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Vertex-wise Examination of Depressive Symptom Dimensions and Brain Volumes in Older Adults

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Abstract

Differences in brain volumes have commonly been reported in older adults with both subthreshold and major depression. However, few studies have examined the association between specific symptom dimensions of depression and brain volumes. This study used vertex-wise analyses to examine the association between specific symptom dimensions of depression and brain volumes in older adults with subthreshold levels of depressive symptoms. Forty-three community-dwelling adults between the ages of 55 and 81 years underwent a structural Magnetic Resonance Imaging scan and completed the Center for Epidemiologic Studies Depression Scale (CES-D). Vertex-wise analyses were conducted using Freesurfer Imaging Suite to examine the relationship between CES-D subscale scores and gray matter volumes while controlling for sex, age, and education. We found distinct associations between depressed mood, somatic symptoms, and lack of positive affect subscales with regional volumes, including primarily positive relationships in temporal regions and a negative association with the lingual gyrus. The relationship between higher depressed mood subscale scores and larger volumes in the left inferior temporal lobe withstood Monte-Carlo correction for multiple comparisons. Results from this preliminary study highlight the importance of examining depression on a symptom dimension level and identify brain regions that may be important in larger studies of depression.

Keywords

Depressive Symptoms; Symptom Dimensions; Aging; Brain; MRI; Vertex-Wise Analysis

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Introduction

Clinically significant depressive symptoms that do not meet the threshold for major depression are common in older adults and have been associated with multiple negative outcomes, including increased health care costs, increased risk for cognitive impairment, functional disability, decreased social support, and increased risk of developing major depression (Lavretsky and Kumar, 2002; Lyness, 2008; Meeks et al., 2011). Increased depressive symptoms have been associated with structural brain changes in fronto-limbic pathways (Kirton et al., 2014; Kumar et al., 1998; Kumar et al., 1997; Taki et al., 2005). These changes include altered brain volumes in frontal and temporal regions including the orbitofrontal cortex, anterior cingulate cortex, temporal pole, amygdala and hippocampus (Disabato and Sheline, 2012; Dotson et al., 2009b; Kumar et al., 1998; Kumar et al., 1997; Naismith et al., 2012; van Eijndhoven et al., 2013). While most studies have reported decreased brain volumes in these regions, variability in the directionality of the relationship between depressive symptoms and structural brain differences have been reported. This variability in the direction and magnitude of brain differences associated with depressive symptoms may be due in part to the heterogeneous nature of depressive symptoms (Hybels et al., 2009). Depression represents a heterogeneous condition, and evidence suggests different depressive symptoms may have unique etiologies and respond differently to treatment (Hasler et al., 2004; Korszun et al., 2004; National Institute of Mental Health, 2003). Examining the different symptom dimensions of depression may provide more insight into the association between depressive disorders and the brain.

Neuroimaging studies examining symptom dimensions of depression are limited, but existing studies have noted dissociable structural and functional brain differences associated with specific symptom dimensions Our group has found that depressed mood symptoms are associated with larger brain volumes in the left posterior cingulate and smaller volumes in the isthmus cingulate (McLaren et al., 2016), and that both depressed mood symptoms and somatic symptoms of depression are associated with increased white matter lesions (Kirton et al., 2014). A recent study showed an inverse relationship of sadness, fatigue and worry with volume in the ventrolateral prefrontal cortex, as well as an inverse relationship of fatigue and irritability with cortical thickness in the rostral anterior cingulate (Lener et al., 2016). Other investigators have reported dissociable functional brain activity associated with different symptom dimensions of depression, including decreased brain activity in the dorsomedial and right ventrolateral prefrontal cortex as a function of higher mood symptoms compared to decreased activity in the pre-genual anterior cingulate as a function of higher somatic-vegetative symptoms (Heinzel et al., 2009). Symptom dimension research is complicated by variations in the measurement and description of specific symptom clusters in depression. Additionally, separately examining different symptom dimensions greatly increases the number of analyses conducted; thus, concerns about type I error lead researchers to limit their analyses to only a few specific regions of interest. The lack of consistency in study methodology and the relatively limited research in this area generally limits researchers' abilities to form strong, a priori hypotheses to guide region of interest selection. As a result, potentially important regions of interest might be missed.

To address this issue, the present study sought to investigate the relationship between symptom dimensions of depression as well as total depressive symptoms and cortical brain volumes in older adults using a vertex-wise analysis that does not require delineation of limited regions of interest. We expected total symptoms to be associated with reduced brain volumes in frontal and temporal regions. As depressed mood and somatic symptoms have been most consistently associated with brain differences, including decreased volumes in frontal regions and increased white matter hyperintensities (Dotson et al., 2009b; Kirton et al., 2014; Périco et al., 2005), we predicted these symptom dimensions would have a stronger association with volume reduction than lack of positive affect symptoms.

Methods

Subjects

Forty-nine healthy older adults (age 55 years and older) were recruited from the University of Florida and the surrounding community. All participants were native English speakers with 9 or more years of education, were right-handed, and had corrected-to-normal vision. All participants obtained a score of 30 or above on the Telephone Interview for Cognitive Status (TICS; Brandt et al., 1988), which has a 94% sensitivity and 100% specificity for detecting dementia (Brandt et al., 1988). Exclusion criteria for the study included self-report of a major medical disorder, including neurological disorder, history of a severe head injury, learning disorder, current use of antiepileptic or antipsychotic medications, current major psychopathology apart from depression or anxiety based on self-report, or in some participants (N = 19), administration of the Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID; First et al., 2002), or not meeting safety criteria for Magnetic Resonance Imaging (MRI). Anxiety disorders were not excluded due to their high comorbidity with depression (Fava et al., 2000); however, only one individual met diagnostic criteria for an anxiety disorder (Anxiety Disorder Not Otherwise Specified). Of the 49 individuals recruited for the study, four were excluded based on these criteria and two were excluded from analyses because of outlier CES-D score values (> 3 standard deviations above the mean). These individuals were removed from analysis out of concern their highly elevated scores may drive the results of the analyses. The final sample included 43 participants (67% female). Sample demographic data are presented in Table 1. The University of Florida's Institutional Review Board approved all study procedures, and participants gave verbal and written informed consent to participate in the study.

Measures

Depressive symptoms were quantified via the Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D is a widely used, 20-item self-report measure of depressive symptoms with a well validated four-factor structure consisting of negative affect, lack of positive affect, somatic symptoms, and interpersonal difficulties subscales (Carleton et al., 2013; Haringsma et al., 2004; Helmes and Nielson, 1998; Radloff, 1977). In this study, the interpersonal difficulties symptom dimension was not analyzed due to its limited range in the sample (0 to 2). Both total and subscale scores for the CES-D were used as continuous measures in the analyses. Three participants were missing one item on the CES-D; thus, analyses did not include their total score or the subscale scores that contained the missing

item. Final sample sizes for each analysis can be found in Table 1. Correlations between the CES-D total and subscale scores are presented in Table 2.

Imaging procedure

Freesurfer Image Analysis Suite (version 5.3) was used for structural data processing and for vertex-wise analyses. Briefly, this processing included motion correction and averaging of T1 weighted images, skull stripping, automated Talairach transformation, subcortical structure segmentation, intensity inhomogeneity correction, gray/white matter boundary tessellation, topology correction, and surface deformation following intensity gradients to insure optimal gray/white and gray/cerebrospinal fluid boarder (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2002; Fischl et al., 2004; Segonne et al., 2004; Segonne et al., 2007; Sled et al., 1998). Images were manually inspected for errors and segmentation errors were corrected. Images were smoothed at 15 full width half maximum. Vertex volumes were calculated by averaging the volume (i.e., surface area * thickness) of the triangles in the cortical surface tessellation that surrounded the vertex. General linear models were conducted in which the total CES-D score or the CES-D subscale scores predicted gray matter volume at each vertex of the brain, controlling for sex, age, and years of education. A Monte Carlo correction for multiple comparisons was implemented to account for type I error (Hagler et al., 2006). We also report the results of analyses using an uncorrected $p \leq 0.001$ threshold for identifying additional ROIs that should be examined in future studies.

Results

Results are summarized in Table 3 and Figure 1. Higher scores on the depressed mood subscale were associated with larger gray matter volumes in the left inferior temporal lobe after correction for multiple comparisons ($k = 399.02$ mm^2, corrected $p < 0.01$), and with larger right paracentral ($k = 66.85$ mm^2, $p < 0.001$) and left superior temporal ($k = 62.09$ mm^2, $p < 0.001$) volumes in uncorrected analyses. Additionally, higher scores on the lack of positive affect subscale were associated with larger gray matter volumes within two clusters in the left lingual gyrus ($k_1 = 89.99$ mm^2, $k_2 = 33.58$ mm^2, $p < 0.001$), and higher levels of somatic symptoms of depression were significantly related to smaller left temporal pole volume ($k = 88.09$ mm^2, $p < 0.001$) in the uncorrected analysis. Total CES-D scores were not associated with gray matter volumes after correction for multiple comparisons, but uncorrected analyses revealed larger right paracentral volumes in individuals with higher total CES-D scores ($k = 45.25$ mm^2; $p < 0.001$).

Given the wide age range in our sample, we performed post-hoc correlations to determine whether or not age was associated with CES-D scores or vertex measurements that were significant in our analyses. Age was not significantly correlated with any of the variables.

Discussion

The present study examined the associations between depressive symptom dimensions and gray matter volumes in a middle-aged to older adult sample with subthreshold levels of depressive symptoms. The primary finding was a relationship between higher severity of depressed mood symptoms and increased left inferior temporal volume. Temporal regions,

including the inferior temporal gyrus, have consistently been implicated in structural imaging studies of both major depression and subthreshold depression (Andreescu et al., 2007; Dotson et al., 2009b; Son et al., 2013; Webb et al., 2014). In contrast to reports of reduced temporal volumes related to depression in many studies, there has been a report of increased grey matter volumes in parts of the left temporal lobe associated with depression (Ballmaier et al., 2004). Additionally, we recently found increased cortical thickness (a component of volume) in the middle temporal gyrus in subthreshold depression within a subset of subjects from the current study (Szymkowicz et al., 2016). Another recent study found increased cortical thickness in the temporal pole of individuals with major depression (van Eijndhoven et al., 2013). Thus, the current findings complement our previous study, are consistent with other investigations, and suggest that the relationship between depressive symptoms and temporal volumes is complex.

In a sample with a similar age range, we previously found that subthreshold depressive symptoms were associated with larger temporal lobe volumes in young-old participants but smaller volumes at more advanced age (Dotson et al., 2009b), suggesting that age is an important moderator of the relationship between depressive symptoms and temporal lobe volumes and might contribute to the variability across studies. We were unable to examine a possible age interaction in the current study due to the sample size. Nonetheless, we extend previous findings by documenting a specific relationship of depressed mood symptoms with the inferior temporal lobes. The inferior temporal lobes have been identified as a component of multiple intrinsic networks, including the central executive network and default mode network, that have been implicated in neuroimaging studies of depression (Kaiser et al., 2015; Wang et al., 2016a; Wang et al., 2016b). The fronto-parietal central executive network, which is involved in external information processing and higher-level cognitive functioning, is thought to contribute to a cognitive vulnerability to depression (Wang et al., 2016b; Zheng et al., 2015). There is evidence that connectivity of the central executive network with the default mode network is decreased in depression and in individuals at high familial risk for depression (Posner et al., 2015; Zheng et al., 2015). The default-mode network is involved in self-referential processing, and aberrant connectivity in this network is thought to have a role in depressive rumination (Hamilton et al., 2015). This interpretation is consistent with the present data since the inferior temporal lobes were specifically associated with depressed mood symptoms, which is more closely tied to depressive rumination than the somatic symptoms and lack of positive affect dimensions of depression.

To further explore potential relationships, we also performed uncorrected analyses, which resulted in distinct relationships of different symptom dimensions with regional volumes in primarily temporal regions. Specifically, depressed mood symptoms were associated with larger paracentral gyrus and superior temporal volume, in addition to the aforementioned relationship with inferior temporal volume; somatic symptoms of depression were associated with smaller volumes in the temporal pole; and lack of positive affect was associated with larger volume in the lingual gyrus. Our findings provide preliminary evidence that symptom dimensions of depression have dissociable relationships with subregions of the temporal lobes. Given the functional heterogeneity of the temporal lobes, identifying the relationship between depressive symptom subtypes and subregions of the temporal lobe represents a

novel approach to enhance our understanding of the underlying etiology and functional consequences of depression.

As previously mentioned, the inferior temporal cortex, associated with depressed mood symptoms in our study, is implicated in depressive rumination. Both the superior temporal gyrus and the temporal pole, associated with lack of positive affect and somatic symptoms in the current study, respectively, have been implicated in emotion processing (Takahashi et al., 2010). The lateral portion of the superior temporal gyrus may play a role in emotional processing as well as social cognition (Allison et al., 2000; Gallagher and Frith, 2003), while the temporal pole is involved in affect regulation (Beauregard et al., 2006; Keedwell et al., 2009). Additional studies in larger samples are needed to verify the link between these temporal regions and symptom dimensions of depression, and to clarify their role in particular symptom dimensions.

We primarily found that higher severity of depressive symptoms was associated with larger regional volumes, but we did find a negative relationship between somatic symptoms and volume in the temporal pole in our exploratory analyses. Depression is often characterized by reduced volumes in frontal and temporal regions (Disabato and Sheline, 2012; Kumar et al., 1998; Naismith et al., 2012), but this is not always found (Frodl et al., 2003; McLaren et al., 2016). Clinical characteristics, such as differences in symptom presentation, might contribute to the variability in findings. In addition, there is evidence that the early stages of first-episode depression are associated with increased volume due to increased metabolic activity and blood flow, and that other mechanisms, such a medication use and stress, over a period of time eventually result in decreased brain volumes (Frodl et al., 2003). Depression-related volumetric enlargement might be driven by increased cortical thickness, which, together with surface area, comprises brain volumes. It has been suggested that early stages of depression may be associated with inflammation that leads to increased cortical thickness (Dowlati et al., 2010; Liberto et al., 2004; Sheline et al., 2003), which is a component of gray matter volume. Subthreshold depressive symptoms, such as those in the present sample, may similarly reflect early stages of the disease. This hypothesis is supported by longitudinal studies demonstrating that subthreshold depressive symptoms increase the risk for clinical depression and can signal the early stages of a clinical episode (Cuijpers et al., 2004; Meeks et al., 2011).

Our findings are consistent with a growing body of research that has demonstrated associations of subthreshold depressive symptoms with both structural and functional brain measures (Dotson et al., 2009a; Dotson et al., 2009b; Dotson et al., 2009c; Hwang et al., 2015; Kumar et al., 1998; Li et al., 2015; Szymkowicz et al., 2016). Of note, we did not find a significant association between frontal lobe volumes and depressive symptoms. This is somewhat surprising, as other studies examining brain volumes in subthreshold depression have identified differences in frontal regions (Dotson et al., 2009b; Taki et al., 2005). Variation in methodologies between studies may have impacted the results. The difference in findings between our study and other similar work highlights the complexities of the relationship between depressive symptoms and brain volumes, and also demonstrates the need for further research in this area.

The study has several limitations. We did not have information about anxiety symptomatology or history of depression for all subjects. Given the common co-occurrence of depressive and anxiety symptoms (Kvaal et al., 2008; Lenze et al., 2000), and the impact of history of depression on neuroimaging measures (Elbejjani et al., 2015; Klauser et al., 2015), future research would benefit from including these variables in analyses. Additionally, given the relatively small sample size, we were unable to examine potentially interesting interactions between depressive symptoms and demographic variables such as age. However, our preliminary results add to the limited literature on structural brain correlates of symptom dimensions of depression by identifying regions of interest for future, larger studies. This line of work has important implications for targeting treatment of depressive disorders based on symptom profiles that map onto specific biological etiologies.

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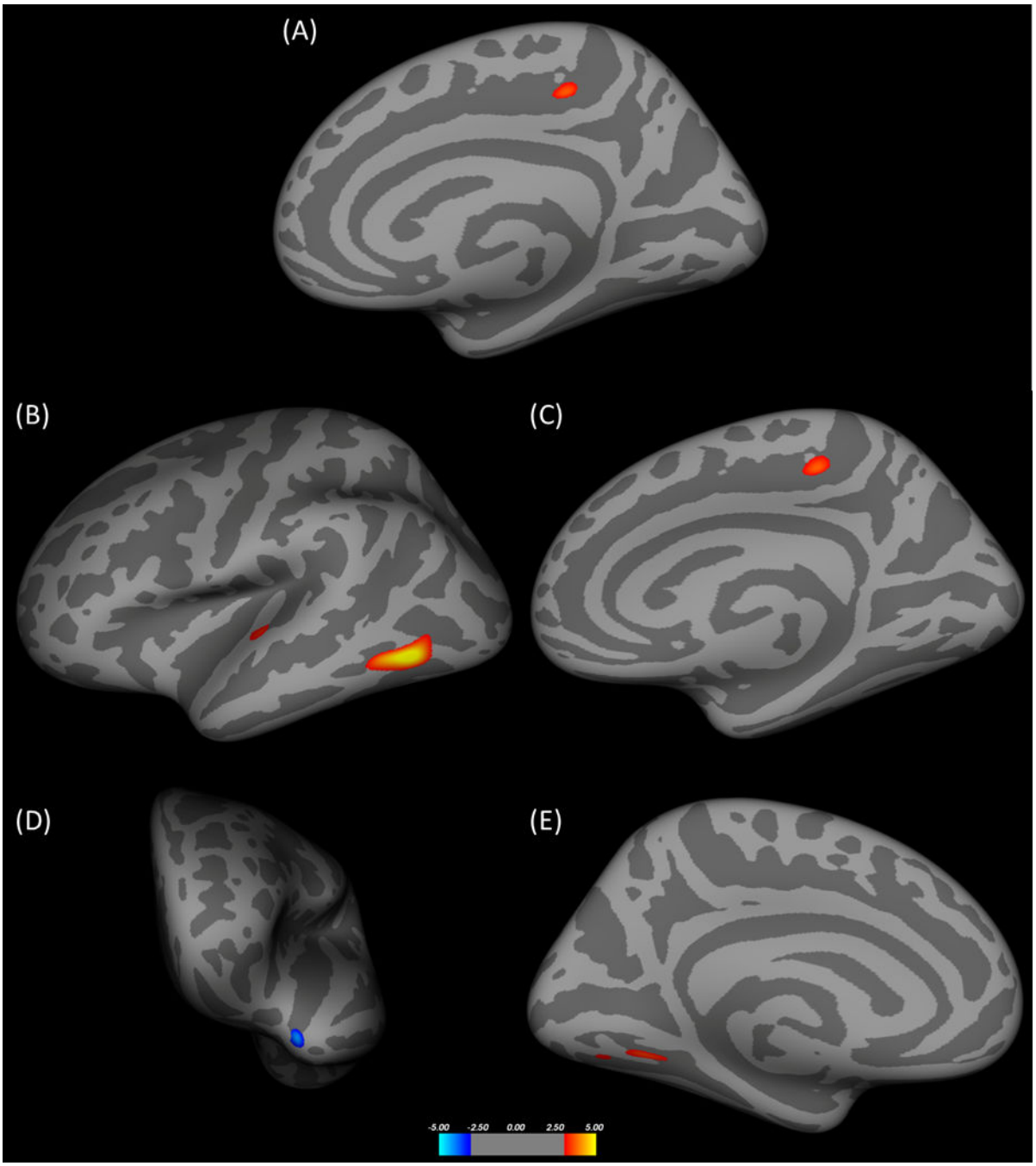

Fig 1.

Significant associations between Center for Epidemiologic Studies Depression Scale scores (CES-D) and brain volumes in the uncorrected analysis. A = total depressive symptoms, B/C = depressed mood subscale, D = somatic symptoms subscale, and E = lack of well-being subscale. Areas in the red to yellow range showed a positive relationship with CES-D scores, with a greater yellow hue representing greater statistical significance. Areas in blue showed

a negative relationship with CES-D scores, with lighter shades representing a greater statistical significance. The color scale is represented as log(p).

Table 1

Sample characteristics and CES-D scores for the sample (67% women)

	Mean	SD	Observed Range	Possible Range
Age (years)	69.45	6.664	55–81	–
Education (years)	15.05	2.581	10–20	–
CES-D total	5.88	4.789	0–20	0–60
Depressed mood	1.05	1.679	0–6	0–21
Lack of well-being	2.38	3.143	0–12	0–12
Somatic	2.35	2.190	0–9	0–21
Interpersonal difficulties	0.12	0.391	0–2	0–6

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

Table 2

Correlations between CES-D total and subscale scores

	Depressed mood	Lack of well-being	Somatic
CES-D total	.629**	.683**	.645**
Depressed mood	–	.085	.451**
Lack of well-being	–	–	.095

Note: The interpersonal difficulties subscale was not included in analyses due to the restricted range of scores. CES-D= Center for Epidemiologic Studies Depression Scale.

** $p < .001$

Table 3

Brain regions showing a significant relationship between volume and CES-D scores.

Region	Side	Coordinates			Cluster Size (mm^2)	*p*
		x	*y*	*z*		
Positive Association						
Total CES-D						
Paracentral Gyrus	R	18.4	−34.2	40.9	45.25	0.0002
Depressed Mood						
Inferior Temporal	L	−48.8	−62.6	−6.0	399.02	<0.0001
Superior Temporal	L	−55.5	−15.6	3.5	62.09	0.0005
Paracentral Gyrus	R	18.3	−34.6	42.7	66.85	0.0002
Lack of Positive Affect						
Lingual Gyrus	L	−24.0	−59.5	−6.4	89.99	0.0003
		−21.1	−74.3	−6.1	33.58	0.0008
Negative Association						
Somatic Symptoms						
Temporal Pole	L	−29.2	8.2	−34.4	88.09	0.0001

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