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Insula thickness asymmetry relates to risk of major depressive disorder in middle-aged to older adults

Erin C. Jones*, Spencer W. Liebel, Emily S. Hallowell, Lawrence H. Sweet

Department of Psychology, University of Georgia, 125 Baldwin Street, Athens, GA 30602, USA

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ABSTRACT

A growing body of research implicates the insula as a critical brain structure in major depressive disorder (MDD), emotional salience, and interoception. Despite a high prevalence of depressive symptoms among middle-aged to older adults and the elevated risks that they confer towards poor outcomes like deteriorating health and suicidality, only limited research has examined the role of the insula in this population. The present study investigates associations between insula thickness and risk of developing MDD in middle-aged to older adults. A composite measure of MDD risk was quantified based upon current Beck Depression Inventory-II scores, current antidepressant medication use, and self-reported history of depression. Linear regressions were performed to analyze the relationships between insula thickness and MDD risk. Linear regression established that left-right insula thickness difference and left insula thickness significantly predicted MDD risk; however, right insula thickness did not. These findings provide evidence of the importance of insula thickness in middle-aged to older adults at elevated risk for MDD, while highlighting the left insula as an area of particular interest.

1. Introduction

Major depressive disorder (MDD) is a persistent, debilitating mood disorder characterized by negative affect, difficulty sleeping, loss of appetite, suicidal thoughts, loss of concentration, anhedonia, and psychomotor agitation or restlessness (American Psychiatric Association, 2013). It is one of the most prevalent psychiatric disorders in the United States, affecting nearly 7% of the American population aged 18 and older at any one time (American Psychiatric Association, 2013). Symptoms of MDD can be cyclical and long-lasting, and affected individuals often experience extended periods of poor functioning in many facets of daily life, including academic achievement, engagement in social activities, and employment (Kessler and Bromet, 2013; World Health Organization, 2017). Furthermore, previous experiences of depressive symptoms are predictive of future depressive episodes and MDD diagnosis (Belmaker and Agam, 2008; Kessler et al., 1997). While the diagnostic criteria for and effects of depressive disorders are well-defined, even depressive symptoms that do not reach the threshold for clinical diagnosis may cause considerable distress and elevate one's risk of symptoms escalating to MDD (APA, 2013; NIMH). This may, in part, be explained by barriers to initial pursuit of treatment that may interact with aging cohort effects, such as lack of education, personal discomfort, and social stigma (Cukrowicz et al., 2011; Epstein et al., 2010; Laborde-Lahoz and Pietrzak, 2015; Pietrzak et al., 2013).

Previous research demonstrates that experiences of depressive symptoms vary over the course of middle to late adulthood, but this relationship is not yet well understood (Newmann et al., 1991). The prevalence rates of MDD in community samples of midlife adults are significantly higher than those of older adults, (Fiske et al., 2009), yet studies utilizing checklists for depressive symptomatology (rather than diagnosis of a depressive disorder) report higher rates of subclinical depressive symptoms among older adults than in midlife (Fiske et al. 2009; Newmann, 1989). Further, evidence suggests that older adults with subclinical depressive symptoms are at a particularly high risk of later converting to MDD (Grabovich et al., 2011). Depressive symptoms in middle-aged to older adults are associated with chronic illness, lower perceived quality of life, and increased risk of suicide (Grabovich et al., 2011; Sapranaviciute-Zabazlajeva et al., 2014; Stahl et al., 2014). Despite endorsing high frequencies of MDD and depressive symptoms, middle-aged to older adults tend to view mild-to-moderate mood symptoms as part of the aging process and believe in the importance of self-reliance to deal with such problems, resulting in the underutilization of effective treatments like cognitive behavior therapy (Fiske et al., 2009; Meadows et al., 2002; Robb et al., 2003; Sapranaviciute-Zabazlajeva et al., 2014; Wetherell et al., 2004). While negative

* Corresponding author.
E-mail address: erin.jones28@uga.edu (E.C. Jones).

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consequences of aging (e.g., loss of close relatives, diminished cognitive abilities, health-related stressors) may partially explain the relatively high occurrence of MDD and depressive symptoms in middle-aged to older adults, the etiology of depressive symptoms and risk for later conversion to MDD in this sample is not well understood (Fiske et al., 2003).

Neural changes in aging adult populations represent one facet that may better explain the underlying etiology of middle-aged to older adults' risk of developing MDD (Ajilore et al., 2015; Szymkowicz et al., 2016). Evidence suggests that the insula, a region associated with emotional salience, allocation of attention during emotional tasks, and interoception (i.e., the sensation of internal states that contribute to emotional experience), may be of particular importance in this relationship (Phan et al., 2002; Critchley et al., 2004; Pandaya et al., 2012; Paulus and Stein, 2010). Other psychiatric disorders associated with heightened awareness of physiological states, such as anxiety disorders (Critchley et al., 2004) and substance use disorders (Naqvi and Bechara, 2009), have been linked to the insula. Thus, abnormal interoceptive awareness may explain the internal and somatic focus of depressive symptoms (Avery et al., 2014; Paulus and Stein, 2010). Consistently, morphometric indices of the insula have been associated with MDD in adolescents and adults, but this relationship has not yet been extended to middle-aged to older adults endorsing depressive symptoms (Foland-Ross et al., 2015; Qiu et al., 2014; Reynolds et al., 2014).

Existing evidence suggests that lateralization of cortical thickness may also be related to MDD risk. To wit, Foland-Ross et al. (2015) found thicker left insula gray matter in adolescent girls who later became clinically depressed compared to those who did not. A substantial literature details lateralized activation abnormalities in the insula and limbic structures during affective stimulation in patients exhibiting depressive symptoms (Pandaya et al., 2012; Schmaal et al., 2017; Singh and Gotlib, 2014). Consistent with these findings, a meta-analysis by Wager et al. (2003) noted increased left insula activation during the experience of negative emotions such as anger, sadness, or anxiety in response to aversive stimuli (Barberini et al., 2012; Spielberg et al., 2008). Additional studies have reported associations between increased left insula activation and higher emotional intelligence scores when viewing sad or fearful facial expressions (Quarto et al., 2016). Finally, increased activity and glutamate levels in the left insula have been linked to other affective disorders such as alexithymia (Ernst et al., 2014). Thus, extant evidence suggests left hemisphere limbic structures may play a unique role in the processing and experiencing of negative emotions such as those associated with depression. Nevertheless, the extent to which asymmetry of insula thickness is associated with MDD risk in middle-aged to older adults remains to be determined.

Considering prior research linking the insula to emotional processing and suggesting that lateralized activation may be a marker of MDD risk, it stands to reason that variation in insula thickness may afford increased sensitivity to MDD risk assessment and inform neural models of depressed mood. Subclinical depressive symptoms have serious implications for present functioning and, along with historical markers (e.g., prior self-reported depression or intervention), suggest increased risk for subsequent MDD onset (Kessler et al., 1997). Thus, it is critical to understand whether fundamental brain processes may provide insights that may inform prevention and intervention efforts in middle-aged to older adults. In the present study, we examined the relationships between left and right insula thickness and MDD risk in a sample of middle-aged to older adults. We hypothesized that increased left and right insula thickness would be significantly and positively predictive of MDD risk composite scores. Based on previous lateralization research, we also expected that this effect would be stronger in the left than the right insula.

Table 1
Participant demographics, MRI measures, self-report depression symptomatology data, and composite CVD and MDD scores.

	M	SD	Minimum	Maximum
Age	63.18	8.08	50	85
Level of education (years)	15.57	2.36	10	23
Left insula thickness (mm)	2.92	0.17	2.48	3.23
Right insula thickness (mm)	2.94	0.16	2.53	3.23
Intracranial Volume (cm^3)	1492.71	149.05	1112.04	1934.58
CVD Risk Score	2.49	1.53	0	7
BDI-II	4.44	4.58	0	17
MDD Risk	5.15	4.58	0	19
MDD Risk (Square-root transformed)	1.97	1.14	0	4.36
	Number of participants		***Proportion of sample***	
"Have you ever had depression in the past?"	Yes = 25		45.5%	
	No = 30		54.5%	
"Are you currently taking medication to treat depression?"	Yes = 14		25.5%	
	No = 41		74.5%	

Note: MRI = Magnetic resonance imaging; BDI-II = Beck Depression Inventory, Second Edition (Beck et al., 1996); MDD = Major Depressive Disorder; MDD risk score = combination of the BDI-II, and Yes/No answers to self-report questions of past presence of depression and current antidepressant medication use; CVD = Cardiovascular Disease; CVD risk score = combination of self-report measures including previous CVD diagnoses, current CVD treatments, and current CVD risk factors.

2. Methods

2.1. Participants

A community sample of 55 healthy middle-aged to older adults (38 female) was recruited from the Providence, Rhode Island area via newspaper ads and flyers as part of a larger study of heart function. Ages ranged from 50 to 85 years (M age = 63.18; SD = 8.08). Mean level of education was 15.57 years (SD = 2.36) (see Table 1). Inclusion criteria were: score ≤ 19 on the Beck Depression Inventory-II (BDI-II), right-handed, English speaking, over the age of 50 years, and normal or corrected vision and hearing at the time of testing. Potential participants were excluded if they had a history of neurological disease (e.g., Alzheimer's disease, stroke, multiple sclerosis, traumatic brain injury with loss of consciousness), substance abuse that resulted in hospitalization, diagnosis of current psychiatric illness, or any magnetic resonance imaging (MRI) contraindications (e.g., ferrous metal implants). All participants provided written informed consent prior to study participation and were monetarily compensated. The present study was carried out in accordance with the latest version of the Declaration of Helsinki and was approved by the Institutional Review Boards of Butler Hospital and Brown University (Providence, Rhode Island).

2.2. Measures

2.2.1. MDD Risk

All participants completed the questionnaires that comprise the MDD risk score prior to MRI. A composite measure of MDD risk was created comprising self-reported history of depression, current antidepressant medication use, and depressive symptoms within the past two weeks using the Beck Depression Inventory-Second Edition (BDI-II; Beck et al., 1996). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) notes that depressive symptom severity and chronicity are key in describing the development and course of MDD (APA, 2013). Indeed, a past episode of depression is the most robust predictor of future episodes (Levinsohn et al., 1989; Rudolph et al., 2009). Further, previous research suggests that sum-score measures of depression alone are not sufficient in encapsulating the

heterogenous nature of depressive symptoms and MDD (Fried and Nesse, 2015). Thus, given the present study's aim to examine neural predictors of MDD risk, we chose both current and historical markers as components of the MDD risk composite measure.

The BDI-II is a 21-item self-report inventory that demonstrates adequate sensitivity and specificity in distinguishing subclinical from clinical depressive symptomology (Smarr and Keefer, 2011; Wang and Gorenstein, 2013). For example, psychiatric, institutionalized, and medical MDD samples exhibit significantly higher mean BDI-II scores than nondepressed control subjects (Wang and Gorenstein, 2013). The BDI-II is considered a reliable and valid measure of depressive symptomatology for individuals aged 13 and older, and studies have confirmed the psychometric utility of using the BDI-II for persons in middle and older adulthood specifically (Segal et al., 2008; Steer et al., 2000). Items are scored on a scale of 0–3 in a list of four statements arranged in increasing severity about a particular symptom of depression. Items are summed to provide a single score. For the current study, participants scoring ≤ 19 on the BDI-II were included in analyses. The score of ≥ 20 is a common cutoff for *moderate* depressive symptomatology (Beck et al., 1996; Smarr and Keefer, 2011; Wang and Gorenstein, 2013). To investigate subclinical depressive symptoms, we included only those participants who scored in the *mild* range or lower. The range of possible MDD risk scores in the present study was calculated by summing its three components for a possible score from 0 to 21 points: 0–19 BDI-II score, 0 or 1 for current antidepressant usage, and 0 or 1 for self-reported history of depression.

2.2.2. Cardiovascular Disease (CVD) Risk

As participants in the current study were recruited for the parent study on heart function, the potential role of CVD risk was explored. CVD risk was measured on a scale from 0–8 by adding one point for each of the CVD diagnoses (angina, arrhythmia, hypertension), treatments (medication for CVD), or risk factors (diabetes, high cholesterol, current smoking, first degree relative with CVD) reported by the participant.

2.2.3. MRI Acquisition and Analysis

Scans were performed using a 3 Tesla Siemens Tim Trio scanner with a 32-channel head receiver array and body resonator transmit coil located on the Brown University campus. Participants were placed head first in the supine position. Following acquisition of a three-axis localizer scan, a 3D T1-MPRAGE scan was acquired with 1 mm isotropic resolution. Scan acquisition parameters (Repetition Time = 1900 ms, Echo Time = 2.98 ms, Inversion Time = 900 ms, and readout flip angle = 9°) were selected to provide a 3D T1 image dataset for gray-white matter segmentation used in the analysis of cortical thickness. Insula thickness was quantified individually in each hemisphere according to the Desikan atlas boundaries using the Freesurfer version 5.3 image analysis suite (Desikan et al., 2006; Fischl and Dale, 2000).

2.3. Statistical Analyses

Linear regressions were performed to analyze the relationships between insula thickness and MDD risk while controlling for participant age, sex, years of education, and intracranial volume. A square root transformation was applied to correct left skewness in MDD risk scores. One extreme outlier (> 2 standard deviations from the mean) was Winsorized to limit influence on the distribution (Dixon, 1960). Given prior literature on insula asymmetry, left-right difference scores (right thickness was subtracted from the left) were calculated for each participant to examine expected asymmetry effects on MDD risk. A paired samples *t*-test was performed to examine group differences in left and right insula thickness. Finally, because the parent study for this data examined cardiac function in middle-aged to older adults, we performed zero-order correlations to explore potential associations between CVD risk, insula thickness, and our MDD risk composite score.

Table 2
Zero-order correlations between variables of interest.

	1	2	3	4	5	6
1. MDD risk score	–					
2. Left insula thickness	0.301*	–				
3. Right insula thickness	0.014	0.450***	–			
4. Left-Right insula thickness difference	0.293*	0.617***	−0.396**	–		
5. Age	0.201	−0.089	−0.378**	0.256	–	
6. Years of education	−0.215	0.082	0.239	−0.069	−0.114	–

Note: BDI-II = Beck Depression Inventory, Second Edition (Beck et al., 1996); MDD = Major Depressive Disorder; MDD risk score = combination of the BDI-II, and Yes/No answers to self-report questions of past presence of depression and current antidepressant medication use. * = $p < 0.05$, ** = $p < 0.01$; *** = $p < 0.001$.

The statistical threshold for all analyses was set at a two-tailed $p < 0.05$. Data were analyzed using Statistical Package for the Social Sciences (SPSS; version 22).

3. Results

Linear regression established that left-right insula thickness difference ($\beta = 2.256$, $t[45] = 2.053$, $p = 0.046$) and left insula thickness ($\beta = 2.046$, $t[45] = 2.118$, $p = 0.040$) significantly predicted MDD risk when controlling for age, sex, years of education, and intracranial volume, but right insula thickness did not ($\beta = 0.106$, $t[45] = 0.091$, $p = 0.928$). The individually quantified difference between left and right insula thickness was significantly associated with MDD risk scores ($r = 0.293$, $p = 0.046$); however there was no significant difference between the two structures when contrasted at the group level ($t[51] = -1.102$, $p = 0.276$). Left ($r = 0.301$, $p = 0.040$) but not right ($r = 0.014$, $p = 0.928$) insula thickness was significantly correlated with MDD risk scores such that a thicker left insula was associated with more MDD risk (see Table 2). Exploratory zero-order correlations showed no significant association between CVD risk and age ($r = 0.120$, $p = 0.400$), years of education ($r = 0.193$, $p = 0.174$), left ($r = -0.104$, $p = 0.476$) or right ($r = 0.012$, $p = 0.933$) insula thickness, left-right insula thickness difference ($r = -0.143$, $p = 0.317$) or MDD risk ($r = -0.134$, $p = 0.347$).

4. Discussion

The primary objective of the present study was to investigate neural predictors of MDD risk in a sample of middle-aged to older adults. We extend the findings of prior studies that have linked insula and depressive symptomatology by reporting associations between insula thickness and MDD risk in middle-aged to older adults. It was hypothesized that insula, and particularly left insula, thickness would predict MDD risk based upon extant literature linking the insula to affective disorders and lower interoceptive awareness (Critchley et al., 2004).

Overall, our results support our hypotheses and extend the findings of prior studies by linking insula thickness and MDD risk in middle-aged to older adults. Congruent with our hypotheses and previous lateralization research, asymmetrical insula thickness, left relative to right, significantly predicted higher MDD risk. Unexpectedly, right insula thickness was not associated with MDD risk, whereas left insula thickness was. These findings suggest that the left insula is uniquely associated with MDD risk among middle-aged to older adults and that its thickness relative to its right hemisphere homologue is particularly informative. Finally, zero-order correlations examining CVD risk yielded no significant results; CVD risk was not significantly associated with age, years of education, MDD risk, or any measure of insula

thickness.

Previous research suggests a notable link between CVD and MDD (Dhar and Barton, 2016; Hare et al. 2014; Musselman et al., 1998). The present sample, drawn from a larger study on heart function, offered a unique opportunity to explore the relationship between various cardiac functions and MDD risk. However, it should be noted that participants in this sample were not current CVD patients. Because the aim of the present study was to examine the relationship between insula thickness and MDD risk in relatively healthy middle-aged and older adults, those with serious cardiac dysfunction were excluded from the present sample. It is possible that the present study yielded no significant link between CVD risk and MDD risk because participants did not have seriously impaired heart function. More research is needed to examine this relationship; future studies could examine the link between insula thickness and MDD risk in cardiac patients specifically.

The present results linking insula thickness and MDD risk may be explained by the role that the insula plays in sensation and reactivity to internal body states. The insula is a primary hub of interoception pathways that links limbic and executive systems, and disruption of insula signaling can affect multiple aspects of current and anticipated feeling states, as well as cognitive and social functions related to decision-making. (Paulus and Stein, 2010). Altered interoceptive awareness has also been linked to heightened negative self-evaluation as well increased anticipation of future pain (Hirsch et al., 2003; Reiss, 1997). In prior studies MDD has been associated with changes in mood, social, and cognitive states, as well as rumination and worse decision-making that have been linked to insula morphometry (Kircanski et al., 2015; Lackner and Fresco, 2016). The present study is the first to demonstrate a link between insula morphometry and middle-aged to older adults' risk of MDD.

The present study is consistent with previous findings that specifically link thicker frontal cortex to depressive symptoms as a function of severity and duration (Foland-Ross et al., 2015). While decreases in cortical thickness have been reported in patients who have been diagnosed with MDD (Ajilore et al., 2010; Tu et al., 2012; van Eijnhoven et al., 2013), the opposite has been found when examining non-clinical participants or those experiencing early signs of the disorder (Qiu et al., 2014; Reynolds et al., 2014; Szymkowicz et al., 2016).

One potential explanation for observed increased cortical thickness in the left insula as a function of depressive symptoms is inflammation (Qiu et al., 2014). Dowlati et al. (2010) suggest that depressed patients exhibit higher than average concentrations of proinflammatory cytokines: proteins that stimulate astrocytes to facilitate neurogenesis, thus potentially increasing cortical thickness (Liberto et al., 2004). It is yet to be determined which areas of the brain are most susceptible to cytokine-related neurogenesis, but the present findings would be consistent with an inflammatory response in the left insula.

Extension of previous research to a sample of middle-aged to older adults is of particular importance as this population faces a unique set of health outcomes secondary to depressive symptoms and MDD (Saint Onge et al., 2014). Many studies suggest that depressive symptoms in middle-aged to older adults follow a chronic course, and that MDD prevention is much more effective than treatment (Comijs et al., 2015; Stahl et al., 2014). Further, older adults especially demonstrate an elevated risk of developing MDD (Grabovich et al., 2011). Because of the potential consequences of depressive symptoms and MDD in middle-aged to older adults, identifying early risk factors for use in screening middle-aged to older adults would also likely mitigate other negative health outcomes. While prophylactic treatment with antidepressant medication is often prescribed in certain adult patient populations at statistically higher risk of developing depression, little research has examined this relationship in otherwise healthy middle-aged to older adults (Lydiatt et al., 2013; Udina et al., 2014). The present study suggests that left insula thickness and hemispheric asymmetry may be important early neural markers of MDD risk in middle-aged to older adults and could help drive targeted monitoring and intervention efforts to prevent depressive symptoms from worsening in late life.

The present study has several notable limitations. First, the modest sample size (N = 55) limits the statistical power of our analyses, and narrow sample demographics (highly educated, predominantly Caucasian) limit the generalizability of these findings to broader populations. Future studies should examine the relationship between insula thickness and risk of depression in more ethnically diverse samples. Another limitation of this study is that the present sample had a wide age range (ages 50 to 85 years; M age = 63.18; SD = 8.08). There is little agreement within MDD literature as to how to define "older" adult populations, and whether "middle-aged" or "young-old adults" constitute a different population than "old-old adults." Finally, because the BDI-II is a self-report measure, the validity of the present study's MDD composite score could be threatened by exaggerated or understated reports of current physical and emotional symptoms of depression.

The present study offers evidence of structural predictors of MDD risk. More research is needed to fully elucidate the specific biological mechanisms by which left insula thickness and insula asymmetry are associated with depressive symptomatology and subsequent MDD risk in middle-aged to older adults. Because many MDD interventions act on interoceptive systems, the present study suggests it is possible that long-term therapeutic efficacy of such treatments may be reflected in less left insula thickness and decreased asymmetry relative to the right insula. Additional research is also needed to better understand the onset and course of depressive symptoms and insula morphometry in middle-aged to older populations.

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Declarations of interest

None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2018.12.011.

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