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Precuneus Abnormalities in Middle-Aged to Older Adults with Depressive Symptoms: An Analysis of BDI-II Symptom Dimensions

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Abstract

We recently reported age-related increases in left precuneus cortical thickness (CT) in older adults with elevated total depressive symptoms. However, it is unclear whether abnormalities in precuneus surface area (SA) are also evident and whether specific symptom dimensions of depression moderated age effects on these measurements. Seventy-three adults completed the Beck Depression Inventory – 2nd edition (BDI-II) and underwent structural neuroimaging. Measures of CT and SA were extracted from the right and left precuneus via FreeSurfer. Regression models included regions of interest as dependent variables, with age, BDI-II subscale scores (e.g., affective, cognitive, and somatic symptoms), and their interactions as independent variables, controlling for mean hemispheric thickness (for CT) or total intracranial volume (for SA). A significant age $\times$ somatic symptom interaction was found for left precuneus CT, such that elevated levels of somatic symptoms were significantly associated with age-related cortical thinning. No depressive symptom dimensions moderated the relationship between age and SA, suggesting that CT may be a more sensitive measure of brain abnormalities in middle-aged to older adults with depressive symptoms.

Keywords

Aging; MRI; Morphometry; Depression

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1. Introduction

The precuneus, a region located in the posterior portion of the medial parietal cortex, is reciprocally connected with various cortical and subcortical structures (Cavanna and Trimble, 2006). It is a core part of the default mode network (Buckner et al., 2008; Utevsky et al., 2014) and is involved in a wide range of higher-order cognitive functions, including self-referential processing, episodic memory, and working memory (Cavanna and Trimble, 2006; Freton et al., 2014; Nejad et al., 2013), all of which have been shown to be affected, to some degree, by both aging and depression (Gutchess et al., 2010; Nejad et al., 2013; Rock et al., 2014; Stanley et al., 2015). Thus, the precuneus may play an important role in age- and depression- related cognitive dysfunction and its structural integrity may provide insight into deficits in the existing neural circuitry that is related to specific cognitive functions.

Cortical volume is an index of the brain's structural integrity that is derived from both cortical thickness (CT) and surface area (SA) measurements. These components have been found to be genetically independent and involve different neurobiological mechanisms (Panizzon et al., 2009; Rakic, 2009). Consistent with this are findings of either non-existent or weak correlations between CT and SA in general across various brain regions (Dotson et al., 2015; Hogstrom et al., 2013; Winkler et al., 2010). In normal aging, CT may be a more sensitive measure of age-related atrophy, particularly in regions outside of the prefrontal cortex (Lemaitre et al., 2012).

While fronto-subcortical structural alterations are most commonly reported in older adults with depressive symptoms (Sacher et al., 2012; Sexton et al., 2013), alterations in other brain regions, such as the precuneus, have also been shown (Frodl et al., 2008; Ries et al., 2009; Smith et al., 2009; Truong et al., 2013). In MDD, discrepant findings with respect to precuneus CT have been reported, with increases in CT reported in younger compared to older individuals with MDD (Truong et al., 2013) and decreases in CT typically reported when comparing individuals with MDD to healthy controls (Frodl et al., 2008; Lim et al., 2012). With respect to subthreshold depressive symptoms, which are clinically relevant symptoms of depression that do not fully meet clinical criteria for MDD, we recently showed that older adults with elevated total depressive symptoms have greater CT in the left precuneus (Szymkowicz et al., 2016b). However, it is unclear whether abnormalities in SA of this region are also evident. By assessing the individual components comprising volumetric measurements, we can obtain a better understanding of the specific brain changes associated with different factors, such as aging and depression.

Of particular interest for the current study are specific symptom dimensions of depression. Depression is a heterogeneous disorder in which symptoms can be broken down into specific symptom factors (e.g., depressed affect, somatic symptoms, etc.; Elhai et al., 2012; Shafer, 2006) that show differential relationships with neural correlates (Dotson et al., 2009; Kirton et al., 2014; McLaren et al., 2016), cognitive functions (Baune et al., 2007; Brailean et al., 2016; Dotson et al., 2014; Turner et al., 2015), and health-related outcomes (Blazer and Hybels, 2004; Gallo et al., 1997). It has been suggested that this symptom dimensional approach to depression may help clarify how different symptom presentations are related to

specific outcomes and neurobiological mechanisms (Brailean et al., 2016; Fried and Nesse, 2015a, b; Fried et al., 2014).

The primary aim of the current study was to examine whether subthreshold depressive symptom dimensions (i.e., cognitive, affective, and somatic symptoms) are differentially associated with morphometric (i.e., CT and SA) measurements of the precuneus in community-dwelling middle-aged to older adults. Of specific interest was whether depressive symptom dimensions moderated age effects on these measurements of the precuneus. Consistent with our previous findings (Szymkowicz et al., 2016a; Szymkowicz et al., 2016b), we hypothesized that we would see age-related declines in SA and that elevated somatic symptoms would be associated with less age-related cortical thinning. We aimed to do so by using a different and larger sample of community-dwelling adults and a different measure of depressive symptoms than in our previous studies.

2. Materials and methods

2.1 Participants

Data were used from the ACTIVE Brain study (Porges et al., 2017; Seider et al., 2016) at the University of Florida, an ongoing study exploring cognitive and multi-modal neuroimaging measures as predictors of age-related cognitive dysfunction. Eighty-nine community-dwelling middle-aged to older adults were recruited from the Gainesville and North Florida region. Participants were excluded from this study if they self-reported a history of major neurological (e.g., stroke, multiple sclerosis), psychiatric (e.g., schizophrenia), or other medical illness (e.g., diabetes), if they failed a brief cognitive screener (Montreal Cognitive Assessment [MoCA] < 20; Nasreddine et al., 2005) or if they had any magnetic resonance imaging (MRI) contraindications ($n = 12$). Our final sample consisted of 77 individuals [6 middle-aged (aged 40–54 years), 14 young-old (aged 55–64 years), 23 middle-old (aged 65–74 years), and 34 old-old (aged 75+ years)]. See Table 1 for presentation of demographic data. Individuals with self-reported MDD were not excluded in order to increase the range of depressive symptom severity in the sample. Eighteen participants had a self-reported MDD diagnoses, three of whom were taking antidepressant medication (all selective serotonin reuptake inhibitors), as were two others who did not self-report a history of depression (serotonin-norepinephrine reuptake inhibitor, tricyclic antidepressants). All procedures were approved by the University of Florida's Institutional Review Board and all participants provided both verbal and written informed consent.

2.2 Measures

Depressive symptoms were measured using the Beck Depression Inventory – 2nd edition (BDI-II; Beck et al., 1996), a widely used 21-item self-report questionnaire assessing the frequency and severity of depressive symptoms over the previous two weeks. Scores on the individual items range from 0–3, with total scores ranging from 0–63. The BDI-II is an adequate tool to screen for depression in various populations and has strong psychometric properties in community-dwelling middle-aged to older adults (Segal et al., 2008). Previous studies have found that the BDI-II can be broken down into separate affective, cognitive, and

somatic subscales (Beck et al., 2002; Vanheule et al., 2008) that hold in both clinical and non-clinical samples. Table 2 notes the items comprising each subscale used in our analyses.

2.3 MRI Data Acquisition

MRI data were collected on a Philips (Amsterdam, Netherlands) 3-Tesla scanner at the University of Florida's McKnight Brain Institute Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) facility. A 32-channel head coil was placed over the participant's head as they lay in a supine position on the scanner bed. To minimize noise while in the scanner, participants were given earplugs and headphones. Foam padding was used to minimize head movement during the scan. Structural images were acquired using a high resolution, T1-weighted turbo field echo anatomical scan using the following parameters: TR = 7 ms, TE = 3.2 ms, 170 slices acquired in a sagittal orientation, field of view = 240×240 , flip angle = 8 degrees, 1 mm cubic resolution.

2.4 MRI Data Extraction

The Freesurfer image analysis suite (version 5.3, <http://surfer.nmr.mgh.harvard.edu>) was used to extract measures of CT and SA for the precuneus in each hemisphere (see Dale et al., 1999; Fischl and Dale, 2000 for technical details of these procedures) from cortical parcellation. Processing included motion correction, removal of non-brain tissue (Segonne et al., 2004), automated Talairach transformation, segmentation of the subcortical structures (Fischl et al., 2002; Fischl et al., 2004), 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 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). Using an automated algorithm, CT estimates were 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). SA was calculated along the white matter surface boundary. This surface was then tessellated and the value for each region of interest represented the sum of the area of all of the triangles that comprise each cortical parcellation. After the automated surface reconstruction, data were manually inspected to ensure adequate quality and accuracy.

2.5 Statistical Analysis

All analyses were conducted using SPSS 22.0 software (Armonk, NY). Prior to statistical analysis, we screened all data for outliers by computing standardized z-scores. Outliers were identified as $z > \pm 3$ standard deviations above the mean and removed from analyses ($n = 1$; BDI-II scores). Correlational analyses were run to determine the relationship between morphometric measures. Separate hierarchical regression analyses were conducted for right and left precuneus CT and SA, with age, BDI-II subscale scores, and their interaction as the independent variables, and mean hemispheric thickness (for CT) or total intracranial volume (for SA) as covariates. The affective, cognitive, and somatic subscales of the BDI-II were entered simultaneously in the same regression models to examine the independent association of each subscale while controlling for other scores. Sex (male/female), education (years), current antidepressant usage (no/yes), and self-reported depression diagnosis

(absent/present) were initially entered as covariates, but were removed from final analyses due to lack of statistical significance. All variables were continuous measures in the models. Age and symptom subscale scores were mean-centered and multiplied to create the interaction terms. We used a statistical significance threshold of $\alpha = 0.05$, uncorrected. Effect sizes are reported as partial eta-squared (η_p^2), for which 0.01 indicates a small effect, 0.06 a medium effect, and 0.14 a large effect (Cohen, 1969).

3. Results

3.1 Correlations

Table 3 depicts the relationship between morphometric measures. Right and left hemispheric measurements for CT and for SA were very strongly correlated (r^2 's > 0.80 , p 's < 0.001). CT measures were not significantly correlated with SA measures (p 's > 0.05).

3.2 Hierarchical Regressions

Results are summarized in Table 4 and Figure 1. Main effects of age were seen for bilateral SA (right: $p = 0.012$; left: $p = 0.003$), such that older age was associated with less SA. Main effects of somatic symptoms were seen for right precuneus CT ($p = 0.018$), such that more symptoms were associated with greater CT. An age $\times$ somatic symptom interaction was found for left precuneus CT ($p = 0.032$), such that higher levels of somatic symptoms at younger ages was associated with greater CT, while higher levels of somatic symptoms at older ages was associated with less CT. There were no other significant main effects or age $\times$ BDI-II subscale interactions for the other regions of interest.

4. Discussion

The present study investigated associations between subthreshold depression in healthy middle-aged to older adults and cortical alterations of the precuneus, particularly with respect to symptom dimensions of depression. Using data from a large sample of community-dwelling adults, our findings suggest that elevated levels of somatic symptoms were associated with age-related decreases in CT. Depressive symptom dimensions did not moderate the relationship between age and SA, suggesting that CT may be a more sensitive measure of brain abnormalities in middle aged to older adults with depressive symptoms.

We previously examined the relationship between depressive symptoms and precuneus CT using a smaller sample of older adults from the same North Florida region. Instead of using the BDI-II, we examined symptom dimensions as measured by subscales of the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). After controlling for age and other demographic variables, total depressive symptom severity was associated with increased precuneus CT (Szymkowicz et al., 2016b). Additional analyses investigating age by CES-D interactions found that higher total depressive symptoms were associated with less age-related cortical thinning and this relationship was driven by somatic symptoms (Szymkowicz et al., 2016a). Reasons for the discrepancy in the association between depressive symptoms and precuneus CT in the previous and current study are unclear. Nevertheless, using a larger community sample with a wider age range and different

depression measure, the current study also highlights the importance of CT alterations of the precuneus in adults with depressive symptoms.

Previous research has found that precuneus CT and SA measurements were not correlated (Bruner et al., 2015; Panizzon et al., 2009), which was also found in the current study. Our findings of age-related decreases in SA are not surprising, as research generally shows consistent declines in these measurements across most cortical regions (Lemaitre et al., 2012; Storsve et al., 2014). In addition, we did not find age-related decreases in CT, which is consistent with previous findings (Dickstein et al., 2007; Freeman et al., 2008; but also see Hutton et al., 2009, Lemaitre et al., 2012); rather, it was the combination of age and increased somatic symptoms that was associated with cortical thinning. It may also be the case that CT measurements are more sensitive to detect possible neurodegeneration in pre-clinical and subthreshold symptom samples. More research is needed to better understand these hypotheses.

Our results add to the limited, but growing, literature on symptom dimensions of depression. Previous work has shown stronger associations of somatic symptoms, compared to other symptom dimensions, with cognitive functioning (Brailean et al., 2016; Korten et al., 2014) and both gray and white matter changes in the brain (Dotson et al., 2013; Kirton et al., 2014; Tang et al., 2014; Thames et al., 2015). Moreover, higher levels of somatic symptoms have been shown to predict more neuroinflammation in women with MDD (Dannehl et al., 2014), suggesting that somatic symptoms, rather than depressive symptoms as a whole, may be related to factors that are known to mediate the cognitive and brain changes seen in MDD.

The association of somatic, but not affective or cognitive, symptoms with the precuneus is also consistent with previous literature. In healthy participants, higher levels of self-reported somatization were associated with abnormal functional connectivity in the precuneus, posterior cingulate gyrus, and anteromedial thalamus (Lemche et al., 2013). The authors suggest that somatization may be related to rumination, which has been shown to alter metabolism and brain activity in default mode regions (Nejad et al., 2013). Moreover, compared to healthy controls, medication-naïve individuals who are experiencing their first-episode of somatization disorder had hypoactivity in the precuneus at rest (Su et al., 2014). This is interesting because default mode regions typically show hyperactivity at rest (Greicius et al., 2003; Raichle et al., 2001), suggesting that there are alterations in precuneus functioning in individuals with elevated somatic symptoms. Additional research is needed to investigate the importance of these precuneus structural and functional alterations and how they affect psychological and cognitive processes across the lifespan.

The current study is not without limitations. Our sample of middle-aged to older adults was highly educated and predominantly white, which may limit the generalizability of these results to other community samples. Our sample also had a wide range of MoCA scores (20–30) and it is possible that a small minority of participants in this study met criteria for mild cognitive impairment (MCI) and/or dementia. The findings reported here may be driven by atrophy secondary to a neurodegenerative process; thus, the current findings should be interpreted with caution until replicated in a larger, independent sample where MCI/dementia status is clearly indicated. Further, information regarding anxiety symptoms was

not available for participants in our study; therefore, we were unable to determine the influence of anxiety on the present results. Additionally, our sample size was not large enough to run our own factor analyses of the BDI-II. It is possible that our own data may have a different factor structure, which could influence our understanding of the current results. Moreover, we assessed depressive symptoms on a continuum of severity, with possibly only a small percentage of participants meeting criteria for clinical depression. Therefore, our conclusions are limited to community-dwelling older adults and more research is needed to determine the extent to which our findings can be replicated in clinically depressed samples. Finally, it is possible that our findings were driven by those individuals who self-reported a history of depression. Additional research investigating current subthreshold depressive symptoms in individuals with and without a history of depression is needed to further elucidate these findings.

In conclusion, increased understanding of the relationship between brain structure and symptom dimensions of depression across the lifespan is important and could benefit future research by encouraging the development of targeted treatments for depression based on an individual's specific symptom presentation. In this study, we found elevated levels of somatic symptoms to be associated with age-related cortical thinning. More research is needed to better understand the possible mechanisms through which symptom dimensions of depression are associated with the precuneus during aging.

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Figure 1.

Age $\times$ BDI-II somatic symptoms interaction for left precuneus cortical thickness, $p = 0.032$. The dotted line signifies the relationship between age and somatic symptoms, on average, on left precuneus cortical thickness. For graphing purposes, and to show the differential relationship of somatic symptom severity, groups were split into low and high somatic symptoms; however, scores were entered into the statistical models as continuous variables. BDI-II = Beck Depression Inventory, 2nd edition.

Table 1

Sample demographic characteristics (n = 77)

	Mean	SD	Range
Age (years)	71.79	10.61	43–93
Sex (% female)	62.33	–	–
Education (years)	16.14	2.68	12–20
Race/Ethnicity	–	–	–
% Caucasian	92.21	–	–
% Non-Hispanic	93.51	–	–
MoCA Total Score	26.00	2.58	20–30
BDI-II Total Score	4.51	5.11	0–33
BDI-II Affective Subscale Score	0.42	1.00	0–7
BDI-II Cognitive Subscale Score	1.05	2.06	0–13
BDI-II Somatic Subscale Score	3.04	2.83	0–13
Precuneus Measurements	–	–	–
R Cortical Thickness (mm)	2.23	0.16	1.81–2.58
L Cortical Thickness (mm)	2.28	0.16	1.85–2.62
R Surface Area (mm ²)	3,677.26	493.34	2,670–4,839
L Surface Area (mm ²)	3,547.99	459.77	2,665–4,728

Note: MoCA: Montreal Cognitive Assessment; BDI-II: Beck Depression Inventory, 2nd edition; R: Right; L: Left.

Table 2

Item content of the BDI-II subscales used in the current study

Affective symptoms	Cognitive symptoms	Somatic symptoms
Sadness	Past Failure	Crying
Pessimism	Guilty Feelings	Agitation
Loss of Pleasure	Punishment Feelings	Loss of Energy
Suicidal Thoughts or Wishes	Self-Dislike	Changes in Sleeping Pattern
Loss of Interest	Self-Criticalness	Irritability
	Indecisiveness	Changes in Appetite
	Worthlessness	Concentration Difficulty
		Tiredness or Fatigue
		Loss of Interest in Sex

Note: BDI-II: Beck Depression Inventory, 2nd edition

Table 3

Correlations between precuneus brain measures

	R cortical thickness	R surface area	L cortical thickness	L surface area
R cortical thickness	–	–	–	–
R surface area	–0.07	–	–	–
L cortical thickness	0.83 [*]	–0.04	–	–
L surface area	0.06	0.89 [*]	0.04	–

Note. R = right. L = left;

^{*}
 $p < 0.001$

Table 4

Regression coefficients for BDI-II symptom dimensions and covariates on precuneus cortical thickness and surface area

	Left Cortical Thickness			Right Cortical Thickness			Left Surface Area			Right Surface Area		
	β	η^2_p	p	β	η^2_p	p	β	η^2_p	p	β	η^2_p	p
Left Mean Thickness	0.68	0.45	<0.01	-	-	-	-	-	-	-	-	-
Right Mean Thickness	-	-	-	0.71	0.48	<0.01	-	-	-	-	-	-
Total ICV	-	-	-	-	-	-	0.63	0.44	<0.01	0.61	0.42	<0.01
Age	-0.17	0.05	0.07	-0.08	0.01	0.35	-0.28	0.13	<0.01	-0.24	0.09	0.01
Affective	-0.01	0.00	0.89	-0.01	0.00	0.89	0.06	0.01	0.52	-0.08	0.01	0.42
Cognitive	-0.08	0.01	0.43	-0.13	0.03	0.20	0.10	0.01	0.42	0.22	0.06	0.05
Somatic	0.12	0.02	0.27	0.25	0.08	0.02	-0.12	0.02	0.27	-0.20	0.05	0.07
Age $\times$ Affective	-0.05	0.01	0.58	0.06	0.01	0.48	-0.05	0.01	0.56	-0.01	0.00	0.90
Age $\times$ Cognitive	0.14	0.03	0.20	-0.06	0.01	0.57	-0.12	0.02	0.34	-0.11	0.02	0.32
Age $\times$ Somatic	-0.23	0.07	0.03	-0.19	0.05	0.06	0.03	0.00	0.81	0.12	0.02	0.29
F	10.58			11.59			8.45			8.16		
R^2	0.56			0.53			0.52			0.50		
Model p			<0.01			<0.01			<0.01			<0.01

Note. BDI-II = Beck Depression Inventory, 2nd edition; ICV = intracranial volume. Bold data indicates significance at $p < 0.05$, uncorrected.