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CORTICAL THICKNESS AND DEPRESSIVE SYMPTOMS IN COGNITIVELY NORMAL INDIVIDUALS: THE MAYO CLINIC STUDY OF AGING

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Conflict of interest disclosures

Dr. Knopman serves as Deputy Editor for Neurology®; serves on a Data Safety Monitoring Board for Lundbeck Pharmaceuticals and for the Dominantly Inherited Alzheimer's Disease Treatment Unit. He has served on a Data Safety Monitoring Board for Lilly Pharmaceuticals; served as a consultant to Tau RX, was an investigator in clinical trials sponsored by Baxter and Elan Pharmaceuticals in the past 2 years; and receives research support from the NIH.

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Abstract

Altered cortical thickness has been observed in aging and various neuro-degenerative disorders. Furthermore, reduced hippocampal volume has been reported in late-life depression. Even mild depressive symptoms are common in the elderly. However, little is known about the structural MRI measures of depressive symptoms in normal cognitive aging. Thus we sought to examine the association between depressive symptoms with cortical thickness and hippocampal volume as measured by brain MRI among community-dwelling participants. We conducted a cross-sectional study derived from the ongoing population-based Mayo Clinic Study of Aging, involving cognitively normal participants (N=1507) aged 70 years. We observed that depressive symptoms were associated with lower global cortical thickness and lower thickness in specific prefrontal and temporal cortical regions, labeled by FreeSurfer software, version 5.3. As expected, the strength of correlation was very small, given that participants were community-dwelling with only mild depressive symptoms. We did not observe associations between hippocampal volume and depressive symptoms. These findings may provide insight into the structural correlates of mild depressive symptoms in elderly participants.

Keywords

aging; depression; depressive symptoms; cortical thickness; MRI

INTRODUCTION

Importance of Subsyndromal Depressive Symptoms

Subsyndromal symptoms of depression are common in the elderly; even in community-dwelling samples.[1, 2] Prevalence estimates for depressive symptoms are at least 2–4 times higher than for major depressive disorder (MDD).[3, 4] In addition, depressive symptoms have been associated with cognitive decline,[5, 6] greater medical comorbidities,[7] decreased quality of life,[8] and increased health care cost.[3, 9] Furthermore, subsyndromal depressive symptoms confer a risk factor for new-onset mood disorders.[7, 10] However, in the literature, symptoms have received much less attention than a clinical diagnosis of MDD, and some have argued that subsyndromal depression in very old participants may be related to normal aging rather than pathology.[11] A recent study showed that depressive symptoms are associated with biomarkers of Alzheimer's disease among cognitively normal elderly participants.[12] In addition, investigators previously recommended dimensional approaches to assess subsyndromal depressive symptoms rather than categorical classifications.[10]

Cortical Thickness

The human cerebral cortex is a highly folded sheet of neurons with regionally varying thickness. Cortical thickness can be measured with high accuracy across the entire cortex and in specific cortical regions.[13] Altered cortical thickness has been observed in

aging[14] and various neurodegenerative disorders.[13, 15] Few studies have examined cortical thickness in MDD.[16–19] However, results were mainly inconsistent and limited by small sample sizes.

Hippocampal Volume

Hippocampal volume has been widely investigated in MDD[20] and also in a small number of studies examining subsyndromal depressive symptoms.[21] However, the association between cortical thickness and mild depressive symptoms remains largely unknown.

We therefore sought to examine the associations between cortical thickness and hippocampal volume as measured by MRI with depressive symptoms in community-dwelling cognitively normal participants. We hypothesized that depressive symptoms in cognitively normal individuals would be associated with 1) lower global cortical thickness; 2) lower thickness in prefrontal cortical regions; and 3) reduced hippocampal volume. Given that this is a community-dwelling study sample, we also hypothesized that the strength of correlation would be small.

MATERIALS AND METHODS

We conducted a cross-sectional study involving cognitively normal participants from the Mayo Clinic Study of Aging (MCSA) on whom depressive symptoms and MRI data were available.

Setting

This study was conducted in the setting of the MCSA. Details of the design and conduct of the MCSA are described elsewhere.[22] Briefly, the MCSA is an ongoing population-based study in Olmsted County, Minnesota that was designed to study prevalence, incidence and risk factors for cognitive aging, mild cognitive impairment and dementia in elderly participants. Only participants who had undergone brain MRI (N=1507) and depressive symptoms assessment were included in this study. We observed small differences between MCSA participants who underwent MRI versus others. As compared to MCSA participants who refused MRI (N=1346), participants who underwent MRI had slightly higher cognitive scores, lower comorbidities, and slightly lower number of depressive symptoms. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards, and informed consent for participation was obtained from every participant.

Cognitive evaluation

Participants of the MCSA underwent extensive cognitive testing and risk factor assessment that is published in detail elsewhere.[22] Briefly, an expert consensus panel of physicians, neuropsychologists, and nurses or study coordinators reviewed the data and made the diagnosis of normal cognition, MCI, or dementia based on published criteria. Participants with MCI or dementia were excluded from this study.

Measurement of depressive symptoms

Depressive symptoms were measured using a validated, self-administered Beck Depression Inventory-II (BDI-II) that has been shown to be sensitive in elderly participants.[23] The BDI-II is an ordinal measure that consists of 21 items that are assessed over the last two weeks and are rated in severity on a Likert scale ranging from 0 to 3; the total score thus ranges from 0 to 63. We primarily examined BDI-II as continuous variable and also compared participants with depressive symptoms – median number of symptoms versus others in this population. There were only 84 (6%) of 1507 participants that scored above the clinically significant cut-off point (BDI-II = 13). This is expected since our study participants are community dwelling cognitively normal persons. Therefore, we considered cut-off points of the median score for the sample (BDI-II = 4) to demonstrate the demographic characteristics. When we investigated the associations between cortical thickness and depressive symptoms, we treated BDI-II as continuous variable.

MRI

Within 150 days of the administration of the BDI-II, magnetic resonance imaging (MRI) was performed using 3-T scanners (Signa; GE Healthcare) equipped with an 8-channel phased array coil (GE Healthcare). A 3-dimensional magnetization–prepared rapid gradient echo sequence was performed [24, 25] and images were corrected for distortion due to gradient nonlinearity and for bias field.[26] Cortical thickness and hippocampal volumes were measured with FreeSurfer software, version 5.3.[27] The following regions of interest (ROIs) of cortical thickness labeled by FreeSurfer were included in the analysis: Anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), and orbitofrontal cortex (OFC). The ACC was created by combining thickness of the rostral, isthmus and caudal anterior cingulate cortex, as labeled by FreeSurfer. The OFC was measured by combining thickness of lateral and medial orbitofrontal cortex; the dlPFC was the combined thickness of the superior frontal, rostral middle frontal and caudal middle frontal cortex; and the vlPFC was created by combining thickness of the pars opercularis, pars triangularis and pars orbitalis, as labeled by FreeSurfer. We further combined various smaller regions as labeled by FreeSurfer and determined the thickness of frontal, parietal and temporal cortices. The composite/global thickness was calculated by averaging thickness of all frontal, occipital, parietal and temporal regions that are labeled by FreeSurfer.

Measurement of Covariates

In addition to traditional confounders such as age, sex, and education, we also included medical comorbidity, antidepressant medication, and global cognition as covariates for the purpose of this study. We measured medical comorbidity by using the Charlson index, which is a widely used weighted index that takes into account the number and severity of diseases (e.g., diabetes, hypertension, dyslipidemia, coronary artery disease, congestive heart failure, myocardial infarction, stroke etc.).[28] Antidepressant medication use was self-reported and included use of Selective serotonin reuptake inhibitor (SSRI), Serotonin–norepinephrine reuptake inhibitor (SNRI), citalopram, tetracyclic, or tricyclic antidepressant medication.

Global cognition was measured based on extensive neuropsychological testing and expressed as z-score, as described in detail elsewhere.[22]

Statistical analysis

We used Wilcoxon two- sided rank sum test to compare two samples, i.e. MCSA participants who refused MRI versus MCSA participants who underwent MRI. We also compared participants with a BDI-II ≤ 4 versus BDI-II > 4 , by using chi-squared test for differences in proportions for the categorical variables. We additionally calculated Spearman rank-order partial correlations between MRI measures (cortical thickness by ROI and hippocampal volume) and BDI-II as continuous variables. The partial correlations accounted for age, sex, education, medical comorbidity, antidepressant medication, and global cognition. Spearman partial correlations are the equivalent of the Spearman rank correlations between the residuals of the linear regression of the ranks of the two variables on the ranks of the variables that are being adjusted or accounted for in the regression models. Hippocampal volumes were additionally adjusted by total intracranial volume (TIV), which was calculated using SPM 12. A sex specific TIV adjustment did not change the results and is not reported. To visually display the data, we computed forest plots of the adjusted correlations with 95% confidence intervals. Statistical testing was done at the conventional 2-tailed α level of $p < 0.05$. Statistical analyses were performed using SAS System, version 9.3 software (SAS Institute, Cary, NC) and R statistical software, version 3.0.2 (R Foundation for Statistical Computing, Vienna).

RESULTS

Demographic Characteristics

In this cross-sectional study, we examined the associations between MRI measures (cortical thickness, and hippocampal volume) and depressive symptoms in cognitively normal participants (N=1507) aged 70 years and above. Participants that agreed to undergo MRI had slightly higher cognitive scores, lower medical comorbidity, and slightly lower number of depressive symptoms as compared to MCSA participants that refused MRI imaging. The complete demographic characteristics are displayed in Table 1. When we categorically defined participants with a BDI-II score ≤ 4 (i.e., the median number of symptoms) as “depressed”, and participants with a BDI-II score > 4 as “not depressed”, we observed the following: “depressed” participants were significantly older, had lower years of education, lower z-scores for cognitive domains, and higher use of antidepressant medication. We did not observe associations with APOE $\epsilon 4$ genotype.

Associations between MRI Measures and Depressive Symptoms

In our unadjusted analysis, we observed significant associations between depressive symptoms and lower hippocampal volume as well as lower cortical thickness in most of the examined regions of interest (ROIs). We observed similar findings after adjusting for age, sex, education, medical comorbidity, antidepressant medication, and global cognition, i.e. depressive symptoms were associated with lower global ($r = -0.09$, $p < 0.01$), frontal ($r = -0.08$, $p < 0.01$) and temporal cortical thickness ($r = -0.09$, $p < 0.01$). We also observed associations with smaller prefrontal and temporal regions, including lower dorsolateral ($r =$

−0.08, $p < 0.01$), ventrolateral prefrontal ($r = -0.08$, $p < 0.01$) insular ($r = -0.07$, $p < 0.01$), and entorhinal ($r = -0.07$, $p < 0.01$) cortical thickness. (Table 2)

Figure 1 visually displays forest plots of the partial Spearman rank-order correlations with 95% confidence intervals.

DISCUSSION

Here we report the cross-sectional associations between cortical thickness and depressive symptoms in a large sample derived from the ongoing population-based Mayo Clinic Study of Aging. Depressive symptoms among cognitively normal elderly participants were associated with reduced cortical thickness in specific prefrontal and temporal regions after adjusting for age, sex, education, medical comorbidity, use of antidepressant medications and global cognition. While we observed significant associations in our large sample size, the effect sizes were very small given that our participants were community-dwelling with only mild depressive symptoms. Similarly, a meta-analysis also reported small effect sizes for associations between late-life depression and regional brain volumes.[29]

Associations between MDD and regional brain volumes have been extensively evaluated in meta-analyses that reported reduced volumes of prefrontal regions, hippocampus, putamen, caudate nucleus, and thalamus.[29, 30] In contrast, subthreshold depression and late-life minor depression have been investigated only in few studies, and they reported volume reductions mainly in frontal[31, 32] and also temporal regions.[31] Furthermore, the association between subsyndromal depressive symptoms and cortical thickness is not well understood among cognitively normal elderly participants.

A few studies have investigated the association between MDD and grey matter volumes[16] or cortical thickness[17–19, 33] in clinical samples; and their findings varied depending on study design and sample sizes. While a few studies reported increased cortical thickness[17] or no significant associations,[33] most studies observed that MDD was associated with reduced cortical thickness in prefrontal,[34] temporal,[19, 34] and entorhinal cortex.[18] Our findings for depressive symptoms add to the literature by indicating that even subsyndromal depressive symptoms in community-dwelling elderly participants are associated with decreased thickness in prefrontal, temporal, and entorhinal cortex.

While little is known about cortical thickness, the field of aging and dementia has extensively investigated the association between hippocampal volume and depression. Most studies reported reduced hippocampal volume in MDD,[20, 35] specifically in late life.[29] In contrast, a study that examined depressive symptoms in a large number of community-dwelling elderly participants observed that mild depressive symptoms were not associated with reduced hippocampal volume.[21] In addition, a small study reported that subthreshold depression was not associated with reduced hippocampal volume, but with reduced gray matter volumes in frontal regions. However, this study sample involved only males.[32] In contrast, we had the opportunity to examine hippocampal volume and cortical thickness in a large community-based sample with about 51% males; and we also did not observe a

significant association between mild depressive symptoms and lower hippocampal volume after adjusting for multiple possible confounders.

In addition, prior studies reported associations between reduced thickness of the parietal cortex and MDD[19] as well as between reduced hippocampal volume and depressive symptoms.[12] Similarly, we observed an association between depressive symptoms and reduced parietal cortex as well as hippocampal volume when we adjusted for age, sex and education (data not shown). However, we did not observe associations when we additionally adjusted for use of antidepressant medication, medical comorbidity and global cognition using z-scores. While studies found associations between syndromal depression and reduced volume of the anterior cingulate cortex (ACC),[16] we did not observe an association between depressive symptoms and ACC thickness, implying that the severity of depression may account for the different findings.

Our study results may be relevant to the recently reported construct of Mild Behavioral Impairment (MBI) [36]. Cognitively normal elderly persons with depressive symptoms can be classified to have MBI. Furthermore, MBI subjects with reduced cortical thickness may need to be closely monitored in order to determine if they are at higher risk for MCI or dementia as compared to MBI individuals without reduction in cortical thickness.

There are several strengths to our study. First, we recruited participants from a subset of a large, well-described population-based sample that also gave us information on antidepressant medication use, comorbidities, and cognition, so we could additionally adjust for these possible confounders. Second, we were able to investigate neuroimaging variables (i.e., cortical thickness and hippocampal volume) in a large sample including more than 1500 community-dwelling participants. Third, we examined associations between cortical thickness and depressive symptoms as continuous variables, as opposed to choosing arbitrary cut-offs for categorical classifications.

The study also has limitations. The BDI-II is a self-reported questionnaire and may therefore be prone to recall bias; however, it is a well validated and widely used scale.[23] In addition, the study is limited by its cross-sectional study design. We aim to replicate the findings in a longitudinal study, which may also provide insight about the direction of causality. It may be considered as a limitation that we did not adjust for multiple comparisons. However, this issue is controversial and while some do not recommend routine Bonferroni correction in order to avoid running into the problem of type 2 error (false negative; [37]), other studies such as genomic research (GWAS type of research) need to routinely correct for multiplicity. [38] We believe that our findings are real, not spurious. We believe that our results are less prone to type 1 error as we conducted our analysis using an a priori hypothesis derived from empirical work. Furthermore, given that composite cortical thickness is composed of regions such as frontal cortex, we did not adjust our specific ROI analyses by composite thickness. Therefore, one may argue that our observed association between frontal thickness and depressive symptoms may partly be explained by reduced thickness across the whole cortex. However, our finding to some degree is in line with previously published research that has shown a relationship between MDD and reduced frontal lobe volume; keeping in mind that

our population-based study design and less severe depressive symptoms differ from clinic sample-based studies that reported on depression and frontal lobe volume.

In this cross-sectional study involving cognitively normal persons, the direction of causality between cortical thickness and depressive symptoms is unknown. However, we would like to propose the following possible mechanisms that may explain the observed relationship between depressive symptoms and cortical thickness: 1) Underlying pathological neurodegeneration may manifest as cortical thinning on MRI. This cortical thinning may, via unknown mechanisms, also lead to depressive symptoms. 2) Cortical thinning may lead to cognitive deterioration which in turn may lead to reactive depressive symptoms. 3) It is also possible that depressive symptoms may modify the relationship between cortical thickness and cognitive outcomes. In this scenario, depressive symptoms serve as mediator/moderator variable. Even though we adjusted for global cognition, we cannot exclude residual confounding by cognition in this analysis. To date, we can only speculate about possible mechanisms linking neuropsychiatric symptoms with neurodegeneration. Further research is needed to address the mechanistic pathways linking neuropsychiatric symptoms with neurodegeneration in the setting of cognitive aging and dementia.

In conclusion, our study adds to prior work by showing associations between depressive symptoms and cortical thinning in prefrontal and temporal regions in a large number of community-dwelling elderly participants. These findings may provide insight into the structural correlates of mild depressive symptoms among cognitively normal elderly participants.

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Abbreviations

MCSA	Mayo Clinic Study of Aging
BDI-II	Beck Depression Inventory-II
MDD	major depressive disorder
dIPFC	dorsolateral prefrontal cortex
vlPFC	ventrolateral prefrontal cortex
ACC	anterior cingulate cortex

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Figure 1. Forest plot of the partial Spearman rank-order correlation estimates and 95% CI between BDI-II and imaging variables

Adjusted for age, sex, education, antidepressant medication, medical comorbidities and global cognition; Hippocampal volume was additionally adjusted for total intracranial volume. Abbreviations: dlPFC = dorsolateral prefrontal cortex; vlPFC = ventrolateral prefrontal cortex; ACC = anterior cingulate cortex.

Table 1

Demographic characteristics

	Not In Study n = 1346	In Study n = 1507	p	BDI-II < 4 n = 753	BDI-II 4 n = 754	p
Males, n (%)	676 (50)	770 (51)	0.64	402 (53)	368 (49)	0.08
APOE ε4 carriers, n (%)	332 (26)	380 (25)	0.90	179 (24)	201 (27)	0.21
Age, yrs (IQR)	78 (74, 83)	77 (74, 82)	0.24	76 (73, 81)	79 (75, 83)	<01
Education, yrs (IQR)	13 (12, 16)	13 (12, 16)	0.01	14 (12, 16)	13 (12, 16)	<01
STMS (IQR)	34 (32, 36)	35 (33, 36)	<01	35 (33, 36)	35 (33, 36)	<01
Cognition Z scores						
Memory (IQR)	0.08 (-0.55, 0.81)	0.50 (-0.21, 1.17)	<01	0.52 (-0.19, 1.19)	0.49 (-0.23, 1.14)	0.30
Language (IQR)	0.15 (-0.45, 0.70)	0.37 (-0.17, 0.95)	<01	0.43 (-0.09, 1.00)	0.31 (-0.26, 0.83)	<01
Attention (IQR)	0.26 (-0.40, 0.77)	0.46 (-0.09, 0.98)	<01	0.55 (0.02, 1.10)	0.35 (-0.17, 0.86)	<01
Visuospatial (IQR)	0.05 (-0.60, 0.69)	0.37 (-0.26, 0.97)	<01	0.42 (-0.12, 1.04)	0.28 (-0.37, 0.85)	<01
Global (IQR)	0.14 (-0.48, 0.79)	0.52 (-0.08, 1.06)	<01	0.62 (0.04, 1.14)	0.38 (-0.17, 0.97)	<01
BDI-II total score (IQR)	4 (1, 8)	4 (1, 7)	<01	1 (0, 2)	7 (5, 9)	<01
Charlson Index (IQR)	4 (2, 6)	3 (2, 5)	<01	3 (1, 5)	4 (2, 5)	<01
Medications						
SSRI/SNR, n (%)	145 (11)	150 (10)	0.47	47 (6)	103 (14)	<01
Citalopram, n (%)	47 (3)	56 (4)	0.75	17 (2)	39 (5)	<01
Tetracyclic, n (%)	14 (1)	13 (1)	0.63	5 (1)	8 (1)	0.40
Tricyclic, n (%)	29 (2)	39 (3)	0.45	20 (3)	19 (3)	0.87
Any, n (%)	184 (14)	196 (13)	0.60	71 (9)	125 (17)	<01

“Not in Study” are MCSA participants who refused MRI, “In Study” are all MCSA participants that underwent MRI and depressive symptom assessment and were included in the analysis; “Not depressed” categorically defined as BDI-II 0–3; “Depressed” is defined as BDI-II 4 (median BDI score). The median (interquartile range, IQR) are reported for the continuous variables and the counts (%) for the categorical variables. Abbreviations: STMS = Kokmen short test of mental status, SSR = selective serotonin reuptake inhibitor, SNR = serotonin-norepinephrine reuptake inhibitor.

Table 2

Spearman rank-order adjusted correlation coefficients (p-values) between BDI-II and MRI measures

	BDI unadjusted r (95% CI)	p	BDI r (95% CI)[‡]	p
Composite	−0.16 (−0.21, −0.11)	<.01	−0.09 (−0.14, −0.03)	<.01
Frontal	−0.13 (−0.18, −0.08)	<.01	−0.08 (−0.13, −0.03)	<.01
Temporal	−0.17 (−0.22, −0.12)	<.01	−0.09 (−0.15, −0.04)	<.01
Parietal	−0.11 (−0.16, −0.06)	<.01	−0.05 (−0.10, 0.00)	0.07
vlPFC	−0.13 (−0.17, −0.08)	<.01	−0.08 (−0.13, −0.03)	<.01
dIPFC	−0.14 (−0.19, −0.09)	<.01	−0.08 (−0.14, −0.03)	<.01
Orbitofrontal	−0.08 (−0.13, −0.02)	<.01	−0.05 (−0.10, −0.00)	0.05
ACC	−0.01 (−0.06, 0.04)	0.65	−0.04 (−0.10, 0.01)	0.10
Insula	−0.10 (−0.15, −0.05)	<.01	−0.07 (−0.12, −0.02)	<.01
Parahippocampal	−0.09 (−0.14, −0.04)	<.01	−0.04 (−0.09, 0.02)	0.18
Entorhinal	−0.13 (−0.18, −0.08)	<.01	−0.07 (−0.12, −0.02)	<.01
Hippocampus volume	−0.14 (−0.19, −0.09)	<.01	−0.04 (−0.09, 0.01)	0.15 [*]

[‡]These correlations are adjusted for age, sex, education, antidepressant medication, medical comorbidities and global cognition.

^{*}Hippocampal volume was also adjusted for total intracranial volume.

Abbreviations: dIPFC = dorsolateral prefrontal cortex; vlPFC = ventrolateral prefrontal cortex; ACC = anterior cingulate cortex.