Title

Anxiety symptoms are associated with smaller insular and orbitofrontal cortex volumes in late-life depression

Authors

Laird, Kelsey T
Siddarth, Prabha
Krause-Sorio, Beatrix
et al.

Publication Date

2019-09-01

DOI

10.1016/j.jad.2019.05.066

Peer reviewed

HHS Public Access

Author manuscript

J Affect Disord. Author manuscript; available in PMC 2020 September 01.

Published in final edited form as:

J Affect Disord. 2019 September 01; 256: 282–287. doi:10.1016/j.jad.2019.05.066.

Anxiety Symptoms are Associated with Smaller Insular and Orbitofrontal Cortex Volumes in Late-life Depression

Kelsey T. Laird, Ph.D., **Prabha Siddarth, Ph.D.**, **Beatrix Krause, Ph.D.**, **Lisa Kilpatrick, Ph.D.**, **Michaela Milillo, B.S.**, **Yesenia Aguilar, B.A.**, **Katherine L. Narr, Ph.D.**, **Helen Lavretsky, M.D. M.S.**[*]

Department of Psychology and Human Development, University of California, Los Angeles (UCLA), 760 Westwood Plaza, Los Angeles, CA 90095, United States

Abstract

Background.—Increasing understanding of the neural correlates of anxiety symptoms in late-life depression (LLD) could inform the development of more targeted and effective treatments.

Methods.—Grey matter volume (GMV) was assessed with volumetric magnetic resonance imaging in a sample of 113 adults ≥60 years with MDD using the following regions of interest: amygdala, anterior cingulate cortex (ACC), insula, orbitofrontal cortex (OFC), and temporal cortex.

Results.—After controlling for demographic (age, sex, education) and clinical variables (antidepressant use, anxiolytic use, duration of illness, medical comorbidity, cognitive functioning), greater severity of anxiety symptoms was associated with lower GMV bilaterally in the insula, $F(1,102) = 6.63$, $p = 0.01$, and OFC, $F(1,102) = 8.35$, $p = 0.005$. By contrast, depressive symptom severity was significantly associated with lower bilateral insula volumes, $F(1,102) = 6.43$, $p = 0.01$, but not OFC volumes, $F(1,102) = 5.37$, $p = 0.02$.

Limitations.—Limitations include 1) the relatively mild nature of anxiety symptoms in our sample; 2) the cross-sectional research design, which prohibits inferences of directionality; 3) the relatively homogenous demographic of the sample, and 4) the exclusion of participants with significant psychiatric comorbidity, suicidality, or cognitive impairment.

Conclusions.—Decreased OFC volumes may serve as a unique biomarker of anxiety symptoms in LLD. Future longitudinal and clinical studies with long-term follow up and more diverse

[*]**Corresponding author:** Helen Lavretsky, M.D., M.S., Professor of Psychiatry In-Residence Director, Late-life Mood, Stress, and Wellness Research Program, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA 760 Westwood Plaza Los Angeles, CA 90095, Phone: (310) 794-4619, Fax: (310) 206-4399 hlavretsky@mednet.ucla.edu.

Contributors

H.L., K.T.L., P.S., B.K., and K.N. designed the study. K.T.L. managed the literature search. B.K. and L.K. processed neuroimaging data. P.S. conducted statistical analyses. K.T.L. wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Dr. Lavretsky received research support from Allergan/ Forest Laboratories. The remaining authors declare no conflicts of interest.

samples will help further elucidate the biological, psychological, and social factors affecting associations between anxiety and brain morphology in LLD.

Keywords

Anxious depression; geriatric; neuroimaging; neural; cortical atrophy; OFC

Anxiety in late life is under-recognized and sub-optimally treated (Tampi & Tampi, 2014). This is in part due to the widespread notion that late-life anxiety is relatively uncommon (Byers, Yaffe, Covinsky, Friedman, & Bruce, 2010; Gum, King-Kallimanis, & Kohn, 2009; Karel, Gatz, & Smyer, 2012; Streiner, Cairney, & Veldhuizen, 2006). Indeed, the prevalence of anxiety disorders in the elderly is somewhat lower than in younger and middle-aged adults, with an estimated prevalence of 3.5–10.2% (Beekman et al., 1998; Bland, Newman, & Orn, 1988). However, rates of clinically-significant *symptoms* of anxiety (i.e., that do not meet DSM criteria) are highly prevalent in the elderly, with rates of 15%–26% in community samples (Mehta et al.,2003). Furthermore, among those with late-life depression (LLD), rates of comorbid anxiety symptoms are as high as 50% (Beekman et al., 2000; Lenze et al., 2000; Livingston, Watkin, Milne, Manela, & Katona, 1997). Existing studies of adults with LLD suggest that comorbid anxiety predicts more severe, persistent, and treatment-resistant depressive illness (Andreescu et al., 2007; Schoevers, Beekman, Deeg, Jonker, & Tilburg, 2003), greater cognitive decline (DeLuca et al., 2005), more disability (Schoevers et al., 2003), and more suicidal ideation (Jeste, Hays, & Steffens, 2006). These results underscore the importance of identifying the psychophysiological correlates of anxiety symptoms in LLD (Fiske, Wetherell, & Gatz, 2009; Lenze et al., 2000).

Several recent studies have investigated the neurobiology of comorbid anxiety in non-geriatric depressed populations (see (Ionescu, Niciu, Mathews, Richards, & Zarate, 2013) for a review). A structural neuroimaging study of German adults compared those with anxious depression (N=49) to those with non-anxious depression (N=96) (Inkster et al., 2011). Participants with anxious depression demonstrated greater grey matter volume (GMV) in the right temporal gyrus, a cortical association area with limbic system input. Another study of Chinese adults (mean age = 29) found that after controlling for demographic covariates, those with anxious depression (N=20) had greater GMV in the frontal lobe, temporal lobes, and insula compared to those with non-anxious depression (N=18) (Qi et al., 2014). Finally, a study of Dutch adults found lower GMV in the anterior cingulate cortex (ACC) in patients with anxiety or depression compared to healthy controls (N=65), and this finding was most robust among those with anxious depression (N=88) (van Tol et al., 2010).

One study recently investigated grey matter correlates of anxiety in older adults with and without a prior history of depression (Potvin et al., 2015). In that sample of 393 individuals ages 65 and older, prior history of depression moderated the association between trait anxiety and grey matter characteristics. Among never-depressed participants, trait anxiety was associated with larger cortical thickness in all regions of interest (ROIs; amygdala, anterior cingulate cortex (ACC), insula, orbitofrontal cortex (OFC), and temporal cortex). In

contrast, among participants with a history of depression, trait anxiety was associated with lower cortical thickness in each ROI.

The extent to which the neural correlates of anxiety in MDD overlap with those associated with depressive symptom severity is unknown. One study of 17 non-geriatric adults with MDD found that GMV was negatively correlated with depressive symptom severity in the ACC and dorsolateral prefrontal cortex (Chen et al., 2007), regions associated with the effortful regulation of affective states (Bush, Luu, & Posner, 2000; Phillips, Drevets, Rauch, & Lane, 2003). These results raise the possibility that previously-observed associations between anxiety and ACC volumes may be the result of greater negative affect more broadly and not necessarily anxiety per se.

To date, no study has investigated possible associations between anxiety symptoms and grey matter characteristics in a large sample of older adults currently meeting criteria for MDD, nor clarified the extent to which these characteristics are distinct from those associated with depression severity. Thus, the aim of the current study was to explore anxiety-specific grey matter correlates in older adults with LLD, focusing on the following previously-implicated regions: amygdala, anterior cingulate cortex (ACC), insula, orbitofrontal cortex (OFC), and temporal cortex (Potvin et al., 2015). We also explored whether total intracranial volume (TIV) was significantly associated with symptoms of anxiety and depression to inform whether ROI results may be attributable to overall brain volume.[1]

Methods

Participants

Data comprised baseline diagnostic interviews and neuroimaging from three clinical trials (NCT02460666, NCT01902004, and NCT02466958) testing the efficacy of tai chi (N=48), memantine (N=43), and levomilnacipran (N=22) for depressed adults ≥ 60 years. Data collection took place between 2015 and 2018 at UCLA. Inclusion criteria were: (1) diagnosis of MDD as defined by Diagnostic and Statistical Manual (DSM)-IV-TR (American Psychiatric Association, 2000) or DSM 5 (American Psychiatric Association, 2013) and (2) normal cognitive functioning as defined by a Mini-Mental State Exam (MMSE) score of 24 or greater. Exclusion criteria were: (1) history of any psychiatric disorder (with the exception of stable comorbid anxiety or stable comorbid insomnia); (2) acute suicidal ideation or suicide attempt within the past year; (3) severe or acute unstable medical illness or neurological disorder; (4) dementia. Participants reported symptoms of anxiety in the mild to moderate range (HAM-A range: 0–17). For the pharmacological trials (NCT02466958, NCT01902004), participants were required to be free of antidepressant medication prior to enrollment. Eligibility for NCT02460666 required that participants were receiving first-line treatment for depression - i.e., either antidepressant medication (N=47) or

[1]The decision to conduct a separate regression of TIV rather than control for TIV in ROI analyses was informed by our primary study aim: to examine whether specific regions are implicated in anxiety comorbid with depression. Although important to control for in between-group comparisons, including TIV as a regressor in models that examine the association of specific regional volumes with clinical variables within a group has potential to absorb all of the variance associated with regional volume and mask any effect of the independent variable

talk therapy (N=1). All study procedures were approved by the UCLA Institutional Review Board.

Measures

Anxiety symptoms were assessed via the 14-item clinician-rated Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959; Maier, Buller, Philipp, & Heuser, 1988). Severity of depressive symptoms was assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979). Cognitive functioning was assessed via the MMSE (Folstein, Anthony, Parhad, Duffy, & Gruenberg, 1985; Folstein, Folstein, & McHugh, 1975). Medical comorbidity was quantified using the clinician-rated Cumulative Illness Rating Scale for Geriatrics (CIRS) (Miller et al., 1992); higher scores indicate greater illness severity.

Image Acquisition

Neuroimaging data was acquired using Siemens 3T Trio (N=20) and Prisma systems (N=93) (Siemens, Erlangen, Germany) with a 32-channel head coil (HEA, HEP) at the Ahmanson & Lovelace Brain Mapping Center at UCLA. A high-resolution T1-weighted structural brain scan was obtained for each participant using a MEMPRAGE sequence (3D multi-echo magnetization-prepared rapid gradient-echo sequences): Prisma: 208 sagittal slices, 0.8mm slice thickness, TR=2400, TE=2.24 ms; FoV=256 mm; 256×256 matrix; TI 1060 ms; flip angle=7°. Trio: 176 sagittal slices, 1 mm^3 isotropic voxel size, TR=2150, TE=1.74 ms, 3.6, 5.46, and 7.32 ms; FoV=256 mm; 256×256 matrix; TI 1260 ms; flip angle=7°. Acquisition time was 6.38 minutes for Prisma and 5.18 minutes for Trio scans.

Freesurfer version 6.0 (http://surfer.nmr.mgh.harvard.edu/) was used for cortical reconstruction of volumetric measures. The preprocessing pipeline included the correction of magnetic field inhomogeneities, removal of non-brain tissues, segmentation of gray matter from white matter and cerebrospinal fluid (CSF), and parcellation of cortical regions using the Desikan-Killany atlas. The reconstructed scans were then carefully inspected for tissue misclassifications and were manually corrected as needed. Cortical maps were smoothed with a Gaussian kernel of 10 mm full-width half-maximum (FWHM). GMV was extracted for the aforementioned atlas labels and included in the statistical analysis.

Statistical Analyses

Prior to analyses, data were inspected for outliers, skewness, and homogeneity of variance to ensure appropriateness of parametric statistical tests. Demographic and clinical data were analyzed using SAS version 9.4 (SAS Institute, Cary, N.C.). We examined the association of regional GMV with anxiety (HAM-A) and depression (MADRS) scores, controlling for age, sex, education, antidepressant use, anxiolytic use, duration of illness, medical comorbidity, cognitive functioning, and scanner, using general linear models with repeated measures. Because HAM-A and MADRS scores are highly correlated ($r = 0.65$, $p<0.0001$), we included these variables one at a time. Based on a previously published study investigating the grey matter correlates of anxiety in older adults with a history of depression, we set the following a priori ROIs: amygdala, ACC, insula, OFC, and temporal cortex (Potvin et al., 2015). A separate general linear model was estimated for each of these ROIs. For amygdala,

ACC and insula, hemisphere (left and right) was used as a repeated measure. For OFC, left and right medial and lateral orbitofrontal regions were used as repeated measures. For temporal cortex, left and right of superior, middle and inferior temporal were used as repeated measures. For all these models, we examined the significance of the interaction term of anxiety/depression scores with hemisphere, to determine if any association present was bilateral or restricted to one hemisphere. If the interaction term was not significant, it was removed from the final model. The significance threshold for each of the five ROIs was set at 0.01 (0.05/5; two-tailed).

Results

Sample Characteristics

The average age of participants (N=113) was 70 years (range=60–84 years). The majority of participants were White (80%) and female (65%), with an average of 16 years of education (see Table 1). Forty-seven participants (42%) were currently taking antidepressant medication.

Regional Grey Matter Volume

Anxiety.—After controlling for covariates, greater severity of anxiety symptoms was associated with lower GMV bilaterally in the insula, $F(1,102) = 6.63$, $p = 0.01$ (Figure 1) and OFC, $F(1,102) = 8.35$, $p = 0.005$ (Figure 2). Anxiety symptoms were not significantly associated with GMV in the amygdala, $F(1,102) = 1.97$, $p = 0.16$, ACC, $F(1,102) = 0.59$, $p = 0.4$, or temporal cortex $F(1,102) = 0.18$, $p = 0.7$.

Depression.—After controlling for covariates, greater severity of depression symptoms was associated with lower GMV bilaterally in the insula, $F(1,102) = 6.43$, $p = 0.01$. Depression was not significantly associated with GMV in the OFC, $F(1,102) = 5.37$, $p = 0.02$, amygdala, $F(1,102) = 2.40$, $p = 0.12$, ACC, $F(1,102) = 0.59$, $p = 0.4$, or temporal cortex, $F(1,102) = 0.94$, $p = 0.3$..

Total Intracranial Volume (TIV)

After controlling for demographic variables (age, sex, education), clinical variables (antidepressant use, anxiolytic use, duration of illness, medical comorbidity, cognitive functioning), and scanner, greater symptoms of anxiety and depression were *each correlated with lower TIV* (HAMA: $F(1,102) = 6.85$, $p = .01$; MADRS: $F(1,102) = 4.45$, $p = .04$).

Discussion

The current study investigated associations between anxiety symptoms and GMV in a sample of 113 adults with LLD. Of our five a priori ROIs, two emerged as statistically significant. Of note, greater symptoms of anxiety and depression were negatively correlated with TIV. The regional heterogeneity in the results, namely that GMV in only two of the identified ROIs were significantly associated with symptoms suggests that these findings are not simply due to the effect of overall brain volumes.

After controlling for clinical and demographic variables, anxiety was associated with lower insula volumes. These results are consistent with those of a previous study in which anxiety correlated with smaller bilateral insula cortical thickness among older adults with a history of depression (Potvin et al., 2015). However, the results of one previous study suggest that anxiety may be associated with *larger* insula volumes in non-geriatric depression (Qi et al., 2014); thus, it is possible that the association between anxiety and brain morphology in MDD may change across the lifespan. Normal aging is associated with heterogeneous grey matter atrophy including accelerated reduction in the insula and prefrontal cortex (Fjell et al., 2013; Good et al., 2001), and increased insula activation in response to emotional stimuli is well-documented among individuals high in trait anxiety (Stein, Simmons, Feinstein, & Paulus, 2007) as well as in social anxiety disorder (Klumpp, Post, Angstadt, Fitzgerald, & Phan, 2013; Shah, Klumpp, Angstadt, Nathan, & Phan, 2009), post-traumatic stress disorder (PTSD)(Etkin & Wager, 2007), and specific phobia (Etkin & Wager, 2007). It is possible that symptoms of anxiety are associated with insula hyperactivation and larger insula volumes among depressed younger adults, but that such anxiety-related insula hyperactivity is absent in late-life depression. Indeed, one study of LLD found no significant association between insula glucose metabolism and anxiety symptoms in a mixed sample of depressed (N=16) and non-depressed (N=13) older adults (Smith et al., 2009). It is also possible that the neurophysiological processes underlying age-related atrophy are exacerbated by frequent anxiety-related activation of the stress response, thereby counteracting positive associations between anxiety symptoms and insula volumes in younger adults with depression (Qi et al., 2014). Furthermore, because insula volume was also significantly negatively correlated with severity of depressive symptoms, it is unknown whether these results are due to anxiety, depression, or negative emotionality more broadly.

Second, we found that anxiety symptoms were associated with smaller bilateral OFC volumes in our sample. In contrast to observed associations with insula volumes, these associations were significant for symptoms of anxiety but not depression. These results implicate smaller OFC volumes as a possibly unique biomarker of anxiety symptoms in LLD. Again, these results are consistent with those of Potvin and colleagues (2015), who found that trait anxiety was associated with lower OFC cortical thickness in older adults with a history of depression. Substantial human neuroimaging research evidence suggests that the OFC, together with other prefrontal cortical areas, plays an important role in affective regulation (Ochsner, Bunge, Gross, & Gabrieli, 2002). OFC lesions increase fear and anxiety behavior in macaques (Shiba, Santangelo, & Roberts, 2016), and lower OFC volumes and functional connectivity have been reported in obsessive-compulsive disorder (Pujol et al., 2004) and PTSD (Zhu et al., 2018). One study found that greater reductions in PTSD symptoms following exposure therapy correlated with greater increases in resting state functional connectivity between the OFC and the amygdala (Zhu et al., 2018), suggesting that the OFC may suppress negative emotion via inhibitory connections to the amygdala and other limbic areas (Davidson, Putnam, & Larson, 2000; Haber, 2008; Zhu et al., 2018). Hypothesized cognitive mediators of this effect include the OFC's potential role in outcome prediction (Gottfried, O'Doherty, & Dolan, 2003; O'Doherty, Deichmann, Critchley, & Dolan, 2002; Seymour et al., 2005; Shiba et al., 2016).

The lack of correlation between anxiety symptoms and GMV in other ROIs (amygdala, ACC, and temporal cortex) was unexpected. However, although research on pathological anxiety has widely implicated GMV abnormalities in the amygdala, few studies have found significant associations between anxiety and amygdala volumes in individuals with a history of depression (Potvin et al., 2015). In addition, the direction of relation between anxiety and GMV is unclear. Studies of individuals with anxiety disorders have documented both decreased (Asami et al., 2009; Hayano et al., 2009; Massana et al., 2003; Szeszko et al., 1999; Uchida et al., 2003; van Tol et al., 2010; Vythilingam et al., 2000) and increased (Schienle, Ebner, & Schäfer, 2011) amygdala volumes compared to healthy controls, while yet others have found no significant differences (Bas-Hoogendam et al., 2017; Sobanski et al., 2010; Szeszko et al., 2004; Uchida et al., 2008). Similarly, studies investigating the association between temporal cortex volumes and anxiety symptoms in individuals with a history of depression have been mixed. While Potvin and colleagues (2015) found that anxiety was correlated *smaller* temporal cortex volumes in their sample of older adults with a history of depression, two studies of non-geriatric depressed adults found the opposite effect (Inkster et al., 2011; Qi et al., 2014). In light of these studies, the null results observed in the current study are not surprising. In contrast, decreased ACC volumes have been associated with anxiety symptoms in both older adults with a history of depression (Potvin et al., 2015) as well as in non-geriatric depressed adults (van Tol et al., 2010). Why no such effect was observed in the current sample is unknown. Recent large database studies have highlighted the importance of large sample imaging and the need for meta-analyses for the reliable detection of neuroanatomical substrates of mental health disorders (Lui, Zhou, Sweeney, & Gong, 2016).

There are several limitations of the current study. First, the degree of current anxiety symptoms was relatively mild (mean HAM-A score = 9.72, SD = 3.84); thus, our results may not generalize to older adults with more severe anxiety. Additional large studies of older adults with comorbid diagnoses of depression and anxiety will help determine underlying brain changes and may inform efforts to identify populations at risk for poor outcomes. Second, because of the cross-sectional nature of the study, we are unable to identify causal relationships. It is possible that symptoms of anxiety decrease GMV in the insula and OFC in older adults with depression. It is also possible that decreased GMV in these areas increase symptoms of anxiety, or that unknown factors contribute to both decreased GMV in these areas as well as anxiety symptoms. Longitudinal clinical studies including multiple levels of analysis (e.g., psychosocial, neurobiological, genetic, immunological) will help elucidate these processes. Third, it is important to note that structural neuroimaging does not provide information about the functional role of our ROIs in anxiety symptoms in LLD. Fourth, our sample was relatively homogenous with regard to demographic features, and participants with significant psychiatric comorbidity, suicidality, or cognitive impairment were excluded. Recruitment of more clinically and demographically diverse samples could help determine group differences in the neural correlates of anxiety in LLD. Recent research suggest that mild cognitive impairment moderates the association between brain morphology and symptoms of anxiety and depression in late life (Lavretsky et al., 2009). Future work may identify similarities and differences in the neural correlates of anxiety in individuals with LLD and co-occurring cognitive impairment or other psychiatric

conditions. Finally, only data on current medication use and present comorbidity were collected in the current study, such that we were unable to investigate the association of previous medication use and diagnostic history with grey matter characteristics.

Conclusion

The current study is the first to our knowledge to identify grey matter characteristics associated with symptoms of anxiety in a relatively large sample of older adults with a current diagnosis of major depression. Our results suggest that even subthreshold anxiety is associated with detectable differences in cortical volumes in the OFC and insula. Decreased OFC volumes, in particular, may serve as a unique biomarker of anxiety symptoms in LLD. The observed sensitivity of key regions involved in LLD to subthreshold anxiety emphasizes the urgency to address anxiety in LLD to mitigate grey matter atrophy in this population. Continued research investigating the biological, psychological, and social factors contributing to anxiety in LLD will increase understanding of underlying neurophysiological mechanisms and help identify potential targets for future intervention.

Acknowledgements

We thank the patients who agreed to participate in this study. We also thank the staff at the Brain Mapping Center who helped collect these data.

Role of the Funding Source

This work was supported by NIH grants AT008383, AT009198, MH097892 as well as a grant from Allergan/ Forest Laboratories to Dr. Lavretsky. The funding sources were not involved in the study design, data collection, data analysis, data interpretation, report writing, or in the decision to submit this article for publication.

References

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders : DSM-IV-TR. Washington, DC: American Psychiatric Association.

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub.

Andreescu C, Lenze EJ, Dew MA, Begley AE, Mulsant BH, Dombrovski AY, . . .Reynolds CF. (2007). Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: controlled study. The British Journal of Psychiatry, 190(4), 344–349. [PubMed: 17401042]

Asami T, Yamasue H, Hayano F, Nakamura M, Uehara K, Otsuka T, . . . Hirayasu Y. (2009). Sexually dimorphic gray matter volume reduction in patients with panic disorder. Psychiatry Research: Neuroimaging, 173(2), 128–134.

Bas-Hoogendam JM, van Steenbergen H, Pannekoek JN, Fouche J-P, Lochner C, Hattingh CJ, . . . Frick A. (2017). Voxel-based morphometry multi-center mega-analysis of brain structure in social anxiety disorder. NeuroImage: Clinical, 16, 678–688. [PubMed: 30140607]

Beekman ATF, Bremmer MA, Deeg DJH, Van Balkom AJLM, Smit JH, De Beurs E,. . . Van Tilburg W. (1998). Anxiety disorders in later life: a report from the Longitudinal Aging Study Amsterdam. International journal of geriatric psychiatry, 13(10), 717–726. [PubMed: 9818308]

Beekman ATF, de Beurs E, van Balkom AJLM, Deeg DJH, van Dyck R, & van Tilburg W (2000). Anxiety and depression in later life: co-occurrence and communality of risk factors. American Journal of Psychiatry, 157(1), 89–95. [PubMed: 10618018]

Bland RC, Newman SC, & Orn H (1988). Prevalence of psychiatric disorders in the elderly in Edmonton. Acta Psychiatrica Scandinavica, 77(S338), 57–63.

Bush G, Luu P, & Posner MI (2000). Cognitive and emotional influences in anterior cingulate cortex. Trends in cognitive sciences, 4(6), 215–222. [PubMed: 10827444]

Byers AL, Yaffe K, Covinsky KE, Friedman MB, & Bruce ML (2010). High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication. Archives of General Psychiatry, 67(5), 489–496. [PubMed: 20439830]

Chen C-H, Ridler K, Suckling J, Williams S, Fu CHY, Merlo-Pich E, & Bullmore E (2007). Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. Biological Psychiatry, 62(5), 407–414. [PubMed: 17217921]

Davidson RJ, Putnam KM, & Larson CL (2000). Dysfunction in the neural circuitry of emotion regulation--a possible prelude to violence. Science, 289(5479), 591–594. [PubMed: 10915615]

DeLuca AK, Lenze EJ, Mulsant BH, Butters MA, Karp JF, Dew MA, . . . Reynolds CF. (2005). Comorbid anxiety disorder in late life depression: association with memory decline over four years. International journal of geriatric psychiatry, 20(9), 848–854. [PubMed: 16116585]

Etkin A, & Wager TD (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. American Journal of Psychiatry, 164(10), 1476–1488. [PubMed: 17898336]

Fiske A, Wetherell JL, & Gatz M (2009). Depression in older adults. Annu Rev Clin Psychol, 5, 363–389. [PubMed: 19327033]

Fjell AM, Westlye LT, Grydeland H, Amlien I, Espeseth T, Reinvang I, . . . Walhovd KB. (2013). Critical ages in the life course of the adult brain: nonlinear subcortical aging. Neurobiology of Aging, 34(10), 2239–2247. [PubMed: 23643484]

Folstein MF, Anthony JC, Parhad I, Duffy B, & Gruenberg EM (1985). The Meaning of Cognitive Impairment in the Elderly. Journal of the American Geriatrics Society, 33(4), 228–235. doi: 10.1111/j.1532-5415.1985.tb07109.x [PubMed: 3989183]

Folstein MF, Folstein SE, & McHugh PR (1975). “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 12(3), 189–198. [PubMed: 1202204]

Good CD, Johnsrude IS, Ashburner J, Henson RNA, Friston KJ, & Frackowiak RSJ (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. NeuroImage, 14(1), 21–36. [PubMed: 11525331]

Gottfried JA, O’Doherty J, & Dolan RJ (2003). Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science, 301(5636), 1104–1107. [PubMed: 12934011]

Gum AM, King-Kallimanis B, & Kohn R (2009). Prevalence of mood, anxiety, and substance-abuse disorders for older Americans in the national comorbidity survey-replication. The American Journal of Geriatric Psychiatry, 17(9), 769–781. [PubMed: 19700949]

Haber S (2008). Parallel and integrative processing through the Basal Ganglia reward circuit: lessons from addiction. Biological Psychiatry, 64(3), 173–174. [PubMed: 18617023]

Hamilton M (1959). The assessment of anxiety states by rating. Br J Med Psychol, 32(1), 50–55. [PubMed: 13638508]

Hayano F, Nakamura M, Asami T, Uehara K, Yoshida T, Roppongi T, . . . Hirayasu Y. (2009). Smaller amygdala is associated with anxiety in patients with panic disorder. Psychiatry and clinical neurosciences, 63(3), 266–276. [PubMed: 19566756]

Inkster B, Rao AW, Ridler K, Nichols TE, Saemann PG, Auer DP, . . . Merlo-Pich E. (2011). Structural brain changes in patients with recurrent major depressive disorder presenting with anxiety symptoms. Journal of Neuroimaging, 21(4), 375–382. [PubMed: 20977527]

Ionescu DF, Niciu MJ, Mathews DC, Richards EM, & Zarate CA (2013). Neurobiology of anxious depression: a review. Depress Anxiety, 30(4), 374–385. [PubMed: 23495126]

Jeste ND, Hays JC, & Steffens DC (2006). Clinical correlates of anxious depression among elderly patients with depression. Journal of affective disorders, 90(1), 37–41. [PubMed: 16325261]

Karel MJ, Gatz M, & Smyer MA (2012). Aging and mental health in the decade ahead: What psychologists need to know. American psychologist, 67(3), 184. [PubMed: 21942364]

Klumpp H, Post D, Angstadt M, Fitzgerald DA, & Phan KL (2013). Anterior cingulate cortex and insula response during indirect and direct processing of emotional faces in generalized social anxiety disorder. Biology of mood & anxiety disorders, 3(1), 7. [PubMed: 23547713]

Lavretsky H, Siddarth P, Kepe V, Ercoli LM, Miller KJ, Burggren AC, . . . Small GW. (2009). Depression and anxiety symptoms are associated with cerebral FDDNP-PET binding in middle-aged and older nondemented adults. The American Journal of Geriatric Psychiatry, 17(6), 493–502. [PubMed: 19472439]

Lenze EJ, Mulsant BH, Shear MK, Schulberg HC, Dew MA, Begley AE, . . . Reynolds Iii CF. (2000). Comorbid anxiety disorders in depressed elderly patients. American Journal of Psychiatry, 157(5), 722–728. [PubMed: 10784464]

Livingston G, Watkin V, Milne B, Manela MV, & Katona C (1997). The natural history of depression and the anxiety disorders in older people:: the Islington community study. Journal of affective disorders, 46(3), 255–262. [PubMed: 9547122]

Lui S, Zhou XJ, Sweeney JA, & Gong Q (2016). Psychoradiology: the frontier of neuroimaging in psychiatry. Radiology, 281(2), 357–372. [PubMed: 27755933]

Maier W, Buller R, Philipp M, & Heuser I (1988). The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. J Affect Disord, 14(1), 61–68. [PubMed: 2963053]

Massana G, Serra-Grabulosa JM, Salgado-Pineda P, Gasto C, Junque C, Massana J, . . . Salamero M. (2003). Amygdalar atrophy in panic disorder patients detected by volumetric magnetic resonance imaging. NeuroImage, 19(1), 80–90. [PubMed: 12781728]

Mehta KM, Simonsick EM, Penninx BWJH, Schulz R, Rubin SM, Satterfield S, & Yaffe K (2003). Prevalence and correlates of anxiety symptoms in well-functioning older adults: Findings from the health aging and body composition study. Journal of the American Geriatrics Society, 51(4), 499–504. [PubMed: 12657069]

Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, Rifai AH, . . . Reynolds CF. (1992). Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry research, 41(3), 237–248. [PubMed: 1594710]

Montgomery SA, & Äsberg M (1979). A new depression scale designed to be sensitive to change. The British Journal of Psychiatry, 134(4), 382–389. [PubMed: 444788]

O'Doherty JP, Deichmann R, Critchley HD, & Dolan RJ (2002). Neural responses during anticipation of a primary taste reward. Neuron, 33(5), 815–826. [PubMed: 11879657]

Ochsner KN, Bunge SA, Gross JJ, & Gabrieli JDE (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. Journal of cognitive neuroscience, 14(8), 1215–1229. [PubMed: 12495527]

Phillips ML, Drevets WC, Rauch SL, & Lane R (2003). Neurobiology of emotion perception II: implications for major psychiatric disorders. Biological Psychiatry, 54(5), 515–528. [PubMed: 12946880]

Potvin O, Catheline G, Bernard C, Meillon C, Bergua V, Allard M, . . . Amieva H. (2015). Gray matter characteristics associated with trait anxiety in older adults are moderated by depression. International psychogeriatrics, 27(11), 1813–1824. [PubMed: 26059837]

Pujol J, Soriano-Mas C, Alonso P, Cardoner N, Menchon JM, Deus J, & Vallejo J (2004). Mapping structural brain alterations in obsessive-compulsive disorder. Archives of General Psychiatry, 61(7), 720–730. [PubMed: 15237084]

Qi H, Ning Y, Li J, Guo S, Chi M, Gao M, . . . Wu K. (2014). Gray matter volume abnormalities in depressive patients with and without anxiety disorders. Medicine, 93(29).

Schienle A, Ebner F, & Schäfer A (2011). Localized gray matter volume abnormalities in generalized anxiety disorder. European archives of psychiatry and clinical neuroscience, 261(4), 303–307. [PubMed: 20820793]

Schoevers RA, Beekman ATF, Deeg DJH, Jonker C, & Tilburg W. v. (2003). Comorbidity and risk-patterns of depression, generalised anxiety disorder and mixed anxiety-depression in later life: results from the AMSTEL study. International journal of geriatric psychiatry, 18(11), 994–1001. [PubMed: 14618550]

Seymour B, O'Doherty JP, Koltzenburg M, Wiech K, Frackowiak R, Friston K, & Dolan R (2005). Opponent appetitive-aversive neural processes underlie predictive learning of pain relief. Nature neuroscience, 8(9), 1234. [PubMed: 16116445]

Shah SG, Klumpp H, Angstadt M, Nathan PJ, & Phan KL (2009). Amygdala and insula response to emotional images in patients with generalized social anxiety disorder. Journal of Psychiatry & Neuroscience.

Shiba Y, Santangelo AM, & Roberts AC (2016). Beyond the medial regions of prefrontal cortex in the regulation of fear and anxiety. Frontiers in systems neuroscience, 10, 12. [PubMed: 26941618]

Smith GS, Kramer E, Ma Y, Kingsley P, Dhawan V, Chaly T, & Eidelberg D (2009). The functional neuroanatomy of geriatric depression. International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences, 24(8), 798–808.

Sobanski T, Wagner G, Peikert G, Gruhn U, Schluttig K, Sauer H, & Schlosser R (2010). Temporal and right frontal lobe alterations in panic disorder: a quantitative volumetric and voxel-based morphometric MRI study. Psychol Med, 40(11), 1879–1886. [PubMed: 20056020]

Stein MB, Simmons AN, Feinstein JS, & Paulus MP (2007). Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. American Journal of Psychiatry, 164(2), 318–327. [PubMed: 17267796]

Streiner DL, Cairney J, & Veldhuizen S (2006). The epidemiology of psychological problems in the elderly. The Canadian Journal of Psychiatry, 51(3), 185–191. [PubMed: 16618010]

Szeszko PR, MacMillan S, McMeniman M, Lorch E, Madden R, Ivey J, . . . Rosenberg DR. (2004). Amygdala volume reductions in pediatric patients with obsessive-compulsive disorder treated with paroxetine: preliminary findings. Neuropsychopharmacology, 29(4), 826. [PubMed: 14970831]

Szeszko PR, Robinson D, Alvir JMJ, Bilder RM, Lencz T, Ashtari M, . . . Bogerts B. (1999). Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder. Archives of General Psychiatry, 56(10), 913–919. [PubMed: 10530633]

Tampi RR, & Tampi DJ (2014). Anxiety disorders in late life: A comprehensive review. Healthy Aging Research, 3, 1–9.

Uchida RR, Del-Ben CM, Busatto GF, Duran FLS, Guimaraes FS, Crippa JAS, . . . Graeff FG. (2008). Regional gray matter abnormalities in panic disorder: a voxel-based morphometry study. Psychiatry Research: Neuroimaging, 163(1), 21–29.

Uchida RR, Del-Ben CM, Santos AC, Araujo D, Crippa JA, Guimaraes FS, & Graeff FG (2003). Decreased left temporal lobe volume of panic patients measured by magnetic resonance imaging. Brazilian Journal of Medical and Biological Research, 36(7), 925–929. [PubMed: 12845380]

van Tol M-J, van der Wee NJA, van den Heuvel OA, Nielen MMA, Demenescu LR, Aleman A, . . . Veltman DJ. (2010). Regional brain volume in depression and anxiety disorders. Archives of General Psychiatry, 67(10), 1002–1011. [PubMed: 20921116]

Vythilingam M, Anderson ER, Goddard A, Woods SW, Staib LH, Charney DS, & Bremner JD (2000). Temporal lobe volume in panic disorder—a quantitative magnetic resonance imaging study. Psychiatry Research: Neuroimaging, 99(2), 75–82.

Zhu X, Suarez-Jimenez B, Lazarov A, Helpman L, Papini S, Lowell A, . . . Schneier F. (2018). Exposure-based therapy changes amygdala and hippocampus resting-state functional connectivity in patients with posttraumatic stress disorder. Depress Anxiety.

Highlights

- Grey matter volumes were assessed in 113 adults with late-life depression (LLD).
- Anxiety symptoms correlated with smaller insula and orbitofrontal cortex volumes.
- Depressive symptoms correlated smaller insula volumes.
- Even subthreshold anxiety may increase risk for cortical atrophy in LLD.
- Smaller orbitofrontal cortex volumes may serve as a unique biomarker of anxiety in LDD.

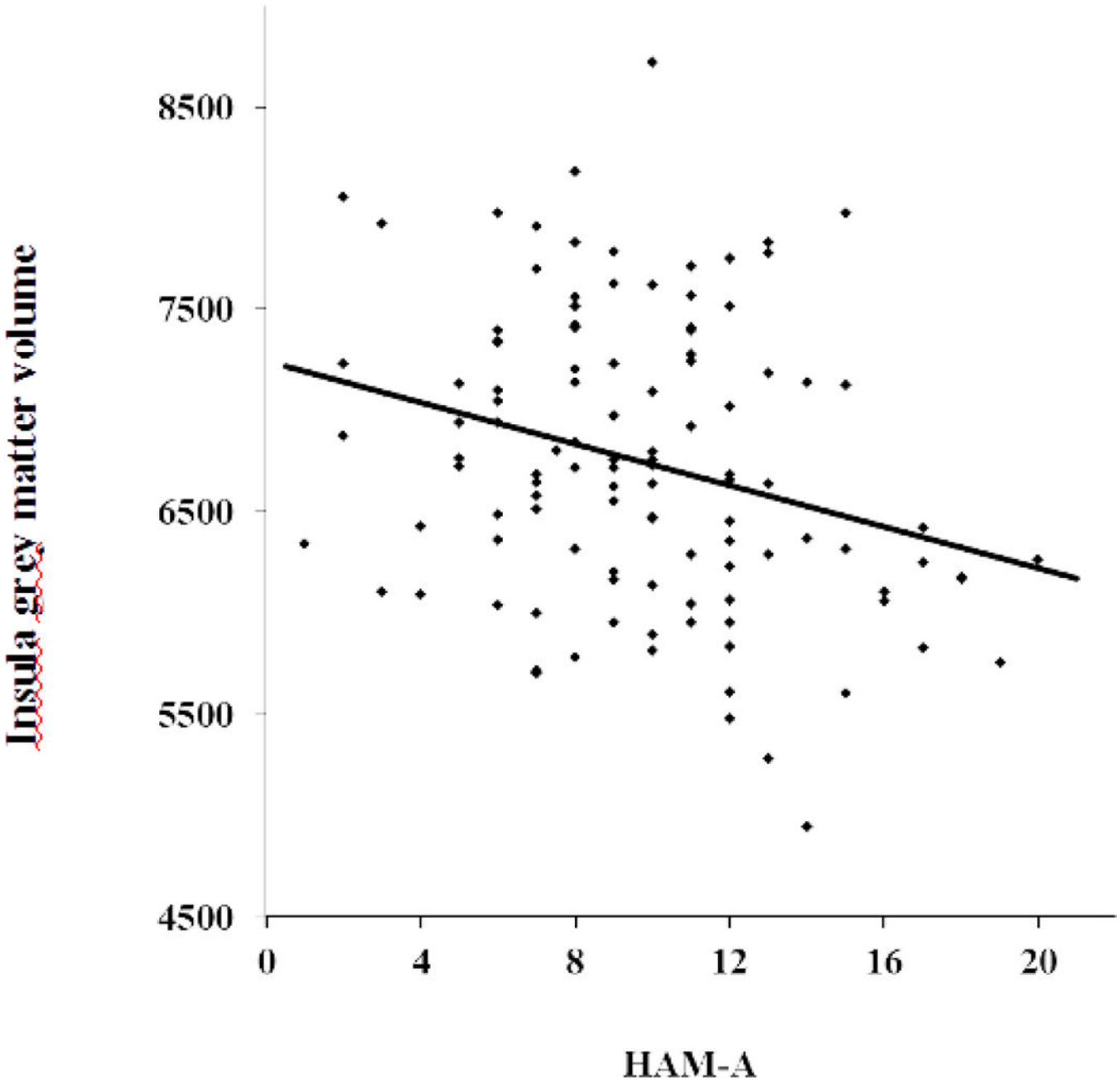

Figure 1.
Association between anxiety symptom severity and bilateral insula grey matter volume after controlling for covariates.

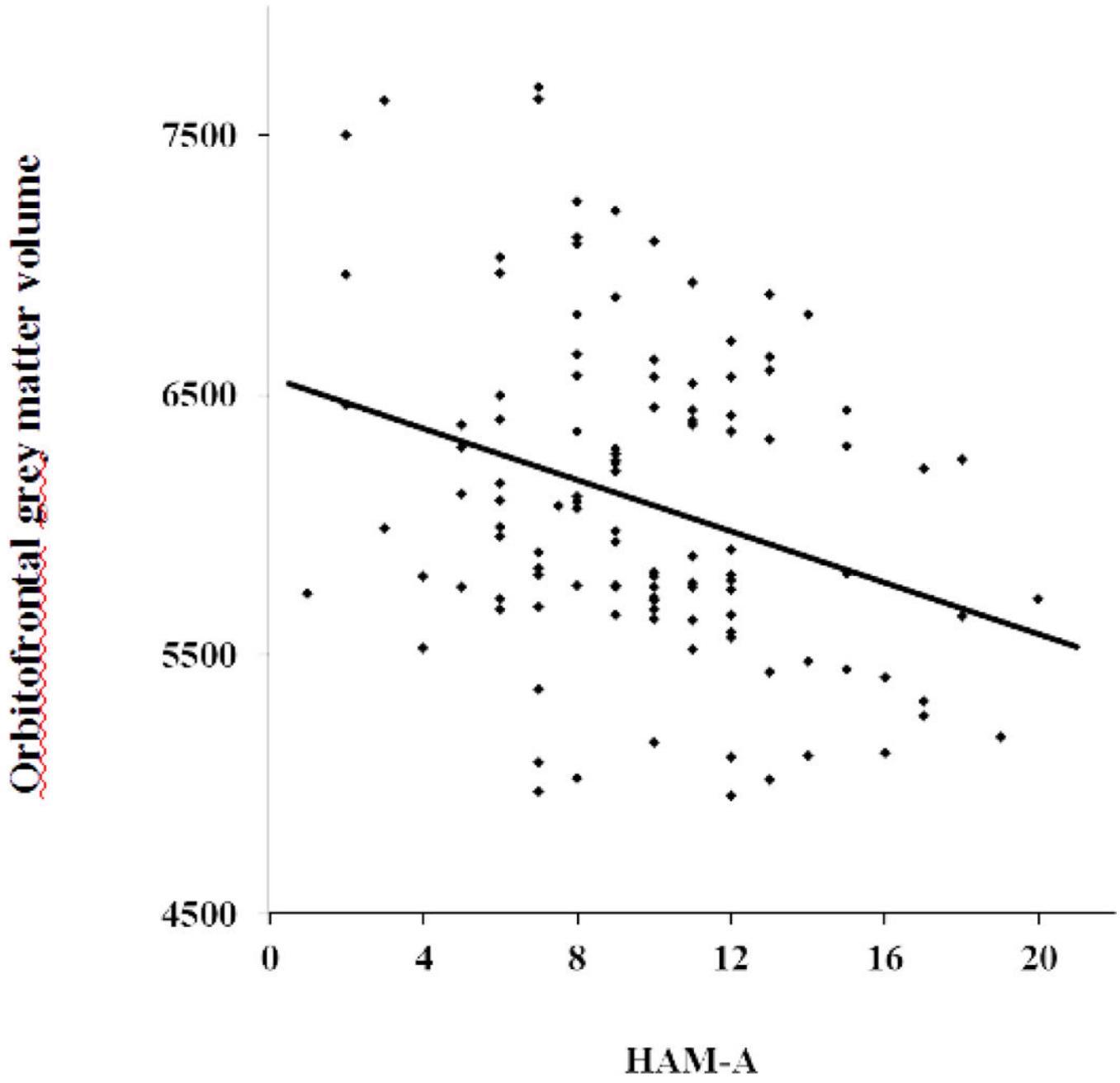

Figure 2.
Association between anxiety symptom severity and bilateral orbitofrontal grey matter volume after controlling for covanates.

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Sample Characteristics

	Mean(SD)/ N(%)
Sex	
Female	74 (65.5%)
Male	39 (34.5%)
Race	
White	90 (80.4%)
Hispanic	11 (9.8%)
Black	7 (6.3%)
Asian	3 (2.7%)
Age	69.7 (6.6)
Depression onset <50 yrs	59 (52.2%)
Years education	16.0 (2.1)
CIRS	4.8 (3.4)
MMSE	28.7 (1.4)
MADRS	16.5 (4.3)
HAM-A	9.7 (3.8)

Note. Total sample N = 113. CIRS = Cumulative Illness Rating Scale for Geriatrics; MMSE = Mini-Mental State Exam; MADRS = Montgomery–Åsberg Depression Rating Scale; HAM-A = Hamilton Anxiety Rating Scale.