International Psychogeriatrics: page 1 of 12 © The Author(s), 2024. Published by Cambridge University Press on behalf of International Psychogeriatric Association
doi:10.1017/S1041610224000012

Anxiety in late-life depression: Associations with brain volume, amyloid beta, white matter lesions, cognition, and functional ability

Maria Kryza-Lacombe,[1,2] Michelle T. Kassel,[1,2] Philip S. Insel,[2] Emma Rhodes,[1,2] David Bickford,[2] Emily Burns,[2] Meryl A. Butters,[3] Duygu Tosun,[4,5] Paul Aisen,[6,7] Rema Raman,[6,7] Susan Landau,[8] Andrew J. Saykin,[9] Arthur W. Toga,[10] Clifford R. Jack Jr,[11] Robert Koeppe,[12] Michael W. Weiner,[2,4,5] Craig Nelson,[2] and R. Scott Mackin[2,4]

[1]*Mental Illness Research Education and Clinical Centers, Veterans Affairs Medical Center, San Francisco, CA, USA*
[2]*Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, CA, USA*
[3]*Department of Psychiatry Western Psychiatric Hospital, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*
[4]*Veterans Affairs Medical Center, San Francisco, CA, USA*
[5]*Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA*
[6]*University of Southern California, Los Angeles, CA, USA*
[7]*Keck School of Medicine, Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA*
[8]*Helen Wills Neuroscience Institute, University of California, Berkeley, CA, USA*
[9]*Department of Radiology and Imaging Sciences and the Indiana Alzheimer's Disease Research Center, Indiana University School of Medicine, Indianapolis, IN, USA*
[10]*Laboratory of Neuro Imaging, Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA*
[11]*Department of Radiology, Mayo Clinic, Rochester, MN, USA*
[12]*Department of Radiology, University of Michigan, Ann Arbor, USA*

ABSTRACT

Objectives: Late-life depression (LLD) is common and frequently co-occurs with neurodegenerative diseases of aging. Little is known about how heterogeneity within LLD relates to factors typically associated with neurodegeneration. Varying levels of anxiety are one source of heterogeneity in LLD. We examined associations between anxiety symptom severity and factors associated with neurodegeneration, including regional brain volumes, amyloid beta (Aβ) deposition, white matter disease, cognitive dysfunction, and functional ability in LLD.

Participants and Measurements: Older adults with major depression ($N = 121$, Ages 65–91) were evaluated for anxiety severity and the following: brain volume (orbitofrontal cortex [OFC], insula), cortical Aβ standardized uptake value ratio (SUVR), white matter hyperintensity (WMH) volume, global cognition, and functional ability. Separate linear regression analyses adjusting for age, sex, and concurrent depression severity were conducted to examine associations between anxiety and each of these factors. A global regression analysis was then conducted to examine the relative associations of these variables with anxiety severity.

Results: Greater anxiety severity was associated with lower OFC volume ($\beta = -68.25$, $t = -2.18$, $p = .031$) and greater cognitive dysfunction ($\beta = 0.23$, $t = 2.46$, $p = .016$). Anxiety severity was not associated with insula volume, Aβ SUVR, WMH, or functional ability. When examining the relative associations of cognitive functioning and OFC volume with anxiety in a global model, cognitive dysfunction ($\beta = 0.24$, $t = 2.62$, $p = .010$), but not OFC volume, remained significantly associated with anxiety.

Conclusions: Among multiple factors typically associated with neurodegeneration, cognitive dysfunction stands out as a key factor associated with anxiety severity in LLD which has implications for cognitive and psychiatric interventions.

Key words: Late-life depression, Anxiety, gray matter volume, Amyloid beta, Cognition

Correspondence should be addressed to: M. Kryza-Lacombe, Mental Illness Research Education and Clinical Centers, San Francisco VA Health Care System, San Francisco, CA 94121, USA. Tel: (415) 221-4810 x23114. E-mail: maria.kryza-lacombe@ucsf.edu. Received 09 Nov 2023; revision requested 16 Nov 2023; revised version received 15 Dec 2023; accepted 22 Dec 2023.

Introduction

Major depressive disorder in older adults, or late-life depression (LLD), is common, associated with

functional decline in old age (Anstey *et al.*, 2007), and frequently co-occurs with neurodegenerative diseases of aging (Diniz *et al.*, 2013). Little is known about how heterogeneity within LLD relates to features associated with neurodegeneration. Anxiety is highly prevalent among individuals with LLD and is one source of heterogeneity in this population. Up to 48% of individuals with LLD present with a concurrent anxiety disorder (Beekman *et al.*, 2000; Jeste *et al.*, 2006; Lenze *et al.*, 2000), which has been associated with poorer depression treatment outcomes and higher rates of recurrence (Andreescu *et al.*, 2007; Steffens & McQuoid, 2005). While LLD often coincides with features commonly associated with neurodegeneration, little is known about how anxiety within LLD relates to such features. Examining how comorbid anxiety relates to factors such as brain structure, amyloid beta (Aβ) deposition, white matter lesions, cognition, and functional ability may elucidate etiological mechanisms implicated in anxiety symptoms in LLD, thereby help parse the heterogeneity of LLD, and may eventually inform precision medicine approaches for both mood symptoms and cognitive dysfunction in LLD.

Anxiety has been linked to neurodegeneration and neuropathology in older adults, including reduced gray matter volume (Karim *et al.*, 2021; Mah *et al.*, 2015) and greater Aβ deposition (Krell-Roesch *et al.*, 2018) and white matter lesion burden (Vogels *et al.*, 2007). These studies suggest that neural circuit disruptions may be elicited by structural abnormalities that diminish emotion regulation capacity and contribute to increased anxious affect. For example, structural and functional abnormalities in the orbitofrontal cortex (OFC), an area involved in emotional processing and behavioral flexibility (Schoenbaum *et al.*, 2009), have been linked to anxiety disorders (Milad & Rauch, 2007) including in older adults with generalized anxiety disorder (Andreescu *et al.*, 2017). In LLD, the association of anxiety with neurodegenerative features is understudied but has been most consistently associated with reduced gray matter in the OFC and insula (Laird *et al.*, 2019), another region involved in emotion processing that is thought to be linked to anxiety-related impairments including threat sensitivity (Klumpp *et al.*, 2012). Both of these regions have been implicated as factors contributing to anxious symptomatology in older adults with a history of depression (Potvin *et al.*, 2015) and in community-dwelling older adults (Pink *et al.*, 2017). Reduced gray matter in the amygdala, anterior cingulate cortex (ACC), and temporal cortex as well as other distributed frontal and parietal areas have also been associated with anxiety in older adults with a history of or current depression, but less consistently (Krause-Sorio *et al.*, 2023; Laird *et al.*, 2019; Potvin *et al.*, 2015). With only two studies conducted specifically in LLD (Krause-Sorio *et al.*, 2023; Laird *et al.*, 2019), more work is needed to elucidate the associations between anxiety and gray matter integrity in this population given the high comorbidity of anxiety and documented vulnerability to lower cortico-limbic volume in LLD (Andreescu *et al.*, 2008).

Previous work has also linked anxiety with neuropathology related to two of the most common neurodegenerative diseases of aging, Alzheimer's disease (AD), and cerebrovascular disease (CVD). AD is characterized by increased Aβ. Associations between Aβ and anxiety have been documented in non-depressed cognitively normal older adults (Johansson *et al.*, 2022; Krell-Roesch *et al.*, 2018; Lewis *et al.*, 2022) and in a mixed sample of older adults with subjective cognitive decline, mild cognitive impairment, and AD dementia (Banning *et al.*, 2020). Research examining associations between anxiety and white matter lesion burden characteristic of CVD has been more limited (Clancy *et al.*, 2021), yet higher white matter lesion burden has been associated with greater anxiety in older adults with a history of ischemic stroke (Kim *et al.*, 2011) and heart failure (Vogels *et al.*, 2007). Overall, although Aβ and white matter pathology appear implicated in anxious symptomatology in older adults, possibly due to related disruptions in emotion circuitry, to our knowledge these factors have not yet been examined in association with anxiety in LLD.

Poorer cognitive functioning in older adults is also known to be associated with anxiety symptoms. For example, in community-based studies, anxiety in older adults has been related to increased likelihood of cognitive dysfunction and impairment (Beaudreau & O'Hara, 2008; Diefenbach *et al.*, 2014; Smith *et al.*, 2021), even when controlling for depression severity and other demographic and clinical covariates (Bierman *et al.*, 2005). Furthermore, community-dwelling older adults with coexisting depression and anxiety exhibited more wide-ranging cognitive deficits compared to individuals with anxiety or depression only (Beaudreau & O'Hara, 2009). In LLD, previous work found no cross-sectional associations between increased anxiety and poorer cognition (DeLuca *et al.*, 2005); however, analyses did not control for depression severity and findings may have been limited by a small sample size. Furthermore, to our knowledge no previous studies have evaluated the relative associations of anxiety in LLD with cognition alongside neurodegenerative features.

Previous work has also shown consistent associations between anxiety and declines in overall functional status among older adults. For example, associations between higher anxiety and poorer

https://doi.org/10.1017/S1041610224000012 Published online by Cambridge University Press

functional status have been found in older adults in nursing care settings (Schultz *et al.*, 2004) and in the community (Krell-Roesch *et al.*, 2020). Furthermore, lower functional ability has also been reported among older adults with anxiety disorders (Porensky *et al.*, 2009). Although evidence suggests that comorbid depression and anxiety are associated with poorer functional status in community samples (Simning & Seplaki, 2020), these associations are understudied within LLD. Some studies suggest that elevated anxiety levels may relate to added functional impairment in LLD (Morin *et al.*, 2020; Schoevers *et al.*, 2003), but no studies have examined relative associations of functional ability and neurodegenerative features with anxiety, despite established links between Aβ and WMH and functional decline.

To elucidate the relation between anxiety and neurodegeneration within LLD, we evaluated the associations of anxiety symptom severity with cortico-limbic volumes, cortical Aβ deposition, WMH, global cognitive functioning, and functional ability in a sample of older adults with LLD. As anxiety and depression have overlapping symptomatology, we controlled for depression severity in our analyses, to highlight the independent effects of anxiety. Our a priori hypotheses were that greater anxiety symptom severity would be associated with smaller cortico-limbic volume in the OFC and insula, greater cortical Aβ deposition and white matter lesion burden, as well as poorer performance on measures of global cognition and functional ability. Additionally, we evaluated the relative associations of these variables with anxiety severity.

Materials & methods

Participants and procedures

Participants were older adults with Major Depressive Disorder (MDD; $N = 121$, Ages 65–91). MDD was determined via multidisciplinary consensus based on the 17-item Hamilton Depression Rating Scale (Hamilton, 1960; total $\geq$ 15), and the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV (American Psychiatric Association, 2000). Participants were eligible if they had unipolar MDD without psychotic features and were currently experiencing an episode of at least six-week duration. Exclusion criteria included other concurrent primary Axis I disorders (except for certain anxiety disorders, e.g., generalized anxiety disorder), neurologic disorders that affect the CNS (e.g., epilepsy, Parkinson's disease, traumatic brain injury), and a clinical dementia diagnosis or evidence of dementia (<25 on the Mini-Mental Status Exam and Clinical Dementia Rating Scale > 1.0).

Participants completed MRI imaging and AV-45 (Florbetapir) amyloid PET imaging and had their blood drawn for DNA/RNA banking with APOE genotyping. They also underwent cognitive testing and comprehensive psychiatric evaluations. The study was designed and executed in accordance with the Declaration of Helsinki for the protection of Human Subjects and approved by the Institutional Review Boards of each study site (University of California, San Francisco, University of Pittsburgh). Written informed consent was obtained from all participants.

Measures

Anxiety

The Generalized Anxiety Disorder 7-item scale (Spitzer *et al.*, 2006; GAD-7), which has been validated in older adults (Wild *et al.*, 2014), evaluated anxiety symptom severity. Participants rated each item on a four-point scale (0 = "not at all," to 3 = "nearly every day") to indicate experienced severity of anxiety symptoms over the past two weeks. Anxiety severity was used as a continuous variable across analyses.

Depression

The Geriatric Depression Scale (Yesavage, 1988; GDS) measured depression severity and was used as a covariate across analyses.

Cortico-limbic volumes and white matter hyperintensities

MRI data were obtained using a 3T scanner to measure cortico-limbic volumes and white matter hyperintensities. MRI protocols included 3D MP-RAGE or IR-SPGR T1-weighted MRI with sagittal slices and voxel size of $1 \times 1 \times 1.2\,mm^3$ and 2D FLAIR MRI with axial slices and voxel size of $0.9 \times 0.9 \times 5\,mm^3$ (Gunter *et al.*, 2017). Cortico-limbic volumes were measured by parcellating the entire cortex of each subject into 41 bilateral regions-of-interest (ROIs) based on a previously published volumetric Desikan-Killiany-Tourville atlas via FreeSurfer v5.3 processing. A Bayesian inference approach was used to noise-correct and segment FLAIR images (Schwarz *et al.*, 2009) for white matter hyperintensities. The OFC and the insula were identified a priori as primary region of interest. In line with previous work, and because sensitivity analyses revealed no significant laterality or subarea effect in the present sample, we used bilateral volumes and combined lateral and medial OFC volumes into single bilateral volumes. Supplemental analyses examined additional regions that have less consistently been shown to be implicated in older adults with anxiety (see Supplemental Materials; Andreescu

https://doi.org/10.1017/S1041610224000012 Published online by Cambridge University Press

et al., 2017; Potvin *et al.*, 2015). White matter lesion burden was defined as the total volume of cerebral white matter hyperintensities (WMH).

Amyloid beta (Aβ)

As previously described (Mackin *et al.*, 2021), all participants underwent Florbetapir PET imaging with four 5-minute frames acquired 50–70 minutes post-injection which were coregistered to a concurrently acquired structural MRI scan. Regional means defined in FreeSurfer 5.3 were used to calculate Florbetapir cortical summary SUVR, which was a composite of frontal, cingulate, temporal, and parietal regions relative to the whole cerebellum (Landau *et al.*, 2013). The composite was used as a continuous variable in our analyses.

APOE genotype

Blood-based DNA/RNA banking determined APOE genotype. A dichotomous variable indicated the absence or presence of the e4 allele (i.e., risk genotypes included 3|4 or 4|4).

Global cognitive functioning

Alzheimer's Disease Assessment Scale-Cognitive Subscale (Rosen *et al.*, 1984; ADAS-Cog) was used to assess global cognitive functioning via 13 subtests designed to measure cognitive dysfunction characteristic of AD. Higher scores indicate more significant impairment.

Functional ability

The Clinical Dementia Rating Scale ([Morris, 1993]CDR) Sum of Boxes (SB) score was used to measure functional ability assessed via semi-structured interviews administered by trained and certified interviewers, with higher scores indicating greater impairment.

Statistical analyses

Anxiety severity in the sample was determined via symptom endorsement on the GAD-7 according to validated published ranges (Spitzer *et al.*, 2006): minimal (≤ 4 points), mild (5–9 points), moderate (10–14 points), and severe anxiety (≥ 15 points). Additionally, the number of individuals with concurrent or lifetime history of a secondary anxiety diagnosis was identified via the SCID.

To examine the associations between anxiety and brain structure (OFC and insula volumes), neuropathology (Aβ SUVR, WMH), and measures of global cognition (ADAS-Cog), and functional ability (CDR-SB), linear regression analyses were conducted with anxiety symptom severity, measured continuously, as the predictor of interest of each of the other variables in separate models. Age, gender, and concurrent depression severity were added as covariates across all models. Intracranial volume was added as an additional covariate in models of cortico-limbic volumes, APOE genotype in the model including Aβ, and education level in the models predicting ADAS-Cog and CDR-SB. This was done to control for known associations between these covariates and respective outcome variables. Given our a priori hypotheses based on prior literature independently implicating the OFC and the insula (Laird *et al.*, 2019; Potvin *et al.*, 2015), cortico-limbic volume analyses were not corrected for multiple comparisons. Log-transformed variables of Aβ SUVR, WMH, and CDR-SB were used in regression analyses as the raw distribution of these variables was significantly skewed. Regression residuals were evaluated for normality and influential cases. Residuals were not normally distributed and/or influential cases were identified in analyses examining Aβ SUVR, WMH, and CDR-SB, and robust regression was conducted as a follow-up analysis for these outcomes. Non-parametric Mann-Whitney tests were additionally conducted to examine whether Aβ SUVR, WMH, and CDR-SB differed by anxiety (i.e., minimal/mild anxiety vs. moderate/severe anxiety).

To evaluate the relative associations of the factors associated with anxiety, a global regression analysis was conducted using anxiety symptom severity, measured continuously, as the outcome. Predictors in this model included factors that emerged as significantly associated with anxiety in initial analyses, as well as demographic characteristics (age, gender, education level) and concurrent depression. Volumes added to this model were adjusted for intracranial volume by creating a variable that represents the proportion of cortico-limbic volume to intracranial volume. Regression residuals were evaluated for normality and influential cases to ensure regression assumptions were met.

Results

Prevalence of anxiety

In the present LLD sample, 50% of individuals endorsed moderate or severe anxiety symptoms (GAD-7), and 27% met criteria for a concurrent anxiety disorder with 7% meeting criteria for more than one anxiety disorder (Table 1). An additional 3% met criteria for lifetime, but not current anxiety disorders. Correlations among variables of interest in this study are presented in Supplemental Table 1.

https://doi.org/10.1017/S1041610224000012 Published online by Cambridge University Press

Table 1. Demographic and clinical characteristics ($N = 121$)

	MEAN ± *SD*	RANGE
Age, years	70.92 ± 5.33	65–91
Education, years	16.34 ± 2.01	12–22
Sex, No. female (%)	82 (68%)	–
Race, No. non-white (%)	15 (13%)	–
Amyloid beta, No. positive (%)	23 (19%)	–
GDS	7.18 ± 3.25	1–15
ADAS-Cog	9.50 ± 5.16	2–30
CDR-SB	0.65 ± 0.65	0–3.5
Any concurrent anxiety disorder^, No. (%)	31 (27%)	–
Generalized anxiety disorder, No. (%)	23 (20%)	–
Social phobia, No. (%)	6 (5%)	–
Specific phobia, No. (%)	9 (8%)	–
Agoraphobia, No. (%)	1 (<1%)	–
Panic disorder, No. (%)	1 (<1%)	–
GAD-7	10.03 ± 4.73	1–21
Minimal anxiety, No. (%)	15 (12%)	–
Mild anxiety, No. (%)	46 (38%)	–
Moderate anxiety, No. (%)	37 (31%)	–
Severe anxiety, No. (%)	23 (19%)	–

Amyloid beta positivity defined as SUVR > 1.11; GAD-7 = Generalized Anxiety Disorder 7-item scale, GDS = Geriatric Depression Scale (15 items), ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, CDR-SB = Clinical Dementia Rating scale Sum of Boxes; Missing data.
Race, 1; GDS, 1; ADAS-Cog, 1; CDR-SB, 3; Concurrent Anxiety Disorder, 6.
^8 individuals met criteria for more than one concurrent anxiety disorder; qualitative labels of the GAD-7 are provided here to illustrate anxiety score distribution in the present sample; however, the continuous GAD-7 total score was used across all analyses.

Association of anxiety with cortico-limbic volumes

Controlling for intracranial volume, age, gender, and concurrent depression severity, anxiety was inversely associated with OFC volume (Table 2; $b = -68.25$, $t = -2.18$, $p = 0.031$, $\eta_p^2 = 0.04$, Figure 1a) but was not associated with insula volume ($b = -19.76$, $t = -0.85$, $p = 0.395$, $\eta_p^2 = 0.01$, Figure 1b). Anxiety was not significantly associated with any of the volumes examined in supplemental analyses (i.e., ACC, amygdala, temporal cortex; see Supplemental Materials).

Association of anxiety with Aβ deposition and white matter lesion burden

After controlling for age, gender, and concurrent depression severity, no significant associations emerged between anxiety severity and Aβ SUVR ($b = 0.002$, $t = 1.15$, $p = 0.253$, $\eta_p^2 < .01$) or WMH ($b = -0.01$, $t = -0.45$, $p = 0.656$, $\eta_p^2 < .01$). Follow-up Mann-Whitney U tests showed no difference between minimal/mild and moderate/severe anxiety for Aβ SUVR ($U = 1720.50$, $p = .570$) or WMH ($U = 1776.50$, $p = .902$).

Association of anxiety with global cognitive functioning

Higher anxiety severity scores were significantly associated with worse performance on ADAS-Cog (Table 2; $b = 0.23$, $t = 2.46$, $p = 0.016$, $\eta_p^2 = .05$), controlling for age, gender, education level, and concurrent depression severity. Older age also emerged as significantly associated with worse ADAS-Cog performance in this model. Table 2 presents result metrics of all model parameters. Examination of model residuals identified two influential cases. Sensitivity analyses that removed these cases from the regression did not change the results or interpretation of the regression.

Association of anxiety with functional ability

Adjusting for age, gender, education, and concurrent depression severity, anxiety severity was not associated with CDR-SB ($b = 0.02$, $t = 1.76$, $p = 0.081$, $\eta_p^2 = .03$). Follow-up Mann-Whitney U showed no difference between minimal/mild and moderate/severe anxiety ($U = 1970.50$, $p = .197$).

Regression analysis evaluating relative associations of cognitive functioning and brain structure with anxiety severity

ADAS-Cog and OFC volume (adjusted for intracranial volume) were entered into the model predicting anxiety severity given their significant associations with anxiety severity in previous models. Worse ADAS-Cog performance was significantly associated with higher anxiety severity ($b = 0.24$, $t = 2.62$, $p = 0.010$, $\eta_p^2 = .06$), but OFC volume did not show a significant association ($b = -399.61$, $t = -1.13$, $p = 0.262$, $\eta_p^2 = .01$). Table 3 displays result metrics of all model parameters and Figure 2 presents a visual representation of the significant effect.

Discussion

The key findings of this study were that greater anxiety severity was associated with greater cognitive dysfunction and lower OFC volume. Additionally, we found that when considering their relative associations with anxiety, only global cognitive functioning remained significantly associated with anxiety severity, independent of OFC volume and concurrent depression severity. We found no associations between anxiety severity and cortical Aβ deposition, WMH, or functional impairment in

https://doi.org/10.1017/S1041610224000012 Published online by Cambridge University Press

Table 2. Summary of demographic and clinical predictors of orbitofrontal cortex volume and cognitive impairment

	OFC volume	ADAS-Cog
Model *R2*	0.48	0.19
F – Statistic	19.54	4.73
DF	5,107	5,114
	b (SE)	***b (SE)***
Intercept	14,168.38** (2761.33)	– 4.37 (7.34)
Age	– 51.96 (27.32)	0.23** (0.08)
Sex	– 267.23 (375.26)	– 0.64 (0.93)
Education	–	– 0.39 (0.22)
ICV	0.01** (0.001)	–
Depression severity	63.52 (45.84)	0.26 (0.14)
Anxiety severity	**– 68.25* (31.27)**	**0.23* (0.09)**

OFC, orbitofrontal cortex; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; DF, degrees of freedom; SE, standard error; ICV, intracranial volume.
*$p < .05$.
**$p < .01$.

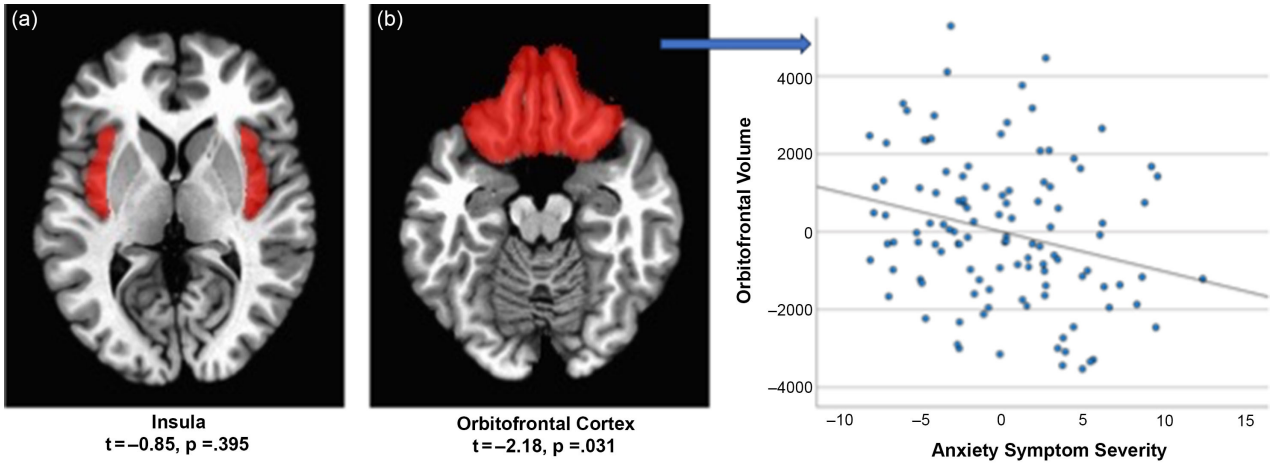

Figure 1. Associations of anxiety with insula (*a*) and orbitofrontal cortex (*b*) volumes.

the present sample. Taken together these findings suggest that cognitive dysfunction and smaller OFC volume, rather than neuropathological indicators more commonly associated with emerging AD or CVD, may be key to understanding anxiety symptoms in LLD.

One major finding is that higher anxiety severity in LLD was associated with poorer performance on a measure of global cognition. This aligns with studies of community-dwelling older adults (Beaudreau & O'Hara, 2008; Bierman *et al.*, 2005; Diefenbach *et al.*, 2014; Smith *et al.*, 2021) and prior work showing that coexisting depression and anxiety among older adults relates to more wide-ranging cognitive deficits compared to individuals with increased anxiety or depression only (Beaudreau & O'Hara, 2009). However, other studies report either no cross-sectional anxiety-related differences in global cognition within LLD (DeLuca *et al.*, 2005) or no additive effect of anxiety on cognitive dysfunction (Martinussen *et al.*, 2019). These discrepancies may be due to our larger sample with higher statistical power compared to previous work (DeLuca *et al.*, 2005) and the outpatient setting of our data collection compared to the inpatient setting of previous work (Martinussen *et al.*, 2019). Overall, our findings, in the context of other work that demonstrated anxiety as a predictor of future cognitive decline (DeLuca *et al.*, 2005; Fung *et al.*, 2018), suggest that screening for anxiety symptoms in individuals with LLD may be important as high symptom severity may put individuals at risk for cognitive dysfunction and cognitive decline over time. However, it is also possible that cognitive dysfunction leads to increased anxiety.

We also found that higher anxiety was associated with lower OFC volume consistent with previous work in older adults with LLD (Laird *et al.*, 2019) and

https://doi.org/10.1017/S1041610224000012 Published online by Cambridge University Press

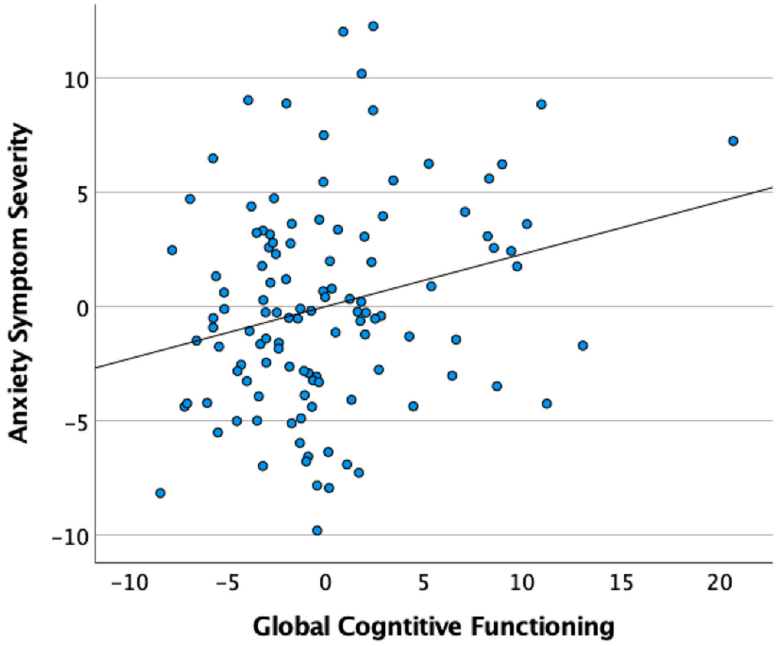

Figure 2. Partial regression plot of the association between anxiety severity and cognitive functioning, controlling for age, gender, level of education, concurrent depression severity, and orbitofrontal volume.

a history of depression (Potvin *et al.*, 2015), as well as with work in older adults with generalized anxiety disorder outside the context of depression (Andreescu *et al.*, 2017). Lower OFC volume, whether life-long or acquired, may be related to functional disruptions in the OFC that may impact behavioral flexibility (Schoenbaum *et al.*, 2009) and emotion regulation (Dixon *et al.*, 2017) and lead to greater anxiety symptoms. Alternatively, individuals with elevated anxiety may be at risk for atrophy in the OFC, which may contribute to cognitive dysfunction and exacerbate emotion processing difficulties. Future work would benefit from further examining these associations to determine the degree to which smaller OCF volume may be an anxiety-specific biomarker across depressed and non-depressed populations. Unlike previous work (Laird *et al.*, 2019; Potvin *et al.*, 2015), we found no associations between anxiety severity and insula volume. This may be due to differences in analytic approaches. For example, prior work (Laird *et al.*, 2019) did not control for depression severity in their analyses with anxiety; however, in a separate model, the same study found that depression severity was also associated with insula volume in LLD. Thus, lower insula volume may be more specific to depression symptom severity, which we controlled in our models.

Another key finding is that cortical Aβ burden was not associated with anxiety in this LLD sample. To our knowledge, this was the first LLD study to examine Aβ burden in relation to anxiety symptom severity. Our findings suggest that emerging AD, as measured by global cortical Aβ burden, may not be a significant contributor to anxiety symptomatology in this population. These results stand in contrast to previous studies demonstrating associations between anxiety and Aβ burden in non-LLD older adult samples (Banning *et al.*, 2020; Johansson *et al.*, 2022; Krell-Roesch *et al.*, 2018; Lewis *et al.*, 2022), which have been interpreted as anxiety possibly increasing risk for Aβ deposition through elevated cortisol levels and brain inflammation (Banning *et al.*, 2020; Krell-Roesch *et al.*, 2018), or that higher Aβ burden may predispose older adults to developing anxiety (Johansson *et al.*, 2022). It is possible that major depression modulates how the brain responds to anxiety and how anxiety influences the development of cortical Aβ pathology. However, given prior work suggesting links between increased anxiety and high subcortical amyloid burden (Hanseeuw *et al.*, 2020) which was not examined here, it will be important to investigate these associations in future LLD work. We also found no associations between anxiety severity and WMH in our sample consistent with multiple previous non-LLD studies that also failed to demonstrate a link between WMH and anxiety (Andreescu *et al.*, 2017; Clancy *et al.*, 2021; Johansson *et al.*, 2022). These findings suggest that despite consistent links between depression and white matter pathology (Lavretsky *et al.*, 2008; Rensma *et al.*, 2018; Teodorczuk *et al.*, 2007), and limited work showing links between anxious symptomatology and WMH in older adults Kim *et al.*, (2011; Vogels *et al.*, 2007), anxiety may not impart

https://doi.org/10.1017/S1041610224000012 Published online by Cambridge University Press

Table 3. Regression analysis predicting anxiety severity in LLD

	b	*SE*	*p* – value
Intercept	14.56	9.40	0.125
Age	– 0.07	0.09	0.439
Sex	– 0.46	1.00	0.641
Education	0.15	0.22	0.502
Depression	0.28	0.14	0.053
OFC Volume^	– 399.61	354.05	0.262
ADAS – Cog	**0.24**	**0.09**	**0.010**

OFC, orbitofrontal cortex.
^adjusted for intracranial volume; bolded variable is a significant predictor of anxiety severity in this model.

additional WMH risk burden in an already clinically depressed older adult population. Altogether, these results suggest that in LLD the pathophysiology of elevated anxiety symptoms may be primarily related to lower OFC volume and not to emerging AD or CVD pathology. However, these results do not prove a cause-effect relationship. Associations may stem from life-long lower OFC volume that predisposes individuals to anxiety. Longitudinal studies are needed to clarify whether lower OFC volume represents atrophy and if volume loss results from anxiety symptoms or whether OFC atrophy increases the risk for anxiety in LLD.

In addition to global cognition and indicators of neurodegeneration and neuropathology, we also examined whether anxiety severity is associated with functional ability and found no associations in the present sample. Although this finding was unexpected, our findings do align with some previous studies examining anxiety in LLD that also found no association between anxiety and functional ability (Jeste *et al.*, 2006; Lenze *et al.*, 2000), but not with others that did demonstrate a link (Morin *et al.*, 2020; Schoevers *et al.*, 2003). It is also possible that our ability to identify an association was limited because our LLD sample exhibited mostly mild levels of functional impairment, as individuals with dementia, where functional impairment is more prevalent, were excluded. As such, it is essential to investigate the temporal relationship between anxiety in LLD and declines in functional ability over time, given longitudinal evidence that anxiety and depression symptoms are associated with risk for functional decline (Dong *et al.*, 2020; Krell-Roesch *et al.*, 2020; Norton *et al.*, 2012), especially when symptoms are comorbid (Kang *et al.*, 2017).

Finally, a global model examining the present study's key findings revealed that among the two factors identified as significantly associated with anxiety severity in initial analyses (i.e., global cognitive functioning and OFC volume) only global cognitive functioning remained associated with anxiety severity, independent of OFC volume and concurrent depression severity. To our knowledge, this is the first LLD study to examine anxiety in the context of its relative associations with neurodegenerative features and our findings suggest that global cognitive dysfunction is most salient to anxiety in LLD among the factors examined here. However, this does not diminish our initial finding that anxiety is associated with OFC volume. A relatively restricted range of OFC volumes and limited sample size may have limited our ability to detect a small significant OFC effect once global cognitive functioning was in the model. Global cognitive functioning is associated with OFC integrity and also represents broader aspects of brain functioning that rely on neural integrity beyond regions assessed in the present study. Thus, OFC volume may not have remained significantly associated with anxiety in the global model because variance associated with OFC volume was subsumed by global cognitive functioning. Nevertheless, our finding that OFC volume is associated with anxiety in initial analyses remains of interest as it suggests that OFC volume is one neural factor that is relevant to anxiety severity in LLD and therefore warrants further investigation in future studies. It is also important for future work to examine additional measures of neural integrity and their association with anxiety severity in LLD, using functional neuroimaging tools for example. Effect sizes of the statistically significant associations identified in this study were small to medium in magnitude which sets the stage for further investigations evaluating the theoretical and clinical relevance of these effects.

The association between anxiety and cognitive dysfunction may be bidirectional, such that increased anxiety leads to poorer cognition and that poorer cognition could lead to increased anxiety, which is supported by prior work (Petkus *et al.*, 2017). Possible clinical implications of this finding are that LLD interventions that address symptoms of anxiety in addition to depression may lead to improved cognitive outcomes and that addressing cognitive dysfunction in interventions could decrease anxiety. Multi-pronged prevention and intervention approaches that address both depression and anxiety symptoms and additionally bolster cognitive functioning may be of value.

It is important to point out that the present cross-sectional study did not examine changes over time, and it is possible that both anxiety and cognitive dysfunction are caused by neurodegenerative changes that were not assessed. The cross-sectional nature of this work also precludes conclusions about risk for future atrophy, neuropathology, and cognitive or functional impairment. Longitudinal studies are needed, especially in light of evidence that anxiety symptoms in mild cognitive impairment

https://doi.org/10.1017/S1041610224000012 Published online by Cambridge University Press

have been linked to increased risk for conversion to AD (Mah *et al.*, 2015). Examining the temporal relations among anxiety, cognition, and neurodegeneration in longitudinal LLD work can further inform treatment of anxiety symptoms and cognitive dysfunction in LLD. Another limitation of the present study is that limited power in our sample may have contributed to our null findings concerning associations between anxiety severity and cortico-limbic volumes other than the OFC, Aβ deposition, white matter lesion burden, and functional ability. Future work with larger samples is needed to further evaluate these associations.

Conclusion

In summary, we found that lower OFC volume may play a role in anxiety symptoms in LLD more so than neuropathological indicators of emerging AD or CVD. Our results further indicated that cognitive dysfunction is a key factor associated with anxiety severity in LLD. Implications for clinical practice include that the potentially bidirectional relationship of anxiety symptoms with cognitive dysfunction may be responsive to cognitive or psychiatric interventions.

Conflict of interest

MWW serves on Editorial Boards for Alzheimer's & Dementia and the Journal for Prevention of Alzheimer's Disease. He has served on Advisory Boards for Acumen Pharmaceutical, Alzheon, Inc., Cerecin, Merck Sharp & Dohme Corp., and NC Registry for Brain Health. He also serves on the USC ACTC grant which receives funding from Eisai for the AHEAD study. He has provided consulting to BioClinica, Boxer Capital, LLC, Cerecin, Inc., Clario, Dementia Society of Japan, Eisai, Guidepoint, Health and Wellness Partners, Indiana University, LCN Consulting, Merck Sharp & Dohme Corp., NC Registry for Brain Health, Prova Education, T3D Therapeutics, University of Southern California (USC), and WebMD. He holds stock options with Alzeca, Alzheon, Inc., ALZPath, Inc., and Anven.

CN has been a consultant to Biohaven, Janssen, Johnson and Johnson, Merck, Novartis, Otsuka.

RSM has received research support from the National Institute of Mental Health, National Institute of Aging, Johnson and Johnson, and Janssen Research and Development LLC.

SL has received research support from the National Institute on Aging, speaking fees from Eisai, and has served on the DSMB for KeifeRX.

The other authors report no biomedical financial interests or potential conflicts of interest.

Funding

Data collection for this project was funded by the National Institute of Mental Health grant R01098062. We acknowledge Ray and Dagmar Dolby Family Fund for research support and Avid Radiopharmaceuticals for providing Florbetapir for this study.

Description of author(s)' roles

Concept and design of original data collection project: RSM. Development of current project and related research questions: MKL, RSM. Acquisition of subjects and/or data: ER, DB, EB, MAB, DT, PA, SL, AJS, AWT, CRJ, RK, MWW, CN, RSM. Analysis and interpretation of data: MKL, MTK, PSI, RSM. Preparation of manuscript: all authors.

Acknowledgements

Writing of this manuscript was supported by the Office of Academic Affiliations, Advanced Fellowship Program in Mental Illness Research and Treatment, Department of Veterans Affairs (M.K.L., M.T.K., E.R.).

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1041610224000012

References

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders, fourth edition, text revision (DSM-IV-TR)*. American Psychiatric Press.

Andreescu, C., Butters, M. A., Begley, A., Rajji, T., Wu, M., Meltzer, C. C., Reynolds C. F.lll, & Aizenstein, H. (2008). Gray matter changes in late life depression—a structural MRI analysis. *Neuropsychopharmacology*, 33(11), 2566–2572. https://doi.org/10.1038/sj.npp.1301655

Andreescu, C., Dew, M. A., Begley, A. E., Mulsant, B. H., Dombrovski, A. Y., Pollock, B. G., Stack, J., Miller, M. D., & Reynolds, C. F. (2007). Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: Controlled study. *The British Journal of Psychiatry*, 190, 344–349. https://doi.org/190/4/344

Andreescu, C., Tudorascu, D., Sheu, L. K., Rangarajan, A., Butters, M. A., Walker, S., Berta, R., Desmidt, T., & Aizenstein, H. (2017). Brain structural changes in late-life generalized anxiety disorder. *Psychiatry Research: Neuroimaging*, 268, 15–21. https://doi.org/10.1016/j.pscychresns.2017.08.004

Anstey, K. J., von Sanden, C., Sargent-Cox, K., & Luszcz, M. A. (2007). Prevalence and risk factors for depression in a longitudinal, population-based study including individuals in the community and residential care. *The American Journal of Geriatric Psychiatry*, 15(6), 497–505. https://doi.org/15/6/497

Banning, L. C. P., Ramakers, I. H. G. B., Köhler, S., Bron, E. E., Verhey, F. R. J., de Deyn, P. P., Claassen, J. A. H. R., Koek, H. L., Middelkoop, H. A. M., van der Flier, W. M., van der Lugt, A., & Aalten, P. (2020). The association between biomarkers and neuropsychiatric symptoms across the Alzheimer's disease spectrum. *The American Journal of Geriatric Psychiatry*, 28(7), 735–744.

Beaudreau, S. A., & O'Hara, R. (2008). Late-life anxiety and cognitive impairment: A review. *The American Journal of Geriatric Psychiatry*, 16(10), 790–803. https://doi.org/10.1097/JGP.0b013e31817945c3

Beaudreau, S. A., & O'Hara, R. (2009). The association of anxiety and depressive symptoms with cognitive performance in community-dwelling older adults. *Psychology and Aging*, 24(2), 507–512. https://doi.org/10.1037/a0016035

Beekman, A. T., De Beurs, E., Van Balkom, A. J., Deeg, D. J., 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.

Bierman, E. J., Comijs, H. C., Jonker, C., & Beekman, A. T. (2005). Effects of anxiety versus depression on cognition in later life. *American Journal of Geriatric Psychiatry*, 13(8), 686–693. https://doi.org/10.1176/appi.ajgp.13.8.686

Clancy, U., Gilmartin, D., Jochems, A. C., Knox, L., Doubal, F. N., & Wardlaw, J. M. (2021). Neuropsychiatric symptoms associated with cerebral small vessel disease: A systematic review and meta-analysis. *The Lancet Psychiatry*, 8(3), 225–236.

DeLuca, A. K., Lenze, E. J., Mulsant, B. H., Butters, M. A., Karp, J. F., Dew, M. A., Pollock, B. G., Shear, M. K., Houck, P. R., & Reynolds C. F.lll (2005). Comorbid anxiety disorder in late life depression: Association with memory decline over four years. *International Journal of Geriatric Psychiatry*, 20(9), 848–854. https://doi.org/10.1002/gps.1366

Diefenbach, G. J., Bragdon, L. B., & Blank, K. (2014). Geriatric anxiety inventory: Factor structure and associations with cognitive status. *The American Journal of Geriatric Psychiatry*, 22(12), 1418–1426. https://doi.org/10.1016/j.jagp.2013.04.014

Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A., & Reynolds, C. F. (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. *British Journal of Psychiatry*, 202(5), 329–335.

Dixon, M. L., Thiruchselvam, R., Todd, R., & Christoff, K. (2017). Emotion and the prefrontal cortex: An integrative review. *Psychological Bulletin*, 143(10), 1033–1081. https://doi.org/10.1037/bul0000096

Dong, L., Freedman, V. A., & de Leon, C. F. M. (2020). The association of comorbid depression and anxiety symptoms with disability onset in older adults. *Psychosomatic Medicine*, 82(2), 158–164.

Fung, A. W. T., Lee, J. S. W., Lee, A. T. C., & Lam, L. C. W. (2018). Anxiety symptoms predicted decline in episodic memory in cognitively healthy older adults: A 3-year prospective study. *International Journal of Geriatric Psychiatry*, 33(5), 748–754. https://doi.org/10.1002/gps.4850

Gunter, J., Thostenson, K., Borowski, B., Reid, R., Arani, A., Bernstein, M. A., Fox, N. C., Thomas, D., Decarli, C., Tosun, D., Thompson, P. M., Weiner, M., & Jack, C. R. (2017). ADNI-3 MRI protocol. *Alzheimer's Dementia*, 13(7), P104–P105.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, 23(1), 56–62.

Hanseeuw, B. J., Jonas, V., Jackson, J., Betensky, R. A., Rentz, D. M., Johnson, K. A., Sperling, R. A., & Donovan, N. J. (2020). Association of anxiety with subcortical amyloidosis in cognitively normal older adults. *Molecular Psychiatry*, 25(10), 2599–2607.

Jeste, N. D., Hays, J. C., & Steffens, D. C. (2006). Clinical correlates of anxious depression among elderly patients with depression. *Journal of Affective Disorders*, 90(1), 37–41. https://doi.org/10.1016/j.jad.2005.10.007

Johansson, M., Stomrud, E., Johansson, P. M., Svenningsson, A., Palmqvist, S., Janelidze, S., van Westen, D., Mattsson-Carlgren, N., & Hansson, O. (2022). Development of apathy, anxiety, and depression in cognitively unimpaired older adults: Effects of Alzheimer's disease pathology and cognitive decline. *Biological Psychiatry*, 92(1), 34–43. https://doi.org/10.1016/j.biopsych.2022.01.012

Kang, H.-J., Bae, K.-Y., Kim, S.-W., Shin, H.-Y., Shin, I.-S., Yoon, J.-S., & Kim, J.-M. (2017). Impact of anxiety and depression on physical health condition and disability in an elderly Korean population. *Psychiatry Investigation*, 14(3), 240–248. https://doi.org/10.4306/pi.2017.14.3.240

Karim, H. T., Ly, M., Yu, G., Krafty, R., Tudorascu, D. L., Aizenstein, H. J., & Andreescu, C. (2021). Aging faster: Worry and rumination in late life are associated with greater brain age. *Neurobiology of Aging*, 101, 13–21.

Kim, J.-T., Park, M.-S., Yoon, G.-J., Jung, H.-J., Choi, K.-H., Nam, T.-S., Lee, S.-H., Choi, S.-M., Kim, B.-C., Kim, M.-K., & Cho, K.-H. (2011). White matter hyperintensity as a factor associated with delayed mood disorders in patients with acute ischemic stroke. *European Neurology*, 66(6), 343–349. https://doi.org/10.1159/000332585

Klumpp, H., Angstadt, M., & Phan, K. L. (2012). Insula reactivity and connectivity to anterior cingulate cortex when processing threat in generalized social anxiety disorder. *Biological Psychology*, 89(1), 273–276. https://doi.org/10.1016/j.biopsycho.2011.10.010

Krause-Sorio, B., Siddarth, P., Milillo, M. M., Kilpatrick, L. A., Narr, K. L., & Lavretsky, H. (2023). Regional gray matter volume correlates with anxiety, apathy, and resilience in geriatric depression. *International Psychogeriatric Association*, 35(12), 698–706.

https://doi.org/10.1017/S1041610224000012 Published online by Cambridge University Press

Krell-Roesch, J., Lowe, V. J., Neureiter, J., Pink, A., Roberts, R. O., Mielke, M. M., Vemuri, P., Stokin, G. B., Christianson, T. J., C. R. Jack Jr., Knopman, D. S., Boeve, B. F., Kremers, W. K., Petersen, R. C., & Geda, Y. E. (2018). Depressive and anxiety symptoms and cortical amyloid deposition among cognitively normal elderly persons: The mayo clinic study of aging. *International psychogeriatrics*, 30(2), 245–251.

Krell-Roesch, J., Syrjanen, J. A., Mielke, M. M., Christianson, T. J., Kremers, W. K., Machulda, M. M., Knopman, D. S., Petersen, R. C., Vassilaki, M., & Geda, Y. E. (2020). Association between neuropsychiatric symptoms and functional change in older non-demented adults: mayo clinic study of aging. *Journal of Alzheimer's Disease*, 78(3), 911–917.

Laird, K. T., Siddarth, P., Krause-Sorio, B., Kilpatrick, L., Milillo, M., Aguilar, Y., Narr, K. L., & Lavretsky, H. (2019). Anxiety symptoms are associated with smaller insular and orbitofrontal cortex volumes in late-life depression. *Journal of Affective Disorders*, 256, 282–287.

Landau, S. M., Lu, M., Joshi, A. D., Pontecorvo, M., Mintun, M. A., Trojanowski, J. Q., Shaw, L. M., Jagust, W. J., & for the Alzheimer's Disease Neuroimaging Initiative (2013). Comparing positron emission tomography imaging and cerebrospinal fluid measurements of β-amyloid. *Annals of Neurology*, 74(6), 826–836.

Lavretsky, H., Zheng, L., Weiner, M. W., Mungas, D., Reed, B., Kramer, J. H., Jagust, W., Chui, H., & Mack, W. J. (2008). The MRI brain correlates of depressed mood, anhedonia, apathy, and anergia in older adults with and without cognitive impairment or dementia. *International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences*, 23(10), 1040–1050.

Lenze, E. J., & ***et al.*** (2000). Comorbid anxiety disorders in depressed elderly patients. *American Journal of Psychiatry*, 157(5), 722–728.

Lewis, C. K., Bernstein, O., Grill, J., Gillen, D., & Sultzer, D. (2022). Anxiety and depressive symptoms and cortical amyloid-β burden in cognitively unimpaired older adults. *The Journal of Prevention of Alzheimer's Disease*, 9(2), 286–296.

Mackin, R. S., Insel, P. S., Landau, S., Bickford, D., Morin, R., Rhodes, E., Tosun, D., Rosen, H. J., Butters, M., Aisen, P., Raman, R., Saykin, A., Toga, A., C. Jack Jr., Koeppe, R., Weiner, M. W., & Nelson, C. (2021). Late-life depression is associated with reduced cortical amyloid burden: Findings from the Alzheimer's disease neuroimaging initiative depression project. *Biological Psychiatry*, 89(8), 757–765.

Mah, L., Binns, M. A., & Steffens, D. C. (2015). Anxiety symptoms in amnestic mild cognitive impairment are associated with medial temporal atrophy and predict conversion to Alzheimer disease. *The American Journal of Geriatric Psychiatry*, 23(5), 466–476. https://doi.org/10.1016/j.jagp.2014.10.005

Martinussen, L. J., Šaltytė Benth, J., Almdahl, I. S., Borza, T., Selbæk, G., Mcpherson, B., & Korsnes, M. S. (2019). The effect of anxiety on cognition in older adult inpatients with depression: Results from a multicenter observational study. *Heliyon*, 5(8), e02235. https://doi.org/10.1016/j.heliyon.2019.e02235

Milad, M. R., & Rauch, S. L. (2007). The role of the orbitofrontal cortex in anxiety disorders. *Annals of the New York Academy of Sciences*, 1121(1), 546–561. https://doi.org/10.1196/annals.1401.006

Morin, R. T., Nelson, C., Bickford, D., Insel, P. S., & Mackin, R. S. (2020). Somatic and anxiety symptoms of depression are associated with disability in late life depression. *Aging & Mental Health*, 24(8), 1225–1228.

Morris, J. C. (1993). The clinical dementia rating (CDR): Current version and scoring rules. *Neurology*, 43(11), 2412–2414. https://doi.org/10.1212/wnl.43.11.2412-a

Norton, J., Ancelin, M. L., Stewart, R., Berr, C., Ritchie, K., & Carrière, I. (2012). Anxiety symptoms and disorder predict activity limitations in the elderly. *Journal of Affective Disorders*, 141(2-3), 276–285. https://doi.org/10.1016/j.jad.2012.04.002

Petkus, A. J., Reynolds, C. A., Wetherell, J. L., Kremen, W. S., & Gatz, M. (2017). Temporal dynamics of cognitive performance and anxiety across older adulthood. *Psychology and Aging*, 32(3), 278–292. https://doi.org/10.1037/pag0000164

Pink, A., Przybelski, S. A., Krell-Roesch, J., Stokin, G. B., Roberts, R. O., Mielke, M. M., Spangehl, K. A., Knopman, D. S., Jack C. R.Jr, Petersen, R. C., & Geda, Y. E. (2017). Cortical thickness and anxiety symptoms among cognitively normal elderly persons: The mayo clinic study of aging. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 29(1), 60–66. https://doi.org/10.1176/appi.neuropsych.15100378

Porensky, E. K., Dew, M. A., Karp, J. F., Skidmore, E., Rollman, B. L., Shear, M. K., & Lenze, E. J. (2009). The burden of late-life generalized anxiety disorder: effects on disability, health-related quality of life, and healthcare utilization. *The American Journal of Geriatric Psychiatry*, 17(6), 473–482. https://doi.org/10.1097/jgp.0b013e31819b87b2

Potvin, O., Catheline, G. B., Bernard, C., Meillon, C., Bergua, V., Allard, M., Dartigues, J.-F., Chauveau, N., Celsis, P., & Amieva, H. (2015). Gray matter characteristics associated with trait anxiety in older adults are moderated by depression. *International Psychogeriatrics*, 27(11), 1813–1824.

Rensma, S. P., van Sloten, T. T., Launer, L. J., & Stehouwer, C. D. (2018). Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, 90, 164–173.

Rosen, W. G., Mohs, R. C., & Davis, K. L. (1984). A new rating scale for Alzheimer's disease. *The American Journal of Psychiatry*, 141(11), 1356–1364.

Schoenbaum, G., Roesch, M. R., Stalnaker, T. A., & Takahashi, Y. K. (2009). A new perspective on the role of the orbitofrontal cortex in adaptive behaviour. *Nature Reviews Neuroscience*, 10(12), 885–892. https://doi.org/10.1038/nrn2753

Schoevers, R. A., Beekman, A. T., Deeg, D. J., Jonker, C., & van Tilburg, W. (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. https://doi.org/10.1002/gps.1001

https://doi.org/10.1017/S1041610224000012 Published online by Cambridge University Press

Schultz, S. K., Hoth, A., & Buckwalter, K. (2004). Anxiety and impaired social function in the elderly. *Annals of Clinical Psychiatry*, 16(1), 47–51. https://doi.org/10.1080/10401230490281429

Schwarz, C., Fletcher, E., DeCarli, C., & Carmichael, O. (2009). *Fully-automated white matter hyperintensity detection with anatomical prior knowledge and without FLAIR*. International Conference on Information Processing in Medical Imaging.

Simning, A., & Seplaki, C. L. (2020). Association of the cumulative burden of late-life anxiety and depressive symptoms with functional impairment. *International Journal of Geriatric Psychiatry*, 35(1), 80–90. https://doi.org/10.1002/gps.5221

Smith, L., Jacob, L., López-Sánchez, G. F., Butler, L., Barnett, Y., Veronese, N., Soysal, P., Yang, L., Grabovac, I., Tully, M. A., Shin, J. I., & Koyanagi, A. (2021). Anxiety symptoms and mild cognitive impairment among community-dwelling older adults from low- and middle-income countries. *Journal of Affective Disorders*, 291, 57–64. https://doi.org/10.1016/j.jad.2021.04.076

Spitzer, R. L., Kroenke, K., Williams, J. B., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine*, 166(10), 1092–1097.

Steffens, D. C., & McQuoid, D. R. (2005). Impact of symptoms of generalized anxiety disorder on the course of late-life depression. *American Journal of Geriatric Psychiatry*, 13(1), 40–47. https://doi.org/10.1176/appi.ajgp.13.1.40

Teodorczuk, A., O'Brien, J. T., Firbank, M. J., Pantoni, L., Poggesi, A., Erkinjuntti, T., Wallin, A., Wahlund, L.-O., Gouw, A., Waldemar, G., Schmidt, R., Ferro, J. M., Chabriat, H., Bäzner, H., & Inzitari, D. (2007). White matter changes and late-life depressive symptoms: Longitudinal study. *British Journal of Psychiatry*, 191(3), 212–217.

Vogels, R. L. C., Oosterman, J. M., van Harten, B., Gouw, A. A., Schroeder-Tanka, J. M., Scheltens, P., van der Flier, W. M., & Weinstein, H. C. (2007). Neuroimaging and correlates of cognitive function among patients with heart failure. *Dementia and Geriatric Cognitive Disorders*, 24(6), 418–423. https://doi.org/10.1159/000109811

Wild, B., Eckl, A., Herzog, W., Niehoff, D., Lechner, S., Maatouk, I., Schellberg, D., Brenner, H., Müller, H., & Löwe, B. (2014). Assessing generalized anxiety disorder in elderly people using the GAD-7 and GAD-2 scales: Results of a validation study. *The American Journal of Geriatric Psychiatry*, 22(10), 1029–1038. https://doi.org/10.1016/j.jagp.2013.01.076

Yesavage, J. A. (1988). Geriatric depression scale. *Psychopharmacology Bulletin*, 24(4), 709–711.