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Journal

Journal of the International Neuropsychological Society, 30(9)

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Publication Date

2024-11-01

DOI

10.1017/S1355617724000262

Peer reviewed

HHS Public Access

Author manuscript

J Int Neuropsychol Soc. Author manuscript; available in PMC 2025 January 16.

Published in final edited form as:

J Int Neuropsychol Soc. 2024 November ; 30(9): 807–811. doi:10.1017/S1355617724000262.

Anxiety in late life depression is associated with poorer performance across multiple cognitive domains

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Abstract

Objective: Anxiety is a common comorbid feature of Late Life Depression (LLD) and is associated with poorer global cognitive functioning independent of depression severity. However, little is known about whether comorbid anxiety is associated with a domain-specific pattern of cognitive dysfunction. We therefore examined group differences (LLD with and without comorbid anxiety) in cognitive functioning performance across multiple domains.

Method: Older adults with Major Depressive Disorder (*N*=228, Ages 65–91) were evaluated for anxiety and depression severity, and cognitive functioning (learning, memory, language, processing speed, executive functioning, working memory, and visuospatial functioning). Ordinary

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least squares regression adjusting for age, sex, education, and concurrent depression severity examined anxiety group differences in performance on tests of cognitive functioning.

Results: Significant group differences emerged for confrontation naming and visuospatial functioning, as well as for verbal fluency, working memory, and inhibition with lower performance for LLD with comorbid anxiety compared to LLD only, controlling for depression severity.

Conclusions: Performance patterns identified among older adults with LLD and comorbid anxiety resemble neuropsychological profiles typically seen in neurodegenerative diseases of aging. These findings have potential implications for etiological considerations in the interpretation of neuropsychological profiles.

Keywords

late life depression; anxiety; cognition; older adults; neuropsychological functioning; neurodegeneration

Introduction

Late Life Depression (LLD) is common and associated with cognitive dysfunction (Masse et al., 2021). Concurrent anxiety disorders are prevalent among individuals with LLD (Suradom et al., 2019) and are associated with poorer depression treatment outcomes and higher rates of recurrence (Andreescu et al., 2007). Elevated levels of anxiety in LLD have also been linked to poorer global cognitive functioning independent of depression severity (Kryza-Lacombe et al., 2024), but only limited work has examined specific domains associated with anxiety. A greater understanding of how anxiety comorbidity in LLD relates to specific cognitive domains may inform clinical practice by establishing anxiety comorbidity as a potential risk factor for domain-specific cognitive dysfunction, and vice versa. This may also inform development of personalized interventions that target anxiety symptoms and/or rehabilitation of specific cognitive domains in addition to depression in LLD.

LLD has been associated with learning and memory deficits (Rhodes et al., 2021) as well as slowed processing speed and executive dysfunction (Sexton et al., 2012). Despite high comorbidity of LLD with anxiety disorders, to our knowledge, only two studies examined cross-sectionally how anxiety relates to domain specific cognitive functioning in LLD (DeLuca et al., 2005; Martinussen et al., 2019). Both studies failed to show cross-sectional associations between anxiety and cognition in these domains in LLD but were conducted in an inpatient sample (Martinussen et al., 2019) and limited by a small sample size (DeLuca et al., 2005). However, evidence from community-dwelling older adults with varying levels of psychiatric symptoms suggests that those with simultaneous depression and anxiety symptoms exhibit cognitive weaknesses in more cognitive domains than individuals with either high anxiety or depression only (Beaudreau & O'Hara, 2009). Specifically, co-existing depression and anxiety symptoms were associated with poorer performance in memory, processing speed, and confrontation naming. Additionally, anxiety on its own is associated with cognitive dysfunction across many domains among older adults, including poorer learning (Butters et al., 2011; Stillman et al., 2012; Yochim et

al., 2013), memory (Laukka et al., 2018; Sabatini et al., 2021; Stillman et al., 2012), processing speed (Beaudreau & O'Hara, 2008, 2009), working memory (Butters et al., 2011; Sabatini et al., 2021), executive functioning (Beaudreau et al., 2013; Beaudreau & O'Hara, 2009; Butters et al., 2011; Laukka et al., 2018; Yochim et al., 2013), visuospatial functioning (Beaudreau & O'Hara, 2008; Stillman et al., 2012), and language, including verbal reasoning (Beaudreau & O'Hara, 2008; Sabatini et al., 2021), verbal fluency (Laukka et al., 2018), and confrontation naming (Shafto et al., 2019). Thus, it is possible that anxiety comorbidity within LLD exacerbates cognitive dysfunction in learning and memory, executive functioning and processing speed typically seen in LLD. However, anxiety comorbidity in LLD may be independently associated with distinct deficits in other domains including language and visuospatial functioning akin to late life anxiety alone. To our knowledge no previous study has examined this in a large outpatient LLD sample.

The objective of the present study is to expand the literature by evaluating differences in cognitive functioning in LLD with and without comorbid anxiety, across multiple domains. Based on previous work examining co-existing depression and anxiety we expected poorer performance in memory, processing speed, and confrontation naming among individuals with LLD and comorbid anxiety, compared to LLD only. Additionally, we expected poorer performance in the domains of learning, working memory, executive functioning, verbal fluency, and visuospatial functioning among individuals with LLD and comorbid anxiety given previous work documenting weaknesses in these domains in the context of anxiety alone. To highlight independent effects of anxiety in LLD our analyses covaried for depression severity and demographic characteristics.

Methods

Participants and Procedures

Data on 228 older adults with Major Depressive Disorder (MDD; Ages 65–91) from two studies were pooled for the present study, including 127 individuals from a longitudinal observational study (Mean Age=71.1, 66%female) and 101 who enrolled in a psychotherapy study (Mean Age=71.4, 58%female). Origin study was included as a covariate in statistical models to account for different recruitment pools. Inclusion criteria across both data pools included unipolar MDD without psychotic features and a current depressive episode duration of ≥6 weeks. Multidisciplinary consensus confirmed MDD diagnosis based on symptom ratings collected via the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorder-IV and the Hamilton Depression Rating Scale (HDRS; observational study: ≥15 on the 17-item HDRS; psychotherapy study: ≥19 on the 24-item GRID-HDRS). Participants were excluded if they had concurrent primary Axis I disorders (except for Generalized Anxiety Disorder, social anxiety, and specific phobia), neurological disorders affecting the brain (e.g., epilepsy, Parkinson's disease, traumatic brain injury, cortical stroke) or evidence of dementia (e.g., <25 on the Mini Mental Status Exam). Additional exclusion criteria for the psychotherapy study included use of antidepressants within the past 6 weeks, electroconvulsive therapy within the past 6 months, and use of cognition enhancing medications. The studies were approved the Institutional Review Boards of the University of California, San Francisco and University of Pittsburgh and were

conducted in accordance with the Declaration of Helsinki for protection of Human Subjects. All participants provided written informed consent.

Across both original studies participants completed comprehensive cognitive testing and questionnaires measuring psychiatric symptoms and psychosocial functioning. For the present study, data were limited to baseline assessments across both studies. Participants were included only if baseline anxiety and depression severity scores and one or more measures of cognitive functioning were available (Table 2 captions list data missingness).

Measures

Anxiety.—The Generalized Anxiety Disorder 7-item scale (GAD-7) measured anxiety severity over the past two weeks. Items are rated on a four-point scale indicating how often participants have experienced a particular anxiety symptom (0="not at all," to 3="nearly every day") with a maximum possible score of 21. Individuals with scores of at least 10, representing moderate or greater levels of anxiety severity (Spitzer et al. 2006), were classified as having LLD with comorbid anxiety (LLD+Anxiety). For the purpose of the present analyses, individuals endorsing minimal to mild anxiety severity levels (score 0–9) were classified as "LLD only." The GAD-7 has been validated in older adults (Wild et al., 2014).

Depression.—Depression severity was measured via the 15-item Geriatric Depression Scale (GDS) which was used as a covariate across analyses. Mood over the past week is rated using a yes/no response format with a maximum score of 15.

Cognitive Functioning.—Learning and memory were assessed via the Rey Auditory Verbal Learning Test (RAVLT) in which a 15-item word list is presented across five learning trials. Learning was measured using the Learning over Trials (LOT) metric; ([sum of trials1–5]–[5x trial1]), and memory was measured using total number of list words recalled after a 30-minute delay. Language was assessed using an abbreviated 30-item version (i.e., odd-numbered items only) of the Boston Naming Test (BNT) and a test of semantic fluency (Animals). The BNT is a test of confrontation naming of visually presented stimuli with total number correct as the outcome variable and semantic fluency is measured via the total number of correct category items (i.e., Animals) generated in 60 seconds as the outcome variable. Processing speed was assessed via number of seconds to complete the Trail Making Test Part A (TMTA) and number of correct items in 120 seconds on the Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Symbol subtest. Executive functioning was assessed using: the number of seconds to complete Trail Making Test Part B (TMTB), which measures rapid set-shifting, the total number of correct words generated across three letter cues (F, A, and S) within 60 seconds each on the Controlled Oral Word Association Test (COWAT), and the number of correct items on the Stroop Color Word Interference test (CWI), which evaluates interference inhibition of a prepotent response. Working memory was assessed using the WAIS-III Digit Span subtest which measures auditory verbal working memory with total correct as the outcome. Finally, visuospatial functioning was assessed via the Benton Judgement of Line Orientation (JOLO) Test with total number of correct items as the outcome.

Statistical Analyses

Group comparisons (LLD only vs. LLD+Anxiety) for key demographic and clinical characteristics were calculated via independent samples t-tests for continuous variables and chi square tests for categorical variables. Group differences in cognitive test performance were evaluated via Ordinary Least Squares regression, with the cognitive variables as the outcome and anxiety group as the predictor of interest. All models included age, gender, years of education, depression severity, and origin study (observational vs. psychotherapy) as covariates. Distributions of regression residuals were examined. Residuals were not normally distributed and/or influential cases were identified in analyses examining TMTA, TMTB, BNT, and JOLO. Additional analyses were subsequently conducted using robust regression and log-transformed variables of TMTA and TMTB, and square-transformed variables of BNT and JOLO. All participants who completed a respective test were included in the associated statistical models and were otherwise excluded.

Results

Demographic and Clinical Characteristics

Table 1 lists the demographic and clinical characteristics of the full LLD sample, 41% of which had at least moderate levels of anxiety and were classified as LLD with comorbid anxiety (LLD+Anxiety). There were no LLD+Anxiety vs. LLD only group differences in age, gender, level of education, race, or ethnicity. Although the entire sample meets criteria for active major depression, there were individual differences in self-reported depression severity and the LLD+Anxiety group had greater depression severity (t=−3.11, p=.003). All analyses comparing group differences in cognition covaried for depression severity. Covariation of anxiety and depression severity was small in magnitude in this sample (r=.26).

Cognitive Functioning

Table 2 displays results of analyses evaluating group differences in cognitive functioning. All models controlled for age, gender, level of education, concurrent depression severity, and origin study. Cognitive performance was significantly lower among LLD+Anxiety compared to LLD-only demonstrating small to medium effects, on the following tests: BNT (t=−3.36, p=.001, η_p^2=.050), JOLO (t=−2.65, p=.009, η_p^2=.031), CWI (t=−2.19, p=.030, η_p^2=.022), COWAT (t=−2.12, p=.034, η_p^2=.022), Digit Span (t=−2.13, p=.034, η_p^2=.021), and Animal Naming (t=−2.01, p=.045, η_p^2=.018). As all findings align with a priori hypotheses that performance would be worse among LLD+Anxiety, findings are interpreted without multiple comparison correction to protect against overcorrection (i.e., Type 2 error). Of note, BNT would remain as the sole significant finding following application of multiple comparison correction via Holm-Bonferroni. Additional analyses examining robustness of findings for models with non-normal residual distributions (TMTA, TMTB, BNT, and JOLO) did not change the results or interpretation of the regression.

Discussion

To our knowledge, this is the first study to examine how anxiety comorbidity relates to cognitive functioning across a range of specific cognitive domains in a large outpatient sample of older adults diagnosed with major depression without dementia. We found that individuals with LLD and comorbid anxiety show significantly poorer performance on confrontation naming and visuospatial functioning compared to LLD with only minimal or mild symptoms of anxiety. We also found worse performance on verbal fluency, inhibition, and working memory in the LLD group with comorbid anxiety. Notably, our analyses controlled for depression symptom severity, and therefore highlight associations between anxiety and cognition distinct from depression severity. Altogether, these findings suggest that anxiety comorbidity in LLD may be associated with distinct patterns of lower performance in confrontation naming and visuospatial functioning, in addition to exacerbation of lower performance that is typically seen in LLD on tests of executive functioning and processing speed. Each of these findings is discussed below.

As expected, we found poorer performance in confrontation naming among LLD with comorbid anxiety vs. LLD only, which aligns with previous reports of co-existing depression and anxiety in community dwelling subclinical older adults (Beaudreau & O'Hara, 2009) as well as work showing that age-related changes in word retrieval are associated with anxiety but not depression (Shafto et al., 2019). Attentional control theory suggests that attentional focus on stimuli perceived to be threatening may be exacerbated in the context of elevated anxiety, limiting attentional resources available for tasks at hand (Eysenck et al., 2007). Word retrieval is critical for interpersonal communication especially in social contexts which may be perceived as threatening. It is possible that anxiety in social contexts limits attentional resources and interferes with word retrieval. However, it is also possible that difficulties with word retrieval generate or exacerbate anxiety. Additionally, we found poorer performance in visuospatial functioning among LLD with comorbid anxiety vs. LLD without clinically significant anxiety. Although no previous work documented visuospatial weaknesses in the context of co-existing anxiety and depression diagnoses, our finding extends previous work documenting evidence of an inverse relationship between anxiety and visuospatial functioning in community dwelling older adults (Stillman et al., 2012; Wetherell et al., 2002). Prior work suggests that visuospatial weaknesses may reflect underlying executive dysfunction (Wasserman et al., 2020) and it is possible that poorer executive functioning contributed to our findings of poorer visuospatial functioning in individuals with LLD and comorbid anxiety. Indeed, we found that this group also had worse performance on several tests with processing speed and/or executive functioning components including verbal fluency, inhibition, and working memory. These findings suggest that anxiety may also be associated with exacerbations of cognitive weaknesses typically seen in LLD. Contrary to a previous report of co-existing depression and anxiety in community dwelling older adults (Beaudreau & O'Hara, 2009), in the present LLD sample we did not find that comorbid anxiety was associated with poorer episodic memory. It is possible that episodic memory is impacted in the context of milder symptoms in the community, but not among individuals with clinically significant depression and anxiety symptoms.

Importantly, lower cognitive performance identified among individuals with comorbid LLD and anxiety in the present work may be responsive to intervention. It is possible that individuals experiencing concurrently elevated levels of depression and anxiety as well as difficulties with word finding, visuospatial functions, and/or processing speed and executive functioning, may experience cognitive improvement when anxiety levels are remediated. It is also conceivable that cognitive training addressing those domains may help decrease anxiety.

Overall, the present findings suggest that LLD with comorbid anxiety is associated with distinct patterns of lower cognitive performance in addition to exacerbation of patterns of lower performance that are typically seen in LLD. This means that individuals with LLD and comorbid anxiety may exhibit lower than expected performance in confrontation naming and visuospatial functioning in addition to weaknesses in executive functioning, processing speed, and memory that are commonly reported in LLD (Rhodes et al., 2021; Sexton et al., 2012). Combined, this pattern of weaknesses resembles a neuropsychological profile reflecting a potential neurodegenerative process. Comorbid anxiety in an older adult with major depression who presents with this type of neuropsychological profile in the absence of dementia may therefore be an important etiological consideration. Specifically, in the absence of dementia, a conservative approach to etiologically linking neuropsychological profiles reflecting neurodegenerative processes may be warranted in individuals with comorbid depression and anxiety. Furthermore, anxiety comorbidity may be a phenotypic risk marker for individuals at risk for greater cognitive dysfunction and a pattern of domain-specific cognitive difficulties which may contribute to specific functional consequences. This may include problems with driving in the context of visuospatial difficulties and social difficulties and the context of naming problems. Furthermore, given poorer cognitive functioning in the context of anxiety comorbidity, disease burden may be higher among these individuals potentially resulting in greater rates of treatment resistance. This would have important implications for treatment selection as well as clinical trials and warrants further examination in future work. Although effects identified in our group-level analyses are mostly small in magnitude, they may be clinically meaningful in the individual patient especially when anxiety severity is high. This highlights the importance of screening for anxiety in individuals who present with depression.

Limitations

Several limitations should be noted. First, this work is correlational and cause-effect relationships cannot be inferred. Relatedly, the cross-sectional nature of this work prevents us from making conclusions about risk for future cognitive decline. Longitudinal work is needed to evaluate the temporal course of these associations and whether psychiatric intervention and/or cognitive training could ameliorate either or both affective and cognitive symptoms. Second, anxiety classification was defined as moderate or severe anxiety over the past 2 weeks on a general anxiety scale which may not be reflective of an anxiety disorder diagnosis. Replication of these findings is necessary in samples with well-characterized anxiety diagnoses and continuous measures of anxiety that distinguish between acute vs. chronic anxiety. Third, the predominantly White and non-Hispanic sample, limits generalizability of findings and highlights the importance of further work in more diverse

samples. Finally, given lower confrontation naming for visual stimuli coupled with poorer visuospatial performance in LLD with comorbid anxiety, future work should additionally employ a verbal naming task that is not reliant on visual perception.

Conclusion

In an outpatient sample of older adults with major depression, we found that individuals with comorbid anxiety exhibited poorer performance in confrontation naming, visuospatial functioning, and executive functioning/processing speed compared to individuals with minimal or mild anxiety, controlling for self-reported depression severity. These findings suggest that anxiety comorbidity in LLD may be associated with distinct patterns of poorer cognitive performance which may inform differential diagnosis in neuropsychology practice. More work is needed to examine whether addressing anxiety symptoms in LLD through intervention may improve some forms of cognitive dysfunction.

Acknowledgements:

Conflicts of Interests:

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

Funding Sources and Other Support:

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. 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.).

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Table 1.

Demographic and Clinical Characteristics

	Full sample (N=228)	LLD only (n=133)	LLD + Anxiety (n=95)	*Test statistic*	*p*
Age, mean years ± SD	71.24 ± 5.49	71.44 ± 5.83	70.96 ± 5.00	$t(226) = 0.66$	0.511
Education, mean years ± SD	16.25 ± 2.19	16.16 ± 2.33	16.39 ± 1.98	$t(226) = -0.79$	0.432
Gender, No. female (%)	143 (62%)	86 (64%)	57 (60%)	$\chi^2(1) = 0.52$	0.473
Race, No. non-white (%)	41 (19%)	21 (16%)	20 (21%)	$\chi^2(6) = 4.81$	0.569
Ethnicity, No. Hispanic (%)	37 (16%)	19 (14%)	18 (18%)	$\chi^2(1) = 0.89$	0.347
GDS	7.87 ± 3.19	7.34 ± 2.99	8.62 ± 3.32	$t(226) = -3.11$	0.003
GAD-7	9.22 ± 4.99	5.71 ± 2.39	14.13 ± 3.23	$t(226) = -22.60$	<.001
Minimal Anxiety, No. (%)	41 (18%)	41 (30.8%)	0%		
Mild Anxiety, No. (%)	92 (40%)	92 (69%)	0%		
Moderate Anxiety, No. (%)	57 (25%)	0%	57 (60%)		
Severe Anxiety, No. (%)	38 (16%)	0%	38 (40%)		

Note. GDS = Geriatric Depression Scale (15-item); GAD-7 = Generalized Anxiety Disorder 7- item Scale.

Table 2.

Mean differences in cognitive functioning raw scores

	Adjusted Means ± Standard Error				
	LLD only (n=133)	**LLD + Anxiety (n=95)**	***t***	***p***	**η_p^2**
Boston Naming Test	27.99 ± .22	26.85 ± .25	−3.36	**0.001**	**0.050**
COWAT Total	41.51 ± 1.05	37.22 ± 1.29	−2.13	**0.034**	**0.022**
Animal Naming Total	20.41 ± .43	19.05 ± .50	−2.01	**0.045**	**0.018**
RAVLT LOT	17.79 ± .72	18.29 ± .85	0.44	0.659	0.001
RAVLT Delayed Recall	8.23 ± .35	7.71 ± .41	−0.93	0.352	<.001
Judgement of Line Orientation	24.44 ± .38	22.85 ± .45	−2.65	**0.009**	**0.031**
Digit Span Total	17.51 ± .32	16.42 ± .38	−2.13	**0.034**	**0.021**
Digit Symbol Test	57.93 ± 1.04	57.82 ± 1.22	−0.07	0.945	<.001
Stroop Color Word Interference	33.98 ± .76	31.38 ± .88	−2.19	**0.030**	**0.022**
Trail Making Test A	37.03 ± 1.08	37.29 ± 1.27	0.16	0.877	<.001
Trail Making Test B	94.80 ± 3.88	98.53 ± 4.60	0.61	0.545	0.002

Note. LLD = Late Life Depression; COWAT = Controlled Oral Word Association Test; RAVLT = Rey Auditory Verbal Learning Test; LOT = RAVLT Learning Over Trials; Missingness: Boston Naming Test, n = 6; COWAT, n = 15; Animal Naming, n = 5; RAVLT LOT, n = 5; AVLT Delay, n = 6; Judgement of Line Orientation, n = 4; Digit Span, n = 4; Digit Symbol Test, n = 5; Stroop Color Word Interference = 5; Trail Making Test A, n = 4; Trail Making Test B, n = 6. Adjusted means are presented as statistical comparisons controlled for age, gender, level of education, concurrent depression severity and origin study; raw scores were used for all measures of cognitive functioning with number correct as the primary outcome variable except for the Trail Making Test Parts A and B in which total completion time in seconds was the outcome; bolded p-values indicate statistically significant findings.