Late-Life Anxiety and Cognitive Impairment: A Review

Sherry A. Beaudreau, Ph.D., Ruth O'Hara, Ph.D.

Emerging research implicates a consistent reciprocal relationship between late-life anxiety and cognition. Understanding this relationship may clarify pathophysiological substrates of cognitive impairment and why co-occurring anxiety and cognitive impairment relates to poorer treatment prognosis for both conditions. This article critically reviews evidence of more prevalent anxiety in cognitively impaired older adults, elevated anxiety related to poorer cognitive performance, and more severe anxiety symptoms predicting future cognitive decline. It considers pathophysiologic mediators and moderators, and the influence of comorbid depression or medical illness in anxiety. Identified directions for future research includes use of in-depth anxiety assessment comparing normal and mild cognitively impaired older adults and use of challenging neuropsychological tests to determine if specific cognitive domains suffer in anxious older adults. (Am J Geriatr Psychiatry 2008; 16:790–803)

Key Words: Late-life anxiety, mild cognitive impairment, dementia, cognitive decline

Anxiety disorders are the most common late-life psychiatric diagnosis with an estimated lifetime prevalence of 15.3% in older adults, surpassing population estimates for mood disorders[1] and severe cognitive impairment.[2] Although investigations of neuropsychiatric concomitants in late-life cognitive impairment primarily focus on depression, the reciprocal relationship between late-life anxiety and cognition merits attention. Improved understanding of this association may elucidate the pathophysiological mechanisms related to age-related cognitive decline. Moreover, the presence of anxiety and other neuropsychiatric symptoms are associated with poorer prognosis for cognitive impairment.[3] Cognitive decrements are also predictive of poorer prognosis and treatment resistance for late-life clinical anxiety;[4] therefore, improving the understanding in this area could guide treatment for anxiety in older adults. Emerging literature on cognition and late-life anxiety focuses primarily on symptoms often associated with generalized anxiety disorder (GAD), thus we limit discussion to general anxiety, worry symptoms, or GAD and exclude other *Diagnostic and Statistical Manual of Mental Disorders, Text Revision* (DSM–IV–TR)[5] anxiety classifications such as posttraumatic stress disorder, social phobia, or panic disorder.

Although the influence of GAD or worry symptoms on cognitive functioning is not well delineated in the literature, there is some evidence for reduced

Received September 31, 2007; revised February 15, 2008; accepted February 19, 2008. From the Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Veterans Affairs Palo Alto Health Care System, and the Sierra Pacific Mental Illness, Research, Education, and Clinical Center (MIRECC), CA. Send correspondence and reprint requests to Sherry A. Beaudreau, Ph.D., Department of Psychiatry, Stanford University, Palo Alto VA Health Care System, and the MIRECC, (151Y), 3801 Miranda Ave., Palo Alto, CA 94304. e-mail: sherryb@stanford.edu

cognitive performance, in particular reduced episodic memory and executive function in young and middle-aged adults with any anxiety disorder.[6] As yet, there has been no investigation of whether worry symptoms per se potentially mediate any negative relationship of GAD to cognitive function in older adults. Worry symptoms, however, may be particularly detrimental in older adulthood[7] due to combined burden of age related reductions in cognitive processing speed[8] and anxiety-related biases in attention to threat information.[9]

Cross-sectional investigations indicate that cognitively impaired older adults exhibit more anxiety symptoms compared with controls, and that elevated anxiety relates to poorer cognitive performance in older adults. Longitudinal support also exists for anxiety as a predictor of future cognitive decline. Two methodologies are typically employed—those comparing anxiety among cognitive diagnostic categories, and those correlating anxiety symptom severity with cognitive performance in community-dwelling older adults or patients. The assumption of the former methodology is that anxiety and other neuropsychiatric symptoms reflect prodromal neurodegenerative cognitive impairment.[10] The latter approach assumes that anxiety depletes cognitive resources,[11] thus increasing risk for late-life cognitive impairment or exacerbating preexisting age-related decrements in memory. Regardless of methodology, most studies measure anxiety symptom presence and severity, and a few examine the presence of an anxiety disorder, the severity of anxious personality traits (i.e., neuroticism, trait anxiety) or transitory states (i.e., state anxiety).

In this article, we first characterize late-life anxiety, and then critically review existing investigations of its relationship to cognitive performance. Next we characterize cognitive difficulties in aging, and critically review studies describing anxiety in older adults with cognitive impairment. Then overlapping pathophysiological mechanisms, comorbidity with depression and medical conditions are discussed. Finally, differential trajectories for older adults who are primarily cognitively impaired or anxious are discussed in light of poorer prognosis, and treatment resistance for anxiety or cognitive deficits.

PREVALENCE AND CHARACTERISTICS OF LATE-LIFE ANXIETY

GAD, characterized by pervasive, excessive, and uncontrollable apprehension or worry about everyday situations, is the most common DSM–IV–TR[5] anxiety disorder in older individuals with a lifetime prevalence of 10.2%.[12] The DSM–IV diagnostic criteria for GAD requires that worry symptoms occur for 6 months or longer, the worry is difficult to control, and that three or more anxiety-related somatic symptoms are present: irritability, concentration problems, restlessness, sleep difficulty, muscle tension, fatigue. Yet about 20% of older adults report subsyndromal anxiety symptoms.[13] Although such symptoms are routinely assessed with self-report measures, or via observation for cognitively impaired older adults, their presence may be clinically significant, i.e., sufficiently impairing to be of note to a clinician and worthy of treatment, even in the absence of a clinical diagnosis. Although GAD and other psychiatric disorders are less prevalent in older compared with younger age groups, estimates may be biased by underreporting, a lack of sensitive late-life anxiety measures, and exclusion of subsyndromal (but impairing) anxiety from epidemiological research (for review see Kogan et al.[14]). Furthermore, the clinical presentation of late-life anxiety is complex with mixed anxiety and depressive symptoms frequently noted in older populations and a preponderance of somatic symptoms in anxious older adults.[14] Evidence is culminating to suggest that anxiety symptoms are a common neuropsychiatric symptom in older adults with mild cognitive impairment (MCI), second only to depressive symptoms.[15]

ANXIETY SYMPTOMS AS CORRELATES AND PREDICTORS OF COGNITIVE IMPAIRMENT IN OLDER ADULTS

Cross-sectional investigations generally support the hypothesis that the presence or severity of anxiety is associated with lower cognitive performance in older adults, with effect sizes generally in the moderate range. Studies assessing measures of learning and

memory (i.e., episodic memory tasks) typically yield larger effects than are observed for other cognitive domains (Table 1). Among older adults with subjective memory complaints, those reporting high anxiety or depressive symptoms performed better than those with mild memory impairment on a memory and learning task and more poorly on attention and working memory compared with those both with no cognitive impairment and minimal anxiety and depressive symptoms.[16] Similarly, another investigation observed a large effect size with respect to poorer episodic memory in older individuals with GAD compared with psychiatric controls.[7] Yet this latter study also observed large effects with respect to the poorer performance of GAD patients on a set shifting task; and in another study a moderate effect of elevated phobic anxiety was observed to be associated with poorer general cognition in community-dwelling adults 55+ on a dementia screening battery.[17] Further, small effects were observed to be associated with poorer performance on delayed verbal memory, executive functions, and information processing speed in community-dwelling older adults who reported more severe state anxiety.[18] In general, the magnitude of the effect may vary less according to the cognitive domain assessed but more according to the difficulty level of the measures selected to assess specific domains, sample size constraints, and whether trait, state, or clinical anxiety measures were used.

Regardless of how anxiety is assessed, the relationship between anxiety and cognitive performance may be complex due to interactions between anxiety and test difficulty or nonlinear associations. For instance, one study found that community-dwelling older adults reporting more severe trait anxiety had poorer reaction time on a divided attention semantic task compared with older adults reporting low trait anxiety.[19] Yet older adults reporting elevated trait anxiety in this same study had facilitated reaction time for a more simple version of the semantic task, selective attention, compared with their low trait anxious counterparts. In Longitudinal Aging Study Amsterdam, older adults reporting clinical levels of anxiety also performed more poorly on a challenging episodic memory task; however, for those reporting subthreshold anxiety symptoms memory performance was facilitated.[20]

Of the few longitudinal investigations of anxiety as a predictor of cognitive decline in older individuals, evidence is mixed—possibly due to investigational differences of how anxiety was measured (Table 1). Despite significant baseline associations between neuroticism and state anxiety on some cognitive tests, even after adjusting for baseline cognitive performance neuroticism failed to predict accelerated cognitive decline on challenging neuropsychological tests over subsequent 3-year follow-up in community-dwelling adults from the Swedish Adoption/Twin Study of Aging.[11] The ability to predict cognitive decline from baseline anxiety, however, may have been attenuated by measuring neurotic traits rather than clinically significant anxiety.

Yet, in two other longitudinal studies, which also adjust for baseline cognitive performance, clinically significant late-life anxiety predicted accelerated cognitive decline. Among older adults referred to a geriatric assessment clinic for memory complaints, clinically significant anxiety status predicted greater cognitive decline on a brief cognitive screen 1 to 5 years later.[10] In another study, accelerated memory decline on a general dementia screen was noted at 4-year follow-up in depressed older adults with comorbid anxiety (GAD or panic disorder) compared with depressed older adults without comorbid anxiety.[21] Although the effect sizes were in the medium range, both studies employed cognitive measures sensitive to frank rather than subtle or very mild cognitive impairment, suggesting a robust relationship between clinically significant anxiety and cognitive impairment.

In summary, considerable variability in the selection of cognitive measures limits the ability to specify cognitive domains or abilities negatively affected by late-life anxiety. Commonly, these studies incorporate screens of general cognitive functioning rather than specific cognitive subtests. Additionally, three of the studies reviewed[10,16,21] examine older patients with mixed anxiety and depression, which may yield different results than focusing on older patients with mostly anxiety symptoms (or an anxiety disorder) but minimal depression. Regardless, there is some support to illustrate that clinically significant anxiety has a detrimental effect on general cognitive abilities. Nevertheless, at least two studies[19,20] demonstrated that anxiety facilitated cognitive performance—at least in the context of mild, nonpathological anxiety[20] or a relatively simple cognitive task.[19] Whether these latter results are replicable in other studies remains to be established. Deficits in specific

TABLE 1. Studies of Anxiety in Relation to Cognitive Performance Among Middle-Aged and Older Adults

Study	Participants	Anxiety Status (Measures)	Cognitive Domains (Measures)	Results	Effect Size
Bierman et al, 2005[a]	2,615 Dutch older adults, Longitudinal Aging Study Amsterdam; mean age: 69–74	Clinically significant anxiety (HADS-anxiety subscale) >7 = anxious	General cognitive functioning (MMSE); episodic memory (AVLT); visual abstract reasoning (RCPM); information processing speed (Coding task)	Curvilinear relationship: mild anxiety facilitated and severe anxiety impeded *episodic memory*	
Booth et al, 2006[b]	398 community-dwelling older adults, Charlotte County Healthy Aging Study; 60–85 years old (M = 72.0)	State anxiety (STPI-SA scale)	General cognitive functioning (3MS); episodic memory (HVLT); inhibition (STROOP); set shifting (TMT-B)	State anxiety explained small amount of variance for reduced *episodic memory* (1.2%) and *set shifting* (1.7%)	
Derouesné et al, 2004	200 community-dwelling French older adults (56–79 years old; M = 69.0) with memory complaints; distressed (n = 18) versus MCI (n = 41) versus controls (n =141)	Clinically significant distress: ≥45% on ZA (n = 8), ≥50% on ZD (n = 1), or both (n = 9)	Episodic memory (CVLT); inhibition (STROOP); attention: (digit and spatial span–forward); working memory (number sequencing)	Distressed and MCI < controls: *Attention (spatial span)* and *working memory.* MCI < distressed: *episodic memory*	0.48 0.63 1.83
DeLuca et al, 2005[c]	79 older Americans with MDD; mean age 72–73; with comorbid GAD or PD (n = 37) versus MDD alone (n = 42)	Generalized anxiety disorder or panic disorder (SCID)	General cognitive functioning (MMSE); General memory (MDRS-memory subscale)	*General memory:* comorbid GAD or PD > decline than MDD alone at 4 year follow-up; *General cognitive functioning*: no group differences at 4-year follow-up	0.44
Hogan, 2003	92 community-dwelling Irish older adults; mean age = 70.1	State and trait anxiety (STAI)	Selective attention (semantic versus motor speed); Divided attention (semantic versus motor speed)	Faster reaction time for *selective attention (semantic)* and slower reaction time for *divided attention (semantic)* for high trait anxious older adults: opposite pattern for low trait anxious older adults	
Mantella et al, 2007	Older Americans with GAD (n = 19), MDD (n = 68), or no psychiatric diagnosis (n = 40); Mean ages 70–71	Generalized anxiety disorder (SCID)	General cognitive functioning (MMSE and MDRS); General executive functioning (EXIT); episodic memory (CVLT); attention (TMT-A); set shifting (TMT-B); naming (BNT)	GAD < normal: *episodic memory-short delay* GAD, MDD[d] < normal: *episodic memory-long delay, episodic memory total recall across learning trials, General Memory subscale on the MDRS and set shifting*	0.82 0.84 1.20 0.47 0.91
Schultz et al, 2005	64 community-dwelling American older adults, > 55 years old	Clinically significant anxiety (SCL-90R-phobic anxiety scale)	General cognitive functioning (RBANS)	*Poorer general cognitive functioning:* greater phobic anxiety	
Sinoff and Werner, 2003[c,e]	137 Israeli older adults, geriatric assessment unit; no depression or cognitive impairment; mean ages 75.9–78.9	Clinically significant anxiety (SAST)	General cognitive functioning (MMSE): Completed at Time 1 and Time 2 (1 to 5 years later)	Anxiety at Time 1 increased risk of decline in *general cognitive functioning* at Time 2 both directly or indirectly via depression	

(*Continued*)

TABLE 1. Continued

Study	Participants	Anxiety Status (Measures)	Cognitive Domains (Measures)	Results	Effect Size
Wetherell et al, 2002[c,f]	704 older adults, Swedish Adoption/Twin study of Aging, >49-years old at and up to 3 three-year follow-up; mean age = 63.7	State anxiety (STPI-SA scale); neuroticism (EPI—neuroticism scale)	Crystallized memory (WAIS INFO and SYN); attention (CVB digits span); visual recognition memory (NF and TPM); abstract reasoning–visual (figure logic) and verbal (analogies); visuospatial (KBD and card Rotations); Processing (FID and SD)	State anxiety—poorer cross-sectional *memory (SYN), verbal abstract reasoning,* and *visual crystallized recognition* (TPM) Neuroticism—poorer cross-sectional *visual recognition memory* (NF), *visuospatial abilities* (KBD), and *processing* (SD) Neither state anxiety or neuroticism predict future cognitive decline	

Notes: [a]Adjusted $R^2 = 0.15$, a moderate effect.
[b]R^2s = 0.012 and 0.017, respectively for verbal fluency and executive functions, very small effects.
[c]Longitudinal design.
[d]Effect sizes reported here are for the GAD group compared with the normal group.
[e]$R^2 = 0.20$, a moderate effect.
[f]*r*s from 0.09 to 0.14, small effects.
Effect size is Cohen's delta; it was computed for original research articles with sufficient information to compare two groups.
HADS: hospital anxiety and depression scale; AVLT: auditory verbal learning test; RCPM: Raven's colored progressive matrices; MMSE: mini mental state exam; STPI-SA: state trait personality inventory-state anxiety scale; 3MS: modified mini mental status exam; CVLT: California verbal learning test; STROOP: Stroop color word test; TMT-B: trail making test-trails B; HVLT: Hopkins verbal learning test; ZA: Zung anxiety scale; ZD: Zung depression scale; MDD: major depressive disorder; SCID: structured clinical interview for DSM-IV axis I disorder; MDRS: Mattis' dementia rating scale; STAI: Speilberger state trait anxiety inventory; EXIT: executive interview; TMT-A: trail making test trails A; SAST: short anxiety screening test; SCL-90R: symptom checklist-90-revised; RBANS: the repeatable battery for assessment of neuropsychological status; EPI: Eysenck personality inventory; WAIS INFO: Weschler adult intelligence scale-information subscale; SYN: synonyms; KBD: Koh's block design; FID: figured identification; SD: symbol digit; NF: names and faces; TPM: Thurstone's picture memory.

cognitive domains, such as those heavily relying upon attentional resources, may be particularly salient to anxiety but have yet to be dissociated.

THE ONSET AND DEVELOPMENT OF ANXIETY IN COGNITIVELY IMPAIRED OLDER ADULTS

Late-life cognitive problems are best conceptualized on a spectrum from normal age-related decline to MCI, and at the extreme, dementia.[22] As many as 30% of older adults in the general population meet diagnostic guidelines for MCI,[23] considered a heterogeneous category varying by the presence or absence of memory impairment, and cognitive impairment in one or multiple domains.[22] Amnestic MCI, in particular, is hypothesized as a prodrome of neurodegenerative dementia.[22] Comorbid anxiety symptoms in MCI may also be a strong indicator of neurodegenerative disease such as Alzheimer[24,25] or Dementia with Lewy Bodies,[26] although these symptoms may not reliably differentiate neurodegenerative dementia subtypes.[27] Dementia involves a significant decline in cognitive function with impairments in memory, and apraxia, agnosia, or aphasia, causing significant impairment in social or occupational function.[5] Dementia severity varies from mild, moderate to severe, occurring in 6%–10% of older adults.[28]

As summarized in Table 2, MCI and dementia status increase the risk of experiencing anxiety and a myriad of other psychiatric symptoms. Epidemiological estimates of the presence of neuropsychiatric symptoms, including anxiety, are as high as 43% in individuals with MCI and 80% in those with dementia.[29] Clinically significant anxiety is also more common in older adults with more severe cognitive impairment, with a small effect across studies comparing controls with those with MCI[30–32] and in one study comparing older controls, MCI, and dementia.[29] An

TABLE 2. Studies of Cognitive Status or Performance in Relation to Anxiety Among Middle-Aged and Older Adults

Study	Participants	Cognitive Status (Measures)	Anxiety Status (Measures)	Results	Effect Size
Collie et al, 2002	174 community-dwelling Australians 50 and older (M = 66–68); matched controls (n = 23) versus MCI (n = 23)	Verbal delayed recall (MCI = <1.5 SD on CERAD during three consecutive assessments)	State anxiety (STAI)	State anxiety: MCI > matched controls (baseline)	0.16
Ferretti et al, 2000	137 older American clinical outpatients with AD; mean age 74; anxiety assessed via self-report (sample 1; n = 62) or by caregiver report on an anxiety subscale (sample 2; n = 75)	General cognitive functioning (Sample 1 by MMSE and DRS; Sample 2 by RMPBC memory subscale)	Clinically significant anxiety via self-report (HARS) or caregiver report (RMBPC anxiety subscale)	Clinically significant anxiety associated with greater cognitive impairment in AD	
Forsell, 2003	443 community-dwelling Swedes, Kung-Holmen Project; 74 and older (M = 83–84); normal controls (n = 353) versus MCI (n = 89)	General cognitive functioning (MCI = MMSE scores 1.0 SD below age and education norms)	Clinically significant anxiety symptoms or an anxiety disorder (CPRS)	Anxiety disorders (presence): MCI > normal controls; anxiety symptoms (presence): no group differences	
Geda et al, 2004	655 community-dwelling Americans; Mean age 77–81; normal controls (n = 514) versus MCI (n = 54) versus early mild AD (n = 87)	General cognitive status (CDR)	Neuropsychiatric anxiety symptoms (NPI)	Neuropsychiatric anxiety (presence): MCI and AD > normal controls	
Hwang et al, 2004	202 community-dwelling Americans; mean age 73–75; normal controls (n = 50) versus amnestic MCI (n = 28) versus mild AD (n = 124)	General cognitive status (NINCDS-ADRDA criteria)	Neuropsychiatric anxiety symptoms (NPI)	Neuropsychiatric anxiety (presence): MCI and AD > Controls	
Lyketsos et al, 2000	1,002 older adults, Cache County, Utah; 65+ (M = 80.8 without dementia; M = 84.2 with dementia); no dementia (n = 673) versus dementia (all stages/types) (n = 329)	General cognitive status (NINCDS-ADRDA criteria; CDR)	Neuropsychiatric anxiety symptoms (NPI)	Neuropsychiatric anxiety (presence): Dementia > no dementia	0.33
Lyketsos et al, 2002[a]	1,335 older adults, mean age 75–77; normal controls, Cache County Study (n = 653) versus MCI (n = 320) versus dementia (n = 362), cardiovascular dementia health study	General cognitive status (DSM-IV)	Neuropsychiatric anxiety symptoms (NPI)	Neuropsychiatric anxiety (presence): Dementia > MCI > general population	
Tatsch et al, 2006	163 community-dwelling Brazilians, 60+ mean age 72–80; normal controls (n = 78) versus CIND (n = 25) versus AD (n = 60)	General cognitive status (CDR)	Neuropsychiatric anxiety symptoms (NPI)	Neuropsychiatric anxiety (presence): CIND and Dementia > Controls; Anxiety and sleep disturbances = most common neuropsychiatric symptoms in CIND	
Teri et al, 1999	523 community-dwelling Americans, 60+ (M = 79), ADPR with probable (n = 439) or possible AD (n = 84)	General cognitive functioning (MDRS; MMSE); general cognitive status (NINCDS-ADRDA criteria)	Clinically significant anxiety (Composite anxiety score >1)[b]	Clinically significant anxiety in 70% of AD patients and related to poorer general cognitive functioning	

(*Continued*)

TABLE 2. Continued

Study	Participants	Cognitive Status (Measures)	Anxiety Status (Measures)	Results	Effect Size
Wilson et al, 2007	219 older clergy, Religious Order Study; no dementia (n = 124) versus dementia (n = 95) at most recent testing before death mean age 83.6–87.8	General cognitive functioning (MMSE); general cognitive status (NINCDS-ADRDA criteria)	Chronic distress (Composite neuroticism, trait anxiety and depression score[c])	Clergy reporting high chronic distress 2× greater risk of dementia during most recent testing	0.38

Notes: AD: Alzheimer dementia; CERAD: consortium to establish a registry for Alzheimer disease; STAI: state trait anxiety inventory; NPI: neuropsychiatric inventory; MDRS: Mattis' dementia rating scale; HARS: Hamilton anxiety rating scale; RMBPC: revised memory and behavioral problems checklist; CPRS: comprehensive psychopathological rating scale; CDR: clinical dementia rating scale; ADPR: Alzheimer disease patient registry; NINCDS-ADRDA: National Institute of Neurologic and Communicative Diseases and Stroke and the Alzheimer Diseases and Related Disorders Association; CIND: cognitively impaired not demented.

[a]The size of the effect between MCI and dementia was small, phi coefficient (ϕ) = 0.20.

[b]4-weighted item from a physician administered checklist (total anxiety score composite ranges from 0 to 5).

[c]Aggregation of *z*-scores from Neuroticism scale of NEO Five-Factor Inventory, Anxiety Trait scale of the State-Trait Anxiety Inventory, and the 10-item Center for Epidemiologic Studies Depression Scale.

Effect size is Cohen's delta; it was computed for original research articles with sufficient information to compare 2 groups.

investigation of older clergy also found a significant, but small effect—those with dementia during their most recent testing before death reported more severe chronic distress (neuroticism, trait anxiety, and depression composite) than those with no dementia.[33] Moreover, the risk of converting to dementia is nearly doubled when anxiety symptoms are present in older adults with MCI.[34]

Furthermore, anxiety or worry symptoms, present in about 70% of older adults with Alzheimer dementia, are related to poorer cognitive outcomes[35,36] and more frequent behavioral disturbances (e.g., verbal threats, wandering, sexual misbehavior).[36] Anxiety differs from agitation in individuals with dementia based on standard behavioral indices, such as the Neuropsychiatric Interview.[37] Behavioral manifestations of agitation in dementia include resistive behaviors and obstinacy, whereas for anxiety key behaviors include nervousness, tension, upset, or inability to relax. Although both are common in people with dementia, the literature investigating their overlap is limited.[38] Some studies suggest agitation is the outward manifestation of anxiety, whereas a few studies suggest they are distinct but overlapping constructs. In their investigation of 40 patients with dementia, Twelftree and Qazi[38] observed a modest relationship between anxiety and agitation, and not all anxiety symptoms correlated with agitation. Less work has been done to consider this issue in cognitively impaired older adults without dementia. A recent hierarchical cluster analysis of older adults with MCI identified two neuropsychiatric symptom clusters; notably, anxiety clustered with mood factors and agitation clustered with other "frontal symptoms" such as behavioral and motor symptoms of executive dysfunction.[39] Further, anxiety but not agitation was one of the most common symptoms observed in individuals with MCI.[25] Yet given the strong relationship typically observed between anxiety and agitation in patients with dementia, agitation may be an advanced form of anxiety that becomes increasingly prevalent as cognitive function deteriorates. Further research is required to elucidate this issue.

Only one of four studies, by Lyketsos et al.,[29] found that anxiety symptoms were more common in dementia compared with MCI. This study differed from the other three[24,25,32] in its inclusion of dementias of various etiologies, not just Alzheimer, although comparable estimates of anxiety are reported for those with dementia across all four studies. A second difference is that the presence of any anxiety symptom was much less common for participants with MCI in the Lyketsos study compared with the other investigations (9.9% versus 25%), further accentuating differences between the MCI and dementia group. Third, Lyketsos et al. used large comparison groups (ns = >300), thus increasing their ability to detect this significant, but modest relationship compared with other studies where the MCI or dementia groups were much smaller (ns = 25–124).

To review, clinically significant anxiety symptoms may predict accelerated cognitive decline. Anxiety of

clinical import a) may differentiate normal older adults from those with MCI or dementia, b) does not consistently distinguish MCI from mild dementia, and c) is associated with both memory and behavioral outcomes in older adults with Alzheimer dementia. The next section describes potential pathophysiological mechanisms linking clinically significant anxiety and cognitive dysfunction.

PATHOPHYSIOLOGICAL MECHANISMS

Structural changes in the brain offer a common potential substrate between late-life anxiety and cognition. Although there are numerous neuroimaging investigations of such anxiety disorders as posttraumatic stress disorder, phobias and obsessive compulsive disorder, very few have directly examined GAD. One of the few such studies of patients implicates functional impairments in the dorsolateral region of the prefrontal cortex,[40] an area strongly influencing diverse cognitive processes, particularly executive functions. In particular, 13 of 15 GAD patients exhibited hyperactivity in this brain region compared with their age and education matched controls. In their recent review, Berkowitz et al.[41] suggest that anxiety disorders such as panic, posttraumatic stress disorder, and phobias are characterized by an underactivity of the prefrontal cortex, thus disinhibiting the amygdala, whereas GAD and obsessive compulsive disorder, which involve worry and rumination rather than fear, may be characterized by overactivity of the prefrontal cortex.[41] This is, however, still speculative given the limited available data addressing this issue.

Neurochemical and structural alterations in emotion-related brain regions (i.e., the limbic system) and interacting brain regions subserving memory and other cognitive functions (i.e., hippocampal and prefrontal regions) might also account for more severe chronic distress in dementia.[33] This supposition is based on empirical evidence that the relationship between chronic distress and dementia is not accounted for by dementia-related neuropathology, such as neuritic plaques, amyloid accumulation, and infarcts.[33] Notably, combined volume reductions in the amygdala (i.e., a significant component of fear and stress neurocircuitry) and the hippocampus are more predictive of dementia than hippocampal volume alone.[42]

Reduced neurotransmitter function is also implicated in late-life neuropsychiatric and cognitive disturbances. Age-related serotonin alterations are postulated to influence directly the emergence of behavioral difficulties (e.g., sleep problems) and neuropsychiatric disturbances (e.g., depression), and to influence indirectly via acetylcholine cognitive impairment in older adults with or without dementia.[43] Animal investigations suggest diminished reuptake and excess extracellular serotonin deteriorates hippocampal dendrites,[44] potentially undermining memory processes. Serotonergic dysfunction affecting both hippocampal and frontal regions is also implicated in GAD;[45] however, it is unknown if prolonged overactivation of these pathways places GAD patients at increased risk for cognitive dysfunction and decline.

In addition, reduced acetylcholine availability is frequently linked to Alzheimer disease, thus targeted by many drug therapies to hasten memory impairment. Consequently, drug treatments for Alzheimer reduce a host of neuropsychiatric symptoms, including anxiety.[46] Activation of cholinergic pathways to the hippocampus in isolation attenuates anxious states[47]; therefore hippocampal neurodegeneration in Alzheimer may reduce the brain's ability to manage anxiety states thus contributing to the excess of anxiety symptoms observed in dementia.

Dementia and anxiety also share a common neuroendocrine substrate—the hypothalamic-pituitary-adrenal (HPA) axis. HPA dysregulation occurs as a consequence of stress and anxiety[48] and serotonergic influences during critical developmental periods on the proliferation of hippocampal glucocorticoid receptors.[49] Chronically elevated cortisol, a byproduct of HPA dysfunction, is hypothesized to damage the hippocampal region, which in turn dampens normal inhibitory regulation of corticosteroids on HPA activity.[48] This forward cascade in HPA response is linked to both smaller hippocampal volume and cognitive dysfunction in older individuals.[50]

Genetic vulnerability is an additional shared influence between anxiety and cognitive impairment. The short form (S variant) serotonin polymorphism transporter (5HTTLPR), associated with reduced transcriptional and reuptake efficiency of the serotonergic system, confers an increased risk for neurotic

personality traits and anxiety disorders, and dampened pharmacological treatment response for anxiety and depressive symptoms in major depressive disorder (for comprehensive review, see Serretti et al.[51]). Empirical evidence for a greater prevalence of the short allele polymorphism in Alzheimer is found in some cultural groups[52–54] but not others.[55–57] Recently, we observed the short allele of the 5HTTLPR to be associated with lower memory and higher waking cortisol (a physiological indicator of high stress or anxiety) in older, healthy adults.[58] Although a different investigation found the interaction between 5HTTLPR and cognitive performance was not associated with phobic anxiety in 64 community-dwelling older adults, the *F*-value of 2.59 ($p = 0.085$) suggests a potential interactive relationship detectable with increased statistical power.[17]

Other genetic markers influencing risk of developing cognitive impairment include the presence of one or more apolipoprotein E (APOE) e4 allele. Among middle-aged adults (mean age: 55), APOE e4 moderated the relationship between elevated clinically significant anxiety and poorer abstract problem solving ability.[59] The strongest association between anxiety and problem-solving was for carriers with homozygous allelic variation of APOE e4, although further replication is needed.

The short allele of the 5HTTLPR and APOE e4 does not appear to have a synergistic effect on dementia risk,[53,54,56] but has a potentially additive effect. In three multinational investigations the short allelic variation of 5HTTLPR conferred a greater risk for Alzheimer dementia independent of APOE e4 status.[52–54] Yet it is unknown if this dual genetic vulnerability further accelerates cognitive decline once it has begun, or how this combined vulnerability might contribute to the development of comorbid neuropsychiatric symptoms in the context of dementia over time.

In summary, although the neuropathophysiological overlap between late-life anxiety disorders and cognitive impairment has only recently been considered, evidence suggests several overlapping biological or physiological mechanisms. Physiological mediating factors to consider include neurotransmitters, brain structure and function, and the HPA axis. Variations or abnormalities in neurotransmitter availability or receptor site functioning, particularly for serotonin, may influence cognition or anxiety. Drastic reductions in acetylcholine availability may also play a role in this relationship, although the nature of anxiety symptoms with regard to this neurotransmitter is not well delineated. Brain structure abnormalities, such as reduced hippocampal volume due to chronic activation of the HPA-axis, or premorbidly small hippocampal volume may increase risk of an anxiety disorder. Genetic polymorphisms or markers may moderate the association between anxiety and cognition, although the support for this view is currently speculative.

COMORBID DEPRESSIVE SYMPTOMS

Another important consideration is the contribution of comorbid depressive symptoms. Lifetime prevalence of developing a mood disorder in the context of GAD is as high as 80%[60] and the incidence of GAD in Alzheimer patients with a mood disorder is 26%.[61] Multiple shared vulnerabilities between GAD and major depressive disorder, including similar genetic risks[60,62] and personality correlates[63] have led to the proposal that the two disorders belong in the same diagnostic category,[62] whereas others suggest the disorders are related but distinct based on differing antecedent risk factors during childhood.[64] Regardless, there is general consensus for the necessity of accounting for depression when studying GAD or its related symptoms. Thus, consideration of the neuropsychiatric correlates of cognitive impairment in older adulthood should focus not only on GAD or related anxiety symptoms, but also on how co-occurring GAD and depressive symptoms or disorders are associated with severity of cognitive impairment. Of the studies already described, the majority examines each symptom or disorder separately or as a general neuropsychiatric aggregate, which is useful but limited if specific comorbidities bestow a greater risk of cognitive impairment. Interesting patterns emerge based on the few studies that have considered co-occurring anxiety and depression in relation to cognitive deficits in aging including a) an inverted U-shaped relationship between anxiety and episodic memory after adjusting for depressive symptoms,[20] b) anxiety as a direct and an indirect (through depression) predictor of cognitive decline,[10] and c) accelerated memory decline for older adults with major depression and GAD or

panic disorder relative to older patient's with pure major depression.[21] More research examining the independent and interactive contributions of anxiety and depression to late-life cognition are needed, particularly if mechanisms of the association are to be parsed and better characterized.

COMORBID MEDICAL CONDITIONS IN ANXIETY: POTENTIAL INTERACTIONS WITH COGNITION

As noted by Cohen,[65] "the diversity of anxiety disorders is remarkable, as is the wide range of conditions with which anxiety is associated" (p. 1). Common comorbidities of anxiety include other psychiatric symptoms or disorders and medical illness. Stress related to chronic medical illness may be the source of anxiety for some older adults. For others, anxiety symptoms (e.g., heart palpitations) may be misinterpreted as health-related problems. Mutual interaction and exacerbation between medical comorbidity and anxiety is most plausible, and particularly salient to older individuals because of an increased prevalence of medical illness with age, a strong relationship between anxiety and comorbid medical illness, and because a predominance of anxiety-related somatic symptoms (e.g., heart palpitations, gastrointestinal problems) are commonly experienced among chronically ill older adults.[14] Indeed, risk of chronic physical illness is much greater in the context of an anxiety disorder, including GAD, and is greatest in the presence of comorbid anxiety and depression.[66]

Elevated anxiety is frequently experienced in diverse medical and disabled populations across a variety of primary care settings.[67] According to one study, 20% of older patients with a recent history of stroke met criteria for GAD.[68] Apart from anxiety, sleep disturbance was the only other neuropsychiatric symptom (and potential medical comorbidity) to distinguish older adults with normal cognition from those with MCI in two different studies.[24,32] Among ethnically diverse older adults, elevated anxiety was also associated with an increased of mortality at 5-year follow-up due to cancer or cardiovascular disease.[69]

Medical illnesses are not only prevalent in anxious older adults, but they also increase risk of developing dementia. Those commonly associated with an increased lifetime prevalence of dementia due to Alzheimer or vascular causes include cardiovascular disease, diabetes, and cerebrovascular illness.[70,71] Additionally, the interaction between the presence of an anxiety disorder and medical burden may also have a detrimental effect on late-life cognition, particularly set shifting.[7] Last, distress about chronic medical illness may also exacerbate the medical condition and increase dementia risk.

In summary, anxiety symptoms and the risk of cognitive impairment are more prevalent in older, medically ill populations. Although there is a dearth of literature linking medical comorbidity with anxiety and cognition, there is increasing recognition that medical illness may be an important factor in late-life anxiety. In this last section, we briefly discuss how anxiety may affect interventions for cognitive impairment in old adults, and then some issues associated with treating late-life anxiety in the presence of cognitive impairment.

TREATMENT CONSIDERATIONS

Pharmacological agents are frequently used to treat dementia and hold promise as an intervention to slow the rate of memory impairment in MCI. Combined pharmacological treatment for memory impairment and emotional problems is not uncommon in clinical settings. Due to the increased risk of nursing home placement when an older adult has anxiety symptoms comorbid to dementia,[72] improving management of anxiety and other neuropsychiatric symptoms is imperative. Additional treatment options for cognitively impaired older adults experiencing anxiety symptoms are certainly needed, including psychological interventions aimed at both improving cognition and reducing anxiety.

With respect to psychological interventions, a recent investigation of cognitive behavior therapy treatment for older GAD patients found that some individuals with executive dysfunction showed positive treatment response, whereas others showed virtually no response.[4] Notably, positive treatment responders with executive dysfunction demonstrated a greater reduction in anxiety symptoms after treatment compared with those with no executive dysfunction. Of interest, positive treatment responders

with executive dysfunction also improved on executive function measures, suggesting that late-life anxiety may affect cognitive resources available to adequately perform executive function tasks, such as problem solving or attention. Although speculative, nonresponders may represent a different subgroup altogether whose anxiety stems from a neurodegenerative process. Improved identification of cognitively impaired older adults at risk for treatment failure is particularly important for treatment selection and optimization. Novel treatment approaches for late-life anxiety, especially those lessening cognitive requirements, may be particularly salient for older adults with MCI. Treatments to consider include emotion-focused psychotherapies and problem-solving therapy, the latter of which has been successful in late-life depression with comorbid executive function deficits.[73]

Modifications to existing treatments or combined approaches may also be necessary in the presence of both conditions. In some instances, older individuals with cognitive impairment fare better in terms of day-to-day functioning, neuropsychiatric symptoms, and memory if their caregivers implement reality orientation techniques, such as regular reminders of the date and cognitively stimulating activities for brief sessions throughout the week.[74] Older adults with dementia and anxiety may respond to behavioral strategies that minimize anxiety cues or respond to the patient's unmet need (e.g., if overstimulated decrease environmental noise).[75] Modified psychotherapy sessions to ensure comprehension and retention of information during sessions may optimize treatment outcome for some anxious and cognitively impaired older adults (e.g., further breaking down information typically presented during sessions, more visual aids, briefer and more frequent sessions). Adjunctive treatment approaches may also derive greater benefit for this comorbid condition (e.g., psychotherapy for anxiety combined with pharmacotherapy for cognitive problems), although further research is needed.

SUMMARY

To review, the importance of the interrelationship between anxiety and cognition depends on the clinical significance of these symptoms. Normal aging decrements in memory or transient, low levels of state anxiety generally do not seem to have a negative impact on older adult, whereas clinically relevant anxiety symptoms and cognitive decrements do. Overlapping pathophysiological mechanisms in the brain (i.e., structures, neurochemicals, endocrine functions) offer a potential substrate for this relationship. Genetic moderators of both cognitive and anxiety disorders provide yet another window into the overlap between these conditions. Ample justification also exists to examine depressive symptoms or disorders in anxiety because of their frequent cooccurrence and overlapping risk factors. Comorbid medical conditions often seen among the aged further complicate this area. Hence, proper consideration of these disorders is necessary when comparing groups of older adults, not only as potential confounds, but also to inform our understanding of the underlying neuropathology between anxiety and cognition. In some cases, treatments targeting anxiety or cognition appear to have reciprocal benefits for both problems.

RECOMMENDATIONS AND FUTURE DIRECTIONS

As illustrated throughout this article, issues associated with anxiety in the context of late-life cognitive impairment are complex, but have the potential to illuminate our understanding of preclinical dementia and optimal treatment approaches for late-life GAD. More research is needed to track the longitudinal course of anxiety and cognition. Moreover, longitudinal observational studies examining the order in which anxiety symptoms or cognitive impairment first appear may be essential for determining etiology. Investigations comparing anxiety and other neuropsychiatric symptom comorbidities between older adults with or without MCI, but excluding those with dementia, would allow for more thorough assessment of anxiety using detailed self-report and semistructured interview questions. The distinction between behavioral manifestations of anxiety and agitation in older adults with dementia also deserves further examination as there is a strong likelihood of overlap between these two neuropsychiatric symp-

toms. Although measures of anxious personality traits and state anxiety provide useful estimations of anxiety tendencies in general populations, use of clinical measures of anxiety are preferable as they more closely estimate pathological anxiety. Shifting from general cognitive batteries to more sophisticated or challenging tests (e.g., select subtests of the Wechsler Adult Intelligence Scale[76] or Delis-Kaplan Executive Functions System)[77] would also allow for better explication of the cognitive domains most susceptible to the effects of anxiety.

Statistical adjustment for gender is common across the studies reviewed, but few examine gender's unique influence on both anxiety and cognition—with the exception of one study that found that older men reporting elevated state anxiety performed more poorly on visuospatial ability and attention—an association not found in the older women.[11] Gender should be considered in future studies of late-life anxiety and cognition in light of a) gender disparities in anxiety and mood disorders[1] and dementia[78] (i.e., greater prevalence in women than in men); b) sex differences in the presentation of these anxiety symptoms in older adults with Alzheimer dementia (e.g., men present with more anger and restlessness, and irritability and agitation)[36]; and c) gender disparities in cognitive performance.[79] The influence of ethnicity is not addressed in this literature. In the studies cited, many of the samples are homogeneous; however, the representation of international older adults represented in these studies is striking (see Tables 1 and 2) suggesting cross-cultural generalizability of the results. In addition to gender and ethnicity, this research should also be expanded to consideration of other anxiety disorders or related anxiety symptoms such as posttraumatic stress disorder and social phobia. Future studies are also required to further parse apart which symptoms of GAD, e.g., worry, might potentially mediate the negative relationship of this disorder to cognitive impairment and decline in older adults.

A significant clinical concern is which problem to treat first when both anxiety and cognitive impairment are present. Augmenting or combining standard treatments (e.g., providing pharmacotherapy for cognitive problems in addition to psychotherapy for GAD) is an important venue for researchers and clinicians to consider. Better characterization of older "nonresponders" to standard treatments for anxiety or cognitive concerns should also be examined more closely in studies to aid in the development of improved treatment strategies for older adults with anxiety and/or cognitive problems.

As has been heavily emphasized throughout this article, common medical and psychiatric comorbidities of GAD and cognitive impairment, including but not limited to depression and chronic medical problems, are critical variables to consider in future studies. Because medical problems in particular can be difficult to quantify in studies, a focus on disability and burden due to medical illness may be a key variable for future research. Future research should also emphasize the use of a broad range of neuroimaging technologies to investigate GAD patients to more fully understand the neurobiological underpinnings of this disorder, how it differs from other anxiety disorders and how it is impacted by normal aging brain changes. Finally, longitudinal studies incorporating imaging techniques would be an ideal method of observing reductions in brain volume in key locations (i.e., hippocampus, prefrontal cortex) and for aiding in the early identification of neurodegenerative illness.

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