Published in final edited form as:

Aging health. 2012 February 1; 8(1): 99–104. doi:10.2217/ahe.11.91.

Anxiety and verbal memory performance in *APOE-4* carriers and noncarriers aged 50 years and above

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Abstract

Aims—The current study sought to explore the relationship between state and trait anxiety and delayed verbal memory performance in *APOE-4* carriers and noncarriers who were aged 50 years and above.

Materials & methods—The study was a retrospective analysis of 267 participants aged 50 years and above who had completed genetic testing for APOE status, the State-Trait Anxiety Inventory, and a comprehensive neuropsychological battery that included three delayed verbal memory measures (Wechsler Memory Scale – 3rd Edition, Logical Memory and Verbal Pairs subtests and the Buschke Selective Reminding Test).

Results—An inverse relationship was found between state anxiety and delayed verbal memory performance. No difference in level of anxiety was found between *APOE-4* carriers versus noncarriers.

Conclusion—State anxiety, but not trait anxiety, was found to have an inverse relationship with delayed verbal memory performance. For example, as self-reported state anxiety increased, delayed verbal memory scores decreased. This relationship did not appear to be influenced by the presence or absence of the *APOE-4* allele.

Keywords

Alzheimer's disease; anxiety; *APOE-4*; cognitive impairment; depression; older adult; State-Trait Anxiety Inventory

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Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Cognitive impairment is devastating to both individuals and families. The prevalence of cognitive impairment in older adults is increasing as the population grows older and diagnostic tools improve. An estimated 15% of older individuals meet diagnostic criteria for mild cognitive impairment (MCI), although the prevalence rates of MCI are difficult to estimate due to lack of conformity over specific diagnostic criteria within the scientific community [1]. MCI is often the precursor for dementia, and Alzheimer's disease (AD) is the most common type of dementia in older adults [2]. A 2011 report from the Alzheimer's Association estimated that 5.4 million people suffer from AD, the fifth-leading cause of death in the USA for those aged 65 years and older [101]. The cost of AD and other dementias was US\$183 billion annually in 2011, with costs projected to reach \$1.1 trillion by the year 2050 [101]. Therefore, research devoted to further understanding of the causes and contributing factors of cognitive impairment is crucial.

Research has found a high comorbidity between depression and cognitive decline [3], with late-life depression potentially appearing as a prodrome rather than a risk factor for dementia [4]. While extensive research has been devoted to the study of depression and cognitive decline, less attention has been focused on the potential role of anxiety and cognition [5,6]. Research that has explored the relationship between anxiety and cognition has yielded mixed results, particularly in older individuals. In a study of older men and women, a curvilinear relationship was found between anxiety and cognition [7]. For example, mild anxiety was associated with better cognitive performance, while severe anxiety was associated with worse cognitive performance [7]. However, other studies found that even subthreshold anxiety symptoms were inversely related to global cognitive function in older adults [6,8].

Anxiety is frequently categorized as a state and trait construct, with state anxiety associated with feelings of tension, apprehension, nervousness and worry accompanied by increased physiological arousal, and trait anxiety associated with a tendency to perceive situations as threatening [9,10]. When research studies on anxiety were classified by state and trait anxiety, results yielded more specific findings. For example, in older adults, increased state anxiety was associated with poorer performance on verbal working memory tasks, although trait anxiety was also associated with decreased verbal learning [10]. Another study suggested that trait anxiety was associated with cognitive impairment and dementia [11]. Consistent findings were demonstrated in a 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl} ethylidene) malononitrile (FDDNP) PET imaging study, which found that trait anxiety correlated with posterior cingulate FDDNP binding in those with MCI and with medial temporal and frontal FDDNP binding in cognitively normal subjects who were middle-aged and older adults [12]. Such findings highlight the possibility that both state and trait anxiety are inversely related to cognitive function.

Another contributing factor in the development of cognitive impairment is genetic composition. Carriers of the *APOE-4* allele are at increased risk for cognitive decline; they are particularly at risk for developing AD [13, 14]. Presence of the *APOE-4* allele has been associated with greater severity of depressive symptoms and decline in verbal memory in middle-aged and older adults [15], reduced semantic fluency [16], and decreased performance on measures of item memory and spatial context retrieval [17].

Based on the aforementioned research, there is reason to believe that anxiety negatively affects cognition in older adults. However, the current research on the relationship between anxiety and verbal memory in older adults is limited. In addition, the presence of the *APOE-4* allele is a well-known contributor to cognitive decline. However, to our knowledge, little is known about the potential role of anxiety in *APOE-4* carriers versus

noncarriers in regards to verbal memory performance. Therefore, the aim of the current study is to investigate the relationship between state and trait anxiety, as measured by the State-Trait Anxiety Inventory (STAI), and verbal memory performance, as measured by a composite of delayed verbal memory test scores, as well as to explore whether *APOE-4* carriers differ in levels of self-reported anxiety.

It is hypothesized that both state and trait anxiety will be inversely related to delayed verbal memory performance, as the aforementioned studies have demonstrated diminished cognitive performance and cognitive change associated with state and trait anxiety. As *APOE-4* carriers have shown more severe depressive symptoms, it is hypothesized that *APOE-4* carriers will have higher levels of self-reported anxiety as well.

Methods

Participants

Participants were recruited through newspaper advertisements, media reports and university-affiliated programs that sought individuals with memory complaints or those with a family history of dementia. To rule out cognitive impairment due to treatable etiologies, all subjects completed neurologic/psychiatric evaluations, neuropsychological assessments and routine laboratory screenings. Some participants completed multiple neuropsychological assessments over the course of 6 years; only scores from the most recent evaluation were utilized in the current analysis. Participants were excluded if they were under the age of 50 years.

A total of 267 participants met inclusion criteria. APOE genotypes were determined through standard techniques from participants' blood samples, as previously described in the literature [18].

Measures & procedures

Each participant completed the STAI prior to completing a full neuropsychological evaluation of approximately 3 h duration (see Box 1 for a list of measures administered). The current study utilized delayed memory scores from three verbal memory measures, including the Wechsler Memory Scale – 3rd Edition (WMS-III), Logical Memory and Verbal Pairs subtests and the Buschke Selective Reminding Test (Buschke). Delayed memory z-scores were derived from the WMS-III [19] and Buschke [20] test manuals (corrected for age and gender when appropriate) and were averaged to formulate a delayed verbal memory domain score.

The STAI is a 40-item self-report measure that evaluates state and trait anxiety separately [9]. As indicated above, state anxiety refers to tension and apprehension that varies in intensity and changes over time, while trait anxiety refers to an individual's characteristic propensity to experience anxiety, which tends to be stable over time [9]. Individuals respond to 20 items that evaluate how they are feeling in the moment (state anxiety) and 20 items that assess how they generally feel (trait anxiety); individuals rate each item on a four-point scale (1 = not at all, 2 = somewhat, 3 = moderately so, 4 = very much so). The range for both the state and trait anxiety measures is 20–80, with a higher number indicating a higher degree of anxiety.

Box 1. Assessment measures comprising the neuropsychological testing battery

- Boston Naming Test

- Buschke Selective Reminding Test
- Clinical Dementia Rating
- Controlled Oral Word Association Test (FAS; animals)
- Functional Abilities Questionnaire
- Hamilton Depression Scale
- Mini Mental State Exam
- Profile of Mood States
- Rey–Osterrieth Complex Figure Test
- State-Trait Anxiety Inventory
- Stroop A, B and C
- Subjective Memory Questionnaire
- Trail Making Test: A and B
- Wechsler Adult Intelligence Scale – 3rd Edition (Block Design, Coding, Digit Span, Picture Completion and Similarities subtests)
- Wechsler Memory Scale – 3rd Edition (Logical Memory, Verbal Pairs and Visual Reproduction subtests)
- Wechsler Test of Adult Reading
- Wisconsin Card Sorting Test

Analytic strategy

A linear multiple regression was used to investigate the effect of anxiety on delayed verbal memory performance. The composite of the delayed verbal memory scores (average of delayed z-scores from WMS-III Logical Memory, WMS-III Verbal Pairs and Buschke) served as the dependent variable. State and trait anxiety total scores, totaled separately (as measured by the STAI), served as the independent variables. Given the *APOE-4* allele's association with increased risk for AD, a *post-hoc* multivariate analysis of variance using APOE status as the independent variable and state and trait anxiety scores as the dependent variables was completed. Also, given that anxiety is commonly comorbid with depression, the results of participants' depression scores on the Hamilton Depression Scale [21, 22] were also analyzed.

Results

There were 267 total participants (see Table 1 for detailed descriptive statistics). The study sample included more female participants than men (62.9 and 37.1%, respectively). The sample's average age was 61.84 years (standard deviation [SD] = 11.76). Participants had a mean of 16.29 years of education (SD = 2.93). While the sample included participants from various racial and ethnic backgrounds, the majority were Caucasian (84.3%). The mean of their Mini Mental State Exam [23] score was 28.59 (SD = 2.17). The sample scored in the non-depressed range on the Hamilton Depression Scale (M = 2.80; SD = 3.45). Over half of the participants did not have an *APOE-4* allele (58.1%), while 41.9% were either heterozygous or homozygous for the *APOE-4* allele.

As can be seen in Table 2, the linear multiple regression revealed a statistically significant inverse relationship between anxiety scores and delayed verbal memory scores ($F[2, 264] = 9.184$; $p < 0.01$; R^2 adjusted = 0.058). An analysis of univariate contributions found that higher state anxiety scores ($M = 34.00$; $SD = 10.99$) were significantly correlated with lower verbal delayed memory scores ($p < 0.01$), while trait anxiety was not ($M = 34.07$; $SD = 10.09$).

A *post-hoc* multivariate analysis of variance using APOE status as the independent variable and state and trait anxiety scores as the dependent variables revealed that there was not a statistically significant difference between individuals possessing the *APOE-4* allele and those who did not with regard to self-reported levels of anxiety ($p > 0.05$). This finding indicates that the association between state anxiety and delayed verbal memory does not seem to be impacted by the presence or absence of the *APOE-4* allele.

Discussion

The current study sought to examine the relationship between state and trait anxiety and delayed verbal memory performance in those aged 50 years and over, along with the relationship between *APOE-4* carrier status and self-reported anxiety. It was hypothesized that both state and trait anxiety would be inversely related to delayed verbal memory performance, and that *APOE-4* carriers would have higher levels of self-reported anxiety. We found that state anxiety, but not trait anxiety, was inversely related to delayed verbal memory performance; this association did not appear to be impacted by the presence or absence of the *APOE-4* allele.

Further investigation into the underlying mechanisms of anxiety provided a possible explanation of the aforementioned findings. According to Eysenck's processing efficiency theory, worry (which Wetherell *et al.* equated to state anxiety [10]) reduces the working memory system's storage and processing efficiency, which could in turn diminish delayed memory performance [24, 25].

It is also possible that an individual's awareness of memory problems and subsequent anxiety over the perceived cognitive decline could explain the current study's findings. For example, a perceived memory problem could have preceded the experience of state anxiety, as perceived cognitive decline could certainly provoke anxiety. In addition, as the current study was cross-sectional in nature, the current analysis does not allow for the conclusion that increased state anxiety causes a decline in delayed verbal memory performance. Future studies might analyze participants' performance and anxiety levels over time to better understand such a relationship.

The lack of association between the *APOE-4* allele and anxiety could not be definitively explained in the literature. While some studies found that the presence of an *APOE-4* allele was associated with increased anxiety symptoms, others did not [26]. However, Panza *et al.* indicated that anxiety measures were often absent in studies assessing neuropsychiatric symptoms and cognition [26].

The current study is not without limitations. First, the study sample included mostly educated, Caucasian individuals. It is unclear whether level of education or ethnicity might impact the findings observed. Second, the mean Mini Mental State Exam score of the study sample was rather high; it is unclear how anxiety might affect a sample that demonstrated poorer global cognitive function. Future studies might examine the potential role of state and trait anxiety in samples with less education, more racial and ethnic diversity, and further reduced cognitive function. Future research might also investigate the potential role of the *APOE-4* allele and anxiety in the aforementioned groups.

Conclusion

State anxiety, but not trait anxiety, was inversely related to delayed verbal memory performance; this association did not appear to be impacted by the presence or absence of the *APOE-4* allele. The relationship between anxiety and cognitive functioning is complex, particularly in older adults, and requires further study to better understand how state and trait anxiety impacts cognition, especially in *APOE-4* carriers.

Future perspective

The number of adults reaching old age is rapidly increasing, as is the number of older adults with memory problems and overall cognitive decline. Given the monumental cost of caring for those with cognitive impairment, research in the area of cognitive decline, its causes, and potentially useful interventions will also likely increase. Research that explores potential mediators of cognitive decline (e.g., mood symptoms) will likely be of particular interest, as practitioners seek meaningful interventions with tangible results.

Executive summary

- We found an inverse relationship between state anxiety and delayed verbal memory performance.
- The association between anxiety and delayed verbal memory performance did not appear to be impacted by the presence or absence of the *APOE-4* allele.
- Future research should examine the potential impact of education, ethnicity and diminished global cognitive functioning (e.g., lower mean Mini Mental State Exam scores) on the relationship between anxiety and memory, with continued consideration of *APOE-4* carrier status.

Acknowledgments

The work was supported by an NIH National Research Service Award 1F31AG035438-01 to JAB and by NIH grants P01-AG025831, AG13308, P50 AG 16570, MH/AG58156, MH52453; AG10123; M01-RR00865, the Department of Energy (DOE contract DE-FC03-87-ER60615); General Clinical Research Centers Program; the Fran and Ray Stark Foundation Fund for Alzheimer's Disease Research; the Ahmanson Foundation. GW Small reports having served as a consultant and/or having received lecture fees from Dakim, Eisai, Forest, Medivation, Novartis and Pfizer. GW Small also reports having received stock options from Dakim.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest

1. Wilson RS, Schneider JA, Boyle PA, Arnold SE, Tang Y, Bennett DA. Chronic distress and incidence of mild cognitive impairment. *Neurology*. 2007; 68:2085–2092. [PubMed: 17562829]
2. Kidd PM. Alzheimer's disease, amnesic mild cognitive impairment, and age-associated memory impairment: current understanding and progress toward integrative prevention. *Altern. Med. Rev.* 2008; 13:85–115. [PubMed: 18590347] • Review of the history, diagnosis, pathophysiology, risk factors and prevention of Alzheimer's disease, amnesic mild cognitive impairment and age-associated memory impairment.
3. Lyketsos CG, Olin J. Depression in Alzheimer's disease: overview and treatment. *Biol. Psychiatry*. 2002; 52:243–252. [PubMed: 12182930]

4. Brommelhoff JA, Gatz M, Johansson B, McArdle JJ, Fratiglioni L, Pedersen NL. Depression as a risk factor or prodromal feature for dementia? Findings in a population-based sample of Swedish twins. *Psychol. Aging*. 2009; 24:373–384. [PubMed: 19485655]
5. Beekman ATF, Bremmer MA, Deeg DJH, et al. Anxiety disorders in later life: a report from the longitudinal aging study Amsterdam. *Int. J. Geriatr. Psychiatry*. 1998; 13:717–726.
6. Stillman AN, Rowe KC, Arndt S, Moser DJ. Anxious symptoms and cognitive function in non-demented older adults: an inverse relationship. *Int. J. Geriatr. Psychiatry*. 2011 • Examines the relationship between subthreshold anxiety symptoms and cognitive functioning in a healthy older adult population.
7. Bierman EJM, Comijs HC, Jonker C, Beekman ATF. Effects of anxiety versus depression on cognition in later life. *Am. J. Geriatr. Psychiatry*. 2005; 13:686–693. [PubMed: 16085784]
8. Deptula D, Singh R, Pomara N. Aging, emotional states, and memory. *Am. J. Psychiatry*. 1993; 150:429–434. [PubMed: 8434658]
9. Spielberger, CD.; Gorsuch, RL.; Lushene, R.; Vagg, PR.; Jacobs, GA. *Manual for the State-Trait Anxiety Inventory (Form Y)*. Palo Alto, CA, USA: Consulting Psychologists Press; 1983.
10. Wetherell JL, Reynolds CA, Gatz M, Pedersen NL. Anxiety, cognitive performance, and cognitive decline in normal aging. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 2002; 57:246–255. • Examines the effects of state anxiety and neuroticism on cognitive functioning in older adults.
11. Gallacher J, Bayer A, Fish M, et al. Does anxiety affect risk of dementia? Findings from the Caerphilly prospective study. *Psychosom. Med*. 2009; 71:659–666. [PubMed: 19553290]
12. Lavretsky H, Siddarth P, Kepe V, et al. Depression and anxiety symptoms are associated with cerebral FDDNP-PET binding in middle-aged and older non-demented adults. *Am. J. Geriatr. Psychiatry*. 2009; 17:493–502. [PubMed: 19472439]
13. Bird, TD. Alzheimer's disease overview. In: Pagon, RA.; Bird, TC.; Dolan, CR.; Stephens, K., editors. *Gene Reviews*. Seattle, WA, USA: University of Washington; 2010.
14. Donix M, Burggren AC, Suthana NA, et al. Longitudinal changes in medial temporal cortical thickness in normal subjects with the *APOE-4* polymorphism. *Neuroimage*. 2010; 53:37–43. [PubMed: 20541611]
15. Lavretsky H, Ercoli L, Siddarth P, Bookheimer S, Miller K, Small G. Apolipoprotein e4 allele status, depressive symptoms, and cognitive decline in middle-aged and elderly persons without dementia. *Am. J. Geriatr. Psychiatry*. 2003; 11:667–673. [PubMed: 14609807]
16. Miller KJ, Rogers SA, Siddarth P, Small GW. Object naming and semantic fluency among individuals with genetic risk for Alzheimer's disease. *Int. J. Geriatr. Psychiatry*. 2005; 20:128–136. [PubMed: 15660408]
17. Kukulja J, Thiel CM, Eggermann T, Zerres K, Fink GR. Medial temporal lobe dysfunction during encoding and retrieval of episodic memory in non-demented APOE epsilon4 carriers. *Neuroscience*. 2010; 168:487–497. [PubMed: 20350587]
18. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993; 261(5123):921–923. [PubMed: 8346443]
19. Wechsler, D. *Wechsler Memory Scale: Third Edition Manual*. San Antonio, TX, USA: The Psychological Corporation; 1997.
20. Buschke H. Selective reminding for analysis of memory and learning. *J. Verb. Learn. Verb. Behav.* 1973; 12:543–550.
21. Hamilton M. The assessment of anxiety states by rating. *Br. J. Med. Psychol.* 1959; 32:50–55. [PubMed: 13638508]
22. Hamilton M. A rating scale for depression. *J. Neurol. Neurosurg Psychiatry*. 1960; 23:56–62. [PubMed: 14399272]
23. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 1975; 12:189–198. [PubMed: 1202204]
24. Eysenck, MW. *Anxiety: The Cognitive Perspective*. Hillsdale, NJ, USA: Erlbaum; 1992.
25. Eysenck MW, Calvo MG. Anxiety and performance: the processing efficiency theory. *Cogn. Emot.* 1992; 6:409–434.

26. Panza F, Seripa D, D'Onofrio G, et al. Neuropsychiatric symptoms, endophenotypes, and syndromes in late-onset Alzheimer's disease: focus on *APOE* gene. *Int. J. Alzheimers Dis.* 2011; 2011:721457. [PubMed: 21559196]

Website

101. Alzheimer's Association. Accessed on 19 April 2011 www.alz.org/downloads/Facts_Figures_2011.pdf • Provides current data on Alzheimer's disease.

Table 1

Summary characteristics for participant sample.

Variables	Total (%)
<i>Gender</i>	
Male	37.1
Female	62.9
<i>Level of education</i>	
High school	6.4
Some college	29.5
College	25.8
Postgraduate	37.1
Less than high school	1.1
<i>Ethnicity</i>	
Caucasian	84.3
African-American	6.0
Latino/Latina	3.4
Asian-American	4.5
Other	0.4
<i>Age (years)</i>	
50–64	51.9
65–79	38.0
80+	10.2
<i>APOE status</i>	
No <i>APOE-4</i> allele	58.1
2/4	0.8
3/4 or 4/4	41.1
<i>Family history of dementia/Alzheimer's disease</i>	
No family history	56.9
Family history	43.1

Table 2

Regression analysis summary for anxiety variables predicting delayed verbal memory scores.

Variable	B	SEB	β
State anxiety	-0.052	0.015	-0.367 *
Trait anxiety	0.023	0.017	0.152

$R^2 = 0.065$ (n = 267; p < 0.01)

*
p < 0.01

β : Standardized regression coefficient; B: Nonstandardized regression coefficient; SEB: Standard error of β .