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Effect of Worry Level on Recall Memory for Odors in ApoE-ε4 Carriers and Non-Carriers

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Abstract

Objective: Increased levels of worry, age, and presence of the apolipoprotein-E (ApoE) ε4-allele are associated with risk for developing cognitive declines and Alzheimer's disease (AD). Odor memory performance has been shown to vary as a function of age and ApoE-genotype, and odor memory tests are sensitive to pre-clinical AD. Worry is known to influence verbal memory; however, its effects on odor memory are unknown. This study aimed to assess the relationships between worry, age, and ε4-status on odor memory.

Method.—Worry was evaluated for young (n= 53) and older (n= 45) adults using the Penn State Worry Questionnaire. Odor memory was assessed using the California Odor Learning Test; an olfactory analogue to the California Verbal Learning Test.

Results.—A significant main effect of worry on long-delay *free* recall was found, such that increasing worry was associated with better recall across age and ε4-status. A significant interaction effect between ε4-status and worry on both short and long-delay *cued* recall was found, such that across age, higher worry was associated with increased cued-recall scores among ε4-negative adults, and decreased scores among ε4-positive adults.

Conclusions.—Findings demonstrate that worry influences odor memory and exerts a particular effect on cued recall among ε4-carriers who are at greater risk for developing AD. Worry is a modifiable predictor of cognitive decline and risk for dementia in aging. Future studies on the effects of treatments aimed at reducing worry (e.g., cognitive behavioral therapies for anxiety) on changes in cognitive functioning are warranted.

Keywords

worry; Apolipoprotein gene; aging; odor memory; cued recall; free recall

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Age-related cognitive decline and neurodegenerative disorders such as Alzheimer's disease (AD) are of great concern, particularly considering the increasing age of the general population. Intervention efforts are most effective in the earliest stages of AD, motivating efforts towards early identification of the disease.

Tests of olfactory function have shown great promise as pre-clinical indicators of AD (Albers, Gilmore, Kaye, Murphy, Wingfield, Bennett et al., 2014; Djordjevic, Jones-Gotman, De Sousa, & Chertkow, 2008; Lehrner, Pusswald, Gleiss, Auff, & Dal-Bianco, 2009; Murphy, 2018 in press; Ottaviano, Frasson, Nardello, & Martini, 2016; Quarmley et al., 2017; Schubert et al., 2008) with prodromal declines in olfactory function occurring due to very early proliferation of AD-related neuropathology in the entorhinal and transentorhinal cortices, regions critical for processing olfactory information (Braak & Braak, 1991; Christen-Zaech et al., 2003). These regions also serve important roles in hippocampal networks critical for memory. For example, impaired odor recognition has been demonstrated in patients with hippocampal lesions (Levy, Manns, Hopkins, Gold, & Squire, 2003). Accordingly, odor tests can serve as early indicators for later cognitive impairment. Indeed, epidemiological research has reported that olfactory function predicts cognitive decline over a five-year period, with results suggesting that odor testing is useful in high-risk settings (Schubert et al., 2008).

The $\epsilon 4$ allele of the apolipoprotein E (ApoE) gene, a genetic risk factor for AD, has also been associated with declines in **a number of** olfactory tasks, even in cognitively normal adults (Calhoun-Haney & Murphy, 2005; Finkel, Reynolds, Larsson, Gatz, & Pedersen, 2011; Gilbert & Murphy, 2004; Larsson et al., 2016; Olofsson et al., 2016). Studies have shown that olfaction declines more rapidly than global cognitive function among carriers of the $\epsilon 4$ allele, with higher-level olfactory processing abilities, such as odor identification, declining faster than more peripheral functions such as odor detection (Calhoun-Haney & Murphy, 2005), and with measurable declines in these abilities occurring as early as middle age in $\epsilon 4/\epsilon 4$ homozygotes (Josefsson, Larsson, Nordin, Adolfsson, & Olofsson, 2017).

However, testing for $\epsilon 4$ -positive status does not carry full sensitivity or specificity for the disease, and approximately 42% of those with non-familial and late-onset AD are not $\epsilon 4$ -carriers (Bekris, Yu, Bird, & Tsuang, 2010; Bird, 2008). Thus, additional factors must be contributing to the pathogenesis of AD, and research into modifiable risk factors has become a growing area of interest. Worry, or the act of dwelling on specific negative or troubling thoughts, is one such modifiable risk factor that has been linked to an increased chance of developing AD, with structural degeneration in the hippocampus and other regions posited as a potential neural mechanism (Mah, Szabuniewicz, & Fiocco, 2016).

Worry is a behavioral (e.g., the act of and actions associated with allowing one's mind to dwell on concerns or problems) and cognitive (e.g., thoughts about concerns, actual or potential problems, or danger) manifestation of negative emotions and physiological experiences (e.g. fear, uncertainty, disgust, stress), and is a hallmark symptom of Generalized Anxiety Disorder (American Psychiatric Association, 2013). Anxiety in aging has been associated with an increased risk for the development of neuropathology associated with Alzheimer's disease, such as proliferation of beta-amyloid (Palmer et al., 2007). The

same biological risk factors for increased amyloid, such as possession of an ApoE $\epsilon 4$ allele, have also been associated with elevated levels of anxiety (Caselli, Reiman, Hentz, Osborne, & Alexander, 2004; Holmes et al., 2016) in older adults. Worry and other perseverative thought processes (i.e., rumination) have been found to predict negative outcomes associated with emotional problems over and above diagnostic categories, even at subsyndromal levels (Ruscio, Seitchik, Gentes, Jones, & Hallion, 2011). Among cognitively normal older adults, those with minimally elevated worry symptoms have been shown to demonstrate poorer performance in visual and paired associate learning and are also more likely to show clinically significant visual learning and memory declines over a two year period than those with minimal levels of worry (Pietrzak et al., 2012). Sub-clinical levels have also been associated with functional impairments, physical disability, and decreased quality of life in cognitively normal older adults (Braam et al., 2014). In line with the Research Domain Criteria (RDoc; Insel, Cuthbert, and Garvey, 2010) initiative, these findings suggest that worry may be a functional mechanism that cuts across diagnostic categories.

Worry is also associated with the physiological stress response, which refers to the biological or physiological symptoms occurring in response to a perceived threat. The perseverative nature of worry serves to prolong the physiological stress response beyond the time constraints of a stressful event, potentially increasing the risk for poor stress-related health outcomes (Ottaviani et al., 2016). Studies of the effect of stress and genetic risk for AD on verbal memory have found that older adults who reported high levels of chronic stress, defined by the authors as at least one high stress event in the past year, performed worse on long delay free recall than those with low stress, and performance was worst in those reporting high stress who also tested positive for the ApoE $\epsilon 4$ allele (Peavy et al., 2007). Similarly, increased cortisol levels, a hormone associated with worry and the experience of stress and anxiety, were negatively correlated with performance on verbal memory and learning and this effect was significantly more pronounced in $\epsilon 4+$ individuals (Lee et al., 2008). Taken together, research exploring the relationships among stress, anxiety, worry, and cognitive function suggest that worry may mediate some of the negative cognitive outcomes associated with stress and anxiety.

While no studies to date have directly examined the relationship between worry and odor memory, links between olfactory, emotion, and memory processing have been reliably shown. A wide variety of cognitive and behavioral studies have demonstrated effects such as olfactory cuing of emotional memories (Galliot et al., 2013), facilitation of the memory for specific unique events as a function of the emotion carried by odors (Saive et al., 2014), and heightened responses to odors in conditions with dysfunction in affective processing, such as Generalized Anxiety Disorder and Post Traumatic Stress Disorder (Cortese, Leslie, & Uhde, 2015).

Connections between olfactory, memory, and emotion have also been demonstrated at the neural level (Soudry, Lemogne, Malinvaud, Consoli, & Bonfils, 2011). The primary olfactory cortex (i.e., piriform cortex) shares a wide number of direct and indirect connections with regions known to be critical for functions such as emotional regulation, integration of affective and sensory information, emotional learning and memory, and reward-based decision making (e.g., the amygdala, cingulate cortex, hippocampus,

orbitofrontal cortex, and insular cortex; (Cerf-Ducastel & Murphy, 2001; Frasnelli et al., 2010; Lehn, Kjørnigsen, Kjølvik, & Håberg, 2013; Smitka et al., 2012). Thus, unlike other sensory systems in which primary sensory information is routed to sensory-association regions via the thalamus, olfactory information is sent directly to regions within the prefrontal cortex and limbic system, resulting in important neurologically-based relationships between mood, emotion, memory, and olfactory processing that affect cognitive, emotional, and social functioning across the lifespan (Sullivan, Wilson, Ravel, & Mouly, 2015).

For example, these fronto-limbic networks have been shown to play important roles in the functional integration of primary olfactory information with information about important associated emotion and memory-related content (Benarroch, 2010; Cerf-Ducastel, Haase, & Murphy, 2012; Murphy, Cerf-Ducastel, Calhoun-Haney, Gilbert, & Ferdon, 2005). A recent study investigating functional connectivity using a cross-modal olfactory recognition memory paradigm also highlights the relationships between medial temporal regions implicated in AD (e.g., entorhinal cortex) and the OFC in odor memory processing, and suggest that associations between regions may vary as a function of memory accuracy and feelings of certainty or familiarity (Haase, Wang, Green, & Murphy, 2013).

Importantly, while genetic and other non-modifiable risk factors for AD serve as useful biomarkers for who will develop the disease; they offer little with regard to intervention and prevention. In contrast, modifiable risk factors for AD such as worry can be directly treated and reduced to potentially improve health and quality of life. Thus, investigations into the relationship between chronic worry, aging, and preclinical markers of risk for AD have important implications.

To the authors' knowledge, no study to date has investigated the effects of worry on odor memory performance. The present study sought to characterize the relationships between worry and odor memory as a function of age and ApoE-ε4 status in healthy young and older adults, which represents an important step towards understanding these relationships in relation to AD. We hypothesized significant differences in odor memory measures as a function of age, ApoE-ε4 status, and worry level, such that: (1) younger adults would perform better than older adults across all odor memory measures (2) odor memory performance would be associated with worry levels, and (3) the effect of worry on odor memory performance would vary as a function of ApoE-ε4 status.

Methods

Participants

Participants were 53 young (18–26 years; 27 males, 26 females) and 45 older (62–84 years; 23 males, 22 females) healthy adults. There were 21 ApoE ε4 positive and 32 ApoE ε4 negative young adults, and 18 ApoE ε4 positive and 23 ApoE ε4 negative older adults. ApoE genotype was not available for four of the older adults, so these cases were excluded from the final analyses.

Younger adults were primarily recruited from undergraduate psychology courses at San Diego State University, and older adults were primarily recruited through information and presentations at community centers and local businesses. The study was in compliance with regulations of the San Diego State University Institutional Review Board (IRB) and subjects gave informed consent. Participants who met the age requirements screened for significant medical or psychiatric conditions that could affect cognition (e.g., history of traumatic brain injury, substance abuse, psychological diagnosis requiring medical or inpatient treatment). The study was part of a larger investigation exploring the effect of cortisol, thus participants were also excluded if they were diagnosed with any condition that could affect cortisol production (e.g. diabetes, uncontrolled hypothyroidism, Post-Traumatic Stress Disorder), or were currently using medications that may affect cortisol production (e.g. corticosteroids, steroid inhalers, antidepressants).

On the day of testing, participants were screened for depression using the Beck Depression Inventory II (BDI-II; Beck, Steer & Brown, 1996) for younger adults, and the Geriatric Depression Scale (GDS; Yesavage et al., 1983) for older adults. Individuals were excluded if they scored a 20 or above on either scale, indicating the presence of moderate to severe depression. Older adult participants were screened for dementia using either the Mini-Mental State Examination (MMSE) or the Dementia Rating Scale (DRS), and excluded if they scored below recommended cutoffs of 26 on the MMSE (Folstein, Folstein, & McHugh, 1975) or 123 on the DRS (Lucas et al., 1998). All participants were assessed by a butanol threshold odor test (procedures are described in Murphy, Gilmore, Seery, Salmon, & Lasker, 1990) and were excluded from the final analyses if testing revealed anosmia or severe hyposmia (i.e., butanol threshold odor test score < 4 in both nostrils).

Procedures

Participants were administered screening tests, mood questionnaires, and tests of olfactory and cognitive function in the laboratory or their home. The testing session lasted approximately 2–3 hours, and participants received either monetary compensation or, when applicable, course credit for their participation.

ApoE Genotyping

All participants were genotyped for apoE allele type using a polymerase chain reaction with oligonucleotide, followed by digestion with the HhaI restriction enzyme and polyacrylamide chain gel electrophoresis. Participants were categorized as $\epsilon 4+$ if they had at least one $\epsilon 4$ allele (i.e., $\epsilon 2/4$, $\epsilon 3/4$, and $\epsilon 4/4$).

California Odor Learning Test

The COLT was developed by Murphy, Nordin, & Acosta (1997) as an olfactory analogue to the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) that uses odors instead of verbally presented words. Odors are distributed into the four semantic categories of spices and herbs, fruits, personal products, and sauces and condiments (e.g. cinnamon, oranges), and were matched on a one-to-one basis with the word items from the

CVLT to allow for calculation of odor memory measures using the computerized scoring system developed for the CVLT (Delis et al., 1987).

Stimuli are presented to participants at suprathreshold level in opaque jars to avoid visual cues. During the odor presentation phases, participants are asked to close their eyes and presented with each odor for 5 seconds, with a 10 second inter-stimulus interval. The test consists of 5 immediate recall trials of 16 odors (List A) followed by a distracter trial of 16 different odors (List B); short delay recall of List A (free and category-cued; SDFR, SDCR), which is assessed directly after immediate recall of List B; long delay recall of List A (free and category-cued; LDFR, LDCR), which is assessed 20 minutes following the short delay portion; recognition memory; and lastly, odor identification.

Penn State Worry Questionnaire

Worry was measured with the Penn State Worry Questionnaire (Meyer, Miller, Metzger, & Borkovec, 1990), which measures the participants' general tendency to worry. The self-report questionnaire includes 16 items that are rated on a 5-point Likert scale ranging from 1, "Not at all typical of me" to 5, "Very typical of me." Possible scores range from 16–80, with higher scores indicating higher worry. Items on the PSWQ measure aspects of worry such as rate, intrusiveness, and pervasiveness. The PSWQ has moderate to excellent psychometric properties across adult age groups (Crittendon & Hopko, 2006; Hopko et al., 2003). It has been shown to have strong internal consistency and adequate convergent validity in both young and older adult samples (Beck, Stanley, & Zebb, 1995) as well as samples with clinical anxiety disorders (Brown, Antony, & Barlow, 1992). It has also been shown to have clinical utility as screening measure for Generalized Anxiety Disorder (Fresco, Mennin, Heimberg, & Turk, 2003) and to be able to identify worry, over and above anxiety and depression (Meyer et al., 1990).

Statistical Analyses

Dependent variables of interest were highly correlated (see Table 2 below for correlations between COLT free and cued recall measures, and PSWQ scores), thus, multivariate analyses of covariance (MANCOVA) were conducted to determine the effect of age (young, older), ApoE ϵ 4 status (negative, positive), PSWQ scores, and all 2-way interaction terms (Age*ApoE, Age*PSWQ, ApoE*PSWQ) on COLT recall memory measures. Two separate MANCOVA's were conducted, one to examine effects on the free odor recall memory dependent variable (i.e., short and long delay free recall) and a second to examine effects on the cued odor recall memory dependent variable (i.e., short and long delay cued recall).

In all cases, Box's Test indicated that the assumption of homogeneity of covariance matrices across groups was met. Follow-up analyses were conducted using univariate analysis of variance tests. To protect the family-wise p-value of .05, a p-value of .025 (.05/# of DVs) was used to determine significance of univariate post-hoc tests. Levene's test indicated the homogeneity of variance assumption was met for each DV. Analyses were performed with SPSS statistical software, version 18.0 (SPSS Inc., Chicago, IL).

Results

Participant Characteristics

Demographic and clinical characteristics are listed in Table 1. All adults scored within the normal range on self report measures of depression and global cognitive function. No significant age or ApoE group differences in odor threshold, MMSE, BDI-II, DRS, and GDS scores were found (p 's > .05). Younger adults rated their current level of worry significantly higher than older adults, $F(3, 90) = 17.64, p < .001$. There was no significant effect of ApoE status on the PSWQ, $F(3, 90) = .001, p > .97$.

Free Odor Recall Memory

There were no significant effects of age or ApoE on free recall (p 's > .09). The main effect of PSWQ was significant, Wilks' $\Lambda = .90, F(2, 86) = 4.73, p = .01, \text{partial eta squared } (\eta^2) = .10$, observed power = .78. No significant two-way interactions were found (p 's > .15).

Follow-up univariate tests of significant multivariate effects indicated that the PSWQ had a significant effect on both short delay free recall, $F(1, 87) = 9.37, p = .003, \eta^2 = .10$, and long delay free recall, $F(1, 87) = 8.38, p = .005, \eta^2 = .09$ such that across age and ApoE groups, higher free recall scores were associated with higher PSWQ scores. In other words, higher self-reported worry was associated with more odors recalled on the free recall tasks.

Cued Odor Recall Memory

Results of the MANCOVA revealed significant main effects of the PSWQ [Wilks' $\Lambda = .85, F(2, 86) = 7.45, p = .001, \eta^2 = .15$], ApoE [Wilks' $\Lambda = .92, F(2, 86) = 3.79, p = .03, \eta^2 = .08$], and age [Wilks' $\Lambda = .93, F(2, 86) = 3.29, p = .04, \eta^2 = .07$] on cued recall. These main effects were qualified by a significant ApoE*PSWQ interaction [Wilks' $\Lambda = .91, F(2, 86) = 4.32, p = .016, \eta^2 = .09$], and a significant age*ApoE interaction [Wilks' $\Lambda = .86, F(2, 86) = 7.19, p = .001, \eta^2 = .14$]. The age*PSWQ interaction was not significant ($p > .24$).

Follow-up testing revealed that the PSWQ had a significant main effect on both short delay cued recall, $F(1, 87) = 15.08, p < .001, \eta^2 = .15$, and long delay cued recall, $F(1, 87) = 12.46, p = .001, \eta^2 = .13$, such that across age and ApoE groups, higher cued recall scores were associated with higher PSWQ scores (i.e., higher self-reported worry).

ApoE also had a significant main effect for both short delay cued recall, $F(1, 87) = 7.64, p = .007, \eta^2 = .08$, and long delay cued recall, $F(1, 87) = 6.68, p < .05, \eta^2 = .07$, such that across age and controlling for PSWQ, $\epsilon 4$ negative adults recalled significantly fewer odors during cued recall than $\epsilon 4$ positive adults (short delay: $M = 3.71$ vs 7.49 ; long delay: $M = 3.85$ vs 7.66).

The main effect of age was only significant for long delay cued recall, $F(1, 87) = 5.17, p = .025, \eta^2 = .06$, (short delay cued recall: $p > .11$). Young adults recalled significantly more odors than older adults ($M = 7.40$ vs 4.10), across ApoE groups and controlling for PSWQ.

Univariate analysis of the ApoE*PSWQ interaction indicated that the effect was significant for both short delay cued recall, $F(1, 87) = 8.50, p = .005, \eta^2 = .09$, and long delay cued

recall, $F(1, 87) = 6.10, p = .015, \eta^2 = .07$ (See Figure 2). Results suggest that cued recall scores have a positive linear association with PSWQ scores in ApoE $\epsilon 4^-$ adults (i.e., higher cued recall scores are associated with higher PSWQ scores) whereas the relationship appeared quadratic in ApoE $\epsilon 4^+$ adults (i.e., lower cued recall scores are associated with low and high PSWQ scores whereas midrange PSWQ scores are associated with higher recall scores). For ease of interpretation, Figures 1 and 2 display the interaction effect with PSWQ categorized according to cutoffs suggested by Korte, Allan, & Schmidt (2016) to represent low, mid, and high levels of worry.

The age*ApoE interaction effect was also significant for both short delay cued recall, $F(1, 87) = 11.85, p = .001, \eta^2 = .12$, and long delay cued recall, $F(1, 87) = 6.13, p = .015, \eta^2 = .07$. One-way ANOVA's were conducted within age groups to examine simple effects of the age*ApoE interaction. However, simple effects of ApoE were not significant within young ($p > .08$) or older ($p > .12$) adults.

Discussion

This is the first study to report on the relationships among odor recall, worry, and ApoE $\epsilon 4$ status. While higher cued recall scores were associated with higher PSWQ worry scores among $\epsilon 4^-$ adults, the positive effect of worry on cued recall memory for odors diminished with high levels of worry among $\epsilon 4^+$ adults (see Figures 1 and 2). Moreover, those with the highest and lowest levels of worry in the $\epsilon 4^+$ group performed comparably low on the odor memory task whereas midrange worry levels were associated with better odor memory, consistent with a quadratic relationship. In contrast, higher worry was associated with better recall among $\epsilon 4^-$ noncarriers, indicating a linear relationship. This effect was found for both short and long delay *cued* recall scores whereas the effect was not significant for free recall scores. Notably, there were no ApoE group differences in PSWQ scores, thus, the significant interaction effect was not driven by group differences in worry.

The present findings are particularly interesting given known deficits in semantic categorization and the ability to use cues to aid recall in AD (Heindel, Salmon, & Butters, 1990). For example, fMRI studies have shown that sustained activity levels in the entorhinal cortex, one of the earliest locations to develop AD-neuropathology, are correlated with subsequent performance on a cued-recall task (Fernández, Brewer, Zhao, Glover, & Gabrieli, 1999). Research also supports utility of cued recall tests in distinguishing depression from MCI and early AD (Dierckx, Engelborghs, De Raedt, De Deyn, & Ponjaert-Kristoffersen, 2007; Vogel, Mortensen, Gade, & Waldemar, 2007), and in predicting conversion from MCI to AD (Dierckx et al., 2009).

There are several possible reasons that might explain the unique impact of worry and apoE on cued recall. A proposed mechanism of action for the expected findings is an overall reduction in neurological reserves as a result of compounding neurodegeneration in neural correlates of worry that overlap with olfactory processing pathways (Canteras, Resstel, Bertoglio, Carobrez, & Guimarães, 2010; Mah et al., 2016; Sapolsky, 1992). For example, hippocampal lesions have been shown to result in reduced levels of anxiety, and the ventral hippocampus has been particularly linked to anxiety-related behavior and cognition

(Bannerman et al., 2004). Effects of anxiety on cognitive functions outside of memory have also been found, with studies showing differences in prefrontal functioning and sustained attention abilities (Forster, Nunez Elizalde, Castle, & Bishop, 2015).

Notably, semantic clustering during encoding, as well as item-specific search during recall, is associated with activity in the prefrontal cortex (Long, Oztekin, & Badre, 2010). Cortical association areas in tempoparietal regions, as well as parahippocampal cortex may also be important for cued memory retrieval (Hayama, Vilberg, Rugg, 2012). Metabolic and functional differences have been observed between apoE $\epsilon 4+$ and $\epsilon 4-$ adults in these regions, and activity in these same regions in younger adults correlates with areas of atrophy in early stages of AD; all of which has led to the hypothesis that alterations in connectivity may create conditions that lead to age- and AD-related atrophy (Buckner et al., 2005; Machulda et al., 2011). Given that brain regions associated with anxiety and anxious responses overlap with these areas (Arnsten, 2009; Pardon & Rattray, 2008), we might speculate that individuals with high levels of worry may be primed to activate anxiety-related networks that are also associated with memory search. ApoE-related metabolic and functional differences within these networks could alter the effect of worry on performance.

Neuropsychological correlates are also important to consider. Previous research has reported impaired executive functioning performance associated with state-anxiety in ApoE- $\epsilon 4$ carriers (Stonnington, Locke, Dueck, & Caselli, 2011). Cued recall invokes executive functions via the use of memory strategy (categorical association), thus, the present findings of significant differences in scores on cued, but not free, recall in ApoE- $\epsilon 4$ carriers may be related to underlying relative differences in executive functioning. Future studies may wish to include measures of additional cognitive abilities (e.g. executive functions, attention, and working memory) in order to determine their influence on the relationship between worry and memory.

An unexpected finding that should be noted was the direction of the main effects for age on PSWQ scores was such that younger adults rated their current level of worry an average of eleven points *higher* than older adults. We speculate that this discrepancy could be understood under the rubric of the socioemotional selectivity theory, which suggests that there is a positivity bias in older adults whereby positive information is more likely to be attended to than negative information, (Carstensen et al., 2011; Lee & Knight, 2009). Some insight into this finding comes from research on stress showing that it can have paradoxical effects on performance, with the direction of the effect changing depending on type, timing, duration, and other factors of the stressor. Under low and high levels of stress, performance tends to be negatively affected; however, under moderate levels of stress, performance may be positively affected (Pardon, 2007). The findings in the present study may be reflecting the positive portion of an underlying quadratic relationship whereby performance is enhanced as worry increases from low to moderate levels, but impaired as worry increases from moderate to high levels.

The lack of an effect of ApoE- $\epsilon 4$ carrier status on free recall of odors is also worthy of discussion given previous findings showing declines in performance on a number of olfactory tasks in those with the $\epsilon 4$ allele. Whereas impairments on odor identification tasks

among ApoE $\epsilon 4$ carriers have been well-documented in the extant literature, the relationship between ApoE $\epsilon 4$ status and recall of odors is less well-studied (for review see Albers et al., 2015 and Murphy, 2018). One possible explanation for the current findings is that the exclusion of individuals with anosmia or severe hyposmia may have inadvertently excluded individuals with underlying $\epsilon 4$ -related pathology. However, complete loss of olfactory function is not typical of preclinical AD, and declines in odor detection (i.e., such as those resulting in hyposmia or anosmia) have been found to occur later than declines in higher-order olfactory processing such as odor identification (Calhoun-Haney & Murphy, 2005); thus, it is not likely that excluding individuals with severe olfactory impairment fully explains the present findings. Performance on free recall tasks can be affected by multiple factors in addition to impaired memory processes, including use of an inefficient memory strategy or impaired attentional processes, and with regards to the current findings this increased variability could have made it more difficult to detect group differences with regard to ApoE $\epsilon 4$ if they existed. Consequently, cued recall tasks that provide a memory strategy scaffolding (i.e., semantic cues) are thought to be better indicators of impaired memory processes, and have been found to be better than free recall at discriminating older adults with dementia from older adults without dementia (Grober & Buschke, 1987). The current findings revealed impaired cued but not free recall among ApoE $\epsilon 4$ carriers, which might suggest that ApoE $\epsilon 4$ carriers may be less able to benefit from the provision of semantic cues, perhaps due to pathology in prefrontal cortex as described earlier. It is also interesting that among the younger adults in the current sample, the trend for ApoE $\epsilon 4$ carriers to perform better than $\epsilon 4$ noncarriers at cued recall of odors approached ($p > .08$), though it did not reach, significance. See Table 1. Mondadori et al. (2007) reported similar findings with regard to verbal episodic memory. Across a series of experiments, the authors found that young $\epsilon 4$ carriers demonstrated better episodic memory performance than $\epsilon 4$ noncarriers, and that $\epsilon 4$ carriers recruited fewer neural resources during the learning and retrieval process even when participants were matched by performance. The authors hypothesized that cellular processes associated with ApoE $\epsilon 4$ that are beneficial to learning and memory early in life may contribute to neuronal damage later in life or be negated by the development of amyloid plaques and neurofibrillary tangles in middle to old age (Mondadori et al, 2007).

Additionally, the finding that those with higher levels of worry have better odor free recall may be unexpected given previous findings of worse cognitive and functional outcomes among those with minimal or subclinical levels of worry. There is some evidence in the literature to support an enhancing effect of worry on performance. Beaudreau et al. (2017) found that elevated worry improved performance on tests of cognitive control and delayed verbal memory in older adults with anxiety or depression; however, this effect was only found among participants with high levels of depressive symptoms, which would not be consistent with the current findings given low depressive symptoms in the current sample. The processing efficiency theory of anxiety (Eysenck & Calvo, 1992) may provide additional insight into these findings. According to the processing efficiency theory, worry interferes with memory processes by consuming attentional resources necessary for holding information in working memory. If attentional resources are not depleted, some individuals may be able to compensate and continue to perform effectively, but with reduced efficiency.

On the other hand, if attentional resources are depleted, performance effectiveness will be impaired. With regards to the current findings, $\epsilon 4$ carriers may be more vulnerable to the negative effect of worry on attentional resources whereas $\epsilon 4$ noncarriers may be better able to recruit additional cognitive resources to maintain or improve performance effectiveness, albeit at reduced efficiency. Such an explanation could explain lower olfactory recall scores among $\epsilon 4$ noncarriers compared to carriers at higher levels of worry (see Figures 1 and 2). The findings of Mondadori et al. (2007) as described above seem to lend some support to this hypothesis, but future studies of worry that include brain imaging methods to compare brain activity between $\epsilon 4$ carriers and noncarriers during olfactory learning and memory tasks are needed to test this hypothesis.

As in all studies several limitations should be noted. In particular, the study was cross-sectional and thus causality cannot be determined. Additionally, the sample included a relatively small number of participants who reported high levels of worry and did not include objective measures of worry or anxiety beyond self-report. Thus, further research including longitudinal data and samples with clinical levels of worry and other symptoms of anxiety measured using a variety of measures (e.g., objective, observational, in vivo) are warranted. However, a notable strength of the current study was the use of a novel and comprehensive odor learning and memory test (i.e., the COLT). While the COLT does not have published reliability and validity information available, a number of olfactory tasks have been shown to be sensitive in detecting neurodegenerative declines, and thus the present results may be particularly helpful in elucidating the role of anxiety and stress-related factors, like worry, on cognitive declines in devastating conditions like AD.

Strikingly, the performance deficits associated with having an $\epsilon 4$ allele and high worry were not only present in older adults, but also were evident in adults below the age of 30 years old. Given that apoE groups did not differ with regard to level of worry, it is plausible that pathological differences among apoE $\epsilon 4$ carriers may affect brain regions that are associated with both memory and worry (e.g., hippocampus, prefrontal cortices), and that these differences may be evident on olfactory testing as early as young adulthood. Given that apoE $\epsilon 4$ carrier status and olfactory declines are associated with increased risk for AD, the present findings also add to evidence that cognitive deficits related to worry levels might compound deficits related to AD pathology. If this mechanism is supported, it suggests that there may be the potential to reduce risk of developing cognitive impairment in those with genetic risk for AD by intervening to reduce worry in those who report chronically high levels of worry.

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References

- Albers MW, Gilmore GC, Kaye J, Murphy C, Wingfield A, Bennett DA...Zang LI (2015). At the interface of sensory and motor dysfunctions and Alzheimer's disease. *Alzheimer's & Dementia*, 11, 70–98.
- American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.
- Bannerman DM, Rawlins JNP, McHugh SB, Deacon RMJ, Yee BK, Bast T, ... Feldon J (2004). Regional dissociations within the hippocampus--memory and anxiety. *Neuroscience and Biobehavioral Reviews*, 28(3), 273–283. 10.1016/j.neubiorev.2004.03.004 [PubMed: 15225971]
- Beaudreau SA, Hantke NC, Mashal N, Gould CE, Henderson VW, and O'Hara R (2017). Unlocking neurocognitive substrates of late-life affective symptoms using the Research Domain Criteria: Worry is an essential dimension. *Frontiers in Aging Neuroscience*, 9, 380. [PubMed: 29249958]
- Beck JG, Stanley MA, & Zebb BJ (1995). Psychometric properties of the Penn State Worry Questionnaire in older adults. *Journal of Clinical Geropsychology*, 1(1), 33–42.
- Beck AT, Steer RA, & Brown GK (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.
- Behar E, Alcaine O, Zuellig AR, Borkovec TD (2003). Screening for generalized anxiety disorder using the Penn State Worry Questionnaire: a receiver operating characteristic analysis. *Journal of Behavior Therapy and Experimental Psychiatry*, 34, 25–43. [PubMed: 12763391]
- Bekris LM, Yu C-E, Bird TD, & Tsuang DW (2010). Genetics of Alzheimer disease. *Journal of Geriatric Psychiatry and Neurology*, 23(4), 213–227. 10.1177/0891988710383571 [PubMed: 21045163]
- Benarroch EE (2010). Olfactory system: functional organization and involvement in neurodegenerative disease. *Neurology*, 75(12), 1104–1109. 10.1212/WNL.0b013e3181f3db84 [PubMed: 20855854]
- Bird TD (2008). Genetic aspects of Alzheimer disease. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, 10(4), 231–239. 10.1097/GIM.0b013e31816b64dc [PubMed: 18414205]
- Braak H, & Braak E (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica*, 82(4), 239–259. 10.1007/BF00308809 [PubMed: 1759558]
- Braam AW, Copeland JRM, Delespaul PAEG, Beekman ATF, Como A, Dewey M, ... Skoog I (2014). Depression, subthreshold depression and comorbid anxiety symptoms in older Europeans: results from the EURODEP concerted action. *Journal of Affective Disorders*, 155, 266–272. 10.1016/j.jad.2013.11.011 [PubMed: 24355647]
- Brown TA, Antony MM, & Barlow DH (1992). Psychometric properties of the Penn State Worry Questionnaire in a clinical anxiety disorders sample. *Behaviour Research and Therapy*, 30(1), 33–37. [PubMed: 1540110]
- Calhoun-Haney R, & Murphy C (2005). Apolipoprotein epsilon4 is associated with more rapid decline in odor identification than in odor threshold or Dementia Rating Scale scores. *Brain and Cognition*, 58(2), 178–182. 10.1016/j.bandc.2004.10.004 [PubMed: 15919549]
- Canteras NS, Resstel LB, Bertoglio LJ, Carobrez A. de P., & Guimarães FS (2010). Neuroanatomy of anxiety. *Current Topics in Behavioral Neurosciences*, 2, 77–96. [PubMed: 21309107]
- Caselli RJ, Reiman EM, Hentz JG, Osborne D, & Alexander GE (2004). A distinctive interaction between chronic anxiety and problem solving in asymptomatic APOE e4 homozygotes. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 16(3), 320–329. 10.1176/jnp.16.3.320 [PubMed: 15377739]
- Cerf-Ducastel B, Haase L, & Murphy C (2012). Effect of Magnitude Estimation of Pleasantness and Intensity on fMRI Activation to Taste. *Chemosensory Perception*, 5(1), 100–109. 10.1007/s12078-011-9109-1 [PubMed: 23227271]
- Cerf-Ducastel B, & Murphy C (2001). fMRI activation in response to odorants orally delivered in aqueous solutions. *Chemical Senses*, 26(6), 625–637. [PubMed: 11473928]
- Christen-Zaech S, Kraftsik R, Pillevuit O, Kiraly M, Martins R, Khalili K, & Miklossy J (2003). Early olfactory involvement in Alzheimer's disease. *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques*, 30(1), 20–25. [PubMed: 12619779]

- Cortese BM, Leslie K, & Uhde TW (2015). Differential odor sensitivity in PTSD: Implications for treatment and future research. *Journal of Affective Disorders*, 179, 23–30. 10.1016/j.jad.2015.03.026 [PubMed: 25845746]
- Crittendon J, & Hopko DR (2006). Assessing worry in older and younger adults: Psychometric properties of an abbreviated Penn State Worry Questionnaire (PSWQ-A). *Journal of Anxiety Disorders*, 20(8), 1036–1054. 10.1016/j.janxdis.2005.11.006 [PubMed: 16387472]
- Delis DC, Kramer JH, Kaplan EF, & Ober BA (1987). California verbal learning test. San Antonio TX: The Psychological Corporation.
- Dierckx E, Engelborghs S, De Raedt R, De Deyn PP, & Ponjaert-Kristoffersen I (2007). Differentiation between mild cognitive impairment, Alzheimer's disease and depression by means of cued recall. *Psychological Medicine*, 37(5), 747–755. 10.1017/S003329170600955X [PubMed: 17164030]
- Dierckx E, Engelborghs S, De Raedt R, Van Buggenhout M, De Deyn PP, Verté D, & Ponjaert-Kristoffersen I (2009). Verbal cued recall as a predictor of conversion to Alzheimer's disease in mild cognitive impairment. *International Journal of Geriatric Psychiatry*, 24(10), 1094–1100. 10.1002/gps.2228 [PubMed: 19280679]
- Djordjevic J, Jones-Gotman M, De Sousa K, & Chertkow H (2008). Olfaction in patients with mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*, 29(5), 693–706. 10.1016/j.neurobiolaging.2006.11.014 [PubMed: 17207898]
- Eysenck MW, & Calvo MG (1992). Anxiety and performance: The processing efficiency theory. *Cognition and Emotion*, 6, 409–434.
- Fernández G, Brewer JB, Zhao Z, Glover GH, & Gabrieli JD (1999). Level of sustained entorhinal activity at study correlates with subsequent cued-recall performance: a functional magnetic resonance imaging study with high acquisition rate. *Hippocampus*, 9(1), 35–44. 10.1002/(SICI)1098-1063(1999)9:1<35::AID-HIPO4>3.0.CO;2-Z [PubMed: 10088898]
- Finkel D, Reynolds CA, Larsson M, Gatz M, & Pedersen NL (2011). Both odor identification and ApoE-ε4 contribute to normative cognitive aging. *Psychology and Aging*, 26(4), 872–883. 10.1037/a0023371 [PubMed: 21517181]
- Folstein MF, Folstein SE, & McHugh PR (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3), 189–198. [PubMed: 1202204]
- Forster S, Nunez Elizalde AO, Castle E, & Bishop SJ (2015). Unraveling the anxious mind: anxiety, worry, and frontal engagement in sustained attention versus off-task processing. *Cerebral Cortex* (New York, N.Y.: 1991), 25(3), 609–618. 10.1093/cercor/bht248
- Frasnelli J, Lundström JN, Boyle JA, Djordjevic J, Zatorre RJ, & Jones-Gotman M (2010). Neuroanatomical correlates of olfactory performance. *Experimental Brain Research*, 201(1), 1–11. 10.1007/s00221-009-1999-7 [PubMed: 19730837]
- Fresco DM, Mennin DS, Heimberg RG, & Turk CL (2003). Using the Penn State Worry Questionnaire to identify individuals with generalized anxiety disorder: a receiver operating characteristic analysis. *Journal of Behavior Therapy and Experimental Psychiatry*, 34(3–4), 283–291. 10.1016/j.jbtep.2003.09.001 [PubMed: 14972674]
- Galliot E, Comte A, Magnin E, Tatu L, Moulin T, & Millot J-L (2013). Effects of an ambient odor on brain activations during episodic retrieval of objects. *Brain Imaging and Behavior*, 7(2), 213–219. 10.1007/s11682-012-9218-8 [PubMed: 23292620]
- Gilbert PE, & Murphy C (2004). The effect of the ApoE epsilon4 allele on recognition memory for olfactory and visual stimuli in patients with pathologically confirmed Alzheimer's disease, probable Alzheimer's disease, and healthy elderly controls. *Journal of Clinical and Experimental Neuropsychology*, 26(6), 779–794. 10.1080/13803390490509439 [PubMed: 15370375]
- Grober E, & Buschke H (1987). Genuine memory deficits in dementia. *Developmental Neuropsychology*, 3, 13–36.
- Haase L, Wang M, Green E, & Murphy C (2013). Functional connectivity during recognition memory in individuals genetically at risk for Alzheimer's disease. *Human Brain Mapping*, 34(3), 530–542. [PubMed: 22102296]

- Heindel WC, Salmon DP, & Butters N (1990). Pictorial priming and cued recall in Alzheimer's and Huntington's disease. *Brain and Cognition*, 13(2), 282–295. 10.1016/0278-2626(90)90053-Q [PubMed: 2143907]
- Holmes SE, Esterlis I, Mazure CM, Lim YY, Ames D, Rainey-Smith S, ... Australian Imaging, Biomarkers, Lifestyle Research Group. (2016). β -Amyloid, APOE and BDNF Genotype, and Depressive and Anxiety Symptoms in Cognitively Normal Older Women and Men. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, 24(12), 1191–1195. 10.1016/j.jagp.2016.08.007 [PubMed: 27742526]
- Hopko DR, Stanley MA, Reas DL, Wetherell JL, Beck JG, Novy DM, & Averill PM (2003). Assessing worry in older adults: confirmatory factor analysis of the Penn State Worry Questionnaire and psychometric properties of an abbreviated model. *Psychological Assessment*, 15(2), 173–183. [PubMed: 12847777]
- Insel T, Cuthbert B, Garvey M, Heinseen R, Pine DS, Quinn K, ... Wang P (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, 167, 748–51. [PubMed: 20595427]
- Josefsson M, Larsson M, Nordin S, Adolfsson R, & Olofsson J (2017). APOE- ϵ 4 effects on longitudinal decline in olfactory and non-olfactory cognitive abilities in middle-aged and old adults. *Scientific Reports*, 7(1), 1286 10.1038/s41598-017-01508-7 [PubMed: 28455505]
- Korte KJ, Allan NP, & Schmidt NB (2016). Factor mixture modeling of the Penn State Worry Questionnaire: Evidence for distinct classes of worry. *Journal of Anxiety Disorders*, 37, 40–47. 10.1016/j.janxdis.2015.11.001 [PubMed: 26615330]
- Larsson M, Hedner M, Papenberg G, Seubert J, Bäckman L, & Laukka EJ (2016). Olfactory memory in the old and very old: Relations to episodic and semantic memory and APOE genotype. *Neurobiology of Aging*, 38, 118–126. 10.1016/j.neurobiolaging.2015.11.012 [PubMed: 26827650]
- Lee BK, Glass TA, Wand GS, McAtee MJ, Bandeen-Roche K, Bolla KI, & Schwartz BS (2008). Apolipoprotein E Genotype, Cortisol, and Cognitive Function in Community-Dwelling Older Adults. *American Journal of Psychiatry*, 165(11), 1456–1464. 10.1176/appi.ajp.2008.07091532 [PubMed: 18593777]
- Lee LO, & Knight BG (2009). Attentional bias for threat in older adults: moderation of the positivity bias by trait anxiety and stimulus modality. *Psychology and Aging*, 24(3), 741–747. 10.1037/a0016409 [PubMed: 19739931]
- Lehn H, Kjørnigsen LJ, Kjølvik G, & Håberg AK (2013). Hippocampal involvement in retrieval of odor vs. object memories. *Hippocampus*, 23(2), 122–128. 10.1002/hipo.22073 [PubMed: 22996310]
- Lehrner J, Pusswald G, Gleiss A, Auff E, & Dal-Bianco P (2009). Odor identification and self-reported olfactory functioning in patients with subtypes of mild cognitive impairment. *The Clinical Neuropsychologist*, 23(5), 818–830. 10.1080/13854040802585030 [PubMed: 19214830]
- Levy DA, Manns JR, Hopkins RO, Gold JJ, & Squire LR (2003). Impaired visual and odor recognition memory span in patients with hippocampal lesions. *Learning & Memory*, 10(6), 531–536. 10.1101/lm.66703 [PubMed: 14657265]
- Lucas JA, Ivnik RJ, Smith GE, Bohac DL, Tangalos EG, Kokmen E, ... Petersen RC (1998). Normative data for the Mattis Dementia Rating Scale. *Journal of Clinical and Experimental Neuropsychology*, 20(4), 536–547. 10.1076/jcen.20.4.536.1469 [PubMed: 9892057]
- Mah L, Szabuniewicz C, & Fiocco AJ (2016). Can anxiety damage the brain? *Current Opinion in Psychiatry*, 29(1), 56–63. 10.1097/YCO.0000000000000223 [PubMed: 26651008]
- Meyer TJ, Miller ML, Metzger RL, & Borkovec TD (1990). Development and validation of the Penn State Worry Questionnaire. *Behaviour Research and Therapy*, 28(6), 487–495. [PubMed: 2076086]
- Mondadori CR, de Quervain DJ, Buchmann A, Mustovic H, Wollmer MA, Schmidt CF, ... Henke K (2007). Better memory and neural efficiency in young apolipoprotein E epsilon 4 carriers. *Cerebral Cortex*, 17, 1934–47. [PubMed: 17077159]
- Murphy C (2018, in press) Olfactory and other sensory impairments in Alzheimer's disease. *Nature Reviews Neurology*.
- Murphy C, Cerf-Ducastel B, Calhoun-Haney R, Gilbert PE, & Ferdon S (2005). ERP, fMRI and functional connectivity studies of brain response to odor in normal aging and Alzheimer's disease. *Chemical Senses*, 30 Suppl 1, i170–171. 10.1093/chemse/bjh168 [PubMed: 15738097]

- Murphy C, Gilmore MM, Seery CS, Salmon DP, & Lasker BR (1990). Olfactory thresholds are associated with degree of dementia in Alzheimer's disease. *Neurobiology of Aging*, 11(4), 465–469. [PubMed: 2381506]
- Murphy C, Nordin S, & Acosta L (1997). Odor learning, recall, and recognition memory in young and elderly adults. *Neuropsychology*, 11(1), 126–137. 10.1037/0894-4105.11.1.126 [PubMed: 9055276]
- Olofsson JK, Josefsson M, Ekström I, Wilson D, Nyberg L, Nordin S, ... Larsson M (2016). Long-term episodic memory decline is associated with olfactory deficits only in carriers of ApoE-ε4. *Neuropsychologia*, 85, 1–9. 10.1016/j.neuropsychologia.2016.03.004
- Ottaviani C, Thayer JF, Verkuil B, Lonigro A, Medea B, Couyoumdjian A, & Brosschot JF (2016). Physiological concomitants of perseverative cognition: A systematic review and meta-analysis. *Psychol Bull*, 142, 231–59. doi: 10.1037/bul0000036 [PubMed: 26689087]
- Ottaviano G, Frasson G, Nardello E, & Martini A (2016). Olfaction deterioration in cognitive disorders in the elderly. *Aging Clinical and Experimental Research*, 28(1), 37–45. 10.1007/s40520-015-0380-x [PubMed: 26003671]
- Palmer K, Berger AK, Monastero R, Winblad B, Bäckman L, & Fratiglioni L (2007). Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology*, 68(19), 1596–1602. 10.1212/01.wnl.0000260968.92345.3f [PubMed: 17485646]
- Pardon M-C (2007). Stress and ageing interactions: a paradox in the context of shared etiological and physiopathological processes. *Brain Research Reviews*, 54(2), 251–273. 10.1016/j.brainresrev.2007.02.007 [PubMed: 17408561]
- Peavy GM, Lange KL, Salmon DP, Patterson TL, Goldman S, Gamst AC, ... Galasko D (2007). The Effects of Prolonged Stress and APOE Genotype on Memory and Cortisol in Older Adults. *Biological Psychiatry*, 62(5), 472–478. 10.1016/j.biopsych.2007.03.013 [PubMed: 17544378]
- Pietrzak RH, Maruff P, Woodward M, Fredrickson J, Fredrickson A, Krystal JH, ... Darby D (2012). Mild worry symptoms predict decline in learning and memory in healthy older adults: A 2-year prospective cohort study. *The American Journal of Geriatric Psychiatry*, 20(3), 266–275. 10.1097/JGP.0b013e3182107e24 [PubMed: 22354117]
- Quarmley M, Moberg PJ, Mechanic-Hamilton D, Kabadi S, Arnold SE, Wolk DA, & Roalf DR (2017). Odor Identification Screening Improves Diagnostic Classification in Incipient Alzheimer's Disease. *Journal of Alzheimer's Disease: JAD*, 55(4), 1497–1507. 10.3233/JAD-160842 [PubMed: 27886011]
- Ruscio AM, Seitchik AE, Gentes EL, Jones JD, & Hallion LS (2011). Perseverative thought: A robust predictor of response to emotional challenge in Generalized Anxiety Disorder and Major Depressive Disorder. *Behaviour Research and Therapy*, 49, 867–74. [PubMed: 22030295]
- Saive A-L, Royet J-P, Ravel N, Thévenet M, Garcia S, & Plailly J (2014). A unique memory process modulated by emotion underpins successful odor recognition and episodic retrieval in humans. *Frontiers in Behavioral Neuroscience*, 8 Retrieved from <http://search.proquest.com/docview/1650980713?accountid=14524>
- Sapolsky RM (1992). *Stress, the aging brain, and the mechanisms of neuron death*. Cambridge, MA: The MIT Press.
- Schubert CR, Carmichael LL, Murphy C, Klein BEK, Klein R, & Cruickshanks KJ (2008). Olfaction and the 5-year incidence of cognitive impairment in an epidemiological study of older adults. *Journal of the American Geriatrics Society*, 56(8), 1517–1521. 10.1111/j.1532-5415.2008.01826.x [PubMed: 18662205]
- Smitka M, Puschmann S, Buschhueter D, Gerber JC, Witt M, Honeycutt N, ... Hummel T (2012). Is there a correlation between hippocampus and amygdala volume and olfactory function in healthy subjects? *NeuroImage*, 59(2), 1052–1057. 10.1016/j.neuroimage.2011.09.024 [PubMed: 21967725]
- Soudry Y, Lemogne C, Malinvaud D, Consoli S-M, & Bonfils P (2011). Olfactory system and emotion: common substrates. *European Annals of Otorhinolaryngology, Head and Neck Diseases*, 128(1), 18–23. 10.1016/j.anorl.2010.09.007

- Sullivan RM, Wilson DA, Ravel N, & Mouly A-M (2015). Olfactory memory networks: From emotional learning to social behaviors. *Frontiers in Behavioral Neuroscience*, 9 Retrieved from <http://search.proquest.com/docview/1692394721?accountid=14524>
- Vogel A, Mortensen EL, Gade A, & Waldemar G (2007). The Category Cued Recall test in very mild Alzheimer's disease: Discriminative validity and correlation with semantic memory functions. *European Journal of Neurology*, 14(1), 102–108. 10.1111/j.1468-1331.2006.01568.x [PubMed: 17222122]
- Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, & Leirer VO (1982). Development and validation of a geriatric depression screening scale: a preliminary report. *Journal of Psychiatric Research*, 17(1), 37–49. [PubMed: 7183759]

Figure 1.
Bar graph depicting the relationship between Penn State Worry Questionnaire and Short Delay Cued Recall Score within ApoE groups, collapsed across age.

Figure 2.
Bar graph depicting the relationship between Penn State Worry Questionnaire and Long Delay Cued Recall Score within ApoE groups, collapsed across age.

Table 1

Means (standard error) for demographic variables, psychophysical tests, self-report measures and the California Odor Learning Test (COLT) outcome variables by Apolipoprotein E (ApoE) ε4 genotype, age, and in total.

	Young		Older		Young (n = 53)	Older (n = 45)	Total (n = 98)
	ε4- (n = 32)	ε4+ (n = 21)	ε4- (n = 23)	ε4+ (n = 18)			
Age	19.7 (0.33)	21.9 (0.68)	72.7 (1.41)	73.8 (1.14)	20.6 (0.37)	72.5 (0.91)	44.4 (2.67)
Education	13.4 (0.29)	14.9 (0.41)	15.7 (0.69)	15.3 (0.71)	14.0 (0.26)	15.5 (0.49)	14.5 (0.27)
Odor threshold	6.9 (0.20)	6.8 (0.27)	6.2 (0.27)	6.8 (0.36)	6.9 (0.16)	6.4 (0.23)	6.6 (0.14)
PSWQ	41.4 (2.70)	42.3 (2.57)	30.8 (2.25)	30.1 (2.76)	41.7 (1.91)	33.3 (2.08)	37.9 (1.46)
Short Delay Free Recall	5.8 (0.44)	7.1 (0.45)	4.3 (0.47)	4.3 (0.60)	6.3 (0.33)	4.1 (0.35)	5.3 (0.26)
Short Delay Cued Recall	5.8 (0.41)	6.9 (0.43)	4.7 (0.48)	3.7 (0.48)	6.2 (0.31)	4.2 (0.33)	5.3 (0.25)
Long Delay Free Recall	6.5 (0.44)	7.5 (0.50)	4.7 (0.50)	4.6 (0.58)	6.9 (0.34)	4.5 (0.36)	5.80 (0.27)
Long Delay Cued Recall	6.1 (0.43)	7.2 (0.44)	4.5 (0.50)	4.1 (0.54)	6.6 (0.32)	4.2 (0.35)	5.5 (0.27)

Note. PSWQ = Penn State Worry Questionnaire.

Table 2.

Pearson's correlations between scores on the California Odor Learning Test (COLT) outcome variables and the Penn State Worry Questionnaire (PSWQ).

	1	2	3	4	5	6
Total Sample						
1. PSWQ	--					
2. Immediate Recall	.23 *	--				
3. Short Free Recall	.28 *	.89 **	--			
4. Short Cued Recall	.31 **	.85 **	.83 **	--		
5. Long Free Recall	.25 *	.92 **	.91 **	.87 **	--	
6. Long Cued Recall	.26 *	.90 **	.87 **	.93 **	.92 **	--
Young ApoE-e4 Positive						
1. PSWQ	--					
2. Immediate Recall	.00	--				
3. Short Free Recall	.01	.95 **	--			
4. Short Cued Recall	-.16	.87 **	.85 **	--		
5. Long Free Recall	-.05	.92 **	.92 **	.85 **	--	
6. Long Cued Recall	-.23	.92 **	.91 **	.94 **	.90 **	--
Young ApoE-e4 Negative						
1. PSWQ	--					
2. Immediate Recall	.35 *	--				
3. Short Free Recall	.44 *	.87 **	--			
4. Short Cued Recall	.55 *	.82 **	.85 **	--		
5. Long Free Recall	.47 **	.87 **	.92 **	.89 **	--	
6. Long Cued Recall	.44 *	.82 **	.86 **	.91 **	.89 **	--
Old ApoE-e4 Positive						
1. PSWQ	--					
2. Immediate Recall	-.06	--				
3. Short Free Recall	.05	.88 **	--			
4. Short Cued Recall	-.04	.76 **	.75 **	--		
5. Long Free Recall	-.02	.95 **	.89 **	.86 **	--	
6. Long Cued Recall	.10	.90 **	.85 **	.90 **	.92 **	--
Old ApoE-e4 Negative						
1. PSWQ	--					
2. Immediate Recall	.40	--				
3. Short Free Recall	.39	.80 **	--			
4. Short Cued Recall	.40	.89 **	.75 **	--		
5. Long Free Recall	.31	.90 **	.82 **	.87 **	--	

	1	2	3	4	5	6
6. Long Cued Recall	.42 *	.90 **	.71 **	.94 **	.90 **	--

Note. ApoE = Apolipoprotein E; PSWQ = Penn State Worry Questionnaire.

*
p < .05.

**
p < .001.

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