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Sex-Based Memory Advantages and Cognitive Aging: A Challenge to the Cognitive Reserve Construct?

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Abstract

Education and related proxies for cognitive reserve (CR) are confounded by associations with environmental factors that correlate with cerebrovascular disease possibly explaining discrepancies between studies examining their relationships to cognitive aging and dementia. In contrast, sex-related memory differences may be a better proxy. Since they arise developmentally, they are less likely to reflect environmental confounds. Women outperform men on verbal and men generally outperform women on visuospatial memory tasks. Furthermore, memory declines during the preclinical stage of AD, when it is clinically indistinguishable from normal aging. To determine whether CR mitigates age-related memory decline, we examined the effects of gender and APOE genotype on longitudinal memory performances. Memory decline was assessed in a cohort of healthy men and women enriched for APOE $\epsilon 4$ who completed two verbal [Rey Auditory Verbal Learning Test (AVLT), Buschke Selective Reminding Test (SRT)] and two visuospatial [Rey-Osterrieth Complex Figure Test (CFT), and Benton Visual Retention Test (VRT)] memory tests, as well as in a separate larger and older cohort [National Alzheimer's Coordinating Center (NACC)] who completed a verbal memory test (Logical Memory). Age-related memory decline was accelerated in APOE $\epsilon 4$ carriers on all verbal memory measures (AVLT, $p = .03$; SRT $p < .001$; logical memory $p < .001$) and on the VRT $p = .006$. Baseline sex associated differences were retained over time, but no sex differences in rate of decline were found for any measure in either cohort. Sex-based memory advantage does not mitigate age-related memory decline in either APOE $\epsilon 4$ carriers or non-carriers.

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Supplementary material

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Keywords

Aging; Preclinical Alzheimer's disease; Mild cognitive impairment; Memory; Sex and cognition; APOE

INTRODUCTION

Focal brain lesions reliably produce characteristic syndromes, yet variability in initial symptoms and ultimate outcomes have long challenged the notion that all brains are created perfectly equal (Mohr, 2004). Applied to dementia, it has similarly been observed that seemingly equivalent neuropathological severity does not necessarily yield equivalent clinical severity. To explain this apparent inconsistency, Katzman introduced the concept of “brain reserve” based upon physical parameters such as brain weight and neuronal size (Katzman et al., 1988). The concept of cognitive reserve (CR) as formulated by Stern and colleagues in 1999 proceeded from the observation that the rate at which patients with Alzheimer's disease (AD) declined on the selective reminding test (SRT) reflected their educational and occupational background (Stern, Albert, Tang, & Tsai, 1999). When matched for dementia severity, patients with higher CR harbored greater pathology (as measured by regional cerebral blood flow) than patients with lower CR arguing that CR mitigated the clinical impact of AD pathology (Scarmeas et al., 2003). Since these relatively early descriptions, investigators have sought to isolate the effects of intellectual and related forms of brain activity that most closely reflect CR from the quantifiable material properties of brain reserve such as brain size, disease susceptibility, and active compensatory mechanisms such as the ability to recruit new brain circuits into the service of damaged ones (Barulli & Stern, 2013; Stern, 2012).

Either in isolation or in various combinations, years of education (most frequently), linguistic skill, intellectually stimulating leisure activity, social engagement, socioeconomic status, occupational complexity, measures of crystallized intelligence, literacy (Barulli & Stern, 2013; Bennett, Arnold, Valenzuela, Brayne, & Schneider, 2014), bilingualism (Craik, Bialystok, & Freedman, 2010), and musical background (Gooding, Abner, Jicha, Kryscio, & Schmitt, 2013) have all been used as proxies for CR, yet all are associated with advantageous environmental factors such as housing, nutrition, access to healthcare, educational opportunities, and cultural resources possibly explaining discrepancies between studies examining their relationships to cognitive aging, incident MCI, incident dementia, rate of decline, mortality, and neuropathology (Sanders, Hall, Katz, & Lipton, 2012; Van Gerven, Van Boxtel, Aulsems, Bekers, & Jolles, 2012; Zahodne et al., 2011; Zahodne, Schofield, Farrell, Stern, & Manly, 2014). Indeed, cerebral amyloid burden has been shown to be diminishing over the course of the twentieth century without any consideration of CR presumably reflecting progress in health and hygiene more generally (Kovari, Herrmann, Bouras, & Gold, 2014). Despite a wealth of studies, there remains therefore, continued uncertainty regarding the significance of CR: is it a purely passive neuropsychological construct in which intellectually advantaged people simply have further to fall before crossing a fixed threshold that defines impairment, or is there evidence that CR confers

active neurobiological protection against AD, transforming itself into a form of acquired brain reserve?

To address this question, a more ideal proxy for CR should have a minimum of potential confounds, should directly reflect cognition, and should be sensitive to the earliest stages of AD. A potential category of proxies meeting these criteria are sex-related memory differences. At a group level, women outperform men on verbal memory tasks (Bleecker, Bolla-Wilson, Agnew, & Meyers, 1988; Kramer & Daniel, 1988; Ruff, Light, & Quayhagen, 1989) and while the data are less consistent, men outperform women on visuospatial tasks generally (Beatty & Troster, 1987; Coltheart, Hull, & Slater, 1975) including some memory tasks (Beinhoff, Tumani, Brettschneider, Bittner, & Riepe, 2008; Orsini et al., 1986; Postma, Izendoorn, & De Haan, 1998; Vecchi & Girelli, 1998). The female advantage for episodic memory has been shown to persist into old age (Beinhoff et al., 2008; Chapman et al., 2011; Gerstorff, Herlitz, & Smith, 2006). Presumably, because these emerge as a function of human development, they are likely less susceptible (but probably not immune) to environmental confounds than all of the previously cited proxies.

Both verbal and visuospatial memory decline during the preclinical stage of AD in apolipoprotein E (APOE) $\epsilon 4$ carriers, earlier than all other cognitive domains (Caselli et al., 2014), including executive skills (Caselli, Dueck, Locke, Hoffman-Snyder, et al., 2011), when such decline may be clinically undetectable and hence indistinguishable from normal aging. Pettigrew et al. found, in a cohort of 227 cognitively normal individuals whose mean age was 57 years that CR and APOE $\epsilon 4$ acted independently with CR reducing risk by 50% in both $\epsilon 4$ carriers and non-carriers while $\epsilon 4$ increased risk by 150%. APOE $\epsilon 2$ interacted with CR so that CR was more protective in non-carriers (Pettigrew et al., 2013). Furthermore, just as APOE $\epsilon 4$ has been correlated with worse outcomes following head trauma and cerebrovascular disease (Caselli, Dueck, Locke, Sabbagh, et al., 2011), so too has APOE been found to interact with physical measures of brain reserve such as head circumference such that physical factors which predispose to cognitive decline have a greater impact in $\epsilon 4$ carriers (Borenstein Graves et al., 2001; Kim et al., 2008).

We, therefore, hypothesized that if CR indeed prevented or reduced the rate of age-related decline, independent of confounding environmental factors, then women should have slower verbal memory decline than men and men slower visual memory decline than women, and such effects might be further influenced by APOE genotype. To determine whether superior memory performance confers neuroprotection against age-related memory decline, we therefore examined whether age-related memory decline was reduced in the advantaged sex.

METHODS

Study Participants

Arizona APOE cohort—We used the Arizona APOE Cohort to test the hypothesis that the advantaged sex would decline less quickly, so that women would decline more slowly than men on verbal memory measures and men more slowly on visual memory measures. From January 1, 1994, through December 31, 2009, cognitively normal residents of Maricopa County age 21 years and older were recruited through local media ads and

underwent APOE genotyping and longitudinal neuropsychological assessment every 2 years. All individuals gave their written, informed consent to participate in the study and have the results of the APOE test withheld from them which was approved by the Mayo Clinic Institutional Review Board. Determination of APOE genotype was performed using Taqman Single Nucleotide Polymorphism assays (Crook, Hardy, & Duff, 1994).

All identified $\epsilon 4$ homozygotes (HMZ) were matched by age, sex, and education to one $\epsilon 4$ heterozygote (HTZ; all with the $\epsilon 3/4$ genotype) and two $\epsilon 4$ non-carriers. Many additional heterozygous persons and non-carriers who were otherwise eligible for enrollment were also recruited. Each participant had screening tests that included a neurological examination, the Folstein Mini-Mental Status Exam (MMSE), Hamilton Depression (Ham-D) Rating Scale, Functional Activities Questionnaire (FAQ), Instrumental Activities of Daily Living (IADL), and Structured Clinical Interview for DSM-IV. We excluded anyone with potentially confounding medical, neurologic, or psychiatric problems. None met published criteria for mild cognitive impairment (MCI) (Petersen et al., 2001), AD (McKhann et al., 1984), or other forms of dementia or major depressive disorder (American Psychiatric Association, 1994). Entry criteria included scores of at least 27 on the MMSE (with at least 1 of 3 on the recall subtest), 10 or less on the Ham-D, and perfect scores on the FAQ and IADL. Data were reviewed at each visit by a neurologist (RJC) and neuropsychologist (DECL) for indications of cognitive impairment, and anyone who developed MCI or dementia during the course of follow-up was excluded from this analysis to avoid skewing the results by a small number of individuals with a more precipitous decline. This resulted in 621 subjects with the following APOE genotypes: $\epsilon 4/4$ $n = 71$, $\epsilon 3/4$ $n = 194$, $\epsilon 3/3$ $n = 317$, $\epsilon 2/3$ $n = 39$.

National Alzheimer's Coordinating Committee (NACC) cohort—The National Institute on Aging (NIA) Alzheimer's Disease Center program contains a central repository of neuro-psychological data obtained at each center available to investigators. We included participants who were normal at entry and remained normal through their most recent follow-up visit. We sought to test our findings from the APOE cohort in this much larger cohort, and so examined the effect of sex on decline on a verbal memory measure involving paragraph recall (Wechsler Memory Scale Logical Memory) that is included in the NACC Uniform Data Set (Weintraub et al., 2009). There were 4575 subjects with the following APOE genotypes: $\epsilon 4/4$ $n = 106$, $\epsilon 3/4$ $n = 1075$, $\epsilon 2/4$ $n = 115$, $\epsilon 3/3$ $n = 2687$, $\epsilon 2/3$ $n = 563$, and $\epsilon 2/2$ $n = 29$.

Neuropsychological testing—We have previously shown that memory is the earliest cognitive domain to decline in healthy appearing APOE $\epsilon 4$ carriers heralding the neuropsychological onset of preclinical AD (Caselli et al., 2009), and subsequently confirmed its greater sensitivity than executive skills (Caselli, Dueck, Locke, Hoffman-Snyder, et al., 2011). Within the context of a previously described comprehensive neuropsychological battery, all APOE cohort participants completed the following four memory measures [two verbal memory and two visuospatial memory tests (Lezak, Howieson, & Loring, 2004)] selected for this study that we have shown are highly sensitive to age-related memory decline; and three of the four are additionally sensitive to APOE $\epsilon 4$ related accelerated decline (Caselli et al., 2014):

Rey Auditory Verbal Learning Test (AVLT): A 15-word list is presented over 5 learning trials followed by a distractor list, a short delay recall trial and a long (30 min) delay recall trial [long term memory (LTM)]. The LTM measure was used for an outcome measure.

Buschke Selective Reminding Test (SRT): A 16-item list of unrelated words pictorially represented and presented over 5 learning trials. Every trial involves selectively presenting cues for those items that were not freely recalled. After a 30-min delay, a free recall and cued recall trial is again administered. Total items recalled without cuing (total free recall) during learning and recall trials was used for an outcome measure.

Rey-Osterrieth Complex Figure Test (CFT): Participants are given up to 10 min to copy a complex 2-dimensional abstract figure, and then are prompted without forewarning to draw it from memory after a 10-min delay. The delayed recall score was used for an outcome measure. This was the only 1 of the 4 measures that did not show a significant APOE ε4 effect, but did show a baseline sex difference.

Benton Visual Retention Test (VRT): Ten relatively simple abstract line drawings are shown to the participant for 10 s each after which they are removed and the participant must draw what they saw. Number correct out of 10 was used for an outcome measure. This was the only 1 of the 4 measures that did not show a baseline sex difference, but it did show an APOE ε4 effect.

Data analysis—To isolate the longitudinal cognitive change for our neuropsychological measures in these cross-sectional and longitudinal samples, we used a quadratic mixed model to gauge change in performance over time and to compare the effect of APOE ε4 status between men and women. The longitudinal growth model used in the current analysis is the same as a previously used model (Caselli, Dueck, Locke, Sabbagh, et al., 2011), replacing the binary cardiovascular risk factor with sex. This mixed model approach isolates the longitudinal effect of age on AVLT-LTM (or other neuropsychological test) in a cross-sectional and longitudinal sample (Fitzmaurice, Laird, & Ware, 2004; Ware et al., 1990) and allows for comparison of the mean annual change in AVLT-LTM within non-carriers between men and women; within carriers between men and women; and a comparison of the longitudinal sex effect between non-carriers and carriers.

The model for Y_{ij} (the j^{th} response for the i^{th} individual) is as follows:

$$\begin{aligned} E(Y_{ij}|b_{1i}) = & \beta_1 + \beta_2 \text{Carrier}_i + \beta_3 \text{Sex}_i + \beta_4 \text{Agec}_{i1} + \\ & \beta_5 \text{Carrier}_i \times \text{Agec}_{i1} + \beta_6 \text{Sex}_i \times \text{Agec}_{i1} + \beta_7 \text{Carrier}_i \times \text{Sex}_i + \\ & \beta_8 \text{Carrier}_i \times \text{Sex}_i \times \text{Agec}_{i1} + \beta_9 \text{Agec}_{i1}^2 + \beta_{10} \text{Carrier}_i \times \text{Agec}_{i1}^2 + \\ & \beta_{11} \text{Agec}_{ij} + \beta_{12} \text{Carrier}_i \times \text{Agec}_{ij} + \beta_{13} \text{Sex}_i \times \text{Agec}_{ij} + \\ & \beta_{14} \text{Carrier}_i \times \text{Sex}_i \times \text{Agec}_{ij} + \beta_{15} \text{Agec}_{ij}^2 + \beta_{16} \text{Carrier}_i \times \text{Agec}_{ij}^2 + b_{1i}, \end{aligned}$$

where Carrier_i is the APOE ε4 carrier status for the i^{th} individual (1 = Carrier; 0 = Non-carrier); Sex_i is the sex for the i^{th} individual (1 = Female; 0 = Male); Agec_{ij} is the age minus 60 (i.e., centered age) of the i^{th} individual at the time of the j^{th} response; and b_{1i} is an

individual specific random effect allowing each subject to have a different intercept. Age is centered to reduce the correlation between the age and age-squared terms. In previous work (Caselli et al., 2009), we found that APOE $\epsilon 4$ carrier status impacted AVLT-LTM at a quadratic level, so quadratic terms for APOE $\epsilon 4$ carrier status are included in all models.

From this cross-sectional and longitudinal model, the longitudinal models for male and female non-carriers are given by:

$$\text{Male: } E(Y_{ij} - Y_{i1}) = \beta_{11}(Agec_{ij} - Agec_{i1}) + \beta_{15}(Agec_{ij}^2 - Agec_{i1}^2),$$

$$\text{Female: } E(Y_{ij} - Y_{i1}) = (\beta_{11} + \beta_{13})(Agec_{ij} - Agec_{i1}) + \beta_{15}(Agec_{ij}^2 - Agec_{i1}^2),$$

and the longitudinal models for male and female carriers are given by:

$$\text{Male: } E(Y_{ij} - Y_{i1}) = (\beta_{11} + \beta_{12})(Agec_{ij} - Agec_{i1}) + (\beta_{15} + \beta_{16})(Agec_{ij}^2 - Agec_{i1}^2),$$

$$\text{Female: } E(Y_{ij} - Y_{i1}) = (\beta_{11} + \beta_{12} + \beta_{13} + \beta_{14})(Agec_{ij} - Agec_{i1}) + (\beta_{15} + \beta_{16})(Agec_{ij}^2 - Agec_{i1}^2).$$

From these longitudinal models, the mean annual change can be estimated based on the following first-order derivatives:

$$\text{Male non-carrier: } dE(Y_{ij} - Y_{i1}) / dAgec_{ij} = \beta_{11} + 2\beta_{15}Agec_{ij},$$

$$\text{Female non-carrier: } dE(Y_{ij} - Y_{i1}) / dAgec_{ij} = \beta_{11} + \beta_{13} + 2\beta_{15}Agec_{ij},$$

$$\text{Male carrier: } dE(Y_{ij} - Y_{i1}) / dAgec_{ij} = \beta_{11} + \beta_{12} + 2(\beta_{15} + \beta_{16})Agec_{ij},$$

$$\text{Female carrier: } dE(Y_{ij} - Y_{i1}) / dAgec_{ij} = \beta_{11} + \beta_{12} + \beta_{13} + \beta_{14} + 2(\beta_{15} + \beta_{16})Agec_{ij}.$$

From these first-order derivatives, the estimate of β_{13} with confidence interval was used to assess the difference in mean annual change in AVLT-LTM between men and women within non-carriers; and the estimate of $\beta_{13} + \beta_{14}$ with confidence interval was used to assess the difference in mean annual change in AVLT-LTM between men and women within carriers. A test of significance of β_{14} was used to assess whether the impact of sex differed between carriers and non-carriers. Given imbalance in baseline covariates between groups, sensitivity analyses incorporate additional baseline covariates (education for the Arizona APOE and NACC cohorts, family history for the NACC cohort only). Modeling was carried out using SAS PROC MIXED (SAS Version 9). Baseline characteristics were compared between groups by using the two-sample *t* test or Pearson chi-square test. Analyses were carried out separately for the APOE cohort and the NACC cohort.

RESULTS

There were 434 women and 187 men from the Arizona APOE Cohort who were included in this study. Another 20 were excluded due to incident MCI or dementia during follow-up testing. Entry data are summarized in Table 1.

Men were moderately older (mean 58.6 vs. 55.8 years, $p = .005$), had an additional year of education (mean 16.2 vs. 15.3 years, $p < .001$), and a higher proportion had multiple epochs of testing (83.4% vs. 74.9%, $p = .02$) but were similar with regard to APOE $\epsilon 4$ carrier status (41.7% vs. 42.7% carriers, $p = .75$), family history of dementia in a first-degree relative (62.6% vs. 65.3%, $p = .51$), and duration of follow-up (6.3 vs. 6.3 years, $p = .92$). At entry, there were no significant differences between APOE $\epsilon 4$ carriers and non-carriers on any memory measure overall or within gender subgroups (supplementary e-table one), but women scored higher than men on both verbal memory tests, and men scored higher than women on 1 of 2 visuospatial memory tests, CFT-recall. Entry advantages on neuropsychological measures were retained throughout follow-up and at all ages.

Age-related memory decline was accelerated in APOE $\epsilon 4$ carriers on both verbal memory measures (AVLT-LTM, $p = .03$; SRT-free recall $p < .001$), as well as on one visuospatial memory measure (VRT $p = .006$), but not on the CFT-recall ($p = .39$). See supplementary e-table two for beta coefficients and standard errors from the mixed model of each outcome. Table 2 summarizes the predicted annual change in men and women at ages 50, 60, and 70 years by APOE $\epsilon 4$ status.

No sex differences between non-carriers and carriers in rate of decline (linear effects) were found for any measure: AVLT-LTM $p = .89$, SRT-free recall $p = .84$, CFT-recall $p = .17$, VRT $p = .49$, and correcting for educational differences did not affect these results. Figure one illustrates the trajectories for the AVLT and shows that while there is a visually evident difference between APOE $\epsilon 4$ carriers and non-carriers, the sex trajectories parallel each other reflecting the absence of sex-related effects on the rates of decline.

There were 3105 women and 1470 men from the NACC cohort who were included. Entry data are summarized in Table 3.

Men were slightly older than women (mean 71.4 vs. 70.5 years; $p = .007$), had more years of education (mean 16.4 vs. 15.4; $p < .001$), and fewer had a first degree relative with dementia (52.8% vs. 57.7%; $p = .002$). APOE $\epsilon 4$ carrier status (28.3% vs. 28.3%; $p = .98$) and mean years of follow-up (3.9 vs. 3.9; $p = .27$) did not differ between the groups. At entry, women scored higher than men on both immediate (mean 14.3 vs. 13.5; $p < .001$) and delayed (13.1 vs. 12.2; $p < .001$) recall scores on the Wechsler Memory Scale-Revised logical memory paragraph recall test, but longitudinally there was no sex difference between non-carriers and carriers in rate of decline (linear effects) on either measure (immediate memory, $p = .21$, delayed memory $p = .95$; see supplementary e-table three for beta coefficients and standard errors from the mixed model of each outcome). Correcting for educational and family history differences did not affect these results. Predicted annual change in men and women at ages 50, 60, and 70 years did not differ when APOE $\epsilon 4$ carriers and non-carriers were considered separately (Table 4).

DISCUSSION

Despite robust APOE $\epsilon 4$ effects on age-related cognitive decline evident on three of four memory measures in the APOE Cohort in quadratic effects (which are more demanding), no similar sex-related effects were found for any measure, including the SRT which was the cornerstone test of Stern's 1999 CR concept (Stern et al., 1999), even in less demanding linear effects. Entry performance advantages were maintained throughout the study at all ages, but there was no indication that such an advantage influenced the rate of decline in the cohort overall or in either APOE $\epsilon 4$ carriers or non-carriers in either cohort. While we cannot completely exclude the possibility of a very subtle effect that our study was not powered to detect, any such effect would be much weaker than the observed APOE $\epsilon 4$ effect (and notably, unlike sex, there was no APOE related advantage at entry).

The sources of sex-related differences in memory are not well understood, and there are multiple conflicting claims with regard to anatomical and physiological differences between male and female brains (Wallentin, 2009). Physiological differences emerge early in life. An event-related potential study in children aged 7–10 years found that developmental changes in basic auditory processing occurred earlier and faster in girls (Nanova, Lyamova, Hadjigeorgieva, Kolev, & Yordanova, 2008). MRI studies of amygdalo-hippocampal growth from infancy through early adulthood have shown that the female amygdala reaches its peak age a year and a half earlier than the male amygdala, and that there is a rightward laterality in the male amygdala (Uematsu et al., 2012). In a functional magnetic resonance imaging (MRI) paradigm, men outperformed women on a spatial navigation task during which they showed larger activation of the right hippocampus relative to women, and when required to indicate the direction of their point of origin on this task, women showed a larger left-sided activation than men, possibly reflecting a bias toward using a verbal mediation strategy (Persson et al., 2013). A consistent finding in multiple studies, in addition to the modestly larger size of the brain in men, is that the anterior cingulate cortex of women is larger than that of men (Chen, Sachdev, Wen, & Anstey, 2007; Good et al., 2001; Paus et al., 1996). Anterior cingulate lesions in patients have been associated with reduced responsiveness ranging from abulia to akinetic mutism (Jurgens & von Cramon, 1982; Laplane, Degos, Baulac, & Gray, 1981; Nemeth, Hegedus, & Molnar, 1988), and anatomically restricted anterior cingulate lesions in primates result in drastically reduced phonation (Sutton, Trachy, & Lindeman, 1981).

Despite the predominant genetic influence on brain development, significant environmentally-influenced differences in cerebral anatomy are evident in cortical thickness, particularly in the heteromodal sensory parietal lobes of adolescent identical twins (Yang et al., 2012), in the arcuate fasciculus of twins discordant for handedness (Haberling, Badzakova-Trajkov, & Corballis, 2013), and in the degree of neurogenesis and exploratory behavior in genetically identical mice (Freund et al., 2013). In each of these cases, sensory stimulation appears to be a key factor. The theory that CR could reflect alterations in the brain's biology, therefore, has a sound neurobiological basis. Achievement and even simply exposure to intellectual and socially engaging stimuli may facilitate more synapses resulting in a larger neuronal ensemble for a given cognitive operation (the larger the target, the more pathology needed to disable it), greater flexibility for alternate networks to assist or replace

the declining function within a damaged network, and more efficient integration so that reduced neuronal activity would generate less Abeta amyloid (Jagust & Mormino, 2011). However, all of these mechanisms may be biologically innate adaptive processes that are not further influenced by “high normal” degrees of environmental stimulation, at least during the course of normal aging and the presymptomatic stages of AD. That is not to say that intellectual advantage, maintaining social activity or achieving greater socioeconomic status does not confer a myriad of benefits, or that frank abuses such as sensory deprivation, cultural impoverishment, disease, and trauma might not harm our brain and diminish our cognitive ability and potential. But if intellectual and related activities enhance CR through physiological or anatomical changes, then it is unclear why sex-related cognitive advantages despite sharing such properties, do not seem to mitigate age-related memory decline even in $\epsilon 4$ carriers who are more susceptible to preclinical AD.

Bennett and colleagues recently reviewed the relationship of environmental stimuli to neuropathological outcomes and showed that effects were largely confined to cerebrovascular pathology (Bennett et al., 2014). If the main effect of environmental stimuli is to reduce cerebrovascular pathology, then might improved cerebrovascular physiology result in improved cognition? Cortical thickness is itself influenced by vascular physiology and mediates the effect of beta-amyloid on memory (Villeneuve et al., 2014). Yet, interventional restoration of blood flow in patients with symptomatic internal carotid artery occlusion that improves oxygen extraction on positron emission tomography does not result in improved cognition (Marshall et al., 2014). Bennett et al. noted 2 exceptions to the finding that CR was related primarily to cerebrovascular pathology: early adult linguistic ability in the Nun study correlated specifically with AD late in life [in women (Snowdon et al., 1996)] and a composite measure comprised of education, occupation, and social engagement (Valenzuela, Brayne, Sachdev, Wilcock, & Matthews, 2011) correlated with greater brain weight, higher prefrontal neuronal density and gray matter thickness (again in women). While both findings are encouraging, both await replication in different patient populations. Once neuropathological burden is excluded, Wilson et al. found that, among members of the Rush Memory and Aging Project whose mean age at death was over 89 years old, a comprehensive measure of intellectual and socially relevant activities during the early, middle, and later stages of life accounted for 14% of the remaining variance in late life cognitive decline, showing that even though this measure of CR did not impact neuropathology it nonetheless did impact cognition (Wilson et al., 2013).

Diagnostic constructs of MCI and dementia are anchored to a threshold of performance that dichotomizes into normal or not, and if the threshold is held constant for all, regardless of premorbid intellectual ability, then it is easy to see how CR, as a passive neuropsychological construct (Stern, 2002), would prolong the time needed for someone with high CR to cross the threshold relative to someone with low CR without necessarily suggesting anything further about neurobio-logical protection against AD. In this case, simply raising the bar for the intellectually advantaged might diminish or even completely erase such an apparent CR effect. Clinically this makes sense since high functioning individuals presenting with subjective cognitive impairment may fail to cross a fixed threshold for defining impairment even when checked a year or two later, but the degree of interval decline itself may exceed what one expects in a healthy individual. Determining what constitutes pathological decline

remains an area of inquiry, but it is clear that domain specific decline, especially memory, correlates with both APOE $\epsilon 4$ carrier status and clinical outcomes (Caselli et al., 2007; Caselli, Chen, Lee, Alexander, & Reiman, 2008). As a passive neuropsychological phenomenon, CR could still have implications for clinical diagnosis. Petersen and colleagues reported that both the incidence (Roberts et al., 2012) and prevalence (Petersen et al., 2010) of MCI was higher among men than women in Olmsted County even though the same was not true for dementia prevalence (Roberts et al., 2012) suggesting that men cross the diagnostic threshold sooner even if fewer go on to develop dementia. Verbal memory measures are used more often than visuospatial memory measures especially in office-based mental status paradigms and men will cross the diagnostic verbal memory threshold sooner than women possibly helping to explain this seeming paradox. Among men and women dying with actual dementia, however, controlling for dementia severity, men show greater levels of pathology at autopsy (Barnes et al., 2005) suggesting women manifest dementia more readily than men. Conceivably there are further CR related effects once memory decline reaches severity levels of frank impairment that might not be evident within the milder spectrum of cognitive aging. If so, it may even be possible that CR effects increase in parallel with disease severity.

A limitation of this study is the possibility that it was underpowered to detect a smaller effect on memory decline, but if such an effect exists, it is clearly less than the APOE $\epsilon 4$ effect that was readily apparent in the Arizona APOE Cohort. In the NACC cohort, the logical memory paragraph recall test may be less sensitive to decline but a recent report showing greater incident MCI conversion in female $\epsilon 4$ carriers in this cohort (Altmann, Tian, Henderson, & Greicius, 2014) is at least suggestive that insensitivity was not a major concern, and the much larger number of participants allays concern that our study was simply underpowered. In addition, we did not analyze the possible influence of estrogen exposure, but the Women's Health Initiative recently reported no significant effect on cognitive function in postmenopausal women (Espeland et al., 2013) making this an unlikely source of error. A third limitation is that neither of our cohorts was community based. There was an over-representation of women, participants with a family history of dementia, and a more limited range of educational backgrounds that were generally higher than average so that we cannot assume our findings would equally apply to poorly educated men, for example. Finally, our study focused on age-related memory decline, but the distinction between healthy aging and preclinical AD is blurred by the fact that age-related cognitive decline is itself associated with a variety of chronic medical conditions including degenerative, vascular, and inflammatory processes among others (DeJager et al., 2012), and by the fact that APOE $\epsilon 4$ may be a risk factor both for AD itself as well as for cognitive aging in the absence of AD (Davies et al., 2014).

In conclusion, sex-associated intellectual advantage on a memory test was retained throughout adulthood, and while we cannot exclude the possibility of an effect during the ninth and tenth decades of life, or after the onset of clinically significant cognitive impairment, there was otherwise no evident effect on the rate of decline associated with age in either APOE $\epsilon 4$ non-carriers or carriers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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REFERENCES

- Altmann A, Tian L, Henderson VW, Greicius MD. Sex modifies the APOE-related risk of developing Alzheimer disease. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Annals of Neurology*. 2014; 75(4):563–573. [PubMed: 24623176]
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV [Internet]. 4th 1994. p. 886 Retrieved from: <http://www.psychiatryonline.com/DSMPDF/dsm-iv.pdf>
- Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA. Sex differences in the clinical manifestations of Alzheimer disease pathology. *Archives of General Psychiatry*. 2005; 62(6):685–691. [PubMed: 15939846]
- Barulli D, Stern Y. Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. [Research Support, N.I.H., Extramural Review]. *Trends in Cognitive Sciences*. 2013; 17(10):502–509. [PubMed: 24018144]
- Beatty WW, Troster AI. Gender differences in geographical knowledge. *Sex Roles*. 1987; 16(11–12): 565–590.
- Beinhoff U, Tumani H, Bretschneider J, Bittner D, Riepe MW. Gender-specificities in Alzheimer's disease and mild cognitive impairment. *Journal of Neurology*. 2008; 255(1):117–122. [PubMed: 18202815]
- Bennett DA, Arnold SE, Valenzuela MJ, Brayne C, Schneider JA. Cognitive and social lifestyle: Links with neuropathology and cognition in late life. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Acta Neuropathologica*. 2014; 127(1):137–150. [PubMed: 24356982]
- Bleecker ML, Bolla-Wilson K, Agnew J, Meyers DA. Age-related sex differences in verbal memory. [Research Support, U.S. Gov't, P.H.S.]. *Journal of Clinical Psychology*. 1988; 44(3):403–411. [PubMed: 3384968]
- Borenstein Graves A, Mortimer JA, Bowen JD, McCormick WC, McCurry SM, Schellenberg GD, Larson EB. Head circumference and incident Alzheimer's disease: modification by apolipoprotein E. *Neurology*. 2001; 57(8):1453–1460. [PubMed: 11673588]
- Caselli RJ, Reiman EM, Locke DEC, Hutton ML, Hentz JG, Hoffman-Snyder C, Osborne D. Cognitive domain decline in healthy apolipoprotein E ϵ 4 homozygotes before the diagnosis of mild cognitive impairment. *Archives of Neurology*. 2007; 64(9):1306–1311. [PubMed: 17846270]
- Caselli RJ, Chen K, Lee W, Alexander GE, Reiman EM. Correlating cerebral hypometabolism with future memory decline in subsequent converters to amnesic pre-mild cognitive impairment. *Archives of Neurology*. 2008; 65(9):1231–1236. [PubMed: 18779428]
- Caselli RJ, Dueck AC, Osborne D, Sabbagh MN, Connor DJ, Ahern GL, Reiman EM. Longitudinal modeling of age-related memory decline and the APOE ϵ 4 effect. *New England Journal of Medicine*. 2009; 361:255–263. [PubMed: 19605830]

- Caselli RJ, Dueck AC, Locke DE, Hoffman-Snyder CR, Woodruff BK, Rapcsak SZ, Reiman EM. Longitudinal modeling of frontal cognition in APOE epsilon4 homozygotes, heterozygotes, and noncarriers. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Neurology*. 2011; 76(16):1383–1388. [PubMed: 21502596]
- Caselli RJ, Dueck AC, Locke DE, Sabbagh MN, Ahern GL, Rapcsak SZ, Reiman EM. Cerebrovascular risk factors and preclinical memory decline in healthy APOE ε4 homozygotes. *Neurology*. 2011; 76:1078–1084. [PubMed: 21325652]
- Caselli RJ, Locke DE, Dueck AC, Knopman DS, Woodruff BK, Hoffman-Snyder C, Reiman EM. The neuropsychology of normal aging and preclinical Alzheimer's disease. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Alzheimer's & dementia: the journal of the Alzheimer's Association*. 2014; 10(1):84–92.
- Chapman RM, Mapstone M, Gardner MN, Sandoval TC, McCrary JW, Guillilly MD, DeGrush E. Women have farther to fall: Gender differences between normal elderly and Alzheimer's disease in verbal memory engender better detection of Alzheimer's disease in women. *Journal of the International Neuropsychological Society*. 2011; 17:654–662. [PubMed: 21486518]
- Chen X, Sachdev PS, Wen W, Anstey KJ. Sex differences in regional gray matter in healthy individuals aged 44–48 years: A voxel-based morphometric study. *Neuroimage*. 2007; 36:691–699. [PubMed: 17499524]
- Coltheart M, Hull E, Slater D. Sex differences in imagery and reading. *Nature*. 1975; 253(5491):438–440. [PubMed: 1110788]
- Craik FI, Bialystok E, Freedman M. Delaying the onset of Alzheimer disease: Bilingualism as a form of cognitive reserve. [Comparative Study Research Support, Non-U.S. Gov't]. *Neurology*. 2010; 75(19):1726–1729. [PubMed: 21060095]
- Crook R, Hardy J, Duff K. Single-day apolipoprotein E genotyping. [Comparative Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Journal of Neuroscience Methods*. 1994; 53(2):125–127. [PubMed: 7823614]
- Davies G, Harris SE, Reynolds CA, Payton A, Knight HM, Liewald DC, Deary IJ. A genome-wide association study implicates the APOE locus in nonpathological cognitive ageing. *Molecular Psychiatry*. 2014; 19:76–87. [PubMed: 23207651]
- DeJager PL, Shulman, Chibnik JM, Keenan LB, Raj BT, Wilson T, Evans RSDA. A genome-wide scan for common variants affecting the rate of age-related cognitive decline. *Neurobiology of Aging*. 2012; 33:1017e1–1017e15.
- Espeland MA, Shumaker SA, Leng I, Manson JE, Brown CM, LeBlanc ES, Resnick SM. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. [Randomized Controlled Trial Research Support, N.I.H., Extramural]. *JAMA Internal Medicine*. 2013; 173(15):1429–1436. [PubMed: 23797469]
- Fitzmaurice, GM.; Laird, NM.; Ware, JH. *Applied longitudinal analysis (Section 15.4)*. Hoboken: John Wiley & Sons, Inc; 2004.
- Freund J, Brandmaier AM, Lewejohann L, Kirste I, Kritzler M, Kruger A, Kempermann G. Emergence of individuality in genetically identical mice. [Research Support, Non-U. S. Gov't]. *Science*. 2013; 340(6133):756–759. [PubMed: 23661762]
- Gerstorf D, Herlitz A, Smith J. Stability of sex differences in cognition in advanced old age: The role of education and attrition. *Journal of Gerontology Series B Psychological Sciences and Social Sciences*. 2006; 618:p245–P249.
- Good CD, Johnsrude I, Ashburner J, Henson RNA, Friston KJ, Frackowiak RSJ. Cerebral asymmetry and the effects of sex and handedness on brain structure: A voxel-based morphometric analysis of 465 normal adult human brains. *Neuroimage*. 2001; 14:685–700. [PubMed: 11506541]
- Gooding LF, Abner EL, Jicha GA, Kryscio RJ, Schmitt FA. Musical training and late-life cognition. *American Journal of Alzheimer's Disease and other Dementias*. 2013; 29(4):333–343.
- Haberling IS, Badzakova-Trajkov G, Corballis MC. Asymmetries of the arcuate fasciculus in monozygotic twins: Genetic and nongenetic influences. [Research Support, Non-U.S. Gov't Twin Study]. *PloS One*. 2013; 8(1):e52315. [PubMed: 23300971]

- Jagust WJ, Mormino EC. Lifespan brain activity, beta-amyloid, and Alzheimer's disease. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Trends in Cognitive Sciences*. 2011; 15(11):520–526. [PubMed: 21983147]
- Jurgens U, von Cramon D. On the role of the anterior cingulate cortex in phonation: A case report. *Brain and Language*. 1982; 15(2):234–248. [PubMed: 7074343]
- Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, Peck A. Clinical, pathological, and neurochemical changes in dementia: A subgroup with preserved mental status and numerous neocortical plaques. [Research Support, U.S. Gov't, P.H.S.]. *Annals of Neurology*. 1988; 23(2): 138–144. [PubMed: 2897823]
- Kim KR, Lee KS, Kim EA, Cheong HK, Oh BH, Hong CH. The effect of the ApoE genotype on the association between head circumference and cognition. *American Journal of Geriatric Psychiatry*. 2008; 16(10):819–825. [PubMed: 18827228]
- Kovari E, Herrmann FR, Bouras C, Gold G. Amyloid deposition is decreasing in aging brains: An autopsy study of 1,599 older people. *Neurology*. 2014; 82(4):326–331. [PubMed: 24363129]
- Kramer JHDCD, Daniel M. Sex differences in verbal learning. *Journal of Clinical Psychology*. 1988; 44(6):907–915.
- Laplane D, Degos JD, Baulac M, Gray F. Bilateral infarction of the anterior cingulate gyri and of the fornices. Report of a case. *Journal of Neurological Science*. 1981; 51(2):289–300.
- Lezak, MD.; Howieson, DB.; Loring, DW. *Neuro psychological assessment*. 4th. New York: Oxford University Press; 2004.
- Marshall RS, Festa JR, Cheung YK, Pavol MA, Derdeyn CP, Clarke WR, Lazar RM. Randomized Evaluation of Carotid Occlusion and Neurocognition (RECON) trial: Main results. [Clinical Trial, Phase III Comparative Study Randomized Controlled Trial Research Support, N.I.H., Extramural]. *Neurology*. 2014; 82(9):744–751. [PubMed: 24477109]
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. [Guideline Practice Guideline]. *Neurology*. 1984; 34(7):939–944. [PubMed: 6610841]
- Mohr JP. Historical observations on functional reorganization. [Editorial Historical Article]. *Cerebrovascular Diseases*. 2004; 18(3):258–259. [PubMed: 15331878]
- Nanova P, Lyamova L, Hadjigeorgieva M, Kolev V, Yordanova J. Gender-specific development of auditory information processing in children: An ERP study. [Research Support, Non-U.S. Gov't]. *Clinical Neurophysiology*. 2008; 119(9):1992–2003. [PubMed: 18579438]
- Nemeth G, Hegedus K, Molnar L. Akinetic mutism associated with bicingular lesions: Clinicopathological and functional anatomical correlates. *European Archives of Psychiatry and Neurological Science*. 1988; 237(4):218–222.
- Orsini A, Chiacchio L, Cinque M, Cocchiari C, Schiappa O, Grossi D. Effects of age, education and sex on two tests of immediate memory: A study of normal subjects from 20 to 99 years of age. [Research Support, Non-U.S. Gov't]. *Perceptual and Motor Skills*. 1986; 63(2 Pt 2):727–732. [PubMed: 3808855]
- Paus T, Otaky N, Caramanos Z, Macdonald D, Zigdenbos A, D'Avirro D, Evans AC. In vivo morphometry of the intrasulcal gray matter in the human cingulate, paracingulate, and superior-rostral sulci: Hemispheric asymmetries, gender differences and probability maps. *Journal of Comparative Neurology*. 1996; 376:664–673. [PubMed: 8978477]
- Persson J, Herlitz A, Engman J, Morell A, Sjolie D, Wikstrom J, Soderlund H. Remembering our origin: Gender differences in spatial memory are reflected in gender differences in hippocampal lateralization. [Research Support, Non-U.S. Gov't]. *Behavioural Brain Research*. 2013; 256:219–228. [PubMed: 23938766]
- Petersen RC, Roberts RO, Knopman DS, Geda YE, Cha RH, Pankratz VS, Rocca WA. Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Neurology*. 2010; 75(10):889–897. [PubMed: 20820000]
- Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review). Report of the

- Quality Standards Subcommittee of the American Academy of Neurology. [Guideline Practice Guideline]. *Neurology*. 2001; 56(9):1133–1142. [PubMed: 11342677]
- Pettigrew C, Soldan A, Li S, Wang MC, Selnes OA, Moghekar A, O'Brien R, Albert M. The Biocard Research Team. *Cognitive Neuroscience*. 2001; 4(3gray matter in healthy individuals aged 44–48 years: A voxel-based 4):136–142. [PubMed: 24168200]
- Postma A, Izendoorn R, De Haan EH. Sex differences in object location memory. [Clinical Trial Randomized Controlled Trial]. *Brain and Cognition*. 1998; 36(3):334–345. [PubMed: 9647682]
- Roberts RO, Geda YE, Knopman DS, Cha RH, Pankratz VS, Boeve BF, Petersen RC. The incidence of MCI differs by subtype and is higher in men: The Mayo Clinic Study of Aging. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Neurology*. 2012; 78(5):342–351. [PubMed: 22282647]
- Ruff RM, Light RH, Quayhagen M. Selective reminding tests: A normative study of verbal learning in adults. *Journal of Clinical and Experimental Neuropsychology*. 1989; 11(4):539–550. [PubMed: 2760186]
- Sanders AE, Hall CB, Katz MJ, Lipton RB. Non-native language use and risk of incident dementia in the elderly. [Research Support, N.I.H., Extramural]. *Journal of Alzheimer's Disease*. 2012; 29(1): 99–108.
- Scarmeas N, Zarahn E, Anderson KE, Habeck CG, Hilton J, Flynn J, Stern Y. Association of life activities with cerebral blood flow in Alzheimer disease: Implications for the cognitive reserve hypothesis. [Research Support, U.S. Gov't, P.H.S.]. *Archives of Neurology*. 2003; 60(3):359–365. [PubMed: 12633147]
- Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *JAMA*. 1996; 275(7):528–532. [PubMed: 8606473]
- Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. [Research Support, U.S. Gov't, P.H.S. Review]. *Journal of the International Neuropsychological Society*. 2002; 8(3):448–460. [PubMed: 11939702]
- Stern Y. Cognitive reserve in ageing and Alzheimer's disease. [Research Support, N.I.H., Extramural Review]. *The Lancet. Neurology*. 2012; 11(11):1006–1012. [PubMed: 23079557]
- Stern Y, Albert S, Tang MX, Tsai WY. Rate of memory decline in AD is related to education and occupation: Cognitive reserve? [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Neurology*. 1999; 53(9):1942–1947. [PubMed: 10599762]
- Sutton D, Trachy RE, Lindeman RC. Primate phonation: Unilateral and bilateral cingulate lesion effects. *Behavioral Brain Research*. 1981; 3(1):99–114.
- Uematsu A, Matsui M, Tanaka C, Takahashi T, Noguchi K, Suzuki M, Nishijo H. Developmental trajectories of amygdala and hippocampus from infancy to early adulthood in healthy individuals. [Research Support, Non-U.S. Gov't]. *PloS One*. 2012; 7(10):e46970. [PubMed: 23056545]
- Valenzuela M, Brayne C, Sachdev P, Wilcock G, Matthews F. Cognitive lifestyle and long-term risk of dementia and survival after diagnosis in a multicenter population-based cohort. [Multicenter Study Research Support, Non-U.S. Gov't]. *American Journal of Epidemiology*. 2011; 173(9): 1004–1012. [PubMed: 21378129]
- Van Gerven PW, Van Boxtel MP, Aulsems EE, Bekers O, Jolles J. Do apolipoprotein E genotype and educational attainment predict the rate of cognitive decline in normal aging? A 12-year follow-up of the Maastricht Aging Study. *Neuropsychology*. 2012; 26(4):459–472. [PubMed: 22642392]
- Vecchi T, Girelli L. Gender differences in visuo-spatial processing: The importance of distinguishing between passive storage and active manipulation. [Research Support, Non-U.S. Gov't]. *Acta Psychologica*. 1998; 99(1):1–16. [PubMed: 9664836]
- Villeneuve S, Reed BR, Wirth M, Haase CM, Madison CM, Ayakta N, Jagust WJ. Cortical thickness mediates the effect of beta-amyloid on episodic memory. [Research Support, N.I. H., Extramural Research Support, Non-U.S. Gov't]. *Neurology*. 2014; 82(9):761–767. [PubMed: 24489134]
- Wallentin M. Putative sex differences in verbal abilities and language cortex: A critical review. *Brain and Language*. 2009; 108:175–183. [PubMed: 18722007]

- Ware JH, Dockery DW, Louis TA, Xu XP, Ferris BG Jr, Speizer FE. Longitudinal and cross-sectional estimates of pulmonary function decline in never-smoking adults. *American Journal of Epidemiology*. 1990; 132(4):685–700. [PubMed: 2403109]
- Weintraub S, Salmon D, Mercaldo N, Ferris S, Graff-Radford NR, Chui H, Morris JC. The Alzheimer's Disease Centers' Uniform Data Set (UDS): The neuropsychologic test battery. [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Alzheimer Disease and Associated Disorders*. 2009; 23(2):91–101. [PubMed: 19474567]
- Wilson RS, Boyle PA, Yu L, Barnes LL, Schneider JA, Bennett DA. Life-span cognitive activity, neuropathologic burden, and cognitive aging. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Neurology*. 2013; 81(4):314–321. [PubMed: 23825173]
- Yang Y, Joshi AA, Joshi SH, Baker LA, Narr KL, Raine A, Damasio H. Genetic and environmental influences on cortical thickness among 14-year-old twins. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Twin Study]. *Neuroreport*. 2012; 23(12):702–706. [PubMed: 22713927]
- Zahodne LB, Glymour MM, Sparks C, Bontempo D, Dixon RA, MacDonald SW, Manly JJ. Education does not slow cognitive decline with aging: 12-year evidence from the victoria longitudinal study. [Research Support, N.I.H., Extramural]. *Journal of the International Neuropsychological Society*. 2011; 17(6):1039–1046. [PubMed: 21923980]
- Zahodne LB, Schofield PW, Farrell MT, Stern Y, Manly JJ. Bilingualism does not alter cognitive decline or dementia risk among Spanish-speaking immigrants. [Research Support, N.I.H., Extramural]. *Neuropsychology*. 2014; 28(2):238–246. [PubMed: 24188113]

Fig. 1.

The longitudinal trajectories for the Long Term Memory (LTM) score of the Auditory verbal memory Test (AVLT) shows that, while there is a visually evident difference between APOE ε4 carriers and non-carriers ($p = .03$), the sex trajectories parallel each other reflecting the absence of sex-related effects on the rates of decline ($p = .89$).

Table 1

Arizona APOE cohort entry data

	Female	Male	<i>p</i>
<i>N</i>	434	187	
Age in years, mean (<i>SD</i>)	55.8 (11.1)	58.6 (11.5)	.005
Education in years, mean (<i>SD</i>)	15.3 (2.3)	16.2 (2.5)	<.001
APOE e4 carriers, %	43.1%	41.7%	.75
First degree relative with dementia, %	65.3%	62.6%	.51
More than 1 epoch, %	74.9%	83.4%	.02
Study participation duration in years, mean (<i>SD</i>)	6.3 (3.2)	6.3 (3.1)	.92
AVLT-LTM, mean (<i>SD</i>)	9.9 (2.9)	7.7 (3.4)	<.001
SRT-free total, mean (<i>SD</i>)	89.7 (9.8)	81.2 (13.6)	<.001
CFT-recall, mean (<i>SD</i>)	17.3 (6.5)	19.0 (6.7)	.002
VRT, mean (<i>SD</i>)	6.9 (2.0)	6.9 (1.9)	.74

AVLT-LTM = Auditory Verbal Learning Test Long Term Memory; CFT = Complex Figure Test; SRT = Selective Reminding Test; VRT = Visual Retention Test; *SD* = standard deviation.

Table 2

Arizona APOE cohort predicted annual change

	Age 50		Age 60		Age 70		Difference ^b (F minus M)	95% CI
	F ^a	M ^a	F ^a	M ^a	F ^a	M ^a		
AVLT-LTM								
ε4+	.10	.05	-.02	-.07	-.14	-.19	.047	-.052 to .145
ε4-	.11	.11	.06	.06	.01	.02	-.006	-.006 to .079
SRT-free								
ε4+	.96	1.21	.12	.37	-.72	-.47	-.251	-.650 to .148
ε4-	1.04	1.08	.74	.77	.43	.46	-.035	-.384 to .314
CFT-recall								
ε4+	.37	.30	.13	.06	-.11	-.18	.075	-.130 to .281
ε4-	.40	.28	.22	.10	.05	-.08	.123	-.054 to .299
VRT								
ε4+	.04	-.02	-.04	-.10	-.12	-.18	.057	-.005 to .118
ε4-	-.00	.02	.02	-.00	-.04	-.02	-.019	-.072 to .034

^a Estimated mean annual change based on the mixed model in original units of the test. See supplementary material for equations and beta coefficients.^b Difference between the estimated mean annual change between males and females, based on the mixed model estimate of β_{13} for non-carriers and $\beta_{13} + \beta_{14}$ for carriers (see Supplementary Material).

Note, the difference estimate is indifferent to age (i.e., does not depend on the age at which the difference is estimated). AVLT-LTM = Auditory Verbal Learning Test Long Term Memory; CFT = Complex Figure Test; SRT = Selective Reminding Test; VRT = Visual Retention Test; F = female; M = male; CI = confidence interval

Table 3

NACC Cohort Entry Data

	Female	Male	<i>p</i>
<i>N</i>	3105	1470	
Age in years, mean (<i>SD</i>)	70.5 (10.3)	71.4 (10.0)	.007
Education in years, mean (<i>SD</i>)	15.4 (2.8)	16.4 (2.9)	<.001
APOE e4 carriers, %	28.3%	28.3%	.98
First degree relative with dementia, %	57.7%	52.8%	.002
More than 1 epoch, %	99.0%	99.3%	.33
Study participation duration in years, mean (<i>SD</i>)	3.9 (2.1)	3.9 (2.2)	.27
Logical memory-immediate recall, mean (<i>SD</i>)	14.3 (3.7)	13.5 (3.7)	<.001
Logical memory-delayed recall, mean (<i>SD</i>)	13.1 (4.0)	12.2 (4.0)	<.001

SD = standard deviation.

Table 4

NACC cohort predicted annual change

	Age 50		Age 60		Age 70		Age 80		Difference ^b (F minus M)	95% CI
	F ^a	M ^a	F ^a	M ^a	F ^a	M ^a	F ^a	M ^a		
Logical memory-immediate										
ε4+	.49	.52	.39	.43	.29	.33	.19	.23	-.037	-.109 to .035
ε4-	.55	.53	.45	.42	.34	.31	.24	.21	.028	-.016 to .071
Logical memory-delayed										
ε4+	.63	.67	.50	.54	.37	.41	.25	.29	-.040	-.114 to .035
ε4-	.69	.69	.55	.55	.42	.42	.29	.29	-.001	-.046 to .044

^a Estimated mean annual change based on the mixed model in original units of the test. See supplementary material for equations and beta coefficients.

^b Difference between the estimated mean annual change between males and females, based on the mixed model estimate of β_{13} for non-carriers and $\beta_{13} + \beta_{14}$ for carriers (see supplementary material).

Note, the difference estimate is indifferent to age (i.e., does not depend on the age at which the difference is estimated). F = female; M = male; CI = confidence interval.