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Paradoxical cognitive trajectories in men from earlier to later adulthood

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Declaration of Interest

L.K. McEvoy has stock options in CorTechs Laboratories, Inc. A.M. Dale is a founder of and holds equity in CorTechs Laboratories, Inc, and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc and receives funding through research agreements with General Electric Healthcare and Medtronic, Inc. The terms of these arrangements have been reviewed and approved by University of California, San Diego in accordance with conflict of interest policies. The author others report no conflicts.

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Abstract

Because longitudinal studies of aging typically lack cognitive data from earlier ages, it is unclear how general cognitive ability (GCA) changes throughout the life course. In 1,173 Vietnam Era Twin Study of Aging (VETSA) participants, we assessed young adult GCA at average age 20 and current GCA at three VETSA assessments beginning at average age 56. The same GCA index was used throughout. Higher young adult GCA and better GCA maintenance were associated with stronger specific cognitive abilities from age 51-73. Given equivalent GCA at age 56, individuals who had higher age 20 GCA outperformed those whose GCA remained stable in terms of memory, executive function, and working memory abilities from age 51-73. Thus, paradoxically, despite poorer maintenance of GCA, high young adult GCA still conferred benefits. Advanced predicted brain age and the combination of elevated vascular burden and *APOE*-ε4 status were associated with poorer maintenance of GCA. These findings highlight the importance of distinguishing between peak and current GCA for greater understanding of cognitive aging.

Keywords

general cognitive ability; cognitive aging; dementia; longitudinal studies; neuropsychology

1. Introduction

Late life cognitive decline and dementia is a major public health concern, with nearly 50 million people affected by dementia worldwide and prevalence projected to reach 130 million by 2050 (Alzheimer's Disease International (ADI) et al., 2015). Longitudinal studies of aging have been central to identifying early predictors of, and mechanisms underlying, late life cognitive decline (Erten-Lyons et al., 2012). However, these studies typically focus exclusively on cognitive change in older adulthood and lack objective cognitive data from earlier ages. It is therefore unclear how and to what extent cognitive change from earlier life is important for predicting later life cognitive performance. While most lifespan research indicates that general cognitive ability (GCA) peaks in young adulthood (Kremen et al., 2019; Salthouse, 2009), there may be substantial variability in maintenance of peak GCA into later life. However, even for studies that begin in midlife, it is exceedingly rare that anything is known about the degree of cognitive change that may have already taken place. This is important, as failure to examine such prior cognitive change could result in mischaracterization of later life cognitive outcomes and overlook the timing of important contributors to cognitive aging. To most accurately assess maintenance of GCA, it is important to have the same measure on every occasion.

Given limited research on maintenance of GCA, contributors to GCA maintenance in midlife are at present unclear. Previous studies exploring midlife change in specific cognitive abilities have identified vascular factors (Anstey et al., 2014; Richards et al., 2003; Tuligenga et al., 2014) and heavy alcohol consumption (Richards et al., 2005; Sabia et al., 2014) as predictors of cognitive decline during this period. In contrast, while the *APOE*-ε4 allele, the largest genetic risk factor for Alzheimer's disease, has been shown to

predict cognitive change in late midlife to older adulthood (Albert et al., 2014; Blair et al., 2005; Bunce et al., 2014; Caselli et al., 2010; Knopman et al., 2009; Zhao et al., 2005), it appears to be less predictive of cognitive change in earlier midlife periods (Deary et al., 2003; Jochemsen et al., 2012). Notably, in some studies, *APOE*-ε4 allele has been shown to moderate the effects of vascular burden, with the greatest degree of midlife cognitive decline observed among *APOE*-ε4 carriers with elevated vascular burden (Bangen et al., 2013; Blair et al., 2005), although these studies have been limited to the transition from late midlife to older adulthood. The absence of an *APOE*-ε4 effect is consistent with early midlife cognitive change representing a decline in cognitive ability rather than reflecting the nascent stages of a neurodegenerative process. However, to our knowledge, no study has explored whether prior cognitive change from young adulthood to midlife predicts subsequent acceleration in cognitive decline.

In the Vietnam Era Twin Study of Aging (VETSA), participants were administered the Armed Forces Qualification Test (AFQT; Bayroff and Anderson, 1963), a measure of GCA, at average age 20 and at all VETSA assessments beginning in midlife (Lyons et al., 2017). For purposes of this article, AFQT and GCA are interchangeable. Consequently, the VETSA is well positioned to evaluate how young adult GCA (indexed by young adult AFQT) and maintenance of GCA (indexed by change in AFQT from young adulthood), predict specific cognitive abilities in later life. In a previous study, we showed that GCA remained largely stable from age 20 to average age 56 (r = .73), although there was a moderate amount of variability in the entire sample, with 45% of participants exhibiting at least a half standard deviation change in GCA over time (Lyons et al., 2009). Therefore, in the present study, we were interested in evaluating (1) how young adult GCA and maintenance of GCA from young adulthood predicts one's level of specific cognitive abilities and one's rate of age-related specific cognitive ability change over the course of three assessments, each approximately 6 years apart, and (2) the extent to which one's young adult GCA is associated with one's level and rate of change in specific cognitive abilities over-and-above one's current level of GCA. To further understand change in GCA from young adulthood, we also explored vascular burden, alcohol consumption, and *APOE* genotype as risk correlates of poor midlife GCA maintenance. Finally, to validate our GCA maintenance measure and to explore its relationship with brain maintenance, we evaluated the association of GCA maintenance as well as young adult GCA with predicted brain age difference (PBAD) score, a commonly used MRI-based measure of advanced brain aging (Franke et al., 2010).

2. Methodology

2.1 Study participants

Participants were men participating in the VETSA, an ongoing longitudinal behavioral genetic study focused on cognitive and brain aging (Kremen, Franz, and Lyons, 2019; Kremen et al., 2013, 2006). The VETSA sample consists of male twin pairs who served in the military sometime between 1965 and 1975. VETSA participants were randomly recruited from a previous study using the Vietnam Era Twin Registry (Tsuang et al., 2001). The VETSA sample is generally representative of American men in their age cohort in terms

health and lifestyle characteristics based on Center for Disease Control and Prevention data (Schoenborn and Heyman, 2009). The sample of the current study consisted of individuals who completed their baseline VETSA assessment between 51 and 61 years of age and who had available data on young adult AFQT and VETSA baseline AFQT (n = 1308). Young adult AFQT was administered at average age 20 (range = 17-26). Participants were excluded from the current study if they reported a history of stroke, multiple sclerosis, HIV, AIDS, seizures, drug dependence, or schizophrenia at any VETSA assessment. The final sample consisted of 1,173 participants (mean VETSA baseline age = 56.02, SD = 2.46). The research protocol was approved by all participating institutions and all participants provided written informed consent at each assessment. Table 1 presents characteristics of the study sample.

Of the 1,173 included participants, 176 participants completed a single VETSA assessment, 292 completed two VETSA assessments, and 705 completed three VETSA assessments. Seventy-two participants were newly recruited and participated in their VETSA baseline assessment at the second wave of VETSA recruitment but were age-matched to the 1,101 other participants recruited at the first VETSA wave. As such, 72 participants underwent up to only two possible VETSA assessments and 1,101 underwent up to three possible VETSA assessments (see Supplementary Figure 1 for a flowchart of participation through VETSA assessments in the sample of this study). The average interval between assessments was 5.7 years for VETSA baseline to follow-up 1 and 6.1 years for follow-up 1 to follow-up 2. Relative to those who completed all possible assessments, those who did not had fewer years of education (13.56 vs. 14.00; $t = -3.83$, $p < .001$), but did not differ in VETSA baseline age (55.95 vs. 56.15; $t = 1.83$, $p = .07$), VETSA baseline GCA ($t = -1.88$, $p = .06$), age 20 GCA ($t = -0.76$, $p = .45$), or race/ethnicity ($Z = 0.17$, $p = .87$).

2.2 Measurements

2.2.1 AFQT—The AFQT is a 100-multiple choice item pencil-and-paper test administered to service members prior to military induction (Bayroff and Anderson, 1963). The AFQT correlates highly with measures of GCA, with documented correlations of .84 between the AFQT and Wechsler Adult Intelligence Scale full scale IQ (Wechsler, 1955) in early adulthood and late midlife (Lyons et al., 2017, 2009; McGrevy et al., 1974). The AFQT consists of items across domains of vocabulary, arithmetic word problems, knowledge and reasoning about tools and mechanical relations, and visual-spatial organization. The average AFQT score in this sample was equivalent to an approximate IQ of 105 in young adulthood and 106 at baseline VETSA assessment. AFQT scores were recorded as percentiles based on military norms and subsequently transformed to standard normal deviates.

To evaluate change in GCA from age 20 to VETSA baseline assessment, VETSA baseline assessment AFQT scores were regressed on age 20 AFQT. Owing to variability in age of VETSA baseline assessment, VETSA baseline assessment age was included as a covariate in this model. Standardized residuals from this regression equation were retained. Use of a regression-based approach was intended to mitigate effects of regression to the mean in calculating change scores (Barnett et al., 2005). Positive residuals thus reflect better than

expected GCA at VETSA baseline assessment based on age 20 GCA and negative residuals reflect worse than expected VETSA baseline GCA.

Age 20 GCA was used as a measure of young adult GCA, VETSA baseline assessment GCA indexed current level of GCA at VETSA baseline assessment, and GCA residuals indexed maintenance of GCA from young adulthood to VETSA baseline assessment. Figure 1 presents the regression of VETSA baseline GCA on age 20 GCA used to derive GCA maintenance scores.

2.2.2 Specific cognitive abilities—In prior work from our group, factor scores were created based on loadings derived from three to seven neuropsychological test scores within six cognitive domains: episodic memory (Kremen et al., 2014); general verbal fluency and semantic fluency (Gustavson et al., 2018a); processing speed (Sanderson-Cimino et al., 2019); and executive function and working memory (Gustavson et al., 2018b). Factor scores were standardized in relation to baseline VETSA assessment and were adjusted for practice effects due to repeat testing at subsequent assessments (Elman et al., 2018).

2.2.3. Vascular burden, alcohol consumption, and APOE genotype—Measures of vascular burden and alcohol consumption were collected at participants' VETSA baseline assessment. Total vascular burden was based on an aggregate score comprising the following: presence of hypertension, angina, diabetes, history of heart attack, history of heart failure, history of heart surgery, current smoking, and erectile dysfunction. Erectile dysfunction was included as an additional vascular factor given its known relationship to microvascular disease (Kendirci et al., 2005) and previous VETSA findings demonstrating its association with cognitive performance independent of other vascular factors (Moore et al., 2014). Presence of hypertension was based on self-reported diagnosis of hypertension by a doctor, mean systolic blood pressure > 140 mm/Hg, or mean diastolic blood pressure > 90 mm/Hg across four measurements. Presence of angina was based on a positive Rose Angina score and/or use of nitroglycerin medications (Lampe et al., 1999). Presence of erectile dysfunction was based on a score of ≤ 25 on the International Index of Erectile Function-6 (Moore et al., 2014; Rosen et al., 1997). Diabetes, heart attack, heart failure, heart surgery, and current smoker status were determined through self-report of doctor diagnosis. Participants with two or more vascular risk factors were designated as having an elevated vascular risk burden. This threshold was chosen based on previous findings showing that two or more vascular risk factors are associated with cerebrovascular pathology at autopsy whereas the presence of any single vascular risk factor is not (Bangen et al., 2015; Nation et al., 2012).

Alcohol consumption groups were defined in accordance with recommendations for alcohol consumption for men (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015). At their baseline VETSA assessment, participants who consumed 1-14 alcoholic beverages in the past two weeks were classified as light drinkers, between 15 and 28 drinks as moderate drinkers, and greater than 28 drinks as heavy drinkers. We consulted data previously collected on these participants at average age 44 as part of the Harvard Drug Study (HDS; Tsuang et al., 2001) to distinguish between never drinkers and former drinkers (Slayday et al., 2020). Participants were classified as never drinkers if they

reported during the HDS that there was no period in which they consumed at least one drink per month for 6 or more months, reported consuming less than 20 drinks lifetime at their VETSA baseline assessment, and reported no alcohol consumption for the last two weeks. Participants were classified as former drinkers if they consumed greater than 20 drinks in their lifetime but did not consume any alcoholic beverages in the past two weeks.

APOE genotype was used as a measure of AD genetic risk. *APOE* was directly genotyped as described previously (Lyons et al., 2013; Schultz et al., 2008). Participants were classified as *APOE*-ε4 positive or negative.

2.2.4. Predicted brain age difference—A subset of the current sample participated in the MRI arm of the VETSA study at VETSA baseline assessment (n = 451). T1 images were acquired on Siemens 1.5 Tesla scanners at one of two sites: University of California, San Diego (UCSD) or Massachusetts General Hospital (MGH). Sagittal T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequences were employed with a T1=1000ms, TE= 3.31ms, TR=2730ms, flip angle=7 degrees, slice thickness =1.33mm, voxel size 1.33x1.0x1.33mm. FreeSurfer version 5.3 was used for subcortical segmentation and surface-based cortical parcellation (Fischl, 2012). All raw and processed images were visually inspected for quality and accuracy. White matter and brain masks were manually edited as necessary, in alignment with standard, objective editing rules.

Predicted brain age was calculated using the *stacked-anatomy* model in BARACUS v0.9.4 (Liem et al., 2017). BARACUS *stacked-anatomy* uses linear support vector regression models on an individual's FreeSurfer-derived measures of cortical thickness, surface area, and subcortical volume to predict their brain age. A predicted brain age difference (PBAD) score was calculated by subtracting predicted brain age from chronological age. Therefore, a negative PBAD score suggests advanced brain aging (older brain age given chronological age). See Figure 2 for a timeline of analyzed measures in this study.

2.3 Statistical analysis

Using the lme4 package (Bates et al., 2015) in R version 4.0.0 (R Core Team, 2020), linear mixed effects models were fit for each specific cognitive ability factor score to evaluate change in specific cognitive ability performance from baseline to second follow-up VETSA assessment. Age was used as the time metric, which ranged from 51 (youngest age at VETSA baseline) to 73 (oldest age at VETSA follow-up 2) and was centered at the mean of VETSA baseline assessment (age 56). Random intercepts and slopes for age were included, which were nested within family pairs to account for repeated observations within individual and the correlated nature of the twin data.

We fit four sets of models. The first set (Model 1) was aimed at determining how young adult GCA (indexed by age 20 GCA) and maintenance of GCA (indexed by residual GCA) contributed to levels of specific cognitive ability performance across age and thus included fixed effects of young adult GCA, GCA maintenance, and age. The second set (Model 2) aimed to determine whether young adult GCA or GCA maintenance was associated with rate of age-related specific cognitive ability change. Therefore, this set of models included fixed effects of young adult GCA, GCA maintenance, age, and the interactions of

young adult GCA x age and GCA maintenance x age. The third set (Model 3) sought to determine if, given similar levels of GCA at the baseline VETSA assessment (i.e., current GCA), earlier young adult GCA contributed anything additional to specific cognitive ability performance. These models were adjusted for current GCA and thus included fixed effects of current GCA, young adult GCA, and age. Finally, the fourth set (Model 4) evaluated whether peak GCA was associated with rate of specific cognitive ability change from age 51-73 among individuals with similar levels of GCA, and thus included fixed effects of current GCA, young adult GCA, age, current GCA x age, and young adult GCA x age.

Subsequent analyses explored correlates of GCA maintenance that were collected at participants' baseline VETSA assessment. Linear mixed effects models with random effects accounting for twin pair clustering were conducted with GCA maintenance as the outcome. Separate models evaluated the association of GCA maintenance with vascular burden, alcohol consumption groups (with never drinkers treated as the reference category), *APOE* genotype as well as the interaction between *APOE* genotype and vascular burden. Each of these models was adjusted for race/ethnicity, which, given the small number of non-white participants in the VETSA sample, was classified as non-Hispanic white versus other. Only participants with complete vascular burden, *APOE* genotype, and alcohol consumption data were included in these analyses (n = 1090).

To further characterize and validate our GCA maintenance score, we explored associations of GCA maintenance as well as young adult GCA with PBAD scores using linear mixed effects models with random effects for twin pair clustering in the subset of the sample with available brain imaging data (n = 451). Recognizing that PBAD scores may not be independent of chronological age (Le et al., 2018; Smith et al., 2019), chronological age was included as a covariate in this model, as was scanner.

Alpha level was set at $p < .05$, two-tailed for all analyses. To correct for false discovery rate inflation due to multiple comparisons, false discovery rate correction was applied to Models 1, 2, 3 and 4 described above.

3. Results

3.1 Specific cognitive abilities

Fixed effect parameter estimates from mixed effects models for each specific cognitive ability are presented in Table 2 and random effect estimates are presented in Supplementary Table 1. All specific cognitive abilities declined with age (all *p*s < .001), with the estimated rate of decline ranging from a .03 standard deviation decline per year for general fluency ability to a .10 standard deviation decline per year for processing speed. Young adult GCA was related to all specific cognitive abilities, with higher young adult GCA associated with better episodic memory ($t = 15.351$, $p < .001$, $R^2 = .221$), semantic fluency ($t = 8.693$, $p < .001$, $R^2 = .095$), general fluency ($t = 9.551$, $p < .001$, $R^2 = .091$), processing speed ($t = 9.164$, $p < .001$, $R^2 = .093$), working memory ($t = 15.356$, $p < .001$, $R^2 = .202$), and executive function ($t = 17.117$, $p < .001$, $R^2 = .256$) from age 51-73. Similarly, better GCA maintenance predicted stronger episodic memory ($t = 10.115$, $p < .001$, $R^2 = .100$), semantic fluency ($t = 6.826$, $p < .001$, $R^2 = .056$), general fluency ($t = 6.868$, $p < .001$, $R^2 = .045$),

processing speed (t = 8.585, p < .001, R^2 = .076), working memory (t = 10.609, p < .001, R^2 = .088), and executive function (t = 11.685, p < .001, R^2 = .112). All effects remained significant after false discovery rate correction. In models incorporating interaction terms of young adult GCA x age and GCA maintenance x age (Model 2), after false discovery rate correction, young adult GCA was not associated with rate of age-related decline in any other specific cognitive ability, nor was GCA maintenance.

Young adult GCA continued to be associated with levels of several specific cognitive abilities in models even after adjusting for current GCA at VETSA baseline (Model 3). After adjusting for current GCA, higher young adult GCA was associated with better episodic memory (t = 3.800, p < .001, R^2 = .013), working memory (t = 3.941, p < .001, R^2 = .016), and executive function (t = 4.059, p < .001, R^2 = .023) from age 51-73, but not with general fluency, semantic fluency, or processing speed (all ps > .05). However, after adjusting for current GCA, young adult GCA was not associated with rate of age-related cognitive decline from age 51-73 for any specific cognitive ability (all ps > .07).

3.2 Correlates of GCA residuals

Maintenance of GCA was significantly associated with elevated vascular burden (b = −.14, t = −2.268, p = .024), but not with *APOE* genotype (b = −.07, t = −0.976, p = .329). However, this was qualified by a vascular risk burden x *APOE* genotype interaction (b = −.27, t = −2.071, p = .030). As shown in Figure 3, elevated vascular burden was associated with poorer GCA maintenance among ε4 carriers (b = −.32, t = −2.972, p = .003), but not among ε4 non-carriers (b = −.05, t = −0.725, p = .468). There was no association between GCA maintenance and any alcohol consumption group (all ps > .06).

GCA maintenance and young adult GCA were also associated with PBAD scores. An older brain relative to chronological age at VETSA baseline assessment (a more negative PBAD score) was associated both with both lower young adult GCA (b = .63, t = 2.606, p = .009, r = .08) and worse GCA maintenance (b = .66, t = 2.904, p = .004, r = .14).

4. Discussion

We examined the association of young adult GCA and change in GCA from young adulthood with one's level and rate of change in specific cognitive abilities over the course of 12 years on average. Change in, or maintenance of, GCA is almost never even considered, most likely because education is by far the most common index of young adult GCA. The fact that formal educational attainment almost never continues beyond young adulthood precludes any examination of change in that index of GCA. In our study, both higher young adult GCA and stronger maintenance of young adult GCA were related to higher levels of specific cognitive abilities between ages 51 and 73 but were not associated with rate of age-related specific cognitive ability decline during this period. Thus, all else being equal, individuals with better young adult GCA and those with better maintenance of GCA from young adulthood to later life exhibit stronger specific cognitive abilities in later life.

Importantly, even after controlling for level of current GCA, stronger young adult GCA remained associated with higher levels of memory, working memory, and executive function

from age 51 to 73. This is notable because individuals matched on current GCA who exhibited a higher GCA at age 20 must by necessity have experienced a greater decline in GCA from age 20 to VETSA baseline than those who started from a lower age 20 GCA. Thus, despite experiencing a relative decline from average ages 20 to 56, some element of young adult GCA still contributed to their specific cognitive ability performance later in life. This represents a paradoxical phenomenon in which, among individuals who are effectively matched for current GCA, those who have experienced an apparent depletion of GCA still outperformed those with a stable but lower level of young adult GCA. Moreover, this benefit of early adult GCA was maintained from age 51 to73 despite their prior GCA decline. Overall, these findings highlight the importance of distinguishing between young adult (often peak) GCA, maintenance of GCA, and current levels of GCA in explaining individual differences in aging-related cognitive performance. Furthermore, they show that without knowledge of earlier GCA, the assumption that older adults equated for current GCA are well matched could be somewhat misleading. Put another way, where you are at now, but also how you got there, is important.

We refer to this phenomenon as paradoxical because experiencing declines is generally associated with poorer functioning. The mechanisms underlying this paradoxical phenomenon are at present unclear. One possibility is that higher peak GCA may be accompanied by stronger metacognitive abilities (e.g., mnemonic strategy knowledge and use), enabling greater compensation capacity when reserve is diminished (Barulli et al., 2013; Frankenmolen et al., 2018). Relatedly, it has been hypothesized that individuals with higher peak GCA may be able to compensate for more recent brain or cognitive change through increased functional brain activation or through activation of alternative brain networks (Cabeza et al., 2018; Steffener et al., 2011). Alternatively, measures of GCA, including the AFQT, have limited coverage of memory and executive function domains. As such, participants who declined in GCA may not have experienced a similar degree of decline in memory, executive function, or working memory abilities. However, half of the AFQT consists of vocabulary and arithmetic, and it seems likely that these abilities would decline less, not more, than memory and executive function (Salthouse, 2009).

These results also have implications for traditional accounts of cognitive reserve. Cognitive reserve is typically invoked to explain the discrepancy between an individual’s level of cognitive performance relative to their brain age or degree of brain pathology. A seminal finding in this literature is that individuals with higher premorbid ability (generally based on educational attainment) exhibit greater Alzheimer’s disease (AD) pathology at equivalent levels of cognitive function relative to those with lower premorbid ability (Stern et al., 1999, 1995). This has been taken as evidence that higher premorbid ability may enable stronger maintenance of cognitive function in the presence of neuropathology (Stern, 2009). Our finding that higher young adult GCA was not associated with an attenuated rate of age-related cognitive decline is partly at variance with this account. For this reason, we believe it is important to distinguish between cognitive reserve, cognitive maintenance, and cognitive resilience. Cognitive reserve may be understood as the total amount of an individual’s cognitive resources at a given time, which appears largely to peak in young adulthood (Kremen et al., 2019; Salthouse, 2009), cognitive maintenance as the degree of preservation of cognitive abilities over time, and cognitive resilience as better than

expected cognitive performance in the face of adverse effects on the brain. Introduced by Nyberg and colleagues (2012), brain maintenance is an important construct that has received considerable attention in the context of studies of cognitive reserve. Our use of cognitive maintenance—or the maintenance of cognitive reserve—may be thought of as directly analogous to brain maintenance.

In this framework, the approach to cognitive reserve may be recast as a question of whether peak cognitive reserve (young adult GCA) supports cognitive resilience, which is manifested by cognitive maintenance in the presence of some adverse factor (e.g., biomarker positivity, genetic risk, etc.). The current results may be understood as failing to provide support for the position that higher cognitive reserve promotes stronger later life cognitive maintenance. We did not incorporate a measure of adversity into our analyses and so were unable to directly examine the relationship between cognitive reserve and cognitive resilience. In other studies, however, we have shown that age 20 GCA moderates the association between hippocampal volume and episodic memory (smaller hippocampal volume was associated with worse episodic memory performance among those with lower age 20 GCA but not among those with higher age 20 GCA) and between lifetime exposure to unhealthy lifestyle factors and advanced brain age (greater exposure to unhealthy lifestyle factors was associated with advanced brain age among those low, but not high, age 20 GCA) (Franz et al., in press; Vuoksimaa et al., 2013). Age 20 GCA then appears to promote resilience, further supporting its use as an index of cognitive reserve. These results might also suggest brain maintenance, but that could not be determined because brain measures in these studies were only at a single point in time.

Similarly, we also observed that both young adult GCA and GCA maintenance were associated with the PBAD score, consistent with previous research positing that PBAD reflects both early life central nervous system integrity and age-related brain deterioration (Elliott et al., 2019). In contrast to specific cognitive ability performance, effect sizes for the association of GCA maintenance with PBAD score were slightly larger than those for young adult GCA. This is likely due to the inclusion of an explicit contrast with chronological age in PBAD calculation, thereby rendering PBAD scores more reflective of accelerated (i.e., greater than expected) brain aging as opposed to a static measure of brain structure. Ultimately, these results suggest that poor cognitive and brain maintenance likely coincide to some degree.

Of note, we did not find that young adult GCA or GCA maintenance was associated with rate of age-related specific cognitive ability change. This is consistent with the bulk of research on this topic, which has similarly shown that early adult GCA influences later life cognitive outcomes not through attenuation of age-related cognitive declines but rather through the higher level of cognitive resources available earlier in life, which is at least partly preserved into older adulthood (Lövdén et al., 2020). The current findings extend this literature in two ways. First, they show that early adult GCA continues to contribute to later life cognitive outcomes by somehow helping to maintain one’s level of ability in specific cognitive domains even among individuals who have experienced a relative decline from their early adult GCA. Second, they show that midlife declines in GCA do not necessarily herald accelerated cognitive decline in early older adulthood.

These results also have implications for traditional accounts of cognitive reserve. Cognitive reserve is typically invoked to explain the discrepancy between an individual's level of cognitive performance relative to their brain age or degree of brain pathology. A seminal finding in this literature is that individuals with higher premorbid ability (generally based on educational attainment) exhibit greater Alzheimer's disease (AD) pathology at equivalent levels of cognitive function relative to those with lower premorbid ability (Stern et al., 1999, 1995). This has been taken as evidence that higher premorbid ability may enable stronger maintenance of cognitive function in the presence of neuropathology (Stern, 2009). Our finding that higher young adult GCA was not associated with an attenuated rate of age-related cognitive decline is partly at variance with this traditional account. For this reason, we believe it is important to distinguish between cognitive reserve, cognitive maintenance, and cognitive resilience. Cognitive reserve may be understood as the total amount of an individual's cognitive resources at a given time, which appears largely to peak in young adulthood (Kremen et al., 2019; Salthouse, 2009), cognitive maintenance as the degree of preservation of cognitive abilities over time, and cognitive resilience as better than expected cognitive performance in the face of adverse effects on the brain.

In this framework, the traditional approach to cognitive reserve may be recast as a question of whether peak cognitive reserve (young adult GCA) supports cognitive resilience, which is manifested by cognitive maintenance in the presence of some adverse factor (e.g., biomarker positivity, genetic risk, etc.). The current results may be understood as failing to provide support for the position that higher cognitive reserve promotes stronger later life cognitive maintenance. We did not incorporate a measure of adversity into our analyses and so were unable to directly examine the relationship between cognitive reserve and cognitive resilience. In other studies, however, we have shown that age 20 GCA moderates the association between hippocampal volume and episodic memory (smaller hippocampal volume was associated with worse episodic memory performance among those with lower age 20 GCA but not among those with higher age 20 GCA) and between lifetime exposure to unhealthy lifestyle factors and advanced brain age (greater exposure to unhealthy lifestyle factors was associated with advanced brain age among those low, but not high, age 20 GCA) (Franz et al., in press; Vuoksimaa et al., 2013). Age 20 GCA then appears to promote resilience, further supporting its use as an index of cognitive reserve.

Among examined correlates, elevated vascular burden was associated with poor GCA maintenance, but only for *APOE*-ε4 carriers. This finding is consistent with several previous studies, which have also shown a moderating effect of *APOE* genotype on the relationship between vascular burden and cognitive decline, albeit in later periods of life than observed in this study (Bangen et al., 2013; Blair et al., 2005). In addition to its known association with Alzheimer's disease, *APOE* plays a central role in cholesterol metabolism, with the ε4 allele contributing to elevated low density lipoprotein levels (Mahley, 2016), and it is associated with vascular disease including myocardial infarction (Anand et al., 2009), carotid atherosclerosis (Elosua et al., 2004), hypertension (Niu et al., 2009), and stroke (McCarron et al., 1999). This raises the possibility that vascular contributors to cognitive decline in midlife may be most pronounced among those with elevated genetic risk for cardiovascular disease. As mentioned above, we did not observe subsequent acceleration of cognitive decline as a function of prior change in GCA. Taken together,

these finding suggest that vascular burden accrued up to late midlife may only contribute to a discrete decline in cognitive function in midlife rather than herald the early stages of a neurodegenerative process characterized by progressive cognitive deterioration.

Here we consider the fact that repeated measurements may be subject to regression to the mean in which individuals who score at the extremes of the distribution at baseline are more likely to score closer to the mean at follow-up. Our use of a regression-based approach in calculating GCA residuals adjusts for this tendency, as can be seen in Figure 1b, and thus mitigates against this potential bias (Barnett et al., 2005). For example, high scorers are expected to decline more, but the residual scores indicate change beyond the amount of expected change. Furthermore, residualized GCA scores were associated with all specific cognitive abilities, with an index of advanced brain age, and with vascular burden, particularly in combination with *APOE*-ε4 carrier status. These associations support the interpretation that the residualized scores are reflective of true change in level of GCA and not simply regression to the mean.

The results of this study should be understood in the context of its limitations. Vascular data from participants' baseline VETSA assessment (at mean age of 56) were examined in relation to GCA maintenance from age 20 to 56, and therefore were not evaluated as prospective predictors of change from young adulthood. Similarly, inferences regarding advanced brain aging were based on a cross-sectional measure of predicted brain age. Although this measure is well-validated and widely used as an index of advanced brain aging (Elliott et al., 2019), measures of brain structure at two or more timepoints are necessary to directly measure accelerated brain aging/brain maintenance. Our measure of PBAD in the baseline VETSA assessment was derived from 1.5T MRI scanners whereas the original BARACUS used 3T MRI. Our data (unpublished) shows that PBAD scores based on 1.5T and 3T MRI had nearly identical heritability estimates and PBAD scores increased linearly in each study wave despite change from 1.5T to 3T scanners. This supports the validity of the PBAD scores in the present study. Finally, the sample was all male and mostly non-Hispanic white. Therefore, generalizability of the current findings to other demographic groups is not clear. Nonetheless, the current study consisted of a large, well-characterized sample with the same test of GCA in both young and middle adulthood. It therefore represents a unique contribution to the literature on peak GCA and the impact of prior cognitive change on subsequent cognitive aging.

Future research should explore the role of peak level and maintenance of GCA in the context of brain pathology. A key question is whether these different aspects of GCA independently contribute to cognitive and brain outcomes in the context of elevated biomarkers of disease (e.g., beta-amyloid or tau). Relatedly, extension of the current analyses to older ages when neurodegenerative pathologies are more prevalent may provide additional insight into the contribution of peak level versus maintenance of GCA during a crucial inflection point for cognitive aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Agriculture, U.S.D. of H. and H.S. and U.S.D. of, 2015. 2015 – 2020 Dietary Guidelines for Americans. 2015 – 2020 Diet. Guidel. Am (8th Ed. 10.1097/NT.0b013e31826c50af

Albert M, Soldan A, Gottesman R, McKhann G, Sacktor N, Farrington L, Grega M, Turner R, Lu Y, Li S, Wang M-C, Selnes O, 2014. Cognitive Changes Preceding Clinical Symptom Onset of Mild Cognitive Impairment and Relationship to ApoE Genotype. Curr. Alzheimer Res 10.2174/1567205011081409101219 20

Alzheimer's Disease International (ADI), Wimo A, Prince M, International, A.D., 2015. World Alzheimer Report 2015, The Global Impact of Dementia. Alzheimer's Dis. Int. (ADI). 10.1111/j.0963-7214.2004.00293.x

Anand SS, Xie C, Paré G, Montpetit A, Rangarajan S, McQueen MJ, Cordell HJ, Keavney B, Yusuf S, Hudson TJ, Engert JC, 2009. Genetic variants associated with myocardial infarction risk factors in over 8000 individuals from five ethnic groups the INTERHEART genetics study. Circ. Cardiovasc. Genet 10.1161/CIRCGENETICS.108.813709

Anstey KJ, Sargent-Cox K, Garde E, Cherbuin N, Butterworth P, 2014. Cognitive development over 8 years in midlife and its association with cardiovascular risk factors. Neuropsychology. 10.1037/neu0000044

Bangen KJ, Beiser A, Delano-Wood L, Nation DA, Lamar M, Libon DJ, Bondi MW, Seshadri S, Wolf PA, Au R, 2013. APOE genotype modifies the relationship between midlife vascular risk factors and later cognitive decline. J. Stroke Cerebrovasc. Dis 10.1016/j.jstrokecerebrovasdis.2013.03.013

Bangen KJ, Nation DA, Delano-Wood L, Weissberger GH, Hansen LA, Galasko DR, Salmon DP, Bondi MW, 2015. Aggregate effects of vascular risk factors on cerebrovascular changes in autopsy-confirmed Alzheimer's disease. Alzheimer's Dement. 10.1016/j.jalz.2013.12.025

Barnett AG, van der Pols JC, Dobson AJ, 2005. Regression to the mean: What it is and how to deal with it. Int. J. Epidemiol 10.1093/ije/dyh299

Barulli DJ, Rakitin BC, Lemaire P, Stern Y, 2013. The influence of cognitive reserve on strategy selection in normal aging. J. Int. Neuropsychol. Soc 10.1017/S1355617713000593

Bates D, Mächler M, Bolker BM, Walker SC, 2015. Fitting linear mixed-effects models using lme4. J. Stat. Softw 10.18637/jss.v067.i01

Bayroff AG, Anderson AA, 1963. Development of the Armed Forces Qualification Test, Technical. ed. U.S. Army Research Institute, Arlington, VA.

Blair CK, Folsom AR, Knopman DS, Bray MS, Mosley TH, Boerwinkle E, 2005. APOE genotype and cognitive decline in a middle-aged cohort. Neurology. 10.1212/01.WNL.0000149643.91367.8A

Bunce D, Bielak AAM, Anstey KJ, Cherbuin N, Batterham PJ, Easteal S, 2014. APOE genotype and cognitive change in young, middle-aged, and older adults living in the community. Journals Gerontol. - Ser. A Biol. Sci. Med. Sci 10.1093/gerona/glt103

Cabeza R, Albert M, Belleville S, Craik FIM, Duarte A, Grady CL, Lindenberger U, Nyberg L, Park DC, Reuter-Lorenz PA, Rugg MD, Steffener J, Rajah MN, 2018. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. Nat. Rev. Neurosci 10.1038/s41583-018-0068-2

Caselli RJ, Dueck AC, Osborne D, Sabbagh MN, Connor DJ, Ahern GL, Baxter LC, Rapcsak Z, Shi J, Woodruff BK, Locke DEC, Snyder H, Alexander GE, Rademakers R, Eric M, 2010. Longitudinal growth modeling of cognitive aging and APOE e4 effect. N. Engl. J. Med 10.1056/NEJMoa0809437.Longitudinal

Deary IJ, Whalley LJ, St. Clair D, Breen G, Leaper S, Lemmon H, Hayward C, Starr JM, 2003. The influence of the ε4 allele of the apolipoprotein E gene on childhood IQ, nonverbal reasoning in old age, and lifetime cognitive change. Intelligence. 10.1016/s0160-2896(02)00114-9

Elliott ML, Belsky DW, Knodt AR, Ireland D, Melzer TR, Poulton R, Ramrakha S, Caspi A, Moffitt TE, Hariri AR, 2019. Brain-age in midlife is associated with accelerated biological aging and cognitive decline in a longitudinal birth cohort. Mol. Psychiatry 10.1038/s41380-019-0626-7

Elman JA, Jak AJ, Panizzon MS, Tu XM, Chen T, Reynolds CA, Gustavson DE, Franz CE, Hatton SN, Jacobson KC, Toomey R, McKenzie R, Xian H, Lyons MJ, Kremen WS, 2018. Underdiagnosis of mild cognitive impairment: A consequence of ignoring practice effects. Alzheimer's Dement. Diagnosis, Assess. Dis. Monit 10.1016/j.dadm.2018.04.003

Elosua R, Ordovas JM, Cupples LA, Fox CS, Polak JF, Wolf PA, D'Agostino RA, O'Donnell CJ, 2004. Association of APOE genotype with carotid atherosclerosis in men and women: The Framingham Heart Study. J. Lipid Res 10.1194/jlr.M400114-JLR200

Erten-Lyons D, Sherbakov LO, Piccinin AM, Hofer SM, Dodge HH, Quinn JF, Woltjer RL, Kramer PL, Kaye JA, 2012. Review of selected databases of longitudinal aging studies. Alzheimer's Dement. 10.1016/j.jalz.2011.09.232

Fischl B, 2012. FreeSurfer. Neuroimage. 10.1016/j.neuroimage.2012.01.021

Franke K, Ziegler G, Klöppel S, Gaser C, 2010. Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: Exploring the influence of various parameters. Neuroimage. 10.1016/j.neuroimage.2010.01.005

Frankenmolen NL, Fasotti L, Kessels RPC, Oosterman JM, 2018. The influence of cognitive reserve and age on the use of memory strategies. Exp. Aging Res 10.1080/0361073X.2017.1422472

Franz CE, Hatton SN, Elman JA, Warren T, Gillespie NA, Whitsel N, Puckett OK, Dale AM, Eyler LT, Fennema-Notestine C, Hagler DJ, Hauger RL, McKenzie R, Neale MC, Panizzon MS, Pearce RC, Reynolds CA, Sanderson-Cimino M, Toomey R, Tu XM, Williams M, Xian H, Kremen WS, Lyons MJ, 2021. Lifestyle and the Aging Brain: Interactive Effects of Modifiable Lifestyle Behaviors and Cognitive Ability in Men from Midlife to Old Age. Neurobiol. Aging

Gustavson DE, Panizzon MS, Elman JA, Franz CE, Beck A, Reynolds CA, Jacobson KC, Xian H, Toomey R, Lyons MJ, Kremen WS, 2018a. Genetic and Environmental Influences on Verbal Fluency in Middle Age: A Longitudinal Twin Study. Behav. Genet 10.1007/s10519-018-9910-6

Gustavson DE, Panizzon MS, Franz CE, Friedman NP, Reynolds CA, Jacobson KC, Xian H, Lyons MJ, Kremen WS, 2018b. Genetic and environmental architecture of executive functions in midlife. Neuropsychology. 10.1037/neu0000389

Jochemsen HM, Muller M, van der Graaf Y, Geerlings MI, 2012. APOE ε4 differentially influences change in memory performance depending on age. The SMART-MR study. Neurobiol. Aging 10.1016/j.neurobiolaging.2011.07.016

Kendirci M, Nowfar S, Hellstrom WJG, 2005. The impact of vascular risk factors on erectile function. Drugs of Today. 10.1358/dot.2005.41.1.875779

Knopman DS, Mosley TH, Catellier DJ, Coker LH, 2009. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: The ARIC MRI Study. Alzheimer's Dement. 10.1016/j.jalz.2009.01.027

Kremen WS, Franz CE, Lyons MJ, 2019. Current status of the Vietnam Era Twin Study of Aging (VETSA). Twin Res. Hum. Genet 22, 783–787. [PubMed: 31933447]

Kremen WS, Beck A, Elman JA, Gustavson DE, Reynolds CA, Tu XM, Sanderson-Cimino ME, Panizzon MS, Vuoksimaa E, Toomey R, Fennema-Notestine C, Hagler DJ, Fang B, Dale AM, Lyons MJ, Franz CE, 2019. Influence of young adult cognitive ability and additional education on later-life cognition. Proc. Natl. Acad. Sci. U. S. A 10.1073/pnas.1811537116

Kremen WS, Franz CE, Lyons MJ, 2013. VETSA: The vietnam era twin study of aging. Twin Res. Hum. Genet 10.1017/thg.2012.86

Kremen WS, Panizzon MS, Franz CE, Spoon KM, Vuoksimaa E, Jacobson KC, Vasilopoulos T, Xian H, McCaffery JM, Rana BK, Toomey R, McKenzie R, Lyons MJ, 2014. Genetic complexity of episodic memory: A twin approach to studies of aging. Psychol. Aging 10.1037/a0035962

Kremen WS, Thompson-Brenner H, Leung YMJ, Grant MD, Franz CE, Eisen SA, Jacobson KC, Boake C, Lyons MJ, 2006. Genes, environment, and time: The Vietnam Era Twin Study of Aging (VETSA). Twin Res. Hum. Genet 10.1375/183242706779462750

Lampe FC, Walker M, Lennon LT, Whincup PH, Ebrahim S, 1999. Validity of a self-reported history of doctor-diagnosed angina. J. Clin. Epidemiol 10.1016/S0895-4356(98)00146-2

Liem F, Varoquaux G, Kynast J, Beyer F, Kharabian Masouleh S, Huntenburg JM, Lampe L, Rahim M, Abraham A, Craddock RC, Riedel-Heller S, Luck T, Loeffler M, Schroeter ML, Witte AV, Villringer A, Margulies DS, 2017. Predicting brain-age from multimodal imaging data captures cognitive impairment. Neuroimage. 10.1016/j.neuroimage.2016.11.005

Lövdén M, Fratiglioni L, Glymour MM, Lindenberger U, Tucker-Drob EM, 2020. Education and Cognitive Functioning Across the Life Span. Psychol. Sci. Public Interes 21, 6–41. 10.1177/1529100620920576

Lyons MJ, Genderson M, Grant MD, Logue M, Zink T, Mckenzie R, Franz CE, Panizzon M, Lohr JB, Jerskey B, Kremen WS, 2013. Gene-environment interaction of ApoE genotype and combat exposure on PTSD. Am. J. Med. Genet. Part B Neuropsychiatr. Genet 10.1002/ajmg.b.32154

Lyons MJ, Panizzon MS, Liu W, McKenzie R, Bluestone NJ, Grant MD, Franz CE, Vuoksimaa EP, Toomey R, Jacobson KC, Reynolds CA, Kremen WS, Xian H, 2017. A longitudinal twin study of general cognitive ability over four decades. Dev. Psychol 10.1037/dev0000303

Lyons MJ, York TP, Franz CE, Grant MD, Eaves LJ, Jacobson KC, Schaie KW, Panizzon MS, Boake C, Xian H, Toomey R, Eisen SA, Kremen WS, 2009. Genes determine stability and the environment determines change in cognitive ability during 35 years of adulthood. Psychol. Sci 10.1111/j.1467-9280.2009.02425.x

Mahley RW, 2016. Apolipoprotein E: from cardiovascular disease to neurodegenerative disorders. J. Mol. Med 10.1007/s00109-016-1427-y

McCarron MO, Delong D, Alberts MJ, 1999. APOE genotype as a risk factor for ischemic cerebrovascular disease: A meta-analysis. Neurology. 10.1212/wnl.53.6.1308

McGrevy DF, Knouse SB, Thompson RA, 1974. Relationships among an individual intelligence test and two air force screening and selection tests, Technical. ed. Personnel Research Division, Air Force Human Resources Laboratory, Brooks Air Force Base, San Antonio, TX.

Moore CS, Grant MD, Zink TA, Panizzon MS, Franz CE, Logue MW, Hauger RL, Kremen WS, Lyons MJ, 2014. Erectile dysfunction, vascular risk, and cognitive performance in late middle age. Psychol. Aging 10.1037/a0035463

Nation DA, Delano-Wood L, Bangen KJ, Wierenga CE, Jak AJ, Hansen LA, Galasko DR, Salmon DP, Bondi MW, 2012. Antemortem pulse pressure elevation predicts cerebrovascular disease in autopsy-confirmed alzheimer's disease. J. Alzheimer's Dis 30, 595–603. 10.3233/JAD-2012-111697 [PubMed: 22451309]

Niu W, Qi Y, Qian Y, Gao P, Zhu D, 2009. The relationship between apolipoprotein e 2/3/4 polymorphisms and hypertension: A meta-analysis of six studies comprising 1812 cases and 1762 controls. Hypertens. Res 10.1038/hr.2009.164

Nyberg L, Lövdén M, Riklund K, Lindenberger U, Bäckman L, 2012. Memory aging and brain maintenance. Trends Cogn. Sci 16. 10.1016/j.tics.2012.04.005

R Core Team, 2020. R: A Language and Environment for Statistical Computing. Vienna, Austria.

Richards M, Hardy R, Wadsworth MEJ, 2005. Alcohol consumption and midlife cognitive change in the British 1946 birth cohort study. Alcohol Alcohol. 10.1093/alcalc/agh126

Richards M, Jarvis MJ, Thompson N, Wadsworth MEJ, 2003. Cigarette Smoking and Cognitive Decline in Midlife: Evidence from a Prospective Birth Cohort Study. Am. J. Public Health 10.2105/AJPH.93.6.994

Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A, 1997. The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. Urology. 10.1016/S0090-4295(97)00238-0

Sabia S, Elbaz A, Britton A, Bell S, Dugravot A, Shipley M, Kivimaki M, Singh-Manoux A, 2014. Alcohol consumption and cognitive decline in early old age. Neurology. 10.1212/WNL.0000000000000063

Salthouse TA, 2009. When does age-related cognitive decline begin? Neurobiol. Aging 10.1016/j.neurobiolaging.2008.09.023

Sanderson-Cimino M, Panizzon MS, Elman JA, Gustavson DE, Franz CE, Reynolds CA, Toomey R, Lyons MJ, Kremen WS, 2019. Genetic and Environmental Architecture of Processing Speed Across Midlife. Neuropsychology. 10.1037/neu0000551

Schoenborn CA, Heyman KM, 2009. Health characteristics of adults aged 55 years and over: United States, 2004-2007. Natl. Health Stat. Report

Schultz MR, Lyons MJ, Franz CE, Grant MD, Boake C, Jacobson KC, Xian H, Schellenberg GD, Eisen SA, Kremen WS, 2008. Apolipoprotein E genotype and memory in the sixth decade of life. Neurology. 10.1212/01.wnl.0000286941.74372.cc

Slayday RE, Gustavson DE, Elman JA, Beck A, McEvoy LK, Tu XM, Fang B, Hauger RL, Lyons MJ, McKenzie RE, Sanderson-Cimino ME, Xian H, Kremen WS, Franz CE, 2020. Interaction between Alcohol Consumption and Apolipoprotein E (ApoE) Genotype with Cognition in Middle-Aged Men. J. Int. Neuropsychol. Soc 1–13.

Steffener J, Reuben A, Rakitin BC, Stern Y, 2011. Supporting performance in the face of age-related neural changes: Testing mechanistic roles of cognitive reserve. Brain Imaging Behav. 10.1007/s11682-011-9125-4

Stern Y, 2009. Cognitive reserve. Neuropsychologia. 10.1016/j.neuropsychologia.2009.03.004

Stern Y, Albert S, Tang MX, Tsai WY, 1999. Rate of memory decline in AD is related to education and occupation: Cognitive reserve? Neurology. 10.1212/wnl.53.9.1942

Stern Y, Tang MX, Denaro J, Mayeux R, 1995. Increased risk of mortality in alzheimer's disease patients with more advanced educational and occupational attainment. Ann. Neurol 10.1002/ana.410370508

Tsuang MT, Bar JL, Harley RM, Lyons MJ, 2001. The Harvard Twin Study of Substance Abuse: What we have learned. Harv. Rev. Psychiatry 10.1080/10673220127912

Tuligenga RH, Dugravot A, Tabák AG, Elbaz A, Brunner EJ, Kivimäki M, Singh-Manoux A, 2014. Midlife type 2 diabetes and poor glycaemic control as risk factors for cognitive decline in early old age: A post-hoc analysis of the Whitehall II cohort study. Lancet Diabetes Endocrinol. 10.1016/S2213-8587(13)70192-X

Vuoksimaa E, Panizzon MS, Chen C-H, Eyler LT, Fennema-Notestine C, Fiecas MJA, Fischl B, Franz CE, Grant MD, Jak AJ, Lyons MJ, Neale MC, Thompson WK, Tsuang MT, Xian H, Dale AM, Kremen WS, 2013. Cognitive reserve moderates the association between hippocampal volume and episodic memory in middle age. Neuropsychologia 51. 10.1016/j.neuropsychologia.2013.02.022

Wechsler D, 1955. Manual for the Wechsler Adult Intelligence Scale., Manual for the Wechsler Adult Intelligence Scale.

Zhao JH, Brunner EJ, Kumari M, Singh-Manoux A, Hawe E, Talmud PJ, Marmot MG, Humphries SE, 2005. APOE polymorphism, socioeconomic status and cognitive function in mid-life. The Whitehall II longitudinal study. Soc. Psychiatry Psychiatr. Epidemiol 10.1007/s00127-005-0925-y

Highlights

- Individuals vary in general cognitive ability (GCA) maintenance through adulthood
- Poor GCA maintenance coincides with advanced brain age
- Even among those with similar current GCA, age 20 GCA confers benefit
- Cognitive aging is affected by both young adult GCA and maintenance of GCA

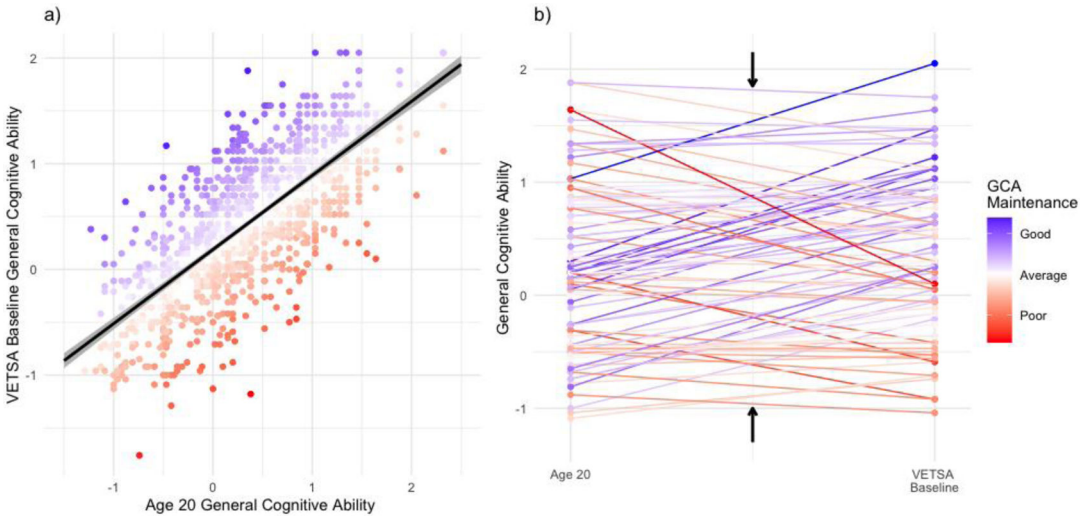

Figure 1. Derivation of general cognitive ability residual scores

Notes. a) Scatterplot with regression line predicting VETSA baseline general cognitive ability from age 20 general cognitive ability; b) random sample of 100 participants depicting change in general cognitive ability from age 20 to VETSA baseline assessment in the context of derived GCA residual scores. Arrows point to cases with similar change scores, but different residual scores, demonstrating adjustment for regression to the mean; Age 20 GCA and age 56 GCA were correlated .73, $p < .001$. GCA = General Cognitive Ability.

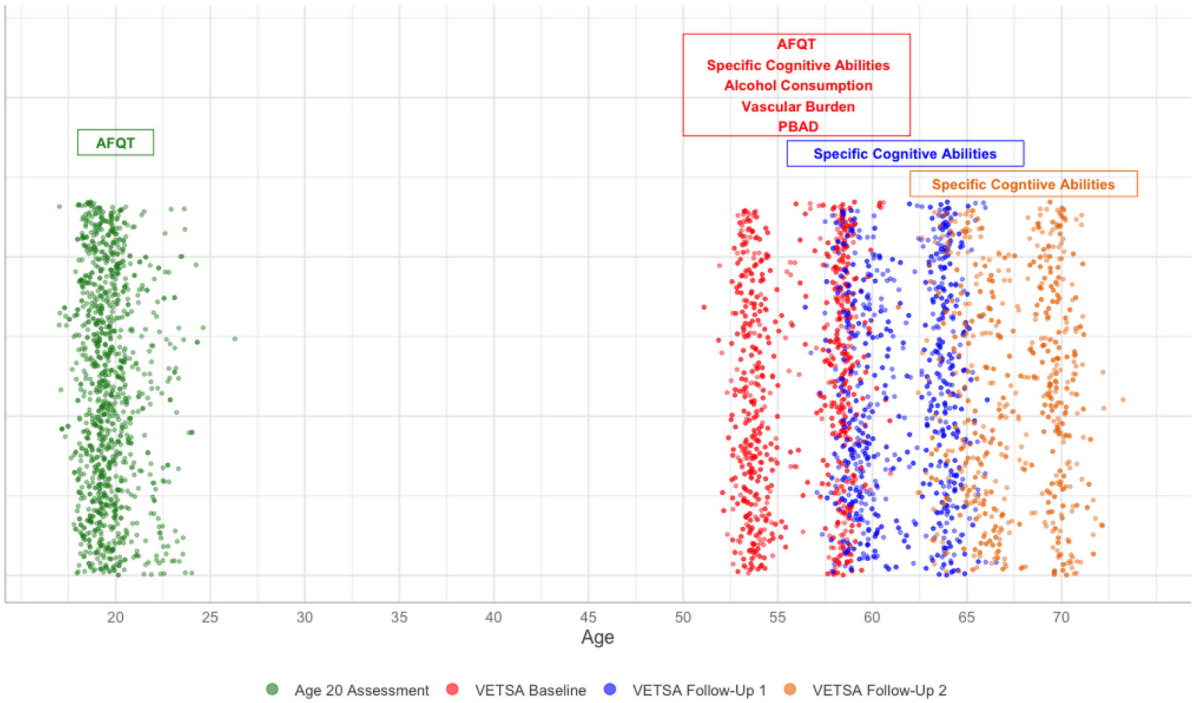

Figure 2. Timeline of analyzed measures

Notes. Points represent age at assessment for each participant and text boxes describe analyzed measures from each assessment. VETSA = Vietnam Era Twin Study of Aging; PBAD = Predicted brain age difference; AFQT = Armed Forces Qualification Test

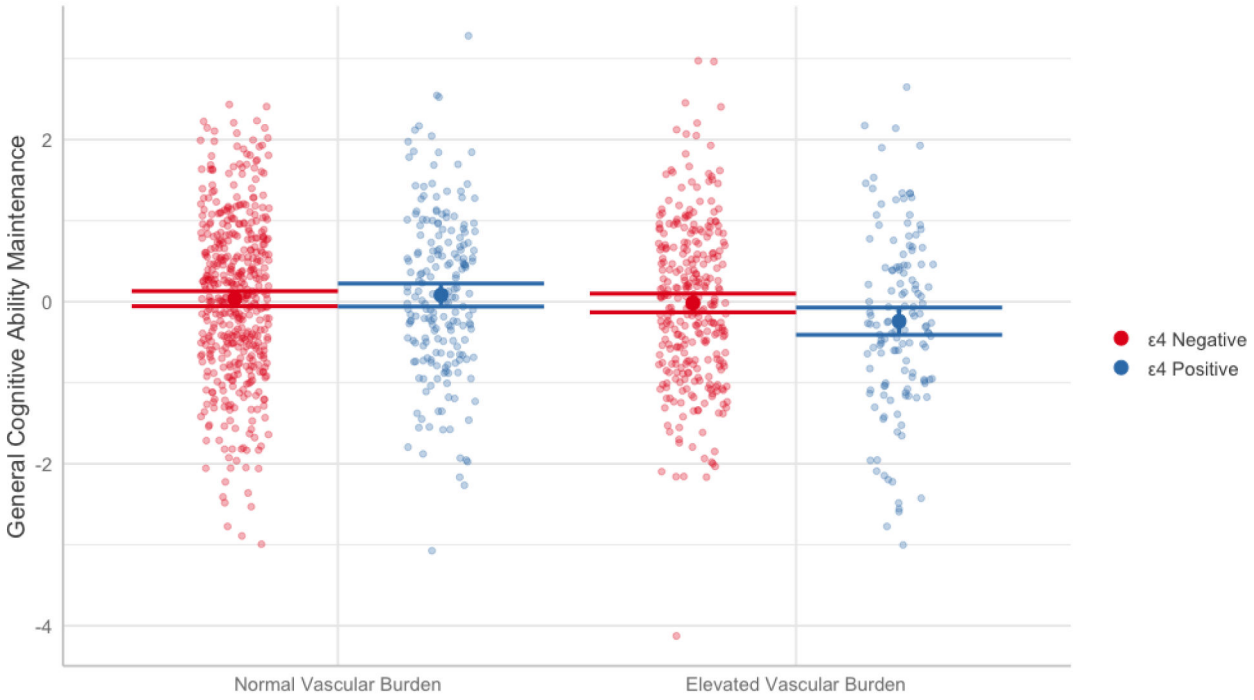

Figure 3. General cognitive ability maintenance score by *APOE* genotype and elevated vascular risk burden

Notes. APOE-ε4 genotype significantly moderated the association between vascular burden and general cognitive ability maintenance (b = −.27, $t = -2.071$, $p = .030$). There was a significant effect of vascular burden among ε4 carriers (b = −.32, t = −2.972, p = .003), but not among ε4 non-carriers (b = −.05, t = −0.725, p = .468). All models adjusted for white race/ethnicity. Error bars reflect 95% confidence intervals.

Table 1.

Sample Characteristics

	Mean or N	SD or %
Demographics		
Age at military enlistment (years)	19.68	1.24
Age at baseline VETSA assessment (years)	55.91	2.43
Education (years)	13.83	2.10
Race/Ethnicity (non-Hispanic white)	1144	91.8
AFQT Performance		
Military Induction AFQT (percentile)	63.57	22.12
First VETSA Assessment AFQT (percentile)	66.69	20.98
Vascular Risk Factors		
Hypertension	488	39.2
Diabetes	142	11.4
Current Smoker	299	24.0
Erectile Dysfunction	543	43.6
Heart Attack	74	5.9
Congestive Heart Failure	11	0.9
Angina	62	5.3
Elevated Vascular Risk Burden	432	40.0
Alcohol Consumption		
Never Drinkers	94	8.2
Former Drinkers	288	25.1
Light Drinkers	479	41.8
Moderate Drinkers	117	10.2
Heavy Drinkers	169	14.7
Alzheimer's Disease Genetic Risk		
APOE-ε4 Positive	344	29.3

Notes. Elevated Vascular Risk Burden was defined as ≥ 2 vascular risk factors.

Table 2.

Mixed effects models examining the effects of residual GCA scores and first VETSA assessment GCA on age 56 cognitive performance and age-related cognitive change

	Memory β (SE)	Semantic Fluency β (SE)	General Fluency β (SE)	Processing Speed β (SE)	Working Memory β (SE)	Executive Function β (SE)
Model 1						
Young adult GCA	.390 (.025)***	.225 (.026)***	.255 (.027)***	0.257 (.028)***	.370 (.024)***	.402 (.024)***
GCA maintenance	.237 (.023)***	.166 (.024)***	.169 (.025)***	0.223 (.026)***	.229 (.022)***	.258 (.022)***
Age	−.049 (.002)***	−.032 (.003)***	−.025 (.002)***	−0.096 (.002)***	−.037 (.002)***	−.070 (.002)***
Model 2						
Age*young adult GCA	.001 (.002)	−.002 (.003)	−.001 (.002)	.004 (.002)	−.002 (.002)	−.005 (.002)*[a]
Age*GCA maintenance	−.003 (.002)	−.003 (.003)	−.002 (.002)	.003 (.002)	−.001 (.002)	.0001 (.002)
Model 3						
Young adult GCA	.130 (.034)***	.037 (.035)	.069 (.036)	.023 (.038)	.131 (.032)***	.124 (.031)***
VETSA baseline GCA	.354 (.035)***	.257 (.036)***	.253 (.036)***	.317 (.038)***	.368 (.033)***	.334 (.032)***
Age	−.045 (.002)***	−.031 (.003)***	−.025 (.002)***	−.095 (.002)***	−.070 (.002)***	−.036 (.002)***
Model 4						
Age*young adult GCA	.003 (.003)	.001 (.004)	.001 (.003)	.005 (.003)	−.002 (.003)	−.006 (.003)
Age*VETSA baseline GCA	−.003 (.003)	−.004 (.004)	−.003 (.003)	−.0002 (.003)	.0002 (.003)	.001 (.003)

Notes. Row labels reflect predictors in specified models, column headers reflect outcomes from distinct models; GCA = General Cognitive Ability

*< .05

**< .01

***< .001

[a]Non-significant effect after false discovery rate correction; Sample sizes differed slightly across specific cognitive abilities due to missing data on neuropsychological measures. Sample sizes were as follows: Memory (n = 1162), Semantic Fluency (n = 1163), General Fluency (n = 1163), Processing Speed (n = 1100), Working Memory (n = 1153), and Executive Function (n = 1148).