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A 35-Year Longitudinal Assessment of Cognition and Midlife Depression Symptoms: The Vietnam Era Twin Study of Aging

Carol E. Franz, Ph.D.[1], **Michael J. Lyons, Ph.D.**[2], **Robert O'Brien, M.S.**[1], **Matthew S. Panizzon, Ph.D.**[1], **Kathleen Kim, M.D., M.P.H.**[1,4], **Reshma Bhat, M.D.**[1,4], **Michael D. Grant, Ph.D.**[2], **Rosemary Toomey, Ph.D.**[2], **Seth Eisen, M.D.**[3], **Hong Xian, Ph.D.**[3], and **William S. Kremen, Ph.D.**[1,4]

[1]University of California, San Diego

[2]Boston University

[3]Washington University

[4]VA San Diego Healthcare System

Abstract

Objective—To determine whether early adult cognitive ability is a risk factor for depressive symptoms in midlife and how genetic and environmental influences explain the association; to examine cross-sectional relationships between depressive symptoms and specific cognitive abilities at midlife.

Design: 35-year longitudinal and cross-sectional twin study of cognitive aging.

Setting: Large multicenter study in the United States.

Participants: 1237 male twins ages 51 to 60.

Measurements: At age 20 and midlife, participants completed the same version of a general cognitive ability test (Armed Forces Qualification Test [AFQT]). Midlife testing included an extensive neurocognitive protocol assessing processing speed, verbal memory, visual-spatial memory, working memory, executive function, and visual-spatial ability. Participants completed the Center for Epidemiologic Studies Depression Scale prior to cognitive testing and provided health and lifestyle information during a medical history interview.

Results—Lower age 20 AFQT scores predicted higher levels of depressive symptoms at age 55 ($r=-.16$, $p<.001$). In bivariate twin modeling, 77% of the correlation between early cognitive ability and midlife depressive symptoms was due to shared genetic influences. Controlling for current age, age 20 AFQT, and non-independence of observations, depressive symptoms were associated with worse midlife AFQT scores and poorer performance in all cognitive domains except verbal memory

Conclusion—Results suggest that low cognitive ability is a risk factor for depressive symptoms; this association is partly due to shared genetic influences. Cross-sectional analyses indicate that

Corresponding author: Carol E. Franz, PhD University of California San Diego Department of Psychiatry Gilman Drive, MC 0738 La Jolla, CA 92093 Tel: 858 822-1793 Fax: 858 822-5856 cfranz@ucsd.edu .

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the association between depressive symptoms and performance is not linked to specific cognitive domains.

Background

In older adults, cognitive impairment is frequently found in conjunction with depression, but whether poor cognitive performance is a risk factor for or a consequence of depressive symptoms remains unresolved. A handful of longitudinal studies find that low cognitive ability early in life may increase liability for later depressive symptoms (1-3). Most longitudinal studies, however, span either from childhood to young adulthood or from mid- to later life; few researchers examine the period from young adulthood to midlife.

With regard to specific cognitive abilities, slower processing speed and poorer functioning on memory tests are reported in many but not all studies of both clinically and sub-clinically depressed adults (4-9). Poorer executive function abilities (e.g., planning, set shifting, cognitive inhibition, mental flexibility, working memory, and organizing) are also more likely in adults with higher levels of depressive symptoms (5,6,10-13). Given that few studies assess pre-morbid cognitive ability, it is difficult to determine whether depressive symptoms increase vulnerability for poorer cognitive performance independent of prior cognitive ability. Most studies examining cognition and depressive symptoms are genetically uninformative; that is, they cannot distinguish the extent to which the co-occurrence of depressive symptoms and poor performance on cognitive measures is influenced by shared genetic and/or environmental influences (9,14,15). In addition, very few studies use cognitive test batteries that evaluate a broad range of specific cognitive abilities, making comparisons among studies difficult. Sorting out the interrelationships among cognitive performance and depressive symptoms is particularly important given the long term implications for functional status and independence in later life (6,16-20).

The Vietnam Era Twin Study of Aging (VETSA) was designed to elucidate the role of genetic and environmental influences on cognitive aging starting at midlife. In the VETSA, we re-administered a test of general cognitive ability at midlife participants had taken at induction into the military 35 years previously. At midlife, participants also were assessed with an extensive neurocognitive battery. Twin studies are a powerful analytic method because they allow the estimation of the relative influences of genes and environment on a particular characteristic (phenotype) or between phenotypes, such as cognitive ability and depression symptoms.

Using this longitudinal twin design, we examined four research questions: 1) Do participants with lower general cognitive ability at age 20 have higher levels of depressive symptoms at midlife? 2) Is decline in general cognitive ability from early to middle adulthood associated with more depressive symptoms? 3) If early adult general cognitive ability and midlife depressive symptoms are related, to what extent do genetic and environmental factors explain the association? And 4) At midlife, do participants with higher levels of midlife depressive symptoms perform more poorly on concurrently assessed measures of executive function, processing speed, and general cognitive ability after controlling for early adult cognitive ability?

Methods

Sample

The Vietnam Era Twin Study of Aging (VETSA) comprises 1237 male twins (614 pairs and 9 unpaired twins) ages 51-60 (mean age 55.4, SD 2.5). The VETSA baseline assessment was conducted between 2003 and 2007. To be eligible, twins had to be between age 51 and 59 at

the time of recruitment, and both members of a pair agreed to participate. We recruited VETSA participants from the Vietnam Era Twin Registry sample of male-male monozygotic (MZ) and dizygotic (DZ) twin pairs. The twin registry was established in the early 1980s based on twins who served in the United States military during the Vietnam era (1965 to 1975). Most participants (68%) did not serve in combat or in Vietnam (21,22). Women are not in the registry due to the lack of women (especially twins) in the military during that era. A combination of DNA testing, questionnaire and blood group methods was used to determine zygosity (23); comparisons of the genotype-based and questionnaire-based zygosity measures indicated 95% accuracy. VETSA twin pairs were randomly selected from a pool of 3322 VET registry twin pairs who had participated in a different study conducted in 1992 (24). Demographic comparisons indicate that VETSA participants were largely representative of the Registry sample (25). The sample was predominantly Caucasian (86%).

Procedures

Twins traveled either to the University of California, San Diego or to Boston University for a day-long assessment involving an extensive neuropsychological test battery, a medical history interview, and functional assessments. When a participant could not travel (n = 33 individuals, 2.6%), research assistants conducted assessments at a facility close to the twin's home. Details of the derivation of the test battery and sample have been described elsewhere (25). A month prior to the day of testing, participants completed a packet of psychosocial and demographic measures. IRB approval was obtained at both sites, and all participants provided signed consent.

Measures

Depressive symptoms—Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D)(26). Participants completed the CES-D as part of the psychosocial packet. The CES-D scale consists of 20 items concerning the frequency of specific moods and behaviors during the past week; ratings range from zero (experienced the symptom less than one day during the past week) to three (experienced on five to seven days). The measure has excellent reliability (alpha >0.92) and is considered a valid indicator of clinically meaningful depressive symptoms (27). As is commonly found in community samples, CES-D scores were significantly skewed to the right, indicating that most participants scored low in depressive symptoms. CES-D scores were log transformed to normalize the data prior to data analyses.

Cognitive Measures—General cognitive ability was assessed with the Armed Forces Qualification Test (AFQT Form 7A)—a 50-minute paper and pencil test with 100 multiple-choice items. The same version of the AFQT was administered to the participants 35 years previously (average age 20, prior to military induction) with the same standardized instructions. Age 20 AFQT scores were acquired from military records and archived at the twin registry (28,29). The AFQT is highly correlated (r=0.84) with measures of general cognitive ability such as the Wechsler Adult Intelligence Scale (30).

In addition to general cognitive ability, the VETSA midlife neurocognitive battery assessed seven domains using standardized measures: processing speed, verbal and visual spatial memory, executive function, working memory, and visual spatial processing. Tests were selected to avoid ceiling effects in middle-aged adults and thus be more sensitive to change in future assessments. Individual measures were standardized and averaged in order to create the cognitive domain scores. Analyses were conducted with domain measures followed by individual measures. For the sake of comparisons with other studies, results for all of the

individual tests are shown for descriptive purposes, but in our explanation of the results, we only consider domain scores.

The Processing Speed domain included measures from the Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test (conditions two and three-- number and letter sequencing, respectively) (31), and the Stroop word reading condition (32,33). Since for all other cognitive tests negative correlations with depressive symptoms indicated worse performance, we reversed the Trails scores so that lower scores indicate slower processing speed. Lower scores on the Stroop reflect poorer performance.

The Verbal Memory domain included the California Verbal Learning Test version two (CVLT) immediate and delayed free recall (34), and the Wechsler Memory Scale-III (WMS-III) (35) Logical Memory Test (immediate and delayed story recall conditions). In our administration, stories were presented only once. The Visual Spatial Memory domain used the WMS-III Visual Reproductions tests (35) in which five designs were each viewed for 10 seconds and then drawn from memory for immediate and delayed recall. Verbal and visual spatial memory domain scores included immediate and delayed recall scores, and delayed recall adjusted for immediate recall. The Short Term Memory domain was based on standardized and averaged scores from WMS-III Digit Span (forward condition) and Spatial Span (forward condition) (35).

Measures included in the Executive Function domain included the D-KEFS Trails condition 4 (number-letter switching), Verbal Fluency Category Switching (fruit-furniture), and the Stroop color-word interference condition. The time score for the Trails switching condition was adjusted for processing speed (Trails 2 and 3) in order to isolate the executive function switching component. Scores on the fluency switching task were adjusted by the score on the animal fluency test to isolate the executive (switching) component. The Stroop interference condition score was adjusted for Stroop word reading performance in order to isolate the executive (cognitive inhibition) component. The Working Memory domain included tests from the WMS III (35): Digit Span backward adjusted for Digit Span forward, Letter-Number Sequencing adjusted for Digit Span forward, and the Spatial Span backward adjusted for Spatial Span forward.

The Visual Spatial Ability domain included the raw scores from the Matrix Reasoning subtest from the Wechsler Abbreviated Scale of Intelligence (30), Thurstone's adaptation of the Gottschaldt Hidden Figures Test (GHFT) (36), and the Card Rotation test (37). Higher scores indicate that the participants completed more items in each test correctly.

Confounders/Covariates—Multiple health and lifestyle factors may confound the association between cognitive performance and depressive symptoms. In order to control for these influences, we included hypertension, cardiovascular risks, diabetes, age, smoking and alcohol consumption, other psychiatric diagnoses, and head injury as covariates in some of the models (38-41). In brief, participants were coded as having hypertension (yes/no) if average blood pressure across four measures taken in the morning and afternoon on the day of testing was greater than or equal to 140 systolic and/or 90 diastolic or if they currently took medication for hypertension (42). The cardiovascular index (yes/no) indicated the presence or absence of having had a heart attack, heart failure, peripheral vascular disease, stroke, heart surgery, catheterization or angioplasty (43). Participants were coded as diabetic (yes/no) if they were taking medication for diabetes and said they had a diagnosis of diabetes. Participants were coded as currently smoking if they smoked at least 100 cigarettes in their lives and currently smoked (1=current smoker/ 0=nonsmoker). Current alcohol consumption was coded as: 0= never drank or did not drink alcohol (beer, wine or hard liquor) in previous 14 days, 1= one or fewer drinks per day, 2= more than one up to two

drinks per day; 3= more than two drinks per day (38). We included an indicator of the presence of other psychiatric problems (yes/no) based on participants' responses to medical history questions regarding whether a physician had ever told them they had an anxiety disorder, post-traumatic stress disorder, drug abuse or alcohol abuse. No participants had a depression diagnosis prior to the early adult AFQT. Head injury was assessed for 1023 out of 1237 participants (the question was added to the protocol late); 300 (29%) men reported at least one head injury.

Statistical analyses

Non-twin analyses—Using SAS 9.2 (44), we performed generalized linear mixed model regressions (proc glimmix) in which the separate cognitive domains or separate cognitive tests were the outcome measures. A family identifier (a variable that identified whether the twins were part of the same family) was entered as a random effect to control for non-independence of the participants. The mixed model approach allowed us to examine the unique effect of age 20 general cognitive ability or change in cognitive ability on age 55 depressive symptoms (first and second hypotheses) and of concurrent depressive symptoms on cognitive performance (fourth hypothesis), adjusting for other variables in the model. In tests of the fourth hypothesis, we conducted three increasingly complex models with each subsequent model including variables from previous models. Model 1 adjusted for age and age 20 general cognitive ability; Model 2 additionally adjusted for other psychiatric problems. Model 3 additionally adjusted for other health and lifestyle influences (smoking, alcohol consumption, head injury, presence of diabetes, hypertension, and cardiovascular disease). Results are reported for the Type III tests of fixed effects.

Twin modeling—Twin studies are a powerful analytic method because they allow the estimation of the relative influences of genes and environment on a particular characteristic (phenotype) or between phenotypes, such as cognitive ability and depression symptoms. Twin modeling was used to examine the extent to which genetic and environmental factors explain the association between age 20 general cognitive ability and depressive symptoms (third hypothesis). Because MZ twins share 100% of their genes whereas DZ twins, like other siblings, share on average 50% of their genes, this approach allows researchers to use the difference in degree of similarity within MZ pairs compared with DZ pairs to estimate the amount of variance or covariance due to three sources: additive genetic (A), common or shared environment (C), and unique or unshared environment (E). Additive genetic influences account for all genetic influences. The common environmental component represents all non-genetic factors that make relatives similar on a phenotype. In contrast, the unique environmental component represents life events that make relatives different (e.g., having a spouse die, losing a job etc.); unique environmental influences include measurement error.

We fit statistical models for the structure of the genetic and environmental covariance of the AFQT measure at age 20 and the CES-D using the Mx package for structural equation modeling (45). The baseline for the twin covariance structure against which other reduced models are compared is the "triple Cholesky ACE model" which factors the phenotypic variance/covariance matrices of MZ and DZ twins into components of variance and covariance due to additive genetic, and common as well as unique environmental effects. Cholesky decompositions have the same number of independent factors as the number of variables in the model (i.e., two). Using this model we can estimate contributions of A, C, and E to each measure, as well as the degree of overlap between genetic, common environmental and unique environmental factors for multiple measures.

Results

Descriptive statistics

Participants averaged 55 years old at the time of the VETSA assessment. Most men were currently married (79%) and employed full-time (78%) with a median family income of 60 to 70 thousand dollars per year. Over half (57%) received some post-secondary school education, and a third of the participants (29%) had at least a college degree. With regard to health and lifestyle factors, as can be seen in Table 1, 56% had hypertension, 8% diabetes, and about one sixth reported cardiovascular disease. One quarter of the men currently smoked and 59% reported having at least one alcoholic drink in the past two weeks. Health and lifestyle characteristics were very comparable to those of the general population of men in the United States in this age group (46,47).

The average CES-D score was 8.31 (SD 8.25; range 0-52); these scores are consistent with scores for community samples (26). Fifteen percent (185) of the men had scores of 16 or higher on the CES-D: a score indicating a clinically meaningful level of depressive symptoms. In the medical history interview, participants were asked if a doctor ever told them they were depressed; 170 (13.7%) responded positively. Two thirds of these men (116) also said they were currently depressed. CES-D scores in the currently depressed group were significantly different from those in the never depressed groups (currently depressed group = 19.70 SD =12.6; non-depressed group=6.99 SD 6.53; $t(1184) = -17.64$ $p<.0001$). Eleven percent reported that they had received a psychiatric diagnosis other than depression in their lifetimes; having a psychiatric diagnosis other than depression was positively correlated with the CES-D. Men with higher levels of depressive symptoms were significantly younger, and more likely to smoke, have cardiovascular disease, and hypertension.

Longitudinal relationship between cognitive ability (AFQT) at age 20 and depressive symptoms at age 55. In support of the first hypothesis, men with lower cognitive ability at age 20 had significantly higher levels of depressive symptoms at age 55 ($r= -.16$, $p<.001$). The second hypothesis was not supported: there was no relationship between change in AFQT scores and the midlife CES-D score. This may be due, in part, to the high stability of general cognitive ability; AFQT scores at age 20 were significantly associated with AFQT scores at age 55 ($r=.74$, $p<.0001$) (48).

Bivariate twin modeling

We examined the extent to which genetic and environmental factors explained the significant association between age 20 general cognitive ability and age 55 depressive symptoms using bivariate twin modeling. Both general cognitive ability and depressive symptoms were significantly heritable (49% and 19% respectively)(48,49). Results indicated that 77% of the correlation between age 20 cognitive ability and midlife depressive symptoms was due to shared genetic influences. The remaining covariance stemmed from shared common environmental influences. In total, genetic influences from the age 20 AFQT accounted for a small but significant portion of the genetic variance in depressive symptoms (13%). Virtually none of the unique environmental variance is shared between measures. Thus unique environmental factors strongly influence development of depressive symptoms (approximately 81% of the variance) and moderately influence general cognitive ability (51% of the variance). However, those aspects of the unique environment that specifically influence general cognitive ability do not influence depressive symptoms (and vice versa).

Cross-sectional analyses at age 55

We tested the fourth hypothesis by examining cross-sectional relationships between depressive symptoms at midlife and concurrently assessed specific and general cognitive abilities. Table 2 provides the descriptive statistics for the cognitive measures and the unadjusted correlations with the CES-D. For the most part, associations were non-specific; that is, they occurred across measures from all domains. Depressive symptoms were significantly correlated (unadjusted) with poorer performance in 17 out of the 22 individual cognitive measures (Table 2). Individual scores for cognitive measures (see Table 2 and 3) are presented for the sake of comparability with other studies.

As described in the methods section, the cognitive measures were collapsed into seven domains representing specific cognitive abilities. We conducted multivariate modeling with depressive symptoms as the predictor variable; the first model controlled for age and cognitive ability at age 20 as fixed effects with family ID as a random effect. As can be seen in Table 3, higher levels of depressive symptoms were significantly associated with poorer performance in five out of the seven cognitive domains: processing speed, visual spatial memory, executive functions, working memory, and visual spatial ability. Correlation coefficients were calculated from the mixed models (Table 3) in order to estimate the effect of depressive symptoms on specific cognitive domains; correlations of .1 are considered equivalent to a low or small effect size (50). Overall, the effect of depressive symptoms on working memory ($r = -.11$), executive functions ($r = -.10$), and general cognitive ability ($r = -.09$) at age 55 was low; weakest/trivial effects were found for verbal memory ($r = -.05$), and processing speed ($r = -.06$).

When health and lifestyle measures (e.g., psychiatric diagnoses, smoking, alcohol consumption, presence of diabetes, hypertension, cardiovascular disease, head injury) were added to the mixed models, concurrent depressive symptoms were still significantly associated with poorer performance in four cognitive domains: visual spatial memory, executive functions, working memory, and visual spatial ability (data not shown). Depressive symptoms were no longer associated with processing speed once health and lifestyle influences were accounted for ($t(574) = -1.54$, $p < .12$)). Participants with slower processing speed were older, more likely to smoke and consume alcohol, or have cardiovascular disease. Health and lifestyle measures neither explained additional variance in the other cognitive domains nor improved the model fit data.

Conclusion

Our goal was to address four research questions

With regard to the first question, the data strongly suggest that low cognitive ability in early adulthood is a risk factor for developing symptoms of depression 35 years later. These results are consistent with some previous studies (1-3). Koenen et al., for instance, found that lower childhood cognitive ability predicted major depression at age 32 and increased the likelihood of experiencing persistent depression between the ages of 18 and 32 (3). Other studies, however, only found support for an indirect association between childhood general cognitive ability and major depression (51,52); other risk factors such as childhood conduct disorder, mediated the association. Our results are also consistent with a co-twin control study that compared pairs of monozygotic twins where one twin had been diagnosed with major depression and the other was not; similar cognitive impairments (language, declarative memory, executive function) were found in both twins regardless of diagnosis (14). These results are unique in that this study is one of the very few genetically informative studies examining cognition and depressive symptoms in midlife adults.

We examined the extent to which genetic and environmental factors explain the association between early adult cognitive ability and depressive symptoms. In keeping with a sizable literature, we found substantial genetic influences on cognitive ability and small to moderate genetic influences on depressive symptoms (48,53). Most of the association between cognitive ability and depressive symptoms appeared to be due to shared genetic influences. Most of the variance, however, was accounted for by unique environmental factors that influenced each phenotype independently (there were no shared unique environmental influences). Thus the environmental factors that specifically influenced cognitive ability were different from the environmental factors that influenced the development of depressive symptoms. These unique environmental factors, by definition, are types of life events or stresses to which only one of the members of the twin pair was exposed. It is beyond the scope of these analyses to examine the possible environmental influences contributing to cognitive ability and depressive symptoms. In part, this is because twin studies historically have identified genetic influences on putatively environmental phenotypes (e.g., marriage, social support, education, stress); future analyses need to proceed with systematic delineation of genetic and environmental covariance.

What might explain the increased risk for depressive symptoms associated with early adult general cognitive ability? Given the cognitive complexity of many adult activities, adults with lower cognitive performance may be exposed to increased stress but have less flexible coping strategies and fewer resources, thereby contributing to greater liability for depressive symptoms. There is also considerable evidence that low cognitive ability is associated with a number of social and psychological factors that increase the likelihood of developing depression such as lower education (and concomitant lower health literacy), lower status jobs, lower income, poorer health care, worse working, living, and social conditions in childhood and adulthood, childhood conduct problems, adult psychiatric problems, greater exposure to health risks associated with poverty, and increased stress (1,41,54-58). With a genetically informative research design, it is possible to tease apart the genetic and environmental influences on these phenotypes as well as on their association with cognitive ability and depressive symptoms.

Decline in general cognitive ability from early to middle adulthood was not associated with higher midlife depressive symptoms; thus worsening cognitive ability did not account for feelings of depression. In general, cognitive ability was highly stable across the 35 years of the study. Finally, cross-sectional analyses indicated that higher levels of midlife depressive symptoms were associated with poorer executive functions (mental flexibility, working memory), slower processing speed, worse visual spatial memory and ability, as well as lower general cognitive function, even when controlling for general cognitive ability assessed 35 years earlier. These results provide further support for a relatively non-specific association between depressive symptoms and cognitive performance (8). There was a suggestion of some specificity for visual spatial memory, as opposed to verbal memory—a pattern that is consistent with the results of a previous meta-analysis (7). Although not predicted, performance on visual spatial ability tasks was poorer in men who had more depressive symptoms; visual spatial abilities have received little attention in previous studies. It may be that the present results largely reflect executive function abilities. As can be seen in Table 3, Matrix Reasoning—which has a strong abstraction component—was the only test in the visual spatial ability domain significantly associated with depressive symptoms. Finally, the association between processing speed and depressive symptoms was no longer significant once health and lifestyle influences were included in the statistical model. Although some studies have found that processing speed is still associated with depression after accounting for health factors, other results have suggested that the relationship may be primarily for more complex speed measures that require some degree of

executive control (4). It may be that the sample is still relatively healthy at middle age so that health effects are not yet evident for other abilities that do not involve speed.

Cognitive ability affects multiple aspects of life thought to be protective against cognitive decline such as education, employment status, income and physical health; these results suggest that higher cognitive ability may also be protective against depressive symptoms. Executive function abilities, in particular, have been shown to have long-term implications across the life course (6,16,17). Among older adults, executive function deficits are associated with lower functional status, making it harder for older adults to maintain their independent activities of daily living (18). Low cognitive ability is also a risk factor for dementia; in some studies of older adults depression also increases vulnerability for dementia and mild cognitive impairment (19,20). The persistence and pervasiveness of impaired cognitive performance in patients with remitted or ongoing depression has also been recognized (8). These results show that longitudinal genetically informed studies can yield a deeper understanding of the complex association between cognition, symptoms of psychological distress, genes and environment that may ultimately improve outcomes for adults with depressive symptoms.

Strengths and Limitations

One limitation of this study may be the use of self-report depressive symptoms rather than a structured diagnostic interview. However, self-report measures are commonly used to assess depressive symptoms in population-based studies and earlier studies point to the effects of even subclinical levels of depressive symptoms on functioning and cognitive performance (10,12,59). Moreover, by using the CES-D, we were able to show that even mild depressive symptoms in a non-patient sample are still associated with poorer cognitive function. It is a limitation that no assessment of depressive symptoms or specific cognitive abilities was conducted at the time of the first cognitive testing (age 20). No twins were diagnosed with depression before age 20 but it is still possible that some depressive symptoms were present at the time. We created separate domains for Short Term and Working Memory, but it should be acknowledged that the internal consistency of the Working Memory domain was lower than that of the other neurocognitive domains. In an earlier version of the manuscript, an anonymous reviewer raised the issue of redundancy in these domains and concern over the internal consistency of the scores within domains. Combining the backward conditions of Spatial Span and Digit Span does substantially increase the internal consistency of the Short Term Memory domain, but it also conflates components of working memory (manipulation of information) and short term memory (maintenance of information). Although there is no ideal solution, our Working Memory domain includes the backward conditions controlling for the forwards conditions (to emphasize manipulation). The Short Term Memory domain now only includes the forwards conditions of Spatial and Digit Span. The correlation between these two domains is .13, suggesting that they capture different components of memory. The higher internal consistency of a Short Term Memory domain that includes both forwards and backwards conditions is likely due to the shared maintenance demands in all of the subtests. This problem is similar to that of high correlations between Trails A and Trails B; this association is likely due to processing speed. Unless Trails B is controlled for processing speed, Trail B is not a good measure of executive (set-shifting) function. We believe that the compromise we propose is important for being able to elucidate the distinction between information maintenance and manipulation in short term memory. Another limitation is that our sample only included men and was predominantly Caucasian, so the results may not generalize to women and minorities. In general, though, middle-aged men have been underrepresented in studies of depression, aging, and cognition. The present study, thus, serves to fill some of that knowledge gap.

Having actual early adult cognitive ability scores is a unique aspect of this study because most studies of depressive symptoms and cognition are limited to using education as a proxy for premorbid cognitive ability. Other strengths of the study include having a large twin middle aged community-dwelling sample, and having longitudinal data based on the same general cognitive ability test over a 35 year period. A few studies may have early cognitive measures, but it is extremely rare to have the same measure of cognitive ability at two time points this far apart. The present study on middle aged adults highlights the need to elucidate the ways in which genetic and environmental factors contribute to cognitive ability and mood in midlife adults, not just in the aged.

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Table 1

Descriptive statistics for CES-Depression, health and lifestyle characteristics

	Mean (SD)	Correlation with CES-D
CES-D: Depression symptoms	8.31 (8.25)	
Age	55.44 (2.48)	**−0.11** **
HEALTH MEASURES	**N (%)**	
Has Hypertension	689 (55.7%)	**0.05** *
Has Diabetes	104 (8.4%)	0.02
Has any Cardiovascular disease	214 (17.3%)	**0.07** **
Current smoker	296 (24%)	**0.10** ***
Alcohol consumption (0-3 scale)		−0.03
Never or not in past 2 weeks	500 (40.4%)	
1 or fewer drinks per day	504 (40.7%)	
> 1 to ≤ 2 drinks per day	105 (8.5%)	
>2 drinks per day	128 (10.4%)	
Has Other Psychiatric Dx	134 (10.8%)	**0.20** ***
Had a head injury (in lifetime)	300 (29.3%)	**0.12** ***

Notes: CES-D=Center for Epidemiologic Studies Depression Scale;

* p<.05;

** p<.01,

*** p<.001 or greater;

Kendall's Tau reported for categorical health measures; N for CES-D = 1231; N's vary slightly (1202-1231) due to missing data.

Table 2

Descriptive statistics for individual cognitive tests and correlations with CES-D

COGNITIVE MEASURES	Mean (SD)	Correlation with CES-D
AFQT (age 20)	61.13 (22.27)	**−0.16** ***
AFQT (age 55)	64.07 (20.94)	**−0.18** ***
Card Rotation	94.16 (24.51)	**−0.07** *
CVLT Short Delay Free Recall	8.63 (2.74)	−0.02
CVLT Long Delay Free Recall	9.06 (2.89)	**−0.06** *
Digit span Forward	10.20 (2.29)	**−0.08** **
Digit span Backward	6.50 (2.17)	**−0.10** **
Hidden Figures	47.9 (20.36)	**−0.12** ***
Letter-Number Sequencing	10.13 (2.38)	**−0.11** ***
Logical Memory immediate	23.45 (6.14)	−0.05
Logical Memory delayed	20.00 (6.64)	−0.04
Matrix Reasoning	23.07 (5.91)	**−0.13** ***
Spatial span Forward	8.05 (1.67)	−0.01
Spatial span Backward	7.41 (1.80)	**−0.12** ***
Stroop Word	93.49 (14.38)	**−0.10** ***
Stroop Color-Word Interference	35.93 (8.43)	**−0.10** ***
Trails 2 (Numeric)[1]	33.50 (12.46)	−0.04
Trails 3 (Letters) [1]	33.73 (13.47)	**−0.08** **
Trails 4 (Letter-Numeric switching) [1]	89.56 (35.32)	**−0.07** **
Verbal Category Fluency--Animals	19.21 (4.46)	−0.03
Verbal Fluency Switching Total	11.48 (3.04)	**−0.12** ***
Visual Reproduction immediate	78.15 (12.45)	**−0.11** ***
Visual Reproduction delayed	54.58 (19.58)	**−0.10** ***

Notes: CES-D=Center for Epidemiologic Studies Depression Scale;; CVLT=California Verbal Learning Test; AFQT: Armed Forces Qualification Test; SD= standard deviation;

* p<.05;

** p<.01,

*** p<.001 or greater;

Kendall Tau reported for health measures; Pearson correlation coefficients reported for cognitive measures; N for CES-D = 1231; N's vary slightly (1202-1231) due to missing data.

1) Scores on Trails measures have been reversed so that negative correlations indicate that slower speeds (poorer performance) are associated with higher CES-D symptoms. For all other cognitive measures, negative correlations indicate that worse performance is associated with higher CES-D symptoms.

Table 3

Depressive symptoms and concurrent cognitive performance, controlling for current age, age 20 general cognitive ability (AFQT), and non-independence of observations.

		Depressive Symptoms (CES-D)		
Cognitive Domains and Tests[1)]	**N**	**Correlation**[2)]	**t-test**	**p**
General Cognitive Ability (AFQT @ age 55)	1214	**−0.09**	**−3.15**	**0.002**
Processing Speed Domain	1208	**−0.06**	**−1.97**	**0.05**
Trails 2	1203	--	−0.81	0.42
Trails 3	1203	--	−1.33	0.19
Stroop Word	1205	**−0.06**	**−2.24**	**0.03**
Verbal Memory Domain	1212	−0.05	−1.78	0.08
Logical Memory immediate	1205	--	−0.34	0.73
Logical Memory delayed	1203	--	−0.58	0.56
Logical Memory delayed adjusted for Logical Memory immediate	1203	--	−0.13	0.90
CVLT Short Delay Free Recall (CVLTSDFR)	1202	--	0.18	0.86
CVLT Long Delay Free Recall (CVLTLDFR)	1201	--	−1.30	0.20
CVLTLDFR adjusted for CVLTSDFR	1201	**−0.08**	**−2.72**	**0.007**
Visual Spatial Memory Domain	1208	**− 0.07**	**−2.35**	**0.02**
Visual Reproduction immediate	1208	**− 0.06**	**−2.05**	**0.04**
Visual Reproduction delayed	1207	**− 0.07**	**−2.30**	**0.02**
Visual Reproduction delayed adjusted for Visual Reproduction immediate	1207	--	−1.31	0.19
Short Term Memory Domain	1213	−0.01	−0.26	0.79
Spatial Span Forward	1208	--	0.66	0.51
Digit Span Forward	1207	--	−1.20	0.23
Executive Function Domain	1209	**− 0.10**	**−3.53**	**0.0004**
Trails 4 Switching adjusted for Trails 2	1200	**−0.07**	**−2.39**	**0.02**
Trails 4 Switching adjusted for Trails 3	1200	**−0.06**	**−2.05**	**0.04**
Stroop Color-Word Interference adjusted for Stroop Word	1202	**− 0.06**	**−2.04**	**0.04**
D-KEFS Verbal Fluency Category Switching adjusted for Animal Fluency	1205	**− 0.10**	**−3.43**	**0.0006**
Working Memory Domain	1212	**−0.11**	**−4.00**	**0.0001**
Spatial span Backward adjusted for Spatial Span Forward	1208	**−0.10**	**−3.59**	**0.0004**
Digit span Backward adjusted for Digit Span Forward	1203	**−0.06**	**−2.21**	**0.03**
Letter-Number Sequencing adjusted for Digit Span Forward	1203	**− 0.06**	**−2.16**	**0.03**
Visual Spatial Ability Domain	1212	**−0.08**	**−2.69**	**0.008**
Matrix Reasoning	1208	**−0.09**	**−2.98**	**0.003**
Hidden Figures	1204	--	−1.57	0.12
Card Rotation	1209	--	−1.16	0.25

[1)] Notes: For all cognitive domain scores, negative values indicate worse performance.

[2)]Correlation derived from the mixed model regressions after controlling for age and age 20 cognitive ability with family ID entered as a random effect; AFQT=Armed Forces Qualification Test; CES-D=Center for Epidemiologic Studies-Depression Scale; p= significance level.

Tests shown under each domain are component tests of that domain. Component tests for cognitive domains were z scored and averaged to create the domain score; in mixed model regressions depressive symptoms were adjusted for age, age 20 cognitive ability, and family ID as a random effect.