Published in final edited form as:
Psychol Aging. 2013 December ; 28(4): 1004–1014. doi:10.1037/a0034838.

Cognitive activities and cognitive performance in middle-aged adults at risk for Alzheimer's disease

Erin Jonaitis, **Asenath La Rue**, **Kim Mueller**, **Rebecca Koscik**, **Bruce Hermann**, and **Mark A. Sager**
University of Wisconsin-Madison

Abstract

Cognitive activity is thought to provide some protection against dementia, but the mechanism and timing of these effects are unknown. Data for this study were drawn from the Wisconsin Registry for Alzheimer's Prevention (WRAP), an at-risk middle-aged sample (mean age = 54 years) enriched for parental family history of Alzheimer's disease (AD). We had two main aims: (1) to determine the relative contribution of three facets of cognitive activity -- education, occupational complexity with data, and cognitive leisure activities – to WRAP participants' cognitive performance; and (2) to assess for interactions between genetic risk factors and cognitive activity in explaining cognitive performance. Results from mixed effects models indicate that some of the variance usually attributed to education may be more closely accounted for by cognitive activities later in life. Overall, our analyses suggest cautious optimism for cognitive activities, especially game-playing, as a strategy for preserving cognitive strengths in midlife.

Introduction

Risk of dementia due to AD is influenced by many factors, including potentially modifiable aspects of health and lifestyle (Barnes & Yaffe, 2011; Fratiglioni, Paillard-Borg, & Winblad, 2004). In particular, low levels of education have been linked to increased odds of developing AD (Sharp & Gatz, 2011; Wight et al., 2002). Work history and leisure-related cognitive activities are additional factors that may influence late-life cognition and AD risk (Fratiglioni & Wang, 2007; Valenzuela & Sachdev, 2006a, b; Wilson & Bennett, 2003). Whereas formal education often ends in late adolescence, work and cognitive activities can provide cognitive stimulation throughout adulthood.

Work history has been linked to cognition and/or AD risk among older adults in several major studies. Both the HARMONY follow-up of the Swedish Twin Registry (Andel et al., 2005; Andel et al., 2007) and the Kungsholmen project (Karp et al., 2009) have found lower AD risk in elderly adults whose main occupations entailed high degrees of complexity in work with data or people. Furthermore, the Canadian Health and Aging Study reported

Correspondence concerning this article should be addressed to: Erin Jonaitis, Wisconsin Alzheimer's Institute, University of Wisconsin, Madison, WI 53719. Contact: jonaitis@wisc.edu.
All authors are affiliated with the Wisconsin Alzheimer's Institute, Department of Medicine, School of Medicine and Public Health, University of Wisconsin-Madison. Bruce Hermann is also affiliated with the Department of Neurology, University of Wisconsin-Madison.

lower AD risk associated with jobs that involved high degrees of complexity in work with things, as well as people (Kröger et al., 2008). Other analyses suggest that particular types of jobs (e.g., manual production of goods) may increase the risk of AD (Qui et al., 2003). In most (e.g., Andel et al, 2005; Andel et al., 2007; Kröger et al., 2008), but not all (e.g., Karp et al., 2009), of these analyses, the predictive significance of occupational complexity remained after statistical adjustment for other relevant factors such as education and socioeconomic status.

Longitudinal studies relating cognitive activities during leisure to cognition and/or AD risk in older adults have also found significant associations (e.g., Akbaraly et al., 2009; Crowe et al., 2003; Hultsch et al., 1999; Wilson et al., 2002, 2003; Verghese et al., 2003; Pillai et al., 2011; Treiber et al., 2011), and the beneficial effects of cognitively stimulating activities typically remain when education, occupation, and other potential confounds are covaried (e.g., Akbaraly et al., 2009; Hultsch et al., 1999; Wilson et al., 2003; Pillai et al., 2011; Treiber et al., 2011; Carlson et al., 2008). Definitions of cognitive activity have varied across studies, and a wide range of specific activities have been found to be protective for cognitive decline and/or AD in epidemiologic research, but most often included are tasks that involve relatively effortful processing of new information (e.g., crossword puzzles, games, etc.).

High education, job complexity, and leisure-related cognitive activities have all been interpreted as building or sustaining cognitive reserve (Fratiglioni & Wang, 2007; Stern, 2009; Valenzuela & Sachdev, 2006a,b). Cognitive reserve refers to the set of cognitive abilities and strategies that an individual can bring to bear to perform cognitive tasks successfully, despite underlying brain illness or injury (Stern, 2009). Individuals with higher estimated levels of cognitive reserve function better in the presence of AD brain pathology than do peers with similar pathology but lower cognitive reserve (Stern, 2009). As a result, identifying ways of building and sustaining cognitive reserve has become a research and clinical priority.

Although higher education, more complex occupations, and cognitively stimulating leisure activities each appear protective against cognitive decline and AD in observational studies, the relative contributions of these factors across the adult lifespan are less well established. For example, although several reviews (Fratiglioni & Wang, 2007; Valenzuela & Sachdev, 2006a) have concluded that education is one of the strongest psychosocial predictors of AD risk, a recent analysis of data from two prospective longitudinal cohorts found that, in comparison to education, mid-life cognitive leisure activity was a better predictor of late-life cognitive variance that could not be directly accounted for by brain pathology (Reed et al., 2011). Correlations among education, occupation, and leisure activities can complicate analyses, as can the possibility that different forms of cognitive activity may selectively sustain different cognitive domains. A further limitation of many studies is the method of retrospective reporting of activities from midlife or younger ages, with elderly adults asked to recall leisure activities or job details from decades earlier in life. The potential for reporting bias may be mitigated by stability in preferred activities, but little is known about consistency in contemporary leisure choices, especially in light of rapidly changing options for leisure pursuits (e.g., digital access and video games).

There is also little known about how potentially modifiable risk factors such as education, occupation, or cognitive leisure activity might interact with genetic susceptibility for AD (Jarvik et al., 2008; Lee, 2003). Having an apolipoprotein allele 4 (APOE-ε4) and/or a family history of AD in a first-degree relative both increase risk of developing the disease (Cupples et al., 2004; Lautenschlager et al., 1996). In an analysis of participants from the Swedish Twin Study evaluated for dementia in old age, Gatz and colleages (2007) found that the association of low education with increased dementia risk was not mediated by genetic influences or accounted for by APOE genotype. Similarly, controlling for APOE genotype did not affect the relationship between cognitive leisure activities and incident AD in an elderly cohort followed longitudinally (Wilson, Mendes de Leon et al., 2002), and there was no interaction between APOE genotype and occupational demands in predicting late-life cognitive change in a sample of aged twins (Potter et al., 2007). However, other research has suggested that sensitivity to certain aspects of the environment may depend on risk gene status, with some studies noting less sensitivity among APOE-e4 carriers (Reynolds, Gatz, Berg, & Pedersen, 2007; Yaffe et al., 2000), and one suggesting more sensitivity, though the interaction was nonsignificant (Carlson et al., 2008). Further, at least one twin study (Potter et al., 2006) suggests that occupational effects on cognitive change in old age are more likely to be observed in dizygotic pairs where there is greater genetic variability. To our knowledge, there have been no studies that have examined baseline risk of AD (based on a positive family history) as a moderator of the effects of occupational complexity and leisure cognitive activity on cognitive decline or AD. In addition, because both genetic and environmental influences may vary in expression across the lifespan (Lee, 2003), it is important to assess for potential interactions in midlife or earlier, as well as old age.

Our study examined the relative contributions of three risk factors – work complexity, concurrent leisure cognitive activities, and education – as predictors of cognitive performance in a middle-aged cognitively-healthy sample at risk for developing dementia by virtue of a parental family history of AD. Research focusing on AD offspring is important because of their increased likelihood of developing the disease, and because of accumulating evidence that biomarkers for AD can be detected in AD offspring years before clinical disease is observed (e.g., Johnson et al., 2006; Honea et al., 2010; Xiong et al., 2011).

We had two main aims: (1) to determine the relative strength of education, occupational complexity with data, and concurrent leisure activities as predictors of different aspects of cognitive performance in a middle-aged sample with increased risk for AD; and (2) to assess for potential interactions between genetic risk factors (FH and APOE-ε4) and cognitive activity measures in explaining cognitive variance. We hypothesized that education effects would be strongest for crystallized intellectual skills such as those measured by verbal IQ subtests, whereas current cognitive activities were expected to relate more closely to skills associated with fluid intelligence such as short-term memory and executive function. Given limited relevant research, we had no a priori hypotheses about the direction of potential interactions between genetic risk factors and cognitive activity effects.

Method

Participants

The Wisconsin Registry for Alzheimer's Prevention (WRAP) is an ongoing longitudinal study of a sample of middle-aged adults enriched for a family history of Alzheimer's disease (Sager et al., 2005). Recruitment began in 2001 and is ongoing. WRAP participants were generally between the ages of 40 and 65 years at baseline, English speaking, and had a parent with either autopsy-confirmed or probable AD (FH+) as defined by NINCDS-ADRDA research criteria (McKhann et al., 1984) or no parental history of AD or other dementia (FH−). FH+ subjects were volunteers whose parent(s) had been evaluated in a memory assessment clinic at the University of Wisconsin-Madison or at affiliated satellite memory assessment clinics, and others who learned about the study from educational presentations or word of mouth. To verify the diagnosis of AD in parents not directly assessed, autopsy reports or parental medical records were reviewed. FH− participants had mothers who survived to at least age 75, and fathers to at least age 70, without Alzheimer's disease, other dementia, or significant memory deficits. These participants were recruited through community presentations and word of mouth.

The WRAP sample currently includes 1510 middle-aged adults recruited predominantly in the upper Midwest and tested at sites in Madison, LaCrosse, and Milwaukee. Because questionnaires about cognitive leisure activities and work history represented new additions to the study after it was underway, and because not all occupations could be classified for job complexity (e.g., homemakers), a subsample of 862 participants provided complete data on our main predictors of interest. Of these, 10 were missing data on APOE and were excluded from final models. Our analyses also excluded subjects who presented with AD (N=3) or other neurological conditions that can impair cognition, including stroke, epilepsy, meningitis, Parkinson's disease, and multiple sclerosis (N=87), leaving a final sample of 762.

General study procedures

Baseline assessment included a battery of commonly used clinical neuropsychological tests (see Sager, Hermann, & La Rue, 2005, for a description of the cognitive battery), completion of questionnaires about health history and lifestyle, laboratory tests, and APOE genotyping. All study procedures have been approved by the Health Sciences IRB of the University of Wisconsin-Madison.

Cognitive outcomes

Factor analysis using promax rotation and maximum likelihood estimation (Grice, 2001) were used to reduce the set of cognitive measures to a smaller number of factors and obtain weights used to combine the measures within each factor. The resulting six weighted factor scores were then standardized (~N (0, 1)) into z-scores, using means and standard deviations obtained from the whole baseline sample (additional details on the factor analysis methods used for the WRAP sample can be found in Dowling et al., 2010). Table 1 shows the factors and the cognitive tests that loaded on each factor. Factors include two general ability indicators, Verbal and Visuospatial Ability, comprised of IQ subtests and related measures.

There are two factors representing new learning and recall (Immediate Memory; Verbal Learning and Memory), both derived from the *Rey Auditory Verbal Learning Test* (Lezak, Howieson, & Loring, 2004), and two factors reflecting components of executive function (Working Memory; Speed and Flexibility).

Education

Participants reported the highest degree they attained. Because only a small number did not finish high school, “some high school” and “high school diploma” were collapsed into one category. Education level was treated categorically, with indicator variables representing completion of at least some college, a bachelor’s degree, and some graduate school, respectively. For example, a participant who reported a bachelor’s degree as their highest education was coded {1, 1, 0}. Participants whose highest education was at the high-school level were coded {0, 0, 0}. This non-orthogonal coding scheme facilitates interpretation of regression coefficients of ordinal variables (Walter et al., 1987).

Job complexity

Occupational information was collected from a series of questions administered via mailed questionnaires and/or in-person interviews. Participants were asked to describe up to three jobs that comprised their “main form(s) of work” and the years spent at each, beginning with their most recent job. Three trained raters coded complexity ratings based on these responses.

Each job was initially coded according to O*NET, the United States Department of Labor Standard Occupational Classification (SOC) Network (United States Department of Labor, 2006), followed by a “crosswalk” search to code each job according to the 1970 U.S. Census Dictionary of Occupational Titles, fourth Edition revised (United States Employment Service, 1991). A matrix developed by Roos and Trieman (1980) was then used to assign work complexity ratings. This matrix is based on an estimation of complexity scores of more than 12,000 occupations in the United States rated by job analysts. There are three complexity ratings for each job: complexity of work with data, complexity of work with people, and complexity of work with things. Following the example of most other studies that have used the job complexity rating system, we did not assign ratings for participants who had mainly worked in homemaking, since the job classification systems had been developed on work for pay. The raw means (SDs) for each rating in our sample are as follows: Complexity with data, 2.1 (1.3); complexity with people, 4.7 (2.2); complexity with things, 5.0 (2.2).

Inter-rater agreement scores of 0.85 for complexity of work with data, 0.87 for complexity of work with people, and 0.46 for complexity of work with things have been previously reported (Cain & Treiman, 1981). For WRAP, a subsample of 5% of cases independently coded by a 4th trained rater yielded 97% agreement with the primary coders. For disagreements and for occupations that were difficult to code (e.g., jobs that were technologically advanced or recently developed), a consensus meeting was held among all three primary raters.

The work-related dependent variable used in the present analyses was a *complexity of work with data* rating, averaged across up to three reported jobs, weighted by years at each job. The correlation between this weighted score and the complexity of participants' longest-held jobs was 0.94. The decision to focus on complexity of work with data was based on preliminary analyses relating each of the three job complexity ratings to cognitive factor scores while controlling for education. In these initial screening analyses, not reported in depth in this manuscript, we compared mean cognitive performance in groups defined by median splits along two dimensions: education and job complexity (with separate analyses for each dimension of complexity). These screening analyses indicated that complexity of work with people or things did not account for any additional cognitive variance beyond that associated with education, whereas complexity of work with data appeared to have an independent effect. Complexity of work with data ratings ranged from highest (0) to lowest (6), representing synthesizing, coordinating, analyzing, compiling, computing, copying, and comparing data, respectively; for analyses, however, these were reverse-coded and standardized (~N(0,1)), so that higher scores represented greater job complexity.

Leisure-related cognitive activity

We used a modified version of the Cognitive Activities Scale (CAS) from the Chicago Health and Aging Study (Wilson et al, 1999) to assess current leisure-related cognitive activity. The original version of the CAS (Wilson et al., 1999) consists of seven items assessing a range of activities selected for the relatively high demands they place on information processing and their comparatively low physical and social demands; among others, these include reading, watching television, playing games, and going to museums. Subjects report their frequency of engaging in each activity on a 5-point scale (1 = once a year or less, 5 = every day or nearly every day). In order to extend the potential utility of this questionnaire for our younger and better educated population, we used a version of the CAS that included attending lectures or continuing education classes and attending concerts or plays, and added an item about leisure use of a personal computer, creating a 10-item scale. Primary analyses used the total score from our modified CAS as a marker for cognitive activity (CAS-TS; theoretical range = 10 to 50). Consistent with findings from other recent studies that have examined statistical properties of cognitive activity scales (e.g., Schinka et al., 2005; Wilson et al., 1999), internal consistency of the CAS was low in our sample (Cronbach's $\alpha = 0.53$). This may relate to the fact that time spent in one activity necessarily reduces time available for other activities (Schinka et al., 2005) and to finding that distributions are often skewed toward very frequent engagement in some activities (e.g., reading) and very infrequent engagement in others (e.g., going to museums). Since game playing figures prominently in public perceptions of activities that may sustain brain fitness (American Society on Aging and Metlife Foundation, 2006), we had an *a priori* interest in examining the utility of the "Games" item (CAS-Games, "Playing games such as cards, checkers, crosswords, or other puzzles", theoretical range = 1 to 5) from the CAS as a proxy for cognitive activity in predicting cognitive outcomes. To protect against Type I error, analyses using CAS-Games instead of CAS-TS were considered secondary analyses. In our sample, the distribution of responses for the games item was closest to normal of all CAS items. Both CAS and Games were standardized (~N(0,1)) for analyses.

Genetic risk

None of the six cognitive outcomes differed between APOE-ε4 heterozygotes and homozygotes (all $p > .05$). Therefore, for simplicity, we modeled APOE-mediated genetic risk as a binary variable coding presence of at least one ε4 allele.

Statistical analysis

To test our hypotheses about the effects of cognitive activity on cognitive performance, we used linear mixed models to examine four groups of independent variables: a) sibling clusters; b) common covariates (age, sex, and site); c) cognitive activity markers (highest degree attained, CAS measure of concurrent cognitive activity, and job complexity with data) and their interactions with age (as a proxy for longitudinal effects); and d) genetic factors (APOE and FH of AD, modeled additively as single binary variables) and their interactions with cognitive activity markers. As a first step, we fit a multivariate mixed model examining the effect of our predictors on cognitive outcomes overall, including sibling cluster as a random effect. The primary purpose of this model was to test whether the effects of a given predictor differed across our six cognitive outcomes. To protect against Type I error inflation, we investigated effects of our predictors on separate cognitive factors only if there was one or more significant predictor-by-cognitive factor interaction in the multivariate model (Gelman and Stern, 2006).

At both steps of the model-fitting process, interaction effects with $p>.10$[1] were rejected and the model was refit iteratively until a final model was obtained for that cognitive outcome. Collinearity and influence diagnostics were examined for final models. Primary analyses used the CAS-TS as the overall measure of participants' concurrent cognitive activity; in secondary analyses, we instead used participants' reported frequency of game-playing, CAS-Games, as our measure of concurrent cognitive activity. We also compared CAS-TS and CAS-Games in terms of correlations with other predictors and predictive consistency across cognitive domains.

Analyses were conducted using SAS (version 9.2) and R (version 2.12.1). All outcomes were examined for normality using PROC UNIVARIATE, with skewnesses and kurtoses < 1.0 (absolute value). Because our design was unbalanced, we used the Kenward-Roger approximation to calculate denominator degrees of freedom for all tests (Schaalje, McBride, & Fellingham, 2002). For significance testing, we set $\alpha=.05$.

Results

Our final sample included data from 772 participants. Demographic and other characteristics of our sample can be found in Table 2. Compared to WRAP subjects not included in this sample, these 772 participants were somewhat older and slightly less likely to be either FH+ or ε4+ ($p<.05$). Continuous cognitive predictors were both z-transformed on the entire sample with data available and distributions were approximately N(0,1).

[1]While a p-value between .05 and .10 is not statistically significant, we chose to keep interaction terms in this range in the model to ensure that our interpretation of related main effects was conservative.

The six cognitive outcomes were approximately normally distributed, with absolute values of skewness and kurtosis less than 0.5 in all cases. As the outcomes were standardized on the larger WRAP sample, the distributions for all were approximately N(0,1). Correlations between the outcomes were moderately positive overall, and strongest for factor scores based on different items from a common test (Verbal Learning and Immediate Memory [Rey AVLT], r=0.65; verbal ability and visuospatial ability [WASI], r=0.52). Standard mixed model diagnostics (Bell et al., 2010) indicated anomalous residuals in some cases. We conducted follow-up analyses using general linear models on a subset containing one randomly-selected member of each family. Results from these models supported the conclusions from the mixed models analyses. In addition, the lack of anomalous residuals in these analyses suggested that those observed in the mixed models were confined to the random portions of the models.

Primary analysis

We fit a multivariate mixed model to our dataset as a whole in order to check for variable by predictor interaction effects. Such effects would allow us to interpret outcome differences in predictor significance as potentially meaningful (Gelman & Stern, 2006). The results suggested domain-specific effects of all predictors of interest. Accordingly, we examined the predictors in the context of particular cognitive outcomes.

Memory—Two sets of mixed models examined the link between measures of cognitive activity and different aspects of memory. Parameter estimates from the final models are displayed in Table 3A. Higher CAS-TS scores significantly predicted better performance on our Immediate Memory factor ($F_{CAS\text{-}TS}(1,750) = 4.88$, $p = .03$). No effect was observed for job complexity ($F_{JOB} < 1$) or education ($F_{ED}(3,748) = 1.48$, $p = .22$). For Verbal Learning & Memory, only Education was a significant predictor ($F_{ED}(3,747) = 9.36$, $p < .0001$), with no effect observed for CAS-TS ($F_{CAS\text{-}TS}(1,750) = 1.54$, $p = .21$) or job complexity ($F_{JOB} < 1$).

Executive function—Separate sets of mixed models explored the relationship between cognitive activity and executive function. Parameter estimates are displayed in Table 3A. For Working Memory, no relationship was found with either CAS-TS ($F_{CAS\text{-}TS}$ (1,746) = 1.71, $p = .19$) or job complexity ($F_{JOB}(1,740) = 2.65$, $p = .10$). No interaction with CAS-TS was significant; however, there was a marginal interaction between APOE and job complexity ($F_{APOE*JOB}(1,740) = 3.61$, $p = .06$), suggesting a possible effect of job complexity in APOE-E4+ participants. In contrast, Speed & Flexibility scores were predicted by both CAS-TS ($F_{CAS\text{-}TS}$ (1,739) = 6.69, $p = .01$) and job complexity ($F_{JOB}(1,706) = 5.25$, $p = .02$), with no significant interaction effects observed. Education was a significant predictor of Working Memory performance ($F_{ED}(3,745)$ 6.26, $p = .0003$), but not of Speed & Flexibility ($F_{ED}(3,737)$ 1.53, $p = .21$).

Verbal & visuospatial ability—Two sets of mixed models examined how verbal and visuospatial ability relate to cognitive activity markers. Parameter estimates are displayed in Table 3A. Visuospatial Ability showed a significant relationship with both CAS-TS ($F_{CAS\text{-}TS}$ (1,732) = 4.14, $p = .04$) and job complexity ($F_{JOB}(1,650) = 5.02$, $p = .03$). No interaction effects were significant. Results were similar for Verbal Ability (CAS: $F_{CAS\text{-}TS}$

(1,735) = 25.60, p < .0001; Job complexity: (F_{JOB}(1,713) = 5.24, p = .02), although the latter effect was qualified by a marginal interaction with APOE ($F_{APOE*JOB}$(1,692) = 2.72, p = .0997) suggesting a possibly-stronger effect of job complexity in APOE-E4+ participants. Education was a significant predictor of both outcomes (Visuospatial Ability: F_{ED}(3,715) = 17.52, p < .0001); Verbal Ability: F_{ED}(3,726) = 65.10, p < .0001).

Secondary analysis

In secondary analyses, we used CAS-Games as a substitute for CAS-TS. Because of its low correlation with other measures of cognitive activity, we felt that CAS-Games had more optimal qualities for linear modeling. Specifically, CAS-Games was not strongly related to either Job complexity (r(760) = −.06, p = .08) or Education (r(760) = −.01); in contrast, CAS-TS was positively correlated with Job complexity (r(760) = .21, p < .0001), and Education (r(760) = .32, p < .0001). As a result of the near-orthogonality of the Games item to the other predictors, we expected to encounter fewer difficulties with multicollinearity in this model.

As with our primary analyses, we started with a multivariate mixed model and removed nonsignificant interactions, which included all interactions with age. Again, several significant outcome variable by predictor interactions emerged. However, in this case, the interaction effect with CAS-Games was nonsignificant, suggesting that the strong positive effect of CAS-Games on cognitive performance did not vary by cognitive domain (F_{GAMES}(1,746) = 29.98, p < .0001). We thus examined the effects of our predictors on each outcome using univariate mixed models.

Memory—More frequent game-playing significantly predicted better performance on both Immediate Memory ($F_{CAS-GAMES}$(1,756) = 8.27, p = .004) and Verbal Learning & Memory ($F_{CAS-GAMES}$ (1,756) = 8.09, p = 0.005). Here, education was a marginal predictor of Immediate Memory (F_{ED}(3,752) = 2.52 p = 0.06) and a significant predictor of Verbal Learning and Memory (F_{ED}(3,751) = 10.77, p < .0001). Again, no effect of job complexity on memory emerged (Immediate Memory: F_{JOB}(1,753) = 1,81, p = .18; Verbal Learning: F_{JOB}(1,750) = 0.56, p = .46). Parameter estimates from these mixed models can be found in Table 3B.

Executive function—Secondary analyses revealed a relationship between game-playing and both measures of executive function (Speed & Flexibility: $F_{CAS-GAMES}$(1,746) = 25.94, p < .0001; Working Memory: $F_{CAS-GAMES}$(1,751) = 6.55, p = .01), with both coefficients significant and positive. As in primary analyses, job complexity was a significant predictor of Speed & Flexibility (F_{JOB}(1,713) = 8.25, p = .004) and had a marginal relationship with Working Memory that was marginally modified by APOE (F_{JOB}(1,745) = 2.75, p = 0.0976; $F_{APOE*JOB}$(1,747) = 3.61, p = .06) . Education was a marginal predictor of Speed & Flexibility (F_{ED}(3,743) = 2.60, p = .05) and a significant predictor of working memory (F_{ED}(3,750) = 5.79, p = .0007). Parameter estimates can be found in Table 3B.

Verbal & visuospatial ability—Secondary analyses revealed quite similar results to primary analyses. Visuospatial Ability showed a significant relationship with both CAS-

Games ($F_{CAS\text{-}GAMES}(1,734) = 20.67$, $p < .0001$) and job complexity ($F_{JOB}(1,667) = 7.94$, $p = .005$). However, in this case, the effect of CAS-Games was modified by an interaction with family history, such that only FH− participants appeared to benefit ($F_{FH*GAMES}(1,751) = 5.15$, $p = .02$). Results were similar for Verbal Ability (Games: $F_{CAS\text{-}GAMES}(1,743) = 11.20$, $p = .0009$; Job complexity: ($F_{JOB}(1,688) = 23.29$, $p < .0001$), with no significant interactions. Education was a significant predictor of both outcomes (Visuospatial Ability: $F_{ED}(3,729) = 19.47$, $p < .0001$); Verbal Ability: $F_{ED}(3,738) = 78.14$, $p < .0001$). Parameter estimates can be found in Table 3B.

Tertiary analysis

Finally, in order to better understand the relative contribution of each of our predictors of interest, we ran the final model from each of the above analyses in three additional ways: including only the covariates and genetic risk factors plus education (and any significant gene*education interactions); covariates plus CAS (and its genetic interactions); and covariates plus job complexity (and its genetic interactions). When considered in this fashion, each of these variables is a highly significant predictor of performance (Table 4). Interestingly, in these analyses, the APOE by job complexity interactions are now nonsignificant, indicating that suppression involving the other predictors of interest plays a role in the marginal significance of this interaction term in the larger models of Working Memory and Verbal Ability.

Discussion

There is a developing consensus in the field of AD research that the pathogenic processes that lead to dementia begin decades before a clinical diagnosis is made, at least by late middle age and possibly sooner (Sperling et al. 2011). WRAP is one of a handful of unique studies that are tracking the course of cognitive change from middle age to later life in persons whose risk of AD is increased by virtue of family history of AD or specific genetic profile. These studies offer the potential of characterizing lifestyle factors such as cognitive activity that may moderate rate of cognitive decline in the critical midlife period and possibly, by enhancing cognitive reserve, delay the onset of clinical AD. In addition, these studies are the only investigations that can determine whether persons at greater or lesser genetic risk benefit equally from protective psychosocial factors, including cognitive activity. Characterizing cognition at baseline in prospective studies, and understanding the factors associated with baseline cognition, are important first steps, paving the way for tracking future change in relation to moderating factors.

Education was a very strong predictor of verbal ability, despite the generally high level of education in our sample. The Verbal Ability factor was a composite of two verbal IQ subtests, word reading, and confrontation naming. These crystallized intellectual skills are built by formal education and sustained or further enhanced by other less formal activities throughout the lifespan (Horn & Cattell, 1967; McGrew, 2005). To a lesser extent, education was also a predictor of Visuospatial Ability and of two important aspects of memory: Working Memory and Verbal Learning and Memory. Because memory is often the first cognitive skill to decline in early AD and is the core area of clinical impairment, our results

are consistent with the idea that higher education may play a role in delaying onset of clinically significant AD symptoms in those that go on to develop this disease. Whether education only affects baseline cognition or also influences cognitive change, remains to be demonstrated by follow-up.

Complexity of work with data was also a significant, and independent, predictor of cognitive speed and flexibility and visuospatial ability. Most of the tasks comprising these cognitive factors are timed, and several make significant demands on attentional skills (e.g., attentional shifting) as well as perceptual and reasoning abilities. These and other skills related to fluid intelligence may require active engagement to build and sustain high levels of performance (e.g., Jaeggi, Buschkuehl, Jonides, & Shah, 2011), and for adults, a job that entails complex data-related tasks may be a naturally-occurring avenue to nurture these abilities. The complexity in working with data distribution in WRAP was skewed toward demanding occupations (e.g., 61% were ranked at the two highest levels, involving tasks that require synthesizing and coordinating data). Given such a high overall level of work complexity, the finding of significant associations with cognitive performance is somewhat surprising. In contrast, complex work with things was underrepresented in our sample, and perhaps for that reason, no associations were observed between this job measure and cognition. We also did not observe associations between cognition and complexity of work with people, as have been reported in some (e.g., Andel et al., 2005; Karp et al., 2009; Kröger et al., 2008), but not all (e.g., Potter et al., 2006, 2007), prior studies. At baseline, a majority (77%) of WRAP participants were working full- or part-time, and as longitudinal follow-ups progress, we will be able to track cognition through the retirement phase. It will be important to determine how far into the life course beneficial effects of complex occupations remain, and whether retirement leads to change in specific cognitive skills (Finkel, Andel, Gatz, & Pedersen, 2009).

Perhaps the most interesting aspect of our results concerns concurrent leisure cognitive activity. Engaging in games (“Playing games like cards, checkers, crossword puzzles, other puzzles”) as a leisure activity was positively associated with scores on all cognitive domains. Engagement in games was the sole activity predictor of immediate memory (initial two learning trials of a verbal list), which entails marshalling of attention and working memory skills to promote an effective initial approach to new learning. Playing games was not correlated with occupational complexity, suggesting that people of diverse work backgrounds chose this as a leisure activity. Spending one’s spare time doing things such as crossword puzzles probably comes closest to current lay views of “brain protective” activities, and as such, our findings provide some indirect support for this popular perception. However, longitudinal data will be needed to determine if there is any benefit of engaging in games for slowing cognitive decline. A limitation in our data on games is that we did not have information on the frequency of engagement in video or electronic games compared to more traditional board or word games. There are recent data to indicate that video games may enhance cognition, especially attention or executive skills, in older adults (e.g., Basak et al., 2008).

Like several prior studies (Wilson et al; 1999; Schincka et al., 2005), we found that the total cognitive activities score, CAS-TS, was also a significant predictor of several aspects of

cognitive performance, although associations were less consistent and slightly weaker than those observed for CAS-Games alone. This may be due to the fact that some items on the CAS scale were engaged in only infrequently (e.g., going to museums), whereas others (e.g., reading) were widely adopted, reducing item variance. It is also possible that the CAS-TS does not provide as good a measure of concurrent cognitive activities in a middle-aged sample as it does in the elderly samples on which it was developed (Wilson et al., 1999).

One question raised by our main findings is whether the nonsignificant relationships observed between some predictor-outcome pairs – for instance, between education and speed and flexibility – truly indicate no relationship, or rather, simply that the variance explained by these predictors of interest is largely shared. Our tertiary analyses support the latter interpretation. This finding is consistent with a mediation model in which more distal variables, such as education, influence mid-life cognition in part through providing a scaffold on which later-life cognitive activities can build. This is similar to the results of Wight and colleagues, who found independent effects of early-life education and later-life training in older men (Wight et al., 2002). However, we caution against drawing strong inferences about the causal chain linking these variables given the correlational and cross-sectional nature of our data.

Our findings could be interpreted as showing variations in cognitive reserve at study baseline that are linked to each of three major domains of cognitive activity. However, as Reed and colleagues (2011) have recently argued, invoking cognitive reserve to explain associations between cognition and risk factors is most convincing when reserve can be measured independently of its hypothesized lifestyle predictors, for example, as residual cognitive variance not explained by brain measures such as volumetric MRI (Reed et al., 2011) or plaque and tangle density (Reed et al., 2011). As neuroimaging data accumulate in WRAP, it may be possible to construct a similar independent measure of cognitive reserve, which would enable us to address the extent to which reserve is responsible for the hypothesized lag between CSF and brain amyloid markers of preclinical AD and the subsequent emergence of cognitive symptoms (Sperling et al., 2011). It will also be important to determine if there are any direct associations between cognitive activity variables and AD biomarkers in this relatively young sample. In a recent study with healthy older adults, higher levels of cognitive engagement, especially in early- and middle life, were associated with lower beta amyloid deposition as measured by PIB (Landau et al., 2012), raising the possibility of a more direct link between cognitive activity and AD pathogenesis.

These analyses also shed some incidental light on how the timing of cognitive stimulation contributes to reserve. The protective effect of education may depend on exposure during a sensitive period of brain development extending into late adolescence; alternatively, it may be that educational activities at any age are beneficial (Howard-Jones et al., 2012; Timiras, 1995; Wight et al., 2002). The data in WRAP do not permit a direct examination of this question. However, the fact that our other measures of cognitive stimulation, which reflect midlife activities, were significant predictors of cognition after controlling for education suggests that a sensitive period is likely not the full story. Future research should address

this question directly, as the answer may have implications for the role of education in public health.

A final and relatively novel aspect of our study concerns the search for interactions between genetic risk factors and cognitive activity measures – a search worth pursuing despite the minimal yield observed in the present analyses. The development and clinical expression of AD most likely reflect a complex interplay of genetic and environmental factors that research is only beginning to address (Jarvik et al., 2008). WRAP is one of only a handful of studies that offer the opportunity to examine genetic and environmental interactions prospectively. In addition to APOE, the major genetic risk factor for AD identified to date, there is accumulating evidence for FH effects on AD biomarkers in preclinical stages of disease that cannot be explained by APOE, and additional candidate genes are being identified that contribute to AD risk (Naj et al., 2011; Hollingsworth et al., 2011). In the currently reported WRAP baseline data, we found a main effect for FH on early trials of a verbal list learning task, with FH+ participants scoring slightly lower than those without a family history of AD, consistent with earlier results (see also, La Rue et al., 2008; Chang et al., 2012). By contrast, only a few interactions between FH, APOE, and cognitive activity predictors were observed, and only one was significant beyond the marginal level. The fact that the beneficial association between games and visuospatial ability was most evident in the FH- group is intriguing, but difficult to interpret at this point. It is possible that cognition in persons who lack genetic risk factors for AD may be more malleable in response to variations in modifiable risk factors than those with AD susceptibility genes, as suggested by a few prior studies (e.g., Reynolds, Gatz, Berg, & Peterson, 2007). However, in the current WRAP data, an interaction with FH was noted on only one cognitive factor, and the stability of this association remains to be established. In addition, because adult offspring and their parents with AD have shared environments, observed FH effects cannot be directly attributed to genetic influences. For APOE, there was a statistically significant main effect on visuospatial function, with lower performance in the ε4+ subgroup, but no significant interactions between APOE genotype and cognitive activity predictors. A recent meta-analysis of associations between APOE genotype and cognitive performance in cognitively normal samples (Wisdom, Callahan, & Hawkins, 2009) found that effect sizes for APOE were smaller among younger-aged groups than elderly adults, and there are large-scale studies of young-adult and middle-aged samples that have failed to find APOE effects on cognition (e.g., Jorm, Mather, Butterworth, Anstey, Christensen, & Easteal, 2007). It will be important to continue to examine associations between genetic and activity risk factors as the WRAP sample ages and risk of clinical AD increases.

Limitations of the current study include the facts that WRAP is a convenience sample with modest demographic range, including educational achievement and types of employment, and that the earliest-enrolled subjects are missing baseline data on work history and cognitive activities. Further, the nature of the FH- cohort required that we select for parental survival to old age, which may bias that group toward better cognitive health. A final limitation is the cross-sectional nature of the present analyses. We do not know whether the positive associations we observed between cognitive activity and cognition at the baseline assessment will prove to be protective in slowing cognitive decline or delaying the onset of clinical dementia. The near-term aim moving forward will be to determine relationships

between these three major activity variables and longitudinal cognitive change, including the subtle types of memory changes that may characterize preclinical AD (Sperling et al., 2011).

Acknowledgments

This research was supported by NIA grant R01AG27161 (Wisconsin Registry for Alzheimer Prevention: Biomarkers of Preclinical AD), NIH grant M01RR03186 (University of Wisconsin Clinical and Translational Research Core), the Helen Bader Foundation, Northwestern Mutual Foundation, and Extendicare Foundation.

The authors gratefully acknowledge the assistance of Shawn Bolin, Maggie Kengott, Gail Lange, Kimberly Mueller, Nia Norris, Janet Rowley, Susan Schroeder, and Pam Winne for WRAP data collection. We especially thank the WRAP participants.

References

Akbaraly TN, Portet F, Fustinoni S, Dartigues JF, Artero S, Rouaud O, Berr C. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. Neurology. 2009; 73(11): 854–861.10.1212/WNL.0b013e3181b7849b [PubMed: 19752452]

Andel R, Crowe M, Pedersen NL, Mortimer J, Crimmins E, Johansson B, Gatz M. Complexity of work and risk of Alzheimer's disease: A population-based study of Swedish twins. Journal of Gerontology: Psychological Sciences. 2005; 60B(5):251–258.10.1093/geronb/60.5.P251

Andel R, Kåreholt I, Parker MG, Thorslund M, Gatz M. Complexity of primary lifetime occupation and cognition in advanced old age. Journal of Aging and Health. 2007; 19(3):397–415.10.1177/0898264307300171 [PubMed: 17496241]

American Society on Aging and Metlife Foundation. Attitudes and awareness of brain health poll. 2006. Retrieved from http://www.asaging.org/asav2/mindalert/pdfs/BH.pdf

Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurology. 2011; 10:819–828.10.1016/S1474-4422(11)70072-2 [PubMed: 21775213]

Basak C, Boot WR, Voss MW, Kramer AF. Can training in a real-time strategy video game attenuate cognitive decline in older adults? Psychology and Aging. 2008; 23:765–77.10.1037/a0013494 [PubMed: 19140648]

Bell, BA.; Schoeneberger, JA.; Morgan, GB.; Kromrey, JD.; Ferron, JM. Fundamental diagnostics for two-level mixed models: The SAS macro MIXED_DX. Proceedings of the annual SAS Global Forum; 2010. Retrieved from: http://support.sas.com/resources/papers/proceedings10/201-2010.pdf

Benton AL. Neuropsychological assessment. Annual Review of Psychology. 1994; 45(1):1–23.

Cain PS, Treiman DJ. The Dictionary of Occupational Titles as a source of occupational data. American Sociological Review. 1981; 46:253–278. http://www.jstor.org/stable/2095059.

Carlson MC, Helms MJ, Steffens DC, Burke JR, Potter GG, Plassman BL. Midlife activity predicts risk of dementia in older male twin pairs. Alzheimers & Dementia. 2008; 4(5):324–31.10.1016/j.jalz.2008.07.002

Chang TS, Coen MH, La Rue A, Jonaitis E, Koscik RL, Sager MA. Machine learning amplifies the effect of parental family history of Alzheimer's disease on list learning strategy. Journal of the International Neuropsychological Society. 2012; 18:428–439.10.1017/S1355617711001834 [PubMed: 22321601]

Crowe M, Andel R, Pedersen NI, Johansson B, Gatz M. Does participation in leisure activities lead to reduced risk of Alzheimer's disease? A prospective study of Swedish twins. Journals of Gerontology B: Psychological Sciences & Social Sciences. 2003; 58(5):249–55.10.1093/geronb/58.5.P249

Cupples LA, Farrer LA, Sadovnick AD, Relkin N, Whitehouse P, Green RC. Estimating risk curves for first-degree relatives of patients with Alzheimer's disease: the REVEAL study. Genetics in Medicine. 2004; 6:192–6.10.1097/01.GIM.0000132679.92238.58 [PubMed: 15266206]

Dowling MN, Hermann B, LaRue A, Sager MA. Latent structure and factorial invariance of a neuropsychological test battery for the study of preclinical Alzheimer's disease. Neuropsychology. 2010; 24(6):742–56.10.1037/a002017610.1037/a0020176.supp [PubMed: 21038965]

Finkel D, Andel R, Gatz M, Pedersen NL. The role of occupational complexity in trajectories of cognitive aging before and after retirement. Psychology and Aging. 2009; 24(3):563–573.10.1037/a0015511 [PubMed: 19739912]

Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurology. 2004; 3(6):242–53.10.1016/S1474-4422(04)00767-7

Fratiglioni L, Wang HX. Brain reserve hypothesis in dementia. Journal of Alzheimer's Disease. 2007; 12(1):11–22.

Gatz M, Mortimer JA, Fratiglioni L, Johansson B, Berg W, Andel R, Petersen NL. Accounting for the relationship between low education and dementia: a twin study. Physiology & Behavior. 2007; 92(1–2):232–237.10.1016/j.physbeh.2007.05.042 [PubMed: 17597169]

Gelman A, Stern H. The difference between "significant" and "not significant" is not itself statistically significant. The American Statistician. 2006; 60:328–331.

Grice JW. Computing and evaluating factor scores. Psychological Methods. 2001; 6(4):430–450.10.1037/1082-989X.6.4.430 [PubMed: 11778682]

Hollingworth P, Harold D, Sims R, Gerrish A, Lambert JC, Carrasquillo MM, Williams J. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nature Genetics. 2011; 43:429–435.10.1038/ng.803 [PubMed: 21460840]

Honea RA, Swerdlow RH, Vidoni ED, Goodwin J, Burns JM. Reduced gray matter volume in normal adults with a maternal family history of Alzheimer disease. Neurology. 2010; 74(2):113–120.10.1212/WNL.0b013e3181c918cb [PubMed: 20065246]

Horn JL, Cattell RB. Age differences in fluid and crystallized intelligence. Acta Psychologica. 1967; 26:107–129.10.1016/0001-6918(67)90011-X [PubMed: 6037305]

Howard-Jones PA, Washbrook EV, Meadows S. The timing of educational investment: A neuroscientific perspective. Developmental Cognitive Neuroscience. 2012; 2(Suppl 1):S18–29.10.1016/j.dcn.2011.11.002 [PubMed: 22682906]

Hultsch DF, Hertzog C, Small BJ, Dixon RA. Use it or lose it: engaged lifestyle as a buffer of cognitive decline in aging? Psychology and Aging. 1999; 14(2):245–263.10.1037/0882-7974.14.2.245 [PubMed: 10403712]

Jarvik L, LaRue A, Blacker D, Gatz M, Kawas C, McArdle JJ, Zonderman AB. Children of persons with Alzheimer disease: what does the future hold? Alzheimer Disease and Associated Disorders. 2008; 22(1):6–20.10.1097/WAD.0b013e31816653ac [PubMed: 18317242]

Jaeggi SM, Buschkuehl M, Jonides J, Shah P. Short- and long-term benefits of cognitive training. Proceedings of the National Academy of Sciences USA. 2011; 108(25):10081–10086.10.1073/pnas.1103228108

Johnson SC, Schmitz TW, Trivedi MA, Ries ML, Torgerson BM, Carlsson CM, Sager MA. The influence of Alzheimer disease family history and apolipoprotein E epsilon4 on mesial temporal lobe activation. Journal of Neuroscience. 2006; 26(22):6069–6076.10.1523/JNEUROSCI.0959-06.2006 [PubMed: 16738250]

Jorm AF, Mather KA, Butterworth P, Anstey KJ, Christensen H, Easteal S. APOE genotype and cognitive functioning in a large age-stratified population sample. Neuropsychology. 1007; 21(1):1–8.10.1037/0894-4105.21.1.1 [PubMed: 17201525]

Kaplan, E.; Goodglass, H.; Weintraub, S. The Boston Naming Test. 2. Philadelphia: Lea & Febiger; 1983.

Karp A, Andel R, Parker MG, Wang H-X, Winblad B, Fratiglioni L. Mentally stimulating activities at work during midlife and dementia risk after age 75: follow-up study from the Kungsholmen Project. American Journal of Geriatric Psychiatry. 2009; 17(3):227–236.10.1097/JGP.0b013e318190b691 [PubMed: 19454849]

Kröger E, Andel R, Lindsay J, Benounissa Z, Verreault R, Laurin D. Is complexity of work associated with risk of dementia? The Canadian Study of Health and Aging. American Journal of Epidemiology. 2008; 167(7):820–830.10.1093/aje/kwm382 [PubMed: 18263600]

Landau SM, Marks SM, Mormino EC, Rabinovici GD, Oh H, O'Neil JP, Jagust WJ. Association of lifetime cognitive engagement and low β-amyloid deposition. Archives of Neurology. 2012; 69(5):623–629.10.1001/archneurol.2011.2748 [PubMed: 22271235]

La Rue A, Hermann B, Jones JE, Johnson S, Asthana S, Sager MA. Effect of parental family history of Alzheimer's disease on serial position profiles. Alzheimer's & Dementia, 2008. 2008; 4:285–290.10.1016/j.jalz.2008.03.009

Lee JH. Genetic evidence for cognitive reserve: variations in memory and related cognitive functions. Journal of Clinical and Experimental Neuropsychology. 2003; 25(5):594–613.10.1076/jcen.25.5.594.14582 [PubMed: 12815498]

Lezak, MD.; Howieson, DB.; Loring, DW. Neuropsychological Assessment. 4. New York: Oxford University Press; 2004.

Lautenschlager NT, Cupples LA, Rao VS, Auerbach SA, Becker R, Burke J, Farrer LA. Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: What is in store for the oldest old? Neurology. 1996; 46:641–50. [PubMed: 8618660]

McGrew, KS. The Cattell–Horn–Carroll theory of cognitive abilities: Past, present, and future. In: Flanagan, DP.; Harrison, PL., editors. Contemporary intellectual assessment: Theories, tests, and issues. 2. New York, NY: Guilford Press; 2005. p. 136-181.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease. Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology. 1984; 34:939–44. [PubMed: 6610841]

Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, Buros J, Schellenberg GD. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nature Genetics. 2011; 43:436–441.10.1038/ng.801 [PubMed: 21460841]

Pillai JA, Hall CB, Dickson DW, Buschke H, Lipton RB, Verghese J. Association of crossword puzzle participation with memory decline in persons who develop dementia. Journal of the International Neuropsychological Society. 2011; 17(6):1006–13.10.1017/S1355617711001111 [PubMed: 22040899]

Potter GG, Helms MJ, Burke JR, Steffens DC, Plassman BL. Job demands and dementia risk among male twin pairs. Alzheimer's & Dementia. 2007; 3(3):192–199.10.1016/j.jalz.2007.04.377

Potter GG, Plassman BL, Helms MJ, Foster SM, Edwards NW. Occupational characteristics and cognitive performance among elderly male twins. Neurology. 2006; 6(8):1377–1382.10.1212/01.wnl.0000240061.51215.ed [PubMed: 17060563]

Qiu C, Karp A, von Strauss E, Winblad B, Fratiglioni L, Bellander T. Lifetime principal occupation and risk of Alzheimer's disease in the Kungsholmen project. American Journal of Industrial Medicine. 2003; 43(2):204–211.10.1002/ajim.10159 [PubMed: 12541276]

Reed BR, Dowling M, Farias ST, Sonnen J, Strauss M, Schneider JA, Bennett DA, Mungas D. Cognitive activities during adulthood are more important than education in building reserve. Journal of the International Neuropsychological Society. 2011; 17:613–624.10.1017/S1355617711000014

Reitan, RM.; Wolfson, D. The Halstead-Reitan Neuropsychological Test Battery: Theory and clinical interpretation. 2. Tucson: Neuropsychology Press; 1993.

Reynolds CA, Gatz M, Berg S, Pedersen NL. Genotype-environment interactions: cognitive aging and social factors. Twin Research and Human Genetics. 2007; 10(2):241–54. [PubMed: 17564514]

Roos, PA.; Treiman, DJ. DOT scales for the 1970 Census classification. In: Miller, AR.; Treiman, DJ.; Cain, PS.; Roos, PA., editors. Work, Jobs, And Occupations: A Critical Review Of Occupational Titles. Washington, DC: National Academy Press; 1980. p. 336-389.

Sager MA, Hermann B, La Rue AL. Middle-Aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer's Prevention. Journal of Geriatric Psychology and Neurology. 2005; 18(4):245–49.10.1177/0891988705281882

Schaalje GB, McBride JB, Fellingham GW. Adequacy of approximations to distributions of test statistics in complex mixed linear models. Journal of Agricultural, Biological, and Environmental Statistics. 2002; 7(4):512–524.10.1198/108571102726

Schinka JA, McBride A, Vanderploeg RD, Tennyson K, Borenstein AR, Mortimer JA. Florida Cognitive Activities Scale: Initial development and validation. Journal of the International Neuropsychological Society. 2005; 11:108–116.10.1017/S1355617705050125 [PubMed: 15686613]

Sharp ES, Gatz M. Relationship between education and dementia: an updated systematic review. Alzheimer Disease and Associated Disorders. 2011; 4:289–304. Epub ahead of print. 10.1097/WAD.0b013e318211c83c [PubMed: 21750453]

Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Phelps CH. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimer's and Dementia. 2011; 7(3):280–292.10.1016/j.jalz.2011.03.003

Stern Y. Cognitive reserve. Neuropsychologia. 2009; 47:2015–2028. doi: 10.10162Fj.neuropsychologia.2009.03.004. [PubMed: 19467352]

Timiras P. Education, homeostasis, and longevity. Experimental Gerontology. 1995; 30(3/4):189–198.10.1016/0531-5565(94)00054-7 [PubMed: 7556502]

Treiber KA, Carlson MC, Corcoran C, Norton MC, Breitner JC, Piercy KW, Deberard MS, Stein D, Foley B, Welsh-Bohmer KA, Frye A, Lyketsos CG, Tschanz JT. Cognitive stimulation and cognitive and functional decline in Alzheimer's disease: the cache county dementia progression study. Journals of Gerontology Series B: Psychological Sciences and Social Sciences. 2011; 66(4): 416–25.10.1093/geronb/gbr023

Trenerry, M.; Crosson, B.; DeBoe, J.; Leber, L. Stroop Neuropsychological Screening Test. Odessa, FL: Psychological Assessment Resources; 1989.

United States Department of Labor, National O*Net Consortium. Occupational information network: O*Net database (O*Net-SOC 2006). National Center for O*Net Development; 2006. Available at http://online.O*Netcenter.org/

United States Employment Service. Dictionary of Occupational Titles. 4. Washington, DC: U.S. Government Printing Office; 1991. revised

Valenzuela MJ, Sachdev P. Brain reserve and cognitive decline: a non-parametric systematic review. Psychological Medicine. 2006a; 36(8):1065–1073.10.1017/S0033291706007744 [PubMed: 16650343]

Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. Psychological Medicine. 2006b; 36(4):441–454.10.1017/S0033291705006264 [PubMed: 16207391]

Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, Buschke H. Leisure activities and the risk of dementia in the elderly. New England Journal of Medicine. 2003; 348:2508–16.10.1056/NEJMoa022252 [PubMed: 12815136]

Walter SD, Feinstein AR, Wells CK. Coding ordinal independent variables in multiple regression analysis. American Journal of Epidemiology. 1987; 125(2):319–323. [PubMed: 3812437]

Wechsler, D. Wechsler Adult Intelligence Scale. 3. San Antonio: The Psychological Corporation; 1997.

Wechsler, D. Wechsler Abbreviated Intelligence Scale. San Antonio: The Psychological Corporation; 1999.

Wight RG, Aneshensel CS, Seeman TE. Educational attainment, continued learning experience, and cognitive function among older men. Journal of Aging and Health. 2002; 14(2):211–236.10.1177/089826430201400203 [PubMed: 11995741]

Wilkinson, G. WRAT3 Administrative Manual. Delaware: Wide Range; 1993.

Wilson RS, Bennett DA. Cognitive activity and risk of Alzheimer's disease. Current Directions in Psychological Science. 2003; 12:87–91.

Wilson RS, Bennett DA, Bienias JL, Mendes de Leon CF, Morris MC, Evans DA. Cognitive activity and incident AD in a population-based sample of older persons. Neurology. 2002; 59(12):1910–14.10.1212/01.WNL.0000036905.59156.A1 [PubMed: 12499482]

Wilson RS, Bennett DA, Bienias JL, Mendes de Leon CF, Morris MC, Evans DA. Cognitive activity and cognitive decline in a biracial community population. Neurology. 2003; 61(6):812–816.10.1212/01.WNL.0000083989.44027.05 [PubMed: 14504326]

Wilson RS, Mendes de Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, Bennett DA. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. Journal of the American Medical Association. 2002; 287(6):742–748.10.1001/jama.287.6.742 [PubMed: 11851541]

Wisdom HM, Callahan JL, Hawkins KA. The effects of apolipoprotein E on non-impaired cognitive functioning: a meta-analysis. Neurobiology of Aging. 2011; 32(1):63–74.10.1016/j.neurobioloaging.2009.02.003 [PubMed: 19285755]

Xiong C, Roe CM, Buckles V, Fagan A, Holtzman D, Balota D, Morris JC. Role of family history for Alzheimer biomarker abnormalities in the Adult Children Study. Archives of Neurology. 2011; 68(10):1311–1317.10.1001/archneurol.2011.208

Yaffe K, Haan M, Byers A, Tangen C, Kuller L. Estrogen use, APOE, and cognitive decline: evidence of gene-environment interaction. Neurology. 2000; 54(10):1949–54.10.1212/WNL.54.10.1949 [PubMed: 10822435]

Table 1

Factor structure of six cognitive domains identified in the WRAP battery.

Factor name	Cognitive test
Immediate Memory	Rey Auditory Verbal Learning Test – Trials 1 & 2[a]
Verbal Learning & Memory	Rey Auditory Verbal Learning Test – Trials 3 through 5 & delayed recall
Working Memory	Digit Span Forward, Digit Span Backward, and Letter-number Sequencing (Wechsler Adult Intelligence Scale-III)[b]
Speed & Flexibility	Stroop Color-Word Test – interference trial[c] Trail-Making Test – Parts A & B[d]
Visuospatial Ability	Block Design and Matix Reasoning subtests (Wechsler Abbreviated Scale of Intelligence) Judgment of Line Orientation[e]
Verbal Ability	Vocabulary and Similarities subtests (Wechsler Abbreviated Scale of Intelligence)[f] Word Reading (Wide Range Achievement Test - 3)[g] Boston Naming Test[h]

[a] Lezak, Howieson, & Loring, 1984

[b] Wechsler, 1999

[c] Trenerry, Crosson, DeBoe, & Leber, 1989

[d] Reitan & Wolfson, 1993

[e] Benton, 1994

[f] Wechsler, 1997

[g] Wilkinson, 1993

[h] Kaplan, Goodglass, & Weintraub, 1983

Table 2

Characteristics of the WRAP sample (N=762).

Age, mean (SD, range)	54.9 (6.60, 36.0–68.9)
Sex, number female (%)	533 (70.0)
APOE, number ε4+ (%)	283 (37.1)
Heterozygous	249 (32.7)
Homozygous	34 (4.5)
Race, number white (%)	689 (90.4)
Education, number with BA (%)	450 (59.1)
Job complexity with data, mean (SD, range)	2.11 (1.27, 0–6)
CAS-Total, mean (SD, range)	31.8 (4.22, 14–42)
CAS-Games, mean (SD, range)	2.80 (1.28, 1–5)
Verbal IQ, mean (SD, range)	109.9 (10.6, 62–135)
Performance IQ, mean (SD, range)	111.1 (11.7, 68–139)
AVLT, mean (SD, range)	50.8 (8.15, 17–75)

Table 3

Regression coefficients for cognitive reserve predictors of six cognitive outcomes.
(A) Models using Cognitive Activity Scale-Total Score (CAS-TS); (B) Models using Games item only (CAS-Games).

Table 3A

	IM	*VLM*	*WM*	*SF*	*VSA*	*VA*
Family ICC	**.11**	**.12**	**.21**	**.26**	**.40**	**.32**
	β (SE)	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**
Age (years)	**−0.0325 (0.00544)**	**−0.0269 (0.00518)**	**−0.0165 (0.00566)**	**−0.0529 (0.00507)**	**−0.0381 (0.00503)**	−0.00659 (0.00434)
Sex (female)	**0.424 (0.0757)**	**0.597 (0.0719)**	−0.0940 (0.0779)	**0.310 (0.0694)**	**−0.369 (0.0679)**	0.00396 (0.0589)
Education						
Some college	0.151 (0.128)	**0.467 (0.121)**	0.160 (0.132)	0.155 (0.117)	**0.242 (0.114)**	**0.347 (0.0991)**
College	0.0926 (0.0940)	0.113 (0.0893)	0.131 (0.0971)	0.0709 (0.086)	**0.416 (0.0847)**	**0.595 (0.0737)**
Postgraduate	0.0332 (0.0910)	0.119 (0.0864)	**0.244 (0.0939)**	0.0394 (0.0837)	0.0794 (0.0828)	**0.320 (0.0714)**
CAS-TS (SD)	**0.0849 (0.0384)**	0.0453 (0.0365)	−0.0517 (0.0395)	**0.0908 (0.0351)**	**0.0704 (0.0346)**	**0.152 (0.0300)**
Job complexity (SD)	0.0342 (0.0376)	0.0137 (0.0357)	0.0794 (0.0488)	**0.0782 (0.0341)**	**0.0747 (0.0333)**	**0.0843 (0.0368)**
FH+	**−0.244 (0.0772)**	−0.0804 (0.0734)	−0.0619 (0.0808)	0.0166 (0.0720)	0.0754 (0.0728)	−0.0716 (0.0626)
APOE-ε4+	−0.0348 (0.0766)	−0.096 (0.0728)	0.0267 (0.0801)	0.0258 (0.0714)	**−0.182 (0.0715)**	−0.0992 (0.0617)
APOE-ε4 x Job	--	--	0.136 (0.0714)	--	--	0.0891 (0.0540)

Table 3B

	IM	*VLM*	*WM*	*SF*	*VSA*	*VA*
Family ICC	**.11**	**.12**	**.21**	**.25**	**.37**	**.29**
	β (SE)	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**
Age (years)	**−0.0315 (0.00537)**	**−0.0269 (0.00510)**	**−0.0178 (0.00557)**	**−0.0529 (0.00498)**	**−0.0375 (0.00493)**	−0.00430 (0.00433)
Sex (female)	**0.432 (0.0747)**	**0.592 (0.0708)**	−0.121 (0.0766)	**0.299 (0.0683)**	**−0.374 (0.0666)**	0.0297 (0.0589)
Education						
Some college	0.199 (0.125)	**0.476 (0.119)**	0.146 (0.129)	0.198 (0.114)	**0.267 (0.111)**	**0.395 (0.0984)**
College	0.111 (0.0929)	0.131 (0.0881)	0.119 (0.0957)	0.0836 (0.0848)	**0.414 (0.0834)**	**0.26 (0.0738)**

Table 3B

	IM	*VLM*	*WM*	*SF*	*VSA*	*VA*
Family ICC	**.11**	**.12**	**.21**	**.25**	**.37**	**.29**
	β (SE)	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**
Postgraduate	0.0430 (0.0899)	0.113 (0.0852)	**0.230 (0.0926)**	0.0539 (0.0825)	0.0839 (0.0813)	0.346 (0.0716)
CAS-Games (SD)	**0.0986 (0.0343)**	**0.0924 (0.0325)**	**0.0901 (0.0352)**	**0.160 (0.0314)**	**0.216 (0.0475)**	**0.0911 (0.0272)**
Job complexity (SD)	0.0500 (0.0372)	0.0263 (0.0353)	0.0799 (0.0482)	**0.968 (0.037)**	**0.0926 (0.0329)**	**0.141 (0.0292)**
FH+	**−0.251 (0.0765)**	−0.0846 (0.0726)	−0.0509 (0.0799)	0.0123 (0.0712)	0.0704 (0.0714)	−0.0749 (0.0625)
APOE-ε4+	−0.0263 (0.0761)	−0.0921 (0.0722)	0.0311 (0.0794)	0.0434 (0.0707)	**−0.177 (0.0704)**	−0.0991 (0.0618)
FH x Games	--	--	--	--	**−0.141 (0.0621)**	--
APOE-ε4 x Job	--	--	0.134 (0.0708)	--	--	--

Coefficients with p<.05 are bold. Note: IM = Immediate Memory (N=762); VLM = Verbal Learning & Memory (N=762); WM = Working Memory (N=760); SF = Speed & Flexibility (N=755); VSA = Visuospatial Ability (N=760); VA = Verbal Ability (N=757)

Table 4

Regression coefficients for cognitive reserve predictors of six cognitive outcomes, when controlling for other predictors of interest (A, C) and when entered alone with non-cognitive-reserve covariates (B, D). Education predictors were entered as a block. Major columns represent coefficients for models including CAS-Total (A, B) and CAS-Games (C, D), respectively.

	CAS-TOTAL		*CAS-GAMES*	
	A. Full model	***B. Single predictor model***	***C. Full model***	***D. Single predictor model***
Immediate memory (N=762)	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**
Education				
Some college	0.151 (0.128)	**0.224 (0.0919)**	0.198 (0.125)	**0.224 (0.0919)**
College	0.0926 (0.0940)	**0.213 (0.0662)**	0.111 (0.0929)	**0.213 (0.0662)**
Postgraduate	0.0332 (0.0910)	0.0245 (0.0659)	0.0430 (0.0899)	0.0245 (0.0659)
CAS (SD)	**0.0849 (0.0384)**	**0.114 (0.0344)**	**0.0986 (0.0343)**	**0.102 (0.0339)**
Job complexity (SD)	0.0342 (0.0376)	**0.0842 (0.0274)**	0.0500 (0.0372)	**0.102 (0.0273)**
Verbal learning & memory (N=762)				
Education				
Some college	**0.467 (0.121)**	**0.310 (0.0892)**	**0.476 (0.119)**	**0.310 (0.0892)**
College	0.113 (0.0893)	**0.224 (0.0546)**	0.131 (0.0881)	**0.224 (0.0645)**
Postgraduate	0.119 (0.0864)	0.0866 (0.0642)	0.113 (0.0852)	0.0866 (0.0643)
CAS (SD)	0.0453 (0.0365)	**0.119 (0.0331)**	**0.0924 (0.0325)**	**0.0948 (0.0326)**
Job complexity (SD)	0.0137 (0.0357)	**0.104 (0.0267)**	0.0263 (0.0353)	**0.129 (0.0265)**
Working memory (N=760)				
Education				
Some college	0.160 (0.132)	**0.224 (0.0936)**	0.146 (0.129)	**0.224 (0.0934)**
College	0.131 (0.0970)	**0.216 (0.0677)**	0.119 (0.0957)	**0.216 (0.0677)**
Postgraduate	**0.244 (0.0939)**	**0.244 (0.0674)**	**0.230 (0.0926)**	**0.244 (0.0674)**
CAS (SD)	−0.0517 (0.0395)	0.0515 (0.0356)	**0.0901 (0.0352)**	**0.102 (0.0349)**
Job complexity (SD)	0.0794 (0.0714)	**0.153 (0.0364)**	0.0799 (0.0482)	**0.170 (0.0363)**
Speed & flexibility (N=755)				
Education				
Some college	0.155 (0.117)	**0.226 (0.0893)**	0.198 (0.114)	**0.226 (0.0893)**
College	0.0709 (0.0860)	**0.173 (0.0642)**	0.0836 (0.0848)	**0.173 (0.0642)**
Postgraduate	0.0394 (0.0837)	0.0796 (0.0641)	0.0539 (0.0825)	0.0796 (0.0641)
CAS (SD)	**0.0908 (0.0351)**	**0.151 (0.0321)**	**0.160 (0.0314)**	**0.143 (0.0327)**
Job complexity (SD)	**0.0782 (0.0341)**	**0.0924 (0.0257)**	**0.0968 (0.0337)**	**0.112 (0.0259)**
Visuospatial ability (N=760)				
Education				
Some college	**0.242 (0.114)**	**0.300 (0.0820)**	**0.267 (0.111)**	**0.300 (0.0821)**

	CAS-TOTAL		*CAS-GAMES*	
	A. Full model	***B. Single predictor model***	***C. Full model***	***D. Single predictor model***
Immediate memory (N=762)	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**
College	**0.416 (0.0847)**	**0.378 (0.0600)**	**0.414 (0.0834)**	**0.378 (0.0600)**
Postgraduate	0.0794 (0.0828)	**0.173 (0.0600)**	0.0839 (0.0813)	**0.173 (0.0600)**
CAS (SD)	**0.0704 (0.0346)**	**0.174 (0.0328)**	**0.216 (0.0475)**	**0.246 (0.0530)**
Job complexity (SD)	**0.0747 (0.0333)**	**0.161 (0.0244)**	**0.0926 (0.0329)**	**0.189 (0.0248)**
Verbal ability (N=757)				
Education				
Some college	**0.347 (0.0991)**	**0.418 (0.0729)**	**0.395 (0.0984)**	**0.418 (0.0729)**
College	**0.595 (0.0737)**	**0.724 (0.0532)**	**0.626 (0.0738)**	**0.724 (0.0532)**
Postgraduate	**0.320 (0.0714)**	**0.392 (0.0530)**	**0.346 (0.0716)**	**0.392 (0.0530)**
CAS (SD)	**0.152 (0.0300)**	**0.303 (0.0318)**	**0.0911 (0.0272)**	**0.0748 (0.0345)**
Job complexity (SD)	**0.0843 (0.0368)**	**0.293 (0.0316)**	**0.141 (0.0292)**	**0.323 (0.0250)**

Coefficients with p<.05 are bold.