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Occupational Cognitive Complexity in Earlier Adulthood is Associated with Brain Structure and Cognitive Health in Mid-Life: The CARDIA Study

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Abstract

Objective—In line with cognitive reserve theory, higher occupational cognitive complexity is associated with reduced cognitive decline in older adulthood. How and when occupational cognitive complexity first exerts protective effects during the lifespan remains unclear. We investigated associations between occupational cognitive complexity during early to mid-adulthood and brain structure and cognition in mid-life.

Methods—Participants were 669 adults from the Coronary Artery Risk Development in Young Adults (CARDIA) study (ages 18-30 at baseline, 52% female, 38% black). We calculated scores reflecting occupational cognitive complexity using Census Occupation Codes (Years 10 and 15) and Occupational Information Network (O*NET) data. At Year 25, participants had structural brain MRI, diffusion tensor imaging, and cognitive testing [Rey Auditory Verbal Learning Test (RAVLT), Digit Symbol Substitution Test (DSST), Stroop]. In adjusted mixed models, we

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examined associations between occupational cognitive complexity during early to mid-adulthood and mid-life brain structure, specifically gray matter volume and white matter fractional anisotropy (FA), and cognition in mid-life (all outcomes converted to z-scores).

Results—Higher occupational cognitive complexity was associated with greater white matter FA (*Estimate* = 0.10, $p = 0.01$), but not gray matter volume. Higher occupational cognitive complexity was associated with better DSST (*Estimate* = 0.13, $p < 0.001$) and Stroop (*Estimate* = 0.09, $p = 0.01$) performance, but not RAVLT performance.

Conclusions—Occupational cognitive complexity earlier in adulthood is associated with better white matter integrity, processing speed, and executive function in mid-life. These associations may capture how occupational cognitive complexity contributes to cognitive reserve.

Keywords

cognitive reserve; cognitive aging; structural MRI; diffusion tensor imaging; occupation

INTRODUCTION

Cognitive reserve theory (Stern, 2012) posits there are factors, like higher education (Meng & D'Arcy, 2012), that help prevent cognitive decline in aging by enabling individuals to develop capacity to maintain good cognition even in the face of neuropathology or other brain changes. In support of cognitive reserve theory, higher educational attainment is known to reduce risk of dementia (Meng & D'Arcy, 2012), and studies have suggested that higher education helps prevent older adults with Alzheimer's neuropathology (e.g., β-amyloid) (Roe et al., 2008) or white matter damage (Mortamais et al., 2013) from exhibiting cognitive deficits. Factors beyond education may also build one's "reserve." A variety of cognitive endeavors have been shown to help prevent cognitive decline in aging, including literacy and reading (Kaup et al., 2015; Kaup et al., 2014), cognitively-stimulating leisure activities (Yates, Ziser, Spector, & Orrell, 2016), and even occupational history. A recent study found older adults who had cognitively-complex occupations were less likely to experience cognitive decline, and this beneficial effect was seen above and beyond the effects of education (Pool et al., 2016).

Although the concept of cognitive reserve is well-supported in older adulthood, few studies have investigated younger populations to understand the role of cognitive reserve earlier in the lifespan. In particular, how one develops "cognitive reserve" throughout life, how this benefits the brain, and how early in life neuroprotective effects first emerge remain unclear (Chapko, McCormack, Black, Staff, & Murray, 2017). We investigated these questions in the context of occupational cognitive complexity (Pool et al., 2016), a factor thought to contribute to cognitive reserve that has been less well-studied compared to education (Arenaza-Urquijo et al., 2013; Chapko et al., 2017; Liu et al., 2012) particularly in terms of associations with brain measures. Utilizing a prospective cohort study of adults followed from young adulthood to middle age, we examined whether occupational cognitive complexity during early to mid-adulthood is associated with brain structure and cognition in mid-life. We hypothesized that greater occupational cognitive complexity in earlier adulthood would be associated with larger gray matter volume as well as greater white matter integrity assessed by fractional anisotropy (FA), reasoning that occupational cognitive complexity might help support brain health by increasing gray matter and white matter connections. We tested our hypotheses by examining global brain measures (total gray matter volume and white matter FA across the brain). We also explored for potential regional differences by testing relationships by lobe, as well as with hippocampal gray matter given the importance of hippocampal changes in cognitive aging (Lister & Barnes, 2009) and Alzheimer's disease (Schuff et al., 2009). In addition, we hypothesized that greater occupational cognitive complexity in earlier adulthood would be associated with better cognitive function in mid-life, including better memory, processing speed, and executive functioning.

METHODS

Participants

Participants were from the Coronary Artery Risk Development in Young Adults (CARDIA) study, a multi-site, community-based prospective cohort study of 5,115 Black and White adults, who were 18-30 years old at baseline (1985–1986). Since baseline, CARDIA participants have been followed prospectively with study visits every 2-5 years (Year 2: 1987–1988, Year 5: 1990–1991; Year 7: 1992–1993; Year 10: 1995–1996; Year 15: 2000–2001, Year 20: 2005–2006, and Year 25: 2010–2011). Please see Cutter et al (1991) for a detailed description of sampling and recruitment methodology. In brief, participants were recruited in four U.S. cities (Birmingham, Alabama; Oakland, California, Chicago, Illinois; and Minneapolis, Minnesota) with the goal of balancing participants at each site by age, race, sex, and education (≤ high school versus > high school) (Friedman et al., 1988; Hughes et al., 1987), and recruitment was primarily by telephone. Eligibility criteria for enrollment included that individuals were in the target age range (18-30 years old) and were healthy and free-living; and enrolled participants were found to be representative of the target population (Cutter et al., 1991).

At Year 25, a total of 3,499 participants remained in the CARDIA study. The Year 25 study visit included cognitive testing, which was not done at prior timepoints. Additionally, at Year 25, a subset of CARDIA participants were invited to also participate in the CARDIA Brain MRI Substudy, which was conducted at three of the sites (Birmingham, Oakland, Minneapolis) (Launer et al., 2015). This substudy aimed to collect neuroimaging data using magnetic resonance imaging (MRI), with the goal of enrolling 700 substudy participants balanced by race and sex. Individuals with contraindications for MRI scans were excluded. In total, 710 participants completed neuroimaging in the CARDIA Brain MRI Substudy.

The CARDIA study was conducted in accordance with the Declaration of Helsinki principles. Institutional review boards at study sites and the CARDIA coordinating center approved the study. Participants provided written informed consent at each CARDIA visit, and CARDIA Brain MRI Substudy participants provided written informed consent separately from the main study.

As shown in Figure 1, for the present study, we utilized data from the main CARDIA study and the CARDIA Brain MRI substudy to investigate the association between occupational cognitive complexity earlier in adulthood (ascertainable from data collected at CARDIA Year 10 and Year 15 study visits) and brain health and cognitive health in mid-life (data collected at Year 25 in CARDIA Brain MRI Substudy and in the main CARDIA study, respectively). Given our focus on brain measures, we defined our analytic cohort for the present study to consist only of individuals who completed neuroimaging at Year 25 in the CARDIA Brain MRI Substudy. Of the 710 total participants who completed neuroimaging, we excluded 33 individuals from inclusion in our analyses due to occupational data that was either missing (n=24) or not translatable into our measure of occupational cognitive complexity (n=9; see detail below; no O*NET data available for their specific occupations). We also excluded an additional 8 individuals who did not complete Year 25 cognitive testing (reasons for missing data unclear). The resulting analytic cohort consisted of 669 individuals [52% female, 38% black, mean years of education = 15.0 (SD = 2.4)]. CARDIA participants not included in this analytic cohort were more likely to be black ($p < .001$), but were not different in age, sex, years of education, or cognition as assessed by the Rey Auditory Verbal Learning Test (RAVLT) (Rosenberg, Ryan, & Prifitera, 1984), Digit Symbol Substitution Test (DSST) (Wechsler, 1997), and Stroop Test (MacLeod, 1991) (all $p > .05$; cognitive measures further detailed below).

Measures

Occupational Cognitive Complexity during Early to Mid-Adulthood—To evaluate the cognitive complexity of participants' occupations during early to mid-adulthood, we utilized occupational data collected in the CARDIA study at Year 10 and Year 15 (1990 Census Occupation Codes) to derive "Occupational Cognitive Requirements" scores (OCRS), a measure which has been utilized in prior studies of occupational cognitive complexity and cognitive aging (Pool et al (2016) and Fisher et al (2014). OCRS, which provide an estimate of the cognitive complexity of particular occupations, are derived from the U.S. Department of Labor's Occupational Information Network (O*NET) database (Peterson, Mumford, Borman, Jeanneret, & Fleishman, 1999). The O*NET database contains survey results from U.S. workers randomly sampled to provide information about their occupations, including for 10 items which asked workers to rate the level of cognitive activity required by their occupation on a scale from 0 to 7. Results from these 10 items can be averaged to calculate an overall OCRS for a particular occupation, with a possible range of 0 to 7 (higher score indicates greater occupational cognitive complexity). The following details how occupational data was collected in CARDIA and how those data were translated into OCRS:

At CARDIA Year 10 (mean age = 35.4; SD = 3.5) and Year 15 (mean age = 40.5; SD = 3.5), participants were asked to report their current occupational status and to indicate what their current or most recent occupation was. Their current (or most recent) occupations were then coded using 1990 Census Occupation Codes. [Though 84 individuals in our analytic cohort endorsed being currently unemployed at the time of either the Year 10 visit and/or the Year 15 visit, Census Occupation Codes were still coded for all of these participants, reflecting occupation most recently held and/or occupation currently held at the other visit when actively employed; thus these 84 individuals were still included in analysis. Only 2 individuals in our analytic cohort indicated being homemakers (both at Year 10 only); both individuals reported occupations outside the home at Year 15 and thus the corresponding Census Occupation Codes for Year 15 were used for these individuals].

Following methods detailed in Pool et al (2016) and Fisher et al (2014), we translated participants' 1990 Census Occupation Codes into overall OCRS. To accomplish this, we merged participants' 1990 Census Occupation Codes (i.e., our CARDIA dataset) with data from the 1998 O*NET database (O*NET 98) (Peterson et al., 1999). Merging of these two datasets required using a crosswalk from the National Crosswalk Service Center (available at http://www.xwalkcenter.org); The O*NET 98 database is organized by a code variable called "onetcode," a unique key code assigned to each "occupational unit" contained within the O*NET database (i.e., reflecting a particular occupation with corresponding ratings data). The crosswalk links these "onetcodes" to their corresponding 1990 Census Occupation Codes. Thus, this made it possible to link individual CARDIA participants' occupations (i.e., their 1990 Census Occupation Codes) with corresponding O*NET ratings of those occupations.

We then calculated participants' Year 10 and Year 15 OCRS (as defined above), and we utilized individuals' maximum OCRS across these two timepoints as our measure of occupational cognitive complexity. Thus, our occupational measure reflects the cognitive complexity of participants' most demanding occupation across Years 10 and 15. We henceforth refer to this maximum OCRS variable as our measure of "occupational cognitive complexity."

Brain Structure in Mid-Life—At Year 25 (mean age = 50.4, SD = 3.5), participants underwent neuroimaging in the CARDIA Brain MRI Substudy, including structural MRI and diffusion tensor imaging (DTI), in 3T MR scanners (Birmingham, AL: Philips 3T Achieva/2.6.3.6 platform; Minneapolis, MN: Siemens 3T Tim Trio/VB 15 platform; Oakland, CA: Siemens 3T Tim Trio/VB 15 platform) using standardized protocols. Methodology including acquisition parameters and data processing methods has been described in detail elsewhere (Launer et al., 2015). Structural MRI images were automatically segmented into gray and white matter, and tissue was classified as normal or abnormal then parcellated into regions of interest using the Jakob Atlas (Goldszal et al., 1998; Kabani, Collins, & Evans, 1998; Shen & Davatzikos, 2002). DTI images were used to calculate maps of fractional anisotropy (FA) using standard methods (Le Bihan et al., 2001). We examined total gray matter volume, gray matter volume within frontal, temporal, parietal, and occipital lobes, and hippocampal gray matter volume, each corrected for intracranial volume (ICV; consisting of total brain volume plus cerebrospinal fluid) to account for variation in head size. Normal gray matter volumes in each lobe were combined across left and right hemispheres, then divided by ICV to calculate the volume to ICV ratio. We examined mean white matter FA across the brain (total FA) as well as white matter FA by lobe, with mean white matter FA values within a particular lobe averaged across the left and right hemispheres. All brain structure outcomes were converted to z-scores (utilizing means and standard deviations from all participants who had these data), with higher z-scores reflecting larger gray matter volumes and higher FA.

Cognition in Mid-Life—At Year 25, participants completed three cognitive tests: 1) Rey Auditory Verbal Learning Test (RAVLT) (Rosenberg, Ryan, & Prifitera, 1984), a word list task that measures episodic memory, and the delayed recall score from this test was utilized in our analyses, 2) Digit Symbol Substitution Test (DSST) (Wechsler, 1997), a measure of processing speed, with score reflecting number of items completed within the time limit, and 3) the Stroop Test (MacLeod, 1991), which measures executive functioning; the interference score calculated from this measure was utilized in our analyses. Raw scores for each measure were converted into z-scores (utilizing means and standard deviations from all participants who completed Year 25 cognitive testing), calculated such that higher z-scores reflect better performance.

Other Variables—The following variables were measured repeatedly throughout the CARDIA study. Age, sex, race, and years of education were self-reported. Hypertension and diabetes were determined via a combination of self-report, clinic assessments, and medication use. Obesity was defined as a body mass index ≥ 30 kg/m^2. To assess depressive symptoms, participants completed the Center for Epidemiologic Studies Depression (CES-D) scale, a 20-item inventory with maximum score of 60 (score ≥ 16 is suggestive of clinical depression) (Radloff, 1977). Participants self-reported current alcohol use (converted to mL/day) and cigarette smoking status (coded as current smoker vs. current non-smoker). We utilized these variables as assessed at Year 25 to correspond in time with the brain structure and cognitive outcomes and enable adjustment for potential confounding factors that could influence the outcome measures.

Statistical Analysis

We examined associations between participants' maximum OCRS (continuous variable), our measure of occupational cognitive complexity, and participant characteristics, including demographics, education, and health factors, using *t*-tests and Pearson's correlations. We then conducted linear mixed models to investigate the association between occupational cognitive complexity and gray matter volumes (z-scores), white matter FA values (z-scores), and cognitive test z-scores. Mixed model analyses were adjusted for demographics (age, sex, race), years of education, as well as health factors found to be associated with occupational cognitive complexity (p <.10) in the *t*-test and correlation analyses. These analyses accounted for site (participants nested within site) as a random effect. To check for problematic multicollinearity among occupational cognitive complexity and the covariates (especially education), we utilized regression diagnostic to examine variance inflation factor (VIF) values. We considered VIF values > 10 to be suggestive of problematic multicollinearity (Belsey, Kuh, & Welsch, 1980).

Since the brain structural and cognitive outcome measures were converted to z-scores, results from the mixed model analyses (estimate values) reflect amount of predicted increase in SD units in the outcome variable per every 1 unit increase in the occupational cognitive complexity variable. For descriptive purposes only, we classified participants into groups based on level of occupational cognitive complexity by tertiles. We utilized these tertile groups to illustrate participant characteristics by occupation cognitive complexity tertile, as well as to graphically depict associations between tertiles and brain structural and cognitive outcomes.

In follow-up to our primary analyses separately testing associations between 1) occupational cognitive complexity and brain structural measures, and 2) occupational cognitive complexity and cognitive function measures, we conducted a secondary analysis in which we followed the Baron and Kenny approach to mediation analysis (Baron & Kenny, 1986; Kenny, 2016) to test whether observed significant associations between occupational cognitive complexity and cognitive function outcomes may be mediated by structural brain measures (i.e., the brain measures found to be significantly associated with occupational cognitive complexity).

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc.).

RESULTS

The distributions of participants' OCRS were similar at Year 10 (mean = 2.6, SD = 1.0, range = 0.8 to 4.9) and Year 15 (mean=2.8, SD=1.1, range = 0.4 to 5.0), and OCRS at the two timepoints were significantly correlated ($r = 0.53$, $p < 0.001$). As stated above, we utilized individuals' maximum OCRS as our measure of occupational cognitive complexity; distribution of this variable was as follows: mean = 3.0, *SD*=1.0, range = 0.8 to 5.0. See Figure 2 for this variable's distribution and descriptive examples of range for occupations in the CARDIA cohort. As detailed in Table 1, higher occupational cognitive complexity was associated with older age, white race, and higher education. There was a trend for occupational cognitive complexity to be higher in women than men. Individuals with higher occupational cognitive complexity were less likely to have hypertension and diabetes, endorsed fewer depressive symptoms, and were less likely to smoke; thus, these factors, along with all the demographic variables, were included as covariates in the below analyses.

Results of mixed models examining the association between occupational cognitive complexity during early to mid-adulthood and brain structure and cognitive z-scores in mid-life are shown in Table 2. Occupational cognitive complexity was not associated with gray matter volume, including no associations with total or regional gray matter volumes. In contrast, higher occupational cognitive complexity was associated with greater white matter FA. In models adjusted for demographics and education, the association between occupational cognitive complexity and white matter FA was significant for total FA and for all four lobes. When additionally adjusting for health factors, associations with total FA, frontal FA, and temporal FA remained statistically significant. Higher occupational cognitive complexity was associated with better performance on the DSST and Stroop in models adjusted for demographics and education as well as models adjusted for demographics, education, and health factors. Occupational cognitive complexity was not associated with RAVLT Delayed Recall performance.

We re-ran the above analyses to explore for potential interactions between occupational cognitive complexity and race or sex, and we found no interaction effects (all $p > 0.05$). Regression diagnostics to check for multicollinearity among the occupational cognitive complexity predictor variable and covariates were not concerning for multicollinearity (VIF values all < 1.7).

To depict associations graphically, Figures 2 and 3 show adjusted white matter FA z-score means and adjusted cognitive z-score means, respectively, by occupational cognitive complexity tertile.

As a follow-up analysis, we explored whether the associations between 1) occupational cognitive complexity and DSST and 2) occupational cognitive complexity and Stroop may be mediated by measures of FA. Specifically, we ran two additional mixed models in which both occupational cognitive complexity and total FA were included as predictors, with the cognitive variables (DSST or Stroop) as the outcome (adjusted for same covariates as above). In the model predicting DSST performance, both occupational cognitive complexity (*Estimate* = 0.12, *SE* = 0.04, $p = .001$) and total FA (*Estimate* = 0.13, *SE* = 0.04, $p < 0.001$) were significantly positively associated with DSST performance, and comparison of these results to those from the prior model that did not include total FA (i.e., results from Table 2) indicates that inclusion of total FA in the model reduces the occupational cognitive complexity estimate by 11%; these results are suggestive of a small partial mediation effect. Similarly, in the model predicting Stroop performance, both occupational cognitive complexity (*Estimate* = 0.08, *SE* = 0.04, $p = 0.03$) and total FA (*Estimate* = 0.08, *SE* = 0.04, $p = 0.03$) were significantly positively associated with Stroop performance, and comparison of these results to those from the prior model that did not include total FA (i.e., results from Table 2) indicates that inclusion of total FA in the model reduces the occupational cognitive complexity estimate by 9%; these results are suggestive of a small partial mediation effect. Results were similar in analyses testing the frontal FA and temporal FA variables as potential mediators, instead of total FA.

DISCUSSION

Given evidence that occupational cognitive complexity is associated with reduced cognitive decline in late life (Pool et al., 2016; Then et al., 2015) and is thought to do so by contributing to cognitive reserve (Pool et al., 2016; Then et al., 2015), we sought to increase understanding of how occupational cognitive complexity may build cognitive reserve during in the lifespan by investigating how individual differences in occupational cognitive complexity earlier in adulthood relate to brain structure and cognition in mid-life. Specifically, among a cohort of adults followed into middle age, we investigated associations between occupational cognitive complexity during early to mid-adulthood and gray matter volume, white matter integrity, and cognitive function (memory, processing speed, and executive function) in mid-life. We found that individuals who had cognitively complex occupations earlier in adulthood had better brain and cognitive health in mid-life. Together with the prior research showing that occupational cognitive complexity is associated with reduced cognitive decline in older age (Pool et al., 2016; Then et al., 2015), our results raise the possibilities that occupational cognitive complexity may serve to preserve or enhance brain structure and cognition even prior to older adulthood. Perhaps beneficial effects seen on brain structure and cognition in mid-life will in turn help individuals to remain more resilient to deleterious effects of aging and neuropathology as they reach older adulthood, in line with cognitive reserve theory (Stern, 2012).

While the above interpretations fit within the larger literature on cognitive reserve in aging (Stern, 2012), an alternative explanation for our results that we cannot rule out is that unmeasured, pre-existing differences may have influenced individuals' occupational cognitive complexity, such as differences in brain structure and cognition earlier in life, which were not measured in the CARDIA study. A previous study that did have the benefit of cognition measured in childhood utilized structural equation modeling to disentangle relationships between childhood cognition, occupational factors (including complexity), and an outcome capturing cognitive, physical, and emotional function in late life; findings highlighted that childhood cognition influences both occupation and late-life function, though there was still an independent effect of occupation on late-life function (Chapko et al., 2016). Though we were not able to account for early-life cognition in this same way, some aspects of our study design help reduce potential impact of reverse causality on our results including 1) that we were able to measure occupational cognitive complexity exposure 10 to 15 years prior to our brain structure and cognitive outcome measures, and 2) because we saw significant associations even when adjusting for educational attainment. Nevertheless, additional studies are needed to further clarify longitudinal associations between occupational cognitive complexity, brain structure, and cognition across the lifespan. Indeed, a study with repeated brain imaging and cognitive assessment beginning in early life continuing through late life is ultimately needed to fully disentangle these longitudinal relationships across the life course, though such a study would certainly be challenging to implement given need for detailed data collection over decades.

With the above caveat in mind, the associations we found generate specific hypotheses about how occupational cognitive complexity may impact brain structure and help protect brain health in aging. We found that higher occupational cognitive complexity during early to mid-adulthood was associated with better white matter integrity (mean FA) in mid-life, but was not associated with gray matter volume. FA values can be influenced by a number of biological factors related to the integrity of white matter structure (Curran, Emsell, & Leemans, 2016), so the exact biological underpinnings of our observed associations remain unclear. Our findings raise the possibility that occupational cognitive complexity may preserve axon tract structure against age-related deterioration, consistent with the concept of "brain maintenance" (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012) which posits that lifestyle variables and other factors may help individuals avoid brain changes in aging. Alternatively, occupational cognitive complexity may help promote neural plasticity or myelination to strengthen or increase white matter connections (Chanraud, Zahr, Sullivan, & Pfefferbaum, 2010). Positive associations with white matter integrity are further supported by findings that engagement in greater cognitive activity during late life is associated with greater FA among older adults (Arfanakis et al., 2015), as well as cognitive training studies that have shown increases in FA following training in older adults (Chapman et al., 2015; Lövdén et al., 2010). To our knowledge, ours is the first study to investigate occupational cognitive complexity in relation to DTI measures. One study examined effects of both education and occupation (as measured by an occupation prestige variable) on FA in 21 older adults with Alzheimer's disease and 18 healthy older adults, and found that education, not occupation, was associated with FA (Teipel et al., 2009). Our results may diverge due to our larger sample size, use of an occupational measure designed to capture cognitive complexity, or focus on middle-aged individuals. That we found no associations between occupational cognitive complexity and gray matter volumes is similar to prior volumetric studies of older adults (Foubert-Samier et al., 2012; Lo & Jagust, 2013). This lack of association with gray matter volume suggests that occupational cognitive complexity's role in supporting brain health may be specific to influencing white matter connections.

Our results exploring the association between occupational cognitive complexity and FA by lobe suggested that associations are not uniform across the brain. Though we found associations between occupational cognitive complexity and white matter FA in all four lobes in our minimally adjusted models, the strongest relationships were for frontal and temporal regions. White matter integrity is known to deteriorate in aging and this occurs most prominently in anterior regions (Chanraud et al., 2010). Therefore, when considering the pattern of our findings in this context, it may be that occupational cognitive complexity helps preserve white matter integrity in regions most vulnerable to age-related deterioration (i.e., frontal and temporal regions). It is also possible that cognitively challenging occupations, on average, place greatest demand on the cognitive processes served by frontal (Koechlin & Hyafil, 2007) and temporal (Squire, Wixted, & Clark, 2007) regions (e.g., reasoning, decision-making, multitasking, learning and memory abilities), potentially leading occupational cognitive complexity to preserve or build neural networks and their white matter connections in these regions in particular. Again, despite these intriguing hypotheses, reverse causality also remains a possible explanation.

With respect to cognition, we found that individuals who had cognitively complex occupations earlier in adulthood performed better on measures of processing speed and executive function in mid-life. In contrast, occupational cognitive complexity was not associated with mid-life memory. Our results are similar to Jonaitis et al (2013), who studied a middle-aged cohort at high-risk for Alzheimer's disease and found that an occupational complexity measure was associated with processing speed, executive functioning, and visuospatial skills but not memory. However, our results diverge from those of Murray et al (2011) who found no association between an occupational measure and cognition in older adulthood (though education was positively related to better cognition). While it is unclear why findings diverge, possibilities include that results may vary in relation to 1) how occupation was measured (our study and Jonaitis et al are similar in basing our occupational measure on ratings of job complexity, while the occupational variable examined in Murray et al classifies individuals based on 9 job categories (e.g., unskilled, managerial), or 2) differences in characteristics of study samples such as differences in age range and range/ distribution of education and occupational histories among participants.

When viewed in combination, the pattern of the associations we found with particular measures of brain structure (white matter integrity, but not gray matter) and particular cognitive domains (processing speed and executive functioning, but not memory) raises the possibility that these associations may be along the same causal pathway. Prior research has shown that white matter integrity is associated with processing speed and executive function (Borghesani et al., 2013), and this indeed was the case in our study as well (as seen as part of our mediation analyses results). Our findings suggesting partial mediation effects, support the possibility that FA may play a contributory role in influencing the positive relationships we observed between occupational cognitive complexity and measures of processing speed and executive functioning. However, given that FA explained a small portion of the variance, our partial mediation results also suggest that other, unmeasured factors may be mediating this relationship as well. The above being said, our mediation results should be interpreted very cautiously and viewed as, at most, as preliminary evidence of a possible pathway. This is because limitations in our study design prevent more rigorous testing of mediation effects and possible causal pathways. Though we were able apply the Baron and Kenny approach to mediation analysis (Baron & Kenny, 1986; Kenny, 2016) in our study, other statisticians, such as Kraemer et al. (Kraemer et al., 2008; Kraemer et al., 2001) have argued for more stringent criteria for mediation analysis including that there is clear temporal sequencing of the constructs of interest and repeated measurement of constructs over time. Unfortunately, our study cannot meet these criteria – namely, since brain MRI and cognitive testing were not done with the CARDIA cohort until Year 25, we cannot directly test whether earlier occupational exposure led to *change* in brain structure and *change* in cognitive function over time. Thus, future studies with repeated measures of brain structure and cognitive function over the life course are needed to begin to explore possible causal pathways.

Strengths of our study include investigation of a well-characterized, diverse community-based cohort of adults from the CARDIA study. This enabled us to conclude that the associations between occupational cognitive complexity and our outcome measures persisted after accounting for other factors, including demographics, education and health variables, suggesting that occupational cognitive complexity may be independently associated with brain and cognitive health. Additional strengths include utilization of an occupational cognitive complexity measure based on prior research (Fisher et al., 2014; Pool et al., 2016) and grounded in rich information provided by O*NET data, as well as examination of two neuroimaging modalities and three domains of cognition. Limitations include that we cannot evaluate how well occupational ratings from the O*NET database match individual CARDIA participants' actual daily experiences in their jobs, and we could not quantify exactly how long individuals held the same job or the extent to which their occupational cognitive complexity may have varied over the years. Finally, although the independent associations we found between occupational cognitive complexity and FA and cognition were statistically significant, effects were modest, which may be due to our middle-aged cohort still being relatively cognitively healthy. It remains unclear whether the associations we observed will translate into clinically-meaningful differences in risk for cognitive decline and dementia as individuals age into older adulthood.

We found that occupational cognitive complexity during early to mid-adulthood is associated with better white matter integrity, processing speed, and executive function in mid-life. Viewed within the broader literature supporting the theory of cognitive reserve and its protective role in older adulthood, the associations we observed point to occupational cognitive complexity as one factor that may help build cognitive reserve across the lifespan, such that its associations with brain health and cognition can be seen as early as in mid-life. Our findings add to a growing body of research that suggests cognitive aging is a lifelong process, that cognitive health in older adulthood may depend on the combination of risk and protective factors individuals were exposed to across their lifetimes from childhood (Seifan, Schelke, Obeng-Aduasare, & Isaacson, 2015) though adulthood and into late life (Deckers et al., 2015).

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PUBLIC SIGNIFICANCE STATEMENT

Cognitively-stimulating activities, such as cognitively-complex occupations, are thought to help prevent cognitive decline in aging. It is unclear how such activities benefit the brain and how early on during the lifespan protective effects first emerge. We found that individuals who had cognitively-complex occupations in earlier adulthood had better brain health (specifically, white matter structure) and better cognitive health (specifically, processing speed and executive function) in mid-life. These associations may help explain why individuals who have cognitively-complex occupations are less likely to show cognitive decline in older adulthood.

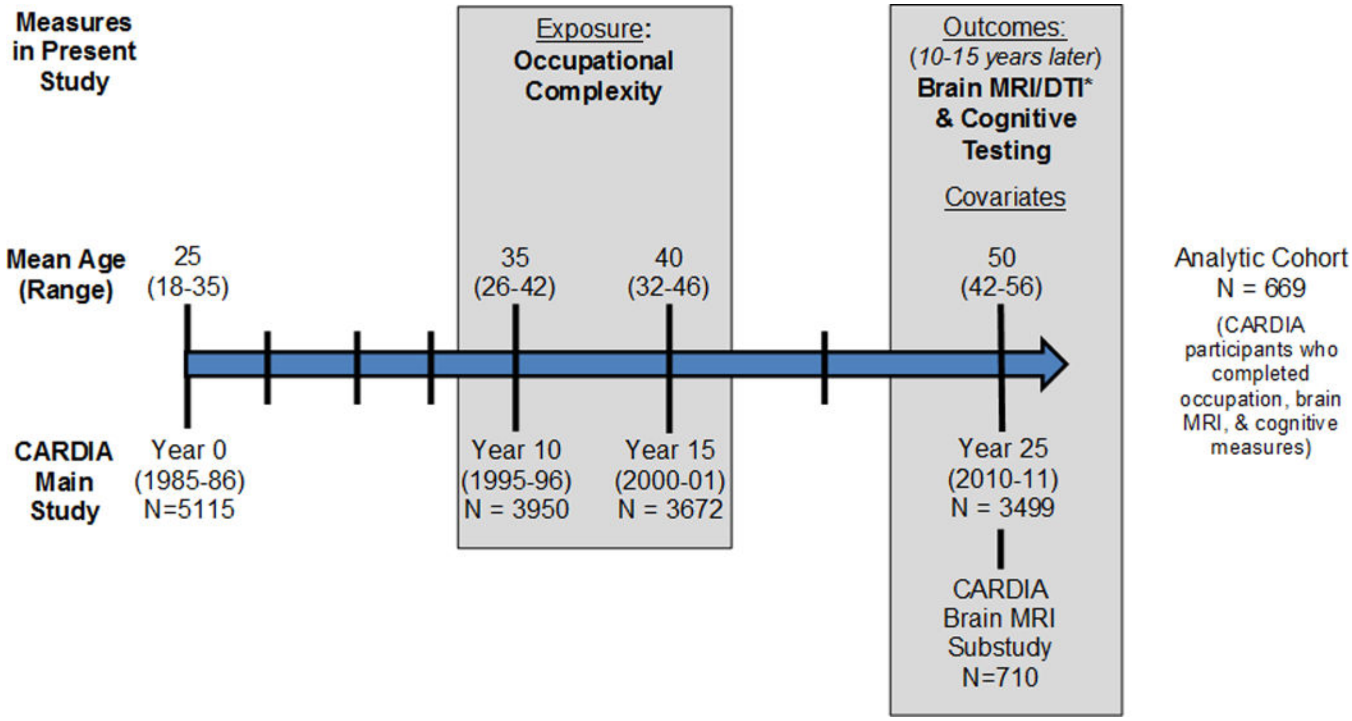

Figure 1. Study Timeline

Timeline of measures utilized in the present study. Tick marks represent study visits that occurred for the main CARDIA study (Years 0, 2, 5, 7, 10, 15, 20, and 25) and the smaller CARDIA Brain MRI Substudy (Year 25). As detailed in the Methods section, the occupational cognitive complexity measure was derived from occupational data coded at Years 10 and 15 in the main CARDIA study. Cognition was assessed at Year 25 in the main CARDIA study; no cognitive measures were given at earlier timepoints. Neuroimaging was conducted among a subset of CARDIA participants at Year 25 in the CARDIA Brain MRI Substudy. *denotes measures collected only among participants in Year 25 Brain MRI Substudy

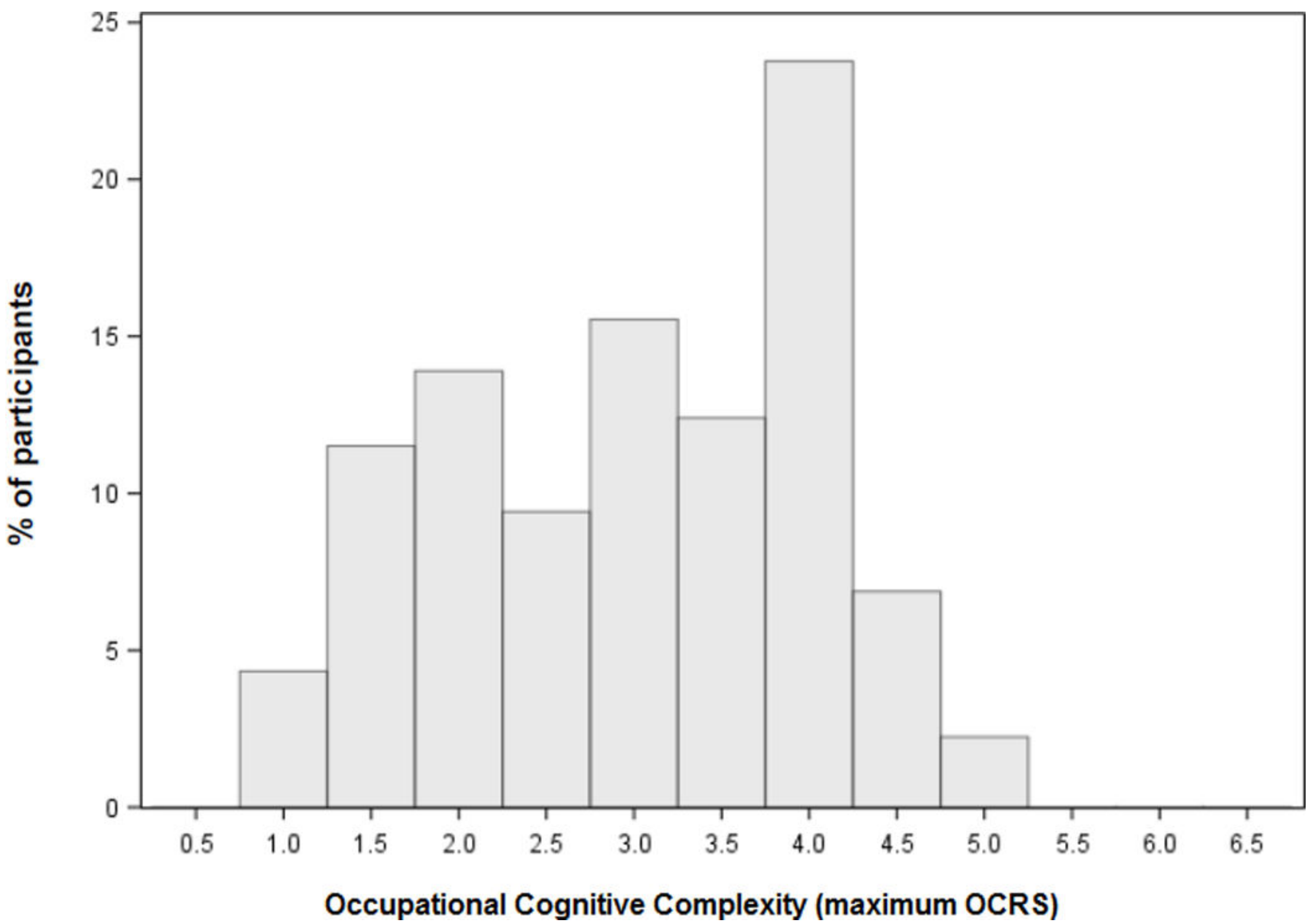

Figure 2. Distribution of the Occupational Cognitive Complexity Variable

Occupational Cognitive Requirements score, possible score range 0 to 7. The following are examples of occupations rated relatively higher in complexity: engineers, financial managers and accountants, scientists, managers and administrators, lawyers, computer programmers, physicians, and psychologists. The following are examples of occupations rated relatively lower in complexity: machine operators, laborers, garbage collectors, bus drivers, private household employees (e.g., cooks, cleaners), construction trades, mail carriers and messengers, and file clerks.

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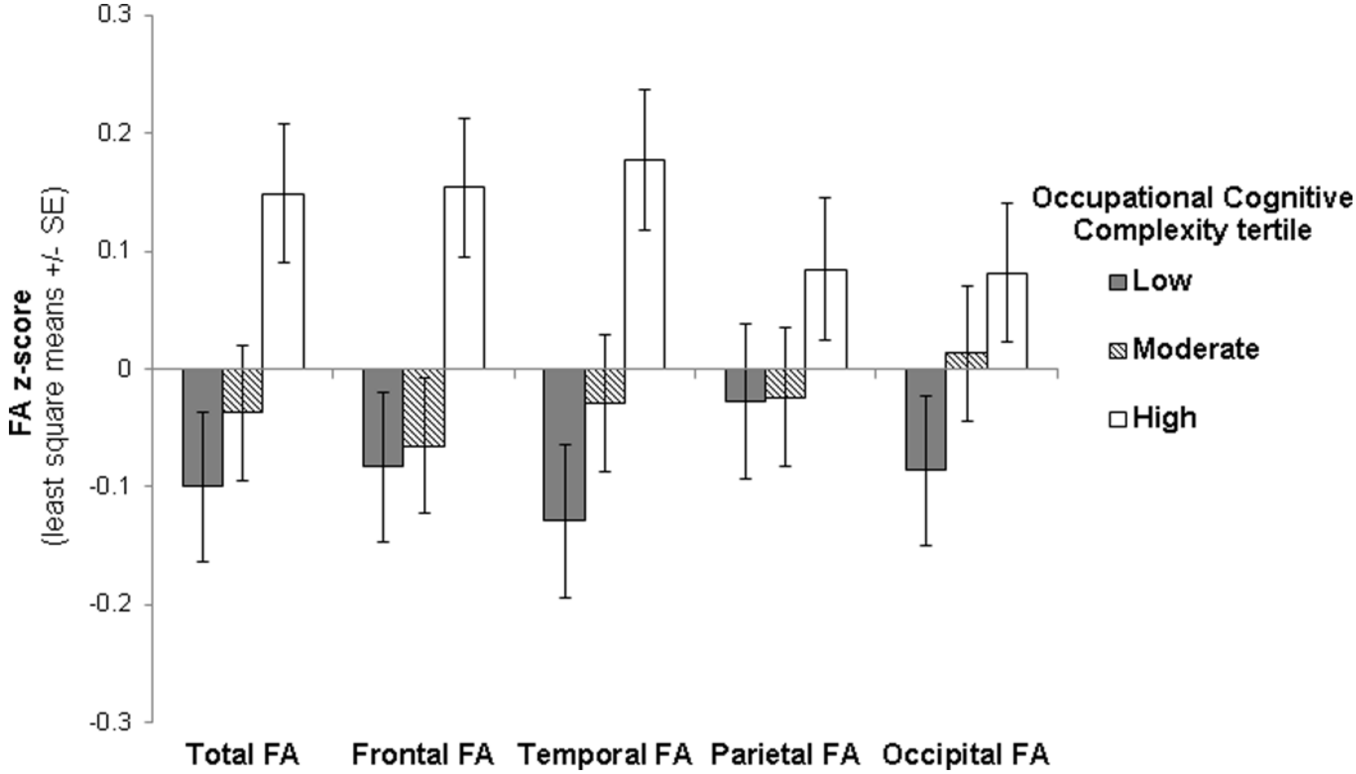

Figure 3. Association between Occupational Cognitive Complexity in Early to Mid-Adulthood (tertiles) and White Matter FA in Mid-life

Results are from mixed models adjusted for age, sex, race, education, hypertension, diabetes, depressive symptoms, and current smoking.

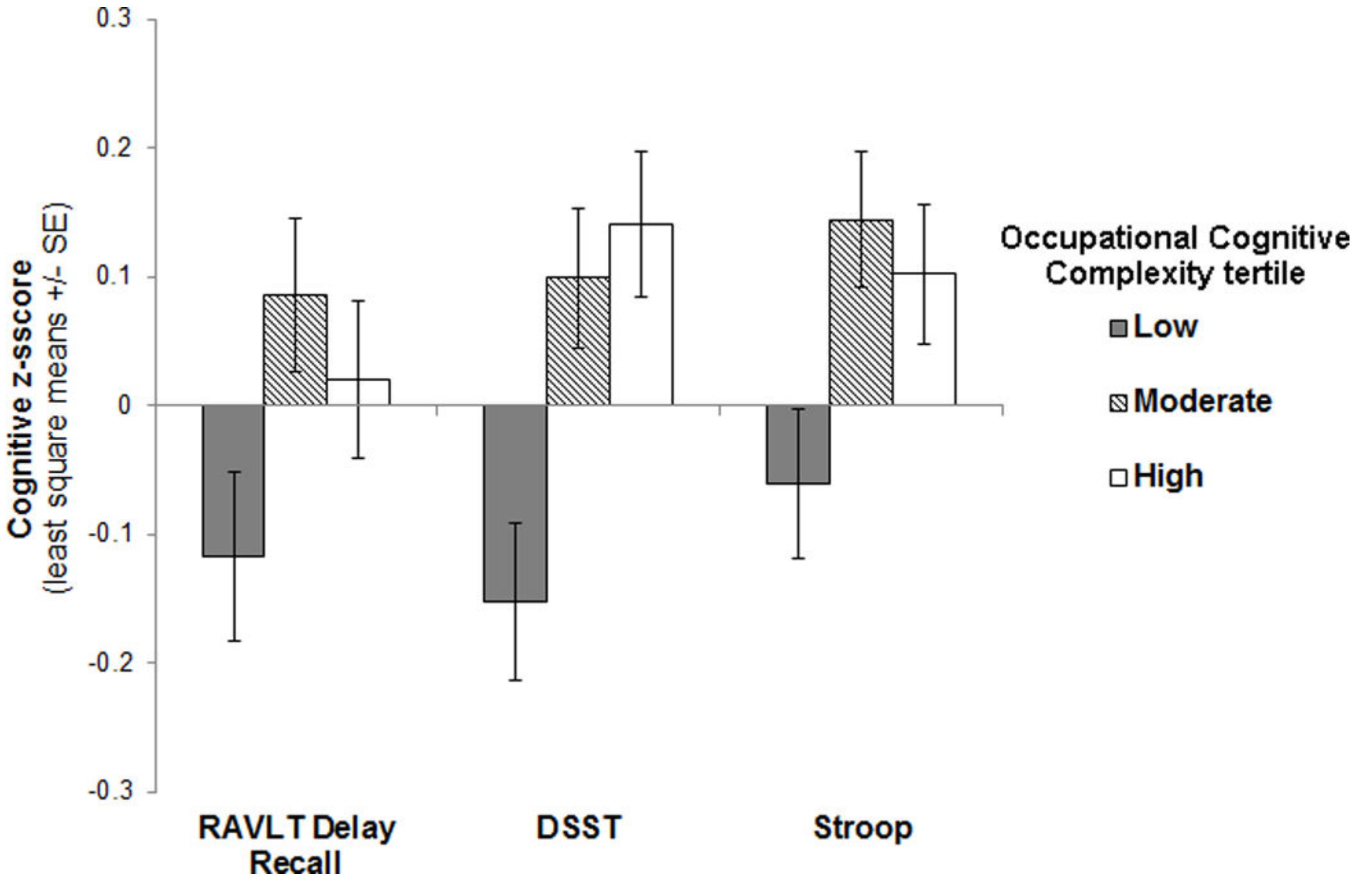

Figure 4. Association between Occupational Cognitive Complexity in Early to Mid-Adulthood (tertiles) and Cognitive Performance in Mid-life

Results are from mixed models adjusted for age, sex, race, education, hypertension, diabetes, depressive symptoms, and current smoking.

Table 1

Association of Participant Characteristics with Occupational Cognitive Complexity

	Overall	Occupational Cognitive Complexity by Tertiles			Association with Occupational Cognitive Complexity *(continuous variable)*	
Mean (SD)/%	**n=669**	**Low n=220**	**Mid n=221**	**High n=228**	***Test Statistic***	***p***
Age, *years* (Y25)	50.4 (3.5)	49.8 (3.6)	50.5 (3.5)	50.8 (3.4)	$r = 0.13$	0.001 *
Sex, *% female*	51.7	48.6	53.9	52.6	$t = -2.0$	0.05
Race, *% black*	38.3	56.8	33.9	24.6	$t = 7.9$	<0.001 *
Education, *years* (Y25)	15.0 (2.4)	13.5 (2.0)	15.4 (2.1)	16.2 (2.2)	$r = 0.50$	<0.001 *
Hypertension (Y25)	28.0	37.3	21.7	25.0	$t = 3.2$	0.002 *
Diabetes (Y25)	9.6	13.7	6.8	8.3	$t = 2.2$	0.03 *
Obesity (Y25)	35.6	41.4	29.6	36.0	$t = 0.93$	0.35
CES-D, out of 60 (Y25)	8.6 (6.9)	10.4 (7.3)	7.9 (6.7)	7.5 (6.3)	$r = -0.19$	<0.001 *
Alcohol, mL/d (Y25)	12.9 (24.5)	14.5 (33.9)	10.9 (18.2)	13.4 (18.5)	$r = -0.06$	0.11
Current Smoker (Y25)	15.5	27.3	11.8	7.9	$t = 6.4$	<0.001 *

* $p < .05$; r = correlation coefficient, t = t-test statistic

Table 2

Association between Occupational Cognitive Complexity during Early to Mid-Adulthood *(continuous variable)* and Brain Structure and Cognition in Mid-Life *(z-scores)*

	Adjusted for demographics and education[a]			Adjusted for demographics, education, and health factors[b]		
	Estimate (95% CI)	***SE***	***p***	***Estimate (95% CI)***	***SE***	***p***
Gray Matter (GM), *z-score*						
Total GM	−0.01 (−0.09, 0.07)	0.04	0.78	−0.03 (−0.12, 0.05)	0.04	0.42
Frontal GM	0.01 (−0.08, 0.09)	0.04	0.86	−0.01 (−0.10, 0.07)	0.04	0.75
Temporal GM	0.01 (−0.07, 0.10)	0.04	0.79	−0.01 (−0.10, 0.08)	0.04	0.80
Hippocampal GM	−0.02 (−0.10, 0.06)	0.04	0.59	−0.02 (−0.10, 0.06)	0.04	0.60
Parietal GM	−0.05 (−0.13, 0.04)	0.04	0.26	−0.07 (−0.15, 0.02)	0.04	0.13
Occipital GM	0.01 (−0.08, 0.10)	0.05	0.83	<0.01 (−0.09, 0.09)	0.05	0.99
Fractional Anisotropy (FA), *z-score*						
Total FA	0.12 (0.05, 0.20)	0.04	0.001*	0.10 (0.02, 0.17)	0.04	0.01*
Frontal FA	0.12 (0.04, 0.19)	0.04	0.003*	0.09 (0.01, 0.16)	0.04	0.03*
Temporal FA	0.15 (0.07, 0.22)	0.04	<0.001*	0.13 (0.05, 0.20)	0.04	0.001*
Parietal FA	0.08 (0.001, 0.15)	0.04	0.049*	0.05 (−0.03, 0.12)	0.04	0.24
Occipital FA	0.10 (0.02, 0.17)	0.04	0.01*	0.07 (−0.002, 0.15)	0.04	0.06
Cognition, *z-score*						
RAVLT Delayed Recall	0.06 (−0.02, 0.14)	0.04	0.12	0.05 (−0.02, 0.13)	0.04	0.17
DSST	0.17 (0.10, 0.24)	0.04	<0.001*	0.13 (0.06, 0.21)	0.04	<0.001*
Stroop Interference	0.10 (0.04, 0.17)	0.03	0.003*	0.09 (0.02, 0.15)	0.04	0.01*

[a] Mixed models adjusted for age, sex, race, education;

[b] Mixed models adjusted for age, sex, race, education, hypertension, diabetes, depressive symptoms, current smoking;

* $p < .05$;

Estimate values reflect amount of predicted increase in SD units in the outcome variable per every 1 unit increase in the occupational cognitive complexity variable.