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Periventricular and Deep Abnormal White Matter Differ in Associations With Cognitive Performance at Midlife

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Abstract

Objective: Abnormal white matter (AWM) on magnetic resonance imaging is associated with cognitive performance in older adults. We explored cognitive associations with AWM during late-midlife.

Method: Participants were community-dwelling men (n = 242; M = 61.90 years; range = 56–66). Linear-mixed effects regression models examined associations of total, periventricular, and deep AWM with cognitive performance, controlling for multiple comparisons. Models considering specific cognitive domains controlled for current general cognitive ability (GCA).

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We hypothesized that total AWM would be associated with worse processing speed, executive function, and current GCA; deep AWM would correlate with GCA and periventricular AWM would relate to specific cognitive abilities. We also assessed the potential influence of cognitive reserve by examining a moderation effect of early life (mean age of 20) cognition.

Results: Greater total and deep AWM were associated with poorer current GCA. Periventricular AWM was associated with worse executive function, working memory, and episodic memory. When periventricular and deep AWM were modeled simultaneously, both retained their respective significant associations with cognitive performance. Cognitive reserve did not moderate associations.

Conclusions: Our findings suggest that AWM contributes to poorer cognitive function in late-midlife. Examining only total AWM may obscure the potential differential impact of regional AWM. Separating total AWM into subtypes while controlling for current GCA revealed a dissociation in relationships with cognitive performance; deep AWM was associated with nonspecific cognitive ability whereas periventricular AWM was associated with specific frontal-related abilities and memory. Management of vascular or other risk factors that may increase the risk of AWM should begin during or before early late-midlife.

Keywords

abnormal white matter; white matter hyperintensities; aging; cognition; midlife

Identifying early biomarkers is important for characterizing the full trajectories of normal and abnormal cognitive aging (Bondi et al., 2017; Sperling et al., 2011). Magnetic resonance imaging (MRI) provides an in vivo measure of brain pathology that may be associated with cognitive decline, including worsening white matter disease. Abnormal white matter (AWM; e.g., white matter hyperintensities on T2-weighted MR images) is related to cerebrovascular incidents, vascular risk factors, and vascular dementia (Debette et al., 2011; Fennema-Notestine et al., 2016; Gorelick et al., 2011; Gunning-Dixon et al., 2009; McEvoy et al., 2015; Prins & Scheltens, 2015; O'Brien & Thomas, 2015). AWM is also an indicator of cerebral small vessel disease, and it may represent axonal loss or demyelination from chronic ischemia (Grueter & Schulz, 2012; Prins & Scheltens, 2015). AWM is prevalent and well studied in older age (Gunning-Dixon et al., 2009); however, AWM volume increases across the life span, and is present to some degree in approximately 50% of adults by their late 40s (Hopkins et al., 2006; Jernigan et al., 2001), when most individuals have reached the peak efficiency of white matter structural connectivity (Zhao et al., 2015). This AWM increase during midlife is largely driven by the advent of cardiovascular and cerebrovascular pathologies as adults enter their 50s (Fennema-Notestine et al., 2016; Gindi et al., 2018; Hopkins et al., 2006; Jernigan et al., 2001). Across ages 20–80, King et al. (2014) found that those over the age of 50 with greater vascular risk factors demonstrated more AWM as well as an increased correlation between AWM and age than those without risk factors. Thus, the earlier midlife age range beginning in the 50s may be important stage of increased AWM development and cerebral small vessel disease progression.

In studies of older adults, more AWM is associated with worse cognitive performance; however, it is not clear how early in life that association manifests. Studies in older age

consistently report associations between total AWM and worse performance on tests of executive function, processing speed, and general cognitive ability (GCA) (Birdsill et al., 2014; Delano-Wood et al., 2008; Grueter & Schulz, 2012; Gunning-Dixon & Raz, 2000), and there is some evidence for associations with other cognitive domains, such as memory (Bolandzadeh et al., 2012; Delano-Wood et al., 2008; Lockhart et al., 2012; Overdorp et al., 2014; Rizvi et al., 2018; Smith et al., 2011; Valdes Hernández et al., 2013). These associations have been shown largely in studies of later life in which the mean age of participants is over 70 and nearly all participants are over 65 years of age (Bangen et al., 2018; Delano-Wood et al., 2008; LADIS, 2011; Overdorp et al., 2014; Rizvi et al., 2018; Smith et al., 2011; Valdes Hernández et al., 2013; Vibha et al., 2018). Little is known about how AWM may impact cognitive performance prior to later life. Studies that do involve middle-aged participants generally group them together with younger adults as a comparison group for older adults (Sun et al., 2017; Vannorsdall et al., 2009). Other studies cover a wide age range (e.g., ages 40–80) that includes middle-aged and older adults (Au et al., 2006; Birdsill et al., 2014; Debette et al., 2011; Lockhart et al., 2012; Rieckmann et al., 2016), making it difficult to characterize the association within middle age specifically. Therefore, despite the importance of middle age in the course of white matter disease progression, there has been little research directly examining the relationship between AWM and cognitive performance at midlife.

AWM can be divided into deep and periventricular regional subtypes that have distinct underlying pathophysiology (Armstrong et al., 2020; Doubal et al., 2010; Fazekas et al., 1993; Fernando et al., 2006; Griffanti et al., 2018). Periventricular AWM is thought to represent changes in short penetrating microvessels which end near larger arterial blood vessels and are susceptible to direct damage from hypertension and other stroke risk factors (Blanco et al., 2017; Fernando et al., 2006; Griffanti et al., 2018; Kim et al., 2008; Wardlaw et al., 2013). In contrast, deep AWM occurs in areas supplied by long microvessels and may reflect damage secondary to hypertension and hypoperfusion (Blanco et al., 2017; Fernando et al., 2006; Griffanti et al., 2018; Kim et al., 2008; Wardlaw et al., 2013). Global AWM is highly heritable (Fennema-Notestine et al., 2016; Sachdev et al., 2016); however, recent work found that periventricular and deep AWM have both shared and unique genetic influences supporting regionally specific differences underlying mechanisms (Armstrong et al., 2020).

There is some evidence that periventricular and deep AWM may also differ in how they relate to cognitive performance (Delano-Wood et al., 2009; Murray et al., 2016; Wiggins et al., 2019); however, the literature is mixed, and few studies have explicitly tested for differences (Bolandzadeh et al., 2012; Soriano-Raya et al., 2012). Greater periventricular AWM is most often correlated with poorer memory, processing speed, and executive function ability, whereas deep AWM may be more correlated with current GCA or widespread cognitive deficits (Bolandzadeh et al., 2012; Cees De Groot et al., 2000; Delano-Wood et al., 2008, 2009; Garde et al., 2000; Soriano-Raya et al., 2012). Few studies, however, have specifically focused on regional AWM during middle age. Within a sample aged 50–65, more deep AWM was negatively related to all cognitive domains, suggesting a negative association with cognition in general, whereas periventricular AWM was not related to cognition (Soriano-Raya et al., 2012). However, other studies across broad age

ranges provide conflicting results, with some finding no cognitive associations with either regional subtype (Baune et al., 2009; Bolandzadeh et al., 2012; Cees De Groot et al., 2000; Debette et al., 2007; Yoon et al., 2014). A systematic review of cognitive associations for regional AWM suggested that the considerable heterogeneity in the field is partially due to differences in analytical approaches and methods of measuring AWM (Bolandzadeh et al., 2012). They also note that the generalizability of results may be limited by some studies' use of categorical AWM variables (e.g., low vs. high groupings; Baune et al., 2009), limited neuropsychological outcome measures (e.g., cognitive screeners; Debette et al., 2007), and small sample sizes (e.g., Bolandzadeh et al., 2012). In the previously mentioned middle-aged study of AWM (Soriano-Raya et al., 2012), investigators used a common rating scale measure of AWM (Fazekas scale) to dichotomize AWM into an absent or low AWM group ($n = 80$) and a moderate-to-high AWM group ($n = 16$). In the current study, we attempted to bolster studies of regional AWM by using a larger middle-aged sample with continuous measures of AWM volume. Moreover, it is unclear to what extent findings for specific cognitive abilities truly reflect specific versus generalized effects, thus, to address this issue in the present study, we examined associations with specific cognitive abilities after controlling for GCA.

Several studies also have evaluated how cognitive reserve factors affect the relationships among AWM and cognition. Cognitive reserve is thought to convey resilience to pathology such that individuals with higher levels of reserve are able to function normally despite higher levels of brain pathology (Stern et al., 2018). Individuals with greater cognitive reserve tend to have weaker associations between AWM and cognitive performance, despite having similar levels of AWM as those with less cognitive reserve (Brickman et al., 2011; Dufouil et al., 2003; Jokinen et al., 2016; Mortamais et al., 2014; Serra et al., 2015). However, these cognitive reserve studies included subjects who were generally older, in their 70s, or included broad age ranges. In one study that focused exclusively on cognitive reserve and total AWM in late middle-aged adults (ages 60–64), no cognitive reserve measure (e.g., intelligence) moderated the relationship between estimated cognitive change and total AWM (Christensen et al., 2007). It is possible that cognitive reserve may have differential effects on periventricular and deep AWM subtypes; therefore, we explored this in the current study as well.

The interpretation of cognitive reserve is often complicated by possible reverse causation. For example, does getting more education increase one's cognitive reserve or do people with more cognitive reserve tend to attain higher levels of education? It has been shown that education, occupational complexity, and engaging in cognitive activities later in life were associated with cognitive function across multiple domains later in life (Kremen et al., 2019). However, after accounting for a direct measure of general cognitive ability administered in young adulthood, the other three variables accounted for very little variance in later cognitive function (Kremen et al., 2019). If available, it is preferable to use a direct measure of GCA collected earlier in life—before age-related declines—as an index of cognitive reserve. In the current study, we use a measure of young adult GCA in this regard.

In the current study, we evaluated the association between AWM and cognitive performance in a sample of late middle-aged (56–66 years) men. Based on findings in the literature

among older adults, we hypothesized that greater total AWM burden would be associated with slower processing speed, worse executive function, and lower current GCA. In exploratory analyses, we also investigated associations of AWM with episodic memory, working memory, and verbal fluency because prior studies have reported conflicting findings for these cognitive domains. We then divided AWM into deep and periventricular regions (Armstrong et al., 2020). Although the literature is mixed, we predicted that deep AWM would be nonspecifically related to cognition (i.e., associated with current GCA) whereas periventricular AWM would be related to specific cognitive domains, that is, memory, executive function, and processing speed (Bolandzadeh et al., 2012; Soriano-Raya et al., 2012). As a further assessment, we included both periventricular and deep AWM in the same linear-mixed regression to better isolate the association between each variable and cognitive ability, essentially examining the effect of each after controlling for the other. We also controlled for current GCA in all analyses of specific cognitive abilities to determine whether associations with AWM were unique to those domains or whether ostensibly domain-specific effects were better attributed to overall cognitive ability. In an effort to improve generalizability of these results to those of other studies, which typically did not include current GCA, we also completed post hoc analyses that removed current GCA as a covariate and included educational attainment instead. Finally, we explored cognitive reserve to assess whether a cognitive reserve index (young adult GCA) moderated the association between cognitive performance and total or regional AWM.

Methods

Participants

Participants in the Vietnam Era Twin Study of Aging (VETSA: Kremen et al., 2006, 2013) cohort were randomly recruited from members of the Vietnam Era Twin Registry who were in a study of psychological health in 1992 (Tsuang et al., 2001). Participants are a nationally distributed sample of male–male twin pairs who served in the U.S. military at some time between 1965 and 1975 (Goldberg et al., 2002; Schoenborn & Heyman, 2009), and were in their 50s at initial recruitment into VETSA. They are similar in health and lifestyle characteristics to American men in their age range, and most (~80%) did not experience combat (Kremen, Franz, et al., 2013; Schoenborn & Heyman, 2009). The original VETSA inclusion criteria were minimal: twins had to be in their 50s when entering the study, and both brothers had to agree to participate in the initial assessment.

The current study includes 242 participants who completed wave 2 of the VETSA MRI study at the University of California, San Diego (UCSD) (Kremen, Franz, et al., 2013; Panizzon et al., 2009). Sample characteristics are presented in Table 1. The average age was 61.9 years (SD = 2.6; range 56–66). Participants completed an average of 13.9 years of education (SD = 2.0) and 85% were non-Hispanic white. We excluded individuals with a history of stroke (n = 6), brain cancer (n = 1), multiple sclerosis (n = 2), or epilepsy (n = 2) as determined by self-report during a medical history interview. Table 2 demonstrates that the rates of vascular risk factors in this sample are reasonably similar to those of the general population. VETSA was approved by the Institutional Review Board at UCSD, and all procedures were in accordance with institutional guidelines.

Neuropsychological Measures

As described previously, participants completed a comprehensive neuropsychological assessment (Kremen et al., 2006, 2013). Factor scores were created for five of the six cognitive domains through structural equation modeling using the statistical program R v3.4.1 (R Development Core Team, 2014). The measures included in each domain score are presented in Table 3. Factor models were based on previously reported work (Gustavson, Panizzon, Elman, et al., 2018; Gustavson, Panizzon, Franz, et al., 2018; Kremen et al., 2014; Sanderson-Cimino et al., 2019). Higher factor scores always indicate better performance. For the sixth domain, visual spatial ability, we used a composite score derived from the average of two standardized (*z*-score) measures.

Individuals who were tested previously at wave 1 of VETSA had their scores adjusted for practice effects using a replacement subjects method of practice effect-adjustment, as previously described (Elman et al., 2018). This method generates a constant for each neuropsychological measure by comparing scores of returnees, dropouts, and subjects who were recruited and tested for the first time at wave 2 of VETSA. The constant was then subtracted from each returnee's wave 2 score. This constant differed across measures. The present analyses utilized practice effect-adjusted wave 2 data for returning participants. No such adjustment was made for subjects who were not tested previously.

Participants also completed the Armed Forces Qualification Test (AFQT) at a mean age of 20 and again concurrently with other cognitive measures. The AFQT is a measure of GCA that correlates highly with other tests of GCA, such as the Wechsler Adult Intelligence Scale ($r = .84$) (Lyons et al., 2017, 2009). The AFQT completed at a mean age of 20 is henceforth referred to as young adult GCA and was used as an index of cognitive reserve that would be unconfounded by aging effects. The AFQT completed concurrently with other cognitive tests is referred to as current GCA, but given that it is based on the same test, it may also viewed as an index of current cognitive reserve. It may differ from young adult reserve because cognitive reserve can be depleted due to aging or pathology. We used the current GCA measure in several ways. We used current GCA as a covariate to determine whether associations of current specific cognitive abilities with AWM were general or truly domain-specific. We also used current GCA as an outcome variable in two sets of analyses. One was to determine if subtypes of AWM were differentially associated with overall cognitive abilities, in addition to examination of the relationship of AWM to specific cognitive domains. The other was the examination of a main effect of young adult cognitive reserve on later cognitive function; outcomes for these analyses included current cognitive domain scores and also current GCA. It is in this the latter case that current GCA may also be viewed as an index of current cognitive reserve. In testing moderation effects, we were only interested in whether associations were moderated by young adult cognitive reserve because, unlike current cognitive reserve, young adult cognitive reserve cannot be confounded with aging-related pathology

MRI Acquisition and Processing

T1-, T2-, and proton-density (PD)-weighted images were acquired at UCSD's Center for Functional Magnetic Resonance Imaging. A GE 3 T Discovery 750 scanner with an eight-

channel phased array head coil was used to acquire the following sequences: Sagittal 3D fast spoiled gradient echo (FSPGR) T1 with TE = min/full, TI = 600 ms, flip angle = 8°, FOV = 25.6 cm, frequency = 256, phase = 192, slices = 172, slice thickness = 1.2 mm; a coronal 2D FRFSE-XL T2 with 2 mm slice thickness, FOV = 24 cm, TE = 94 ms, TR = 4.6s, ETL = 16, frequency = 256, phase = 256, 2 NEX; and a coronal 2D FSE-XL PD with 2 mm slice thickness, FOV = 24 cm, TE = min/full, TR = 3s, ETL = 4, frequency = 256, phase = 256. We used a multichannel segmentation approach to measure AWM in addition to total white matter, gray matter, cerebrospinal fluid (CSF), and intracranial volume (ICV) (Fennema-Notestine et al., 2016). This approach leverages complementary information in three volumes to increase measurement sensitivity while reducing the impact of MR acquisition noise. Steps include standard alignment of the T1 (i.e., 6 degrees-of-freedom, rigid transformation to an anterior/posterior commissure aligned space), registration of T2 and PD to T1 using a mutual information method (Maes et al., 1997), intensity nonuniformity correction using N3 (Sled et al., 1998), and a three-class tissue segmentation utilizing Scott's L2E method (Scott, 2001) to determine robust means and covariances for white matter, gray matter, and CSF. AWM was classified using morphological operators (Yoo et al., 2002) to identify voxel clusters originally segmented as gray matter that fell within anatomically defined white matter regions. Results were visually reviewed and manually edited when necessary to correct misclassifications. Since partial voluming of CSF and white matter along the edges of ventricles results in voxels with AWM-like signal, even in healthy individuals, we did not allow any voxels that touched (i.e., shared a common face, edge, or vertex with) a ventricular fluid voxel to be classified as AWM; such voxels were excluded from the estimated volumes. We separated global AWM volume into periventricular and deep AWM with a method based on a widely used approach that was leveraged for a large-scale, multicohort study by the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) group (Armstrong et al., 2020; DeCarli et al., 2005). The approach defined a Euclidean boundary of 1 cm beyond the ventricular wall such that AWM beyond that boundary was defined as deep and AWM proximal as periventricular (Figure 1). Further details regarding the AWM quantification and the frequency atlas can be found elsewhere (Fennema-Notestine et al., 2016).

Statistical Analysis

AWM and white matter volumes were log-transformed to reduce skewness in their distributions and to stabilize their variances. For ease of interpretation, the log-transformed volume values were then standardized (*z*-scores). Three individuals with AWM *z*-scored volumes greater than three standard deviations from the mean were Winsorized to reduce the effect of outliers (Ruppert, 2004). Linear-mixed effects models were conducted with the packages *lme4* and *lmerTest* in R v3.4.1 (Bates et al., 2014; Kuznetsova et al., 2015; R Development Core Team, 2014). We controlled for correlated twin pair data by including a random intercept in all regressions. In all models, the outcome was a cognitive domain score and the predictor was an AWM variable.

We examined associations between AWM and performance in six cognitive domains and current GCA. Model 1 examined associations between cognition and total AWM; Model 2 between cognition and deep AWM; and Model 3 between cognition and periventricular

AWM. Model 4 included both periventricular and deep AWM to identify associations between one subtype of AWM and cognition after accounting for the other subtype of AWM. As deep AWM and periventricular AWM were correlated, we tested for multicollinearity via a variance inflation factor (VIF) (Craney & Surles, 2002). We also examined whether cognitive reserve moderated these associations by testing for interactions between AWM and a measure of cognitive reserve (young adult GCA). As such, we ran four additional models that included an interaction term of young adult GCA × AWM variable: young adult GCA × total AWM (Model 5), young adult GCA × deep AWM (Model 6), young adult GCA × periventricular AWM (Model 7); and a model that included an interaction term for young adult GCA × deep AWM and young adult GCA × periventricular AWM (Model 8). We chose to model cognitive reserve as an interaction term in accordance with cognitive reserve guidelines (Christensen et al., 2007; Stern et al., 2018). In post hoc analyses, to improve comparability of our results to the broader AWM literature, we repeated our main analyses, replacing current GCA with educational attainment.

All analyses controlled for age and total white matter volume to adjust for individual differences in head size. Because associations with specific cognitive domains might reflect one's level of overall cognitive ability, we covaried for current GCA in most models. By covarying for current GCA, we attempted to isolate the variance within each cognitive domain that was separate from the individual's overall cognitive ability. We could then identify the relationship between AWM and that domain-specific variance, without confounding for overall cognitive ability. Current GCA was not included as a covariate when current GCA was the outcome variable, in the cognitive reserve models, or in the educational attainment models. To correct for multiple tests and for correlations among the outcome measures, we applied the method of Li and Ji to the false discovery rate (Li & Ji, 2005). This method limits the number of false positives in analyses to 5%. The false discovery rate correction was conducted separately 3 times. The first included all analyses focused on main effects of AWM variables (Models 1–4; 35 variables of interest). The second included all cognitive reserve analyses (Models 5–7; 35 variables of interest). The third was done for a set of post hoc educational attainment analyses (35 variables of interest).

For descriptive purposes, we used Pearson's correlations or *t* tests to show the simple associations between AWM variables and the following: total white matter, age, education, systolic and diastolic blood pressure, hypertension, diabetes, and number of head injuries (0 vs. 1 or more than 1) (Supplemental Table 1).

Results

Sample Characterization

Tables 1 and 2 provide a description of the sample. Pearson correlations and *t* tests demonstrated that total AWM was significantly related to periventricular AWM, deep AWM, total white matter, years of education, systolic blood pressure, and diastolic blood pressure ($ps < .05$). Periventricular AWM was also significantly related to total white matter, deep AWM, systolic, and diastolic blood pressure ($ps < .01$). Deep AWM was also significantly related to total white matter, education, diabetes, and systolic blood pressure ($ps < .04$). No

AWM variable was related to a diagnosis of hypertension or a history of head injury (*p*s > .06). Full results are displayed in the supplement (Supplemental Table 1).

Association of AWM With General and Domain Specific Cognitive Performance

As shown in Table 4, after multiple comparison correction, total AWM (Model 1) and deep AWM (Model 2) were significantly associated with current GCA only. In contrast, periventricular AWM (Model 3) was significantly associated with executive function, working memory, and episodic memory. When both deep and periventricular AWM were simultaneously included in the regression (Model 4), deep AWM remained significantly associated with current GCA and periventricular AWM remained significantly associated with executive function, working memory, and episodic memory. Figure 2 displays these relationships. The variance inflation factor estimates were all under 2.0, suggesting that collinearity did not invalidate Model 4 regressions (Craney & Surles, 2002). Supplemental Table 2 lists the false discovery correction alphas for Models 1 through 4.

Cognitive Reserve

Young adult GCA did not moderate the association between any AWM measure and performance in any cognitive domain (interaction *p*s range: .05–.89). The main effect of young adult GCA on cognition was significant across all domains (β range: .20–.71; *p*s < .005). Results are presented in Supplemental Table 3.

Post Hoc Educational Attainment Analyses

To improve generalizability of these results to those of other studies, we also completed post hoc analyses that removed current GCA as a covariate and included educational attainment. After controlling for multiple comparisons, total AWM was significantly associated with episodic memory (β = −.17; $p = .01$). Deep AWM was significantly associated with processing speed (β = −.17; $p = .01$) and visual spatial ability (β = −.18; $p = .009$). Periventricular AWM was significantly associated with working memory (β = −.20; $p = .004$) and episodic memory (β = −.16; $p = .01$). When deep and periventricular AWM were included in the same regression, periventricular AWM was significantly associated with working memory (β = −.23; $p = .006$). Full results are presented in Supplemental Table 4. Supplemental Table 5 provides a comparison of educational attainment-adjusted results to current GCA-adjusted results, demonstrating differential associations.

Discussion

In this sample of late middle-aged men, we found negative relationships between AWM and cognition approximately 10 years prior to most studies of age-related AWM. Total AWM and deep AWM were associated with current GCA, whereas periventricular AWM was associated with performance in specific cognitive domains, namely, executive function, working memory, and episodic memory (Figure 2). The associations between periventricular AWM and the same three cognitive domains remained significant when periventricular and deep AWM were simultaneously examined in a regression (Model 4). All models controlled for age and total white matter. Current GCA was also a covariate within individual domains; thus, the significant results for periventricular AWM suggest a specificity for

functioning within specific cognitive domains rather than overall cognitive ability. Models that simultaneously included deep and periventricular AWM further support that the conclusion that the observed region-specific associations are truely specific and not simply driven by overall AWM.

Covarying for current GCA is a unique feature of this study that better isolates the associations between specific cognitive domains and each AWM measure. At first glance, the present results appear to differ from the only other extensive study of regional AWM at midlife that we are aware of (Soriano-Raya et al., 2012). In that study, deep AWM was significantly associated with executive function, verbal fluency, attention, visual memory, visuospatial ability, and psychomotor speed, whereas periventricular AWM was not associated with any measures of cognitive performance (Soriano-Raya et al., 2012). In contrast to the present analyses, Soriano-Raya et al. (2012) had a small sample size and used a dichotomous AWM measure (i.e., high vs. low groups) derived from visually scored data, which limit generalizability of the study (Bolandzadeh et al., 2012). The studies also differ because we covaried for current GCA while Soriano-Raya et al. (2012) covaried for education. It is possible that the associations between deep AWM and cognitive domains found in Soriano-Raya et al. (2012) may be explained by an overall correlation between deep AWM and nonspecific cognitive ability, that is, current GCA. To test this hypothesis, we performed post hoc analyses in which we reran models without the current GCA covariate and instead controlled for education. These analyses are also more readily comparable to the general AWM literature. Total and deep AWM were significantly associated with specific cognitive abilities while controlling for education, but not when controlling for current GCA. When controlling for education, total and deep AWM were associated with current GCA. In our view, these results suggest that the associations of total and deep AWM with specific cognitive abilities are likely due to associations of these measures with overall cognitive ability. In contrast, periventricular AWM appears to have a relatively specific impact on working memory, regardless of whether education or current GCA is included as a covariate (Supplementary Table 5). In the education-adjusted Model 4, which also included deep AWM, periventricular AWM was still related to working memory. In the current GCA-adjusted Model 4, periventricular AWM was related to working memory, episodic memory, and executive function. In our view, these results suggest that removing variance associated with current GCA helped reveal periventricular AWM's associations with specific cognitive domains at midlife. Future studies of AWM may benefit from covarying for current GCA to investigate the relationship of AWM with specific cognitive domains. Our results also suggest that the cognitive effects of AWM are likely obscured or weakened if deep and periventricular AWM are combined into a total AWM measure.

Although our results do not appear consistent with review studies that found frequent significant associations between total AWM and processing speed or executive function (Bolandzadeh et al., 2012; Debette & Markus, 2010; Gunning-Dixon & Raz, 2000), the present analyses included a multiple comparison correction based on 34 total variables of interest in six cognitive domains plus current GCA, in addition to our adjustment for overall cognitive function. Few of the studies cited in the review articles simultaneously examine more than three cognitive domains and do not control for this many comparisons

(Bolandzadeh et al., 2012; Debette & Markus, 2010; Gunning-Dixon & Raz, 2000). More recent studies not included in the review articles also typically examine a smaller set of cognitive domains (e.g., Bangen et al., 2018; Griffanti et al., 2018; Murray et al., 2016; Rizvi et al., 2018). If results are considered for total AWM (Table 4; Model 1) without controlling for multiple comparisons ($\alpha = .05$), total AWM was significantly associated with processing speed ($p = .048$) and was at a trend level with the executive function ($p = .08$) domain. In the present sample, periventricular AWM was significantly associated with executive function, working memory, and episodic memory, while deep AWM was not. Total AWM was only significantly associated with current GCA. Although nonsignificant after multiple test correction, periventricular AWM was associated with processing speed at $p = .05$. Thus, there is some consistency with prior findings of mostly older adults, but our results indicate that it is important to examine deep and periventricular AWM separately, as well as to adjust for overall cognitive function. Combining them into a single total measure appears to reduce precision when evaluating cognitive associations. Future studies will thus benefit from evaluating subtypes of AWM rather than a global measure.

In our sample, there was no moderation effect of cognitive reserve on the associations between AWM and cognition. This result is consistent with a study of similarly aged participants (age range 60–64 years) in which the association between total AWM and cognition was not significantly moderated by multiple cognitive reserve measures (Christensen et al., 2007). In contrast, studies of AWM in older adults have observed a cognitive reserve effect (Brickman et al., 2011; Dufouil et al., 2003; Jokinen et al., 2016; Mortamais et al., 2014; Serra et al., 2015). The lack of cognitive reserve moderation effects in late midlife may be because participants in these samples have less AWM burden and cognitive decline than studies with older samples. As these participants age, it is possible that increases in AWM burden and cognitive decline may demonstrate a significant cognitive reserve effect.

Most studies of AWM have included wide age ranges [e.g., 42–73 years (Birdsill et al., 2014; 55–85, Delano-Wood et al., 2009)], or focused on older adults [e.g., mean age = 75.8; $SD = 8.06$ (Overdorp et al., 2014)]. Those studies did include some middle-aged adults, but the mean age of the samples was older by 10 years or more than the present sample. The older mean age and wide age range of those studies makes it difficult to know precisely if or how AWM may relate to cognitive performance in middle-aged adults. It is possible that previous associations with AWM were primarily driven by individuals at the upper end of the sample age ranges. Our findings, based on a sample with both a narrow age range (56–66) and a mean age (61.9; $SD = 2.6$) that is a decade younger than most AWM studies indicate that the negative association of AWM with cognitive function is detectable earlier in life than previous studies have generally reported. Because AWM is associated with a faster progression to mild cognitive impairment and dementia (Bangen et al., 2018; Gunning-Dixon & Raz, 2000), as well as greater depression, reduced mobility, and decreased independence (LADIS, 2011), our results suggest that prevention of AWM development should begin prior to or early in midlife.

Strengths and Limitations

We separated periventricular and deep AWM with an automatic quantification method based on an established procedure (DeCarli et al., 2005) as implemented for a large-scale, multicohort study by the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) (Armstrong et al., 2020). Although this method is useful and was found to be driven by some unique genes underlying each AWM subtype (Armstrong et al., 2020), it is relatively simplistic in its delineation, and it may oversample the volume of deep AWM in comparison to manual scoring methods that tend to quantify more periventricular AWM lesions (Bolandzadeh et al., 2012). Future studies will benefit from implementing methods that explore regional AWM in a more specific, neuroanatomically driven fashion. In particular, a study that incorporates three dimensional reconstructions of AWM and examines lesion growth would better quantify AWM. Also, these findings may not generalize to women or across race and ethnicity as the sample is entirely male and largely white, non-Hispanic.

This study also has several strengths. First, the sample is representative of American men with respect to lifestyle and health, including vascular risk factors that may contribute to AWM development. Second, the broad neuropsychological battery contained multiple tests within each of several cognitive domains, allowing a rigorous assessment of the association of cognitive function with AWM. Third, the narrow age range allowed us to conclude that AWM was, in fact, already associated with cognitive performance in late midlife. Fourth, we were able to covary for current GCA and assess both types of regional AWM in the same regression. These models tested the specificity of associations between cognitive domains and each regional AWM measure.

Conclusion

Greater total AWM and deep AWM were associated with lower overall cognitive ability (GCA) while periventricular AWM was linked more specifically to poorer executive function, working memory, and episodic memory. These effects were evident 10 years earlier than found in most prior studies of AWM. Separating AWM into periventricular and deep regions and controlling for current GCA allowed us to differentiate specific cognitive domain associations from more generalized cognition. The identification of regional cognitive associations may be important as periventricular and deep AWM demonstrate some different etiologies and genetic risk factors (Armstrong et al., 2020). Although some prior studies included age ranges that overlapped with the age range in the present study, the narrow age range here provides definitive evidence that cognitive effects of AWM are already present at late midlife. Given that greater AWM was associated with poorer cognition, aggressive management of vascular or other risk factors that may increase the AWM development (Gouw et al., 2008; Jeerakathil et al., 2004) prior to or early in midlife is likely to be important for reducing the risk of cognitive impairment later in life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question:

We describe how abnormal white matter (AWM) associations with cognitive performance in late midlife differ when considering AWM as a global measure or as regional measures (periventricular AWM and deep AWM).

Findings:

Regional measures of AWM have unique associations with cognitive performance and these associations are present in late-midlife, years before most AWM studies have demonstrated.

Importance:

These findings suggest that regional measures of AWM may be more precisely linked to cognitive performance than a global measure, and that AWM may have effects on cognitive performance during late midlife.

Next Steps:

To examine how regional AWM in late midlife predicts decline in cognitive performance in old age.

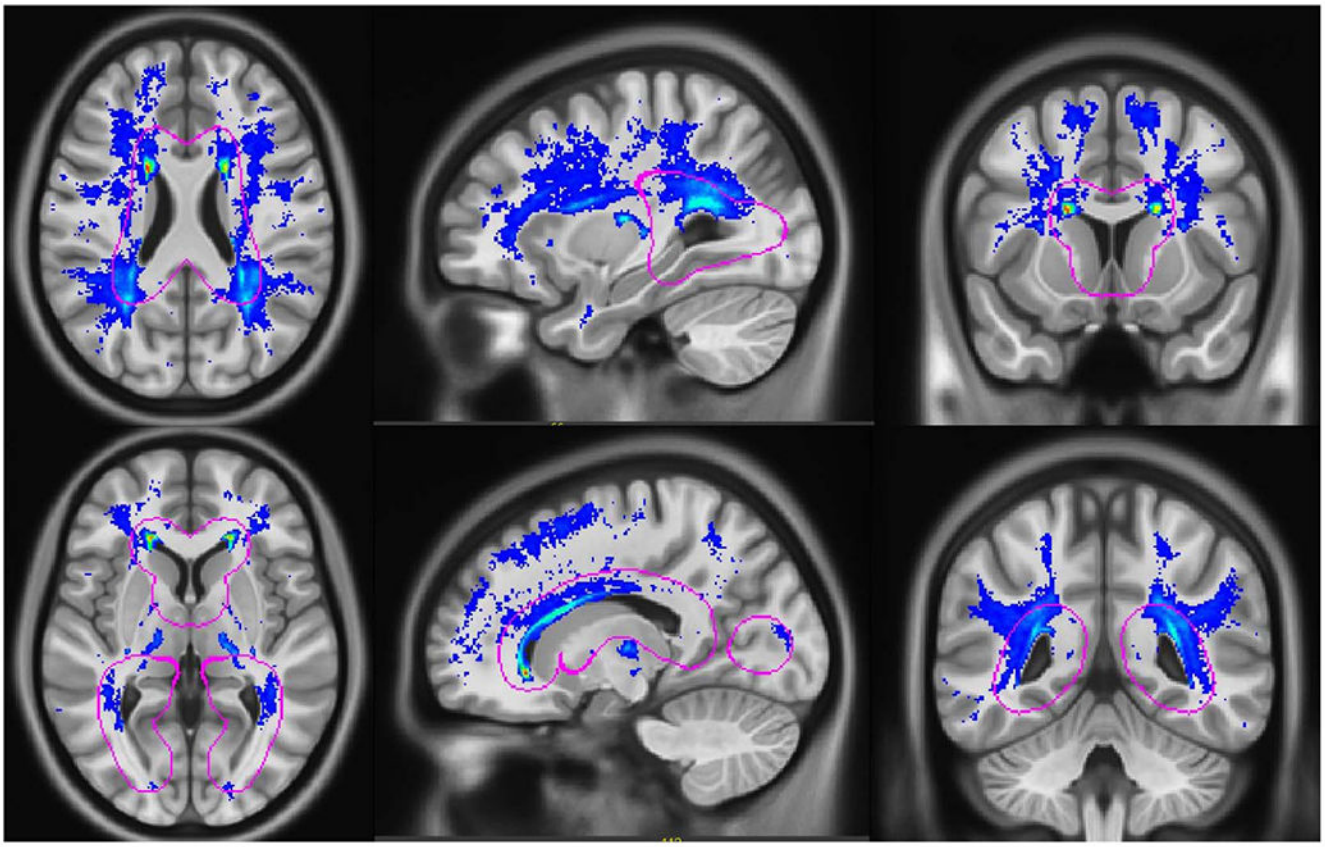

Figure 1. Periventricular and Deep AWM Frequency Atlas

Note. Abnormal white matter (AWM) frequency atlas with periventricular/deep 10mm boundary (pink). The spatial distribution and most common areas of AWM are shown overlaid on an averaged T1 [see (Fennema-Notestine et al., 2016) for methods related to the frequency atlas]. High to low frequency ranged from 0.77 (red) to 0.01 (dark blue) of the sample with AWM in a given voxel. Voxels displayed were designated as AWM with minimum threshold of 0.01 ($n = 3$). Therefore, areas in darkest blue indicate that only three subjects had enough AWM in that area to be included. Axial (left), sagittal (middle), and coronal (right) views. Boundary between periventricular and deep AWM is shown in pink, where voxels within the boundary are periventricular, and voxels on and outside the boundary are deep based on methods used in Armstrong et al. (2020); DeCarli et al. (2005). See the online article for the color version of this figure.

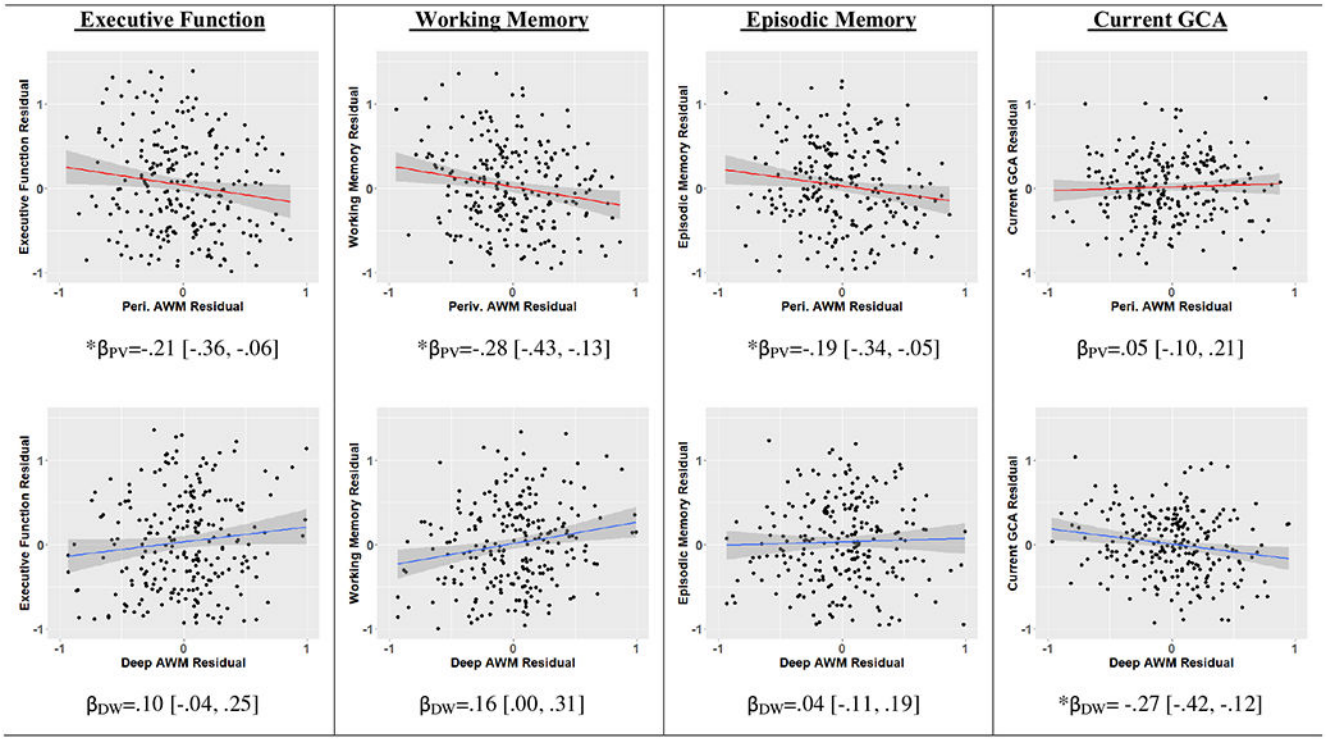

Figure 2. Plots of Residual Associations Between AWM Subtype and Cognition From Model 4 With Significance Denoted

Note. Presents the associations between cognition and abnormal white matter (AWM) subtypes from Model 4 for working memory, episodic memory, executive function, and current global cognitive ability (GCA). All variables represent residual values from linear mixed effects models. Thus, the *X*- and *Y*-axes show the remaining variance in AWM subtype (*X*-axis) or cognition (*Y*-axis), after controlling for age, total white matter, and twinness (random intercept). Additionally, the bottom row of graphs (displaying associations for deep AWM, blue line) control for periventricular AWM; the top row of graphs (displaying associations for periventricular AWM, red line) control for deep AWM. All graphs displaying relationships for specific cognitive domains also control for current GCA. Each graph contains a trend line displaying the relationship between an AWM subtype and cognition. Beta values are presented below each graph and those with asterisks (*) are significant after multiple test correction. The shaded area displays 95% confidence intervals. See the online article for the color version of this figure.

Table 1

Sample Characteristics (n = 242)

	Mean (*SD*)	**[Range]**
Age (years)	61.9 (2.6)	[56.0, 65.9]
Education (years)	13.9 (2.0)	[6, 20]
Systolic pressure	126.3 (14.5)	[94.5,176.5]
Diastolic pressure	77.3 (8.4)	[56.0, 103.0]
BMI (kg/m^2)	28.8 (4.3)	[14.4, 44.2]
	% (n)	
History of head injury	28.5% (69)	
History of tobacco smoking	60.3% (146)	

Note. Presents descriptives for the sample. Systolic and diastolic blood pressure measurements are the average of four seated blood pressure readings by trained observers with an electronic sphygmomanometer. Body Mass Index (BMI) was calculated using measured height and weight. History of head injury and history of tobacco smoking are based on self-report.

SD = standard deviation.

Table 2

Prevalence of Vascular Risk Factors in Relation to National Data

	Sample	National comparisons
Hypertension	50.4% (122)	57.6% (ages 55–64)[a]
High cholesterol	49.6% (120)	46.0% (men age 55–64)[b]
Diabetes	11.6% (28)	12.7% (ages 45–64)[c]
Obese (≥30 kg/m^2)	35.5% (86)	38.5% (ages 60+)[d]

Note. Participants were classified as having hypertension based on systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-report of a physician diagnosis. Diagnoses of diabetes and high cholesterol were based on participant self-report during an interview with a trained psychometrist. Obesity was calculated from measurements of height and weight collected by staff during the neuropsychological assessment.

[a](Benjamin et al., 2018).

[b](National Center for Health Statistics, 2017).

[c](Centers for Disease Control and Prevention, 2017).

[d](Hales et al., 2017).

Table 3

Neuropsychological Measures Used to Create Cognitive Domain Scores

Cognitive domains	Neuropsychological measures
Visual spatiala	Mental rotation; Hidden figures
Executive function factor and working memory factorb	D-KEFS Trails Switching condition, adjusted for Trails number sequencing & letter sequencing conditions; D-KEFS Category Switching Accuracy, adjusted for verbal fluency; Stroop: Color-Word Interference condition, adjusted for Color Naming and Word Reading conditions; AX-Continuous Performance Test WMS-III Digit Span: Forward & Backward; Reading Span; WMS-III Letter-Number Sequencing
Episodic memory	CVLT Long Delay Free Recall and Short Delay Free Recall; WMS-III Logical Memory—Immediate Recall and Delayed Recall; WMS-III Visual Reproduction: Immediate Recall and Delayed Recall
Processing speed	Stroop Word Reading, Stroop Color Naming; DKEFS Trail-Making Test Number Sequencing subtest, DKEFS Trail-Making Test Letter Sequencing, and ten trials of three Reaction Time tasks (left hand, right hand, and left or right)
Verbal fluency	D-KEFS Letter Fluency (three conditions) and Category Fluency (three conditions)

Note. D-KEFS = Delis-Kaplan Executive Function System (Delis et al., 2001); CVLT = California Verbal Learning Test-II (Delis et al., 2000); WMS-III = Wechsler Memory Scale-III (Corporation, 1997).

[a]The Visual Spatial domain is a composite score created by standardizing (*z*-score) the individual tests and averaging.

[b]The Executive Function factor and the Working Memory factor share some of the same tasks. The factor analysis that created the Executive Function factor extracted variance that was distinct from that associated with the Working Memory factor.

Table 4

Current GCA-Corrected Linear Mixed Effect Models

AWM variable	Processing speed	Visual spatial	Executive function	Working memory	Episodic memory	Verbal fluency	Current GCA
Model 1	β = −.13	β = −.08	β = −.10	β = −.11	β = −.15	β = −.07	β = **−.18**
Total AWM	[−.26, .00]	[−.19, .03]	[−.22, .02]	[−.24, .01]	[−.27, .03]	[−.20, .06]	[**−.31**, **−.05**]
	p = .048	*p* = .14	*p* = .09	*p* = .07	*p* = .017	*p* = .297	***p* = .006**
Model 2	β = −.11	β = −.07	β = −.02	β = −.006	β = −.08	β = −.08	β = **−.24**
Deep AWM	[−.24, .01]	[−.18, .04]	[−.14, .10]	[−.13, .12]	[−.20, .04]	[−.22, .05]	[**−.37**, **−.11**]
	p = .08	*p* = .20	*p* = .70	*p* = .92	*p* = .21	*p* = .20	***p* < .001**
Model 3	β = −.13	β = −.05	β = **−.15**	β = **−.18**	β = **−.17**	β = −.04	β = −.11
Periv. AWM	[−.25, .00]	[−.16, .06]	[**−.27**, **−.03**]	[**−.31**, **−.06**]	[**−.29**, **−.05**]	[−.17, .09]	[−.23, .02]
	p = .05	*p* = .38	***p* = .01**	***p* = .003**	***p* = .005**	*p* = .51	*p* = .10
Model 4	β_{DW} = −.6	β_{DW} = −.07	β_{DW} = .10	β_{DW} = .16	β_{DW} = .04	β_{DW} = −.09	$\beta_{\mathbf{DW}}$ = **−.27**
Deep AWM	[−.21, .10]	[−.20, .07]	[−.04, .25]	[.00, .31]	[−.11, .19]	[−.26, .07]	[**−.42**, **−.12**]
	p_{DW} = .45	p_{DW} = .34	p_{DW} = .17	p_{DW} = .04	p_{DW} = .61	p_{DW} = .26	p_{DW} < **.001**
Periv. AWM	β_{PV} = −.09	β_{PV} = −.01	$\beta_{\mathbf{PV}}$ = **−.21**	$\beta_{\mathbf{PV}}$ = **−.28**	$\beta_{\mathbf{PV}}$ = **−.19**	β_{PV} = .01	β_{PV} = .05
	[−.25, .07]	[−.15, .12]	**[−.36, −.06]**	**[−.43, −.13]**	**[−.34, −.05]**	[−.15, .17]	[−.10, .21]
	p_{PV} = .26	p_{PV} = .88	$p_{\mathbf{PV}}$ = **.005**	$p_{\mathbf{PV}}$ < **.001**	$p_{\mathbf{PV}}$ = **.01**	p_{PV} = .89	p_{PV} = .50

Note. Presents regression coefficients (β), confidence intervals, and *p* values for an abnormal white matter (AWM) variables within each model. Models 1, 2, and 3 include only one AWM variable. Model 4 includes both deep AWM and periventricular AWM. All models include a random effect of twin. Models examining a cognitive domain control for total white matter, age, and current general cognitive ability (GCA). Models examining current GCA (right most column) do not include current GCA as a predictor. Values in bold type are significant after correction for multiple testing. All variables were *z*-scored before being entered into the model.