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Educational attainment, MRI changes and cognitive function in older postmenopausal women from the Women's Health Initiative Memory Study

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Abstract

The relationship between neuropathology and clinically manifested functional and cognitive deficits is complex. Clinical observations of individuals with greater neuropathology who function better than some individuals with less neuropathology are common and puzzling. Educational attainment, a proxy for 'cognitive reserve', may help to explain this apparent contradiction. The objective of this study is to determine if educational attainment is correlated with cognitive decline, brain lesion volume and total brain atrophy. One thousand three hundred ninety of the 7,479 community-dwelling women 65 years of age and older enrolled in the Women's Health Initiative Memory Study, two parallel randomized, placebo-controlled clinical trials comparing unopposed and opposed post-menopausal hormone therapy with placebo, were studied. Study participants received annual assessments of global cognitive function with the Modified Mini

Mental State exam. One thousand sixty-three participants also received a supplemental neurocognitive battery and neuroimaging studies. Magnetic resonance imaging was used to calculate total ischemic lesion and brain volumes. Incident cases of probable dementia and mild cognitive impairment were centrally adjudicated. After adjustment for total lesion and total brain volumes (atrophy), higher educational attainment predicted better cognitive performance ($p<0.001$). Following conversion to dementia/MCI, higher education predicted steeper declines in cognitive function ($p<0.001$). Thus, higher educational attainment was associated with a delay in diagnosis of dementia/MCI in the face of a growing neuropathological load.

Keywords

cognition; MRI; cognitive reserve; aging; women; WHIMS

Introduction

The relationship between neuropathology and clinically manifested functional and cognitive deficits is complex and inconsistent. Clinical observations of individuals with greater neuropathology who function better than some individuals with less neuropathology are common and puzzling. It has been hypothesized that *cognitive reserve* (CR) may help to explain this phenomenon [1, 2]. The CR hypothesis predicts that individuals with greater CR will utilize more varied cognitive processing approaches and/or compensatory strategies which help the individual to perform better under the increased neuropathological load [3]. Accordingly, the same amount of neuropathology should affect people differently depending upon their level of CR with greater CR being associated with better cognitive performance on neurocognitive tests, better observable functioning, and longer time until a clinical diagnosis of dementia. A larger neuropathology load at the time of clinical diagnosis, however, predicts a faster post-diagnosis cognitive and functional decline for individuals with greater CR. Increased intellectual challenges and stimulations, which result from education, cognitively challenging occupations and other activities, are thought to contribute to more efficient neural pathways and an increased ability to recruit alternative pathways to compensate for damage [2, 4]. Common proxies for CR have included educational attainment, occupational, IQ, literacy, and leisure activities.

Support for the CR hypothesis [1, 3, 5] comes from studies reporting lower incident dementia [6–9] and better functioning [10–13] in persons with higher education compared to those with less education and a more precipitous loss of function among persons with more education once diagnosed with Alzheimer's dementia (AD) [14–21]. For example, Stern, et al. matched AD patients for clinical severity and observed that those with greater educational or occupational attainment died sooner than those with less attainment [22]. Further support comes from studies reporting negative correlations between years of education, premorbid IQ, occupation, leisure activities, and resting cerebral blood flow in patients matched for clinical severity [22–25] and a positive relation between linguistic ability at an early age and the presence of AD pathology at autopsy [26]. A recent review of studies correlating structural and functional imaging variables with CR concluded that there is reasonable support for its positive association with brain volume among healthy elders

and for its protective effect against progressive brain burden; evident in the observation that among individuals with established cognitive impairment at comparable levels of clinical severity, higher levels of reserve correlate with greater amounts of brain pathology [27]. However reliance on small ($n < 100$), clinical, convenience samples and cross-sectional study designs limit conclusions.

This study examines the relationship between educational attainment and both cognitive performance and MRI-derived measures of neuropathology--total lesion volume and total brain atrophy--in a large, well-characterized, geographically diverse sample of post-menopausal women including women with adjudicated diagnoses of all-cause dementia or mild cognitive impairment (MCI) who were followed prospectively. It was predicted that (1) greater lesion volume and lower total brain volumes will be associated negatively with cognitive performance, (2) educational attainment will be positively associated with cognitive test performance (after controlling for neuropathological load) and (3) the trajectory of cognitive test performance (decline) will be steeper for women with more education compared to women with less education, after diagnosis of dementia or MCI.

Methods

Context and participants

The Women's Health Initiative Memory Study (WHIMS) [28] is an ancillary study to the Women's Health Initiative (WHI) trials of Hormone Therapy (HT), [29] two large, randomized, double-blind, placebo-controlled, clinical trials of hormone-related outcomes. WHIMS was conducted to assess the relative effect of 0.625 mg/day conjugated equine estrogen (CEE) alone or in combination with 2.5 mg/day of continuous medroxyprogesterone acetate (CEE+MPA) on the incidence of dementia and global cognitive functioning in postmenopausal women. Women were excluded for concerns about competing risks, safety, or for adherence. Participants ($N=7,479$) in the WHIMS trials were recruited between May 1996 and December 1999 from women in the WHI trials who were at least 65 years of age and free of dementia. Annual follow-up of the cohort continues.

Fourteen of the 39 WHIMS clinical sites participated in the Women's Health Initiative Study of Cognitive Aging (WHISCA) [30], an ancillary study to WHIMS in which 2,303 non-demented women were administered a supplemental neurocognitive battery during an average of 3.0 years (range 1.1–5.5 years) after being enrolled in the WHI.

The WHIMS Magnetic Resonance Imaging sub-study (WHIMS-MRI) was designed to contrast neuroradiologic outcomes among women over age 70 who had been assigned to active versus placebo therapy during the WHIMS trials. It was conducted in a subset of 1,407 women participating in WHISCA. Exclusion criteria included the presence of pacemakers, defibrillators, neurostimulators, prohibited medical implants, and foreign bodies (e.g. bullets, shrapnel, metal slivers) that would pose a hazard to the participant during the MRI procedure. Other exclusion criteria included shortness of breath and/or inability to lie flat and conditions that can be exacerbated by stress (e.g. anxiety panic disorders, claustrophobia, uncontrolled high blood pressure, or seizure disorders) severe

enough to preclude an MRI. MRI scans were obtained an average of 8.0 years after enrollment in WHI.

Written informed consent was obtained from all participants separately for each of the three studies. The NIH and institutional review boards approved the protocol and consent forms.

Assessment of cognitive function

Global and domain specific cognitive performance were assessed. Global cognitive function was measured annually in WHIMS participants with the Modified Mini Mental State (3MS) exam.[31] The 3MS exam consists of 15 items that sum to 0–100; higher scores reflect better cognitive functioning. Participants scoring below the designated 3MS cut-point of 72 for those with 8 years of formal education and 76 for those with 9 years of education received a complete neurological evaluation to determine incident dementia or MCI as described below [28]. (After 16 months new cut points of 80 and 88, respectively, were implemented prospectively to increase sensitivity of case ascertainment)

The WHISCA supplemental neurocognitive battery consisted of nine tests measuring domain-specific cognitive performance: the Primary Mental Abilities Vocabulary Test (PMAVoc) [32] to measure verbal knowledge, the Letter (sum of three letters: F-A-S) and Category Fluency-Animals [33, 34] to measure phonemic and category verbal fluency, the Benton Visual Retention Test (BVRT, errors) [35] to measure short-term figural memory and visuo-construction, the California Verbal Learning Test (CVLT) [36] to measure verbal learning and memory (sum of three trials learning List A), the Digit Span Test (DST) [37] to measure attention and working memory, the Card Rotations Test (CRT) [38] to measure spatial rotational ability, and the Finger Tapping Test (FTT) [39] to measure fine motor speed.

MRI assessment

MRI scanning was conducted using a standardized protocol. MR scanning pulse sequences were performed in the following order:

- Series 1 – 3 plane gradient echo localizer for positioning
- Series 2 – Sagittal T1-weighted mid-slice image to demonstrate anatomical location of the AC/PC for slice angle and slice position
- Series 3- Oblique Axial Spin Density/T2-weighted from the vertex to skull base parallel to the AC/PC plane
- Series 4 - Oblique Axial FLAIR T2-weighted images matching slice positions in Series 3
- Series 5 - Oblique Axial 3D SPGR T1 weighted-images from the vertex to skull base parallel to the AC/PC plane

All scans were reviewed on-site before transmission for central reading. The two measures used in this report were total ischemic lesion volume (small-vessel ischemic disease in the basal ganglia and in the white and gray matter outside the basal ganglia) [40] and total brain atrophy defined as $100\% \times (1 - \text{total brain volume} / \text{intracranial volume})$.

Assessment of educational attainment and dementia risk factors

At WHI baseline, data on education and other dementia risk factors were collected via self-report and standardized assessments. Education was divided into four levels (no high school degree, high school degree or GED, some college or post-high school technical education, or college graduate); some levels were combined to add clarity in some presentations. Also included in our analyses as covariates were age, ethnicity, family income, use of tobacco, body mass index, hypertension, cardiovascular disease, diabetes, prior use of hormone therapy, alcohol intake, and WHI hormone intervention assignment.

Ascertainment of incident probable dementia and mild cognitive impairment

The WHIMS protocol has been described previously [28]. In brief, participants who scored below pre-established 3MS cut-points at the annual assessments were scheduled for a comprehensive dementia work-up that included an assessment with the CERAD neurocognitive battery [41], a complete neuropsychiatric clinical exam by a board certified physician experienced in diagnosing dementia, interviews with the participant and a knowledgeable friend or family member regarding acquired cognitive and behavioral changes, a computerized tomography brain scan (without contrast) and blood assay. Final classification of dementia, mild cognitive impairment or normal cognition was centrally adjudicated by an expert panel using DSM-III diagnostic criteria for dementia [42] and Petersen's criteria for MCI [43]. Regardless of adjudicated status, women continued to be scheduled for their annual cognitive assessments with the 3MS.

Statistical methods

Analysis of variance was used to compare mean differences in total lesion volume and the index of atrophy among women grouped according to dementia risk factors. Analyses of covariance, applied to scores from cognitive function tests administered within one year prior to the MRI, were used to assess cross-sectional associations that individual cognitive test scores had with education level. In these, adjustments for age and total ischemic lesion volume and total brain atrophy were used to align women with similar levels of pathology. Analyses were repeated with additional adjustment for other dementia risk factors.

We investigated associations between education and longitudinal cognitive change in women with high, intermediate, and low levels of MRI-derived brain changes (see Table 4 for definitions). We examined whether the rate that 3MS scores changed over time, as portrayed by slopes, varied by education level in each of these groups.

To examine the trajectory of cognitive function of women across time spanning incident dementia or MCI, we grouped women who were adjudicated to have dementia and any cognitive impairment (either dementia or MCI) during follow-up according to their level of education and used generalized mixed effects linear models [44] to compare the trajectory of 3MS scores during the ± 3 years spanning this classification.

Results

Figure 1 shows the composition of study samples. WHIMS-MRI provided data on 1,403 women, of which 1,390 (99.4%) had at least one 3MS test within five years prior to the MRI scan and education level recorded. Of these women, 91.6% (n=1,273) had their most recent 3MS test within one year of the scan; these women were used to describe cross-sectional relationships between 3MS scores and MRI outcomes. A subset of the WHIMS-MRI women, N=1,063 (76.5%), also had at least one WHISCA cognitive battery administration within the five years prior to the MRI scan; of these women, 56.0% (n=779) had a battery within the year prior to the date of the scan.

Table 1 displays the distribution of dementia risk factors for the 1,390 women with cognitive data and the mean levels of total ischemic lesion volume and total brain atrophy for women grouped according to these risk factors. Mean ischemic lesion volume was greater for women who were older, former or current smokers, had lower BMI, or had uncontrolled hypertension or a history of cardiovascular disease. The mean total brain atrophy index was greater among women who were older, were White or Asian, had lower BMI, or who had uncontrolled hypertension or a history of cardiovascular disease.

Cross-sectional relationships with cognitive function

As shown in Table 2, MRI measures were significantly related to performance on each WHISCA cognitive test, with R^2 ranging from 0.02 to 0.10. After control for MRI measures, education was significantly related to each cognitive domain except spatial ability. Lastly, for each outcome, educational level was linearly and positively related to cognitive performance---women who did not complete high school had poorer mean scores and women with post college education had better mean scores, after adjustment for MRI outcomes. (Note that higher scores on the BVRT test signify worse performance) Further adjustment for the dementia risk factors in Table 1 did not materially alter these relationships (Table 3).

Longitudinal relationships with cognitive function

The median MRI parameter scores for women with at least one 3MS administration within 5 yrs. prior to the scan were: ischemic lesion volume = 4.6 mm^3 and brain atrophy = 26.5%. The high MRI neuropathological load group consisted of 381 women with a mean ischemic lesion volume of 15.2 mm^3 and mean total brain atrophy equal to 29.4%. In this group, 11 women had less than a high school education, 74 were high school graduates, and 296 had post-high school education (the highest two levels of education were collapsed in these analyses to portray relationships more clearly). The low MRI neuropathological load group included 380 women with a mean ischemic lesion volume equal to 2.0 mm^3 and a mean total brain atrophy of 23.6%. It had 30 women with less than a high school education, 107 had high school graduates, and 243 had post-high school education. The intermediate MRI neuropathological load group consisted of 629 women with a mean ischemic lesion volume of 8.6 mm^3 and a mean total brain atrophy of 26.5%. It had 21 women with less than high school, 142 were high school graduates, and 466 had post-high school education. Table 4 lists annual rates of changes in 3MS scores during the five years prior to MRI scans. Among

women with high neuropathological load, the rates and standard errors of measurement (SE) of declines in 3MS test scores over time varied significantly by education level ($p=0.03$). Among women with intermediate and lower levels of neuropathological load, rates of decline did not vary by education level ($p=0.34$ and $p=0.31$, respectively).

Among the 7,479 women enrolled in WHIMS, 461 total of incident cases of dementia ($n=199$) and MCI ($n=262$) were adjudicated as of June, 2007. Figure 2 portrays the mean (± 1 standard error) 3MS scores that were collected during the ± 3 years spanning the initial classification of cognitive impairment for women grouped according to whether they had post-high school education (women with less than high school education were grouped with high school graduates due to small sample sizes). General linear mixed effects models were used to produce means from the longitudinal sequences of scores; time=0 corresponds to the first on-study classification of any cognitive impairment. Prior to this diagnosis, more highly educated women had higher 3MS scores, however their downward trajectory was steeper through the entire time span circumscribing the diagnoses: -1.48 (0.18) units/yr. for high school education or less versus -2.64 (0.15) units/yr. for greater than high school education ($p<0.001$). This is particularly noticeable following diagnosis when the more highly educated group had lower mean 3MS scores than the less educated group. Parallel analyses were done among the subset of women with dementia classifications. In these women, the differences in the slopes of the 3MS trajectories did not reach statistical significance (-4.30 ($SE=0.37$) units/yr. for high school education or less versus -4.99 (0.28) units/yr. for greater than high school education ($p=0.14$). The statistical power to detect an interaction between education and neuropathological groups was limited; this interaction was not statistically significant.

Discussion

We predicted that neuropathological load would be negatively associated with cognitive performance; that after adjusting for MRI derived brain changes, women with higher educational attainment would perform better on cognitive tests than women with less attainment; and that the decline in cognitive performance following incident dementia or mild cognitive impairment would be steeper for more highly educated women compared to less educated women because of the higher neuropathological load they have at the time of diagnosis. Our findings generally support these predictions.

Other studies have reported that higher education is associated with reduced risk of incident AD [6, 8, 9, 45–52]. In our study as well, education was associated with better cognitive test performance even after controlling for dementia risk factors and MRI measures. Women with less educational attainment performed more poorly than women with post high school education on both global and domain specific cognitive measures. While these correlations are not a direct test of the CR hypothesis, they demonstrate expected relationships between this proxy for CR and measures of current cognitive functioning.

In women with greater ischemic lesion volumes and greater brain atrophy, higher educational attainment was associated with better longitudinal cognitive performance. In contrast, education was not related to changes in cognitive performance among women with

lower lesion volumes and atrophy. These data suggest that as neuropathology increases, the protective effects of education become more evident presumably as the individual faces a greater challenge to maintain cognitive and behavioral functioning. It has been suggested that having greater capacity for adaptability including the ability to utilize alternate cognitive processing [1] or brain networks [2, 53] may explain the better performance of individuals with more education. For example, Scarmeas, et al., found that high CR subjects utilized additional brain regions during challenging memory tasks compared with individuals with less CR [53].

While more highly educated women outperformed less educated women on cognitive tests, the decline over time was steeper among women who developed dementia or MCI. This may have been due to the greater neuropathological load carried by the more highly educated WHIMS participants at the time of incident classification. Other studies also have found a faster rate of cognitive decline among more highly educated individuals diagnosed with dementia compared to less well educated individuals [15, 16, 19, 20] and non-demented controls [17]. Scarmeas, et al., studied 312 incident AD cases in New York who were given serial neuropsychological assessments over a mean of 5.6 years [21]. A composite cognitive score calculated from 12 tests declined by 9% of a standard deviation (SD) per year. They observed similar rates of decline before and after AD incidence. For each additional year of education there was annual 0.3% SD decline during follow-up.

Several studies also found, as we did, that when subjects are matched for clinical severity (i.e., diagnosis), those with higher education have more abnormal brain changes. Bennett, et al., performed brain autopsies on 130 older Catholic clergy in the Religious Orders Study who had undergone annual cognitive testing [11]. Both years of formal education and AD pathology scores were related to cognitive function. Moreover, higher education was associated with greater AD pathology (neuritic and diffuse plaques) after controlling for age and gender indicating that the relation between AD neuropathology and cognitive function is modulated by educational attainment. Stern, et al., tested whether individuals with more education have more advanced AD before it is clinically observed [23]. When patients were matched on clinical severity, cerebral blood flow was less in the parietotemporal region and this effect was greater in the group with the highest level of education. In another study, 46 patients with AD premorbid intellectual ability were inversely related with cerebral metabolism after controlling for demographic variables and dementia severity [25] Finally, Kidron, et al., found greater cerebral ventricular enlargement in the parietal area among AD patients with high education relative to controls [54].

There are several limitations to our research. First, our measure of global cognitive functioning, the 3MS, is a coarse measure and may not accurately reflect actual overall cognitive performance. We were obliged to use it for this analysis due to study design. Also, the statistically significant differences in 3MS scores may not be clinically significant. Second, educational attainment may not be the best proxy for CR; however studies using different proxies such as premorbid IQ, occupational attainment, literacy and leisure activities have yielded similar results. Third, MRI parameters of total ischemic volume and total brain atrophy are blunt expressions of underlying neuropathology and do not capture all relevant pathologies. Our choice of these two parameters may have excluded other relevant

indicators and analysis of specific brain regions (e.g., medial temporal lobe, hippocampus) might have yielded a finer grained picture. Lastly the women we describe volunteered and were eligible for clinical trials of hormone therapy and do not represent more general populations [55].

Important strengths of WHIMS are that the sample studied is large, well-characterized cohort of geographically diverse and community-residing post-menopausal women; the methodology used to identify incident dementia and mild cognitive impairment is comprehensive and well-validated; and the prospective design. WHIMS has provided the opportunity to draw together serial cognitive test scores, standardized MRI readings, and centrally adjudicated assessments of cognitive impairment in a large cohort.

These results suggest that an individual's educational attainment might be a marker for a neuroprotective process that supports better cognitive and behavioral functioning of older adults with neuropathologies like Alzheimer's disease. Answering whether this potential protection might be conferred by helping develop a larger repertoire of compensatory cognitive strategies or neuroanatomical or neurophysiologic changes was not within the scope of this study. The possibility that cognitive experiences might enhance and protect cognitive functioning into later life when the brain is more vulnerable to neuropathologies is exciting and points to important studies for the future.

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Figure 1.
WHIMS, WHISCA and WHIMS MRI sub-groups

Figure 2. Mean (± 1 standard error) 3MS scores circumscribing first classification of 461 incident cases of dementia or mild cognitive impairment: 189 with high school education or less and 272 with post high school education.

Table 1

Age-adjusted relationships that dementia risk factors have with MRI-based measures (n=1,390).

Risk Factor	Distribution N (%)	Mean Total Ischemic Lesion Volume (mm³) (p-value)	Mean Percent Total Brain Atrophy (%) (p-value)
Age at time of MRI --yrs, N (%) ¹			
70–74	710 (50.9)	7.01 (8.78)	25.70 (0.13)
75–79	490 (35.2)	9.70 (0.58)	27.14 (0.15)
80–89	194 (13.9)	11.74 (0.95)	27.98 (0.26)
		<0.001	<0.001
Race/ethnicity, N (%)			
African-American	4 (0.3)	15.32 (5.54)	24.35 (1.71)
American Indian	23 (1.7)	6.70 (2.31)	24.99 (0.71)
Asian	60 (4.3)	7.58 (1.43)	26.65 (0.44)
Hispanic	21 (1.5)	5.73 (2.42)	24.78 (0.75)
White	1271 (91.5)	8.76 (0.31)	26.59 (0.10)
Other/multiple	11 (0.8)	5.71 (3.34)	25.92 (1.03)
		0.40	0.03
Smoking status at WHI enrollment, N (%)			
Never	800 (57.9)	7.70 (0.39)	26.35 (0.12)
Former	523 (37.8)	9.78 (0.48)	26.70 (0.15)
Current	59 (4.3)	10.60 (1.44)	27.36 (0.45)
		0.001	0.03
Body mass index at WHI enrollment, kg/m ² , N (%)			
<25	415 (29.9)	9.63 (0.54)	27.01 (0.17)
25–29	523 (37.7)	8.84 (0.48)	26.45 (0.15)
30–34	298 (21.5)	7.71 (0.64)	26.11 (0.20)
35	153 (11.0)	7.01 (0.90)	26.24 (0.28)
		0.03	0.003
Hypertension status at WHI enrollment, N (%)			
None	734 (52.7)	7.69 (0.41)	26.46 (0.13)
Current/controlled ²	206 (14.8)	8.25 (0.77)	25.88 (0.24)
Current/uncontrolled	454 (32.6)	10.28 (0.52)	26.91 (0.16)
		<0.001	0.001
Alcohol intake at WHI enrollment, N (%)			
None	616 (44.3)	8.37 (0.45)	26.59 (0.14)
1–6/week	619 (44.5)	8.80 (0.44)	26.42 (0.14)
7+/week	157 (11.3)	8.83 (0.88)	26.64 (0.27)
		0.76	0.60
Prior CVD at most recent WHI visit, N (%)			

Risk Factor	Distribution N (%)	Mean Total Ischemic Lesion Volume (mm³) (p-value)	Mean Percent Total Brain Atrophy (%) (p-value)
No	1306 (93.7)	8.36 (0.32)	26.42 (0.10)
History of stroke	13 (0.9)	12.90 (1.84)	27.48 (0.57)
History of other CVD ³	75 (5.4)	9.70 (0.92)	27.15 (0.28)
		0.02	0.01
Diabetes at WHI enrollment, N (%)			
No	1244	8.51 (0.31)	26.47 (0.10)
Yes	150	9.48 (0.90)	27.01 (0.28)
		0.31	0.06
WHI HT assignment, N (%)			
HT	690	8.62 (0.42)	26.68 (0.13)
Placebo	704	8.61 (0.42)	26.37 (0.13)
		0.99	0.10

Table 2

Mean cognitive test score within one year preceding MRI with adjustment for age, total intracranial volume, total ischemic lesion volume, and total brain volume by education

Cognitive Function (Cognitive Test)	Partial Correlation ¹		Combined R ² For MRI Outcomes (p-value) ²	< HS graduate N WHIMS=54 WHISCA=31 Mean (SD)	High School or GED N WHIMS=298 WHISCA=167 Mean (SD)	Post HS N WHIMS=512 WHISCA=320 Mean (SD)	College Graduate N WHIMS=409 WHISCA=261 Mean (SD)	P-value
	With Lesion Volume	With Brain Atrophy						
Global cognitive function (3MS)	-0.12*	-0.18*	0.05 (<0.001)	93.85 (0.50)	96.43 (0.21)	96.80 (0.16)	97.47 (0.18)	<0.001
Verbal knowledge (PMA Voc)	-0.07*	-0.12*	0.05 (<0.001)	31.33 (1.50)	37.09 (0.65)	38.69 (0.47)	42.33 (0.52)	<0.001
Verbal fluency (F-A-S) (Category- Animals)	0.00 -0.12*	-0.02 -0.12*	0.02 (<0.001) 0.04 (<0.001)	37.74 (2.15) 24.76 (1.13)	42.02 (0.92) 27.61 (0.49)	41.33 (0.67) 27.75 (0.35)	46.79 (0.74) 29.80 (0.39)	<0.001 <0.001
Figural memory (BVRT, errors)	0.11*	0.16*	0.05 (<0.001)	8.85 (0.63)	6.87 (0.27)	6.29 (0.20)	5.41 (0.22)	<0.001
Verbal learning (CVLT, Sum of 3 learning trials)	-0.01	-0.13*	0.03 (0.003)	26.54 (1.13)	28.31 (0.49)	28.84 (0.35)	31.23 (0.39)	<0.001
Attention/working memory (Digit span)	0.01	-0.03	0.03 (<0.001)	6.23 (0.32)	6.97 (0.14)	7.13 (0.10)	7.37 (0.11)	0.004
Spatial ability (CRT)	-0.11*	-0.27*	0.10 (<0.001)	59.68 (5.12)	67.61 (2.20)	67.45 (1.60)	65.70 (1.77)	0.46
Fine motor speed (Finger Tapping)	-0.05*	-0.07*	0.02 (0.01)	36.92 (1.06)	37.88 (0.46)	38.79 (0.33)	39.83 (0.37)	0.002

Notes. SD = standard deviation; HS = high school; GED = General Equivalent Degree; MRI = magnetic resonance imaging; 3MS = Modified Mini Mental State Exam; PMA = Primary Mental Abilities; BVRT = Benton Visual Retention Test; CVLT = California Verbal Learning Test; CRT = Card Rotation Test;

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After adjustment for age and intracranial volume;
2 Multivariable relationship with intracranial volume, total ischemic lesion volume, and total brain volume; Type I error is not controlled across individual cognitive functions; Education level is missing for
4 participants;
* p 0.05

Table 3

Mean cognitive test scores within 1 yr prior to MRI with adjustment for age, total intracranial volume, total ischemic lesion volume, total brain atrophy, and other covariates in Table 1 by education.

Cognitive Function (Cognitive Test)	Not HS Graduate N WHIMS=54 WHISCA=31 Mean (SD)	High School or GED N WHIMS=298 WHISCA=167 Mean (SD)	Post High School N WHIMS=512 WHISCA=320 Mean (SD)	College Graduate N WHIMS=409 WHISCA=261 Mean (SD)	P-value
Global cognitive function (3MS)	94.22 (0.51)	96.41 (0.21)	96.82 (0.16)	97.47 (0.18)	<0.001
Verbal knowledge (PMA Voc)	32.36 (1.52)	37.03 (0.65)	38.78 (0.46)	42.06 (0.52)	<0.001
Verbal fluency (F-A-S) (Category-Animals)	38.96 (2.18) 25.90 (1.16)	42.24 (0.93) 27.60 (0.49)	41.21 (0.67) 27.56 (0.35)	46.51 (0.74) 29.70 (0.40)	<0.001 <0.001
Figural memory (BVRT)	8.38 (0.64)	6.95 (0.27)	6.33 (0.20)	5.38 (0.22)	<0.001
Verbal learning (CVLT)	27.30 (1.18)	28.26 (0.50)	28.75 (0.36)	31.21 (0.40)	<0.001
Attention/working memory (Digit span)	6.39 (0.33)	7.00 (0.14)	7.10 (0.10)	7.36 (0.11)	0.02
Spatial ability (CRT)	64.06 (5.29)	67.42 (2.24)	67.39 (1.61)	65.47 (1.80)	0.81
Fine motor speed (Finger Tapping)	36.97 (1.10)	38.07 (0.47)	38.80 (0.34)	39.68 (0.38)	0.02

Notes. SD = standard deviation; HS = high school; GED = General Equivalent Degree; MRI = magnetic resonance imaging; 3MS = Modified Mini Mental State Exam; PMA = Primary Mental Abilities; BVRT = Benton Visual Retention Test; CVLT = California Verbal Learning Test; CRT = Card Rotation Test.

Table 4

Fitted slopes (SE) for 5-year changes in 3MS scores across three MRI brain pathology groups by education level (3MS units/year).

Education	Neuropathological Load Groups ^I		
	High neuropathological load	Intermediate neuropathological load	Low neuropathological load
Not HS graduate	N=11 -0.94 (0.28)	N=21 -0.27 (0.17)	N=30 0.14 (0.13)
HS graduate	N=74 -0.13 (0.11)	N=142 -0.11 (0.06)	N=107 -0.04 (0.06)
Post HS	N=296 -0.22 (0.57)	N=466 -0.04 (0.03)	N=243 0.05 (0.04)
	P=0.03	P=0.24	P=0.33

Notes. MRI = magnetic resonance imaging; 3MS = Modified Mini Mental State Exam; HS = high school; SE = standard error;

^I High = lesion volume above median and brain atrophy above median; Low = lesion volume below median and brain atrophy below median; Intermediate = remaining women.