

# White matter hyperintensities and cognition across different Alzheimer's biomarker profiles

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## Abstract

**Background/Objectives:** To examine the association between white matter hyperintensities (WMH) and cognitive domains such as memory and executive function (EF) across different clinical and biomarker categories of Alzheimer's disease (AD).

**Design:** Cross-sectional study.

**Setting:** Alzheimer's Disease Neuroimaging Initiative.

**Participants:** A total of 216 cognitively normal (CN) participants and 407 participants with mild cognitive impairment (MCI) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) at baseline.

**Measurements:** Based on the 2018 research framework, participants were classified using AT(N) (amyloid- $\beta$  deposition [A], pathologic tau [T], and neurodegeneration [(N)]) biomarkers into one of three categories: biomarker negative [A – T – (N)–], amyloid negative but other biomarker positive [A – T  $\pm$  (N)+ or A – T + (N) $\pm$ ] or amyloid positive [A + T  $\pm$  (N) $\pm$ ]. Linear regression models were then used to examine the association between WMH and memory composite scores and EF composite scores.

**Results:** Higher WMH burden was associated with worse EF in both CN and MCI subgroups while a significant association between WMH and memory was only found in the MCI subgroup. Furthermore, WMH was associated with EF in the group with A – T  $\pm$  (N)+ or A – T + (N) $\pm$  biomarker category, but not for A – T – (N)– (normal biomarker) and A + T  $\pm$  (AD pathology).

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu/>). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found in [https://adni.loni.usc.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List.pdf](https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf)

The association between higher WMH and worse memory was independent of amyloid levels in individuals with MCI with evidence of AD pathology.

**Conclusion:** Vascular disease, as indexed by WMH, independent of AD pathology affects cognitive function in both CN and MCI subgroups. Future studies using the AT(N) research framework should consider white matter lesions as a key biomarker contributing to the clinical presentation of AD.

#### KEY WORDS

Alzheimer's disease pathology, AT(N) research framework, cognitive decline, white matter hyperintensities

## INTRODUCTION

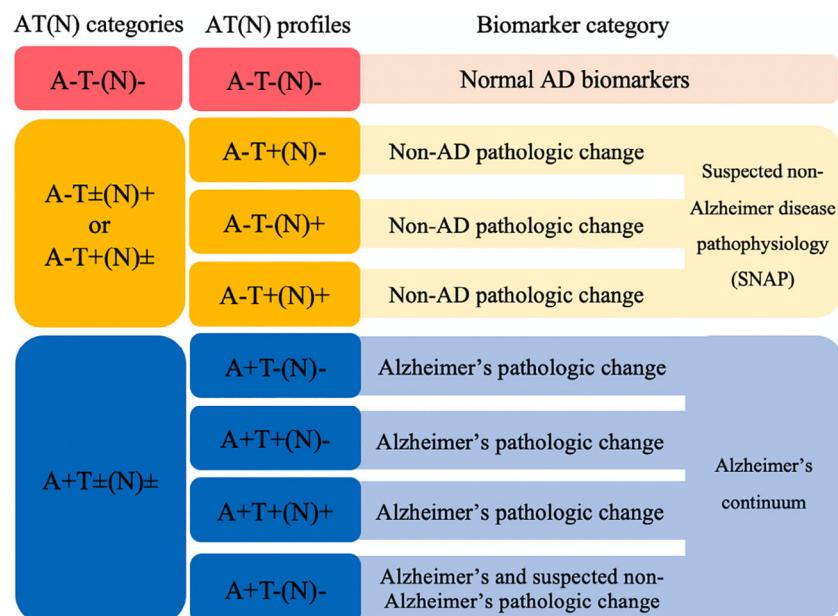
Increasing evidence supports the idea that Alzheimer's disease (AD) is heterogeneous, with multiple factors contributing to its pathophysiology and to cognitive impairment.<sup>1</sup> The 2018 National Institute on Aging and Alzheimer's Association (NIA-AA) research framework proposed a biological definition for AD, which outlines a biomarker system to classify individuals along the AD continuum.<sup>2</sup> In this framework, imaging biomarkers and cerebrospinal fluid (CSF) biomarkers are used to define amyloid- $\beta$  [A], tau [T], and neurodegeneration [(N)] status as part of the "AT(N)" biomarker system (Figure 1). While the AT(N) system defines a biomarker-based approach to diagnose AD for research studies, it leaves the door open for inclusion of additional biomarkers that might explain the order of events, causality, and the relationships among biomarkers, cognition, or other symptoms.

### Key Points

- Association between white matter hyperintensities and memory performance was independent of amyloid levels in mild cognitive impairment individuals with Alzheimer's pathology.
- White matter hyperintensities (WMH) was associated with executive function in the suspected non-Alzheimer disease pathophysiology biomarker category.

### Why Does this Paper Matter?

WMH may be a key contributor to cognitive decline in AD independent of amyloid.



**FIGURE 1** Amyloid- $\beta$  deposition [A], pathologic tau [T], and neurodegeneration [(N)] [AT(N)] biomarker measurement system defined by diagnostic and clinical meaning [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

White matter lesions appearing as hyperdense areas in T2-weighted magnetic resonance imaging (MRI), referred to as white matter hyperintensities (WMH), commonly coexist with AD.<sup>3</sup> WMH burden increases with age and has been associated with cardiovascular risk factors and linked to cerebral small vessel disease.<sup>4</sup> The neuropathological basis of WMH is thought to be primarily driven by ischemia due to chronic hypoperfusion.<sup>5</sup> Based on post-mortem MRI studies of white matter lesions, decreased small vessel density contributes to increased vacuolization of white matter, which allows for fluid accumulation and elevated FLAIR seen in WMH.<sup>6</sup> The underlying mechanism of ischemia could cause both vascular brain injury and the neurodegenerative changes of AD.<sup>7</sup> Another plausible theory is that WMH is the result of Wallerian degeneration secondary to neurodegenerative changes.<sup>8</sup>

There is strong evidence that WMH is associated with cognitive decline, and increased rate of disease progression in both early<sup>9</sup> and late-onset dementia.<sup>10</sup> Concurrent presence of cerebrovascular pathology in individuals in preclinical and prodromal AD stages as well as clinically diagnosed AD-type dementia can lead to worse performance in most cognitive domains.<sup>11</sup> Prior studies suggest that greater WMH is associated with decline in global cognition or specific cognitive domains.<sup>12</sup> Furthermore, greater WMH can lower the threshold of clinical expression of dementia due to AD.<sup>13</sup> Despite these consistent observations, white matter lesions are not included in the current conceptual models of the pathogenesis<sup>14</sup> or the biological definition of AD that was proposed in the NIA-AA research framework.<sup>2</sup>

Because vascular disease plays a role in AD pathophysiology and contributes to cognitive status and decline, it has been suggested that the NIA-AA research framework should be extended to include biomarkers of vascular dysfunction to the biomarker system.<sup>15</sup> There are two opposing views on the extent to which WMH represent a core feature of AD: one view considers WMH as a marker of vascular pathology, a comorbid disease process that is independent of AD pathology. The other view considers WMH as a core feature of AD pathology, which predicts the clinical onset and course of AD at least as well as the cardinal biological markers of AD.<sup>16</sup> According to this view, there are vascular forms of AD pathology.<sup>3</sup> To assess these hypotheses, in this study, we aimed to investigate if the association between WMH and memory performance is independent of A $\beta$  in non-demented older adults.

The literature on relationships between amyloid or tau burden and cognition is large and findings vary among studies. Many large-scale studies indicate a stronger association of amyloid burden with memory than

with other cognitive domains.<sup>17</sup> The relationship between white matter disease and cognition may be less specific, but executive function (EF) may be somewhat more affected than other cognitive domains.<sup>18</sup> The Alzheimer's Disease Neuroimaging Initiative (ADNI), with a large collection of biomarkers and neurocognitive tests, provides the opportunity to assess the association of biomarkers with specific cognitive domains. While it is known that biomarkers of AD and biomarkers of vascular pathology contribute to cognitive decline, the associations between WMH and cognition among individuals categorized by AD biomarker status remain unclear. In this study, we aimed to investigate the association between WMH and cognitive domains such as EF and memory within the AT(N) research system. We hypothesize that greater WMH burden will be associated with worse EF in individuals with suspected non-AD pathophysiology [SNAP; A – T ± (N)+ or A – T + (N)±].

## METHODS

### Study design

This study used data obtained from the ADNI database. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Individuals in the current study were recruited as part of ADNI-GO and ADNI-2 between 2009 and 2016. ADNI was approved by the institutional review boards of all participating institutions and written informed consent was obtained from all participants at each site. For up-to-date information on ADNI, see <http://adni.loni.usc.edu/>

Eligible participants for this study were cognitively normal (CN) or had MCI at their initial visit. MCI participants in ADNI are diagnosed as amnestic MCI, which requires a Mini Mental State Examination (MMSE) score between 24 and 30 (inclusive), a memory complaint, objective memory loss measured by education-adjusted scores on the Wechsler Memory Scale Logical Memory II, a Clinical Dementia Rating (CDR) of 0.5, absence of significant impairment in other cognitive domains, essentially preserved activities of daily living, and the absence of dementia. Participants with a baseline diagnosis of AD (clinical dementia) were excluded from this study. Additional inclusion criteria were having measures of amyloid PET, CSF biomarkers, <sup>18</sup>F-fluorodeoxyglucose (FDG) PET, and MRIs at the same visit. Participants with

missing data for at least one of these biomarkers were excluded. This study included 216 individuals who were CN and 407 with MCI. Figure S1 summarizes the participant selection process for this study.

## Study measures

### Cognitive measures

The primary cognitive measures of interest were the memory and the EF composite scores. Methods for developing these composite scores are previously described in detail.<sup>19,20</sup> In brief, the memory composite score was developed using a longitudinal single factor model on Mplus and includes the Rey Auditory Verbal Learning Test (RAVLT, 2 versions), AD Assessment Schedule—Cognition (ADAS-Cog, 3 versions), MMSE, and Logical Memory data. The EF composite score was developed using an iterative process in which a model was constructed using bi-factor confirmatory factor analysis. The final model included WAIS-R Digit Symbol Substitution, Digit Span Backwards, Trails A and B, Category Fluency, and Clock Drawing.

### CSF biomarkers

CSF A $\beta$ <sub>42</sub> and p-tau were measured at the ADNI Biomarker Core Laboratory (University of Pennsylvania) using the multiplex xMAP Luminex platform (Luminex Corp) with Innogenetics (INNO-BIA AlzBio3; for research use only reagents) immuno-assay kit-based reagents.<sup>21</sup> All CSF biomarker assays were performed in duplicate and averaged.

### Neuroimaging

Amyloid PET imaging was measured with Florbetapir. Florbetapir binding images were averaged, spatially aligned, interpolated to a common voxel size (1.5 mm<sup>3</sup>), and smoothed to a common resolution of 8 mm full width at half maximum. FDG-PET data were acquired and reconstructed according to a standardized protocol (<http://adni.loni.usc.edu/>). A brief overview of the protocol is described in Text S1.

### Statistical analysis

AT(N) biomarker profiles were determined by applying a cutoff value to each biomarker based on values reported

in prior studies. The threshold of 1.11 was used for Florbetapir standardized uptake value ratio (SUVr) to designate whether participants were amyloid abnormal (A+) or normal (A-).<sup>22</sup> CSF p-tau levels were determined as tau abnormal (T+) or normal (T-) by using the cutoff value of 23 pg/ml.<sup>22</sup> The cutoff value of 1.21 was used for FDG PET (N) (average of angular, temporal, and posterior cingulate).<sup>23</sup> Eight AT(N) biomarker profiles were originally created as previously described.<sup>2</sup> However, sample sizes were too small for some of these profiles [A + T - (N)+, n = 9; A + T - (N)-, n = 23; A - T - (N)+, n = 28; A - T + (N)+, n = 34]. Therefore, to define subgroups with increased sample size that are adequate for analysis, we used AT(N) biomarkers to categorize participants to three major categories: (1) normal AD biomarkers [A - T - (N)]; (2) Alzheimer's continuum [A + T ± (N)±], and (3) suspected non-AD pathophysiology [SNAP; A - T ± (N)+ or A - T + (N)±].

WMH values were log transformed before inclusion rendering their distribution nearly normal. Linear regression models were used to test for cross-sectional relationships between WMH and memory and EF in different diagnostic and biomarker subgroups. Initially, we looked at the association between WMH and cognitive domains separately for CN and MCI subgroups. Potential confounders such as age, sex, and years of education were added as covariates to each regression model. We ran similar models to see if WMH volume was associated with memory or EF in participants stratified by AT(N) biomarker categories. Next, participants were categorized to six subgroups using combinations of clinical diagnoses (CN, MCI) and ATN biomarker categories outlined above; linear regressions were repeated separately for each subgroup. Finally, to test if the effect of WMH was independent from amyloid levels, Florbetapir PET was added as an additional covariate in supplementary models.

All statistical analyses were conducted using SPSS, version 26.0 (SPSS, Inc.).

## RESULTS

### Demographics and sample characteristics

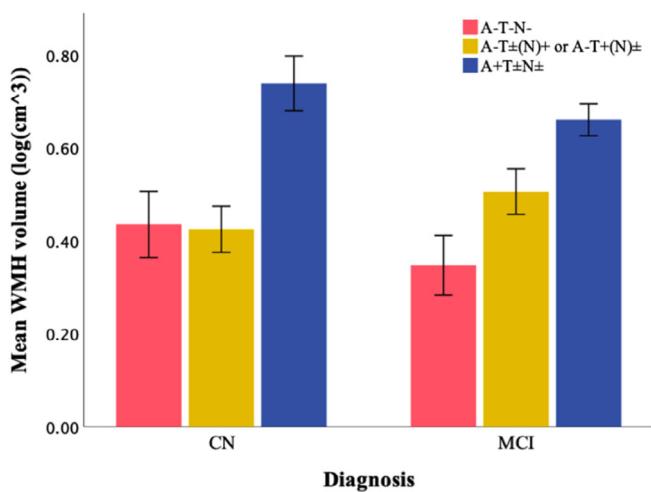
Characteristics of participants categorized by AT(N) biomarker profiles are shown in Table 1. The mean ( $\pm$ SD) age of all participants was  $72.1 \pm 7.0$  years; 52.3% were male; and on average had  $16.3 \pm 2.6$  years of education. A - T - (N)- individuals had an average memory composite score of  $0.88 \pm 0.63$  and average EF composite score of  $0.74 \pm 0.73$ . Comparatively, the SNAP group [A - T ± (N)+ or A - T + (N)±] individuals had lower memory ( $0.84 \pm 0.69$ ) and EF composite scores

**TABLE 1** Characteristics of 623 participants by amyloid- $\beta$  deposition [A], pathologic tau [T], and neurodegeneration [(N)] [AT(N)] biomarker profiles

Variable	A - T - (N) -	A - T $\pm$ (N) + or A - T + (N) $\pm$	A + T $\pm$ (N) $\pm$	All participants
n	106	213	304	623
Age, mean (SD), years	69.2 (6.3)	71.8 (7.5)	73.3 (6.6)	72.1 (7.0)
Male, n (%)	55 (51.9)	120 (56.3)	151 (49.7)	326 (52.3)
Education, mean (SD), years	16.7 (2.5)	16.6 (2.5)	16.0 (2.7)	16.3 (2.6)
WMH, mean (SD)	4.61 (6.4)	5.39 (6.4)	9.05 (12.5)	7.04 (10.1)
Memory composite score, mean (SD)	0.88 (0.63)	0.84 (0.69)	0.33 (0.72)	0.60 (0.74)
EF composite score, mean (SD)	0.74 (0.73)	0.78 (0.87)	0.32 (0.89)	0.55 (0.89)
ADAS-COG 13 score, mean (SD)	10.11 (4.70)	10.99 (5.66)	15.29 (7.17)	12.94 (6.71)
MMSE score, mean (SD)	28.83 (1.38)	28.71 (1.41)	27.98 (1.79)	28.37 (1.64)
Hippocampus, mean (SD), cm <sup>3</sup>	7.58 (0.93)	7.40 (1.07)	6.89 (1.00)	7.19 (1.06)
Entorhinal, mean (SD), cm <sup>3</sup>	3.87 (0.62)	3.84 (0.69)	3.56 (0.68)	3.72 (0.69)

Note: Data are mean (SD) or number (SD) unless otherwise stated.

Abbreviations: A-, amyloid normal using amyloid PET; A+ amyloid abnormal using amyloid PET; ADAS-Cog 13, Alzheimer's Disease Assessment Scale-Cognitive Subscale 13; EF, executive function; MMSE, Mini-Mental State Examination; N-, neurodegeneration normal using FDG; N+, neurodegeneration abnormal using FDG; SD, standard deviation; T-, tau normal using CSF p-tau; T+, tau abnormal using CSF p-tau; WMH, white matter hyperintensities.



**FIGURE 2** Bar graph of white matter hyperintensities (WMH) volume distribution among participants categorized by both amyloid- $\beta$  deposition [A], pathologic tau [T], and neurodegeneration [(N)] [AT(N)] biomarker profiles and clinical diagnoses. Error bars are  $\pm 1$  SE [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

( $0.78 \pm 0.87$ ) than the biomarker negative group. The A + T  $\pm$  (N)  $\pm$  individuals had an average memory composite score of  $0.33 \pm 0.72$  and average EF composite score of  $0.32 \pm 0.89$ . A - T - (N) - had the lowest average WMH levels at  $4.61 \pm 6.4$ ; A - T  $\pm$  (N) + or A - T + (N)  $\pm$  had an intermediate average of  $5.39 \pm 6.4$ ; and A + T  $\pm$  (N)  $\pm$  subgroup had the highest WMH average at  $9.05 \pm 12.5$ . When participants were stratified based on clinical diagnoses, CN individuals had an average memory

composite score of  $1.09 \pm 0.58$  and average EF composite score of  $0.89 \pm 0.82$ . MCI individuals had lower memory and EF composite scores:  $0.33 \pm 0.68$  and  $0.37 \pm 0.87$ , respectively. WMH volume distribution among participants categorized by both AT(N) biomarker categories and clinical diagnoses is shown in Figure 2. Table S1 shows a simple correlation between WMH and AT(N) biomarkers.

### Association between WMH and cognitive domains among CN and MCI subgroups

Table S2 summarizes results of regression models assessing the relationship between WMH and EF separately in CN and MCI subgroups. Higher baseline WMH volumes were associated with lower EF in CN ( $\beta = -0.161$ ,  $p = 0.012$ ) and MCI individuals ( $\beta = -0.104$ ,  $p = 0.048$ ).

Regression models were used to assess the association between WMH and memory separately for both CN and MCI individuals (Table S2). Higher baseline WMH volumes were associated with worse memory in the MCI subgroup ( $\beta = -0.114$ ,  $p = 0.035$ ), but the association was not significant in the CN subgroup ( $\beta = -0.027$ ,  $p = 0.663$ ).

### Association between WMH and cognitive domains among different AT(N) biomarker categories

Table 2 shows the results of regression models investigating the association between WMH and EF in subgroups

	Executive function			Memory		
	$\beta$	<i>t</i>	<i>p</i>	$\beta$	<i>t</i>	<i>p</i>
AT(N) biomarker categories						
Normal AD biomarkers ( <i>n</i> = 106)						
Sex	0.097	0.986	0.326	0.310	3.272	0.001***
Age	-0.176	-1.628	0.107	-0.202	-1.943	0.055
Education	0.139	1.426	0.157	0.138	1.468	0.145
WMH	-0.111	-1.037	0.302	0.081	0.784	0.435
Suspected non-Alzheimer disease pathophysiology ( <i>n</i> = 213)						
Sex	0.108	1.784	0.076	0.281	4.553	<0.001***
Age	-0.277	-4.304	<0.001***	-0.284	-4.318	<0.001***
Education	0.307	5.046	<0.001***	0.207	3.320	0.001***
WMH	-0.133	-2.075	0.039*	-0.064	-0.979	0.329
Alzheimer's continuum ( <i>n</i> = 304)						
Sex	0.088	1.734	0.084	0.242	4.773	<0.001***
Age	-0.198	-3.710	<0.001***	0.003	0.061	0.951
Education	0.148	3.003	0.003**	0.157	3.174	0.002**
WMH	-0.053	-1.007	0.315	-0.059	-1.098	0.273

Note: WMH values were log transformed.

Abbreviations: A-, amyloid normal using amyloid PET; A+ amyloid abnormal using amyloid PET; N-, neurodegeneration normal using FDG; N+, neurodegeneration abnormal using FDG; T-, tau normal using CSF p-tau; T+, tau abnormal using CSF p-tau; WMH, white matter hyperintensities.

\*Significance at  $p < 0.05$ ; \*\*Significance at  $p \leq 0.01$ ;

\*\*\*Significance at  $p \leq 0.001$ .

defined by AT(N) biomarker categories. Higher WMH volume was associated with worse EF in individuals with the A - T  $\pm$  (N)+ or A - T + (N) $\pm$  biomarker category ( $\beta = -0.133$ ,  $p = 0.039$ ), but not in A - T - (N)- ( $\beta = -0.108$ ,  $p = 0.304$ ) and A + T  $\pm$  (N) $\pm$  ( $\beta = -0.053$ ,  $p = 0.315$ ).

The association between WMH and memory was examined separately for each of the A - T - (N)-, A-T  $\pm$  (N) + or A - T + (N) $\pm$ , and A + T  $\pm$  (N) $\pm$  biomarker categories. There was no significant association between WMH and memory in any of the three biomarker categories (Table 2).

## Association between WMH and cognitive domains among different AT(N) biomarker categories and CN/MCI subgroups

Participants were then categorized according to both the AT(N) framework and baseline clinical diagnoses. Separate regression models were used to examine the association between WMH and EF in each subgroup as shown in Table S3. Higher WMH volumes were associated with worse EF in A - T  $\pm$  (N)+ or A - T + (N) $\pm$  individuals

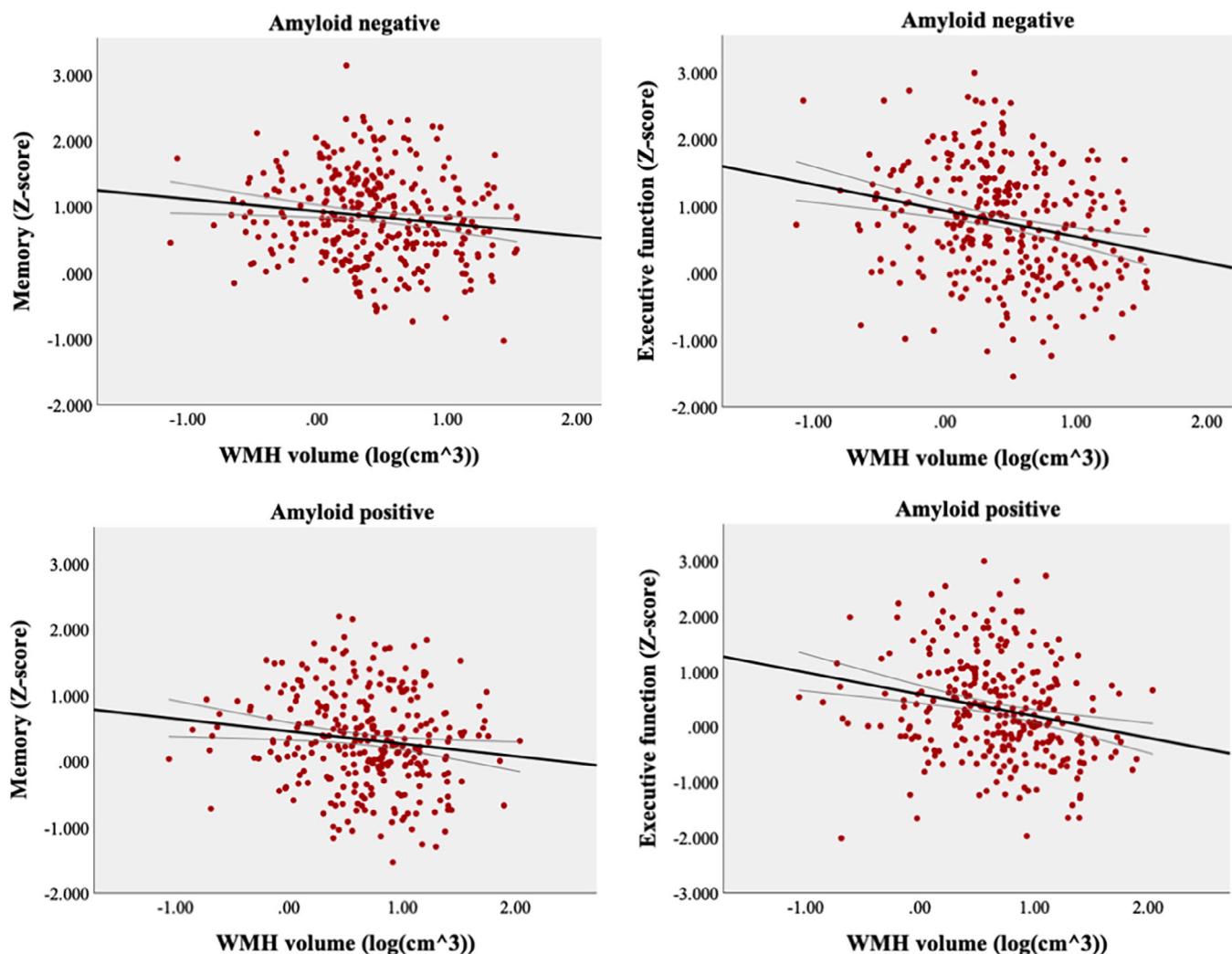
**TABLE 2** Association between white matter hyperintensities (WMH) and cognitive domains among different amyloid- $\beta$  deposition [A], pathologic tau [T], and neurodegeneration [(N)] [AT(N)] categories

within the CN subgroup ( $\beta = -0.205$ ,  $p = 0.018$ ). However, no significant difference was detected in other biomarker categories.

Regression models were next used to assess the association between WMH and memory in each AT(N) biomarker category (Table S3). For A + T  $\pm$  (N) $\pm$  individuals diagnosed with MCI, higher WMH was associated with worse memory ( $\beta = -0.158$ ,  $p = 0.032$ ) (Table S3). However, there was no significant association among A - T  $\pm$  (N)+ or A - T + (N) $\pm$  individuals within the CN subgroup ( $\beta = -0.017$ ,  $p = 0.852$ ).

To further investigate whether the effect of WMH on memory was independent of baseline A $\beta_{42}$  levels within each biomarker category, we added amyloid as a covariate to the model in A + T  $\pm$  (N)  $\pm$  individuals with MCI (Table S4). In these regression models, both amyloid levels ( $\beta = -0.262$ ,  $p < 0.001$ ) and WMH ( $\beta = -0.159$ ,  $p = 0.024$ ) showed significant associations with memory in the A + T  $\pm$  (N) $\pm$  and MCI subgroup. The associations between WMH and memory and EF among amyloid positive and negative participants are shown in Figure 3.

In the current study, both the ADNI memory composite score and the diagnosis criteria for amnestic MCI include the MMSE and logical memory. This might cause



**FIGURE 3** Simple scatter plots of the associations between white matter hyperintensities (WMH) and cognitive domains among amyloid positive and negative participants

a circularity problem that may lead to inaccurate measures of association. Circular analysis is a well-known issue in statistics, which might inflate the apparent statistical strength of any results reported.<sup>24</sup> To address this issue, as a sensitivity analysis, separate regression models were conducted using the ADAS-Cog score as the dependent variable instead of the ADNI memory composite score. Results are shown in Tables S5 and S6. Higher WMH volumes were similarly associated with worse memory for individuals who had MCI ( $\beta = 0.159$ ,  $p = 0.004$ ). Higher WMH was additionally found to be associated with worse memory for individuals classified as amyloid positive ( $\beta = 0.148$ ,  $p = 0.017$ ).

## DISCUSSION

We investigated the effect of WMH on cognitive domains of memory and EF in the context of AT(N) biomarker

classification. We found that higher WMH was associated with worse EF in both CN and MCI subgroups. Furthermore, there was a significant association between higher WMH and lower memory function in the MCI subgroup but not in the CN subgroup. We also showed that the association between WMH and memory is independent of amyloid levels in individuals with MCI with in vivo evidence of AD pathology.

Although many studies indicate that higher burden of white matter lesions is inversely associated with memory and EF in older adults,<sup>25</sup> this has not been a consistent finding across different clinical stages of disease.<sup>26</sup> Our results suggest that in the CN subgroup, WMH is associated with EF but not with memory. In the MCI subgroup, WMH was associated with both memory performance and EF. These findings might be explained by the differential effect of WMH on various neuronal pathways. WMH is thought to have greater effects in the frontal and prefrontal regions, which may play a pivotal role in

preserving normal EF.<sup>27</sup> WMH can also affect memory when white matter lesions are localized in deep frontal and occipital areas.<sup>28</sup> The MCI participants in ADNI were all diagnosed with *amnestic* MCI at enrollment. We may not see an effect on WMH on memory in the normal subgroup because their range of scores was attenuated.

A key finding of our study was that WMH was associated with EF in the subgroup with A – T ± (N)+ or A – T + (N)± (SNAP) biomarker category, but not for A – T – (N)– (normal biomarker) or A + T ± (N)± (AD pathology) subgroups. In addition, higher WMH burden was associated with lower memory composite scores for individuals with MCI who have AD pathology. In vivo imaging studies indicate distinct topographic stages of A $\beta$ , tau, and neurodegeneration in different clinical stages of AD and other dementia.<sup>29</sup> These studies indicate that the pattern of sequential involvement of the cognitive function domains largely corresponded to the distribution of tau pathology in the brain.<sup>30</sup> Decline in executive performance may occur prior to memory impairment in preclinical AD due to the sequential amyloid deposition in the basal isocortex and then the hippocampus.<sup>31</sup> These findings support the notion that topographic patterns of pathology may influence patterns of domain-specific cognitive decline. EF impairment in participants with SNAP may occur early in disease, as a process that is independent of amyloid deposition. A longitudinal study monitoring the spatial expansion of A $\beta$ , tau, and other biomarkers along with measurement of cognitive function in specific domains can help with establishing the causal chain of global and domain-specific cognitive decline.

There are several limitations that should be noted. Based on its design, ADNI exclude participants who might have primary vascular dementia. The inherent selection bias in ADNI, may prevent our study findings to be generalized to the population at large. The categorization of participants based on the AT(N) biomarker categories was based on single cutoff values, which may introduce misclassification. Furthermore, since the number of individuals within some of the profiles were relatively small, assessment of the association between WMH and cognitive domains for individual AT(N) subgroups was not possible; we thus combined subgroups [A – T – (N)–, A – T ± (N)+ or A – T + (N)±, A + T ± (N)±] to gain statistical power but cannot exclude heterogeneity within the groups we defined. To avoid type I error, our study limited the number of comparisons by looking at specific associations based on the prespecified hypothesis. Furthermore, considering the small sample in some subgroups, we were underpowered to detect weaker associations among our measures of interest. This study should therefore be considered as an exploratory study and replication of this work in population-based cohorts with larger

biomarker datasets may provide better insight on the association between WMH and cognitive domains across different biomarker profiles. The relationships with WMH in this study were assumed to be linear and monotonic in our analysis and WMH was not differentiated based on its localization: periventricular and subcortical. Finally, the cross-sectional design of this study precludes establishing a direct causal relationship between tested measures. Future longitudinal studies in larger samples are needed to confirm our findings in individual biomarker groups and to establish the causal relationships between individual biomarkers and cognitive function.

Our findings support that WMH is a critical component of AD pathology, independent of amyloid deposition. Further studies are needed to disentangle the neuropathological mechanisms and synergism between vascular diseases and neurodegenerative changes that lead to AD. However, our findings suggest individuals with high levels of amyloid and WMH volume should be closely monitored for changes in cognition over time. Furthermore, our results support that decline in specific cognitive domains occur early in the course of disease when pathologic brain changes—such as WMH—are already forming but impairment in cognition is not significant enough to make clinical diagnosis of dementia. Therefore, aggressive medical management of the vascular risk factors (e.g., hypertension and diabetes) is warranted for asymptomatic individuals found to have significant WMH burden.

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## CONFLICT OF INTEREST

The authors report no conflict of interest.

## AUTHOR CONTRIBUTIONS

Sharon Lam: data analysis, interpretation of data, manuscript preparation, and intellectual contributions to content. Richard B. Lipton: interpretation of data, manuscript editing, and intellectual contributions to content. Andrea R. Zammit: interpretation of data, manuscript editing, and intellectual contributions to content. Danielle J. Harvey: interpretation of data, manuscript editing, and intellectual contributions to content. Ali Ezzati: conception and design, acquisitions of data, interpretation of data, manuscript preparation, intellectual contributions to content, and study supervision.

## SPONSOR'S ROLE

None.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**Figure S1** Flow chart of study participants

**Text S1.** Detailed information on the calculation of Florbetapir, FDG-PET, and white matter hyperintensities (WMH) values

**Table S1.** Simple correlation (Pearson) among white matter hyperintensities (WMH), amyloid, tau, and neurodegenerative biomarkers of 623 participants

**Table S2.** Association between white matter hyperintensities (WMH) and cognitive domains among cognitively normal (CN) and mild cognitive impairment (MCI) subgroups

**Table S3.** Association between white matter hyperintensities (WMH) and memory among different amyloid- $\beta$  deposition [A], pathologic tau [T], and neurodegeneration [(N)] [AT(N)] profiles and cognitively normal/mild cognitive impairment (CN/MCI) subgroups

**Table S4.** Association between white matter hyperintensities (WMH), amyloid- $\beta$ , and memory among A + T ± (N)± and mild cognitive impairment (MCI) subgroup

**Table S5.** Association between white matter hyperintensities (WMH) and memory measured by ADAS-Cog 13 among cognitively normal (CN) and mild cognitive impairment (MCI) subgroup

**Table S6.** Association between white matter hyperintensities (WMH) and memory measured by ADAS-Cog 13 among amyloid- $\beta$  deposition [A], pathologic tau [T], and neurodegeneration [(N)] [AT(N)] categories

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