



## Tract-defined regional white matter hyperintensities and memory

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### ABSTRACT

White matter hyperintensities (WMH) are common radiological findings among older adults and strong predictors of age-related cognitive decline. Recent work has implicated WMH in the pathogenesis and symptom presentation of Alzheimer's disease (AD), which is characterized clinically primarily by a deficit in memory. The severity of WMH volume is typically quantified globally or by lobe, whereas white matter itself is organized by tracts and fiber classes. We derived WMH volumes within white matter tract classes, including association, projection, and commissural tracts, in 519 older adults and tested whether WMH volume within specific fiber classes is related to memory performance. We found that increased association and projection tract defined WMH volumes were related to worse memory function but not to a global cognition summary score that excluded memory. We conclude that macrostructural damage to association and projection tracts, manifesting as WMH, may result in memory decline among older adults.

### 1. Introduction

White matter hyperintensities (WMH) are areas of increased signal best visualized on T2-weighted images, thought to reflect the presence and severity of small vessel cerebrovascular disease (CVD) (Biesbroek et al., 2016). White matter hyperintensities are considered to be core etiological features of vascular cognitive impairment (Biesbroek et al., 2016; van der Flier et al., 2018; Vannorsdall et al., 2009), which is typically characterized by deficits in executive function and processing speed (Jokinen et al., 2009; Schmidt et al., 2005; Vannorsdall et al., 2009). However, WMH severity has been implicated both in the pathogenesis and symptom presentation of Alzheimer's disease (AD) and its antecedent risk states (e.g., Brickman, 2013; Luchsinger et al., 2009), which are characterized clinically by a deficit in memory, and in memory functioning *per se* among older adults (Burton et al., 2004; Rizvi et al., 2018; Swardfager et al., 2018).

Studies that examine the relationship between WMH and cognition in older adults typically quantitate WMH as a global phenomenon (Yoshita et al., 2005) or grossly by cerebral lobe (Gootjes et al., 2004). White matter fiber tracts, however, are organized systematically throughout the brain and can be divided into three major classes of

fiber bundles: association, projection, and commissural fiber bundles. Despite the known differential association of white matter fibers within these different tract classes and cognition (Bennett and Madden, 2014; Hasan et al., 2010; Makris et al., 1997; Mandonnet et al., 2018), less is known about how WMH severity within them is associated with cognitive functioning.

Association fibers are long and short fiber tracts that connect cortical areas within hemispheres, and include long tracts such as the superior longitudinal fasciculus (Lee et al., 2015), inferior fronto-occipital fasciculus (IFOF), and inferior longitudinal fasciculus (ILF). Long association fibers are well known to be critical for supporting cognitive processes, including executive function, language, visuospatial functioning, and memory (Duffau, 2015; Friederici, 2009; Mabbott et al., 2009; Thiebaut de Schotten et al., 2012; Voineskos et al., 2012; Wendelken et al., 2015). Commissural tracts are interhemispheric fibers that connect cortical regions of both hemispheres, such as the corpus callosum. Commissural tracts are implicated in functional integration (Aralasmak et al., 2006; Catani et al., 2002), memory and executive functioning (Voineskos et al., 2012; Zahr et al., 2009). Projection tracts are fibers that connect subcortical structures and cortex, and include fibers such as corticospinal tract and thalamic radiations. The anterior

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thalamic radiation connects thalamic nuclei to the prefrontal cortex and anterior cingulate cortex (Torso et al., 2015; Wakana et al., 2004). Functions of projection fibers are related to aspects of motor and sensory abilities (Kuypers, 1964; Lemon, 2008). However, specific projection fibers, such as the anterior thalamic tract, can contribute to episodic memory function and are vulnerable to the effects of Alzheimer's disease (Aggleton et al., 2016).

In a previous study, we demonstrated the relationship between WMH volume and cognition is statistically mediated by global cortical thickness (Rizvi et al., 2018). In this follow-up study, we were interested in how WMH within the three classes of white matter fiber tracts are differentially associated with memory in older adults. We hypothesized, given that the connections among frontal, temporal and parietal areas form networks supporting memory (Cabeza et al., 2008; Fletcher and Henson, 2001), that increased WMH within association tracts would be negatively associated with memory functioning in older adults. We investigated the specificity of the relationship of tract WMH and memory relative to a global measure of cognition that excluded memory. To compare our results with previous DTI studies on individual tracts, and to reveal any driving sources of tract WMH associations with memory, we also explored the association between WMH and memory in individual tracts within the tract classes that were associated with memory.

## 2. Material and methods

### 2.1. Participants

Participants came from the Washington Heights Inwood Columbia Aging Project (WHICAP), a community-based study of cognitive aging and dementia in northern Manhattan New York. Participants from a third recruitment wave, beginning in 2010, who had 3T MRI acquired were included in the study. Only participants with complete WMH, cognitive, and demographic data from the 2010 subset were included in the analyses ( $n = 519$ ). WHICAP participants receive semi-structured and structured interviewing to query for histories of common medical morbidities and risk factors, including multiple sclerosis and history of traumatic brain injury with loss of consciousness, two conditions that can confound measurement of WMH related to cerebrovascular disease.

### 2.2. Neuropsychological testing

Participants were administered a comprehensive and validated neuropsychological battery in their preferred language (English or Spanish) (Siedlecki et al., 2010). Testing covered multiple cognitive domains, including memory, executive function/speed, language, and

visuospatial function. Domain scores (Siedlecki et al., 2010) were derived by averaging z-scores of individual tests within each domains. Z-scores were computed from test means and standard deviations of the entire WHICAP sample at baseline. The memory domain comprised scores from the Selective Reminding Test, including total recall, delayed recall, and delayed recognition (Buschke and Fuld, 1974). The language domain included letter and category fluency, 15-item Boston Naming Test (Goodglass et al., 1983), Repetition and Comprehension subtests from the Boston Diagnostic Aphasia Examination (Goodglass and Kaplan, 1972), and the Similarities subtest from the Wechsler Adult Intelligence Scale - Revised (Wechsler and De Lemos, 1981). The visuospatial domains included matching and recognition trials from the Benton Visual Retention Test (Benton, 1974), Identities and Oddities from the Mattis Dementia Rating Scale (Mattis, 1976), and the Rosen Drawing Test (Rosen, 1981). The executive function/speed domain consisted of scores from Color Trails 1 and Color Trails 2 (D'Elia et al., 1996). We created a non-memory cognition variable by averaging performance scores in all the other domains (executive function/speed, language, visuospatial function). Our hypothesis pertained to the relationship of WMH in white matter tract classes with memory; to test the specificity of this relationship we also compared WMH volumes with non-memory cognition.

### 2.3. Magnetic resonance imaging

#### 2.3.1. Image acquisition

Magnetic resonance images were collected on a 3T Philips Achieva scanner at Columbia University between 2011 and 2015. T1-weighted (resolution = 1 mm × 1 mm × 1 mm, repetition time = 6.6 ms, echo time = 3.0 ms, field of view = 256 × 200 × 165 mm with 1-mm slice thickness) and T2-weighted fluid-attenuated inversion recovery (FLAIR; resolution = 0.6 mm × 0.43 mm × 0.43 mm, repetition time = 8000 ms, echo time = 332.0 ms, inversion time = 2400 ms, field of view = 240 × 240 × 180 mm with 1.20-mm slice thickness) images were acquired in the transverse orientation.

#### 2.3.2. White matter hyperintensity quantification

Total WMH volumes were quantified with previously developed methods (Brickman et al., 2011, 2015). Each T2-weighted FLAIR image was brain extracted and a single Gaussian curve was fit to voxel intensity values. An intensity threshold of 2.1 SD above the mean intensity value defined the lower boundary of hyperintense voxels and voxels above that threshold were labeled. Each labeled mask was visually inspected and manually corrected, removing any voxels that were mislabeled as WMH voxels (Fig. 1).

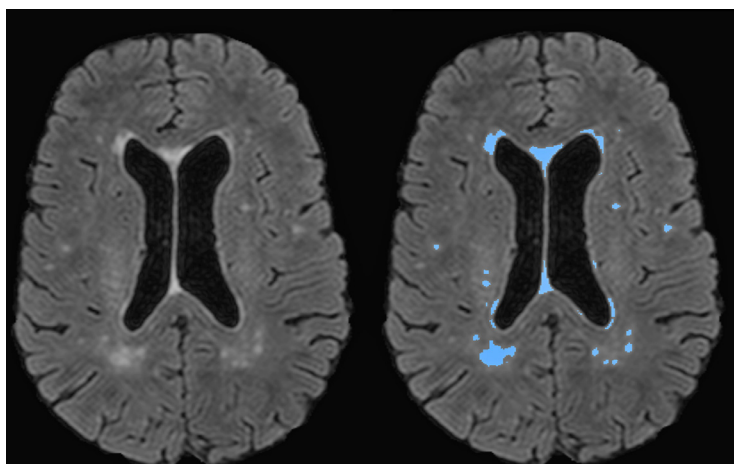


Fig. 1. Axial slice of a FLAIR sequence with unlabeled white matter hyperintensities (left), and labeled white matter hyperintensities (right).

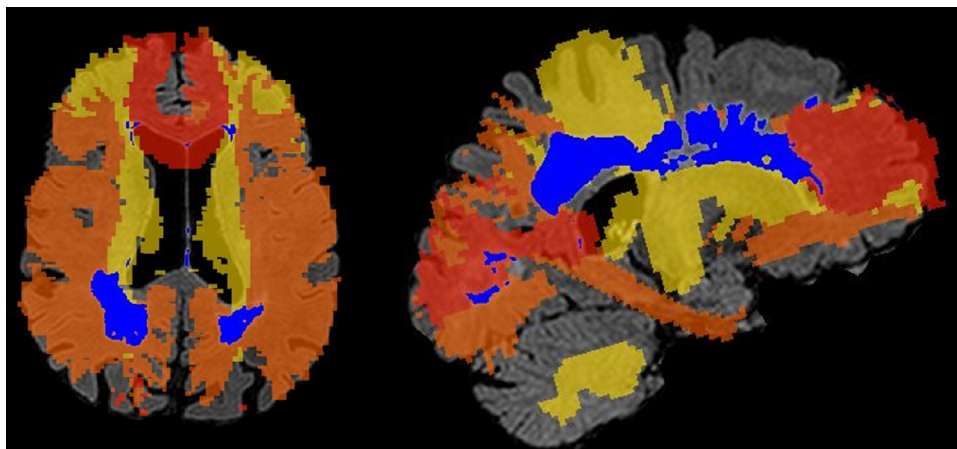


Fig. 2. The three tract classes using the JHU White Matter Tractography Atlas with corresponding colors (red = commissural, yellow = projection, orange = association) are visualized here, with an overlaid segmented WMH image (in blue) on top.

### 2.3.3. Tract-defined white matter hyperintensity classification

FLAIR and T1-weighted images were brain extracted using Brain Extraction Tool (Smith, 2002) in FMRIB Software Library (FSL). The T1-weighted and FLAIR images were coregistered with FMRIB's Linear Image Registration Tool in FSL with trilinear interpolation and correlation ratio as the cost function. Next, the Montreal Neurological Institute (MNI) standard brain template (MNI-152 T1 brain) was transformed into each subject's coregistered T1-weighted and FLAIR image space, using trilinear interpolation and the resulting transformation matrix was applied to move the Johns Hopkins University (JHU) white matter tractography mask (Mori and van Zijl, 2007) into the FLAIR image space using the nearest neighbor method (Fig. 2). The JHU ICBM tract atlas had a probability threshold of 0% with 2 mm isotropic resolution.

The regional WMH volumes were derived by extracting the labeled WMH voxels within each tract and summing them according to the class of tract fibers. The three classes included the association, commissural, and projection white matter fiber tracts. A relative WMH volume within each class of tracts was derived by dividing the volume of WMH within each class by the total volume of the tracts. The specific tracts within each class (Fig. 3) are listed below:

*Association fiber tracts:* cingulum-cingulate gyrus, cingulum-hippocampus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, uncinate fasciculus, and superior longitudinal fasciculus temporal part.

*Commissural fiber tracts:* forceps major, and forceps minor.

*Projection fiber tracts:* anterior thalamic radiation, and corticospinal tract.

### 2.4. Statistical analysis

Three sets of general linear models were used to test the relationship between relative WMH volumes within the three tract categories and memory. For these analyses, relative WMH volume within each tract class and the memory summary scores were the independent and dependent variables, respectively. We repeated this analysis with the cognition summary score that excluded memory as the dependent variable. We further tested the specificity of the memory relationships by dividing participants into high and low memory groups, based on their median memory performance, and compared regional WMH volumes across these groups. A mixed design general linear model was implemented with Memory Group (low, high) as a between-groups factor and WMH Region (association, commissural, and projection) as a within-subjects factor. Covariates included age, sex, race/ethnicity, and education. Within the tract classes for which WMH were related to memory, we examined the correlation between WMH volume and

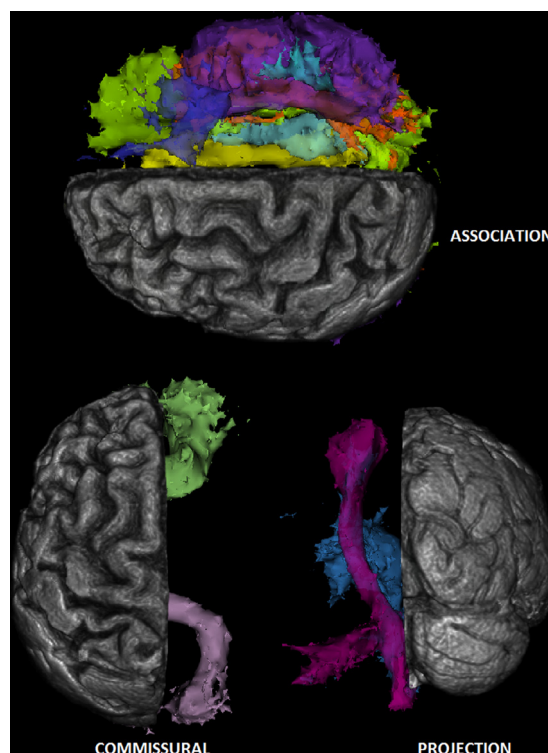


Fig. 3. A representation of the three classes of white matter tract fibers. Each tract class was 3D rendered in 3D slicer, and displayed next to a cortical hemisphere.

memory within the individual tracts in a series of multiple regressions with the same covariates listed above. To ensure that relationships between regional WMH and memory were not due to differential effects related to diagnosis, we re-ran the primary analysis after removing from the data the individuals with AD dementia ( $n = 8$ ). Next, we re-ran the primary analysis while covarying for MCI diagnosis ( $n = 83$ ). These analyses did not lead to different results from our main findings.

## 3. Results

### 3.1. Participant characteristics

Participant characteristics, WMH volume measures, and cortical thickness are displayed in Table 1. No participants reported a history of multiple sclerosis. Eighteen participants reported a history of head

**Table 1**  
Descriptive information regarding the participants studied.

Variable	
<b>N</b>	519
<b>Age, mean years (SD)</b>	73.98 (5.64)
<b>Sex, n (%) Women</b>	292 (56.3%)
<b>Education, mean years (SD)</b>	12.78 (4.51)
<b>Diagnostic Category</b>	
NC, n (%)	411 (81.9%)
MCI, n (%)	83 (16%)
AD, n (%)	8 (1.5%)
Missing diagnosis (%)	17 (3%)
<b>Race / Ethnicity</b>	
White, n (%)	159 (30.6%)
Black, n (%)	188 (36.2%)
Hispanic, n (%)	158 (30.4%)
Other, n (%)	14 (2.7%)
<b>WMH volume, cm<sup>3</sup></b>	
Total, mean (SD)	5.50 (7.11)
Association WMH ratio, mean (SD)	0.0098 (0.0123)
Projection WMH ratio, mean (SD)	0.0043 (0.0077)
Commissural WMH ratio, mean (SD)	0.0099 (0.0092)
<b>Domain score</b>	
Memory, mean (SD), range	0.44 (0.73), -2.63-2.04
Average Cognition (no memory), mean (SD), range	0.63 (0.54), -1.39-1.68

NC = Normal Controls, MCI = Mild cognitive impairment, AD = Alzheimer's disease.

injury with loss of consciousness. White matter hyperintensity volume did not differ between individuals reporting history of head injury with loss of consciousness and those reporting no such history ( $t = 1.468, p = .143$ ).

### 3.2. Relationships between tract class-defined WMH and memory

Increased WMH volumes within association tracts and projection tracts were related to poorer memory performance (see Table 2). White matter hyperintensity volume within commissural tracts was not associated with memory. In all three models, memory performance was negatively associated with age, and positively associated with education. Memory scores were also lower in men compared with women and in African American and Hispanic participants, compared with non-Hispanic Whites. Individuals with lower memory had particularly elevated WMH volume in projection tracts (Memory Group x WMH Region interaction,  $F = 3.419, p = .037$ , Fig. 4).

### 3.3. Relationships between tract class-defined WMH and non-memory cognition

White matter hyperintensity volumes in the three tract classes were

**Table 2**  
Results of multiple regressions of relationships between WMH volumes and memory.

Tract Class WMH Volume	Standardized $\beta$ coefficient	Significance (p-value)	95% CI
<b>Association tract WMH</b>	-0.115	0.005	(-18.606, -3.433)
<b>Projection tract WMH</b>	-0.121	0.003	(-12.165, -2.445)
<b>Commissural tract WMH</b>	-0.063	0.120	(-11.505, 1.337)
<b>Individual Tract WMH Volume</b>			
Anterior Thalamic Radiation WMH	-0.112	0.006	(-0.113, -0.019)
Corticospinal Tract WMH	-0.117	0.005	(-0.190, -0.035)
Cingulum cingulate gyrus WMH	-0.072	0.077	(-0.253, 0.013)
Cingulum hippocampus WMH	-0.027	0.513	(-1.819, 0.909)
Inferior Fronto-occipital Fasciculus WMH	-0.081	0.049	(-0.122, 0.000)
Inferior Longitudinal Fasciculus WMH	-0.068	0.096	(-0.247, 0.020)
Superior Longitudinal Fasciculus WMH	-0.126	0.002	(-0.090, -0.020)
Uncinate Fasciculus WMH	-0.144	0.000	(-2.027, -0.593)
Superior Longitudinal Fasciculus temporal part WMH	-0.067	0.101	(-2.441, 0.218)

Covariates included: age, sex, education, race/ethnicity.

not related to non-memory cognition (see Table 3). The effect sizes were largest for the relationships between tract WMH volumes and memory compared with the relationships between tract WMH volumes and non-memory cognition.

### 3.5. Relationships between individual tract WMH and memory

We tested which individual tracts WMH within association and projection tracts were associated with memory in a series of multiple regressions. Within projection tracts, increased WMH volume in the anterior thalamic tract and the corticospinal tract were related to poorer memory. Within association tracts, increased WMH in the inferior fronto-occipital fasciculus, the superior longitudinal fasciculus, and the uncinate fasciculus were associated with poorer memory (see Table 2).

## 4. Discussion

We demonstrated that higher WMH volumes within association and projection tracts were associated with lower memory performance in older adults. These relationships were specific to memory when comparing to a global measure of cognition that excluded memory. Within association tracts, WMH volumes within the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and the uncinate fasciculus were most reliably related to memory. Both projection tract WMH volumes, including those within the corticospinal and anterior thalamic tracts, were associated with memory. These observations were not systematically influenced by diagnosis of MCI or dementia.

The consideration of white matter tract classification has been predominantly applied to diffusion tensor imaging (DTI) analyses to study the effects of white matter integrity on cognitive function (Madden et al., 2009). Metrics derived from DTI in cross-sectional analyses capture aspects of white matter microstructure, which may reflect a combination of individual developmental differences and damage or neurodegenerative changes. White matter hyperintensities, on the other hand, reflect the degree of macrostructural damage to white matter and change from younger age because young, healthy individuals do not typically have WMH. Our observations linking WMH volume to memory indicate that the relationship between regional white matter damage and memory may be tract specific. No studies to our knowledge have examined the effects of WMH volume in tract-defined classes of white matter – namely association, projection, and commissural – on memory. As cognitive functions are supported by multiple white matter tracts performing similar and complementary functions, it is useful to group these tracts into the three established types of fibers.

Our findings do, however, complement those from DTI studies, which also suggest a role of association tracts in supporting memory

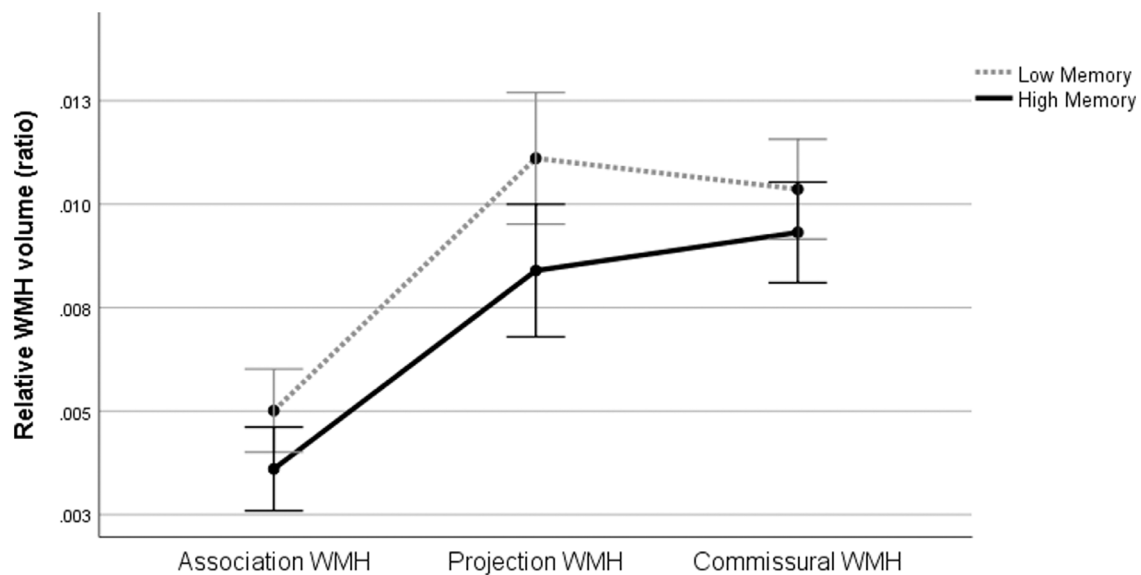


Fig. 4. The interaction plot of Memory Group by WMH Region ( $F = 3.419, p = .037$ ) illustrating that individuals with lower memory had particularly elevated WMH volume in projection tracts.

Table 3

Results of multiple regressions of relationships between WMH volumes and global cognition (excluding memory).

Tract Class WMH Volume	Standardized $\beta$ coefficient	Significance ( $p$ -value)	95% CI
Association tract WMH	-0.049	0.145	(-8.514, 1.261)
Projection tract WMH	-0.057	0.097	(-5.759, 0.477)
Commissural tract WMH	-0.033	0.328	(-6.174, 2.070)

Covariates included: age, sex, education, race/ethnicity.

functioning in older adults. Diffusion tensor imaging studies typically report relationships between integrity of association tracts, including fronto-temporal tracts the parahippocampal cingulum and the uncinate fasciculus, and episodic memory (Metzler-Baddeley et al., 2011). A previous study reported that fractional anisotropy of the inferior longitudinal fasciculus and posterior and anterior cingulum was associated with memory function (Kantarci et al., 2011). Lockhart and colleagues (Lockhart et al., 2012) extended this line of work on microstructure by finding that macrostructural white matter injury, as measured by WMH, within tracts connecting frontal and temporal cortex, and frontal-subcortical regions, were also associated with memory in older adults. We add to this body of work by confirming that not only that macrostructural damage to association tracts, but also projection tracts, have a role in memory function. Our unexpected finding regarding the relationship between WMH in projection white matter tracts, particularly the relationship between corticospinal tract and memory, deviates from previous DTI studies, which suggested a role of the corticospinal tract in sensorimotor functions rather than cognitive functions (Carter et al., 2012; Karahan et al., 2019). A plausible explanation of the relationship between corticospinal tract WMH and memory may simply be due to the tract's proximity to the lateral ventricles, where periventricular WMH reside and are known to be associated to memory (Munoz Maniega et al., 2019; Smith et al., 2011).

Our findings have implications for the potential role of WMH, as a marker of small vessel cerebrovascular disease, in the pathogenesis of AD. We found previously (Tosto et al., 2015) that WMH predicts accumulation of tau protein in the cerebrospinal fluid over time, but not vice versa. Data from animal models support the idea that small vessel cerebrovascular disease may promote neurodegenerative changes through its direct effect on tau hyperphosphorylation, mediated by an inflammatory cascade (Raz et al., 2019). Furthermore, higher WMH within specific tract classes may contribute to the disruption of cortical

networks that support memory, the primary cognitive domain typically affected in AD, possibly contributing additively to an AD-like symptoms (Greicius et al., 2004), perhaps lowering a clinical diagnostic threshold. Tract WMH, which we hypothesize disrupt structural and functional networks, leading to cognitive dysfunction, may also increase the propagation and trans-synaptic spread of tau in affected networks (Ahmed et al., 2014; De Calignon et al., 2012; Lehmann et al., 2013). Thus, overall, we believe that there is accumulating evidence that WMH, as a marker of small vessel cerebrovascular disease, may contribute directly to the pathogenesis of AD through tau pathology, and also to an Alzheimer's "phenotype" of memory dysfunction independent of primary AD pathology through network disruption. The possibility that some degree of white matter macrostructural change can result from Alzheimer's-related neurodegeneration may also be contributing (McAleese et al., 2017).

In considering potential limitations of the study, we acknowledge that there may be other possible causes of WMH formation, such as through white matter degenerative diseases, like multiple sclerosis and traumatic brain injury. In our sample, no participants reported a history of multiple sclerosis. A small number of participants reported a history of traumatic brain injury with loss of consciousness, but these individuals did not differ in terms of their WMH volumes from those with no history of traumatic brain injury. Wallerian-like degeneration, secondary to AD-related neurodegeneration may be an additional source of WMH (McAleese et al., 2017). Although we cannot rule out this possibility entirely, we feel that the extant literature overwhelmingly supports the primary role of small vessel cerebrovascular disease in WMH formation and that the temporality (i.e., only 8 participants in this study had dementia and others who may have had preclinical disease were presumably in stages prior to widespread neurodegeneration) speak against this possibility. We are also restricted in our ability to infer causality of our findings, due to the cross-sectional

design of the study. We recognize that while focusing on macrostructural markers of white matter damage, we did not account for microstructural abnormalities within areas of normal appearing white matter. This issue can be addressed using diffusion tensor imaging metrics in future analysis.

We suggest our findings of the impact of tract-defined WMH on memory performance is partially explained by the previously proposed concept of “disconnection” (Lockhart et al., 2012; Munoz Maniega et al., 2019; O’Sullivan et al., 2001; Ritchie et al., 2015), which may mediate the effect of tract WMH on cognitive performance. Neuroimaging studies suggest that long-term memory is dependent on multiple cortical and subcortical regions, which are integrated via neural networks (Charlton et al., 2010; Grady et al., 2003; Ranganath et al., 2005). White matter hyperintensities within tracts may disrupt pathways that support memory performance.

## 5. Conclusion

The study examined the role of WMH within three tract categories and found that association and projection WMH are related to memory functioning in older adults.

## CRedit authorship contribution statement

**Batool Rizvi:** Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Patrick J. Lao:** Formal analysis, Writing - review & editing. **Juliet Colón:** Investigation, Data curation, Project administration. **Christiane Hale:** Investigation, Data curation, Project administration. **Kay C. Igwe:** Software, Data curation. **Atul Narkhede:** Software, Data curation. **Mariana Budge:** Investigation, Data curation, Project administration. **Jennifer J. Manly:** Investigation, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Nicole Schupf:** Investigation, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Adam M. Brickman:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

## Declaration of Competing Interest

None.

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