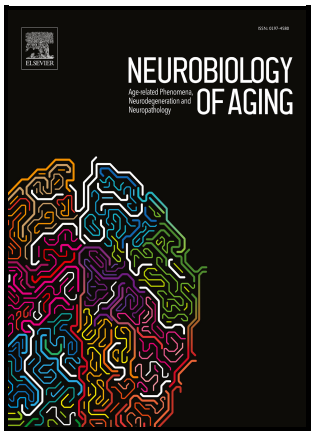


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# Impact of white matter hyperintensities on structural connectivity and cognition in cognitively intact ADNI participants

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**Abstract**

We used indirect brain mapping with virtual lesion tractography to test the hypothesis that the extent of white matter tract disconnection due to white matter hyperintensities (WMH) is associated with corresponding tract-specific cognitive performance decrements. To estimate tract disconnection, WMH masks were extracted from FLAIR MRI data of 481 cognitively intact participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) and used as regions of avoidance for fiber tracking in diffusion MRI data from 50 healthy young participants from the Human Connectome Project. Estimated tract disconnection in the right inferior fronto-occipital fasciculus, right frontal aslant tract, and right superior longitudinal fasciculus mediated the effects of WMH volume on executive function. Estimated tract disconnection in the left uncinate fasciculus mediated the effects of WMH volume on memory and in the right frontal aslant tract on language. In a subset of ADNI control participants with amyloid data, positive status increased the probability of periventricular WMH and moderated the relationship between WMH burden and tract disconnection in executive function performance.

***Keywords:*** Cognition, Structural connectivity, White matter hyperintensity (WMH), White matter fiber tract

**Abbreviations:**

AD: Alzheimer's Disease
ADAS13: Alzheimer's Disease Assessment Scale-Cognitive 13
ADNI: Alzheimer's Disease Neuroimaging Initiative
AF: Arcuate Fasciculus
ANTs: Advanced Normalization Tools
CDT: Clock Drawing Test
CSF: Cerebrospinal Fluid
CST: Corticospinal Tract
DTI: Diffusion Tensor Imaging
FAT: Frontal Aslant Tract
FDR: False Discovery Rate
FLAIR: Fluid-attenuated Inversion Recovery
HCP: Human Connectome Project
IFOF: Inferior Fronto-occipital Fasciculus
ILF: Inferior Longitudinal Fasciculus
MCI: Mild Cognitive Impairment
MMSE: Mini-Mental Status Examination
MNI: Montreal Neurological Institute
MoCA: Montreal Cognitive Assessment
MRI: Magnetic Resonance Imaging
PET: Positron Emission Tomography
QA: Quantitative Anisotropy
QSDR: Q-space Diffeomorphic Reconstruction
RAVLT: Rey Auditory Verbal Learning Test
ROA: Region of Avoidance
SD: Standard Deviation
SDF: Spin Distribution Function
SLF: Superior Longitudinal Fasciculus
SPSS: Statistical Package for the Social Sciences
SUVR: Standardized Uptake Value Ratio
SVD: Cerebral Small Vessel Disease
TE: Time to Echo
TI: Inversion Time
TMT A: Trial Making Test A
TMT B: Trial Making Test B
TR: Repetition Time
UF: Uncinate Fasciculus
VCF: Verbal Category Fluency
VCID: Vascular Cognitive Impairment and Dementia
VPF: Verbal Phonemic Fluency
WM: White Matter
WMH: White Matter Hyperintensity

## 1. Introduction

White matter hyperintensities (WMH) on T2-weighted fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) are nearly ubiquitous in older adults (Prins and Scheltens, 2015), including asymptomatic individuals (Brant-Zawadzki et al., 1985), and currently provide the most widely accepted biomarker of cerebral small vessel disease (SVD) (Wardlaw et al., 2013). WMH lesions are also linked to clinical progression in mild cognitive impairment (MCI) and Alzheimer's disease (AD) (Coutu et al., 2017; Zhang et al., 2011). While mounting evidence describes the association between global WMH lesion burden and cognitive decline (Prins and Scheltens, 2015; Yoshita et al., 2005), studies also suggest that spatial distribution of WMH and tract-specific lesions may be more predictive of cognitive performance than the overall volume of WMH lesions (Biesbroek et al., 2013; Cremers et al., 2016; Lampe et al., 2019; Langen et al., 2018; Smith et al., 2011).

White matter (WM) infarcts typically cause disconnection syndromes by interrupting WM tracts connecting gray matter structures (Duering et al., 2012; Duering et al., 2015). Brain structural connectivity can be studied noninvasively using MRI diffusion tensor imaging (DTI) and tractography methods (Bullmore and Sporns, 2009) and recent evidence demonstrates that network properties derived from diffusion tractography have significant explanatory power for cognitive performance decrements in older participants (Bergamino et al., 2022; Lombardi et al., 2020). To date, limited data are available regarding the effect of WMH lesions on tract specific connectivity and corresponding cognitive performance. A study on individuals with SVD including both normal and cognitively abnormal participants found that WMH lesion burden in the anterior thalamic radiation and forceps minor are strongly associated with deficits in executive function, visuomotor

speed, and memory performance, independent of global WMH lesion volume (Biesbroek et al., 2016). Another study aimed to investigate the association of WMH burden within three tract categories and memory function concluded that macrostructural damage in the form of WMH in association and projection tracts may contribute to memory decline in older adults (Rizvi et al., 2020).

However, the effects of WMH are challenging to study using diffusion tractography because they are diffuse and often occur in regions of crossing fiber tracts. In addition, WMH lesions can alter WM diffusion parameters and interfere with computerized tract-tracing algorithms, leading to inaccurate estimation of structural connectivity (Muñoz Maniega et al., 2019; Reginold et al., 2016; Reginold et al., 2018; Seiler et al., 2018; Wardlaw et al., 2015). An alternative approach for estimating the effects of WMH on the structural connectome is to use FLAIR-based WMH data as regions of avoidance for indirect fiber tracking in high-quality DTI data acquired from normal participants. This indirect 'virtual lesion connectome' approach alleviates the difficulties related to conducting tractography using participants' diffusion MRI data containing WMH lesions (Li et al., 2021). In this study, we applied the virtual lesion approach to MRI and cognitive performance data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to test the hypothesis that the spatial distribution and extent of WM tract disconnection due to WMH is associated with tract-specific cognitive performance decrements. Cognitively intact participants from the ADNI were included in this study in an effort to minimize the effect of other potential mechanisms (e.g. neurodegeneration) associated with AD or other types of dementia on cognitive function.

A fundamental interaction between vascular disease and AD pathogenesis has been proposed, sometimes referred as the vascular hypotheses of AD (Casado et al., 2008), whereby vascular dysfunction causes neuronal dysfunction through a complex process, including blood brain barrier compromise (Bell and Zlokovic, 2009; Van De Haar et al., 2016), diminished capillary perfusion causing focal ischemic or hypoxic micro-injuries, reduced Aβ clearance, and formation of neurotoxic oligomers (Canobbio et al., 2015; Janota et al., 2016; Kapasi and Schneider, 2016). Consistent with these hypotheses, studies have shown that baseline WMH lesion burden has been associated with both the severity and progression rate of amyloid burden (Gordon et al., 2015; Soldan et al., 2020; Wong et al., 2021). Additionally, a positive interaction between WMH burden and Aβ deposition on the fractional anisotropy of WM tracts has been identified (Bendlin et al., 2012; Chao et al., 2013). In this context, we also examined the effects of amyloid status on the relationship between structural connectivity and cognition to test the hypothesis that amyloid status impacts both the overall and tract-specific association between WMH and cognition in cognitively intact older adults.

## 2. **Materials and methods**

### 2.1. Human participant data

This study used data from two publicly available datasets. The first sample consisted of 481 individual healthy control older adults from the ADNI database (adni.loni.usc.edu). 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 MCI and early AD. For up-to-date information, see

www.adni-info.org. Demographic information, structural MRI data, PET imaging, neuropsychological test scores, and cerebrospinal fluid (CSF) analysis were obtained for these participants. All selected participants scored greater than 24 on the Mini-Mental Status Examination (MMSE). Participants who were cognitively impaired or were diagnosed with MCI, AD, or other types of dementia were excluded from the study. The second dataset included high-resolution DTI data of a cohort of 50 healthy young (27 female, mean (SD) age of 39.2 (1.6) years) participants randomly selected from the publicly available Human Connectome Project-Aging lifespan 2.0 release (Bookheimer et al., 2019). In both studies, participants' data were acquired using protocols approved by the Institutional Review Board of each center.

### 2.2. Neuropsychological assessment of ADNI controls

All ADNI participants underwent comprehensive neuropsychological evaluation based on a standardized battery of tests. In this study, cognitive data collected closest to the time of the MRI data acquisition for each participant were used for analyses. The selected ADNI cognitive data set included the following cognitive domains: Measures of global cognition (Mini-Mental Status Exam; MMSE, and Montreal Cognitive Assessment; MoCA, Alzheimer's Disease Assessment Scale-Cognitive; ADAS13), episodic memory (Rey Auditory Verbal Learning Test immediate recall; RAVLT), language (Verbal Category Fluency test; VCF, Verbal Phonemic Fluency; VPF), visuospatial construction (Clock Drawing Test; CDT), processing speed (Trial Making Test A; TMT A) and executive function (Trail Making Test B; TMT B). The difference between the time taken to complete TMT B and the time taken to complete TMT A, results in a relatively pure measurement of executive function in part B, while reducing the visual search and psychomotor functioning requirements (Vazzana et al., 2010). This provides a better indication of an individual's

executive control abilities (Sánchez-Cubillo et al., 2009). Cognitive data were transformed into z-scores for each domain.

### 2.3. Beta Amyloid status of ADNI controls

We used Aβ-PET or CSF Aβ data to classify ADNI participants into two groups based on cerebral amyloid beta deposition status. For ADNI images PET tracer [$^{18}$F] florbetapir was used to visualize Aβ deposition. PET data were available for 300 participants enrolled in this study. A florbetapir cortical summary measurement (SUVR) cut-off of 1.11 using the whole cerebellum reference region was considered for the beta-amyloid positive group (Landau et al., 2012). For the participants without Aβ-PET, beta-amyloid status was determined by CSF assay of Aβ42 concentration using the Elecsys assay (Roche Diagnostics GmbH). Those below the cut-off of 980 pg/ml were considered beta-amyloid positive (McCollum et al., 2021). Aβ data for 60 participants was not available.

### 2.4. MRI acquisition in the ADNI controls and HCP Lifespan cohort

A standardized MRI protocol for image acquisition was implemented across ADNI sites and validated across platforms (Jack Jr et al., 2008). A 3T MRI scanner was used to acquire FLAIR MRI scans with the following parameters: TR/TE/TI=4800/119/1655 ms, resolution 1.2x1x1 mm, and acquisition matrix=256x256x160 slices.

The diffusion MRI images of the HCP participants were acquired using a Siemens 3T Prisma scanner and the following parameters were used: TR/TE=3230/89.20 ms, resolution 1.5 mm isotropic, 92 slices, and multiband acceleration factor of 4. A total of 185 diffusion-weighting

directions of 2 shells of b=1500 and 3000 s/mm$^2$ in addition to 28 b=0 s/mm$^2$ images were acquired (Harms et al., 2018).

### 2.5. WMH Lesion segmentation of FLAIR MRI images

FLAIR images were skull-stripped using automated brain extraction HD-BET (Isensee et al., 2019). The nnU-Net, a deep learning-based method developed for automatic medical image segmentation, was adopted to segment WMH lesions on FLAIR MRI of ADNI participants for the present study (Isensee et al., 2021). PyTorch 1.5.1 and Nvidia Quadro RTX 5000 GPUs were used to train the models using 100 manually segmented images. WMH lesions were defined as hyperintense lesions in the periventricular and deep WM compared to NAWM on FLAIR MRI and were annotated manually using ITK-SNAP (Yushkevich et al., 2006). We implemented nnU-Net with the default settings for 500 epochs. The model was tested on a total of 100 participants. The Dice coefficient for the five-fold cross-validation was 86.06 ± 1.48%. Then, the model was employed to segment the remaining 381 FLAIR images. These generated binary FLAIR-based WMH masks were manually inspected and revised, if required. All masks co-registered to the T1 images and non-linearly transformed to Montreal Neurological Institute (MNI) space using Advanced Normalization Tools (ANTs) (Avants et al., 2011).

Convert3D software was used to calculate the volume of segmented lesions for each mask (Yushkevich et al., 2006). WMH lesion volume (units of cubic millimeters) was measured as the number of detected voxels multiplied by voxel dimensions. The lesion volume was normalized by the intracranial volume provided in the ADNI dataset to adjust for the difference in brain size (DeCarli et al., 2005). These relative volume measures were log-transformed to normalize

population variance. WMH masks were averaged using FSL (v6.0.6) to create WMH Lesion frequency maps across all or subsets of participants (Jenkinson et al., 2012).

### 2.6. DTI structural connectivity analysis

HCP Diffusion MRI data of young participants were preprocessed using the standard HCP pipelines including eddy current distortion and head motion correction (Glasser et al., 2013). Then the images were reconstructed using q-space diffeomorphic reconstruction (QSDR) with a diffusion sampling length ratio of 1.25 to calculate the spin orientation distribution (SDF), and were aligned to the MNI quantitative anisotropy map using DSI Studio (Yeh and Tseng, 2011). Individual reconstructed images were visually inspected and data with artifacts, co-registration errors, and incorrect tensor calculations were excluded.

To mimic the effect of WMH lesions on brain structural connectivity, WMH lesion masks were used as ROA for indirect fiber tracking in the 50 HCP participants' DTI data. Deterministic streamline tractography was conducted to extract 8 WM bundles using the HCP1065 white matter tractography atlas in right and left brain hemispheres (Yeh et al., 2018). For each WM pathway, $10^6$ seeds were placed within the atlas tract volume, and streamlines were generated using the following tracking parameters: tracking index quantitative anisotropy (QA), angular threshold 0, minimum length 20 mm, maximum length 300 mm, termination of the process after $10^6$ seeds, 0 iterations of topology-informed pruning, and an autotrack tolerance of 16. The Extracted WM pathways included eight tracts that were in proximity to high-frequency WMH lesions and had established relations with distinct cognitive domains (Barbeau et al., 2023; Conner et al., 2018; Dick et al., 2019; Janelle et al., 2022; Voineskos et al., 2012; Von Der Heide et al., 2013): arcuate

fasciculus (AF), corticospinal tract (CST), fornix, frontal aslant tract (FAT), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UF) (Figure 1). Tract disconnection for each WM pathway was defined as the ratio of the number of the affecting streamline in the presence of simulated WMH lesion masks (streamlines passing through the ROA) to the number of streamlines without the presence of any lesion. 50 sets of DTI fiber tracking were carried out for each WMH lesion mask to determine a mean virtual lesion tract disconnection that is not biased by individual biological variations in anatomy or coregistration errors between the FLAIR MRI data and the diffusion MRI data (Figure 2).

### 2.7. Statistical analysis

The statistical analyses were conducted in Statistical Package for the Social Sciences (SPSS v28). Data were presented using mean and standard deviation (SD) for the continuous variable, and frequencies for categorical variables. independent t-test or Wilcoxon rank-sum test for the continuous variable and Chi-square test or Fisher's exact test for categorical variables were used to compare the difference between the two groups.

Logarithmic (log) transformation was performed to achieve a normal distribution for the WMH volume ratio. Z scores of cognitive measures, WMH volume ratio (log-transformed), and tract disconnection were used in all analyses described below. Linear regression models were used to examine the relationship between the global WMH volume or tract disconnection and cognitive functions considering age, sex, and level of education as covariates. The interaction effect of beta-amyloid status on these relationships was investigated by a general linear model. The false

discovery rate (FDR) method was utilized to account for multiple comparisons. Further, we assessed the mediation effect of global WMH lesion burden and tract disconnection on the relationship between age and cognitive performance using PROCESS for SPSS v4.1 framework (Hayes, 2017). To adjust the confidence intervals in the mediation analysis for multiple comparisons, we used the fdrci package in R (version 4.1.2) (Millstein et al., 2022).

Voxel-based analysis was performed using Statistical non-Parametric Mapping (SnPM13.1.09, http://nisox.org/Software/SnPM13/) toolbox for the SPM12 framework to compare the voxel-wise WMH lesion probability between the beta-amyloid positive and negative groups (Holmes et al., 1996; Nichols and Holmes, 2002; Penny et al., 2001). The significance threshold was set at FDR corrected $p<0.05$.

## 3. **Results**

### 3.1. Characteristics of ADNI controls

Table 1 provides the demographic characteristics, neuroimaging, and cognitive variables of the control participants from the ADNI database. There were 481 ADNI participants, 40.3% females, with a mean age of 72.3 ± 6.3 years. Age was significantly correlated to the severity of WMH lesion burden, as expected ($p < 0.001$). Data for beta-amyloid status was available for 421 (87.5%) participants. Age was significantly higher in the beta-amyloid positive group than in the negative group ($P<0.001$). Both groups were of similar sex ratio and education level. In terms of cognitive measures, beta-amyloid positive participants had worse performance on MoCA, ADAS13, TMT A, TMT B, RAVLT, and VCF tests but showed no differences in MMSE, VPF, and clock drawing test scores.

Table 1. Characteristics of the ADNI participants included in this study and comparison of variables across different beta-amyloid status groups.

| | | Amyloid – (N=272) | Amyloid + (N=149) | p-value | Total (N=481) |
|---|---|---|---|---|---|
| Sex (Female%) | | 86 (57.7%) | 63 (42.3%) | 0.543 | 194 (40.3%) |
| Age (Mean±SD) | | 70.0 ± 6.3 | 72.3 ± 6.3 | **<0.001** | 70.7 ± 6.3 |
| Race (%) | White | 241 (88.6%) | 133 (89.3%) | 0.561 | 426 (88.6%) |
| | Black | 15 (5.5%) | 12 (8.1%) | | 31 (6.4) |
| | Asian | 6 (2.2%) | 2 (1.3%) | | 11 (2.3) |
| | American Indian/Alaskan | 2 (0.7%) | 0 (0.0%) | | 2 (0.4%) |
| | More than one | 6 (2.2%) | 2 (1.3%) | | 9 (1.9%) |
| | Unknown | 2 (0.7%) | 0 (0.0%) | | 2 (0.4%) |
| Education year (Mean±SD) | | 16.9 ± 2.3 | 16.6 ± 2.5 | 0.245 | 16.8 ± 2.3 |
| MMSE (Mean±SD) | | 29.1 ± 1.2 | 28.9 ± 1.3 | 0.086 | 29.0 ± 1.2 |
| MoCA (Mean±SD) | | 26.5 ± 2.5 | 25.7 ± 2.8 | **0.002** | 26.2 ± 2.6 |
| ADAS13 (Mean±SD) | | 8.0 ± 4.2 | 9.0 ± 5.0 | **0.040** | 8.3 ± 4.5 |
| Trail A (Mean±SD) | | 30.2 ± 8.5 | 31.7 ± 9.0 | **0.075** | 30.4 ± 8.6 |
| Trail B (Mean±SD) | | 72.8 ± 33.8 | 81.7 ± 42.0 | **0.019** | 75.4 ± 36.4 |
| Trail B – A (Mean±SD) | | 40.2 ± 29.3 | 49.9 ± 39.6 | **0.009** | 43.6 ± 32.8 |
| RAVLT immediate (Mean±SD) | | 47.8 ± 10.8 | 45.5 ± 10.2 | **0.035** | 46.9 ± 10.6 |
| Verbal category fluency (Mean±SD) | | 22.3 ± 5.3 | 20.9 ± 5.4 | **0.008** | 21.8 ± 5.4 |
| Verbal phonemic fluency (Mean±SD) | | 15.1 ± 4.9 | 14.7 ± 4.2 | 0.405 | 14.9 ± 4.6 |
| Clock drawing test (Mean±SD) | | 4.75 ± 0.54 | 4.67 ± 0.59 | 0.152 | 4.74 ± 0.55 |
| WMH Volume (log-transformed) (Mean±SD) | | -2.81 ± 0.60 | -2.58 ± 0.65 | **<0.001** | -2.74 ± 0.62 |



3.2. Quantification and distribution of WMH across different amyloid status

The overall volume of WMH lesion burden was significantly higher in the beta-amyloid positive group compared to the negative group ($p<0.001$). This difference between the two groups remained significant after controlling for age ($p=0.027$). Figure 3 illustrates the lesion frequency maps for 110 age-matched beta-amyloid negative and positive participants along with the voxel-wise

difference map between the two groups (See also Supplementary Figure 1). Using a previously defined periventricular region mask as a region of interest (Dolui et al., 2019), the mean frequency of WMH lesions in the periventricular area was significantly higher in the beta-amyloid positive group compared to the beta-amyloid negative group (26.4 ± 11.3% vs 20.8 ± 12.3%, $p<0.001$).

### 3.3. Associations between overall WMH lesion burden and cognitive performance

Two linear regression models were used to examine the association between normalized WMH volume and cognition. Model 1 included sex and level of education as covariates, and Model 2 added age to Model 1 (Table 2). WMH was significantly associated with global cognitive measures (ADAS13, p=0.025), episodic memory (RAVLT immediate, p=0.016), and executive function and processing speed (TMT B, p=0.019; TMT B minus A, p=0.027), even after controlling for age. We did not find an association between WMH lesion volume and visuospatial construction abilities or language performance in our cohort of cognitively normal older participants. The scatter plots in Figure 4 illustrate the association between WMH lesion burden and various cognitive tests. Additionally, mediation analysis was conducted to investigate the mediating role of WMH lesion burden on age-related cognitive decrement while controlling for sex and level of education. The global volume of WMH lesions significantly mediated the association between age and scores on the ADAS13, TMT B minus A, and RAVLT immediate recall tests (Supplementary Figure 2).

The interaction of amyloid status on WMH lesion related cognitive decline was also assessed for each cognitive task. A significant interaction was seen for the relation between WMH lesion volume and amyloid status for TMT B minus A times (p=0.023) (Figure 5).

Table 2. Linear regression model of the association between WMH volume and cognitive tests before and after adding age to the model.

| | **MOCA** | **ADAS13** | **TMT B-A** | **RAVLT** | **VCF** | **VPF** | **CDT** |
|---|---|---|---|---|---|---|---|
| ***Model 1*** | B (p-value) | | | | | | |
| sex | 1.30 (<0.001) | -2.76 (<0.001) | -0.27 (0.934) | 7.51 (<0.001) | 1.08 (0.038) | 1.24 (0.006) | 0.10 (0.069) |
| Level of education | 0.8 (<0.001) | -0.25 (0.004) | -1.44 (0.035) | 0.89 (<0.001) | 0.53 (<0.001) | 0.27 (0.005) | 0.004 (0.693) |
| WMH Volume | -0.68 (0.001) | 4.31 (<0.001) | 10.89 (<0.001) | -3.32 (<0.001) | -1.32 (0.002) | -0.97 (0.008) | -0.08 (0.054) |
| ***Model 2*** | B (p-value) | | | | | | |
| sex | 1.12 (<0.001) | -2.46 (<0.001) | 2.11 (0.516) | 6.81 (<0.001) | 0.72 (0.163) | 1.15 (0.012) | 0.08 (0.163) |
| Level of education | 0.29 (<0.001) | -0.28 (0.001) | -1.65 (0.015) | 0.93 (<0.001) | 0.56 (<0.001) | 0.29 (0.003) | 0.01 (0.585) |
| Age | -0.08 (<0.001) | 0.14 (<0.001) | 1.05 (<0.001) | -0.30 (<0.001) | -0.16 (<0.001) | -0.05 (0.173) | -0.01 (0.040) |
| WMH Volume | -0.30 (0.173) | 0.82 (0.025) | 6.30 (0.027) | -2.03 (0.016) | -0.63 (0.166) | -0.73 (0.071) | -0.04 (0.368) |

3.4. Association between estimated WMH tract disconnection and cognitive performance

A higher WMH burden was associated with higher disconnection for all examined WM tracts (Supplementary Tables 1). After adjusting for age, sex, and level of education, the relationships between WM tract disconnection and cognitive scores, both before and after adding WMH lesion volume as a covariate are presented in Supplementary Tables 2 and 3. Scatter plots illustrating the Z scores of cognitive tests in relation to tract disconnection Z scores, while controlling for age, sex, and level of education, can be found in Supplementary Figures 3 and 4. Table 3 provides a summary of WM tract-specific disconnections that exhibited significant associations with each cognitive domain.

In addition, the moderation effect of amyloid status on the relationship between tract disconnection and cognitive measures was assessed. Amyloid positivity significantly moderated the correlation of TMT B minus A with right IFOF (p=0.028) and right UF tract disconnection (p=0.005).

Table 3. Tract disconnection predicting each cognitive performance test score using linear regression.

| **Cognitive test** | **WM tract (FDR corrected p-value)** |
|---|---|
| ADAS13 | Right SLF (0.021), right FAT (0.021), left fornix (0.019) |
| TMT B - A | Right ILF (0.041), left ILF (0.021), right IFOF (0.011), left IFOF (0.013), right SLF (0.019), right FAT (0.006), right AF (0.019), left UF (0.025), right CS (0.006), left CS (0.006) |
| RAVLT | Right SLF (0.041), left UF (0.021) |
| VCF | Right FAT (0.025) |

### 3.5. Mediation effect of tract disconnection and WMH lesion burden on the age-related cognitive decrement

Mediation analyses were used in a serial manner to assess the effect of WMH lesion burden and tract disconnection on the age-related cognitive decrement. Sex and level of education were included as covariates in the analysis. In this model, both global WMH lesion burden and tract disconnection were treated as mediator variables within the same model (Figure 6). For every cognitive domain, 16 separate mediation analyses were conducted for each tract disconnection, and the significant outcomes are presented in Table 4. For the relationship between age and TMT B minus A scores, the mediating effects of WMH volume through disconnection in the right IFOF, right FAT, and right SLF tracts were significant. We found that WMH volume via disconnection in the left UF tract mediated the effect of age on the RAVLT immediate test and WMH volume through disconnection in the right FAT mediated the effect of WMH lesion volume on VCF test

scores. After applying FDR correction across various tract disconnections within each cognitive test, the mediation effect of WMH lesion volume through right FAT and right SLF remained significant for the relationship between age and TMT B minus A scores.

Furthermore, another mediation analysis was used to assess the extent to which associations between WMH volume and decrements in specific cognitive domains were mediated by corresponding tract-specific disconnection. In this model age, sex, and level of education were included as covariates. For the relationship between WMH volume and TMT B minus A scores, the mediating effects of right IFOF, right FAT, and right SLF tract disconnection, for the relationship between WMH volume and RVLT immediate the mediating effects of left UF tract disconnection, and for the relationship between WMH volume and VCF scores the mediating effects of right FAT tract disconnection were significant (Supplementary Figure 5).

Table 4. Mediation effect of WMH burden and tract disconnection on age-related cognitive decrement.

| **Cognitive test** | **Tract** | **Total effect** (P value) | **Direct effect** (P value) | **Indirect effect (BootLLCI-BootULCI)** | **Indirect effect (BootLLCI-BootULCI)** | **Indirect effect (BootLLCI-BootULCI)** |
|---|---|---|---|---|---|---|
| | | | | ***Age->WMH->Cognition*** | ***Age->Tract->Cognition*** | ***Age->WMH->Tract->Cognition*** |
| ADAS13 | Left Fornix | **0.0394 (<0.001)** | **0.0300 (<0.001)** | 0.0044 (-0.0021, 0.0117) | 0.0017 (-0.0002, 0.0049) | **0.0033 (0.0004, 0.0068) (p=0.022)** |
| | Right SLF | **0.0383 (<0.001)** | **0.0306 (<0.001)** | -0.0002 (-0.0083, 0.0081) | 0.0000 (-0.0022, 0.0025) | **0.0078 (0.0023, 0.0145) (p=0.004)*** |
| | Right FAT | **0.0381 (<0.001)** | **0.0315 (<0.001)** | 0.0002 (-0.0081, 0.0084) | -0.0010 (-0.0035, 0.0012) | **0.0075 (0.0018, 0.0140) (p=0.008)** |
| TMT B - A | Right IFOF | **0.0413 (<0.001)** | **0.0328 (<0.001)** | -0.0007 (-0.0119, 0.0106) | 0.0011 (-0.0006, 0.0039) | **0.0082 (0.0003, 0.0170) (p=0.025)** |
| | Right SLF | **0.0416 (<0.001)** | **0.0340 (<0.001)** | 0.0005 (-0.0088, 0.0097) | 0.0001 (-0.0019, 0.0025) | **0.0070 (0.0019, 0.0131) (p=0.007)*** |
| | Right FAT | **0.0412 (<0.001)** | **0.0349 (<0.001)** | -0.0026 (-0.0116, 0.0069) | -0.0012 (-0.042, 0.0018) | **0.0101 (0.0035, 0.0175) (p=0.002)*** |
| RAVLT | Left UF | **-0.0385 (<0.001)** | **-0.0286 (<0.001)** | -0.0051 (-0.0121, 0.0018) | -0.0017 (-0.0041, 0.0001) | **-0.0031 (-0.0065, -0.0003) (p=0.024)** |

| | | | | | | |
|---|---|---|---|---|---|---|
| VCF | Right FAT | **-0.0352 (<0.001)** | **-0.0306 (<0.001)** | -0.0005 (-0.096, 0.0084) | 0.0007 (-0.0009, 0.0024) | **-0.0048 (-0.0103, -0.0009) (p=0.031)** |

Statistically significant results are bolded.

*****Significant p value after FDR correction for multiple comparisons.

## 4. Discussion

In this study, we utilized the virtual lesion approach, an indirect method of estimating structural connectivity changes, to examine the relationship between WM tract disconnection caused by WMH and cognitive performance in cognitively intact older individuals from the ADNI dataset. We found a direct effect of WMH lesion burden on cognitive performance, as well as an indirect effect of WMH-induced tract disconnection on specific cognitive domain tests. Additionally, we observed tract-specific associations between WM disconnection and cognitive function, as well as a moderating effect of amyloid status on the relationship between structural connectivity changes and performance in certain cognitive domains, particularly executive function. Taken together, our findings suggest that some of the correlation between WMH lesions and cognitive performance can be attributed to the effect of lesions on WM tracts, and provide new evidence regarding the underlying mechanisms of WMH-related cognitive decline.

### 4.1. Advantages and limitations of the virtual lesion approach

In our prior study using the virtual lesion disconnectome approach, indirect mapping of structural connectivity showed a significantly stronger correlation with the functional connectivity of the older participants compared to the direct mapping of structural connectome using the older participants' own DTI data (Li et al., 2021). This observation supports the assertion that the changes in diffusion properties within the WMH lesion and adjacent area can confound tract-tracing algorithms (Ciccarelli et al., 2008; Muñoz Maniega et al., 2019; Reginold et al., 2016; Reginold et al., 2018).

Most clinical research studies of brain aging, and dementia include FLAIR MRI data that could be leveraged to elucidate brain-behavior relationships between WMH-based disconnection and cognitive performance, including interactions with clinical or demographic factors and comorbid pathologies such as Alzheimer's pathophysiology. Although there is the potential for misregistration errors when applying virtual lesion masks onto normative data from younger individuals, we recently demonstrated, using DTI data from the HCP (Van Essen et al., 2013), that normative DTI data from young and older participants produce comparable disconnectome metrics. However, we concluded that the utilization of young, healthy participants' diffusion MRI data for virtual lesion tractography was preferable over older participants due to their higher streamline counts and the absence of WMH lesions (Taghvaei et al., 2023).

A potential drawback of this method is that lesion masks serve as ROA in DTI tractography, meaning that any streamlines passing through the lesion are considered fully deleted. WMH lesions may partially and heterogeneously impact WM tracts that pass through them. Thus, this model likely results in an overestimation of true structural disconnection. However, most of the impacted WM pathways in our study were not fully disconnected by the lesion (ROA), and modeling partial instead of complete disconnection for streamlines passing through the lesion should only cause a scaling effect, rather than alter the spatial connectivity pattern (Wang et al., 2017). Nevertheless, this partial model fails to account for the non-uniform effects of WMH lesions on WM tracts.

### 4.2.Association of WMH lesion burden, tract disconnection, and cognitive performance

Multiple studies have suggested that WMH lesions as a marker of small vessel disease related to cognitive decline. In line with them, we found WMH lesions are particularly associated with performance decrements in processing speed, executive function, and episodic memory (Banerjee et al., 2018; Dong et al., 2015; Kloppenborg et al., 2014; Lampe et al., 2019; Staals et al., 2015; Sun et al., 2014; Van Den Berg et al., 2018; Zeng et al., 2020). We did not find an association between WMH lesions volume and verbal fluency or visuospatial construction in our cohort, which is consistent with the findings of a previous study (Kim et al., 2022). These findings might be due to the low variance of visuospatial construction and verbal fluency tests scores in our cohort of cognitively intact participants or the tests' insufficient sensitivity to detect differences in these cognitive domains.

The correlation between WMH lesions' location and specific cognitive performance was previously investigated in cognitively normal and impaired participants (Biesbroek et al., 2013; Lampe et al., 2019; Smith et al., 2011). Those studies found that WMH lesion burden in the frontal lobe was associated with a decline in executive function, while parieto-temporal lesion burden was associated with poor episodic memory performance (Biesbroek et al., 2013; Lampe et al., 2019; Zeng et al., 2020). More recent studies have demonstrated that connectivity and microstructural integrity of specific tract depends on the burden of WMH lesion within the tract (Hilal et al., 2021; Seiler et al., 2018; Vernooij et al., 2009). Together, these findings emphasize the importance of the spatial distribution of WMH regarding their effects on cognitive performance and suggest that the relationship between regional WMH lesions and different cognitive domains may be tract specific. Our current study confirms and extends these observations.

We found a significant correlation between disconnection in different tracts and performance on specific cognitive tests (Table 2). In general, right-side association tracts had a relation with processing speed and executive function, and left-side tracts were associated with language, verbal working, and episodic memory, with the exception of the right FAT. After correction for multiple comparisons, the correlation between left-side association tracts and language did not survive. While verbal working memory did not show a correlation with global WMH burden, right FAT tract disconnection was related to alterations in this domain (Supplementary Table 2). This tract-specific effect suggests that the specific spatial distribution of WMH lesion is more predictive of language performance decrement than global WMH lesion burden.

In the domain of executive function, disconnections in the right ILF and right IFOF were the strongest predictors of TMT A and TMT B functions. ILF supports visuomotor dexterity and fast visual processing (Voineskos et al., 2012), and IFOF supports goal-oriented behavior, visual switching tasks, and semantic language processing (Conner et al., 2018). The performance on TMT A is primarily influenced by visual processing speed. Conversely, TMT B is a more complex task, which involves alternating between numbers and letters in ascending order, necessitating the integration of additional cognitive abilities, including cognitive flexibility and visual switching ability. Right IFOF, right SLF, and right FAT disconnections all significantly mediated the global WMH lesion burden effect on TMT B minus A, which more specifically measures executive function. Our findings suggest that executive function decrements are linked to disconnections in multiple tracts rather than to a specific WM pathway, which is in line with previous studies (Haász et al., 2013; Kuznetsova et al., 2016). Timed task function and processing speed depend on the coordination of multiple brain regions and WMH lesions potentially can interfere with WM

association fibers, causing a slowdown in neural transmissions (Kandiah et al., 2009; Vannorsdall et al., 2009). The roles of Right SLF and FAT on executive performance were previously described (Dick et al., 2019; Janelle et al., 2022).

In the language domain, prior to adjustments for multiple comparisons, we observed significant relationships between the VPF performance and left ILF and left IFOF. The involvement of these tracts in the processing of semantic language has been established (Conner et al., 2018; Mandonnet et al., 2007; Sierpowska et al., 2019). Of note, right FAT disconnection mediated the effect of WMH lesion on the verbal working memory test. While in general, left FAT supports speech production and verbal fluency, and right FAT supports executive function in right-handed individuals (Dick et al., 2019), there is some evidence suggesting the involvement of the right FAT in language function. One study found a relationship between speech fluency and the fractional anisotropy of the right FAT in children with autism (Chenausky et al., 2017), and impairments in white matter integrity of the right FAT have been observed in adults with stuttering (Neef et al., 2018). Furthermore, the right FAT has been implicated in recovery from speech deficits associated with left FAT lesions (Berthier et al., 2017; Young et al., 2020).

With regard to memory, left UF disconnection showed the strongest relationship with episodic memory (RAVLT immediate) and mediated the WMH-related memory decline. The UF supports associative and episodic memory functions (Von Der Heide et al., 2013) and changes in UF microstructure were found to predict cognitive performance in the memory (Metzler-Baddeley et al., 2011; Tariq et al., 2020). The ADAS13 cognitive test assesses multiple cognitive domains including memory, language, praxis, and orientation (Skinner et al., 2012). We found that the

effect of WMH lesions burden on ADAS13 was mediated by the left fornix, right SLF, and right FAT disconnection. Fornix is well known to support episodic memory (Douet and Chang, 2015) and SLF plays a major role in language, memory, and visuospatial functioning (Janelle et al., 2022).

However, the mechanisms underlying the relationship between WMHs and cognitive decline remain to be fully elucidated. One proposed theory is that WMH lesions may promote neurodegeneration, resulting in a decline in cognitive function. Rizvi et al. found evidence to support this theory through their examination of cortical thinning as a mediator of the relationship between WMHs and cognition. They also demonstrated that medial temporal lobe atrophy volume mediates the relationship between WMH volume and memory functioning (Rizvi et al., 2018). Other research has shown that WMH-associated tract-specific injury is related to specific lobar gray matter atrophy, with the integrity of the associated WM tracts and gray matter volumes having a differential impact on episodic memory and processing speed (Seiler et al., 2018).

By demonstrating that specific tract disconnection mediated the effect of global WMH lesions on associated cognitive domains even in cognitively intact participants where the extent of cognitive decrements was small, our study provides additional support for the "disconnection hypothesis" that WMH lesions have a tract-specific effect on distinct cognitive domains. An alteration to a specific tract may result in the deterioration of a specific functional domain related to the regions that were connected by the tract. To ensure the robustness of our methodology we conducted mediation analysis across various cognitive domains for all tracts and did not find any unanticipated associations between tract disconnection and cognitive performance, such as the relation between the corticospinal tract disconnection and memory function. In future studies, it

could be beneficial to use resting-state functional MRI (fMRI) to assess how region-specific cortico-cortical connectivity changes are influenced by subcortical structural connectivity changes. In addition, future work assessing connectivity changes due to WMH in data from participants with vascular cognitive impairment might be expected to yield even stronger correlations.

Studies by Boes et al. (Boes et al., 2015), Griffis et al. (Griffis et al., 2019), and Thiebaut de Schotten et al. (Thiebaut de Schotten et al., 2020) used resting-state functional MRI to examine connectivity changes due to focal infarcts. While this differs considerably from our focus on age associated diffuse WMH, some comparisons can still be made. Because functional connectivity considers connections between gray matter parcels, it captures second-order connections that may be important for functional recovery and are not assessed in our approach. However, Griffis et al. demonstrated that subcortical disconnections significantly mediated functional connectivity changes, which supports the validity of examining direct structural connectivity changes (Griffis et al., 2019). In our prior study using indirect tractography, we found a significant correlation between functional and structural connectivity due to diffuse WMH (Li et al., 2021). In contrast with the atlas-based approach used by Griffis et al., in the current study, we used 50 sets of individual diffusion MRI to capture individual variability in the structural connectome. Thiebaut de Shotten et al. developed statistical WM function maps for each cognitive task based on functional connectivity changes in a large dataset of patients with stroke lesions (Thiebaut de Schotten et al., 2020). Although they did not assess the function of each white matter tract separately, they provided statistical probability maps of the WM function for each cognitive task that are in agreement with our findings. As in our study, deficits in verbal fluency, verbal working

memory, and executive function were associated with a white matter region compatible with the FAT while visuomotor function was associated with the SLF region.

Future research on the significance of SVD in dementia should encompass not only the total volume of WMH, but also consider their spatial distribution and the tract-wise effects of WMH. In this study we focused on connectivity changes in tracts intersecting with high-frequency WMH, but lower frequency WMH may also cause tract disconnection and connectivity may also be affected by microstructural changes in WM that occur prior to the manifestation of WMH on FLAIR MRI (Muñoz Maniega et al., 2019). Abnormalities in WM are believed to be among the initial changes in AD in its pre-dementia stages (Gunning-Dixon et al., 2009; Nasrabady et al., 2018). Hence, our findings may also provide insight into the early processes of cognitive decline associated with AD.

### 4.3. Amyloid effect

The primary pathologies of AD include Aβ plaques and neurofibrillary tangles that accumulate years before the onset of dementia (Thal et al., 2014). VCID and Alzheimer's disease (AD) have traditionally been conceptualized as having different mechanisms, but there is mounting evidence of overlap between these categories (Iadecola, 2010; Sahathevan et al., 2012). Both VCI and AD share common risk factors such as hypertension, hyperlipidemia, and ApoE genotype, and there are well-documented mechanistic interactions between VCID and AD (Helzner et al., 2009; Petrovitch et al., 2005). WMH lesions have been found to be more strongly linked with cerebral Aβ accumulation than any other established biomarker or cognitive examination (Kandel et al., 2016). In this study, we observed that the frequency of periventricular WMH lesions was higher

in Aβ positive participants and Aβ positive status significantly moderated the relationship of WMH lesion burden and tract disconnection with executive function performance. These findings provide further evidence for the synergistic effect of WMH lesions and Aβ deposition on the decrement of cognitive performance (Vemuri et al., 2015). A previous study on cognitively healthy populations also reported a significant relationship between Aβ with memory and executive function (Harrington et al., 2013; Hedden et al., 2013; Insel et al., 2020). A recent study on cognitively unimpaired adults showed that Aβ accumulation independently of tau pathology and cortical thickness was associated with worse performance on the executive tests, but not memory function (Tideman et al., 2022). They suggested that the underlying cause of the effect of Aβ on executive function could be due to either a direct regional effect of Aβ accumulation on functional networks such as the central executive network, or a disruption of the cholinergic neurotransmission system (Lim et al., 2015; Tideman et al., 2022). Our findings provide indirect support for the first of these potential mechanisms.

### 4.4.Limitation

There are additional limitations in our study that must be acknowledged, beyond the limitation of modeling virtual WMH lesions as causing complete disconnection mentioned previously. First, neuropsychological tests are not completely specific for each cognitive domain and some of our cognitive function tests employed in this study, particularly the clock drawing test, may not be sensitive enough to detect subtle variability in cognitively intact participants. Second, the findings derived from the ADNI database may not be generalized to the broader population, as the participants are typically healthy, predominantly white, and well-educated, which might not represent the full diversity of individuals found in the general population (Gianattasio et al., 2021).

Finally, the design of the current study, being cross-sectional, cannot establish causal relationships of the observed associations, though it stands to reason that WMH lesions are probably not caused by decrements in cognitive performance. To better understand these issues, further larger studies with longitudinal data are required to confirm our findings and establish the causal relationships between WMH-induced WM structural disconnections and corresponding cognitive function.

## 5. Conclusion

Using a virtual lesion approach to estimate disconnections in major white matter tracts due to white matter hyperintensities, we demonstrated that tract-specific disconnections mediate cognitive domain-specific decrements in cognitive performance in cognitively intact older adults. Amyloid status further moderated the effects of WMH lesions or tract disconnection on executive function.



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**References:**


Avants, B.B., Tustison, N.J., Song, G., Cook, P.A., Klein, A., Gee, J.C., 2011. A reproducible evaluation of ANTs similarity metric performance in brain image registration. Neuroimage 54(3), 2033-2044. DOI:10.1016/j.neuroimage.2010.09.025

Banerjee, G., Jang, H., Kim, H.J., Kim, S.T., Kim, J.S., Lee, J.H., Im, K., Kwon, H., Lee, J.M., Na, D.L., 2018. Total MRI small vessel disease burden correlates with cognitive performance, cortical atrophy, and network measures in a memory clinic population. Journal of Alzheimer's Disease 63(4), 1485-1497. DOI: 10.3233/JAD-170943

Barbeau, E.B., Kousaie, S., Brass, K., Descoteaux, M., Petrides, M., Klein, D., 2023. The importance of the dorsal branch of the arcuate fasciculus in phonological working memory. Cerebral Cortex, bhad226. DOI: 10.1093/cercor/bhad226

Bell, R.D., Zlokovic, B.V., 2009. Neurovascular mechanisms and blood–brain barrier disorder in Alzheimer's disease. Acta neuropathologica 118, 103-113. DOI: 10.1007/s00401-009-0522-3

Bendlin, B.B., Carlsson, C.M., Johnson, S.C., Zetterberg, H., Blennow, K., Willette, A.A., Okonkwo, O.C., Sodhi, A., Ries, M.L., Birdsill, A.C., 2012. CSF T-Tau/Aβ42 predicts white matter microstructure in healthy adults at risk for Alzheimer's disease. PloS one 7(6), e37720. DOI: 10.1371/journal.pone.0037720

Bergamino, M., Schiavi, S., Daducci, A., Walsh, R.R., Stokes, A.M., 2022. Analysis of Brain Structural Connectivity Networks and White Matter Integrity in Patients With Mild Cognitive Impairment. Frontiers in Aging Neuroscience 14, 23. DOI: 10.3389/fnagi.2022.793991

Berthier, M.L., De-Torres, I., Paredes-Pacheco, J., Roé-Vellvé, N., Thurnhofer-Hemsi, K., Torres-Prioris, M.J., Alfaro, F., Moreno-Torres, I., López-Barroso, D., Dávila, G., 2017. Cholinergic potentiation and audiovisual repetition-imitation therapy improve speech production and communication deficits in a person with crossed aphasia by inducing structural plasticity in white matter tracts. Frontiers in Human Neuroscience 11, 304. DOI: 10.3389/fnhum.2017.00304

Biesbroek, J.M., Kuijf, H.J., van der Graaf, Y., Vincken, K.L., Postma, A., Mali, W.P., Biessels, G.J., Geerlings, M.I., Group, S.S., 2013. Association between subcortical vascular lesion location and cognition: a voxel-based and tract-based lesion-symptom mapping study. The SMART-MR study. PloS one 8(4), e60541. DOI: 10.1371/journal.pone.0060541

Biesbroek, J.M., Weaver, N.A., Hilal, S., Kuijf, H.J., Ikram, M.K., Xu, X., Tan, B.Y., Venketasubramanian, N., Postma, A., Biessels, G.J., 2016. Impact of strategically located white matter hyperintensities on cognition in memory clinic patients with small vessel disease. PloS one 11(11), e0166261. DOI: 10.1371/journal.pone.0166261

Boes, A.D., Prasad, S., Liu, H., Liu, Q., Pascual-Leone, A., Caviness Jr, V.S., Fox, M.D., 2015. Network localization of neurological symptoms from focal brain lesions. Brain 138(10), 3061-3075. DOI: 10.1093/brain/awv228

Bookheimer, S.Y., Salat, D.H., Terpstra, M., Ances, B.M., Barch, D.M., Buckner, R.L., Burgess, G.C., Curtiss, S.W., Diaz-Santos, M., Elam, J.S., 2019. The lifespan human connectome project in aging: an overview. Neuroimage 185, 335-348. DOI: 10.1016/j.neuroimage.2018.10.009

Brant-Zawadzki, M., Fein, G., Van Dyke, C., Kiernan, R., Davenport, L., de Groot, J., 1985. MR imaging of the aging brain: patchy white-matter lesions and dementia. American Journal of Neuroradiology 6(5), 675-682.

Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nature reviews neuroscience 10(3), 186-198. DOI: 10.1038/nrn2575

Canobbio, I., Abubaker, A.A., Visconte, C., Torti, M., Pula, G., 2015. Role of amyloid peptides in vascular dysfunction and platelet dysregulation in Alzheimer's disease. Frontiers in cellular neuroscience 9, 65. DOI: 10.3389/fncel.2015.00065

Casado, A., Encarnación López-Fernández, M., Concepción Casado, M., de La Torre, R., 2008. Lipid peroxidation and antioxidant enzyme activities in vascular and Alzheimer dementias. Neurochemical Research 33, 450-458. DOI: 10.1007/s11064-007-9453-3

Chao, L.L., DeCarli, C., Kriger, S., Truran, D., Zhang, Y., Laxamana, J., Villeneuve, S., Jagust, W.J., Sanossian, N., Mack, W.J., 2013. Associations between white matter hyperintensities and β amyloid on integrity of projection, association, and limbic fiber tracts measured with diffusion tensor MRI. PloS one 8(6), e65175. DOI: 10.1371/journal.pone.0065175

Chenausky, K., Kernbach, J., Norton, A., Schlaug, G., 2017. White matter integrity and treatment-based change in speech performance in minimally verbal children with autism spectrum disorder. Frontiers in Human Neuroscience 11, 175. DOI: 10.3389/fnhum.2017.00175

Ciccarelli, O., Catani, M., Johansen-Berg, H., Clark, C., Thompson, A., 2008. Diffusion-based tractography in neurological disorders: concepts, applications, and future developments. The Lancet Neurology 7(8), 715-727. DOI: 10.1016/S1474-4422(08)70163-7

Conner, A.K., Briggs, R.G., Sali, G., Rahimi, M., Baker, C.M., Burks, J.D., Glenn, C.A., Battiste, J.D., Sughrue, M.E., 2018. A connectomic atlas of the human cerebrum—chapter 13: tractographic description of the inferior fronto-occipital fasciculus. Operative Neurosurgery 15(Suppl 1), S436. DOI: 10.1093/ons/opy267

Coutu, J.-P., Lindemer, E.R., Konukoglu, E., Salat, D.H., Initiative, A.s.D.N., 2017. Two distinct classes of degenerative change are independently linked to clinical progression in mild cognitive impairment. Neurobiology of Aging 54, 1-9. DOI: 10.1016/j.neurobiolaging.2017.02.005

Cremers, L.G., de Groot, M., Hofman, A., Krestin, G.P., van der Lugt, A., Niessen, W.J., Vernooij, M.W., Ikram, M.A., 2016. Altered tract-specific white matter microstructure is related to poorer cognitive performance: The Rotterdam Study. Neurobiology of aging 39, 108-117. DOI: 10.1016/j.neurobiolaging.2015.11.021

DeCarli, C., Fletcher, E., Ramey, V., Harvey, D., Jagust, W.J., 2005. Anatomical mapping of white matter hyperintensities (wmh) exploring the relationships between periventricular WMH, deep WMH, and total WMH burden. Stroke 36(1), 50-55. DOI: 10.1161/01.STR.0000150668.58689.f2

Dick, A.S., Garic, D., Graziano, P., Tremblay, P., 2019. The frontal aslant tract (FAT) and its role in speech, language and executive function. Cortex 111, 148-163. DOI: 10.1016/j.cortex.2018.10.015

Dolui, S., Tisdall, D., Vidorreta, M., Jacobs Jr, D.R., Nasrallah, I.M., Bryan, R.N., Wolk, D.A., Detre, J.A., 2019. Characterizing a perfusion-based periventricular small vessel region of interest. NeuroImage: Clinical 23, 101897. DOI: 10.1016/j.nicl.2019.10189

Dong, C., Nabizadeh, N., Caunca, M., Cheung, Y.K., Rundek, T., Elkind, M.S., DeCarli, C., Sacco, R.L., Stern, Y., Wright, C.B., 2015. Cognitive correlates of white matter lesion load and brain atrophy: the Northern Manhattan Study. Neurology 85(5), 441-449. DOI: 10.1212/WNL.0000000000001716

Douet, V., Chang, L., 2015. Fornix as an imaging marker for episodic memory deficits in healthy aging and in various neurological disorders. Frontiers in aging neuroscience 6, 343. DOI: 10.3389/fnagi.2014.00343

Duering, M., Righart, R., Csanadi, E., Jouvent, E., Hervé, D., Chabriat, H., Dichgans, M., 2012. Incident subcortical infarcts induce focal thinning in connected cortical regions. Neurology 79(20), 2025-2028. DOI: 10.1212/WNL.0b013e3182749f39

Duering, M., Righart, R., Wollenweber, F.A., Zietemann, V., Gesierich, B., Dichgans, M., 2015. Acute infarcts cause focal thinning in remote cortex via degeneration of connecting fiber tracts. Neurology 84(16), 1685-1692. DOI: 10.1212/WNL.0000000000001502

Gianattasio, K.Z., Bennett, E.E., Wei, J., Mehrotra, M.L., Mosley, T., Gottesman, R.F., Wong, D.F., Stuart, E.A., Griswold, M.E., Couper, D., 2021. Generalizability of findings from a clinical sample to a community‐based sample: a comparison of ADNI and ARIC. Alzheimer's & Dementia 17(8), 1265-1276. DOI: 10.1002/alz.12293

Glasser, M.F., Sotiropoulos, S.N., Wilson, J.A., Coalson, T.S., Fischl, B., Andersson, J.L., Xu, J., Jbabdi, S., Webster, M., Polimeni, J.R., 2013. The minimal preprocessing pipelines for the Human Connectome Project. Neuroimage 80, 105-124. DOI: 10.1016/j.neuroimage.2013.04.127

Gordon, B.A., Najmi, S., Hsu, P., Roe, C.M., Morris, J.C., Benzinger, T.L., 2015. The effects of white matter hyperintensities and amyloid deposition on Alzheimer dementia. NeuroImage: Clinical 8, 246-252. DOI: 10.1016/j.nicl.2015.04.017

Griffis, J.C., Metcalf, N.V., Corbetta, M., Shulman, G.L., 2019. Structural disconnections explain brain network dysfunction after stroke. Cell reports 28(10), 2527-2540. e2529. DOI: 10.1016/j.celrep.2019.07.100

Gunning-Dixon, F.M., Brickman, A.M., Cheng, J.C., Alexopoulos, G.S., 2009. Aging of cerebral white matter: a review of MRI findings. International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences 24(2), 109-117. DOI: 10.1002/gps.2087

Haász, J., Westlye, E.T., Fjær, S., Espeseth, T., Lundervold, A., Lundervold, A.J., 2013. General fluid-type intelligence is related to indices of white matter structure in middle-aged and old adults. Neuroimage 83, 372-383. DOI: 10.1016/j.neuroimage.2013.06.040

Harms, M.P., Somerville, L.H., Ances, B.M., Andersson, J., Barch, D.M., Bastiani, M., Bookheimer, S.Y., Brown, T.B., Buckner, R.L., Burgess, G.C., 2018. Extending the Human Connectome Project across ages: Imaging protocols for the Lifespan Development and Aging projects. Neuroimage 183, 972-984. DOI: 10.1016/j.neuroimage.2018.09.060

Harrington, M.G., Chiang, J., Pogoda, J.M., Gomez, M., Thomas, K., Marion, S.D., Miller, K.J., Siddarth, P., Yi, X., Zhou, F., 2013. Executive function changes before memory in preclinical Alzheimer's pathology: a prospective, cross-sectional, case control study. PloS one 8(11), e79378. DOI: 10.1371/journal.pone.0079378

Hayes, A.F., 2017. Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. Guilford publications.

Hedden, T., Oh, H., Younger, A.P., Patel, T.A., 2013. Meta-analysis of amyloid-cognition relations in cognitively normal older adults. Neurology 80(14), 1341-1348. DOI: 10.1212/WNL.0b013e31828ab35d

Helzner, E.P., Luchsinger, J.A., Scarmeas, N., Cosentino, S., Brickman, A.M., Glymour, M.M., Stern, Y., 2009. Contribution of vascular risk factors to the progression in Alzheimer disease. Archives of neurology 66(3), 343-348. DOI: 10.1001/archneur.66.3.343

Hilal, S., Liu, S., Wong, T.Y., Vrooman, H., Cheng, C.-Y., Venketasubramanian, N., Chen, C.L., Zhou, J.H., 2021. White matter network damage mediates association between cerebrovascular disease and cognition. Journal of Cerebral Blood Flow & Metabolism 41(8), 1858-1872. DOI: 10.1177/0271678X21990980

Holmes, A.P., Blair, R., Watson, J., Ford, I., 1996. Nonparametric analysis of statistic images from functional mapping experiments. Journal of Cerebral Blood Flow & Metabolism 16(1), 7-22. DOI: 10.1097/00004647-199601000-00002

Iadecola, C., 2010. The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. Acta neuropathologica 120, 287-296. DOI: 10.1007/s00401-010-0718-6

Insel, P.S., Donohue, M.C., Sperling, R., Hansson, O., Mattsson-Carlgren, N., 2020. The A4 study: β-amyloid and cognition in 4432 cognitively unimpaired adults. Annals of Clinical and Translational Neurology 7(5), 776-785. DOI: 10.1002/acn3.51048

Isensee, F., Jaeger, P.F., Kohl, S.A., Petersen, J., Maier-Hein, K.H., 2021. nnU-Net: a self-configuring method for deep learning-based biomedical image segmentation. Nature methods 18(2), 203-211. DOI: 10.1038/s41592-020-01008-z

Isensee, F., Schell, M., Pflueger, I., Brugnara, G., Bonekamp, D., Neuberger, U., Wick, A., Schlemmer, H.P., Heiland, S., Wick, W., 2019. Automated brain extraction of multisequence MRI using artificial neural networks. Human brain mapping 40(17), 4952-4964. DOI: 10.1002/hbm.24750

Jack Jr, C.R., Bernstein, M.A., Fox, N.C., Thompson, P., Alexander, G., Harvey, D., Borowski, B., Britson, P.J., L. Whitwell, J., Ward, C., 2008. The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine 27(4), 685-691. DOI: 10.1002/jmri.21049

Janelle, F., Iorio-Morin, C., D'amour, S., Fortin, D., 2022. Superior longitudinal fasciculus: a review of the anatomical descriptions with functional correlates. Frontiers in Neurology 13. DOI: 10.3389/fneur.2022.794618

Janota, C., Lemere, C.A., Brito, M.A., 2016. Dissecting the contribution of vascular alterations and aging to Alzheimer's disease. Molecular neurobiology 53, 3793-3811. DOI: 10.1007/s12035-015-9319-7

Jenkinson, M., Beckmann, C.F., Behrens, T.E., Woolrich, M.W., Smith, S.M., 2012. Fsl. Neuroimage 62(2), 782-790. DOI: 10.1016/j.neuroimage.2011.09.015

Kandel, B.M., Avants, B.B., Gee, J.C., McMillan, C.T., Erus, G., Doshi, J., Davatzikos, C., Wolk, D.A., Initiative, A.s.D.N., 2016. White matter hyperintensities are more highly associated with preclinical Alzheimer's disease than imaging and cognitive markers of neurodegeneration. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 4, 18-27. DOI: 10.1016/j.dadm.2016.03.001

Kandiah, N., Narasimhalu, K., Lee, J., Chen, C., 2009. Differences exist in the cognitive profile of mild Alzheimer's disease and subcortical ischemic vascular dementia. Dementia and geriatric cognitive disorders 27(5), 399-403. DOI: 10.1159/000210387

Kapasi, A., Schneider, J., 2016. Vascular contributions to cognitive impairment, clinical Alzheimer's disease, and dementia in older persons. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 1862(5), 878-886. DOI: 10.1016/j.bbadis.2015.12.023

Kim, T., Aizenstein, H.J., Snitz, B.E., Cheng, Y., Chang, Y.-F., Roush, R.E., Huppert, T.J., Cohen, A., Doman, J., Becker, J.T., 2022. Tract specific white matter lesion load affects white matter microstructure and their relationships with functional connectivity and cognitive decline. Frontiers in Aging Neuroscience 13, 1008. DOI: 10.3389/fnagi.2021.760663

Kloppenborg, R.P., Nederkoorn, P.J., Geerlings, M.I., van den Berg, E., 2014. Presence and progression of white matter hyperintensities and cognition: a meta-analysis. Neurology 82(23), 2127-2138. DOI: 10.1212/WNL.0000000000000505

Kuznetsova, K.A., Maniega, S.M., Ritchie, S.J., Cox, S.R., Storkey, A.J., Starr, J.M., Wardlaw, J.M., Deary, I.J., Bastin, M.E., 2016. Brain white matter structure and information processing speed in healthy older age. Brain Structure and Function 221, 3223-3235. DOI: 10.1007/s00429-015-1097-5

Lampe, L., Kharabian-Masouleh, S., Kynast, J., Arelin, K., Steele, C.J., Löffler, M., Witte, A.V., Schroeter, M.L., Villringer, A., Bazin, P.-L., 2019. Lesion location matters: the relationships between white matter hyperintensities on cognition in the healthy elderly. Journal of Cerebral Blood Flow & Metabolism 39(1), 36-43. DOI: 10.1177/0271678X17740

Landau, S.M., Mintun, M.A., Joshi, A.D., Koeppe, R.A., Petersen, R.C., Aisen, P.S., Weiner, M.W., Jagust, W.J., Initiative, A.s.D.N., 2012. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. Annals of neurology 72(4), 578-586. DOI: 10.1002/ana.23650

Langen, C.D., Cremers, L.G., de Groot, M., White, T., Ikram, M.A., Niessen, W.J., Vernooij, M.W., 2018. Disconnection due to white matter hyperintensities is associated with lower cognitive scores. NeuroImage 183, 745-756. DOI: 10.1016/j.neuroimage.2018.08.037

Li, Z., Dolui, S., Habes, M., Bassett, D.S., Wolk, D., Detre, J.A., 2021. Predicted disconnectome associated with progressive periventricular white matter ischemia. Cerebral Circulation-Cognition and Behavior 2, 100022. DOI: 10.1016/j.cccb.2021.100022

Lim, Y.Y., Maruff, P., Schindler, R., Ott, B.R., Salloway, S., Yoo, D.C., Noto, R.B., Santos, C.Y., Snyder, P.J., 2015. Disruption of cholinergic neurotransmission exacerbates Aβ-related cognitive impairment in preclinical Alzheimer's disease. Neurobiology of aging 36(10), 2709-2715. DOI: 10.1016/j.neurobiolaging.2015.07.009

Lombardi, A., Amoroso, N., Diacono, D., Monaco, A., Logroscino, G., De Blasi, R., Bellotti, R., Tangaro, S., 2020. Association between structural connectivity and generalized cognitive spectrum in Alzheimer's disease. Brain sciences 10(11), 879. DOI: 10.3390/brainsci10110879

Mandonnet, E., Nouet, A., Gatignol, P., Capelle, L., Duffau, H., 2007. Does the left inferior longitudinal fasciculus play a role in language? A brain stimulation study. Brain 130(3), 623-629. DOI: 10.1093/brain/awl361

McCollum, L.E., Das, S.R., Xie, L., de Flores, R., Wang, J., Xie, S.X., Wisse, L.E., Yushkevich, P.A., Wolk, D.A., Initiative, A.s.D.N., 2021. Oh brother, where art tau? Amyloid, neurodegeneration, and cognitive decline without elevated tau. NeuroImage: Clinical 31, 102717. OI: 10.1016/j.nicl.2021.102717

Metzler-Baddeley, C., Jones, D.K., Belaroussi, B., Aggleton, J.P., O'Sullivan, M.J., 2011. Frontotemporal connections in episodic memory and aging: a diffusion MRI tractography study. Journal of Neuroscience 31(37), 13236-13245. DOI: 10.1523/JNEUROSCI.2317-11.2011

Millstein, J., Battaglin, F., Arai, H., Zhang, W., Jayachandran, P., Soni, S., Parikh, A.R., Mancao, C., Lenz, H.-J., 2022. fdrci: FDR confidence interval selection and adjustment for large-scale hypothesis testing. Bioinformatics Advances 2(1), vbac047. DOI: 10.1093/bioadv/vbac047

Muñoz Maniega, S., Meijboom, R., Chappell, F.M., Valdés Hernández, M.d.C., Starr, J.M., Bastin, M.E., Deary, I.J., Wardlaw, J.M., 2019. Spatial gradient of microstructural changes in normal-appearing white matter in tracts affected by white matter hyperintensities in older age. Frontiers in neurology, 784. DOI: 10.3389/fneur.2019.00784

Nasrabady, S.E., Rizvi, B., Goldman, J.E., Brickman, A.M., 2018. White matter changes in Alzheimer's disease: a focus on myelin and oligodendrocytes. Acta neuropathologica communications 6(1), 1-10. DOI: 10.1186/s40478-018-0515-3

Neef, N.E., Anwander, A., Bütfering, C., Schmidt-Samoa, C., Friederici, A.D., Paulus, W., Sommer, M., 2018. Structural connectivity of right frontal hyperactive areas scales with stuttering severity. Brain 141(1), 191-204. DOI: 10.1093/brain/awx316

Nichols, T.E., Holmes, A.P., 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Human brain mapping 15(1), 1-25. DOI: 10.1002/hbm.1058

Penny, W., Ashburner, J., Kiebel, S., Henson, R., Glaser, D., Phillips, C., Friston, K., 2001. Statistical parametric mapping: An annotated bibliography. Wellcome Department of Imaging Neuroscience. London: University College London.

Petrovitch, H., Ross, G.W., Steinhorn, S.C., Abbott, R.D., Markesbery, W., Davis, D., Nelson, J., Hardman, J., Masaki, K., Vogt, M.R., 2005. AD lesions and infarcts in demented and non-demented Japanese-American men. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society 57(1), 98-103. DOI: 10.1002/ana.20318

Prins, N.D., Scheltens, P., 2015. White matter hyperintensities, cognitive impairment and dementia: an update. Nature Reviews Neurology 11(3), 157-165. DOI: 10.1038/nrneurol.2015.10

Reginold, W., Itorralba, J., Luedke, A., Fernandez-Ruiz, J., Reginold, J., Islam, O., Garcia, A., 2016. Tractography at 3T MRI of corpus callosum tracts crossing white matter hyperintensities. American Journal of Neuroradiology 37(9), 1617-1622. DOI: 10.3174/ajnr.A4788

Reginold, W., Sam, K., Poublanc, J., Fisher, J., Crawley, A., Mikulis, D.J., 2018. Impact of white matter hyperintensities on surrounding white matter tracts. Neuroradiology 60(9), 933-944. DOI: 10.1007/s00234-018-2053-x

Rizvi, B., Lao, P.J., Colón, J., Hale, C., Igwe, K.C., Narkhede, A., Budge, M., Manly, J.J., Schupf, N., Brickman, A.M., 2020. Tract-defined regional white matter hyperintensities and memory. NeuroImage: Clinical 25, 102143. DOI: 10.1016/j.nicl.2019.102143

Rizvi, B., Narkhede, A., Last, B.S., Budge, M., Tosto, G., Manly, J.J., Schupf, N., Mayeux, R., Brickman, A.M., 2018. The effect of white matter hyperintensities on cognition is mediated by cortical atrophy. Neurobiology of aging 64, 25-32. DOI: 10.1016/j.neurobiolaging.2017.12.006

Sahathevan, R., Brodtmann, A., Donnan, G.A., 2012. Dementia, stroke, and vascular risk factors; a review. International Journal of Stroke 7(1), 61-73. DOI: 10.1111/j.1747-4949.2011.00731.x

Sánchez-Cubillo, I., Periáñez, J.A., Adrover-Roig, D., Rodríguez-Sánchez, J.M., Ríos-Lago, M., Tirapu, J., Barceló, F., 2009. Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. Journal of the International Neuropsychological Society 15(3), 438-450. DOI: 10.1017/S1355617709090626

Seiler, S., Fletcher, E., Hassan-Ali, K., Weinstein, M., Beiser, A., Himali, J.J., Satizabal, C.L., Seshadri, S., DeCarli, C., Maillard, P., 2018. Cerebral tract integrity relates to white matter hyperintensities, cortex volume, and cognition. Neurobiology of aging 72, 14-22. DOI: 10.1016/j.neurobiolaging.2018.08.005

Sierpowska, J., Gabarrós, A., Fernández-Coello, A., Camins, À., Castañer, S., Juncadella, M., François, C., Rodríguez-Fornells, A., 2019. White-matter pathways and semantic processing: intrasurgical and lesion-symptom mapping evidence. NeuroImage: Clinical 22, 101704. DOI: 10.1016/j.nicl.2019.101704

Skinner, J., Carvalho, J.O., Potter, G.G., Thames, A., Zelinski, E., Crane, P.K., Gibbons, L.E., Initiative, A.s.D.N., 2012. The Alzheimer's disease assessment scale-cognitive-plus (ADAS-Cog-Plus): an expansion of the ADAS-Cog to improve responsiveness in MCI. Brain imaging and behavior 6, 489-501. DOI: 10.1007/s11682-012-9166-3

Smith, E., Salat, D., Jeng, J., McCreary, C., Fischl, B., Schmahmann, J., Dickerson, B., Viswanathan, A., Albert, M., Blacker, D., 2011. Correlations between MRI white matter lesion

location and executive function and episodic memory. Neurology 76(17), 1492-1499. DOI: 10.1212/WNL.0b013e318217e7c8

Soldan, A., Pettigrew, C., Zhu, Y., Wang, M.-C., Moghekar, A., Gottesman, R.F., Singh, B., Martinez, O., Fletcher, E., DeCarli, C., 2020. White matter hyperintensities and CSF Alzheimer disease biomarkers in preclinical Alzheimer disease. Neurology 94(9), e950-e960. DOI: 10.1212/WNL.0000000000008864

Staals, J., Booth, T., Morris, Z., Bastin, M.E., Gow, A.J., Corley, J., Redmond, P., Starr, J.M., Deary, I.J., Wardlaw, J.M., 2015. Total MRI load of cerebral small vessel disease and cognitive ability in older people. Neurobiology of aging 36(10), 2806-2811. DOI: 10.1016/j.neurobiolaging.2015.06.024

Sun, X., Liang, Y., Wang, J., Chen, K., Chen, Y., Zhou, X., Jia, J., Zhang, Z., 2014. Early frontal structural and functional changes in mild white matter lesions relevant to cognitive decline. Journal of Alzheimer's Disease 40(1), 123-134. DOI: 10.3233/JAD-131709

Taghvaei, M., Cook, P.A., Sadaghiani, S., Shakibajahromi, B., Tackett, W., Dolui, S., De, D., Brown, C., Khandelwal, P., Yushkevich, P.A., Das, S., Wolk, D.A., Detre, J.A., 2023. Young versus Older Subject Diffusion MRI Data for Virtual White Matter Lesion Tractography? Human brain mapping 44( 10), 3943– 3953. DOI: 10.1002/hbm.26326

Tariq, S., Tsang, A., Wang, M., Reaume, N., Carlson, H., Sajobi, T.T., Longman, R.S., Smith, E.E., Frayne, R., d'Esterre, C.D., 2020. White matter tract microstructure and cognitive performance after transient ischemic attack. Plos one 15(10), e0239116. DOI: 10.1371/journal.pone.0239116

Thal, D.R., Attems, J., Ewers, M., 2014. Spreading of amyloid, tau, and microvascular pathology in Alzheimer's disease: findings from neuropathological and neuroimaging studies. Journal of Alzheimer's Disease 42(s4), S421-S429. DOI: 10.3233/JAD-141461

Thiebaut de Schotten, M., Foulon, C., Nachev, P., 2020. Brain disconnections link structural connectivity with function and behaviour. Nature communications 11(1), 5094. DOI: 10.1038/s41467-020-18920-9

Tideman, P., Stomrud, E., Leuzy, A., Mattsson-Carlgren, N., Palmqvist, S., Hansson, O., Initiative, A.s.D.N., 2022. Association of β-Amyloid accumulation with executive function in adults with unimpaired cognition. Neurology 98(15), e1525-e1533. DOI: 10.1212/WNL.0000000000013299

Van De Haar, H.J., Burgmans, S., Jansen, J.F., Van Osch, M.J., Van Buchem, M.A., Muller, M., Hofman, P.A., Verhey, F.R., Backes, W.H., 2016. Blood-brain barrier leakage in patients with early Alzheimer disease. Radiology 281(2), 527-535. DOI: 10.1148/radiol.2016152244

Van Den Berg, E., Geerlings, M.I., Biessels, G.J., Nederkoorn, P.J., Kloppenborg, R.P., 2018. White matter hyperintensities and cognition in mild cognitive impairment and Alzheimer's disease: a domain-specific meta-analysis. Journal of Alzheimer's disease 63(2), 515-527. DOI: 10.3233/JAD-170573

Van Essen, D.C., Smith, S.M., Barch, D.M., Behrens, T.E., Yacoub, E., Ugurbil, K., Consortium, W.-M.H., 2013. The WU-Minn human connectome project: an overview. Neuroimage 80, 62-79. DOI: 10.1016/j.neuroimage.2013.05.041

Vannorsdall, T.D., Waldstein, S.R., Kraut, M., Pearlson, G.D., Schretlen, D.J., 2009. White matter abnormalities and cognition in a community sample. Archives of clinical neuropsychology 24(3), 209-217. DOI: 10.1093/arclin/acp037

Vazzana, R., Bandinelli, S., Lauretani, F., Volpato, S., Lauretani, F., Di Iorio, A., Abate, M., Corsi, A.M., Milaneschi, Y., Guralnik, J.M., 2010. Trail Making Test predicts physical impairment and mortality in older persons. Journal of the American Geriatrics Society 58(4), 719-723. DOI: 10.1111/j.1532-5415.2010.02780.x

Vemuri, P., Lesnick, T.G., Przybelski, S.A., Knopman, D.S., Preboske, G.M., Kantarci, K., Raman, M.R., Machulda, M.M., Mielke, M.M., Lowe, V.J., 2015. Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. Brain 138(3), 761-771. DOI: 10.1093/brain/awu393

Vernooij, M.W., Ikram, M.A., Vrooman, H.A., Wielopolski, P.A., Krestin, G.P., Hofman, A., Niessen, W.J., Van der Lugt, A., Breteler, M.M., 2009. White matter microstructural integrity and cognitive function in a general elderly population. Archives of general psychiatry 66(5), 545-553. DOI: 10.1001/archgenpsychiatry.2009.5

Voineskos, A.N., Rajji, T.K., Lobaugh, N.J., Miranda, D., Shenton, M.E., Kennedy, J.L., Pollock, B.G., Mulsant, B.H., 2012. Age-related decline in white matter tract integrity and cognitive performance: a DTI tractography and structural equation modeling study. Neurobiology of aging 33(1), 21-34. DOI: 10.1016/j.neurobiolaging.2010.02.009

Von Der Heide, R.J., Skipper, L.M., Klobusicky, E., Olson, I.R., 2013. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. Brain 136(6), 1692-1707. DOI: 10.1093/brain/awt094

Wang, M.B., Owen, J.P., Mukherjee, P., Raj, A., 2017. Brain network eigenmodes provide a robust and compact representation of the structural connectome in health and disease. PLoS computational biology 13(6), e1005550. DOI: 10.1371/journal.pcbi.1005550

Wardlaw, J.M., Smith, E.E., Biessels, G.J., Cordonnier, C., Fazekas, F., Frayne, R., Lindley, R.I., T O'Brien, J., Barkhof, F., Benavente, O.R., 2013. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. The Lancet Neurology 12(8), 822-838. DOI: 10.1016/S1474-4422(13)70124-8

Wardlaw, J.M., Valdés Hernández, M.C., Muñoz-Maniega, S., 2015. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. Journal of the American Heart Association 4(6), e001140. DOI: 10.1161/JAHA.114.001140

Wong, F.C.C., Saffari, S.E., Yatawara, C., Ng, K.P., Kandiah, N., Initiative, A.s.D.N., 2021. Influence of white matter hyperintensities on baseline and longitudinal amyloid-β in cognitively normal individuals. Journal of Alzheimer's Disease 84(1), 91-101. DOI: 10.3233/JAD-210333

Yeh, F.-C., Panesar, S., Fernandes, D., Meola, A., Yoshino, M., Fernandez-Miranda, J.C., Vettel, J.M., Verstynen, T., 2018. Population-averaged atlas of the macroscale human structural connectome and its network topology. Neuroimage 178, 57-68. DOI: 10.1016/j.neuroimage.2018.05.027

Yeh, F.-C., Tseng, W.-Y.I., 2011. NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. Neuroimage 58(1), 91-99. DOI: 10.1016/j.neuroimage.2011.06.021

Yoshita, M., Fletcher, E., DeCarli, C., 2005. Current concepts of analysis of cerebral white matter hyperintensities on magnetic resonance imaging. Topics in Magnetic Resonance Imaging 16(6), 399-407. DOI: 10.1097/01.rmr.0000245456.98029.a8

Young, J.S., Morshed, R.A., Mansoori, Z., Cha, S., Berger, M.S., 2020. Disruption of frontal aslant tract is not associated with long-term postoperative language deficits. World Neurosurgery 133, 192-195. DOI: 10.1016/j.wneu.2019.09.128

Yushkevich, P.A., Piven, J., Hazlett, H.C., Smith, R.G., Ho, S., Gee, J.C., Gerig, G., 2006. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage 31(3), 1116-1128. DOI: 10.1016/j.neuroimage.2006.01.015

Zeng, W., Chen, Y., Zhu, Z., Gao, S., Xia, J., Chen, X., Jia, J., Zhang, Z., 2020. Severity of white matter hyperintensities: lesion patterns, cognition, and microstructural changes. Journal of Cerebral Blood Flow & Metabolism 40(12), 2454-2463. DOI: 10.1177/0271678X19893600

Zhang, N., Song, X., Zhang, Y., Chen, W., D'Arcy, R.C., Darvesh, S., Fisk, J.D., Rockwood, K., Initiative, A.s.d.N., 2011. An MRI brain atrophy and lesion index to assess the progression of structural changes in Alzheimer's disease, mild cognitive impairment, and normal aging: a follow-up study. Journal of Alzheimer's Disease 26(s3), 359-367. DOI: 10.3233/JAD-2011-0048

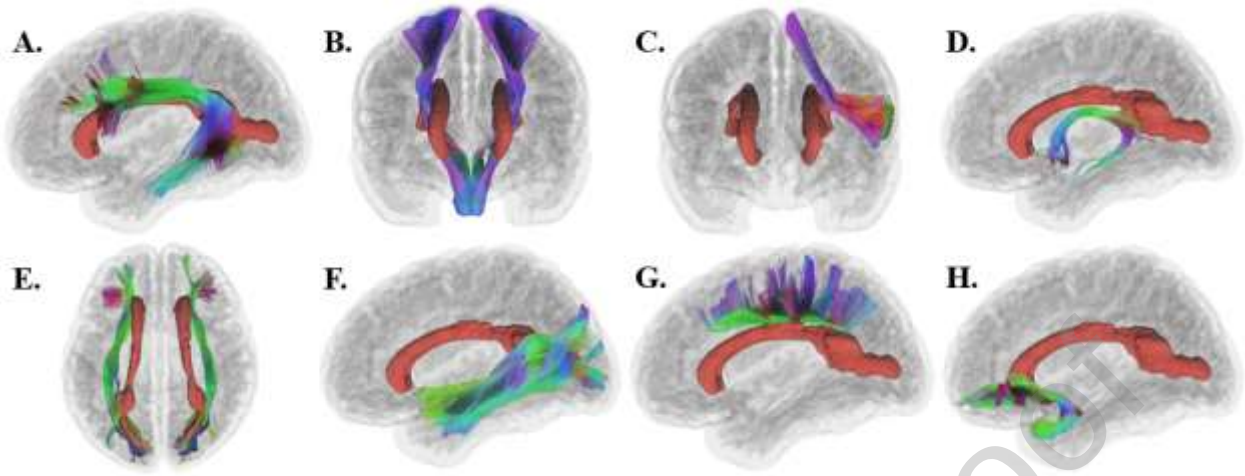


Figure 1. The spatial proximity of different white matter tracts with WMH lesions. The WMH lesion mask extracted from WMH lesion frequency map containing voxels with greater than 10% probability of lesion in our study participants is shown in red in each rendering. A: Arcuate fasciculus, B: Corticospinal tract, C: Frontal aslant tract, D: Fornix, E: Inferior fronto-occipital fasciculus, F: Inferior longitudinal fasciculus, G: Superior longitudinal fasciculus, H: Uncinate fasciculus.

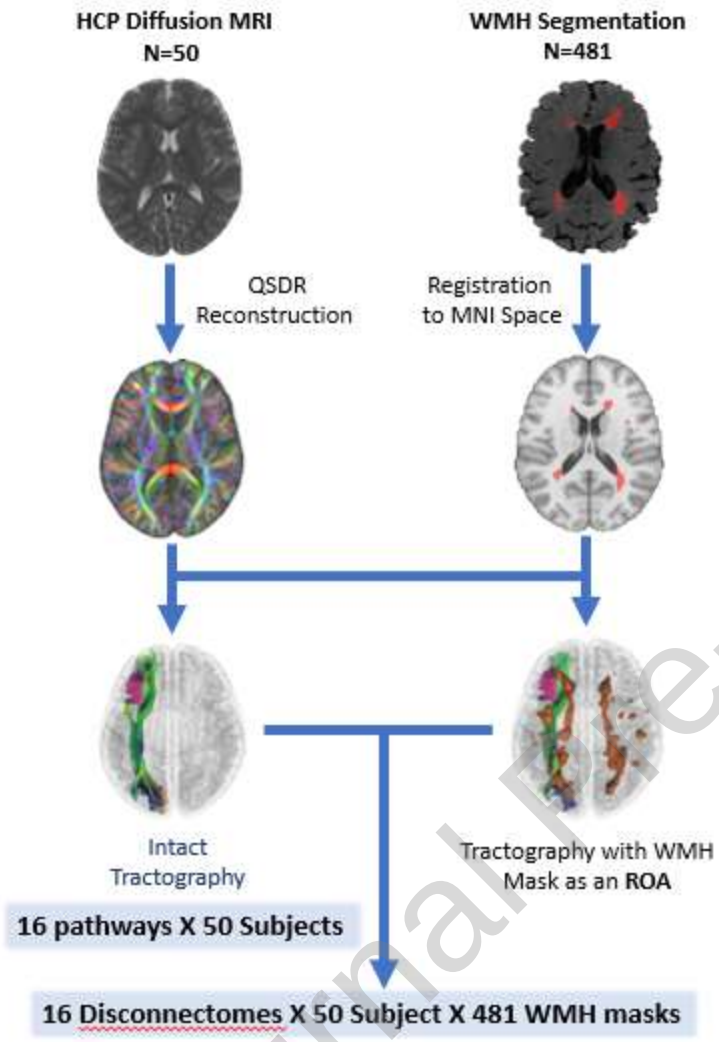


Figure 2. Virtual lesion tact-based disconnectome pipeline.

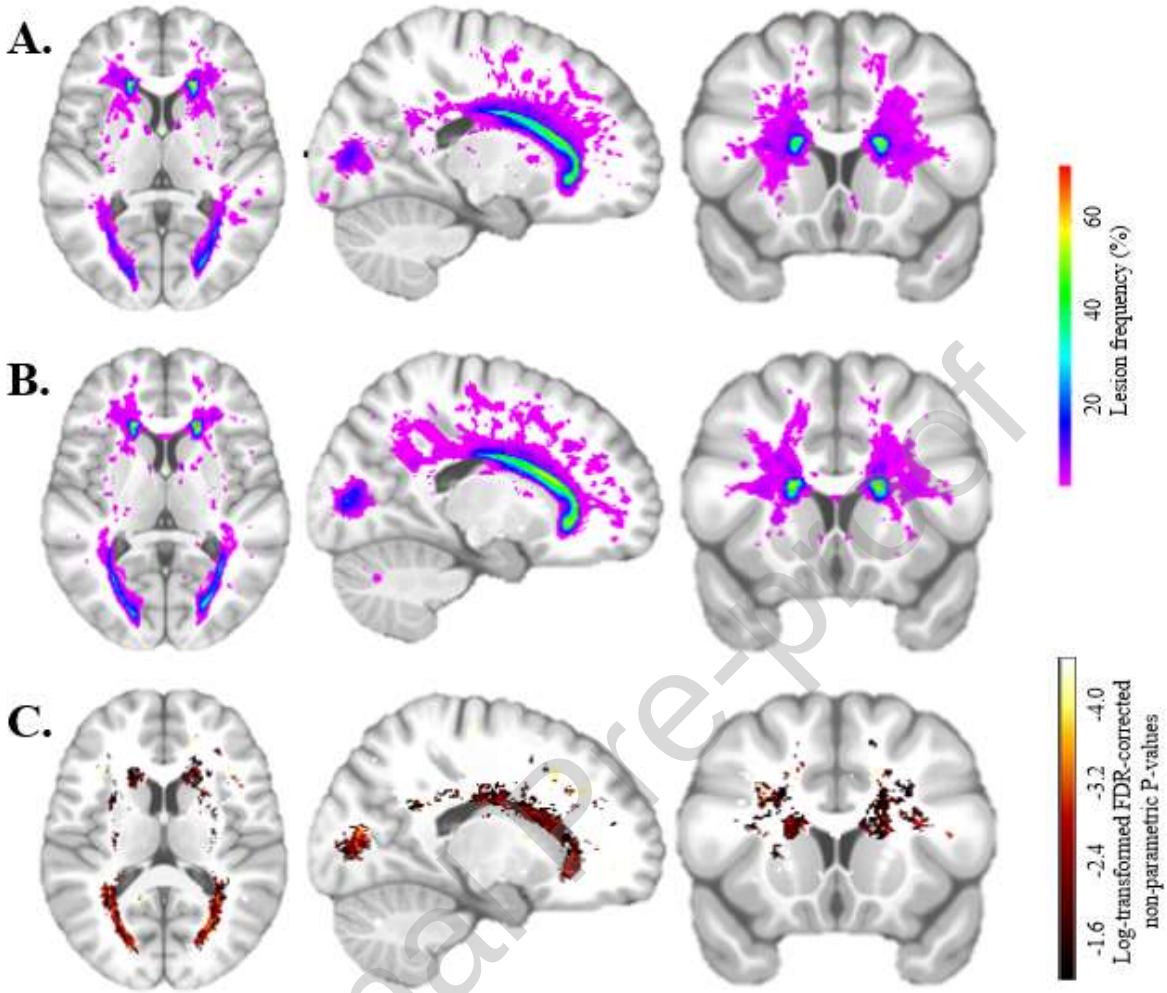


Figure 3. Lesion frequency distribution maps for 110 age-matched beta-amyloid negative (A) and positive (B) participants. C. Voxel-wise difference map between two groups. WMH lesions in highlighted areas are significantly more frequent in beta-amyloid positive participants compared to the negative group (FDR corrected $p<0.05$).

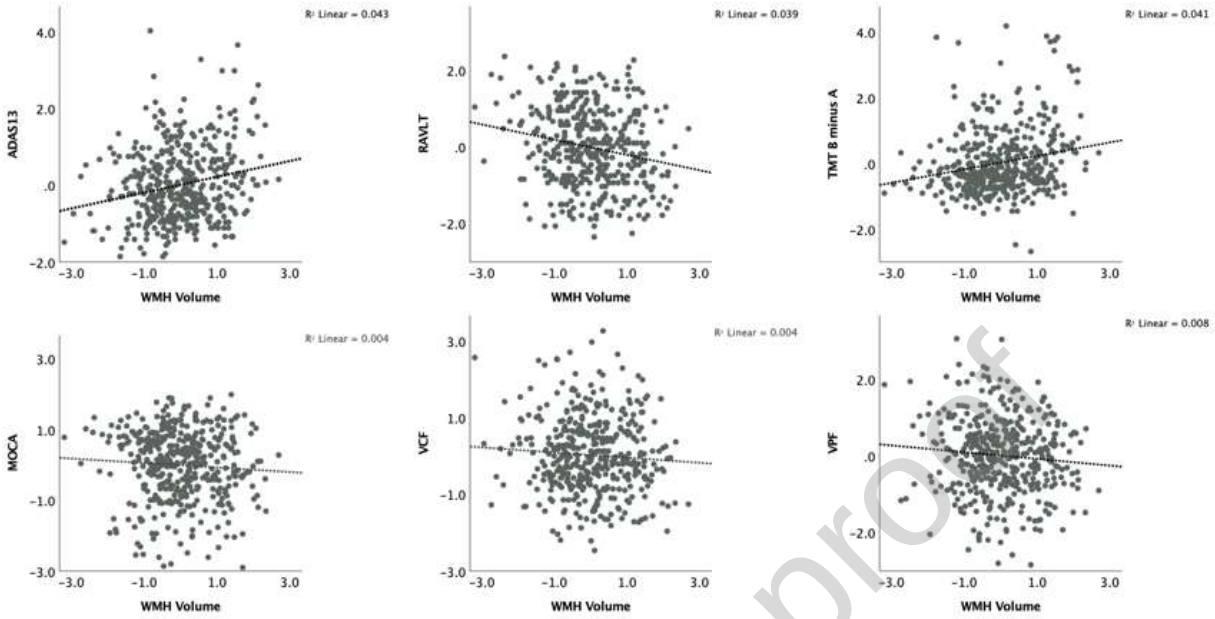


Figure 4. Scatter plot of cognitive tests' Z scores on tract disconnection Z score controlling for age, sex, and level of education.

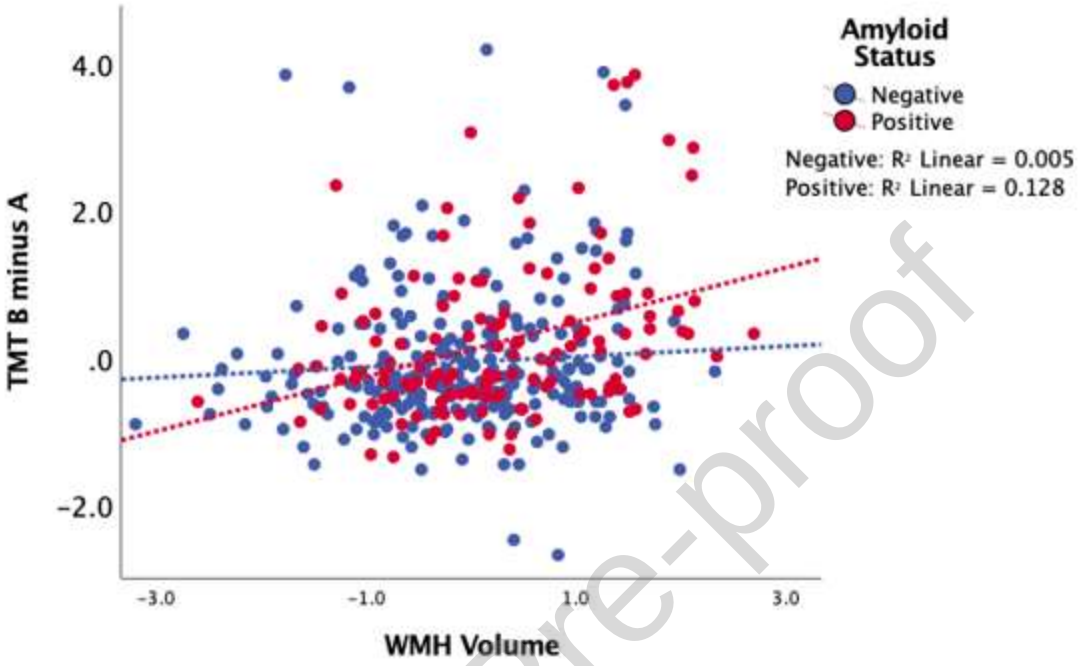


Figure 5. Scatter plot of TMT B minus A times residual on WMH volume Z scores across beta-amyloid positive and negative groups.

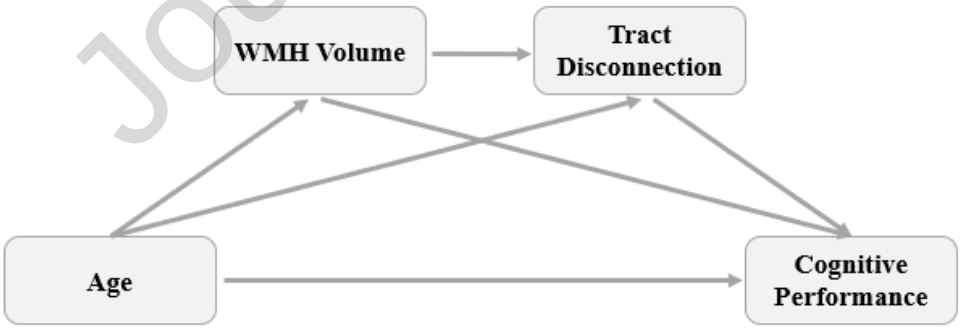

Figure 6. Mediation model of global WMH lesions and tract disconnection on age-related cognitive decrement.

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**Highlights:**

- Global WMH burden was associated with episodic memory and executive function.
- Estimated disconnections due to WMH correlated to cognitive performance decrements.
- The probability of periventricular WMH was higher in amyloid-positive subjects.
- Amyloid status moderated the effect of tract disconnection on executive function.