

White Matter Hyperintensity Load Drives Differential Grey Matter Changes in Mild Cognitive Impairment

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Abstract

Background: Small-vessel cerebrovascular disease often represented as white matter hyperintensities on magnetic resonance imaging, is considered an important risk factor for progression to dementia. Grey matter volume alterations in Alzheimer's disease-specific regions comprising the default mode network and executive control network are also key features of early Alzheimer's disease. However, the relationship between increasing white matter hyperintensity load and grey matter volume needs further examination in the cognitively normal and mild cognitive impairment. Here, we examined the load-dependent influence of white matter hyperintensities on grey matter volume and cognition in the cognitively normal and mild cognitive impairment stages.

Methods: Magnetic resonance imaging data from 93 mild cognitive impairment and 90 cognitively normal subjects were studied and white matter hyperintensity load was categorized into low, medium and high terciles. We examined how differing loads of white matter hyperintensities related to whole-brain voxel-wise and regional grey matter volume in the default mode network and executive control network. We further investigated how regional grey matter volume moderated the relationship between white matter hyperintensities and cognition at differing white matter hyperintensity loads.

Results: We found differential load-dependent effects of white matter hyperintensity burden on voxel-wise and regional grey matter atrophy in only mild cognitive impairment subjects. At low load, white matter hyperintensity load was positively related to grey matter volume in the executive control network but at high load, white matter hyperintensity load was negatively related to grey matter volume across both the executive control and default mode networks and no relationship was observed at medium white matter hyperintensity load. Additionally, negative associations between white matter hyperintensities and domains of memory and executive function were moderated by regional grey matter volume.

Conclusions: Our results demonstrate dynamic relationships between white matter hyperintensity load, grey matter volume and cognition in the mild cognitive impairment stage. Interventions to slow the progression of white matter hyperintensities, instituted when white matter hyperintensity load is low could potentially prevent further cognitive decline.

1. Background

Mild cognitive impairment (MCI) is considered a high-risk prodromal stage of Alzheimer's disease (AD) with more than a third of patients at increased risk of progression to dementia (1). A diagnosis of MCI is characterized by objective cognitive impairment, related to memory as well as other cognitive domains, but without functional impairment that interferes with activities of daily life (2, 3). Additionally, the presence of cerebrovascular risk factors are also thought to place cognitively normal individuals at increased risk of progression along the AD spectrum (4).

Indeed, studies show that small-vessel cerebrovascular disease, represented by surrogate Magnetic Resonance Imaging (MRI) measures particularly white matter hyperintensities (WMH) (5, 6), is an

important risk factor for the clinical manifestation of MCI and progression to dementia (7–9). Moreover, high WMH volume itself has been associated with greater risk of progression from cognitively normal to MCI (2). Indeed, increased WMH burden has been associated with medial temporal lobe atrophy and cognitive impairment in AD (10, 11). Specifically, WMH-related global reductions in grey matter volume (GMV) together with frontal and parietal-lobe specific structural alterations have been widely observed in AD (12). Recent work also suggests that WMH is an independent risk factor for medial temporal atrophy in amyloid positive subjects (13). The topographic pattern of WMH in the brain has also been associated with amyloid beta deposition, indicating close relationships between these brain pathologies (14). However, the pathophysiological process underlying how WMH and AD neuropathology interact to accelerate degeneration and influence progression in early AD stages involving MCI and cognitively normal individuals remains to be elucidated. Therefore, it is of interest to study the effect of WMH on atrophy patterns and cognition in the cognitively normal and prodromal MCI, to allow for development of strategies to reduce irreversible structural and cognitive damage.

Previous studies have demonstrated that WMH plays a role in grey matter (GM) structural changes and cognitive decline even at the MCI stage (14–19). Structural decline has been shown to involve temporal and frontal regions comprising the AD-related default mode and executive control networks (20–22). Recent findings have shown that even at low levels of WMH in cognitively unimpaired middle-aged individuals, higher WMH lesion volume is significantly associated with a widespread pattern of lower GMV in temporal, frontal, and cerebellar areas (23). However, results have been mixed with some studies suggesting that higher WMH is associated with higher network-based GMV and functional connectivity involving the default mode and executive control networks in the cognitively normal, MCI and AD (21, 24, 25). This relationship thus needs further elucidation in early disease stages. While our previous work has also shown that derogatory influences of WMH on GMV are most widespread at the MCI stage, compared to both cognitively normal and AD stages (26), the possible differential effects of WMH load on GMV in the cognitively normal and MCI remain to be elucidated.

Greater baseline WMH burden is also predictive of accelerated neuro-cognitive decline as well as increase in clinical dementia rating longitudinally(27). Additionally, cross-sectional studies illustrate associations between high WMH and decline in memory and executive function in healthy controls and MCI(15, 28, 29). Global and regional cortical thickness have also been shown to mediate the relationship between WMH and global cognition in cognitively healthy individuals, MCI and AD patients(11). Additionally, GMV has also been shown to mediate the association between WMH burden with both executive function and memory, in mixed populations of individuals with cardiovascular risk factors and AD patients(30). However, few studies have explored how differing loads of WMH can influence relationships between WMH, GMV and cognition. The extent to which these associations are present in the early stages of disease involving both cognitively normal elderly and MCI, especially in the Asian context, has not yet been fully assessed.

In light of these uncertainties, we sought to assess the load-dependent influence of WMH on whole-brain voxel-wise and region of interest-based GMV and cognition in cognitively normal individuals and

individuals with MCI from an Asian cohort. Based on prior evidence of the influence of WMH on default mode and executive control networks, we assessed the effect of WMH on major regions comprising these networks. We hypothesized that increasing WMH load would result in lower voxel-wise and regional GMV. We also investigated the influence of WMH load on memory and executive function. We hypothesized that increasing load of WMH would be related to greater impairment in domains of memory and executive function. Additionally, we also examined the mediating and moderating effect of GMV on the relationship between WMH and cognition.

2. Methods

2.1 Study Participants

Cognitively normal individuals and participants with a diagnosis of MCI were recruited from tertiary neurology centres in Singapore between August 2013 and August 2018. Inclusion criteria included diagnosis of MCI based on the NIA-AA criteria (31). Subjects with MCI were required to have cognitive symptoms, deficits on neuropsychological evaluation, CDR of 0.5 and to not meet criteria for dementia. For cognitively normal subjects, inclusion criteria included absence of subjective cognitive symptoms and a CDR of 0. Exclusion criteria included: 1) a history of alcohol or drug abuse; 2) a current or known history of major depression; 3) comorbid neurodegenerative disease such as Parkinson's disease; 4) history of stroke; 5) presence of contraindications to MRI.

Informed consent for both studies was sought from each patient according to the Declaration of Helsinki and local clinical research regulations. The study was granted approval by the Singhealth Centralized Review Board. Following quality control, we included 90 cognitively normal individuals and 93 participants with MCI in our study.

2.2 Neuropsychological assessments

Patients underwent a standardized battery of neuropsychological assessments administered by trained research staff. Cognitive information collected examined domains of 1) episodic memory, assessed using Alzheimer's Disease Assessment Scale (ADAS)–Cognitive 10-word delayed recall (32) and ADAS-Immediate Recall (33); and 2) executive function, assessed using Frontal Assessment Battery (34) and Color Trails 2 (35). Measures of global cognition included the Mini-Mental State Examination (36) and the Montreal Cognitive Assessment (37). Performance on the individual tasks was transformed into z-scores based on normative scores (38–40).

2.3 Image Acquisition

MRI scans were performed on a 3T Prisma Fit System (Siemens, Erlangen, Germany). High resolution T1-weighted MPRAGE (MagnetizationPrepared Rapid Gradient Echo: 192 continuous sagittal slices, TR/TE/TI = 2300/2.28/900 ms, flip angle = 8°, FOV = 256 × 240 mm², matrix = 256 × 240, isotropic voxel size = 1.0 × 1.0 × 1.0mm³, bandwidth = 200 Hz/pixel and FLAIR (Fluid Attenuated Inversion Recovery) sequences (192 continuous sagittal slices, TR/TE/TI = 5000/387.0/1800 ms, flip angle = 15°, FOV = 256 ×

256 mm², matrix = 256 × 256, isotropic voxel size = 1.0 × 1.0 × 1.0mm³) were obtained. Scan images were reviewed at acquisition and subjects with motion artifacts and gross pathological findings were excluded.

2.4 Image pre-processing

We used the Computational Anatomy Toolbox (<http://dbm.neuro.uni-jena.de/cat12/>) protocol in Statistical Parametric Mapping (SPM12) (<http://www.fil.ion.ucl.ac.uk/spm/>), to process the T1 images for voxel-based morphometry (VBM) analysis. Specifically, all 3D T1-weighted MRI scans were normalized using an affine transformation followed by non-linear registration, corrected for bias field inhomogeneities. Images were then segmented to derive subject-level GM, white matter (WM), and cerebrospinal fluid (CSF) components (41). The Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm was used to normalize the segmented scans into the standard MNI space which provides better precision in spatial normalization to the template (42). Subsequently, the modulation step performed a non-linear deformation on the normalized segmented images. The modulation step provides a comparison of the absolute amounts of tissue corrected for individual differences in brain size. All obtained segmented, modulated, and normalized GM and WM images were then smoothed using an 8-mm full-width-half-maximum isotropic Gaussian smoothing kernel.

2.5 White matter hyperintensity derivation

We used the Lesion Segmentation Toolbox (LST version 2.0.15), a MATLAB (https://www.mathworks.com/?s_tid=gn_logo) and SPM12-based automated tool for WMH detection, to extract binary WMH lesion belief maps (43, 44). We employed the automated lesion growth algorithm from LST on T1 anatomical and FLAIR images to quantify WMH as reported previously (24). This algorithm first co-registers the T2 FLAIR to T1 and subsequently segments T1 images into GM, WM and CSF tissue maps. This information is then combined with the co-registered T2 FLAIR images to estimate the WMH lesion belief maps. By thresholding these maps with a pre-determined initial kappa threshold (κ), an initial binary lesion map is obtained and is subsequently grown along voxels that appear hyperintense on the T2 FLAIR image. To define the optimal threshold, T1 and FLAIR images of 10 randomly chosen subjects with mild to severe WMH load were segmented at $\kappa = 0.3$, $\kappa = 0.2$ and $\kappa = 0.10$. After further visual inspection of segmentation results at these threshold levels, the WMH visual raters determined $\kappa = 0.10$ as the optimal threshold. The total lesion volume in each subject was then obtained using the extract values of interest option in the LST toolbox. The obtained lesion volume was categorized into terciles i.e. low (0.00-1.57), medium (1.58–3.16) and high (≥ 3.17) terciles in the cognitively normal and low (0.00-1.49 ml), medium (1.50–4.19 ml) and high (≥ 4.20 ml) terciles for MCI. Using published methods, total lesion volume was log-transformed and normalized using total intracranial volume for use in the statistical analyses(45). In the following sections, WMH load will thus refer to this log transformed ratio of WMH over total intracranial volume. Additionally, the lesion probability maps generated by the algorithm were used for lesion filling to correct for the presence of white matter lesions which may lower the estimated grey matter fraction on the T1-weighted images (43). These lesion-filled images were used for subsequent analyses.

2.6 Region of interest derivation

We applied a multiple seed-based approach to test the association between GMV and WMH load specifically in regions of interest (ROIs) belonging to the Default mode network (DMN) and executive control network (ECN). We selected six ROIs covering the DMN and ECN based on a prior study (46). The DMN ROIs included the posterior cingulate cortex (PCC) and precuneus (PCN) and the ECN ROIs included the left and right dorsolateral prefrontal cortex (L and R DLPFC) and the left and right posterior parietal cortex (L and R PPC) in standard space. Average GMV from these network ROIs were derived using the MarsBar package in SPM12 (47).

2.7 Statistical analyses

Group differences on participant characteristics across the WMH terciles were assessed using one-way ANOVA analyses for continuous variables and chi-square tests for categorical variables (Table 1a-b).

Table 1
a: Subject Demographics: Cognitively normal participants

	Tercile 1 (n = 30)	Tercile 2 (n = 29)	Tercile 3 (n = 31)	<i>p value</i>
Age at visit (years)	58.80 (6.44) ^{b,c}	64.9 (6.61)	65.6 (6.18)	<i>p</i> < 0.001
Sex (M/F), n	17/13	17/12	16/15	<i>p</i> = 0.852
Education (years)	13.30 (4.41)	13.2 (2.92)	12.6 (3.01)	<i>p</i> = 0.661
MMSE	28.8 (1.35)	28.4 (1.76)	28.7 (1.47)	<i>p</i> = 0.616
MOCA	28.2 (1.38)	27.3 (2.31)	27.7 (1.81)	<i>p</i> = 0.183
WMH (ml)	0.92 (0.36) ^c	2.27 (0.51) ^c	8.03 (5.18)	<i>p</i> < 0.001
Total GMV (ml)	580.52 (40.7)	581.38 (47.2)	559.52 (63.4)	<i>p</i> = 0.179
Average SBP (mmHg)	126.59 (17.36)	127.24 (14.89)	136.07 (16.59)	<i>p</i> = 0.060
ADAS Delayed recall z-score	0.168 (0.98)	0.166 (0.73)	-0.051 (0.99)	<i>p</i> = 0.566
ADAS Immediate recall z-score	-0.364 (0.88)	-0.099 (0.85)	-0.208 (1.33)	<i>p</i> = 0.625
Color Trails 2 z-score	0.450 (0.608)	0.437 (0.95)	0.406 (1.78)	<i>p</i> = 0.99
FAB z-score	0.683 (0.41)	0.589 (0.45)	0.552 (0.59)	<i>p</i> = 0.568
Values represent mean (SD) unless otherwise indicated				
Superscript letters indicate whether group mean was significantly different compared with ^b Tercile 2, ^c Tercile 3, based on post-hoc comparisons (<i>p</i> < 0.05) following one-way analysis of variance. Chi-square tests were carried out on sex.				
Abbreviations: MMSE, mini-mental state examination; MOCA, Montreal Cognitive Assessment; WMH, white matter hyperintensity; GMV, grey matter volume; SBP, systolic blood pressure; ADAS, Alzheimer's disease assessment scale; FAB, frontal assessment battery.				

Table 1
b: Subject Demographics – Mild cognitive impairment

	Tercile 1 (n = 31)	Tercile 2 (n = 30)	Tercile 3 (n = 32)	<i>p</i> value
Age at visit (years)	56.40 (6.78) ^{b,c}	57.09 (6.38) ^c	62.28 (6.75)	<i>p</i> < 0.001
Sex (M/F), n	10/21	17/13	20/12	<i>p</i> = 0.040
Education (years)	12.80 (3.15)	13.63 (3.80)	11.62 (3.84)	<i>p</i> = 0.094
MMSE	28.16 (1.44)	27.30 (2.08)	27.46 (1.52)	<i>p</i> = 0.115
MOCA	26.32 (2.65)	24.96 (3.05)	25.62 (2.82)	<i>p</i> = 0.183
WMH (ml)	0.72 (0.39) ^{b,c}	2.55 (0.87) ^c	10.75 (8.01)	<i>p</i> < 0.001
Total GMV (ml)	590.85 (58.39)	605.31 (59.90)	575.05 (51.92)	<i>p</i> = 0.116
Average SBP (mmHg)	126.94 (18.34)	131.09 (15.74)	131.36 (16.32)	<i>p</i> = 0.514
ADAS Delayed recall z-score	0.311 (1.11)	1.17 (1.85)	0.772 (0.99)	<i>p</i> = 0.056
ADAS Immediate recall z-score	0.435 (1.29)	0.998 (1.59)	0.848 (1.55)	<i>p</i> = 0.315
Color Trails 2 z-score	-0.092 (0.97)	0.127 (0.84)	-0.78 (3.49)	<i>p</i> = 0.27
FAB z-score	0.395 (0.68)	0.371 (0.78)	0.113 (1.10)	<i>p</i> = 0.38
Values represent mean (SD) unless otherwise indicated				
Superscript letters indicate whether group mean was significantly different compared with ^b Tercile 2, ^c Tercile 3, based on post-hoc comparisons (<i>p</i> < 0.05) following one-way analysis of variance.				
Chi-square tests were carried out on sex.				
Abbreviations: MMSE, mini-mental state examination; MOCA, Montreal Cognitive Assessment; WMH, white matter hyperintensity; GMV, grey matter volume; SBP, systolic blood pressure; ADAS, Alzheimer's disease assessment scale; FAB, frontal assessment battery.				

Association between WMH and voxel-wise GMV

To assess the positive and negative effect of WMH on voxel-wise GMV, we built a voxel-wise multiple regression model with GMV as the dependent variable and log-transformed WMH and total intracranial volume ratio as the independent variable of interest. Age at visit and sex were added as covariates to the analysis. The GM clusters showing significant effect of WMH were examined using a threshold of uncorrected *p* < 0.001 and a minimum cluster size of 100 voxels(26, 48). Significant GM clusters were identified using the Automated Anatomical Labelling atlas. This analysis was conducted separately for MCI and cognitively normal subjects.

Associations between default mode network and executive control network regions of interest GMV and WMH load

Pearson's correlation analysis was used to assess the association between ROI GMV and WMH load in each tercile separately. Significant effect of WMH is reported at $p < 0.05$ following False Discovery Rate (FDR) correction for multiple comparisons across the six regions of interest and then at a lower uncorrected threshold of $p < 0.05$. Partial correlation analysis was used to assess the association between ROI GMV and WMH load while controlling for age at visit, hypertension status and systolic blood pressure, separately.

Associations between WMH load and cognition

Pearson's correlation analysis was used to assess the association between WMH load and cognition separately at each WMH tercile. Cognitive test z-scores comprising the ADAS delayed recall and ADAS immediate recall as well as Color Trails 2 and Frontal assessment battery were used in the analyses to represent memory and executive function assessments, respectively.

Mediation and Moderation effect of WMH load on the association between ROI GMV and cognition

A mediation analysis was conducted to test whether ROI GMV mediated the effect of WMH on cognition. Individual mediation models were fitted for each GMV ROI and each cognitive test at tercile 1 and tercile 3. Specifically, each model included WMH load as the predictor, ROI GMV as the mediator, and cognitive test scores as the outcome. Each model controlled for age at visit and sex. The mediation model was significant if the relationship between WMH load and cognition was reduced when controlling for the mediator. The absence of a significant direct relationship between WMH and cognition after including the mediator was considered a full mediation. On the other hand a significant direct relationship after including the mediator was considered a partial mediation.

A moderation analysis was conducted to assess whether ROI GMV moderated the relationship between WMH and cognition. For this, we carried out a linear regression analysis at each WMH tercile. Cognitive test z-scores comprising the ADAS delayed recall, ADAS immediate recall, Color Trails 2 and Frontal assessment battery were used in the linear regression model to represent memory and executive function assessments. An interaction term between ROI GMV and WMH load was included to assess the moderation effect. Age at visit and sex were added as nuisance covariates in the linear regression model. Multiple comparisons correction across the six ROIs and four cognitive tests was conducted using False Discovery Rate (FDR) correction for multiple comparisons and then at a lower uncorrected threshold of $p < 0.05$.

The statistical analyses for mediation models was carried out using the Statistical Package for Social Sciences (SPSS, Inc; Chicago, IL, USA) version 23.0 macro PROCESS (49). Effect size estimation was applied using bias-corrected bootstrap estimation with 5,000 resamples (50). A bias-corrected 95% bootstrapped confidence interval (CI) that did not contain zero indicated a significant effect (50). All other

statistical analyses were conducted using R 3.0.3 (R CoreTeam, 2014) with RStudio (RStudio Team, 2012).

3. Results

90 cognitively normal participants (Table 1a) with a mean age of 63.1 (SD 7.04), mean WMH of 3.80 (SD 4.35) and 93 MCI participants (Table 1b) with a mean age of 58.65 (SD 7.09) years and mean WMH volume of 4.76 (SD 6.44) ml were studied. Participant demographics and cognitive characteristics categorized by tercile of WMH are summarized in Table 1a-b. Participant age were significantly different between WMH terciles. Participants did not differ on disease severity as indicated by their similar global cognition and memory and executive function test profiles (Table 1a-b).

3.1 Associations between voxel-wise grey matter volume and WMH load in the cognitively normal and mild cognitive impairment

In the cognitively normal, at tercile 2, higher WMH load was associated with lower GMV in the left precuneus, right middle temporal gyrus, right superior parietal and bilateral lingual gyrus ($p < 0.001$, minimum cluster size = 100 voxels). WMH load was not associated with GMV at either tercile 1 or tercile 3 (Table 2a).

Table 2

Associations between white matter hyperintensity load and voxel-wise grey matter volume in normal controls and mild cognitive impairment

a) Normal Controls	Region	Peak t-statistics	Cluster size	MNI Coordinates
Negative association between WMH load and GMV				
Tercile 2	Left rectus	5.60	193	-9 26 - 14
	Left precuneus; right superior parietal gyrus	5.01	168	-14 -75 56
	Right middle temporal gyrus	4.69	341	63 - 48 -4
	Right superior parietal; right precuneus	4.60	329	16-60 63
	Left lingual gyrus	4.58	208	14-69 -10
	Right lingual gyrus	4.44	146	-20 -60 -12
b) Mild cognitive impairment	Region	Peak t-statistics	Cluster size	MNI Coordinates
Positive association between WMH load and GMV				
Tercile 1	Left angular gyrus	4.92	196	-48 -64 28
Negative association between WMH load and GMV				
Tercile 1	Right postcentral gyrus	5.83	805	46 - 16 38
	Right middle/superior frontal gyrus	5.60	277	33 6 57
	Right middle cingulum	5.49	428	15-39 40
	Right anterior cingulum	4.75	183	3 39 22
	Left middle/inferior frontal gyrus	4.57	221	-40 44 - 10
	Left superior/medial frontal gyrus	4.50	118	-10 42 24
	Right lingual gyrus	4.40	117	26-90 -16
	Left inferior frontal, triangular part	4.25	190	-36 27 6

All voxel-wise analyses controlled for age at visit and sex.

Abbreviations: WMH, white matter hyperintensity; GMV, grey matter volume.

a) Normal Controls	Region	Peak t-statistics	Cluster size	MNI Coordinates
Tercile 3	Left supramarginal gyrus	6.08	909	-54 -34 32
	Right superior parietal gyrus; right postcentral gyrus; right inferior parietal gyrus	5.08	1172	26–57 58
		4.49	388	-39 -54 52
	Left inferior parietal gyrus	4.39	127	42 28 30
	Right middle/inferior frontal gyrus	4.13	207	9–46 42
	Right precuneus; right middle cingulum	3.78	102	45–68 36
	Right angular gyrus			
All voxel-wise analyses controlled for age at visit and sex.				
Abbreviations: WMH, white matter hyperintensity; GMV, grey matter volume.				

In MCI participants, at tercile 1, WMH load show positive and negative associations with voxel-wise GMV (Table 2b). Specifically, WMH was positively associated with GMV in areas involving the left angular gyrus including voxels within the posterior parietal cortex ($p < 0.001$, minimum cluster size = 100 voxels). Additionally, WMH load was also negatively associated with GMV primarily in frontoparietal regions involving the bilateral middle and superior frontal gyrus, bilateral anterior cingulum and left inferior frontal gyrus ($p < 0.001$, minimum cluster size = 100 voxels). At tercile 3, WMH was only negatively associated with GMV in frontoparietal regions involving the right superior parietal gyrus, left inferior parietal, right middle and inferior frontal gyrus, left supramarginal gyrus, right precuneus and right angular gyrus ($p < 0.001$, minimum cluster size = 100 voxels). In MCI, regions showing differential voxel-wise GMV changes overlapped with frontoparietal DMN (precuneus, cingulate cortex) and ECN (dorsolateral posterior parietal cortex, posterior parietal cortex).

Thus, due to the presence of differential associations between WMH and voxel-wise GMV in MCI in frontoparietal regions involving the ECN and DMN, we further investigated the influence of WMH on ROI-based GMV in these networks as well as on the association between GMV and cognition at the MCI stage only.

3.2 Associations between ROI grey matter volume and WMH load in mild cognitive impairment

In individuals with WMH load within tercile 1, WMH volume was positively associated to GMV in the LPPC ($r = 0.48$; $p = 0.0061$, FDR-corrected $p < 0.05$; Fig. 1A). No association between WMH volume and GMV was observed at tercile 2.

However, at tercile 3, a negative relationship was observed between WMH and GMV such that increasing WMH load was associated with lower GMV across both the DMN and ECN: PCC ($r = -0.44$; $p = 0.011$, FDR-

corrected $p < 0.05$), PCUN ($r = -0.35$; uncorrected $p < 0.05$), LDLPFC ($r = -0.42$; $p = 0.016$, FDR-corrected $p < 0.05$), RDLPFC ($r = -0.38$; uncorrected $p < 0.05$), LPPC ($r = -0.47$; $p = 0.006$, FDR-corrected $p < 0.05$; Fig. 1A); RPPC ($r = -0.515$; $p = 0.0025$, FDR-corrected $p < 0.05$; Fig. 1B). Importantly, these results remained significant after controlling for age at visit, hypertension status and systolic blood pressure.

3.3 ROI grey matter volume moderates the relationship between WMH load and cognition in mild cognitive impairment

A Pearson's correlation analyses between log WMH/TIV in each tercile and cognitive performance on episodic memory (ADAS delayed recall, ADAS immediate recall) and executive function (color trails 2, frontal assessment battery) was carried out. No significant associations were observed between low, medium or high WMH and cognitive performance.

We found no mediation effect of DMN or ECN ROI GMV on the relationship between WMH load and cognition for any of the cognitive tests.

On the other hand, significant moderation effects between cognition and WMH load were observed in conjunction with ROI GMV. Specifically, at tercile 1, the interaction of increasing WMH load and RDLPFC GMV ($\beta = 75.38$; uncorrected $p < 0.05$; Fig. 2A) related to worse performance on the ADAS delayed recall test. Similarly, the interaction of increasing WMH load and PCUN GMV ($\beta = 60.19$; uncorrected $p < 0.05$; Fig. 2B) associated with worse performance on the ADAS immediate recall test. Higher WMH load and LDLPFC ($\beta = 127.80$; $p = 0.001$, FDR-corrected $p < 0.05$; Fig. 2C) and RPPC ($\beta = 101.40$; $p = 0.0053$, FDR-corrected $p < 0.05$; Fig. 2D) GMV related to worse performance on the ADAS immediate recall test.

No associations between WMH, GMV and memory/executive function were observed at tercile 2 in MCI.

At tercile 3 i.e. the highest load of WMH, increasing WMH load interaction with ECN GMV related to lower FAB scores i.e. the LDLPFC ($\beta = -41.9$; uncorrected $p < 0.05$; Fig. 3A), RDLPFC ($\beta = -40.8$; uncorrected $p < 0.05$) and LPPC ($\beta = -61.90$; uncorrected $p < 0.05$; Fig. 3B). Additionally, increasing WMH load interaction with PCC GMV ($\beta = 36.50$; uncorrected $p < 0.05$; Fig. 4A) related to worse performance on the ADAS delayed recall and increasing WMH load interaction with LDLPFC GMV ($\beta = 59.03$; uncorrected $p < 0.05$; Fig. 4B) related to worse performance on the ADAS immediate recall test.

4. Discussion

We demonstrate differential relationships between WMH load and voxel-wise and regional GM atrophy in the DMN and ECN with low WMH being positively associated with GMV and high WMH being negatively associated with GMV. Such a differential relationship was only observed in the MCI stage with cognitively normal individuals showing primarily reduced GMV associated with WMH. Specifically, in MCI, low WMH load was related to higher GMV in the ECN and lower voxel-wise frontoparietal GMV, however as the load of WMH increased, only a negative relationship was seen. At high WMH load, frontoparietal voxel-wise GMV and within the DMN and ECN ROIs demonstrated a negative relationship with increasing WMH

burden. We also demonstrate GMV to be a key moderator in the relationship between WMH and cognition in MCI. Specifically, higher WMH was related to worse memory and executive function moderated by GMV in the DMN and ECN. While at low WMH load, only memory performance was affected, at high WMH load, both memory and executive function were affected. Our results highlight variable relationships between WMH and GMV, dependent on the amount of cerebral WMH burden and their subsequent association with cognition in participants with MCI, indicating that such associations cannot be assumed to be linear in nature. This variable relationship may have important implications in the clinical management of MCI patients with varying loads of WMH.

Cerebral WMH has been associated with several mechanisms including small vessel cerebrovascular disease, GM atrophy and neuroinflammation (15, 21, 26, 51, 52). It has been widely assumed that irrespective of the underlying mechanism, increasing WMH load will result in progressive increase in GMV loss. Our study demonstrates that this assumption is dependent on the baseline WMH load. While we demonstrate GMV decline in both the DMN and ECN ROI with high WMH volume, at low levels of WMH, this relationship is reversed such that increasing WMH is associated with higher GMV, primarily in the ECN. We additionally show, that at an intermediate load of WMH, the relationship between WMH load and GMV is stable and a negative relationship between increasing WMH load and ROI GMV is only observed when a certain threshold of WMH is reached. Our results are thus one of the first to shed light on a differential relationship between increasing WMH load and GMV, especially in the ECN, a network affected by the presence of cerebrovascular disease. In support of such findings, a few prior studies have illustrated increased cortical thickness related to the presence of WMH in older subjects without dementia (21, 53). Such findings suggest that mechanisms that have not been clearly elucidated may occur in response to low loads of WMH in frontoparietal regions especially in the absence of dementia. Increased cortical thickness has also been found in ageing studies likely indicative of local plasticity (54, 55). In patients with early stage cerebrovascular disease, inflammatory responses related to blood-brain barrier disruption may lead to the build-up of WMH accompanied by an increase in brain structural measures (52, 56). Such processes may underlie the relative sparing of GMV at low and intermediate WMH loads in our study in early stages of disease. However, the functional implications of these associations still remain under conjecture.

The finding of widespread negative association between WMH load and GMV at both the voxel-wise and ROI level at high WMH load evidenced in our study is supported by numerous prior studies (11, 15–22, 26). However, the mechanisms underlying this relationship need to be examined further. One possible mechanism includes anatomical disruptions due to the presence of subcortical WMH lesions subsequently leading to structural alterations of the cortex because of anterograde degeneration (57) as well as damage to specific white matter tracts connecting these regions (25, 58). Additionally, changes in cortical structures themselves can lead to axonal loss and demyelination due to Wallerian degeneration (59). Furthermore, the presence of WMH likely reflects microvascular damage, hypoperfusion and ischaemia within the cortex which may also underlie reduced GMV in overlapping regions and those connecting tracts affected by WMH (60, 61). Notably, in the present study, the relationships between WMH and GMV remain unchanged after controlling for both hypertension status and systolic blood

pressure, thus suggesting other independent WMH-related factors might be involved. Thus, in line with and in addition to previous findings, our results lend evidence to differential load-dependent relationships between WMH and brain structure.

The influence of WMH on cognition is predominantly thought to result in poor outcomes with prior studies showing reduction in executive function, memory and global cognition including perceptual speed (15, 27). However, in our study there were no pairwise associations between WMH and cognition, nor between GMV and cognition. Instead, the negative association between WMH and cognition was significant only when GMV in the ECN and DMN were taken into account. Specifically, at tercile 1, memory decline was associated with increasing WMH moderated by lower GMV in the DMN and ECN. At tercile 3, more widespread associations were observed. Memory function and executive function were negatively associated with increasing WMH moderated by GMV in the DMN and ECN. Our results thus support the notion that increasing WMH burden is related to more widespread cognitive decline, with this relationship being strengthened by GMV loss in frontoparietal regions. These findings are in line with prior studies showing cortical atrophy mediating the relationship between WMH and cognition including memory (11, 21, 22, 30). Since GMV moderated the relationship between WMH and cognition at both low and high WMH loads, it is likely that GMV is an important moderator regardless of WMH load. Additionally, increasing load of WMH, specifically periventricular WMH may result in damage to cholinergic neurotransmitter systems, and result in cognitive decline (62). Thus, further studies assessing the effect or varying WMH load on cognition and the role of regional GMV in this association at various stages of disease are required.

The clinical relevance of our study may be that specifically in patients with MCI, presence of low burden of WMH may be indicative of an early stage of cortical neurodegeneration (especially in regions critical for memory and executive function) wherein there is no grey matter loss, but instead there is compensatory grey matter increase (21, 53). Detection of this stage (MCI with low burden of WMH) may provide a window of opportunity to institute interventions to retard the neurodegenerative process. However, when WMH load crosses a certain threshold, irreversible GMV loss begins and disease modifying interventions to slow GMV loss may be less beneficial.

Limitations and future directions

Our study has several limitations. Since our analyses are based on cross-sectional data, our findings need to be further validated using a longitudinal dataset. Some of our findings did not pass multiple comparisons correction due to our moderate sample size though we used normalised data and data-driven methods to classify our levels of WMH load. In addition, although our MCI group was comprised of largely the amnesic sub-type, the presence of non-amnesic MCI subjects might confound the relationship between WMH, GMV and cognition. Notably, our cohort is representative of urban populations in Asia and worldwide. The generalizability of our findings to older populations and patients with lower education attainment will need to be studied further in future studies. We also do not have a sufficient sample size to study this effect on patients with AD dementia. Moreover, the amyloid and tau

status of our subjects was not known, thus we were unable to assess the influence of these AD biomarkers on the relationship between WMH and brain structure. Thus, future work will need to involve understanding the interaction between AD risk factors, WMH and GMV as well as the effect of white matter disruption on cognition across the AD spectrum.

Conclusions

In summary we demonstrate differential effects of WMH burden on frontoparietal atrophy in the DMN and ECN in a load-dependent manner ranging from sub-threshold to high WMH levels. Our results further shed light on the dynamic relationship between WMH load, GMV and cognitive performance. Detection of MCI with low WMH, may enable targeted therapeutic interventions to delay neurodegenerative changes in ECN and DMN regions.

Abbreviations

AD: Alzheimer's disease

ADAS: Alzheimer's Disease Assessment Scale

CSF: Cerebrospinal Fluid

DLPFC: Dorsolateral Prefrontal Cortex

DMN: Default Mode Network

ECN: Executive Control Network

FDR: False Discovery Rate

FLAIR: Fluid Attenuated Inversion Recovery

GM: Grey Matter

GMV: Grey Matter Volume

L: Left

LST: Lesion Segmentation Toolbox

MCI: Mild Cognitive Impairment

MPRAGE: MagnetizationPrepared Rapid Gradient Echo

MRI: Magnetic Resonance Imaging

PCC: Posterior Cingulate Cortex

PCN: Precuneus

PPC: Posterior Parietal Cortex

R: Right

ROIs: Regions of Interest

SPM12: Statistical Parametric Mapping

WM: White Matter

WMH: White matter hyperintensity

Declarations

Ethics approval and consent to participate

Informed consent for both studies was sought from each patient according to the Declaration of Helsinki and local clinical research regulations. The study was granted approval by the Singhealth Centralized Review Board.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Disclosures and Competing Interests

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Authors' Contributions

AV conceptualized and designed the study, carried out data analyses and drafted the manuscript and figures; NK conceptualized and designed the study, drafted the manuscript and figures and carried out the final review; KPN contributed to the study design and drafting of the manuscript and figures and carried out the final review; BYXW contributed to the acquisition of the data and design of study; DK contributed to the acquisition of the data and design of study; AL contributed to the acquisition of the data and design of study.

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Figures

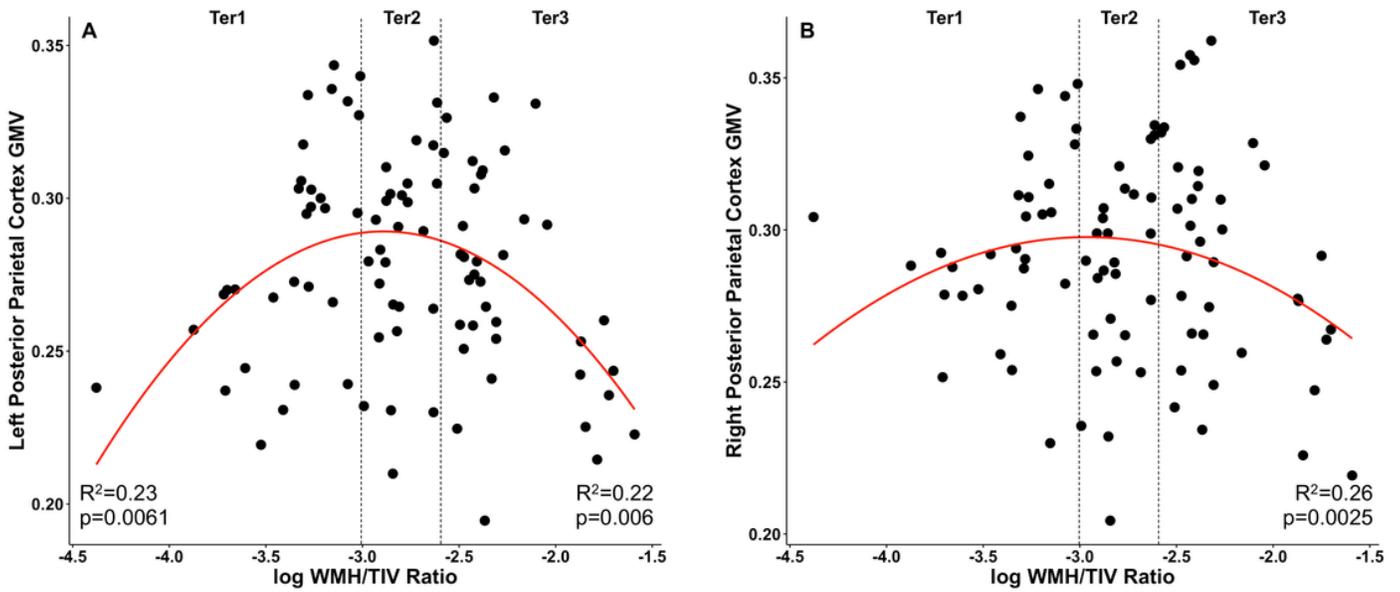


Figure 1

Load-dependent differential relationships between grey matter and white matter hyperintensity load in mild cognitive impairment. A) In tercile 1, GMV in the left posterior parietal cortex was positively related to WMH load. No relationship was observed at tercile 2. At tercile 3, on the other hand, the inverse was observed, with increasing WMH load relating to lower GMV in the posterior parietal cortex. B) Similarly, in the right posterior parietal cortex, increasing WMH load in the highest tercile 3 was related to lower GMV. Abbreviations: GMV, grey matter volume; WMH, white matter hyperintensity.

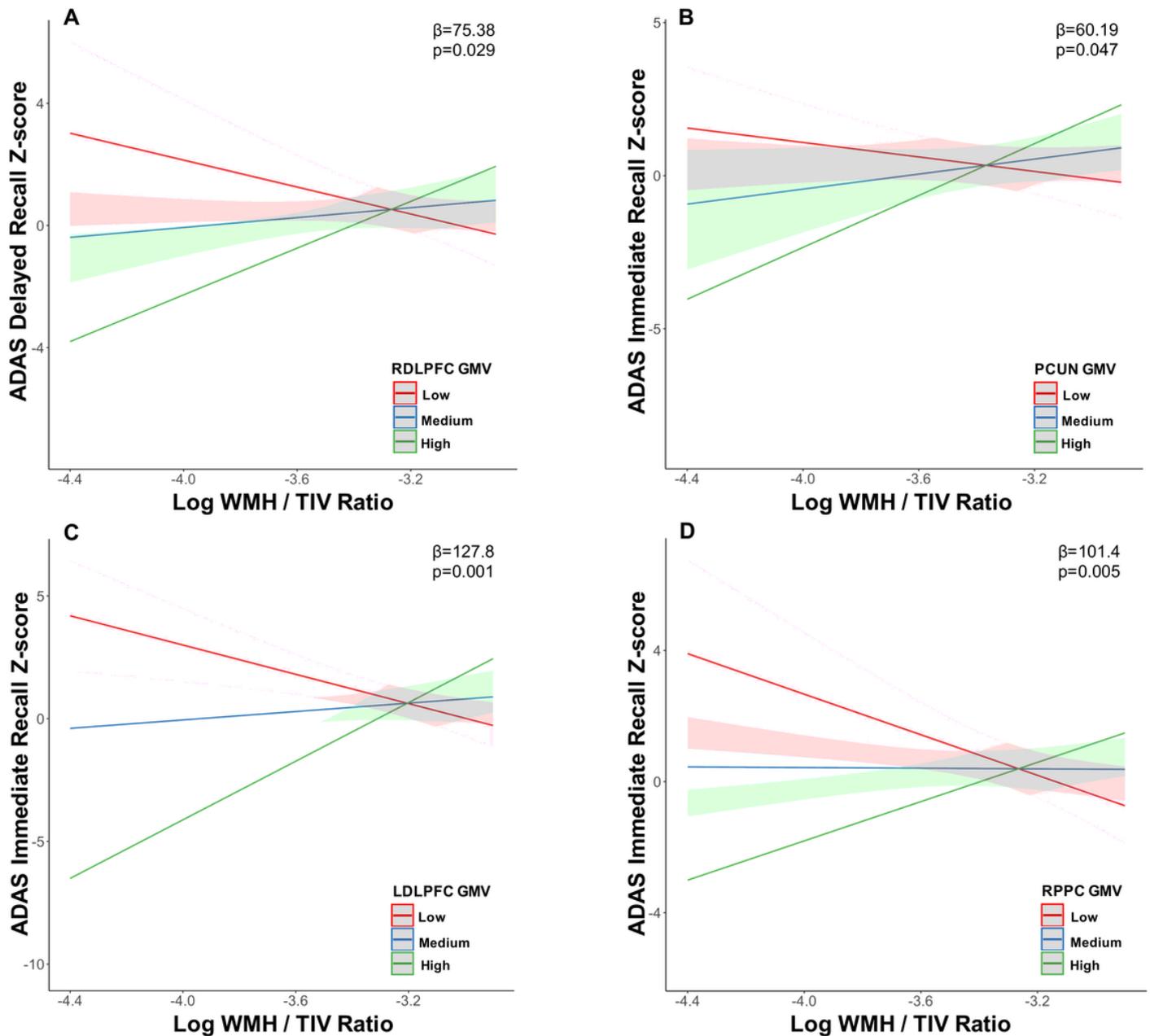


Figure 2

Grey matter volume in the default mode and executive control networks moderates the relationship between white matter hyperintensity volume and memory at low white matter hyperintensity load. In tercile 1, default mode network (PCUN) and executive control network (LDLPFC, RDLPFC, RPPC) grey matter volume moderated the relationship between memory (ADAS delayed recall, ADAS immediate recall) impairment and increasing WMH load. Abbreviations: ADAS, Alzheimer's disease assessment scale; WMH, white matter hyperintensity; TIV, total intracranial volume; LDLPFC, left dorsolateral prefrontal cortex; RDLPFC, right dorsolateral prefrontal cortex; RPPC, right posterior parietal cortex; PCUN, precuneus; GMV, grey matter volume.

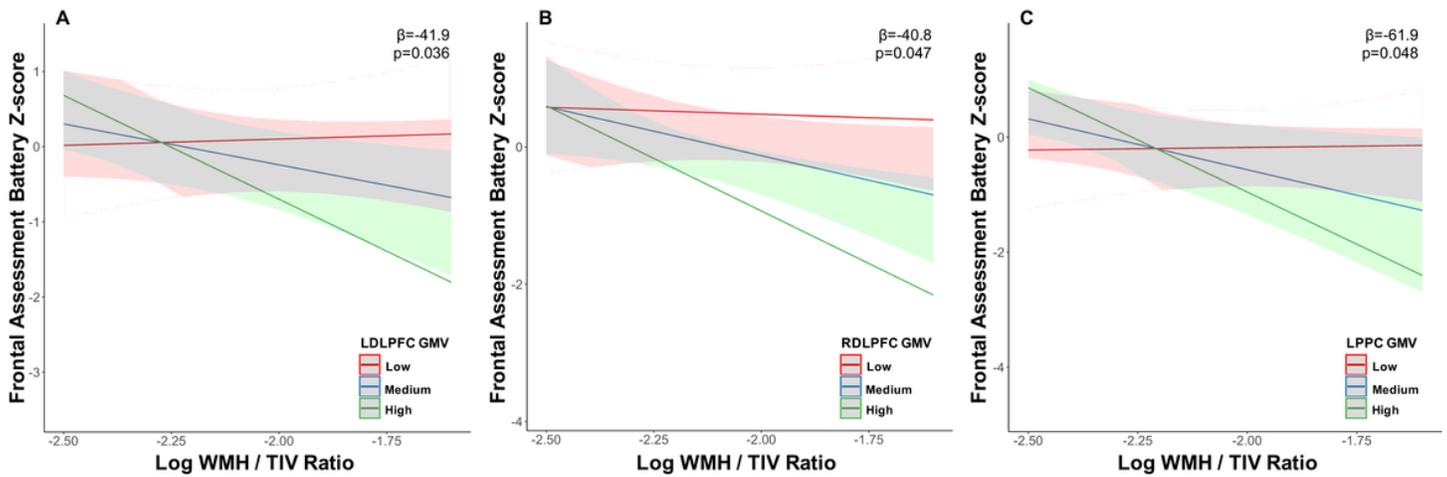


Figure 3

Grey matter volume in the executive control network moderates the relationship between white matter hyperintensity volume and executive function at high white matter hyperintensity load. The association between executive function (frontal assessment battery) decline and increasing WMH load in tercile 3 was moderated primarily by executive control network (LDLPFC, RDLPFC, LPPC) grey matter volume. Abbreviations: WMH, white matter hyperintensity; TIV, total intracranial volume; LDLPFC, left dorsolateral prefrontal cortex; RDLPFC, right dorsolateral prefrontal cortex; LPPC, left posterior parietal cortex; GMV, grey matter volume.

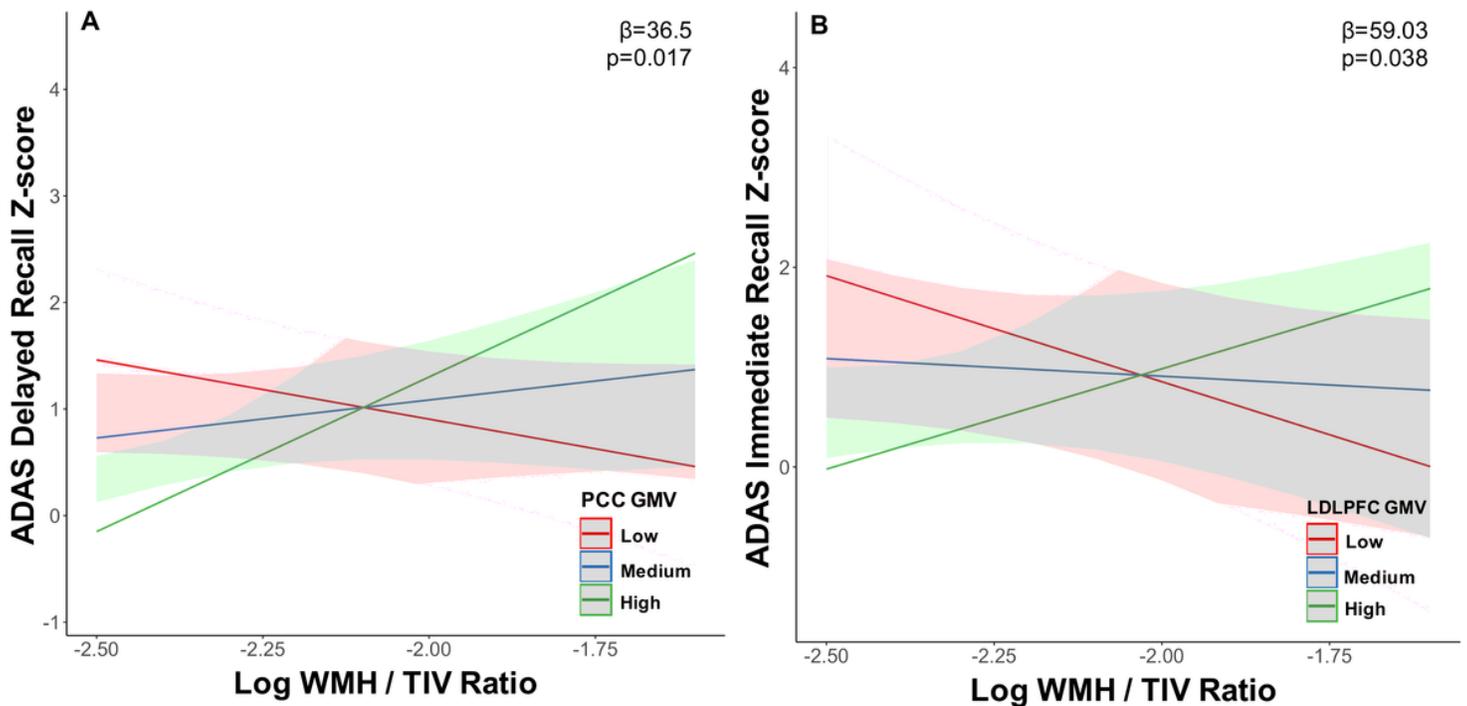


Figure 4

Grey matter volume in the default mode and executive control networks moderates the relationship between white matter hyperintensity volume and memory at high white matter hyperintensity load. In tercile 3, default mode network (PCC) and executive control network (LDLPFC) grey matter volume moderated the relationship between memory (ADAS delayed recall, ADAS immediate recall) impairment and increasing WMH load. Abbreviations: ADAS, Alzheimer's disease assessment scale; WMH, white matter hyperintensity; TIV, total intracranial volume; LDLPFC, left dorsolateral prefrontal cortex; RDLPFC, PCC, posterior cingulate cortex; GMV, grey matter volume.