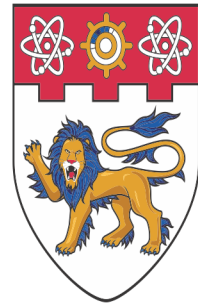


Arterial Transit Time and Blood-brain Barrier Exchange Reflect Early Cognitive Vulnerability in White Matter Hyperintensities



NANYANG
TECHNOLOGICAL
UNIVERSITY

SINGAPORE

LEE KONG CHIAN SCHOOL OF
MEDICINE

James Xiao Yuan Chen (BEng)¹, Ashwati Vipin (PhD)¹, Jessie Siew-Pin Leuk (PhD)¹, Kiirtaara Aravindhan (PhD)¹, Gursimar Bhalla (BSc)¹, Bocheng Qiu (MEng)¹, Jacklyn Leonardo (MSc)¹, Deneshan Peranantharajah (MBBS)¹, Nagaendran Kandiah (FRCP)^{1,2,3},

¹Dementia Research Centre (Singapore), 11 Mandalay Road, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore 308232; ²Neuroscience and Mental Health Programme, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; ³National Healthcare Group, Singapore;

In 594 community participants, Arterial Transit Time (ATT) showed widespread white matter hyperintensity (WMH) related disruption and the strongest cognitive association profile, while blood-brain barrier water exchange (T_{ex}) provided complementary evidence of early neurovascular vulnerability, particularly for processing speed and executive function.

Introduction

Background:

- White matter hyperintensities (WMH) are imaging markers of cerebral small vessel disease and are associated with cognitive impairment¹.
- Cognitive vulnerability may reflect not only lesion burden, but also altered vascular delivery and blood-brain barrier function¹.
- Multi-echo arterial spin labelling enables non-contrast estimation of arterial transit time (ATT), cerebral blood flow (CBF), and blood-brain barrier water exchange time (T_{ex}).

Research Gap:

- It remains unclear whether these hemodynamic metrics identify early vascular dysfunction across WMH burden, and whether they relate to cognitive domains most vulnerable to small vessel disease, particularly processing speed and executive function.

Aim:

- To explore whether ATT, CBF, and T_{ex} act as candidate hemodynamic biomarkers of early vascular pathology and cognitive vulnerability across low and high WMH burden.

Methodology

Study cohort:

- Analysed 594 adults from the Biomarkers and Cognition Study, Singapore (BIOCIS), with neuropsychological assessment and multi-echo arterial spin labelling magnetic resonance imaging.

White matter hyperintensity stratification:

- White matter hyperintensity burden was rated on fluid-attenuated inversion recovery magnetic resonance imaging using a modified Fazekas scale and classified as low burden scores 0-4, n = 538, or high burden scores 9-12, n = 56.

Cognitive outcomes:

- Domain level z-scores were derived for episodic memory, executive function, processing speed, and visuospatial function.

Hemodynamic imaging:

- Three Tesla multi-echo pseudocontinuous arterial spin labelling estimated ATT, CBF, and T_{ex} across Hammers-atlas grey matter regions and global grey matter.

Statistical analysis:

- Group differences in hemodynamic metrics were tested using age, sex, and education adjusted analysis of covariance with Benjamini-Hochberg false discovery rate (FDR) correction. Within each WMH burden group, regression models tested associations between hemodynamic metrics and cognitive domains.

Results

Demographic profile

- High WMH burden was associated with older age and fewer years of education.

Cognitive profile

- High-burden participants showed lower performance across all assessed cognitive domains.

Global imaging profile

- High-burden participants showed greater WMH volume, prolonged global ATT, reduced global CBF, and shorter T_{ex} .

Modelling implication

- Subsequent regional and cognitive association models adjusted for age, sex, and education.

Category	Low WMH burden (N = 538)	High WMH burden (N = 56)	p-value
Age (years)	54.2 (9.7)	70.1 (7.7)	<0.001*
Sex (F %)	352 (65.4)	25 (44.6)	0.003*
Education Years, (years)	15.8 (3.0)	13.4 (3.3)	<0.001*
Episodic Memory (Z-score)	0.17 (0.7)	-0.54 (1.2)	<0.001*
Executive Function (Z-score)	0.12 (0.9)	-0.68 (0.8)	<0.001*
Processing Speed (Z-score)	0.38 (1.0)	-0.73 (1.1)	<0.001*
Visuospatial (Z-score)	0.10 (0.8)	-0.17 (0.8)	0.009*
White Matter Hyperintensity volume (mL)	1.07 (0.7)	9.96 (8.0)	<0.001*
Global Arterial Transit Time (S)	1.29 (0.2)	1.51 (0.1)	<0.001*
Global Cerebral Blood Flow (mL/100g/min)	67.1 (12.8)	59.0 (13.3)	<0.001*
Global T_{ex} time (S)	0.25 (0.1)	0.20 (0.04)	<0.001*

Figure 1. Baseline characteristics stratified by white matter hyperintensity burden. Participants were classified by modified Fazekas score into low burden, scores 0-4, and high burden, scores 9-12. Continuous variables are shown as mean (standard deviation) unless otherwise stated; p-values represent unadjusted between-group comparisons.

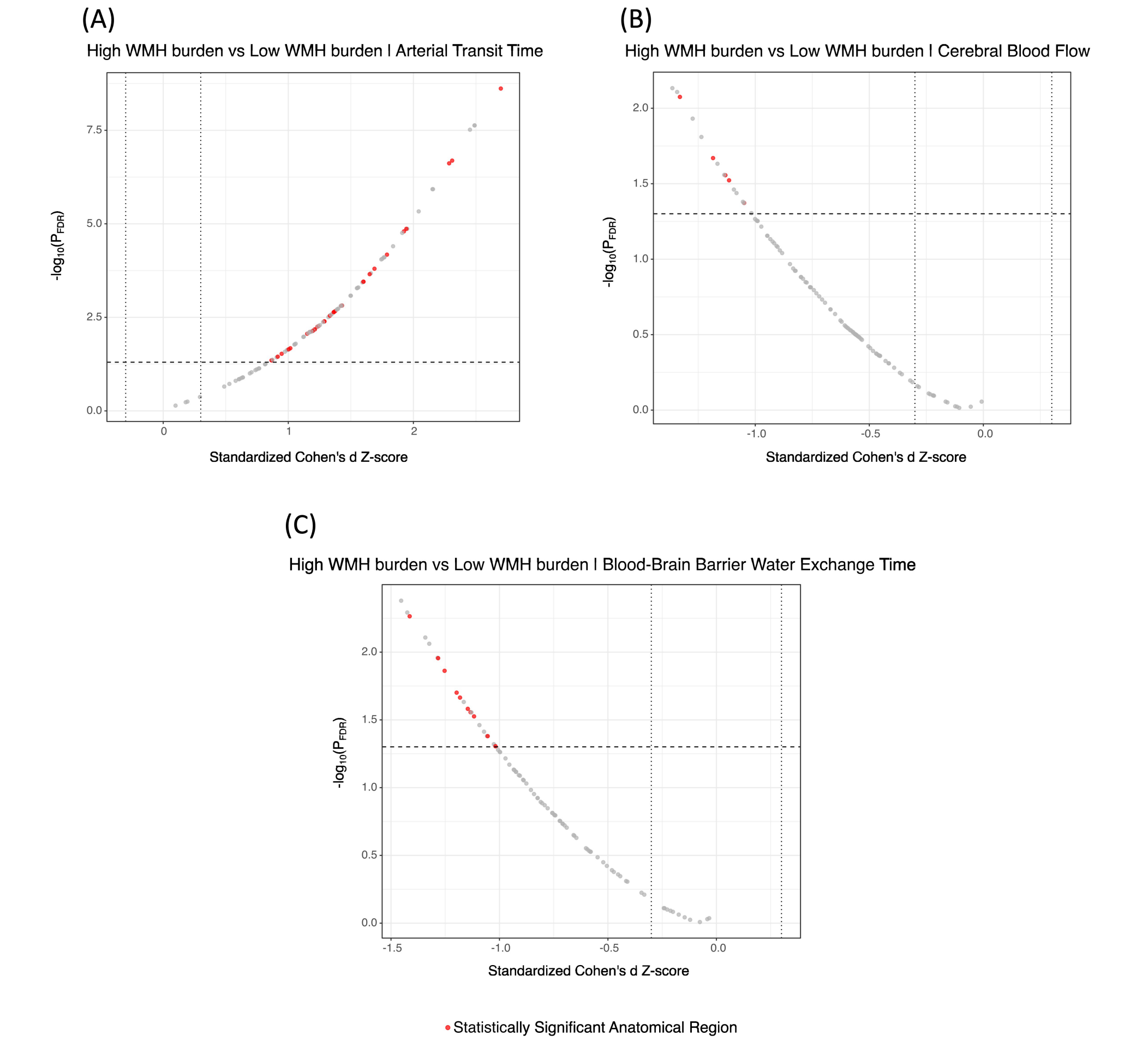


Figure 2. Regional hemodynamic differences between high and low WMH burden. Volcano plots show covariate-adjusted group differences in (A) ATT, (B) CBF, and (C) T_{ex} across anatomical regions and global grey matter. Each point represents one region; red points indicate regions surviving BH-FDR correction. WMH, white matter hyperintensity; ATT, arterial transit time; CBF, cerebral blood flow; T_{ex} , blood-brain barrier water exchange time; FDR, false discovery rate; BH, Benjamini-Hochberg.

- ATT showed the broadest burden related regional abnormality, predominantly reflecting prolongation in high WMH burden.
- CBF and T_{ex} showed fewer significant regions, indicating more spatially selective abnormalities.
- Overall, ATT appeared to be the most spatially extensive hemodynamic marker of WMH burden.

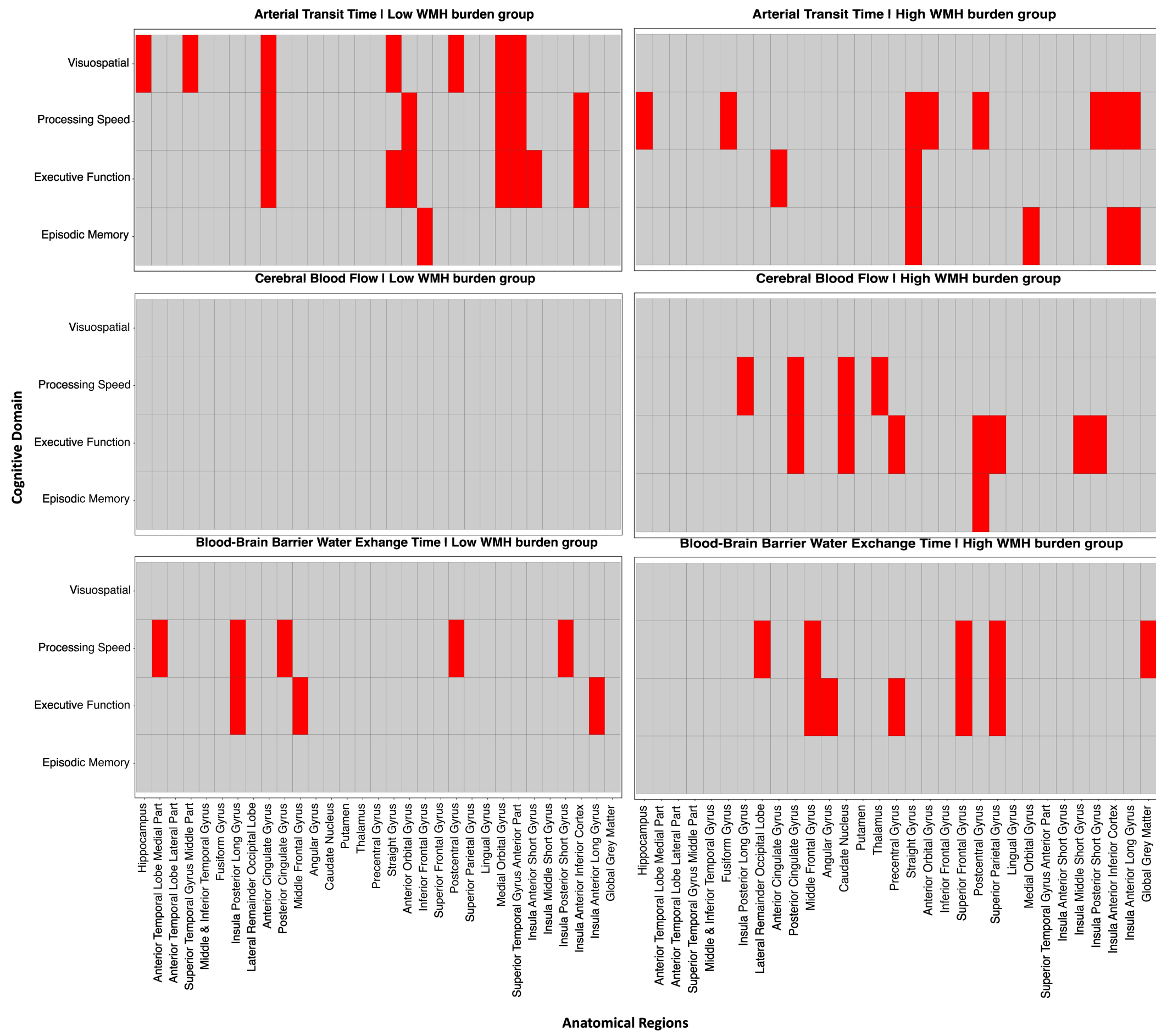


Figure 3. Hemodynamic-cognition association maps by WMH burden. Heatmaps show within-group associations between ATT, CBF, T_{ex} , and cognitive domains. Rows represent cognitive domains and columns represent anatomical regions. Red cells indicate statistically significant associations; grey cells indicate non-significant associations. WMH, white matter hyperintensity; ATT, arterial transit time; CBF, cerebral blood flow; T_{ex} , blood-brain barrier water exchange time.

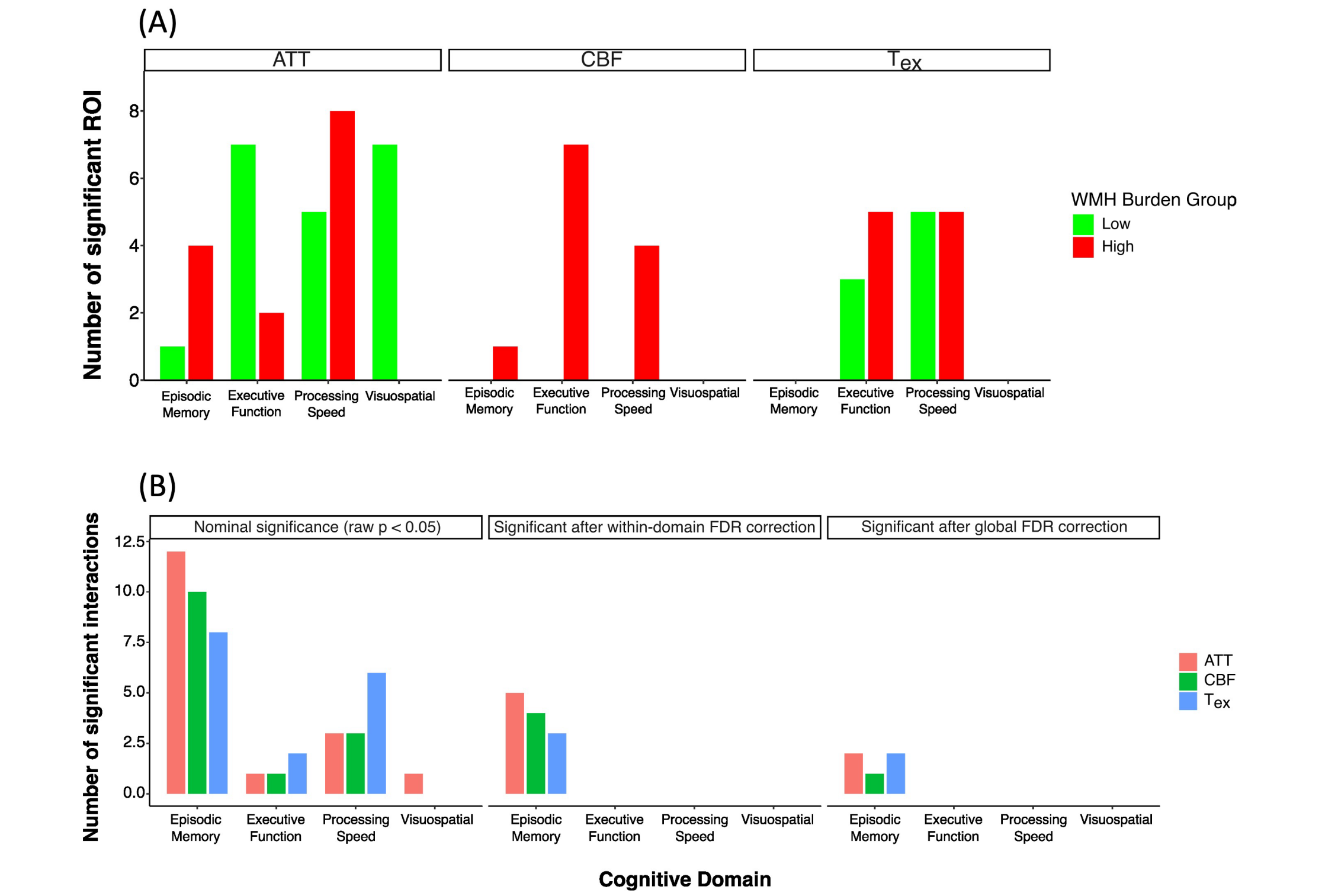


Figure 4. Domain-level association and interaction density. (A) Counts of significant region-level associations between hemodynamic metrics and cognitive domains within low and high WMH burden groups. (B) Counts of significant hemodynamic metric $\times$ WMH burden interaction terms across cognitive domains, shown at nominal significance, within-domain FDR correction, and global FDR correction thresholds. WMH, white matter hyperintensity; ATT, arterial transit time; CBF, cerebral blood flow; T_{ex} , blood-brain barrier water exchange time; FDR, false discovery rate.

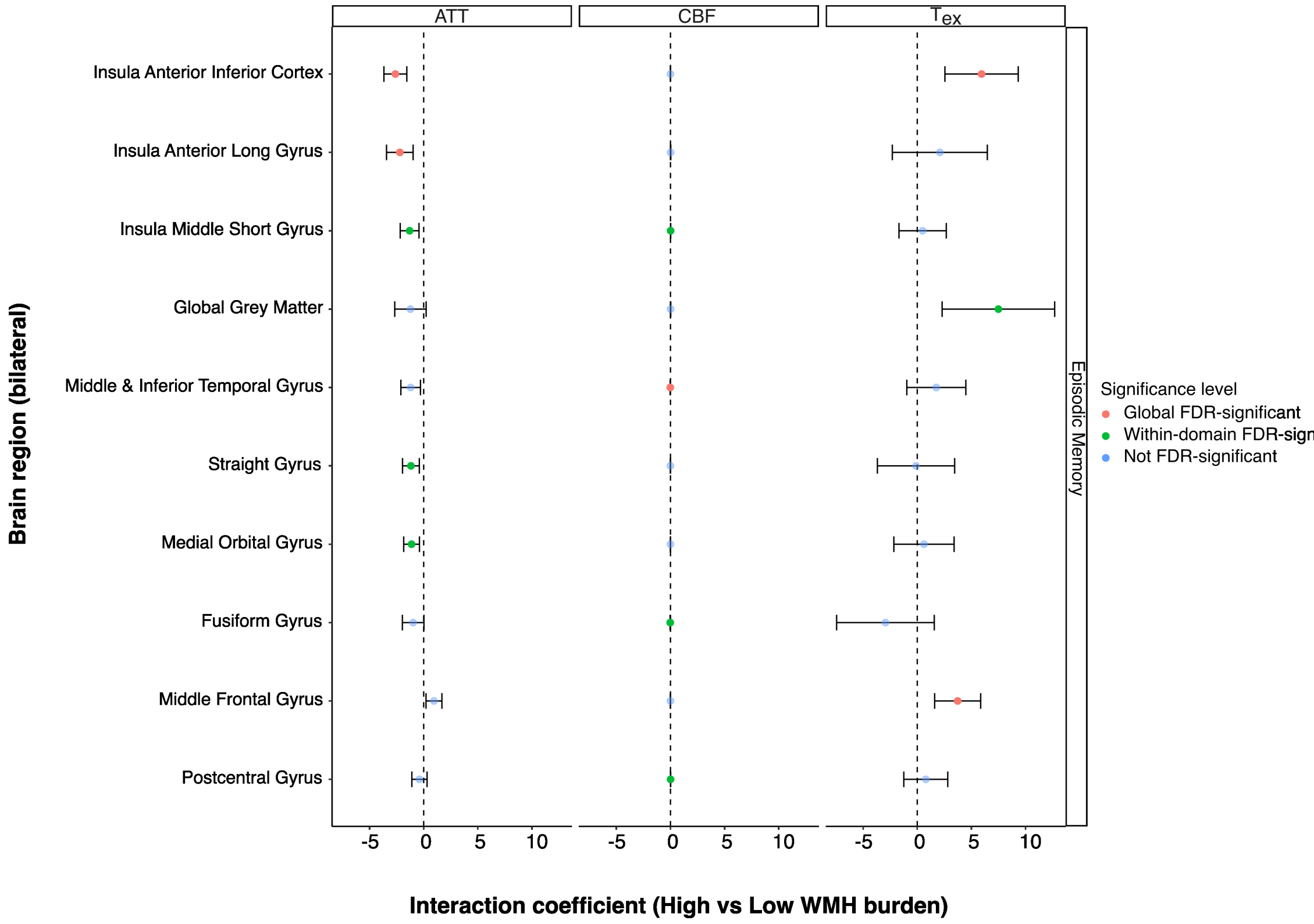


Figure 5. Regional interaction effects for episodic memory. Forest plots show hemodynamic metric $\times$ white matter hyperintensity burden interaction coefficients across selected bilateral regions. Points indicate estimated effects and horizontal lines indicate confidence intervals

- Within-group analyses highlighted **processing speed** and **executive function** associations.
- Interaction analyses revealed an emerging **episodic memory** burden modulated signal.
- Cognitive vulnerability signals were more evident for **ATT** and T_{ex} than for cerebral blood flow.

Conclusion

- ATT showed the broadest WMH related hemodynamic disruption.
- T_{ex} provided complementary evidence of neurovascular dysfunction and cognitive vulnerability.
- Together, these metrics may help identify early vascular cognitive vulnerability beyond WMH burden alone.

Acknowledgement

- We thank the Dementia Research Centre (Singapore), Nanyang Technological University, Singapore, for supporting participant recruitment, cognitive assessment, neuroimaging acquisition, and data curation.

Reference

- Markus HS, Joutel A. The pathogenesis of cerebral small vessel disease and vascular cognitive impairment. *Physiological Reviews*. 2025;105(3):1075-1171. doi:10.1152/physrev.00028.2024