

WMH and Cardiovascular Risk Jointly Shape NAWM Microstructure and Cognitive Function in Ageing

Fábio Carneiro^{1,2}, Camille Cathala³, Cristina Ramponi¹, Mihály Gayer^{1,2}, Aurélie Bussy¹, Bogdan Draganski^{1,4}

1 - inAGE Lab, Department of Neurology, Inselspital, Bern; 2 - Graduate School for Health Sciences, University of Bern; 3 - Signal Processing Lab 5, EPFL, Lausanne; 4 - Institute for Diagnostic & Interventional Neuroradiology, Inselspital, Bern



- White matter hyperintensities (WMH) on FLAIR are linked to cardiovascular risk factors (CVRF) and cognitive impairment in ageing. Microstructural damage extends beyond FLAIR-visible lesions into normal-appearing white matter (NAWM)^{1,2}, which may reflect diffuse "pre-lesional" damage³ from upstream drivers or arise secondary to WMH^{1,4}. WMH-related cognitive change may likewise stem from focal lesions or NAWM alterations⁵. Quantitative MRI (qMRI) and multishell diffusion-weighted imaging (DWI) yield in-vivo indices of myelin/iron, axonal, and unbound-water content⁶.
- In two **population-based cohorts** with available **FLAIR, qMRI and DWI** (BrainLaus and SACR; n=343, age 71.2±7.9, 56% female), we aimed to: (1) clarify how **CVRF (SCORE2^{7,8})** and **WMH** burden jointly relate to **NAWM microstructure**; (2) characterize **WMH-related cognitive effects** and whether they are **mediated by NAWM microstructure**.

Methods & Results

1 WMH and CVRF jointly shape NAWM microstructure

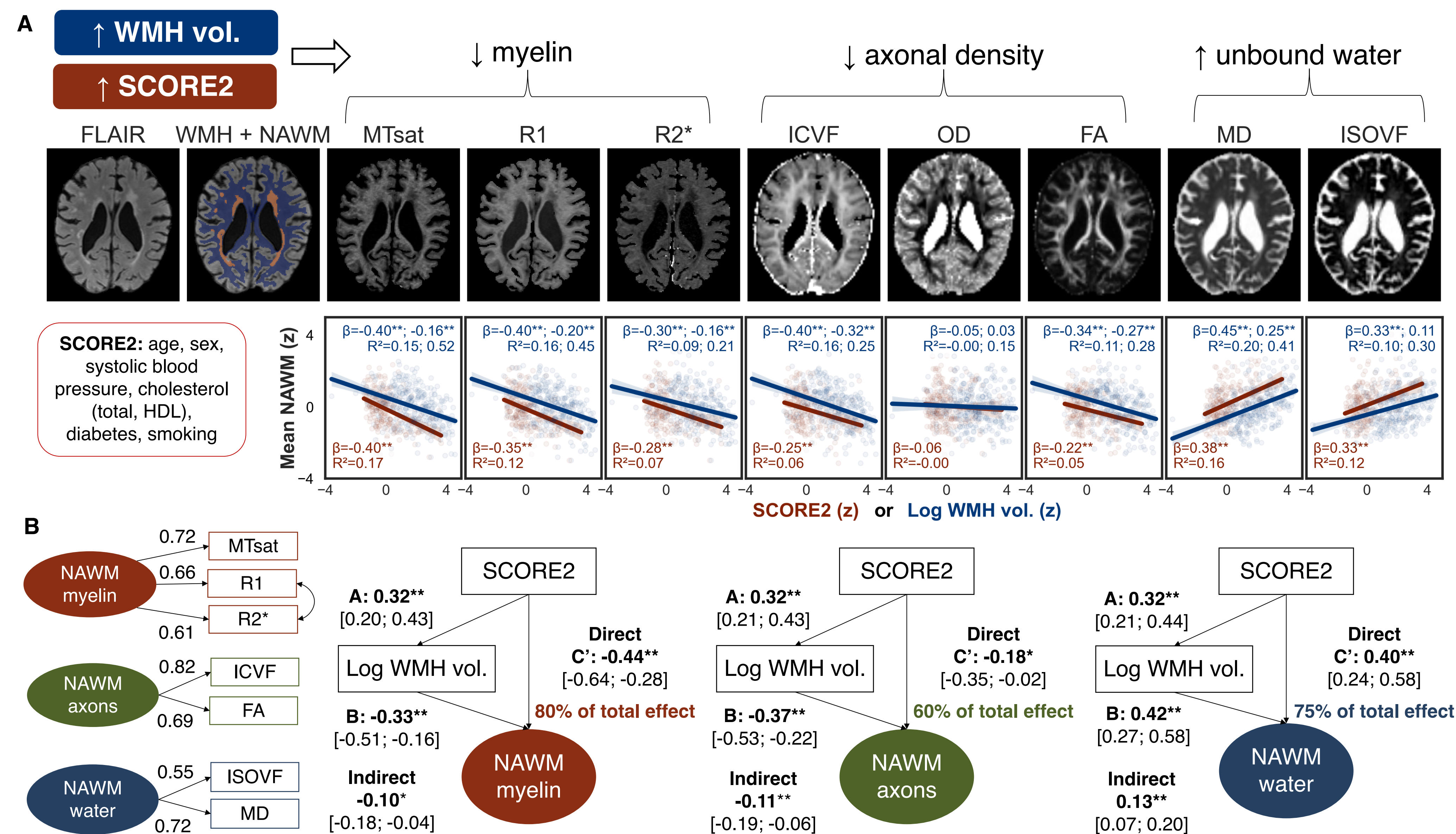


Figure 1. (A) WMH masks generated with White-Net⁹; CVRF burden by SCORE2; NAWM microstructure by qMRI and DWI. In multiple linear regression, higher WMH volume and SCORE2 were associated with reduced myelin- and axonal-sensitive and increased unbound-water metrics. β /R² annotations: WMH volume — unadjusted; adjusted (age, sex, total WM volume); SCORE2 — unadjusted only (age and sex captured by SCORE2). **(B)** Structural equation models (SEM) with microstructural latent variables: direct and WMH-mediated (indirect) effects of SCORE2 on NAWM; direct effects were smaller for axonal metrics. OD was excluded from axonal latent variable (no association with SCORE2 or WMH in A). All models corrected for total WM volume. Bootstrap CIs, 5,000 resamples. **p<0.001; *p<0.05, FDR-corrected.

2 Cognitive effects of WMH and related NAWM alterations

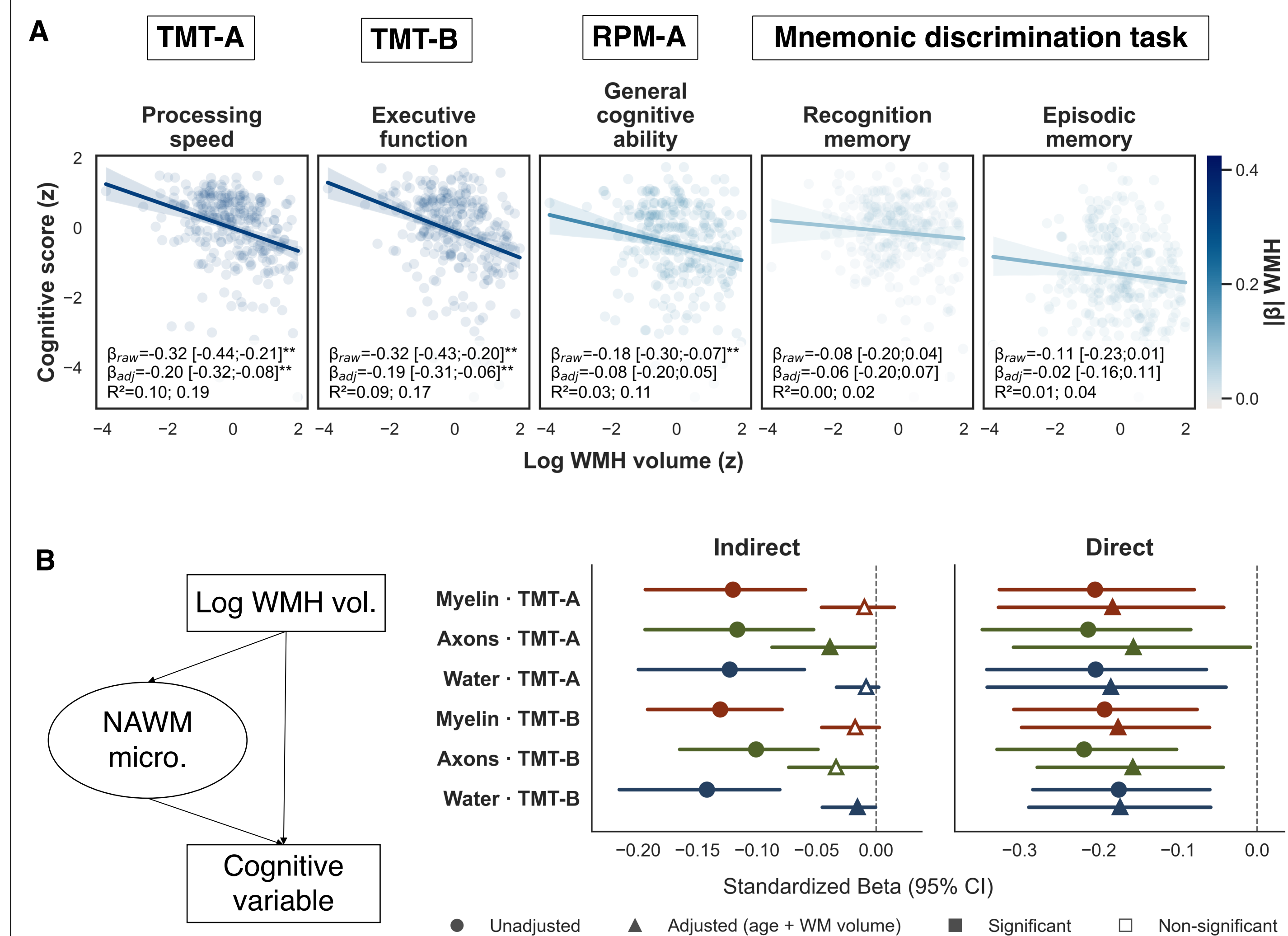


Figure 2. (A) Cognitive battery: Trail Making Test A and B (TMT-A/B), Raven's Progressive Matrices - abbreviated (RPM-A), and a mnemonic discrimination task yielding recognition and episodic (similarity discrimination) memory scores. All cognitive scores were adjusted for education. TMT-A/B scores were inverted. Higher WMH volume was associated with reduced processing speed (TMT-A) and executive function (TMT-B). β /R² annotations: unadjusted (β_{raw}) and adjusted (β_{adj} : age, sex, total WM volume). **(B)** SEM with microstructural latent variables, showing direct and NAWM-mediated (indirect) effects of WMH volume on TMT-A and TMT-B; effects were predominantly direct, with indirect effects attenuated after age adjustment. Bootstrap CIs, 5,000 resamples. **p<0.001; *p<0.05, FDR-corrected.

Discussion

qMRI and DWI detect NAWM microstructural alterations related to CVRF and WMH. CVRF acted predominantly through direct effects on myelin- and water-sensitive metrics, with smaller direct effects for axonal metrics. This suggests **lesion-related axonal involvement**, contrasting with **lesion-independent** (potentially more diffuse and/or pre-lesional) **myelin injury and oedema**, in line with pathological studies^{10,11,12}. CVRF-independent NAWM alterations linked to WMH may implicate upstream mechanisms beyond CVRF^{12,13} and reinforce the presence of lesion-related injury. WMH-related cognitive impairment primarily affected **processing speed and executive function**, reflecting mainly focal lesion effects and, to a lesser degree, age-associated NAWM changes.

References

- Wardlaw JM et al. Lancet Neurol. 2019;18(7):684–696.
- Bussy A et al. Brain. 2026;awag200.
- Jochems ACC et al. J Am Heart Assoc. 2024;13(3):e032259.
- Li H et al. Brain. 2023;146(11):4659–4673.
- Tuladhar AM et al. NeuroImage Clin. 2015;7:518–524.
- Weiskopf N et al. Nat Rev Phys. 2021;3:570–588.
- SCORE2 Working Group. Eur Heart J. 2021;42(25):2439–2454.
- SCORE2-OP Working Group. Eur Heart J. 2021;42(25):2455–2467.
- Cathala C et al. Under revision.
- Englund E, Brun A. Histopathology. 1990;16(5):433–439.
- McAleese KE et al. Acta Neuropathol. 2017;134(3):459–473.
- McAleese KE et al. Brain Pathol. 2019;29(3):414–424.
- Garner-Crussard A et al. Alzheimers Dement. 2023;19(9):3738–3748.

Acknowledgments

This project was funded by SNF grant number 213595. We thank BrainLaus and SACR participants for their participation.

Contact

