

Complementary Associations of Plasma Neurofilament Light and DTI-Derived Free Water with Cognitive Function

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Free water and plasma NfL provide complementary information about cognition. Free water is associated with executive function across the cognitive spectrum, whereas plasma NfL is most informative among cognitively impaired individuals.

INTRODUCTION

- Neurofilament light chain (NfL) is a neuron-specific protein that can serve as a **minimally invasive biomarker for neurodegeneration**.
- Our previous work shows diffusion tensor imaging (DTI)-derived free water (FW) is a **sensitive marker of white matter injury** linked to cognition.
- NfL and FW** capture distinct processes of brain injury and examining their independent **and joint associations with cognition may clarify how axonal and microstructural damage relates to cognitive function**.

METHODS

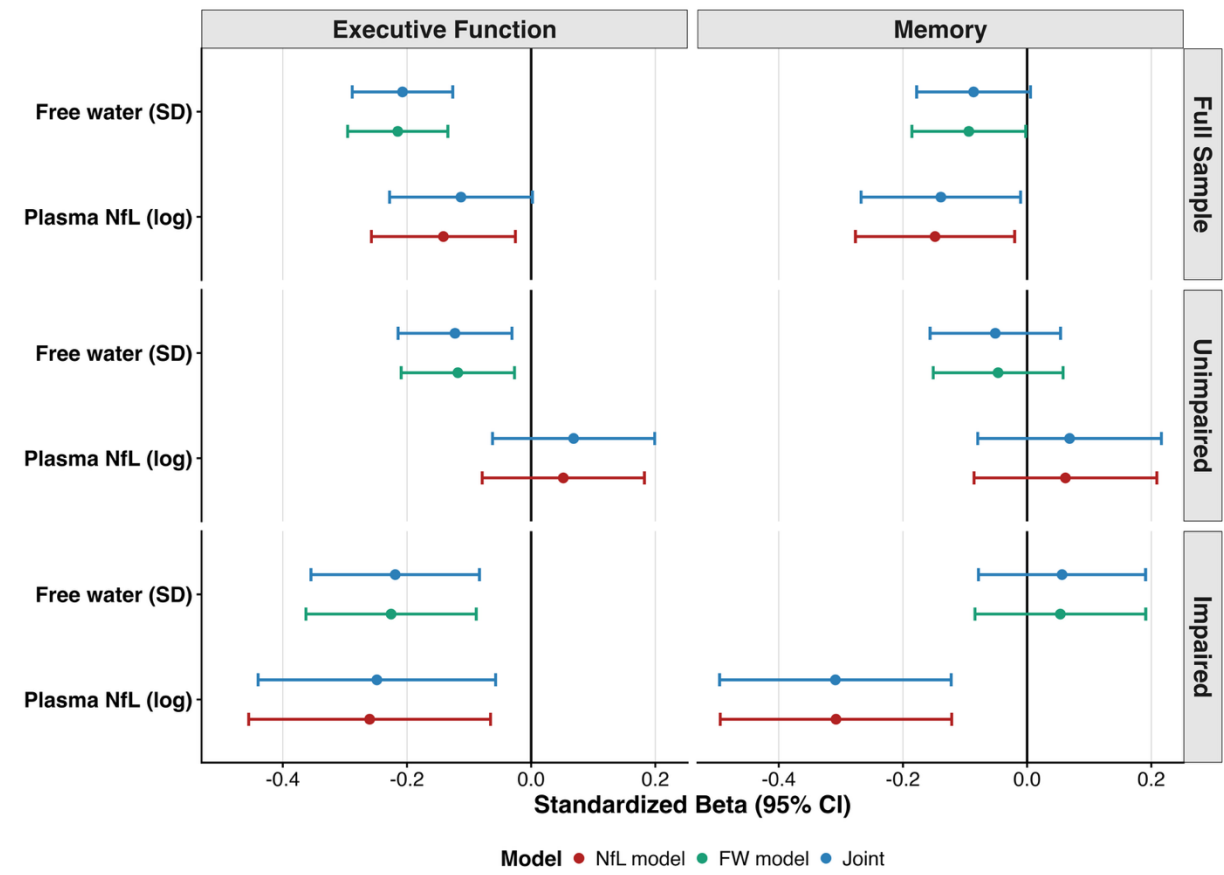
- Sample:** N = 960 (Diverse VCID); unimpaired and impaired (MCI/dementia),
- Imaging:** 3T MRI; standardized FW; log-WMH residualized on TCV
- Biomarker:** Plasma NfL (log-transformed)
- Cognition:** Standardized Executive Function (sEF) and Memory (sEM)
- Analysis:** Adjusted linear regression (age, sex, education, race, and ethnicity)
- Outcomes:** sEF and sEM
- Analyses were conducted in the full sample and stratified by cognitive status.

Table 1: Participant Characteristics.

	Overall (N=960)	Unimpaired (N=671)	Impaired (N=245)
Age, years	74.2 ± 5.8	74.0 ± 5.7	74.8 ± 6.2
Female sex, n (%)	680 (70.8)	465 (69.3)	175 (71.4)
Race, n (%)			
White	597 (62.2)	458 (68.3)	125 (51.0)
Black	318 (33.1)	179 (26.7)	109 (44.5)
Other	45 (4.7)	34 (5.1)	11 (4.5)
Hispanic, n (%)	268 (27.9)	191 (28.5)	69 (28.2)
Neurofilament light	2.94 ± 0.57	2.91 ± 0.55	3.06 ± 0.62
Free water	0.208 ± 0.035	0.205 ± 0.033	0.217 ± 0.040
Executive function (sEF)	0.08 ± 0.97	0.32 ± 0.89	-0.58 ± 0.88
Memory (sEM)	0.05 ± 0.98	0.35 ± 0.90	-0.71 ± 0.88

RESULTS

Figure 1. Independent and joint associations of plasma NfL and FW with cognition.



Executive Function

- FW associated in: Full sample, Unimpaired, and mpaired
- NfL strongest in impaired participants

Memory

- NfL associated in: Full sample and Impaired
- FW weaker association

FW remained independently associated with executive function, while NfL remained independently associated only among cognitively impaired individuals.

CONCLUSIONS

- FW and plasma NfL demonstrate distinct yet complementary associations with cognitive function.**
- FW was consistently associated with **executive function**, suggesting that microstructural white matter injury contributes early and broadly to cognitive vulnerability.
- Plasma **NfL** showed stronger associations among **cognitively impaired** individuals, consistent with axonal injury.
- These findings support the integration of **multimodal biomarkers** to improve the characterization and staging of vascular-related cognitive impairment.

Clinical Implications

- Plasma biomarkers and MRI biomarkers reflect different biological processes.
- Combining them may improve risk stratification.
- Multimodal biomarkers could improve participant selection for future clinical trials.

CONTACT

Acknowledgement: We thank all study participants and staff for their invaluable contributions to this research. This work was supported by National Institutes of Health (NIH) grants P30 AG072972, U19NS120384, R01 AG075758, RF1 AG077639, and RF1 NS130659..

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