

The association between Neurofilament Light Chain and Glial Fibrillary Acidic Protein with Apathy in Neurocognitive Disorders

Krushnaa Sankhe^{1,2}, Amer M. Burhan^{3,8}, Barry Campbell⁴, Philippe Desmarais⁵, Corinne Fischer³, Zahra Goodarzi⁶, Nathan Herrmann³, Zahinoor Ismail⁶, Dallas Seitz^{3,6}, Mabelle Wilchesky⁷, Krista L. Lanctôt^{1,2,3}

¹ Sunnybrook Research Institute, Toronto, ON, Canada; ² Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada; ³ Department of Psychiatry, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada; ⁴ Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada; ⁵ Université de Montréal, Montréal, QC, Canada; ⁶ Department of Psychiatry, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada; ⁷ Department of Family Medicine and Division of Geriatric Medicine, McGill University, Montréal, QC, Canada; ⁸ Ontario Shores Centre for Mental Health Sciences, Whitby, ON, Canada.

Background

- Apathy is a persistent neuropsychiatric symptom (NPS) present across the neurocognitive disorder (NCD) spectrum.
- Neuronal and astroglial injury contribute to cognitive dysfunction but links to NPS such as apathy remain unknown.

Aim

- Here, we investigated associations between apathy and neuronal and astroglial injury markers across the NCD spectrum.

Methods

Participants:

- Data were obtained from the Comprehensive Assessment of Neurodegeneration and Dementia: Canadian Cohort Study (COMPASS-ND).
- Participants included cognitively unimpaired (CU) individuals, individuals with subjective cognitive impairment (SCI), mild NCD and major NCD.
- Major NCD included Alzheimer's disease dementia, Frontotemporal dementia, Lewy Body dementia, and Parkinson's Disease (PD) dementia.
- Mild NCD included mild cognitive impairment (MCI) and PD-MCI.

Measures:

- Apathy: Apathy severity was measured using the caregiver-rated Apathy Inventory (IA) scale.
- Cognition: Global cognition was assessed using Montreal Cognitive Assessment (MoCA).

Biomarkers:

- Neuronal injury was assessed using plasma neurofilament light chain (NfL).
- Astroglial injury was assessed using plasma Glial Fibrillary Acidic Protein (GFAP).
- Biomarker concentrations were measured using the Simoa Neurology 4-Plex E Advantage Kit (Quanterix, Billerica, MA, USA) on the HD-X platform.

Statistical analysis:

- Multivariable linear regression examined associations between apathy severity and log-transformed plasma NfL and GFAP, adjusted for age, sex, MoCA score, and diagnostic group.
- Secondary analyses examined associations across apathy domains (initiative, interest, emotion).
- Exploratory analyses assessed whether associations differed by diagnostic group by including biomarker × diagnostic group interaction terms in the models.

Results

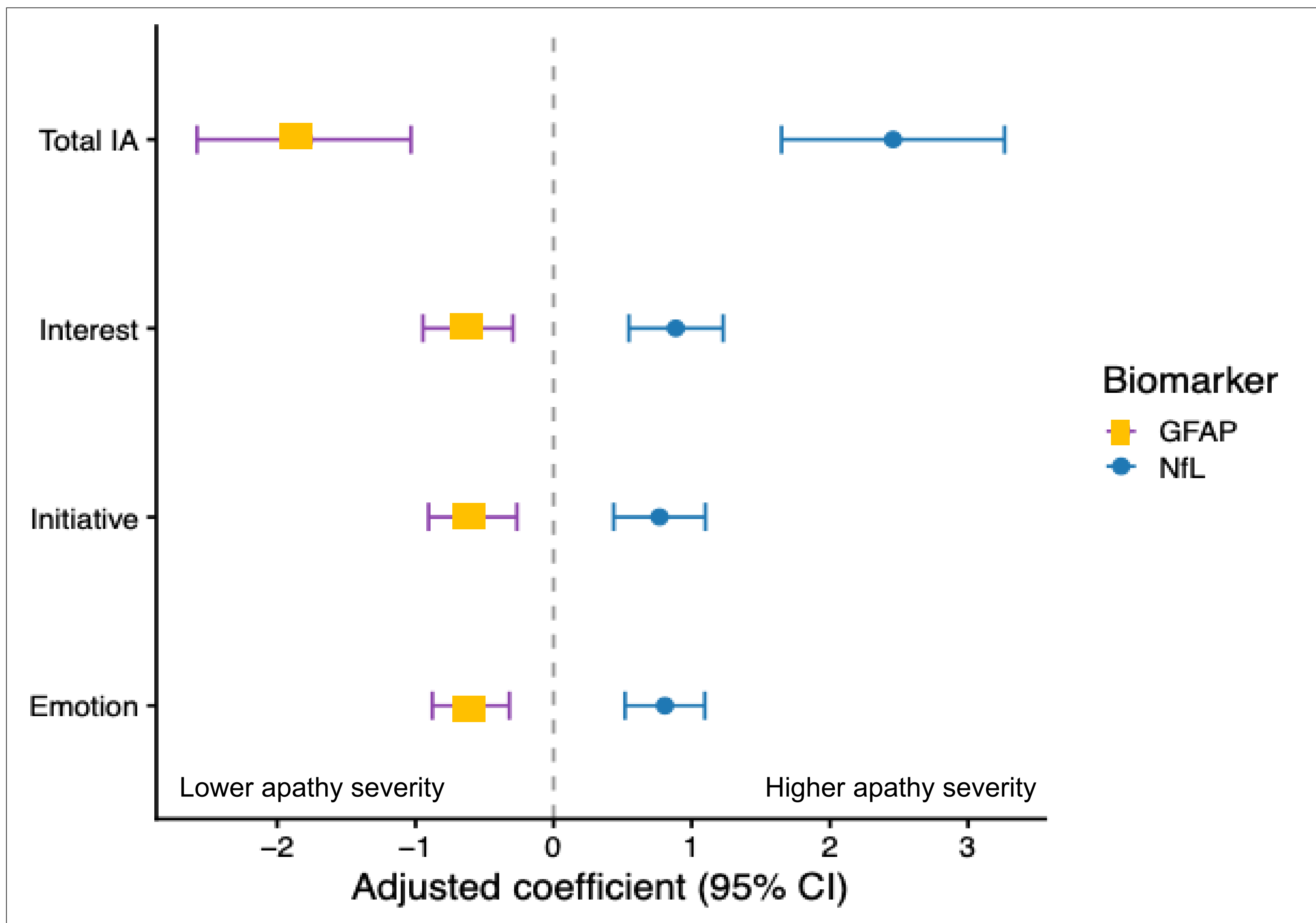
- 809 participants [mean (SD) age= 72.0 (7.2) years; 54% male] were included.
- Primary results:** Higher plasma NfL and lower plasma GFAP were independently associated with greater total IA scores (**Figure 1**).
- Secondary results:** Associations were consistent across the initiative, interest and emotion domains (**Figure 1**).
 - Initiative:** NfL: 0.77 [0.17], p < 0.001; GFAP: -0.59 [0.16], p < 0.001
 - Interest:** NfL: 0.89 [0.17], p<0.001; GFAP: -0.62 [0.17], p<0.001
 - Emotion:** NfL: 0.81 [0.15], p<0.001; GFAP: -0.60 [0.14], p<0.001

Table 1. Demographics and clinical characteristics of study sample.

	Overall (N=809)	CU (N=123)	SCI (N=99)	Mild NCD (N=382)	Major NCD (N=205)
Age, mean (SD)	72.0 (7.17)	69.5 (5.89)	69.8 (5.70)	73.0 (6.66)	72.7 (8.74)
Male, n (%)	435 (53.8%)	52 (42.3%)	34 (34.3%)	227 (59.4%)	122 (59.5%)
MoCA, mean (SD)	22.9 (4.83)	27.5 (1.57)	27.6 (1.69)	22.9 (3.38)	18.0 (4.52)
NfL, mean (SD)	27.1 (26.5)	21.6 (39.0)	19.4 (10.3)	26.8 (25.9)	34.5 (23.3)
GFAP, mean (SD)	163 (140)	145 (292)	118 (57.8)	152 (80.6)	215 (117)
IA, mean (SD)	2.03 (4.83)	0.390 (1.51)	0.404 (1.08)	1.70 (4.31)	4.41 (6.85)

Abbreviations: NCD, neurocognitive disorder; MoCA, Montreal Cognitive Assessment; CU, cognitively unimpaired; SCI, subjective cognitive impairment; NfL, neurofilament light chain; GFAP, Glial Fibrillary Acidic Protein; IA, Apathy Inventory

Figure 1. Associations of plasma NfL and GFAP with apathy severity.



Notes: Higher plasma NfL and lower plasma GFAP were independently associated with higher apathy severity (NfL: B [SE]= 2.46 [0.41], p<0.001; GFAP: B [SE]= -1.81 [0.39], p<0.001). Estimates were derived from multivariable linear regression models adjusted for age, sex, MoCA score, and diagnostic group. Error bars represent 95% confidence intervals. Positive coefficients indicate greater apathy severity with higher biomarker concentrations.

Results (Cont'd)

- Exploratory interaction analyses suggested a significant NfL × diagnostic group interaction for Major NCD, whereas no significant interactions were observed for GFAP or other diagnostic groups (**Table 3**).
- Sensitivity analyses additionally adjusting for the alternate biomarker yielded similar findings, with a significant NfL × Major NCD interaction, and no significant GFAP × Major NCD interaction.

Table 2. Exploratory biomarker x diagnostic group interaction analyses

Biomarker	Interaction term	B (SE)	p-value
NfL	NfL x Major NCD	2.64 (1.07)	0.01***
GFAP	GFAP x Major NCD	-1.55 (1.05)	0.14

Abbreviations: NfL, neurofilament light chain; GFAP, Glial Fibrillary Acidic Protein; IA, Apathy Inventory. Separate interaction models were adjusted for age, sex and MoCA scores. ***p<0.05

Conclusions

- Independent associations between plasma biomarkers and apathy severity were observed after adjustment for age, sex, cognition, and diagnostic group, with higher NfL and lower GFAP linked to greater apathy.
- Associations were consistent across initiative, interest, and emotional apathy domains.
- Exploratory analyses suggested stronger NfL-apathy associations among individuals with Major NCD.
- Greater neuronal injury and lower astroglial injury may be associated with apathy in NCD, consistent with the differential vulnerability of neurons and astrocytes in the neurovascular unit.



UNIVERSITY OF
TORONTO



COMPASS-ND
The Comprehensive Assessment of
Neurodegeneration and Dementia



Sunnybrook
HEALTH SCIENCES CENTRE

Acknowledgements

Dr. Krista Lanctôt, COMPASS-ND study participants, CCNA Team 11 members and the Geriatric Psychopharmacology Research Group.