

Neural embedding of frailty in cognitively unimpaired aging and dementia across Latin America

Joaquin Migeot^{#1,2}, Olivia Wen^{#1}, Raul Gonzalez-Gomez¹, Hernan Hernandez¹, David Aguillon³, Jose Alberto Avila-Funes^{4,5}, Maria I Behrens^{6,7,8,9}, Martin A Bruno^{10,11}, Nilton Custodio^{12,13}, Carolina Delgado^{14,15}, Claudia Duran-Aniotz¹, Dafne Duron-Reyes^{2,16}, Adolfo M Garcia^{17,18,19}, Maria E Godoy¹⁹, Kun Hu^{20,21,22}, Brian Lawlor², Peng Li^{20,21,22,23,24}, Marcelo Adrian Maito¹⁹, Diana L Matallana^{25,26}, Bruce Miller^{18,27}, Maira Okada de Oliveira^{18,28}, Stefanie D Pina-Escudero^{18,27}, Katherine L Possin^{18,27}, Elisa de Paula Franca Resende^{18,29,30}, Pablo Reyes³¹, Hernando Santamaria-Garcia^{31,32}, Andrea Slachevsky^{33,34,35,36}, Leonel T Takada³⁷, Paulina Vergara², Kristine Yaffe^{18,38}, Jennifer S Yokoyama^{18,27,39}, Roman Romero-Ortuno^{2,39}, Agustín Ibáñez^{1,2,18,19*}

*Corresponding authors, ^equal contribution



Introduction

- Frailty, resulting from the cumulative burden of biopsychosocial health deficits, influences dementia risk and severity.
- Few studies have differentiated dementia subtypes and associations with structural and functional brain alterations in Latin America, despite high regional prevalence.

Objectives

- Construct a frailty index comprised of 32 health variables
- Test if frailty distinguishes between dementia and cognitively unimpaired
- Examine whether frailty is associated with gray matter volumes and functional connectivity

Methods

Sample:

- 3,461 participants (mean age 63.5; 65.8% female) from ReDLat across six Latin American countries (CU: 1,924, AD: 1,126, FTLD: 411).

Frailty index: 32 health variables across six domains.

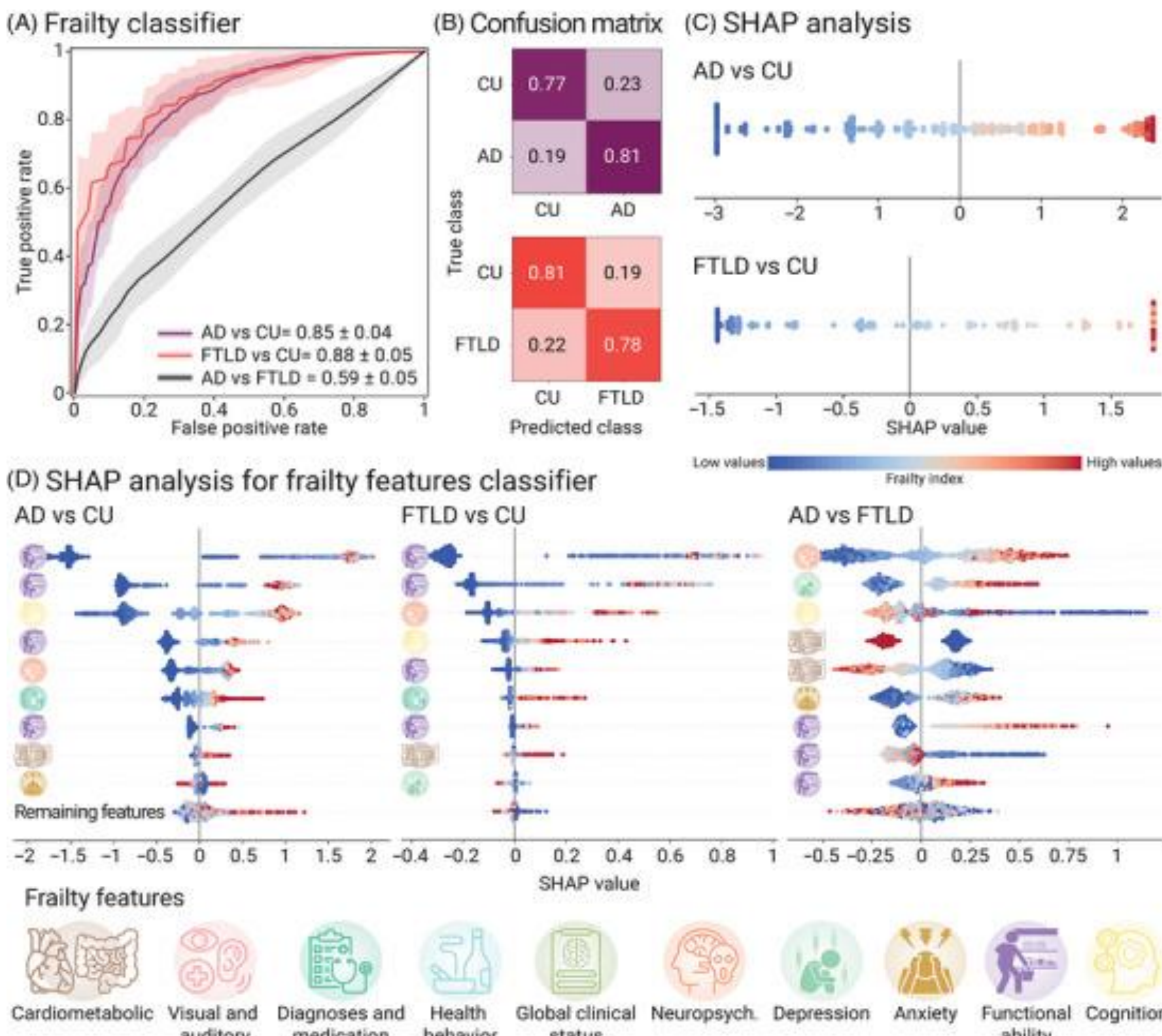
- Cardiometabolic, sensory, health behaviors, global clinical status, neuropsychiatric/mood, and cognitive/functional ability.

Statistical analyses:

- XGBoost classification and SHAP analysis identified the most predictive frailty features.
- Linear regression models tested associations between frailty and gray matter volume and resting-state functional connectivity

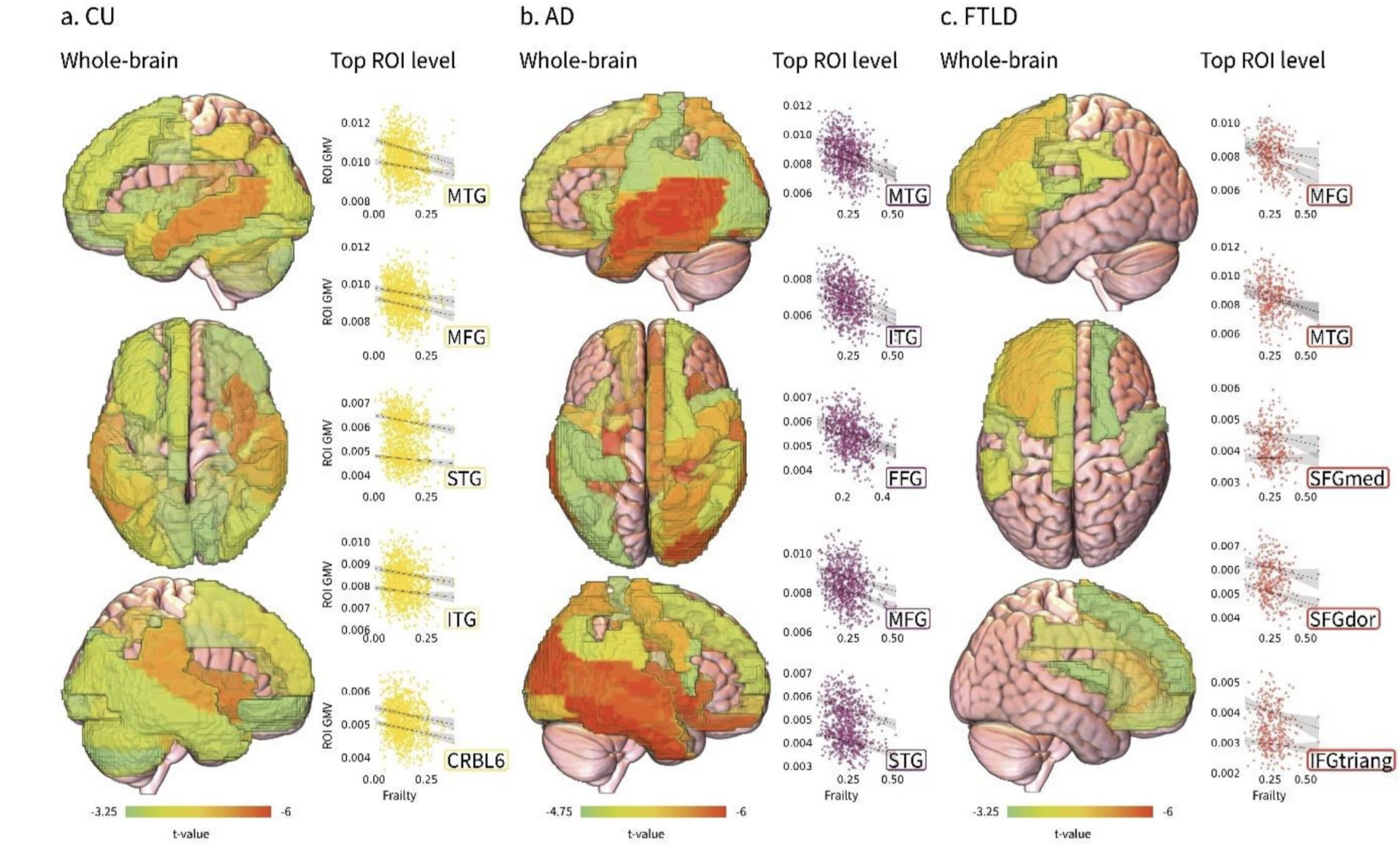
Results

Figure 1. Frailty classification performance.



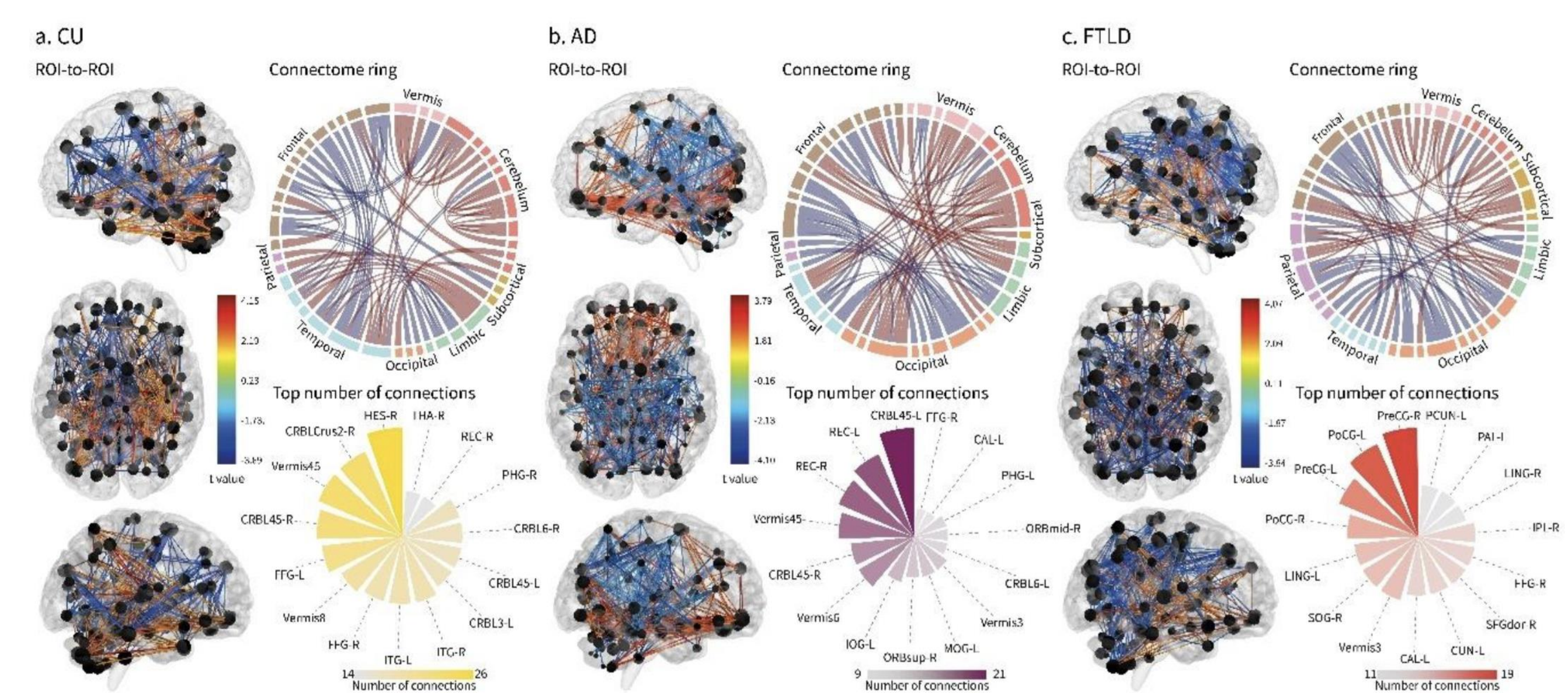
- Frailty robustly classified AD vs. CU (AUC = 0.85) and FTLD vs. CU (AUC = 0.88)
- Frailty showed poor discrimination between AD and FTLD (AUC = 0.59)
- Functional ability, cognition, neuropsychiatric symptoms, and number of diagnoses/medications were the strongest drivers of CU-vs-dementia classification

Figure 2. Association between frailty and gray matter volumes.



- Greater frailty linked to widespread gray matter loss, with temporal involvement in CU and frontotemporal effects in dementia, particularly FTLD.

Figure 3. Association between frailty and brain connectivity.



- Connectivity analyses showed fronto-temporo-posterior reductions and increased connectivity in the frailty network.

Discussion

- Frailty differentiated dementia CU but did not distinguish between AD and FTD, indicating a shared vulnerability signal. However; frailty-related atrophy and connectivity disruption converged on known disease-vulnerable brain regions.
- Findings support the integration of the frailty index into dementia risk characterization and prevention strategies, given substantial overlap between frailty domains and modifiable risk factors in Latin American populations.

Full paper and author affiliations

