Frailty and young-onset cognitive decline: Fluid biomarkers and multimodal neuroimaging correlates in Mild Cognitive Impairment before age 65

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Background & Aims

Frailty is a multidimensional construct increasingly recognized as a predictor of adverse outcomes in cognitive disorders. Yet, its neurobiological underpinnings in young-onset mild cognitive impairment (YO-MCI, <65y) remain poorly understood.

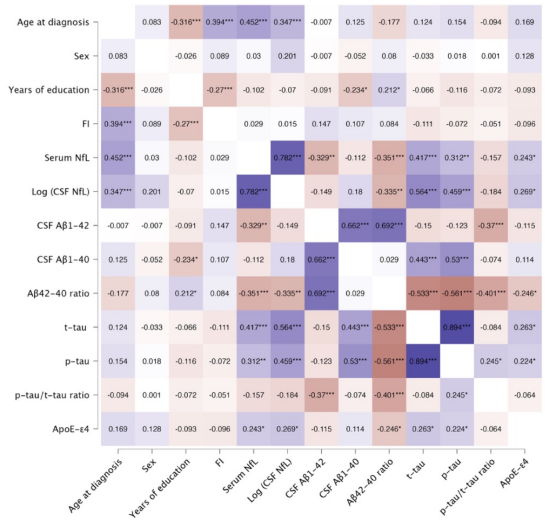
This study aimed to examine cross-sectional associations between a 40-item **Frailty Index (FI)** and:

- **Fluid biomarkers** (CSF Aβ, tau, NfL; serum NfL);
- **MRI** features: voxel-based morphometry (VBM) and diffusion tensor imaging (DTI).

Methods

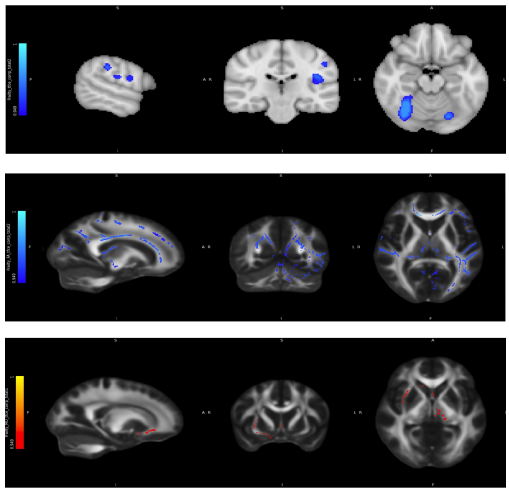
- Multicentric, consecutive, **clinic-based cohort (n= 146)** from the Cognitive Neurology Clinics of Modena & Reggio Emilia, 2019–2023; with **symptom onset < 65 y**.
- T1-weighted data were analysed with FSL-Voxel Based Morphometry (**VBM**)
- **CSF** $A\beta_{1-42}$, $A\beta_{1-40}$, total tau, p-tau, NfL; serum NfL.
- **FI** consisting of **40 items**; analyzed as **continuous**.

Results



Heatmap of Spearman correlations between frailty, socio-demographic variables, and fluid biomarkers in YO-MCI. Frailty (FI) correlated positively with age and negatively with education, but showed no significant associations with CSF Aβ, tau, or NfL.

MRI correlates of frailty in YO-MCI. Higher frailty was associated with reduced grey matter volume in bilateral cerebellum (lobule VI, Crus I) and perirolandic cortices (top row), decreased fractional anisotropy in widespread commissural, projection and association tracts (middle row), and increased mean diffusivity in anterior thalamic radiations and projection fibres (bottom row).



Conclusions

- **Independence from AD biology**: Frailty in YO-MCI was **uncoupled from CSF/PET amyloid, tau, and NfL**, suggesting a vulnerability dimension distinct from canonical Alzheimer's pathology.
- **Structural and functional footprint**: Frailty was mirrored in **cerebellar, perirolandic, and occipito-temporal atrophy**, alongside widespread **microstructural degradation** and altered cerebellar connectivity.
- **Clinical implications**: Frailty represents a **neurobiological marker of reduced reserve**, reflecting systemic dysregulation and network compromise even before age 65.
- **Future directions**: Longitudinal studies should clarify whether interventions targeting frailty (e.g., mobility, vascular, lifestyle) can mitigate structural decline and delay dementia progression.

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