

Plasma and cerebrospinal fluid proteomic signatures for cognitive decline and dementia in a Brazilian cohort



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Background

Plasma and cerebrospinal fluid (CSF) biomarkers of dementia have impacted the field significantly in recent years. Biomarkers now allow for increasingly accurate classification of patients in terms of amyloid status (e.g. pTau217), neuroinflammation (e.g. GFAP), and neurodegeneration (e.g. NfL), aiding in diagnosis and prognosis. Dementia, however, is a heterogeneous condition, and specific endophenotypes exist beyond these general classifications. Proteomic profiling of patients may allow for a better understanding of disease subtypes and reveal therapeutic targets. Brazil has the world’s largest recently admixed population, with remarkable genetic diversity, but it remains severely understudied in dementia research. Here we report on the first affinity proteomics dataset from a Brazilian dementia cohort. This study contributes proteomic data from an understudied population and may provide insights into the molecular dynamics between brain amyloidosis and cognitive decline.

Methods

The study was conducted at the Memory Clinic at the D’Or Institute for Research and Education (IDOR) in Rio de Janeiro. A total of 1034 protein targets were measured in 104 paired plasma and CSF samples from 96 elderly participants, using the Olink platform. Participants were volunteers referred to the service by physicians or other healthcare professionals. All provided written informed consent approved by the local Research Ethics Committee, were native Brazilians, over 55 years of age, and had plasma and CSF samples available. They were clinically categorized as cognitively unimpaired (CU, n=35), mild cognitive impairment (MCI, n=25), Alzheimer’s disease (AD, n=19), or non-AD dementia (n=17). Clinical diagnoses outside the scope of the study were excluded. AD was diagnosed according to criteria included in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for probable major neurocognitive disorder due to AD. Amyloid status was determined for all participants using plasma pTau217 or CSF biomarkers. Locally defined cutoff values of <1.2 for CSF Aβ₁₋₄₂/t-Tau ratio, >346.9 pg/ml for CSF pTau181, >22.72 pg/ml for CSF pTau217, and >0.34 pg/ml for plasma pTau217 were used. Thirty-three participants had follow-up clinical data available, up to 6.9 years after the first assessment. Standard non-parametric approaches were used for group comparisons. Analytes with low detectability were not removed from the dataset, to avoid losing data relevant only to specific disease states.

Support:



Results

Clinical diagnosis (at baseline)	Cognitively unimpaired	Mild cognitive impairment	Alzheimer's Disease	Other dementias	Data availability
Participants (n)	35	25	19	17	
Total samples (baseline+follow-ups)	39	26	20	19	
Sex (M/F)	15 / 24	13 / 13	7 / 13	8 / 11	104 / 104
Age (years, mean±SD)	67.7 ± 5.89	72.07 ± 5.04	75.35 ± 7.34	74.57 ± 8.0	104 / 104
Education (years, mean±SD)	14.67 ± 2.51	12.69 ± 3.59	11.65 ± 4.86	8.90 ± 4.68	104 / 104
MMSE (mean±SD)	27.89 ± 1.69	26.09 ± 2.10	21.22 ± 3.98	20.71 ± 4.69	91 / 104
CSF pTau181 (pg/ml, mean±SD)	335.9 ± 276.3	371.7 ± 158.9	844.0 ± 497.9	504.8 ± 274.3	80 / 104
CSF pTau217 (pg/ml, mean±SD)	16.17 ± 21.44	25.32 ± 23.94	51.12 ± 35.13	39.05 ± 39.36	89 / 104
Plasma pTau217 (pg/ml, mean±SD)	0.33 ± 0.28	0.46 ± 0.31	1.0 ± 0.49	0.85 ± 0.78	94 / 104
Plasma GFAP (pg/ml, mean±SD)	157.2 ± 74.81	196.7 ± 101.2	335.5 ± 131.2	238.0 ± 120.3	83 / 104
Plasma NfL (pg/ml, mean±SD)	15.64 ± 6.02	18.88 ± 10.63	26.40 ± 13.95	43.01 ± 59.54	83 / 104

Table 1 – Demographic table. Demographical, clinical, and laboratory data of the sample are summarized. Data availability shows the number of datapoints available for each measurement.

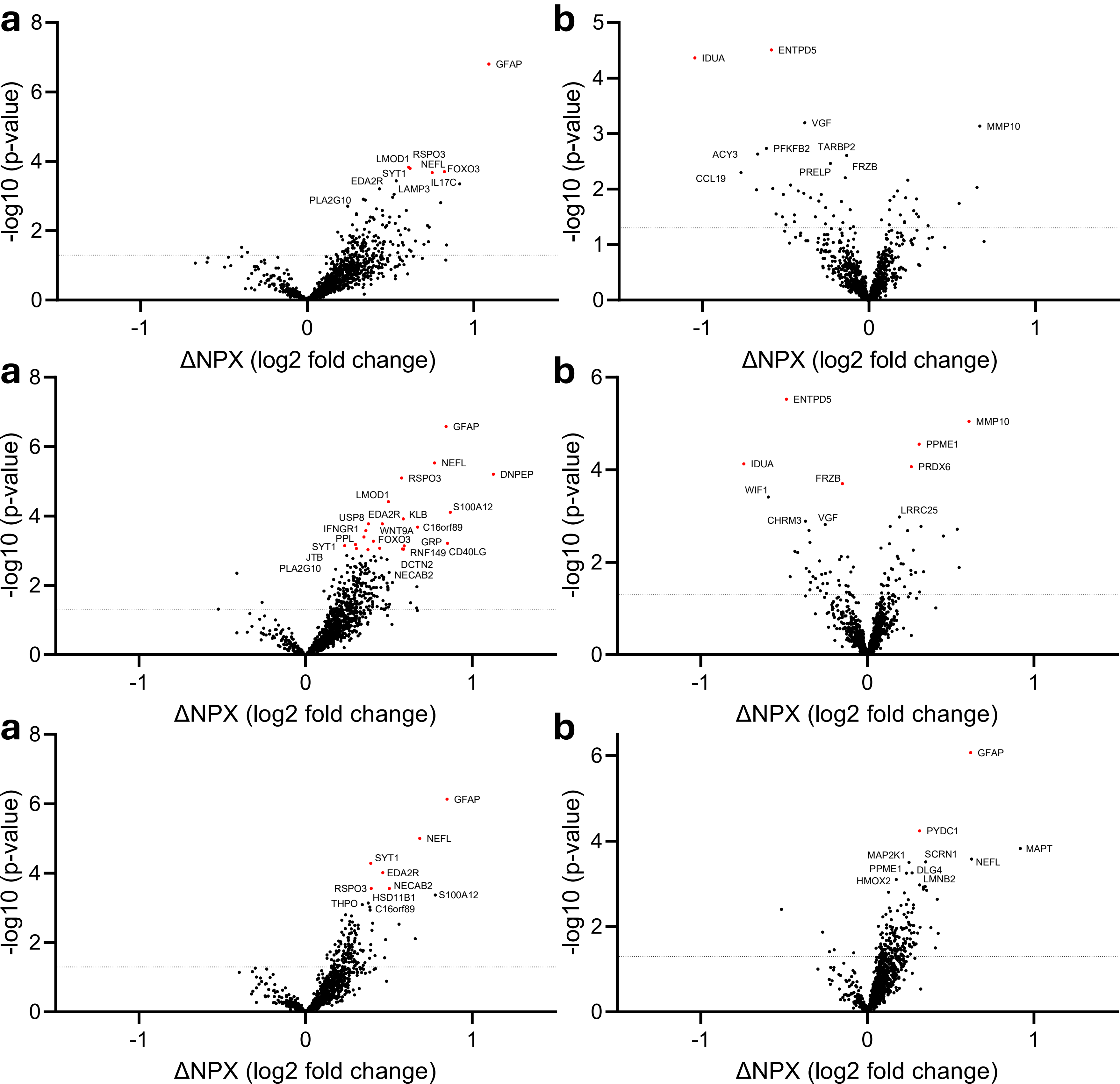


Figure 1 – Differential protein expression in Alzheimer's disease.

Protein expression (NPX, relative units) is shown as volcano plots for all plasma (A) and CSF (B) samples, comparing AD X cognitively normal participants (baseline). Two-tailed Wilcoxon rank-sum test; nominal p-value threshold is shown as a dotted line, FDR-corrected hits are shown in red.

Figure 2 – Differential protein expression in all-cause dementia.

Protein expression (NPX, relative units) is shown as volcano plots for all plasma (A) and CSF (B) samples, comparing participants with a clinical diagnosis of dementia X those without dementia (baseline). Two-tailed Wilcoxon rank-sum test; nominal p-value threshold is shown as a dotted line, FDR-corrected hits are shown in red.

Figure 3 – Differential protein expression driven by amyloid status.

Protein expression (NPX, relative units) is shown as volcano plots for all plasma (A) and CSF (B) samples, comparing participants with AD pathology X those without AD pathology (baseline). Two-tailed Wilcoxon rank-sum test; nominal p-value threshold is shown as a dotted line, FDR-corrected hits are shown in red.