

Multi-omics uncovers pathophysiological alterations underlying neuropsychiatric symptoms in Alzheimer's disease

Miriam Rabl^a*, Daniel Trejo Banos^b*, Sebastian Salzmann^b, Ekaterina Krymova^b, Julius Popp^{a,c}, for the Alzheimer's Disease Neuroimaging Initiative

^a University Hospital of Psychiatry and University of Zurich, Switzerland; ^b Swiss Data Science Center, EPFL and ETH Zurich, Switzerland

^c Old Age Psychiatry Service, Lausanne University Hospital, Switzerland;

*contributed equally

Background

Neuropsychiatric symptoms (NPS) are common in cognitive decline and Alzheimer's disease (AD), yet the underlying pathology is poorly understood. We investigated cerebrospinal fluid (CSF) proteome and metabolome alterations to identify CNS pathophysiological alterations related to

(a) the overall presence of NPS

(b) the presence of depression, anxiety, and apathy

Results

	Total n = 661	CN n = 146	MCI n = 351	AD n = 140
Demographic data				
Age, $\pm$ s.d.	73.5 $\pm$ 7.7	74.8 $\pm$ 6.1	72.3 $\pm$ 7.7	75.3 $\pm$ 8.6
Female, n (%)	280 (42.4%)	65 (44.5%)	147 (41.9%)	58 (41.4%)
Education (years)	15.9 $\pm$ 2.8	16.3 $\pm$ 2.7	16.0 $\pm$ 2.8	15.4 $\pm$ 2.9
Biological data, n (%)				
Amyloid positivity	403 (61.0%)	51 (34.9%)	214 (61.0%)	124 (88.6%)
APOE ϵ 4 carrier	322 (48.7%)	35 (24.0%)	179 (51.0%)	97 (69.3%)
Other				
MMSE score, $\pm$ s.d.	26.9 $\pm$ 3.3	29.0 $\pm$ 1.1	27.8 $\pm$ 1.8	22.4 $\pm$ 3.8
Presence of NPS, n (%)	292 (44.2%)	17 (11.6%)	170 (48.4%)	95 (67.9%)
Depression, n (%)	163 (24.7%)	7 (4.8%)	89 (25.4%)	57 (40.7%)
Anxiety, n (%)	105 (15.9%)	2 (1.4%)	54 (15.4%)	44 (31.4%)
Apathy, n (%)	126 (19.1%)	4 (2.7%)	66 (18.8%)	53 (37.9%)

Fig. 2 Cohort characteristics

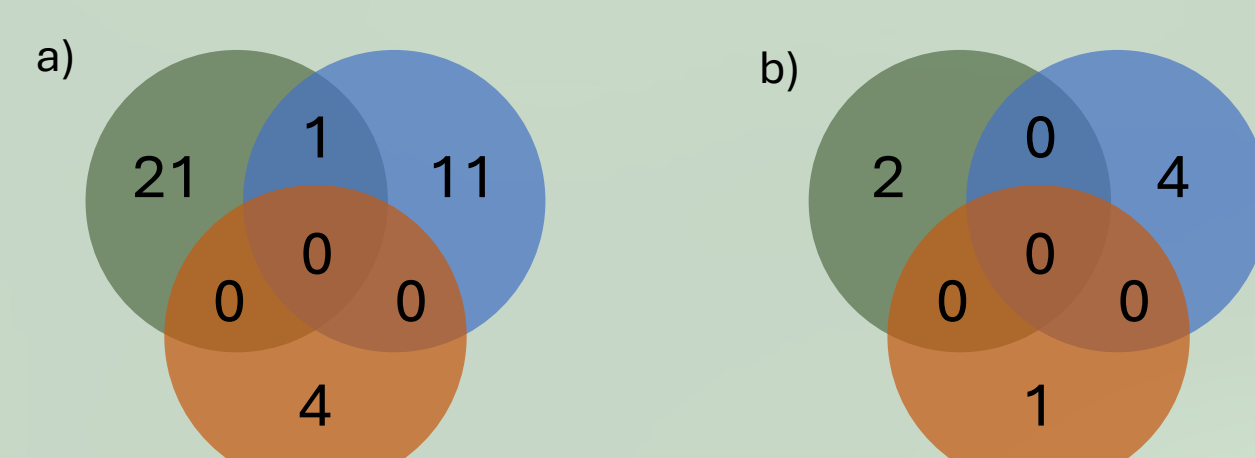


Fig. 3 Overlap of proteins (a) and metabolites (b) selected from the parsimonious model for depression, anxiety, and apathy

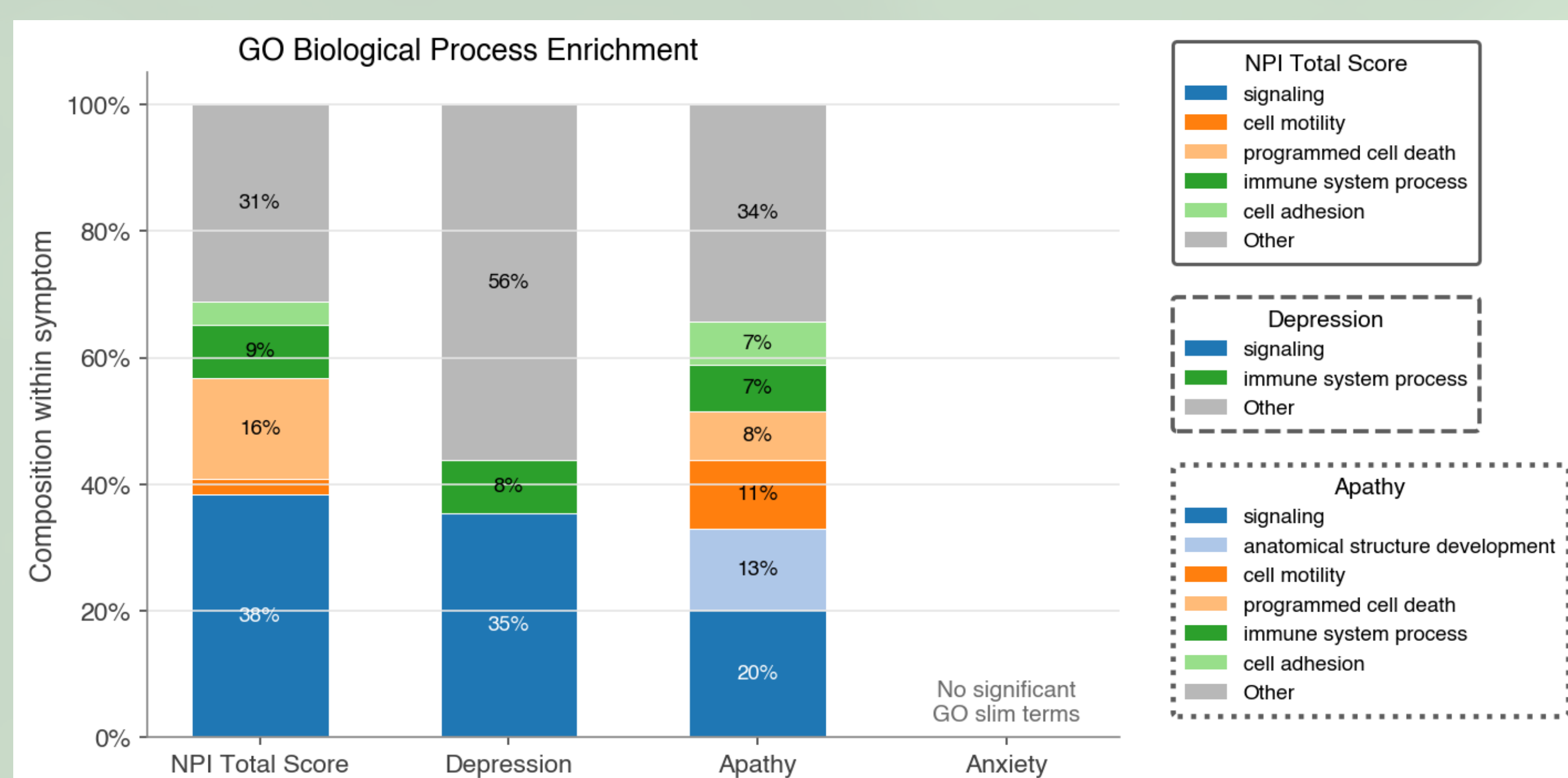


Fig. 4 Frequency of enriched pathways based on GO slim categories and the selected proteins of the exploratory model

	pQTLs UK biobank	overlap exploratory model	overlap parsimonious model
Depression	821	54	3 (HNRNPA1, PABPN1, MMP9)
Anxiety	583	47	1 (CHIT1)

Fig. 5 External comparison with pQTLs from the UK biobank (2)

Conclusion

Applying a multi-omics approach, we identified distinct CSF molecular alterations suggesting specific biological pathway alterations in depression, apathy, and anxiety. Further external validation and the investigation of less frequent symptoms such as agitation, disinhibition, or psychosis are needed.

Methods

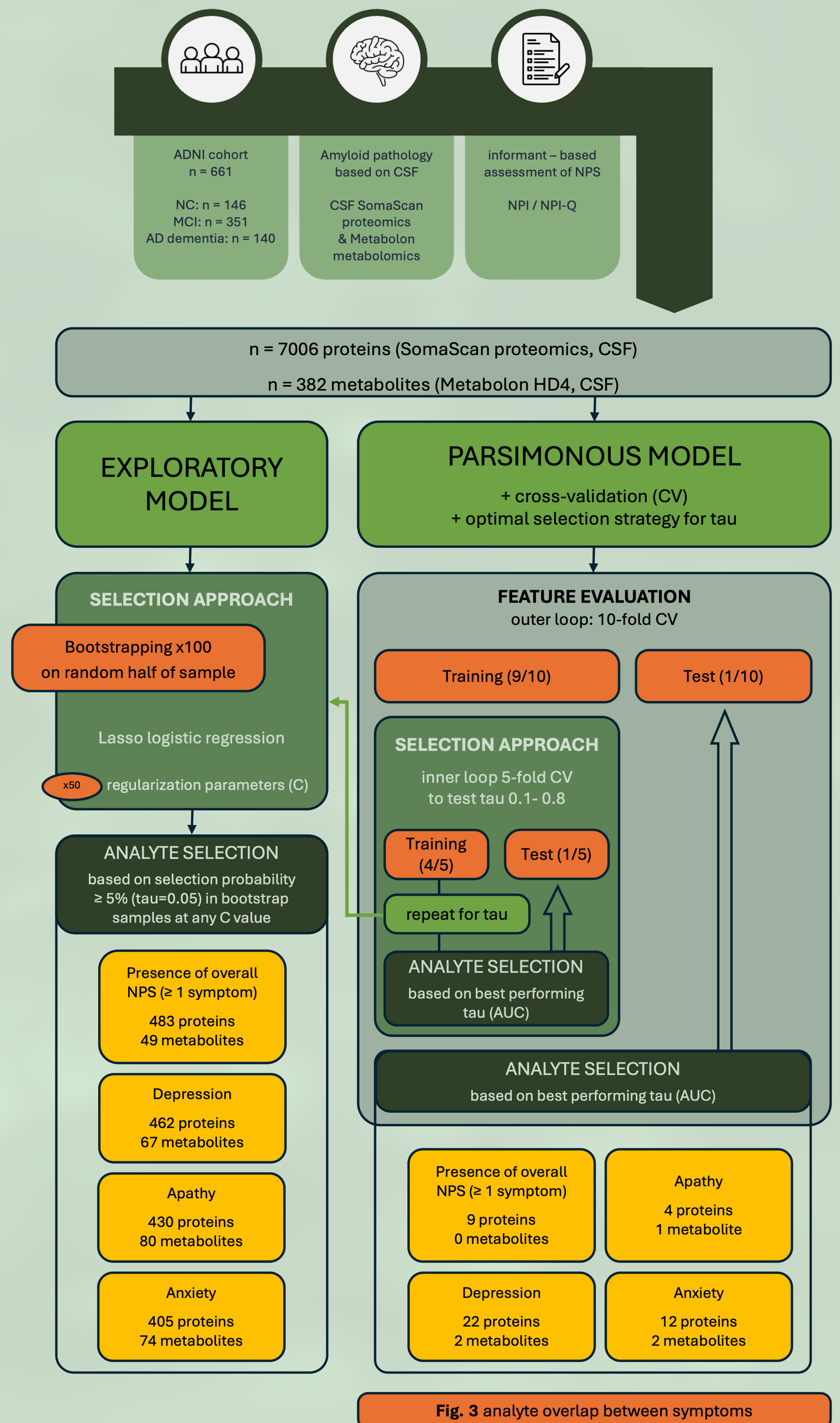


Fig. 4 GO enrichment analysis

Fig. 5 external validation

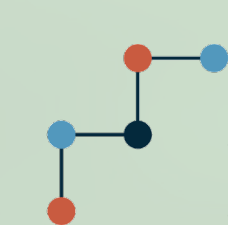
Fig. 1 Statistical approach, stability selection based on (1)

References

- Meinshausen, N. and Bühlmann, P., 2010. Stability selection. *Journal of the Royal Statistical Society Series B: Statistical Methodology*, 72(4), pp.417-473.
- Eldjarn, G.H., Ferkingstad, E., Lund, S.H., et al., 2023. Large-scale plasma proteomics comparisons through genetics and disease associations. *Nature*, 622(7982), pp.348-358.

Funding & Contact

miriam.rabl@bli.uzh.ch



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University of
Zurich^{UZH}