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Plasma profiles of neurology-related proteins in at-risk mental state and first-episode psychosis: Associations with psychotic symptoms and cognitive performance

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ABSTRACT

Background: Early diagnosis of psychosis is crucial, and biomarker detection may provide insights into the pathophysiology of psychosis and the potential for the development of early diagnostic tools. In particular, blood-based proteomic profiling has yielded promising results for psychiatric disorders because of the use of novel high-throughput techniques and the feasibility of performing blood extractions in routine clinical practice.
Study design and methodology: Here, we studied 182 participants (33.3 % females, $\overline{X}_{age}$ = 24.66 ± 5.05), comprising 50 healthy controls (HCs), 37 patients with an at-risk mental state (ARMS) and 95 patients with a first episode of psychosis (FEP). We used a panel of 92 neurology-related proteins in a multiplex immunoassay to identify the plasma protein profiles of each group, their coexpression patterns and biological relevance, and their associations with psychotic symptoms and cognitive performance.
Results: CPA2 was overexpressed in both ARMS participants (β = 0.876, adj. p = 0.009) and FEP participants (β = 0.568, adj. p = 0.011) compared with HCs. In FEP participants, in addition to CPA2, 31 other proteins were overexpressed, with GFRA1 being the most differentially expressed protein (β = 1.159, adj. p < 0.001). Coexpression clusters in FEP patients were involved in several biological processes, such as the regulation of myelination, cell adhesion, multicellular organismal processes and axon guidance. In ARMS patients, THY1 expression was inversely correlated with symptom severity (ρ = −0.640, adj. p = 0.039), and IL12 expression was correlated with cognitive performance (ρ = 0.707, adj. p = 0.007); however, no further correlations were found after the false discovery rate adjustment.
Conclusions: Our findings suggest the involvement of CPA2, GFRA1 and IL12, among other neurology-related proteins, in the early phases of psychosis, which, if confirmed, could become promising biomarkers for diagnosis, psychotic symptom development and psychosis-associated cognitive impairment. However, future studies with larger samples, a longitudinal design, and more extensive proteomic panels are needed to validate these biomarkers and refine their clinical applicability.

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1. Introduction

Psychotic disorders pose a global medical challenge because of their significant impact on patients' well-being, relatively high prevalence (greater than 1 %), and complex pathophysiology (Świtaj et al., 2012). Patients experience a first episode of psychosis (FEP), which is defined as the full onset of psychotic symptoms. Up to 80 % of FEP patients experience a high-risk phase or at-risk mental state (ARMS) marked by subtle prodromal symptoms prior to overt psychosis (Addington and Heinssen, 2012; Benrimoh et al., 2024; van Os and Kapur, 2009), although clinical detection remains challenging.

The main features of psychosis include positive symptoms (delusions, hallucinations, and disorganized thinking), negative symptoms (avolition, social withdrawal, and diminished emotional expression), mood symptoms (depression and mania), and cognitive symptoms (problems in processing speed, executive functions and social cognition). Positive and depressive symptoms are generally more responsive to antipsychotic (AP) and antidepressant treatment than are negative or cognitive symptoms (Puranen et al., 2020; Sabe et al., 2021; Spark et al., 2022). While negative symptoms also present treatment-related challenges, cognitive assessment is often more exhaustive.

Cognitive impairment frequently progresses before the onset of full psychotic symptoms, substantially affecting daily functioning (Nuechterlein et al., 2014; Schaefer et al., 2013). Compared with symptom severity alone, cognitive status provides a broader measure of functional impairment, encompassing multiple psychological processes (Kaneko, 2018; McCutcheon et al., 2023).

Psychotic disorders are primarily diagnosed on the basis of clinical signs and symptomatology, with evaluations influenced by the variability in presentation, interpretation, and the patient's ability to report experiences accurately (van Os et al., 2019). Symptom overlap with other psychiatric and neurological conditions can lead to diagnostic delay and misdiagnosis, limiting the potential for timely and targeted interventions (Fusar-Poli et al., 2020). Given the relevance and early presence of cognitive impairment, integrating biomarkers of cognitive performance into diagnostic frameworks could improve accuracy and prognostic assessment.

Among biomarker-based approaches, fluid biomarker profiling offers the potential to complement clinical evaluations by providing biological signatures that reflect underlying pathophysiological processes, allowing earlier and more individualized treatment strategies (Perkins et al., 2015; Schwarz et al., 2011). However, the identification of biological components that reflect cognitive changes remains challenging. Recent advances in proteomic technologies have facilitated highly sensitive identification of biomarker candidates in psychiatric disorders (García-Gutiérrez et al., 2020). To date, research on fluid biomarkers in patients with psychosis spectrum disorders is limited, with methodological heterogeneity hindering replicability and clinical translation (Fuentes-Claramonte et al., 2024). A key consideration is the biofluid from which biomarkers are extracted, which is typically whole blood, plasma or cerebrospinal fluid (CSF). While CSF analyses can provide detailed insights into brain-related pathologies (Gaetani et al., 2020), the invasiveness of the sample collection procedure restricts its use in clinical settings, underscoring the need for reliable blood-based biomarkers.

Protein expression profiling of plasma samples from patients with psychosis has yielded preliminary evidence. Lee et al. (2024) profiled samples from patients with ARMS and FEP using untargeted mass spectrometry and identified several proteins that were differentially expressed in both groups compared with healthy controls (HCs), such as PRDX2, ITIH4 and FLNA. Tsang et al. (2025) and Eren et al. (2023) used a protein panel based on proximity extension assay (PEA) technology to assess the blood levels of inflammation-related proteins. Both studies revealed higher interleukin (IL6) levels in the plasma of individuals with early psychosis than in that of control individuals, confirming the results obtained from single-biomarker studies (Stojanovic et al., 2014) and aligning with previous results obtained from patients with schizophrenia (SCZ) (Goldsmith et al., 2016).

Associations between specific blood biomarkers and the severity of psychotic symptoms have scarcely been reported. For example, Cao et al. (2023a) reported that specific complement factors are positively correlated with positive and negative symptoms in FEP patients, and previous studies linked high levels of complement factors to psychotic experiences and the transition to psychosis in high-risk individuals (Madrid-Gambin et al., 2019; Mongan et al., 2021). Using PEA, Lee et al. (2024) also identified several proteins that are mostly associated with positive symptom severity (e.g., MIF, VWF, and PRDX2), and Eren et al. (2023) reported that the levels of proteins identified (AXIN1, STAMBP and IL7) in both FEP and SCZ patients were associated with positive symptoms. To our knowledge, no further studies have investigated blood proteomic markers of psychotic symptomatology.

With respect to cognitive impairment, studies in which PEA was used revealed associations between protein levels and cognitive performance, mostly associated with dementia, Alzheimer's disease and age-related cognitive impairment (Chen et al., 2023; Ehtewish et al., 2023; Kivisäkk et al., 2022). In these studies, the most commonly used immunoassay panel was the one that determines the levels of neurology-related proteins. Owing to extensive research on fluid biomarkers of Alzheimer's disease, a certain consensus has been reached regarding the expected changes in the levels of certain proteins in this population (Simrén et al., 2023). However, the scenario is very different for patients with other conditions. Neurology-related proteomic biomarkers of cognition in the general adult population and of cognitive impairment derived from other medical conditions, such as post-traumatic stress disorder, overweight/obesity and metabolic syndrome, and HIV, have been reported in only a few studies, in which some proteins (RSPO1, TNFRSF12A, EDA2R, EFNA4, MSR1, ULBP2 and GFRA1) overlapped in at least two studies (Ellegaard Nielsen et al., 2020; Y. Guo et al., 2024; Harris et al., 2020; Jiang et al., 2022; Llaurador-Coll et al., 2023; Tin et al., 2023). Analogous studies have not been reported for psychosis spectrum disorders. Taken together, existing studies report fragmented information restricted to inflammation and psychosis and to cognitive impairment in patients with other pathologies.

Considering the lack of neurological blood-based biomarker research on psychosis, the present study has two main aims: first, to identify the plasma protein profiles of patients with ARMS and FEP using a neurology-related multiplex immunoassay, and second, to explore the associations between plasma protein levels and psychotic symptom severity and cognitive performance.

2. Materials and methods

2.1. Participants

ARMS and FEP patients and HCs were recruited from the early intervention program in the psychosis unit at the Hospital Universitari Institut Pere Mata (Reus, Catalonia, Spain) and Hospital Universitari Parc Taulí (Sabadell, Catalonia, Spain). This study included 182 participants (50 HCs, 37 ARMS patients, 95 FEP patients) from whom we collected information about clinical characteristics, cognitive function, biometric features, and plasma samples. Part of the cohort recruited in Reus has already been included in previous studies (Stojanovic et al., 2014).

FEP was defined as the onset of a full psychotic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and confirmed by the Spanish version of the Structural Clinical Interview for DSM-IV (SCID-I). ARMS participants fulfilled the criteria for any of the three risk groups defined by the International Early Psychosis Association and the Comprehensive Assessment of At-Risk Mental States (Schultze-Lutter et al., 2015; Yung and McGorry, 2007).

The exclusion criteria for ARMS and FEP patients were psychosis

induced by substances or other medical conditions, intellectual disability, severe head injury, and the inability to understand or speak Spanish or Catalan fluently. The HCs included patients' friends and nongenetic relatives and university students, and the exclusion criteria were being genetically related to patients and having previous or current psychiatric disorders, as determined through the General Health Questionnaire (Goldberg and Hillier, 1979).

Ethical approval was obtained from the ethics committees of the Institut d'Investigació Sanitària Pere Virgili (approval number: 09-1-26/aclproj1) and Hospital Universitari Parc Taulí (approval number: 2018/647). Written informed consent was obtained from all participants.

2.2. Procedure

All participants were assessed when they were clinically stable enough to understand and sign the informed consent form and to undergo the cognitive assessment. At study entry, participants underwent biometric, clinical, and cognitive assessments.

2.2.1. Biometric assessment and blood sampling

The biometric weight and height examinations were performed by trained nurses. Body mass index (BMI) was calculated, and a fasting blood sample was obtained in the morning between 8:30 and 9:30 a.m. under resting conditions. Blood was collected in EDTA-containing tubes, and after centrifugation (at 1800×*g* for 15 min at room temperature), plasma aliquots were stored at −80 °C in the IISPV biobank until the biochemical analysis was performed. Plasma samples were used for the protein analysis, and high-sensitivity C-reactive protein (hs-CRP) was used as an inflammatory biomarker.

2.2.2. Clinical assessment

Sociodemographic, clinical, and treatment-related information was obtained through direct interviews by trained psychiatrists. Sociodemographic data included sex, age, years of education and ethnicity. The clinical assessments included the Spanish versions of the Positive and Negative Syndrome Scale (PANSS, Kay et al. (1987)) to assess the severity of psychotic symptoms (higher scores indicating greater severity) and the Calgary Depression Scale (CDS, Sarró (2004)) to assess the severity of depressive symptoms (higher scores reflecting greater severity). Illness duration was calculated for FEP patients from the first date of the presentation of psychotic symptoms, and comorbidities were assessed according to the SCID-I as previously described (Labad et al., 2015). Information on the AP dosage was transformed into chlorpromazine equivalents (CPZE) in mg/day (Gardner et al., 2010), and substance use was categorized as frequent (≥1 time/week) or nonfrequent (<1 time/week).

2.2.3. Cognitive assessment

The cognitive tests were administered by experienced psychologists, and all the participants completed the tests in a specific order. The MATRICS Consensus Cognitive Battery (MCCB; Kern et al. (2008); Nuechterlein et al. (2008)) was administered to the participants. The MCCB is a neuropsychological battery comprising ten tests that measure seven cognitive domains, including the Trail Making Test Part A (TMT-A), the Brief Assessment of Cognition in Schizophrenia–Symbol Coding (BACS-SC) subtest and the Category Fluency Test–Animal Naming (Fluency) to measure processing speed; the Hopkins Verbal Learning Test–Revised (HVLT-R) to measure verbal learning and memory; the Weschler Memory Scale III–Spatial Span (WMSIII-SS) and the Letter–Number Span (LNS) subtests to measure working memory; the Neuropsychological Assessment Battery–Mazes (NAB-Mazes) subtest to measure reasoning and problem solving; the Brief Visuospatial Memory Test–Revised (BVMT-R) to measure visual learning and memory; the Mayer–Salovey–Caruso Emotional Intelligence Test–Managing Emotions (MSCEIT-ME) subtest to measure social cognition; and the Continuous Performance Test–Identical Pairs (CPT-IP) to measure attention and vigilance. The z scores of the MCCB subtests were obtained by calculating the means and standard deviations of the whole sample. The z score for the TMT-A was inverted to reflect better performance with a higher score, as this subtest is scored indirectly. Z scores for each cognitive domain were calculated by averaging the z scores of the tests assessing each domain. Additionally, a global z score was obtained from the means of all tests to reflect global cognitive performance.

2.3. Blood protein analysis

Coded 50 µl plasma samples were randomly distributed in 96-well plates and sent to Olink Proteomics (Uppsala, Sweden). A total of 92 neurology-related protein biomarkers were measured by multiplex PEA technology, in which matched pairs of antibodies were used to quantify proteins through high-sensitivity and high-specificity PCR (Assarsson et al., 2014). Protein levels are presented as normalized protein expression (NPX) units. NPX is the arbitrary unit on the $\log_2$ scale of the quantification cycle in the sample defined by Olink Proteomics, where a larger number represents a higher protein level. The proteins measured in the Olink Target 96 Neurology Panel include established biomarkers related to neurobiological processes and neurological diseases according to widely used databases (UniProt, Human Protein Atlas, Gene Ontology and DisGeNET), in addition to other exploratory proteins with broader roles in processes such as cellular regulation, immunology, development and metabolism (Olink Proteomics, 2019).

Quality control (QC) of the protein expression levels was performed as follows. First, 2 samples (1 HC and 1 ARMS sample) did not pass the initial Olink QC ($SD_{NPX} > 0.3$ NPX from the median of the control samples), and they were excluded. Second, the NPX values were scaled and plotted in Q−Q plots to reevaluate the distribution of the protein data. Values falling below or above a defined threshold of −4 to 4 quantiles were considered outliers, and as such, 21 data points were removed throughout the dataset. After the quantile distribution was checked, all the proteins were included because they followed a normal distribution, except for MANF, which had a nonnormal distribution. Two proteins, MAPT and NGF, had several values below the limit of detection (LOD), and their results should be interpreted carefully.

2.4. Statistical analysis

2.4.1. Sample description

Sample sociodemographic and clinical variable distributions were assessed using the Kolmogorov−Smirnov test, and comparisons between groups were performed using the chi-square test, analysis of variance (ANOVA), Kruskal−Wallis test, Mann−Whitney *U* test and Student's *t*-test, according to the type and distribution of each variable.

2.4.2. Plasma protein profiles

The preliminary association of acute inflammation with protein expression was determined through Spearman's correlation analysis between protein expression levels and hs-CRP levels.

Linear models were constructed to assess the differentially expressed proteins among the sample groups, and p values were corrected for multiple testing by calculating the false discovery rate (FDR) using the Benjamini−Hochberg method at the 0.05 threshold (limma R package, Ritchie et al. (2015)). Volcano plots were generated to display the results of the linear models (before and after FDR adjustment). Linear models included covariates that were significantly associated with the expression levels of most proteins in a previous bivariate analysis, namely, age, sex and BMI. The levels of hs-CRP and several other proteins correlated; however, some values were missing for hs-CRP levels and hs-CRP levels had a strong correlation with BMI ($\rho = 0.401$, $p < 0.001$). Thus, BMI was employed as a covariate to account for inflammation instead of hs-CRP levels. Using the differentially expressed proteins between groups, a locally estimated scatterplot smoothing (LOESS) curve was generated to visualize trends in the variation in protein expression between groups. A

logistic regression model was used to check the power of the 32 differentially expressed proteins to discriminate between HCs and FEP patients, again controlling for age, sex, and BMI. A 10-fold cross-validation approach repeated 1000 times was used to ensure robustness. Model performance was assessed using a receiver operating characteristic (ROC) curve analysis, and the mean area under the curve (AUC) across all iterations was calculated to summarize the results. A power analysis was performed using the Olink Insight statistical tool (Olink Proteomics, 2024).

2.4.3. Hierarchical clustering of protein expression and pathway enrichment analysis

Proteins showing significant differences in expression between groups were subjected to hierarchical clustering within each group using Ward's clustering method with the Euclidean distance to identify coexpression patterns. Clusters were selected through bootstrap resampling (N boots = 1000) using the pvclust R package (Suzuki and Shimodaira, 2006) to ensure their significance. Additionally, a pathway enrichment analysis of the significant clusters was subsequently performed using the g:Profiler database (Kolberg et al., 2023) with the whole genome as the background gene set to provide a consistent reference framework independent of platform-specific detection limits. Only the biological processes that survived the FDR adjustment (Benjamini–Hochberg method at the 0.05 threshold) were considered.

2.4.4. Associations between protein expression and psychotic symptoms

The associations between protein levels and disease features were determined by calculating Spearman's partial correlation coefficient, controlling for age, sex, BMI, AP dosage and years of education and adjusting for the FDR. The selected disease features included positive (P), negative (N) and general (G) symptoms, as assessed by the PANSS.

2.4.5. Associations between protein expression and cognitive performance

The association between protein levels and cognitive performance was also assessed by calculating Spearman's partial correlation coefficient between protein expression levels and global cognition in the whole sample, controlling for age, sex, BMI, years of education and diagnostic group, and adjusting for the FDR. In parallel, we analyzed the associations within each group using the same procedure, but added the AP dosage as a covariate in patients with ARMS and FEP and applied the FDR adjustment. The MCCB global z score was considered to indicate global cognitive performance. Furthermore, exploratory correlation analyses of each MCCB cognitive domain were performed using the same approach.

All the statistical analyses were performed and plots were generated with R Studio (version 2024.9.0.375 with R version 4.4.1), and the figures were arranged with Affinity Designer 2 (version 2.5.6).

Table 1
Descriptive characteristics and summary statistics of the sample.

	Total (N = 180)	HCs (N = 49)	ARMS patients (N = 36)	FEP patients (N = 95)	Statistical value (X^2/F/U/t)	p value
Sociodemographic variables						
Sex: female *(n, %)*	60 (33.3)	20 (40.8)	10 (27.8)	30 (31.6)	1.866[a]	0.393
Age: years *(m, SD)*	24.66 (5.05)	24.06 (4.70)	24.15 (5.49)	25.17 (5.05)	1.014[b]	0.365
Years of education *(med, IQR)*	10 (10–13)	13 (11–15)	10 (10–11)	10 (0–12)	24.723[c]	<0.001
Ethnicity: Caucasian *(n, %)*	166 (92.2)	47 (95.9)	32 (88.9)	87 (91.6)	1.546[a]	0.462
Inflammation variables						
BMI *(m, SD)*	23.18 (3.86)	22.69 (3.78)	22.27 (3.29)	23.77 (4.03)	2.539[b]	0.082
hs-CRP *(N = 143; med, IQR)*	0.9 (3.00–2.22)	1.10 (0.40–2.20)	1.20 (0.40–3.10)	0.80 (0.20–2.10)	0.688[c]	0.709
Substance use variables						
Frequent tobacco use *(n, %)*	97 (53.9)	13 (26.5)	15 (41.7)	69 (72.6)	30.354[a]	<0.001
Frequent cannabis use *(n, %)*	49 (27.2)	7 (14.3)	7 (19.4)	35 (36.8)	9.676[a]	0.008
Frequent alcohol use *(n, %)*	65 (36.1)	21 (42.9)	9 (25.0)	35 (36.8)	2.915[a]	0.233
Clinical variables						
PANSS Positive *(med, IQR)*	9 (8–12)	–	9.00 (8.00–11.00)	9.00 (8.00–13.00)	1707.500[d]	0.551
PANSS Negative *(med, IQR)*	14 (10–19.75)	–	11.50 (10.00–15.00)	15.00 (10.25–20.00)	1952.500[d]	0.055
PANSS General *(med, IQR)*	29 (23–35.75)	–	32.00 (29.00–40.75)	28.00 (23.00–34.00)	1095.500[d]	0.007
PANSS Total *(med, IQR)*	54 (45–64.75)	–	55.50 (47.25–62.75)	54.00 (45.00–64.75)	1490.500[d]	0.562
CDS *(m, SD)*	3.92 (5.34)	–	6.15 (6.18)	3.09 (4.77)	2.610[e]	0.006
Illness duration: days *(m, SD)*	–	–	–	168.38 (171.22)	–	–
Psychiatric comorbidities *(n, %)*	12 (6.15)	0	7 (19.44)	5 (5.26)	13.25[a]	0.001
Substance use disorder *(n, %)*	3 (1.67)	0	0	3 (3.16)	2.730[a]	0.255
Personality disorder *(n, %)*	4 (2.22)	0	3 (8.33)	1 (1.05)	7.899[a]	0.019
ADHD *(n, %)*	1 (0.50)	0	1 (2.78)	0	4.022[a]	0.134
Anxiety disorder *(n, %)*	4 (2.22)	0	3 (8.33)	1 (1.05)	7.899[a]	0.019
Treatment variables						
AP intake (yes, %)	103 (57.2)	–	13 (36.1)	90 (94.7)	53.392[a]	<0.001
AP dosage, CPZE *(med, IQR)*	225 (100–400)	–	0 (0.00–127.50)	300 (200–450)	2917.000[d]	<0.001
Cognitive domain z scores* (MCCB) *(m, SD)*						
AtteVi	−0.99 (1.10)	−0.44 (0.90)	−1.19 (1.07)	−1.20 (1.11)	9.354[b]	<0.001
ProcSp	−0.42 (0.92)	0.26 (0.67)	−0.49 (0.82)	−0.74 (0.88)	24.320[b]	<0.001
ReasPS	0.20 (0.98)	0.40 (0.84)	0.19 (1.04)	0.09 (1.01)	1.624[b]	0.189
VerbLe	−0.62 (0.94)	−0.16 (0.90)	−0.88 (0.82)	−0.77 (0.92)	9.426[b]	<0.001
VisuLe	0.06 (1.04)	0.26 (0.93)	0.03 (1.05)	−0.04 (1.08)	1.323[b]	0.269
WorkMe	−0.59 (0.80)	−0.31 (0.70)	−0.84 (0.86)	−0.64 (0.80)	5.184[b]	0.006
SociCo	−0.67 (1.23)	−0.31 (1.05)	−0.49 (1.02)	−0.93 (1.33)	4.745[b]	0.010
Global cognition score	−0.45 (0.70)	−0.01 (0.53)	−0.55 (0.62)	−0.64 (0.72)	15.592[b]	<0.001

Abbreviations: HC = healthy controls; ARMS = at-risk mental state; FEP = first episode of psychosis; m = mean; med = median; SD = standard deviation; IQR = interquartile range; BMI = body mass index; hs-CRP = high-sensitivity C-reactive protein; PANSS=Positive and Negative Symptom Scale; CDS=Calgary Depression Scale; ADHD = attention deficit and hyperactivity disorder; AP = antipsychotic; CPZE = chlorpromazine equivalents; MCCB = MATRICS Consensus Cognitive Battery; AtteVi = attention and vigilance; ProcSp = processing speed; ReasPS = reasoning and problem solving; VerbLe = verbal learning and memory; VisuLe = visual learning and memory; WorkMe = working memory; SociCo = social cognition; a Chi-squared test; b ANOVA; c Kruskal–Wallis test; d Mann–Whitney *U* test; e Student's T test.
* Tukey's post hoc test for the global cognition score showed significant differences between HCs and ARMS patients ($p < 0.001$) and between HCs and FEP patients ($p < 0.001$) but not between ARMS and FEP patients ($p = 0.779$). The results for Tukey's post hoc tests of each cognitive domain are shown in Figure S3.

3. Results

3.1. Sample description

Sample features and statistics for between-group comparison are presented in Table 1. Thirty-three percent of the individuals were female, and the mean age of the whole sample was 24.66 ± 5.05 years. The number of years of education was significantly greater in HCs than in ARMS and FEP patients. With respect to substance use, the frequent consumption of tobacco and cannabis differed significantly between the groups, with higher consumption in the ARMS and FEP groups than in the HC group. As expected, the percentages of AP intake and AP dosage were significantly higher in FEP patients than in ARMS patients. The PANSS general and CDS scores were significantly higher in the ARMS group than in the FEP group. Notably, compared with both HCs and FEP patients, ARMS patients had higher plasma hs-CRP levels, although the difference was not significant. Similar results were observed for both the ARMS and FEP groups in several cognitive domains as well as in the global cognitive domain; in some cases, the ARMS and FEP groups had significantly lower scores than did the HCs (Supplementary Fig. S1, Table 1).

3.2. Plasma protein profiles

The protein expression levels in each group are shown in Supplementary Table S1. A specific exploratory analysis was conducted to test whether inflammation (hs-CRP levels) was associated with protein expression, and significant relationships with 20 proteins in the whole sample were observed, indicating the association of these proteins with acute inflammatory stages (Supplementary Table S2), although only one protein (DRAXIN) remained significant after the FDR adjustment ($\rho = -0.321$, $p = 0.021$).

Linear models comparing protein expression levels between groups revealed several significant differences (Fig. 1A, Supplementary Table S3). Comparisons between HCs and FEP patients revealed 32 proteins that were significantly overexpressed in FEP patients after the FDR correction: GFRA1, ULBP2, SCARA5, ACVRL1, DDR1, MSTN, FLRT2, ROBO2, KYNU, NMNAT1, NTRK2, TNFRSF21, ASAH2, CPA2, WFIKKN1, CD300C, EFNA4, SIGLEC1, UNC5C, EPHB6, THY1, ADAM22, GFRA3, PDGFRA, CSF3, CDH3, LAYN, JAM2, SCARB2, SCARF2, CPM, and SMPD1 (Supplementary Table S4). In the model comparing ARMS patients and HCs, the expression of one protein, namely, CPA2, which was overexpressed in ARMS patients, differed significantly between the groups. In the model comparing ARMS patients and FEP patients, no

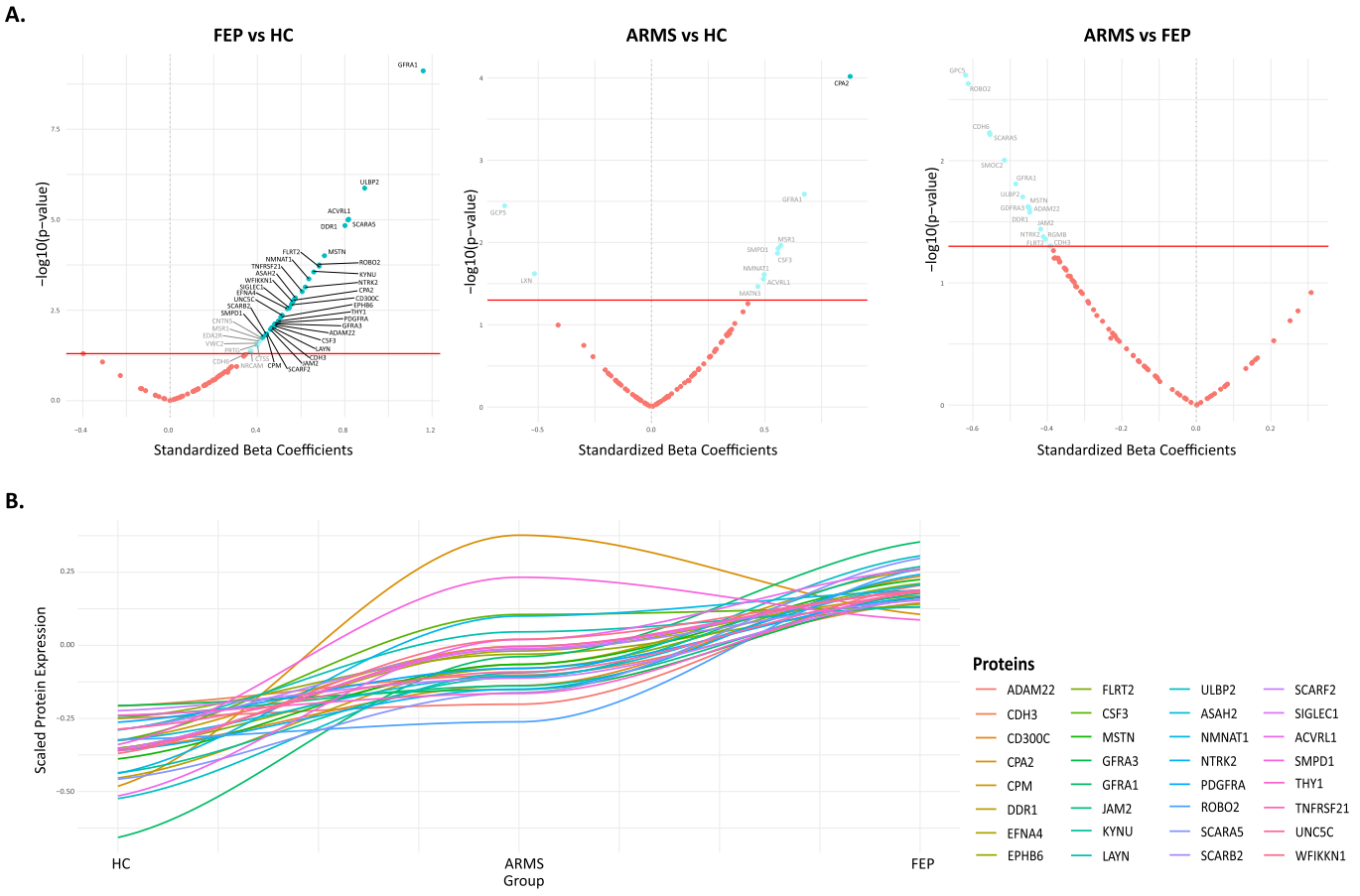

Fig. 1. Comparison of protein expression levels between groups.
(A) Volcano plots showing the standardized beta coefficients and their respective p values. Linear regression models comparing protein expression levels between groups (controlling for age, sex and BMI) were constructed as described in the Materials and Methods section**.** The horizontal red line represents the threshold at a p value = 0.05; proteins below this threshold were not statistically significant. The clear blue dots in gray were statistically significant but did not survive the FDR (Benjamini–Hochberg) adjustment threshold at 0.05. Stronger blue dots, shown in black, were statistically significant and survived the FDR (Benjamini–Hochberg) adjustment threshold at 0.05. The number of proteins with positive coefficients was greater in patients with FEP, ARMS and FEP, respectively in the three plots. **(B) LOESS curve showing trends in protein expression levels across groups**. The 32 differentially expressed proteins in FEP patients are represented in the LOESS curve, and expression levels were scaled to allow presentation in a single plot. FDR, false discovery rate; FEP, first episode of psychosis; ARMS, at-risk mental state; LOESS, locally estimated scatterplot smoothing. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

significant differences were observed between these groups. Boxplots of each of the 32 differentially expressed proteins between the groups are shown in Supplementary Fig. S2. Interestingly, a gradual increasing trend in the expression of most proteins was observed from HCs to ARMS patients and from ARMS patients to FEP patients. These results were confirmed by the LOESS curve (Fig. 1B), in which a trend for the 32 differentially expressed proteins was observed across the three stages (HC–ARMS–FEP). Notably, although not significantly different, CPA2 and SMPD1 were the only proteins that were overexpressed in ARMS patients compared with both HCs and FEP patients.

Finally, the repeated 10-fold cross-validation logistic regression analysis yielded an average AUC of 0.703 (95 % CI: 0.701–0.707), an average specificity of 0.728 (95 % CI: 0.725–0.730) and a sensitivity of 0.534 (95 % CI: 0.530–0.539) at the optimal thresholds, indicating the poor ability of the 32 differentially expressed proteins to differentiate FEP patients from HCs. The power analysis considering the sample size and protein assays revealed a power of 0.26 for detecting an effect size (Cohen's f) of 0.24 at a Bonferroni-corrected significance level of 0.0005 (0.05 overall), indicating that the study had low sensitivity; thus, nonsignificant results should be interpreted with caution and should not be taken as evidence of no effect.

3.3. Hierarchical clustering and biological functions

The 32 differentially expressed proteins were used for hierarchical clustering and pathway enrichment analyses. Five statistically significant clusters were defined in the HCs, six in the ARMS patients, and three in the FEP patients (Fig. 2A). The results of the pathway enrichment analysis using the g:Profiler database within each cluster in FEP patients and the proteins involved in each Gene Ontology (GO) biological process are shown in Fig. 2B. Clusters in HCs and ARMS patients did not show significant enrichment in any biological process, whereas in FEP patients, one cluster (THY1, CPA2, KYNU, and SCARA5) was not significantly enriched in any biological process; another cluster (hereafter referred to as cluster A: CPM, TNFRSF21, CDH3, JAM2, ACVRL1, DDR1, and GFRA1) was enriched in cell adhesion (GO:0007155), negative regulation of myelination (GO:0031642), and negative regulation of nervous system processes (GO:0031645); and one last cluster (hereafter referred to as cluster B: ADAM22, GFRA3, EPHB6, UNC5C, SCARB2, SMPD1, ASAH2, MSTN, CSF3, ULBP2, WFIKKN1, NMNAT1, EFNA4, and FLRT2) was enriched in axon guidance (GO:0007411), multicellular organismal process (GO:0032501), and neuron projection guidance (GO:0097485).

Regarding biological processes, first, the g:Profiler database (Kolberg et al., 2023) was used to determine the top 10 significant GO biological processes in which the 92 proteins were involved (Supplementary Table S5). The pathway enrichment analysis of the 32 differentially expressed proteins using the g:Profiler database revealed their roles in several biological processes regardless of their cluster (Supplementary Fig. S3). Except for axon guidance and neuron projection guidance, all the enriched biological processes were linked to more than one cluster. The top 5 significant biological processes associated with the proteins were cell adhesion (GO:0007155), axon development (GO:0061564), the enzyme-linked receptor protein signaling pathway (GO:0007167), neuron projection development (GO:0031175), and the transmembrane receptor protein tyrosine kinase signaling pathway (GO:0007169). All FDR-corrected p values were <0.001, and 60 % of the biological processes overlapped with the top 10 biological processes identified

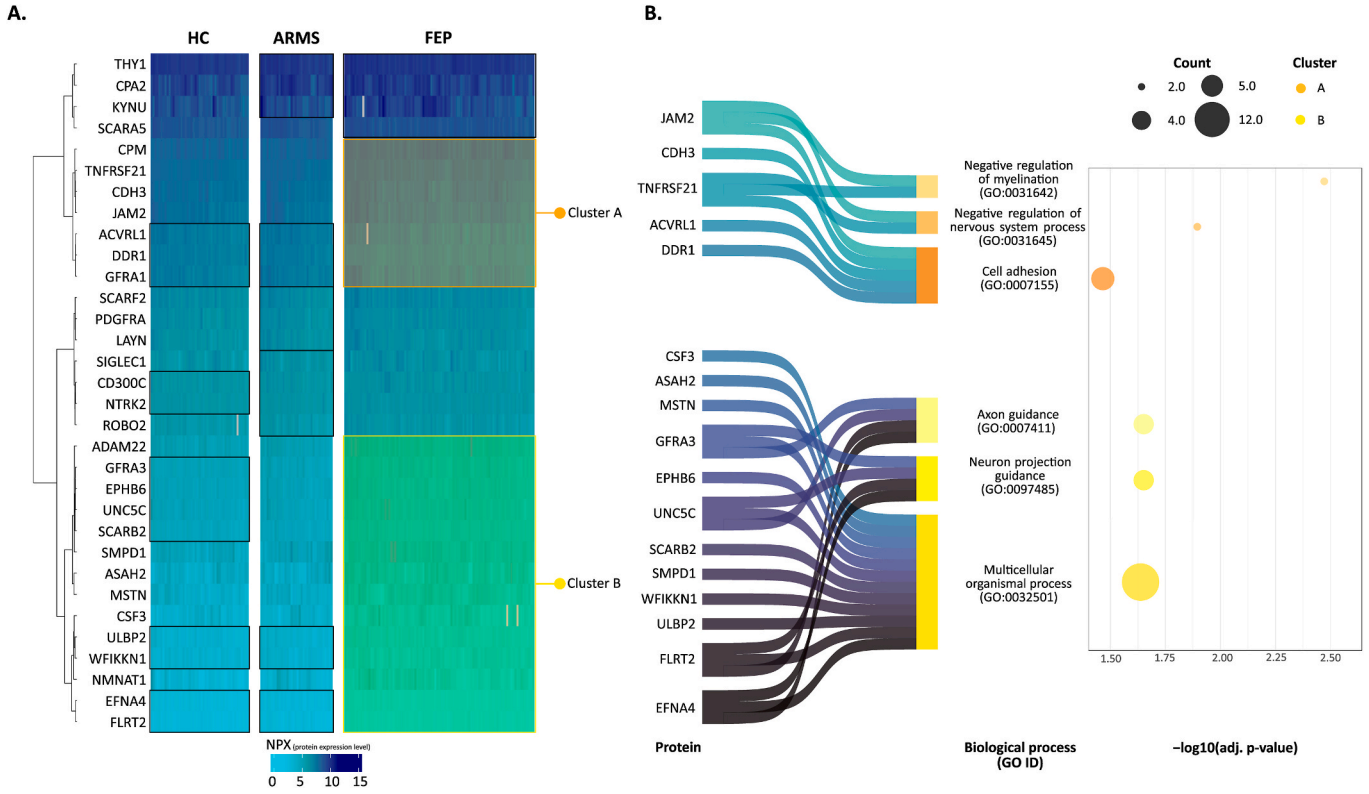

Fig. 2. Identification of clusters based on protein expression and pathway enrichment analysis of significant clusters.
(A) Heatmap showing protein expression levels by group (blocks), sorted by protein expression similarity (left side dendrogram) within clusters after hierarchical clustering (only 32 differentially expressed proteins). Significant clusters in each group are squared. Clusters that were not enriched in any biological process after the enrichment analysis are shown in black. Clusters A and B are shown in orange and yellow, respectively, and are enriched in some biological processes. **(B) Sankey and bubble plots showing proteins in clusters A and B and the biological pathways in which they are enriched**. The color indicates the cluster, and the circle size indicates the number of proteins enriched in the biological process. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

through an enrichment analysis of the whole set of proteins. In addition, we explored the links among the 32 differentially expressed proteins using the STRING database and found that the cluster composed of NTRK2, PDGFRA, ROBO2, EFNA4, FLRT2, GFRA1, GFRA3, EPHB6, UNC5C and NMNAT1 was supported by experimental evidence and related to neuron development and receptor-dependent signaling (Supplementary Fig. S4 and Supplementary Table S6). Notably, enzyme-linked receptor protein signaling and the transmembrane receptor protein tyrosine kinase signaling pathway were not among the top 10 biological processes identified for the whole protein set, indicating that neurology-related receptor signaling processes are involved in psychosis.

3.4. Associations between protein expression and psychotic symptoms

Heatmaps showing partial correlations between the expression levels of all the proteins and the PANSS scores of ARMS and FEP patients are presented in Fig. 3. Spearman's correlation coefficients are presented in Supplementary Table S7. In ARMS patients, positive symptoms were not significantly correlated with the expression of any protein; negative symptoms were negatively correlated with the expression of CSF3, IL5RA and MAPT; and general symptoms were negatively correlated with the expression of nine proteins (SIGLEC9, ADAM22, EDA2R, CD300C, TNFRSF21, ULBP2, GFRA1, MAPT, and THY1). MAPT was the only protein whose expression correlated with both negative and general symptom severity in ARMS patients. After the FDR adjustment, the only significant correlation was between THY1 expression and general symptoms.

In FEP patients, positive symptoms were significantly negatively correlated with the expression of two proteins (GFRA1 and CD300LF), negative symptoms were significantly negatively correlated with the expression of two proteins (VWC2 and CD300LF), and general symptoms were significantly positively correlated with the expression of one protein (CSF3) and significantly negatively correlated with the expression of four proteins (EDA2R, GFRA1, VWC2, and CLM1). GFRA1, VWC2 and CD300LF expression were negatively correlated with two or more symptom scores. After the FDR adjustment, none of the correlations in FEP patients remained significant. Notably, the expression levels of EDA2R and GFRA1, although they did not pass FDR correction, were negatively associated with PANSS general symptoms in both ARMS and FEP patients.

3.5. Associations between protein expression and cognitive performance

On the one hand, the partial correlation analysis between protein expression and cognitive performance in the whole sample (controlling for age, sex, years of education and diagnostic group) revealed significant nominal correlations with five proteins (CPM, SMPD1 and MME with negative correlations and CRTAM and DRAXIN with positive correlations; Supplementary Table S8). None of the correlations remained significant after the FDR adjustment.

On the other hand, within-group partial correlation analyses (controlling for age, sex, years of education and AP dosage in ARMS and FEP patients) revealed different profiles (Fig. 4B), with significant correlations identified depending on the diagnostic group (Supplementary Table S8). In HCs, CTSC, SMPD1, PLXNB1, ASAH2 and CSF3 expression levels were negatively correlated with cognition, whereas MDGA1 was the only protein whose expression was significantly positively correlated with cognition. In ARMS patients, the expression levels of IL12, SIGLEC1, EPHB6, CD200, CSF2RA, MDGA1, CDH3, CDH6, CRTAM, UNC5C, DRAXIN, CD300C, TNFRSF21, NTRK2, PRTG, FCRL2, EZR, CNTN5 and MSR1 were positively correlated with cognition, but the none of the proteins showed a negatively correlation with cognition. Finally, in FEP patients, negative correlations were only observed with IL5RA, LAT, LGALS8, PLXNB3, CLEC1B, CNTN5 and NTRK2. However, after the FDR correction, only IL12 was strongly correlated with global cognition in ARMS patients ($\rho = 0.707$, adj. $p = 0.007$).

The results from the exploratory analysis of the cognitive domains are shown in Supplementary Fig. S5, and the correlation coefficients and p values are presented in Supplementary Table S9. From a general perspective, correlations were stronger in HCs and in ARMS patients, but absolute coefficients were closer to 0 in the FEP group. In HCs, proteins whose expression levels were negatively correlated with global cognition were correlated mainly with processing speed (ProcSp) and working memory (WorkMe), some of which were also correlated with reasoning and problem solving (ReasPS). MDGA1, the only protein with a positive correlation, was significantly correlated with attention and vigilance (AtteVi) and WorkMe. Thus, in HCs, the WorkMe domain was correlated most strongly with protein expression levels. Additionally, global cognition could be driven by WorkMe, as they shared the same significant correlations. In ARMS patients, all the significant correlations were positive except for CPM and ReasPS. The domains with more positive associations were AtteVi and WorkMe. Some of the proteins showing significant correlations with global cognition showed no significant correlations with cognitive domains. In FEP patients, all the significant correlations were negative. Most of the proteins whose expression levels were correlated with global cognition were significantly correlated with ProcSp, but in contrast with those in HCs and ARMS patients, no domains were clearly correlated with the expression levels of most proteins.

4. Discussion

4.1. Plasma protein profiles, hierarchical clustering of protein expression and biological functions

In the present study, we used a multiplex immunoassay to identify the plasma profiles of differentially expressed neurology-related proteins in ARMS and FEP patients compared with HCs and the associations of the expression levels of these proteins with disease features. Several of these proteins were also significantly associated with cognitive performance and symptom severity, underscoring their potential roles in disease pathophysiology.

Our findings revealed that one protein, CPA2, was overexpressed in ARMS patients and that 32 proteins, including CPA2, were overexpressed in FEP patients compared with HCs. Carboxypeptidase A2 (CPA2) is a carboxypeptidase that acts on aromatic C-terminal residues; it is synthesized mainly in the pancreas and is involved in various metabolic processes (Uhlén et al., 2015). CPA2 is also associated with conditions such as celiac disease, type 1 and type 2 diabetes, and renal failure (Olink Proteomics, 2024). Moreover, the CPA2 gene is highly expressed in oligodendrocytes and is associated with white matter and myelination (Uhlén et al., 2015), both of which are disrupted in individuals with psychosis (Mighdoll et al., 2015). The altered plasma CPA2 levels in both groups may reflect metabolic disturbances or inflammation, which are frequently observed in patients with psychosis spectrum disorders and even in at-risk populations (Alonso et al., 2022; Cordes et al., 2017; Stojanovic et al., 2014). Alternatively, our results of CPA2 overexpression in plasma may mirror myelin alterations in ARMS and FEP patients.

The 32 differentially expressed proteins were involved mainly in 3 groups of biological functions: (1) cell development, differentiation and adhesion; (2) enzyme-linked receptor, cell surface and transmembrane receptor tyrosine kinase signaling pathways; and (3) neuron development, axon and neuron projection development and neurogenesis. Taken together, these findings suggest that these pathways are altered during early psychosis and that plasma analyses can identify these alterations.

More specifically, the upregulated proteins in FEP patients included in cluster A (CPM, TNFRSF21, CDH3, JAM2, ACVRL1, DDR1, and GFRA1) were enriched in cell adhesion and, interestingly, in the negative regulation of myelination and nervous system processes. Cell

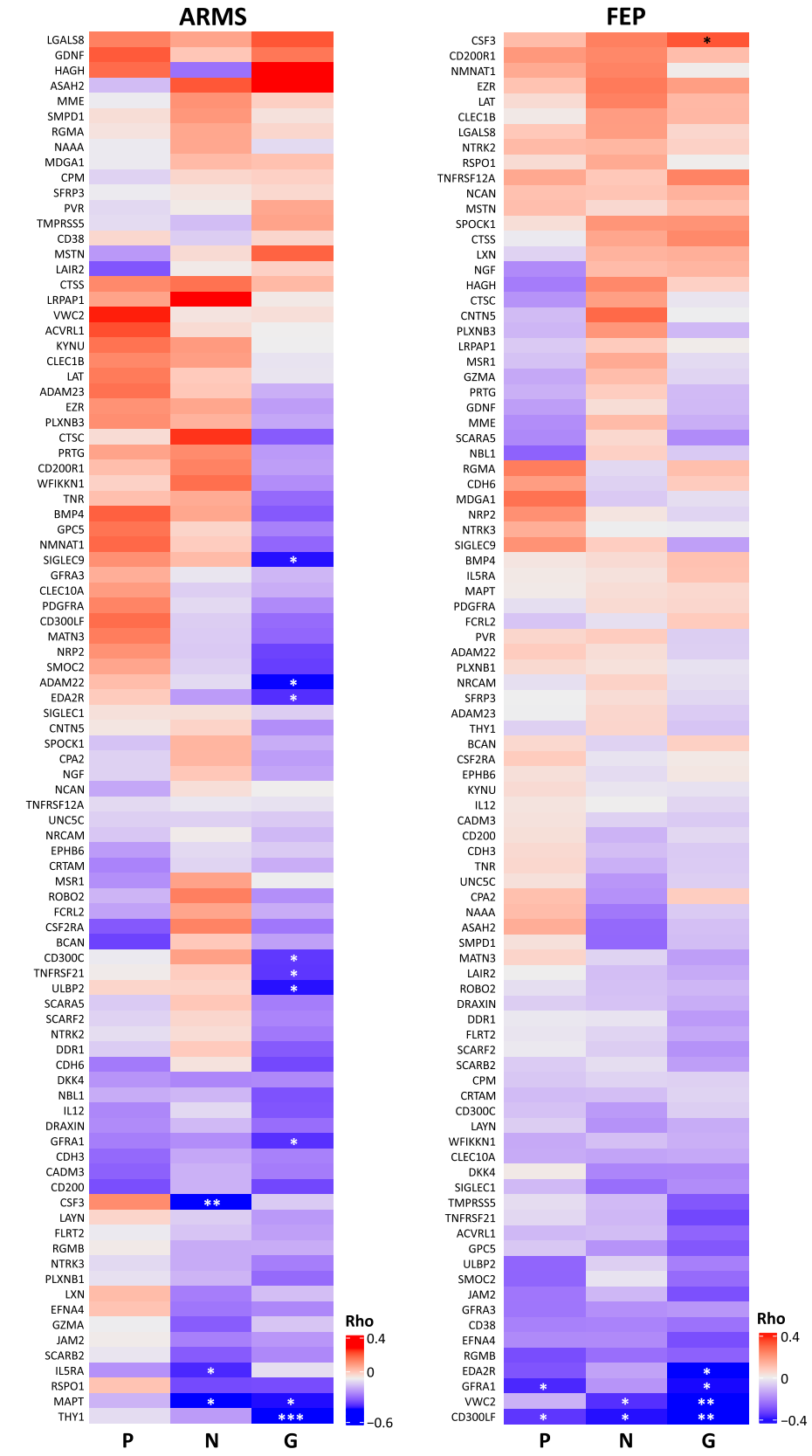

Fig. 3. Heatmaps showing correlations between protein expression levels and symptoms assessed with the PANSS in the ARMS and FEP groups. P = PANSS positive score; N = PANSS negative score; G = PANSS general score. *p value < 0.05, **p value < 0.01, ***p value < 0.001, # significant after the FDR adjustment. PANSS, Positive and Negative Syndrome Scale; ARMS, at-risk mental state; FEP, first episode of psychosis.

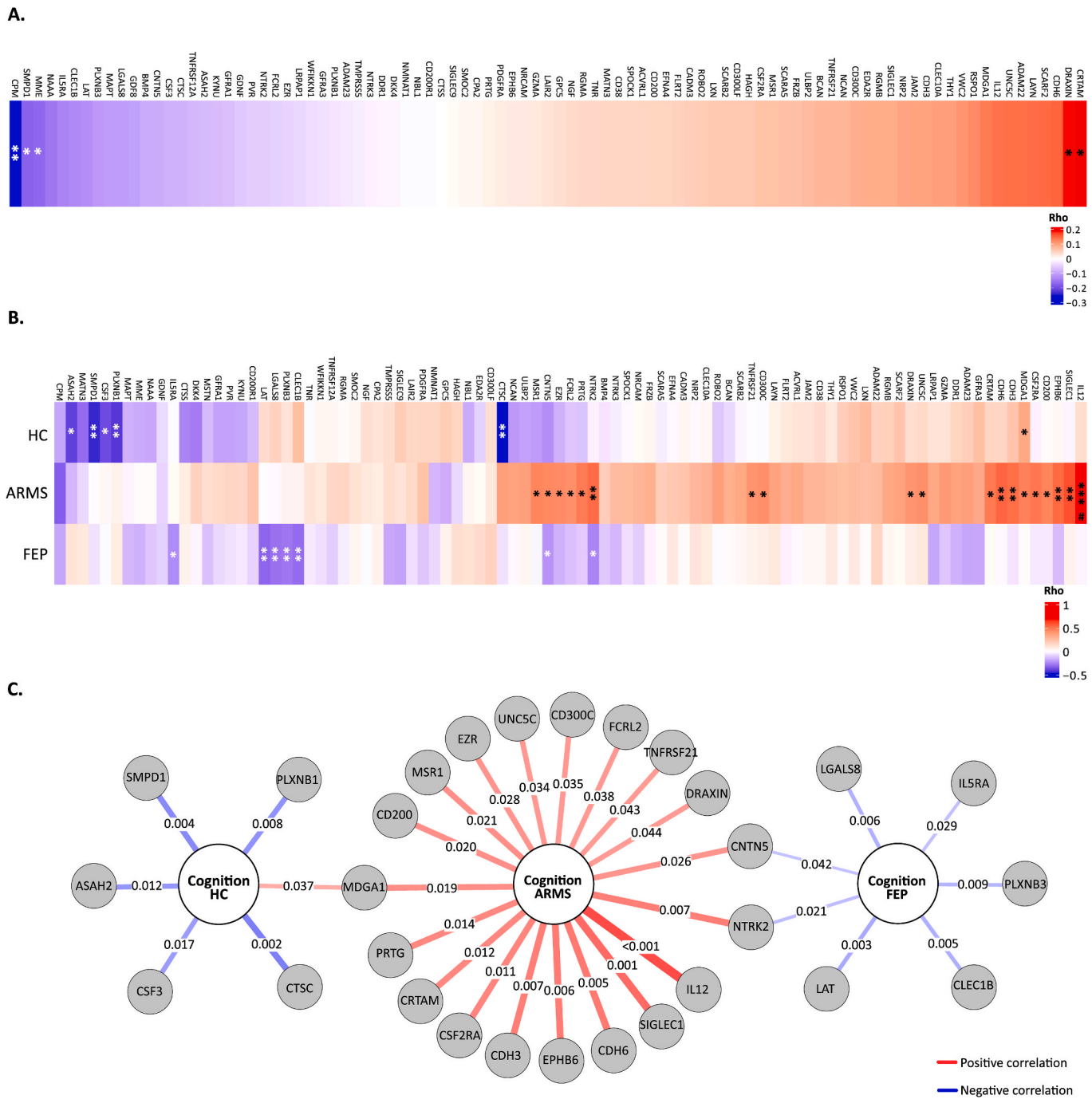

Fig. 4. Correlation analysis between protein expression levels and global cognition assessed with the MCCB in the whole sample and across groups. **(A) Heatmap showing the correlations between protein expression levels and global cognition in the whole sample** (partial Spearman's correlation analysis controlling for age, sex, years of education and diagnostic group). *p value < 0.05, **p value < 0.01. **(B) Heatmaps showing the correlations between protein expression levels and global cognition within each group** (partial Spearman's correlation analysis controlling for age, sex, years of education and AP dosage). *p value < 0.05, **p value < 0.01, ***p value < 0.001, #significant after the FDR (Benjamini–Hochberg) adjustment threshold at 0.05. **(C) Network diagram showing the nominally significant correlations between protein expression levels and global cognition within each group** (partial Spearman's correlation analysis controlling for age, sex, years of education and AP dosage). The edge colors (red and blue) indicate positive and negative correlations, respectively. The edge width and opacity reflect absolute correlation values. Nominal p values are shown at the edges. MCCB, MATRICS Consensus Cognitive Battery; AP, antipsychotic; FDR, false discovery rate. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

adhesion and negative regulation of myelination are associated with psychotic disorders and SCZ (Fryar-Williams and Strobel, 2015; Fuentes-Claramonte et al., 2024; Paterson et al., 2006). Notably, our research group described a relevant role for DDR1 in the myelination process (Vilella et al., 2019) and reported that the expression of this gene, specifically isoform c, is upregulated in the brain tissue of patients with SCZ (Aranda et al., 2024; Roig et al., 2012). Moreover, in brain tissue coexpression networks, a module in which DDR1 and JAM3 (junctional adhesion molecule 3) were strongly coexpressed was identified, and the cell type enrichment analysis identified this module as an "oligodendrocyte cell type" (Aranda et al., 2024). JAM3 and JAM2 (junctional adhesion molecule 2; upregulated in FEP patients and present in cluster

A) interact and are highly expressed by endothelial cells, where they promote cell–cell adhesion (Szklarczyk et al., 2023). These results indicate that alterations in the adhesion of the oligodendrocyte cell lineage are implicated in psychosis. Glial cell line-derived neurotrophic factor receptor alpha 1 (GFRA1) was the top upregulated protein in FEP patients. Together with GFRA3, GFRA1 forms a complex with RET (Porcari et al., 2025), which is involved in neuronal processes and nervous system development and has been previously linked to SCZ (Souza et al., 2010). Through PEA, high blood levels of GFRA1 have been found to be associated with dementia (Y. Guo et al., 2024; Jiang et al., 2022) and cognitive impairment (Harris et al., 2020). Glial cell line-derived neurotrophic factor (GDNF) is a ligand of GFRA1, and its signaling pathway plays an essential role in the plasticity of adult circuits, controlling the integration of newly generated neurons. Additionally, previous studies have shown that GDNF expression is downregulated in the blood and CSF of SCZ patients (Hidese, 2024; Turkmen et al., 2021), which may explain the increase in the level of the receptor GFRA1 as a compensatory mechanism to increase sensitivity to GDNF. However, in our sample, the plasma levels of GDNF did not differ among the groups. In summary, upregulated proteins in cluster A may indicate increased negative regulation of the nervous system and, more specifically, of the myelination process.

Furthermore, cluster B (ADAM22, GFRA3, EPHB6, UNC5C, SCARB2, SMPD1, ASAH2, MSTN, CSF3, ULBP2, WFIKKN1, NMNAT1, EFNA4, and FLRT2) was significantly enriched in axon guidance, multicellular organismal process, and neuron projection guidance. Axon guidance and neuronal projections are associated with psychotic disorders and SCZ (Biederman et al., 2009; Kristensen and Cadenhead, 2007; Merico et al., 2015; Wang et al., 2018). Notably, these two processes were exclusively linked to cluster B proteins when we analyzed the enrichment of all the differentially expressed proteins. According to the data in Supplementary Fig. S4, both cluster A and B proteins strongly overlapped with the network created using the STRING platform, in which the 32 proteins were preferentially enriched in cell/neuron development, neuron projection and membrane receptors. In addition, data from this database experimentally support the relationships among several of these proteins. Taken together, these findings suggest that these interrelated proteins are key elements involved in the disruption of the brain during the early stages of psychosis. Despite the specific neurology-focused design of the panel, these results indicate the importance of nervous system processes, myelination regulation, and axonal and neuronal guidance in psychotic disorders.

Our analysis did not reveal any significant differences in protein expression levels between ARMS patients and FEP patients after the FDR adjustment. However, the expression levels of most proteins were higher in FEP patients than in ARMS patients. Potential explanations could be the low statistical power due to the difference in sample size, the proinflammatory stage of the ARMS participants that we already published for part of this cohort (Labad et al., 2015; Stojanovic et al., 2014), or the heterogeneity of the ARMS group, comprising participants with a genetic risk and participants presenting attenuated symptoms. Although disruptions in shared biological processes might be present in both groups, the diversity within the psychosis risk period might attenuate the proteomic differentiation (Fusar-Poli et al., 2013). However, a gradual increasing trend in the expression of most proteins was observed across the three groups, from HCs to ARMS patients and from ARMS patients to FEP patients, which could be interpreted as three stages of a disease continuum. Although the differences were not statistically significant, CPA2 and SMPD1 were overexpressed in ARMS patients compared with both HCs and FEP patients, and GFRA3 was also underexpressed in ARMS patients compared with both HCs and FEP patients.

4.2. Association of protein expression with symptom severity

In terms of positive, negative and general symptom severity, EDA2R (ectodysplasin A2 receptor) and GFRA1 were negatively correlated with general symptoms in both the ARMS patients and the FEP patients, suggesting that EDA2R and GRFA1 levels may be indicators of anxiety, depression, impulsivity and other factors related to general psychopathology. Interestingly, CSF3 (colony-stimulating factor 3) expression was negatively correlated with negative symptoms in ARMS patients, whereas it was positively correlated with general symptoms in FEP patients. Given the immunological and inflammatory roles of CSF3 (The Gene Ontology Consortium et al., 2023), this difference could be due to stage-specific proteomic dynamics and a dysregulated immune response in individuals with psychotic disorders (Fusar-Poli et al., 2013). For example, the elevated depressive symptoms and hs-CRP levels in our ARMS patients may also reflect stage-specific features.

MAPT (microtubule-associated protein tau) was linked to several nervous system-related processes; MAPT expression was negatively correlated with both general symptoms and negative symptoms in ARMS patients, which is consistent with the results of previous research indicating that low levels of this protein are associated with early-onset psychosis (Andreou et al., 2021). Additionally, the expression levels of THY1, ADAM22, CD300C, TNFRSF21, ULBP2 and SIGLEC9 were negatively correlated with general symptoms in ARMS patients. In addition to the negative associations between cognition and CD300C (immunoglobulin superfamily member 16), TNFRSF21 (TNF receptor superfamily member 21), ULBP2 (UL16 binding protein 2) and THY1 (Thy-1 cell surface antigen) reported by Harris et al. (2020) and the negative association between the CSF levels of TNFRSF21 and bipolar disorder (Göteson et al., 2021), other studies have not reported similar results or associations with psychosis spectrum disorders. IL5RA levels were also negatively correlated with symptoms in patients with ARMS; however, to our knowledge, this association has not been previously reported.

In FEP patients, regardless of previously mentioned findings concerning EDA2R and CSF3 expression, negative correlations between general symptom severity and VWC2 (von Willebrand factor C domain containing 2) and CD300LF (CD300 molecule-like family member F) expression have been reported, and even though these proteins participate in the immune response and neural function and development, respectively (Stelzer et al., 2016), no previous research has linked them to psychosis. However, the correlations between symptoms and protein levels must be carefully considered, as they were no longer statistically significant after the FDR adjustment except for a negative association between THY1 expression and general symptoms in ARMS patients. The lack of significance after the FDR adjustment could be due to the low statistical power of the study, considering the limited sample size and the large number of variables tested.

4.3. Association of protein expression with cognitive performance

The analysis of the associations between protein levels and cognition in the whole sample revealed nominally significant positive associations between cognitive performance and CRTAM (cytotoxic and regulatory T-cell molecule) and DRAXIN (dorsal inhibitory axon guidance protein). CRTAM has not been linked to cognitive performance or any similar feature. CRTAM is expressed mainly in the cerebellum and is involved in immunological processes (Boles et al., 2005). DRAXIN expression is associated with several neurodevelopmental and psychiatric disorders, such as autism spectrum disorder and SCZ, according to genome-wide association studies (GWASs) (W. Guo et al., 2017; Sullivan et al., 2008), but it has not been associated with cognition in previous studies. DRAXIN was the only protein in our study that correlated with hs-CRP levels, thus supporting the findings of previous studies linking metabolic disturbances with cognition (Abubakar et al., 2025; Cordes et al., 2017; Llaurador-Coll et al., 2023). Additionally, nominally significant negative associations were found between cognitive performance and the expression of CPM (carboxypeptidase M), SMPD1 (sphingomyelin phosphodiesterase 1) and MME (membrane metalloendopeptidase). CPM expression has previously been negatively associated with

cognition in older adults by Harris et al. (2020) and in HIV-related cognitively impaired men by Sun et al. (2019). SMPD1 expression is associated with Parkinson's disease (Alcalay et al., 2019), but along with MME, it has not been previously associated with cognition.

When associations with cognition in each group were assessed separately, some proteins were significantly correlated in all three groups, but only IL12 (interleukin 12) survived the FDR adjustment. IL12 is associated with proinflammatory and immune processes (Olink Proteomics, 2024). This positive association is intriguing, as previous research has often linked elevated IL12 levels to cognitive decline in older adults (Lin et al., 2019; Llaurador-Coll et al., 2023). However, as stated previously, the transitory inflammation stage found in the ARMS patients can lead to temporary proteomic dysregulation, and in this case, the results should be interpreted carefully. Before the FDR adjustment, MDGA1 (MAM domain containing glycosylphosphatidylinositol anchor 1) was the only protein positively correlated with cognition in both HCs and ARMS patients, but no correlation was observed in FEP patients. The MDGA1 gene is associated with bipolar disorder (Rappaport et al., 2017) and phenotypically with cognitive decline (Harris et al., 2020; Llaurador-Coll et al., 2023; Sherva et al., 2020). Additionally, the expression levels of CLEC1B (C-Type lectin domain family 1 member B), PLXNB3 (plexin B3), LGALS8 (galectin 8) and LAT (linker for the activation of T cells) were significantly negatively correlated in FEP patients, and the expression levels of all of these proteins were positively but not significantly correlated with cognitive performance in HCs. The expression levels of these 4 proteins showed similar correlation patterns with cognition within groups but dissimilar correlation patterns between groups, and they were negatively associated with cognitive performance in a previous study by our group (Llaurador-Coll et al., 2023). Regarding the correlations between protein expression levels and cognitive domains, the most remarkable finding was that the correlation strength changed between groups for all the cognitive domains. Compared with those in the HCs, the correlations in the ARMS patients were mainly negative and stronger, which may be due to immune-mediated dysregulation and greater symptom severity in the ARMS patients in our sample.

4.4. Study limitations

While this study provides valuable insights into the discovery of biomarkers for psychosis, several limitations should be considered. Even though our sample is properly characterized, its limited size and the imbalances between groups must be considered limitations. Consequently, the power of our linear regression model is limited (0.26 for an effect size of 0.24), and the logistic regression model also has a certain overfitting probability since the mean event-per-variable ratio (EPV) is lower than that recommended for prediction models (EPV = 1.71). These two characteristics may explain the poor predictive value, whereas other studies in which PEA was used in neurological disorder research (Ehtewish et al., 2023; Y. Guo et al., 2024) and studies using other methodologies in similar populations (Cao et al., 2023b; Kopczynska et al., 2019) revealed higher predictive values. These factors might limit the generalizability of the results, and they should be interpreted carefully. Moreover, the assay used to determine plasma protein levels is a target panel limited to detecting 92 proteins specifically selected for neurological disorder research. Additionally, the requirement for the patients to be clinically stable enough to appropriately administer clinical and cognitive tests did not allow us to capture alterations in the acute phase.

4.5. Final discussion

In summary, we identified distinct plasma profiles of neurology-related proteins associated with ARMS and FEP, providing insights into their potential roles in psychosis spectrum disorders. The upregulation of CPA2 expression in ARMS and FEP patients might be associated with the psychosis risk. In FEP patients, the expression of 32 proteins involved in neuron guidance and the regulation of nervous system processes was upregulated compared with that in HCs, suggesting alterations in these pathways in patients with psychosis. Notably, GFRA1 was the most upregulated protein in FEP patients and was strongly associated with psychosis-related pathways, suggesting that it represents a candidate biomarker of early psychosis. Our results also revealed a negative correlation between THY1 expression and general symptoms and a positive correlation between IL12 expression and cognitive performance in ARMS patients. Taken together, these findings provide a foundation for future research into neurology- and psychiatry-related plasma proteomic biomarkers of psychosis and their potential roles in clinical strategies for managing disease features.

5. Conclusions

From the discussion, several conclusions can be drawn as follows:

- Elevated plasma CPA2 levels may indicate a risk of psychosis and could reflect metabolic or myelin-related disturbances before psychosis onset.
- GFRA1 may become a potential biomarker for psychosis onset.
- Cell adhesion, the regulation of myelination, axon guidance and neuron projection processes, which involve several proteins, may be dysregulated during early psychosis.
- IL12 and THY1 expression levels may be associated with psychosis-related features (cognitive impairment and general symptoms, respectively) in patients with ARMS.
- Further studies with larger, more diverse cohorts and expanded protein panels are needed to validate and refine these candidate biomarkers.

CRediT authorship contribution statement

Martí Llaurador-Coll: Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Itziar Montalvo:** Investigation, Data curation. **Francesc Estrada:** Investigation. **Vanessa Sanchez-Gistau:** Writing – review & editing, Supervision, Project administration, Investigation, Data curation. **Henrik Zetterberg:** Writing – review & editing, Supervision, Resources. **Javier Labad:** Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Andrea L. Benedet:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis. **Elisabet Vilella:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

Henrik Zetterberg has served at scientific advisory boards and/or as a consultant for AbbVie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, Roche, and WebMD and is a cofounder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

The other authors have nothing to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.101134.

Data availability

Data will be made available on request.

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