Disease Severity Across Psychiatric Disorders Is Linked to Pro-Inflammatory Cytokines

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Disclosure:

Volker Arolt has been working as a counselor for Sanofi-Aventis Germany and Springer-Nature Verlag, Germany.

Ion-George Anghelescu has served as a counselor, advisor or CME speaker for the following entities: Aristo Pharma, Janssen Pharmaceutica, Merck, Dr. Willmar Schwabe, Recordati Pharma.

Jens Wiltfang acted as a consultant for Immungenetics, Noselab, Roboscreen, served on a scientific advisory board for Abbott, Biogen, Boehringer Ingelheim, Lilly, Immungenetics, MSD Sharp-Dohme, Noselab, Roboscreen, Roche, and received honoraria for presentations by Beeijing Yibai Science and Technology Ltd, Eisai, Gloryren, Janssen, Pfizer, Med Update GmbH, Roche, Lilly.

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Peter Falkai is currently president of the WFSBP. Peter Falkai has been EPA president in 2022 and is a co-editor of the German (DGPPN) schizophrenia treatment guidelines and a co-author of the WFSBP schizophrenia treatment guidelines. Peter Falkai received speaking fees from Boehringer-Ingelheim, Janssen, Otsuka, Lundbeck, Recordati, and Richter and was a member of the advisory boards of these companies and Rovi.

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Abstract

Importance: Numerous studies indicate that the traditional categorical classification of severe mental disorders (SMD), such as schizophrenia, bipolar disorders, and major depressive disorders, does not align with the underlying biology of those disorders as they frequently overlap in terms of symptoms and risk factors.

Objective: This study aimed to identify transdiagnostic patient clusters based on disease severity and explore the underlying biological mechanisms independently of the traditional categorical classification.

Design: We utilized data from 443 participants of the PsyCourse Study diagnosed with SMD, a longitudinal study with deep phenotyping across four visits. We performed longitudinal clustering to group patients based on symptom trajectories and cognitive performance. The resulting clusters were compared on cross-sectional variables, including independent measures of severity as well as polygenic risk scores, serum protein quantification, miRNA expression, and DNA methylation.

Results: We identified two distinct clusters that exhibited marked differences in illness severity. However, these clusters did not differ significantly in age, sex, or diagnostic proportions. We found that inflammatory serum proteins showed significant differences between the two clusters.

Conclusion: Our findings demonstrate that transdiagnostic clustering can effectively differentiate patients based on disease severity. The association of disease severity with pro-inflammatory proteins highlights the potential role of inflammation in the pathophysiology of SMD. These results underscore the importance of considering illness severity in psychiatric research and clinical practice and suggest that targeting inflammatory pathways may offer novel therapeutic strategies for patients with SMD.

Keywords: severe mental disorders, transdiagnostic clustering, disease severity, inflammation, proteomics, PLAUR, cognitive dysfunction, multi-omics analysis

Key points

Question: Can analyzing symptom trajectories and cognitive profiles across diagnostic categories reveal clinically relevant subgroups in severe mental disorders?

Findings: In this longitudinal study of 443 individuals with severe mental disorders, two distinct clusters emerged, differing significantly in illness severity, with the more severe group displaying elevated pro-inflammatory serum proteins, suggesting an association between disease severity and inflammation.

Meaning: These findings suggest that transdiagnostic clustering clarifies shared mechanisms, underscores the importance of inflammation in severe mental disorders, and highlights a promising avenue for novel therapeutic approaches.

Introduction

Severe mental disorders (SMD) such as schizophrenia (SCZ), schizoaffective disorder (SCZA), bipolar disorder (BD), and major depressive disorder (MDD), are complex and multifaceted syndromes that have common symptoms and risk factors(1). Many characteristics such as cognitive dysfunction, functional impairment, and psychiatric symptoms are shared among SMD. There is evidence from behavioral genetic and genome-wide association studies (GWAS) that SMD are heritable, with a common phenomic(2,3) and genomic basis(4). Different nosological frameworks have been proposed based on account for these commonalities, with RDoC and HiTOP(5) emphasizing dimensionality rather than categorical classification. Also, the DSM-5 is now emphasizing dimensionality in addition to diagnostic categories. Moreover, multiple studies have associated SMD with a dysregulation of the immune system. For example, SMD are marked by an augmentation of pro-inflammatory proteins in the blood (6,7). Treatments of pro-inflammatory cytokines can induce SMD symptoms(8). The link between the immune system and SMD is so important that those disorders are recognized as neuroimmune disorders (9–11). However, a challenge that remains for clinicians, regardless of the diagnostic system used is how to differentiate individuals who will experience a severe form of psychopathology from milder cases. The gold standard is population-based longitudinal studies with a duration of several years or decades, ideally prior to disease onset. However, such studies are extremely challenging and costly to conduct and in the end most longitudinal studies have emphasized highly heterogeneous illness trajectories over time(12). Here, we take a different approach and instead focus on the short-term course of the five core aspects of SMD: we focus on these five core aspects, cognitive dysfunction, functional impairment, and psychotic, manic, and depressive symptoms, because they collectively represent the fundamental dimensions of impairment across diagnostic categories, allowing for a more nuanced and transdiagnostic perspective on the severity and course of SMD. We take advantage of The PsyCourse Study(13), a deeply phenotyped longitudinal sample of the psychotic-to-affective spectrum, collected specifically for this purpose. To identify clusters of patients that differ in their longitudinal course, we used *longmixr* a R toolbox that enables longitudinal clustering of mixed data types(14,15). We identified two patient clusters that are similar in diagnostic proportions but exhibited distinct levels of severity. We then conducted comprehensive multi-omics analyses and found that proinflammatory cytokines are strongly associated with disease severity.

Methods

Longitudinal clustering

Participants data and samples were obtained from the PsyCourse Study (www.psycourse.de, supplementary Methods).

Clustering was performed using longmixr (Figure 1A)(14). First, longitudinally measured phenotypic data were meaningfully divided into five groups representing different domain SMD, namely depressive, SCZ, manic, and cognitive symptoms, and functioning. (supplemental material).

Phenotypic characterization of the clusters

To validate the clustering, we compared the clusters for the sums of the scales and the scores of neuropsychological tests used for clustering. To ensure that there were no biases, we checked for differences in age, sex, and diagnosis.

We also compared the clusters on three severity indicators not used for clustering: Operational Criteria Checklist for Psychotic and Affective Illness (OPCRIT) item 90 (16) , the body mass index (BMI), and childhood trauma using Childhood Trauma Screener (17) (Supplementary Methods).

Statistics included X^2 tests for categorical variables, T-tests for single measurements, and ANOVA for multiple time-points. Analysis and figures were realized with R.

Polygenic risk score analysis (PRS)

To assess whether genetics contributed to the differences in clusters, we compared PRS for MDD, BD, SCZ and for antipsychotic treatment resistance and the P-factor (18,19). Genotyping was described previously (20) (supplemental Methods).

Multiomics analysis

Propensity score matching was used to control for age, sex, and diagnosis across clusters. Serum from the first visit was used to quantify 384 proteins in 176 participants using Olink Explore Inflammation panel. The *OlinkAnalyze* package was used for QC. Proteins were compared using T tests, followed by a Gene Ontology (GO) analysis to identify biological pathways. Spearman correlations were computed between the normalized expression values of proteins (NPX) and variables from neuropsychological tests (Trail Making Test A (TMT-A) and B (TMT-B) (time), Verbal digit span forward (DGT_SP_FRW), Verbal digit span backward (DGT_SP_BW), Digit-Symbol-Test (DST)) and age of the participants.

To account for age, we selected proteins with one significant correlation with a test variable and recomputed partial correlations between proteins and each test.

For DNA methylation 192 participants were analyzed (Illumina EPIC V2). The ages were imputed using the *methylclock* package and probes were filtered out if variance <0.05 resulting in 693 probes. Differential analysis was performed with *minfi* and *limma* packages while adjusting for age and sex.

The miRNAome was obtained from the first visit and processed as previously described(20,21). *DESeq2* compared the two clusters while adjusting for age, sex, and sequencing batches. Multiple hypothesis correction (Benjamini-Hochberg) was used.

Results

Longitudinal clustering of participants

Our aim was to characterize the study samples independently of their ascertained DSM-IV diagnoses (Figure 1A, Methods, Table I). We explored different clustering solutions and used the cumulative distribution function (CDF) to determine the optimal number of clusters (Figure 1B). The CDF indicated that the two-cluster solution was optimal, as it demonstrated better binary separation characterized by a flatter curve with steep ascents at 0 and 1 (14).

The clusters showed significant differences across various symptom scales and neuropsychological assessments. Cluster B had higher scores on schizophrenia, manic and depressive symptoms (Figure 1C-E). They also showed poorer functioning scores (Figure 1F).

In addition, patients in Cluster B performed worse for cognition, i.e. they had a higher error rate on the TMT Part B with longer completion times (for both Parts A and B) and had lower scores for Verbal Digit Span (VDS) tests, and DST (Figure 1G-H; Supplementary Figures 1A-E). In summary, Cluster B consists of participants with a higher illness severity compared to cluster A.

Our clustering algorithm used longitudinal data from these symptom scales and neuropsychological tests to group patients based on their symptom trajectories and cognitive performance over time. Since the clusters were derived by analyzing patterns in these specific measures, it is logical that the resulting clusters would differ significantly on these variables. However, it is noteworthy that the differences across these diverse scales and tests converge in the same direction, consistently indicating greater severity in Cluster B. The convergence of these independent measures across different domains supports the conclusion that clustering differentiates patients primarily by severity.

Comparison of Cross-Sectional Phenotypic Variables

Since age and sex were regressed out during clustering, we anticipated that these variables would not differ significantly between clusters. Indeed, there were no significant differences in age (Figure 1I; *t*-test *p*-value = 0.36) or sex (Figure 1J; χ^2 *p*-value = 0.46). Importantly, the clusters did not differ significantly in the proportions of diagnoses among SCZ, SCZA, BD, and MDD (Figure 1K; χ^2 *p*-value = 0.18). Additionally, the proportions of male and female subjects in the clusters were also similar (Supplementary Figure 1F and Supplementary Table I, X^2 padj = 1 for each test). Age was also similar when stratified by sex and diagnosis individually, indicating that age and sex are similar in both clusters (Supplementary Figure 1G).

Comparison of Polygenic Profiles

To assess whether genetic factors contribute to the differences between our clusters, we used several PRS (see methods). We did not find significant differences between the clusters regarding PRS for MDD (Figure 2A; *t*-test adjusted *p*-value = 0.15), BD

(Figure 2B; *t*-test adjusted *p*-value = 0.674), or SCZ (Figure 2C; *t*-test adjusted *p*-value = 0.894). Similarly, the sum of the PRS for these three disorders did not differ significantly between the clusters (Figure 2D; *t*-test adjusted *p*-value = 0.674). Furthermore, no significant differences were observed for SCZ treatment resistance PRS (Figure 2E; adjusted *p*-value = 0.674) or for the P factor PRS (Figure 2F; *t*-test adjusted *p*-value = 0.971).

Independent Measures of Severity

To further characterize the differences in severity between the clusters, we analyzed independent measures not used in the clustering process. We found a significant difference in the distribution of OPCRIT categories between the clusters (Figure 2G; χ^2 p-value < 0.001). Specifically, Cluster B had a higher proportion of patients experiencing partial remission or ongoing chronic illness compared to Cluster A, indicating a more severe illness trajectory.

Significant differences were found in BMI between the clusters (figure 2H, ANOVA *p*-value = 1e-07). However, there was no significant difference in the rate of BMI change over time between the clusters (t-test estimate=0.07; *p*-value = 0.33). Additionally, although not statistically significant, there was a trend toward a higher proportion of participants with a history of childhood trauma (CHT) in Cluster B compared to Cluster A (Figure 2I; χ^2 *p*-value = 0.07).

Multi-omics Analysis

To identify associated molecular alterations between the clusters we carried out 3 distinct molecular profiling approaches during the first visit for each patient group (Figure 3A).

miRNA Expression and Methylome Comparisons

We compared the miRNA profiles from the first visit of the PsyCourse Study of 125 participants (64 low-severity patients and 61 high-severity patients). PCA analysis did not reveal any major differences or batch effects (Supplemental figure 2A). Furthermore, none of the 465 miRNAs analysed were differentially expressed between the two groups, suggesting that miRNA expressions are unlikely to be associated with differences observed between the clusters (Figure 3B).

Similarly, we explored the methylomes of 192 patients using DNA samples (see supplemental figure 2B). We performed differential methylation analyses on the top variable methylation sites (see method). However, no methylation sites were significantly different between the groups (Figure 3C). To further investigate a possible relationship between DNA methylation and severity we explored whether epigenetic age acceleration was distinct between the clusters. The imputed epigenetic age correlated strongly with the actual age of the participants (Supplemental Figure 2C) and did not differ between the two groups (Figure 3D; Wilcoxon p-value = 0.44).

Proteomic Differences in a targeted inflammatory protein Panel

We characterized 363 circulating serum proteins, using the Olink Inflammatory panel (Supplementary Figure 3A). Comparing the 363 circulating proteins between the clusters revealed 25 down-regulated and 48 up-regulated proteins in the serum of the high-severity cluster compared to the low-severity cluster (Figure 4A). Top differential expressed proteins are illustrated to reveal that differences are not due to extreme outliers (Figure 4B, Supplementary Table II). GO analyses were performed to identify biological pathways associated with these proteins. The down-regulated proteins were linked to six GO terms related to the regulation of cell adhesion and interleukin-13 (IL-13) production, a cytokine with anti-inflammatory properties(22) (Figure 4C). In contrast, the up-regulated proteins were associated with multiple GO terms indicative of a pro-inflammatory state, such as "response to interferon-gamma" and "response to interleukin-1" (Figure 4D). This indicates that a higher severity is associated with a deregulation of inflammation state.

Spearman correlations between protein expression levels and neuropsychological assessments identified 7 proteins correlated with at least one of the test variables (Supplementary Figure 3D). Notably, proteins up-regulated in the high-severity cluster were positively correlated with the time taken to complete the TMT-A and TMT-B and negatively correlated with the scores of the DST as well as VDS_FRW and VDS_BW. Conversely, the down-regulated proteins ENPP5 and CDON showed opposite correlations.

Many of the correlations between proteins and neuropsychological variables were accompanied by similar correlations with the age of the participants (10 proteins; Supplementary Figure 3D). To disentangle the effect of age on cognition, we calculated partial correlations between these proteins and the test variables, adjusting for age. This resulted in nine significant correlations while controlling for age, with five of these correlations related to the PLAUR gene (Figure 4E). We further investigated the relationship between the expression of PLAUR and disease severity encoded by the ordered categories of the OPCRIT. A significant association was found (ANCOVA p-value < 0.001 after adjusting for age). We also identified differences between patients with ongoing chronic illness and those with good or partial remission (Wilcoxon Rank Sum test, p-value < 0.05, Figure 4F-G).

Discussion

Our study leverages comprehensive longitudinal phenotyping over four visits to demonstrate that disease severity in severe mental disorders can be characterized independently of traditional diagnostic categories. By employing a transdiagnostic clustering approach, we identified patient groups that differ primarily in illness severity. While there were no significant differences in age and sex overall, we did observe a difference in the proportion of female patients with schizoaffective disorder between the clusters. This specific variance may be due to unique clinical features within this subgroup, but overall, the similar diagnostic proportions highlight that the clusters represent groups differentiated by severity across diagnostic categories.

This finding underscores the significant overlap in symptoms across disorders such as schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder, highlighting the limitations of categorical diagnoses in capturing the complexity of psychiatric conditions.

The overlapping symptoms between different psychiatric disorders have been well-documented and suggest that common underlying mechanisms may contribute to disease manifestation(3,4). Cognitive dysfunction, functional impairment, and mood disturbances are prevalent across multiple diagnoses. Our results demonstrate that these shared symptoms coalesce to define severity levels that transcend diagnostic boundaries. This supports dimensional models of psychopathology, such as RDoC and HiTOP, which advocate for assessing mental disorders along continuous dimensions rather than discrete categories(23,24).

Importantly, we found that independent measures not used in the clustering process, especially the OPCRIT item and BMI also differed between the clusters, further confirming the robustness of our severity classification. The high-severity cluster had a higher proportion of patients experiencing partial remission or ongoing psychiatric chronic illness according to the OPCRIT item, indicating a more severe overall illness trajectory. Additionally, patients in the high-severity cluster exhibited higher BMI, which has been associated with increased psychiatric symptom severity, poorer cognitive performance and poorer clinical outcomes in patients with affective disorders (25,26). Weight gain is also a common side effect of antipsychotic treatment and is associated with poorer medication adherence in patients with schizophrenia, which increases the risk for recurrent illness episodes and poorer outcome long term(27). Although the difference in CHT was not statistically significant, there was a trend toward a higher proportion in the high-severity cluster, aligning with literature that associates CHT with more severe psychiatric outcomes(28,29). These independent measures, which were not part of the clustering variables, reinforce our finding that the clusters are differentiated primarily by severity.

The genetic analysis revealed no significant differences in PRS for SCZ, BP, or MDD between the high-severity and low-severity clusters. This suggests that genetic variants identified in GWAS may be more closely associated with disease susceptibility rather than the severity of illness. In psychiatry, the largest GWAS focus on the risk of developing a disorder by comparing cases to controls, which may not capture genetic factors influencing the course or severity of the disease once it manifests. It is also possible that rare variants, structural variations, or gene–environment interactions play a more significant role in determining illness severity.

Our proteomic analysis revealed that disease severity is associated with proteomic changes indicative of a pro-inflammatory state associated to psychiatric severity. Specifically, patients in the high-severity cluster showed up-regulation of proteins associated with pro-inflammatory pathways while anti-inflammatory pathways

associated with IL-13 were down-regulated. This shift suggests that systemic inflammation may be linked to increased illness severity in SMD. Given that cognitive dysfunction is a critical aspect of disease severity, we investigated whether the expression levels of these proteins were associated with cognitive performance. Our analysis identified 4 proteins that correlated with at least one neuropsychological test variable. It is noteworthy that some of these proteins have been previously associated with psychosis or nervous system development. For example, ENPP5 was found positively associated to intelligence by a Mendelian analysis (30), while negative association were found for the expression of PLAUR and CD4 (31,32). The CRIM1 gene is expressed in neurons and is implicated in central nervous system development(33). Among them, PLAUR deserves particular attention due to its multiple associations with cognitive function and neurological processes. Literature searches confirmed the association of PLAUR expression with cognitive function in multiple studies. This gene is also expressed by microglial cells in the CNS. Its inactivation is known to induce changes in GABA A-receptor subunits, highlighting its importance in CNS development(34). Additionally, the urokinase plasminogen activator system, of which PLAUR is a part, is involved in leukocyte recruitment, with the soluble form of PLAUR in serum and cerebrospinal fluid being implicated in neurological disorders(35,36). Taken together, these findings demonstrate that disease severity is associated with proteomic changes indicative of a pro-inflammatory state.

In contrast to the proteomic findings, our analysis revealed no significant differences in miRNA expression or DNA methylation profiles between the high-severity and low-severity clusters. miRNA expression and DNA methylation are regulatory mechanisms that may require longer timescales to manifest significant changes. These epigenetic modifications are often more stable and may not fluctuate significantly over the short-term course captured in our study(37).

An important consideration is that our analyses of miRNA and DNA methylation were conducted using blood which may not capture alterations occurring in the brain. The brain and blood can have distinct epigenetic landscapes, and peripheral markers may not fully represent central nervous system processes.

Despite the strengths of our comprehensive multi-omics approach and longitudinal design, our study has several limitations. First, the use of peripheral blood samples for miRNA and DNA methylation analyses may not accurately reflect brain-specific epigenetic changes associated with psychiatric disorders or be a consequence of lack of statistical power due to the sample size. Second, due to a reasonable but limited sample size in a homogenous population it is relevant to replicate our findings in larger and heterogenous populations in future studies.

In conclusion, our study emphasizes the importance of comprehensive, longitudinal phenotyping in capturing the complexity of SMD beyond categorical diagnoses. Our multi-omics analysis further reveals that increased disease severity is associated

with a pro-inflammatory proteomic profile, potentially contributing to cognitive dysfunction.

Our work underscores the importance of considering illness severity as a key dimension in psychiatric research and clinical practice. Tailoring interventions based on severity rather than diagnosis alone may improve patient outcomes, and targeting inflammatory pathways could offer new therapeutic avenues for patients with SMD.

Author contribution

UH, TGS and JP designed the study. MB, KA, PF, MH, UH, ANF, MOK, SP, DRE, ECS, TGS, FS, TV, IGA, VA, BTB, UD, DED, AJF, CF, FL, GJ, CK, FL, JR, EZR, MS, CS, JW, and JZ contributed to acquisition and/or processing and/or managing of data (phenotype data and/or biological data). SP carried out the quality control of the genotyping, imputation and (in parts) PRS calculation. LK coordinated the RNA isolation and small-RNA-seq of the entire PsyCourse samples with the help of SB and ALS. DMK and TP contributed to the sequencing design and performed QC analysis. FS and AF planned the sequencing experiments. PS performed all analyses including the clustering, the omics comparisons and generated the figures. JP supervised the analyses. PS, UH, MB, JP & TGS wrote the first draft of the paper.

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Legends of the figures and tables

Table I: Variables measured by the PsyCourse Study

Figure 1

(A) Graph representing the strategy to classify the longmixr participants based on clinical evaluations. The consensus matrix displayed is the one computed by longmixr for the 2 clusters solution, while the consensus CDF was used to identify the optimal number of clusters. (B) Consensus CDF (upper) and consensus matrix (bottom) plots of our longmixr clustering. Spaghetti plots comparing the sum of the PANSS (negative, positive, and general) scales (C, ANOVA p-value < 0.001), the sum of the YMRS scale across the two clusters (D, ANOVA p-value < 0.001), the sum of the IDSC scale across the two clusters (E, ANOVA p-value < 0.001), the sum of the GAF scale across the two clusters (F, ANOVA p-value < 0.001), the time needed to finish Part B of the TMT tests across the two clusters (G, ANOVA, p-value < 0.001), and the number of errors made during the Part B of the TMT test (H, ANOVA p-value = 0.005). Boxplot comparing the age at the first visit of the two clusters (I, T Test p-value = 0.36), and barplots representing the sex (J, X^2 p-value = 0.458) and the diagnosis proportions in each cluster (K, X^2 p-value = 0.18).

Figure 2

Boxplot comparing PRS between the two clusters, namely PRS for MD (A, T test adjusted p-value = 0.150), BD (B, T test adjusted p-value = 0.674), SCZ (C, T test adjusted p-value = 0.894), all 3 disorders (D, T test adjusted p-value = 0.674, sum of the individual PRS), SCZ treatment resistance (E, T test adjusted p-value = 0.674) and for the P factor (F, T test adjusted p-value = 0.971). Barplot representing the proportion of OPCRIT categories measured at the fourth visit of the PsyCourse study in each cluster (G, X^2 p-value < 0.001). Spaghetti plot comparing the BMI of the two clusters (H, ANOVA p-value < 0.001), and barplot representing the proportion of childhood trauma presence in each cluster (I, X^2, p-value = 0.07)

Figure 3

Flowchart that describes the multiomics analyses that were performed in this study (A) and volcano plot of the analysis comparing the miRNAome (B) and the methylome (C) of the two clusters. Boxplot comparing the age acceleration (imputed age – real age) of the two clusters (D).

Figure 4

Volcano plot of the olink analysis (A, T test), and expression boxplot of 4 dysregulated proteins across the two clusters (B). Network graph of the GO process enriched in the proteins down-regulated (C), or up-regulated (D) in the high severity clusters. The color and size of the nodes correspond respectively to the p-value and the number of genes associated to the GO terms. The size of the edges represents the number of proteins in common between the GO terms. Correlation heatmap of the partial correlation of spearman between the protein's expression and the

neuropsychological assessment variables (E, * $p<0.05$, ** $p<0.005$). The DE column indicates if the proteins were differentially expressed in our analysis comparing the high and low severity patients' groups. Boxplot representing the expression of the PLAUR gene according to the different OPCRIT categories (F), and heatmap representing the partial correlation of spearman of the PLAUR gene to the different neuropsychological assessments (G). The text in the tyle is the adjusted p-value.

Supplementary Figure 1

Spaghetti plots showing the time needed to finish (A, ANOVA p-value < 0.001) and the number of errors (B, ANOVA p-value =0.146) made during Part A of the TMT test, as well as the scores of the Digit Symbol test (C, ANOVA p-value < 0.001), Verbal Digit Span test forward (D, ANOVA p-value < 0.001) and backward (E, ANOVA p-value < 0.001) in both clusters. (F) Barplots indicate the sex proportion in the two clusters across the different categorical diagnoses, and (G) Comparison of age between the clusters grouped by age and diagnosis using T tests (pvalues adjusted with BH method).

Supplementary Figure 2

PCA plot of the miRNAome expression data (A) of the methylation state of CpG site (B) of the patients. Correlation between real age of the participants during the first visit of the PsyCourse study and the DNA imputed age using the Levine model of the methylClock R package (C),

Supplementary Figure 3

PCA plot of the protein expression in NPX (A). Barplot of the GO process significantly enriched for the down-regulated (B) and up-regulated (C) proteins in the high severity cluster. Correlation heatmap of the partial correlation of spearman between the proteins' expression and the neuropsychological assessment variables (* $p<0.05$, ** $p<0.005$). The DE column indicates if the proteins were differentially expressed in our analysis comparing the high and low severity patients' groups (D).

Supplementary Table I

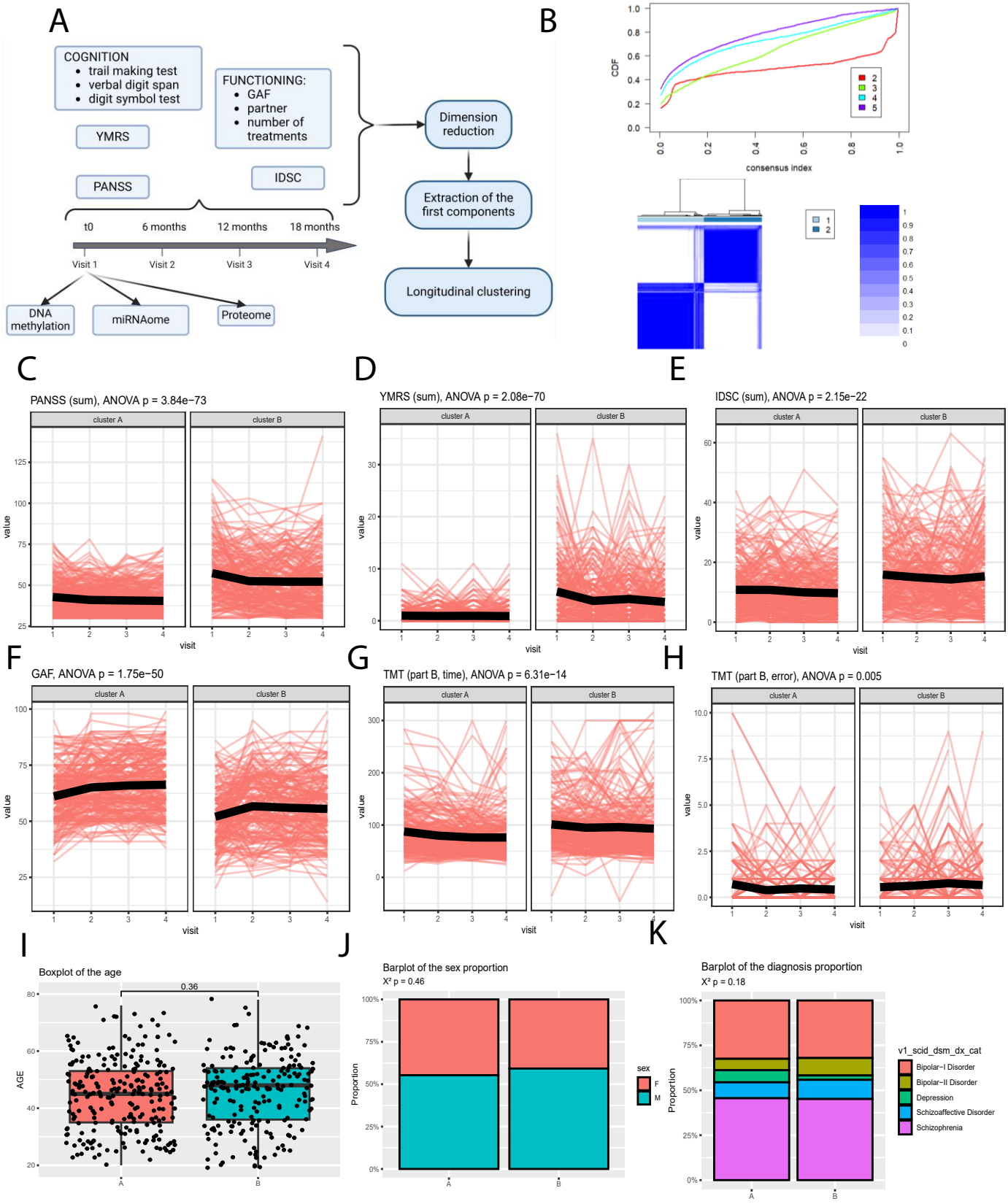
Sex Proportions across the clusters for each diagnosis and results of their comparisons (X^2).

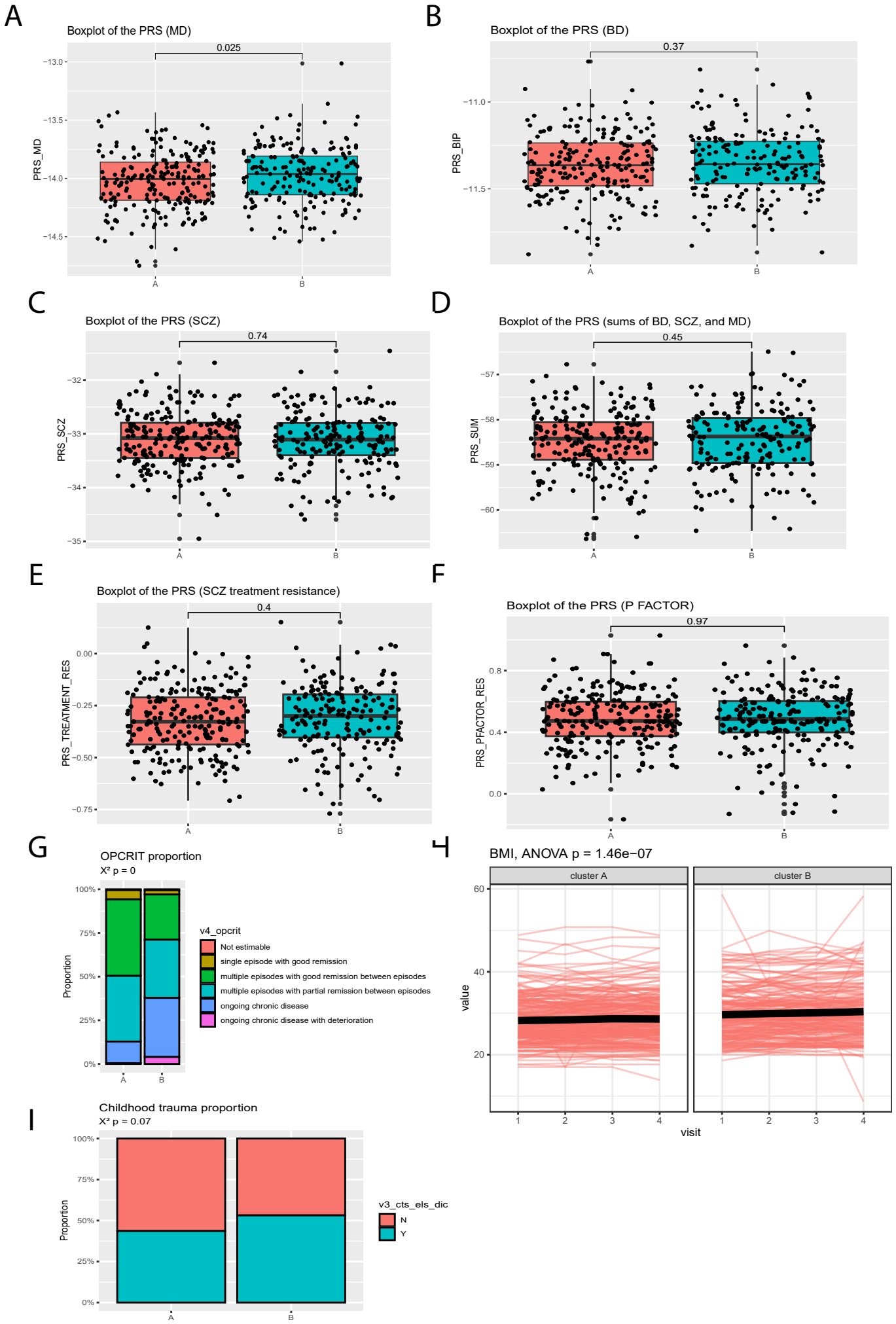
Supplementary Table II

Results of the proteomic analysis comparing the two clusters (Estimate = numeric difference in mean NPX between the two groups, Low and High severity columns indicate the mean NPX of each group)

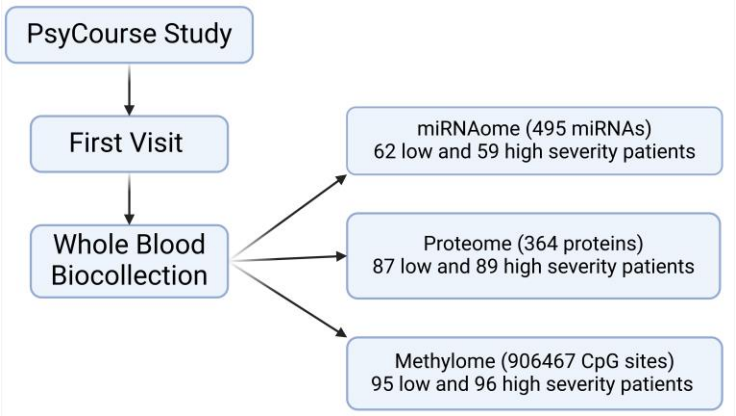
Table I:

Variable measured at each visit				
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**
PANSS sum score*	49.58 (16.17)	46.34 (13.95)	46.03 (14.02)	45.89 (15.5)
IDSC sum score*	13.16 (10.83)	12.72 (9.92)	11.96 (10.37)	12.29 (10.77)
YMRS sum score*	3.14 (4.98)	2.28 (3.89)	2.46 (4.09)	2.17 (3.63)
GAF score*	56.87 (13.11)	61.17 (13.6)	61.31 (13.86)	61.26 (14.56)
Variable measured at a single visit				
Sex (visit 1)				
F	190 (42.9%)			
M	253 (57.1%)			
Age (mean; SD)	19-79 (45.93; 12.49)			
Diagnosis (visit 1)				
Bipolar-I Disorder	143 (32.1%)			
Bipolar-II Disorder	35 (7.8%)			
Depression	21 (4.7%)			
Schizoaffective Disorder	43 (9.6%)			
Schizophrenia	204 (45.7%)			
OPCRIT (visit 4)				
Not estimable	2			
Single episode with good remission	17			
multiple episodes with good remission between episodes	151			
multiple episodes with partial remission between episodes	152			
ongoing chronic disease	96			
ongoing chronic disease with deterioration	9			
-999 (not measurable)	16			
Presence of childhood trauma (visit 3)				
No	218			
Yes	201			
-999 (not measurable)	24			
Current psychiatric treatment (visit 1)				
No	9			
Yes. outpatient	295			
Yes. day patient	22			
Yes. inpatient	114			
NA	3			
First-episode patient (visit 1)				
No	410			
Yes	16			
NA	17			

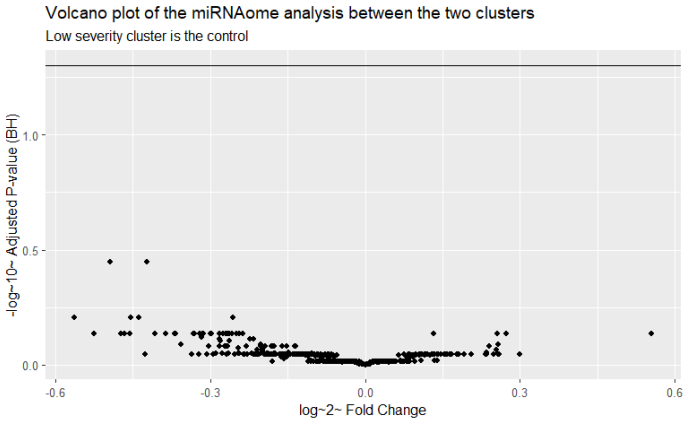

A
COGNITION
trail making test
verbal digit span
digit symbol test
YMRS
PANSS
FUNCTIONING:
GAF
partner
number of treatments
IDSC
t0
6 months
12 months
18 months
Visit 1
Visit 2
Visit 3
Visit 4
DNA methylation
miRNAome
Proteome
Dimension reduction
Extraction of the first components
Longitudinal clustering
B
CDF
consensus index
C
PANSS (sum), ANOVA p = 3.84e−73
D
YMRS (sum), ANOVA p = 2.08e−70
E
IDSC (sum), ANOVA p = 2.15e−22
F
GAF, ANOVA p = 1.75e−50
G
TMT (part B, time), ANOVA p = 6.31e−14
H
TMT (part B, error), ANOVA p = 0.005
cluster A
cluster B
value
visit
I
Boxplot of the age
0.36
AGE
J
Barplot of the sex proportion
X² p = 0.46
Proportion
sex
F
M
K
Barplot of the diagnosis proportion
X² p = 0.18
v1_scid_dsm_dx_cat
Bipolar−I Disorder
Bipolar−II Disorder
Depression
Schizoaffective Disorder
Schizophrenia


A
Boxplot of the PRS (MD)
0.025
PRS_MD
−13.0
−13.5
−14.0
−14.5
A
B
B
Boxplot of the PRS (BD)
0.37
PRS_BIP
−11.0
−11.5
A
B
C
Boxplot of the PRS (SCZ)
0.74
PRS_SCZ
−32
−33
−34
−35
A
B
D
Boxplot of the PRS (sums of BD, SCZ, and MD)
0.45
PRS_SUM
−57
−58
−59
−60
A
B
E
Boxplot of the PRS (SCZ treatment resistance)
0.4
PRS_TREATMENT_RES
0.00
−0.25
−0.50
−0.75
A
B
F
Boxplot of the PRS (P FACTOR)
0.97
PRS_PFACTOR_RES
0.8
0.4
0.0
A
B
G
OPCRIT proportion
X² p = 0
Proportion
100%
75%
50%
25%
0%
A
B
v4_opcrit
Not estimable
single episode with good remission
multiple episodes with good remission between episodes
multiple episodes with partial remission between episodes
ongoing chronic disease
ongoing chronic disease with deterioration
H
BMI, ANOVA p = 1.46e−07
cluster A
cluster B
value
60
40
20
1
2
3
4
visit
I
Childhood trauma proportion
X² p = 0.07
Proportion
100%
75%
50%
25%
0%
A
B
v3_cts_els_dic
N
Y

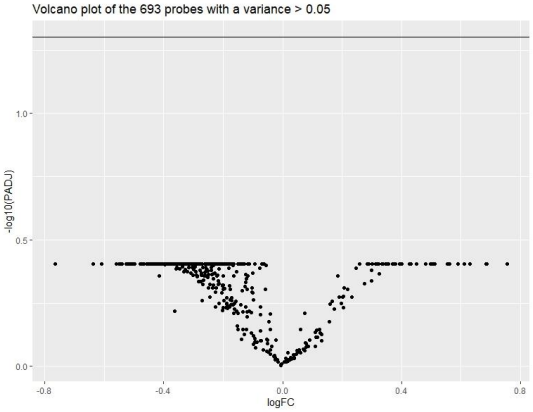
A


PsyCourse Study
First Visit
Whole Blood Biocollection
miRNAome (495 miRNAs)
62 low and 59 high severity patients
Proteome (364 proteins)
87 low and 89 high severity patients
Methylome (906467 CpG sites)
95 low and 96 high severity patients

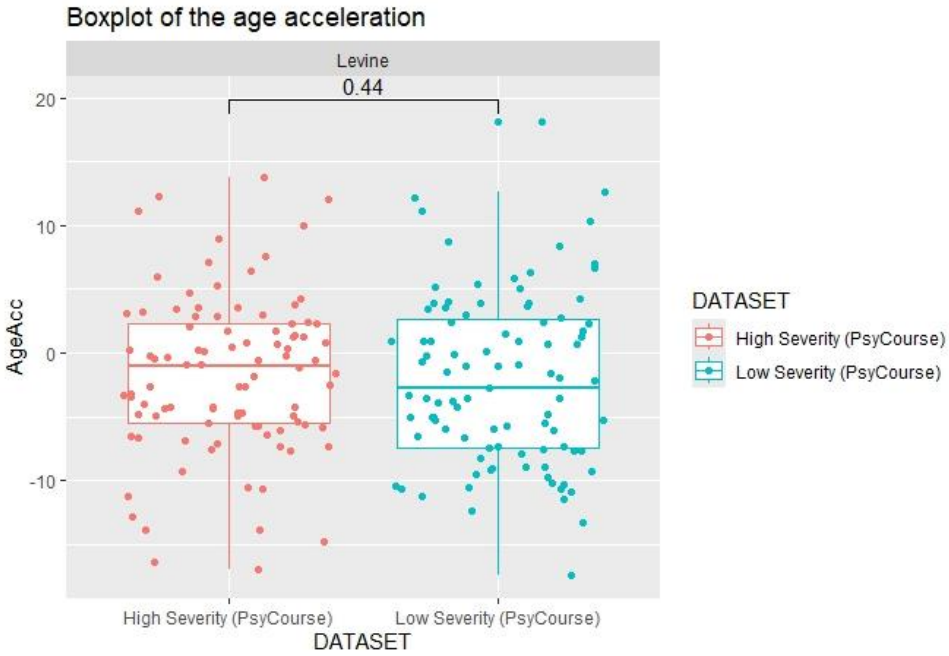
B

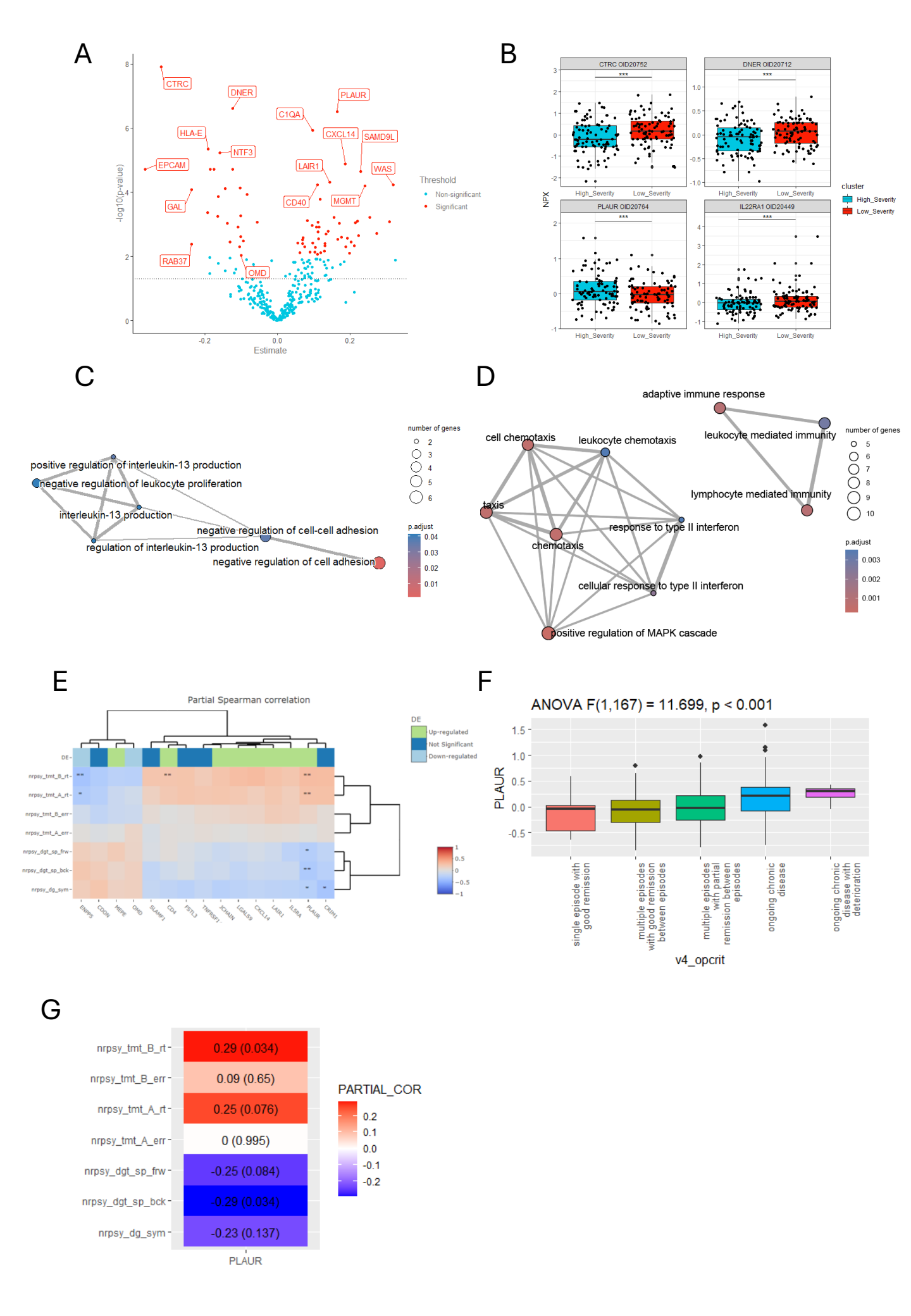

Volcano plot of the miRNAome analysis between the two clusters
Low severity cluster is the control
-log~10~ Adjusted P-value (BH)
1.0
0.5
0.0
-0.6
-0.3
0.0
0.3
0.6
log~2~ Fold Change

C


Volcano plot of the 693 probes with a variance > 0.05
-log10(PADJ)
1.0
0.5
0.0
-0.8
-0.4
0.0
0.4
0.8
logFC

D


Boxplot of the age acceleration
Levine
0.44
AgeAcc
20
10
0
-10
High Severity (PsyCourse)
Low Severity (PsyCourse)
DATASET
DATASET
High Severity (PsyCourse)
Low Severity (PsyCourse)


A
CTRC
DNER
PLAUR
C1QA
HLA-E
CXCL14
SAMD9L
NTF3
EPCAM
LAIR1
WAS
GAL
CD40
MGMT
RAB37
OMD
-log10(p-value)
Estimate
Threshold
Non-significant
Significant
B
CTRC OID20752
DNER OID20712
PLAUR OID20764
IL22RA1 OID20449
NPX
High_Severity
Low_Severity
cluster
C
positive regulation of interleukin-13 production
negative regulation of leukocyte proliferation
interleukin-13 production
negative regulation of cell-cell adhesion
regulation of interleukin-13 production
negative regulation of cell adhesion
number of genes
p.adjust
D
adaptive immune response
leukocyte mediated immunity
cell chemotaxis
leukocyte chemotaxis
lymphocyte mediated immunity
taxis
response to type II interferon
chemotaxis
cellular response to type II interferon
positive regulation of MAPK cascade
number of genes
p.adjust
E
Partial Spearman correlation
DE
Up-regulated
Not Significant
Down-regulated
nrpsy_tmt_B_rt
nrpsy_tmt_A_rt
nrpsy_tmt_B_err
nrpsy_tmt_A_err
nrpsy_dgt_sp_frw
nrpsy_dgt_sp_bck
nrpsy_dg_sym
ENPP5
CDON
MEPE
OMD
SLAMF1
CD4
FSTL3
TNFRSF1
JCHAIN
LGALS9
CXCL14
LAIR1
IL5RA
PLAUR
CRIM1
F
ANOVA F(1,167) = 11.699, p < 0.001
PLAUR
single episode with good remission
multiple episodes with good remission between episodes
multiple episodes with partial remission between episodes
ongoing chronic disease
ongoing chronic disease with deterioration
v4_opcrit
G
nrpsy_tmt_B_rt
0.29 (0.034)
nrpsy_tmt_B_err
0.09 (0.65)
nrpsy_tmt_A_rt
0.25 (0.076)
nrpsy_tmt_A_err
0 (0.995)
nrpsy_dgt_sp_frw
-0.25 (0.084)
nrpsy_dgt_sp_bck
-0.29 (0.034)
nrpsy_dg_sym
-0.23 (0.137)
PLAUR
PARTIAL_COR