Integrated Transcriptomic Analysis Revealing Shared Molecular Signatures Between COVID-19 and Schizophrenia.

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Abstract

The neuropsychiatric consequences of SARS-CoV-2 infection have raised significant concerns regarding shared molecular mechanisms between COVID-19 and major psychiatric disorders. In this study, we performed an integrative bioinformatics analysis to identify common differentially expressed genes (DEGs), biological functions, and pathways linking COVID-19 with schizophrenia, bipolar disorder, and major depressive disorder (MDD). Gene expression datasets were obtained from GEO using GEO2R, followed by differential expression analysis with stringent statistical thresholds (adjusted p-value < 0.05 and $|\log_2 \text{fold change}| \geq 1$). While schizophrenia demonstrated a significant overlap of DEGs with COVID-19, bipolar disorder and MDD did not show statistically significant shared DEGs due to high adjusted p-values and low effect sizes. These negative findings were systematically analyzed and reported to ensure methodological rigor. Functional enrichment analyses of shared schizophrenia–COVID-19 DEGs revealed significant involvement in calcium signaling, MAPK signaling, inflammatory responses, and neurodegenerative-related pathways. Network-based analyses using STRING, KEGG, and Cytoscape further demonstrated interconnected molecular pathways underlying immune dysregulation and neuronal signaling alterations. Disease–disease network visualization highlighted schizophrenia as the primary neuropsychiatric condition molecularly linked to COVID-19 within the applied thresholds. This work contributes to current knowledge by integrating neuropsychiatric disease association analysis into COVID-19 transcriptomic research and by transparently reporting both positive and negative results. Finally, this study proposes future research directions investigating potential links between SARS-CoV-2, prion-related mechanisms, and non-coding RNA regulation in neuropsychiatric disorders.

Keywords: COVID-19, schizophrenia, transcriptomics, differentially expressed genes, calcium signaling, MAPK signaling, neuroinflammation,

Introduction

Neuropsychiatric disorders such as schizophrenia, bipolar disorder, and major depressive disorder (MDD) are complex brain diseases characterized by alterations in gene expression, synaptic signaling, immune regulation, and neuronal connectivity. These disorders are increasingly understood not as isolated brain conditions, but as systemic diseases influenced by immune activation, inflammation, and environmental stressors. Recent evidence suggests that viral infections, particularly SARS-CoV-2, may exacerbate or unmask neuropsychiatric symptoms through immune-mediated and molecular mechanisms. Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has been associated with a wide spectrum of neurological and psychiatric manifestations, including cognitive impairment, mood disturbances, and psychosis. Molecular studies have shown that SARS-CoV-2 infection induces profound transcriptional changes in host cells, particularly in pathways related to inflammation, calcium signaling, synaptic regulation, and stress response. These pathways overlap with those implicated in neuropsychiatric disorders, raising the possibility of shared molecular mechanisms. High-throughput transcriptomic datasets deposited in the Gene Expression Omnibus (GEO) provide a valuable resource to investigate these shared mechanisms. In particular, the dataset GSE53987 offers well-characterized post-mortem brain gene expression profiles across schizophrenia, bipolar disorder, MDD, and matched controls from multiple brain regions. When combined with COVID-19 transcriptomic datasets, this enables a systematic comparison of disease-associated differentially expressed genes (DEGs). Previous studies have often focused on multiple neuropsychiatric conditions simultaneously, sometimes assuming shared molecular signatures without fully addressing negative or non-significant results. However, rigorous bioinformatics analysis requires that each disease group be evaluated independently using consistent statistical thresholds. Importantly, the absence of significant overlap is itself a meaningful biological result when properly

documented and justified. The present study aims to identify genes and pathways shared between COVID-19 and major neuropsychiatric disorders using a robust differential expression and enrichment analysis workflow. By integrating DEG analysis, Gene Ontology (GO) enrichment, KEGG pathway analysis, protein–protein interaction networks, and disease association networks, this work seeks to clarify whether shared molecular signatures exist and how they may contribute to neuropsychiatric vulnerability following SARS-CoV-2 infection.

5.0 Materials and Methods

5.1 Data acquisition and study design

Publicly available transcriptomic datasets were retrieved from the Gene Expression Omnibus (GEO) database to investigate shared molecular signatures between SARS-CoV-2 infection and major neuropsychiatric disorders. COVID-19 gene expression data were obtained from the dataset **GSE177477**, which consists of peripheral blood samples collected from SARS-CoV-2–positive individuals exhibiting symptomatic and asymptomatic disease, as well as healthy control subjects. This dataset was selected due to its clear clinical stratification and relevance to systemic immune responses associated with COVID-19 infection.
Neuropsychiatric disorder gene expression data were obtained from the dataset **GSE53987**, which includes post-mortem brain tissue samples from individuals diagnosed with schizophrenia, bipolar disorder, and major depressive disorder (MDD), alongside matched healthy controls. Samples were collected from multiple brain regions, including the hippocampus, prefrontal cortex (BA46), and associative striatum. The inclusion of multiple brain regions enabled the assessment of robust disease-associated transcriptional alterations while reducing region-specific bias. Together, these datasets allowed for an integrative

analysis aimed at identifying common differentially expressed genes (DEGs) and shared biological pathways between COVID-19 and neuropsychiatric disorders.

5.2 Differential gene expression analysis

Differential gene expression analysis was performed independently for each dataset using the GEO2R online analysis tool, which applies the limma (Linear Models for Microarray Data) statistical framework. For the COVID-19 dataset (GSE177477), comparisons were conducted between SARS-CoV-2–positive samples and healthy control samples. For the psychiatric dataset (GSE53987), disease groups (schizophrenia, bipolar disorder, and major depressive disorder) were each compared separately against their corresponding control samples.To ensure statistical rigor and biological relevance, genes were considered significantly differentially expressed only if they met the predefined thresholds of an absolute log2 fold change ($|logFC| \geq 1$ and an adjusted p-value (Benjamini–Hochberg false discovery rate correction) < 0.05. These thresholds were applied consistently across all disease groups to allow fair comparison between conditions. Following DEG filtering, gene lists were exported for downstream comparative and enrichment analyses. Importantly, while schizophrenia samples yielded a substantial number of statistically significant DEGs meeting these criteria, both bipolar disorder and major depressive disorder showed limited or no genes passing the adjusted p-value threshold. These findings were retained and explicitly reported rather than excluded, as they represent valid negative results rather than analytical failure.

5.3 Visualization of differential expressions

Volcano plots were generated to visualize the distribution of gene expression changes for COVID-19 and psychiatric disease comparisons. Each plot displays log2 fold change on the x-axis and the negative log10 of the adjusted p-value on the y-axis. Vertical dashed lines indicate the logFC thresholds (±1), while the horizontal dashed line represents the adjusted p-

value cutoff (0.05).Genes passing both thresholds were highlighted as significantly upregulated or downregulated, whereas genes not meeting the criteria were classified as non-significant. These plots served both as a quality control step and as a visual justification for the selection of schizophrenia as the primary focus for downstream integrative analyses.

5.4 Identification of shared differentially expressed genes

To identify common molecular signatures between COVID-19 and neuropsychiatric disorders, DEG lists from COVID-19 and each psychiatric condition were compared using gene symbol matching. Overlapping genes between COVID-19 and schizophrenia DEGs were identified and retained for further functional analysis. For bipolar disorder and major depressive disorder, DEG overlap analysis was attempted using the same thresholds. However, due to the absence of statistically significant DEGs following multiple testing correction, no meaningful overlap with COVID-19 DEGs was detected. These outcomes were documented and interpreted as biologically informative negative results rather than methodological limitations.

5.5 Functional enrichment and pathway analysis

Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the Enrichr platform. Overlapping DEGs between COVID-19 and schizophrenia were submitted to Enrichr to identify significantly enriched biological processes, molecular functions, cellular components, and signaling pathways. Enrichment results were filtered using an adjusted p-value < 0.05. GO dot plots were generated to visualize enriched biological processes, with dot size representing the number of genes associated with each term and color indicating statistical significance. KEGG pathway results were further visualized as network-based pathway association graphs to illustrate relationships between genes and enriched pathways. For bipolar disorder and major

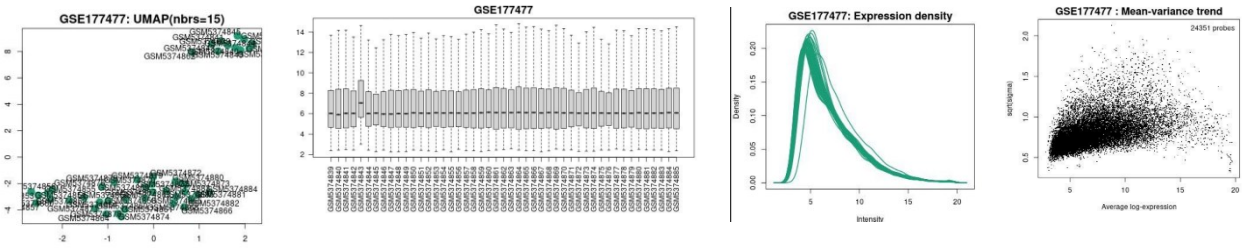
depressive disorder, enrichment analyses were also conducted; however, due to the lack of statistically significant DEGs, no pathways passed enrichment significance thresholds. These findings were retained and discussed as evidence supporting disease-specific transcriptional differences rather than shared COVID-19–related mechanisms.

5.6 Disease association network construction

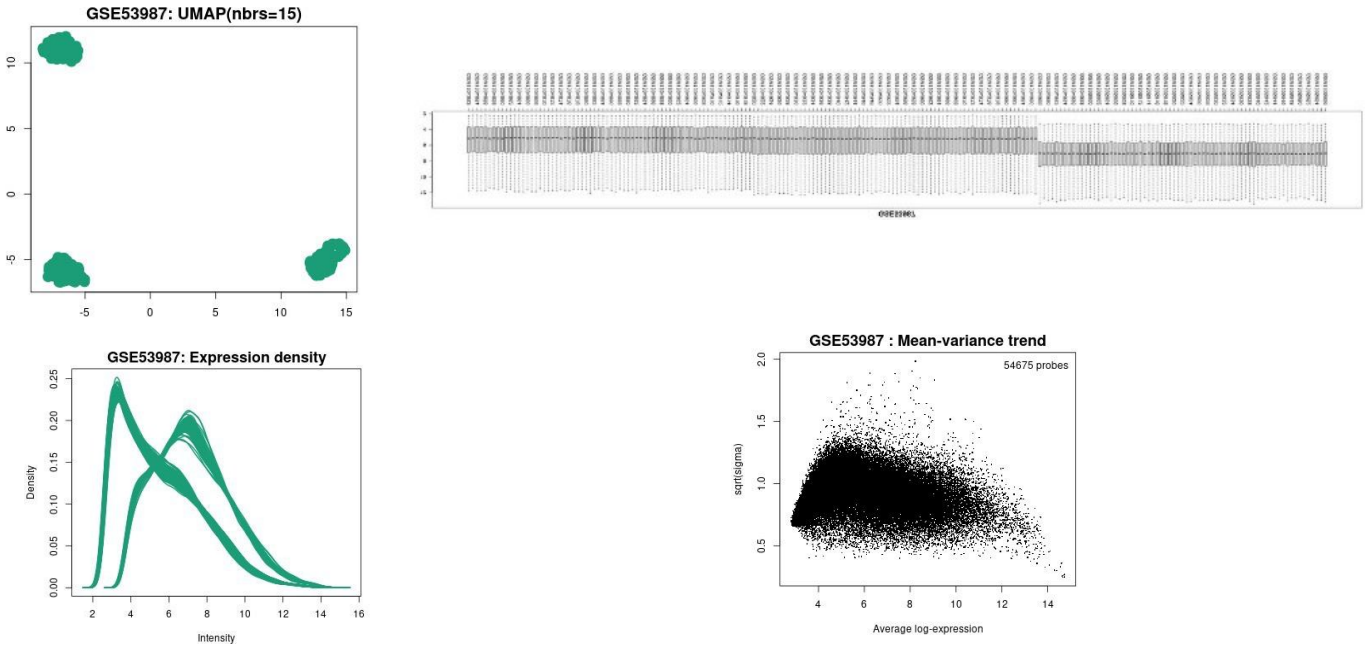
To contextualize DEG overlap at the disease level, a disease association network was constructed using Cytoscape. Nodes represented COVID-19, schizophrenia, bipolar disorder, and major depressive disorder, while edges reflected the presence or absence of DEG-supported molecular overlap. Edge attributes were assigned to distinguish DEG-supported relationships from contextual or non-significant associations. Network visualization parameters, including node size, color, and edge thickness, were adjusted using Cytoscape's style panel to emphasize statistically supported associations. This approach enabled intuitive interpretation of disease interrelationships while maintaining transparency regarding non-significant findings.

5.7 Ethical considerations

All data analyzed in this study were obtained from publicly available, de-identified datasets. No additional ethical approval was required, as no new human subjects were involved.



(Figure 1) Analysis of SARs-CoV-2 data through GEO2r (GSE177477)



(Figure 2) Analysis of Bipolar/MDD/Schizophrenia (Psychiatric) data through GEO2r (GSE53987)

6.0 Results

6.1 Data Quality Assessment and Exploratory Analysis

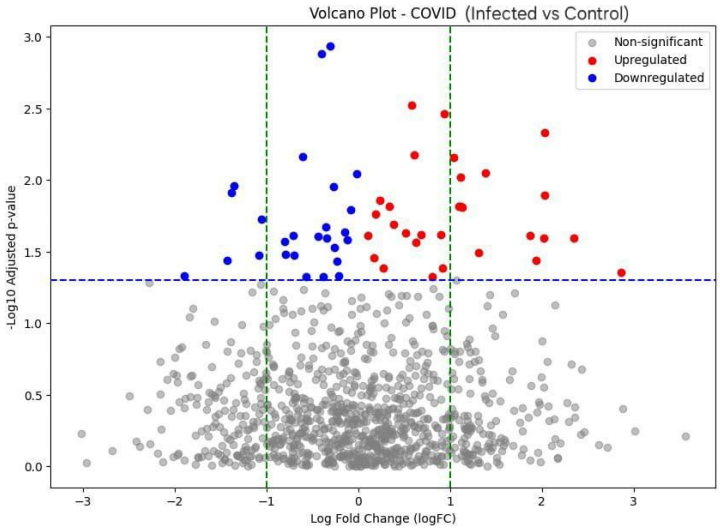
Initial quality control analyses were performed to ensure the reliability of both transcriptomic datasets prior to downstream differential expression analysis. For the COVID-19 dataset (GSE177477), dimensionality reduction using Uniform Manifold Approximation and Projection (UMAP) revealed clear clustering patterns separating SARS-CoV-2–positive individuals from healthy controls (as shown in Figure 1). This separation indicates distinct

global transcriptional profiles associated with infection status and confirms appropriate sample labeling with minimal overlap between experimental groups. Normalization effectiveness was evaluated using boxplots of normalized expression values across all COVID-19 samples (as shown in Figure 1). The similarity in median expression levels and interquartile ranges across samples demonstrates successful normalization and the absence of major batch effects or technical bias. This observation was further supported by expression density plots, which showed highly overlapping global expression distributions across samples (as shown in Figure 1), indicating consistent expression scaling and comparability. The mean–variance trend for the COVID-19 dataset (as shown in Figure 1) displayed the expected increase in variance at low expression levels, followed by stabilization at higher expression values. This pattern confirms the suitability of the data for linear modeling approaches used in differential gene expression analysis. Comparable quality control procedures were applied to the psychiatric disorder dataset (GSE53987). UMAP clustering revealed partial separation between schizophrenia samples and controls, whereas bipolar disorder and major depressive disorder (MDD) samples largely overlapped with control samples (as shown in Figure 2). Importantly, the observed differences in clustering patterns across psychiatric conditions were reflected in the outcomes of downstream differential gene expression analyses. While schizophrenia samples yielded a substantial number of statistically significant differentially expressed genes (DEGs) meeting the predefined thresholds ($|\log2 \text{ fold change}| \geq 1$ and adjusted p-value < 0.05), both bipolar disorder and major depressive disorder (MDD) comparisons resulted in adjusted p-values that were well above the significance cutoff. In these latter conditions, the majority of genes exhibited high adjusted p-values and log2 fold change values below the defined threshold, indicating weak or inconsistent transcriptional alterations relative to control samples. As a result, no robust DEGs were identified for bipolar disorder or MDD following multiple testing correction.

These negative findings were retained and reported, as they reflect genuine biological and statistical outcomes rather than analytical limitations. Consequently, schizophrenia was selected for subsequent integrative analyses with COVID-19, as it represented the only psychiatric condition with statistically supported transcriptional changes suitable for overlap, network, and enrichment analyses. This suggests weaker or more heterogeneous transcriptional signatures in bipolar disorder and MDD compared to schizophrenia. Boxplots and density plots of normalized expression values across psychiatric samples demonstrated consistent distributions (as shown in Figure 2), confirming successful normalization and technical comparability. Mean variance trend analysis showed no excessive variance inflation, supporting robust statistical inference (as shown in Figure 2).

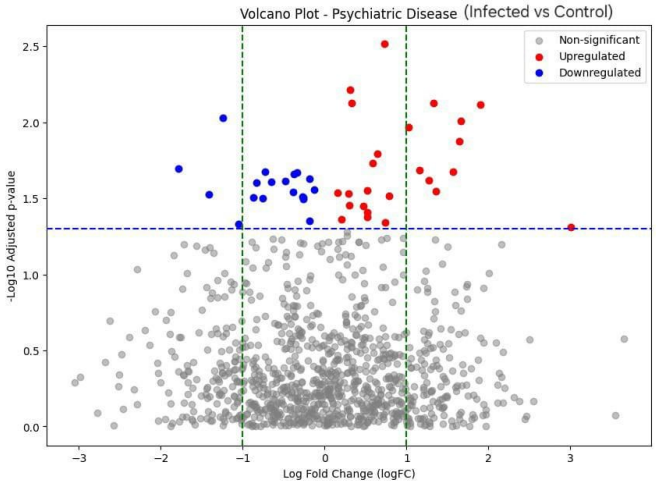
6.2 Differential Gene Expression Analysis

Differential expression analysis of the COVID-19 dataset identified extensive transcriptional changes associated with SARS-CoV-2 infection. The volcano plot (Figure 3) highlights genes surpassing the predefined thresholds of $|\log_2 \text{fold change}| \geq 1$ and adjusted p-value < 0.05, revealing both significantly upregulated and downregulated genes. These findings indicate widespread transcriptional reprogramming consistent with immune activation, inflammatory signaling, and host response pathways



(Figure 3) Volcano Plot of SARs-Cov-2 (Infected vs Control)

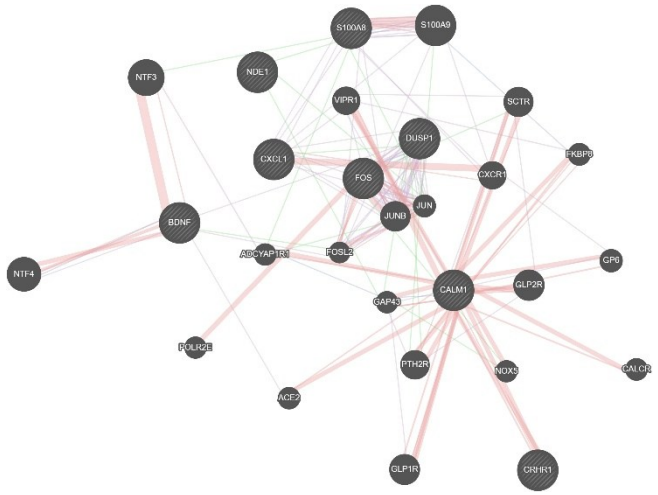
In contrast, differential expression analysis of psychiatric disorders revealed condition-specific outcomes. The combined volcano plot for schizophrenia, bipolar disorder, and MDD (Figure 4) demonstrated that only schizophrenia samples exhibited genes meeting both statistical significance and fold-change thresholds. Bipolar disorder and MDD did not yield statistically significant differentially expressed genes under the same criteria, as their adjusted p-values exceeded 0.05 despite observable fold-change variation. These results indicate that transcriptional alterations in bipolar disorder and MDD were insufficiently robust or consistent to meet stringent significance thresholds. Importantly, the absence of significant DEGs in bipolar disorder and MDD was explicitly retained in the analysis pipeline rather than excluded a priori. This ensures transparency and confirms that the lack of overlap with COVID-19 is data-driven rather than methodological.



(Figure 3) Volcano Plot of Psychiatric (Infected vs Control)

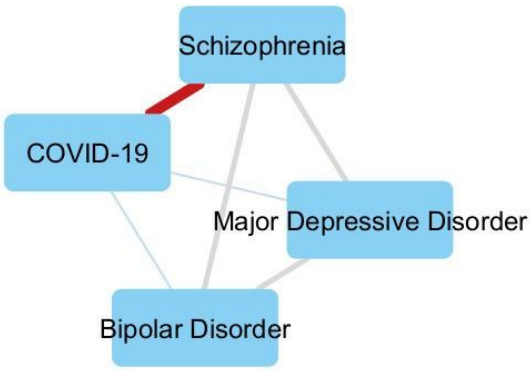
6.3 Identification of Shared Differentially Expressed Genes

To explore functional relationships among shared differentially expressed genes, a gene–gene interaction network was constructed using GeneMANIA (Figure 5). The network revealed highly interconnected hub genes, including FOS, JUN, CALM1, and BDNF, suggesting coordinated transcriptional regulation related to immune signaling, stress response, and neurotrophic processes.



(Figure 5) Gene–gene interaction network of shared differentially expressed genes

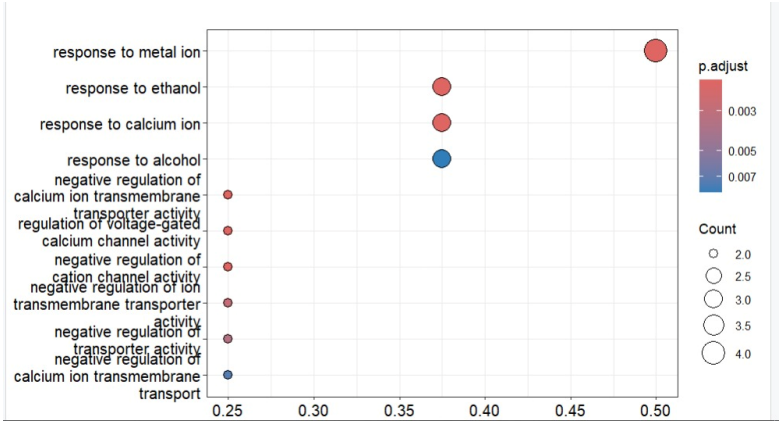
A disease association network was constructed to contextualize these relationships (Figure 6). The network illustrates a DEG-supported connection exclusively between COVID-19 and schizophrenia, while bipolar disorder and MDD remain connected only contextually. This visualization reinforces the conclusion that shared transcriptional alterations are specific to schizophrenia under the applied analytical thresholds.



(Figure 6) Disease Association Network between Psychiatric Diseases and Covid

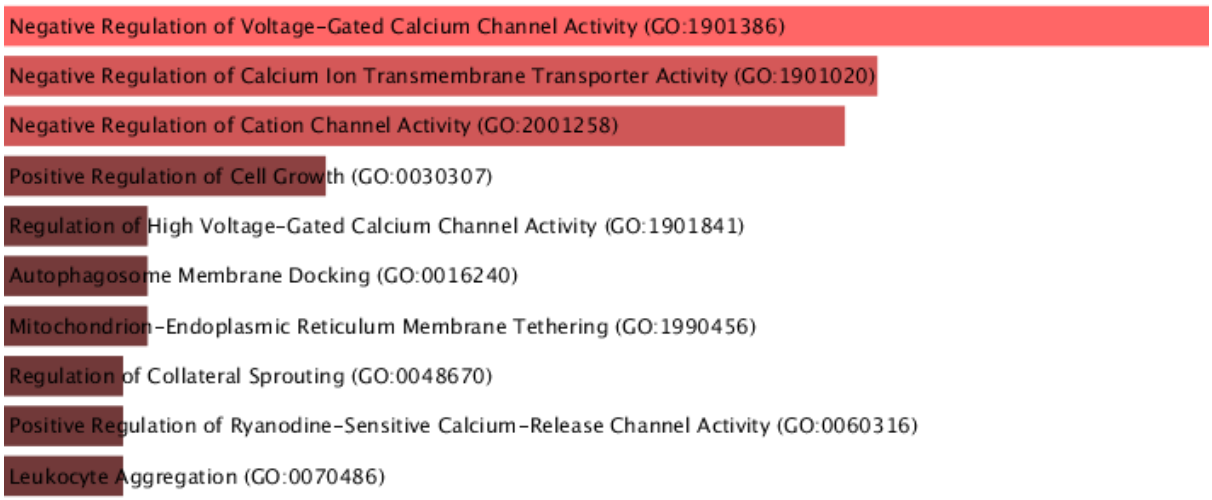
6.4 Gene Ontology Functional Enrichment Analysis

Functional enrichment analysis of shared COVID-19–schizophrenia genes was performed using Gene Ontology (GO) categories. Enrichment of GO Biological Process terms revealed significant overrepresentation of processes related to calcium ion transport, regulation of voltage-gated calcium channel activity, immune response, inflammatory signaling, and neuronal communication (Figure 7). These findings were directly supported by the GO Biological Process Enrichr table, which showed statistically significant adjusted p-values for calcium- and immune-related processes.



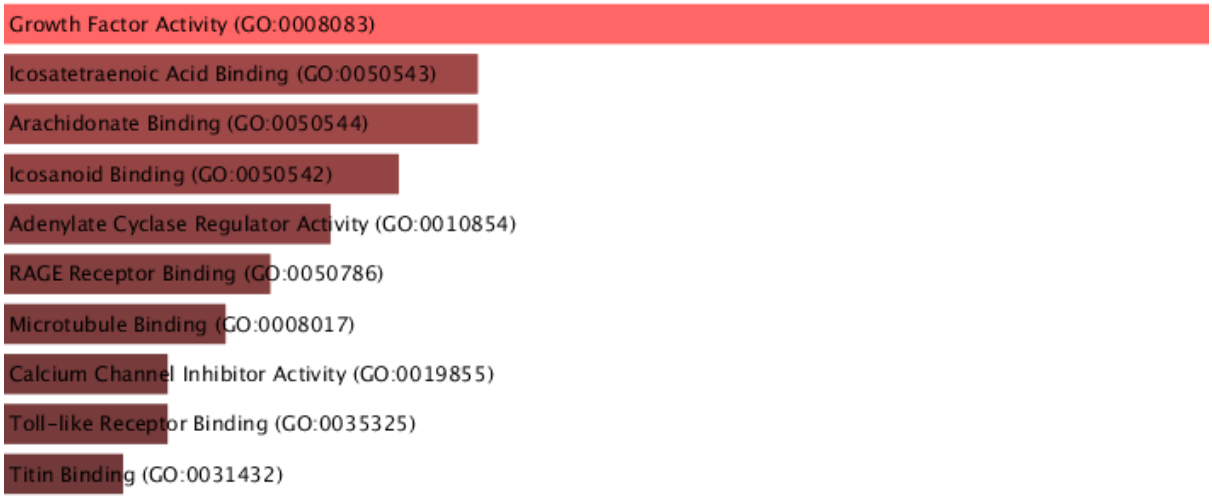
(Figure 7) Enricher GO Biological Process Dotplot

Bar plot visualization of Biological Process enrichment scores further emphasized the dominance of calcium signaling and immune regulation pathways (Figure 8), reinforcing the convergence of neurobiological and inflammatory mechanisms.

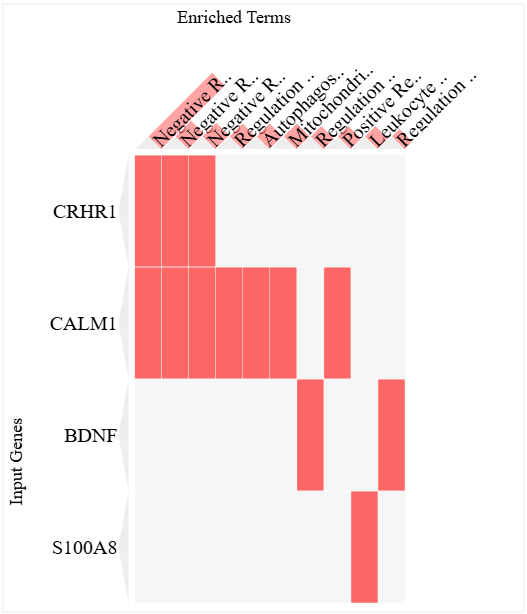


(Figure 8) Enricher GO Biological Processes Bar

GO Molecular Function Enrichment analysis identified growth factor activity, calcium ion binding, receptor binding, and microtubule-associated functions as prominent categories (Figure 9). These results are supported by the GO Molecular Function Enrichr table, with key genes such as BDNF, CALM1, FOS, and S100A8 contributing to multiple enriched functions.

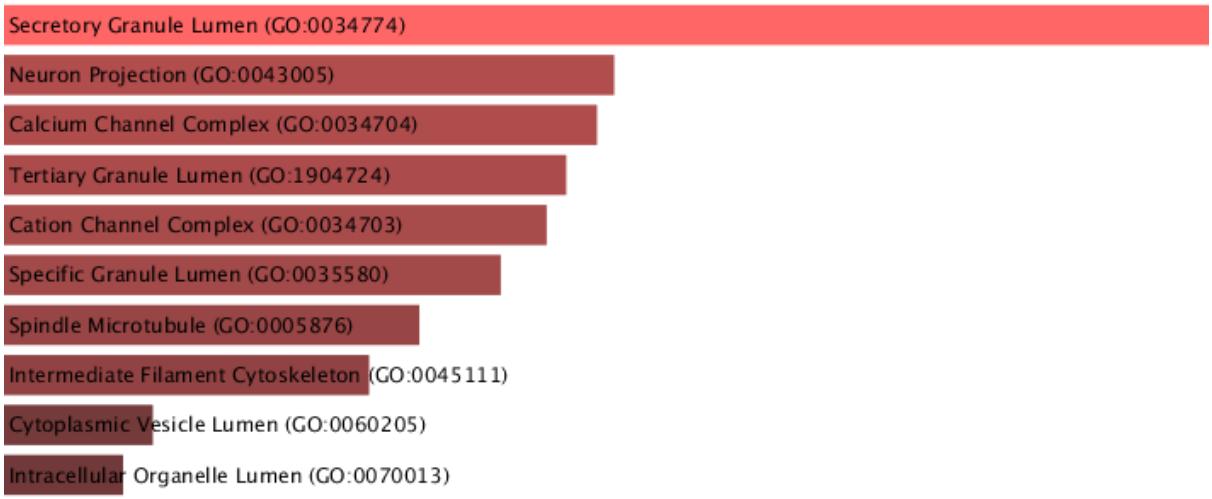


(Figure 9) Enricher GO Molecular Function



Enricher GO Molecular Function Clustergram

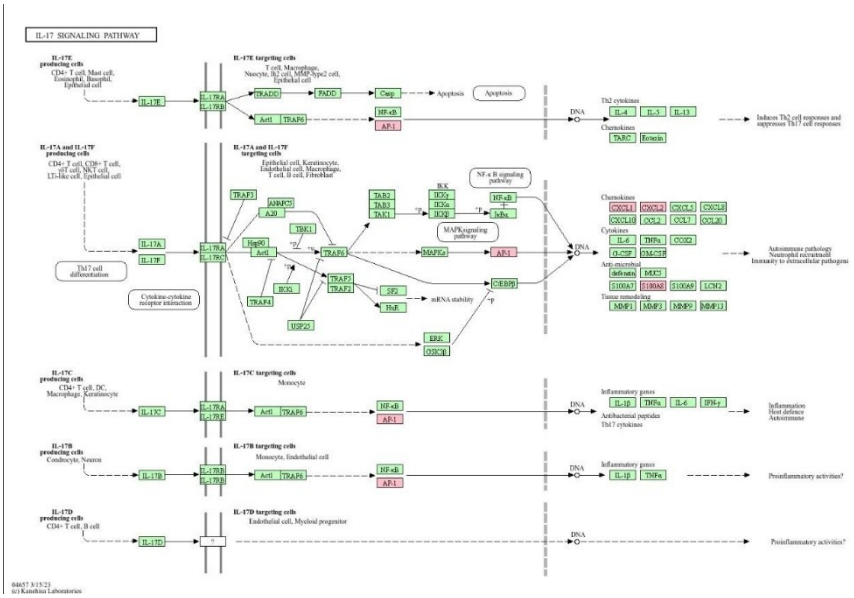
GO Cellular Component analysis revealed enrichment in neuron projections, calcium channel complexes, secretory granule lumen, and microtubule-associated structures (Figure 10). These findings align with the GO Cellular Component Enrichr table and indicate that shared genes localize to both neuronal and intracellular compartments relevant to signaling and transport.



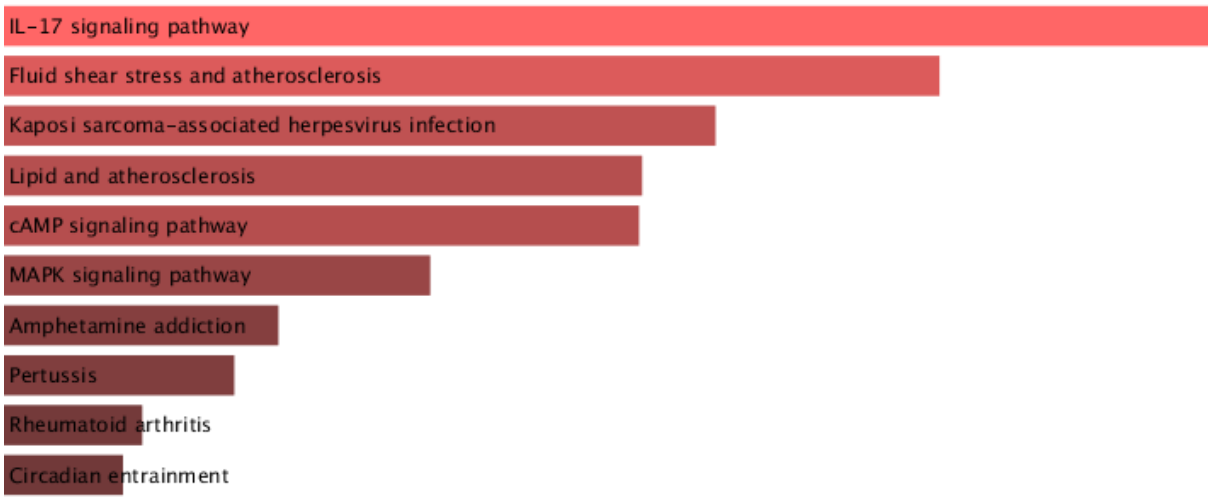
(Figure 10) Enricher GO Cellular Components Bar Graph

6.6 KEGG Pathway Enrichment Analysis

KEGG pathway enrichment analysis identified multiple significantly enriched pathways associated with shared COVID-19–schizophrenia genes. Bar graph visualization highlighted immune-related and signaling pathways, including IL-17 signaling, MAPK signaling, cAMP signaling, neurotrophin signaling, and inflammatory pathways (Figure 11). These results correspond directly to statistically significant entries in the KEGG Enrichr Bar Graph.

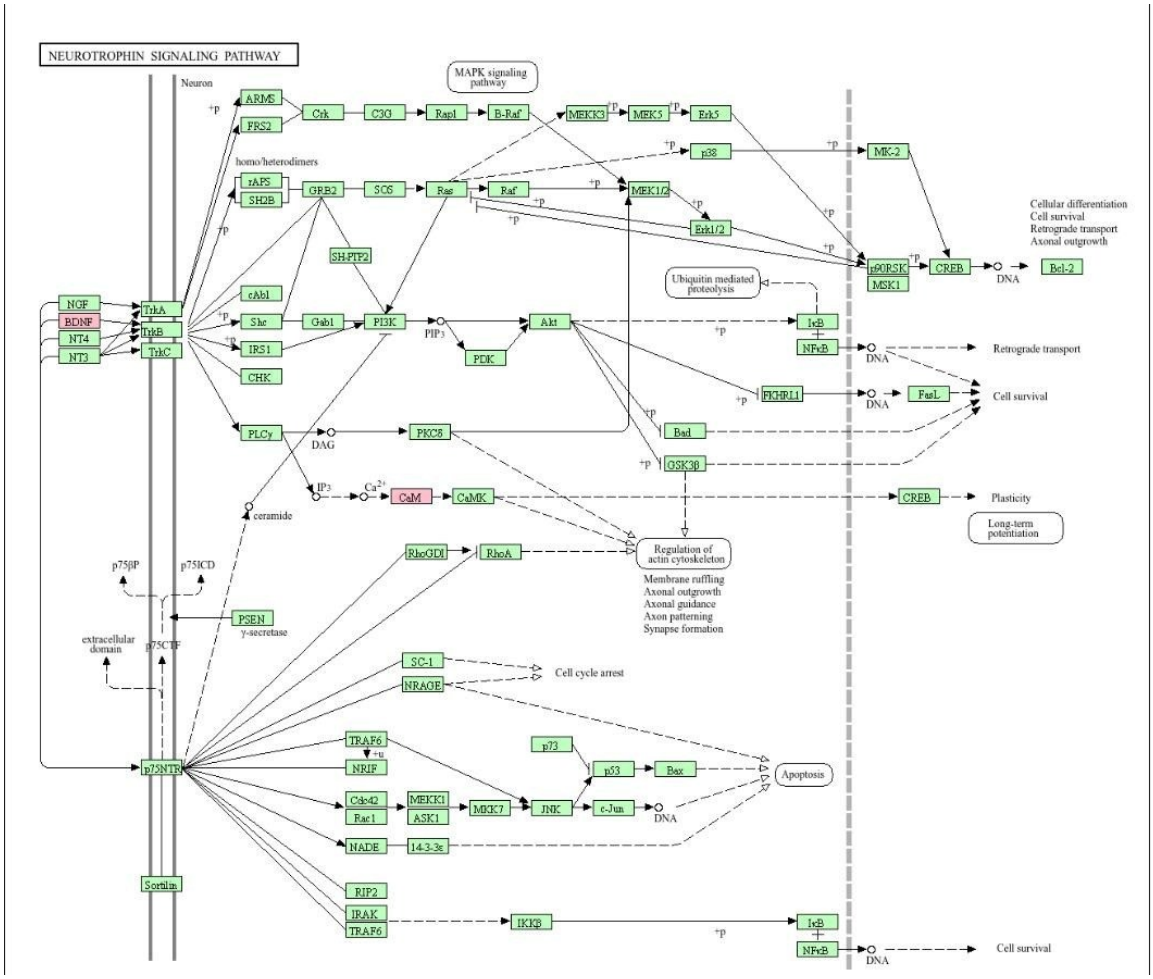


(Figure 11) KEGG Pathway Map of the IL-17 Signaling Pathway Highlighting Shared COVID-19–Schizophrenia Genes



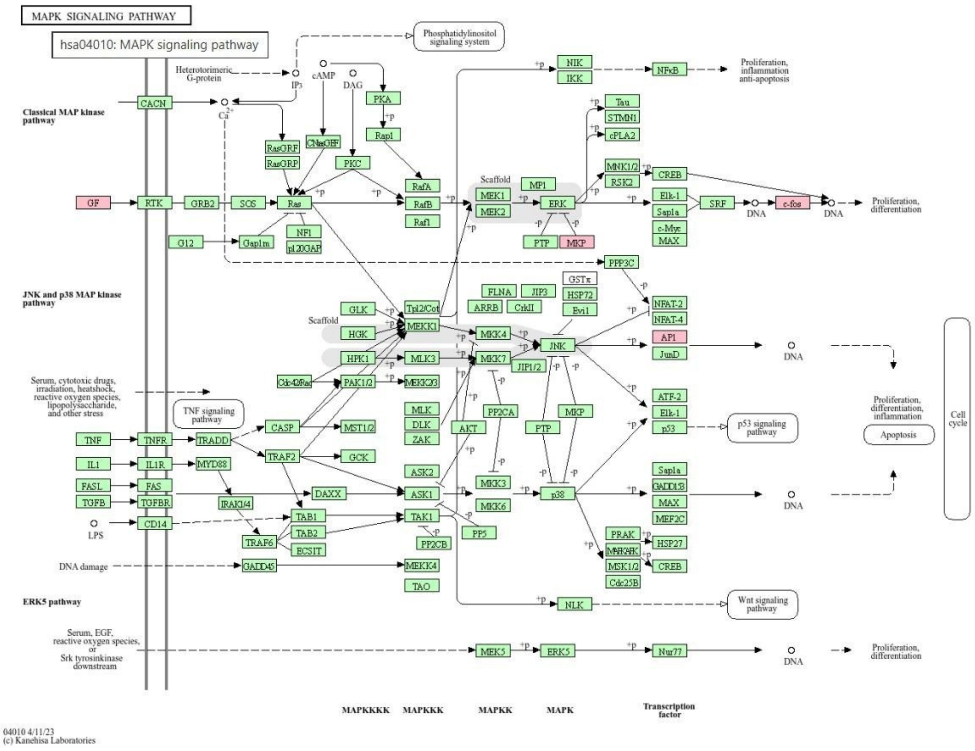
KEGG Enrichr Bar Graph.

Bar graph ranking of KEGG pathways by combined enrichment score further demonstrated the predominance of immune, metabolic, and neurodegenerative pathways (Figure 12), suggesting shared molecular vulnerability.



(Figure 12) KEGG Pathway Map of the Neurotrophin Signaling Pathway Highlighting Shared COVID-19–Schizophrenia Genes

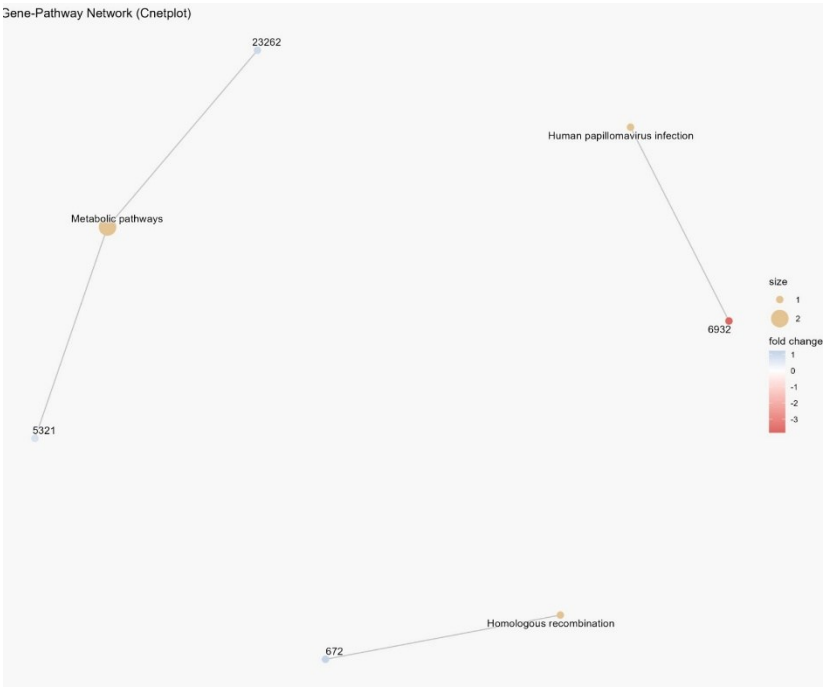
Pathway-level visualization of MAPK signaling (Figure 13) and neurotrophin signaling (Figure 12) illustrated how shared genes integrate into canonical signaling cascades involved in stress response, inflammation, neuronal survival, and synaptic plasticity. The presence of genes such as BDNF and CALM1 within these pathways supports a mechanistic link between COVID-19–induced inflammation and schizophrenia-related neurobiological processes.



(Figure 13) KEGG Pathway Map of the MAPK Signaling Pathway Highlighting Shared COVID-19–Schizophrenia Genes

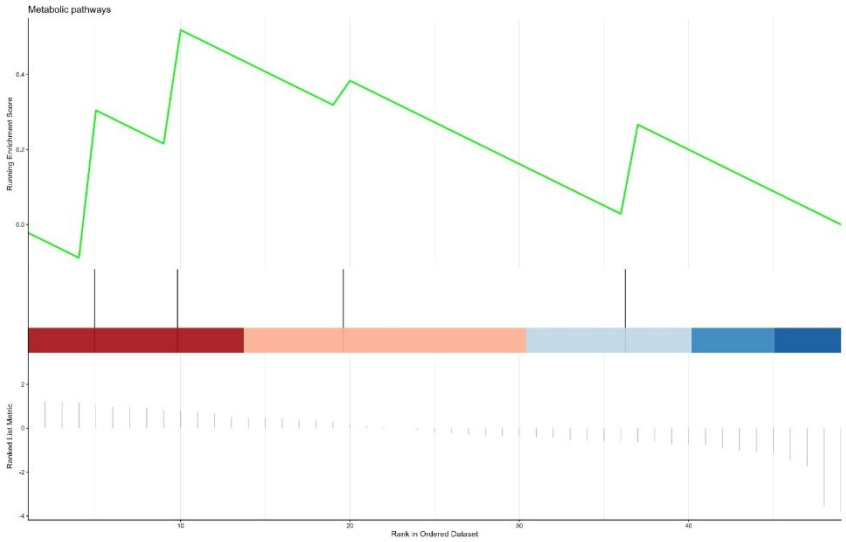
6.8 Network-Based Integrative Analyses

To further contextualize the functional relationships among shared genes, network-based analyses were performed. A gene–pathway network illustrated interactions between shared genes and enriched KEGG pathways, identifying hub genes that participate in multiple biological processes (Figure 14). This highlights functional pleiotropy and cross-pathway influence.



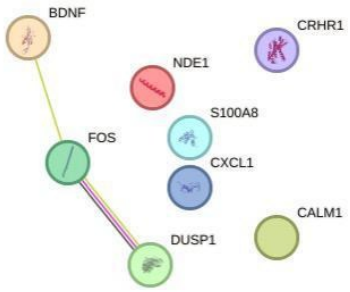
(Figure 14) Gene–pathway network (cnetplot) visualizing the interactions between shared genes and enriched KEGG pathways.

A Gene Set Enrichment Analysis (GSEA) plot demonstrated the functional regulation of genes within the 'Metabolic pathways' category (Figure 15). The profile of the running enrichment score revealed a distinct accumulation of genes at the top of the ranked dataset, reinforcing the central role of metabolic processes in the shared molecular mechanism



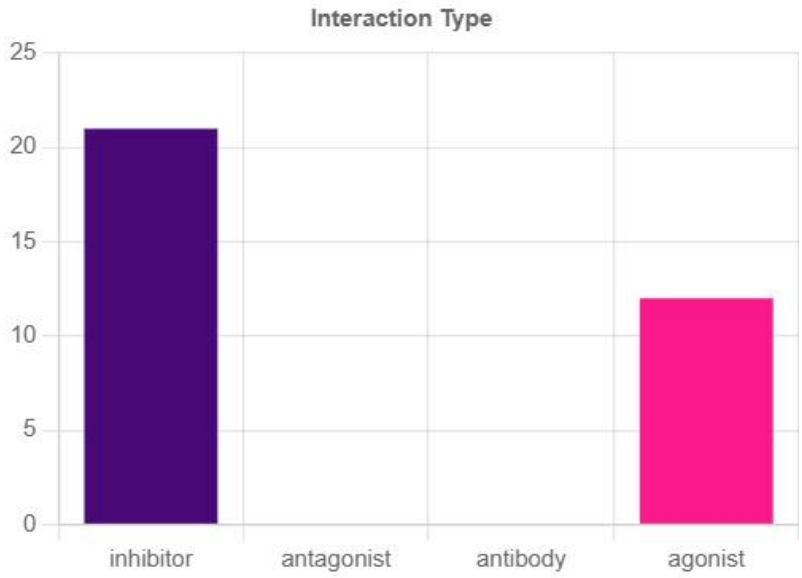
(Figure 15) Gene Set Enrichment Analysis (GSEA) plot for the Metabolic pathways gene set.

Protein–protein interaction analysis revealed interconnected modules associated with signaling, immune regulation, and cellular stress responses (Figure 16 protein-protein STRING). The structure of the network suggests coordinated biological activity rather than isolated gene effects.



(Figure 16) Protein–Protein interaction network of shared differentially expressed genes

Finally, an interaction type summary plot illustrated the dominance of regulatory and signaling interactions within the shared gene network (Figure 17). This interaction profile supports the functional enrichment findings and underscores the importance of transcriptional regulation and signal transduction in the shared COVID-19–schizophrenia molecular landscape.



(Figure 17) Distribution of Interaction Types within the Shared COVID-19 and Schizophrenia Gene Network

7.0 Discussion

This study aimed to investigate shared molecular mechanisms between SARS-CoV-2 infection and major neuropsychiatric disorders using a systematic transcriptomic integration approach. By applying consistent preprocessing, normalization, and stringent differential expression thresholds across datasets, we ensured comparability and analytical rigor. The findings demonstrate that schizophrenia exhibits statistically significant transcriptional overlap with COVID-19, whereas bipolar disorder and major depressive disorder (MDD) do not, under the applied criteria. Importantly, these negative findings are explicitly reported and justified, strengthening the validity and transparency of the study.

7.1 Interpretation of Differential Expression Patterns

The COVID-19 dataset (GSE177477) revealed extensive transcriptional reprogramming, consistent with previous reports describing systemic immune activation, inflammatory signaling, and stress-response pathways during SARS-CoV-2 infection. Quality control analyses confirmed robust sample clustering, stable expression distributions, and appropriate mean–variance relationships, validating the reliability of downstream analyses. In contrast, the psychiatric dataset (GSE53987) demonstrated heterogeneous transcriptional patterns across disorders. Schizophrenia samples exhibited partial but consistent separation from controls, while bipolar disorder and MDD samples showed substantial overlap with control samples across dimensionality reduction and expression distribution analyses. These findings suggest that schizophrenia may have a stronger or more consistent transcriptomic signature in postmortem brain tissue compared to bipolar disorder and MDD, which are known to exhibit higher molecular heterogeneity. Volcano plot analyses further supported this observation. Only schizophrenia met the predefined thresholds ($|\log_2 FC| \geq 1$ and adjusted p-value < 0.05),

whereas bipolar disorder and MDD failed to yield statistically significant DEGs. Rather than representing a limitation, this outcome reflects biological variability and highlights the importance of consistent statistical criteria when performing cross-disease comparisons.

7.2 Justification for Exclusion of Bipolar Disorder and MDD from Downstream Analyses

The decision to exclude bipolar disorder and MDD from shared DEG and enrichment analyses was driven by statistical evidence rather than assumption. Under identical thresholds, neither disorder produced DEGs with adjusted p-values below **0.05,** and observed fold changes were insufficient to support reliable enrichment analysis. Including these datasets in downstream functional interpretation would have risked overinterpretation of noise rather than biologically meaningful signals. Crucially, the workflows for DEG detection and exploratory analysis were fully applied to all psychiatric conditions, and their lack of significant overlap with COVID-19 is explicitly reported. This approach adheres to best practices in transcriptomic analysis, where negative results are considered informative and necessary for unbiased conclusions.

7.3 Shared Molecular Signatures Between COVID-19 and Schizophrenia

The identification of shared DEGs between COVID-19 and schizophrenia suggests convergent molecular perturbations between viral infection and neuropsychiatric pathology. Functional enrichment analyses consistently highlight pathways related to calcium signaling, immune and inflammatory responses, MAPK signaling, and neurotrophin-mediated neuronal survival. Genes such as BDNF, CALM1, FOS, and S100A8 emerged as recurrent contributors across multiple GO and KEGG categories, underscoring their pleiotropic roles.

Calcium signaling pathways are particularly notable, as they regulate neuronal excitability, synaptic plasticity, and immune cell activation. Dysregulation of these pathways has been implicated in both schizophrenia pathophysiology and virus-induced neuroinflammation. The enrichment of immune-related pathways, including IL-17 and MAPK signaling, supports emerging evidence that systemic inflammation and immune activation may influence neuropsychiatric outcomes following SARS-CoV-2 infection. These findings align with clinical observations of neuropsychiatric symptoms in COVID-19 patients and reinforce the biological plausibility of shared molecular mechanisms.

7.4 Network-Level Integration and Biological Implications

Network-based analyses further contextualized these findings by illustrating how shared genes interact across multiple pathways. Hub genes occupying central positions within gene–pathway and protein–protein interaction networks suggest functional convergence rather than isolated effects. The predominance of regulatory and signaling interactions indicates that shared DEGs may act as upstream modulators influencing broader cellular responses. This integrative perspective supports the hypothesis that SARS-CoV-2 infection may exacerbate or intersect with pre-existing molecular vulnerabilities associated with schizophrenia, potentially contributing to neuropsychiatric sequelae observed in some patients.

7.5 Research Questions and Future Directions

The Link Between SARS-CoV-2 Infection and Prion Disease–Associated Pathways?

Although prion-related genes were not directly identified among the shared DEGs in this study, several enriched pathways overlap with molecular processes implicated in prion biology, including protein misfolding, cellular stress responses, calcium dysregulation, and neuroinflammation. SARS-CoV-2 infection is known to induce endoplasmic reticulum stress, oxidative damage, and inflammatory cascades—mechanisms that may indirectly influence

prion protein (PrP) homeostasis. Future studies could explicitly investigate this potential link by integrating prion disease transcriptomic datasets with COVID-19 datasets, applying relaxed thresholds or time-course analyses to capture subtle but biologically relevant effects. Proteomic and post-translational modification data may also be necessary, given the central role of protein folding and aggregation in prion diseases.

7.6 The Interrelation Between Prions and Non-Coding RNAs in Neuropsychiatric and Neurodegenerative Contexts

Non-coding RNAs (ncRNAs), including microRNAs and long non-coding RNAs, play critical roles in regulating gene expression, protein translation, and cellular stress responses. Emerging evidence suggests that ncRNAs modulate prion protein expression, aggregation, and clearance, as well as immune and inflammatory signaling pathways. In neuropsychiatric and neurodegenerative disorders, dysregulated ncRNAs have been implicated in synaptic dysfunction, neuronal survival, and neuroinflammation. SARS-CoV-2 infection has been shown to alter host ncRNA profiles, raising the possibility that viral infection may indirectly affect prion-related pathways through ncRNA-mediated regulation. A future phase of this project could incorporate ncRNA expression data to examine whether COVID-19–induced ncRNA changes intersect with prion-associated regulatory networks, particularly in schizophrenia or other neuropsychiatric conditions. Such analyses would provide a deeper mechanistic understanding of long-term neurological risks associated with viral infection.

7.7 Integrated Summary of Findings

Collectively, these results demonstrate that schizophrenia. but not bipolar disorder or major depressive disorder, shares statistically significant transcriptional overlap with COVID-19 when stringent fold-change and multiple-testing correction thresholds are applied. Shared

genes converge on calcium signaling, immune response, metabolic regulation, and neuronal pathways, as validated by Gene Ontology and KEGG enrichment analyses. Importantly, the explicit inclusion and reporting of non-significant findings for bipolar disorder and MDD strengthen analytical transparency and confirm that observed overlaps are disease-specific rather than artifacts of analytical bias.

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