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# *In Silico* Analysis Reveals Overlapping Molecular Mechanisms Between COVID-19 and Attention-Deficit/Hyperactivity Disorder

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**Background: Coronavirus disease 2019 (COVID-19) has been increasingly associated with neurological complications, mainly through mechanisms involving neuroinflammation and cytokine dysregulation. Attention-deficit/hyperactivity disorder (ADHD), a neurodevelopmental disorder with known immunological and neurotrophic components, has emerged as a potential risk factor for adverse COVID-19 outcomes. This study investigates the genetic interplay between COVID-19 and ADHD using *in silico* methods, aiming to identify shared molecular pathways and uncover convergent mechanisms that may inform pathophysiology, risk stratification, and potential therapeutic interventions.**

**Methods: Genes associated with COVID-19 and ADHD were retrieved from the DisGeNET database. Shared genes were identified using FunRich software, and protein-protein interactions were analyzed using the Search Tool for Retrieval of Interacting Genes database. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analyses were performed to further elucidate the shared molecular mechanisms.**

**Results: Overall, 216 overlapping genes, including key genes, such as *neuropilin-1*, *brain-derived neurotrophic factor*, *insulin-like growth factor 1*, and *interleukin-6*, were identified. These genes were involved in three key functional categories: (1) vascular and endothelial function, (2) neurodevelopment and synaptic activity, and (3) immune modulation and inflammatory response generation. These findings indicate the potential shared molecular mechanisms between COVID-19 and ADHD.**

**Conclusions: The identified overlapping genes highlight potential therapeutic targets for both conditions. The study underscores the significance of their shared molecular pathways and proposes the use of animal models to validate these genetic associations. Further investigation into these pathways may inform strategies for disease prevention and management of COVID-19 and ADHD.**

**Keywords:** ADHD; brain-derived neurotrophic factor; COVID-19; *in silico* analysis; insulin-like growth factor 1; interleukin-6; neuropilin-1

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic raises global concern not only for its immediate health effects but also for its long-term effects on human physiology, particularly the central nervous system. Although early research focuses primarily on respiratory symptoms, increasing evidence shows that SARS-CoV-2 can affect the brain through mechanisms involving cytokine storms, neuroinflammation, and neurovascular dysfunction [1–4].

Attention-deficit/hyperactivity disorder (ADHD), a common neurodevelopmental disorder characterized by inattention, impulsivity, and executive dysfunction, is linked to immune dysregulation and aberrant neurotrophic signaling [5]. ADHD serves as a focal comparator in this study due to its well-established immunoneurological profile and emerging evidence of heightened vulnerability to COVID-19-related neurocognitive complications. Observational studies [6,7] report that individuals with ADHD experience elevated risks of infection, severe COVID-19 outcomes, and long-term neuropsychiatric sequelae—possibly mediated by shared molecular mechanisms such as disrupted cytokine signaling and impaired neurovascular integrity. Additionally, pathway analysis has revealed that shared genes between COVID-19 and ADHD may exacerbate COVID-19 symptoms in ADHD patients through immune-related pathways [8].

According to the WHO, ADHD prevalence in Southeast Asia ranges from 5% to 18%, which is in contrast with the global estimate of 7% to 7.6% among children and adolescents [9,10]. A behavioral study on the association between ADHD and COVID-19 have reported higher infec-

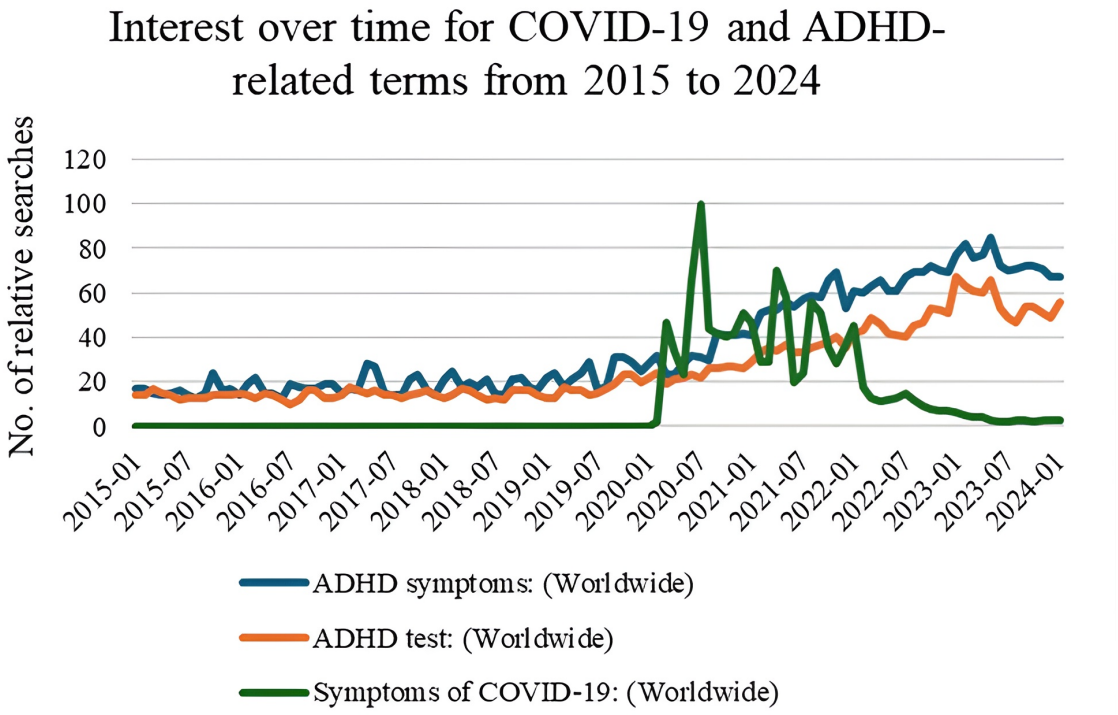


**Fig. 1. Google search trends for COVID-19 and ADHD-related terms.** Line graphs depict the global relative search trends for "ADHD symptoms", "ADHD test", and "Symptoms of COVID-19" from 1 January, 2015, to 1 January, 2024. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; COVID-19, coronavirus disease 2019.

tion rates in ADHD patients compared to non-ADHD populations [6]. However, these findings are attributable to the psychological impact of COVID-19 rather than an immunoneurological relationship between the two conditions. This highlights the need for a genetic approach to elucidate the significant molecular overlap between the two conditions.

Given its global prevalence and distinct immunological profile, ADHD provides a relevant framework for examining potential molecular overlap with COVID-19. This study investigates whether the two conditions, despite their differing etiologies, share convergent genetic and molecular features that could explain observed clinical parallels. Genetic studies on COVID-19 have largely focused on its associations with respiratory diseases, such as asthma, implicating genes including Alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase (*ABO*) and ataxin-2 (*ATXN2*) in susceptibility [11]. However, the genetic relationship between COVID-19 and ADHD remains underexplored.

The pandemic also underscores the utility of *in silico* methodologies in biomedical research. These tools have been essential in analyzing the SARS-CoV-2 structure, identifying drug targets, and optimizing clinical trial design [12–14]. Techniques such as gene expression profiling and machine learning offer powerful means to decipher the molecular underpinnings of complex diseases. Despite the availability of robust genomic databases, few studies have utilized these resources to explore genetic overlaps between COVID-19 and ADHD. This study leverages these approaches to efficiently assess genetic correlations and their translational relevance.

Parallel to growing academic interest, public attention to ADHD surged during the pandemic. Google Trends data show a significant increase in global searches for "ADHD symptoms" and "ADHD tests" during 2022–2023, suggesting heightened awareness and potentially greater symptom recognition. Although these data do not establish causality, they reflect shifting health-seeking behaviors during the pandemic. Restricted access to healthcare led to increased reliance on digital platforms for medical information. Google Trends offers valuable insights into public interest, but it has limitations, including anonymized data and demographic exclusions [15–17].

Fig. 1 illustrates the trajectory of global search interest from 2015 to 2024, with notable spikes in ADHD-related queries peaking in 2023 and COVID-19 symptom-related searches reaching their highest point in July 2020. These patterns support the hypothesis that the pandemic may have amplified public and clinical attention to ADHD, driving further investigation into the shared biological mechanisms between the two conditions.

Therefore, this study aims to identify and characterize the shared molecular pathways linked to COVID-19 and

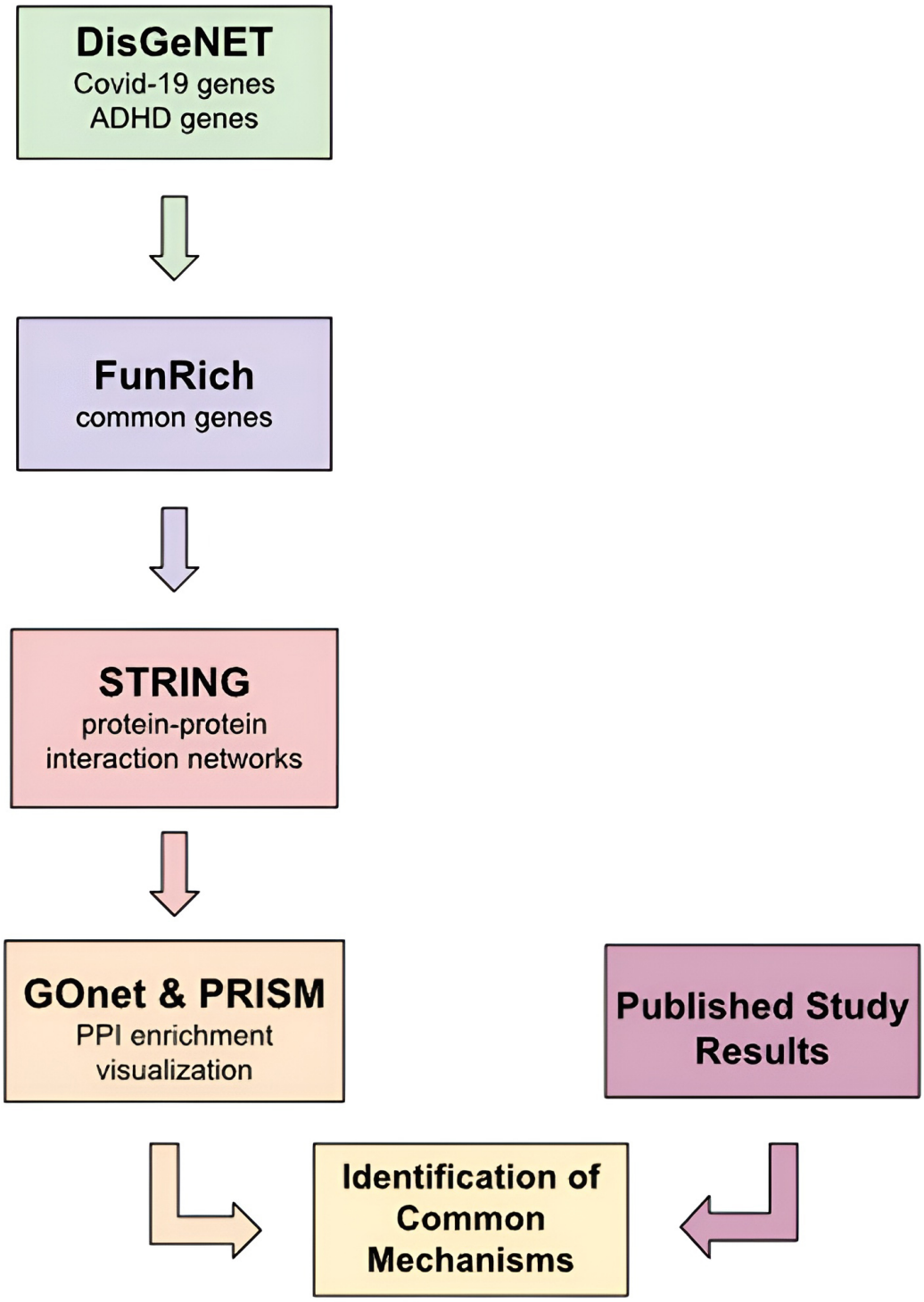


**Fig. 2. Schematic representation of the *in silico* analysis conducted in this study.** The flowchart outlines the methodology. Genes related to COVID-19 and ADHD were obtained from DisGeNET while overlapping genes were identified using FunRich. The identified gene sets were analyzed in STRING to construct PPI networks. Gene set enrichment analyses were performed using GO and KEGG pathways. To further visualize PPI enrichment, GOnet and PRISM were used. Additionally, findings from existing studies on shared Molecular Functions between COVID-19 and ADHD were compared. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; COVID-19, coronavirus disease 2019; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, protein-protein interaction; STRING, Search Tool for Retrieval of Interacting Genes.

ADHD by identifying genes associated with both conditions, analyzing their protein-protein interaction (PPI) networks, and investigating underlying biological functions and molecular mechanisms. By integrating findings from contemporary genetic databases, this study could enhance our understanding of the molecular overlap between these two conditions and offer a foundation for future research on targeted therapeutic strategies.

## Materials and Methods

To investigate molecular commonalities between COVID-19 and ADHD, we conducted an *in silico* bioinformatics analysis (Fig. 2). This comprehensive approach integrated gene selection, PPI network construction, functional enrichment, and literature-based prioritization to delineate overlapping molecular mechanisms.

### *Data Selection and Data Acquisition*

Gene selection was performed using the DisGeNET database (https://www.disgenet.com), a curated platform that integrates gene-disease associations (GDAs) from multiple sources. Searches were conducted on 20 February, 2024, using the official disease terms "COVID-19" and "Attention Deficit Hyperactivity Disorder". Inclusion was limited to *Homo sapiens* genes with a GDA score $\geq$0.1. To ensure robustness, genes were included only if statistically significant findings were reported by at least two independent studies ($p < 0.05$ with confidence intervals excluding zero). Studies with small sample sizes or preliminary data lacking empirical validation were excluded. The resulting gene lists were analyzed using FunRich software (http://funrich.org/), and overlapping genes were identified via Venn diagram analysis.

### *Protein-Protein Interaction Data*

In total, 216 genes common to COVID-19 and ADHD were analyzed using the Search Tool for Retrieval of Interacting Genes (STRING) database (v11.5; https://string-db.org/) to construct a PPI network. Default STRING parameters with a medium confidence score cutoff ($\geq$0.4) were employed. The interaction network was used to assess gene connectivity and identify clusters suggestive of shared biological pathways.

### *Functional Enrichment Analysis (Gene Ontology and Kyoto Encyclopedia of Genes and Genomes Pathway)*

To characterize the functional roles of the overlapping genes, enrichment analysis was performed using STRING. Enrichments were classified into Gene Ontology (GO) Molecular Function, GO Cellular Component, GO Biological Process, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. The top 20 enriched terms in each category were selected for further analysis.

GO analysis was conducted using the GO database (https://geneontology.org), a standardized cross-species resource describing gene functions [18,19]. KEGG analysis was performed via the KEGG database (https://www.kegg.jp), which integrates genomic data with higher-order functional information [20,21]. To control for false positives, enrichment *p*-values were adjusted utilizing the Benjamini-Hochberg false discovery rate (FDR) correction method.

To validate the findings, a parallel enrichment analysis was conducted using g:Profiler (https://biit.cs.ut.ee/gprofiler), applying the same significance threshold (adjusted $p$-value $< 0.05$). Analyses encompassed GO Biological Processes, Molecular Functions, Cellular Components, and KEGG pathways, with *Homo sapiens* specified as the reference organism. This two-platform strategy ensured robust and reproducible identification of shared molecular pathways.

### *Summary and Visualization of Results*

Results were visualized using GOnet, a web-based tool for interactive GO annotation and enrichment analysis [22]. A stringent q-value threshold ($q < 0.05$) was employed, and genes were grouped according to cerebral cortex expression levels to underscore potential neurobiological relevance. Supplementary analyses and data visualization were conducted using GraphPad Prism (version 8.0.0; GraphPad Software, San Diego, CA, USA; https://www.graphpad.com). Only statistically significant GO terms and KEGG pathways were retained to ensure biological interpretability.

### *Data Comparison and Analysis*

To further contextualize the shared genes, literature-based gene prioritization was performed. Each of the 216 overlapping genes was queried in Google Scholar using the format: "[gene name] AND (COVID-19 OR SARS-CoV-2) AND ADHD". Genes were considered relevant if supported by at least two independent, peer-reviewed studies providing mechanistic insights, such as altered expression, molecular interactions, or demonstrated functional roles. Speculative mentions or citations from review articles lacking primary data were excluded. This rigorous approach identified four key candidate genes—neuropilin-1 (NRP1), brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and interleukin-6 (IL-6)—consistently implicated in both COVID-19 and ADHD.

## Results

### *Overview of Common Genes Between COVID-19 and ADHD*

Using DisGeNET, genes associated with COVID-19 and ADHD were identified and analyzed to uncover shared biological functions. FunRich mapped 1627 of 1843 COVID-19-related genes and 626 of 842 ADHD-related

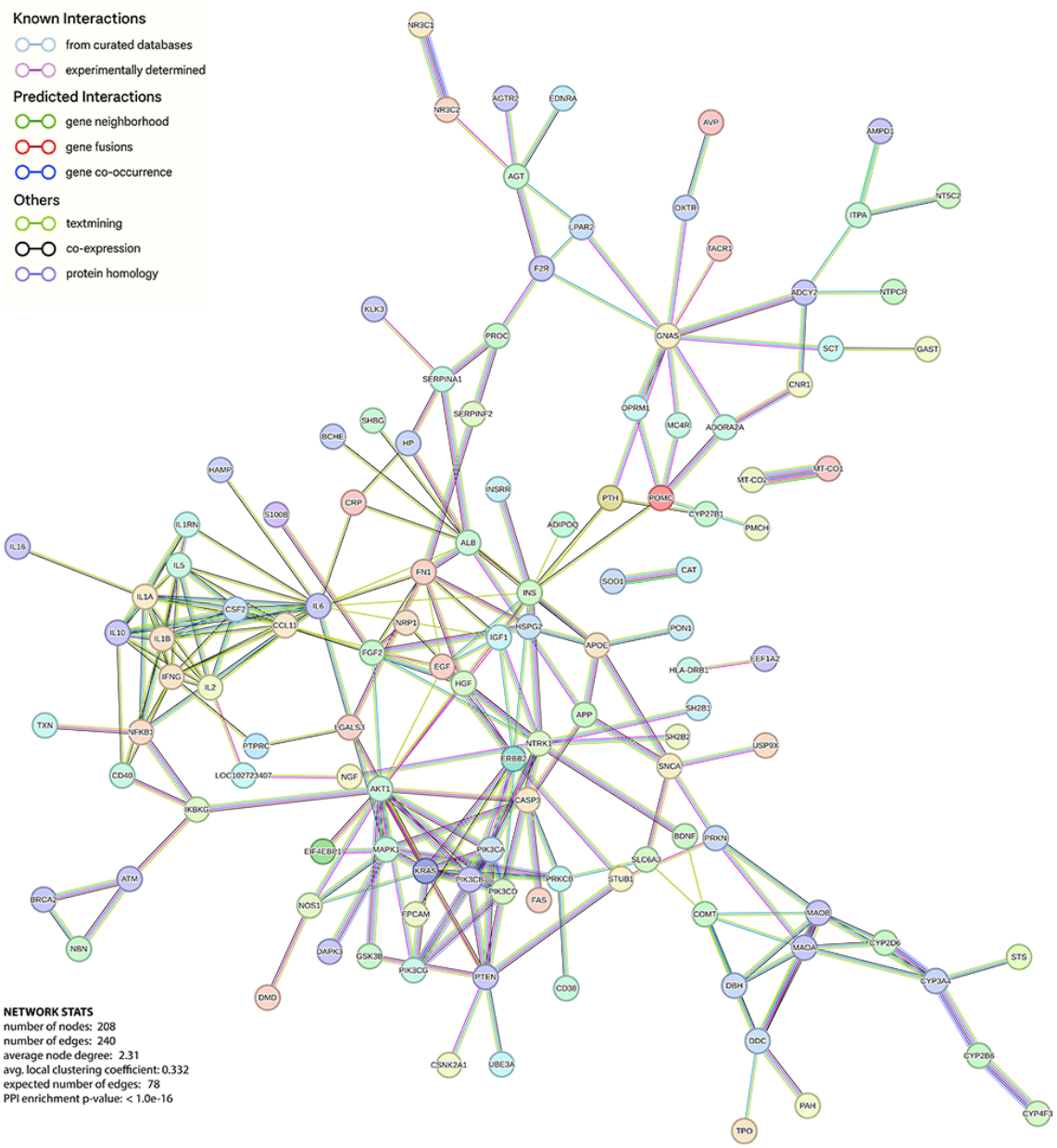


**Fig. 3. PPI networks of overlapping genes between COVID-19 and ADHD generated using STRING.** This shows interactions among the 216 shared genes. Hub genes such as IL-6, BDNF, IGF-1, and NRP1 indicate key roles in immune, neurodevelopmental, and vascular processes common to both conditions. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BDNF, brain-derived neurotrophic factor; COVID-19, coronavirus disease 2019; IGF-1, insulin-like growth factor 1; IL-6, interleukin 6; NRP1, neuropilin 1; PPI, protein-protein interaction; STRING, Search Tool for Retrieval of Interacting Genes.

genes, revealing 216 genes common to both conditions (Table 1). GDA scores for these 216 genes varied in strength. For the four genes selected for detailed discussion, the GDA scores were as follows: BDNF (COVID-19: 0.4, ADHD: 0.4), NRP1 (COVID-19: 0.35, ADHD: 0.1), IGF-1 (COVID-19: 0.3, ADHD: 0.35), and IL-6 (COVID-19: 1.0, ADHD: 0.2). Although some ADHD GDA scores were relatively low, these genes were retained due to their biological relevance to overlapping pathways involved in immune signaling and neurodevelopment.

Table 1 differentiate between "mapped genes" used in enrichment analysis from "recognized genes" supported by prior empirical evidence, helping to distinguish computational findings from previously established associations.

### *Interaction Networks Between COVID-19 and ADHD*

PPI analysis using the STRING database revealed a network comprising 208 nodes and 240 edges, with an average node degree of 2.31 and a local clustering coefficient

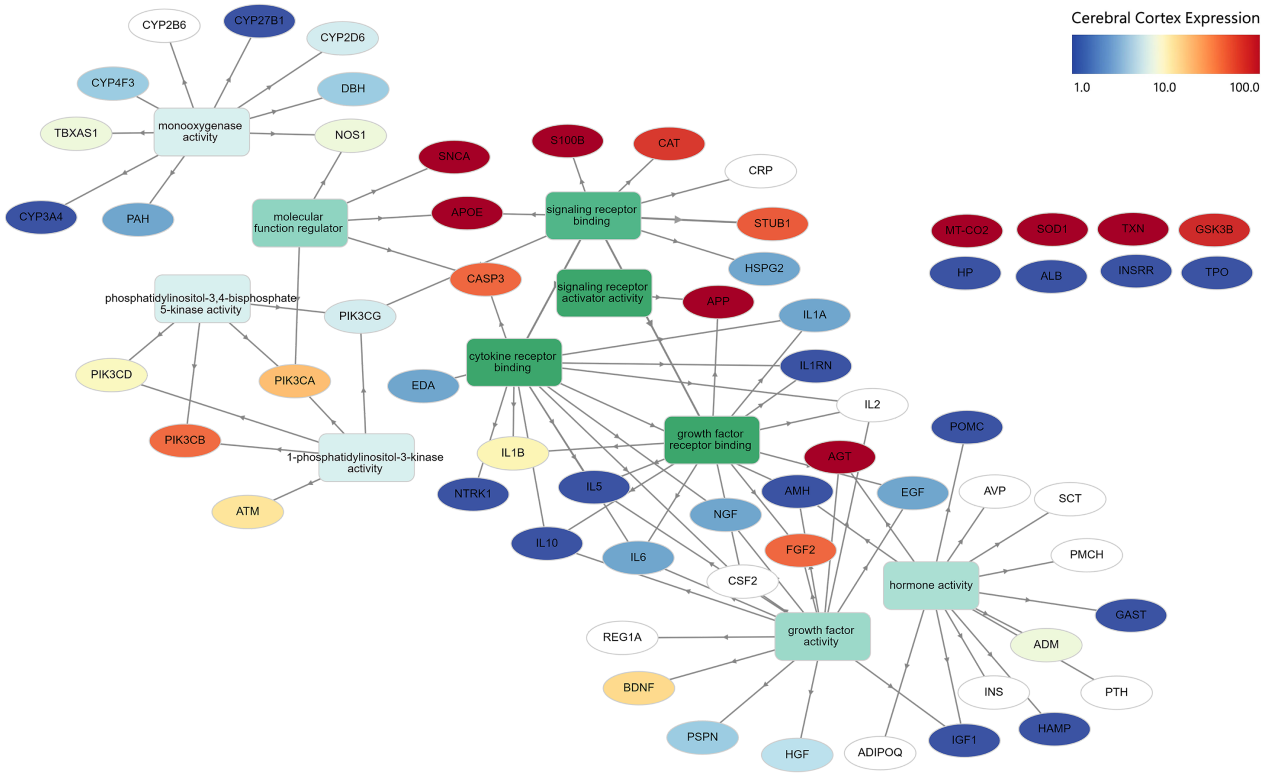


**Fig. 4. Network illustrating the GO functional enrichment analysis of Molecular Function pathways in genes shared between COVID-19 and ADHD.** The analysis reveals enrichment for cytokine receptor binding, neurotrophic factor activity, and growth factor binding, highlighting the immune-neurotrophic axis. The eight genes displayed on the right represent individual gene nodes that are highly expressed in the cerebral cortex (indicated by color intensity) and are functionally enriched within the Molecular Function category of the GO analysis despite not being directly connected to other genes included in the network. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; COVID-19, coronavirus disease 2019; IL-6, interleukin-6.

**Table 1. Number of mapped and recognized genes for COVID-19 and ADHD and the total number of shared genes between the two diseases.**

| Disease | Mapped genes | Recognized genes | Common genes |
|---|---|---|---|
| COVID-19 | 1843 | 1632 | 216 |
| ADHD | 842 | 752 | |

"Mapped genes" are those identified through our computational pipeline and successfully annotated for subsequent analyses. "Recognized genes" are those previously reported in peer-reviewed studies as associated with the respective condition(s). Abbreviations: ADHD, attention-deficit/hyperactivity disorder; COVID-19, coronavirus disease 2019.

of 0.332 (Fig. 3). The expected number of edges was 78, and the enrichment $p$-value was $<1.0 \times 10^{-16}$, indicating significant interaction beyond chance.

### *Functional and Pathway Enrichment Analyses of Gene Products Between COVID-19 and ADHD*

GO enrichment analysis was performed across the Biological Process, Molecular Function, and Cellular Component categories using GOnet. Functional terms are displayed in green boxes, with darker shades indicating stronger correlations. Gene expression levels in the cerebral cortex are color-coded from blue to red. Figs. 4,5,6 lists the genes associated with enrichment terms in each GO category. All enrichment analyses, including KEGG pathways, were corrected for multiple testing using the Benjamini-Hochberg FDR method, reducing the risk of false positives [23]. Bar graphs summarize the top 20 enriched GO and KEGG pathways, with yellow bars representing $p$-values and gray bars indicating gene counts.

Fig. 7 illustrates the enriched terms and associated genes in the GO Molecular Function, GO Cellular Component, GO Biological Process, and KEGG pathways. Additionally, **Supplementary Tables 1–4** provides detailed gene lists corresponding to each enrichment term across all analyzed categories.

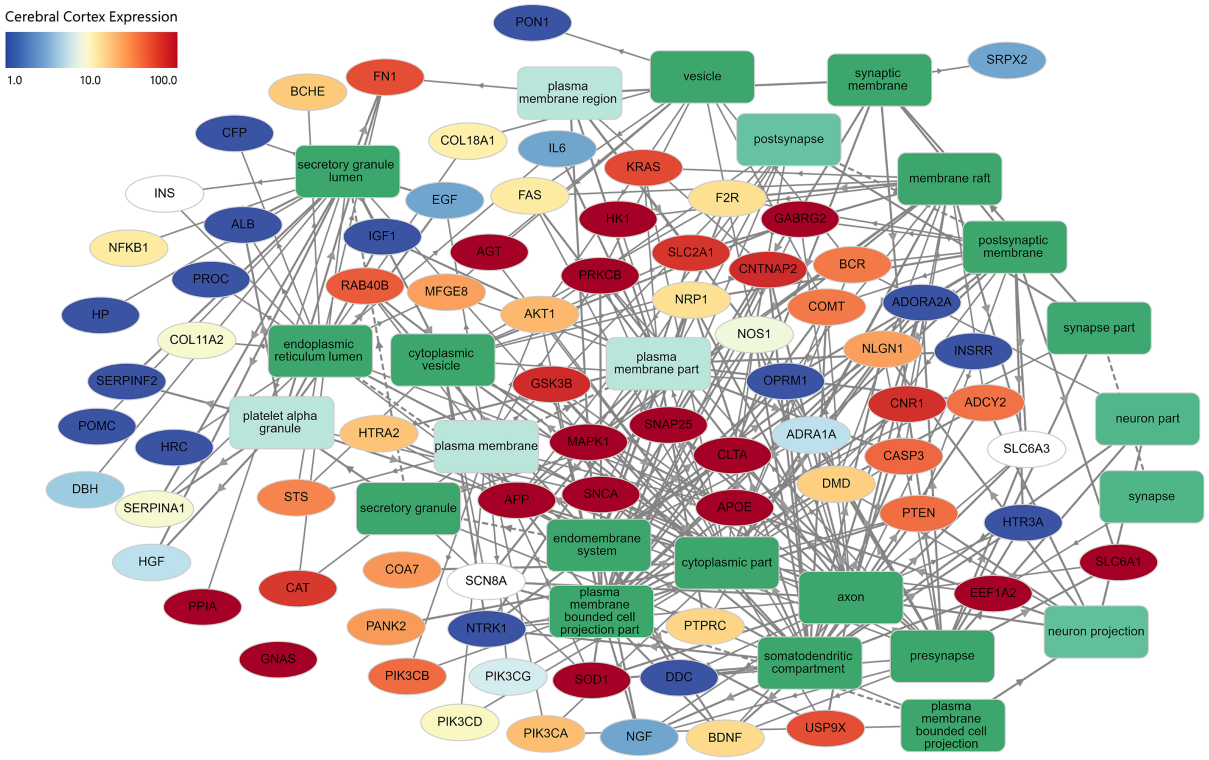


**Fig. 5. Network illustrating the GO functional enrichment analysis of Cellular Component pathways in genes shared between COVID-19 and ADHD.** The analysis reveals enrichment in plasma membrane-bound and synaptic vesicle-associated proteins, consistent with roles in neural communication and signal transduction. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; COVID-19, coronavirus disease 2019; BDNF, brain-derived neurotrophic factor.

### *Systemic Review of Common Genes Between COVID-19 and ADHD*

To identify genes of functional relevance to COVID-19 and ADHD, we employed a systematic, two-step filtering strategy. First, 216 overlapping genes were identified using a DisGeNET-based *in silico* pipeline. Second, each gene underwent a structured literature review to determine whether prior peer-reviewed studies provided mechanistic or empirical evidence of its involvement in both conditions. Only genes supported by at least two independent studies per disorder were retained, while those cited in speculative or low-evidence contexts were excluded to minimize bias and strengthen interpretation.

Although certain genes, such as IL-6, are widely implicated in inflammatory responses and immune activation, their recurrence across both conditions may indicate convergence at key regulatory nodes within shared biological pathways rather than being specific to one condition. Accordingly, the final gene list prioritized biologically plausible candidates with consistent cross-condition relevance.

Based on these criteria, four genes—NRP1, BDNF, IGF-1, and IL-6—were selected for in-depth analysis. Each gene was mapped to one or more of three functional domains central to both disorders: (1) vascular and endothelial regulation, (2) neurodevelopment and synaptic plasticity, and (3) immune modulation and inflammatory response.

These shared genes were identified from aggregated datasets and were not stratified by phenotype, age, sex, or disease severity. Given the clinical and demographic heterogeneity of ADHD and COVID-19, the functional relevance of these genes may vary across subgroups. Therefore, the findings presented here are intended to generate hypotheses that should be validated in more targeted, stratified clinical and experimental cohorts.

## Discussion

This study identifies overlapping molecular mechanisms underlying the genetic interplay between COVID-19 and ADHD. Although both conditions have distinct etiologies, our findings suggest convergence on shared biological pathways related to immune modulation, neurodevelopment, and vascular function. However, we acknowledge the substantial phenotypic heterogeneity of both disorders.

ADHD presents in multiple subtypes with varying cognitive and behavioral profiles [24], while COVID-19 outcomes range widely depending on age, immune status, and comorbidities [25]. Consequently, although the shared genes identified are statistically enriched, their clinical relevance may differ across subpopulations.

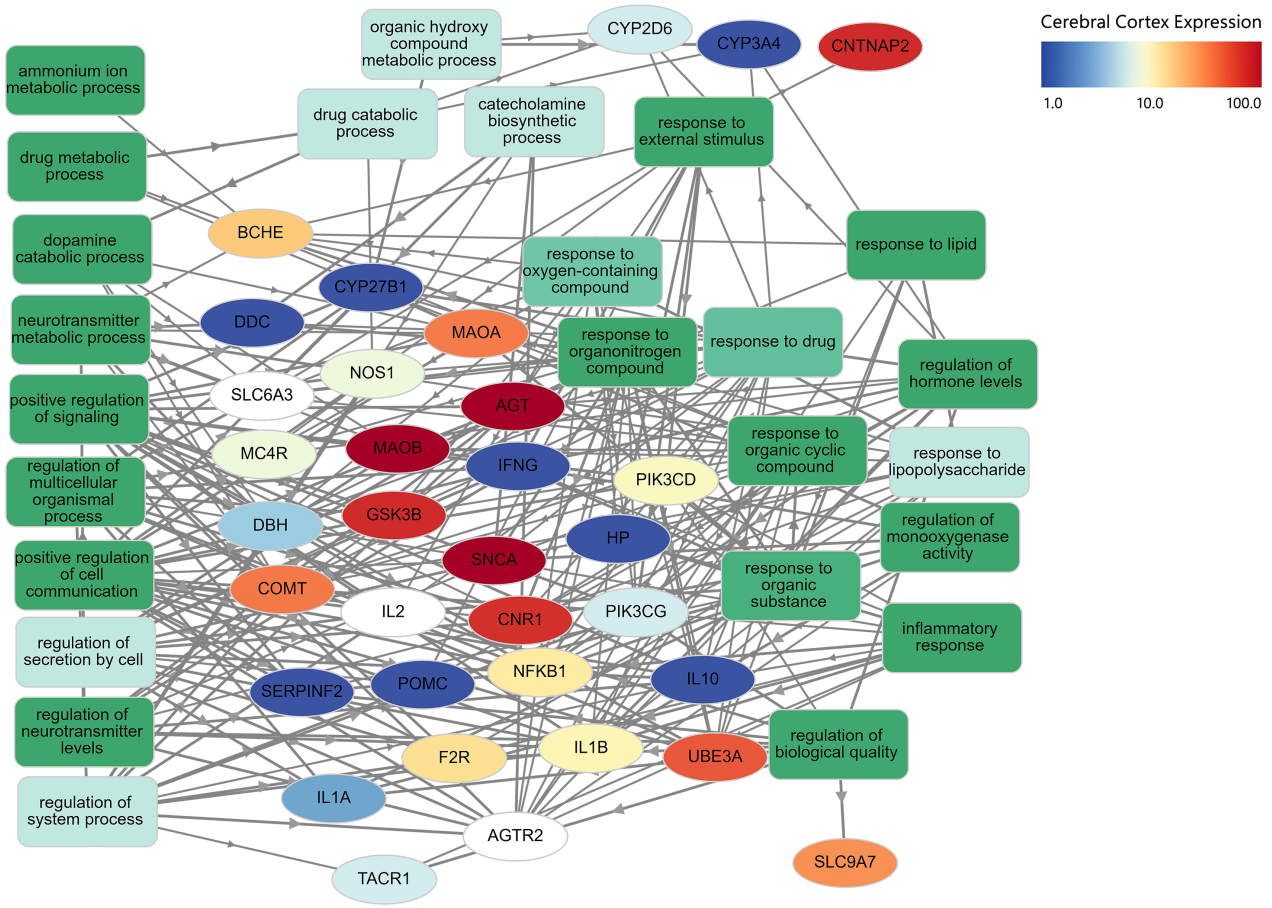


**Fig. 6. Network illustrating the GO functional enrichment analysis of Biological Process pathways in genes shared between COVID-19 and ADHD.** The network is dominated by pathways related to cytokine-mediated signaling, inflammatory responses, and axon guidance—reflecting mechanisms involved in SARS-CoV-2 pathogenicity and ADHD neurodevelopmental anomalies. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; COVID-19, coronavirus disease 2019.

This analysis does not stratify findings by phenotype, age, or sex and it should be interpreted as a population-agnostic framework. Genes such as IL-6 may reflect general inflammatory responses rather than condition-specific drivers [26]. Thus, this exploratory *in silico* approach offers a foundation for future hypothesis-driven research, especially when experimental validation is not yet feasible. Although the "common genes" strategy limits causal inference and may capture housekeeping or pleiotropic genes, it remains valuable for identifying mechanistic intersections [11,26].

Using a DisGeNET-guided pipeline, we identified 216 overlapping genes and selected four for further analysis—NRP1, BDNF, IGF-1, and IL-6—based on their biological plausibility and consistent representation in the peer-reviewed literature [13,27–29]. These genes represent three major biological themes relevant to both disorders: (1) vascular and endothelial function, (2) neurodevelopment and synaptic activity, and (3) immune modulation and inflammatory response.

### *Vascular and Endothelial Function*

Vascular and endothelial integrity is critical in systemic and neurological health. COVID-19 disrupts vascular function through endothelial damage, contributing to inflammation and coagulopathy [25]. ADHD is also linked to altered neurovascular processes that may affect attention and cognition [24].

NRP1 is a membrane-bound coreceptor involved in angiogenesis and axon guidance [30,31]. It is expressed in endothelial and neural cells and interacts with vascular endothelial growth factors (VEGFs) and semaphorins [31]. NRP1 enhances SARS-CoV-2 infectivity by facilitating viral entry, functioning more efficiently than Angiotensin-converting enzyme 2 (ACE2) and Transmembrane serine protease 2 (TMPRSS2) *in vitro* [32,33]. In the nervous system, NRP1 regulates thalamocortical axon migration, an essential process in neural circuit formation [34], which is disrupted in ADHD and externalizing behavior disorders [35–37]. Its role in viral pathogenesis and brain development positions NRP1 as a promising candidate for dual therapeutic targeting.

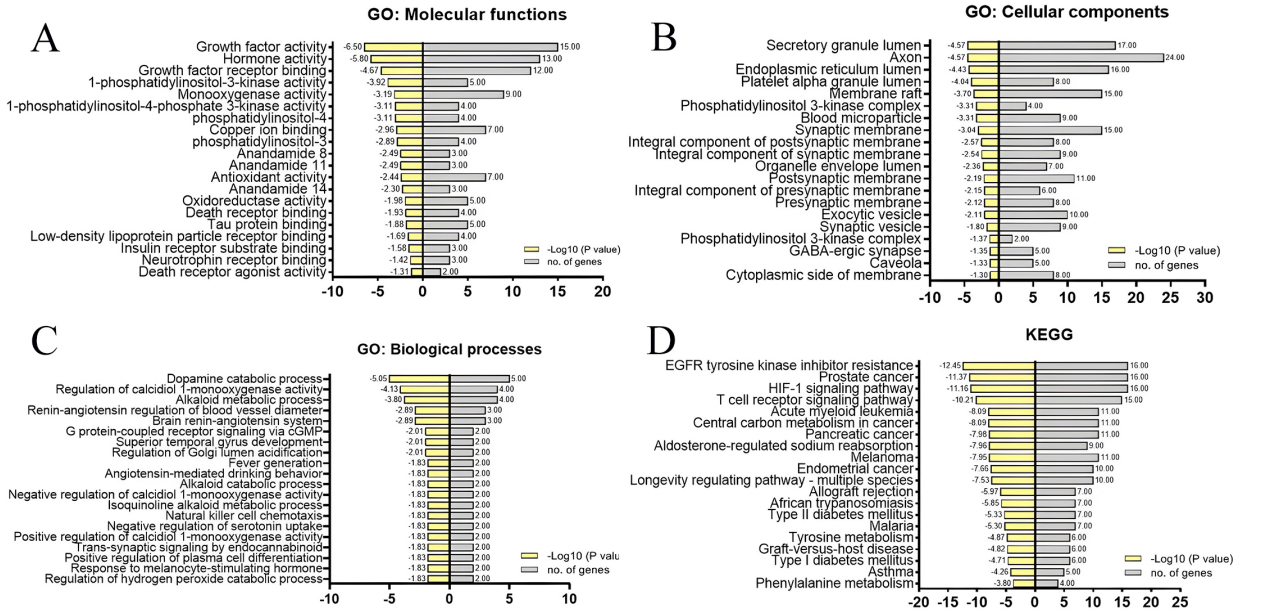


**Fig. 7. Top 20 enriched pathways of shared genes between COVID-19 and ADHD based on GO analysis.** (A) Enriched Molecular Function pathways. (B) Enriched Cellular Component pathways. (C) Enriched Biological Process pathways. (D) Enriched KEGG pathways. Bar graphs display the top 20 enriched GO and KEGG pathways, along with corresponding *p*-values and gene counts for COVID-19 and ADHD. Yellow bars indicate *p*-values, while gray bars denote the number of genes. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; COVID-19, coronavirus disease 2019; KEGG, Kyoto Encyclopedia of Genes and Genomes.

### *Neurodevelopment and Synaptic Activity*

COVID-19 and ADHD are associated with disruptions in neurodevelopmental signaling. COVID-19 impairs cognitive function through inflammation and altered neurotrophic factor activity [38], while ADHD is characterized by deficits in synaptic connectivity and dopaminergic signaling [24].

BDNF plays a vital role in neuroplasticity, neurogenesis, and neuronal survival [24,38–40]. It is highly expressed in the hippocampus and cortex and it circulates in peripheral blood [41]. A study by Petrella *et al.* [39] reports altered Brain-derived neurotrophic factor (BDNF) levels in symptomatic patients with COVID-19, with low levels predicting poor prognosis, particularly in adult males [42–44]. In ADHD, reduced BDNF activity is related to dysfunction in midbrain dopaminergic pathways and abnormalities in the frontal-striatal-cerebellar and ventral limbic circuits [45–47]. Adults with ADHD exhibit lower BDNF levels [48], whereas children often show elevated levels [46,49], suggesting developmental stage-specific effects. In animal models, BDNF deficiency is linked to hyperactivity and behavioral phenotypes resembling ADHD [46].

IGF-1 is a neurotrophic and immunomodulatory molecule primarily produced by the liver [50–52]. It influences long-term cell survival, growth, and immune cell activation [53–55]. Elevated IGF-1 levels are associated with milder COVID-19 symptoms in children [54,56], while reductions correlate with disease progression [57,58]. IGF-1 could also mitigate cytokine storms [57,58]. In ADHD, IGF-1 levels are lower than those in healthy controls [59], and treatment with stimulant medications may further suppress IGF-1 [60,61]. These changes may influence growth and pubertal development, particularly in children [62,63]. Together, BDNF and IGF-1 exemplify neurodevelopmental regulators with shared relevance to both disorders.

### *Immune Modulation and Inflammatory Response*

Immune system dysregulation is central to COVID-19 and ADHD. In this study, IL-6, a pleiotropic cytokine, emerged as a highly connected gene associated with both conditions. In COVID-19, IL-6 is a key driver of the cytokine storm, contributing to acute respiratory distress syndrome, disease severity, and mortality [64–67]. It is produced by multiple immune cell types and it mediates pro-inflammatory and anti-inflammatory responses [68–70]. Overproduction leads to systemic inflammation and coagulopathy [64].

In ADHD, elevated IL-6 levels correlate with cognitive impairment and hyperactivity [26,71]. Polymorphisms in IL-6 are linked to neurodevelopmental outcomes, potentially through their effect on dopaminergic signaling [72–74]. IL-6 also regulates neurotrophin activity, which may influence learning and memory [75]. Although IL-6 is not specific to either condition, its central role across enriched pathways, including “cytokine-mediated signaling” and “JAK-STAT signaling” [69], makes it a strong candidate for further mechanistic and therapeutic investigation.

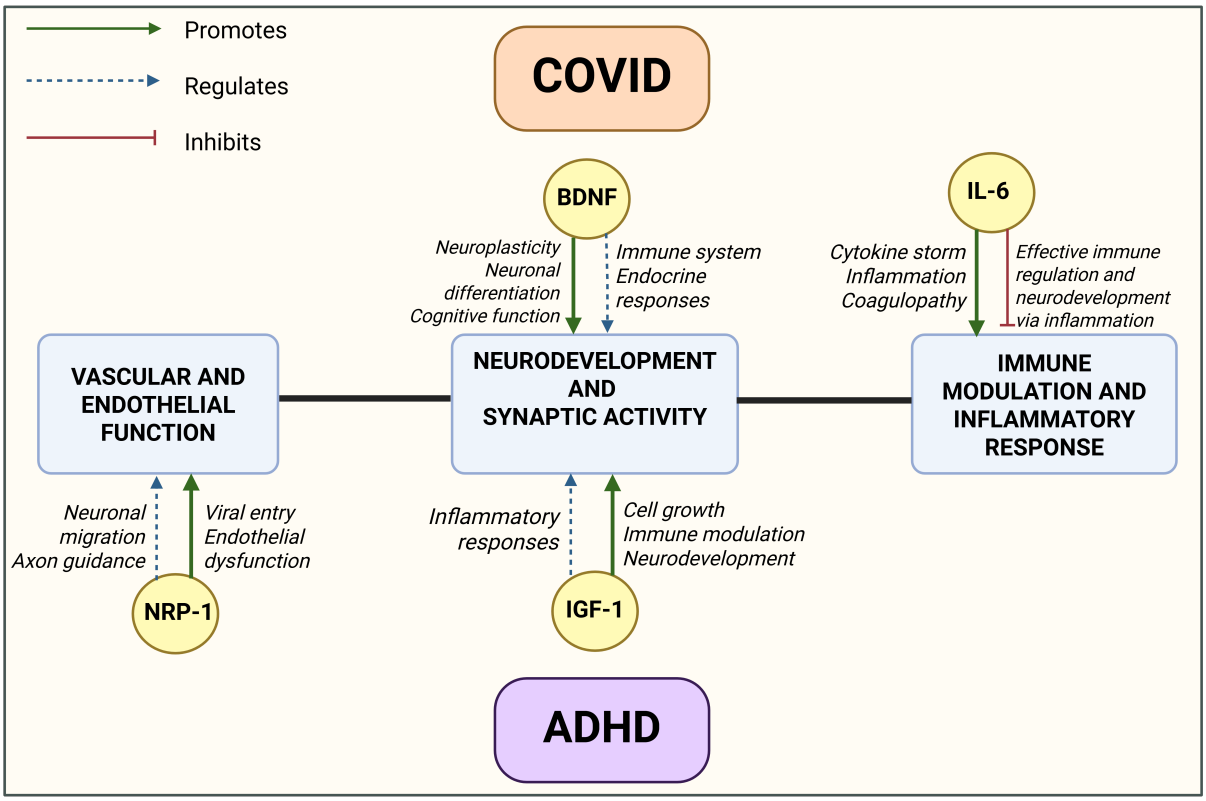


**Fig. 8. Schematic diagram illustrating the molecular mechanisms linking key genes to COVID-19 and ADHD.** This integrative figure synthesizes the findings of the study into a mechanistic map. It positions NRP1 at the interface of viral entry and axon guidance, BDNF and IGF-1 in neurotrophic support and synaptic plasticity regulation, and IL-6 as a central mediator of immune dysregulation. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BDNF, brain-derived neurotrophic factor; COVID-19, coronavirus disease 2019; IGF-1, insulin-like growth factor 1; IL-6, interleukin 6; NRP1, neuropilin 1.

The convergence of NRP1, BDNF, IGF-1, and IL-6 across computational and empirical analyses supports the hypothesis that COVID-19 and ADHD share underlying vulnerabilities in immune regulation, neurodevelopment, and vascular integrity. These genes are enriched in KEGG and GO pathways, such as "VEGF signaling", "axon guidance", "PI3K-Akt signaling", "neurotrophin TRK receptor signaling", and "cytokine–cytokine receptor interaction" [11–13,28,76]. Although supported by multiple *in silico* analyses, our findings remain correlative. To validate these hypotheses, future studies should incorporate experimental approaches, including gene knockdown or overexpression in animal models, transcriptomic profiling of human cohorts using platforms such as GEO or ArrayExpress, cytokine assays (e.g., ELISA, qPCR) using patient-derived samples, and involve co-expression network and hub gene analyses using ADHD and COVID-19 datasets. Moreover, analyses stratified by age, sex, COVID-19 severity, and ADHD subtype will be essential to contextualize the functional relevance of these genes. The exclusion of broadly expressed housekeeping genes may improve specificity in further analyses.

Finally, the focus on four genes introduces selection bias; however, our dual-filtering approach—combining computational identification and structured literature review (requiring $\geq$2 peer-reviewed studies per condition)—enhances credibility. IL-6 and BDNF align closely with enriched GO and KEGG terms, whereas IGF-1 and NRP1 occupy central roles in PPI networks and relevant signaling pathways. Together, these findings support a biologically coherent model of convergence between COVID-19 and ADHD.

NRP1 facilitates SARS-CoV-2 entry and contributes to endothelial dysfunction in COVID-19, while also regulating axonal guidance and neural circuitry related to attention and behavior, implicating its role in ADHD. Likewise, BDNF and IGF-1 are crucial for neuronal survival and immune regulation; disruptions in their expression are associated with cognitive deficits and immune dysregulation in both conditions. IL-6, a major cytokine, whose levels are elevated during the COVID-19-induced inflammatory response, also contributes to ADHD pathophysiology by promoting neuroinflammation and behavioral dysregulation. These convergent roles suggest that shared molecu-

lar mechanisms may contribute to overlapping clinical features and offer potential targets for integrated therapeutic approaches. As illustrated in Fig. 8, *NRP1*, *BDNF*, *IGF-1*, and *IL-6* are involved in overlapping neuroimmune and signaling pathways relevant to both COVID-19 and ADHD, highlighting their functional interconnectedness and therapeutic significance.

Although this study provides valuable insights, it remains exploratory and relies exclusively on *in silico* analyses and literature-based gene prioritization. Direct experimental validation processes—encompassing transcriptomic profiling, clinical biomarker assessment, or mechanistic assays—were not conducted. Thus, the identified genes should be considered putative candidates that could be used to generate hypotheses rather than confirmed therapeutic targets. Future studies should incorporate patient-derived expression datasets, functional studies, and clinical cohort analyses to assess the biological and translational relevance of these genes.

Given the large number of identified overlapping genes (n = 216), we applied a filtering strategy that prioritized genes whose inclusion was supported by evidence from at least two independent studies. This criterion was used to enhance the robustness and translational relevance of the highlighted targets by ensuring that the selection of genes, including *NRP1*, *BDNF*, *IGF-1*, and *IL-6*, was supported by reproducible evidence across both COVID-19 and ADHD contexts. While this approach may omit potentially novel or understudied genes, it allows for a more focused analysis of genes for which existing evidence is stronger, thereby improving the mechanistic clarity and clinical interpretability of our findings. We acknowledge this trade-off and have added a note to highlight this limitation, to encourage future studies to explore the broader gene set.

The identification of *NRP1*, *BDNF*, *IGF-1*, and *IL-6* as overlapping genes across both COVID-19 and ADHD highlights opportunities for translational research. These genes may inform the development of biomarker-based diagnostics, risk stratification tools, and targeted therapies. For example, IL-6, a pro-inflammatory cytokine elevated in severe COVID-19, could serve both as a marker of neuroinflammatory vulnerability and as a therapeutic target through existing IL-6 inhibitors. BDNF and IGF-1, which play key roles in neuroplasticity and cognitive regulation, may support interventions aimed at mitigating cognitive impairments occurring commonly in both disorders. The involvement of NRP1 in SARS-CoV-2 entry and neural signaling suggests that its inhibition could simultaneously reduce viral neuroinvasion and support neurodevelopmental stability in ADHD.

Future research should aim to validate these pathways in clinical cohorts and explore gene-specific therapeutic strategies. This includes evaluating NRP1 inhibitors for their dual antiviral and neuroprotective effects, modulating BDNF and IGF-1 to enhance cognitive resilience, and repurposing IL-6-targeted therapies in patients exhibiting overlapping symptomatology. Such efforts can move us toward precision medicine approaches that integrate molecular insights into clinical management strategies for both COVID-19 and ADHD.

Ultimately, validating these shared molecular targets in clinical settings and assessing their therapeutic potential through well-designed trials is imperative. Integrating genomic, clinical, and pharmacological data within interdisciplinary frameworks will be essential to advancing precision medicine approaches. This approach may improve risk stratification, inform individualized treatment strategies, and optimize clinical monitoring, thereby enhancing outcomes for patients affected by COVID-19, ADHD, or both these conditions.

## Conclusions

This study provides preliminary evidence of a genetic link between COVID-19 and ADHD, highlighting shared molecular mechanisms that may underlie overlapping neurological and immune-related dysfunctions. Through an *in silico* bioinformatics approach, we identified NRP1, BDNF, IGF-1, and IL-6 as central genes involved in pathways related to vascular regulation, neurodevelopment, and immune signaling. These genes are implicated in key Biological Processes such as viral entry, synaptic plasticity, and inflammation, offering a potential explanation for comorbidity or shared pathophysiology between the two conditions.

While exploratory, our findings demonstrate a cost-effective and scalable strategy for uncovering mechanistic overlaps between seemingly distinct disorders. We recommend that future studies use *in vivo* models or patient-derived samples to experimentally validate the candidate genes identified here. Overall, this work serves as a foundation for gene prioritization and hypothesis generation, particularly in early-stage or resource-limited research settings, and provides a framework for advancing translational studies at the intersection of infectious and neurodevelopmental disorders.

## Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

## Author Contributions

MMR and MJA conceptualized and designed the literature research. MMR and MJA collected the literature. MMR, SK, MJA and CM were critically involved in conceptualization, reviewing and editing. MMR and MJA were responsible for drafting the manuscript. CM was responsi-

ble for funding acquisition. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest. Changjong Moon is serving as one of the Editorial Board members of this journal. We declare that Changjong Moon had no involvement in the review of this article and has no access to information regarding its review.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202537199.136.

## References

[1] Raza ML, Imam MH, Zehra W, Jamil S. Neuro-inflammatory pathways in COVID-19-induced central nervous system injury: Implications for prevention and treatment strategies. Experimental Neurology. 2024; 382: 114984. https://doi.org/10.1016/j.expneurol.2024.114984.

[2] Thepmankorn P, Bach J, Lasfar A, Zhao X, Souayah S, Chong ZZ, *et al*. Cytokine storm induced by SARS-CoV-2 infection: The spectrum of its neurological manifestations. Cytokine. 2021; 138: 155404. https://doi.org/10.1016/j.cyto.2020.155404.

[3] Ando M, Takeda T, Kumagai K. A Qualitative Study of Impacts of the COVID-19 Pandemic on Lives in Adults with Attention Deficit Hyperactive Disorder in Japan. International Journal of Environmental Research and Public Health. 2021; 18: 2090. https://doi.org/10.3390/ijerph18042090.

[4] Bobo E, Fongaro E, Lin L, Gétin C, Gamon L, Picot MC, *et al*. Mental Health of Children With Attention Deficit and Hyperactivity Disorder and Their Parents During the COVID-19 Lockdown: A National Cross-Sectional Study. Frontiers in Psychiatry. 2022; 13: 902245. https://doi.org/10.3389/fpsyt.2022.902245.

[5] Du J, Fang L, Dong K, Zhou Z. Exploring the complex relationship between attention deficit hyperactivity disorder and the immune system: A bidirectional Mendelian randomization analysis. Journal of Affective Disorders. 2025; 369: 854–860. https://doi.org/10.1016/j.jad.2024.10.050.

[6] Heslin KP, Haruna A, George RA, Chen S, Nobel I, Anderson KB, *et al*. Association Between ADHD and COVID-19 Infection and Clinical Outcomes: A Retrospective Cohort Study From Electronic Medical Records. Journal of Attention Disorders. 2023; 27: 169–181. https://doi.org/10.1177/10870547221129305.

[7] Merzon E, Manor I, Rotem A, Schneider T, Vinker S, Golan Cohen A, *et al*. ADHD as a Risk Factor for Infection With Covid-19. Journal of Attention Disorders. 2021; 25: 1783–1790. https://doi.org/10.1177/1087054720943271.

[8] Chen F, Cao H, Baranova A, Zhao Q, Zhang F. Causal associations between COVID-19 and childhood mental disorders. BMC Psychiatry. 2023; 23: 922. https://doi.org/10.1186/s12888-023-05433-0.

[9] Kamila G, Gulati S. Navigating the Frontiers in Childhood Neurodevelopmental Disorders: Unravelling Challenges in South-East Asia. WHO South-East Asia Journal of Public Health. 2023; 12: 81–84. https://doi.org/10.4103/WHO-SEAJPH.WHOSEAJPH_6_24.

[10] Salari N, Ghasemi H, Abdoli N, Rahmani A, Shiri MH, Hashemian AH, *et al*. The global prevalence of ADHD in children and adolescents: a systematic review and meta-analysis. Italian Journal of Pediatrics. 2023; 49: 48. https://doi.org/10.1186/s13052-023-01456-1.

[11] Baranova A, Cao H, Chen J, Zhang F. Causal Association and Shared Genetics Between Asthma and COVID-19. Frontiers in Immunology. 2022; 13: 705379. https://doi.org/10.3389/fimmu.2022.705379.

[12] Abdelmoneim AH, Khalil SI, Awadelkareem Osman Fadl H, Rewane A, Elbager SG. Exploring the Power and Promise of In Silico Clinical Trials with Application in COVID-19 Infection. Sudan Journal of Medical Sciences. 2021; 16.

[13] Moradi M, Golmohammadi R, Najafi A, Moosazadeh Moghaddam M, Fasihi-Ramandi M, Mirnejad R. A contemporary review on the important role of *in silico* approaches for managing different aspects of COVID-19 crisis. Informatics in Medicine Unlocked. 2022; 28: 100862. https://doi.org/10.1016/j.imu.2022.100862.

[14] Murray D, Doran P, MacMathuna P, Moss AC. In silico gene expression analysis–an overview. Molecular Cancer. 2007; 6: 50. https://doi.org/10.1186/1476-4598-6-50.

[15] Arora VS, McKee M, Stuckler D. Google Trends: Opportunities and limitations in health and health policy research. Health Policy (Amsterdam, Netherlands). 2019; 123: 338–341. https://doi.org/10.1016/j.healthpol.2019.01.001.

[16] Ming WK, Huang F, Chen Q, Liang B, Jiao A, Liu T, *et al*. Understanding Health Communication Through Google Trends and News Coverage for COVID-19: Multinational Study in Eight Countries. JMIR Public Health and Surveillance. 2021; 7: e26644. https://doi.org/10.2196/26644.

[17] Seifter A, Schwarzwalder A, Geis K, Aucott J. The utility of "Google Trends" for epidemiological research: Lyme disease as an example. Geospatial Health. 2010; 4: 135–137. https://doi.org/10.4081/gh.2010.195.

[18] Johnson ZJ, Krutkin DD, Bohutskyi P, Kalyuzhnaya MG. Metals and methylotrophy: Via global gene expression studies. Methods in Enzymology. 2021; 650: 185–213. https://doi.org/10.1016/bs.mie.2021.01.046.

[19] Thomas PD. The Gene Ontology and the Meaning of Biological Function. In Dessimoz C, Škunca N, (eds.) The Gene Ontology Handbook (pp. 15–24). Springer New York: New York, NY. 2017. https://doi.org/10.1007/978-1-4939-3743-1.

[20] Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. Nucleic Acids Research. 2000; 28: 27–30. https://doi.org/10.1093/nar/28.1.27.

[21] Kanehisa M, Sato Y, Kawashima M, Furumichi M, Tanabe M. KEGG as a reference resource for gene and protein annotation. Nucleic Acids Research. 2016; 44: D457–62. https://doi.org/10.1093/nar/gkv1070.

[22] Pomaznoy M, Ha B, Peters B. GOnet: a tool for interactive Gene Ontology analysis. BMC Bioinformatics. 2018; 19: 470. https://doi.org/10.1186/s12859-018-2533-3.

[23] Szklarczyk D, Nastou K, Koutrouli M, Kirsch R, Mehryary F, Hachilif R, *et al*. The STRING database in 2025: protein networks with directionality of regulation. Nucleic Acids Research. 2025; 53: D730–D737. https://doi.org/10.1093/nar/gkae1113.

[24] Magnus W, Anilkumar AC, Shaban K. Attention Deficit Hyperactivity Disorder. StatPearls: Treasure Island (FL). 2023.

[25] Karakasis P, Nasoufidou A, Sagris M, Fragakis N, Tsioufis K. Vascular Alterations Following COVID-19 Infection: A Comprehensive Literature Review. Life (Basel, Switzerland). 2024; 14: 545. https://doi.org/10.3390/life14050545.

[26] Misiak B, Wójta-Kempa M, Samochowiec J, Schiweck C, Aichholzer M, Reif A, *et al*. Peripheral blood inflammatory markers in patients with attention deficit/hyperactivity disorder (ADHD): A systematic review and meta-analysis. Progress in Neuro-psychopharmacology & Biological Psychiatry. 2022; 118: 110581. https://doi.org/10.1016/j.pnpbp.2022.110581.

[27] Eadeh HM, Bourchtein E, Langberg JM, Eddy LD, Oddo L, Molitor SJ, *et al*. Longitudinal Evaluation of the Role of Academic and Social Impairment and Parent-Adolescent Conflict in the Development of Depression in Adolescents with ADHD. Journal of Child and Family Studies. 2017; 26: 2374–2385. https://doi.org/10.1007/s10826-017-0768-7.

[28] Pathan M, Keerthikumar S, Ang CS, Gangoda L, Quek CYJ, Williamson NA, *et al*. FunRich: An open access standalone functional enrichment and interaction network analysis tool. Proteomics. 2015; 15: 2597–2601. https://doi.org/10.1002/pmic.201400515.

[29] Piñero J, Ramírez-Anguita JM, Saüch-Pitarch J, Ronzano F, Centeno E, Sanz F, *et al*. The DisGeNET knowledge platform for disease genomics: 2019 update. Nucleic Acids Research. 2020; 48: D845–D855. https://doi.org/10.1093/nar/gkz1021.

[30] Kielian M. Enhancing host cell infection by SARS-CoV-2. Science (New York, N.Y.). 2020; 370: 765–766. https://doi.org/10.1126/science.abf0732.

[31] Neufeld G, Cohen T, Shraga N, Lange T, Kessler O, Herzog Y. The neuropilins: multifunctional semaphorin and VEGF receptors that modulate axon guidance and angiogenesis. Trends in Cardiovascular Medicine. 2002; 12: 13–19. https://doi.org/10.1016/s1050-1738(01)00140-2.

[32] Cantuti-Castelvetri L, Ojha R, Pedro LD, Djannatian M, Franz J, Kuivanen S, *et al*. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science (New York, N.Y.). 2020; 370: 856–860. https://doi.org/10.1126/science.abd2985.

[33] Daly JL, Simonetti B, Klein K, Chen KE, Williamson MK, Antón-Plágaro C, *et al*. Neuropilin-1 is a host factor for SARS-CoV-2 infection. Science (New York, N.Y.). 2020; 370: 861–865. https://doi.org/10.1126/science.abd3072.

[34] López-Bendito G, Cautinat A, Sánchez JA, Bielle F, Flames N, Garratt AN, *et al*. Tangential neuronal migration controls axon guidance: a role for neuregulin-1 in thalamocortical axon navigation. Cell. 2006; 125: 127–142. https://doi.org/10.1016/j.cell.2006.01.042.

[35] Arcos-Burgos M, Vélez JI, Solomon BD, Muenke M. A common genetic network underlies substance use disorders and disruptive or externalizing disorders. Human Genetics. 2012; 131: 917–929. https://doi.org/10.1007/s00439-012-1164-4.

[36] Ivanov I, Bansal R, Hao X, Zhu H, Kellendonk C, Miller L, *et al*. Morphological abnormalities of the thalamus in youths with attention deficit hyperactivity disorder. The American Journal of Psychiatry. 2010; 167: 397–408. https://doi.org/10.1176/appi.ajp.2009.09030398.

[37] Shaw P. The shape of things to come in attention deficit hyperactivity disorder. The American Journal of Psychiatry. 2010; 167: 363–365. https://doi.org/10.1176/appi.ajp.2010.10010037.

[38] Rios M. BDNF and the central control of feeding: accidental bystander or essential player? Trends in Neurosciences. 2013; 36: 83–90. https://doi.org/10.1016/j.tins.2012.12.009.

[39] Petrella C, Nenna R, Petrarca L, Tarani F, Paparella R, Mancino E, *et al*. Serum NGF and BDNF in Long-COVID-19 Adolescents: A Pilot Study. Diagnostics (Basel, Switzerland). 2022; 12: 1162. https://doi.org/10.3390/diagnostics12051162.

[40] Shafiee A, Seighali N, Teymouri Athar M, Abdollahi AK, Jafarabady K, Bakhtiyari M. Levels of brain-derived neurotrophic factor (BDNF) among patients with COVID-19: a systematic review and meta-analysis. European Archives of Psychiatry and Clinical Neuroscience. 2024; 274: 1137–1152. https://doi.org/10.1007/s00406-023-01681-z.

[41] Savic G, Stevanovic I, Mihajlovic D, Jurisevic M, Gajovic N, Jovanovic I, *et al*. MMP-9/BDNF ratio predicts more severe COVID-19 outcomes. International Journal of Medical Sciences. 2022; 19: 1903–1911. https://doi.org/10.7150/ijms.75337.

[42] Mahboubi Mehrabani M, Karvandi MS, Maafi P, Doroudian M. Neurological complications associated with Covid-19; molecular mechanisms and therapeutic approaches. Reviews in Medical Virology. 2022; 32: e2334. https://doi.org/10.1002/rmv.2334.

[43] Minuzzi LG, Seelaender M, Silva BSDA, Cunha EDBB, Deus MDC, Vasconcellos FTF, *et al*. COVID-19 Outcome Relates With Circulating BDNF, According to Patient Adiposity and Age. Frontiers in Nutrition. 2021; 8: 784429. https://doi.org/10.3389/fnut.2021.784429.

[44] Motaghinejad M, Gholami M. Possible Neurological and Mental Outcomes of COVID-19 Infection: A Hypothetical Role of ACE-2\Mas\BDNF Signaling Pathway. International Journal of Preventive Medicine. 2020; 11: 84. https://doi.org/10.4103/ijpvm.IJPVM_114_20.

[45] Baroni A, Castellanos FX. Neuroanatomic and cognitive abnormalities in attention-deficit/hyperactivity disorder in the era of 'high definition' neuroimaging. Current Opinion in Neurobiology. 2015; 30: 1–8. https://doi.org/10.1016/j.conb.2014.08.005.

[46] Liu DY, Shen XM, Yuan FF, Guo OY, Zhong Y, Chen JG, *et al*. The Physiology of BDNF and Its Relationship with ADHD. Molecular Neurobiology. 2015; 52: 1467–1476. https://doi.org/10.1007/s12035-014-8956-6.

[47] Tsai SJ. Attention-deficit hyperactivity disorder may be associated with decreased central brain-derived neurotrophic factor activity: clinical and therapeutic implications. Medical Hypotheses. 2007; 68: 896–899. https://doi.org/10.1016/j.mehy.2006.06.025.

[48] Corominas-Roso M, Ramos-Quiroga JA, Ribases M, Sanchez-Mora C, Palomar G, Valero S, *et al*. Decreased serum levels of brain-derived neurotrophic factor in adults with attention-deficit hyperactivity disorder. The International Journal of Neuropsychopharmacology. 2013; 16: 1267–1275. https://doi.org/10.1017/S1461145712001629.

[49] Shim SH, Hwangbo Y, Kwon YJ, Jeong HY, Lee BH, Lee HJ, *et al*. Increased levels of plasma brain-derived neurotrophic factor (BDNF) in children with attention deficit-hyperactivity disorder (ADHD). Progress in Neuro-psychopharmacology & Biological Psychiatry. 2008; 32: 1824–1828. https://doi.org/10.1016/j.pnpbp.2008.08.005.

[50] Dyer AH, Vahdatpour C, Sanfeliu A, Tropea D. The role of Insulin-Like Growth Factor 1 (IGF-1) in brain development, maturation and neuroplasticity. Neuroscience. 2016; 325: 89–99. https://doi.org/10.1016/j.neuroscience.2016.03.056.

[51] Sherbet GV. 8-Insulin-Like Growth Factors. Growth Factors and Their Receptors in Cell Differentiation, Cancer and Cancer Therapy. 2011; 87–104. https://doi.org/10.1016/B978-0-12-387819-9.00008-6.

[52] Wang X, Cao L, Liu S, Zhou Y, Zhou J, Zhao W, *et al*. The critical roles of IGFs in immune modulation and inflammation. Cytokine. 2024; 183: 156750. https://doi.org/10.1016/j.cyto.2024.156750.

[53] Hakuno F, Takahashi SI. IGF1 receptor signaling pathways. Journal of Molecular Endocrinology. 2018; 61: T69–T86. https://doi.org/10.1530/JME-17-0311.

[54] Hazrati E, Gholami M, Farahani RH, Ghorban K, Ghayomzadeh M, Rouzbahani NH. The effect of IGF-1 plasma concentration on COVID-19 severity. Microbial Pathogenesis. 2022; 164: 105416. https://doi.org/10.1016/j.micpath.2022.105416.

[55] Hoyek S, Cruz NFSD, Patel NA, Al-Khersan H, Fan KC, Berrocal AM. Identification of novel biomarkers for retinopathy of prematurity in preterm infants by use of innovative technologies and artificial intelligence. Progress in Retinal and Eye Research. 2023; 97: 101208. https://doi.org/10.1016/j.preteyeres.2023.101208.

[56] Ashpole NM, Sanders JE, Hodges EL, Yan H, Sonntag WE. Growth hormone, insulin-like growth factor-1 and the aging brain. Experimental Gerontology. 2015; 68: 76–81. https://doi.org/10.1016/j.exger.2014.10.002.

[57] Fan X, Yin C, Wang J, Yang M, Ma H, Jin G, *et al*. Pre-diagnostic circulating concentrations of insulin-like growth factor-1 and risk of COVID-19 mortality: results from UK Biobank. European Journal of Epidemiology. 2021; 36: 311–318. https://doi.org/10.1007/s10654-020-00709-1.

[58] Zhao M, Liu Z, Shao F, Zhou W, Chen Z, Xia P, *et al*. Communication Pattern Changes Along With Declined IGF1 of Immune Cells in COVID-19 Patients During Disease Progression. Frontiers in Immunology. 2022; 12: 729990. https://doi.org/10.3389/fimmu.2021.729990.

[59] Wang LJ, Huang YH, Chou WJ, Lee SY, Chang HY, Chen CC, *et al*. Interrelationships among growth hormone, thyroid function, and endocrine-disrupting chemicals on the susceptibility to attention-deficit/hyperactivity disorder. European Child & Adolescent Psychiatry. 2023; 32: 1391–1401. https://doi.org/10.1007/s00787-021-01886-4.

[60] Bereket A, Turan S, Karaman MG, Haklar G, Ozbay F, Yazgan MY. Height, weight, IGF-I, IGFBP-3 and thyroid functions in prepubertal children with attention deficit hyperactivity disorder: effect of methylphenidate treatment. Hormone Research. 2005; 63: 159–164. https://doi.org/10.1159/000084683.

[61] Sisley S, Trujillo MV, Khoury J, Backeljauw P. Low incidence of pathology detection and high cost of screening in the evaluation of asymptomatic short children. The Journal of Pediatrics. 2013; 163: 1045–1051. https://doi.org/10.1016/j.jpeds.2013.04.002.

[62] Mei H, Xie R, Li T, Chen Z, Liu Y, Sun C. Effect of Atomoxetine on Behavioral Difficulties and Growth Development of Primary School Children with Attention-Deficit/Hyperactivity Disorder: A Prospective Study. Children (Basel, Switzerland). 2022; 9: 212. https://doi.org/10.3390/children9020212.

[63] Wang LJ, Huang YH, Chou WJ, Lee SY. Growth Hormone and Thyroid Function in Children With Attention Deficit Hyperactivity Disorder Undergoing Drug Therapy. The Journal of Clinical Endocrinology and Metabolism. 2022; 107: 2047–2056. https://doi.org/10.1210/clinem/dgac139.

[64] Falahi S, Zamanian MH, Feizollahi P, Rezaiemanesh A, Salari F, Mahmoudi Z, *et al*. Evaluation of the relationship between IL-6 gene single nucleotide polymorphisms and the severity of COVID-19 in an Iranian population. Cytokine. 2022; 154: 155889. https://doi.org/10.1016/j.cyto.2022.155889.

[65] Gong J, Dong H, Xia QS, Huang ZY, Wang DK, Zhao Y, *et al*. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19: a retrospective study. BMC Infectious Diseases. 2020; 20: 963. https://doi.org/10.1186/s12879-020-05681-5.

[66] Liu BM, Martins TB, Peterson LK, Hill HR. Clinical significance of measuring serum cytokine levels as inflammatory biomarkers in adult and pediatric COVID-19 cases: A review. Cytokine. 2021; 142: 155478. https://doi.org/10.1016/j.cyto.2021.155478.

[67] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England). 2020; 395: 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3.

[68] Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochimica et Biophysica Acta. 2011; 1813: 878–888. https://doi.org/10.1016/j.bbamcr.2011.01.034.

[69] Smieszek SP, Przychodzen BP, Polymeropoulos VM, Polymeropoulos CM, Polymeropoulos MH. Assessing the potential correlation of polymorphisms in the IL6R with relative IL6 elevation in severely ill COVID-19 patients'. Cytokine. 2021; 148: 155662. https://doi.org/10.1016/j.cyto.2021.155662.

[70] Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harbor Perspectives in Biology. 2014; 6: a016295. https://doi.org/10.1101/cshperspect.a016295.

[71] Drtilkova I, Sery O, Theiner P, Uhrova A, Zackova M, Balastikova B, *et al*. Clinical and molecular-genetic markers of ADHD in children. Neuro Endocrinology Letters. 2008; 29: 320–327.

[72] Donfrancesco R, Nativio P, Borrelli E, Giua E, Andriola E, Villa MP, *et al*. Serum cytokines in pediatric neuropsychiatric syndromes: focus on Attention Deficit Hyperactivity Disorder. Minerva Pediatrics. 2021; 73: 398–404. https://doi.org/10.23736/S2724-5276.16.04642-9.

[73] Kozłowska A, Wojtacha P, Równiak M, Kolenkiewicz M, Huang ACW. ADHD pathogenesis in the immune, endocrine and nervous systems of juvenile and maturating SHR and WKY rats. Psychopharmacology. 2019; 236: 2937–2958. https://doi.org/10.1007/s00213-019-5180-0.

[74] Zalcman S, Green-Johnson JM, Murray L, Nance DM, Dyck D, Anisman H, *et al*. Cytokine-specific central monoamine alterations induced by interleukin-1, -2 and -6. Brain Research. 1994; 643: 40–49. https://doi.org/10.1016/0006-8993(94)90006-x.

[75] Borovcanin MM, Jovanovic I, Radosavljevic G, Pantic J, Minic Janicijevic S, Arsenijevic N, *et al*. Interleukin-6 in Schizophrenia-Is There a Therapeutic Relevance? Frontiers in Psychiatry. 2017; 8: 221. https://doi.org/10.3389/fpsyt.2017.00221.

[76] Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 Cytokine Storm; What We Know So Far. Frontiers in Immunology. 2020; 11: 1446. https://doi.org/10.3389/fimmu.2020.01446.