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Shared interactions of six neurotropic viruses with 38 human proteins: a computational and literature-based exploration of viral interactions and hijacking of human proteins in neuropsychiatric disorders

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Abstract

Introduction Viral infections may disrupt the structural and functional integrity of the nervous system, leading to acute conditions such as encephalitis, and neuropsychiatric conditions as mood disorders, schizophrenia, and neurodegenerative diseases. Investigating viral interactions of human proteins may reveal mechanisms underlying these effects and offer insights for therapeutic interventions. This study explores molecular interactions of virus and human proteins that may be related to neuropsychiatric disorders.

Methods Herpes Simplex Virus-1 (HSV-1), Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Influenza A virus (IAV) (H1N1, H5N1), and Human Immunodeficiency Virus (HIV1&2) were selected as key viruses. Protein structures for each virus were accessed from the Protein Data Bank and analyzed using the HMI-Pred web server to detect interface mimicry between viral and human proteins. The PANTHER classification system was used to categorize viral-human protein interactions based on function and cellular localization.

Results Energetically favorable viral-human protein interactions were identified for HSV-1 (467), CMV (514), EBV (495), H1N1 (3331), H5N1 (3533), and HIV 1&2 (62425). Besides immune and apoptosis-related pathways, key neurodegenerative pathways, including those associated with Parkinson's and Huntington's diseases, were frequently interacted. A total of 38 human proteins, including calmodulin 2, Ras-related botulinum toxin substrate 1 (Rac1), PDGF-β, and vimentin, were found to interact with all six viruses.

Conclusion The study indicates a substantial number of energetically favorable interactions between human proteins and selected viral proteins, underscoring the complexity and breadth of viral strategies to hijack host cellular mechanisms. Further in vivo and in vitro validation is required to understand the implications of these interactions.

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1 Introduction

Mental health disorders arise from a dynamic interplay between genetic and environmental factors. Environmental exposures, like genetics, consist of interconnected elements that influence shared biological and psychological pathways, shaping the development of mental illness. Studying these exposures from conception onward and understanding their cumulative effects provide insights into the intricate relationship between multigenic and multi environmental influences on mental health [1–3]. Among these environmental exposures, exposure to infectious agents is increasingly recognized as a significant contributor to mental health risks [4]. Emerging evidence suggests that such exposures can affect brain development and function, leading to a range of mental health disorders, from mood disorders like depression to neurodegenerative conditions and autoimmune disorders such as multiple sclerosis (MS) [5–9].

Viral encounters, in particular, have been strongly linked to neuropsychiatric conditions, influencing the brain either through direct invasion of neural tissue, or indirectly by triggering complex immune responses [6]. Viruses that directly enter the central (CNS) or peripheral (PNS) nervous system are termed 'neuroinvasive', while those that infect and replicate within neural cells are classified as 'neurotropic' [10]. In contrast, viruses that are neither neuroinvasive nor neurotropic affect the CNS primarily through the induction of immune responses, leading to CNS inflammation and neuronal death facilitated by the enhanced secretion of proinflammatory cytokines [6–13]. This immune-mediated dysfunction can be further exacerbated by the production of autoantibodies that erroneously target neuronal structures. Specifically, antibodies against CNS cell surface antigens, known as 'neuronal surface antibodies' (NSAbs), have been implicated in the pathogenesis of a range of neuropsychiatric disorders, including mood disorders, psychosis, and autoimmune encephalitis [10–18]. Notably, immunotherapy targeting these NSAbs has shown considerable success in treating these conditions [19].

Another proposed mechanism of CNS dysfunction associated with viral infections involves molecular mimicry [18, 20]. During their life cycle, viruses exploit host cellular machinery to produce viral proteins. These viral proteins, which are present within human cells during infection, may interact with human proteins through matching amino acid sequences and forming non-covalent bonds. Such interactions could enable viral proteins to mimic human proteins with structurally similar interaction surfaces, potentially hijacking their binding sites in physiologically relevant interactions. This mimicry can lead to either a gain or loss of function in host proteins [21–23]. Loss of function in critical proteins involved in neurophysiological processes or gain of function in proteins associated with neurodegenerative pathways could underlie the neuropsychiatric effects observed during viral infections. Additionally, viral proteins may interact with human proteins involved in inflammatory pathways, exacerbating inflammatory responses. Furthermore, if viral proteins resemble CNS cell surface antigens, they could trigger autoimmune responses, further contributing to CNS dysfunction. A deeper understanding of the complex interplay between viral exposure, immune response, and the development of neuropsychiatric diseases is essential for advancing mental health research.

A diverse range of viruses have been implicated in CNS dysfunction, each utilizing distinct pathways to infect neural tissue. Alphaviruses, such as herpes simplex virus type 1 (HSV-1) and varicella-zoster virus (VZV), initially target the PNS through sensory endings. HSV-1, rabies virus (RABV), influenza A, and SARS-CoV-2 infect the olfactory epithelium before progressing to the CNS. Poliovirus and RABV primarily affect motor neurons, while viruses like HIV and certain picornaviruses breach the blood–brain barrier (BBB) by hijacking infected leukocytes. Additional mechanisms include the infection of brain microvasculature, as seen with West Nile virus (WNV) and Epstein-Barr virus (EBV), or the disruption of the BBB through cytokine storms, as observed with Borna disease virus (BDV) and influenza A variants [6, 10]. Notably, viruses such as HSV-1, EBV, cytomegalovirus (CMV), human immunodeficiency virus (HIV), and certain strains of influenza A (H5N1, H1N1) are particularly associated with widespread neurological effects and they are selected as the key viruses analyzed and reviewed for this study.

Herpes simplex virus type 1 infects approximately 63.6% of adults [24] and its reactivation can lead to serious neurological complications upon viral replication within the CNS. Studies suggest that HSV-1 reaches the CNS via the trigeminal and olfactory pathways [25–28], and can spread to the contralateral temporal lobe, potentially causing herpes simplex encephalitis (HSE) [29]. As an acute condition, HSE primarily affects the temporal and frontal lobes, causing neuronal death through necrosis, apoptosis, and inflammation [30, 31]. Despite antiviral treatment, many HSE survivors experience lasting neurological issues, such as epilepsy and cognitive impairments [32–34]. Almost 40% of HSE patients develop neuronal surface antibodies, leading to autoimmune encephalitis (AE) with symptoms like choreoathetosis, seizures and behavioral changes [35]. Several mechanisms have been proposed to explain the pathogenesis of post-HSV autoimmune encephalitis, including molecular mimicry and immune responses triggered by the exposure of previously concealed antigens following infection-induced cellular damage.

In the long term, HSV-1 infections may reduce cortical gray matter gradually, contributing to cognitive decline and psychiatric disorders like schizophrenia and bipolar disorder [36, 37]. Elevated C-reactive protein (CRP) levels in HSV-1 positive individuals have been linked to cognitive impairment in bipolar disorder and schizophrenia patients, although no direct causal relationship has been proven [38, 39].

HSV-1 is also associated with Alzheimer's Disease (AD). The virus induces amyloid-beta production, tau hyperphosphorylation, and disrupts calcium homeostasis and autophagy, leading to AD-related pathologies like neuroinflammation, oxidative stress, and mitochondrial dysfunction [40–44]. In individuals with the APOE-ε4 genotype, a major AD risk factor, HSV-1 infection can be more severe. Genes linked to AD susceptibility, such as CR1, CLU, PICALM and NC-2, also participate in HSV-1's life cycle, contributing to amyloid plaque formation [45, 46]. In alignment with these observations, proteomic analyses demonstrate considerable quantities of HSV-1 and immune-related proteins within amyloid plaques and neurofibrillary tangles in AD [44–47]. These findings highlight HSV-1's significant role in AD pathogenesis.

Epstein-Barr virus, a gamma herpes virus, affects nearly 90% of the global population [48, 49]. It transforms B cells, elevating RNA levels and viral genome copies, with viral genes like Epstein-Barr nuclear antigen (EBNA) expressed [50]. EBV infection of brain microvascular endothelial cells (HBMECs) increases intercellular adhesion molecule-1 (ICAM-1) and chemokine ligand 5 (CCL-5) expression, leading to peripheral blood mononuclear cell (PBMC) adhesion to endothelial cells [51]. Active EBV replication in the CNS, evidenced by the presence of lytic cycle gene BZLF-1 in cerebrospinal fluid (CSF), compromises the blood–brain barrier, contributing to neurological and psychiatric disorders [52].

EBV seroprevalence is higher in MS patients, and MS patients are more likely to have symptomatic EBV infection, like infectious mononucleosis (IM). Anti-EBV antibody titers, influenced by the HLA-DRB1*1501 genotype, play a role in MS risk. EBV triggers CNS inflammation, dysregulated immune responses, and autoantibody production through viral proteins, particularly the EBNA-1 [53]. EBV facilitates immune escape by inhibiting caspase-mediated apoptosis, thereby reducing immune exposure to EBNA-1. EBNA-1 expression correlates with increased major histocompatibility complex (MHC) expression, altered immune signaling, and enhanced angiogenesis, which may further exacerbate MS [54, 55].

CSF analysis in MS patients reveals increased EBV-specific T-cell activity, particularly against lytic proteins, indicating a localized immune response [56]. EBNA-1-specific Th1 cells with high antigen sensitivity may cross-react with autoantigens, promoting autoimmune activity [57]. EBV-specific CD4+ T cells target myelin basic protein in the CNS, contributing to demyelination [58], while EBV-specific CD8 T cells increase CNS inflammation [59]. Post-mortem studies show significant infiltration of EBV-infected B cells and plasma cells in MS brains [60], with EBV-expressing B cells in lesions and ectopic follicles, suggesting a role in B cell tolerance and viral persistence [61].

EBV infection is linked to psychiatric conditions like schizophrenia, where patients show abnormal antibody responses and cognitive decline associated with EBV exposure [62]. Similar immune alterations, including decreased reactivity against EBNA-1, are seen in major depressive disorder [63], and a US study showed EBV seropositivity in children with learning disabilities [64].

EBV-induced chronic neuroinflammation, driven by immortalized B cells and enhanced secretion of pro-inflammatory cytokines, accelerates amyloid-beta (Aβ) plaque accumulation and neuronal death, contributing to AD progression [65, 66]. Epidemiological studies also associate EBV infection with increased AD risk, particularly in individuals carrying the APOE-4 allele [44, 67].

Human cytomegalovirus, also known as Human Herpesvirus-5 (HHV-5), is a widespread herpesvirus, with about 50% of U.S. adults under 50 being seropositive. However, global prevalence requires further study [68–71]. Congenital CMV (cCMV) is the most common congenital infection, affecting 0.64% of live births in Europe and the U.S. [71, 72]. CMV establishes lifelong infections through latency, immune evasion, and reactivation. While asymptomatic in immunocompetent individuals, it presents serious risks for the elderly, immunocompromised, critically ill, and neonates, leading to severe complications and higher morbidity and mortality [69, 70, 73–75].

Neuropathological research has identified several CMV-induced CNS pathologies, such as microglial nodular encephalitis and necrotizing encephalitis, with hallmark "owl eye" morphologies found in the basal ganglia, brainstem, and cortex [76–79]. CMV-related inflammation has been linked to Alzheimer's disease pathogenesis by modulating amyloid-beta levels, and may also contribute to conditions like Parkinson's, Huntington's, and ataxia, though further research is needed [80–83].

Kenneson et al. reported a birth prevalence of 0.64% for congenital cytomegalovirus based on data from 27 culture-based universal studies, with 11% of identified cases presenting symptomatic infection [71]. Several studies have highlighted that congenital CMV infection is associated with an increased risk of developmental and neurological complications, including learning disabilities, epilepsy, cerebral palsy, hearing impairment, and visual deficits [84–88]. Additionally,

cCMV has been linked to autism spectrum disorders (ASD), potentially due to maternal immune activation and the transfer of antibodies to the fetus [89–91].

Influenza viruses, typically recognized as respiratory pathogens, can also induce significant neurological and psychiatric complications. Studies on mouse models have shown that the H5N1 strain can invade the CNS, primarily through the olfactory route, causing nonsuppurative encephalitis and vasculitis with brain hemorrhage [92–94]. In contrast, while the H1N1 strain does not invade the brain tissue, it has been linked to a wide range of neurological conditions, including encephalitis, seizures, multiple sclerosis, and Guillain-Barré syndrome during acute phases, as well as chronic conditions like schizophrenia, Parkinson's disease, and dementia [92, 95–98].

Notably, data from large-scale genetic datasets, such as FinnGen and UK Biobank, revealed a connection between influenza infection and an increased risk of developing neurodegenerative diseases like AD, amyotrophic lateral sclerosis (ALS), vascular dementia (VAS), and Parkinson's disease (PD), up to 15 years post-infection [7]. Additionally, several studies, including those from Denmark and Canada, suggest that severe influenza infections can elevate the long-term risk of PD [99, 100]. Vaccination against influenza has been shown to reduce the risk of AD and PD, supporting the protective role of vaccines in neurodegenerative disease prevention [100, 101].

These associations are primarily linked to chronic neuroinflammation. In mouse models, the neurotropic H5N1 strain increased microglial activity in the substantia nigra (SN), with persistent inflammation leading to significant dopaminergic neuron loss by 60 days post-infection, even after the virus became undetectable in the brain [93, 102]. Similarly, the H1N1 strain activates the peripheral immune system, elevating proinflammatory cytokines like TNF-α, IL-1β, and IL-6, causing neuroinflammation, microglial overactivation, and subsequent behavioral and cognitive impairment [11–15]. Chronic microglial overactivation in the SN and hippocampus persisted up to 90 days post-infection without blood–brain barrier disruption or T-cell infiltration [96]. Inflammation, coupled with suppressed neurotrophic factors like BDNF and GDNF, worsens neural plasticity and contributes to cognitive decline [96, 103].

However, studies on younger mice did not show significant morphological changes in the brain [97], suggesting that age might be a key determinant of vulnerability to infection-induced neuroinflammation [11]. Additionally, even in the absence of morphological changes in the SN and the hippocampus, infected individuals might still undergo destructive chronic inflammation through microglial priming [104].

Historical evidence links influenza infections to postencephalitic parkinsonism (PEP) following the encephalitis lethargica pandemic, with neuronal loss and neurofibrillary tangles found in the substantia nigra of affected individuals [105–107]. The frequency of prior influenza infections had been significantly associated with the development of parkinsonian symptoms, suggesting a cumulative inflammatory damage from each infection [107]. Both H5N1 and H1N1 have been shown to trigger persistent accumulation of alpha-synuclein in the CNS, a process potentially predisposing individuals to synucleinopathies such as PD [93, 108]. Alpha-synuclein may act as part of the body's antiviral defense, while antiviral treatments like Oseltamivir phosphate have been shown to prevent its accumulation [108, 109]. Similarly, beta-amyloid, known for its role in Alzheimer's disease, may act as an antiviral agent against H1N1 by inhibiting viral replication and promoting viral aggregation [110]. The structural similarities between the H5N1 hemagglutinin fusion domain and beta-amyloid proteins may help explain the increased risk of AD in individuals with a history of influenza infection [111].

Human Immunodeficiency Virus remains a significant global health challenge, with an estimated 39 million individuals living with HIV/AIDS as of 2023 [112, 113]. Beyond its profound immunological impact, HIV significantly influences the central nervous system. As a neurotropic virus, it gains access to the CNS via cerebrospinal fluid or infected CD4+ T cells that cross the blood–brain barrier. This infiltration is associated with neuropsychiatric complications, including cognitive impairment, HIV-associated neurocognitive disorders (HAND), and depression [114–118].

Chronic HIV-induced inflammation further exacerbates neuronal damage and fosters neurodegeneration. Key viral proteins such as trans-activator of transcription (Tat), viral protein R (Vpr), and envelope glycoprotein GP120 (gp120) play critical roles in this process, primarily by enhancing the secretion of proinflammatory cytokines [16, 17, 119, 120]. Additionally, Tat disrupts microRNA expression, impairing neuronal function, while gp120 induces neuronal death through the CXCR4-PKC signaling pathway [16, 17]. These mechanisms contribute to a range of neurological complications, including peripheral neuropathies, motor dysfunction, and vascular myelopathies [121].

Psychiatric disorders are notably prevalent among people living with HIV (PLWH), with rates of major depressive disorder (MDD) exceeding 35%, generalized anxiety disorder affecting 15%, and bipolar disorder observed in 10.8%—all significantly higher than in the general population [122–125]. Furthermore, PLWH face a 58% greater risk of dementia, including Alzheimer's, vascular, and Parkinson's types, compared to HIV-negative individuals [126, 127]. While highly active antiretroviral therapy (HAART) has reduced CNS lesions and improved neurocognitive outcomes, mild cognitive

impairments persist in some individuals, reflecting the complex interplay between viral mechanisms and brain function [128–131]. These findings underscore the urgent need for adjunctive therapies to enhance neuroprotection and improve cognitive and psychiatric outcomes in PLWH.

Based on the knowledge reviewed above, this study focused on HSV-1, EBV, CMV, HIV, and Influenza viruses H5N1 and H1N1 due to their significant impact on CNS function. These viruses can infect and persist in the CNS, disrupting normal neurological processes through molecular mimicry, immune evasion, and inflammation. Such mimicry involves viral proteins interacting with host proteins, potentially triggering autoimmune responses and neuroinflammation that mirror or exacerbate conditions like Alzheimer's, Parkinson's, and other neurodegenerative diseases. Understanding these interactions helps elucidate the broader impact of viral infections on neurological health. Using a validated computation model, this study aimed to analyze the human protein interactions of the six key viruses, and document the location and molecular functions of the interacted proteins, so as to guide researchers for further in vivo and in vitro targets to study the viral effects on neuropsychiatric functions.

2 Methods

For computational analyses, a technique similar to that introduced by Yapici-Eser et al. [20] was adopted. Initially, the selected viral agents HSV-1, CMV, EBV, HIV, Influenza A virus serotypes H1N1 and H5N1 were studied for their known protein structures. Protein Data Bank (PDB) was used for the composition of protein lists for each virus. Subsequently, all identified viral chains were investigated for their structural availability for human protein interactions using the HMI-Pred web server. Lastly, all human proteins that were highly likely to be interacting with viral proteins were classified based on their molecular and cellular functions, which cellular component they belong to, and the pathways they are involved in, using the PANTHER Classification System version 18 released on 2023-08-01 [132].

2.1 Protein Data Bank

The Protein Data Bank is an open-access database that stores experimentally derived 3D protein structures across a wide range of organisms [133]. In our study, using the advanced search tool, the scientific names of the viral agents were written in the "full text" section and structural specifications were made using the "structure attributes" section. Method of crystallization was specified as "experimental" and further as "x-ray diffraction", and refinement resolution was specified as "≤2.5 Å", to allow for a reliable structural analysis [134–136].

For this study, we focused only on viral proteins from the identified complexes, selecting structure chains that belong exclusively to viruses. If a complex included both viral and non-viral proteins, only the viral chains belonging to the organism of interest were considered for further analysis of viral mimicry. To make this specification, we initially utilized the "source organism taxonomy name" option, followed by retrieving the chains for mimicry analysis through a script that accessed data from the PDBe REST API [137]. The script is available at the following GitHub repository: [https://github.com/ku-cosbi/ViralMimicry].

2.2 Proteins

Viral proteins meeting specified quality standards were extracted from the Protein Data Bank as of February 2024. Specifically, the Herpes Simplex Virus 1 proteome contained 55 proteins and 113 chains stored in the PDB, while Cytomegalovirus exhibited 50 proteins and 81 chains. The Epstein-Barr Virus proteome comprised 61 proteins and 93 chains, while the Influenza H1N1 virus featured 202 proteins and 397 chains. Influenza H5N1 virus had 71 proteins and 210 chains, and the combined Human Immunodeficiency Virus 1 & 2 proteome encompassed 1734 proteins and 3459 chains [138]. Statistics provided here exclusively consider viral chains as detailed in Sect. 2.1. The list of PDB IDs of proteins found for each virus is provided in the following GitHub repository: https://github.com/ku-cosbi/ViralMimicry/ under Viral_Chains section.

2.3 HMI-Pred

HMI-PRED is a web server designed to predict protein–protein interactions (PPIs) between human and microbial species, based on structural availability and affinity. It identifies potential interactions by analyzing microbial proteins with

surface patches structurally resembling one face of the template interface, along with evolutionarily conserved "hot spots", facilitating interaction with complementary sites on host proteins. The algorithm utilizes a template interface dataset containing structurally available endogenous and exogenous human PPIs and microbial target proteins. The latest version utilized in this study had access to all PPIs uploaded to the PDB as of January 3rd, 2019 as the templated interface dataset [139]. In a stepwise approach, HMI-Pred initially extracts the surface of microbial target proteins, followed by the structural matching of the target protein surface with the constituent partners of the template interfaces. Finally, it performs local flexible refinement of predicted interactions and evaluates their likelihood using Rosetta scoring [140] based on energetic favorability. This refinement step is crucial because structurally complementary host-microbe interaction (HMI) complexes may lack electrochemical compatibility, meaning that even if two proteins fit together well, they may not bind effectively due to unfavorable chemical interactions. For a predicted interaction to be considered energetically favorable, it must lower the system's energy upon binding. Specifically, complexes with interface scores (I_sc) below − 5 and total energy scores less than zero are classified as energetically favorable, indicating a higher likelihood of biologically relevant interactions. While Rosetta is a well-established method for scoring protein–protein interactions, it has certain limitations [141, 142]. Its total energy score can be noisy due to structural variations distant from the binding interface, caused by the stochastic nature of the optimization process and the system's high degree of flexibility. Relying solely on the interface energy score (I_sc) to reduce this noise is not physically accurate and can introduce artifacts. Over-optimization at the interface may distort individual protein structures, such as causing loop regions to adopt unrealistic conformations. Additionally, I_sc lacks physical units and does not represent true binding free energy, offering only a qualitative assessment of interaction favorability. Despite limitations, this criterion helps filter out false positives, making predicted HMIs more biologically relevant. A schematic representation of the HMI-PRED algorithm can be found in Fig. 1 [23, 143, 144]. HMI-PRED is available at https://interactome.ku.edu.tr/hmi/index.php.

Using the HMI-Pred webpage, we inputted the viral protein PDB IDs with chain specifications into the designated section. The default template was applied for target human protein structures, and the structural alignments were performed

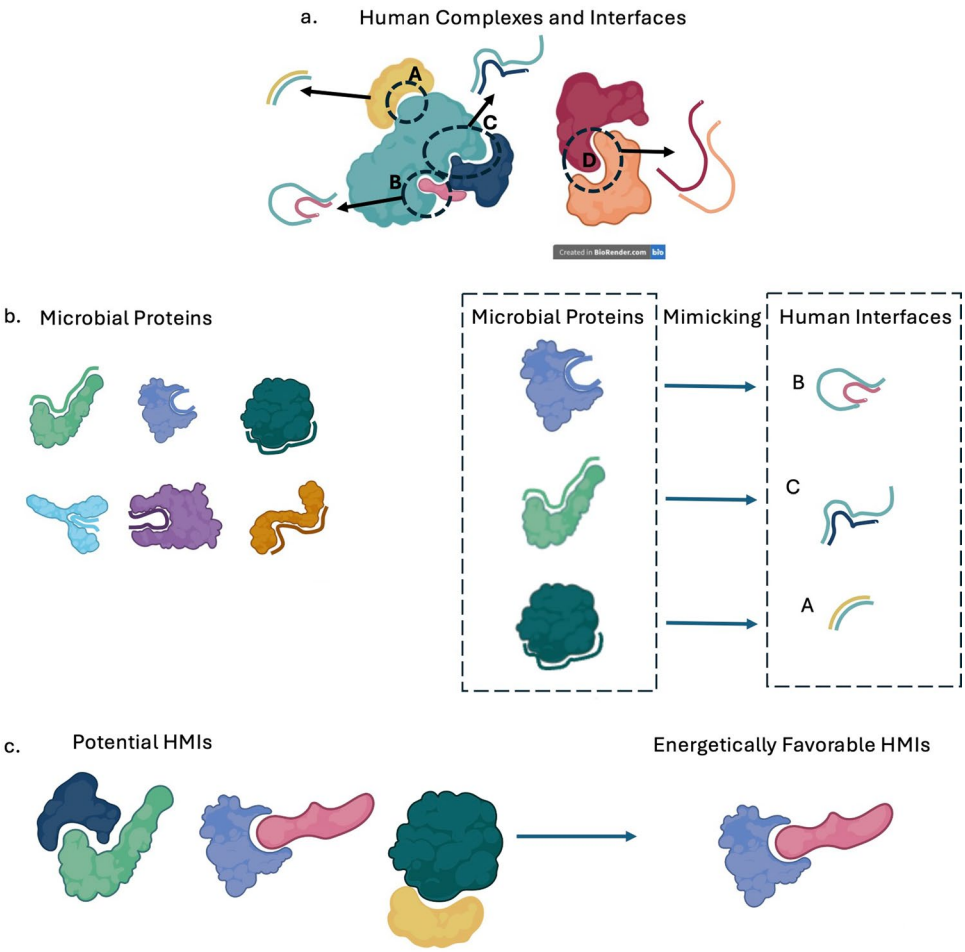


Fig. 1 A schematic representation of HMI-PRED (**a**) Human complexes are retrieved from the Protein Data Bank, and interfaces are extracted to create HMI template dataset (**b**) Given an input microbial structure, surface of the microbial protein is extracted and searched against the human interfaces in the HMI database. If the surface structurally matches to one side of the template human interface, the microbial protein is considered to be a candidate for interaction with the other side of the template (**c**) Potential HMIs are systematically evaluated for their energetic favorability; interactions having a Rosetta interface score (I_sc) below − 5 and total energy score below zero are considered to be energetically favorable, and reported as potential host-microbe interaction

using TM-align algorithm [145]. Subsequently, we downloaded the result files and organized them in a shared folder for each viral agent. Upon completion of the result gathering process for each chain, the contents within these folders were converted into Microsoft Excel Worksheet® format. We filtered our results by eliminating synthetic constructs and chimeric structures. The codes utilized for pre and post-analysis required for HMI-PRED workflow as well as input and output files can be found in the following repository: https://github.com/ku-cosbi/ViralMimicry/. The final dataset includes energetically favorable protein–protein interactions between viral antigens and human proteins, along with additional metrics assessing the likelihood of interaction. These metrics include the number of aligned residues, the length of the template interface, percent match score, and the probability of representing a biological interface (as detailed in Online Resource 1). Additionally, a separate list of interacting human proteins for each viral agent was extracted from this worksheet for utilization in subsequent steps.

2.4 Classification

The PANTHER (Protein ANalysis THrough Evolutionary Relationships) Classification System categorizes proteins according to their gene families, facilitating scientific investigations into the molecular bases underlying biological processes. It offers insights into the proteins' family and protein classes, their functional roles, and the cellular pathways they participate in, leveraging gene ontology principles and phylogenetic gene family trees [132, 146, 147]. The PANTHER system can be reached at https://www.pantherdb.org.

In this part of the study, we performed six independent analyses using the PANTHER platform. For each viral agent, we uploaded the corresponding list of interacting human protein IDs, designating the list type as ID lists, and specifying *Homo sapiens* as the organism. The resulting data were visualized through graphical charts. Functional classifications including molecular functions, cellular components, and pathway analyses were conducted and subsequently exported for further interpretation.

To identify human proteins that consistently interact with proteins from various viral agents, we utilized Microsoft Excel® to create a pivot table, aggregating the interacting protein lists for each virus. The proteins that interacted with each virus for at least one time were extracted (n = 38). These proteins were then collectively analyzed via the PANTHER search engine using the 'functional classification viewed in gene list' feature, which retrieved the UniProt IDs for 37 of the proteins. The one remaining protein, which could not be identified automatically, was manually searched in the UniProt database and added to the list. The functions of these 38 proteins were subsequently cataloged using UniProt, followed by a targeted literature review to more thoroughly explore their associations with neurological disorders.

For a detailed examination of mimicry in neurons and synapses, we utilized the PANTHER "cellular component" classification tool. Proteins categorized under the "cellular anatomical entity" were further analyzed, with a particular focus on those localized in neuron-specific regions such as the "distal axon", "presynapse", "postsynapse", "somatodendritic compartment", and "cell projection". Proteins that consistently appeared in the analyses of more than four viral agents were flagged for further investigation regarding their potential associations with CNS dysfunction.

3 Results

3.1 Human protein interactions of each virus

The majority of viral proteins revealed energetically favorable interactions with human proteins across different cellular sites. Table 1 presents the total number of predicted protein–protein interactions and the ratios of viral proteins that mimic human proteins relative to the total number of viral proteins. Specifically, 95% of all HSV-1 proteins in the PDB database interacted with 467 human proteins, resulting in 2892 human-viral protein interaction pairs. For EBV, 48% of its proteins showed predicted interactions with 495 distinct human proteins, leading to a total of 2240 interactions. Similarly, 46% of CMV proteins interacted with 201 human proteins, resulting in 514 interaction pairs. In the case of influenza viruses, 47% of IAV H1N1 proteins interacted with 565 human proteins, forming 3331 distinct interaction pairs. Additionally, 75% of IAV H5N1 proteins exhibited energetically favorable interactions with 539 human proteins, totaling 3533 interactions. Finally, 66% of all HIV-1 and HIV-2 proteins combined revealed interactions with 1420 different human proteins, culminating in a total of 62425 interactions. A comprehensive list of these interactions, including the names of human and viral proteins, PDB IDs, mimicked interactions, and interaction Rosetta scores, can be found in Online Resource 1.

Table 1 Total number of energetically favorable interactions between viral proteins and human proteins

Viral Agent	Number of interactions (n)	Number of human proteins interacting (n)	Percentage of viral proteins interacting (%)[a]
HSV-1	2892	467	95
EBV	2240	495	48
CMV	514	201	46
IAV H1N1	3331	565	47
IAV H5N1	3533	539	75
HIV 1&2	62425	1420	66

[a] Percentage of viral proteins interacting with human proteins over all viral proteins extracted from the PDB
HSV: Herpes Simplex Virus, EBV: Epstein-Barr Virus, CMV: Cytomegalovirus, IAV: Influenza A Virus, HIV: Human Immunodeficiency Virus

The human proteins interacting with the viral agents have been categorized based on their molecular functions, cellular localizations, and the functional pathways in which they participate. In the case of HSV-1, 49.89% of the interacting human proteins are found in organelles, 39.19% in the cytoplasm, and 20.56% in the cell membrane. In terms of molecular functions, 39.40% of the proteins are involved in binding, 21.62% in catalysis, and 8.35% in transcription regulation. Additionally, 8 proteins are linked to ATP-dependent processes, and 2 proteins are involved in antioxidant activity. Of those classified by functional pathways, 15.24% belong to the CCKR signaling pathway, 10.98% to the gonadotropin-releasing hormone receptor pathway, and 10.37% to both the apoptosis signaling and Parkinson's disease pathways. Moreover, 9.15% of proteins are associated with angiogenesis, PDGF signaling, inflammation mediated by chemokines, cytokine signaling, and Huntington's disease pathways. Online Resource 2 provides a detailed overview.

For CMV, 37.31% of the interacting proteins are located in organelles, 29.35% in the cytoplasm, and 18.41% in the cell membrane. In terms of functionality, 39.80% are involved in binding, 22.89% in catalysis, and 7.96% in molecular transducer activity, with 3 proteins related to ATP-dependent processes. Classified by functional pathways, 15.71% are involved in the gonadotropin-releasing hormone receptor pathway, 14.29% in integrin signaling, and 12.86% in both the CCKR signaling pathway and inflammation mediated by chemokines and cytokines. Additionally, 10% of proteins are implicated in Huntington's disease, Parkinson's disease, EGF receptor signaling, and PDGF signaling pathways, with 8.57% related to angiogenesis. Details are available in Online Resource 3.

For EBV, 47.27% of the interacting proteins are localized in organelles, 35.76% in the cytoplasm, and 22.63% in the cell membrane. Functionally, 41.41% participate in binding, 16.57% in catalytic processes, and 8.08% in transcription regulation. Moreover, 14 proteins are associated with ATP-dependent processes, while 2 are linked to antioxidant activity. Of the proteins classified by functional pathways, 14.72% are part of the CCKR signaling map, 13.50% are involved in apoptosis signaling, 10.43% in the gonadotropin-releasing hormone receptor pathway, and 9.20% in chemokine-mediated inflammation and cytokine signaling. Additionally, 8.59% are linked to Huntington's disease, and 6.75% to angiogenesis. A detailed list can be found in Online Resource 4.

For the Influenza A Virus H5N1 strain, 52.13% of interacting proteins are located in organelles, 37.48% in the cytoplasm, and 22.26% in the cell membrane. Functionally, 41.19% are involved in binding, 25.60% in catalysis, and 7.79% in transcription regulation, with 12 proteins linked to ATP-dependent processes and 3 associated with antioxidant activity. Of the proteins classified by functional pathways, 16.30% are part of the CCKR signaling map, 14.13% in the gonadotropin-releasing hormone receptor pathway, 11.96% in apoptosis signaling, and 10.33% in chemokine-mediated inflammation and Huntington's disease pathways. Furthermore, 9.24% are linked to both Parkinson's disease and angiogenesis. Full details are available in Online Resource 5.

For the Influenza A Virus H1N1 strain, 50.80% of the interacting proteins are found in organelles, 36.81% in the cytoplasm, and 20.85% in the cell membrane. Functionally, 40.35% participate in binding, 22.65% in catalysis, and 8.32% in transcription regulation, with 13 proteins linked to ATP-dependent processes and 4 associated with antioxidant functions. Among the classified pathways, 14.44% are involved in the CCKR signaling pathway, 13.33% in the gonadotropin-releasing hormone receptor pathway, 12.22% in apoptosis signaling, 10% in both Parkinson's disease and chemokine-mediated inflammation, and 8.89% in angiogenesis and PDGF signaling. Additionally, 7.78% are involved in Huntington's disease. Online Resource 6 contains detailed information.

Finally, for HIV 1&2, 42.75% of interacting proteins are located in organelles, 33.03% in the cytoplasm, and 19.58% in the cell membrane. Functionally, 38.45% are involved in binding, 24.51% in catalytic activities, and 7.18% in transcription regulation, with 32 proteins linked to ATP-dependent processes and 5 associated with antioxidant functions. Among functional pathways, 9.83% are part of the CCKR signaling map, 9.41% are involved in chemokine-mediated inflammation, 8.79% in the gonadotropin-releasing hormone receptor pathway, 7.53% in both angiogenesis and integrin signaling, and 7.11% in Huntington's disease and apoptosis signaling. Furthermore, 5.86% are associated with Parkinson's disease. Online Resource 7 provides detailed information. Additionally, the interaction times of each interacting viral protein are provided in detail for each viral agent in Online Resource 8.

An overview of the affected functional pathways relevant to CNS dysfunction is presented in Fig. 2.

3.2 Shared interactions of six neurotropic viruses

In total, 38 human proteins were found to consistently interact with proteins of all six viruses. Table 2 presents a detailed list of these shared interacting proteins, including their PDB IDs, names, and a brief overview of their nervous system functions.

Additionally, proteins that were interacting with all six viral agents were grouped together for analysis. Of these, 50% are located in organelles, 42.11% in the cytoplasm, and 23.68% in the cell membrane. In terms of molecular function, 63.16% are involved in binding, 15.79% in catalysis, and 5.26% in transcription regulation. When classified by pathways, 28.57% are linked to angiogenesis, the CCKR signaling map, and the gonadotropin-releasing hormone receptor pathway. Another 21.43% are associated with B cell activation, inflammation mediated by chemokines, integrin signaling, PDGF signaling, and T cell activation. Other commonly affected pathways include Huntington's disease (14.29%), VEGF

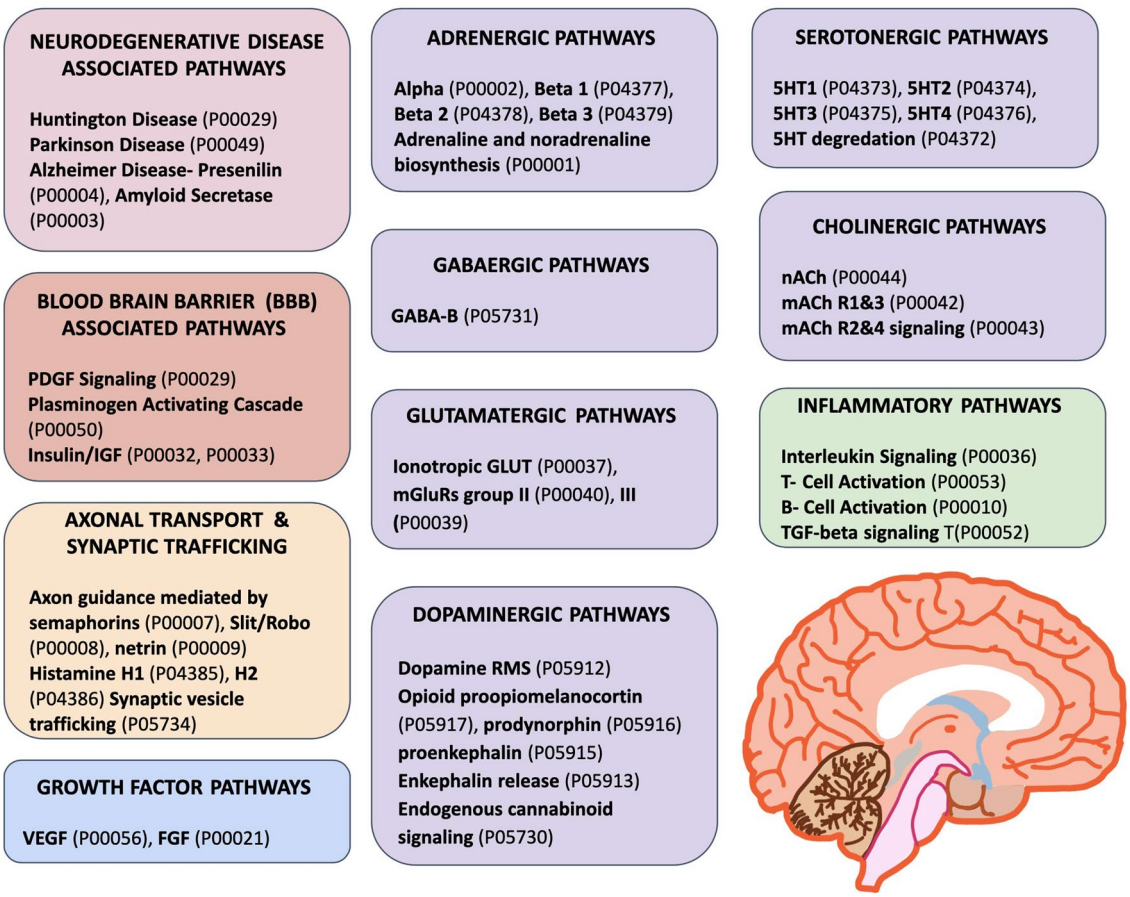


Fig. 2 A summary of the affected functional pathways possibly linked to CNS dysfunction (*mGluRs* metabotropic glutamate receptors, *GLUT* glutamate, *nACh* nicotinic acetylcholine, *mACh* muscarinic acetylcholine)

Table 2 Names and functions of proteins consistently mimicked by six key viruses

PDB ID	Protein name	Function
AF10	Protein AF-10	The AF-10 protein is involved in chromatin remodeling and transcriptional regulation through its leucine zipper domain, which interacts with GAS41, a protein linked to glioblastoma. In leukemia, AF-10 forms chimeric fusion proteins, such as MLL/AF10 and CALM*/AF10, that retain the leucine zipper motif, potentially disrupting normal gene regulation by interacting with chromatin remodeling complexes [148, 149]
BRMS1	Breast cancer metastasis suppressor 1	A transcriptional repressor that encourages the deacetylation of certain histone proteins by suppressing NF-kappa-B pathway activity. It contributes to the inhibition of metastasis by encouraging non-adherent cell death [150]
CALM2	Calmodulin-2	Calmodulin II is a calcium-binding protein that is essential for regulating various cellular processes influenced by the changes in intracellular calcium levels. Its functions include the modulation of neurotransmitter production and synaptic activity, and it plays a critical role in synaptic plasticity and brain development [151]
CCM2	Cerebral cavernous malformations 2	CCM2, part of the CCM signaling complex, is essential for maintaining BBB integrity. Malfunctioning of this protein can disrupt intercellular junctions, increase vascular permeability, and elevate the risk of hemorrhagic stroke, alongside promoting neuroinflammation [152, 153]
CHM4B	Charged multivesicular body protein 4b	A vital component of the ESCRT-III complex involved in membrane remodeling and scission processes. It plays a crucial part in lens development through interacting with gap junction proteins Cx46 and Cx50, which are essential for lens fiber cell differentiation and communication [154]
CSF3	Granulocyte colony-stimulating factor (G-CSF)	G-CSF has neuroprotective properties and regulates the formation of blood cells in the bone marrow. With potential therapeutic uses in neurodegenerative illnesses, it strengthens the blood–brain barrier and improves motor function to enhance neurological recovery. Through anti-apoptotic mechanisms, it improves cognitive performance [155]
CSN5	COP9 signalosome complex subunit 5	The COP9 signalosome subunit CSN5/JAB1 is crucial for neurodevelopment, influencing neuronal differentiation, synaptic morphogenesis, and myelination. It interacts with transcription factors and cell cycle regulators to support neuronal growth and function [156]
CTIP	DNA endonuclease RBBP8 (CtIP)	An essential endonuclease for homologous recombination-mediated double-strand break repair in particular. It controls checkpoints in the cell cycle and is involved in chromosomal translocations that occur during immunological responses [157]
CTNB1	Catenin beta-1	An important part of the Wnt signaling pathway, ß-Catenin is crucial for synapse assembly and plasticity, binding to cadherins at synaptic junctions to regulate dendritic spine dynamics and memory formation [158]
DPY30	Protein dpy-30 homolog	Through H3K4 methylation, Dpy30 is necessary for the proliferation and development of neural stem cells. Due to epigenetic alterations, loss of Dpy30 causes anatomical abnormalities in the brain as well as a decrease in the populations of neural stem cells. Dpy30 is important for neurodevelopment and has been linked to illnesses such as schizophrenia [159]
EMAL4	Echinoderm microtubule associated protein-like 4	Essential for the correct attachment of kinetochores during mitosis as well as the development and stability of microtubules. It encourages the recruitment of proteins necessary for the process of mitosis [160]
FRIL	Ferritin light chain	Stores iron in a non-toxic, readily available form, playing a crucial role in iron homeostasis. It also mediates iron uptake in developing kidney cells and aids in the autophagic degradation of iron [161]
IL2	Interleukin-2	IL-2 is essential for immune regulation, primarily by activating regulatory T cells, which help manage inflammation, and emerging evidence links IL-2 to neurodegenerative mechanisms [162], schizophrenia [163, 164], depression, and bipolar disorder [165]
INADL	InaD-like protein	Through its interactions with tight junction proteins like CRB3, INADL, it contributes to the preservation of tight junction integrity. It controls other important proteins' locations at tight junctions, including ZO1 and ZO3, which is necessary for healthy cell polarity and junction formation [166, 167]
INCE	Inner centromere protein	As a component of the chromosomal passenger complex, it is a crucial regulator of mitosis that maintains appropriate chromosomal alignment and segregation during cell division. It regulates kinetochore localization and kinase activation [168]

Table 2 (continued)

PDB ID	Protein name	Function
INS	Insulin	Insulin is vital for brain health and neuroplasticity throughout development and adulthood [169]. Disruptions in insulin signaling are linked to neuroinflammation, BBB compromise, cognitive decline, and neurodegeneration [170–172]
JUN	Transcription factor Jun	A transcription factor that is critical for multiple cellular processes, including cell cycle regulation, apoptosis, and neuronal differentiation. It plays a key role in neurodevelopment and synaptic plasticity [173]
MDM2	E3 ubiquitin-protein ligase	MDM2 regulates the degradation of p53, mitochondrial respiration and oxidative stress. Its proper functioning in neurons is essential to prevent excessive cell death and maintain neuronal health [174, 175]
MSL1	Male-specific lethal 1 homolog	A part of the MSL complex, acetylating histone H4 at Lys-16 for maintaining chromosome stability and regulating gene expression. It plays a role in modulating gene expression associated with the X chromosome and promotes histone ubiquitination, influencing transcription [176]
NEMO	NF-kappa-B essential modulator	NF-kappa-B essential modulator, also known as IKKγ, is a subunit of the IκB kinase (IKK) complex that plays a role in the activation of the NF-κB signaling pathway. It facilitates the phosphorylation and degradation of IκB proteins, allowing the release of NF-κB dimers, such as p65/p50, which then translocate to the nucleus to regulate gene expression involved in immune responses, cell survival, and inflammation [177]
NKG2D	NKG2-D type II integral membrane protein	An immunological receptor that detects and eliminates abnormal cells, contributing to neuroinflammation. It is essential in the inflammatory pathways of linking immune dysregulation and disease progression by influencing natural killer cell activity and neurodegeneration [178]
NUP58	Nucleoporin p58/p45	Facilitates trafficking between the cytoplasm and nucleus by regulating the movement of molecules across the nuclear membrane. It forms part of the nuclear pore complex [179]
PAXI	Paxillin	Paxillin is a focal adhesion protein that interacts with signaling pathways involving focal adhesion kinase (FAK) and Rho GTPases, regulating cytoskeletal dynamics, cell adhesion, and immune cell migration [180–182]. It significantly influences neuronal development and synaptic formation, and plays a key role in leukocyte transmigration into the central nervous system [181]
PGFRB	Platelet-derived growth factor receptor beta	PDGFR-ß is crucial for neural cell development and function, playing key roles in neuroprotection, synaptic plasticity and BBB integrity. It protects neurons from excitotoxicity and oxidative stress, modulates synaptic function, and supports cell survival [183]
PLMN	Plasminogen	Plasminogen plays a dual role in neuronal processes, aiding neuronal development and synaptic formation through the degradation of extracellular matrix proteoglycans via microglial activation, while also mediating neurodegeneration in response to excitotoxicity [184]. It is also essential for maintaining blood–brain barrier (BBB) integrity [185]
RABX5	Rab5 GDP/GTP exchange factor (RAP1)	Acting as a Rab effector, connects endosome recycling with endocytic membrane fusion. It aids in membrane trafficking by acting as a ubiquitin ligase [186]
RAC1	Ras-related C3 botulinum toxin substrate 1	Rac1, a Rho family GTPase, is vital for synaptic plasticity, influencing dendritic spine morphology and facilitating new neural circuit development that is critical for memory formation [187]
RFIP2	Rab11 family-interacting protein 2	Controls vesicle transport from endosomes to the plasma membrane and contributes to insulin granule exocytosis and receptor-mediated endocytosis. It plays a role in phagocytosis and the regulation of cell polarity [188]
SHRPN	Sharpin	Part of the linear ubiquitin chain assembly complex (LUBAC), modulating NF-κB signaling. It protects against cell death and inflammation by attaching linear polyubiquitin chains to proteins [189]
SKA2	Spindle and kinetochore associated protein 2	As part of the SKA1 complex, it is crucial for accurate chromosome segregation during mitosis. It interacts with microtubules, facilitating chromosome movement during cell division, ensuring the proper timing of anaphase onset, and maintaining correct kinetochore-microtubule attachments [190]

Table 2 (continued)

PDB ID	Protein name	Function
STIM1	Stromal interaction molecule 1	A calcium sensor for modulating the activity of calcium channels located in the plasma membrane. It plays a role in store-operated calcium entry (SOCE) and controls calcium signaling in different functions, such as enamel formation and cellular response to calcium depletion [191]
TLR3	Toll-like receptor 3	A component of the immune system detects double-stranded RNA, which is usually an indicator of viral infection. This triggers inflammatory responses via NF-κ-B and other signaling pathways, aiding in pathogen defense by promoting the release of type I interferons (IFNs), proinflammatory cytokines, and chemokines [192]
TYOBP	TYRO protein tyrosine kinase-binding protein (TYROBP)	Facilitates the binding activity of signaling receptors and participates in various processes, such as myeloid cell activation in immune response, cytokine production regulation, and lymphocyte activation control. It functions upstream of or within the differentiation of osteoclasts and the regulation of osteoclast development [193]
UBAP1	Ubiquitin-associated protein 1 (UBAP-1)	A component of the ESCRT-I complex that oversees vesicular trafficking and directs ubiquitinated proteins into multivesicular bodies for degradation. It contributes to the breakdown of cell-surface proteins [194]
UBB	Polyubiquitin-B	Gene products that produce ubiquitin, a small regulatory protein, play a key role in numerous cellular processes, especially in protein degradation through the ubiquitin–proteasome system (UPS) [195, 196]
UBC	Polyubiquitin-C	Gene products that produce ubiquitin, a small regulatory protein, play a key role in numerous cellular processes, especially in protein degradation through the ubiquitin–proteasome system (UPS) [195, 196]
VIME	Vimentin	A type III intermediate filament protein broadly expressed in mesenchymal cells, essential for preserving cell integrity, structure, and stability. It aids in the stabilization of collagen mRNAs [197]
VINC	Vinculin	A cytoplasmic protein that binds to actin, playing a role in cell adhesion and communication between cells and the extracellular matrix. It helps regulate mechanotransduction and ensures the maintenance of cellular integrity [198]

BBB Blood Brain Barrier, *CALM** Clathrin Assembly Lymphoid Myeloid, *COP9* Constitutive photomorphogenesis 9, *CRB* Crumbs Cell Polarity Complex Component, *CSN* COP9 signalosome, *DPY30* dpy-30 histone methyltransferase complex regulatory subunit, *ESCRT* Endosomal Sorting Complexes Required for Transport, *GAS* Glioma Amplified Sequence, *H3K4* Histone H3 lysine K4, *InaD* inactivation no afterpotential D, *JAB1* c-Jun activation domain binding protein, *ZO* Zonula Occludens

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signaling (14.29%), Alzheimer's disease-presenilin (7.14%), apoptosis signaling (7.14%), and oxidative stress response (7.14%). A detailed breakdown of these pathways, molecular functions, and cellular localizations can be found in Table 3.

In the context of mimicry in neuronal cells, the following human proteins (n = 16) were identified for their consistent interactions with more than four key viruses: CDC42, CYFP1, EPHA8, GSK3B, USH1C, HOME3, HIP-1, MERL, NPTN, FAK2, RAC1, RB11A, RAB8A, STRN3, TY3H, and VIME. Notably, proteins such as Homer protein analog homolog 3 (HOME3), Huntingtin-interacting protein 1 (HIP-1), Ras-related C3 botulinum toxin substrate 1 (RAC1), tyrosine 3 monooxygenase (TY3H), and vimentin (VIME) were highlighted for their well-documented roles in neuronal functions. An overview of the mean match scores for these proteins in viral interactions, along with their significance in the nervous system, is provided in Table 4.

4 Discussion

4.1 Viral proteins highly interact with human proteins

In this study, we explored the human protein interactions of the six key viruses that are associated with various neuropsychiatric disorders. Our findings revealed that virus proteins interact with a significant number of human proteins. Notably, some human protein interactions were shared across all six viruses, suggesting the involvement of common pathways. In addition, we found that viral proteins engage with multiple pathways at various cellular locations. Understanding the timing, mechanisms, and conditions under which these interactions occur is crucial for elucidating their role in the neuropsychiatric effects associated with these viral agents. Further in vivo and in vitro studies should examine these interactions to establish direct associations and uncover the underlying mechanisms.

Over the centuries, viruses have co-evolved with their hosts to acquire traits that increase their adaptability to the host. By these traits, viruses can obtain faster replication times, longer infectious periods, and strategies to evade the host immune system [206]. Some viruses mimic protein structures of their host. Mimicked proteins are defined as a safeguard to viruses by reducing the number of pathogenic epitopes available for recognition by the host's immune system. The low epitope recognition interferes with the host's immune response, making it more difficult to identify and combat the viral invaders [207]. However, the mimicry may not always confer a net advantage to the virus. Thus, to adopt mimicry, the virus must pay a cost, such as longer replication times due to longer protein sequences or loss of protein function due to mutations acquired for mimicry. On the other hand, short linear mimicry at the size of an immune epitope may be able to offer substantial evasion of the adaptive immune system while minimizing unfavorable effects to viral protein function or length [208]. Our study reveals that among the interacting proteins, there are multiple proteins that take role in important human cellular functions and pathways. It needs further exploration to study if these interactions are short-time interactions or if they are used for latency, by in vivo and in vitro assessments. Studies may involve viral-infected cell cultures to analyze associated protein changes, alongside animal models that explore the impact of the infectome on cellular and neuronal functions in relation to behavioral outcomes.

Our study utilized a computational approach to analyze our hypothesis, which was under some limitations. HMI-PRED, an interface mimicry-based prediction workflow, falls within the category of structure-based protein–protein interaction (PPI) prediction methods, specifically modeling pairwise interactions. While PPI prediction methods that incorporate structural information offer a significant advantage by providing 3D details, a key limitation of such methods is the availability of protein structural data, which remains incomplete due to the limited availability of experimentally resolved 3D structures. This gap becomes more pronounced when viral proteins are considered, as many pathogenic proteins still lack crystal structure. Therefore, HMI-PRED algorithm with its reliance on protein structural data may not identify all expected interactions between viral and human proteins and our results may not cover all interactions. Consequently, the number of real time interactions may be higher than reported in this analysis. Furthermore, the template set used by HMI-PRED has not been updated since 2019, potentially overlooking newly resolved structural interfaces. Despite these challenges, research from over a decade ago has shown that the current structural data adequately covers most biologically relevant structural space for PPIs [145]. HMI-PRED, by employing a template-based approach, capitalizes on recurring structural scaffolds, enabling the exploration of evolutionarily conserved interaction modes [143]. Another limitation stems from the usage of PANTHER classification system to document the cellular localizations and functions of the found human proteins. Some proteins from our interaction lists were not classified by PANTHER and we also needed to carry out a manual approach to dissect the possible interactome pathways. Some viral proteins were observed to interact with multiple sites on a single human protein, potentially indicating a more significant functional impact of

Table 3 Cellular localizations, molecular functions, and pathways of the 38 human proteins commonly interacting with all viruses

Cellular Localizations

	(n)	(%)
intracellular anatomical structure (GO:0005622)	21	55,26
organelle (GO:0043226)	19	50,00
cytoplasm (GO:0005737)	16	42,11
membrane (GO:0016020)	9	23,68
cell periphery (GO:0071944)	9	23,68
endomembrane system (GO:0012505)	5	13,16
cell junction (GO:0030054)	4	10,53
extracellular space (GO:0005615)	3	7,89
extracellular region (GO:0005576)	3	7,89
supramolecular complex (GO:0099080)	2	5,26
cytosol (GO:0005829)	2	5,26
cell projection (GO:0042995)	2	5,26
cell surface (GO:0009986)	1	2,63
apical part of cell (GO:0045177)	1	2,63
side of membrane (GO:0098552)	1	2,63
somatodendritic compartment (GO:0036477)	1	2,63
envelope (GO:0031975)	1	2,63
extrinsic component of membrane (GO:0019898)	1	2,63
membrane-enclosed lumen (GO:0031974)	1	2,63
microtubule organizing center (GO:0005815)	1	2,63
postsynapse (GO:0098794)	1	2,63
chromosomal region (GO:0098687)	1	2,63
nucleoplasm (GO:0005654)	1	2,63
external encapsulating structure (GO:0030312)	1	2,63

Molecular Functions

	(n)	(%)
Binding (GO:0005488)	24	63,16
Catalytic activity (GO:0003824)	6	15,79
Transcription regulator activity (GO:0140110)	2	5,26
Molecular transducer activity (GO:0060089)	2	5,26
Structural molecule activity (GO:0005198)	2	5,26
Molecular function regulator activity (GO:0098772)	2	5,26
Molecular adaptor activity (GO:0060090)	1	2,63

Pathways

	(n)	($\%_c$)
Angiogenesis (P00005)	4	28,57
CCKR signaling map (P06959)	4	28,57
Gonadotropin-releasing hormone receptor pathway (P06664)	4	28,57
B cell activation (P00010)	3	21,43
Inflammation mediated by chemokine and cytokine signaling pathway (P00031)	3	21,43
Integrin signalling pathway (P00034)	3	21,43
PDGF signaling pathway (P00047)	3	21,43
T cell activation (P00053)	3	21,43
EGF receptor signaling pathway (P00018)	2	14,29
Huntington disease (P00029)	2	14,29
Insulin/IGF pathway-protein kinase B signaling cascade (P00033)	2	14,29
p53 pathway feedback loops 2 (P04398)	2	14,29
Ras Pathway (P04393)	2	14,29
Toll receptor signaling pathway (P00054)	2	14,29
VEGF signaling pathway (P00056)	2	14,29
Alzheimer disease-presenilin pathway (P00004)	1	7,14
Apoptosis signaling pathway (P00006)	1	7,14
Axon guidance mediated by netrin (P00009)	1	7,14
Axon guidance mediated by semaphorins (P00007)	1	7,14
Axon guidance mediated by Slit/Robo (P00008)	1	7,14
Blood coagulation (P00011)	1	7,14
Cadherin signaling pathway (P00012)	1	7,14
Cytoskeletal regulation by Rho GTPase (P00016)	1	7,14
FAS signaling pathway (P00020)	1	7,14
FGF signaling pathway (P00021)	1	7,14
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway (P00026)	1	7,14
Heterotrimeric G-protein signaling pathway-rod outer segment phototransduction (P00028)	1	7,14
Insulin/IGF pathway-mitogen activated protein kinase kinase/MAP kinase cascade (P00032)	1	7,14
Interleukin signaling pathway (P00036)	1	7,14
Oxidative stress response (P00046)	1	7,14
p38 MAPK pathway (P05918)	1	7,14
p53 pathway (P00059)	1	7,14
P53 pathway feedback loops 1 (P04392)	1	7,14
Plasminogen activating cascade (P00050)	1	7,14
TGF-beta signaling pathway (P00052)	1	7,14
Ubiquitin proteasome pathway (P00060)	1	7,14
Wnt signaling pathway (P00057)	1	7,14

Note n: number of human proteins, %: percentage of proteins among all 38 proteins, $\%_c$: percentage of proteins among proteins that could be classified using the PANTHER system

Table 4 Human proteins that commonly interact with the viral agents in neural cells and their clinical relevance

Protein name	Mean match score (%)[a]	Clinical associations
Homer protein analog homolog 3 (HOME3)	87.46	Cerebellar disease (subacute degeneration-cerebellitis), Cognitive dysfunction [199], Regulation of glutamate transmission within the limbo-corticostriatal circuit [200]
Huntingtin-interacting protein 1 (HIP1)	72.73	Regulates apoptosis and gene expression implicated in the Huntington's Disease [201]
Ras-related C3 botulinum toxin substrate 1 (RAC1)	77.11	Axonal regeneration in the injured brain, stimulation of neuronal intrinsic growth and counteraction against the growth inhibitory signaling [202] Prevents synaptic degeneration, neuronal number loss and memory impairment [203]
Tyrosine 3 monooxygenase (TY3H)	95.67	Catalysator of the initial and rate-limiting step of catecholamine biosynthesis, when downregulated, dopamine deficiency leads to impaired motor control & operant learning during postnatal development Point mutations that downregulate TY3H can lead to l-DOPA-responsive dystonia, parkinsonism in infancy, and progressive encephalopathy [204]
Vimentin (VIME)	76.32	Regulates axonal regrowth, myelination, apoptosis, and neuroinflammation [205]

[a]The mean of %match scores for all documented interactions of the protein, as provided in Online Resource 1

these interactions. However, in this study, we primarily focused on identifying at least one interaction between human and viral proteins. We provide the list of all interactions in the supplementary files for the interested readers to use the data for their further research.

4.2 Viral proteins interact with human proteins linked to key cellular pathways

Among the many pathways listed for the interacted proteins, inflammatory pathways take the lead. Psychiatric disorders are also known to be related to abnormal inflammation and inflammatory cytokine levels [209, 210], however the bidirectional relationship between these is less known. The link between infections and psychiatric disorders is also suggested to be mediated through prolonged low-level chronic inflammatory responses, as well as autoimmunity triggered by the infections [211]. Altered B and T cell lymphocyte responses are a new area of research for the development of neuropsychiatric disorders. The virus triggered alterations in human lymphocytes may produce a peripheral vulnerability factor that affects the nervous system and produce a vulnerability for neuropsychiatric disorders.

Another significant pathway associated with viral infections is the neurotransmitter release machinery. Many of the viruses interact with synaptosomal associated protein-25 (SNP-25), VAMP2 like proteins that play an active role in the vesicle formation and release [20]. SNP-25 is interacting with all viruses except for CMV, and synaptosomal associated protein-29 (SNP-29) is interacting with all viruses except for CMV and IAV H5N1. SNAP-25 is a part of SNARE complex responsible for vesicle release [212, 213], and it has been associated with many disorders such as schizophrenia, epilepsy and attention-deficit hyperactivity disorder. Gain or loss of function, in addition to slowing of the processes related to these proteins, would affect the release machinery and thereby cortical excitability [214] and synaptic stability [215]. These interactions may be important especially during the prenatal period where cortical development and synapse formation are being generated.

Other than the general synaptic mechanisms, the six viruses were found to be interacting with the serotonin, beta adrenergic, glutamatergic, GABAergic and opioidergic pathways (see Online Resources 2, 3, 4, 5, 6, 7). Low number of interactions were also found with dopaminergic, histaminergic and oxytocinergic pathways. Although the PANTHER classification guides to interactions with different neurotransmitter systems, it is seen from the interacting proteins lists (see Online Resources 2, 3, 4, 5, 6, 7) that the association with different neurotransmitter pathways mainly stems from the interactions with vesicular or presynaptic vesicle release machinery related proteins, instead of a direct interaction with neurotransmitter receptors. More interestingly, all 6 viruses except CMV interacted with gamma-aminobutyric acid type B receptor subunit 1 (GABR1) and gamma-aminobutyric acid type B receptor subunit 2 (GABR2) (see Online Resources 2, 3, 4, 5, 6, 7). Such an interaction was not observed for other neurotransmitter receptors. Autoantibodies against gamma-aminobutyric acid type B receptor (GABABR) were reported in cases of limbic encephalitis and refractory seizures [216, 217]. GABABR are found widespread in the brain, they are metabotropic receptors composed of mainly two

subunits GABR1 and GABR2. GABAB1 binds GABA or other ligands like baclofen, while GABAB2 couples the receptor to the G protein. Activation occurs through conformational changes across both subunits, with GABA binding to GABAB1 inducing movements that trigger G protein activation via the transmembrane domain. GABAB receptors couple to Gi/o proteins, inhibiting presynaptic Ca2+ channels, activating postsynaptic K+ channels, and modulating adenylyl cyclase, and they regulate neural network oscillations in thalamocortical and temporal circuits [218]. Recently, in addition to its association with obsessive compulsive disorder [219], GABABR's role on stress responses, depression and anhedonia is being discussed [220]. The infectome may be altering GABABR function, thereby causing neuropsychiatric disorders.

Growth factors are crucial for the neuronal tissue, playing an integral part in both the development and progression of psychiatric and neurological disorders. Our findings reveal that viruses interact with pathways such as FGF, PDGF, VEGF. These pathways are important for the survival of central and peripheral nervous system cells, as well as for the maintenance of vascular health [221–223]. Other than these, neurodegenerative pathways as grouped under Huntington and Parkinson's disease pathways were found to be interacting with all viruses. Clinical studies also reveal a significant association of viruses with neurodegenerative pathways, as summarized in the introduction, in accordance with our findings.

4.3 Six neurotropic viruses have a shared interaction with 38 human proteins

Our findings interestingly reveal that all six selected viruses have shared interactions with 38 human proteins. Other than these interactions, there are also some human proteins that interact with 5 of the selected viruses (n = 150), which can be further investigated from Online Resource 9. Here, we focused mainly on those that are interacting with all six viruses.

Current literature supports the importance of the listed proteins interacting with all viruses and their association with neuropsychiatric disorders. Below, we represent the current literature about each interacting protein.

4.3.1 Calmodulin 2 (CALM2)

Calmodulin II, a calcium-binding protein, which is notably abundant in the mammalian central nervous system, plays a pivotal role in regulating numerous enzymes, ion channels, and proteins that are sensitive to intracellular calcium fluctuations. These include processes such as neurotransmitter production, synaptic function, neurotransmitter release, cyclic nucleotide metabolism, and the modulation of microtubule dynamics [224]. Moreover, calmodulin is crucial for activating Ca^2+/calmodulin-dependent protein kinases (CAMKs), which are essential for synaptic plasticity, learning, memory, and brain development, particularly in the developing brain. Alterations or mutations in calmodulin proteins, including Calmodulin II, have been linked to neurological conditions like epilepsy, intellectual disability, and developmental delays, which stem from abnormalities in neural circuits, synaptic structures, and dendritic spine development, as well as dysregulated neurodevelopmental gene expression. Calmodulin's ability to modulate enzymes and ion channels underscores its fundamental role in maintaining neuronal homeostasis and activity [225–228].

Calmodulin also interacts with and regulates several proteins implicated in the onset and progression of Alzheimer's disease, such as beta-amyloid precursor protein enzyme 1 (BACE1), beta-secretase, amyloid precursor protein (AbPP), and presenilin-1 (PSEN-1). In addition, it governs tau protein phosphorylation through CAMKII and cyclin-dependent kinase 5, contributing to both pro-inflammatory and antioxidant responses that influence AD pathology as well as other neurodegenerative disorders [229–232].

In Parkinson's disease, the loss of dopaminergic neurons is linked to increased intracellular calcium levels and hyperactivation of calmodulin-binding proteins (CaMBPs), including L-type calcium channels, ryanodine receptors (RyR), SK channels, and nitric oxide synthase (NOS). This neuronal damage can be mitigated in experimental settings by pharmacologically inhibiting CaMBPs. Similarly, inhibiting CaM-activated phosphatase (calcineurin, CaN) has been shown to protect against neurotoxicity and neuroinflammation, while improving cognitive function in PD and other neurodegenerative disease models [233].

In the context of depression, CaMKII is overexpressed in the lateral habenula (LHb), where it contributes to depressive behaviors by increasing synaptic activity. Targeted knockdown of CaMKII has been found to reverse these effects. Emerging studies also point to the involvement of CaMKs in disorders like schizophrenia and autism, where mutations in CaMK genes are associated with synaptic dysfunction and behavioral alterations [234]. In our analysis, HSV-1 interacts with 11 different sites of CALM2, which shows the high level of mimicry and functional coupling.

4.3.2 Ras-related C3 botulinum toxin substrate 1 (RAC1)

Rac1, a member of the Rho family of GTPases, is critical for various processes that underlie synaptic plasticity, a fundamental mechanism for memory formation and consolidation. Rac1 activity directly impacts dendritic spine morphology, which is essential for synaptic transmission in brain regions involved in memory-related functions [235]. Rac1 also plays a significant role in axonal morphogenesis and neurogenesis, facilitating the development of new neural circuits required for learning and memory [236, 237]. At the synapse, Rac1 is activated by synaptic stimuli such as NMDA receptor activation, which is mediated by signaling intermediates like kalirin-7 and CaMKII. This activation leads to the rapid enlargement and stabilization of dendritic spines, which are critical for maintaining synaptic connectivity [235, 238]. Beyond its role in synaptic plasticity, Rac1 regulates key cellular processes across different neural cell types, including promoting oligodendrocyte myelination [239], shaping astrocyte morphology [240], and enabling microglia to adapt to their microenvironment within the central nervous system [241].

In Alzheimer's disease, Rac1 is critically involved in neurodegenerative processes. Recent studies have shown a significant downregulation of Rac1 in the entorhinal cortex and frontal cortex of AD patients, suggesting its involvement in synaptic loss, one of the earliest pathological features of the disease [242, 243]. Rac1 regulates the actin cytoskeleton and dendritic spine stability; thus, its downregulation may contribute to the loss of neuronal connectivity in AD [235, 244]. Moreover, Rac1 activation appears to exacerbate amyloid precursor protein (APP) processing and tau hyperphosphorylation, both key factors in AD pathogenesis [243]. This suggests that Rac1 may contribute to both amyloid and tau pathology. Interestingly, while Rac1 is reduced in AD brain tissue, it is increased in the plasma of AD patients with severe cognitive decline (Mini-MSE < 18), indicating a potential compensatory or diagnostic biomarker role [242, 243]. These findings suggest that modulating Rac1 activity can offer therapeutic avenues to mitigate neurodegeneration by balancing its protective versus pathogenic roles in AD.

In Parkinson's disease, Rac1 is associated with neuroinflammation and oxidative stress, contributing to neuronal injury and the progression of neurodegeneration. Rac1 is a subunit of NADPH oxidase, and its dysregulation can promote the generation of reactive oxygen species (ROS), leading to oxidative stress, a key pathological mechanism in PD [245]. Studies have shown that inhibiting Rac1 can reduce oxidative stress, apoptosis, and inflammatory responses in cellular models of PD, suggesting its role in neuronal injury. Moreover, miR-185-5p was found to mitigate MPP+-induced neuronal cell injury by targeting Rac1, further implicating Rac1 in PD pathology [246, 247]. Additionally, the tumor suppressor protein HACE1 has been identified as a regulator of Rac1 activity in PD, modulating neuroinflammation and offering a neuroprotective role. These findings suggest that Rac1 activity may exacerbate neurodegeneration in PD, positioning it as a potential therapeutic target [245].

Rac1 also plays a significant role in mood disorders, such as depression. Chronic social stress has been shown to reduce Rac1 activity in the nucleus accumbens (NAc), a brain region associated with reward and emotional regulation, leading to depression-like behaviors. This reduction in Rac1 contributes to the increase in stubby spines in the NAc, which are characteristic of depression-related neural adaptations [248]. Conversely, increasing Rac1 activity in the NAc has been demonstrated to improve early-life stress-induced depression-like behaviors, suggesting a protective role for Rac1 in spine remodeling and stress resilience [249]. Furthermore, Rac1's involvement in actin cytoskeleton dynamics and synaptic structure highlights its critical role in the neural adaptations underlying depressive behavior [250, 251]. Thus, Rac1 modulation could serve as a therapeutic strategy for treating stress-related psychiatric disorders.

Rac1 has been implicated in the pathophysiology of schizophrenia, particularly in relation to synaptic development and neuronal connectivity [252]. Genome-wide DNA methylation studies have identified altered RAC1 methylation levels in individuals with schizophrenia or intellectual disability, who also have multiple family members suffering from the same condition [253]. Additionally, Rac1 is part of the DISC1/Kal-7 signaling pathway, which regulates synapse formation and neuronal maturation. Disruptions in this pathway, particularly in conjunction with mutations in genes like NX1 and DISC1, have been associated with schizophrenia and autism spectrum disorders, indicating that abnormalities in Rac1 signaling may contribute to the onset of these psychiatric conditions [254–256]. The regulation of Rac1 activity at synapses is crucial for maintaining proper neural connectivity, and its dysregulation may underlie the synaptic deficits observed in schizophrenia [256].

4.3.3 COP9 signalosome complex subunit 5 (CSN5/JAB1)

The COP9 signalosome (CSN), particularly its subunit CSN5, also known as JAB1, plays a pivotal role in neurodevelopment and neuroprotection. CSN5/JAB1 is involved in several key neurodevelopmental processes, including neuronal

differentiation, synaptic morphogenesis, and myelination. It works synergistically with copines (CPNEs) to promote neuronal outgrowth and is essential for the development of photoreceptors and neural stem cells, as demonstrated in Drosophila experimental models [257, 258]. Additionally, JAB1 interacts with the transcription factor Brn-2, which is crucial for neuronal differentiation [259]. It also regulates dendritic spine development, an essential aspect of synaptic plasticity and function [260]. In Schwann cells, JAB1 controls axonal sorting and motor function by modulating the cell cycle inhibitor p27, whose dysregulation can lead to myelination defects and neurological disorders, such as autism, Down syndrome, and Smith-Magenis syndrome [258, 261].

JAB1's role extends beyond neurodevelopment into various neurological diseases. In AD, JAB1 promotes β-secretase processing of amyloid precursor protein, leading to increased amyloid-β production. Elevated levels of JAB1 in AD brains contribute to cognitive decline by stabilizing RanBP9, which accelerates Aβ pathology [262]. In MS, JAB1 deficiency in oligodendrocytes causes demyelination and premature cellular senescence, aggravating disease progression [263]. JAB1 is also implicated in neuropathic pain, where it is upregulated following injury and contributes to pain signaling via the JNK and NF-κB pathways [264]. In peripheral nerve injury, JAB1 regulates Schwann cell proliferation and axonal sorting through its interaction with p27, highlighting its importance in nerve regeneration [258, 265].

Furthermore, JAB1 plays a protective role in ischemic brain disease by regulating microglial inflammatory responses, preserving endothelial barrier integrity, and reducing neuronal death. It modulates NF-κB-driven inflammatory mediators, such as CCL2, and regulates the release of macrophage migration inhibitory factor (MIF) through the JNK/AP-1 pathway, which is linked to the activation of integrins involved in inflammation [266, 267]. Additionally, JAB1 enhances tight junctions in cerebral endothelial cells, reducing blood–brain barrier permeability and offering protection against ischemic injury [268].

Despite its therapeutic potential, JAB1's roles in different diseases are complex and often contradictory. While reducing JAB1 levels may benefit conditions like AD, its downregulation in MS exacerbates disease pathology. Therefore, tissue-specific interventions targeting JAB1 may be necessary to minimize adverse effects [258, 263, 264].

4.3.4 Catenin beta (ß-catenin)

β-catenin binds to cadherins, which are calcium-dependent cell adhesion molecules involved in synapse assembly, synaptic plasticity, memory formation, and the regulation of dendritic spine dynamics [269]. The cadherin-catenin complex is localized at synaptic junctions, and disruptions in this complex are believed to affect synapse development, connectivity, and function [269, 270]. Through the Wnt/β-catenin signaling pathway, β-catenin also regulates processes such as cell proliferation, survival, migration and differentiation [271]. Recent studies highlight β-catenin's role in learning and memory in animal models [269, 272]. Additionally, activation of the Wnt/β-catenin pathway reduces inflammation and promotes neuroprotection by mediating interactions between microglia, macrophages, and astrocytes [273].

The WNT/β-catenin signaling pathway has been implicated in several neurodegenerative and psychiatric disorders, including AD, PD, Huntington's disease, and affective disorders like depression and bipolar disorder. In AD, mutations in familial Alzheimer's disease genes, such as presenilin-1 (PS-1), affect β-catenin stability. PS-1 mutations decrease β-catenin levels and are associated with overproduction of amyloid-beta, contributing to AD pathology. PS-1 also inactivates GSK3, a kinase that negatively regulates β-catenin. Increased GSK3 activity in AD brains correlates with reduced β-catenin stability, suggesting that β-catenin dysregulation may be involved in Aβ pathology and synaptic dysfunction [269, 274, 275]. In PD, WNT/β-catenin dysregulation plays a central role in disease progression, influencing axonal function, microtubule stability, and membrane trafficking, all of which are impaired in PD. Furthermore, dysregulated β-catenin signaling may contribute to neuroinflammation and neurodegeneration [273], affecting dopaminergic neurons and exacerbating the progression of PD. In affective disorders like depression and bipolar disorder, the β-catenin/GSK3 pathway is linked to synaptic plasticity dysregulation. Lithium, a mood stabilizer, inhibits GSK3, stabilizing β-catenin, which mimics antidepressant effects in animal models. DISC1, a gene associated with psychiatric disorders, also stabilizes β-catenin by inhibiting GSK3, further linking this pathway to mood regulation [269, 276, 277].

4.3.5 Interleukin-2 (IL-2)

Interleukin-2 (IL-2) is crucial in modulating immune responses, particularly by stimulating regulatory T cells (Tregs), which are essential for controlling inflammation. Emerging evidence underscores IL-2's significant involvement in neurodegenerative mechanisms, particularly through its regulation of neuroinflammation. For instance, IL-2-deficient mice exhibit hippocampal alterations and cognitive impairments that resemble those observed in Alzheimer's disease. Studies have

revealed a marked reduction in IL-2 levels within the hippocampus of AD patients. In AD mouse models, prolonged IL-2 administration has been shown to significantly expand regulatory T cell populations, activate astrocytes surrounding amyloid plaques, reduce amyloid plaque burden, enhance synaptic plasticity, and improve memory deficits. These findings highlight the therapeutic potential of IL-2 in targeting neuroinflammation and mitigating neurodegenerative processes in AD [162].

IL-2 plays a significant role in the pathogenesis of schizophrenia, affecting various neurobiological processes, including the Glutamate neurotransmitter system. Studies have shown that IL-2 alters Glutamate and GABA synthesis and release in hippocampal neurons, potentially contributing to schizophrenia's cognitive and behavioral symptoms. Genetic studies also suggest a potential link between IL-2 gene variants and schizophrenia susceptibility. Additionally, reduced IL-2 levels have been correlated with more severe negative symptoms in schizophrenia patients [163, 278, 279]. Interestingly, alterations in cytokine levels, including IL-2, have been found to overlap in schizophrenia, depression, and bipolar disorder, suggesting a shared inflammatory pathway underlying these psychiatric conditions [280].

4.3.6 Transcription factor jun

Transcription factor jun plays a pivotal role in various cellular processes, including cell cycle regulation, apoptosis, and axogenesis, and is essential for neuronal development and differentiation [281]. It is also crucial in the pathological cell death seen in neurodegenerative diseases and contributes to synaptic plasticity and memory formation, with impaired c-Jun signaling linked to memory deficits [282]. Additionally, alterations in c-Jun activity are involved in the neuroinflammatory response induced by microglia following cerebral ischemia [283]. Elevated phosphorylation of c-Jun N-terminal kinase (JNK) may contribute to stress-induced release of alarmins, key mediators of neurovascular inflammation, which are prominently involved in the pathogenesis of neurodegenerative disorders such as AD, PD, and MS [284].

4.3.7 Paxillin

Paxillin is a focal adhesion (FA) protein that interacts with signaling pathways involving focal adhesion kinase (FAK) and Rho GTPases to regulate various cellular processes, including cytoskeletal dynamics, cell adhesion, migration, and the transmigration of immune cells [182, 285]. These interactions enable paxillin to influence cell behavior, neuronal development, and synaptic formation [286]. Paxillin also plays a crucial role in the transmigration of leukocytes into the central nervous system, contributing to neuroinflammation following traumatic brain injury [181]. Additionally, paxillin, in conjunction with Hic-5, may modulate tau phosphorylation or associate with hyperphosphorylated tau in vivo, contributing to AD pathogenesis [287].

4.3.8 E3 ubiquitin-protein ligase MDM-2

MDM2 regulates the degradation of p53, a key mechanism for maintaining cellular homeostasis [288]. In neurons, proper regulation of p53 by MDM2 is critical to prevent excessive neuronal death or dysfunction and ensure cellular health [289]. Furthermore, MDM2 upregulation has been strongly linked to amyloid-beta-induced synaptic spine loss, a critical event in the pathogenesis of AD [290]. Moreover, recent studies have shown that tau, a key protein in AD, directly binds to the E3 ubiquitin ligase MDM2 in vitro, in cultured human cells, and in human brain tissue. This interaction impairs the ubiquitination of p53, indicating a potential involvement of the p53/MDM2 axis in the neurodegenerative processes underlying AD [291].

4.3.9 Platelet derived growth factor receptor beta (PDGF-ß)

PDGF-β, a key platelet-derived growth factor, is essential for the development and functioning of neural cells. It plays critical roles in neuroprotection, synaptic plasticity, cell survival, differentiation, and maintaining blood–brain barrier integrity. It is mainly expressed in endothelial cells and binds its receptor at pericytes. This interaction with endothelial cells and pericytes is important for proper BBB integrity. When either PDGF-β or its receptor knock-down, it leads to

significant vascular developmental problems [292] and BBB disruption. Additionally, soluble form of PDGF-β is suggested as a biomarker of cognitive decline and brain capillary damage associated with mural cell pericyte injury [293, 294].

In addition to BBB functions, PDGF provides neuroprotection by inhibiting excitotoxicity and oxidative stress, shielding neurons from NMDA receptor-mediated damage and oxidative injury, largely through the PI3-K/Akt signaling pathway. PDGF-ß also modulates synaptic function by reducing NMDA-evoked currents, regulating excitatory postsynaptic potentials, and enhancing long-term depression (LTD) in hippocampal neurons. Additionally, it influences dendritic spine morphology and synaptic plasticity, both essential for memory and learning. PDGF-ß supports cell survival by activating anti-apoptotic pathways and promotes the differentiation of oligodendrocyte progenitors for myelination, as well as neural stem/progenitor cells. Furthermore, it plays a crucial role in maintaining BBB integrity by recruiting pericytes during development and following brain injury [183].

PDGF-β has been associated with multiple neurodegenerative and psychiatric conditions, such as AD, depression, and schizophrenia. In AD, PDGF-β signaling is disrupted, likely due to pericyte loss, which contributes to reduced vascular density, decreased cerebral blood flow, and breakdown of the BBB, all hallmark features of AD pathogenesis [295]. In the context of depression, inhibition of GABAergic neurons within the medial septum-dentate gyrus circuit has been shown to alleviate chronic stress-induced depressive-like behavior. This effect is mediated through upregulation of PDGF-β expression, which in turn promotes adult hippocampal neurogenesis [296]. Additionally, the PDGFβ and PDGFRβ genes are implicated in the potential etiology of schizophrenia, suggesting a broader role for PDGF signaling in neuropsychiatric disorders [297].

4.3.10 Plasminogen

Plasminogen plays a dual role in neuronal processes, facilitating both neuronal development and synaptic formation through the degradation of extracellular matrix proteoglycans via microglial activation, while also mediating critical steps in excitotoxin-induced neurodegeneration [298]. Additionally, plasminogen and plasmin are essential for maintaining the integrity of the BBB, with animal models demonstrating the beneficial effects of recombinant tPA treatment in reducing BBB permeability following stroke [299]. Alterations in the levels of tissue plasminogen activator (tPA), plasminogen, and plasmin, whether excessive or deficient, are linked to neurodevelopmental disorders and a range of CNS pathologies [300]. Plasmin also plays a key role in the activation of neurotrophic factors, which are critical for neuronal growth, survival, and differentiation [301].

Plasminogen and plasmin play significant roles in neurodegeneration in both AD and PD. Plasminogen accumulates in areas of neural injury, promoting tissue regeneration and aiding in the degradation of misfolded proteins such as α-synuclein and tau [302]. Plasmin is also capable of cleaving amyloid-beta [303], and studies using AD mouse models have shown its effectiveness in clearing Aβ42 peptides and tau protein aggregates, both in vivo and ex vivo. This process is further associated with the upregulation of choline acetyltransferase (ChAT) and the downregulation of acetylcholinesterase (AChE), contributing to improved memory functions and reduced neurodegeneration [304]. Similarly, in PD, plasmin degrades α-synuclein deposits, preventing their accumulation and reducing the activation of microglia and astrocytes, which are implicated in disease progression [305].

4.3.11 Insulin

Insulin plays a crucial role in maintaining brain health and supporting neuroplasticity, both during neurodevelopment and throughout adulthood in the central nervous system [169]. It regulates a wide range of CNS functions, and disruptions in insulin signaling are associated with neurological disorders such as Alzheimer's disease, age-related cognitive decline, and mild cognitive impairment [306]. Most of the insulin present in the CNS is derived from peripheral sources, transported across the BBB [307]. Peripheral insulin resistance, often caused by metabolic conditions like elevated serum glucose levels and lipid imbalances, can impair brain insulin signaling, contributing to neuroinflammation and cognitive deficits [308, 309]. This impairment compromises BBB integrity, increases its permeability, and allows excess glucose to enter the brain and leads change in perivascular cells to myofibroblastic character and increased extracellular matrix formation [310, 311]. In response, microglia are activated into a pro-inflammatory state, which drives cytokine release and neuroinflammatory cascades, ultimately leading to reactive astrogliosis [310]. This neuroinflammation further weakens the BBB, creating a vicious cycle of hyperglycemia and neuroinflammation that accelerates neurodegeneration [312–314]. Additionally, insulin influences brain energetics by affecting glucose utilization, and reduced insulin action in the brain exacerbates mitochondrial dysfunction and energy deficits, contributing to cognitive decline [315].

In Alzheimer's disease, insulin signaling in the CNS is severely disrupted, with lower cerebrospinal fluid-to-plasma insulin ratios and diminished brain insulin pathways compared to healthy individuals, particularly in the cerebral cortex and hippocampus, contributing to cognitive decline [316–319]. Similarly, while the link between insulin resistance and Parkinson's disease is less conclusive, insulin's role in suppressing neuroinflammation and pro-inflammatory cytokine release highlights its importance in PD pathogenesis [320]. In schizophrenia, insulin interacts with dopamine, glutamate, and AKT pathways, enhancing dopamine transporter activity and modulating cognitive function through glutamate signaling. Disruptions in these pathways, along with a genetic overlap between insulin resistance and schizophrenia, suggest insulin's role in schizophrenia [315].

4.3.12 Cerebral cavernous malformations 2 (CCM2)

CCM2, along with CCM1 and CCM3, forms the CCM signaling complex (CSC), which plays a critical role in preserving blood–brain barrier integrity within the CSC-mPRs-PRG signaling network [152]. Mutations that cause loss of function in any of the three genes encoding these proteins have been linked to disruptions in intercellular junctions, elevated reactive oxygen species, enhanced angiogenesis, changes in basement membrane composition, and increased vascular permeability. These alterations can result in the formation of abnormally dilated intracranial sinusoids, significantly raising the risk of hemorrhagic stroke [152, 153]. In addition, malfunctioning of CCM proteins has been associated with astrocyte reactivation, leukocyte recruitment, and subsequent neuroinflammation [153, 321]. Beyond its role in vascular integrity, CCM2 is also identified as a key regulator of TrkA-dependent cell death in pediatric neuroblastomas [321]. In summary, dysfunction of the CCM2 protein primarily impacts the brain's vascular structure and integrity, potentially leading to neurological complications through bleeding, inflammation, and disrupted neurovascular development.

4.3.13 Toll-like receptor 3 (TLR3)

Toll-like receptor 3 (TLR3), an important part of the innate immune system, recognizes double-stranded RNA, typically associated with viral infections. It is expressed in neurons, oligodendrocytes, astrocytes, endothelial cells, and microglia in both rodents and humans. Upon activation, TLR3 in astrocytes and microglia promotes the release of neuroprotective factors, such as anti-inflammatory cytokines, which help prevent neuronal damage [322, 323].

However, chronic or excessive TLR3 activation is linked to neurodegenerative conditions like Alzheimer's and Parkinson's diseases, as it promotes inflammatory pathways that increase the production of pro-inflammatory cytokines [324, 325]. Moreover, TLR3 involvement has been implicated in several psychiatric disorders, including depression, schizophrenia, and bipolar disorder, where dysregulated immune responses are believed to have a significant effect [326–329]. While TLR3 contributes to antiviral defense in the CNS, its overactivation may exacerbate neurodegeneration and contribute to the pathology of mental health disorders.

4.3.14 Vinculin

Vinculin is a cytoskeletal protein critical in cell adhesion, mechanotransduction, and maintaining cellular integrity. It is primarily localized at focal adhesions and adherens junctions, where it links the actin cytoskeleton to the plasma membrane. Vinculin plays an essential role in mechanosensing, enabling cells to respond to mechanical stimuli, such as changes in the extracellular environment [330, 331].

In neurodegenerative diseases like Alzheimer's, vinculin's disruption may contribute to synaptic dysfunction, reducing synaptic plasticity and exacerbating tau pathology [332–334]. Similarly, in Parkinson's disease, alterations in vinculin may affect the cytoskeletal organization, contributing to dopaminergic neuronal loss and motor dysfunction. In psychiatric disorders such as schizophrenia vinculin's involvement in synaptic stability and cell adhesion may underlie the observed structural and synaptic abnormalities [334]. Changes in vinculin expression and function could disrupt neuronal connectivity, leading to the cognitive and mood disturbances characteristic of these conditions.

4.3.15 Ubiquitin-associated protein 1 (UBAP-1)

Ubiquitin-associated protein 1 (UBAP-1) plays a significant role in the endosomal sorting complex required for the transport (ESCRT) system, which is crucial for membrane remodeling processes, such as vesicular trafficking and the degradation of ubiquitinated proteins. UBAP-1 contains a ubiquitin-associated (UBA) domain that facilitates its interaction with

ubiquitinated proteins. Disruptions in this protein's function, particularly mutations or dysregulation, have been linked to impaired protein degradation pathways, contributing to cellular stress and damage accumulation [335, 336].

Emerging research suggests a potential relationship between UBAP-1 dysfunction and neurodegenerative diseases, particularly amyotrophic lateral sclerosis [336, 337]. While clear connections between UBAP-1 and neurodegenerative or psychiatric conditions like Alzheimer's or schizophrenia have not yet been confirmed, UBAP-1 is recognized as a genetic risk factor for frontotemporal lobar dementia (FTLD) due to its interaction with TAR DNA binding protein (TDP-43) [338].

4.3.16 Polyubiquitin-B and polyubiquitin-C

Polyubiquitin-B (UBB) and polyubiquitin-C (UBC) are gene products that encode ubiquitin, a small regulatory protein involved in various cellular processes, particularly in protein degradation via the ubiquitin–proteasome system (UPS). Polyubiquitination refers to the attachment of multiple ubiquitin molecules to a substrate protein, marking it for degradation. Both UBB and UBC play crucial roles in maintaining cellular homeostasis by regulating protein turnover, DNA repair, and stress responses. Dysregulation of ubiquitin-mediated processes has been implicated in the accumulation of misfolded proteins, a hallmark of many neurodegenerative and psychiatric disorders [339, 340].

In neurodegenerative diseases such as Alzheimer's and Parkinson's, the accumulation of ubiquitinated proteins suggests an impairment in the UPS [341, 342]. Mutant or truncated forms of UBB, such as UBB+1, have been shown to accumulate in neurons, leading to proteasomal dysfunction and contributing to neuronal death and cognitive decline in Alzheimer's disease [343, 344]. Similarly, alterations in UBC expression have been linked to schizophrenia where abnormal protein degradation pathways could affect synaptic plasticity and neurotransmitter systems [345].

4.3.17 Vimentin

Vimentin is a type III intermediate filament protein widely expressed in mesenchymal cells, playing a crucial role in maintaining cell integrity, structure, and stability [197]. It is also involved in various cellular processes, including wound healing, cell migration, and immune responses. Vimentin is increasingly recognized for its involvement in neurodegenerative diseases and psychiatric disorders. Recent studies have demonstrated that vimentin is upregulated in reactive astrocytes and microglia in response to brain injury or neuroinflammation, which is a common hallmark in conditions such as AD, PD, and MS [205, 346–348]. Furthermore, vimentin's role in cytoskeletal dynamics is believed to influence neuroinflammation, which can exacerbate neurodegenerative processes [205].

In psychiatric disorders, vimentin has been linked to depression and schizophrenia, primarily through its involvement in neuroinflammation and oxidative stress pathways [349–351]. Research suggests that the altered expression of vimentin may contribute to the inflammatory processes observed in major depressive disorder and schizophrenia [352, 353]. Studies also indicate that vimentin may interact with key molecules involved in stress responses, such as glucocorticoid receptors, which could explain its role in these conditions [197].

4.3.18 Sharpin

SHARPIN (SHANK-associated RH domain-interacting protein) is a multifunctional protein that plays key roles in various cellular processes, including immune regulation, cell survival, and inflammation [354]. As part of the linear ubiquitin chain assembly complex (LUBAC), SHARPIN is crucial in modulating NF-κB signaling, a pathway involved in inflammation and immune responses [355, 356]. Therefore, mutations or dysregulation of SHARPIN have been linked to neuroinflammation, a hallmark of many neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease [357, 358]. Furthermore, the role of SHARPIN in NF-κB signaling pathways suggests it may play a role in psychiatric disorders, such as bipolar disorder [359]. However, more research is needed to fully elucidate the precise mechanisms by which SHARPIN contributes to these conditions.

4.3.19 Stromal interaction molecule 1 (STIM1)

Stromal interaction molecule 1 (STIM1) is a crucial protein that acts as a calcium sensor in cells, playing a significant role in the regulation of intracellular calcium levels [191, 360]. Upon depletion of calcium in the endoplasmic reticulum, STIM1 undergoes a conformational change, translocating to the plasma membrane to activate store-operated calcium entry (SOCE) through the Orai channels [361, 362]. This mechanism is vital for various physiological processes, including muscle contraction, hormone secretion, and gene expression. Recent studies have indicated that deficiency of STIM1 and subsequent altered calcium signaling pathways may contribute to the pathophysiology of Alzhemer`s diseases, where impaired calcium signaling may lead to synaptic dysfunction and neuronal apoptosis [363–365].

4.3.20 NF-kappa-B essential modulator (NEMO)

NF-Kappa-B essential modulator (NEMO), also known as IKKγ, is a crucial regulatory subunit of the IκB kinase (IKK) complex that plays a vital role in the activation of the NF-κB signaling pathway [177]. NEMO facilitates the phosphorylation and degradation of IκB proteins, allowing the release of NF-κB dimers, such as p65/p50, which then translocate to the nucleus to regulate gene expression involved in immune responses, cell survival, and inflammation. Dysregulation of NEMO can lead to aberrant NF-κB activation, contributing to various pathological conditions, including neuroinflammation and neurodegeneration [366–368]. Recent studies have indicated aberrant NF-κB signaling increases β-amyloid precursor protein and A β processing, contributing to the pathogenesis of AD [366]. Additionally, polymorphism in NF-κB has been associated with MS [366, 369].

4.3.21 NKG2-D type II integral membrane protein

NK-cell activity is regulated by a balance between stimulatory and inhibitory signals, with the activating receptor NKG2D capable of overriding inhibitory signals to drive effector functions [370]. NKG2D plays a key role in T cell and NK cell functions, including proliferation, migration, cytotoxicity, and cytokine production [371–373].

Several studies have linked NKG2D to neurodegenerative pathologies, with Qi et al. (2022) reporting reduced NKG2D expression in Alzheimer's disease, while Garofalo et al. (2020) observed increased expression of NKG2D ligands in mouse models of Amyotrophic Lateral Sclerosis [374–376], and Mihara et al. (2008) highlighting differences in NKG2D-related pathways between Parkinson's disease patients and non-PD individuals [377].

Zhang et al. (2021) demonstrated that in mouse models of major depressive disorder, NKG2D expression is increased in the spleen, while no changes were observed in the parietal cortex compared to the control group. These findings suggest that elevated NKG2D expression in the spleen may contribute to depression-like behavior in mice susceptible to chronic social defeat stress, highlighting the role of the brain-spleen axis in stress-related psychiatric disorders. This supports the broader implication of NKG2D in neuroinflammatory processes across various conditions [378].

4.3.22 Granulocyte colony-stimulating factor (G-CSF)

Granulocyte colony-stimulating factor (G-CSF; filgrastim), primarily recognized for regulating blood cell production in the bone marrow [379], and it is present in neurons and neural progenitor cells within the hippocampus [380]. G-CSF has shown neuroprotective benefits in addition to its hematological roles. Elevated BBB scales, inclined plane test results, electrophysiological evaluations, and lower apoptotic cell counts suggest that G-CSF therapy is effective in promoting neurological recovery. These results show significant promise in strengthening BBB function and improving motor and neurological performance [155]. Tsai et al. demonstrated that even in the absence of a decrease in amyloid burden, G-CSF treatment enhanced cognitive function in Tg2576 Alzheimer's disease animal models [381]. Several previous investigations have verified that G-CSF can reverse cognitive deficits in APP+PS1 Tg mice via both Aβ-dependent and Aβ-independent mechanisms, including increased neurogenesis, improved synaptic plasticity, and microglial activation [379, 382, 383].

Additionally, G-CSF's neuroprotective role extends to chronic neurodegenerative diseases. Its capacity to retain striatal dopamine levels and preserve neuronal shape in such mice was shown in a study by Meuer, indicating its promise as a therapeutic agent [384]. G-CSF physiologically regulates the survival, differentiation, and proliferation of neutrophil leukocytes through anti-apoptotic mechanisms that are preserved in neurons [380, 385]. Its potential as a treatment

for neurodegenerative illnesses like Parkinson's disease has been bolstered by its proven neuroprotective properties in cerebral ischemia models. According to Tsai's study, Parkinson's patients' UPDRS part III scores stayed steady for two years following G-CSF treatment, indicating the potential for long-term neuroprotection [386].

4.3.23 Ferritin light chain

Ferritin, a key iron storage protein, is essential for regulating iron bioavailability and preventing the overproduction of reactive oxygen species, which is capable of causing cellular damage and death [387, 388]. Ferritin light chain dysfunction has been widely implicated in several neurodegenerative diseases, particularly the Parkinson's and Alzheimer's diseases [388–390]. Dopaminergic neurons in the substantia nigra are especially prone to iron-related oxidative damage in PD, likely due to ROS accumulation in the case of impaired ferritin light chain production [391, 392]. Neuroferritinopathy, also referred to as hereditary ferritinopathy, belongs to the group of neurodegeneration with brain iron accumulation disorders and typically results from a frameshift mutation in the FTL gene, which encodes ferritin light chain. This leads to iron buildup and the formation of abnormal intracellular aggregates containing mutant ferritin [393,395].

4.3.24 Protein dpy-30 homolog

In their study, Shah et al. demonstrated that Dpy30 and H3K4 methylation are crucial for the proliferation and differentiation of postnatal neural stem cells (NSCs) [396]. Loss of Dpy30 resulted in structural brain abnormalities, including enlarged lateral ventricles, a malformed dentate gyrus (DG), and a reduction in cerebellar folia, which were accompanied by a global reduction in H3K4 methylation [159, 396]. Immunostaining further revealed a significant decrease in NSCs within the postnatal knockout (KO) DG and subventricular zone (SVZ), along with a reduced astrocytic population in both regions and a decline in neuronal numbers specifically in the KO DG. Shah et al. also demonstrated, through in vitro assays, that KO NSCs showed a diminished capacity to form neurospheres, confirming the essential role of Dpy30 in NSC self-renewal [396]. These findings align with earlier research by Jiang et al., which showed that Dpy30, along with Rbbp5, is necessary for the neuronal differentiation of embryonic stem cells, highlighting the epigenetic priming role of H3K4 methylation [397].

Dpy30's significant expression within both the hippocampus and cerebellum during late embryonic and postnatal stages suggest that its regulatory function spans multiple stages of neural development, with defects resulting from its loss likely stemming from disruptions at both stages. Moreover, emerging evidence links deficient H3K4 methylation to various mental disorders. For instance, loss-of-function mutations in SETD1A, an H3K4 methyltransferase, have been identified in individuals with schizophrenia and other neurodevelopmental disorders [398]. Given the crucial function of H3K4 methylation regarding brain development, these findings offer novel understanding of the molecular mechanisms underlying neurodevelopmental disorders [159].

5 Conclusion

In conclusion, this study's analyses and related literature review highlight the significant role that viral protein interactions with human proteins may play in neuropsychiatric diseases. Our findings suggest that the six key viruses, HSV-1, EBV, CMV, HIV, and influenza viruses, can interact with many human proteins across multiple pathways, both in the peripheral and central systems, that can possibly lead to neuropsychiatric dysfunction. The common interactions of all six viruses and 38 human proteins emphasize the potential for future in vivo and in vitro targets that can be modified for infectome-pathology associations. These studies could explore how viral infections influence neuropsychiatric disease development through mechanisms like molecular mimicry, immune evasion, and chronic neuroinflammation.

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Aleyna Keskin, Yusuf Huseyin Berrak, Fatma Cankara and Hale Yapici-Eser, and all authors commented on previous versions of the manuscript. Figures have been prepared by Elif Asli Özer and Fatma Cankara. All authors read and approved the final manuscript.

Data availability The datasets generated during and/or analysed during the current study are available in the following repository, [https://github.com/ku-cosbi/ViralMimicry/]. The codes utilized for pre and post-analysis required for HMI-PRED workflow as well as input and output files can be found here.

Declarations

Competing interests The authors declare no competing interests.

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