Integrative Multi-Omics and Network Biology Approaches to Understanding Viral-Host Interactions in Neurodegenerative Diseases: From Pathogenesis to Therapeutic Targets

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Abstract

Neurodegenerative diseases (NDs) result from multiple causes which include both genetic elements and environmental factors and possibly infectious pathogens. Research studies show that the human brain contains dormant viral species which do not cause active infections[1], [2]. Recent studies have renewed interest in the hypothesis that viral infections may contribute to the initiation or progression of neurodegenerative diseases[3]. The review evaluates how integrative multi-omics and network biology methods analyze viral–host interactions in NDs to understand disease mechanisms and discover new therapeutic options. Scientists now study how various pathogens lead to brain diseases through high-throughput virus detection methods which show that diseased brains contain multiple viruses instead of focusing on individual pathogens. The modern analysis of the central nervous system now uses single-cell and spatial omics technologies with systems bioinformatics and artificial intelligence to provide complete examination. The methods allow scientists to link genomic data with transcriptomic and proteomic and metabolomic information for constructing complete interaction networks. Wongchitrat et al. (2024) report molecular mechanisms through which neurotropic viruses may promote chronic neuroinflammation and metabolic dysregulation and protein aggregation in the brain which leads to neuronal dysfunction based on network-driven analysis[4]. The review integrates current knowledge about viral–host interactions in neurodegeneration through discussions of new computational and experimental findings and suggests ways to use this information for creating biomarkers and personalized treatments for Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

Keywords: Neurodegenerative diseases; viral–host interactions; brain virome; multi-omics; network biology; neuroinflammation; Alzheimer's disease; Parkinson's disease; amyotrophic lateral sclerosis; therapeutic targets.

Introduction

Neurodegenerative diseases (NDs) including Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS) develop from multiple causes which include inherited elements and outside environmental triggers. Scientists study CNS infections because these diseases result in rare neurodegenerative cases which do not show any genetic markers[5]. The primary focus of neurodegenerative disease research used to be protein-based theories which identified amyloid-β and α-synuclein misfolded proteins as the primary disease-causing agents. The proteinopathy models have generated essential knowledge, yet they fail to explain the beginning and development of disease in numerous patients. Scientists now study the "infection hypothesis" because they understand that microbial pathogens, including viruses, could cause neurodegenerative diseases through their direct toxic effects on cells and their ability to create long-lasting brain inflammation [5]. Multiple types of viruses, bacteria, fungi, and parasites have been found in human brains and linked to ND development, which supports the theory that neurodegeneration results from infectious agents[5]. Studies about viral infections causing neurodegenerative diseases have expanded their findings through extensive research during the last few years. Deep sequencing studies have reported viral genetic signatures in brain tissues. However, interpretation of these findings requires careful control for contamination, sequencing artifacts, and other technical biases. Some studies suggest that aging or diseased brains may harbor diverse viral signatures, although the biological significance of these observations remains under investigation. One 2024 study using the ViroFind sequencing technology found an unexpectedly broad variety of viral species in deceased brains which did not display CNS infection symptoms[2]. A 2023 transcriptomic data mining study reported viral signatures in brain transcriptomic datasets and suggested possible associations between neurotropic viruses and neurodegenerative disease pathways[1]. These findings have contributed to a growing hypothesis that multiple viral exposures may interact with host susceptibility factors in neurodegenerative disease development, instead of the previous belief that single pathogens caused single diseases (e.g., herpes simplex virus in Alzheimer's disease). The evidence suggest that Alzheimer's disease and Parkinson's disease may involve interactions between host susceptibility factors and multiple infectious exposures rather than a single pathogen or virus family, because host susceptibility factors together with multiple infections determine disease progression[5]. The discovery of new scientific knowledge generates fundamental inquiries about viral agents' mechanisms of interaction with host brain systems which influence disease progression.

Detection of viral sequences in brain tissue must be interpreted cautiously. Many sequencing-based virome studies involve extremely low microbial biomass samples, where environmental contamination, reagent-derived sequences, or peripheral blood contamination may introduce non-host viral reads. In several virome studies, the most abundant viral sequences detected were not human neurotropic viruses but viruses associated with environmental sources or parasites. Such findings highlight the importance of rigorous validation using orthogonal approaches such as quantitative PCR, in situ hybridization, and immunohistochemistry before concluding that detected viral sequences represent true CNS infection.

Comprehending the intricate interactions between viruses and host neuronal systems in NDs constitutes considerable computational and experimental challenges. Traditional neurovirology methods studied individual viruses separately, but these methods fail to detect the complex viral interactions which scientists now recognize. The brain responds to infections through modifications that affect genomic sequences, transcriptomic patterns, proteomic and metabolomic profiles, and changes in cellular networks and brain region functions. Conventional single-omics methods together with targeted research approaches provide limited understanding of this intricate system. Researchers need to develop complete analytical systems for studying viral infections in neurodegenerative diseases because these systems must link data from different biological scales to prove their relationship[6]. Systems bioinformatics enables researchers to understand the complex networks of genes, proteins, metabolites, and cells which become disrupted during infection-associated neurodegeneration[6]. Scientists use network biology to study disease-related molecular interactions by combining different omics data for complete disease network analysis[7]. Scientists analyze virus–host interaction networks with disease-specific molecular data to discover essential hub molecules and pathways which reveal the mechanisms of neurodegenerative processes triggered by viral disruptions.

Scientists can now study viral effects in detail because modern technological systems provide advanced capabilities. Single-cell transcriptomics combined with spatial omics enables identification of viral markers in particular cell groups while also showing their connection to neuropathological changes that result from localized infections, avoiding the tissue averaging effect of bulk studies. The application of machine learning and artificial intelligence (AI) techniques for detecting complex patterns in multi-omics data and predicting virus-associated biomarkers or drug repurposing targets in virus–host networks continue to grow. These new technologies allow network biology to examine large complex datasets and find relationships that traditional analytical methods cannot identify [6], [7]. This review evaluates current scientific breakthroughs about viral infections leading to neurodegenerative diseases, using modern multi-omics and network-based methods that drive faster research advancement in this field. The first part of the review examines the wide range of viruses present in aging and diseased brains and the evidence for their established role in neurodegenerative disease development. We then discuss methodological advances in detecting and analyzing the brain virome, from next-generation sequencing to new computational pipelines. The review emphasizes integrative methods which combine single-cell and spatial omics with proteomics, metabolomics, and network medicine approaches to study viral–host interactions at a systems level. These research methods reveal molecular mechanisms (virus-induced protein aggregation, metabolic rewiring, and immune dysregulation) which explain the relationship between infections and neuronal death[4]. The last part of the paper outlines how combined methods can create new biomarkers and therapeutic targets, while also discussing the current research challenges that need to be resolved.

Background

Recent research has renewed interest in investigating viral infections as potential contributors to neurodegenerative diseases.

The idea that infections lead to neurodegenerative diseases has existed since ancient times, but scientists only started to take it seriously in the last few decades. Previous research from the last few decades established connections between particular pathogens and Alzheimer's disease through the identification of herpesvirus DNA in Alzheimer's brain tissue and the occurrence of Parkinsonian symptoms after viral encephalitis. The research results were interesting, yet scientists treated them as anecdotal evidence which took a backseat to established protein-based mechanisms. Multiple neurodegenerative diseases develop as a direct result of infections, according to epidemiology and molecular science research studies[5]. The infection hypothesis of neurodegeneration suggests that pathogens start neurotoxic processes through two mechanisms: either direct brain cell destruction or sustained neuroinflammation that results in neuronal and glial cell damage[5]. The effects of viral infections differ from single genetic mutations because pathogens create multiple effects by producing toxins, modifying immune responses, breaching the blood-brain barrier, and triggering protein misfolding and cell death[5]. These various routes of infection enable pathogens to cause the intricate neurodegenerative disease processes.

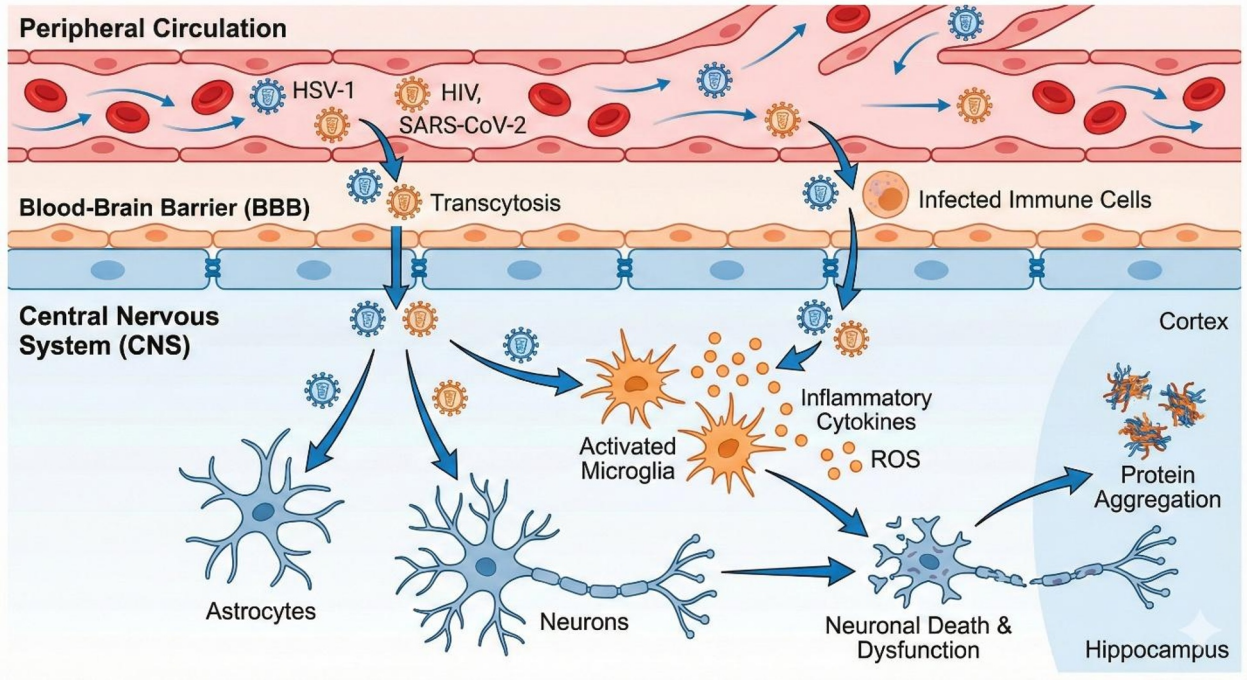

Figure 1. Conceptual schematic illustrating proposed mechanisms Viral Entry Routes and Mechanisms Driving Neurodegeneration

Schematic illustration of how neurotropic viruses contribute to neurodegenerative pathology. Viruses such as HSV-1, HIV, and SARS-CoV-2 infiltrate the central nervous system through routes including blood–brain barrier disruption, infected immune-cell trafficking, and neural pathways. Once inside the CNS, viruses infect neurons, microglia, and astrocytes, inducing chronic neuroinflammation, cytokine release, oxidative stress, and impaired autophagy. These processes converge on hallmark neurodegenerative mechanisms, including protein aggregation, synaptic dysfunction, mitochondrial impairment, and neuronal loss. This figure summarizes the infection-driven pathways discussed in the Introduction and Background sections.

The current understanding shows that neurodegeneration cannot be caused by a single infectious agent affecting all patients. No single pathogen (or group of pathogens) is solely responsible for diseases like Alzheimer's or Parkinson's in every case[5]. An individual's disease risk and progression will depend on the interaction between their exposures and their individual susceptibility. How people respond to infections depends on their genetic makeup, immune system strength, and microbiome diversity, because these host factors determine which individuals will develop neurodegenerative changes after infection[5]. The risk of neurodegeneration becomes higher when multiple infections occur simultaneously or in succession compared to a single infection[8]. Scientists are developing models to analyze multiple pathogens simultaneously, because neurodegenerative diseases show distinct features. Recent high-throughput studies reinforce this view: rather than finding one "smoking gun" microbe, researchers often detect entire communities of viruses present in aging or diseased brains. Research on human brain viruses shows that herpesviruses and polyomaviruses exhibit typical neurotropic behavior, but scientists have also found novel viral species which demonstrate different brain virome patterns between normal and pathological brains[1], [5]. The human body hosts multiple brain viruses, which makes it difficult to prove their direct disease-causing potential or their ability to infect damaged brain tissue. More research is required because these viruses exist in multiple forms and affect numerous people worldwide. They present new targets for investigating how persistent viral infections or reactivations might seed neurodegenerative pathology.

Research has shown that viral infections activate multiple molecular pathways which are also implicated in neurodegenerative diseases. Neurotropic viruses cause disease-related misfolded protein accumulation through two distinct mechanisms that affect protein clearance and create pathological protein aggregates[4]. The CNS can become chronically infected with viruses, which activates glial cells permanently while releasing pro-inflammatory cytokines that produce an inflammatory environment resembling – and possibly accelerating – the immune system problems found in degenerating brains[4]

The presence of viruses leads to oxidative stress and mitochondrial damage in neurons, as demonstrated by studies showing that HIV and other viruses cause neural cell mitochondrial dysfunction and autophagy impairment resulting in Alzheimer's- and Parkinson's-like damage[4]. The brain experiences two main changes in cellular metabolism and neurotransmitter systems when viral infections occur. Viruses modify glutamate and serotonin pathways to enable their replication process while causing harm to brain cells[4]. These convergent mechanisms show that viruses, although external pathogens, can invade internal neurodegenerative processes through different entry points. Studying how viruses disrupt these pathways yields a two-fold benefit: it reveals disease triggers and creates new understanding of disease mechanisms. Investigating the role of viral infections in neurodegeneration poses significant scientific challenges, owing to the complexity of both the infections and the diseases. Neurodegenerative disorders develop gradually over many years or decades, whereas viral infections can be short-term or chronic with sporadic reactivations. Disentangling a timeline of cause and effect thus requires longitudinal data and inventive models. Traditional experimental methods (e.g., infecting animal models with a candidate virus) have provided important data, yet they do not accurately represent the multifactorial nature of human disease. Postmortem human tissue studies, while valuable, mostly reveal correlations (virus present in brain tissue alongside pathology) but often fail to establish that the viral presence in brain tissue leads to neuropathological changes[5]. There is also the problem of specificity: certain viruses can reside in the CNS without triggering noticeable harm in most people (for instance, JC polyomavirus usually remains dormant without symptoms), yet these viruses still cause disease in specific instances. Answering such questions demands large amounts of data and sophisticated analytical techniques that go beyond basic one-virus-one-effect approaches.

The main problem stems from the need to combine data points that exist at different biological scales. During virus-induced neurodegenerative processes, viral genes may integrate into or episomally persist in the host genome, host gene expression profiles are altered, proteins and metabolites involved in inflammation and cell death pathways are modulated, and crosstalk occurs between neurons, microglia, astrocytes, and peripheral immune cells. Capturing this full picture requires multiple omics methods: genomics to detect viral sequences and relevant host mutations, transcriptomics for studying host gene expression changes, proteomics and metabolomics for downstream effects, and so on[6]. Analyzing each of these layers separately provides a piecemeal view, and critical insights could be missed if, for example, a viral protein's effect on a metabolic enzyme is only apparent when gene and metabolite data are integrated. Integrative frameworks thus become indispensable, and recent translational studies have demonstrated that multi-omics integration can markedly advance our understanding of complex disease biology [6]. Network biology and systems medicine approaches provide powerful solutions for grappling with this complexity. Instead of viewing each gene or protein in isolation, network-based approaches map interactions across molecules, cells, and tissues. In the context of virus–host interactions, such approaches connect viral factors to host pathways holistically. For instance, the study of virus–host protein–protein interaction networks shows how a viral protein might bind to various human proteins that serve as essential nodes in neurodegenerative pathways[7]. Scientists can detect the points of intersection between viral infection and disease pathology by overlaying known ND-associated molecules onto these networks. Network analyses have identified master regulator molecules of inflammation and metabolism that are activated by viral infections and in neurodegenerative brains, which could serve as therapeutic targets[7].

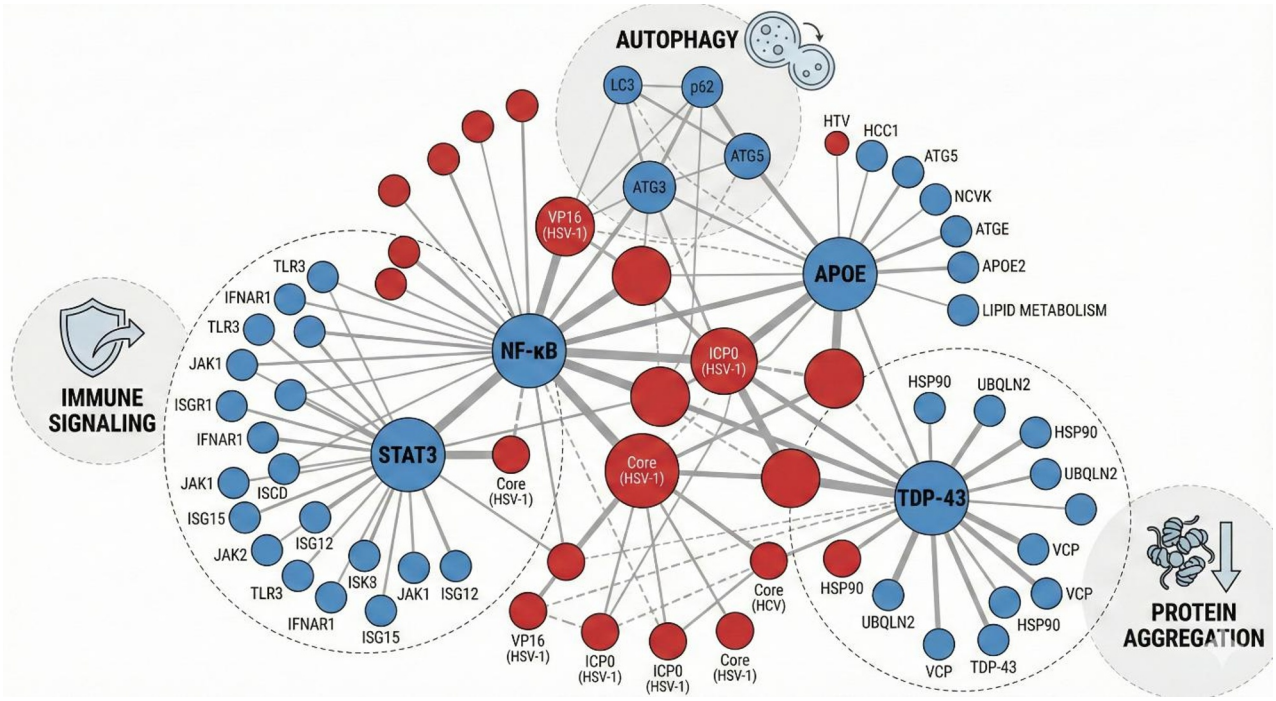

Figure 2. Illustrative network representation based on published interaction datasets of Virus–Host Protein Interaction Network in Neurodegenerative Pathways.

Network representation of viral proteins interacting with human host proteins implicated in neurodegenerative disease mechanisms. Viral proteins (red nodes) and host proteins (blue nodes) form interaction clusters revealing shared pathways such as immune signaling, autophagy, metabolic regulation, and protein aggregation. Hub host proteins—those with high centrality—highlight potential molecular bottlenecks where viral perturbation may accelerate neurodegenerative processes. This network visualization supports the systems-biology perspective described in the "Network Biology and Systems Medicine" discussion.

Table 1. Major molecular and cellular mechanisms through which viral infections contribute to neurodegenerative pathology.

Mechanism	Molecular/Cellular Process	Example Viruses	Supporting Evidence	References
Chronic Neuroinflammation	Sustained microglial and astrocyte activation; cytokine overproduction (IL-6, TNF-α).	HSV-1, HIV-1, SARS-CoV-2	Elevated neuroinflammatory cytokines in infected brains.	Kettunen et al., 2024; Wongchitrat et al., 2024
Protein Misfolding and Aggregation	Viral proteins promote amyloid-β or α-synuclein aggregation.	HSV-1, EBV	Viral infections promote amyloid deposition and tau phosphorylation.	Sait et al., 2021; Bovis et al., 2025

Mechanism	Molecular/Cellular Process	Example Viruses	Supporting Evidence	References
Mitochondrial Dysfunction	Impaired oxidative phosphorylation and increased ROS leading to neuronal apoptosis.	HIV-1, HSV-1	Viral proteins alter mitochondrial dynamics and energy metabolism.	Wongchitrat et al., 2024
Immune-Mediated Demyelination	Cross-reactive viral antigens target myelin proteins (molecular mimicry).	EBV, Varicella-Zoster Virus	Viral epitopes similar to host CNS proteins trigger autoimmune demyelination.	Mielcarska & Rouse, 2025
Epigenetic Reprogramming	Viral infection modifies DNA methylation and histone acetylation in neurons.	HHV-6, CMV	Infected neurons show altered chromatin states regulating neurodegeneration genes.	O'Connor et al., 2023

The mechanisms summarized here represent associations reported in the literature and do not necessarily imply direct causation. The table summarizes the primary pathways affected by neurotropic and systemic viral infections—including neuroinflammation, protein aggregation, mitochondrial impairment, autoimmunity, and epigenetic changes—highlighting representative viruses and supporting literature.

The last set of challenges includes both operational and technological obstacles.

The process of detecting viruses in brain tissue becomes extremely challenging when searching for latent viruses that exist at minimal concentrations. The detection of brain-resident viruses requires highly sensitive sequencing methods together with strict bioinformatic analysis to prevent false positive results (since tiny viral fragments could stem from contamination or blood components rather than actual brain infection). The ability to distinguish active viral replication versus dormancy is also essential, because active replication produces more direct harmful effects. Scientists can determine which brain cells contain viral transcripts through single-cell RNA sequencing with viral read detection[9]. Similarly, spatial transcriptomics can map viral RNA and host responses within intact brain tissue, capturing the microanatomical context of infection (for example, a virus localized to an amyloid plaque or specific brain region)[10]. These high-resolution technologies produce enormous amounts of data that require AI/ML solutions for analysis. AI technology enables doctors to study patient data regarding their virome and immune signature, showing that viral infections can lead to distinct neurodegenerative subtypes[7], [8].

Scientists can address some research problems by combining computational progress with cloud computing infrastructure and international data-sharing collaborations. Identifying the viral factors that contribute to neurodegeneration is difficult, but multi-omics integration combined with network biology and advanced analytical tools shows strong potential for progress. These frameworks both explain the biological mechanisms and create opportunities to find new biomarkers and develop new treatments.

Case Studies: Specific Disease Applications

Alzheimer's Disease (AD) and Viral Connections

Alzheimer's disease has been at the forefront of research into microbial triggers of neurodegeneration. Research indicates that hidden neurotropic viruses play a role in creating the pathologies that lead to Alzheimer's disease. Herpes simplex virus type 1 (HSV-1) in particular has been detected at higher frequencies in the brains of patients with AD, and carriers of HSV-1 who also possess specific genetic risk factors (e.g., the APOE-ε4 allele) show an increased risk of developing Alzheimer's[11]. HSV-1 reactivation in the brain results in localized neuroinflammation which leads to the formation of amyloid plaques or tau tangles. Research has shown that

herpesviruses exist in AD brains, but scientists have also found other viral signatures in these brains. Studies have detected human herpesvirus 6 (HHV-6) DNA and RNA in Alzheimer's samples, and a 2025 study found that viral infections can harm neurotransmitter systems which may trigger neurodegenerative processes[12]. A study by Bovis et al. (2025) found that viral infections caused by HIV-1 or HSV-1 disrupt glutamate and nitric oxide pathways in neurons, leading to calcium influx, tau phosphorylation, and synaptic damage[12]. These molecular changes in brain tissue correspond to all the main characteristics of Alzheimer's disease pathology. Several studies have suggested possible viral involvement in AD, although the strength and consistency of this association remain actively debated, scientists are now considering viruses as potential contributors to both the onset and progression of the disease[13]. The direct evidence needed to prove that viral infections cause Alzheimer's disease remains elusive, but researchers have identified common pathways between viral brain infections and Alzheimer's progression, which indicates that infections could accelerate Alzheimer's in susceptible individuals.

Amyotrophic Lateral Sclerosis (ALS) and TDP-43 Proteinopathy

Some studies have proposed that viral infections may influence ALS-related molecular pathways, which causes progressive motor neuron degeneration and TDP-43 protein aggregation in the brain. The first clue of a virus-ALS link came when scientists discovered that TDP-43 binds to HIV-1 transcripts to suppress viral gene expression, revealing a connection between viral infection and TDP-43 biology[14]. Scientists are now investigating how viral infections might affect the process of TDP-43 mislocalization and aggregation in ALS patients. A 2023 review by Rahic et al. presented various connections between viruses and TDP-43 pathology, showing that viral infections affect host neuronal RNA processing and stress granule behavior, which are fundamental to TDP-43 disease mechanisms[14]. Scientists have also found endogenous retroviral elements (HERVs) in the human genome – remnants of ancient viral infections – that show unusual activity in certain ALS patients. These elements produce toxic viral proteins which can damage motor neurons. Studying ALS through computational network analysis reveals how viral infections disrupt essential pathways, leading to the identification of viral proteins that interact with host proteins controlling proteostasis and neuroinflammation, thus worsening ALS symptoms. The current lack of direct evidence for viral causes of ALS does not rule out the possibility that viral infections or reactivations, including endogenous retrovirus activation, could trigger ALS in genetically or age-vulnerable neurons. Studies are now examining whether antiviral treatments or vaccines might reduce ALS risk or slow disease progression in specific groups of people, as scientists increasingly consider viral factors in what was once viewed as a non-infectious neurodegenerative disorder.

HIV-Associated Neurocognitive Disorder (HAND)

HIV infection provides a clear example of an infectious disease that causes neurodegeneration. HIV-positive patients continue to develop HIV-associated neurocognitive disorders (HAND) despite effective antiretroviral therapy because the virus enters the CNS and causes chronic inflammation leading to neurological impairments. The direct involvement of HIV in HAND differs from Alzheimer's and ALS because HIV infects brain-resident macrophages and microglia, resulting in neurotoxic viral products and cytokines that harm neurons. Moreover, HIV infection creates an immunosuppressed environment that allows other latent viruses in the brain to reactivate. For example, JC polyomavirus can lead to progressive multifocal leukoencephalopathy (PML) when it infects someone with HIV/AIDS, and herpesviruses can remain active in the body, continuously activating the CNS immune system. Research into the brain virome of HIV patients has begun using multi-omics analysis of brain tissue samples to identify its full scope. Dang et al. (2024) used the ViroFind sequencing pipeline to characterize viral signatures present in brain tissues from HIV-positive and HIV-negative individuals. The analysis identified multiple viral sequences, including herpesviruses, torque teno virus, and several low-abundance viral reads. Notably, some of the most abundant detected sequences corresponded to viruses not typically associated with human CNS infection, highlighting the possibility of environmental contamination or sequencing artifacts in metagenomic datasets[2]. These observations emphasize the importance of careful interpretation when assessing brain virome composition. They further found that HIV-positive individuals with substance use disorder had more brain viruses and higher levels of Torque teno virus and Epstein–Barr virus[2]. These findings indicate that HIV infection, together with other health conditions, changes the brain virome composition in ways that might increase the risk of neurodegenerative diseases. Scientists have used systems-biology approaches to investigate HIV protein interactions with human neuronal proteins, revealing that the virus interferes with host pathways that regulate metabolic processes, synaptic functions, and cell survival mechanisms[5]. The medical management of HAND is difficult because HIV viremia can be kept under control, yet viral proteins together with secondary infections continue to drive neuroinflammatory reactions. The HAND case demonstrates that viral brain infections – by altering the

secondary virome – can cause progressive neurodegenerative effects, a phenomenon that may help explain other neurodegenerative diseases that do not have direct viral involvement.

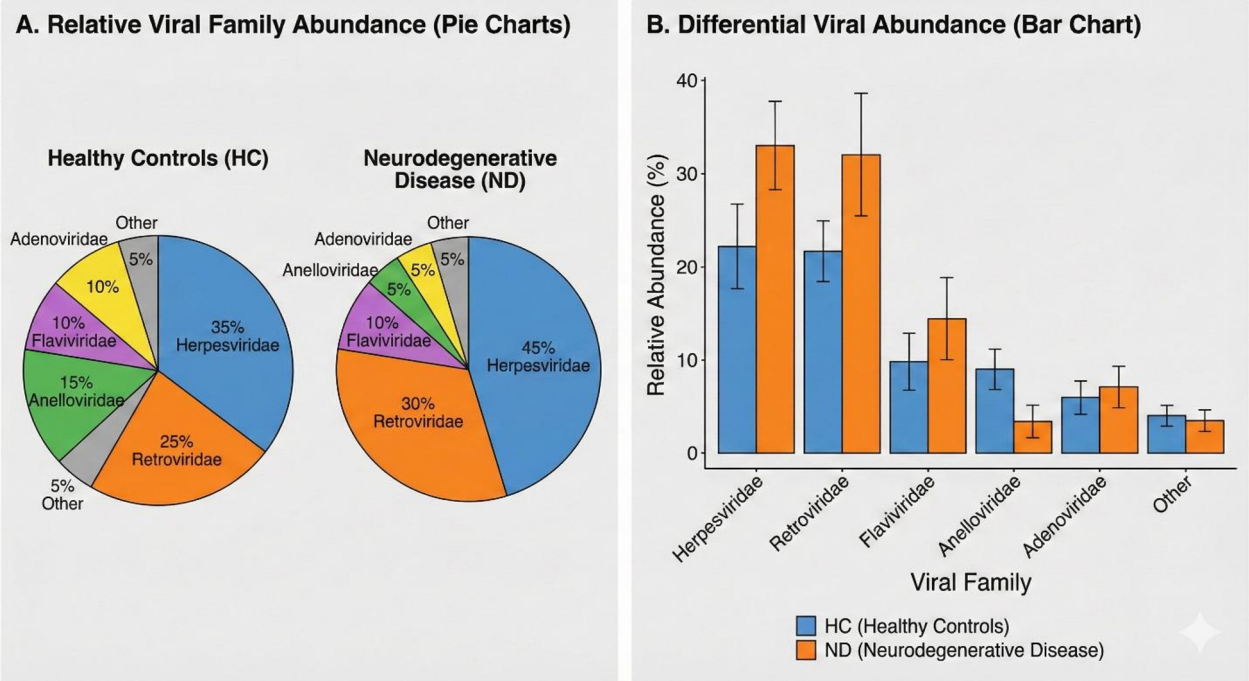

Figure 3. Conceptual visualization representing viral community patterns reported in sequencing studies. *Data visualization of viral community structure ("brain virome") derived from sequencing-based studies of human brain tissue. Relative abundances of major viral families detected in neurodegenerative disease versus healthy control brains are shown (e.g., Herpesviridae, Retroviridae, Polyomaviridae). Optional diversity indices or ordination plots highlight group-level differences in viral richness and community variation. These visualizations represent the expanding evidence that aging and diseased brains harbor complex viral communities with potential mechanistic roles in neurodegeneration, as described in the Background and Case Studies sections.*

COVID-19 and Long-Term Neurological Effects

The COVID-19 pandemic has brought new attention to viral impacts on the brain. The virus SARS-CoV-2 primarily causes respiratory problems, but severe or prolonged COVID-19 cases show neurological and cognitive symptoms in many patients. Acute COVID-19 can lead to encephalitis, stroke, anosmia, and other neurological complications in a subset of individuals. A UK Biobank study utilizing longitudinal imaging detected brain structural changes even in mild cases[15]. This raises concern that SARS-CoV-2 infection might accelerate neurodegenerative processes in some individuals or at least produce lasting deficits in cognitive function (often referred to as "brain fog"). The mechanisms behind these effects are still under study. SARS-CoV-2 has some capacity for neuroinvasion – it can infect cells in the olfactory epithelium and, in certain experimental models, neurons or glial cells – but direct viral infection of the brain appears relatively limited and infrequent in humans. Instead, the virus creates a more critical impact through its ability to activate systemic inflammation, which can break through the blood–brain barrier and trigger microglia and astrocytes in the brain, establishing a long-lasting inflammatory state after the initial infection. This neuroinflammatory state shows characteristics similar to those of chronic neurodegenerative diseases. COVID-19 infection can also lead to autoimmune reactions and vascular damage that result in microclotting and small vessel injuries, which could explain post-infection cognitive decline. Research studies have established that long COVID (post-acute sequelae of SARS-CoV-2 infection) shows similarities with other virus-related neurodegenerative

diseases, because severe viral infections have been hypothesized to potentially accelerate neurodegenerative processes in susceptible individuals, although long-term evidence remains limited[13]. Ongoing studies are tracking large cohorts of COVID-19 survivors to see if their long-term rates of neurodegenerative disease are elevated. The COVID-19 pandemic highlights that COVID-19 and similar respiratory viruses can cause neurological and neurodegenerative effects in older brains, underscoring the need for continued scientific investigation to understand these outcomes.

Table 2. Summary of viral associations with major neurodegenerative diseases.

Disease	Associated Virus(es)	Proposed Mechanism	Key Evidence / Findings	References
Alzheimer's Disease (AD)	Herpes Simplex Virus-1 (HSV-1), Human Herpesvirus-6 (HHV-6), Cytomegalovirus (CMV)	Viral reactivation triggers amyloid-β aggregation and tau phosphorylation via neuroinflammation.	HSV-1 DNA detected in AD brains; APOE-ε4 carriers more susceptible; viral proteins colocalize with amyloid plaques.	Sait et al., 2021[11]; Bovis et al., 2025; Mielcarska & Rouse, 2025[13]
Parkinson's Disease (PD)	Epstein–Barr Virus (EBV), Influenza Virus, SARS-CoV-2	Immune-mediated dopaminergic neuron loss; α-synuclein misfolding via inflammatory pathways.	Post-infection parkinsonism seen after viral encephalitis; COVID-19 associated with accelerated PD onset.	Mielcarska & Rouse, 2025[13]; Douaud et al., 2022[15]
Amyotrophic Lateral Sclerosis (ALS)	Endogenous Retroviruses (HERV-K), HIV-1	Viral proteins interact with TDP-43, causing aggregation; retrovirus reactivation induces motor neuron death.	Elevated HERV-K expression in ALS patients; HIV-1 infection linked with ALS-like symptoms.	Rahic et al., 2023[14]; Wongchitrat et al., 2024[4]
HIV-Associated Neurocognitive Disorder (HAND)	HIV-1, JC Polyomavirus, Epstein–Barr Virus	Direct CNS infection; chronic neuroinflammation and oxidative stress; immune exhaustion.	HIV and secondary viruses detected in brain tissues via deep sequencing (ViroFind).	Dang et al., 2024[2]; Kettunen et al., 2024[5]
COVID-19 (Long COVID)	SARS-CoV-2	Neuroinflammation, microvascular damage, autoimmunity, and persistent immune activation.	MRI evidence of cortical thinning and neuronal loss; increased inflammatory markers.	Douaud et al., 2022[15]; Mielcarska & Rouse, 2025[13]

These viral associations are based on reported correlations and mechanistic hypotheses rather than definitive causal relationships. This table compiles key viruses implicated in Alzheimer's disease, Parkinson's disease, ALS, HIV-associated neurocognitive disorder, and COVID-19–related neurological decline, along with proposed pathogenic mechanisms and supporting evidence from recent studies.

Emerging Methods and Technological Innovations

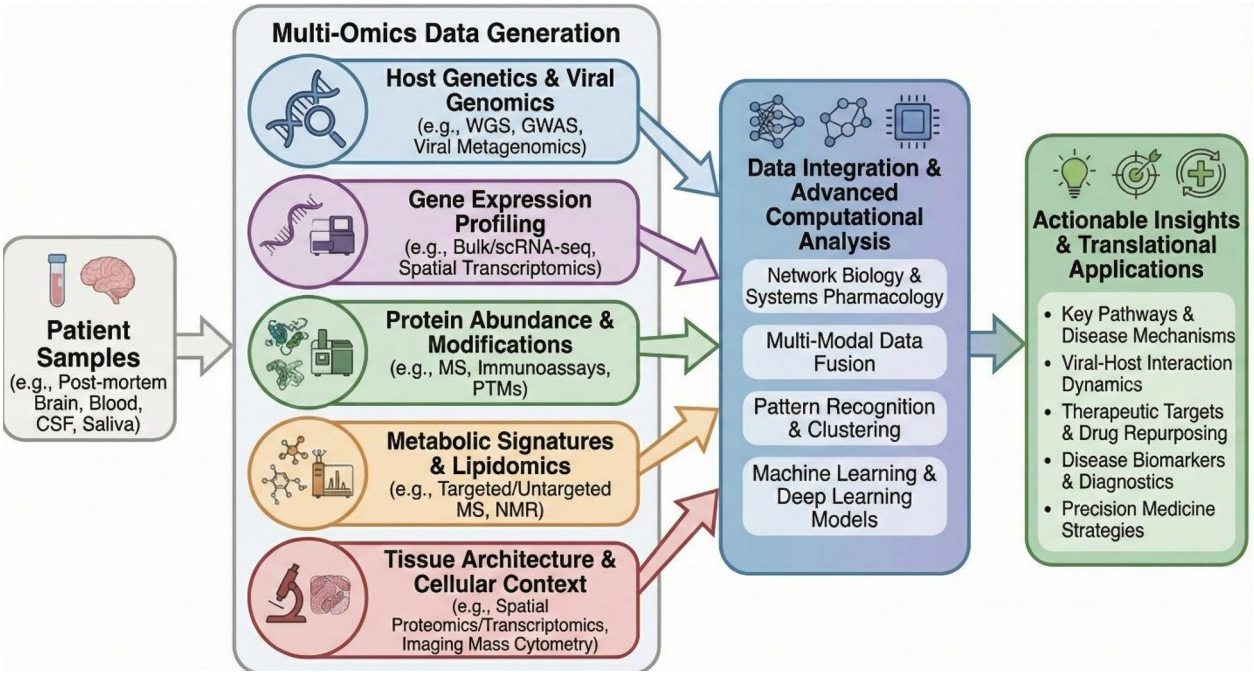

Figure 4. Proposed Conceptual Integrative Multi-Omics Workflow for Studying Viral–Host Interactions
Overview of the multi-omics and systems-biology framework applied to dissect virus–host interactions in neurodegenerative diseases. Patient-derived samples undergo genomics, viral metagenomics, transcriptomics, proteomics, metabolomics, and spatial or single-cell omics profiling. These datasets are systematically integrated using computational pipelines, network biology, and AI/ML algorithms to identify host pathways disrupted by viral infection, molecular signatures of susceptibility, and potential therapeutic targets. This workflow reflects the integrative strategies detailed in the "Emerging Methods and Technological Innovations" section.

Spatial and Single-Cell Omics Technologies

Scientists study virus–host interactions in the brain using spatially resolved and single-cell omics methods. Traditional bulk tissue analysis combines signals from millions of cells, which can mask critical localized effects of viral infection. Researchers can now examine gene expression patterns of both host and viral components at cellular and subcellular levels by combining new spatial transcriptomics platforms with single-cell RNA sequencing (scRNA-seq). These methods have ushered in a new era for neurodegenerative disease studies. Single-cell transcriptomic analyses have uncovered previously unrecognized brain cell diversity in ND patients by examining glial and immune responses[9]. Analyzing virus-exposed or infected brain tissues via scRNA-seq allows scientists to track viral RNA in specific cell types and study associated gene expression changes. He et al. (2024) identified distinct glial and immune cell populations with differential inflammatory gene expression profiles across neurodegenerative disease subtypes, highlighting previously unrecognized cellular heterogeneity within lesion microenvironments[9]. The distribution of viral genes and host response genes in whole tissue sections can be studied through spatial transcriptomics and multiplexed in situ profiling methods (e.g., MERFISH and NanoString GeoMX). **Fangma et al. (2023)** describe the suite of spatially resolved multi-omics platforms — including

MERFISH and imaging mass spectrometry — that are now capable of detecting viral RNA and host responses within their precise microanatomical context, creating the technical basis for future studies mapping viral signatures

relative to amyloid pathology and microglial activation[10]. Spatially resolved data illustrate how infection and degeneration occur together in specific brain regions. The field of transcriptomics has now extended to spatial proteomics and metabolomics via techniques like imaging mass spectrometry and high-plex immunofluorescence, enabling researchers to study proteins and metabolites in their native locations. These approaches allow detection of viral proteins in specific neurons and analysis of how local metabolite changes (such as lactate accumulation or neurotransmitter alterations) affect neighboring infected cells. The analysis of spatial and single-cell datasets is challenging due to their large volume and complexity, which demands powerful computational systems and artificial intelligence to identify meaningful patterns. Nonetheless, applying these advanced methods has led to groundbreaking discoveries about how viral infections alter cellular environments and their relationship to disease progression.

Real-Time and Longitudinal Analyses

Researchers are developing advanced methods to monitor virus–host interactions both in real time and over extended periods. Traditional experiments often provide only static "snapshots" of the brain at a given time point (frequently at end-stage disease). To study infection and neurodegeneration progression, scientists need to observe changes across multiple time points. Live-cell imaging combined with in-vivo longitudinal imaging now allows observation of cellular behavior over time. For instance, two-photon microscopy can be used to watch viral spread in animal brains while simultaneously monitoring real-time immune cell activation. Similarly, scientists track synaptic spine loss and the spread of protein aggregates over days to weeks by observing neurons and glial cells in models of viral encephalitis or chronic infection. The progression of brain inflammation and degeneration can also be followed in patients or animal models through longitudinal MRI and PET imaging, starting before infection, continuing during infection, and after recovery. Such methods have been applied to COVID-19 patients: serial MRI scans have monitored brain changes (e.g., inflammation resolving and atrophy developing) over months of recovery. Time-course multi-omics experiments are increasingly feasible for molecular studies as well. Scientists infect neural cell cultures or organoids and then collect samples at multiple time points for transcriptomic, proteomic, and metabolomic analyses to track molecular changes over time. Using these time-series approaches, researchers can identify the timing of initial responses and subsequent events (for example, demonstrating that interferon production precedes prolonged neuronal metabolic dysfunction). Analysis of time-dependent data requires dynamic network modeling approaches to understand how initial viral perturbations propagate through biological networks over time, resulting in cell death. By applying predictive modeling, researchers can also simulate therapeutic interventions at various time points to pinpoint optimal windows for halting the degenerative process with antiviral or anti-inflammatory treatments.

Table 3. Overview of multi-omics platforms and computational approaches used to characterize viral–host interactions in the brain.

Omics Type	Key Techniques	Primary Insights	Applications in ND Research	References
Metagenomics / Viromics	Shotgun NGS, targeted viral capture (ViroFind, VIRSorter)	Identification of latent and novel viral genomes in brain tissues.	Brain virome mapping in AD and HAND.	Dang et al., 2024; Balakrishnan et al., 2023

Omics Type	Key Techniques	Primary Insights	Applications in ND Research	References
Transcriptomics (Bulk & scRNA-seq)	RNA-seq, Smart-seq, 10x Genomics	Host and viral transcript detection at single-cell level.	Identifying viral RNA in specific cell types; immune activation mapping.	He et al., 2024
Proteomics	LC-MS/MS, SWATH-MS	Host–virus protein interaction identification and pathway enrichment.	Discovery of viral targets in Alzheimer's and ALS.	Wongchitrat et al., 2024; Santiago et al., 2017
Metabolomics	GC-MS, NMR	Detection of virus-induced metabolic rewiring (e.g., kynurenine pathway).	Neuroinflammation and oxidative stress pathway analysis.	O'Connor et al., 2023
Spatial Omics	MERFISH, GeoMX, Imaging Mass Spectrometry	Spatial localization of viral RNA/proteins in brain tissue.	Mapping viral foci relative to amyloid plaques and glial activation.	Fangma et al., 2023
Integrative Network Biology	Multi-omics integration via network analysis and ML pipelines.	System-wide mapping of viral impact on host pathways.	Identification of hub proteins and biomarkers.	Morselli Gysi et al., 2021; Vicidomini et al., 2024

This table lists major omics technologies (metagenomics, transcriptomics, proteomics, metabolomics, spatial omics) together with their key applications in neurodegenerative disease research and representative peer-reviewed sources.

Big Data, AI, and Collaborative

Scientists are developing novel experimental approaches and improving their analytical methods and collaboration to integrate virome research fully. The enormous datasets generated by sequencing, omics, and imaging technologies exceed the capacity of conventional analytical techniques. The field now operates with big data infrastructure and AI-driven analytics as standard practice. Researchers utilize cloud computing platforms to store and jointly analyze multi-terabyte datasets that include genomic reads, proteomic spectra, and imaging files. Processing virome sequencing data from hundreds of brain samples across multiple neurodegenerative diseases is now feasible through cloud-based pipelines that perform uniform data processing and enable powerful meta-analyses. AI systems, coupled with machine learning techniques, excel at detecting complex patterns in large datasets. Unsupervised learning algorithms can discover new patterns – such as specific combinations of viral strains and host gene expression changes – that classify patients into distinct groups. Researchers have applied machine learning to multi-omics data to identify viral infection markers, which allowed them to distinguish subgroups of Alzheimer's disease patients with unique clinical trajectories[8]. Scientists also use deep learning models (neural networks) to predict virus–host protein interactions and to uncover drug targets within these networks, as demonstrated in various studies[16], [17], [18], [19]. Similar network-based approaches are being explored for neurodegenerative drug discovery[20]. International consortia and data-sharing initiatives are vital for collaborative progress. The scientific community has established brain banking programs to obtain tissue samples for virome studies and to conduct epidemiological research linking past infections (from medical records) to neurodegenerative disease incidence[21]. These platforms enable global teams to perform joint analyses using common tools and dashboards. The development of federated learning provides a privacy-preserving solution by allowing models to be trained across multiple hospitals and

biobanks without moving patient data from its home institution. The combination of big data methods with AI analysis and worldwide collaboration has accelerated discoveries in understanding the brain virome and neurodegenerative disease mechanisms. The field is moving toward predictive models that could enable future risk assessments based on individual's past viral exposures and the precise identification of intervention points in the virus–neurodegeneration cascade.

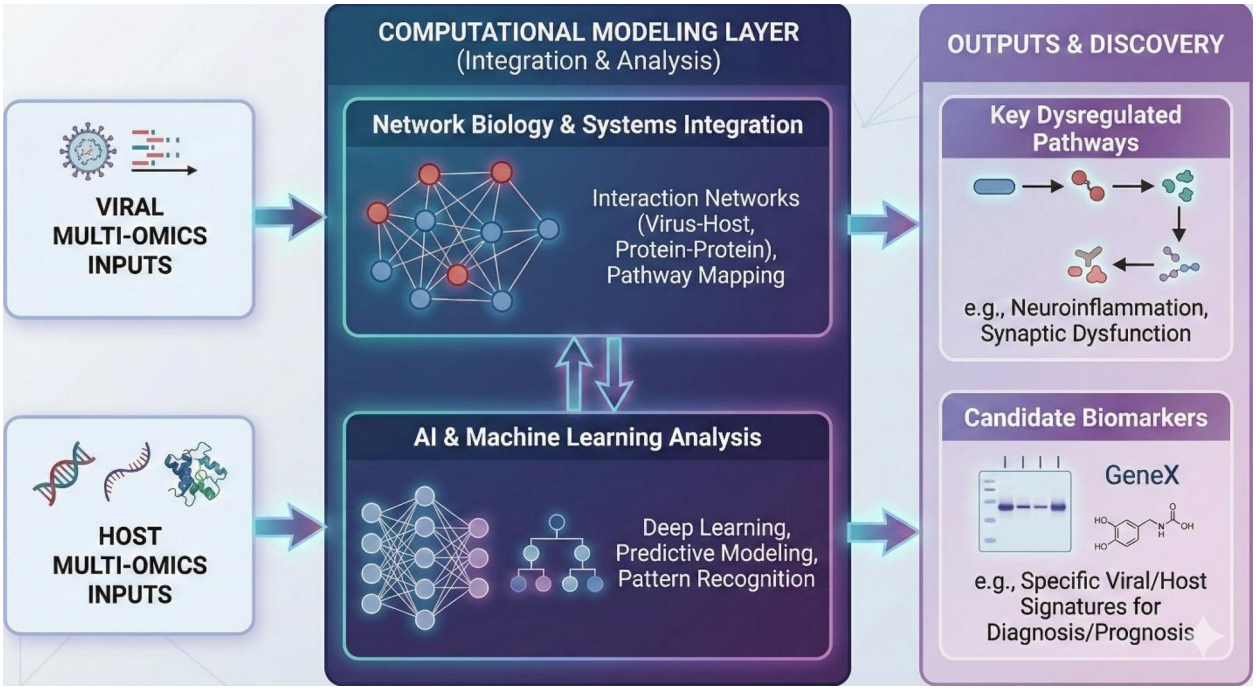

Figure 5. AI/ML-Driven Prediction of Biomarkers and Drug Targets in Virus-Linked Neurodegeneration. *Conceptual diagram illustrating artificial-intelligence pipelines applied to viral–host multi-omics data. Viral genomic sequences, host transcriptomic and proteomic profiles, and PPI networks are processed by machine-learning models—including deep neural networks and graph algorithms—to predict biomarkers, classify patient subgroups, and identify candidate drug-repurposing targets. This figure reflects the computational and predictive approaches outlined in the "Big Data, AI, and Collaborative Platforms" section.*

Current Challenges and Limitations

The interdisciplinary field has made substantial advancements, yet various obstacles and limitations continue to slow its progress.

The main technical and methodological problem lies in data integration and standardization. Different studies use different approaches to detect viruses (different sequencing platforms and bioinformatic pipelines) and to study host responses (different omics technologies). This wide range of data types makes it difficult for researchers to achieve consistent results between studies or to combine datasets. The human microbiome field created benchmarking methods which demonstrate the need to develop standardized analytical methods and reference data for brain virome research. Analyzing multi-omics data from thousands of patients faces a major technical hurdle because it requires substantial computational power. Research groups that do not have access to high-performance computing systems may experience delays, as they cannot easily conduct big-data research – leading to a bias where only well-funded laboratories pursue certain studies. The study of Alzheimer's disease has also faced reproducibility issues, because certain findings about virus detection in Alzheimer's brains have not produced consistent results when researchers

attempted to verify them in independent studies. These results indicate that virus detection needs rigorous validation, for example through sequencing, qPCR, and immunohistochemistry on multiple patient populations. Data analysis also needs strict controls, because noise and artifacts (such as viral reads from contamination) can lead to incorrect conclusions.

Biological and interpretational challenges are equally pressing, the question of causality vs. correlation. Many studies can identify that viruses and neurodegenerative pathology co-exist but proving that viruses cause or exacerbate the degeneration is difficult. The lack of human longitudinal data forces researchers to rely on animal models and cell culture models, which do not perfectly replicate human disease states. Moreover, each patient's situation is unique – host genetic variation means that a virus triggering disease in one person might be harmless in another. The same viral infection can produce severe encephalitis in one individual but be completely benign in another, because of genetic differences in their immune system. The diversity of infections also makes it hard to understand the relationship between infections and NDs in epidemiological studies. There is a further distinction between tissue-specific and systemic effects: some viruses can contribute to neurodegeneration through peripheral infection and inflammation (such as a systemic viral infection that never penetrates the brain but causes chronic inflammation or autoimmunity that harms the CNS). Research studies need specific designs to evaluate CNS tissue and blood markers separately, to distinguish direct neurotropic effects from systemic effects that occur elsewhere in the body. Identifying individual pathogens is additionally complicated when patients have multiple co-infections, because it becomes difficult to determine which specific infection (or combination of infections) causes brain damage, or if the combined infections together create the problem.

Platforms Contamination and Interpretation Challenges in Brain Virome Studies

Low microbial biomass tissues such as the brain present significant challenges for virome detection. Viral reads detected through metagenomic sequencing may originate from laboratory reagents, sequencing adapters, environmental contamination, or peripheral blood contamination rather than genuine CNS infection. Several studies have reported unexpected viral taxa, including viruses associated with parasites or environmental sources, among the most abundant reads. These findings emphasize the need for stringent contamination controls, including negative controls, independent replication, and orthogonal validation techniques such as quantitative PCR or imaging-based methods. Without such validation, it remains difficult to distinguish true viral presence from sequencing artifacts.

Additional issues involve ethical, regulatory, and training challenges. Gene editing technologies and other experimental interventions face heightened ethical scrutiny when moving from the laboratory into medical practice. Combining genomic data with infection records and neurological health information generates privacy concerns – patient anonymity and robust consent procedures are critical when sharing data internationally. The identification of viral markers and development of antiviral treatments for NDs will also require adjustments to regulatory procedures. For example, testing antiviral drugs or vaccines for managing neurodegenerative risk (such as administering anti-herpes medications to asymptomatic APOE4 carriers to slow Alzheimer's progression) will demand substantial evidence of safety and efficacy, given the long-term risks of such interventions. Implementing public health measures for infections linked to NDs faces challenges because these measures must reach all segments of the population equally, yet lower-income and marginalized groups often lack adequate healthcare access. Training the next generation of researchers is another challenge – it requires education in virology, neuroscience, and data science. New cross-disciplinary programs and funding initiatives to support such training have only recently begun. The field needs to solve these operational and ethical problems before scientists can transition from discovery research to intervention efforts.

Conclusion

Research findings show that scientists now understand neurodegenerative diseases **do not develop** from internal factors alone, as viral infections represent one of several environmental factors contributing to neurodegenerative disease development. Researchers are no longer searching for a single microbial origin of Alzheimer's or Parkinson's, instead, they study how individual virome elements and immune system components influence existing neurodegenerative disease processes. Scientists have reached a more complete understanding through the integration of multi-omics methods with network biology techniques. They use genomics, transcriptomics, proteomics, metabolomics, and computational modeling to study the intricate molecular interactions between viruses and aging brain cells. This research has generated important results, which include the identification of concealed viruses in

brain tissue, the discovery that viral proteins accelerate proteinopathies, and the identification of critical network sites that connect antiviral and neurodegenerative pathways.

These research results carry significant implications for translation. The field of biomarkers could benefit from incorporating viral signatures – such as specific viral DNA sequences or antiviral antibody patterns – to enhance the detection of NDs alongside established markers like amyloid and tau. For instance, a combination of certain herpesvirus antibody titers and inflammatory markers could help identify patients who will experience cognitive decline. The findings also present new possibilities to develop antiviral and immunomodulatory treatments for neurodegenerative diseases. It is intriguing to consider that antivirals (e.g., anti-HSV medications) or vaccines might reduce the risk or slow the progression of diseases like Alzheimer's in subsets of patients – clinical trials are now beginning to test such possibilities. Studying virus–host interaction networks enable researchers to discover new drug applications, because medications that affect immune system functions or viral processes could potentially reduce neurodegenerative disease symptoms. Scientists are already using AI technology together with network medicine to discover new compounds that block pathogen–host interactions, as demonstrated in COVID-19 network-based drug repurposing studies and AI-driven host–pathogen protein interaction mapping[16], [17], [18], [19], [22], [23].

Multiple recommendations and future directions become apparent. Establishing causal relationships will require longitudinal cohort studies, especially now that population-based biobank research shows viral infections are associated with higher neurodegenerative risks[21]. Research efforts should include additional mechanistic laboratory experiments to expand upon current findings. Future studies need to focus on individualized virology for neurological patients, because each patient carries different infections – a scenario that would benefit from precision medicine via tailored virus screening, surveillance, and treatment plans. Ongoing technological advancement is also essential, since improved methods are needed to detect rare viruses, perform single-cell assays for viral proteins, and conduct high-throughput functional screens to understand fundamental mechanisms. Progress in this field will depend on interdisciplinary collaboration as a fundamental element. Successfully investigating challenges like COVID-19 has required virologists, neurologists, data scientists, and immunologists to collaborate through established systems for data exchange and research. Similarly, studying the brain virome's involvement in neurodegenerative diseases requires multiple experts and different research approaches due to its complex nature.

The field of virus–neurodegenerative disease research faces multiple obstacles while also offering various potential discoveries. The analysis of large datasets through integrative modeling has already suggested potential associations between past infections and neurological deterioration in older individuals. Despite growing evidence linking viral infections and neurodegenerative processes, establishing direct causality remains a major challenge and requires further experimental validation. Through continued collaborative efforts, the scientific community can better understand and ultimately control neurodegenerative diseases by examining and managing the viral factors that initiate these conditions. This new perspective builds upon existing knowledge about neurodegeneration to create innovative strategies for treating major diseases that cause serious harm to human health.

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