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REVIEW ARTICLE

Predicting the Impact of Viral Infections on Neuronal Aging and Cognitive Decline Using AI-Based Brain Transcriptomics

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ABSTRACT

Neuronal aging is a complex process characterized by cognitive decline and susceptibility to neurodegenerative diseases, including AD, MS, and PD. As individuals age, brain undergoes structural and functional alterations, leading to impaired synaptic plasticity, neuroinflammation, and oxidative stress. Additionally, aging weakens immune response, ultimately CNS more vulnerable to latent viral infections and reactivations. HSV-1 and EBV have been strongly implicated in neurodegenerative pathologies. HSV-1, a neurotropic virus, has been found in postmortem brains of AD patients, suggesting a role in amyloid-beta accumulation and chronic neuroinflammation. Similarly, EBV has been linked to MS, with viral reactivation triggering inflammatory cascades that contribute to demyelination and neurodegeneration. Other viruses, including CMV, HIV, and SARS-CoV-2, have also been associated with long-term neurological complications, worsening cognitive decline in aging individuals. By integrating deep learning and machine learning approaches, AI can predict disease progression, assess individual susceptibility to viral-induced neurodegeneration, and aid in early diagnosis. Brain transcriptomics, which involves RNA sequencing and gene expression profiling, provides insights into molecular pathways disrupted by viral infections. These technologies enhance our ability to identify biomarkers for neurodegenerative diseases, paving the way for targeted interventions. This study highlights the intersection of viral neuropathology, aging, and AI-based transcriptomics, emphasizing the need for computational tools to unravel the complexities of neurodegeneration. Understanding viral contributions to neuronal aging can lead to innovative therapeutic strategies, potentially mitigating the impact of chronic viral infections on cognitive health. As AI continues to evolve, its integration with

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neurobiology and bioinformatics will revolutionize early detection, personalized treatment, and preventive measures for age-related neurodegenerative disorders.

KEYWORDS

• Neuronal aging • Neurodegeneration • Viral infections • Brain transcriptomics • Artificial intelligence

INTRODUCTION

Neuronal Aging and Cognitive Decline: Cellular and Molecular Mechanisms

Neuronal aging is a complex biological process characterized by progressive declines in neuronal function and structure, leading to cognitive impairment and an increased predisposition to neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS). This decline is driven by cellular and molecular changes that disrupt neuroglial integrity, microtubule cytoskeleton stability, and neuronal connectivity, ultimately affecting cognitive reserve and neural plasticity (Verkhratsky, 2025). Understanding these mechanisms is critical for developing interventions aimed at mitigating cognitive decline and preventing neurodegeneration (Figure 1).

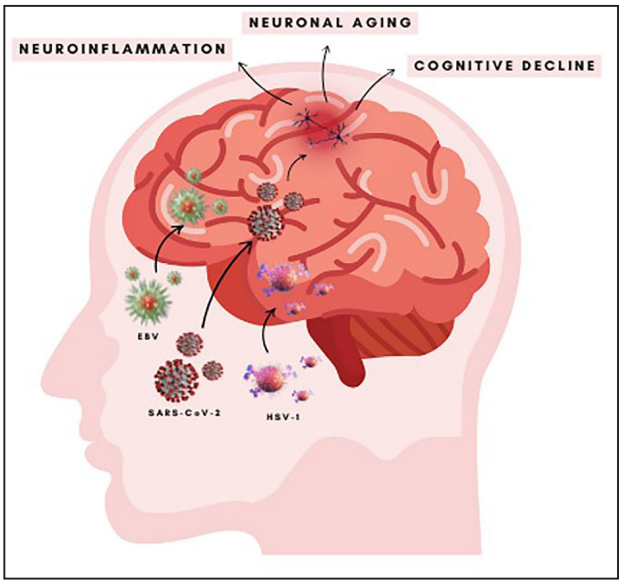


Figure 1: Viral Infections and their Role in Neuronal Aging

Neuroglial Decline and Cognitive Impairment

Neuroglial cells, including astrocytes and oligodendrocytes, play important role in maintaining neuronal health and cognitive function. However, aging leads to structural and functional deterioration in these cells, compromising neural homeostasis and increasing risk of neurodegeneration. Astrocytes exhibit significant atrophy, resulting in impaired synaptic support and neuroinflammatory responses, which contribute to cognitive dysfunction (Verkhratsky, 2025). Additionally, oligodendrocytes lose their ability to sustain myelination, reducing white matter integrity and slowing neural transmission, thereby worsening cognitive decline and neurodegenerative pathology (Verkhratsky, 2025). The decline in neuroglial support mechanisms underlines importance of therapeutic strategies aimed at preserving glial function to enhance cognitive longevity.

Microtubule Cytoskeleton Decay and Neuronal Aging

The microtubule cytoskeleton plays fundamental role in maintaining neuronal structure, axonal transport, and synaptic function. Aging disrupts microtubule stability, leading to axonal swellings, synaptic terminal degradation, and impaired intracellular transport, which are hallmarks of cognitive decline and neurodegenerative diseases (Okenve-Ramos *et al*., 2024). This cytoskeletal decay leads other neuronal aging hallmarks and is associated with tau hyperphosphorylation, a key pathological feature of AD. Studies have demonstrated that interventions targeting microtubule stability, such as genetic modulation and pharmacological agents, can moderate neuronal aging and slow cognitive decline (Okenve-Ramos *et al*., 2024).

Cellular Senescence and Cognitive Aging

Cellular senescence, process by which cells lose their ability to proliferate and function efficiently, is a major contributor to brain/neural ageing and cognitive decline. Accumulation of senescent cells in brain interrupts neuronal function, increases neuroinflammation, and worsens neurodegenerative processes (Shafqat *et al*., 2023). Senescent neurons and

glial cells secrete pro-inflammatory factors, together known as senescence-associated secretory phenotype (SASP), which promotes neurodegeneration and impairs cognitive function (Luzy *et al*., 2024). Emerging sign suggests that senotherapies, including senolytics (drugs that selectively eliminate senescent cells) and senomorphics (agents that modulate SASP factors), may offer therapeutic potential for cognitive decline and thereby brain health in aging populations (Shafqat *et al*., 2023).

Environmental and Lifestyle Modulators of Neuronal Aging

While intrinsic cellular and molecular processes initiative neuronal aging, environmental and lifestyle factors also play significant role in modulating cognitive decline. Diet, physical activity, cognitive engagement, and sleep quality have been shown to influence neuroplasticity and brain pliability against aging related worsening. Caloric restriction, for instance, has been linked to reduced neuroinflammation and enhanced synaptic function, while regular physical exercise promotes neurogenesis and synaptic plasticity (Gonzales *et al*., 2022). Furthermore, cognitive training and social engagement have been found to improve cognition, delaying onset of neurodegenerative conditions (Ridderinkhof&Krugers, 2022). Understanding relationship between genetic predisposition and lifestyle interferences can help in development of personalized strategies for maintaining cognitive function during aging.

Aging, Immunosenescence, and Viral Reactivation: The Role of Immune Decline in Latent Viral Infections

Aging is a multipart biological process associated with systemic physiological decline, including a weakened immune response that older individuals more susceptible to infections and viral reactivation. Among the key contributors to this phenomenon, they are immunosenescence and inflammaging, which compromise ability of immune system to mountaeffective response against latent viruses such as herpes simplex virus type 1 (HSV-1), Epstein-Barr virus (EBV) and etc (Chen *et al*., 2024). While immune aging is widely recognized as increased infection risk, recent studies suggest that relationship between immune decline and viral perseverance is complex, requiring further research into its fundamental mechanisms (Autio *et al*., 2022).

Immunosenescence and Altered Immune Cell Function

Immunosenescence refers to gradual decline of immune system due to aging. One of most critical indicators of immunosenescence is alteration of immune cell populations, particularly in adaptive immune system. The thymus, which is responsible for T cell maturation, experiencesinvolvement with age, lead to decline in production of naive T cells. This reduction results in a reduced capacity to recognize and respond to novel antigens, increasing vulnerability and more chanceof infections and viral reactivation (Wrona *et al*., 2024). Additionally, aging causesexpansion of memory T cells, particularly those specific to persistent viral infections like cytomegalovirus (CMV) and EBV. This shift in T cell composition reduces immune resources and also reducesability to fight new pathogens effectively (Lee *et al*., 2022). Moreover, older individuals exhibit impaired cytokine production, particularlydecline in type-I interferons, which play a crucial role in antiviral defence (Srivast *et al*., 2023). The delayed production of anti-inflammatory cytokines further worsens immune dysregulation, contributing to extended inflammation and impaired pathogen clearance.

Inflammaging: A Persistent Pro-Inflammatory State

Inflammaging is characterized by chronic, low-grade inflammation that continues even in absence of active infection stage. This inflammatory state is driven by several factors, including cellular senescence, oxidative stress, and persistent antigenic stimulation from latent viral infections (Quiros-Roldan *et al*., 2024). Senescent cells, which accumulate with aging, secrete a pro-inflammatory situation known as senescence-associated secretory phenotype (SASP), further amplifying systemic inflammation and impairing immune homeostasis (Chen *et al*., 2024). This relationship between immunosenescence and inflammaging creates an environment encouraging to viral reactivation. For instance, studies suggest that HSV-1 and EBV remain under control in young individuals due to robust immune surveillance. However, in aging individuals, the decline in immune

efficiency, coupled with chronic inflammation, weakens viral suppression, leading to increased viral shedding and potential symptomatic reactivation (Wrona *et al*., 2024). This phenomenon underscores the complex relationship between immune aging and persistent viral infections, necessitating deeper investigation into potential interventions.

Viral Reactivation and Aging

While immune decline generally correlates with increased viral reactivation, some studies suggest that the relationship is more nuanced. Autio *et al*. (2022) found that despite immunosenescence, the rate of EBV reactivation does not significantly differ with age, indicating that additional factors, such as genetic predisposition and environmental influences, may modulate viral persistence. Similarly, Quiros-Roldan *et al*. (2024) noted that while aging increases susceptibility to infections, factors such as prior viral exposure history and host immune resilience also play a critical role in determining outcomes. Understanding these dynamics is crucial for developing targeted therapeutic strategies to mitigate the impact of immune aging on viral reactivation. Lifestyle interventions, such as regular physical activity, balanced nutrition, and stress management, have been shown to enhance immune resilience and delay immunosenescence (Wrona *et al*., 2024). Additionally, emerging research on gerotherapeutics, including senolytics and immune-modulating drugs, holds promise for counteracting age-related immune decline and improving antiviral defense mechanisms (Hieber *et al*., 2023).

In conclusion, aging-induced immune decline, characterized by immunosenescence and inflammaging, significantly impacts the body's ability to control latent viral infections. While the risk of viral reactivation is generally heightened in older adults, the exact relationship between aging and persistent infections remains complex and warrants further investigation. By integrating lifestyle interventions, targeted therapies, and immunological advancements, it may be possible to enhance immune resilience and improve health outcomes in aging individuals.

The Role of AI and Brain Transcriptomics in Understanding the Impact of Viral Infections on the Aging Brain

The integration of artificial intelligence (AI) with brain transcriptomics has emerged as a groundbreaking approach to decipher the effects of viral infections on neurodegenerative processes, particularly in aging populations. Transcriptomics, which involves the large-scale study of RNA transcripts, allows researchers to analyze gene expression patterns associated with various diseases. AI-driven models enhance this analysis by identifying intricate patterns and predicting potential disease trajectories. This review explores the role of AI in transcriptomic studies related to viral infections and their implications for neurodegeneration in aging individuals.

AI in Transcriptomic Studies

AI-powered algorithms, particularly machine learning (ML) models, are revolutionizing transcriptomic research by analyzing vast datasets with high precision. These models can identify correlations between gene expression changes and clinical outcomes, thereby facilitating a deeper understanding of disease mechanisms. For instance, deep learning approaches applied to transcriptomic data have enabled the identification of biomarkers for neurological disorders linked to viral infections (Guo *et al*., 2023). Furthermore, AI-driven natural language processing (NLP) techniques have been instrumental in aggregating and analyzing large-scale transcriptomic studies, providing comprehensive insights into the molecular pathways affected by infections such as SARS-CoV-2 and herpes simplex virus-1 (HSV-1) (Zhang *et al*., 2024).

Brain Transcriptomics and Viral Infections

Transcriptomic studies have demonstrated that viral infections can significantly alter gene expression patterns in the brain, potentially accelerating neurodegenerative processes. Postmortem analyses of COVID-19 patients have revealed dysregulation in key neuroinflammatory and mitochondrial pathways, mirroring changes observed in aging brains (Mavrikaki *et al*., 2022). These findings suggest that SARS-CoV-2 may contribute to cognitive decline by inducing transcriptomic alterations associated with neurodegeneration. Similarly, research on HSV-1 infection in human cerebral organoids has shown perturbations in Alzheimer's disease (AD)-related genes. Orszulak *et al*. (2023) demonstrated that HSV-1 infection

leads to transcriptomic shifts that mimic the molecular signatures observed in AD patients. This highlights the potential role of chronic viral infections in neurodegenerative disease progression.

Implications for Aging and Neurodegeneration

Chronic viral infections may exacerbate neuroinflammation and cognitive decline in aging individuals. Studies on influenza virus infections in aged mice have revealed heightened expression of genes linked to neurocognitive dysfunction, suggesting that viral exposure could accelerate aging-related neurological deterioration (Wu *et al*., 2024). Moreover, persistent SARS-CoV-2 infections have been associated with prolonged neuroinflammatory responses, further implicating viral pathogens in the exacerbation of age-related cognitive decline (Sarkar & Ghosh, 2024). Understanding the interplay between viral infections and aging through AI-powered transcriptomics is crucial for developing targeted interventions. By identifying key molecular markers and disrupted pathways, researchers can design precision medicine approaches to mitigate the neurological impact of viral infections in older adults. AI models trained on extensive transcriptomic datasets can also enhance early detection and personalized treatment strategies for neurodegenerative conditions.

The convergence of AI and brain transcriptomics offers unprecedented insights into how viral infections influence the aging brain. By leveraging machine learning and deep learning techniques, researchers can decipher complex gene expression patterns and their implications for neurodegenerative diseases. While challenges remain, continued advancements in AI-driven transcriptomic research hold the potential to revolutionize our understanding of viral-induced cognitive decline and inform the development of targeted therapeutic strategies for aging populations.

Viral Infections and Neurodegeneration

Relationship between viral infections and cognitive decline has gained increasing attention in recent years, particularly concerning the role of Herpes Simplex Virus 1 (HSV-1) and Epstein-Barr Virus (EBV). HSV-1 has been linked to Alzheimer's disease (AD) through mechanisms involving neuroinflammation, amyloid-beta (Aβ) deposition, and tau pathology, while EBV has been implicated in multiple sclerosis (MS) and associated neuronal inflammation (Cairns *et al*., 2025; Wang *et al*., 2024). In addition, emerging evidence suggests that other viruses, such as SARS-CoV-2, Cytomegalovirus (CMV), and Human Immunodeficiency Virus (HIV), may also contribute to cognitive impairment through similar neurodegenerative pathways.

HSV-1 has long been recognized for its neurotropic properties, with the ability to establish lifelong latency in the trigeminal ganglia and reactivate under conditions of stress or immunosuppression. The reactivation of HSV-1 in the central nervous system (CNS) has been associated with the accumulation of Aβ plaques and tau tangles, which are hallmarks of AD pathology. Studies using human brain tissue models have demonstrated that repetitive injury can induce HSV-1 reactivation, leading to neuroinflammatory cascades and promoting AD-like changes, including gliosis and the deposition of phosphorylated tau (Cairns *et al*., 2025). Moreover, HSV-1 infection has been found to alter synaptic and immune gene expression, mirroring patterns observed in the early stages of AD (Funk *et al*., 2024). Furthermore, HSV-1 accelerates disease progression by triggering microglial phagocytosis and activating the NLRP3 inflammasome, further exacerbating neuronal damage (Wang *et al*., 2024).

The role of EBV in cognitive decline is particularly evident in its association with MS, a chronic inflammatory demyelinating disease of the CNS. EBV is believed to contribute to MS pathogenesis by inducing an aberrant immune response that leads to neuronal inflammation and demyelination. The presence of EBV-infected B cells in the CNS of MS patients suggests a possible mechanism by which the virus perpetuates neuroinflammation, ultimately affecting cognitive function. Although the exact mechanisms remain under investigation, EBV infection appears to play a pivotal role in modulating the immune landscape of the brain, thereby influencing disease progression and severity (Schreiner *et al*., 2024, Zhang *et al*., 2022).

Beyond HSV-1 and EBV, other viral infections have been implicated in cognitive decline. The recent SARS-CoV-2 pandemic has shed light on the potential long-term neurological consequences of viral infections, with many

COVID-19 survivors experiencing persistent cognitive dysfunction, commonly referred to as "brain fog." The neurotropic potential of SARS-CoV-2 has been demonstrated through its ability to invade the CNS via the olfactory epithelium and disrupt the blood-brain barrier, leading to neuroinflammation and neuronal damage. Emerging studies suggest that SARS-CoV-2 infection may accelerate neurodegenerative processes, potentially increasing the risk of developing AD and other forms of dementia (Sarkar & Ghosh, 2024, Naffaa, 2025).

CMV and HIV have also been linked to neurodegeneration through chronic inflammation and immune system dysregulation. CMV, a common herpesvirus, is known to persist in the CNS and has been associated with increased Aβ burden and neuroinflammatory responses in aging individuals. Similarly, HIV associated neurocognitive disorders (HAND) arise due to chronic HIV infection, which leads to persistent neuroinflammation, synaptic dysfunction, and neuronal loss. Despite antiretroviral therapy, HIV-infected individuals remain at an elevated risk for cognitive impairment, highlighting the need for further research into viral contributions to neurodegenerative diseases(Sian-Hulsmann& Riederer, 2024, Römer, 2021).

While the role of HSV-1 in AD is well-documented, the impact of other viruses such as EBV, SARS-CoV-2, CMV, and HIV on cognitive decline remains an area of active research. The growing body of evidence underscores the need for further investigation into the mechanisms by which viral infections contribute to neurodegenerative processes. Understanding these interactions could pave the way for novel therapeutic strategies aimed at mitigating the long-term cognitive effects of viral infections and improving overall brain health.

AI-Driven Transcriptomic Approaches for Viral Detection and Neurodegeneration Prediction

Artificial intelligence (AI) is revolutionizing transcriptomic analysis by providing powerful tools for viral detection and neurodegeneration prediction. The integration of AI with RNA sequencing (RNA-seq) data has facilitated the identification of crucial biomarkers, advancing early diagnosis and targeted therapeutic interventions. AI-driven models, including machine learning (ML) and deep learning (DL), enable the automated extraction of biologically relevant features, enhancing our understanding of disease mechanisms at the molecular level.

AI in Viral Detection

Transcriptomic studies have demonstrated potential of AI models in distinguishing between viral infections and their associated NDs. Machine learning techniques, such as ensemble learning, have been successfully applied to differentiate between neuromyelitis optica and multiple sclerosis based on RNA biomarkers, achieving an accuracy of over 90% (Wylezinski *et al*., 2024). Additionally, deep learning models like EdeepVPP, a convolutional neural network (CNN), have demonstrated high efficiency in viral genome prediction, reaching an AUC-ROC score of 0.992 (Dasari & Bhukya, 2021). Such AI-driven approaches offer significant improvements in the precision and speed of viral detection, contributing to better disease management strategies.

Bioinformatics analyses have further revealed distinct transcriptomic signatures in viral infections. For instance, RNA-seq data from Zika virus-infected human neural stem cells (hNSCs) identified critical alterations in gene expression related to congenital neurological defects (Rolfe *et al*., 2016). These findings underscore the role of AI in uncovering disease associated pathways, enabling early intervention strategies for viral infections with neurodevelopmental implications.

AI in Neurodegeneration Prediction

Emerging evidence suggests a strong association between viral infections and neurodegenerative diseases. Large-scale transcriptomic analyses have identified viral infection-related genes that correlate with neurological disorders, suggesting a possible mechanistic link between viral exposure and neurodegeneration (Guo *et al*., 2023). AI models are instrumental in deciphering these complex interactions by analyzing multi-omics data to predict disease progression.

Deep learning frameworks specifically designed for neurodegenerative disease prediction have been developed using RNA-

seq data. For instance, models such as the Deep Learning Framework for AD effectively characterize transcriptomic signatures associated with Alzheimer's disease (AD), demonstrating high predictive accuracy across multiple datasets (Wang *et al*., 2021). Similarly, UnCOT-AD, a multi-omics AI model, integrates gene expression, DNA methylation, and proteomic data using variational autoencoders and adversarial training, resulting in enhanced prediction accuracy compared to single-omics approaches (Abir *et al*., 2024). These advancements underscore the importance of AI in improving diagnostic accuracy and understanding disease mechanisms at the molecular level (Table 1).

Table 1: Deep Learning Models for Neurodegeneration Prediction

Model Name	Disease Targeted	Data Type	Key Features	Reference
Deep Learning Framework for AD	Alzheimer's Disease	RNA-seq	Characterizes transcriptomic signatures for AD progression	Wang *et al*., 2021
UnCOT-AD	Alzheimer's Disease	Multi-omics (Gene Expression, DNA Methylation, Proteomics)	Uses Variational Autoencoders and adversarial training for multi-omics integration	Abir *et al*., 2024

In addition to deep learning, traditional machine learning models have also been applied to neurodegeneration research. For instance, logistic regression classifiers trained on postmortem transcriptomic data have demonstrated an F1 score of 90.9% in classifying amyotrophic lateral sclerosis (ALS) (Bain *et al*., n.d.). Likewise, the Cox proportional hazards model has been utilized for predicting the progression of mild cognitive impairment (MCI) to AD, highlighting the utility of AI in early disease detection (Park *et al*., 2024). Moreover, ensemble AI predictors such as AITeQ leverage multiple classifiers including logistic regression, naive Bayes, and support vector machines (SVM) to achieve superior classification performance in AD detection (Ahammad *et al*., 2024) (Table 2).

Table 2: Machine Learning Models for Neurodegeneration Prediction

Model Name	Disease Targeted	Data Type	Key Features	Reference
Logistic Regression Classifier	Amyotrophic Lateral Sclerosis (ALS)	Postmortem transcriptomic data	Supervised learning approach for ALS classification	Bain *et al*., n.d.
Cox Proportional Hazards Model	Alzheimer's Disease	Mild Cognitive Impairment (MCI) Transcriptomics	Predicts progression from MCI to AD	Park *et al*., 2024
AITeQ	Alzheimer's Disease	RNA-seq	Five-gene signature-based ensemble model with logistic regression, naive Bayes, and SVM	Ahammad *et al*., 2024
AI Predictor for AD	Alzheimer's Disease	Blood Transcriptomics	Multiple classifiers (logistic regression, SVM, decision trees, neural networks)	Chiricosta *et al*., 2022

AI Tools and Datasets in Neurodegeneration Research

Several AI-driven tools have been developed to facilitate transcriptomic analysis in neurodegenerative diseases. IBM Watson, for example, employs semantic similarity analysis to identify RNA-binding proteins associated with ALS, providing valuable insights into disease pathology (Bakkar *et al*., 2018). Similarly, explainable AI models incorporating SHAP (SHapley Additive exPlanations) have been utilized to analyze single-cell RNA-seq data, revealing novel disease-related mechanisms in Huntington's disease (Usman *et al*., 2025) (Table 3).

Tool Name	Application	AI Techniques Used	Key Findings	Reference
IBM Watson	RNA-binding protein identification in ALS	Semantic similarity analysis	Identified novel RNA-binding proteins linked to ALS	Bakkar *et al*., 2018
Explainable AI Model	Huntington's Disease	Neural Networks with SHAP (SHapley Additive exPlanations)	Revealed disease-related mechanisms from single-cell RNA-seq	Usman *et al*., 2025

AI-powered transcriptomic analysis holds immense potential for advancing both viral detection and neurodegeneration prediction. By leveraging ML and DL techniques, researchers can identify unique biomarkers, uncover disease associated pathways, and improve diagnostic accuracy. Despite these advancements, challenges remain, particularly in model interpretability and clinical validation. Future research should focus on refining AI models to enhance their applicability in real-world clinical settings, ultimately contributing to better disease management and personalized medicine.

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