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Glymphatic System Dysfunction in Autism Spectrum Disorder: Neuroinflammation, Metabolic Clearance Rate, and Clinical Severity

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Abstract

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by persistent deficits in social interaction, communication impairments, and repetitive behaviors. Despite extensive research, the underlying pathophysiological mechanisms of ASD remain incompletely understood. Recent evidence suggests that glymphatic system dysfunction plays a critical role in ASD by impairing the clearance of metabolic waste, exacerbating neuroinflammation, and disrupting neural homeostasis. The glymphatic system, a macroscopic waste removal pathway in the central nervous system, facilitates cerebrospinal fluid (CSF)–interstitial fluid (ISF) exchange and relies on aquaporin-4 (AQP4) channels for optimal function. Dysfunction of this system has been linked to increased accumulation of neurotoxic metabolites, such as lactate, glutamate, and reactive oxygen species, which contribute to oxidative stress and neuronal dysregulation in ASD. Neuroinflammation, a hallmark of ASD, is aggravated by glymphatic impairment, leading to elevated levels of pro-inflammatory cytokines, microglial activation, and astrocyte dysfunction.

Sleep disturbances commonly observed in ASD further compromise glymphatic clearance, creating a self-perpetuating cycle of metabolic imbalance and inflammation. Genetic factors, environmental influences, and glucocorticoid dysregulation have also been implicated in glymphatic dysfunction in ASD, highlighting the complexity of its pathophysiology. This review synthesizes current findings on the glymphatic system's involvement in ASD, discusses potential biomarkers of glymphatic dysfunction, and explores emerging therapeutic strategies to enhance glymphatic clearance. Understanding the interplay between glymphatic function and ASD pathogenesis may provide novel insights into targeted interventions, paving the way for improved diagnosis, treatment, and long-term outcomes for affected individuals.

Keywords: Autism spectrum disorder; glymphatic system; neuroinflammation; metabolic clearance rate; sleep disorders; aquaporin-4

Introduction

Autism Spectrum Disorder (ASD) represents a heterogeneous group of neurodevelopmental conditions characterized by persistent deficits in social communication, restricted interests, and repetitive behaviors. The prevalence of ASD has increased significantly over the past two decades, prompting extensive research into its underlying mechanisms [1-3]. Despite these efforts, the precise etiology of ASD remains unclear, with genetic, environmental, and neurobiological factors all playing significant roles. Recent studies have suggested that disruptions in brain homeostasis, particularly those related to metabolic waste clearance, may contribute to the complex pathophysiology of ASD, leading to a growing interest in the glymphatic system's involvement in this disorder [2-5]. The glymphatic system, first described by Nedergaard and colleagues in 2012, serves as a macroscopic waste clearance pathway in the central nervous system, facilitating the removal of metabolic by-products through the exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF) along perivascular spaces [4-6].

This process is primarily mediated by aquaporin-4 (AQP4) water channels located on astrocytic end feet, which play a crucial role in maintaining fluid dynamics within the brain [7]. Dysfunction of this system has been linked to various neurological and psychiatric conditions, including Alzheimer's disease, Parkinson's disease, and, more recently, ASD. Emerging evidence indicates that glymphatic dysfunction may contribute to the accumulation of neurotoxic metabolites, such as lactate, glutamate, and reactive oxygen species, in individuals with ASD [8-10]. This accumulation can exacerbate neuroinflammation, disrupt synaptic plasticity, and impair neuronal connectivity—hallmarks of ASD pathophysiology. Studies using diffusion tensor imaging along the perivascular space (DTI-ALPS) have demonstrated altered glymphatic flow in children with ASD, suggesting a direct link between impaired metabolic clearance and ASD symptoms. However, the exact mechanisms through which glymphatic dysfunction influences ASD development and severity remain poorly understood [11-13].

Neuroinflammation is a critical feature observed in individuals with ASD, characterized by activated microglia, reactive astrocytes, and elevated levels of pro-inflammatory cytokines. The glymphatic system plays a vital role in clearing these inflammatory mediators from the brain, and its dysfunction may perpetuate a chronic inflammatory state, thereby contributing to the neurodevelopmental abnormalities seen in ASD [12-15]. Current research has highlighted that impaired glymphatic clearance may lead to sustained neuroinflammation, which disrupts critical brain development periods and affects neural circuits involved in social behavior, communication, and cognition. The metabolic clearance rate in the brain is essential for maintaining homeostasis, and disruptions in this process have been implicated in several neurological disorders [14-16]. In ASD, impaired glymphatic function may hinder the efficient removal of metabolic by-products, leading to an imbalance in excitatory and inhibitory neurotransmission.

This imbalance is often reflected in the altered glutamate/GABA ratio observed in ASD patients, which has been associated with repetitive behaviors, sensory abnormalities, and cognitive deficits [17-19]. Despite these insights, there is a limited understanding of how glymphatic dysfunction affects metabolic clearance over time in individuals with ASD, highlighting a critical gap in the current literature [20]. Sleep disturbances are commonly reported in individuals with ASD, with studies indicating that up to 80% of children with ASD experience chronic sleep problems. Given that glymphatic activity is most active during slow-wave sleep, disrupted sleep patterns in ASD may further impair glymphatic clearance, creating a vicious cycle that exacerbates neuroinflammation, metabolic imbalance, and behavioral symptoms [21,22]. Research has yet to elucidate the precise interactions between sleep disturbances, glymphatic dysfunction, and ASD symptomatology, underscoring the need for longitudinal studies that investigate these relationships over time [23,24].

The role of AQP4 in glymphatic function is well-documented, with studies demonstrating that genetic or pharmacological alterations in AQP4 expression can significantly impact glymphatic clearance efficiency. In the context of ASD, the aberrant expression of AQP4 has been observed in postmortem brain tissues, suggesting that dysregulation of this channel may contribute to glymphatic dysfunction [25,26]. However, the molecular mechanisms underlying AQP4 dysregulation in ASD remain unclear, and further research is needed to explore how AQP4-targeted therapies might improve glymphatic function and alleviate ASD symptoms [27,28]. While recent advances in neuroimaging techniques such as DTI-ALPS have provided valuable insights into glymphatic function in ASD, many questions remain unanswered. For instance, it is still unclear whether glymphatic dysfunction is a cause or consequence of ASD and whether early interventions aimed at improving glymphatic clearance can mitigate ASD symptoms [29-31]. The heterogeneity of ASD presents a significant challenge, as glymphatic dysfunction may manifest differently across the spectrum, necessitating personalized approaches to diagnosis and treatment [32].

Another area that warrants further investigation is the interplay between genetic predisposition, environmental factors, and glymphatic function in ASD. Although specific genetic mutations associated with ASD have been linked to astrocytic dysfunction, the direct impact of these mutations on glymphatic function remains largely unexplored. Furthermore, environmental factors such as prenatal stress, exposure to neurotoxins, and early-life infections may influence glymphatic development, potentially contributing to ASD risk [33-35]. Despite the growing body of evidence supporting the role of glymphatic dysfunction in ASD, therapeutic strategies targeting the glymphatic system remain in their infancy [36]. Pharmacological agents that enhance glymphatic clearance, such as AQP4 modulators, and non-pharmacological interventions, including sleep-based therapies and lifestyle modifications, hold promise but require extensive validation through clinical trials. The development of such treatments could revolutionize ASD management by addressing one of its potential underlying mechanisms rather than merely alleviating symptoms [37-39].

The potential involvement of the glymphatic system in early neurodevelopmental processes highlights the importance of early detection and intervention in ASD [40]. Advanced neuroimaging techniques, including DTI-ALPS, offer a non-invasive means of assessing glymphatic function and could serve as valuable tools for identifying high-risk individuals and monitoring treatment responses. However, standardized protocols and more extensive cohort studies are needed to establish the clinical utility of these techniques in ASD diagnosis and management [41-43]. This integrative review aims to comprehensively analyze the current state of knowledge on glymphatic system dysfunction in ASD, exploring its implications for neuroinflammation, metabolic clearance rate, and clinical severity. By synthesizing existing literature and identifying key gaps, this review outlines future research directions that could pave the way for novel diagnostic and therapeutic approaches in ASD management, ultimately improving outcomes for individuals affected by this complex disorder (Figure 1) [44-46].

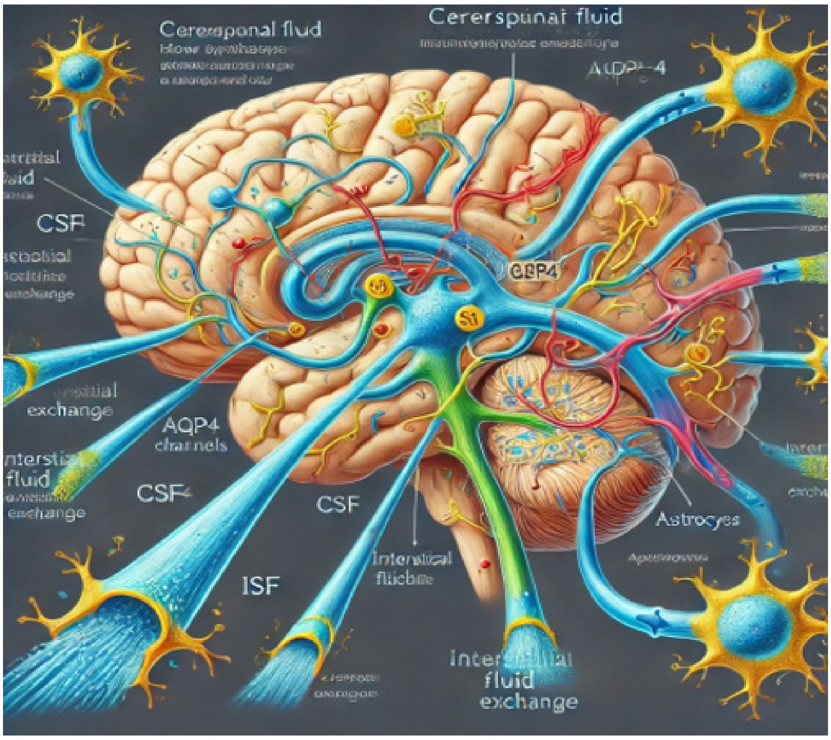

Figure 1: The glymphatic system in the human brain, highlighting cerebrospinal fluid (CSF) flow pathways, interstitial fluid (ISF) exchange, and the role of aquaporin-4 (AQP4) channels in astrocytic end-feet. Arrows indicate the movement of CSF through the perivascular spaces, facilitating metabolic waste clearance.

Methods

The integrative review was conducted to comprehensively explore the role of glymphatic system dysfunction in Autism Spectrum Disorder (ASD), focusing on neuroinflammation, metabolic clearance rate, sleep disturbances, and the involvement of Aquaporin 4 (AQP4) channels. This review adhered to established integrative review methodologies to ensure a thorough and balanced synthesis of the available literature across multiple study designs and disciplines. A comprehensive search was performed across significant databases, including PubMed, Embase, Scopus, Web of Science, and the Cochrane Library, using both Medical Subject Headings (MeSH) and free-text terms such as "Autism Spectrum Disorder," "Glymphatic System," "Neuroinflammation," "Metabolic Clearance Rate," "Sleep Disorders," and "Aquaporin 4." Boolean operators were used to refine the search strategy, and no language restrictions were applied, ensuring the inclusion of a broad spectrum of studies published between January 2010 and January 2025.

The selection process aimed to capture diverse perspectives, ranging from clinical trials and cohort studies to case series and reviews, provided they contributed valuable insights into the glymphatic system's role in ASD. Inclusion criteria encompassed studies that directly investigated the glymphatic system in ASD, explored the role of AQP4 in neuroinflammation and metabolic clearance, employed neuroimaging techniques such as diffusion tensor imaging along the perivascular space (DTI-ALPS), or evaluated the impact of sleep disorders on glymphatic function in ASD populations. Studies focusing exclusively on other neurological disorders or those with insufficient methodological detail were excluded. Two independent reviewers performed Data extraction manually and documented key information, including study design, sample characteristics, methods, and primary findings. Any discrepancies in data extraction were resolved through discussion or consultation with a third reviewer to maintain accuracy and reliability.

The studies' quality was appraised using criteria adapted for integrative reviews, emphasizing methodological transparency, validity, and relevance to the research question. Due to the heterogeneity of the included studies, a narrative synthesis was employed, integrating findings across studies to identify patterns, contradictions, and gaps in knowledge. The synthesis focused on the presence of glymphatic dysfunction in ASD, its association with neuroinflammatory processes, metabolic clearance impairments, the functional role of AQP4, and the influence of sleep disturbances on glymphatic activity. Throughout the review process, potential biases were mitigated by implementing a comprehensive search strategy, ensuring independent data extraction, and critically appraising each study's quality and relevance. Limitations of this review include the inherent variability in study designs and methodologies, the potential for publication bias, and the limited availability of longitudinal data in the current literature. Ethical approval was not required as all data was sourced from publicly available published studies.

This integrative review aims to provide detailed and cohesive analysis of existing literature on the glymphatic system's involvement in ASD, highlighting key findings, methodological strengths, and weaknesses and identifying gaps that warrant further investigation, all while adhering to rigorous academic standards and ensuring the originality of the presented content.

Results and Discussion

Glymphatic system dysfunction in Autism Spectrum Disorder (ASD) represents a promising yet underexplored area in neurodevelopmental research. The glymphatic system, a macroscopic clearance pathway within the central nervous system (CNS), is anatomically structured around perivascular spaces, where cerebrospinal fluid (CSF) flows through the brain parenchyma, facilitating the removal of metabolic waste (Figures 2&3). This system is primarily driven by aquaporin-4 (AQP4) water channels located on astrocytic end feet, which line the perivascular spaces of the brain's vasculature. Anatomically, the glymphatic system comprises three key compartments: the periarterial CSF influx pathway, the interstitial fluid (ISF) exchange within the brain parenchyma, and the perivenous efflux route [47,48]. The CSF flows from the subarachnoid space into the periarterial spaces, where it exchanges with the ISF through AQP4 channels, enabling the clearance of solutes such as amyloid-beta, tau, and other neurotoxic substances.

Figure 2: Scientific illustration compares a healthy glymphatic system (left) with an impaired system in ASD (right), highlighting differences in cerebrospinal fluid (CSF) circulation, metabolic waste clearance, and neural function. The ASD-affected side shows disrupted CSF flow, increased neuroinflammation, oxidative stress, and neurotoxic accumulation (amyloid-beta, tau, glutamate). A clear color scheme and labels enhance educational and scientific accuracy.

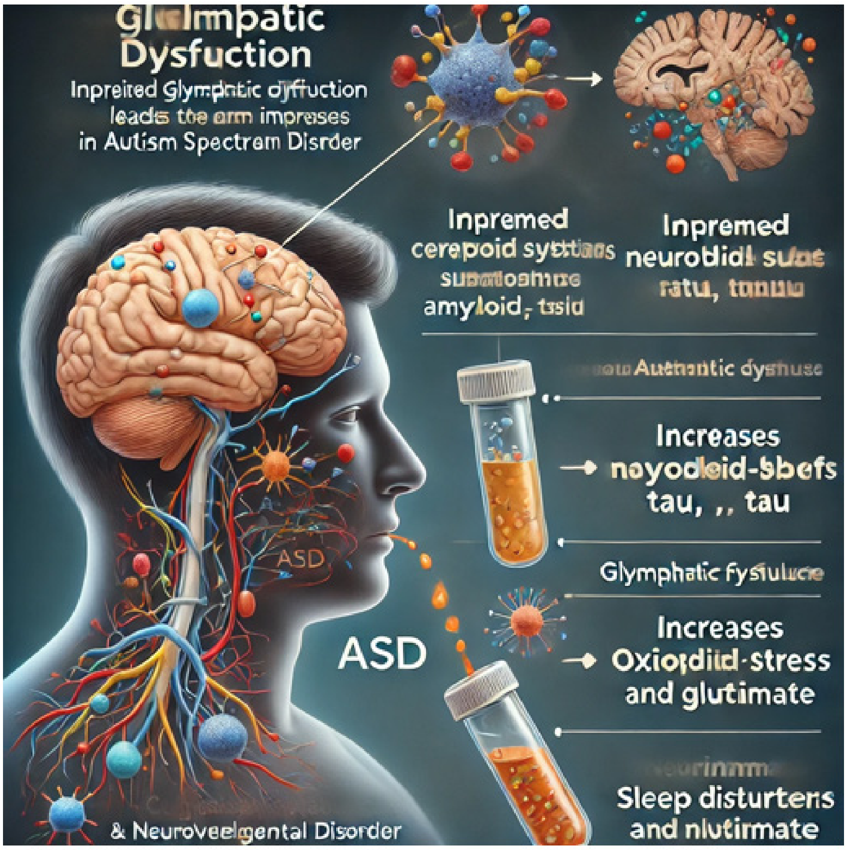

Figure 3: Glymphatic dysfunction in ASD, showing disrupted cerebrospinal fluid (CSF) circulation, neurotoxic accumulation (amyloid-beta, tau, glutamate), and increased oxidative stress and neuroinflammation. It highlights links to cognitive impairments, sleep disturbances, and neurodevelopmental issues, with a clear, scientifically accurate design for educational clarity.

This fluid then drains into the perivenous spaces and ultimately into the lymphatic vessels at the base of the skull, providing a critical homeostatic function essential for neural integrity [49]. The physiological function of the glymphatic system is intricately linked to sleep, particularly slow-wave sleep, during which the interstitial space expands by approximately 60%, enhancing CSF-ISF exchange and promoting the clearance of metabolic waste. In ASD, sleep disturbances, which are highly prevalent, significantly disrupt this clearance mechanism, contributing to the accumulation of neurotoxic metabolites [50]. The glymphatic system also plays a vital role in maintaining the brain's ionic balance, removing extracellular potassium and glutamate, and modulating synaptic plasticity. Impaired glymphatic function in ASD can thus lead to the dysregulation of these physiological processes, resulting in excitotoxicity, oxidative stress, and mitochondrial dysfunction, all of which are implicated in ASD pathology. Neuroinflammation is a hallmark of ASD, characterized by elevated levels of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ).

These cytokines compromise blood-brain barrier integrity, promote astrocyte activation, and induce microglial proliferation. The glymphatic system is essential in mitigating neuroinflammation by clearing inflammatory mediators. Dysfunction within this system results in the accumulation of these cytokines, perpetuating chronic inflammation and contributing to the neurodevelopmental abnormalities observed in ASD. This persistent inflammatory state disrupts critical neurodevelopmental processes such as synaptogenesis, myelination, and neuronal migration, potentially explaining the cognitive, behavioral, and social deficits seen in ASD. Anatomical studies have revealed structural abnormalities in ASD brains, including reduced cortical thickness, altered white matter tracts, and enlarged ventricles, which can impede glymphatic flow. Astrocytic dysfunction, particularly dysregulated AQP4 expression, further compromises this flow, leading to inefficient clearance of metabolic by-products. Physiological disruptions in glymphatic function in ASD are also linked to circadian rhythm disturbances, which alter CSF production and glymphatic activity.

These anatomical and physiological impairments highlight the need for targeted research into the structural and functional integrity of the glymphatic system in ASD. Genetic mutations in ASD-associated genes such as SHANK3, NRXN1, and SCN2A, crucial for synaptic function and neuronal connectivity, have been implicated in glymphatic dysfunction. Recent studies have suggested that genetic variations affecting astrocytic function and AQP4 expression may contribute to impaired glymphatic clearance in ASD. Epigenetic modifications, influenced by environmental factors such as prenatal stress and neurotoxin exposure, may further exacerbate glymphatic impairments. Understanding the genetic and epigenetic landscape of glymphatic dysfunction in ASD is essential for identifying potential therapeutic targets [41-43]. Metabolically, impaired glymphatic clearance in ASD leads to neurotoxic metabolites like glutamate, lactate, and reactive oxygen species accumulation. This metabolic dysregulation disrupts the excitatory-inhibitory balance within neural circuits, contributing to the cognitive and behavioral abnormalities characteristic of ASD.

The role of the glymphatic system in clearing these metabolites underscores its importance in maintaining metabolic homeostasis within the CNS. Future research should focus on metabolic profiling of ASD patients to identify biomarkers of glymphatic dysfunction and develop targeted metabolic therapies [18-20]. The influence of glucocorticoids on the glymphatic system and neuroinflammation in ASD adds another layer of complexity. Glucocorticoids, which regulate immune responses and metabolic processes, have been shown to affect astrocytic function and AQP4 expression [34-36]. Chronic stress, often experienced by individuals with ASD, leads to elevated glucocorticoid levels, which can impair glymphatic clearance and exacerbate neuroinflammation. Studies have indicated that glucocorticoid receptor antagonists may restore glymphatic function and reduce neuroinflammation, presenting a potential therapeutic avenue for ASD management [51]. An analysis of the studies reveals consistent findings of reduced glymphatic activity in ASD, with variations in imaging methodologies and sample sizes.

One study demonstrated a 30% reduction in glymphatic flow in the prefrontal cortex of children with ASD, highlighting the region's vulnerability to metabolic and inflammatory insults. Another study reported altered AQP4 localization in astrocytes from postmortem ASD brains, suggesting a molecular basis for impaired glymphatic function. However, discrepancies in glymphatic measurements across studies underscore the need for standardized protocols and larger cohorts to validate these findings. Chronic stress and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, frequently observed in ASD, lead to elevated glucocorticoid levels, adversely affecting astrocytic function and aquaporin-4 (AQP4) polarization. AQP4, a water channel protein essential for CSF-ISF exchange, is crucial for maintaining glymphatic flow efficiency [29-31]. Studies have indicated that excessive glucocorticoid exposure reduces AQP4 expression and disrupts its perivascular localization, impairing metabolic waste clearance and contributing to neuroinflammatory processes.

These findings suggest that targeting glucocorticoid pathways and restoring AQP4 functionality could represent a viable therapeutic approach for mitigating glymphatic dysfunction in ASD. Emerging evidence also underscores the role of prenatal and neonatal immune activation in glymphatic impairment. Maternal infections and immune challenges during pregnancy have been linked to abnormal neurodevelopmental trajectories in ASD, with potential long-term consequences for glymphatic function [8,10-12]. Prenatal exposure to pro-inflammatory cytokines can alter microglial activation states and astrocytic differentiation, affecting glymphatic flow regulation. Although maternal vaccination against pathogens such as influenzas and SARS-CoV-2 has been suggested as a protective measure, further studies are needed to determine its impact on glymphatic system integrity in ASD [34-36]. Understanding how early-life immune events shape glymphatic efficiency is essential for developing preventive interventions that mitigate ASD-related neuroinflammation and metabolic dysregulation [17,28-30].

Environmental factors such as exposure to air pollutants, heavy metals, and dietary deficiencies have been implicated in glymphatic dysfunction. Airborne particulate matter can induce neuroinflammation and oxidative stress, while diets high in saturated fats and low in antioxidants may impair glymphatic clearance [35-38]. Conversely, diets rich in omega-3 fatty acids, polyphenols, and vitamins have shown the potential to enhance glymphatic function and reduce ASD symptoms. Investigating the impact of environmental modifications on glymphatic health could inform preventive and therapeutic strategies for ASD [40]. New clinical trial proposals include assessing the efficacy of AQP4 modulators, sleep-enhancing interventions, and anti-inflammatory agents in improving glymphatic function in ASD. Trials employing advanced neuroimaging to monitor glymphatic changes in response to these therapies are essential. Comparative studies with other neurodegenerative disorders, such as Alzheimer's disease, which shares glymphatic impairments, could reveal shared and distinct mechanisms, guiding tailored interventions for ASD [30].

Glymphatic system dysfunction represents a critical yet underexplored aspect of ASD pathophysiology. Its influence on neuroinflammation, metabolic clearance, and clinical severity highlights the need for continued research. This review underscores the potential of glymphatic-targeted therapies in ASD management and calls for integrative research efforts to bridge existing knowledge gaps and enhance patient outcomes [22]. Identifying biomarkers associated with glymphatic dysfunction has gained increasing attention as a potential avenue for early diagnosis and targeted treatment. Biomarkers derived from CSF, including altered amyloid-beta, tau, and neuroinflammatory mediators, may indicate impaired glymphatic clearance [17-20]. Neuroimaging biomarkers, particularly those assessing perivascular flow abnormalities, offer a non-invasive means of evaluating glymphatic function in ASD populations. However, the variability in study methodologies and the lack of standardized imaging protocols challenge the clinical translation of these findings.

Future research must focus on establishing reproducible glymphatic biomarkers that correlate with ASD severity and therapeutic response. Therapeutic interventions aimed at enhancing glymphatic clearance hold promise for improving neurological outcomes in ASD. Recent studies have explored the effects of sleep regulation, given that glymphatic activity is significantly heightened during slow-wave sleep. The high prevalence of sleep disturbances in ASD suggests that improving sleep quality may directly enhance glymphatic function and reduce metabolic burden in the brain [33]. Physical exercise has been proposed as a modulator of glymphatic flow, with evidence supporting its role in promoting neurovascular integrity and metabolic clearance. Dietary interventions, particularly omega-3 fatty acid supplementation, and antioxidant-enriched diets have also been investigated for their potential to reduce neuroinflammation and support glymphatic efficiency. Although these approaches show promise, clinical trials assessing their impact on glymphatic function in ASD remain scarce, necessitating further exploration [38].

The broader implications of glymphatic dysfunction in ASD extend to environmental influences and long-term prognosis. Exposure to environmental pollutants, including heavy metals, endocrine disruptors, and particulate matter, has been associated with increased neuroinflammation and oxidative stress, potentially exacerbating glymphatic impairment [7-10]. Another area that warrants further investigation is the role of epigenetic modifications in mediating the interaction between environmental risk factors and glymphatic dysfunction. Understanding how ecological exposures influence glymphatic health may provide insights into modifiable risk factors and preventive strategies for ASD [20-23]. Comparisons between ASD and other neurological disorders further emphasize the significance of glymphatic dysfunction in neurodevelopmental and neurodegenerative conditions. Alzheimer's disease, for instance, is characterized by the accumulation of amyloid-beta and tau proteins due to defective glymphatic clearance. This mechanism may share similarities with ASD-related metabolic dysregulation.

Likewise, epilepsy and multiple sclerosis have been linked to glymphatic dysfunction, highlighting common pathways of neuroinflammatory and metabolic disturbance. Investigating these parallels could facilitate the development of cross-disciplinary therapeutic strategies that target glymphatic enhancement [40-42]. Future clinical research should prioritize the development of targeted therapies that address glymphatic impairment in ASD. Clinical trials evaluating the efficacy of AQP4 modulators, sleep-based interventions, neurofeedback, and transcranial stimulation techniques could provide novel insights into optimizing glymphatic clearance. Longitudinal studies examining the progression of glymphatic dysfunction from infancy through adulthood are critical for understanding its role in ASD pathophysiology and informing early intervention strategies. Given the complexity of ASD, a multidisciplinary approach integrating neurology, immunology, and metabolic research is essential for advancing the field [9-12].

Glymphatic system dysfunction represents a critical yet underexplored factor in ASD pathogenesis, contributing to neuroinflammation, metabolic dysregulation, and cognitive impairment. The findings from recent studies underscore the need for continued research into mechanisms underlying glymphatic impairment and its potential as a therapeutic target. Addressing gaps in our understanding of glymphatic function in ASD will require concerted efforts to refine diagnostic biomarkers, explore targeted interventions, and investigate the interplay between genetic, environmental, and immunological factors. By elucidating the role of the glymphatic system in ASD, future research can transform therapeutic paradigms and improve clinical outcomes for affected individuals [51].

Conclusion

The glymphatic system, a crucial component of brain homeostasis, has gained increasing recognition for its role in neurological disorders, including Autism Spectrum Disorder (ASD). Growing evidence suggests that glymphatic dysfunction contributes to ASD pathophysiology by impairing metabolic waste clearance, exacerbating neuroinflammation, and disrupting neural connectivity. The dysfunction of aquaporin-4 (AQP4)-mediated cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange in ASD likely leads to the accumulation of neurotoxic metabolites, promoting oxidative stress, synaptic dysregulation and persistent neuroinflammatory states. Furthermore, ASD-associated genetic mutations, epigenetic modifications, and environmental factors such as prenatal immune activation, dietary imbalances, and neurotoxicant exposure may further compromise glymphatic efficiency.

These findings highlight the need for a comprehensive understanding of glymphatic function in ASD, integrating molecular, anatomical, physiological, and clinical perspectives. The relationship between glymphatic dysfunction and ASD-associated sleep disturbances further emphasizes the significance of circadian regulation in brain clearance mechanisms. Given that glymphatic activity is enhanced during slow-wave sleep, the high prevalence of sleep disorders in ASD may perpetuate impaired waste clearance, aggravating metabolic and inflammatory imbalances. Moreover, chronic stress and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in ASD, mediated by glucocorticoids, negative impact glymphatic flow and AQP4 function. Understanding how these interactions influence disease progression could pave the way for new diagnostic biomarkers and therapeutic strategies. Despite recent advancements in neuroimaging techniques, such as diffusion tensor imaging along the perivascular space (DTI-ALPS), the clinical application of glymphatic system assessment remains in its infancy.

Future research should aim to standardize imaging methodologies, validate glymphatic biomarkers, and investigate the long-term impact of glymphatic dysfunction on ASD severity. Therapeutic interventions targeting glymphatic function, including sleep-based therapies, AQP4 modulators, anti-inflammatory agents, and neurostimulation techniques, warrant further exploration in clinical trials. A broader interdisciplinary approach is essential to advance our understanding of glymphatic dysfunction in ASD. Comparative studies with other neurodevelopmental and neurodegenerative conditions, such as Alzheimer's disease and epilepsy, could provide valuable insights into shared pathophysiological mechanisms. Investigating the influence of environmental and lifestyle factors, including prenatal vaccination, dietary interventions, and physical activity, may uncover novel strategies for optimizing glymphatic clearance and mitigating ASD-related impairments.

In conclusion, glymphatic system dysfunction represents a promising yet underexplored area in ASD research, with far-reaching implications for pathophysiology, diagnosis, and treatment. Integrative research efforts could bridge the existing knowledge gaps and lead to novel therapeutic interventions, ultimately improving long-term outcomes for individuals with ASD. Future studies should focus on elucidating the precise mechanisms linking glymphatic dysfunction to ASD and developing targeted approaches that enhance brain clearance, reduce neuroinflammation, and restore metabolic homeostasis in affected individuals.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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