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STRESS-INDUCED GLIAL HISTOPATHOLOGY AS A MEDIATOR OF NEUROPSYCHIATRIC VULNERABILITY: INSIGHTS FROM RODENT AND ZEBRAFISH MODELS

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REVIEW **OPEN ACCESS**

ABSTRACT

Introduction – Glial cells, including astrocytes, microglia, and oligodendrocytes, are active regulators of neural plasticity, synaptic integrity, and connectivity. Chronic and early-life stress are major risk factors for neuropsychiatric disorders, yet the role of glial histopathology in mediating this vulnerability remains incompletely understood. This thematic narrative review aims to synthesize integrative evidence on stress-induced glial histopathology as a mediator of neuropsychiatric risk, with emphasis on findings from rodent and zebrafish models and their translational implications.
Methods – A structured thematic narrative review was conducted across PubMed, Scopus, and Embase for studies published between 2000 and 2025. Inclusion criteria prioritized high-quality experimental research and reviews on glial responses to stress, synaptic alterations, and biomarker potential in rodent and zebrafish models.
Results – Evidence consistently demonstrates astrocyte atrophy, microglial activation with pro-inflammatory profiles, and oligodendrocyte dysfunction leading to myelin disruption, collectively contributing to synaptic instability, neuroinflammation, and impaired connectivity.
Discuss – Rodent models provide detailed insights into cellular and regional pathology, while zebrafish models offer translational value through high-throughput behavioral and neuroimmune profiling. Species differences in glial structure and stress responsiveness remain a barrier to direct clinical translation.
Conclusion – Glial pathology represents a unifying mechanism linking stress exposure to neuropsychiatric vulnerability. Future studies should integrate cross-species, longitudinal designs and translational biomarkers to advance therapeutic strategies for stress-related mental health disorders.

Keywords: glial histopathology, neuropsychiatric risk, chronic stress, astrocytes, microglia

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INTRODUCTION

Early-life adversity, including chronic and prenatal stress, is increasingly recognized as a critical risk factor for the development of neuropsychiatric disorders. Epidemiological studies consistently link exposure to adverse environmental conditions during sensitive developmental periods with heightened vulnerability to conditions such as major depressive disorder (MDD), anxiety disorders, post-traumatic stress disorder (PTSD), and schizophrenia. This vulnerability is thought to arise from stress-induced alterations in brain development, plasticity, and connectivity, mediated in part by non-neuronal elements such as glial cells.[1-3] Glial cells, comprising astrocytes, microglia, and oligodendrocytes, are not merely supportive components of the central nervous system (CNS) but are active participants in shaping neural circuits and modulating synaptic function. Under conditions of chronic or early-life stress, these cells undergo profound molecular and morphological changes that can disrupt neural networks and contribute to enduring behavioral abnormalities.[4,5]

The critical role of glia in brain development and plasticity has been increasingly highlighted by experimental studies using rodent and, more recently, zebrafish models. Rodent models provide detailed insight into region-specific glial alterations under stress, including astrocyte atrophy, microglial activation, and oligodendrocyte dysfunction, which together compromise synaptic integrity, neural connectivity, and behavioral regulation.[6-11] Zebrafish models have added unique translational value by enabling real-time imaging, high-

throughput behavioral screening, and molecular profiling of stress responses, revealing conserved neuroendocrine and neuroimmune mechanisms.[12-14]

Despite these advances, key translational challenges persist. Much of our understanding is derived from animal models that only partially recapitulate the complexity of human neurodevelopment and pathology.[15,16] Cross-species differences in glial morphology, marker expression, and stress reactivity limit direct extrapolation to humans.[17,18] For example, human astrocytes display greater size and complexity compared to rodents, and microglial and oligodendroglial responses to stress show species-specific regulatory features. Moreover, the temporal and regional heterogeneity of glial pathology complicates efforts to identify universal biomarkers or therapeutic targets.

The search for reliable glial biomarkers of neuropsychiatric risk has yielded promising candidates, such as glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), and an astrocyte protein (S100β), detectable in cerebrospinal fluid or peripheral blood. Elevated levels of these proteins have been associated with neuroinflammation, neurodegeneration, and cognitive decline, yet their specificity for primary psychiatric conditions remains uncertain.[19-21] Advances in neuroimaging and liquid biopsy approaches, including the analysis of glial-derived extracellular vesicles, offer further potential for translational biomarker development, though validation in longitudinal and clinical studies is still needed.[22,23]

Against this backdrop, the present review aims to provide a thematic synthesis of stress-induced glial histopathology as a mediator of early neuropsychiatric risk, with an emphasis on integrative evidence from rodent and zebrafish models. We seek to delineate conserved and divergent patterns of glial dysfunction across species, developmental stages, and brain regions, and to evaluate their relevance for biomarker discovery and intervention strategies. This narrative synthesis aspires to bridge experimental findings with clinical relevance, highlighting opportunities and challenges for future research in the prevention and treatment of stress-related neuropsychiatric disorders.

METHOD

Study design

This work is a thematic narrative review that synthesizes preclinical and translational literature on stress-induced glial histopathology and neuropsychiatric vulnerability.

Databases and timeframe

We searched PubMed, Scopus, and Embase for studies published January 2000–June 2025, a period spanning major advances in rodent and zebrafish models and glial biology.

Literature Search Strategy

Search terms combined free-text keywords and controlled vocabulary (MeSH terms) relevant to the review's core focus areas. Keywords included *glial cells*, *astrocytes*, *microglia*, *oligodendrocytes*, *stress*, *chronic stress*, *early-life stress*, *neuropsychiatric disorders*, *biomarkers*, *zebrafish*, *rodent models*, *myelin integrity*, *synaptopathy*, *neuroinflammation*, *translational neuroscience*.

Boolean operators (AND, OR) were applied to refine results. For example, *(glial cells OR astrocytes OR microglia) AND (stress OR early-life adversity) AND (neuropsychiatric disorders OR biomarkers OR translational)*.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were carefully defined to ensure that the curated literature reflected high scientific quality, relevance, and translational value. We included peer-reviewed, indexed publications (original studies and reviews) that examined glial responses to stress, synaptic alterations, behavioral correlates, or biomarker potential in rodent and/or zebrafish models (January 2000–June 2025). We also considered high-relevance grey literature where appropriate (e.g., conference proceedings, theses, and preprints on established servers such as bioRxiv/medRxiv) when methods were transparent and results filled clear thematic gaps. Studies were not excluded on the basis of journal quartile.

Studies were excluded if they focused solely on peripheral glial populations without relevance to the central nervous system, addressed disease contexts unrelated to neuropsychiatric risk (such as primary brain tumors), or were published in non-indexed or predatory journals. Single case reports without broader applicability were similarly excluded. Where possible, we favored comparative studies that advanced cross-species insights—particularly those integrating rodent, zebrafish, and human data—or that contributed meaningfully to translational or biomarker frameworks.

Terminology note

To maintain consistency with preclinical conventions, we use "anxiety-like behavior(s)" and "depression-like behavior(s)" throughout (including tables), and American English spelling.

RESULTS

The synthesis of experimental evidence demonstrates that stress exposure leads to distinct and cell-specific glial alterations, which contribute to neuropsychiatric vulnerability. Findings consistently reveal that astrocytes undergo atrophy and network disruption, microglia exhibit activation with pro-inflammatory profiles, and oligodendrocytes show impaired myelin maintenance, particularly in prefrontal-limbic circuits. These cellular changes collectively compromise neural plasticity, connectivity, and behavior.

Astrocyte Responses to Stress

Rodent models of chronic and early-life stress have consistently reported astrocyte atrophy, reduced glial fibrillary acidic protein (GFAP) expression, impaired gap junction coupling, and diminished process complexity. For example, Aten et al. demonstrated that chronic mild stress results in astrocyte atrophy, downregulation of GFAP, and reduced connexin-43, correlating with depression-like behavior.[10] Machado-Santos et al. observed decreased astrocyte density and impaired gap junctions in recurrent depression models,[11] whereas Lin et al. linked downregulation of ezrin to reduced astrocyte complexity and increased stress susceptibility.[24] Hao et al. highlighted astrocyte-mediated neuronal inhibition contributing to depression-like behavior,[25] while zebrafish models by Demin et al. reported anxiety-like behavior with elevated neuroinflammatory markers despite no significant GFAP change.[14] These findings are summarized in **Table 1**, providing an integrated view of model systems, key results, behavioral correlates, and translational implications.

Table 1. Experimental Evidence on Astrocyte Responses to Stress

Author-Year	Model	Key Findings	Behavioral Correlates	Translational Relevance
Aten et al., 2023[10]	Rodent CMS	Astrocyte atrophy, ↓ GFAP, ↓ Cx43	Depression-like behavior	Target astrocyte network for therapy
Machado-Santos et al., 2021[11]	Rodent recurrent depression	↓ Astrocyte density, impaired gap junctions	Mood disorder phenotypes	Astrocyte network restoration as intervention
Lin et al., 2024[24] [Preprint]	Rodent chronic stress	↓ Ezrin expression, reduced astrocyte complexity	Stress susceptibility	Ezrin modulation as resilience factor
Hao et al., 2020[25]	Rodent chronic stress	Astrocyte-mediated neuronal inhibition	Depression-like behavior	Glutamate modulation beneficial
Demin et al., 2020[14]	Zebrafish chronic stress	No GFAP change, ↑ neuroinflammation markers	Anxiety-like behavior	Alternative glial markers needed

Microglial Responses to Stress

Microglia in stress models display hypertrophy, increased density, and enhanced production of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α.[7,26] These changes drive excessive synaptic pruning, neuroinflammation, and behavioral manifestations such as anxiety- and depression-like phenotypes.[27] Rodent studies further identify molecular pathways such as TREM-1/SYK and NF-κB as key mediators of maladaptive microglial remodeling.[28,29] Zebrafish models, while less detailed in glial morphology, show conserved neuroimmune activation with elevated IL-1β and IL-6, contributing to anxiety-like behaviors.[14] These patterns are synthesized in **Table 2**, highlighting key findings and translational relevance.

Table 2. Experimental Evidence on Microglial Responses to Stress

Author-Year	Model	Key Findings	Behavioral Correlates	Translational Relevance
Wang et al., 2018[7]	Rodent CMS	Microglial hypertrophy, ↑ pro-inflammatory cytokines	Anxiety- and depression-like behavior	Target neuroinflammatory cascades
Afridi & Suk, 2023[26]	Review rodent studies	Microglial remodeling, synaptic pruning	Behavioral deficits	Molecular targets: TREM-1/SYK, NF-κB
Andoh & Koyama, 2021[27]	Rodent chronic stress	Microglial activation linked to neuroinflammation	Stress-induced behavioral changes	Modulate microglial activation therapeutically
Chu et al., 2021[29]	Rodent social defeat	Stress impacts microglial plasticity	Cognitive dysfunction, mood symptoms	Microglial plasticity as therapeutic target
Demin et al., 2020[14]	Zebrafish chronic stress	↑ IL-1β, IL-6, neuroimmune activation	Anxiety-like behavior	Need for zebrafish glial marker validation

Oligodendrocyte Responses to Stress

Stress exposure impairs oligodendrocyte maturation and myelin integrity, particularly in circuits governing mood and cognition. Kokkosis et al. reported reduced oligodendrocyte maturation and prefrontal hypomyelination following chronic stress,[8] while Poggi et al. demonstrated decreased proliferation and impaired myelin protein expression in social stress models.[9] These cellular changes are linked to functional deficits and emotional dysregulation, consistent with neuroimaging studies showing reduced white matter integrity in stress-related psychiatric conditions.[30,31] Evidence from zebrafish remains limited, though neuroimmune activation may indirectly affect myelin pathways.[14] These findings are summarized in **Table 3**.

Cross-Species and Translational Synthesis

Rodent models offer detailed insights into region- and cell-specific glial pathology, whereas zebrafish models contribute complementary behavioral and neuroimmune data, enabling high-throughput screening. Despite these strengths, species-specific differences in astrocyte complexity, microglial reactivity, and myelination dynamics limit direct extrapolation to human pathology.[17,18] Emerging platforms, including iPSC-derived glia and human glial chimeras, promise to bridge these gaps and advance translational relevance.[32,33]

Table 3. Experimental Evidence on Oligodendrocyte Responses to Stress

Author-Year	Model	Key Findings	Behavioral Correlates	Translational Relevance
Kokkosis et al., 2022[8]	Rodent chronic stress	↓ oligodendrocyte maturation, prefrontal hypomyelination	Cognitive impairment, emotional dysregulation	Link myelin disruption to mood disorders
Poggi et al., 2022[9]	Rodent social stress	↓ proliferation, impaired myelin protein expression	Anxiety-, depression-like behavior	Myelin repair as therapeutic target
Maas et al., 2017[30]	Rodent chronic stress	↓ white matter integrity in hippocampus, prefrontal cortex	Cognitive deficits	Supports imaging markers for myelin disruption
Lehmann et al., 2017[31]	Human imaging study	↓ gray/white matter volumes	Functional impairments	Myelin-related biomarkers for clinical translation
Demin et al., 2020[14]	Zebrafish chronic stress	Neuroimmune activation, potential myelin impact	Anxiety-like behavior	Need for zebrafish myelin studies

DISCUSSION

The present synthesis consolidates evidence that glial dysfunction is not a secondary or incidental feature of stress-related neuropsychiatric disorders, but rather a central pathological axis linking environmental adversity to structural and functional brain alterations. This review reinforces the concept that glial cells—once considered passive scaffolding—serve as dynamic regulators of neuroplasticity, synaptic integrity, and immune homeostasis. Their perturbation under stress conditions contributes directly to enduring behavioral and cognitive vulnerabilities.[4,34] Although we favored peer-reviewed evidence, we additionally incorporated select preclinical preprints when methods were explicit and findings addressed clear thematic gaps; these are flagged as [Preprint] to support transparency.

Astrocyte dysfunction under stress emerges as a key mechanism undermining synaptic stability. As illustrated in **Table 1**, rodent models consistently demonstrate astrocyte atrophy, reduced GFAP expression, impaired gap junctions, and altered cytoskeletal integrity, culminating in compromised regulation of neurotransmitter clearance, ion homeostasis, and metabolic support.[10,11,24] These cellular deficits parallel functional connectivity disruptions seen in neuroimaging studies of mood and anxiety disorders.[30] Importantly, therapeutic efforts targeting astrocyte dysfunction—such as glutamate modulators (e.g., riluzole) and agents enhancing cytoskeletal resilience—show promise in preclinical models.[24,35] Yet, significant translational hurdles persist, including species-specific differences in astrocyte complexity, molecular profiles, and regional vulnerability.[17]

Microglial activation represents another conserved response to stress, with dual pathogenic and homeostatic roles. The evidence consolidated in **Table 2** underscores that microglial hypertrophy, increased density, and pro-inflammatory cytokine release contribute to maladaptive synaptic pruning and neuroinflammation, driving anxiety- and depression-like behaviors.[7,27] However, microglia also engage in neuroprotection and repair, underscoring the complexity of their involvement in stress pathology. Therapeutic strategies must balance inhibition of harmful activation with preservation of essential microglial functions. Targeting molecular checkpoints such as TREM-1/SYK or NF-κB holds potential but requires nuanced modulation to avoid collateral disruption of neural homeostasis.[28,29]

Oligodendrocyte dysfunction and myelin disruption further reinforce the link between stress and impaired connectivity. Findings synthesized in **Table 3** reveal consistent reductions in oligodendrocyte proliferation, myelin protein expression, and structural integrity of white matter in prefrontal-limbic circuits.[8,9] These changes correlate with cognitive deficits and emotional dysregulation, mirroring neuroimaging evidence of compromised white matter in individuals exposed to chronic stress.[30,31] Despite these advances, the development of targeted therapies to promote remyelination in psychiatric populations remains an underexplored area of translational research.

Integration of rodent and zebrafish models has provided valuable cross-validation of stress-induced glial pathology. Rodents offer unparalleled detail in cellular and regional changes, while zebrafish models contribute high-throughput behavioral and neuroimmune insights.[12,14] However, translational limitations arise from species differences in glial architecture, immune signaling, and developmental timelines, highlighting the need for caution when extrapolating preclinical findings to human conditions.[18,36]

Biomarker discovery represents a critical translational goal. Candidates such as GFAP, NfL, and S100β show potential as indicators of glial damage or dysfunction, yet their specificity, sensitivity, and predictive value for psychiatric disorders remain to be conclusively established.[19,20] Advances in liquid biopsy technologies, including extracellular vesicle profiling, and in vivo imaging offer promising avenues for validation but necessitate integration into longitudinal, cross-species clinical studies.[22,23]

Emerging technologies, including iPSC-derived glial models, human glial chimeras, spatial transcriptomics, and live imaging, promise transformative opportunities for advancing glial research in neuropsychiatry.[32,33,37] These platforms can help dissect glial heterogeneity, dynamic interactions, and temporal trajectories in health and disease. However, realizing their translational potential requires coordinated, multidisciplinary collaboration across molecular neuroscience, bioengineering, psychiatry, and clinical science.

CONCLUSION

This review highlights that glial histopathology, characterized by astrocyte atrophy, microglial activation, and oligodendrocyte dysfunction; represents a core mechanism linking stress exposure to neuropsychiatric vulnerability. Evidence from rodent and zebrafish models consistently associates these glial changes with synaptic instability, neuroinflammation, and disrupted connectivity, reinforcing foundational models of mood and stress-related disorders. In sum, glial pathology represents a unifying mechanistic bridge between stress exposure and neuropsychiatric risk, and underscores the importance of targeting glial dysfunction in prevention and treatment strategies. Future research must prioritize integrative frameworks that combine cross-species, developmental, and longitudinal perspectives, with an emphasis on translational endpoints that support biomarker validation and therapeutic innovation. Such efforts will be essential for moving from mechanistic understanding toward clinical applications for stress-related mental health disorders.

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