

Review

Beyond the Neuron: The Integrated Role of Glia in Psychiatric Disorders

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Abstract: In recent decades, substantial evidence has highlighted the integral roles of neuroglia, particularly astrocytes, microglia, oligodendrocytes, and ependymal cells, in the regulation of synaptic transmission, metabolic support, and immune mechanisms within the central nervous system. In addition to their structural role, these cells actively modulate neurotransmitter homeostasis and influence neuronal plasticity, thereby affecting cognition, mood, and behavior. This review discusses how neuroglial alterations contribute to the pathophysiology of five common psychiatric disorders: major depression, bipolar disorder, anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and schizophrenia. We synthesized preclinical and clinical findings illustrating that glial dysfunction, including impaired myelination and aberrant neuroinflammatory responses, often parallels disease onset and severity. Moreover, we outline how disruptions in astrocytic glutamate uptake, microglia-mediated synaptic pruning, and blood–brain barrier integrity may underlie the neurobiological heterogeneity observed in these disorders. The therapeutic implications range from anti-inflammatory agents to investigational compounds that aim to stabilize glial function or promote remyelination. However, challenges due to interindividual variability, insufficient biomarkers, and the multifactorial nature of psychiatric illnesses remain. Advances in neuroimaging, liquid biopsy, and more precise molecular techniques may facilitate targeted interventions by stratifying patient subgroups with distinct glial phenotypes. Continued research is essential to translate these insights into clinically efficacious and safe treatments.



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Keywords: neuroglia; neuroinflammation; depressive disorder; major; bipolar disorder; attention deficit disorder with hyperactivity; schizophrenia

1. Introduction

Over the past few decades, it has become increasingly evident that glial cells, traditionally viewed merely as supporting elements in the function of the central nervous system (CNS), play fundamental roles in regulating and maintaining the neuronal milieu. Although neurons are recognized as the primary drivers of electrical signaling, neuroglia, which consist mainly of astrocytes, microglia, oligodendrocytes, and ependymal cells, actively contribute to synaptic communication, metabolic support, and the modulation of inflammatory processes [1]. A deeper understanding of these interactions is important to elucidate the pathophysiology of various psychiatric disorders, including depression, bipolar disorder, anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and schizophrenia [2,3].

The clinical relevance of this topic is evident from the high prevalence of these conditions in the general population and the associated social and economic burdens. Depression

is estimated to be one of the leading causes of disability worldwide, whereas anxiety disorders affect millions of individuals, resulting in personal and societal problems. In the context of bipolar disorder, mood fluctuations and the chronicity of the disease result in severe outcomes for both patients and their families. Schizophrenia, which is characterized by cognitive and psychotic manifestations, poses a significant therapeutic challenge, necessitating integrated approaches. Furthermore, ADHD, especially in children and adolescents, is widely diagnosed and surrounded by controversial neurobiological research lines [4].

Traditionally, the pathogenesis of these illnesses has been attributed to neuronal dysfunction involving neurotransmitters (dopamine, serotonin, norepinephrine, GABA, and glutamate) and synaptic plasticity. However, recent evidence has suggested that glial cells play an active role beyond structural support. For instance, astrocytes modulate the ionic and molecular environment by participating in the regulation of the release and uptake of neurotransmitters, in addition to influencing synaptic signaling and the blood–brain barrier [1]. Microglia function as the primary resident immune cells of the CNS and are indispensable for sustaining homeostasis and mediating inflammatory responses [5]. Meanwhile, oligodendrocytes are vital for the formation and maintenance of the myelin sheath, ensuring appropriate neuronal conduction velocity; their dysfunction has been linked to psychiatric disorders such as schizophrenia [2].

This review examines the relationship between neuroglia and five clinically significant psychiatric disorders: depression, bipolar disorder, anxiety disorders, ADHD, and schizophrenia. We begin with an overview of the normal function of glial cells and then examine the key findings linking glial alterations to each condition. Preclinical data (animal models and histological and molecular investigations) and clinical observations (neuroimaging, biomarker analysis, and symptom correlation) are reviewed. Finally, future perspectives are discussed, focusing on therapeutic interventions geared toward glial modulation.

2. Methods

In this narrative review, we sought to integrate current data on the roles of glial cells (astrocytes, microglia, oligodendrocytes, and ependymal cells) in psychiatric disorders, such as major depression, bipolar disorder, anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and schizophrenia. This comprehensive review was conducted by searching PubMed, Web of Science, and Scopus for English language articles published between 2000 and 2025. We used a combination of controlled vocabulary and free-text keywords such as “astrocytes”, “microglia”, “oligodendrocytes”, “ependymal cells”, “glial cells”, “neuroinflammation”, “bipolar disorder”, “depression”, “anxiety”, “ADHD”, and “schizophrenia”. Although no formal systematic protocol was employed, we prioritized studies with a robust methodological design, clinically relevant and recent data, and a clear explanatory approach to enhance the didactic value of this review.

3. Basic Concepts and Physiology of Neuroglia

To understand the contributions of glial cells to the pathogenesis of psychiatric disorders, it is imperative to first understand their physiological roles under baseline conditions. Although glial cells do not generate action potentials in the same manner as neurons, they fulfill multiple critical functions necessary for the central nervous system (CNS), including structural support, the regulation of the extracellular microenvironment, and the modulation of synaptic transmission [6].

3.1. Astrocytes

Astrocytes are the most abundant and versatile glial cells, representing approximately half of the brain volume. Histologically, their processes envelop blood vessels as well as synapses, thereby forming what is often termed the “neurovascular unit” [7]. Astrocytes regulate cerebral blood flow and deliver nutrients and oxygen in accordance with neuronal activity. They are also central to maintaining the extracellular microenvironment, particularly through the regulation of ion concentrations such as potassium and the buffering of neurotransmitters such as glutamate [8].

A pivotal aspect of astrocyte function lies in their participation in “tripartite neurotransmission”, a conceptual framework that redefines the synapse as comprising not only the presynaptic terminal, synaptic cleft, and postsynaptic terminal, but also the astrocytic processes that envelop and detect neuronal signals [9]. In this context, shifts in astrocytic reactivity, such as the enhanced expression of glial fibrillary acidic protein (GFAP), a hallmark of reactive astrocytes, can signify ongoing pathological or adaptive processes, including neuroinflammatory or degenerative changes [10].

3.2. Microglia

Microglia account for approximately 10% of the cellular population in the CNS and serve as the principal immune defense in the brain [11]. Originating from mesodermal precursors, these cells display notable plasticity and swiftly adapt their phenotypes to local environmental cues. Under homeostatic conditions, microglia assume a “ramified” morphology and continuously survey their microenvironment. However, upon exposure to injurious or inflammatory stimuli, they transition into a “reactive” or “amoeboid” state, migrating to the lesion site, phagocytosing cellular debris, and secreting both pro- and anti-inflammatory cytokines [12].

In certain pathological contexts, sustained microglial activation can promote a neurotoxic milieu characterized by the release of mediators such as nitric oxide and pro-inflammatory factors such as IL-1 β and TNF- α , which may compromise synaptic signaling and neuronal viability [13]. Consequently, dysregulated microglial function has been implicated in numerous neurological and psychiatric conditions, as chronic low-grade inflammation is a common feature of many disorders, including schizophrenia [14].

3.3. Oligodendrocytes

Oligodendrocytes are tasked with myelinating CNS nerve fibers, a function essential for efficient electrical impulse conduction. The preservation of myelin sheaths underpins the integrity of neural communication, and disruptions in these processes can manifest as cognitive and behavioral deficits [15].

While oligodendrocyte research has traditionally focused on demyelinating diseases, such as multiple sclerosis, emerging evidence suggests that their dysfunction may also contribute to mood and psychotic disorders. For instance, alterations in both the number and morphology of oligodendrocytes have been reported in patients with schizophrenia, suggesting a connection between myelination and the regulation of cortico-subcortical pathways [16]. Furthermore, exacerbated microglial activation has been proposed as a mechanism driving oligodendrocyte damage in individuals with schizophrenia, ultimately compromising white matter integrity [17].

3.4. Other Glial Interactions

The blood–brain barrier (BBB) is a highly selective interface that influences the exchange of substances between the bloodstream and central nervous system (CNS). Its composition includes endothelial cells sealed by tight junctions, pericytes, and astrocytic

end-feet, all of which play key roles in preserving barrier integrity [18,19]. Proper BBB function is vital for shielding the CNS from pathogens, toxins, and abrupt shifts in blood composition. Through the secretion of factors, such as angiopoietin-1 and TGF- β , astrocytes directly sustain BBB homeostasis and modulate capillary permeability within the brain [20].

Disturbances in glial activity can compromise BBB integrity, leading to increased permeability and facilitating neuroinflammatory processes. Evidence indicates that under pathological conditions such as neuroinflammation and neurodegenerative disorders, astrocytes and microglia become activated and can degrade tight junctions, permitting plasma proteins to leak into the brain parenchyma [21].

In addition to their role in participating in the regulation of classical neurotransmitters such as glutamate, glial cells also secrete signaling molecules, including ATP, D-serine, and cytokines, which directly influence neuronal excitability and synaptic plasticity [22]. Therefore, astrocytes and microglia not only provide metabolic support for neurons, but also execute essential functions in modulating neuronal network activity. This dynamic interplay underlies the key processes of learning, memory, and emotional behavior, underscoring the active involvement of glia in cognitive performance and neural homeostasis [23].

Table 1 summarizes the fundamental differences between neuronal and glial functions, emphasizing how glial dysfunction contributes to psychiatric pathology.

Table 1. Functional comparison of neurons and glial cells in psychiatric disorders. Neurons have traditionally been considered primary drivers of psychiatric pathology because of their roles in neurotransmission, synaptic plasticity, and circuit connectivity. However, increasing evidence has highlighted the crucial involvement of glial cells (astrocytes, microglia, and oligodendrocytes) in neuropsychiatric disorders. While neurons directly mediate neurotransmitter release and the propagation of action potentials, glial cells regulate synaptic homeostasis, immune responses, and metabolic support. Dysfunctional glial processes, including astrocytic glutamate imbalance, microglia-mediated neuroinflammation, and oligodendrocyte-related myelination deficits, contribute to psychiatric disorders, such as major depression, bipolar disorder, schizophrenia, anxiety disorders, and ADHD. Understanding the complementary and interdependent roles of neurons and glia offers a more comprehensive framework for developing novel therapeutic strategies that extend beyond traditional neurotransmitter-based pharmacology.

Feature	Neurons	Glial Cells
Primary Function	Neurotransmission via action potentials	Structural, metabolic, and immune support
Synaptic Regulation	Release and reuptake of neurotransmitters	Modulation of synaptic homeostasis, synaptic pruning
Inflammatory Response	Limited response to immune signals	Microglia-mediated neuroinflammation, astrocyte reactivity
Neurotransmitter Role	Direct synthesis and release	Indirect modulation through uptake, metabolism, and signaling
Involvement in Psychiatric Disorders	Dopaminergic, noradrenergic, serotonergic, and glutamatergic dysfunction	Neuroinflammation, oxidative stress, and demyelination
Therapeutic Implications	Targeted with psychotropic drugs (SSRIs, antipsychotics, or stimulants)	Potential target for anti-inflammatory, myelin-restorative, and glia-stabilizing therapies

4. Neuroglia and Psychiatric Disorders

Evidence suggests that both inflammation and glial dysfunction contribute to the pathophysiology of mental health disorders. An expanding body of literature indicates that altered astrocytic or microglial reactivity can upregulate the neuronal circuits implicated in mood, cognition, and emotional regulation [24]. Figure 1 illustrates the integration of neurobiological mechanisms underlying major psychiatric disorders.

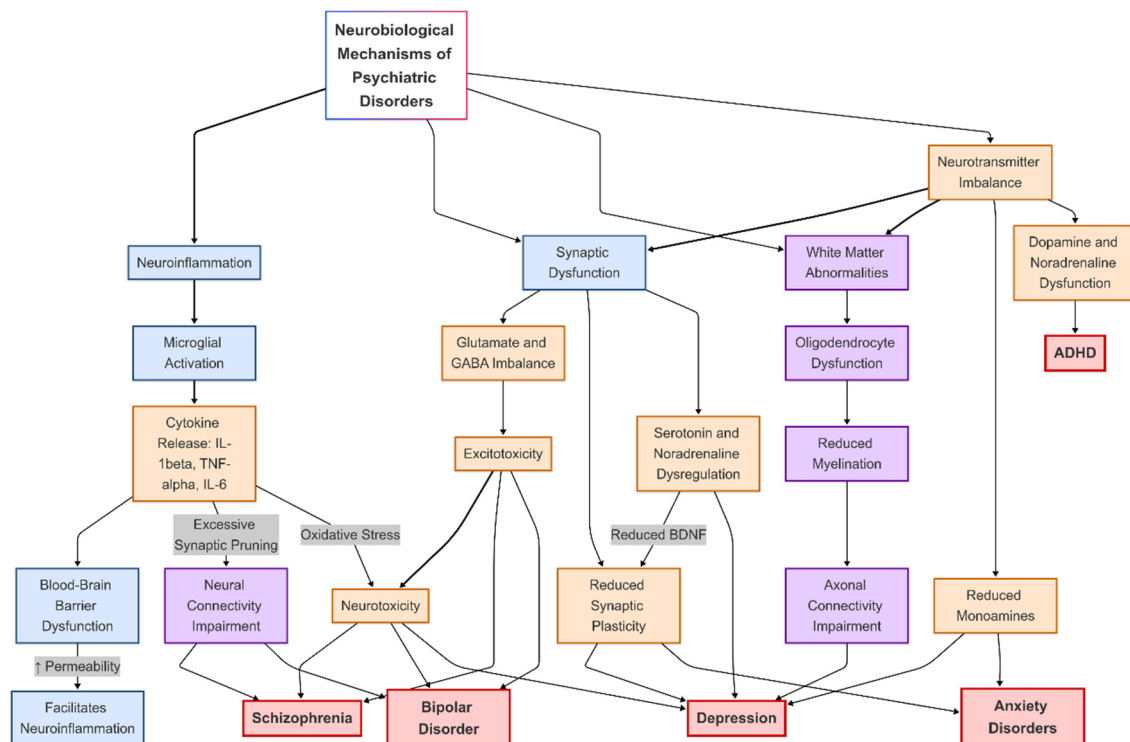


Figure 1. Neurobiological mechanisms of psychiatric disorders. This diagram illustrates the core neurobiological mechanisms underlying psychiatric disorders, emphasizing the role of glial dysfunction in conjunction with neurotransmitter imbalance, synaptic impairments, and white matter abnormalities. Neuroinflammation, primarily mediated by microglial activation and the release of pro-inflammatory cytokines (e.g., IL-1 β , TNF- α , and IL-6), contributes to excessive synaptic pruning, oxidative stress, and blood–brain barrier dysfunction, which collectively impair neural connectivity and facilitate the onset of schizophrenia and bipolar disorder. Synaptic dysfunction, driven by glutamate and GABA imbalances, excitotoxicity, and reduced synaptic plasticity, further disrupts mood and cognitive processes and plays a central role in bipolar disorder and depression. White matter abnormalities, particularly oligodendrocyte dysfunction and impaired myelination, lead to the axonal connectivity deficits that have been implicated in depression and other affective disorders. Neurotransmitter imbalances, including dopamine and noradrenaline dysregulation, are closely associated with attention-deficit/hyperactivity disorder (ADHD) and anxiety disorders. The complex interplay between these mechanisms underscores the multifactorial nature of psychiatric disorders, highlighting the need for an integrative approach in order to understand their pathophysiology.

The so-called “inflammatory hypothesis” of psychiatric disorders has gained traction based on observations of elevated levels of pro-inflammatory cytokines (e.g., IL-6 and TNF- α) in patients with major depression, schizophrenia, and related clinical conditions. When systemic inflammation extends into the CNS, it can activate or dysregulate microglial function, potentially triggering a harmful cycle of exaggerated inflammatory responses [25]. Within this framework, the excessive release of neurotoxic mediators and the promotion of maladaptive synaptic changes may adversely affect behavior and cognition [26].

In animal models, rodents exhibiting depression-like behaviors frequently display increased expression of microglial activation markers and reactive astrocytes [27]. Likewise, postmortem analyses of the brains of individuals diagnosed with psychiatric disorders have revealed shifts in the density or morphology of astrocytes and microglia in regions such as the prefrontal cortex, hippocampus, and amygdala [28].

Functional neuroimaging studies, particularly PET imaging employing TSPO ligands (a marker for microglial activation), have indicated that patients with treatment-resistant depression may show heightened tracer binding in certain brain regions, suggesting neuroinflammation [29]. Peripheral biomarkers (such as C-reactive protein and various cytokines) frequently correlate with the severity of mood and anxiety symptoms. Although cross-sectional data alone do not establish direct causality, converging evidence suggests that chronic inflammation, largely mediated by glial cells, may be integral to both the onset and persistence of psychiatric disorders [30].

Nonetheless, not all investigations corroborate this hypothesis. Some studies failed to detect significant differences in glial activation between psychiatric patients and healthy controls or yielded conflicting results depending on the illness stage or prior medication exposure. Moreover, the clinical heterogeneity of these disorders, including the distinct subtypes of depression and schizophrenia, complicates the establishment of a unifying model. Additional factors, such as medical comorbidities, substance use, genetic variation, and shape, sometimes confound these findings [31].

To provide a structured overview of glial involvement in psychiatric disorders, Table 2 summarizes the key findings derived from different methodologies, including neuroimaging, biomarker analyses, postmortem studies, and preclinical models. This comparative perspective highlights how each approach contributes to the understanding of the role of neuroglia in mental health conditions. Each psychiatric disorder will be further explored in detail.

Table 2. Glial-related findings in psychiatric disorders using different methodologies. PET (positron emission tomography), TSPO (Translocator Protein, a marker of microglial activation), MRS (Magnetic Resonance Spectroscopy), DTI (Diffusion Tensor Imaging, used to assess white matter integrity), fMRI (functional magnetic resonance imaging, used to study brain connectivity), CSF (cerebrospinal fluid), CRP (C-reactive protein, an inflammatory marker), GFAP (glial fibrillary acidic protein, an astrocytic marker), S100B (calcium-binding protein B, associated with astrocytic function and reactivity), MBP (Myelin Basic Protein, related to oligodendrocyte function and myelination), and CNP (2',3'-Cyclic-nucleotide 3'-phosphodiesterase, an enzyme involved in myelin regulation and oligodendrocyte function).

Methodology	Findings	Potential Implications
Neuroimaging (PET, MRS, DTI, fMRI)	PET (TSPO ligands): Some studies report increased tracer binding in individuals with treatment-resistant depression and schizophrenia. MRS: Altered glutamate/glutamine levels observed in mood disorders. DTI: Reduced white matter integrity reported in schizophrenia and bipolar disorder. fMRI: Functional connectivity alterations noted in anxiety and schizophrenia.	PET findings suggest possible neuroimmune activation in specific psychiatric conditions. MRS data indicate potential disruptions to glutamatergic homeostasis. DTI studies raise the possibility of white matter abnormalities, which may be related to changes in myelination. fMRI results suggest altered network connectivity, which could be influenced by neuroglial activity.

Table 2. Cont.

Methodology	Findings	Potential Implications
Biomarkers (CSF and blood)	Inflammatory markers: Increased levels of IL-6, TNF- α , and CRP reported in some individuals with depression, schizophrenia, and bipolar disorder. Astrocytic markers: Elevated S100B and GFAP detected in CSF of patients with depression in certain studies. Kynurenine pathway metabolites: Altered levels identified in mood disorders and schizophrenia.	Findings suggest that immune-related processes may contribute to psychiatric conditions, though causality remains unclear. Changes in astrocytic markers may reflect glial reactivity, but further validation is needed. Alterations in the kynurenine pathway could have implications for neurotransmitter balance and neuroimmune interactions.
Postmortem brain studies	Astrocytes: Lower astrocyte density reported in the prefrontal cortex and hippocampus of individuals with depression and schizophrenia. Microglia: Some studies indicate increased microglial marker expression in schizophrenia. Oligodendrocytes: Altered expression of myelin-related genes (e.g., MBP, CNP) observed in schizophrenia.	Reduced astrocyte density may be associated with changes in synaptic function. Microglial activation patterns suggest a potential role in neuroimmune responses, though variability exists across studies. Oligodendrocyte-related changes could impact white matter integrity and neural communication.
Animal models	Depression: Increased expression of microglial activation markers observed in stress-induced models. Bipolar disorder: Variability in microglial activity across mood states in some models. Anxiety and PTSD: Associations between microglial activation and stress-related behavioral responses.	Experimental findings suggest that neuroglial alterations may be linked to behavioral changes in preclinical models. Microglial responses appear to be dynamic and may vary depending on disease state. Translational relevance requires further investigation to determine how these mechanisms relate to human pathology.

4.1. Major Depression Disorder

Major depression (MD) is one of the most prevalent and debilitating psychiatric disorders, characterized by a persistently depressed mood, anhedonia (loss of interest or pleasure in previously enjoyable activities), disturbances to appetite and sleep, and, in severe cases, cognitive impairment and suicidal ideation. Early neurobiological hypotheses of depression were largely centered on neurotransmitter imbalances, particularly involving serotonin and norepinephrine. However, a growing body of evidence underscores the role of inflammatory processes and glial dysfunction, especially those involving astrocytes and microglia, in the pathophysiology of depression [32].

Research using animal models of depression (e.g., those induced by chronic stress) has shown that microglia may assume a hyperreactive state in several brain regions, including the prefrontal cortex and hippocampus [33,34]. Conversely, some studies have reported reduced microglial density or functionality at certain stages of the disorder, which may reflect distinct phases of the illness or the influence of pharmacological interventions [35]. Therefore, “microglial activation” during depression is non-uniform. Instead, it may vary in both intensity and regional distribution within the brain.

In humans, positron emission tomography (PET) using the Translocator Protein (TSPO) ligand has enabled the indirect in vivo quantification of activated microglia. Some findings suggest that individuals with treatment-resistant depression exhibit elevated TSPO binding in areas implicated in mood regulation, indicating neuroinflammation [32]. Nevertheless,

replicating these observations remains challenging given methodological differences across studies and the clinical heterogeneity of patient populations.

In addition to microglia, growing attention has been focused on the role of astrocytes in depression. These cells regulate glutamate homeostasis, which is a key excitatory neurotransmitter essential for synaptic plasticity and neuronal communication. Astrocytic dysfunction can lead to glutamate accumulation in the synaptic cleft, contributing to excitotoxicity and synaptic loss in regions critical for mood regulation, such as the hippocampus [36,37]. In this context, an increased expression of glial fibrillary acidic protein (GFAP), a hallmark of astrocyte reactivity, has been detected in postmortem brain samples from individuals with depression [38]. However, other studies have documented a decrease in the number of astrocytes within certain regions, such as the prefrontal cortex, highlighting the heterogeneity of these findings [31].

Astrocytes also secrete a range of trophic factors (e.g., BDNF and GDNF) and cytokines (e.g., IL-1 β and TNF- α), placing them at the nexus between inflammatory responses and neuroprotective mechanisms [39]. Perturbations in the secretion of these molecules can modulate the inflammatory milieu of the brain, thereby exacerbating or alleviating depressive symptoms. Therapeutically, this is an expanding frontier, with ongoing investigations into pharmacological agents that specifically restore or modulate astrocytic function by mitigating excessive reactivity or re-establishing glutamate uptake capacity [40].

Major depression is often accompanied by elevated levels of peripheral inflammatory markers such as C-reactive protein (CRP), IL-6, and TNF- α . One plausible hypothesis posits that these pro-inflammatory cytokines in the bloodstream may signal to the central nervous system either by crossing or altering the blood–brain barrier, subsequently triggering or perpetuating glial activation [41,42]. This “neuroimmune axis” is part of a model wherein chronic stressors—whether psychological, metabolic, or infectious—favor the emergence of inflammatory states that, in turn, contribute to depressive symptomatology via disrupted synaptic plasticity and glial dysfunction [43].

The recognition of glial involvement in depression has spurred the development of therapeutic strategies aimed at modulating inflammatory pathways and astrocytic/microglial functions rather than focusing solely on classical neurotransmitter targets (serotonin, dopamine, and norepinephrine). For instance, minocycline, an antibiotic with anti-inflammatory properties, has shown promising results in certain clinical trials, suggesting symptomatic improvement along with a reduction in inflammatory markers [36]. Other agents such as N-acetylcysteine (NAC) have been explored for their antioxidant and microglial-modulating activities [31].

4.2. Bipolar Disorder

Bipolar disorder (BD) is characterized by mood swings that alternate between episodes of mania or hypomania and depression. Its underlying pathophysiology is multifaceted, encompassing disruptions in cerebral energy metabolism, monoamine neurotransmission, intracellular signaling pathways, and more recently, the neuroimmune and glial systems [44].

Similarly to findings in depression, postmortem analyses of brains of patients with BD have suggested alterations in astrocyte density and morphology. Some reports point to a reduced astrocyte count in the prefrontal and limbic structures, potentially correlating with deficits in emotional regulation and impulsive behavior [45]. The modulation of glutamate, along with interactions between astrocytes and endothelial cells, may be particularly pertinent to BD, as extreme mood states could arise from the instability of the neuronal extracellular milieu [46].

Microglial cells have received considerable attention in recent years. Experimental evidence implies that the manic phase may be associated with a pro-inflammatory mi-

croglial profile, whereas the depressive phase may involve different forms of microglial dysfunction [47,48]. Although the transition between mood states in BD is undoubtedly influenced by multiple factors, the involvement of glia offers an additional perspective, especially concerning synaptic plasticity and “inflammatory neurotoxicity” [49].

Clinically, patients with BD frequently exhibit elevated levels of inflammatory cytokines (e.g., IL-1 β and IL-6) during acute manic or depressive episodes compared with those in patients with euthymia. This fluctuation suggests that inflammation may vary according to the phase of the disorder, which is potentially mediated by glial processes [50]. Moreover, external factors such as stress, infections, and diet can trigger or exacerbate episodes by intensifying systemic inflammation [51].

Another area of interest in BD is oligodendrocyte abnormality. Neuroimaging studies, most notably magnetic resonance imaging, have highlighted white matter alterations in individuals with BD, implicating possible disturbances in myelination or oligodendrocyte functionality [43]. Disrupted communication between regions such as the prefrontal cortex and limbic system may partly explain the cognitive and affective dysregulation that characterizes the condition. Although oligodendrocytes have been explored less extensively than astrocytes and microglia, they nonetheless represent a plausible link between glial disturbances and BD pathophysiology [52].

Several mood stabilizers, including lithium and valproate, possess anti-inflammatory and neuroprotective properties that modulate glial functions. For instance, lithium inhibits microglial activation, enhances astrocyte survival, and regulates the critical neurotrophic factors involved in neuroplasticity [53]. Accordingly, the glial regulatory actions of these agents may underlie their therapeutic efficacy in mood stabilization. Identifying more targeted molecular pathways in glial cells holds promise for the development of novel pharmacological interventions with improved efficacy and fewer side effects.

4.3. Anxiety Disorders

Anxiety disorders, which include generalized anxiety disorder (GAD), phobias, panic disorder, and related conditions, such as post-traumatic stress disorder (PTSD), are primarily characterized by excessive fear or worry that interferes with daily functioning. Similarly to findings in depression and bipolar disorder, emerging evidence suggests that neuroinflammation and glial dysfunction may play pivotal roles in the development or persistence of anxiety symptoms [54].

It is well established that an imbalance between inhibitory neurotransmission (e.g., GABA) and excitatory neurotransmission (e.g., glutamate) contributes to the neuronal hyperexcitability observed in anxiety disorders. Astrocytes are integral to glutamate re-uptake, converting it into glutamine, which can be subsequently utilized by neurons to synthesize either GABA or glutamate. When astrocyte function is compromised, such as by the reduced expression of glutamate transporters, glutamate may accumulate in the extracellular space, creating a milieu of enhanced neural excitability and elevated anxiety [55].

Under conditions of intense or chronic stress, activation of the hypothalamic–pituitary–adrenal (HPA) axis leads to the release of hormones that can influence microglial cells, inducing a pro-inflammatory phenotype. This state may promote the secretion of cytokines, thereby affecting emotional processing circuits in regions such as the amygdala and prefrontal cortex and heightening fear and anxiety responses [56]. Experimental animal models have shown that blocking or modulating microglial activation can mitigate anxiety-like behaviors, further supporting the involvement of neuroimmune mechanisms [57].

PTSD, which arises following exposure to extreme trauma, is characterized by the intrusive recollection of traumatic events, hypervigilance, and recurrent flashbacks. Neuroimaging and biomarker studies have indicated that chronic inflammation and glial

dysfunction, particularly within fear-processing regions such as the amygdala and hippocampus, may underpin these persistent traumatic memories [56].

4.4. ADHD

Attention-deficit/hyperactivity disorder (ADHD) typically emerges during childhood but often persists into adulthood, and is characterized by inattention, impulsivity, and hyperactivity. The etiology is multifactorial, encompassing genetic, environmental, and neurobiological elements, with conventional research focusing on the dopaminergic and noradrenergic systems [58]. However, recent findings indicate that glial cells may play a salient role in the pathophysiology of this disorder [59].

Dopamine (DA) is central to the regulation of motivation and inhibitory control, both of which are compromised in ADHD. Evidence suggests that astrocytes and microglia can modulate DA release and reuptake in the striatum and prefrontal cortex [60]. Inflammatory alterations within these glial populations can disrupt dopaminergic metabolism and contribute to core ADHD symptoms [61]. Although this remains an emerging area of study, functional magnetic resonance imaging (fMRI) and molecular assays have reported correlations between inflammatory markers and ADHD severity [62].

Susceptibility to glial dysfunction in ADHD may also be influenced by genetic factors that affect immune signaling and myelination. Polymorphisms in genes related to inflammation, for example, may increase microglial reactivity in response to infections or environmental toxins, exacerbating attentional deficits [63]. Additionally, prenatal exposure to substances such as alcohol or tobacco can precipitate an intrauterine inflammatory response, potentially impairing glial development and increasing the likelihood of ADHD onset during childhood [64].

Currently, the first-line treatment for ADHD comprises psychostimulants (e.g., methylphenidate and amphetamines) that target the dopaminergic and noradrenergic pathways [65]. Nonetheless, given the possible contribution of glial dysregulation, future research should explore pharmacological strategies that enhance astrocytic function or mitigate excessive inflammatory responses, offering a complementary avenue for ADHD management.

4.5. Schizophrenia

Schizophrenia is a complex psychiatric disorder characterized by positive symptoms (hallucinations and delusions), negative symptoms (apathy, social withdrawal, and anhedonia), and cognitive impairments (difficulties in concentration, memory, and executive functions). While early research efforts focused on dopaminergic or glutamatergic abnormalities, recent studies have increasingly highlighted the significance of inflammation and glial cells in the pathophysiology of schizophrenia [49]. Evidence suggests that microglial, astrocytic, and oligodendroglial alterations may contribute to the functional deficits that define this disorder [66].

A prominent line of research concerns the involvement of microglia in the onset and progression of schizophrenia. Neuroimaging studies employing positron emission tomography (PET) with Translocator Protein (TSPO) ligands have provided evidence of heightened microglial activation in individuals with schizophrenia, especially during acute psychotic episodes [13]. Activated microglia are thought to release pro-inflammatory cytokines and reactive oxygen species (ROS), potentially inducing neurotransmission disturbances and synaptic damage. In certain instances, excessive microglial-mediated synaptic pruning may lead to the loss of connections essential for cortico-subcortical network integrity [67]. Such alterations could manifest as cognitive and behavioral disruptions typical of schizophrenia, including difficulties in integrating information and sustaining coherent thought processes.

Nevertheless, the literature remains divided regarding which stages of the illness exhibit pronounced microgliosis, and whether certain subgroups of patients display more marked inflammatory components than others do.

In recent years, there has been growing interest in the role of astrocytes in schizophrenia. In addition to their pivotal functions in ion homeostasis and neurotransmitter uptake, astrocytes are also crucial for synaptic organization. Changes in the expression of glial fibrillary acidic protein (GFAP) have been reported in the brains of individuals with schizophrenia, but findings vary according to brain region and disease stage [41]. Some investigators have proposed that, in specific cases, reduced astrocytic reactivity could impair neuronal support and disrupt the glutamatergic equilibrium.

Another relevant aspect of astrocyte function involves the release of D-serine, an essential cofactor for the activation of N-methyl-D-aspartate (NMDA) receptors in neurons. The dysregulation of D-serine production or release may contribute to disruptions in glutamatergic signaling, a hypothesis often linked to psychotic symptoms [68]. Accordingly, elucidating how astrocytes modulate NMDA-mediated pathways may offer valuable insights into the pathophysiological mechanisms underlying schizophrenia.

White matter integrity and the efficiency of electrical conduction along cortico-subcortical pathways are critical for higher-order processes including cognition and reality testing. Neuroimaging studies have revealed structural white matter abnormalities in many individuals with schizophrenia, suggesting that oligodendrocyte-related dysfunction or impaired myelination may play a significant role [69]. Multiple studies have reported the diminished expression or disruption of genes related to oligodendrocytes (e.g., CNP and MBP) in postmortem brain samples from patients with schizophrenia [66]. Insufficient myelination could compromise the synchronous firing of neuronal populations, thus exacerbating cognitive deficits and possibly contributing to hallucinations. Although the causal link between oligodendroglial dysfunction and schizophrenic symptoms has not been fully established, these findings underscore the importance of coordinated glial activity for integrated brain function.

As a multifactorial disorder, schizophrenia arises from the interplay between susceptibility genes, epigenetic factors, environmental stressors, and immunoinflammatory components. The polymorphisms in genes involved in immune responses or microglial activity may predispose certain individuals to chronic neuroinflammation, setting in motion pathological processes that culminate in psychotic manifestations [70].

5. Future Directions: Possibilities, Challenges, and Dangers

Glial cell involvement in the pathophysiology of various psychiatric disorders prompts a crucial question: How can these recent discoveries be harnessed to create effective therapeutic interventions? The roles of astrocytes, microglia, and oligodendrocytes in inflammatory, neurotrophic, and synaptic processes suggest promising pharmacological targets and novel therapeutic strategies. Despite significant progress, however, major hurdles remain. These include defining target specificity, ensuring safety, and elucidating precise mechanisms of action that can support robust clinical benefits [71].

5.1. Possibilities

The inflammatory component is among the most extensively investigated aspects of the glia–psychiatric disorder interface. Chronic microglial activation, marked by elevated levels of pro-inflammatory cytokines (IL-1 β , TNF- α , and IL-6) and neurotoxic substances (nitric oxide and reactive oxygen species), has been linked to major depression, schizophrenia, and bipolar disorder [72]. Consequently, molecules capable of modulating the hyperreactive response have emerged as potential therapeutic candidates.

Non-steroidal anti-inflammatory drugs (NSAIDs), antioxidants, and immunobiologicals, such as monoclonal antibodies targeting specific cytokines, have been investigated as adjuvants in the treatment of resistant depression. However, from a translational standpoint, there is a pressing need to identify subgroups of patients with heightened inflammatory profiles (e.g., elevated C-reactive protein or IL-6 levels) who might derive particular benefits from such interventions [73].

Astrocytes play a pivotal role in glutamate reuptake via specialized transporters (EAAT1/2). The dysregulation of these transporters or astrocytic hyperreactivity can lead to excessive extracellular glutamate, exacerbating excitotoxicity, an established mechanism of neuronal loss in mood disorders and schizophrenia [74]. Theoretically, pharmacological agents that enhance astrocytic transporter activity or curb glial glutamate release could alleviate this pathological imbalance.

Furthermore, there is a growing interest in compounds that boost the astrocyte-driven production of neurotrophic and neuroprotective factors (e.g., BDNF and GDNF), thereby sustaining or restoring synaptic plasticity. Interventions aimed at stabilizing astrocyte function may thus serve as either adjunctive or primary therapies for conditions such as major depression, bipolar disorder, and anxiety disorders [11].

Oligodendrocytes, the cells responsible for generating and maintaining myelin sheaths, also exhibit functional alterations in schizophrenia and possibly in bipolar disorder [3]. Because myelin dysfunction undermines neuronal conduction and disrupts the integration of signals across cerebral regions, therapeutic strategies designed to safeguard or restore white matter could enhance functional connectivity, with positive repercussions for both cognitive and affective symptoms.

Preclinical investigations have focused on factors that facilitate the maturation of oligodendrocyte precursor cells (OPCs) or counteract inflammatory processes that lead to oligodendroglial damage. Nonetheless, specificity remains a challenge. Myelination is tightly regulated, and excessive or inappropriate stimulation may induce functional imbalances [75]. Thus, identifying safe and targeted approaches to modulating myelination represents a key frontier in glial-based therapies for psychiatric disorders.

5.2. Challenges

Depression, bipolar disorder, anxiety disorders, ADHD, and schizophrenia do not constitute single, uniform entities; rather, they are complex syndromic spectra characterized by heterogeneous symptoms and clinical outcomes. This clinical diversity corresponds to the underlying neurobiological variability; distinct patient subgroups may exhibit divergent inflammatory profiles, genetic variations in immune pathways, and unique microglial activation signatures [49]. Such heterogeneity complicates the design of clinical trials and underscores the difficulty of identifying reliable biomarkers to stratify the patients most likely to benefit from glia-targeting interventions.

Although current insights into the relationship between neuroglia and psychiatric disorders highlight new facets of this complexity, the translation of glial research into therapeutic applications is still in its early stages. Several factors have contributed to this challenge.

1. Breadth of Glial Functions

Astrocytes, microglia, and oligodendrocytes perform multiple, often overlapping functions and operate in intricate networks alongside neurons. Hence, the modulation of one particular process (e.g., microglial-mediated inflammation) can trigger unintended consequences in other domains (e.g., alterations in synaptogenesis or blood–brain barrier permeability), leading to potential off-target effects [76].

2. Difficulty Accessing Brain Tissue

Unlike other medical conditions in which biopsies of the affected organ are readily obtainable, such procedures are seldom feasible in the central nervous system, except in rare or extreme cases (e.g., tumor resections). As a result, studies of human glial function rely primarily on neuroimaging, cerebrospinal fluid analysis, or postmortem examination, and each method is constrained by its inherent limitations [77].

3. *Interindividual Variability*

Genetic, epigenetic, and environmental factors can profoundly influence glial response. Consequently, pharmacological agents that are efficacious in certain patient subgroups may fail in others, making it difficult to achieve robust outcomes in large-scale clinical trials [78].

4. *Systemic Nature of Inflammation*

Many pro-inflammatory pathways implicated in central nervous system disorders also operate peripherally (and vice versa). Consequently, drugs targeting glial processes may exhibit unpredictable bioavailability and produce unwanted systemic changes [25].

5. *Scarcity of Specific Biomarkers*

The lack of reliable biomarkers to detect “astrocytic dysfunction” or “excessive microglial reactivity” in humans impedes the validation of new therapies, as no universally accepted indicators exist to track pharmacological responses in glial cells [41].

Glial function is also highly susceptible to metabolic shifts (e.g., fluctuations in glucose or thyroid hormones and changes in stress hormones) and peripheral inflammatory insults (e.g., infections, obesity, and metabolic syndrome). Even when a plausible “glial target” is identified, its modulation may be confounded by medical comorbidities and lifestyle factors (diet, sedentary behavior, and alcohol consumption) [28]. Consequently, findings that show promise in animal models or tightly selected patient subgroups may fail to be replicated in broader clinical settings.

Moreover, anti-inflammatory agents can interfere with peripheral immune processes, increasing the risk of infection or compromising immune surveillance against neoplasms. Similarly, compounds that enhance astrocyte or oligodendrocyte activity may produce unanticipated effects on other cellular pathways, given the overlap in signaling mechanisms inside and outside the CNS. Thus, long-term safety remains a pressing concern, calling for extensive Phase II and III trials as well as post-marketing surveillance if such glia-targeting drugs ultimately gain approval [79].

Despite these obstacles, several indicators suggest that progress is on the horizon. Advances in neuroimaging, the development of liquid biopsies (e.g., extracellular vesicles released by glial cells), and efforts to delineate more homogeneous inflammatory subgroups have paved the way forward. Investments in multidisciplinary research, including neurology, psychiatry, immunology, and stem cell biology, are poised to accelerate our understanding of glial mechanisms and facilitate the design of targeted clinical trials.

5.3. *Dangers*

Due to the notion that inflammatory processes and glial dysfunction may be linked to psychiatric disorders, there is an accompanying risk of unvalidated therapeutic practices seeking to capitalize on a “mechanistic” discourse—often grounded in preliminary or preclinical findings—to justify questionable interventions. It is important to emphasize that although discoveries about neuroglia offer promising new pathophysiological hypotheses for depression, bipolar disorder, anxiety disorders, ADHD, and schizophrenia, no evidence to date supports the direct or indirect manipulation of glial function as an established, clinically effective treatment [80].

Within this context, certain practitioners may exploit the widespread enthusiasm surrounding glia-related research by promoting supplements, antioxidants, or other sub-

stances under claims of “anti-inflammatory action” or “restoring glial health”. Although some compounds, such as minocycline and N-acetylcysteine, have been systematically investigated, the current clinical outcomes remain inconsistent and often show modest effects or fail to replicate in larger trials [81,82]. Demonstrations of inflammatory alterations or astrocyte/microglial dysfunction in experimental studies should not be construed to indicate that isolated antioxidant regimens or purported neuroprotective substances can significantly improve clinical outcomes.

Given the complexities of mental disorders, including genetic, epigenetic, and environmental factors, it is improbable that a single unvalidated therapy could reverse these pathophysiological processes. Moreover, demonstration of efficacy in animal or in vitro models does not guarantee safety and effectiveness in humans. Any extrapolation of such data requires controlled clinical studies that rigorously assess not only potential symptom improvement, but also adverse events and the durability of gains over the long term [83].

Clinicians, researchers, and patients should thus maintain a critical stance when confronted with “therapies” targeting glial modulation that lack a robust scientific foundation. As with any biomedical field in its infancy, progress in our understanding of glial functions and their relationship with psychiatric disorders requires time, replication of findings, and well-designed studies. It is essential to distinguish evidence-based expectations from speculative claims, lest the promise of glial research be overshadowed by ineffective or even harmful treatments [84].

6. Final Considerations

As our understanding of psychiatric disorders continues to evolve, evidence increasingly implicates glial cells (astrocytes, microglia, and oligodendrocytes) as active participants in both the onset and progression of mental illnesses. Far from being passive bystanders, these cells influence critical processes of neurotransmitter homeostasis, synaptic plasticity, immune surveillance, and myelination, thereby influencing the core aspects of emotional regulation, cognition, and behavior. Equally compelling is the notion that inflammation, especially when chronic, can undermine glial function and perpetuate a pathophysiological cycle that includes excitotoxicity, oxidative stress, and the maladaptive remodeling of the neural networks. Although the extent and nature of glial contributions vary across major depression, bipolar disorder, anxiety disorders, ADHD, and schizophrenia, convergent findings underscore the relevance of glial cells in the neurobiology of each condition.

This growing body of work suggests potential therapeutic approaches beyond conventional monoaminergic strategies. By targeting inflammatory cascades, modulating astrocytic glutamate uptake, or restoring oligodendrocyte integrity, it may be possible to mitigate some of the key pathophysiological mechanisms shared by many psychiatric disorders. Nevertheless, these concepts are largely in the exploratory phase. Methodological challenges, ranging from heterogeneity in clinical phenotypes to difficulties in measuring glial activity in vivo, have thus far limited our ability to translate glial-based interventions into the clinical arena. Moreover, the pleiotropic roles of glial cells require nuanced approaches that minimize the unintended consequences of neuronal and systemic functions.

Moving forward, the priority lies in identifying validated biomarkers capable of monitoring glial states in real time. Multi-omics platforms, advanced neuroimaging with refined TSPO ligands, and tissue-specific transcriptomic analyses may yield the precision necessary to distinguish specific inflammatory or glial signatures between patient subgroups. Such efforts will allow for more personalized treatment regimens and enable the robust stratification of clinical trials. Likewise, targeted research into glial–vascular interactions and neuroimmune crosstalk promises to bridge the gap between peripheral markers and

central pathology, offering a cohesive view of how external stressors and systemic factors may drive or exacerbate glial dysfunction.

In this landscape of guarded optimism, it is crucial to maintain scientific rigor. Overzealous claims of “glial cures” risk eroding the legitimate progress made in this burgeoning field, particularly when extrapolated from preclinical findings or small clinical cohorts. Advances in glial research must be anchored in large-scale, rigorously designed studies that systematically evaluate both efficacy and long-term safety. Nonetheless, as mechanistic insights deepen and translational hurdles are surmounted, the targeted modulation of neuroglia is poised to redefine therapeutic strategies for psychiatric disorders. By highlighting the complexity of glial–neuronal interactions, we can progress toward a more integrative and potentially transformative approach to mental healthcare.

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