Chapter

Astrocytic Abnormalities in Schizophrenia

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Abstract

Astrocytes are glial cells in the central nervous system (CNS), which contribute to CNS health and disease by participating in homeostatic, structural, and metabolic processes that play an essential role in facilitating synaptic transmission between neurons. Schizophrenia (SCZ) is a neuropsychiatric disorder associated with various positive and negative behaviors and interruption of executive function and cognition thought to be due partly to aberrations in signaling within neural networks. Recent research has demonstrated that astrocytes play a role in SCZ through various effects, including influencing immune system function, altering white matter, and mediating changes in neurotransmitters. Astrocytes are also known to play a role in inducing SCZ-associated changes in neuroplasticity, which includes alterations in synaptic strength and neurogenesis. Also, astrocyte abnormalities are linked to neurobehavioral impairments seen at the clinical level. The present chapter details general information on SCZ. It highlights the role of astrocytes in SCZ at molecular and behavioral levels, including neural changes seen in the disease, and the therapeutic implications of targeting astrocytes in SCZ.

Keywords: astrocytes, neurobehavioral disorders, schizophrenia, neurosciences, neuroimmunology

1. Introduction

Schizophrenia (SCZ) is a severe mental illness with typical onset during early adulthood, which confers a lifetime disability. The main signs of the disease comprise positive symptoms, such as delusions and hallucinations; negative symptoms, such as blunted emotions, social withdrawal, and apathy; and executive and cognitive neurobehavior interruption. Additionally, SCZ is associated with a greater suicide possibility and a shorter lifetime. The illness puts a substantial socioeconomic burden on caregivers, families, patients, and society [1].

While the mechanisms underlying SCZ remain unknown, dysfunctions in synaptic signaling are implicated. A synapse relying on chemical transmission is

comprised of a neural presynaptic and neural postsynaptic component. However, an astrocyte is a vital member of the synapse leading to the term "tripartite synapse" and among other functions, plays a role in synaptic plasticity [2, 3]. Astrocytic processes are considered crucial members of the tripartite synapse because they enclose the pre- and postsynaptic components and are close to the synaptic cleft [4]. They can quickly reuptake excess glutamate produced by the presynaptic terminals because of their great expression of the high-affinity glutamate transporters EAAT1 and EAAT2, which limits excitatory transmission [5]. In turn, astrocytes provide a significant contribution to synaptic plasticity and transmission. Even though they are electrically inactive, they react to presynaptic activation by sending G-protein-mediated Ca^{2+} signals, which cause the release of "gliotransmitters" such as glutamate, ATP, and GABA, which influence local synaptic transmission [6–8]. The likelihood of inducing LTP is increased by astrocyte-derived glutamate-mediated of NMDA receptor activation on the postsynaptic sites [9]. Furthermore, astrocytic processes surrounding synapses undergo fast structural remodeling due to stimuli that cause synaptic long-term potentiation (LTP), altering their capacity to control synaptic transmission. When taken as a whole, the anatomical and functional data strongly suggest that astrocytes are essential active mediators of synaptic plasticity [10]. Recently, a fourth player at the synapse has been recognized as the important role of the extracellular matrix (ECM), especially in synaptic plasticity has emerged. Accordingly, synapses consist of four pre- and postsynaptic elements, glial processes, and an ECM [11, 12]. In SCZ, it has been shown that interactions between all synapse elements disrupt synaptic functions and alter plasticity [13], and a breakdown in communication between synaptic components and changes in synaptic plasticity is believed to cause SCZ. Given the clinical, genetic, and pathological diversity of SCZ, synaptic dysfunction in specific brain areas may represent a point of convergence, perhaps resulting from various unique molecular processes in different people [13].

The evidence supporting a role of astrocytes in altered synaptic signaling in SCZ is diverse and often includes changes seen in glutamate transmission. Transplanted Human Induced Pluripotent Stem Cell (hiPSC)-astrocyte progenitors from SCZ patients transformed into mature astrocytes in a mouse created behavioral alterations consistent with cognitive and olfactory changes seen in SCZ patients. Healthy neurons co-cultured with astrocytes from SCZ patients of both males and females showed a drastically heightened reaction to glutamate, suggesting modifications in gliotransmitter liberation and/or inadequate turnover of neurotransmitters [14]. Additionally, synaptic dysfunction, demyelination, and alterations in inflammation pathways were noted [14]. Dysregulated glia functions have been associated with endothelial cell stimulation and increased systemic inflammatory markers in brain pathology [15, 16].

Further evidence for a role of altered glutamate signaling in astrocytes playing a role in SCZ are findings that the astrocyte-derived N-methyl-D-aspartate (NMDA) receptor antagonist kynurenic acid (KYNA) is higher in SCZ patients [17, 18]. In addition, KYNA is not only produced in astrocytes but also in a diversity of cell types through activation of the kynurenine pathway (KP) resulting in tryptophan metabolism. As high concentrations of KYNA are associated with the pathophysiology of SCZ, enhanced knowledge of mechanisms leading to high KYNA production in patients with SCZ could aid in the design of novel diagnostics and therapeutics, which could focus on targeting astrocytes [19].

Astrocytes synthesize and release D-serine, which is a co-agonist of the NMDAR where it modulates synaptic activity. Reductions in D-serine release by astrocytes could play a role in SCZ by leading to inhibition of synaptic transmission and synaptic

plasticity mediated by NMDA receptors. Hypofunctionality of NMDA receptors has been shown to be associated with behaviors reminiscent of SCZ, and further, a risk factor for SCZ is reduced functioning of NMDAR in cortical pyramidal neurons and interneurons. While astrocytes are not the sole source of D-serine, they do con¬tribute to the available pool, and their contribution can be local and region-specific. Accordingly, targeting astrocytic D-serine synthesis in SCZ represents a potential clinical strategy in order to reverse cortical hypofunctionality.

Neuroinflammation has been implicated in a role in SCZ, and astrocytes could play a role in this process [20, 21]. These comprise reduced astrocyte cellular characteristics and gene expression in chronic stress, anxiety, depression, and enhanced inflammation in SCZ [22]. Targeting changes in inflammatory markers in astrocytes might also represent a therapeutic strategy for SCZ patients.

In the present chapter, we review molecular aspects of astrocyte abnormality in SCZ, focusing on neuroplasticity in line with clinical features. We also summarize animal studies of the behavioral aspects of this topic. Finally, we propose therapeutic and diagnostic strategies focused on targeting astrocytes.

2. Overview of SCZ

2.1 Clinical presentation

The word SCZ originated by Eugen Bleuler in 1908, is derived from the Greek words 'schizo' (splitting) and 'phren' (mind) and defines a functional psychotic illness typified by the occurrence of hallucinations, delusional opinions, and disruptions of perception, thought, and behavior. Conventionally, symptoms have been separated into two major classifications: positive symptoms that comprise delusions, hallucinations, and formal thought disorders, and negative symptoms such as poverty of speech, anhedonia, and lack of motivation. SCZ diagnosis is clinical, solely done after acquiring a detailed psychiatric record and excluding further reasons for psychosis. Risk factors comprise the season of birth, severe maternal malnutrition, maternal influenza in pregnancy, family history, childhood trauma, social isolation, cannabis use, minority ethnicity, complications of giving birth, and urbanization [23–25].

SCZ is a developmental disorder and it is now widely accepted that astrocytes play an important role during both pre and postnatal development and continue their important role in development into adulthood by regulating establishment of neuronal circuits [26] and by regulating multiple homeostatic functions, such as buffering extracellular potassium or modulation of synaptic activity [27] and functional hyperemia [28], respectively. They offer metabolic support for synaptic activity and are also required for creating and maintaining synapses [29]. Changes in astrocytic numbers have been demonstrated to cause cognitive impairment, which is consistent with the essential roles of astrocytes in neural circuit functioning. In the astrocyte-specific toxin L-aminoadipate (L-AA) model [30] or in a transgenic mouse line with inducible and selective tetanus neurotoxin (TeNT) expression in astrocytes [31], mice exhibited deficits in set-shifting attention, working memory, reversal learning [30], recognition memory, and abnormal cortical gamma oscillations [31]. Similarly, decreased expression of the astrocytic glutamate transporter GLT-1 lowered prepulse suppression of the acoustic startle response [32], which is a well-established characteristic of SCZ. Changes in astrocytic cell density and morphology in the mouse prefrontal cortex (PFC) cause cognitive dysfunctions associated with the subcortical zone (SCZ) [30, 31].

2.2 Epidemiology

The prevalence of SCZ is around 0.6% and 1.9% in the U.S. population [33]. Based on insurance claims for the management of SCZ, the yearly prevalence in the U.S. is 5.1 per 1000 lives [34]. The illness prevalence appears identical in men and women, although the onset of symptoms occurs younger in men than in women [35]. Men tend to encounter their initial episode of SCZ in their early 20s, while women commonly encounter their initial episode in their late 20s or early 30s [36].

Study regarding a potential connection between geographical birthplace and the origination of SCZ has given inconsistent outcomes. A cooperative survey by the World Health Organization in 10 countries discovered that SCZ occurred with similar rates throughout the diverse geographically-stratified populations [37].

3. Molecular mechanisms

3.1 Neuroplasticity mechanisms

3.1.1 Synaptic plasticity and neurotransmitter alterations

3.1.1.1 Astrocyte function in synaptic plasticity and SCZ

Patients with SCZ exhibit profound cognitive impairment and negative symptoms resistant to current medication. Evidence supports the theory that these deficiencies are caused, at least in part, by changes in cortical synaptic plasticity, which is the ability of synapses to strengthen or weaken their activity. Targeting synaptic plasticity is a promising therapeutic approach to managing SCZ as synaptic transmission is a well-understood process, and the biochemical mechanisms behind short-term and long-term changes in synaptic strength are becoming even more evident as players at the molecular level are identified [38].

Long-term depression (LTD) and potentiation (LTP) of synaptic transmission are essential processes by which the brain changes the strength of synapses [39]. Many forms of synaptic plasticity depend on alterations in AMPA and NMDA receptors within the membrane, as these excitatory glutamate receptors are essential for synaptic transmission [38]. SCZ brains show reductions in synaptic functioning due to the loss of AMPA and NMDA receptors and loss of dendritic spines and synaptic markers. Loss of synapses and markers is consistent with microscopic analysis in patients showing reductions in brain volume, notably in the hippocampus, prefrontal and superior temporal cortices, and frontolimbic circuitry, which is accompanied with an increase in ventricular size [38].

3.1.1.2 Neurotransmitter hypotheses of SCZ

The role of dysfunctions in neurotransmitters, many of which are gliotransmitters, has been explored in SCZ and as many of these transmitters are gliotransmitters, alterations in astrocytic functioning have been suggested.

3.1.1.2.1 Glutamate

Glutamate is the principal excitatory neurotransmitter in the central nervous system (CNS) that initiates fast signal transmission. Its activity is critically

involved in routine behaviors, including learning and memory, which mechanistically processes relying on synaptic plasticity. Dysfunctions in glutamate transmission are seen in SCZ [40]. Given the significance of astrocytes in altering glutamatergic transmission, it is probable that they are involved in the glutamate dysfunction seen in SCZ.

Activity of astrocytes regulates extracellular glutamate levels [41]. As high glutamate levels can be toxic, following impulse transmission, EAATs, immediately terminate glutamate transmission by removing glutamate from the tripartite synapse (**Figure 1**). In astrocytes, EAAT1 and EAAT2 are the most prominent EAATs [42]. Once transported into astrocytes by EAATs, glutamate is converted to glutamine-by-glutamine synthase. This newly created glutamine can then be transported back to

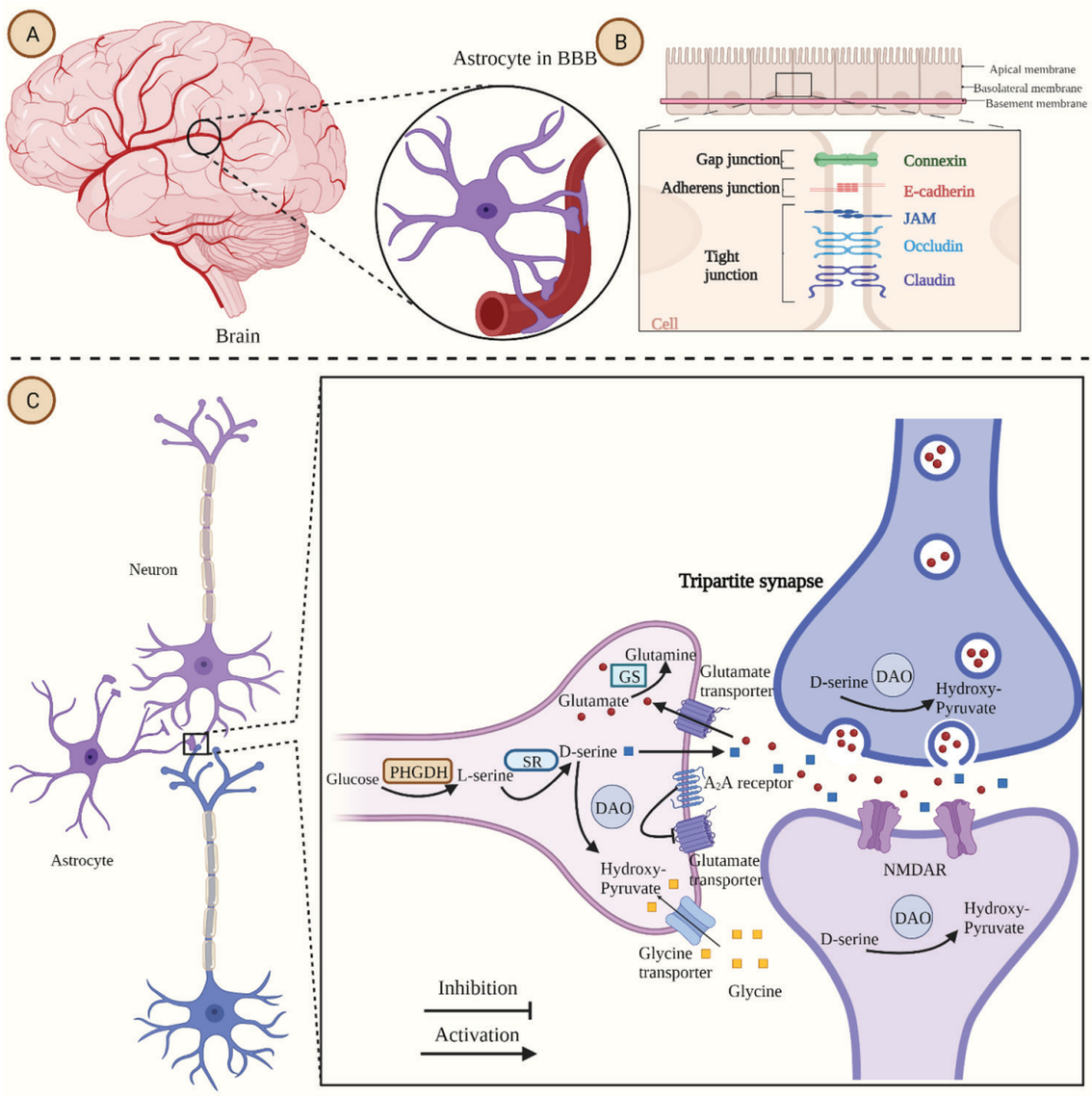

Figure 1.
A general depiction of the position of the astrocyte in the tripartite synapse and BBB. A) Astrocytes protect the brain from blood borne toxins and microbes by close opposition of their end feet on blood vasculature. B) Gap junctions play a crucial role in cellular communications between astrocytes. C) Astrocytes play a vital role in neuronal communication via participation in the tripartite synapse which is shown with important glial and neuronal intracellular and extracellular pathways. Created with BioRender.com. Abbreviations: BBB: Blood brain barrier, D: Dextro, DAO: D-amino acid oxidase, GS: Glutamine synthetase, L: Levo, NMDAR: N-methyl D-aspartate receptor, PHGDH: 3-phosphoglycerate dehydrogenase, and SR: Serine racemase.

presynaptic neurons in a process known as glutamate-glutamine cycling, where it is converted into glutamate [43].

The glutamate theory of SCZ is based in part on findings that NMDA antagonists like ketamine and phencyclidine induce an SCZ-like psychosis exhibiting positive symptoms [40]. Further evidence of a role played by the NMDA receptor in SCZ is that disruptions in NMDA receptors in interneurons result in the lack of inhibitory signals to glutamate neurons, mainly in the prefrontal cortex, which may be associated with negative symptoms of SCZ [40]. The endogenous NMDAR antagonist KYNA can mimic SCZ-like symptoms similar to other exogenous NMDAR antagonists such as phencyclidine and ketamine. Studies of the role it could play in SCZ have been conducted [19, 44]. At low concentrations, KYNA acts as an antagonist at the strychnine-insensitive glycine-binding site of NMDARs. However, higher concentrations also block the glutamate-binding site of NMDARs [19]. Furthermore, KYNA has modest antagonistic effects on kainate and amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-sensitive glutamate receptors, with concentration-dependent effects on AMPA receptor-mediated actions [19, 44]. In addition, KYNA is an endogenous antagonist of α7 nicotinic acetylcholine receptors, which would also be expected to reduce synaptic excitability. Increased KYNA levels have been noted in the CSF and cortical brain areas in SCZ patients due to alterations in enzyme activity/expression in the kynurenine pathway (KP), which transfers tryptophan metabolism to KYNA synthesis [19, 44].

3.1.1.2.2 Glycine

Glycine, a nonessential amino acid that plays a critical role in inhibitory and excitatory neurotransmission is upregulated in SCZ. SCZ patients have higher glycine levels, particularly in the parietal and occipital cortex [45]. Astrocytes are a major source of glycine. While thought of as a classic inhibitory amino acid as it interacts with the inhibitory canonical strychnine glycine receptor (GlyR), which is a chloride channel [46], glycine also functions as a potentiator of excitatory transmission by acting as a co-agonist of NMDAR. Interestingly, it is glycine's actions at the NMDAR which appear to play a crucial role in the neurodevelopmental phases of SCZ pathogenesis [47]. D-serine is an endogenous ligand at the NMDAR glycine B-site [48] and has been proposed to activate NMDARs in the amygdala, however, upon high afferent activity glycine released from astrocytes enhanced NMDAR activity, which affected induction of LTP [49].

Glycine concentration in the synaptic cleft is carefully controlled by glycine transporters, particularly GlyT1 and GlyT2, located in astrocytes, which regulate neurotransmitter reuptake. Accordingly, targeting the astrocytic glycine transporters represents a potential treatment for SCZ [50].

3.1.1.2.3 Dopamine and adenosine systems

Alteration of striatal D2 dopamine receptors leads to positive symptoms, whereas the alteration of the prefrontal cortex D1 dopamine receptor leads to negative and cognitive symptoms. Dopamine transmission within the striatum is also impaired [51]. The number of synapses in the lateral part of the ventral tegmental area and the substantia nigra is reduced in SCZ. Among other effects, loss of synapses would lead to loss of NMDA receptors, which would result in reductions of activity of these striatal dopamine-containing cells, resulting in alterations in dopamine release at terminals. This is supported by findings that there is a deficiency of dopaminergic activation in the prefrontal cortex in SCZ. This could also result from decreased communication between the striatum and the prefrontal cortex, due in part to NMDAR

dysfunction that has been shown in both prefrontal cortex and the striatum in postmortem SCZ brain [52].

Adenosine has two known types of receptors: A1 and A2. A1 receptors block the release of neurotransmitters including glutamate. Activating A2A-receptors causes glutamate release, which activates NMDA receptors and inhibits A1-receptors [53]. A2A receptors are found in dopamine-rich locations, such as the prefrontal cortex and the striatum, and their activation causes reduced dopaminergic innervation [53]. Hypofunction of A2A receptors in the striatum leads to hyperfunction of D2 receptors, which are implicated in disorders linked to neuroinflammatory processes, as well as to triggering immunological responses and heightening dopaminergic neurons' vulnerability to neurotoxic injury. Striatal astrocytes express A2A-D2 receptor heterodimers. While D2 receptor activation decreases presynaptic glutamate release, stimulation of A2A receptor reverses this action [53]. Dysfunction of the striatal astrocytic A2A receptor, which causes damage to the D2 receptor and disrupts glutamate homeostasis, is believed to be linked to SCZ [53, 54].

3.1.1.2.4 GABA

Postmortem investigations have extensively identified changes in various GABA-related markers in SCZ patients. Some studies show the reduction of inhibitory GABAergic neurotransmission across several brain regions affected by SCZ. These anomalies may cause difficulties in emotional functioning and cognitive control. Furthermore, one clinical investigation found reduced GABA concentrations in CSF samples from patients with first-episode psychosis compared to healthy volunteers, which were linked to total and general positive and negative syndrome scale ratings, disease severity, and poor performance on attention testing [55].

Astrocytes react to GABA through various pathways, including GABA receptors and transporters. GABA-activated astrocytes may then influence local neuronal activity by releasing gliotransmitters such as glutamate and ATP. Furthermore, astrocyte activation through various inputs can influence GABAergic neurotransmission. The complexity of communication within the brain is enhanced by reciprocal signaling between GABAergic neurons and astrocytes, and our improved understanding of this complexity could lead to new treatments for brain disorders [55].

3.1.1.2.5 Endocannabinoid systems

The endocannabinoid system (ECS), which consists of two well-characterized receptors and enzymes responsible for their production and degradation, is engaged in various physiological and pathological processes of the CNS [19].

There are two types of cannabinoid receptors (CBRs), cannabinoid receptor type 1 (CB1R) and cannabinoid receptor type 2 (CB2R), belonging to the family of Gi/o protein-coupled receptors (GPCRs). Therefore, activating them inhibits cAMP production, activates mitogen-activated protein kinases, and presynaptically inhibits several neurotransmitters involved in SCZ through presynaptic mechanisms [56, 57].

CB1Rs are involved in regulation of mood or emotion, antinociception, energy balance, immunological function, and endocrine activities [58]. CB2Rs, on the other hand, are expressed mainly in immunological and hematopoietic cells. CB2Rs have a protective function by reducing inflammation-induced pain via cytokine modulation and immune cell migration [58, 59].

Several alterations in the ECS have been reported in SCZ patients, including changes in CB1R availability, density, and/or mRNA expression, differences in levels of endocannabinoid in specific brain regions and CSF have been noted in SCZ

patients. Endogenous CBR ligands are lipid-derived hydrophobic molecules, the best researched of which are N-arachidonoylethanolamine (AEA) and 2-arachidonoyl glycerol (2-AG). The fatty acid amide hydrolase (FAAH) enzyme quickly metabolizes AEA, whereas the monoacylglycerol lipase (MAGL) enzyme hydrolyzes 2-AG. Blocking the FAAH enzyme in order to heighten effects of AEA has been proposed as a potential therapy for SCZ. Furthermore, phytocannabinoids produced from plants, such as 9-tetrahydrocannabinol (9THC), the main psychoactive component of cannabis, and non-psychoactive cannabidiol (CBD) have intriguingly been suggested as potential treatments for SCZ due to actions involving glutamate release from astrocytes [60, 61]. This is supported by findings that CB1R is located on internal PFC astrocytes and reduces the negative symptoms of SCZ by reducing glutamate release [62]. On the other hand, exogenously applied cannabinoids can induce SCZ-like symptoms in adolescents if exposure is frequent and early in life [62].

3.1.2 Myelination and white matter

Astrocytes play a significant role in the repair and recovery of neurons, which includes a role in the repair of damage to white matter through their regulation of oligodendrocytes. White matter damage has been linked to developing various demyelinating conditions, including SCZ.

White matter astrocytes differ from those in gray matter in terms of development, morphology, residence, protein synthesis, and the role they play in supporting neighboring cells. During demyelination and remyelination, the functions of astrocytes are dynamic and are modified in response to specific stimuli or reactive processes, leading to vastly different biological outcomes. The effect of astrocytes on oligodendrocytes and various cellular subtypes in the oligodendrocyte lineage includes serving as an energy supply, a modulator of immune system function, a mediator of inflammation processes, a resource for trophic factors, and a regulator of iron. Features of astrocytes that lead to their neuroprotective properties include anti-oxidative properties, stabilization of glutamate homeostasis, and production of growth factors.

Ultrastructural evaluations showed induced microglia near dystrophic and apoptotic oligodendroglia, demyelinating and demyelinating axons, and swollen and vacuolated astroglia in cases with SCZ, in contrast to healthy subjects [15]. Theoretically, targeting astrocyte function represents a rational approach to repair injured myelin white matter-associated diseases such as SCZ [63] and cell therapy using stem cells or progenitor cell-derived astroglia has been recommended for patients with neuropsychiatric disorders associated with white matter degeneration or synaptic loss, [64]. Unfortunately, re-myelinating strategies have to date proved inadequate, which could stem from an unsuitable microenvironment. When taken together, although white matter alterations are implicated in SCZ, the astrocyte-specific alterations in this disease need to be explored further and those alterations need to take into account the vast array of cell types that astrocytes interact with before we can use astrocytic cell therapy for management of SCZ.

3.1.3 Adult neurogenesis

Adult neurogenesis could play a role in the pathological mechanisms of SCZ, but also could perhaps be exploited therapeutically. In the process of adult hippocampal neurogenesis, neural stem cells (NSCs) in the dentate gyrus (DG) transform into neurons, which is a process that continues throughout life [65]. Natural proliferation and

maturation of NSCs in DG contribute to emotional behaviors and cognitive function, and disturbances to this process can cause neuropsychiatric disorders such as anxiety, mood disorders, and memory and learning disorders [66–70]. Transformation of NSCs into neurons is regulated by adult astrocytes in the hippocampus [71]. Following transformation, astrocytes contribute to the maturation and integration of neurons in the hippocampal circuit. Inhibiting the exocytosis of astrocytes leads to a decrease in dendritic spine count and dendritic branching, as well as disrupted dendrite survival and maturation of the new neurons [72]. Astrocytes control neurogenesis by releasing a variety of factors. D-Serine, BDNF, fibroblast growth factor 2 (FGF-2), glial cell line-derived neurotrophic factor (GDNF), and VEGF are examples of astrocyte-derived factors that may promote neurogenesis [73].

3.1.3.1 D-serine

Astrocytic D-serine is believed to play a role in neurogenesis. Obstruction of vesicle proliferation in astrocytes led to a decrease in dendritic formation in adult-born granule cells (abGCs) associated with a reduction in extracellular D-serine [72]. Further, mutations leading to decreases in D-serine result in changes reminiscent of SCZ. The DISC1 (disrupted-In-SCZ 1) gene is located on chromosome 1q42 and the product binds to and stabilizes serine racemase (SR), resulting in an increase in the conversion of L-Serine to D-Serine in astrocytes. A mutation in the DISC1 gene was first detected and linked to SCZ in a Scottish family with several major mental disorders, and now this gene mutation is recognized as a major risk factor for disorders involving abnormalities of neural development [74]. As a dominant-negative molecular tool, DISC1 mutants truncated at the C end of the full-length protein are used to elucidate the role of DISC1 in astrocytes [75]. In the mouse, dominant-negative C-terminus-truncated human DISC1 resulted in dendritic dysplasia and reduced neurogenesis [65]. Further, dominant-negative effects resulted in SR degradation, decreases in NMDA neurotransmission, and reductions in neurogenesis [65]. Further, this mutation appears to affect the neurogenesis of DG neurons more than other brain regions, such as the subventricular zone [76]. Therefore, it is tempting to speculate that D-serine depletion plays a role in SCZ.

3.1.3.2 BDNF and FGF2

Another astrocyte secretory factor that is involved in adult neurogenesis is BDNF. Astrocytes regulate the removal and recycling of pro-BDNF [77]. Pro-BDNF neuronal precursors are taken up by astrocytes through endocytosis and then converted to adult BDNF. Overexpression of BDNF-containing hippocampal astrocytes promotes the survival and maturation of abGCs and was associated with an anxiolytic/antidepressant-like effect in mice [78]. The process of neurogenesis is also supported by FGF-2, which is mainly produced by astrocytes. In addition, astrocyte-derived FGF-2 facilitates abGC differentiation and function [73].

3.1.3.3 Lactate and VEGF

Astrocytes store large amounts of glycogen as a source of energy for cells [79]. Astrocytes break down glycogen into lactate that is released from cells by a monocarboxylate transporter 4 (MCT4). The neurotransmitter MCT2 takes lactate up as an energy source for neurons. This pathway is called the astrocyte-neuron lactate shuttle [80, 81].

Increasing lactate concentrations in the blood can raise brain VEGF levels by binding to the hydroxycarboxylic acid 1 receptor, which presents on vascular endothelial cells [82]. Then the VEGF stimulates angiogenesis and neurogenesis. Intraperitoneal administration of lactate to mice increases abGC viability via MCT2 [83], however, further research is needed to understand how increased lactate mediates this action on neurogenesis.

3.2 Immune mechanisms

3.2.1 Innate immunity

Individuals affected by neuropsychiatric conditions usually present with hyperinflammation-associated dysfunctions in the peripheral blood, such as raised concentrations of inflammatory cytokines or chemokines, augmented quantities of circulating monocytes and neutrophils, along with a higher reactivity of astrocytes, microglia, as well as brain endothelial cells to different proinflammatory signals [84].

Due to the prominent role of inflammation in neuropsychiatric conditions, it is important to understand the role of inflammasomes. These essential multimeric complexes regulate inflammation by mediating the secretion of cytokines. Specifically, inflammasome pathways can be categorized into canonical and noncanonical signaling, which depend on caspase-1 and caspase-4/5 activation in humans, respectively [85]. Caspase-1 activation helps the maturation of IL-1β and IL-18, two vital inflammatory cytokines. Two neuroimaging studies also showed a link between carrier status for a functional single nucleotide polymorphism (SNP) in the IL-1β gene and aberrant white and gray matter proportions in SCZ patients, unlike healthy patients individuals [15]. Researchers also found that orbitofrontal white matter neuronal compactness was enhanced in SCZ cases with high transcription concentrations of proinflammatory cytokines compared to those with low concentrations [15]. In another study, the animals presented SCZ-like neurobehavior at 45 postnatal days linked with the increase of NLRP3 inflammasome expression and IL-1β levels on 7, 14, and 45 postnatal days [86]. This study shows maternal immune activation (MIA) may be associated with an SCZ-like neurobehavior. This neurobehavior can be induced to a neuroinflammatory profile in the brain. This evidence may base future studies on the relationship between neuroinflammation and psychiatric disorders [87].

Extracellular adenosine triphosphate (ATP) and the metabolite adenosine are key mediators of the immune response. Excess shedding of ATP into the intercellular area from induced/injured nerve cells or abnormal purinergic signaling induces the nod-like receptor proteins (NLRPs) of inflammasomes in astrocytes/microglia [84]. A new review article details the involvement of aberrant purinergic signaling in the pathogenesis of SCZ, in addition to other neuropsychiatric disorders such as major depressive disorder, bipolar disorder, autism, anxiety, and attention-deficit/hyperactivity disorders (ADHDs) [88]. Each of these conditions could be attributed to abnormalities in signaling from P1 and P2 receptors along with enzymes processing the metabolism of purinergic mediators.

In addition, SCZ patients are often treated with antipsychotic medications that cause brain volume reduction and astrocyte expiry in a process called pyroptosis or proinflammatory cellular expiry [89]. This process involves the formation of inflammatory bodies and enhanced production of complexes such as NLRP3, parallel with the induction of caspases and gasdermin D (GSDMD). These components are strongly linked to innate immunity, hyperinflammation, and cell damage/expiry.

The same study found the main effect of antipsychotic treatments on astrocyte pyroptotic pathways and the molecular processes that could be exerted through inflammasome pathways [89]. In this experiment, 72-h therapy with olanzapine, quetiapine, risperidone, or haloperidol strongly attenuated the astrocytes' viability. 24-h therapy by olanzapine, quetiapine, risperidone, or haloperidol dose dependently augmented the protein synthesis of astrocytic NLRP3, NLRP6, caspase-1, caspase-4, and GSDMD. Co-administration with a histamine H1 receptor agonist, 2-(3-trifluoromethylphenyl) histamine (FMPH), attenuated the raised synthesis of NLRP3, caspase-1, and GSDMD activated via olanzapine, quetiapine, risperidone, or haloperidol [89]. Moreover, olanzapine, quetiapine, risperidone, or haloperidol treatment-induced pore formation in the astrocyte membranes was suppressed via FMPH co-treatment [89].

When taken together, astrocytic inflammasomes and hyperinflammation are implicated in SCZ, and activation of astrocyte pyroptotic pathways could be due to antipsychotic-activated astrocyte expiry. Further, H1 receptor activation could be a robust therapeutic approach to inhibit antipsychotic-activated astrocyte pyroptosis and hyperinflammation [90]. However, more studies should assess astrocyte-specific (or other CNS cell-specific) inflammasomes and consider the noncanonical pathways to understand more fully how these innate complexes contribute to hyperinflammatory cytokine secretion and neuronal/glial damage. Also, various toll-like receptors (TLKs) are involved in SCZ. These receptors are essential as they bridge innate and adaptive immunity and interact with inflammasomes. More studies are needed to decipher the role of astrocyte-specific TLRs in SCZ patients.

3.2.2 Adaptive immunity

Adaptive immunity, which arises following activity of the innate immune system, occupies a pivotal function in neurodevelopment [91]. A key component of the adaptive immune response is specialized immune cells known as T lymphocytes (T cells). The ability of T cells to penetrate the brain, stimulate microglia, and cause neuroinflammation is widely established, and these activities have been shown to disrupt several brain functions and cause progressive neuro alterations [92, 93]. While a role of inflammatory states has been noted in SCZ [94, 95], the impact of the adaptive immune system, particularly T lymphocyte cells, on the essential characteristics and severity of SCZ is unknown; however, epidemiological, immunological, and gene expression research do suggest a degree of dysfunction of T cells-related processes in SCZ [95–98]. Higher concentrations of T cells in the hippocampus and an elevated number of activated lymphocytes in the CSF have been noted in SCZ patients suggesting blood-brain barrier disruption and T-cell infiltration [99]. Multiple genome-wide association studies (GWAS) have noted genetic variations in SCZ patients of CD28 and CTLA-4 genes, which code for regulatory molecules of the adaptive immune system suggesting that these proteins modulate T-cell activity and are associated with T-cell functions, including antigen processing and cell adhesion, this provides further evidence that the adaptive immune system plays a role in SCZ [100, 101].

SCZ is linked to modestly elevated blood cytokines, which are thought to be the result/stimulus for the activation of microglia [102]. Overlap between activated microglia, proinflammatory cytokines, and translocator protein (TSPO) leads to the basis of using TSPO-PET imaging to monitor neurodegeneration. In SCZ patients, findings of lower levels of TSPO in frontal and subcortical regions, including caudate,

putamen, and thalamus, lead to the speculation that suppression of microglial inflammation results in reduced TSPO binding [103]. However, discrepancies that exist in this literature and utility of this technique in SCZ have been debated given differences in degeneration seen in SCZ when compared to other neurodegenerative diseases [104, 105]. The discrepancy between experiments that show an increase, decrease, or no change in TSPO in the subcortical regions of schizophrenic patients has prompted several follow-up investigations employing first and second-generation tracers with mixed results [106, 107].

Postmortem immunohistochemistry analysis, genetic association studies, and transcriptome investigations indicate increased astrocyte activity in SCZ [29].

The expression of marker gene profiles of various cortical cell types was investigated in a prior study, which gave compelling evidence of an increase in astroglial gene expression in SCZ [108].

Further studies strengthened these results and suggested that increased astroglial gene expression followed by a decrease in microglial gene expression is a primary cause of disease rather than a side effect [109, 110].

Astrocytes play a significant role in microglial excitation and function via TGF-β. TGF-β regulates microglial previous studies discovered that TGF-β regulates microglial activation and activity, and astrocytes are crucial actors in this process [111–113]; A critical process that actively suppresses the inflammatory TSPO-expressing phenotype of microglia via elimination of the TGF-β receptor type 2 from adult microglia could be pertinent to the SCZ patient debate [111].

3.3 Other mechanisms

3.3.1 Gap junction

Connexins make gap junction channels that facilitate the transmission of intercellular calcium currents. Most brain gap junctions are situated among glial cells and gap junctions between astrocytes and astrocytic processes are known as reflexive gap junctions and together an astroglial system is created [114]. Gap junctions allow two-sided interchange of molecules, ions, nutrients, etc. The gating of brain gap junction channels is modulated dynamically by alterations in the number of cell connections, conductance properties, and subunit configurations. Astrocyte signaling happens primarily via intercellular calcium currents in response to neuronal activity and/or through flux in the endoplasmic reticulum.

Gap junctions comprise hemichannels (connexons) that attach through their extracytoplasmic processes. Each hemichannel is an oligomer of six connexin proteins (Cx). An astrocytic syncytium gap junction is comprised of four connexins, Cx32, Cx26, Cx43, and Cx45, which can create homotypic (*i.e.,* gap junction channels created by hemichannels of the identical type) or heterotypic gap junction channels (*i.e.,* created by hemichannels of various types) [115].

Loss of gap junction function in astrocytes has been hypothesized to play a role in SCZ [116]. Use of computational modeling of astrocyte gap junction activity also supported the conclusion that a loss of astrocytic gap junctions would alter activity in the neural network which could play a role in neuronal-glial changes seen in SCZ [117]. Finally, reduced gap junctions between astrocytes were found to concentrate signaling among the most connected astrocytes, which would be expected to impact communication at the tripartite synapse [118] that could lead to cognitive deficits.

3.3.2 Extracellular matrix system (ECM)

Neurons and glial synthesize the ECM, which impacts the maturing and maintenance of synapses. Moreover, at the hyaluronan level, the ECM divides the exterior of neurons, restricting the exterior movement of integrated membrane proteins. In the pathogenesis of SCZ, failures in ECM development have been suggested. The ECM is comprised in part of chondroitin sulfates. Patients diagnosed with SCZ demonstrated a massive rise in chondroitin sulfate proteoglycan (CSPG) - positive glia in the entorhinal cortex and deep amygdala, whereas the density of GFAP – positive cells was not altered. As CSPGs mediate adult synaptic plasticity, higher levels in SCZ could play a role in alterations in this process. Further, modification of the ECM could result in differences in distribution of receptors and transmitters. For example, decreased expression of Reelin, a component of the ECM primarily expressed in adult GABA neurons, was observed in patients with SCZ in caudate nucleus, cerebellum, hippocampus, and prefrontal and temporal cortices. A decrease in Reelin is typically associated with a reduction in glutamic acid decarboxylase expression, suggesting a robust functional correlation between Reelin expression and GABAergic neurotransmission. Consequently, the variations in ECM could be expected to have an impact on release of inhibitory neurotransmitter [119].

3.3.3 Epigenetics

A connection between SCZ risk and epigenetic pathways has been suggested based on association studies. In a study of the promotor hypermethylation status of the glutathione S-transferase TI (GSTT1) and glutathione S-transferase P1 (GSTP1) genes in a Tunisian SCZ population, a significant relationship between SCZ and the GSTT1 and GSTP1 active genotype was noted [120]. A similar relationship was noted in another study [121].

The single nucleotide polymorphisms rs1043618 and rs2075799 in *HSPA1A* (heat shock protein family A "HSP70" member 1A) have been linked to SCZ [122, 123], which is interesting as HSP70 facilitates astrocytic neuroinflammation [124]. No epigenetic processes have been defined that might modulate the expression of HSP70 in SCZ.

Valproic acid (VPA) and other HDAC inhibitors are molecules that facilitate chromatin remodeling to modify gene transcription selectively, such as MS-275, trichostatin A, sodium butyrate, and apicidin appear to enhance H3K4Me3 and H3K4Me2 levels at the *HSP70* astrocytic promoter. H3K4me3 and H3K4me2 are related to transcriptionally active chromatin areas. Curiously, VPA provoked stimulation of the astrocytic *HSP70* promoter through employing histone acetyltransferase p300 in astrocytes of the rat cortex [125].

Moreover, there are data for enhanced *HSPA1A* expression and additional genes associated with immune function, such as the proinflammatory mediators *IFITM2*, *IFITM1*, and *IFITM3* in postmortem dorsolateral prefrontal cortex (dlPFC) sections from SCZ [120]. A considerable link was noted between first-episode psychosis in Greek schizophrenic patients and *the HSPA8* variant (rs1136141) [126].

Regulator of G-protein–signaling 4 (RGS4) is a GTPase-triggering protein that regulates G-protein-coupled receptor signaling, regulating receptor-facilitated synaptic neural signaling [127]. A variant of the *RGS4* polymorphism (rs951436) leads to declines in the structural volume of the white matter [128]. Downregulation of *RGS4* transcripts in the dlPFC of SCZ patients has been reported that suggest that this gene could be a candidate gene for SCZ [129].

Type of OMICS	Findings	Reference
Genomics	Quantitative-PCR determination of Human Induced Pluripotent Stem Cells (hiPSC)-obtained Neural progenitor cells (NPCs), neurons, NGN2 neurons, and astrocytes revealed a baseline expression of all five SCZ risk genes, TOAK2, NRXN1, SNAP91, KCTD13, and CLCN3.	[133]
Proteomics	In comparison with the controls, astrocytes acutely treated with 20 μM MK-801 demonstrated 11 differentially expressed proteins and those acutely treated with 50 μM demonstrated 30. The expressed proteins most often regulate cell development and/or protection (28%) or energy pathways (24%). Additionally, 10 of these proteins (33.3%) were also observed differentially expressed in specific areas of SCZ human brain samples.	[134]
Proteomics	A whole of 124 PFC proteins were observed to be substantially differentially expressed among the isolated-rearing (IR) group and the social-rearing (SR) group, the most notable of them were Annexin A2 (ANXA2), glial fibrillary acidic protein (GFAP), and vimentin (VIM), three astrocyte biomarkers. Additional Western blot tests proved that the GFAP, ANXA2 and VIM levels were improved considerably in IR rats. Adolescent social isolation promoted SCZ-like behaviors and considerably different expression of 124 PFC proteins in mature rats, particularly ANXA2, GFAP, and VIM, that proposes that astrocyte development could be implicated in the neuronal process of SCZ.	[135]
Transcriptomics	Four differentially expressed miRNAs (miR-206, miR-127-5p, miR-337-3p, miR-1185-1-3p) were found in SCZ astrocytes that demonstrated significantly lesser basic expression relative to controls.	[136]
Transcriptomics	There was seen an ongoing detection of an enhancement in the expression of cortical astrocytes. No alterations in astrocyte expression were detected in subcortical areas.	[108]

Table 1.
An overview of studies evaluating OMICS approaches for astrocytic abnormalities in SCZ.

A different study demonstrated that *RSG4* expression of the lengthiest variant, *RGS4*-1, was reduced in schizophrenic patients' dlPFC [130]. The methylation of *RGS4* regulatory region CpG islands in the *postmortem* dlPFC sections was evaluated in SCZ and results showed that the reduced *RGS4*-1 mRNA expression levels were not related to hypermethylation of the 5′ region CpG islands. Moreover, the more deficient *RGS4*-1 expression was associated with the 5′ regulatory regions SNPs rs2661347, rs951436, rs10917670, and rs2661319 [131].

Research by Vrajová *et al*. assessed the potential epigenetic process of *RGS4* expression via silenced *RGS4* gene utilizing siRNA targeted toward human *RGS4* and analyzed the impact of neuroblastoma cell lines differential expression. They noted that downregulated *RGS4* mRNA alters the expression of 67 genes comprising crucial transcription factors, such as brain-derived neurotrophic factor (BDNF) and DISC1, related to the pathology of SCZ [132]. Additionally, several OMICS approaches have evaluated the interaction among astrocytes and SCZ (**Table 1**).

4. Behavioral outcomes

Development of preclinical models of astrocyte dysfunction in SCZ is quickly expanding. We will summarize the existing animal models, which have relied on

altering key functions of astrocytes that have been discovered to be aberrant in SCZ. We will focus on genetic models. However, nongenetic preparations will be discussed in the case of modifying the astrocytes to trigger SCZ-like behavioral phenotypes. For further details, the readers are referred to the comprehensive review paper by Xia *et al.* [137].

4.1 Models with structural change

To reduce glia in cortical areas in order to model changes seen in SCZ patients, an astrocyte-exclusive toxin, L-alpha-aminoadipic acid (L-AAA), was administered in the prefrontal cortex (PFC) of adult rats. L-AAA triggered anhedonia in sucrose preference evaluation, anxiety, and helplessness in forced swim test (FST). Of note, these effects were not seen following ibotenate-triggered neurotoxic lesion of the PFC, highlighting the specificity of astrocyte deterioration in inducing the affective neurobehaviors. The toxin also influenced attentional set-shifting, working memory, and reversal learning. The influences of L-AAA seem to support the role of astrocytes in behavioral disorders due to dysfunction of the medial PFC. The limitation of utilizing this toxin for neurobehavioral exploration is progressive neuronal death and dendritic degeneration in the surviving nerve cells in L-AAA-treated animals [138, 139].

4.2 Models related to glutamate signaling

Glutamate uptake is one of the major functions of astrocytes [140]. GLT-1 actions are heightened in the PFC of SCZ [141]. To model this scenario, the antibiotic ceftriaxone that specifically augments GLT-1 production and activity was administered to rodents. In this model, evaluation of the inhibition of prepulse inhibition (PPI) of the acoustic startle reflex, which is a biomarker of SCZ was conducted. Ceftriaxone-triggered GLT-1 up-regulation was linked to attenuated PPI that was reversed via dihydrokainate (DHK), a GLT-1 blocker [142]. Intriguingly, ceftriaxone's PPI suppressive influences were further augmented by administering only one dosage of phencyclidine (PCP) [143]. However, the NMDAR antagonist, MK-801, exhibited conflicting results regarding ameliorating sensorimotor, cognitive, and memory performance in environmental enrichment (EE) models [144–146].

Other models relate to D-serine, purine, trophic factors, and extracellular matrix proteins [137].

4.3 Models with hyperinflammation

Intraperitoneal injection in rodents of kynurenine (100 mg/kg) resulting in a 37-fold CNS enhancement likely leading to immune system activation was associated with a higher rate of error in the radial arm maze, although no alteration was found in locomotor function or the latency to obtain food reward [147]. When kynurenine was applied on postnatal days 7–10 and rats were evaluated as adults' social neurobehavior and locomotor activity was attenuated; however, no effects on attention or fear conditioning were detected [148].

While the dosages of kynurenine utilized in these studies were high, the outcomes suggest that neuroinflammation can affect cognitive function, which could involve astrocytes [137], and that early life activation of the processes of neuroinflammation can have long-lived consequences. Further evidence of this is provided by data showing that infection by *Toxoplasma gondii* (*T. gondii*) is a predisposing factor for

SCZ [149]. *T. gondii* induces the synthesis of KYNA, potentially in astrocytes [150]. *T. gondii* involvement may play a role in the disease by enhancing KYNA synthesis within astrocytes. While *T. gondii*-infected animals have exhibited SCZ-like neurobehaviors in multiple studies, the contribution of KYNA or other astrocyte-related elements needs further study because the parasite exerts a plethora of direct and indirect influences on the brain [151].

Short-term one-week exposure of mice to cuprizone resulted in flawed working memory and augmented responses to methamphetamine and phencyclidine. These cognitive behaviors were associated with perturbation of astrocytes/microglia and enhancement of IL-6 in GFAP+ cells as well as an increase in other proinflammatory biomarkers, which have been observed in SCZ [152].

The production of many proinflammatory elements is mediated through the transcription of nuclear factor-kappa B (NF-κB) [153]. Several genetic, biomarker, and postmortem data indicate the role of NF-κB in SCZ. In transgenic rodents in which NF-κB function was specifically blocked in astrocytes while there were no differences in overall health outcomes, locomotor function, sensorimotor actions, or anxiety, female GFAP-IκBα-dn rodents exhibited mild deficiencies in the terminal stage of the non-cued type of the Barnes maze, as corroborated via the increased latency to the first correct nose poke and reduced time length in the portion of the maze already enclosing the goal box [154].

5. Therapeutic and diagnostic approaches for SCZ: Focus on astrocytes

5.1 Therapeutic targets for SCZ

Astrocytes are involved in numerous critical physiological processes in the brain, which directly or indirectly contribute to the pathogenesis of SCZ, including receptor trafficking, development and maturation of synapses, synaptic glutamate metabolism, regulation of CNS homeostasis, maintenance of integrity of the blood-brain barrier (BBB), nutrient provision to neural tissues, and regulation of neurogenesis. Based on data showing astrocyte involvement in the pathology of SCZ, astrocytes should be considered as therapeutic targets for treating this disease. In SCZ, abnormalities in neurons and neurotransmitters mainly result from the malfunction of astrocytes. Hence, correct functioning of astrocytes is required for the processes of synaptic activity and synaptic plasticity within neural networks, which is activity necessary for normal cognitive functions [155]. Therefore, targeting pathways associated with astrocytes' abnormal function may help ameliorate SCZ complications.

As hypofunctionality of NMDA receptors is believed to be one of the leading causes of SCZ, modifying NMDA receptors' function can be considered a therapeutic strategy for SCZ treatment. Targeting astrocytic glutamate reuptake presents a viable strategy for increasing glutamate sufficient to restore NMDA functionality [156]. Clozapine decreases glutamate reuptake through downregulation of glutamate transporter (GLT1) in astrocytes resulting in ameliorating hypofunctionality of NMDA receptors [157].

In addition to glutamate, several small molecules that can affect NMDA receptor functioning are linked to astrocyte activity. In preliminary trials, the NMDA receptor co-agonists glycine and D-serine have been applied as well as D-cycloserine [158]. An encouraging effect of high-dose D-serine administration was seen in SCZ patients [159]. Unfortunately, while small studies showed promising results, more extensive

trials indicated no significant difference between intervention and placebo groups when D-serine was exogenously applied [160].

An alternative approach to enhance D-serine levels in the synaptic space is to inhibit its metabolism in astrocytes. D-serine is metabolized by D-amino acid oxidase (DAAO) in astrocytes; thus, DAAO inhibitors may enhance NMDA activity by increasing endogenous D-serine concentrations. However, none of the identified human DAAO inhibitors have been approved for use in SCZ patients. Low bioavailability, high clearance rate, and inability to cross the BBB are considered the primary restrictions of these inhibitors [161].

Strategies focused on suppressing glycine reuptake in order to increase glycine's extracellular concentration in the synaptic space where it might be able to enhance NMDA functionality have been implemented, and inhibiting glycine transporter 1 (GlyT1) in astrocytes has been one approach considered for management of some SCZ symptoms. Among various GlyT1 inhibitors that have been trialed, only bitopertin has reached phase III clinical trials [155]. However, lack of efficacy has led to the discontinuation of its development as an antipsychotic [162].

In addition to glycine and D-serine, Kynurenic acid (KYNA), a metabolite of tryptophan degradation in astrocytes, can influence the function of NMDA receptors. KYNA has a preferential affinity for the NMDA receptor and can inhibit NMDA activity. According to the direct relationship between KYNA concentration and cognitive impairments in SCZ, interventions that lower brain KYNA levels may be clinically beneficial. Regrettably, at the current time, it is not feasible to target degradative enzymes or reuptake sites to enhance the removal of excess KYNA from its effector site in the brain. Moreover, exploiting the ability of depolarization events or cellular energy scarcity to reduce cerebral KYNA production is not possible. Pharmacological kynurenine aminotransferase (KAT) inhibitors are the most effective strategy to reduce KYNA production in the brain. The practicality of this approach is supported by findings that the nonspecific aminotransferase inhibitor aminooxyacetic acid readily prevents cerebral KYNA neosynthesis *in vivo*. In this regard, KAT II is the preferential target to suppress KYNA synthesis in the brain due to its high specificity toward kynurenine [158]. According to previous preclinical studies, the administration of selective KAT II inhibitors could successfully reduce extracellular KYNA levels in various rat brain regions. When taken together, considering KYNA's inhibitory effects on several neurotransmitters with a critical role in cognitive processes, any therapeutic agent or intervention that decreases KYNA levels or otherwise hinders KYNA function in the brain may lead to cognitive enhancement in SCZ or other psychiatric disorders, and the data suggest that KAT II inhibitors or pharmacological agents that weaken the function of KYNA at its receptor(s) have a high potential to be used for cognitive deficits in SCZ [158].

Astrocytes can also be a target to repair synaptic functions by moderating their effects on glycogen/lactate metabolism, as glucose uptake into astrocytes is reduced in SCZ due to a decrease in glycolysis and decreased lactate production. The decrease in lactate could have a profound effect on reductions in neurogenesis. Therefore, modifying glycogen/lactate metabolism sufficient to compensate for reduction of lactate could facilitate lactate-mediated neurogenesis, and lead to improvement of behavioral deficits in SCZ patients [163].

Reducing inflammation resulting from astrocytes can also be considered a therapeutic approach for SCZ and this approach has been shown to improve SCZ symptoms. For instance, minocycline, an antibiotic with anti-inflammatory effects, induced improvements in some SCZ patients. COX2 inhibitors, which are non-steroid anti-inflammatory drugs, have been shown to improve SCZ symptoms.

Lending support to the effectiveness of this strategy, many antipsychotic drugs exhibit anti-inflammatory effects, which could be important in their therapeutic efficacy. Given the link between inflammation and SCZ, a clear understanding of the cytokines involved in SCZ and the role played by astrocytes in linking inflammation and SCZ could lead to therapeutic strategies [156].

5.2 Diagnostic approach for SCZ

Postmortem studies identified significant changes in astrocyte density and morphology, as well as deregulated expression of several common astrocyte markers, including glial fibrillary acidic proteins (GFAP), aquaporin 4 (AQ-4), S100, glutaminase, thrombospondin (TSB-1), and excitatory amino acid transporter 2 (EAAT2) [22, 164–166]. When taken together, while data are suggestive of a role of altered astrocytic function in SCZ, the findings do differ, with some studies indicating a drop in marker levels and the number of astroglial cells compared to controls and others a rise. Although dysregulation in developing astroglial cells may have profound effects on the formation and maturation of neuronal networks, few studies have examined the status of astroglial cells during postnatal brain development, instead focusing on the postmortem examination of adult brain tissues [36]. Due to confounding factors associated with the use of postmortem tissues, differences in the brain regions evaluated, variety in the severity of the disease, and disparities in pharmacological treatments, it remains to be determined what the contribution of these markers to the disease is and if they play a role, at which developmental stage their role is most important. In light of the profound changes in astrocytic morphology and function, monitoring of alterations in astrocytes has been considered a diagnostic approach in SCZ. However, it is difficult to know what can easily be monitored from tissue non-invasively extracted in patients, which reflects astrocytic status. At the present time, identification of peripheral biomarkers that reflect neuropathological changes in SCZ has received a great deal of interest and in this arena, exosomes have been a focus of study as they are relatively easy to detect and have been proposed to be involved in psychiatric disorders [167]. Intriguingly, it is possible to identify the parent cell from which exosomes source.

Exosomes are nano-sized extracellular vesicles containing nucleic acids, proteins, lipids, and other bioactive substances secreted by cells into the surrounding body fluids, which regulate cellular communications in addition to neuroplasticity [168], trafficking of microRNA (miRNA) [169], and neuroinflammation [170, 171]. They can cross the BBB and be assayed peripherally, Exosomes derived from astrocytes would be expected to exhibit changes across the progression of SCZ. As proof of concept that exosomes can be detected and traced back to their parent cell, a high concentration of exosomal GFAP, resulting from astrogliosis was detected in plasma obtained from SCZ patients [172]. Thus, astrocytes-derived exosomes have the potential to be used for SCZ diagnosis and assessment of disease progression. However, further studies are needed to clarify to what extent circulating exosomes can serve as novel peripheral biomarkers of SCZ.

6. Conclusions

Astrocytic changes have been linked to SCZ at the neurobehavioral, structural, functional, and molecular levels. ECM, gap junctions, and epigenetics are also

Highlights
1. SCZ is a debilitating disorder with an estimated prevalence of 0.6% to 1.9% in the US population.
2. Astrocytic abnormalities end in cognitive disturbances such as memory, learning, and attention, and also abnormal cortical gamma oscillations in SCZ.
3. Various neurotransmitters such as glutamate, glycine, dopamine, adenosine, GABA, and the endocannabinoid system are implicated in astrocytic abnormalities in SCZ
4. Astrocyte-meditated remyelination is impaired in SCZ.
5. Neurogenesis-regulating molecules including D-serine, BDNF, FGF2, Lactate, and VEGF apparently fail in modulating neurogenesis via astrocytes in SCZ.
6. Innate (TLRs and Inflammasomes) and adaptive (T lymphocytes) immune responses exacerbate astroglial mediated abnormalities in SCZ.
7. The synaptic microenvironment (ECM, and Gap junctions) is highly altered in astrocyte-neuron communications in SCZ.
8. Epigenetic studies highlight a derailed cascade of regulatory molecular pathways.
9. Animal models of SCZ also demonstrate astrocytic abnormalities.
10. Astrocytes show promise as therapeutic and diagnostic targets in SCZ.

Table 2.
A summary of important points from this chapter.

implicated in the astrocytic abnormalities associated with SCZ. Various neurotransmitter systems that are regulated by astrocytes including GABA, glutamate, and adenosine are involved in SCZ. Also, different types of neuroplasticity governed by astrocytes are altered in SCZ. Moreover, hyperinflammation that is in part regulated by astrocytic inflammasomes (e.g., NLRPs) is present in SCZ patients and is affected by pharmacotherapy with antipsychotics. Clinical behavioral deficits in animal models are also related to aberrancies in astrocytes. When taken together, the plethora of studies that indicate a link between astrocytic dysfunction and SCZ should warrant future research to explore the role played by astroglial cells in SCZ to bridge the clinical and molecular findings and pave the path for developing future therapeutics that correct, or exploit, astrocyte functions in SCZ (**Table 2**).

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Conflict of interest

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References

[1] Tayeb HO et al. Pharmacotherapy of schizophrenia: Toward a metabolomic-based approach. CNS Spectrums. 2019;**24**(3):281-286

[2] Genoud C et al. Plasticity of astrocytic coverage and glutamate transporter expression in adult mouse cortex. PLoS Biology. 2006;**4**(11):e343

[3] Ventura R, Harris K. Three-dimensional relationships between hippocampal synapses and astrocytes. Journal of Neuroscience. 1999;**19**(16):6897-6906

[4] Witcher MR, Kirov SA, Harris KMJG. Plasticity of perisynaptic astroglia during synaptogenesis in the mature rat hippocampus. Glia. 2007;**55**(1):13-23

[5] Danbolt N. Glutamate Uptake. Progress in Neurobiology. 2001;**65**(1): 1-105

[6] Araque A et al. Gliotransmitters travel in time and space. Neuron. 2014;**81**(4):728-739

[7] Harada K, Kamiya T, Tsuboi T. Gliotransmitter release from astrocytes: Functional, developmental, and pathological implications in the brain. Frontiers in Neuroscience. 2016;**9**:499

[8] Rivera A, Vanzulli I, Butt A. A central role for ATP signalling in glial interactions in the CNS. Current Drug Targets. 2016;**17**(16):1829-1833

[9] Perea G, Araque AJS. Astrocytes potentiate transmitter release at single hippocampal synapses. Science. 2007;**317**(5841):1083-1086

[10] Perez-Alvarez A et al. Structural and functional plasticity of astrocyte processes and dendritic spine interactions. Journal of Neuroscience. 2014;**34**(38):12738-12744

[11] Dityatev A et al. Extracellular matrix and synaptic functions. Cell Communication in Nervous and Immune System. 2006;**43**:69-97

[12] Song I, Dityatev A. Crosstalk between glia, extracellular matrix and neurons. Brain Research Bulletin. 2018;**136**:101-108

[13] Chelini G et al. The tetrapartite synapse: A key concept in the pathophysiology of schizophrenia. European Psychiatry. 2018;**50**:60-69

[14] Koskuvi M et al. Patient iPSC-astrocytes show transcriptional and functional dysregulation in schizophrenia. bioRxiv. 2020

[15] Najjar S, Pearlman DM. Neuroinflammation and white matter pathology in schizophrenia: Systematic review. Schizophrenia Research. 2015;**161**(1):102-112

[16] Dieset I et al. Association between altered brain morphology and elevated peripheral endothelial markers — Implications for psychotic disorders. Schizophrenia Research. 2015;**161**(2):222-228

[17] Takahashi N, Sakurai T. Roles of glial cells in schizophrenia: Possible targets for therapeutic approaches. Neurobiology of Disease. 2013;**53**:49-60

[18] Cohen SM et al. The impact of NMDA receptor hypofunction on GABAergic neurons in the pathophysiology of schizophrenia. Schizophrenia Research. 2015;**167**(1-3):98-107

[19] Plitman E et al. Kynurenic acid in schizophrenia: A systematic review and meta-analysis. Schizophrenia Bulletin. 2017;**43**(4):764-777

[20] Khandaker GM et al. Inflammation and immunity in schizophrenia: Implications for pathophysiology and treatment. The Lancet Psychiatry. 2015;**2**(3):258-270

[21] Miyaoka T et al. Remission of psychosis in treatment-resistant schizophrenia following bone marrow transplantation: A case report. Frontiers in Psychiatry. 2017;**8**:174

[22] Kim R et al. Astroglial correlates of neuropsychiatric disease: From astrocytopathy to astrogliosis. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018;**87**:126-146

[23] Davis J et al. A review of vulnerability and risks for schizophrenia: Beyond the two hit hypothesis. Neuroscience and Biobehavioral Reviews. 2016;**65**:185-194

[24] Messias EL, Chen CY, Eaton WW. Epidemiology of schizophrenia: Review of findings and myths. The Psychiatric Clinics of North America. 2007;**30**(3):323-338

[25] Banazadeh M et al. Evaluating the effect of black myrobalan on cognitive, positive, and negative symptoms in patients with chronic schizophrenia: A randomized, double-blind, placebo-controlled trial. Phytotherapy Research. 2022;**36**(1):543-550

[26] Eroglu C, Barres BA. Regulation of synaptic connectivity by glia. Nature. 2010;**468**(7321):223-231

[27] Hu W et al. The glutamate hypothesis of schizophrenia: Evidence from human brain tissue studies. Annals of the New York Academy of Sciences. 2015;**1338**(1):38-57

[28] Verkhratsky A, Nedergaard M. Physiology of astroglia. Physiological Reviews. 2018;**98**(1):239-389

[29] Chung WS, Allen NJ, Eroglu C. Astrocytes control synapse formation, function, and elimination. Cold Spring Harbor Perspectives in Biology. 2015;**7**(9):a020370

[30] Lima A et al. Astrocyte pathology in the prefrontal cortex impairs the cognitive function of rats. Molecular Psychiatry. 2014;**19**(7):834-841

[31] Lee HS et al. Astrocytes contribute to gamma oscillations and recognition memory. Proceedings of the National Academy of Sciences. 2014;**111**(32):E3343-E3352

[32] Bellesi M et al. GLT-1 upregulation impairs prepulse inhibition of the startle reflex in adult rats. Glia. 2009;**57**(7):703-713

[33] van Os J, Kapur S. Schizophrenia. Lancet. 2009;**374**(9690):635-645

[34] Wu EQ et al. Annual prevalence of diagnosed schizophrenia in the USA: A claims data analysis approach. Psychological Medicine. 2006;**36**(11):1535-1540

[35] Dipiro JT et al. Pharmacotherapy: A Pathophysiologic Approach. Vol. 4. Connecticut: Appleton and Lange; 2014. pp. 141-142

[36] American Psychiatric Association, D. and A.P. Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Vol. 5. Washington, DC: American Psychiatric Association; 2013

[37] Sartorius N et al. Early manifestations and first-contact

incidence of schizophrenia in different cultures. A preliminary report on the initial evaluation phase of the WHO collaborative study on determinants of outcome of severe mental disorders. Psychological Medicine. 1986;**16**(4):909-928

[38] Blanco-Suárez E, Caldwell ALM, Allen NJ. Role of astrocyte-synapse interactions in CNS disorders. The Journal of Physiology. 2017;**595**(6):1903-1916

[39] Malenka RC, Bear MF. LTP and LTD: An embarrassment of riches. Neuron. 2004;**44**(1):5-21

[40] Moghaddam B, Javitt D. From revolution to evolution: The glutamate hypothesis of schizophrenia and its implication for treatment. Neuropsychopharmacology. 2012;**37**(1):4-15

[41] Jia M et al. Taming glutamate excitotoxicity: Strategic pathway modulation for neuroprotection. CNS Drugs. 2015;**29**(2):153-162

[42] Pajarillo E et al. The role of astrocytic glutamate transporters GLT-1 and GLAST in neurological disorders: Potential targets for neurotherapeutics. Neuropharmacology. 2019;**161**:107559-107559

[43] Andersen JV et al. Glutamate metabolism and recycling at the excitatory synapse in health and neurodegeneration. Neuropharmacology. 2021;**196**:108719

[44] Zádor F et al. Kynurenines and the endocannabinoid system in schizophrenia: Common points and potential interactions. Molecules (Basel, Switzerland). 2019;**24**(20):3709

[45] Pei J-C et al. Directly and indirectly targeting the glycine modulatory site to modulate NMDA receptor function to address unmet medical needs of patients with schizophrenia. Frontiers in Psychiatry. 2021;**12**:742058-742058

[46] de Bartolomeis A et al. Glycine signaling in the framework of dopamine-glutamate interaction and postsynaptic density. Implications for treatment-resistant schizophrenia. Frontiers in Psychiatry. 2020;**11**:369-369

[47] Yoshikawa M et al. Expression of the mRNA and protein of serine racemase in primary cultures of rat neurons. European Journal of Pharmacology. 2006;**548**(1-3):74-76

[48] Chatterton JE et al. Excitatory glycine receptors containing the NR3 family of NMDA receptor subunits. Nature. 2002;**415**(6873):793-798

[49] Li Y et al. Identity of endogenous NMDAR glycine site agonist in amygdala is determined by synaptic activity level. Nature Communications. 2013;**4**:1760-1760

[50] Betz H et al. Glycine transporters: Essential regulators of synaptic transmission. Biochemical Society Transactions. 2006;**34**(Pt 1):55-58

[51] Juárez Olguín H et al. The role of dopamine and its dysfunction as a consequence of oxidative stress. Oxidative Medicine and Cellular Longevity. 2016;**2016**:9730467-9730467

[52] Errico F et al. Decreased levels of D-aspartate and NMDA in the prefrontal cortex and striatum of patients with schizophrenia. Journal of Psychiatric Research. 2013;**47**(10):1432-1437

[53] Guidolin D et al. Chapter eight—Adenosine A2A-dopamine D2 receptor-receptor interaction in neurons and astrocytes: Evidence and perspectives.

In: Giraldo J, Ciruela F, editors. Progress in Molecular Biology and Translational Science. London, United Kingdom: Academic Press; 2020. pp. 247-277

[54] Tarasov VV et al. Alterations of astrocytes in the context of schizophrenic dementia. Frontiers in Pharmacology. 2020;**10**:1612-1612

[55] Losi G, Mariotti L, Carmignoto G. GABAergic interneuron to astrocyte signalling: A neglected form of cell communication in the brain. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2014;**369**(1654):20130609

[56] Matsuda LA et al. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature. 1990;**346**(6284):561-564

[57] Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. Nature Reviews. Drug Discovery. 2004;**3**(9):771-784

[58] Maccarrone M et al. Endocannabinoid signaling at the periphery: 50 years after THC. Trends in Pharmacological Sciences. 2015;**36**(5):277-296

[59] Hashimotodani Y, Ohno-Shosaku T, Kano M. Endocannabinoids and synaptic function in the CNS. The Neuroscientist. 2007;**13**(2):127-137

[60] Devane WA et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 1992;**258**(5090):1946-1949

[61] Mechoulam R et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochemical Pharmacology. 1995;**50**(1):83-90

[62] Secci ME et al. Astrocytic mechanisms involving Kynurenic acid control Δ(9)-tetrahydrocannabinol-induced increases in glutamate release in brain reward-processing areas. Molecular Neurobiology. 2019;**56**(5):3563-3575

[63] Li J et al. Astrocytes in oligodendrocyte lineage development and white matter pathology. Frontiers in Cellular Neuroscience. 2016;**10**:119-119

[64] Li J et al. Astrocytes in oligodendrocyte lineage development and white matter pathology. Frontiers in Cellular Neuroscience. 2016;**10**:119-125

[65] Terrillion CE et al. DISC1 in astrocytes influences adult neurogenesis and hippocampus-dependent behaviors in mice. Neuropsychopharmacology. 2017;**42**(11):2242-2251

[66] Christian KM, Song H, Ming G-L. Functions and dysfunctions of adult hippocampal neurogenesis. Annual Review of Neuroscience. 2014;**37**:243-262

[67] Clelland C et al. A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science. 2009;**325**(5937):210-213

[68] Revest J et al. Adult hippocampal neurogenesis is involved in anxiety-related behaviors. Molecular Psychiatry. 2009;**14**(10):959-967

[69] Snyder JS et al. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature. 2011;**476**(7361):458-461

[70] Zhou M et al. mTOR inhibition ameliorates cognitive and affective deficits caused by Disc1 knockdown in adult-born dentate granule neurons. Neuron. 2013;**77**(4):647-654

[71] Song H, Stevens CF, Gage FH. Astroglia induce neurogenesis from adult neural stem cells. Nature. 2002;**417**(6884):39-44

[72] Sultan S et al. Synaptic integration of adult-born hippocampal neurons is locally controlled by astrocytes. Neuron. 2015;**88**(5):957-972

[73] Araki T, Ikegaya Y, Koyama R. The effects of microglia-and astrocyte-derived factors on neurogenesis in health and disease. European Journal of Neuroscience. 2021;**54**(5):5880-5901

[74] Millar JK et al. Disruption of two novel genes by a translocation co-segregating with schizophrenia. Human Molecular Genetics. 2000;**9**(9):1415-1423

[75] Ma TM et al. Pathogenic disruption of DISC1-serine racemase binding elicits schizophrenia-like behavior via D-serine depletion. Molecular Psychiatry. 2013;**18**(5):557-567

[76] Bernstein H-G et al. Reduced density of DISC1 expressing astrocytes in the dentate gyrus but not in the subventricular zone in schizophrenia. Neuropsychopharmacology. 2018;**43**(3):457-458

[77] Bergami M et al. Uptake and recycling of pro-BDNF for transmitter-induced secretion by cortical astrocytes. The Journal of Cell Biology. 2008;**183**(2):213-221

[78] Quesseveur G et al. BDNF overexpression in mouse hippocampal astrocytes promotes local neurogenesis and elicits anxiolytic-like activities. Translational Psychiatry. 2013;**3**(4):e253-e253

[79] Brown AM, Ransom BR. Astrocyte glycogen and brain energy metabolism. Glia. 2007;**55**(12):1263-1271

[80] Suzuki A et al. Astrocyte-neuron lactate transport is required for long-term memory formation. Cell. 2011;**144**(5):810-823

[81] Zhou J et al. Lactate potentiates angiogenesis and neurogenesis in experimental intracerebral hemorrhage. Experimental & Molecular Medicine. 2018;**50**(7):1-12

[82] Morland C et al. Exercise induces cerebral VEGF and angiogenesis via the lactate receptor HCAR1. Nature Communications. 2017;**8**(1):1-9

[83] Lev-Vachnish Y et al. L-lactate promotes adult hippocampal neurogenesis. Frontiers in Neuroscience. 2019;**13**:403

[84] Ratajczak MZ et al. ATP-Nlrp3 Inflammasome-complement Cascade Axis in sterile brain inflammation in psychiatric patients and its impact on stem cell trafficking. Stem Cell Reviews and Reports. 2019;**15**(4):497-505

[85] de Zoete MR et al. Inflammasomes. Cold Spring Harbor Perspectives in Biology. 2014;**6**(12):a016287

[86] Ventura L et al. Involvement of NLRP3 inflammasome in schizophrenia-like behaviour in young animals after maternal immune activation. Acta Neuropsychiatr. 2020;**32**(6):321-327

[87] Ventura L et al. Involvement of NLRP3 inflammasome in schizophrenia-like behaviour in young animals after maternal immune activation. Acta Neuropsychiatrica. 2020;**32**(6):321-327

[88] Pasquini S et al. Adenosine receptors in neuropsychiatric disorders: Fine regulators of neurotransmission and potential therapeutic targets. International Journal of Molecular Sciences. 2022;**23**(3):1219

[89] He M et al. NLRP3/Caspase-1-mediated Pyroptosis of astrocytes induced by antipsychotics is inhibited by a histamine H1 receptor-selective agonist. Frontiers in Aging Neuroscience. 2022;**14**:847561

[90] He M et al. NLRP3/Caspase-1-mediated Pyroptosis of astrocytes induced by antipsychotics is inhibited by a histamine H1 receptor-selective agonist. Frontiers in aging. Neuroscience. 2022;**14**:847561

[91] Filiano AJ, Gadani SP, Kipnis J. Interactions of innate and adaptive immunity in brain development and function. Brain Research. 2015;**1617**:18-27

[92] Amor S et al. Inflammation in neurodegenerative diseases. Immunology. 2010;**129**(2):154-169

[93] González H, Pacheco R. T-cell-mediated regulation of neuroinflammation involved in neurodegenerative diseases. Journal of Neuroinflammation. 2014;**11**:201

[94] Najjar S et al. Neuroinflammation and psychiatric illness. Journal of Neuroinflammation. 2013;**10**(1):816

[95] Kirkpatrick B, Miller BJ. Inflammation and schizophrenia. Schizophrenia Bulletin. 2013;**39**(6):1174-1179

[96] Nyland H, Naess A, Lunde H. Lymphocyte subpopulations in peripheral blood from schizophrenic patients. Acta Psychiatrica Scandinavica. 1980;**61**(4):313-318

[97] Smith RS. A comprehensive macrophage-T-lymphocyte theory of schizophrenia. Medical Hypotheses. 1992;**39**(3):248-257

[98] Matloubi H et al. Decreased T cell response to mitogen and increased anti-cytoplasmic antibody in drug-free schizophrenic patients. Iranian Journal of Immunology. 2007;**4**(1):32-37

[99] Busse S et al. Different distribution patterns of lymphocytes and microglia in the hippocampus of patients with residual versus paranoid schizophrenia: Further evidence for disease course-related immune alterations? Brain, Behavior, and Immunity. 2012;**26**(8):1273-1279

[100] Aberg KA et al. A comprehensive family-based replication study of schizophrenia genes. JAMA Psychiatry. 2013;**70**(6):573-581

[101] Frydecka D et al. The role of genetic variations of immune system regulatory molecules CD28 and CTLA-4 in schizophrenia. Psychiatry Research. 2013;**208**(2):197-198

[102] Pillinger T et al. A meta-analysis of immune parameters, variability, and assessment of modal distribution in psychosis and test of the immune subgroup hypothesis. Schizophrenia Bulletin. 2019;**45**(5):1120-1133

[103] Corsi-Zuelli F, Deakin B. Impaired regulatory T cell control of astroglial overdrive and microglial pruning in schizophrenia. Neuroscience and Biobehavioral Reviews. 2021;**125**:637-653

[104] Schain M, Kreisl WC. Neuroinflammation in neurodegenerative disorders-a review. Current Neurology and Neuroscience Reports. 2017;**17**(3):25

[105] Enache D, Pariante CM, Mondelli V. Markers of central inflammation in major depressive disorder: A systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain

tissue. Brain, Behavior, and Immunity. 2019;**81**:24-40

[106] Marques TR et al. Neuroinflammation in schizophrenia: Meta-analysis of in vivo microglial imaging studies. Psychological Medicine. 2019;**49**(13):2186-2196

[107] Plavén-Sigray P et al. Meta-analysis of the glial marker TSPO in psychosis revisited: Reconciling inconclusive findings of patient-control differences. Biological Psychiatry. 2021;**89**(3):e5-e8

[108] Toker L et al. Transcriptomic evidence for alterations in astrocytes and Parvalbumin interneurons in subjects with bipolar disorder and schizophrenia. Biological Psychiatry. 2018;**84**(11):787-796

[109] Gandal MJ et al. Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. Science. 2018;**362**(6420):eaat8127

[110] González-Peñas J et al. Enrichment of rare genetic variants in astrocyte gene enriched co-expression modules altered in postmortem brain samples of schizophrenia. Neurobiology of Disease. 2019;**121**:305-314

[111] Zöller T et al. Silencing of TGFβ signalling in microglia results in impaired homeostasis. Nature Communications. 2018;**9**(1):4011

[112] Schilling T et al. Astrocyte-released cytokines induce ramification and outward K+ channel expression in microglia via distinct signalling pathways. The European Journal of Neuroscience. 2001;**14**(3):463-473

[113] Travis MA, Sheppard D. TGF-β activation and function in immunity. Annual Review of Immunology. 2014;**32**:51-82

[114] Miterauer B, Baer W. Disorders of human consciousness in the tri-partite synapses. Medical Hypotheses. 2020;**136**:109523

[115] Mitterauer BJ. Pathophysiology of schizophrenia based on impaired glial-neuronal interactions. Open journal of medical. Psychology. 2014;**03**(02):15

[116] Mitterauer B. Loss of function of glial gap junctions may cause severe cognitive impairments in schizophrenia. Medical Hypotheses. 2009;**73**(3):393-397

[117] Genocchi B, Lenk K, Hyttinen J. Influence of Astrocytic Gap Junction Coupling on in Silico Neuronal Network Activity. Berlin: Springer;

[118] Lenk K et al. Larger connection radius increases hub astrocyte number in a 3-D neuron–astrocyte network model. IEEE Transactions on Molecular, Biological and Multi-Scale Communications. 2021;**7**(2):83-88

[119] Tarasov VV et al. Alterations of astrocytes in the context of schizophrenic dementia. Frontiers in Pharmacology. 2019;**10**:1612

[120] Arion D et al. Molecular evidence for increased expression of genes related to immune and chaperone function in the prefrontal cortex in schizophrenia. Biological Psychiatry. 2007;**62**(7):711-721

[121] Kordi-Tamandani DM et al. Association of glutathione s-transferase gene methylation with risk of schizophrenia in an Iranian population. Pharmacology. 2014;**94**(3-4):179-182

[122] Kim JJ et al. Association analysis of heat shock protein 70 gene polymorphisms in schizophrenia. European Archives of Psychiatry

and Clinical Neuroscience. 2008;**258**(4):239-244

[123] Kowalczyk M et al. Heat shock protein 70 gene polymorphisms are associated with paranoid schizophrenia in the polish population. Cell Stress & Chaperones. 2014;**19**(2):205-215

[124] Yu WW et al. Heat shock protein 70 suppresses neuroinflammation induced by α-synuclein in astrocytes. Molecular and Cellular Neurosciences. 2018;**86**:58-64

[125] Marinova Z et al. Histone deacetylase inhibition alters histone methylation associated with heat shock protein 70 promoter modifications in astrocytes and neurons. Neuropharmacology. 2011;**60**(7-8):1109-1115

[126] Bozidis P et al. HSP70 polymorphisms in first psychotic episode drug-naïve schizophrenic patients. Life Sciences. 2014;**100**(2):133-137

[127] Gerber KJ, Squires KE, Hepler JR. Roles for regulator of G protein signaling proteins in synaptic signaling and plasticity. Molecular Pharmacology. 2016;**89**(2):273-286

[128] Buckholtz JW et al. Allelic variation in RGS4 impacts functional and structural connectivity in the human brain. The Journal of Neuroscience. 2007;**27**(7):1584-1593

[129] Liu YL et al. Evaluation of RGS4 as a candidate gene for schizophrenia. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics. 2006;**141b**(4):418-420

[130] Mirnics K et al. Disease-specific changes in regulator of G-protein signaling 4 (RGS4) expression in schizophrenia. Molecular Psychiatry. 2001;**6**(3):293-301

[131] Ding L et al. Expression of the longest RGS4 splice variant in the prefrontal cortex is associated with single nucleotide polymorphisms in schizophrenia patients. Frontiers in Psychiatry. 2016;**7**:26

[132] Vrajová M et al. The effects of siRNA-mediated RGS4 gene silencing on the whole genome transcription profile: Implications for schizophrenia. Neuro Endocrinology Letters. 2011;**32**(3):246-252

[133] Ho SM et al. Evaluating synthetic activation and repression of neuropsychiatric-related genes in hiPSC-derived NPCs, neurons, and astrocytes. Stem Cell Reports. 2017;**9**(2):615-628

[134] Martins-de-Souza D, Lebar M, Turck CW. Proteome analyses of cultured astrocytes treated with MK-801 and clozapine: Similarities with schizophrenia. European Archives of Psychiatry and Clinical Neuroscience. 2011;**261**(3):217-228

[135] Sun L et al. Adolescent social isolation affects schizophrenia-like behavior and astrocyte biomarkers in the PFC of adult rats. Behavioural Brain Research. 2017;**333**:258-266

[136] Akkouh IA et al. Transcriptome analysis reveals disparate expression of inflammation-related miRNAs and their gene targets in iPSC-astrocytes from people with schizophrenia. Brain, Behavior, and Immunity. 2021;**94**:235-244

[137] Xia M et al. Behavioral sequelae of astrocyte dysfunction: Focus on animal models of schizophrenia. Schizophrenia Research. 2016;**176**(1):72-82

[138] Banasr M, Duman RS. Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. Biological Psychiatry. 2008;**64**(10):863-870

[139] Lima A et al. Astrocyte pathology in the prefrontal cortex impairs the cognitive function of rats. Molecular Psychiatry. 2014;**19**(7):834-841

[140] Danbolt NC. Glutamate uptake. Progress in Neurobiology. 2001;**65**(1):1-105

[141] Matute C et al. Increased expression of the astrocytic glutamate transporter GLT-1 in the prefrontal cortex of schizophrenics. Glia. 2005;**49**(3):451-455

[142] Bellesi M et al. GLT-1 upregulation impairs prepulse inhibition of the startle reflex in adult rats. Glia. 2009;**57**(7):703-713

[143] Melone M, Bellesi M, Conti F. Synaptic localization of GLT-1a in the rat somatic sensory cortex. Glia. 2009;**57**(1):108-117

[144] Nozari M et al. Postnatal MK-801 treatment of female rats impairs acquisition of working memory, but not reference memory in an eight-arm radial maze; no beneficial effects of enriched environment. Psychopharmacology. 2015;**232**(14):2541-2550

[145] Nozari M et al. Sex-specific restoration of MK-801-induced sensorimotor gating deficit by environmental enrichment. Neuroscience. 2015;**299**:28-34

[146] Nozari M et al. Enriched environment prevents cognitive and motor deficits associated with postnatal MK-801 treatment. Psychopharmacology. 2014;**231**(22):4361-4370

[147] Chess AC et al. Elevations of endogenous kynurenic acid produce spatial working memory deficits. Schizophrenia Bulletin. 2007;**33**(3):797-804

[148] Iaccarino HF et al. The effect of transient increases in kynurenic acid and quinolinic acid levels early in life on behavior in adulthood: Implications for schizophrenia. Schizophrenia Research. 2013;**150**(2-3):392-397

[149] Yolken R, Dickerson F, Fuller Torrey E. Toxoplasma and schizophrenia. Parasite Immunology. 2009;**31**(11):706-715

[150] Notarangelo F et al. Evaluation of kynurenine pathway metabolism in toxoplasma gondii-infected mice: Implications for schizophrenia. Schizophrenia Research. 2014;**152**(1):261-267

[151] Kannan G, Pletnikov MV. Toxoplasma gondii and cognitive deficits in schizophrenia: An animal model perspective. Schizophrenia Bulletin. 2012;**38**(6):1155-1161

[152] Tezuka T et al. Cuprizone short-term exposure: Astrocytic IL-6 activation and behavioral changes relevant to psychosis. Neurobiology of Disease. 2013;**59**:63-68

[153] Petegnief V et al. Neuronal injury-induced expression and release of apolipoprotein E in mixed neuron/glia co-cultures: Nuclear factor κB inhibitors reduce basal and lesion-induced secretion of apolipoprotein E. Neuroscience. 2001;**104**(1):223-234

[154] Brambilla R et al. Inhibition of astroglial nuclear factor κB reduces

inflammation and improves functional recovery after spinal cord injury. The Journal of Experimental Medicine. 2005;**202**(1):145-156

[155] Singer P, Dubroqua S, Yee KB. Inhibition of glycine transporter 1: The yellow brick road to new schizophrenia therapy? Current Pharmaceutical Design. 2015;**21**(26):3771-3787

[156] Takahashi N, Sakurai T. Roles of glial cells in schizophrenia: Possible targets for therapeutic approaches. Neurobiology of Disease. 2013;**53**:49-60

[157] Vallejo-Illarramendi A et al. Clozapine reduces GLT-1 expression and glutamate uptake in astrocyte cultures. Glia. 2005;**50**(3):276-279

[158] Pocivavsek A et al. Chapter 25—Astrocytes as pharmacological targets in the treatment of schizophrenia: Focus on Kynurenic acid. In: Pletnikov MV, Waddington JL, editors. Handbook of Behavioral Neuroscience. Amsterdam, Netherlands: Elsevier; 2016. pp. 423-443

[159] Kantrowitz JT et al. High dose D-serine in the treatment of schizophrenia. Schizophrenia Research. 2010;**121**(1):125-130

[160] Girgis RR et al. The past and future of novel, non-dopamine-2 receptor therapeutics for schizophrenia: A critical and comprehensive review. Journal of Psychiatric Research. 2019;**108**:57-83

[161] Egerton A et al. Glutamate in schizophrenia: Neurodevelopmental perspectives and drug development. Schizophrenia Research. 2020;**223**: 59-70

[162] Kantrowitz JT et al. Neurophysiological effects of Bitopertin in schizophrenia. Journal of Clinical Psychopharmacology. 2017;**37**(4):447-451

[163] Powell CL, Davidson AR, Brown AM. Universal glia to Neurone lactate transfer in the nervous system: Physiological functions and pathological consequences. Biosensors. 2020;**10**(11):183

[164] Katsel P et al. Astrocyte and glutamate markers in the superficial, deep, and white matter layers of the anterior cingulate gyrus in schizophrenia. Neuropsychopharmacology. 2011;**36**(6):1171-1177

[165] Tarasov VV et al. Alterations of astrocytes in the context of schizophrenic dementia. Frontiers in Pharmacology. 2020;**10**:1612

[166] Trépanier MO et al. Postmortem evidence of cerebral inflammation in schizophrenia: A systematic review. Molecular Psychiatry. 2016;**21**(8):1009-1026

[167] Lee EE et al. Plasma levels of neuron- and astrocyte-derived Exosomal amyloid Beta1-42, amyloid Beta1-40, and phosphorylated tau levels in schizophrenia patients and non-psychiatric comparison subjects: Relationships with cognitive functioning and psychopathology. Frontiers. Psychiatry. 2021;**11**:532624

[168] Tavakolizadeh J et al. MicroRNAs and exosomes in depression: Potential diagnostic biomarkers. Journal of Cellular Biochemistry. 2018;**119**(5):3783-3797

[169] Banigan MG et al. Differential expression of exosomal microRNAs in prefrontal cortices of schizophrenia and bipolar disorder patients. PLoS One. 2013;**8**(1):e48814

[170] Saeedi S et al. The emerging role of exosomes in mental disorders. Translational Psychiatry. 2019;**9**(1):122

[171] Zhang Y et al. Exosomes: Biogenesis, biologic function and clinical potential. Cell & Bioscience. 2019;**9**(1):19

[172] Ranganathan M et al. Analysis of circulating exosomes reveals a peripheral signature of astrocytic pathology in schizophrenia. The World Journal of Biological Psychiatry. 2022;**23**(1):33-45