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REVIEW ARTICLE

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Astrocyte regulation of synaptic signaling in psychiatric disorders

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Over the last 15 years, the field of neuroscience has evolved toward recognizing the critical role of astroglia in shaping neuronal synaptic activity and along with the pre- and postsynapse is now considered an equal partner in tripartite synaptic transmission and plasticity. The relative youth of this recognition and a corresponding deficit in reagents and technologies for quantifying and manipulating astroglia relative to neurons continues to hamper advances in understanding tripartite synaptic physiology. Nonetheless, substantial advances have been made and are reviewed herein. We review the role of astroglia in synaptic function and regulation of behavior with an eye on how tripartite synapses figure into brain pathologies underlying behavioral impairments in psychiatric disorders, both from the perspective of measures in postmortem human brains and more subtle influences on tripartite synaptic regulation of behavior in animal models of psychiatric symptoms. Our goal is to provide the reader a well-referenced state-of-the-art understanding of current knowledge and predict what we may discover with deeper investigation of tripartite synapses using reagents and technologies not yet available.

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INTRODUCTION

Over the 150 years [1] since astroglia were discovered and described as the most abundant glial type in the brain [2], they have mostly been silent bystanders to neurons and synapses in the field of neuroscience. It wasn't until the 1990s that research began in earnest from a perspective that through metabolic activity, and expression of glutamate transporters, astroglia can contribute indirectly to excitatory neurotransmission [3, 4]. However, a minority perspective for a more direct astrocytic regulation of synaptic activity and synaptic regulation by astroglia also began to emerge [5–9] and in 1999 the term 'tripartite synapse' was coined to acknowledge an equivalent partnership between perisynaptic astroglial processes (PAPs) and the neuronal pre- and postsynapse [10]. Thus, by the turn of the current century researchers were beginning to accept and investigate tripartite synaptic activity and plasticity, although astroglia-neuron interactions were still being examined largely from the perspective of pathologies arising from neurotoxicity, such as in stroke-induced ischemia, amyotrophic lateral sclerosis and vascular dementia [11–15]. The possibility that astroglia contributed to psychiatric disorders was formally broached in 2007 [16, 17]. Since that time, our understanding of the mechanisms by which astroglia bidirectionally regulate synaptic transmission and plasticity, and how this contributes to the neuronal pathologies underpinning psychiatric disorders has become a growing area of investigation with the potential to yield innovative clinical therapies.

While substantial evidence supports neuroimmune, metabolic, and homeostatic roles for astroglia in shaping neural function and cognition (for excellent reviews, please see refs. [18–21]), here we explore current data and perspectives on mechanisms whereby astroglia regulate synaptic activity and plasticity through bidirectional release of neuroactive molecules (gliotransmission onto neurons and the release of transmitters and modulators from neurons onto astroglia). In describing bidirectional transmission, we focus on how the morphological positioning of astroglia relative to synapses and the expression of astroglial membrane receptors and transporters regulate neuronal synaptic activity and plasticity. The three primary mechanisms whereby astroglia regulate neuronal synapses, including morphology, expression and surface diffusion of membrane transporters, and gliotransmission, are summarized in Box 1. We also examine studies from humans and animal models of psychiatric disorders that support a consequential role for astroglia in the initiation, progression and symptoms of psychiatric disorders. In evaluating the literature, we noted that a majority of studies quantifying the intersection between tripartite synapses and behavior were made in a brain circuit containing frontal cortical, allocortical (hippocampus and amygdala) and dopaminergic projections to the nucleus accumbens or striatum, and the accumbens projection to the ventral pallidum. This interconnected circuit is well-established to be involved in regulating normal and maladaptive motivated behaviors in both animals and humans [22–24]. Box 2 orients the reader to the nuclei in this circuit and briefly summarizes findings on tripartite synaptic plasticity from each nucleus in the circuit. To organize the literature, we focus on tripartite physiology and signaling at excitatory synapses separate from inhibitory synapses in the different loci of the circuit. This is followed by incorporating tripartite physiology into astroglial pathologies

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Box 1. Three mechanisms whereby astroglia modulate neuronal synapses

Astroglia employ three general approaches to regulate synaptic activity. The three astroglial mechanisms are not mutually exclusive and can be constitutive to provide long-term homeostasis in synaptic transmission, or they can be transient in response to environmental stimuli that trigger behavioral symptoms of psychiatric disorders.

Morphological mechanisms of astroglial plasticity: This mechanism is primarily how physically close an astroglial process is to the synaptic cleft. Closer proximity of an astroglial process has three primary effects on synaptic activity. 1) The process can provide steric interference to water soluble synaptic transmitters, thereby decreasing diffusion coefficients and slowing access of transmitters into the extracellular space and access to extrasynaptic receptors [346, 347]. 2) Closer proximity to either the pre- or postsynapse can locally decrease diffusion constants and guide transmitters towards extrasynaptic receptors on the opposite side of the synapse [348]. For example, at excitatory synapses closer proximity to the postsynapse can guide glutamate toward presynaptic metabotropic glutamate release-regulating autoreceptors. 3) Closer morphological proximity between astroglial surface and the neuronal synapse brings astroglial surface proteins closer to the synapse that can profoundly regulate neurotransmission. Notably this includes transmitter uptake transporters that can remove synaptically-released transmitter when near the synapse and thereby limit access to extrasynaptic receptors.

Expression of astroglial membrane transporters and receptors: Astroglia express surface proteins that respond to synaptic activity. Two key types of protein are transporters that eliminate extracellular transmitter to reduce synaptic transmitter spillover and ionotropic or metabotropic receptors that can signal to induce astroglial plasticity. For example, stimulating Gq-coupled metabotropic receptors promotes astroglial process elongation toward synapses. Importantly, many of these proteins are expressed on the astroglial perisynaptic surface in higher density than elsewhere. This is particularly well-characterized for the astroglial glutamate transporter, GLT-1 and NA^+/K^+-ATPase that show patterned astroglial surface expression adjacent to the synapse [349, 350].

Gliotransmission: Through a variety of mechanisms [351], astroglia release molecules that can regulate neurotransmission via stimulation of extrasynaptic receptors situated on the pre- or postsynapse. Release can be calcium-dependent or via astroglial transporters [352, 353]. For example, glutamate is released following Gq-coupled metabotropic receptor stimulation [287] and via the cystine-glutamate exchanger that scavenges cystine from the extracellular space in a 1:1 stoichiometric exchange for intracellular astroglial glutamate [354]. Recognized gliotransmitters include classical neurotransmitters like glutamate and GABA, as well as neuromodulators like ATP/adenosine and D-serine.

associated with psychiatric disorders and animal models of psychiatric behavioral symptoms. Finally, we conclude with what to anticipate in the immediate future from research on tripartite synaptic plasticity and psychiatric disorders.

ASTROCYTE REGULATION OF EXCITATORY SYNAPSES

Astrocytes are crucial for glutamatergic synaptic transmission (Fig. 1). Not only do astroglia supply neurons with glutamine, the precursor required for glutamate biosynthesis [25, 26], they are also required for terminating glutamatergic signaling and are responsible for the vast majority of glutamate clearance in the brain [27]. Astroglial glutamate uptake is coordinated primarily by the Na^+-dependent glial glutamate transporter (GLT-1) [28] and the glutamate-aspartate transporter (GLAST) [29]. While glutamate clearance is required for effective glutamatergic synaptic communication, it is also required to prevent excitotoxic buildup of glutamate, a biomarker often associated with the progression of neuropsychiatric and neurodegenerative disorders [30, 31]. Once removed from the synapse, glutamate is converted to glutamine in astrocytes, which is then supplied back to neurons [32]. Appropriate glutamate and glutamine transfer between astrocytes and neurons is critical for excitatory signaling and cognitive function and is often described as the glutamate-glutamine cycle [25, 33] (Fig. 1). Additionally, astrocytes also express a variety of neurotransmitter receptors including ionotropic and metabotropic glutamate receptors [34–40], the activation of which engages Ca^{2+} signaling, a major second messenger in astrocytes regulating numerous astrocytic functions. Ultimately, chemical communication between neurons and astrocytes allows astrocytes to decode afferent

Box 2. Circuit most well-studied for tripartite synapses

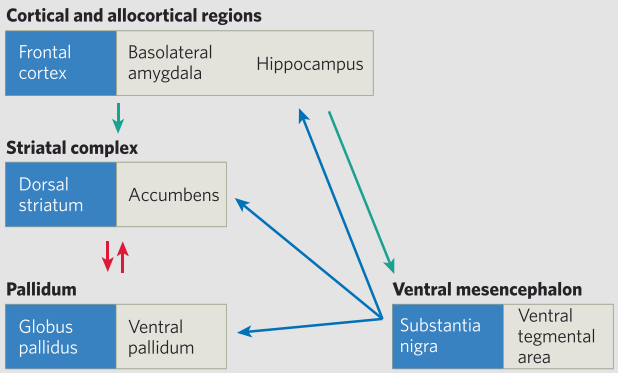
This brain circuit encompasses the majority of studies on astroglial regulation of synaptic activity, as summarized below and in detail in the text. The circuit is also characterized in both humans and animal models to harbor tripartite and behavioral pathologies characteristic of many psychiatric disorders. Within boxes the gradient from white to blue reflects the general topography of how the different regions are wired together through their respective nuclei. Green arrow = glutamatergic, red = GABAergic and blue = dopaminergic.

Cortical and allocortical regions: In these structures astroglial regulation of synaptic activity is largely focused on glutamatergic synapses, with work in hippocampal slices showing how the different forms of astroglial plasticity (see Box 1) regulate synaptic strength [52–54]. For example, increased morphological proximity and expression of GLT-1 decreases synaptic glutamate spillover and reduces synaptic potentiation. Behaviorally these adaptations have been studied most intensely with regard to learning and memory, and the implications of astroglial plasticity on disorders such as dementia [355, 356]. However, studies in the amygdala and prefrontal cortex demonstrate how tripartite synaptic plasticity also modulates motivation in animal models of substance use disorder and depression. Human studies showing astroglial pathologies in postmortem tissue from patients with various psychiatric disorders are also most abundant in the cortical and allocortical regions, especially for major depression [123, 127–136].

Striatal complex: As with the cortical and allocortical regions, most studies within the striatal complex also focus on astroglial regulation of excitatory transmission. In particular, some efforts have been made to show distinctions between astroglial synaptic regulation of striatal medium spiny neurons expressing D_1- versus D_2-dopamine receptors [304]. A number of studies also examine a role for astroglial regulation of dopamine transmission [114]. Regarding psychiatric disorders, studies in the striatal complex most frequently employ animal models of substance use disorder. However, gliotransmission of adenosine binds to A_{2A} receptors and interacts directly with D_2-dopamine receptors to dampen the effects of dopamine release, with implications for the role of striatal dopamine transmission in schizophrenia and Parkinson's disease [111].

Pallidum: There are relatively fewer studies on tripartite synapses in the pallidum. However, because of the dense GABAergic input to the pallidum from the striatal complex, it is a site where inhibitory tripartite synaptic plasticity and physiology can be readily examined [357]. To date, most studies involve the role of these GABAergic tripartite synapses in substance use disorders [357], with no studies conducted we are aware of regarding astroglia as pathogenic in the pallidum of psychiatric patients, although astroglia in the globus pallidus have been implicated in some movement disorders, especially regarding astroglial regulation of iron metabolism [358].

Ventral mesencephalon: This region is the source of ascending dopamine innervation to the other regions in the circuit. While little is known regarding tripartite synaptic regulation in the ventral mesencephlon, as mentioned above, astroglial regulation of dopamine synapses in the striatum has recently become a topic of interest in models of psychiatric and motor disorders.



information and generate functional outputs via the release of neuroactive molecules [41].

Apart from their central role in glutamate synthesis and glutamate clearance, astroglia also directly influence ionotropic glutamate receptor activation. The NMDA ionotropic glutamate receptor requires binding of a co-agonist (L-glycine or D-serine) to function [42], with D-serine serving as a primary modulator of excitatory transmission and an important factor in the pathophysiology of anxiety and depression-related disorders [43, 44]. D-serine is generated via enzymatic conversion of astrocyte-derived L-serine by serine racemase [45] (however, see ref. [46] for an in depth discussion on the cellular source of D-serine). In forebrain regions D-serine serves as the primary co-agonist for

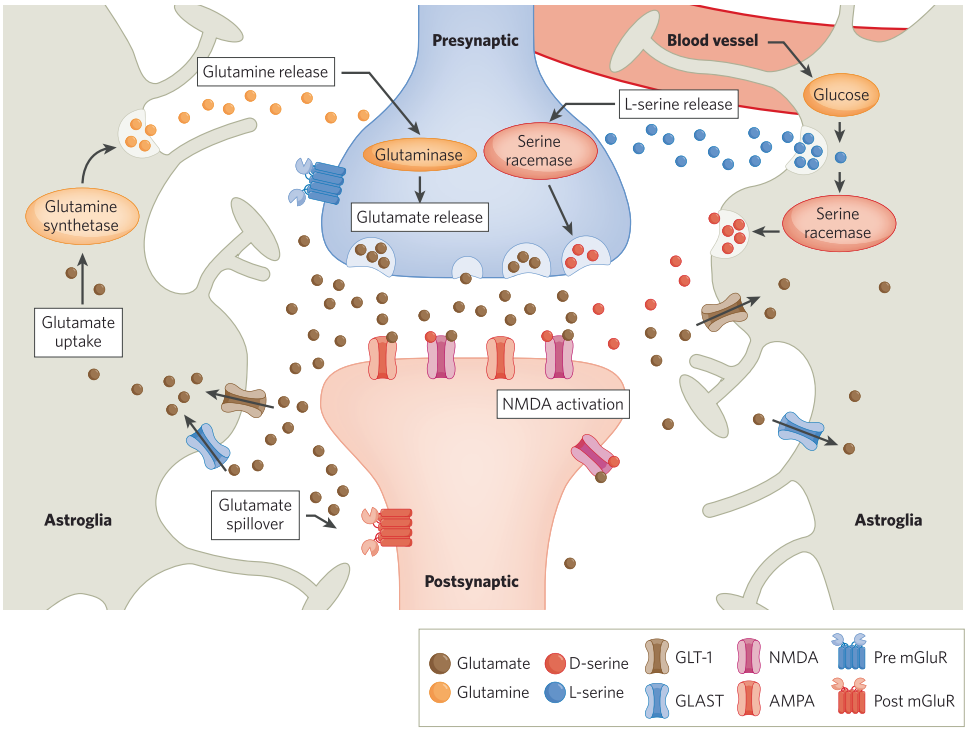


Fig. 1 Astroglial regulation of excitatory synapses. Astroglia adjacent to excitatory synapses express GLT-1 and GLAST transporters responsible for clearance of glutamate. Glutamate transporter activity also dictates extrasynaptic glutamate levels, which can influence glutamate receptor activation located at both pre- and post-synaptic sites. Once taken up by astroglia, glutamate is converted to glutamine, which is in turn released by astroglia and taken up by neurons. Importantly, neuronal glutamate biosynthesis requires glutamine release from astrocytes and transport into neurons, where it is converted to glutamate. Apart from the glutamate-glutamine cycle, astrocytes also produce L-Serine, which is converted to D-Serine via serine racemase, which also serves to facilitate synaptic glutamate signaling through its role as a co-agonist at NMDA receptors expressed in the synaptic cleft and extrasynaptically on both neurons and astroglia. Astroglial expression of mGluRs as well as astroglial release of glutamate through a Ca^{2+}-dependent process and cystine-glutamate exchange has been omitted here for for illustrative clarity.

NMDA receptors, with studies supporting a role for cortical D-serine in depression, fear conditioning, anxiety, and cognitive function [43, 47–49]. NMDA receptors are positioned within the synaptic cleft and extrasynaptically, with extrasynaptic receptor stimulation predicted to result from glutamate spillover consequent to astrocyte retraction from synapses, or from gliotransmission directly [50].

Finally, astroglia modulate excitatory neurotransmission through their physical interaction with neurons. Astrocytes ensheathe synapses with their membranous PAPs [51], allowing for dynamic regulation of the physical space where neurotransmission occurs. Indeed, alterations in the extent of the astroglial embrace allow astrocytes to influence the local concentration of neurotransmitters like glutamate [52–55]. Accordingly, reorganization of astroglial morphology can have a direct impact on the profile of synaptic and extrasynaptic neurotransmitter receptor activation during synaptic transmission, with severe retraction allowing glutamate to engage in inter-synaptic signaling [53, 56]. Further, it has been repeatedly demonstrated that modifications in the association of peripheral astroglial processes with synapses and dendritic spines is activity dependent [57–59], making the morphological properties of astrocytes and by extension their physical interaction with synapses, a coordinated means for tripartite astroglial regulation of excitatory synaptic transmission [60].

ASTROCYTE REGULATION OF INHIBITORY SYNAPSES

As detailed above, the majority of CNS synapses are approached by astroglial peripheral processes [61], including inhibitory synapses [62] (Fig. 2). Astrocytes express $GABA_A$ and $GABA_B$ receptors and as in neurons, $GABA_A$ activation is coupled with chloride currents [63]. $GABA_B$ stimulation on astroglia triggers astroglial Ca^{2+} flux and in the dorsal striatum can drive excitatory synapse formation through astroglial thrombospondin signaling [64, 65]. Similar patterns of neuron-glial communication have been observed in the hippocampus and cortex, where astrocytic $GABA_B$ stimulation triggers astroglial Ca^{2+} oscillation and subsequent glutamate release that potentiates synaptic activity [65–67]. This pattern of signaling underlies goal-directed behavior when it occurs in the prefrontal cortex [67], and produces disordered attention and locomotor hyperactivity when occurring in the dorsal striatum [64]. Notably, $GABA_B$ stimulation on hippocampal astrocytes has also been shown to trigger heterosynaptic depression in an ATP/adenosine-dependent manner [68]. That astroglia can bidirectionally modulate neuronal activity in a single brain region underscores the sensitivity of astrocytes to changes in neuronal firing frequency and duration of activity [69].

Just as astroglial processes adjacent to excitatory synapses play an important role in retrieving synaptically released glutamate, astroglia situated near inhibitory synapses participate in GABA uptake through expression of high-affinity GABA transporters GAT-1 and GAT-3. GAT-1 is expressed to a similar extent at neuronal terminals and on perisynaptic astroglial processes [70]. In contrast, GAT-3 is most densely expressed by astroglia and targeted extrasynaptically >500 nm from synaptic active zones [71]. Given the predominantly extrasynaptic location and high affinity for GABA, GAT-3 serves to regulate inhibitory tone at extrasynaptic receptors and minimizes synaptic GABA spillover between inhibitory synapses, while still permitting GABA access to the immediate perisynaptic environment [72, 73].

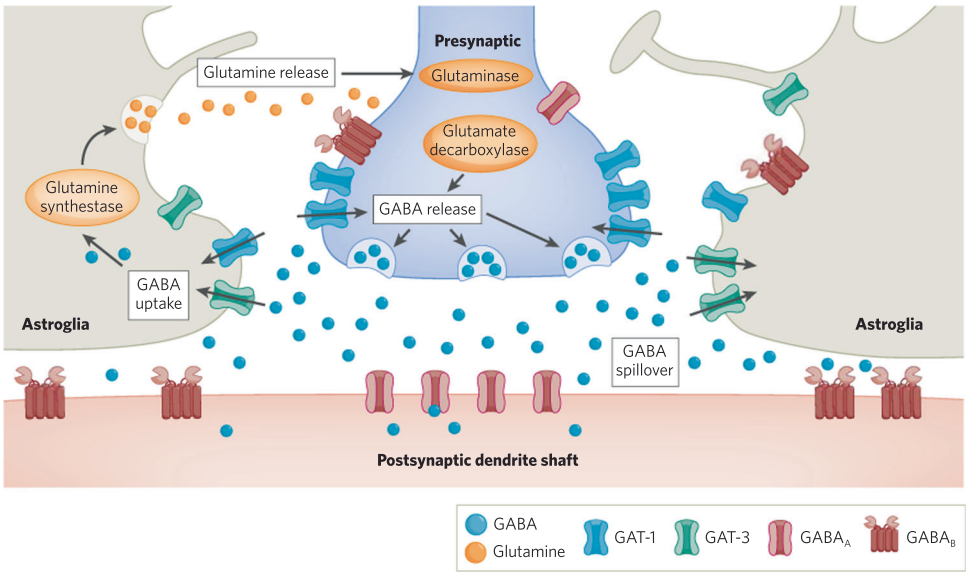


Fig. 2 Astroglial regulation of inhibitory synapses. GABAergic synapses are frequently on the dendritic shaft. Astroglia adjacent to GABA release sites express $GABA_A$ and $GABA_B$ receptors as well as GABA transporters GAT-1 and GAT-3. GAT-1 is also expressed on presynaptic terminals. GAT-3 on astroglia is targeted extrasynaptically, where it regulates GABA spillover and stimulation of extrasynaptic receptors on neurons. As is also true for replenishment of neuronal glutamate, neuronal GABA pools depend upon glutamine release from astrocytes that can be converted to GABA within neurons. Elevated Na^+ in astrocytes due to Na^+ co-transport coupled to GABA or glutamate uptake directly stimulates glutamine synthesis and efflux from astroglia through glutamine transporters. In some cases, increased intracellular Na^+ in astrocytes also leads to extrusion of GABA through GAT reversal.

Similar to their role in facilitating excitatory transmission, astrocytes and their synaptic adjacency are essential to provide glutamine for neuronal synthesis of GABA via the decarboxylation of glutamate [74]. Elevation of sodium ions in astroglia, largely generated by sodium co-transport coupled to GABA or glutamate transport directly stimulate glutamine synthesis, as well as glutamine efflux through glutamine transporters on astroglia [75, 76]. In this way, neuronal activity is both coupled to glutamine efflux from astrocytes and is also dependent on astrocyte-neuron proximity and functional transport activity to replenish pools of glutamate and GABA [77]. Thus, it stands to reason that up- or downregulation of transporters by astroglia, which occurs in a number of brain regions and psychiatric disorders discussed below and elsewhere (see ref. [78] for example), may impact synaptic release dynamics [79] leading to changes in basal transmitter levels characteristic of disease states [80–83].

While GABAergic release by astroglia is not as well documented as glutamatergic gliotransmission [84], astrocytes synthesize GABA via monoamine oxidase B [85, 86], or diamine oxidase and aldehyde dehydrogenase a1a and release GABA through Best1 channels [87]. Astroglial GABA release through Best1 mediates GABA tone in the thalamus and permits tactile discrimination in mice [87]. Additionally, the increases in intracellular Na^+ in astrocytes arising from glutamate transport can lead to extrusion of GABA via reversal of GAT transport [88–91].

ASTROCYTE REGULATION OF NEUROMODULATORS

Neuromodulation is the process by which endogenous molecules, including ATP/adenosine, dopamine, serotonin, and others influence pre-synaptic release or post-synaptic action of ionotropic transmitters that directly hyperpolarize or depolarize neurons [92, 93]. Thus, neuromodulators regulate classic excitatory or inhibitory synaptic transmission, adding complexity and fine-tuning control over synaptic activity (Fig. 3). Among neuromodulators, ATP/adenosine has emerged as a relevant player in the bidirectional chemical communication between neurons and astroglia [93]. ATP/adenosine can be released by neurons or astroglia via equilibrative nucleoside transporters (ENTs) that transport ATP across the plasma membrane according to its concentration gradient [94, 95]. ATP is then converted, serving as a source of extracellular adenosine. Adenosine is also generated intracellularly and transported directly [96]. Since adenosine levels increase intracellularly in neurons as a function of neural activity and ATP/adenosine transport can occur passively, neural activity increases levels of extracellular adenosine [96]. Researchers also find co-transport of adenosine in synaptic vesicles [97–99] and astrocytes release ATP in response to both excitatory and inhibitory synaptic activity [100, 101]. Thus, a number of mechanisms are engaged by both neurons and glia to increase synaptic and extrasynaptic adenosine levels [96].

Adenosine receptors are G-protein coupled receptors expressed on astrocytes and both pre- and post-synaptically on neurons [99, 102, 103] and adenosine neuromodulation has been observed at GABAergic, glutamatergic, and dopaminergic synapses [101, 102, 104–106]. G_i-coupled A_1 and G_s-coupled A_{2A} adenosine receptors have received the most attention for their regulation of synaptic physiology in recent years [95, 107, 108]. Both A_1 and A_{2A} adenosine receptors form heteromeric complexes with other GPCRs, most notably dopamine D_1 and D_2 receptors, respectively, further tuning the outcome of ligand binding [95, 96]. For example, A_{2A} heteromerization with D_2 receptors in the striatum decreases the affinity of dopamine for the D_2 receptor [109, 110]. Moreover, it is thought that the pairing of G_i- and G_s-coupled receptors serves to disrupt the traditional GPCR signaling cascades at the level of adenylyl cyclase [110]. Adenosine antagonists like caffeine derive their behavioral effects through disrupting these interactions in the striatum, where D_2-A_{2A} pairing is predominant [111], and in the spinal cord, where D_1-A_1 pairing is observed, serving to disinhibit dopaminergic signaling [107, 110].

In addition to ATP/adenosine signaling, astrocytes are tuned to detect and respond to monoaminergic signaling, including dopamine and serotonin [112]. Indeed, some serotonin (5-HT) receptors, including 5-HT_2 are more abundant in astroglia than in neurons [113]. Synaptically released dopamine directly increases Ca^{2+} in nucleus accumbens astrocytes by stimulating astroglial

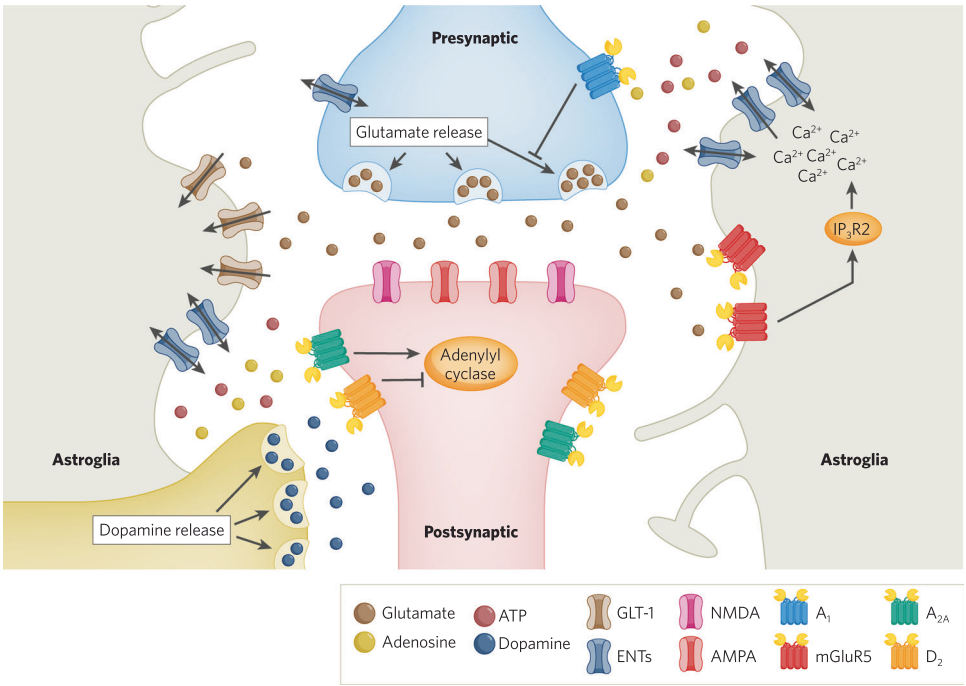


Fig. 3 Neuromodulation by astroglia. Astrocytes modulate glutamate release via ATP/adenosine transport through ENTs. In the dorsolateral striatum, cortical terminals release glutamate that binds astroglial mGluR5, triggering IP_3R2-dependent Ca^{2+} flux and ultimately ATP/adenosine release that inhibits further synaptic glutamate release via action on presynaptic A_1 receptors. This signaling cascade has been shown to act selectively on D_1 receptor-expressing neurons of the direct pathway (D_1 receptors not shown). Instead, on D_2 receptor-expressing neurons of the indirect pathway, postsynaptic G_i-coupled D_2 receptors interact with G_s-coupled A_{2A} adenosine receptors such that ATP/adenosine binding consequent to astroglia ATP/adenosine release overrides dopaminergic action on D_2 receptors to inhibit D_2-receptor mediated locomotor activation.

dopamine D_1 receptors [114]. This increase in astroglial Ca^{2+} depresses excitatory transmission by promoting gliotransmission of ATP/adenosine at presynaptic A_1 receptors, a mechanism that contributes to amphetamine-induced hyperlocomotion [114]. While some evidence supports expression of dopamine transporters in astrocytes [115], the monoamine transporter most densely expressed by astroglia is the norepinephrine transporter, which has high affinity for both dopamine and epinephrine [116, 117]. It has been shown that astrocytes insulate glutamatergic terminals at a much closer range compared with dopaminergic terminals [118], consistent with their dense expression of GLT-1 [27], when compared with monoamine transporters. Finally, astrocytes are capable of monoamine catabolism, through their expression of monoamine oxidase B, the main enzyme for norepinephrine, dopamine and serotonin catabolism [119, 120].

ASTROCYTE INVOLVEMENT IN PSYCHIATRIC DISORDERS

Given the prominent role of astroglial glutamate and GABA transporters in regulating synaptic and extrasynaptic levels of synaptically released glutamate and GABA, as well as evidence of both glutamate and GABA gliotransmission, examining postmortem brain tissue for astroglial protein biomarkers and morphology reveals the likelihood that astroglial adaptations are consequential regulators of many psychiatric disorders. This has resulted in using rodent models of psychiatric disorders to reveal parallel adaptations and a deeper analysis of potential molecular and morphological adaptations in astroglial regulation of tripartite synaptic transmission. Our understanding of astroglial involvement in synaptic transmission and psychiatry is incomplete, especially regarding regulation of GABAergic transmission and neuromodulators. We next discuss what is known regarding how astroglia may contribute to the etiology and expression of symptoms in various psychiatric disorders.

Major depressive disorder

Mounting evidence suggests that the pathophysiology of major depressive disorder (MDD) involves substantial adaptations in astroglial function [121]. In post-mortem analyses of human tissue, reduced expression of key players in the astroglial systems that regulate excitatory neuronal transmission is often observed [122]. For example, there are alterations in astroglial signaling systems involved in the glutamate-glutamine cycle evident in cortical structures of MDD patients including reduced GLT-1, GLAST and glutamine synthetase levels [123–126]. A large amount of evidence indicates that MDD patients exhibit profound loss of cortical astroglia indicated via reduced cell counts and astroglial cell density [123, 127–136], with substantial decreases in expression of glial fibrillary acidic protein (GFAP), a cytoskeletal protein selectively synthesized in a population of astroglia, in prefrontal cortex (PFC) samples from MDD patients [122, 137]. Morphologically, gray matter cortical astrocytes in MDD patients exhibit enlarged glial cell nuclei [129] with larger cell bodies as well as longer, more ramified processes observed in white matter astrocytes [138]. Apart from gross morphological adaptations, MDD astrocytes also exhibit decreased coverage of blood vessels in gray matter [139, 140].

When considering loss of astroglia, a likely consequence is dysregulation of the homeostatic functions these cells normally perform [141] and the extracellular buildup of synaptically released glutamate. Consistent with this, pharmacological blockade of GLT-1 in the PFC elevates extracellular glutamate concentrations and produces depressive-like behaviors in rodents including anhedonia, increased latency to drink sucrose, increased intracranial self-stimulation and decreased social interaction [142, 143]. Several rodent models of depression also exhibit reductions in cortical GLT-1 and GLAST mRNA and protein content, including models that utilize chronic dexamethasone administration [144] or chronic learned helplessness paradigms

[145]. Another function of astroglia potentially impacted by MDD is the metabolic support that astrocytes provide for neurons in the form of astrocyte-neuron lactate shuttling [146, 147], a signaling cascade directly linked to synaptic plasticity and memory formation [148–151]. Indeed, peripheral administration of lactate evokes antidepressant-like effects likely through lactate's ability to increase excitability of nearby neurons [152], and levels of cortical lactate correlate with coping behavior in rodents, with astrocyte-derived lactate directly enhancing the excitability of layer V pyramidal neurons [153]. Recently, it was demonstrated that chemogenetic activation of cortical astroglia releases ATP from astrocytes, which in rodent models of depression induces antidepressant-like effects mediated by purine receptors [154].

The connection between astroglia and the pathophysiology of MDD is further supported by rodent studies where selective ablation of cortical astrocytes with the gliotoxin L-α-aminoadipic acid (L-AA) is sufficient to trigger a depressive-like phenotype [155, 156]. In concert with loss of cortical astroglia, cortical administration of L-AA impairs cognitive function and promotes dendritic atrophy [157]. Generally, several studies support the hypothesis that reductions in astroglial density in the cortex contributes to the development of MDD. For example, akin to human MDD [158], rodent models of depression and anxiety exhibit decreased PFC astroglial counts, reduced GFAP levels [159, 160] and decreased blood vessel coverage with concomitant reductions in astroglial complexity [133, 161]. Interestingly, administration of fluoxetine reverses maladaptive decreases in astroglial complexity, suggesting that MDD- and anxiety-induced structural adaptations in cortical astrocytes could be therapeutic targets of antidepressant drugs. Consistent with this hypothesis, several studies have explored astroglia as mediators of the effects of antidepressant therapies [162–165]. As an example, selective serotonin reuptake inhibitors (SSRIs) engage cortical astroglia in rodents as evidenced by their enhanced intracellular Ca^{2+} levels [166]. Also, SSRIs directly stimulate astroglial 5-HT_{2B} receptors [167] and chronic SSRI treatment upregulates 5-HT_{2B} in astrocytes, but not neurons [168]. Furthermore, SSRIs stimulate glucose metabolism in astrocytes [162], a process that is necessary for memory improvements associated with antidepressant treatment [169, 170]. SSRIs also stimulate astroglial release of ATP/adenosine, with therapeutic consequences on brain-derived neurotrophic factor expression [171].

Astrocytes have also been implicated in the anti-depressant mechanisms of action of various other traditional and non-traditional antidepressant therapies, including tricyclic antidepressants [172], transcranial direct current stimulation [173], lithium [174], ketamine [175–177], and electroconvulsive therapy [171, 178, 179]. Much like SSRIs, electroconvulsive therapy stimulates ATP/adenosine release from astroglia [171] and downregulation of astrocyte-derived ATP/adenosine induces depressive-like symptoms in rodents [154], a pathology reversed by SSRIs [180]. Thus, impairments in astrocyte ATP/adenosine release have been cited as a causative factor in MDD and the hypothesis that astrocyte ATP/adenosine signaling plays an important role in antidepressant action is gaining traction [171, 181].

Both depression and anxiety have been associated with alterations in glutamate receptor expression and/or function [182–184]. Recently, the NMDA receptor antagonist ketamine has garnered attention for its ability to rapidly induce potent antidepressant effects [185–187]. In a rat model of MDD, ketamine treatment increases astrocyte size in the hippocampus and increases the number and length of astroglial processes, supporting the idea that astroglial atrophy, at least in the hippocampus, is associated with MDD [188]. Interestingly, ketamine dose-dependently engages glutamatergic communication between astrocytes and neurons [189]. Further, overexpression of serine racemase and subsequent elevation of D-serine reduces anxiety-like phenotypes in rodents, with dietary D-serine supplementation also mimicking these effects [48]. Taken together, mounting evidence indicates that astroglial regulation of NMDA receptor activation is a reliable means to produce antidepressant-like effects [190], providing an attractive target for therapeutic intervention in MDD.

Finally, stress exposure, which is known to contribute to depression in both animal models and humans [191, 192], leads to enduring astrocyte morphological changes [193, 194]. For example, acute or chronic stress in adult rats results in astrocyte process atrophy and reductions in astrocyte volume, as well as decreased GFAP-positive astrocyte number in the prefrontal cortex [193, 194]. For more in-depth discussion on the potential role of astroglia in mood disorders and in the mechanistic action of antidepressant drugs see refs. [125, 195–201].

Bipolar disorder

Direct evidence for cortical glutamatergic dysfunction in bipolar disorder (BD) is somewhat varied, which may reflect clinical heterogeneity in BD and the impacts of mood-stabilizing medication use common in BD patients [127]. Investigations of astrocyte density and expression of GFAP in cortical tissue from BD patients yield largely heterogenous results [127, 202–207]. However, thinning of cortical gray and white matter [208, 209], and decreased astroglial numbers are observed in BD cortical tissue, with enhanced activity of the glutamatergic system observed in BD patient magnetic resonance imaging studies [210, 211]. Further, clear adaptations in astroglial gene expression networks is evident in tissue isolated from BD patients [212, 213]. Generally, glutamate transporter GLAST and GLT-1 mRNA levels are not impacted in BD patients [127]. However, astrocyte atrophy has been observed in the prefrontal and anterior cingulate cortices, leading to suspicions that homeostatic function of cortical astroglia may be impaired in BD and that abnormal glutamatergic neurotransmission and neuron-glial coupling may be present [210, 214]. Further, evidence for elevation of cortical glutamate levels and enhanced excitatory transmission has been observed in BD patients [210, 211] and genetic variants in the GLT-1 gene are associated with increased susceptibility to BD and schizophrenia [215, 216]. Finally, astrocytes derived from BD patients exhibit altered gene expression profiles and conditioned media from these cells negatively impacts neuronal excitability in culture models [217]. Together, these data also support a role for cortical astroglia in the pathophysiology of BD progression [218].

Several therapeutics for BD have direct impacts on astroglial homeostatic regulation of glutamate [219]. As an example, valproic acid treatment increases promoter activity of GLAST and GLT-1, prevents manganese-induced downregulation of GLAST and GLT-1 and improves glutamate clearance [220]. Similarly, riluzole increases GLT-1 activity [221], and promotes cortical glutamate-glutamine cycling likely enhancing neuronal plasticity as a means to reduce BD symptoms [222]. Lithium affects expression of astroglial genes and modifies astroglial signaling [223], and rodent studies using cultured astroglia reveal a network of lithium-responsive astroglial genes [174]. Acutely, lithium inhibits glutamate clearance, yet when administered chronically it enhances glutamate uptake in samples derived from the murine cortex [224] and lithium protects cultured neurons from glutamate excitotoxicity [225]. Together, these data indicate that manipulating astroglia function may be a common cellular consequence of existing BD therapeutics.

While the effects of lithium on glutamate transport are discussed above, lithium also acts to inhibit astroglial glycogen synthase kinase-3β, a serine/threonine kinase involved in many cellular functions [226]. Additionally, lithium treatment or genetic deletion of glycogen synthase kinase-3β increases astroglial density, pointing to the therapeutic efficacy of lithium potentially being derived in part from its ability to reverse cortical thinning and loss of astroglia [174, 227]. Lithium also targets the extracellular matrix-modifying enzyme lysyl oxidase, as well as

peroxisome proliferator-activated receptor gamma, both of which have been linked to astrocyte proliferation and adaptations in astroglial morphology [174]. These findings support a wide body of evidence indicating that lithium directly targets astrocytes, and that lithium can reverse cortical thinning and altered astroglial morphometrics observed in BD patients.

Schizophrenia

Akin to BD, evidence for alterations in mRNA and protein levels of GLT-1 and GLAST in cortical postmortem tissue from patients with schizophrenia (SCZ) is varied depending on the cortical region investigated [127]. While GLT-1 mRNA and protein levels are increased in prefrontal cortex in SCZ patients [228, 229], reductions in GLT-1 expression have also been observed [230], with others reporting no change [231]. Despite these somewhat disparate findings, reductions in posttranslational modification of GLAST and GLT-1 required for appropriate localization of these proteins to the astroglial plasma membrane are observed in SCZ patient samples [232]. Further, knock out of GLAST expression in mice produces a variety of behavioral changes considered rodent analogues of symptoms in SCZ [233], providing additional support for the hypothesis that aberrant glutamate homeostasis could be present in SCZ astrocytes. Additionally, a mutation in Disrupted-In-Schizophrenia 1 (DISC1) is a genetic risk factor implicated in major mental disorders that disrupts neurodevelopment and synaptic signaling [234, 235], and astroglial expression of the mutated variant of DISC1 reduces excitatory synapse formation in cultured neurons, an effect that is rescued by D-serine administration [235].

The adaptations in GFAP levels observed in samples derived from SCZ patients are also somewhat varied depending on the cortical subregions investigated, with evidence existing for increases [236, 237], decreases [238–240] and no change in GFAP levels [240] (see ref. [127] for in depth review). Interestingly, astrocyte distribution is altered in PFC white matter of SCZ patients with enhanced clustering of astrocytes observed, supporting the hypothesis that heterogeneity in the fidelity of homeostatic or metabolic support by astroglia may contribute to SCZ progression [207]. Consistent with this observation and similar to what has been shown in MDD, the labeling of astrocytes adjacent to blood vessels [241] is decreased in the prefrontal cortex of SCZ postmortem tissue. Direct analyses of altered function in SCZ astroglia has also been obtained in elegant chimera studies where glial progenitor cells derived from schizophrenic patients were implanted in mice. In these studies, SCZ-derived cells exhibit delayed astrocytic differentiation and altered astrocyte morphology, with astrocytes derived from SCZ patients exhibiting fewer processes and less branching [242]. These data also point to shifts in the structure-function relationship of astroglia in the pathophysiology of SCZ. Consistent with this hypothesis, astrocytes derived from SCZ patients also exhibit reduced expression of neuroligin, a cell adhesion protein that controls the balance of excitatory and inhibitory synaptic connections and regulates astrocyte morphology [243, 244].

Alcohol use disorder

Changes in astrocyte morphology in patients with alcohol use disorder (AUD) have long been known [245]. Many of these changes involve GFAP upregulation and morphological changes indicative of reactive astrogliosis occurring in cortical and subcortical brain structures [246–248]. Likewise, in animal models chronic ethanol exposure induces reactive astrogliosis, characterized by increased astrocyte density, hypertrophy and/or increased expression of astrocyte filament proteins including vimentin and GFAP [249–251]. As an example, increased astrocyte density is observed in the prelimbic cortex of alcohol-withdrawn rats, and astrocyte density correlates positively with alcohol consumed prior to withdrawal [250].

In some studies, reduced astrocyte density is observed. These differences may have to do with disease stage as well as brain region studied. For example, reduced astrocyte number has been noted in the hippocampus of abstinent patients who were formerly chronic alcohol users [252] and in the orbitofrontal cortex of alcohol-dependent patients [253]. In either case, dysregulated astrocyte function, from astrocyte atrophy or reactive astrogliosis, is likely to disrupt synaptic activity. Adaptations are also observed in synaptic adjacency of astroglia in the central amygdala, a region linked to alcohol dependence in rodent models (Chandler lab unpublished observation). Ethanol also directly impacts cortical glutamate homeostasis [254]. In cortical culture systems, ethanol treatment enhances glutamate clearance, with upregulation of both GLAST and GLT-1 observed [255–258]. In rodents, prolonged ethanol exposure followed by a period of abstinence increases the number of GFAP and glutamine synthetase immunoreactive astroglia in the prelimbic PFC, an effect that correlates with the extent of ethanol consumption [250], suggesting that ethanol increases glutamate processing and could engage a positive feedback loop linked to excessive ethanol consumption. Comparatively few studies have examined GFAP levels, astroglial density or morphological adaptations in cortical astroglia in human patients with substance use disorder (SUD) or in rodent models of drug taking and drug seeking. However, reduced GFAP staining and reduced numbers of astrocytes are observed in the prefrontal cortex in AUD patients [253, 259] and packing density of astrocytes labeled for expression of gap junction proteins is also reduced in alcohol-dependent subjects [260]. Similarly, reduced astrocyte numbers are observed in rodents exposed to ethanol following a period of abstinence [261]. Moreover, cortical astrocyte gene expression profiles are robustly impacted by ethanol exposure in rodents [262], indicating that akin to MDD, BD and SCZ cortical astroglia are likely involved in the neural systems underlying the progression of AUD. Consistent with a role for astroglial glutamate homeostasis in ethanol-related behaviors, GLAST knock out mice do not show conditioned place preference for ethanol and exhibit reduced voluntary ethanol intake [263] and intracerebral ventricular infusion of a GLT-1 antagonist attenuates binge drinking in mice [264]. In recent studies, chemogenetic activation of cortical astroglia has been shown to potentiate ethanol consumption in ethanol-naïve animals, enhancing both ethanol-induced acute hyperlocomotion and subsequent sedation, with inhibition of cortical astroglial function via disruption of intracellular Ca^{2+} signaling producing the opposite effect [265].

Astroglial regulation of inhibitory GABAergic transmission is also altered by ethanol. In rats undergoing 10-hours of alcohol withdrawal after weeks of chronic exposure, astrocytes in the central amygdala increase their synaptic adjacency as well as their expression of GAT-3 [266]. Furthermore, rats with low GAT-3 expression in the central amygdala exhibit compulsive drinking behavior and alcohol dependent individuals show similar GAT-3 reductions [267, 268]. Since GABA spillover in the central amygdala is causally linked with escalation of alcohol intake, as well as withdrawal symptoms in dependent animals [269], these findings support the hypothesis that GAT-3 upregulation and increased synaptic adjacency by astrocytes in the central amygdala are compensatory adaptations that may serve to counteract extrasynaptic GABA spillover and withdrawal symptoms.

Substance use disorder

Although outside of AUD there is little clinical data regarding astroglial involvement in SUDs, a large body of work from rodent models of SUDS has emerged showing that cocaine or heroin self-administration produces both enduring and transient adaptations in astroglial morphology and membrane transporter expression.

Extinction training after cocaine or heroin self-administration downregulates GLT-1 expression in accumbens astroglia [270–274], yet in the prelimbic PFC just a splice variant of GLT-1, GLT-1B, is downregulated, which requires both long access cocaine self-administration and an extended period of withdrawal [271]. Alternatively, rodent studies utilizing non-contingent methamphetamine demonstrate GLT-1 upregulation in the striatum [275, 276], while methamphetamine self-administration and extinction do not alter GLT-1 in the accumbens [277]. No changes in GLT-1 expression in the PFC following amphetamine exposure have been identified [278]. Notably methamphetamine exposure increases astroglial glutamate release thought to be involved in microglial activation and neuroinflammation associated with methamphetamine use [279]. It is perhaps surprising that cocaine and methamphetamine self-administration and extinction training do not induce similar adaptations in GLT-1 expression in the accumbens, given their similar effects on monoamine transport [280]. Instead, heroin and nicotine both result in downregulation of GLT-1 in the accumbens when self-administered, much like cocaine [281, 282], and treatment of primary cortical astrocyte cultures with morphine downregulates expression of GLT-1 [283], with similar results observed in the cortex of rodents following morphine treatment [284]. In addition to adaptations in GLT-1, cocaine, methamphetamine, and heroin self-administration induce morphological changes in astroglia in the nucleus accumbens that consist of a reduction in the proximity of astroglial processes to synapses [274, 277, 285, 286]. Further, chemogenetic activation of nucleus accumbens astrocytes inhibits cue-induced cocaine [287] and methamphetamine seeking [277], an effect likely mediated by gliotransmitter release and/or morphological reorganization of astroglia [287, 288]. Additionally, chemogenetic activation of nucleus accumbens astrocytes also reduces motivation for ethanol in a behavioral economics paradigm [289]. Remarkably, reinstated drug seeking induced by drug-conditioned cues transiently increases astroglial proximity to accumbens synapses [274], an effect that is most pronounced surrounding large dendritic spines [290]. Astrocyte fine process elongation during cued reinstatement coincides with degradation of the extracellular matrix [291], a process that is necessary for expansion of dendritic spines during drug seeking [292]. See Brown and Sorg in this issue of NPP for further detail on the extracellular matrix, perineuronal nets and SUDS. Moreover, the reinsertion of astroglial processes towards accumbens synapses dampens cued reinstatement of heroin seeking, as preventing this reinsertion by knocking down the actin binding protein ezrin increases cued heroin seeking [293]. Finally, this dynamic of astroglial withdrawal from accumbens synapses after heroin use and transient restoration by heroin cues occurs selectively around D_2-medium spiny neuron (MSN) dendrites, while the pattern surrounding D_1-MSNs is the opposite [294].

In animal models, relapse behavior is linked to activity of excitatory corticostriatal terminals [295], which are regulated by astroglial uptake of both glutamate and GABA in the basal ganglia [296–298]. As discussed above, astrocytes undergo remodeling in subtler ways than was previously appreciated [62, 294], and microscopic alterations in perisynaptic astroglial processes are linked with synaptic adaptations in disorders of motivation including drug relapse [50]. Astrocytes in the ventral pallidum, a brain structure receiving GABAergic projections from the nucleus accumbens that orchestrates both reward seeking [299, 300] and hedonic liking [301], undergo synapse-selective morphological plasticity after extinction training that abolishes heroin-seeking behavior [62]. The increased adjacency of astrocytes with synapses in the dorsolateral ventral pallidum following extinction training is selective for D_1-MSN afferents from the nucleus accumbens core. Notably, astrocytes in the ventral pallidum also increase their expression of GAT-3 during extinction training, and both the increased adjacency with D_1-MSN terminals and the increase in GAT-3 expression are necessary for extinction of heroin-seeking behavior, given that knockdown of either phenotype stimulates reward-seeking in the extinguished context [62]. Remarkably, manipulating either synaptic adjacency of pallidal astrocytes or GAT-3 expression does not affect natural reward seeking [62]. The signaling events that drive transient astrocyte morphological adaptations to limit drug-seeking have not been characterized, but are known to involve phosphorylation of ezrin, an astroglial-selective actin-binding protein that permits astrocyte fine process elongation [302, 303].

It is intriguing that astrocytes exhibit the same pattern of synaptic insulation after heroin withdrawal at both excitatory terminals that synapse onto D_1-MSN dendrites in the nucleus accumbens core, and at GABAergic D_1-MSN terminals in the ventral pallidum [62, 294, 303]. Likewise, astrocytes retract from D_1-MSN-containing synapses during cued reinstatement of heroin seeking in both brain regions, upon glutamate or GABA release, in the accumbens or pallidum, respectively. This observation raises the possibility that astroglia are tuned via receptor and/or transporter expression to nearby synapses, such that synaptic activity triggers similar morphological adaptations. For example, Na^+ currents triggered by glutamate uptake in the accumbens, or GABA uptake in the ventral pallidum, could elicit similar forms of morphological plasticity upon synaptic transmitter release and subsequent neurotransmitter transport at either site. Alternatively, astrocytes may be tuned to signal uniquely with specific neural subtypes (as in ref. [304]), rather than simply in response to excitatory or inhibitory synaptic activity. For example, astrocytes in the dorsal striatum engage in ATP/adenosine signaling selectively with D_1-MSNs, but not D_2-MSNs [101], suggesting neural release of certain molecules may recruit different patterns of gliotransmission, as well as degrees of synaptic insulation by astroglial processes (as in ref. [294]).

Finally, thrombospondin (TSP) is secreted by astroglia, and when activated in the extracellular matrix binds to the α2δ-1 auxiliary subunit on presynaptic Ca^{2+} channels and promotes synaptogenesis during brain development [305]. TSP secretion and activation is also produced following cocaine-induced increases in astroglial Ca^{2+} [306]. This process mediates the induction of silent synapses in the nucleus accumbens by cocaine and since the astroglial Ca^{2+} increases often occur simultaneously in multiple adjacent astroglia [307] this may contribute to ensemble formation encoding learning associated with cocaine use [308]. Stimulation of the α2δ-1 subunit by thrombospondin may be consequential in cocaine relapse since blockade of this receptor reduces cocaine prime-induced cocaine seeking [309].

Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is thought to arise from an imbalance of excitatory and inhibitory neurotransmission in the brain [310, 311]. In keeping with this framework, animal models of OCD exhibit increased excitatory drive, or loss of inhibitory regulation [312]. Given their essential role in regulating both excitatory and inhibitory signaling, astrocytes have been the subject of several studies seeking to uncover relevant pathophysiology in OCD [311, 313]. Since astroglial GAT-3 expression reduces tonic inhibition of postsynaptic cells, abnormal GAT-3 expression can tip the excitatory:inhibitory balance. For example, disrupting functionally critical Ca^{2+} dynamics in astroglia in the dorsolateral striatum leads to maladaptive GAT-3 upregulation along with a number of alterations in striatal MSN physiology, and triggers excessive self-grooming behavior [314], an obsessive-compulsive-like trait in mice [314, 315]. While neural activity is generally disrupted by Ca^{2+} extrusion from astroglia, and MSNs exhibit hyperpolarized resting membrane potentials, higher rheobase, and right-shifted input-output curves overall, reduced tonic inhibition is noted selectively on D_1-MSNs [314]. Moreover, excessive grooming in these animals is partially reversed by GAT-3 blockade, indicating its direct contribution to OCD-like behavior.

FUTURE DIRECTIONS

Over the last decade the field of neuroscience has begun turning toward a realization that we need a deeper understanding of the role played by astroglia to understand how neuronal synapses are tuned by astrocytes which in-turn regulate brain circuits and behavior. This is true not only for homeostatic functions performed by astroglia to constitutively maintain aspects of synaptic metabolism and boundaries of synaptic transmitter release, spillover and postsynaptic signaling, but also for understanding the dynamic changes in synaptic plasticity that are induced by important environmental stimuli to initiate adaptive learning and behavior, as well as pathological behaviors characteristic of psychiatric disorders. These advances require not only improved technologies for measuring and observing astroglia and tripartite synaptic function, but also require us to ask questions about brain and synaptic function from an astroglial perspective. Below, we approach future directions from this point of view by asking four fundamental questions from an astroglial perspective, then describing existing and future technologies that might be useful in answering these questions.

What is the functional relevance of astrocyte heterogeneity? Recent analyses of astrocyte morphology, protein expression, and function within and across brain regions have highlighted considerable functional heterogeneity in astroglia [316–319], as well as the existence of unique forms of astroglial plasticity in subpopulations of brain astrocytes [294, 304, 320]. For example, relapse to heroin use induces morphological plasticity in a subpopulation of astrocytes that insert peripheral processes toward synapses. Another subpopulation of accumbens astrocytes remain retracted from synapses during heroin relapse but increase their extrasynaptic expression of GLT-1. Though non-overlapping, both adaptations are transient and serve to reduce drug-seeking behavior in rodents [294]. These findings paired with the fact that expression of certain classic astrocyte markers only occurs in subpopulations of brain astrocytes [321] point to astrocytes as a heterogeneous cell type in morphology, protein expression, and function. Like in neurons, identifying reliable markers of unique astroglial types is an important goal that will permit functional characterization of different astrocyte subpopulations. High throughput quantification of morphology and protein expression across large numbers of astrocytes in critical brain regions, paired with appropriate statistical methods for identifying unique populations, and plasticity in these populations in various disease states is an existing strategy that has yet to be conducted on a large scale.

How do astroglia switch from constitutive homeostatic regulation of synapses to dynamic regulators of synaptic transmission and behavior induced by salient environmental stimuli? Resolving this primary issue requires a shift toward in vivo technologies. In vitro and ex vivo technologies have provided us with the knowledge that synaptic activity and plasticity are strongly regulated by the proximity of astroglia and the expression of various proteins that can control transmitter spillover to extrasynaptic receptors (both neuronal and astroglial). Culture systems and brain slice experimentation have allowed for breakthroughs in understanding how astroglial Ca^{2+} dynamically regulates astroglial plasticity which in turn influences neuronal synapses. However, in vitro and ex vivo preparations do not perfectly mimic in vivo homeostatic environments. For example, much of the subtle compartmentalization of extracellular neuromodulators is disrupted in tissue slices and may not exist in culture. More importantly, the physiological or pathological processes by which environmental stimuli lead to learning and behavior requires in vivo models. A key advance that is needed is improved sensitivity of Ca^{2+} sensors in astroglia [322–329]. For example, while it is now possible to image Ca^{2+} fluxes in peripheral perisynaptic astroglial processes in fixed-head 2-photon imaging of cortex, deep brain structures require implantation of a lens that causes a loss of both resolution and fluorescence intensity. Given the advances currently being made in genetic indicators for Ca^{2+}, studies utilizing visualization and analyses of adaptations in astroglial activity patterns during behaviors indicative of psychiatric symptoms, such as cue-induced stress or drug seeking, will provide much needed insight into the role that astroglia play in these processes.

How do we test for astroglial necessity or sufficiency in mediating behavioral pathologies? Viral strategies for influencing neuronal activity are starting to be adapted for brain region-specific stimulation of astrocytes [314, 330–333], but much work remains in developing astroglial specific promoters and transgenes for selective regulation of astroglia proteins [306, 334–336] and for astroglial expression of genetic indicators of specific neurotransmitters including dopamine, GABA and glutamate [337, 338]. As described above for astroglial Ca^{2+} sensors, visualizing these sensors in vivo in deep brain structures remains a hurdle, and as astroglial subtypes are genetically and functionally defined, new reagents selective for individual subtypes will need to be developed, including viral transgene expression and transgenic experimental animals.

Do astroglia coordinate circuit activity? Sufficient data are now being accumulated regarding how astroglia are adapting in two interconnected brain nuclei relative to specific neuronal subtypes. As discussed above, recent studies show that drug cues produce enhanced astroglia-synapse interaction with specific regulation around D_1- and D_2-MSN dendrites in the nucleus accumbens in parallel with adaptations selectively around D_1- and D_2-MSN synapses in the ventral pallidum. The cell-type subcircuit specificity raises the possibility that these adaptations may be coordinated to modulate cued drug seeking. Simultaneous in vivo imaging of astroglial Ca^{2+} transients in the behaving animal paired with recordings of neuronal activity in the same brain region, would be an ideal approach, yet this will undoubtedly be technically challenging (see above). However, methods for genetically tagging neurons activated during behavioral tasks [339], called targeted recombination in active populations or TRAP [340], could be adapted to use in astroglia to provide insight on how signaling activity within astroglia in interconnected nuclei may be shaping circuit activity. While work remains to be done to identify relevant immediate early gene promoter activity in astroglia that is induced by receptor stimulation or ionic flux, studies illustrate the possibility [341, 342]. On one hand, behaviorally stimulated ensembles of astroglia could be filled with a membrane targeted reporter and synaptic proximity to specific neuronal subtypes could be determined. On the other hand, astrocytic TRAP can be combined with chemogenetic or optogenetic tools to manipulate astroglial activity in subsets of cells engaged by various stimuli. Additionally, once astrocytic TRAP vectors become widely utilized, when combined with vectors that allow for Cre-dependent manipulation of gene expression in astroglia, (a relatively minor extension of the existing astroglia shRNA vector technology [306]), it will be possible to target subsets of astrocytes active during a particular task or behavior and discreetly manipulate expression of neurotransmitter receptor and release systems in these cells. This approach will help investigators code how astroglial ensembles are being regulated by neuro- and gliotransmission. With these approaches, astrocytes and tripartite physiology can be amalgamated into the developing ensemble-based hypotheses of how activity within small sets of neurons dictate complicated behaviors [343, 344].

A final exciting approach toward understanding how astroglia and tripartite synapses may regulate brain circuits is framed by reports detailing axo-astrocytic transfer of viral vectors encoding recombinases from neurons to astroglia, which when combined with various intersectional viral vector approaches, allows for the specific transduction of astrocytes that contact synapses with anatomically specific presynaptic inputs. These strategies allow for

the discreet microcircuit level manipulation and analyses of astrocyte roles in regulating activity of circuits such as those outlined in Box 2 [345].

In summary, the field of neuroscience appears to be on the verge of having a toolkit to more directly observe how astroglia regulate neuronal synapses in real time. This combined with deeper understanding of how astroglial subtypes shape neural activity will permit incorporating astroglial functions and plasticity into existing circuit schema that are thought to underpin psychiatric disorders. Accompanying this expansion in basic knowledge, drug discovery efforts aimed at reversing astroglial pathologies identified in postmortem human brain and the more subtle pathologies currently being identified in animal models hold great promise in developing novel therapeutic approaches for treating psychiatric disorders.

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ADDITIONAL INFORMATION

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