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Astroglial correlates of neuropsychiatric disease: from Astrocytopathy to Astrogliosis

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Abstract

Complex roles for astrocytes in health and disease continue to emerge, highlighting this class of cells as integral to function and dysfunction of the nervous system. In particular, escalating evidence strongly implicates a range of changes in astrocyte structure and function associated with neuropsychiatric diseases including major depressive disorder, schizophrenia, and addiction. These changes can range from astrocytopathy, degeneration, and loss of function, to astrogliosis and hypertrophy, and can be either adaptive or maladaptive. Evidence from the literature indicates a myriad of changes observed in astrocytes from both human postmortem studies as well as preclinical animal models, including changes in expression of glial fibrillary protein, as well as changes in astrocyte morphology and astrocyte-mediated regulation of synaptic function. In this review, we seek to provide a comprehensive assessment of these findings and consequently evidence for common themes regarding adaptations in astrocytes associated with neuropsychiatric disease. While results are mixed across conditions and models, general findings indicate decreased astrocyte cellular features and gene expression in depression, chronic stress and anxiety, but increased inflammation in schizophrenia. Changes also vary widely in response to different drugs of abuse, with evidence reflective of features of astrocytopathy to astrogliosis, varying across drug classes, route of administration and length of withdrawal.

Keywords

astrocyte; GFAP; depression; schizophrenia; addiction

I. Introduction

A neurocentric view of the brain has long dominated neuroscience research and the search for pharmacological treatments for neuropsychiatric disorders [1, 2]. In this approach, glial and vascular cells have been largely ignored, with focus on neuronal and synaptic function. However, current research on neuropsychiatric disorders is challenging neurocentrism, as glia have been found to play vital roles in a wide range of neuropsychiatric disorders

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including schizophrenia, major depressive disorder, and addiction, in both preclinical animal models, as well as in human studies [3–7].

The need for investigation of glial cells in neuropsychiatric disorders, and as candidates for therapeutic development, is highlighted by the limitations of current pharmacotherapies that are predominantly designed to counteract neuronal signaling deficits. For example, existing first line pharmacotherapeutic treatments for depression, primarily designed to functionally elevate monoamine signaling, offer modest success rates with a variety of side effects such as difficulty sleeping, lack of energy, anxiety, anhedonia, impaired cognition and pain [8–11]. Further, those that do see mood improvement with these anti-depressants must wait 3–6 weeks before the drugs can take effect. Similarly, treatment for schizophrenia has focused on the development of dopamine and serotonin receptor antagonists, including typical and atypical antipsychotics, which are associated with adverse side effects such as extrapyramidal effects, gastrointestinal effects, dizziness, sexual dysfunction, somnolence, headache and nausea [12, 13]. Moreover, roughly one-fifth of first episode schizophrenic patients are non-responders to antipsychotic treatment [14, 15], and they tend to remain unresponsive [16–18].

There is an even greater lack of effective pharmacotherapies for prevention of relapse in substance use disorders. While FDA-approved treatments are available for opioid, alcohol and nicotine use disorders, there are no currently approved medications for psychostimulant or cannabis use disorders [19]. Therapies available for alcohol and opiate disorders largely target opiate receptors as partial agonists or antagonists to reduce the rewarding effects of these drugs, and as such these drugs have side effects akin to withdrawal symptoms such as nausea, dysphoria and fatigue [20, 21]. It is important to note that a majority of these treatments reduce drug intake and craving, however they do not effectively increase the long-term abstinence from drugs of abuse [21–23]. Additionally, there is a need for therapies that can help combat polydrug abuse, which make up just under half of all drug abusers [24]. Given the overall need for new approaches toward effective pharmacotherapeutic interventions for depression, schizophrenia, and substance use disorders, emerging evidence for the engagement of astrocytes and impaired astrocyte function as a contributing cellular mechanism can assist in this pursuit. Accordingly, the overall goal of this review will be to investigate the existing literature regarding specific changes in astrocytes associated with these conditions, in an effort to identify candidate mechanisms for pharmacotherapeutic development.

II. Astrocytes are critical mediators of neural function

Among the three primary types of glial cells (astrocytes, oligodendrocytes, and microglia), astrocytes are the most numerous, outnumbering neurons by a wide margin in several species [25–27]. Astrocytes are named for their star-like appearance and serve many important functions, from providing energy and metabolic support to neurons, to roles in synaptic development and signaling, glutamate uptake and release, regulation of blood flow, and neuroprotection (for review, see [27–30]). Astrocytes in healthy tissue have clearly defined non-overlapping microdomains creating a complex architecture to modulate synaptic neuronal firing with blood flow and to monitor neuronal activity [31–34]. Because of these

diverse and critical functions in both the healthy and dysfunctional central nervous system (CNS), it is paramount to appreciate how adaptations or dysfunction of astrocytes contribute to the etiology of neuropsychiatric disease.

Astrocytes are classified based on morphology and astrocyte-specific biomarkers such as glial-fibrillary acid protein (GFAP), the glutamate transporter GLT-1, Ca+ binding protein S100β, glutamine synthetase (GS), connexin, the aquaporin receptor (AQP4) [35–38], and aldehyde dehydrogenase 1 L1 (ALDH1L1) [39, 40]; for review [27] and [41]. In addition to these markers, ALDH1L1 positive cells have similar gene expression profiles as GLT-1 positive cells [40], and fluorescent proteins expressed under the ALDH1L1 promoter have been used to reliably identify astrocytes in transgenic mice [39, 40]. In addition to the astroglial markers mentioned above, transcriptome studies in isolated astrocytes have shown a distinct enrichment of genes [42–44]. Most notably, fluorescence-activated cell sorting and isolation have revealed astrocyte enrichment in metabolic pathways, including an enrichment of enzymes related to glycolysis and the tricarboxylic acid/Krebs cycle [43, 44], which was functionally verified using mass spectrometric analysis [43]. An enrichment of astrocytes has also been found in pathways related to amino acid synthesis/degradation (including glycine, serine, and cysteine), glutamate production/degradation and lipid synthesis [44], indicating roles for astrocytes in seminal cellular functions.

The most common way to identify astrocytes is GFAP expression; however, not all astrocytes express GFAP [41, 45] and GFAP expression levels vary among brain region [27, 46]. While GFAP is a reliable marker for reactive astrocytes, many astrocytes in the healthy CNS do not exhibit detectable levels of GFAP [27]. As such, elevated GFAP expression is one of the primary features associated with reactive astrocytes in the context of injury and inflammation [46–48]. However, despite a large literature on reactive astrocytes as reflective of nervous system injury or inflammation, it is complex to define a reactive astrocyte. The reactive astrogliosis response is a spectrum of changes, including both gain and loss of astrocytic function, that is dependent on the type and severity of the insult, and can result in either beneficial or detrimental effect on the surrounding neural tissue (for a review, see [46]). Mild to moderate astrogliosis may look no different than astrocytes in healthy CNS tissue. However, at the severe end of astrogliosis, reactive astrocytes invade individual domains, and proliferating astrocytes further disrupt the domain architecture, with the formation of a glial scar in response to dense glial compacting in the most severe cases (for a review see [27]).

The dynamic changes of astrocytes are not limited to astrogliosis, and atrophic astrocytes, where astrocytes are smaller and less arborized have also been described. Accordingly, Pekney and colleagues [49] have proposed two pathways of astrogliopathology: the commonly known reactive astrogliosis where astrocytes can either have neuroprotective or anisomorphic/severe scar forming effects, and a second pathway characterized as astrocytopathy, that includes the atrophy/degeneration, with loss of function and pathological remodeling of astrocytes. Atrophic astrocytes are smaller, do not ensheath the synapse as tightly, and have reduced expression of GFAP, AQP4 and GLT-1 [49]. The consequences of these morphological and biochemical changes include an inability to mediate glutamate homeostasis at the synapse, reduced tone of signaling molecules and

trophic factors due to volume distribution and reduced production, altered glucose metabolism and reduced network connectivity of astrocytes [49, 50]. Additionally, atrophic astrocytes have been shown to increase their production of kynurenic acid (NMDA and acetylcholine receptor antagonist), which in turn inhibits excitatory synaptic transmission, further antagonizing the system [51–53].

Astrogliosis has been a well-described hallmark of neuropsychiatric disorders, however there is increasing evidence that astrocytopathy is also characteristic of neuropsychiatric disorders such as frontotemporal dementia, stress, major depressive disorders, schizophrenia and substance use disorders [7, 54–58]; for a review see [59]. In this review, we will outline the evidence for astrogliopathology associated with neuropsychiatric disorders ranging from astrocytopathy to astrogliosis, as indicated by changes in GFAP expression and astrocyte morphology, as well as impairments in function including glutamate uptake and synaptic regulation by astrocyte-derived modulators of synaptic and neuronal function.

III. Depression, Stress and Anxiety

Glial fibrillary acidic protein (GFAP)

Reported changes in GFAP expression related to mood disorders including depression, stress and anxiety have been remarkably consistent (Table I). In postmortem brain tissue from patients diagnosed with major depressive disorder (MDD), a consistent decrease in GFAP expression has been found across diverse brain regions. For example, decreases in GFAP have been found using both immunohistochemistry and immunocytochemistry in parts of the frontal cortex, including prefrontal cortex (PFC) [60], dorsolateral prefrontal cortex (DLPFC [61]) and orbitofrontal cortex [62]. However, one study reported no differences in GFAP expression between patients with MDD and control subjects in the DLPFC [63]. In this case, the age of MDD patients was found to be a factor in the results from this study, with younger but not older MDD patients showing more pronounced decreases in GFAP expression vs. control subjects [63].

In addition to a decrease in GFAP expression in the frontal cortex, decreases in GFAP expression in subcortical brain regions have also been reported in patients diagnosed with MDD. For example, a decrease in GFAP expression has been found in the hippocampus [64], amygdala [65], thalamus [66], caudate [66] and cerebellum [67]. Likewise, gene expression of GFAP is decreased in the locus coeruleus [68], thalamus [66], and various white matter of brain regions [69], indicating the decrease in GFAP protein expression may be at the transcriptional level. The above-mentioned studies all indicate that a decrease in GFAP expression in corticolimbic brain regions may be a common neurobiological deficit associated with depression.

Animal models of mood disorders including depression, stress and anxiety, have consistently revealed decreases in GFAP (Table I). The Wistar-Kyoto rat, a commonly used rodent model of depression and anxiety, is behaviorally characterized by an increase in behaviors associated with depression including increased immobility during the forced swim test, and neurochemically by an increase in adrenocorticotropin hormone (ACTH) and corticosterone in response to stress [70]. Immunohistochemistry studies examining GFAP expression in

these rats showed a decrease in GFAP in a wide variety of brain regions including the PFC, basolateral amygdala and hippocampus [71]. However, no changes in GFAP were reported in the insular cortex and somatosensory cortex [71], perhaps indicating that a downregulation of GFAP in Wistar-Kyoto rats may be brain region specific. Other animal models of depression have shown similar decreases in GFAP expression. For example, an early life stressor induced by maternal deprivation in Fischer rats leads to decreased GFAP expression in adulthood in a variety of different brain regions including the dentate gyrus, hippocampus, basolateral amygdala, cingulate cortex and PFC [72].

A wealth of animal studies have used different stress paradigms to induce behaviors associated with both depression and anxiety. The chronic unpredictable stress (CUS) model, which consists of a variety of stressors including cage-tilting, cage-rotation, lights on/off for an extended period of time, food/water deprivation, strobe lights, isolation, crowding and exposure to different odors, results in depressive behaviors including anhedonia (decreased preference for sucrose) and learned helplessness (increased immobility in forced swim test) [73]. In rodents exposed to the CUS procedure, decreased GFAP expression has been found in the hippocampus [74], and decreased GFAP protein and mRNA have been found in the PFC [75] and hippocampus [76–78]. Furthermore, this decrease in GFAP expression has been consistently found in other animal models that have used stress to induce behaviors associated with depression or anxiety. Chronic restraint stress has been shown to decrease GFAP in the hippocampus and frontal cortex [79, 80], the rostral ventromedial medulla [81] and periaqueductal gray [82]. Moreover, chronic psychosocial stress has been reported to decrease GFAP expression in the hippocampus of male tree shrews [57]. Similarly, in rodent models of post-traumatic stress disorder (PTSD), which is characterized by heightened anxiety-like behavior, inducing PTSD in rodents using an inescapable foot shock protocol decreased GFAP expression in the hippocampus [83]. Similar results have been found in other rodent models of PTSD, including exposure to a single prolonged stressor, which also decreased GFAP in the hippocampus [84]. Another experiment examined GFAP levels and the correlation between GFAP and anxiety like behaviors in guinea pig pups born from mothers that were stressed during pregnancy [85]. During childhood, these pups showed an increase in anxiety behaviors when tested in an open field test, and showed decreased GFAP expression in the hippocampus [85]. Another experiment examined the effects of the neurotoxic agent aluminum citrate on both anxiety behaviors and GFAP expression [86]; Wistar rats administered aluminum citrate via an oral gavage showed increased anxiety like behavior when tested in an open field or elevated T-maze, and further showed a decrease in GFAP expression in the hippocampus [86]. In summary, the above-mentioned studies indicate that inducing depression or anxiety-like behaviors in animals using different models of stress can lead to a universal downregulation of GFAP in different brain regions. Furthermore, an increase in either depressive or anxiety like behaviors is associated with a decrease in GFAP expression, indicating that downregulation of GFAP may be a common neurobiological link across mood disorders.

It remains unclear precisely what role decreased GFAP, a cytoskeletal protein, may play in mood disorders. In fact, genetic deletion of GFAP in mice leads to a remarkably normal phenotype [87, 88]. However, the prominent decrease in expression of a canonical cellular marker may serve as a marker of atrophic cells with impaired functional capacities. The

contribution of decreased GFAP under conditions of astrocytopathy, similarly as increased GFAP under conditions of astrogliosis, are observed in concordance with numerous other changes, and accordingly it is a challenge to isolate specific roles of individual molecules. Current evidence supports a structural role for GFAP, and an indicator of general cellular responsiveness. For example, transplantation of astrocyte human progenitors into murine cortex leads to development of more complex human astrocytes in the murine brain, including more complex GFAP arborizations, and an increase in LTP and learning performance [89] suggesting that while a reduction in GFAP may indeed reflect a reduction in inflammation, it may also reflect reduced support for induction of synaptic and behavioral plasticity. Accordingly, future studies will be required to clarify this role more fully.

Changes in Astrocyte Morphology

In addition to a prominent decrease in GFAP expression associated with mood disorders, changes in the morphometric properties of astrocytes have also been reported (Table I). Initial reports indicated that the size of glial cells was increased in the DLPFC of MDD patients [90], but other studies have reported no change in the overall glial cell size, as well as no change in the size of glial cell nuclei in the frontal cortex [91, 92]. One experiment was able to reconstruct protoplasmic and fibrous astrocytes from the anterior cingulate cortex of patients with MDD to examine area of the cell body, as well as the number/length/diameter of branching points [93]. Using this method, the authors reported that fibrous astrocytes from MDD patients who committed suicide had larger cell bodies, as well as an increase in the number of branching points which were also longer in length [93]. In contrast to the downregulation of GFAP found in mood disorders, the results from this study suggest that astrogliosis, and hence an inflammatory response, may also be associated with depression.

Although the results from studies that have examined the morphology of astrocytes in human post-mortem tissue samples has been mixed, animal studies have consistently found a decrease in the morphometric properties of astrocytes associated with depression and chronic stress. For example, male tree shrews show a decrease in the somal volume of astrocytes in the hippocampus after psychosocial stress [57], a finding which has also been found in C57/BL6 mice after treatment with chronic corticosterone [94]. Using Sholl analysis of branching of fine astrocytic processes, a rat model of PTSD induced by inescapable shocks showed a decrease in the number of peripheral processes, as well as a decrease in the number of branching points of astrocytes in the hippocampus [83]. A similar result was found in astrocytes in the cortex of rats subject to chronic restraint stress [95]. After chronic restraint stress, a significant decrease in the number of astrocytic processes, as well as a decrease in the length and volume of fine processes was found [95]. In macaque monkeys that exhibit self-injurious behaviors, a behavioral characteristic often associated with increased anxiety, a decrease in both branching and arbor length of astrocytes was found in the frontal cortex [96]. Similar to the findings demonstrating a consistent and prominent decrease in GFAP expression associated with mood disorders, these preclinical studies examining the morphology of astrocytes and mood disorders indicate that a decrease in the number of peripheral astrocytic processes is also associated with mood disorders.

Changes in astrocyte function-glutamate uptake

Similar to the downregulation of GFAP associated with mood disorders, decreases in GLT-1 (human analog-excitatory amino acid transporter 2/EAAT2) expression is broadly found associated with depression and stress (Table I), providing further support for an astrocytopathy hypothesis for depression [50]. GLT-1 (EAAT2) is one member of the high affinity family of glutamate transporters, also including GLAST (EAAT1), EAAT3, EAAT4, EAAT5 and the vesicular transporters VGLUT1–3 [97]. GLT-1 is especially important in glutamatergic signaling as it is responsible for approximately 90% of glutamate uptake and thus plays an important role in maintaining glutamate homeostasis at neuronal synapses [98–100]. Similarly, to the downregulation of GFAP, studies examining changes in GLT-1 (EAAT2) in mood disorders have broadly found a decrease in GLT-1 expression. For example, immunohistochemistry studies examining EAAT2 protein expression in MDD patients have shown a decrease in EAAT2 expression in the orbitofrontal cortex [62]. Another study has shown that in addition to EAAT2, EAAT1 is also downregulated in DLPFC of MDD patients who committed suicide [101]. Interestingly, MDD patients who died of non-suicidal causes showed an increase in EAAT1 and EAAT2 expression in the DLPFC, indicating that the neurobiological mechanisms behind suicidal tendencies may also play a role in EAAT1 and EAAT2 expression. In addition to decreased protein expression of EAAT2, a decrease in EAAT2 gene expression has also been found in MDD patients, providing one mechanism for the decrease in EAAT2 protein expression. For example, decreased EAAT2 mRNA has been found in the locus coeruleus [102], hippocampus [103] and cortex [104].

Animal models of chronic stress which have been used as models for depression, have also found a decrease in GLT-1 expression. For example, multiple different models of chronic stress, including CUS [105, 106], restraint stress [82], social defeat [107] and post-natal stress [108] have all been shown to decrease GLT-1 expression in brain areas such as the hippocampus and PFC. However, two studies have shown an increase in GLT-1 expression in the hippocampus following unpredictable stress [109] and maternal separation [110]. One hypothesis suggests that the time course of GLT-1 downregulation may be dependent on when expression is examined [105]. Immediately following exposure to a stressor, GLT-1 expression may be temporarily increased, which is then followed by a prolonged decrease [105]. Future studies are needed examine this hypothesis.

Similar to the decrease in GLT-1 gene expression found in human MDD patients, GLT-1 mRNA levels have also been found to be decreased in animal models of stress and anxiety. For example, GLT-1 mRNA levels are decreased in the hippocampus following learned helplessness in rats [111]. Furthermore, the offspring of rats exposed to stress show decreased GLT-1 mRNA levels, indicating heritable epigenetic mechanisms may play a role in the stress induced downregulation of GLT-1 expression [112]. Further highlighting the role of GLT-1 in mood disorders, antidepressants can increase GLT-1 expression. For example, fluoxetine has been shown to reverse behavioral symptoms of depression, as well as increase GLT-1 protein expression in the hippocampus [105]. Riluzole, a neuroprotective agent approved to treat ALS, upregulates GLT-1 expression, and importantly, has been

shown to act as an antidepressant in both animal models [113] and patients diagnosed with MDD [114, 115].

In neuropsychiatric disorders and most notably depression, a strong correlation exists between the downregulation in GFAP expression and the decrease in GLT-1 (Table I, Table VI). The decrease in both GFAP and GLT-1 is observed in numerous different brain regions, and across both post-mortem human studies and animal models of depression. Most notably in the hippocampus, multiple different animal models of depression including chronic stress, restraint stress, pre-natal stress, and learned helplessness, all show decreases in both GFAP and GLT-1 (Table VI). Similarly, a decrease in GFAP and GLT-1 is observed in the hippocampus of patients with depression (Table VI). These results suggest that in brain regions such as the hippocampus, GFAP expression may correlate with GLT-1 expression. GLT-1 trafficking has been shown to be impaired in transgenic mice lacking GFAP, further suggesting a functional role for GFAP in regulating GLT-1 expression [116]. However, the relationship between GFAP and GLT-1 expression is not always straightforward or direct. For example, in disorders including schizophrenia (Table II, Table VI) and in cases of brain injury, astrogliosis and increased GFAP is often found together with decreased GLT-1 expression [117]. However, in a rat model of traumatic brain injury, ceftriaxone reverses both the decrease in GLT-1 and the increase in GFAP expression [117], further suggesting a mechanistic link between bidirectional GFAP and GLT-1 expression. Based on these findings, it can be hypothesized that a change in astrocyte morphology from basal levels (either atrophy or hypertrophy) can lead to subsequent decreases in GLT-1 expression. However, the causal relationship between GFAP and GLT-1 expression remains unclear and an important area for future research. Relatedly, the functional relationships between changes in GFAP, GLT-1, and neuronal function and synaptic plasticity must be more systematically assessed in order to effectively evaluate the consequences of experience- and drug-induced adaptations in astrocytes.

Modulation of synaptic function

Synaptic function can be significantly modulated by release of gliotransmitters, including glutamate, ATP, D-serine, and others [118, 119]. D-serine is a critical NMDA receptor co-agonist which is racemized in neurons and astrocytes from L-serine synthesized in astrocytes [119]. Accordingly, deficits in synaptic function by insufficient D-serine agonism may reflect an astroglial basis.

Evidence for the role of NMDA receptors in mood disorders is shown by treatment with sub-anesthetic doses of the NMDA receptor antagonist ketamine, which elicits rapid anti-depressive behaviors in both patients with MDD (reviewed in [120, 121]), and animal models [122, 123]. Elevated or impaired levels of NMDA receptor co-agonist D-serine represent one way in which dysregulation of NMDA function associated with mood disorders may occur. Patients with depression have higher levels of D-serine and L-serine in blood serum [124]. In contrast, animal models have shown that elevating D-serine levels leads to anti-depressive behaviors [125]. Elevating D-serine levels via transgenic manipulation of serine racemase (SR), or by the addition of D-serine to the drinking water of mice, leads to decreased immobility time in a forced swim test [125]. Confirming the results

from this study, another experiment has shown that acute D-serine treatment via i.p. injections also reduces immobility time in a forced swim test and moreover, reverses learned helplessness [126]. Additional studies have indicated that D-serine may be involved in other mood disorders as well. For example, transgenic mice lacking D-amino-acid oxidase, the enzyme that degrades D-serine, demonstrate increased anxiety-like behaviors [127].

One clinical trial showed that D-serine treatment may also be effective in reducing PTSD symptoms [128]. Future studies can include quantification of D-serine levels in post-mortem tissue samples from patients with MDD and animal models of depression, along with examining levels of serine racemase and the metabolizing enzyme D-amino-acid oxidase in both human and animal models of depression, which will further characterize the role of D-serine and NMDA receptors in mood disorders. It is unclear why D-serine treatment, and NMDA receptor inhibition via low-dose ketamine, might exert similar antidepressant effects; nonetheless, the implications of efficacy in targeting this mechanism merits further investigation.

It is important to note that the role of astrocytes in D-serine synthesis and transmission is not universally agreed upon. While D-serine was for years thought to be astrocyte-derived, recent publications indicate that neurons, not astrocytes, are the primary source of serine racemase, the bidirectional enzyme that converts L-serine to D-serine and vice versa [129], and congruent with this, serine racemase knockout studies have indicated a reduction in D-serine in neurons and not astrocytes [130]. Additionally, there is minimal evidence supporting D-serine release machinery in astrocytes [131]; for a review see [132]). As a result of this evidence, Wolosker and colleagues support the hypothesis that neurons are the dominant synthesizer and transmitter of D-serine [132]. Countering these claims, Oliet and colleagues point to established research that indicates astrocytes have the most optimal conditions for D-serine synthesis, whereas neurons have the ideal conditions for D-serine degradation [129, 133, 134]. Because serine racemase is a bidirectional enzyme, differences in experimental conditions can reverse serine racemase to primarily degrading D-serine, and Oliet and colleagues suggest this may be the case with some of the experiments staining for D-serine [134]. Further, using staining methods for serine racemase in neurons and astrocytes is confounded by the difference in makeup of the neuropil (~5–5% astrocytic and 70–75% neuronal [134]). Nonetheless, regardless of the cellular source of D-serine, it is acknowledged that astrocytes are the primary cellular source of 3-phosphoglycerate dehydrogenase (Phgdh), the rate limiting enzyme in the synthesis of L-serine, and accordingly astrocyte physiology remains central to the production of D-serine [119, 135].

Astrocyte-derived ATP has also been shown to be involved in depressive behaviors [136, 137]. A chronic social defeat protocol to induce depressive like behaviors in mice leads to reduced astrocytic levels of ATP in the prefrontal cortex and hippocampus, which is markedly reversed by systemic and intracerebroventricular injection of ATP [136]. Furthermore, ATP acts on purinergic receptors, which have also been shown to be involved in mood disorders. Polymorphisms for the gene encoding for the P2X7 purinergic receptor have been shown to lead to increased vulnerability for the diagnosis of mood disorders [138] and P2X7 knockout mice show anti-depressive behaviors including decreased immobility time in a forced swim test [139].

IV. Schizophrenia

Glial fibrillary acidic protein (GFAP)

In contrast to the preponderance of evidence indicating downregulation of astrocyte markers in MDD and in animal models of stress and depression, results are more mixed in the case of schizophrenia (Table II). A recent meta-analysis of changes in GFAP expression in postmortem human brain tissue indicated an increase, decrease, or lack of change in GFAP from 6, 6, and 21 studies, respectively [140]. This is likely attributable to a combination of individual genetic differences, heterogeneity of schizophrenic symptoms [141, 142], diversity of astrocytes [143, 144], and brain region specific differences in GFAP expression [71].

Multiple different animal models of schizophrenia have reported an increase in GFAP expression in a number of different brain areas [145–148]. Moreover, repeated injections of the NMDA receptor antagonist MK-801 in rodents, which has been used to induce schizophrenic symptoms, leads to an increase in GFAP expression in the hippocampus [148]. Likewise, other rodent models of schizophrenia including the maternal immune activation model and the early maternal deprivation model, have shown increased GFAP in parts of the frontal cortex [145, 147]. Although these studies suggest a correlation between possible astrogliosis and the presence of schizophrenic symptoms, numerous other preclinical studies have reported no changes in GFAP expression associated with schizophrenia. For example, mouse models of schizophrenia with overexpression of Munc-18a or mutant DISC-1 show no changes in cortical or hippocampal GFAP expression, respectively [149, 150].

In contrast, some preclinical animal models have indicated decreased GFAP association with Schizophrenia models. For example, a separate study using sub-chronic MK-801 treatment showed a decrease in GFAP in the prefrontal cortex (PFC) [151], in contrast to the hippocampal findings discussed above [148]. Additional studies observed a decrease in GFAP density in the cingulate cortex and corpus callosum of schizophrenic patients [152] and a decrease in the density of glial cells in the frontal cortex [142, 153]. In short, the above studies indicate that the association between GFAP expression and schizophrenia is more complex than originally hypothesized. Some studies have reported an increase in GFAP expression which may indicate astrogliosis, while others have shown decreased or no change.

Changes in astrocyte morphology

Although a wealth of experiments have quantitatively and qualitatively identified the changes in GFAP with schizophrenia, very few studies have examined the morphology of astrocytes in relation to schizophrenia. Much like the literature on GFAP and schizophrenia, experiments investigating the morphometric changes in astrocytes have shown differential results. One study examining the volume fraction, density, and size of astrocytes in the hippocampus using electron microscopy reported evidence of astrogliosis in schizophrenia [154]. In contrast, several studies have reported no change in the area and size of the nucleus

and cytoplasm of astrocytes [155, 156]. Future experiments are needed to further clarify the morphometric changes in astrocytes associated with schizophrenia.

Changes in astrocyte function-glutamate transport

The majority of studies examining changes in EAAT2 in schizophrenic patients have shown an increase in mRNA encoding EAAT2 (Table II). For example, increased EAAT2 mRNA has been shown in the thalamus [157], ACC [158] and PFC [159, 160] of schizophrenic patients. An increase in astroglial EAAT2 expression can lead to a decrease in glutamatergic transmission, which may underlie some of the symptoms observed in schizophrenia [159]. In contrast, one study examining EAAT1 and EAAT2 protein expression in an elderly schizophrenic population found a decrease in both astroglial glutamate transporters in the mediodorsal and ventral nuclei of the thalamus [161]. Interestingly, this study also showed cell type specific differences in gene expression of EAAT1 and EAAT2, with lower transcription levels in astrocytes, but higher transcription levels in neurons [161]. These results suggest that in schizophrenia, a loss of glutamate uptake in astrocytes may lead to compensatory neuronal changes in glutamate uptake [161]. Similarly, another study showed a loss of astroglial but not neuronal glutamate transporters is associated with schizophrenia [162]. A decrease in both astroglial EAAT1 and EAAT2 expression was found in the superior temporal gyrus, and a decrease in EAAT2 was found in the hippocampus of elderly patients diagnosed with schizophrenia [162]. However, no changes were found in the neuronal glutamate transporter EAAT3, or vesicular glutamate transporters VGLUT1 and 2, further indicating that the maintenance of glutamate homeostasis by astroglial glutamate transporters may play a critical role in schizophrenia.

In animal studies, administration of antipsychotics has shown that the efficacy of these drugs in treating schizophrenic symptoms may be due in part to suppression of GLT-1 expression [163–166]. For example, chronic administration of both atypical and typical antipsychotics in rodents decrease GLT-1 expression in the striatum [164], frontal cortex [163, 166] and hippocampus [163]. In contrast, upregulating GLT-1 expression has been shown to induce schizophrenic symptoms. Ceftriaxone, a β-lactam antibiotic that increases GLT-1 expression [167], has been shown to impair pre-pulse inhibition (PPI) of the acoustic startle reflex in rodents [168], a behavioral maladaptation often associated with schizophrenia. Furthermore, missense and 5’-UTR variants in the gene encoding for EAAT2 has been associated with an increased susceptibility for neuropsychiatric disorders including schizophrenia in humans [169]. These studies indicate that schizophrenia may be associated with an increase in GLT-1 expression, which in turn leads to a decrease in glutamatergic signaling. Antipsychotics may relieve psychotic symptoms by decreasing GLT-1 expression and restoring basal levels of glutamatergic signaling.

It is important to also note that a few studies have observed no changes in EAAT2 expression associated with schizophrenia [170, 171]. In addition, other studies have reported changes in GLAST, which may also influence glutamatergic signaling [162, 170]. These results again indicate that the relationship between glutamate transporters and schizophrenia is complex, and future studies are needed to further clarify these findings.

Modulation of synaptic function

A decrease in glutamatergic signaling as a result of impaired NMDA receptor (NMDAR) function has been widely hypothesized as an important contributing cellular mechanism for schizophrenia [172–175]. This hypothesis has been supported by multiple lines of evidence, including observations that antagonists of NMDAR can induce schizophrenic symptoms in healthy subjects, analysis on NMDA receptor subunit expression/localization in postmortem brain, and genetic linkage analyses. For example, NMDAR antagonists such as phencyclidine (PCP) have been shown to induce positive symptoms of schizophrenia including psychosis [176], and others such as ketamine have been shown to induce negative symptoms [177]. Furthermore, a wealth of NMDAR antagonists including PCP and ketamine have also been shown to induce schizophrenic symptoms in animals [178–181]. As discussed above, NMDA receptors are modulated by the glio- and neurotransmitter D-serine [119]. The relationship between schizophrenia and D-serine levels has been studied extensively, and directly implicates astroglial modulation of NMDA receptors in the development of schizophrenic symptoms. A meta-analysis of 20 experiments examining the levels of D-serine in schizophrenic patients indeed shows a decrease in D-serine levels in the serum of schizophrenic patients, and further, combined treatment of D-serine and antipsychotics generally improves the negative symptoms associated with schizophrenia [182].

While less information is available regarding a role for gliotransmitters beyond D-serine in schizophrenia, one study examined astrocyte specific deletion of adenosine A2A receptors, and the subsequent effects on several behavioral characteristics of schizophrenia [5]. The results from this study showed that mice lacking adenosine A2A receptors in astrocytes show a potentiated response to the NMDAR antagonist MK-801 in a test of locomotor activity, and deficits in working memory, two behavioral characteristics of schizophrenia [5]. Interestingly, these mice also exhibit deficits in GLT-1 activity, indicating a common link between astrocyte derived adenosine and glutamate uptake [5]. Further studies are needed to investigate the role of adenosine, as well as other gliotransmitters in schizophrenia.

V. Other Neuropsychiatric Disorders- Bipolar Disorder, Obsessive Compulsive Disorder (OCD), Tourette Syndrome, Autism

While information regarding adaptations in astroglial protein expression and cell morphology is more limited in the context of other psychiatric conditions, evidence exists for a role for astrocytes in conditions including bipolar disorder, OCD, Tourette Syndrome, and autism. Initial studies examining the number and density of glial cells showed no differences between bipolar patients and control subjects in a variety of different brain regions including the amygdala [65, 183], hippocampus, and entorhinal cortex [183]. However, in other brain regions including the PFC and anterior cingulate cortex, a decrease in glial cell number and density has been reported in patients diagnosed with bipolar disorder [183]. When examining GFAP, the findings have also been mixed. Although some studies have reported no change in GFAP expression in the entorhinal cortex [184] and PFC [60], one study has shown an increase in GFAP in the DLPFC in patients diagnosed with bipolar disorder [185]. Studies examining GFAP mRNA expression in patients with bipolar

disorder have also shown contrasting results. For example, although one study reported an increase in GFAP gene transcription in brain regions including thalamic nuclei, internal capsule and putamen [186], another study has reported a decrease in GFAP mRNA expression in the anterior cingulate cortex [69]. These studies suggest that GFAP expression in bipolar patients may vary depending on a wide range of factors including brain region examined and severity of symptoms.

In addition to GFAP expression, a few studies have examined other characteristics of astrocytes including morphology and expression of glutamate transporters. One study examining the area fraction and spatial distribution of GFAP-positive astrocytes reported a decrease in patients diagnosed with bipolar disorder [187]. Studies examining expression of astroglial glutamate transporters in bipolar patients have shown an increase in protein and mRNA expression of EAAT1 but a decrease in EAAT2 expression in the cortex of bipolar patients [188]. The heterogeneity of findings in astrocyte-related changes in bipolar disorder again perhaps reflects the diverse range of behavioral symptoms found in this disease. One way this can be remedied is by differentiating between bipolar I and bipolar II diagnosis, and by examining changes in astrocytes in animal models of bipolar disorder which may then clarify these diverse findings in clinical studies.

One study has reported that astroglial GLT-1 expression may play a role in the behaviors associated with obsessive compulsive disorder (OCD), as astrocyte specific knockout of GLT-1 expression in transgenic mice was shown to lead to excessive repetitive behaviors including grooming and head tics, which was then diminished by treatment with an NMDA receptor antagonist [189]. Other studies have also shown that astroglial glutamate transporters may be involved in Tourette Syndrome. For example, one missense variant in the gene encoding for EAAT1 (*SLC1A3*), is associated with Tourette Syndrome diagnosis [190]. Furthermore, a gene-set analysis study using a genome wide association data set of patients with Tourette Syndrome showed that this neuropsychiatric disorder is associated with a variety of different genes related to astrocyte functions [191]. These above-mentioned studies indicate that astroglial glutamate transporters may be involved in the repetitive behaviors associated with OCD and gene expression of genes related to astrocyte functions may be associated with Tourette Syndrome, warranting further investigation.

Astrocytes have also been implicated in autism spectrum disorder. In post mortem tissue samples from patients with autism, an increase in GFAP immunoreactivity has been reported in the ACC white but not gray matter; however, gene expression of GFAP was not reported to be different between autism patients and control subjects in either gray or white matter areas of the ACC [192]. In contrast, a separate gene expression study reported increased expression of GFAP in the PFC and cerebellum of patients with autism [193], suggesting that in autism, changes in GFAP gene expression may be brain region specific. In an animal model of autism induced using valproic acid, although GLAST expression did not change in the hippocampus, GLT-1 protein expression was decreased at P15 but increased at P120 [194], indicating possible developmental effects of GLT associated with autism. However, how this related to a clinical setting remains to be examined.

VI. Substance Use Disorders

Similar to the other psychiatric conditions discussed above, engagement of astrocytes in the development of substance use disorders has emerged in recent years [195, 196]. As the contributions of drug-induced adaptions in astrocyte physiology and function toward the development of substance use disorders emerge, there are similarities and contrasts between drug categories and between substance use disorders and other psychiatric diseases which can be drawn.

A. Cocaine

Glial fibrillary acidic protein (GFAP)—Collective results from a number of preclinical animal studies have revealed that the effects of cocaine exposure on GFAP expression can vary substantially based on administration paradigm, length of withdrawal, and brain region (Table III). For instance, increases in hippocampal GFAP have been reported in mice and rats following both acute and chronic non-contingent cocaine [197, 198], however these changes normalized in mice following 14 days of withdrawal [197]. In contrast, adolescent rats (PND 28–42) exposed to non-contingent cocaine exhibit increased hippocampal GFAP and S-100β expression in adulthood after both short and long withdrawal periods [199]. A different profile has been observed in the striatum, as GFAP was found to be increased following acute non-contingent administration, but decreased following 4 days of administration [198]. Chronic non-contingent cocaine treatment leads to activation of ER stress and autophagy pathways, consequently leading to increased GFAP expression in the striatum, suggesting a mechanism for non-contingent cocaine-induced astrogliosis [200]. Other studies have shown further contrasting results in GFAP expression following abstinence in acute vs chronic cocaine exposure. While acute exposure followed by abstinence did not alter GFAP expression in the rat caudate-putamen, PFC, or NAc core, an increase in GFAP has been observed in the NAc following abstinence from chronic administration [201, 202]. Adding to the complexity of results, it has also been reported that chronic non-contingent cocaine exposure causes different changes in GFAP expression depending on the rat strain used [203].

A few studies have also reported cocaine-induced decreases in GFAP expression. For example, prenatal cocaine exposure in rhesus monkeys leads to decreased cortical and white matter GFAP expression at 2 months [204], which is normalized in 3 year old animals [205]. Further, cocaine self-administration and extinction training in rats leads to decreased GFAP expression in NAc core astrocytes [55]. These findings are reminiscent of decreases in GFAP expression and astrocyte morphology observed in clinical and preclinical animal models of depression and stress described above; however, more experiments are needed to more conclusively assess the effects of cocaine on GFAP across varying administration paradigms. Numerous differences exist between these models, including not only operant behavior required for self-administration, but also the dosing and pharmacokinetic effects of cocaine.

Astrocyte quantity and morphology—Chronic non-contingent cocaine leads to reduced area and lengh of dorsal hippocampal astrocytic processes after 7 and 14 days of

cocaine injections; however, increased GFAP expression was also found in these animals after 7 days of cocaine but not 14 days (described above) suggesting that the degenerative effects of cocaine may be independent of gross GFAP measurements [197]. Similarly, Scofield et al. [55] showed that in a model of cocaine self-administration and extinction training, NAc core astrocytic synaptic contacts, surface area and volume are reduced, along with a decrease in GFAP expression [55]. In a separate study, George et al. [206] showed that the density of GFAP-positive astrocytes was unchanged in the dmPFC among rats that were drug naïve, or self-administered cocaine under a short- or long-access schedule. Again, further investigations across models will be important to more fully appreciate the effects of cocaine on the structure of astrocytes in different brain regions.

Changes in astrocyte function-glutamate transport—Rodent cocaine self-administration followed by extinction or forced abtinence has been broadly described to lead to a decrease in expression and function of GLT-1 within the NAc; moreover, decreased GLT-1 expression correlates with cocaine exposure and has been proposed as an important cellular mechanism for relapse to cocaine seeking [207–212]. Interestingly, GLT-1 expression in the NAc core decreases progressively with degree of cocaine exposure, as well as degree of withdrawal period [213]. In addition, the expression and function of astroglial cystine-glutamate exchanger (xC^-, catalytic subunit xCT), responsible for the maintinance of basal extrasynaptic glutamate levels, is decreased in the NAc following cocaine self-administration, contributing to the cocaine-induced impairment in glutamate homeostasis and driving cocaine seeking behavior [210, 214–216]. In contrast, a change in GLT-1 and xC^- expression has not been observed in the prefrontal cortex or dorsal striatum following cocaine self-administration and extinction training or forced abstinence [207, 208, 211, 217], indicating brain region specific decreases in astroglial GLT-1/xC- expression after cocaine exposure.

Modulation of synaptic function—The functional consequence of drug-induced adaptations to astrocytes are largely unknown. However, there is considerable evidence for modulation of synaptic function by astrocytes [218], as well as the effects of cocaine on synaptic strength and plasticity [219, 220], leaving astrocytes well positioned to contribute to synaptic mechanisms of cocaine-induced synaptic pathologies. Accumulating evidence indicates that deficits in astrocyte-derived D-serine may be a contributing mechanism [221]. For example, non-contingent cocaine exposure disrupts LTP and LTD, elicits hypofunctional NMDA receptors and reduces D-serine levels in the NAc [222]. Application of exogenous D-serine attenuates these deficits in synaptic plasticity and restores NMDA receptor function [222]. The effects of cocaine on D-serine levels is in part mediated by an increase in the enzyme responsible for the degradation of D-serine, D-amino acid oxidease (DAO), and a decrease in serine racemase. A separate, recent study has also indicated reduced D-serine levels and increased DAO in the hippocampus of adult, drug-naïve progeny of cocaine-exposured sires [223].

In addition, accumulating evidence indicates that astrocytic lactate transport contributes to drug associated memories [224]. The astrocyte-neuron lactate shuttle hypothesis posits that astrocyte-derived lactate provides the primary metabolic energy support for neuronal and

synaptic function [225, 226]. Disruption of lactate transport impairs acquisition and expression of cocaine conditioned place preferance (CPP) and reduces cue-primed seeking behavior [224, 227]. Similarly, lactate-mediated metabolic coupling between astrocytes and neurons specifically within the basolateral nucleus of the amygdala (BLA) is required for cocaine-associated memories. Specifically, inhibition of lactate transport in the BLA blocks reconsolidation of cocaine CPP as well as cocaine self-administration, indicating that astrocyte-neuron coupling is required for drug-associated memories and behaviors [228]. Of relevance, it has recently been proposed that lactate may modulate synaptic signaling indepently from it's role as an energy source [229, 230]. Accordingly, impaired function of astrocytes would carry consequences for not only neuronal energy demands, but also synaptic function. These studies also indicate that astrocytes likely facilitate the neural processes which mediate development of drug reward and drug-paired associations.

Lastly, there are a few studies which have shown that manipulations of astrocytes can influence drug seeking behaviors. For example, genetic expression of a dominant negative vesicular release protein (dnSNARE) specifically in astrocytes blocks drug-induced reinstatement of CPP as well as cue-induced reinstatement in the operant self-administration paradigm [231]. Moreover, stimulation of astroglial Gq-coupled DREADD receptors (designer receptors activated by a designer drug) in the NAc blocks cue-primed reinstatement via astroglial glutamate release and stimulation of presynaptic inhibitory mGluR2/3 receptors [232]. A similar inhibitory effect of astroglial Gq-DREADD stimulation has been observed on alcohol self-administration [233].

B. Amphetamine and Methamphetamine

Glial fibrillary acidic protein (GFAP)—Within the psychostimulant class of drugs, amphetamine and methamphetamine generally both result in higher levels of dopamine release, with greater evidence of neurotoxicity than other stimuluants such as cocaine [234, 235]. Despite conflicting results regarding the direction of effects of cocaine administration on changes in GFAP expression, most studies have indicated either increased or null changes in GFAP expression following amphetamine or methamphetamine administration. Similarly to the cocaine studies discussed above, administation paradigm and withdrawal periods have varied considerably across studies. For example, in one study, while acute administration of D-amphetamine did not alter GFAP expression in the hippocampus and cerebral cortex, chronic administration increased GFAP expression specifically in the hippocampus [236]. Relatedly, chronic amphetamine administration also has been reported to increase GFAP immunoreactivity in the NAc [237], PFC, and hippocampus [238]. Another study also reported an increase in GFAP expression in female mice after chronic methamphetamine treatment, as an escalating dose treatment paradigm was shown to increase GFAP in the hippocampus [239]. These results then suggest that changes in GFAP expression after amphetamine/methamphetamine may be dependent on variables including length of administration and brain region.

There are also conflicting reports of changes in GFAP expression following limited or extended withdrawal periods from amphetamine/methamphetamine treatment. For example, GFAP expression does not change in the mouse olfactory bulb, substantia nigra (SNr),

hippocampus, hypothalamus, midbrain, cerebellum, and brain stem after 3 days of abstinence from acute methamphetamine (4 × 10 mg/kg s.c. injections, every 2 hours) treatment [240]. In support of this result, GFAP expression is not altered in the hippocampus after a short period of abstinence (3 days) from acute binge methamphetamine administration (1 day/4 × 5 mg/kg) [241]. However results from another study showed that after either amphetamine or methamphetamine treatment, GFAP mRNA and protein expression increased 6–72 hrs later in the mouse brain [242]. Similarly, abstinence from methamphetamine, at the same time point of 72 hours, resulted in increased GFAP expression in the dorsal striatum of adult rats [240, 243–246]. Moreover, 12 or 72 hours of abstinence following methamphetamine treatment resulted in a hypertrophy of astrocytes in the striatum [242], indicating that limited abstinence from methampetamine can induce astrogliosis, in agreement with measurements of GFAP expression. In female mice, GFAP immunofluorescence is also increased in the striatum following 1 or 7 days of abstinence from methamphetamine treatment [247]. Similarly, although abstinence following chronic amphetamine administration was also shown to increase GFAP immunoreactivity in the dorsal striatum, there was no change in the NAc and PFC [248]. GFAP expression was also increased in the somatosensory cortex after 17 days of abstinence from chronic non-contingent amphetamine administration [249]. In support of these findings, one month or 2 days after administration of a neurotoxic methamphetamine regimen, GFAP expression was persistently increased [250] In brief, although some studies have reported no changes in GFAP expression after withdrawal from amphetamine or methamphetamine treatment, a number of others have shown an increase in GFAP expression. Future studies are needed to clarify these findings, with an emphasis on the effects of a binge vs. non-binge and neurotoxic vs. non-neurotoxic treatment of amphetamine/methamphetamine on GFAP expression.

Changes in astrocyte function-glutamate transport—While numerous studies have found suppressive effects of cocaine exposure on expression and activity of GLT-1, the same is not true for amphetamines. Neither acute nor chronic administration (5 days) of amphetamine alters GLT-1 expression in the NAc, PFC, SN, VTA or striatum (STR) [251]. Also, no difference in GLT-1 expression was found in the NAc, amygdala, hippocampus, thalamus, or various cortical regions following 7 days of abstinence from chronic methamphetamine administration (5 times/week for 3 weeks); however, an increase in GLT-1 expression in the striatum was observed [252]. Following restraint stress-induced methamphetamine CPP, increased GLT-1 expression was also found in the mPFC, but not in the dorsal hippocampus [253]. In support of these results, GLT-1 expression increased after 2 hours of 3 i.p. methamphetamine injections/day in the mPFC but not in the hippocampus [254]. In contrast to these findings, however, six days of amphetamine administration results in decreased xCT expression within the thalamus and frontal cortex [255]. Similar to the observed changes in GFAP expression, changes in GLT-1 expression after amphetamine/methamphetamine may be dependent on the dose, length of administration, and brain region.

C. Nicotine

Glial fibrillary acidic protein (GFAP)—In comparison to the other drugs in the psychostimulant class such as cocaine and amphetamine, relatively fewer studies are

available on the effects of nicotine on GFAP expression. In one study, chronic administration of nicotine increased nocifensive behaviors in response to a mechanical stimulus in the rat trigeminal system, which correlated with elevated GFAP expression in the medullary horn of the upper spinal cord [256]. In another study, maternal rat exposure to chronic nicotine via osmotic pump led to sensorimotor deficits in adulthood, which correlated with an increase of GFAP expression in the cerebellum [257]. In support of this, Abdel-Rahman and colleagues [258] reported an increase in GFAP immunostaining in the hippocampus, cerebellar white matter and granular cell layer of female and male offspring of mothers treated with nicotine. Interestingly, prenatal nicotine exposure increased GFAP immunoreactivity in fetal guinea pig but decreased expression in adult offspring guinea pig hippocampus [259].

Other studies have reported a lack of effect or a decrease in GFAP following nicotine exposure. For example, chronic nicotine administration has been reported to be without effect on GFAP expression in adult hippocampus [260, 261]. Also, chronic nicotine administration via osmotic pump does not alter GFAP expression in rat SNr [262]. Moreover, GFAP expression is not changed in the frontal cortical grey and white matter in a mouse model of Alzheimer's disease, after chronic nicotine administration in drinking water [263]. Interestingly, other studies have shown a decrease in GFAP expression after nicotine administration. Adolescent rats exposed to nicotine exhibit decreased hippocampal GFAP expression in adult female but not male rats [264]. Also, a postmortem human study found GFAP immunoreactivity decreased in the hippocampus and entorhinal cortices from humans with chronic nicotine history [265].

Changes in astrocyte function-glutamate transport—Two studies have reported effects of nicotine on GLT-1 expression. Similarly to cocaine, GLT-1 expression is decreased in the NAc core after nicotine self-adminitration and extinction [266]. After extended (12 hours/day) nicotine self-administration, GLT-1 and xCT expression are also reduced in the NAc shell [267].

E. Opiates

Glial fibrillary acidic protein (GFAP)—The majority of studies which have investigated GFAP expression following exposure to opiates have reported increases in expression (Table IV). GFAP protein and mRNA levels have been reported to be upregulated in the striatum after chronic morphine administration [268] and in whole brain following naloxone-induced withdrawal of chronic morphine treatment [269]. Moreover, chronic (but not acute) morphine treatment increased GFAP expression in the NAc shell, VTA and frontal cortex, which is prevented by the α2-adrenoceptor antagonist yohimbine [270]. Additionally, increased GFAP expression in the hippocampus, spinal cord, midbrain and posterior cingulate cortex has been reported in morphine tolerant rats, while no difference was found in the thalamus [271–274]. Interestingly, acute or naloxone-induced withdrawal from chronic morphine administration increases GFAP expression by a mechanism requiring matrix metalloprotein-9 (MMP-9) in the dorsal root ganglia [275, 276]. Supporting these findings, morphine withdrawal increases GFAP expression in the periaqueductal gray, suggesting astrocyte activation correlates with the release of TNFα [277]. Further, GFAP expression is increased in the locus coeruleus (LC) and nucleus of the solitary tract (NST)

after chronic morphine treatment [278]. Further still, one day following chronic morphine treatment, GFAP expression is increased in the NAc, but decreased in the mesencephalon [279]. Lastly, morphine induced conditioned place preference (CPP) elicits dynamic changes in GFAP expression in the amygdala, as GFAP is reduced following extinction of morphine CPP but not after morphine-induced reinstatement to CPP [280].

Astrocyte quantity and morphology—Early studies with primary glial cells in culture found that morphine inhibits astrocyte proliferation, but increases area and complexity of astrocyte cytoplasmic processes [281–285]. Subsequent *in vivo* studies have shown that chronic morphine administration does not affect astrocyte numbers in the caudate nucleus (CN), NAc, and lateral septal nucleus (LSN) [286]. However, the total length of astrocyte processes and astrocyte branching is increased in the LSN and NAc but decreased in CN [286]. Moreover, morphine-induced CPP elicits an increase hippocampal astrocyte quantity both in male and female rats [287, 288].

Changes in astrocyte function-glutamate transport—GLT-1 expression is reduced in the cerebrum of male but not female mice following repeated morphine treatment [289]. A separate *in vitro* study showed that GLT-1 expression is reduced after morphine treatment in primary culture astrocytes [290]. Moreover, GLT-1 surface expresion is decreased in the NAc core, while xCT surface expression is increased, following heroin self-administration and extinction [291].

F. Alcohol

Glial fibrillary acidic protein (GFAP)—A growing body of literature indicates substantive effects of alcohol on astrocytes, as well as roles for astrocytes in alcohol use and relapse [292, 293] (Table V). In postmortem tissue from human alcoholics, a decrease in glial cell density has been reported in the DLPFC [294], suggesting a decrease in the number and size of glial cells following alcohol use. However, in the superior frontal gyrus and primary motor cortex of alcoholics, decreased GFAP expression was found [295], supporting a hypothesis of alcohol-induced atrophy of astrocytes.

Findings from preclinical studies examining changes in GFAP expression after alcohol exposure have predominantly shown an increase in GFAP expression, suggesting astrogliosis and an increased inflammatory response after alcohol drinking [296]. For example, following 6 weeks of ethanol exposure in the drinking water of rats, increased GFAP expression was reported in the hippocampus, striatum, and cortex [297]. Likewise, increased GFAP expression has also been reported after exposure to different concentrations of ethanol at different exposure times. Prolonged exposure to either a 5 or 10% ethanol concentration increased GFAP expression in the hippocampus [298], and chronic exposure to increasing concentrations of ethanol increased GFAP expression in various brain regions including the hippocampus, globus pallidus, internal capsule, corpus callosum, and cortex [299]. Similarly, exposure to both low (20%) or high (40%) concentrations of ethanol for 3 weeks, 3 months or 6 months all increased GFAP expression in the hippocampus and cingulate cortex [300]. Moreover, one week exposure to 6% ethanol also increased GFAP expression in the hippocampus [301]. Interestingly, in the offspring of rats who were administered

ethanol by oral gavage, increased GFAP expression was found in the cortex [302], hippocampus and striatum [303], suggesting epigenetics may be one mechanism for increased GFAP following ethanol exposure.

Although exposure to ethanol drinking appears to increase GFAP expression, results from other methods have been mixed. For example, an oral gavage treatment of 6.5 g/kg/day of ethanol was shown to decrease GFAP expression in the cortex [304], while an intermittent ethanol access paradigm did not lead to any changes in GFAP expression in the infralimbic cortex and orbitofrontal cortex [305]. Other studies have shown that withdrawal from ethanol also decreases GFAP expression. For example, 3 weeks of abstinence from either chronic ethanol treatment or exposure to ethanol in operant conditioning chambers was shown to decrease GFAP expression in the prelimbic cortex and orbitofrontal cortex [305]. Another study has shown that 6 weeks of exposure to ethanol increased GFAP expression, but 10 weeks of abstinence normalized GFAP levels in the hippocampus, striatum and cortex [297]. In short, these above-mentioned studies suggest mixed results regarding the effects of ethanol exposure on GFAP expression. Future studies are then needed to assess how other methods of ethanol exposure induce changes in GFAP, and the time course of withdrawal induced changes in GFAP.

Astrocyte Morphology—Although few studies have examined morphological changes in astrocytes in response to ethanol treatment *in vivo*, studies utilizing astrocyte cultures have shown ethanol-induced changes in astrocyte morphology. For example, acute ethanol exposure induces swelling of astrocyte cultures from the rat cortex [306, 307]. Furthermore, prolonged exposure to ethanol for 1, 3, or 7 days leads to increased cell volume of rat astrocytes in culture [307]. Increased cell volume and swelling of astrocytes is one possible mechanism for the increase in GFAP expression observed after ethanol treatment.

Existing *in vivo* studies corroborate these results. One study *in vivo* has shown that adolescent intermittent ethanol exposure leads to increased astrocyte volume and branch length in the CA1 region of the hippocampus in adulthood, 24 days after the last ethanol administration [308]. A separate study has also shown that packing density of astrocytes is increased in the NAc core during abstinence from ethanol self-administration [233].

Changes in astrocyte function-glutamate transport—Alcohol has also been shown to induce changes in expression of the astroglial glutamate transporters, most notably GLT-1 (human analog EAAT2) and GLAST (human analog EAAT1), associated with changes in glutamate uptake. In blood samples from human alcoholics, withdrawal from alcohol use has been shown to increase EAAT2 expression [309]. In the central nervous system, an increase in EAAT1 expression was found in the PFC of human alcoholics [310]. In contrast to these findings in human alcoholics, some preclinical studies using animal models of alcohol use have reported a decrease in GLT-1 expression [311–313]. For example, withdrawal from a binge treatment of ethanol has been shown to lead to a decrease in GLT-1 expression in the striatum and PFC [311, 312]. Similarly, five weeks of free choice ethanol was shown to decrease GLT-1 expression in the NAc [313]. However, other studies using intermittent alcohol exposure paradigms have found no effect of alcohol on NAc GLT-1 expression and/or function [314–316]. A functional role for glutamate transporters in alcohol use has

been demonstrated by pharmacotherapeutic treatment with drugs that increase GLT-1 expression. For example, the β-lactam antibiotic ceftriaxone increases GLT-1 expression, and importantly, has been shown to reduce alcohol intake [313, 317–319]. Other drugs that increase GLT-1 have also been shown to reduce alcohol intake [320, 321].

In contrast to reduced GLT-1 expression associated with exposure to alcohol, withdrawal from a binge treatment of ethanol did not result in any changes in GLAST expression [312]. Moreover, GLAST knockout mice do not exhibit a place preference for ethanol but do show reduced ethanol intake compared to wild-type mice, [322]; accordingly, the role of GLAST expression in alcohol intake is not straightforward.

Modulation of synaptic function—The role NMDA receptors in alcohol intake has been demonstrated by studies showing that systemic treatment of the NMDA receptor co-agonist D-serine and D-cycloserine can reduce aversion resistant alcohol intake [323]. Furthermore, D-cycloserine has been shown to modulate behaviors induced by ethanol including reducing the anxiolytic effects of ethanol [324], and enhancing tolerance to ethanol [325]. D-cycloserine has also been shown to facilitate extinction of alcohol seeking [326]. Furthermore, D-serine treatment 15 minutes before ethanol administration can increase latency for mice to lose the loss of righting reflex, without effect on ethanol-induced deficits in the rotarod test [327]. Importantly, a one-week treatment regimen of D-serine reduces preference for ethanol, indicating that D-serine may be a promising pharmacotherapeutic candidate for alcoholism. However, another study reported that systemic treatment of D-serine or D-cycloserine had no effect on measures of ethanol intoxication including ataxia, hyperthermia and loss of righting reflex [328].

Adenosine signaling and transport have also been implicated in ethanol-induced intake and ethanol-induced behaviors. Alcohol can increase adenosine levels [329], and increased adenosine can influence glutamatergic release and signaling. For example, the equilibrative nucleoside transporter (ENT-1) transports adenosine across the plasma membrane is expressed primarily on astrocytes [330]. Ethanol can decrease adenosine uptake by modulating ENT-1 expression and activity [331]. In astrocyte cultures, ENT-1 antagonists and siRNA-induced knockdown of ENT-1 lead to decreased GLT-1 mRNA expression, which is reversed by overexpression of ENT-1 [332]. Importantly, ENT-1 knockdown is sufficient to prevent the ethanol-induced increase in GLT-1 expression, indicating an interaction between ethanol, GLT-1 and ENT-1 expression [332]. This interaction is further demonstrated by studies showing that ENT-1 knockout mice consume more significantly more alcohol than wild-type littermates [333, 334]. Deletion of ENT-1 has also been shown to decrease expression of AQP-4, a water protein channel specific to astrocytes [335]. Moreover, administration of ceftriaxone in ENT-1 knockout mice increases both GLT-1 and aquaporin-4, and importantly, reduces ethanol intake [335]. These studies indicate that alcohol has effects on astrocyte-derived gliotransmitters which influence both glutamate uptake and alcohol intake. And in addition to adenosine, astrocyte-derived ATP has also been shown to be influenced by alcohol. The P2X7 receptor, a target of ATP, was shown to be increased by chronic ethanol treatment in the striatum, hippocampus and midbrain [336].

G. Marijuana (THC)

The main psychoactive component in marijuana (*cannabis sativa*), (−)-Δ^9-Tetrahydrocannabinoid (THC), is a partial agonist of the cannabinoid type 1 and 2 receptors (CB1, CB2) [337, 338]. CB1, in particular, is expressed on astrocytes and its activation causes the release of calcium from internal stores, stimulating glutamate release and potentiating synaptic transmission [337–340]. Additionally, THC affects energy metabolism in astrocytes as it reduces glucose uptake at THC blood levels of > 10 ng/ml *in situ* [341], and THC application to primary astrocyte cultures stimulates glucose metabolism [342]. These primary effects of THC on astrocytes indicate that there could be long-term effects on morphology and functioning.

There is a lack of information on THC administration and withdrawal in adulthood, however there are a limited number of studies regarding the effects of adolescent THC exposure on astrocytes throughout development and into adulthood. Chronic THC exposure during prenatal development through PND 20 reduces GFAP expression during prepuberty, periadolescence and adulthood (PND 21, 30 and 70) in the SNr and at prepuberty and adulthood (PND 20 and 70) in the cerebellar cortex in male rats [343, 344]. However, hippocampal and hilus GFAP expression is elevated in adulthood compared to controls when THC is given in increasing doses (2.5 mg/kg, 5 mg/kg and 10 mg/kg) throughout adolescence (PND 28 or 35 through PND 45) [345, 346].

Additionally, prenatal THC exposure into preadolescence in males and females attenuates cerebellar cortex glutamate uptake in astrocytes shown by sustained, reduced GS protein throughout adolescence (PND 30) and a trend for males in adulthood (PND 70) [343]. Further, it was found that these astrocytic changes were accompanied with hippocampal NMDA receptor subunit GluN2B and AMPA subunits GluA1 and GluA2 upregulation, along with increased expression of pro-inflammatory markers TNF-α, iNOS and COX-2, but a reduction in IL-10 [346]. As animal models of THC use and dependence continue to emerge and develop, it will be of interest to determine the degree to which effects of THC are similar or different to those of other drug classes.

VII. Astrocytes as candidate pharmacotherapeutic targets for psychiatric disease

Emerging roles for astrocytes in addiction and psychiatric disease continue to grow, garnering attention toward astroglial mechanisms. In particular, several reviews have addressed the potential of glial cells as pharmacotherapeutic targets for addiction [347–349]. However, the myriad of changes observed in these oft-comorbid conditions – e.g., addiction, depression, and schizophrenia – merits consideration of possible similar or opposing cellular mechanisms. For example, upregulation of GLT-1/EAAT-2 and amelioration of glutamate homeostasis has been proposed as a candidate mechanism for pharmacotherapeutic treatment of substance use disorders [350, 351]; however, evidence for an opposing adaptation for GLT-1 in schizophrenia raises the question of whether this would be an effective pharmacological target in substance use disorders comorbid with schizophrenia. This complexity underscores the importance of a complete picture of highly variable and

individual conditions, as well as normalizing conditions behavioral preclinical models. Nonetheless, the efficacy of glial modulators in reducing reinstatement and drug seeking behaviors in preclinical animal addiction models underscores the potential of astrocytes as therapeutic targets for substance use disorders. Moreover, the striking consistency of evidence for atrophic astrocytes in animal models of stress and depression as well as human MDD suggests that this may well represent a central cellular feature of chronic stress and depression, and accordingly a potentially important pharmacotherapeutic target for mood disorders.

VIII. Summary and conclusions

Responsiveness of astrocytes to compromised nervous systems – injury, inflammation, drugs of abuse, neuropsychiatric disease – ranges from astrocytopathy to astrogliosis, with a continuum of phenotypes including decreased gene expression and cell size, to increased GFAP, cell size, and release of pro-inflammatory molecules [27, 49]. A substantive body of literature indicates comprehensive adaptations in astrocytes that are complicated by the variables which contribute to the complexity of neuropsychiatric disease. However, themes are beginning to emerge, such as a preponderance of evidence for astrocytopathy associated with depression, to generally inflammatory effects of drugs of abuse that may normalize or revert to astrocytopathy over a period of withdrawal. Particularly in the case of drugs of abuse, it is paramount to consider time course, route of administration, dose, and other methodological factors when considering the effects of drugs on properties and function of astrocytes. Nonetheless, continued focus on the relationship between psychiatric disease and astrocytes will provide critically needed insight into the cellular mechanisms of these complex problems, as well as their solutions.

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Highlights

- Astrocytes perform many vital functions in the central nervous system
- Both astrogliosis and astrocytopathy have been associated with CNS disorders
- A decrease in GFAP and astrocyte morphology is associated with mood disorders
- Increased GFAP expression is more associated with schizophrenic symptoms
- Drugs of abuse induce broad changes in astrocyte gene expression and structure

Table I

Astrocyte-related changes in Depression, Stress and Anxiety

Effects on Astrocyte Marker	Study design	Brain Region	Reference
No change in GFAP; but younger MDD patients show decreased GFAP	MDD patients	DLPFC	Miguel-Hidalgo et al, 2000
No change in GFAP	MDD patients	Entorhinal cortex	Damadzic et al, 2001
No difference in GFAP	Wistar-Kyoto rat model of depression	Insular cortex, somatosensory cortex	Gosselin et al, 2009
No changes in glial cell size or density	MDD patients	OFC	Cotter et al, 2005
No change in size of glial nuclei	MDD patients	Cortex	Cotter et al, 2002
↑ GFAP protein and mRNA	Behaviorally depressed monkeys	CA1	Willard et al, 2014
↑ Cell bodies, longer/ ramified processes of fibrous astrocytes	MDD patients who committed suicide	Layer 6	Torres-Platas et al, 2011
↑ GLT-1	Chronic unpredictable stress in rats	Hippocampus	Raudensky and Yamamoto, 2007
↑ GLT-1	Early maternal separation in rats	Hippocampus	Martisova et al, 2012
↓ GFAP	MDD patients	Hippocampus	Cobb et al, 2016
↓ GFAP labeled astrocytes adjacent to blood vessels	MDD patients	PFC	Webster et al, 2001
↓ GFAP	MDD patients	DLPFC	Si et al, 2004
↓ GFAP	MDD patients	Locus coeruleus	Chandley et al, 2013
↓ GFAP	MDD patients	Amygdala	Altshuler et al, 2010
↓ GFAP	MDD patients	Cerebellum	Fatemi et al, 2004
↓ GFAP area fraction	MDD patients	OFC	Miguel-Hidalgo et al, 2010
↓ GFAP protein and mRNA	MDD patients who completed suicide	Thalamus, caudate nucleus	Torres-Platas et al, 2016
↓ GFAP mRNA (but not statistically significant)	MDD patients	White Matter	Webster et al, 2005
↓ GFAP	Wistar-Kyoto rat model of depression	PFC, basolateral amygdala, hippocampus	Gosselin et al, 2009
↓ GFAP	Early life deprivation in rats	PFC, amygdala, hippocampus,	Leventopoulos et al, 2007
↓ GFAP mRNA	Chronic unpredictable stress in rats	PFC	Banasr et al, 2010
↓ GFAP protein and mRNA	Chronic unpredictable mild stress in mice	Hippocampus	Yang et al, 2014
↓ GFAP protein and mRNA	Chronic unpredictable stress in rats	Hippocampus	Liu et al, 2011
↓ GFAP protein and mRNA	Chronically stressed mice	Hippocampus	Ding et al, 2017
↓ GFAP	Chronic unpredictable mild stress in rats	Hippocampus	Ye et al, 2011
↓ GFAP	Juvenile stress in *Octon degus*	Medial PFC	Braun et al, 2009
↓ GFAP	Chronic immobilization stress in rats	Hippocampus, frontal cortex	Shilpa et al, 2017
↓ GFAP	Restraint stress in rats	Hippocampus, frontal cortex	Santha et al, 2015
↓ GFAP	Inescapable shock protocol in rats (PTSD model)	Hippocampus	Saur et al, 2016

Effects on Astrocyte Marker	Study design	Brain Region	Reference
↓ GFAP	Single prolong stress in rats (PTSD model)	Hippocampus	Han et al, 2015
↓ GFAP	Chronic restraint stress	Rostral ventromedial medulla	Imbe et al, 2013
↓ GFAP	Chronic psychosocial stress in male tree shrews	Hippocampus	Czeh et al, 2005
↓ GFAP	Chronic restraint stress in rats	Periaqueductal gray	Imbe et al, 2012
↓ GFAP	Neonate guinea pigs born from stressed mothers (show increased anxiety)	CA1 Hippocampus	Bennett et al, 2015
↓ GFAP	Aluminum citrate intoxication in rats to increase anxiety	Hippocampus	Silva et al, 2013
↓ Size of glial cells	MDD patients	DLPFC	Rajkowska et al, 1999
↓ Somal volume of astrocytes	Male tree shrews subject to psychosocial stress	Hippocampus	Czeh et al, 2005
↓ Arbor length in Astrocytes, bifurcations	Macaques with self-injurious behavior	Frontal Cortex	Lee et al, 2013
↓ Astrocyte primary processes	Inescapable shock protocol in rats (PTSD model)	Hippocampus	Saur et al, 2016
↓ Astrocyte process length, branching and volume	Chronic stress in rats	Cortex	Tynan et al, 2013
↓ Somal volume of astrocytes and protrusion length	Chronic corticosterone treatment in mice	Hippocampus	Zhang et al, 2015
↓ SLC1A3 and SLC1A2 mRNA	MDD patients	Locus coeruleus	Chandley et al, 2014
↓ SLC1A2, SLC1A3	MDD patients	Cortex	Choudary et al, 2005
↓ SLC1A2, SLC1A3	MDD patients	Hippocampus	Medina et al, 2016
↓ EAAT2	MDD patients	OFC	Miguel-Hidalgo et al, 2010
↓ EAAT1, EAAT2	MDD patients	DLPFC	Zhao et al, 2016
↓ EAAT2	Chronic restraint stress in rats	Periaqueductal gray	Imbe et al, 2012
↓ GLT-1 mRNA	Prenatal stress in rats	Hippocampus, striatum, frontal cortex	Zhang et al, 2013
↓ GLT-1	Chronic unpredictable mild stress in rats	Hippocampus	Zhu et al, 2017
↓ GLT-1 mRNA	Learned helplessness in rats	Hippocampus, cortex	Zink et al, 2010
↓ GLT-1	Chronic unpredictable stress in rats	Hippocampus	Chen et al, 2014
↓ GLT-1	Chronic unpredictable stress for 42 days in rats	Hippocampus	Liu et al, 2016
↓ GLT-1	Chronic post-natal stress in rats	Hippocampus and frontal cortex	Odeon et al, 2015
↓ GLT-1	Social defeat in mice	PFC	Veeraiah et al, 2014
↓ Astrocyte derived ATP	Chronic social defeat in mice	Hippocampus and prefrontal cortex	Cao et al, 2013

Table II

Astrocyte-related changes in Schizophrenia

Astrocyte Marker	Study design	Brain Region	Reference
No change in GFAP	Escalating amphetamine treatment in rats	Caudate Putamen	Peleg-Raibstein et al, 2008
No change in GFAP	Munc-18 overexpressing mice	Cortex	Gil-Pisa et al, 2014
No change in GFAP	DISC-1 mutant mice	Hippocampus	Abazyan et al, 2014
No change in GFAP	Schizophrenic patients	ACC	Katsel et al, 2011
No change in GFAP	Schizophrenic patients	DLPFC, visual cortex, Hippocampus	Steffek et al, 2008
No change in GFAP	Schizophrenic patients	Entorhinal cortex	Damadzic et al, 2001
No change in GFAP	Schizophrenic patients	Ventromedial temporal, frontal, calcarine cortices	Arnold et al, 1996
No change in area of astrocyte nucleus and cytoplasm	Schizophrenic patients	Hippocampus	Kolomeets and Uranova, 2010
No change in glial somal size	Schizophrenic patients	OFC, OFC	Rajkowska et al, 1998
No change in density of astrocytes	Schizophrenic patients	Hippocampus	Schmitt et al, 2008
No change EAAT2	Schizophrenic patients	DLPFC, ACC	Bauer et al, 2008
No changes EAAT1, EAAT2A, EAAT2B, EAAT3	Schizophrenic patients	DLPFC, primary visual cortex	Lauriat et al, 2006
No change in D-amino acid oxidase (DAO)	Schizophrenic patients	Parietal cortex	Bendikov et al, 2007
↑ GFAP	MK-801 treatment in rats	Hippocampus	Yu et al, 2015
↑ GFAP protein and mRNA	Cultured astrocytes bathed in MK-801	Hippocampus	Yu et al, 2015
↑ GFAP	Maternal Immune Activation (MIA) in rats	Frontal Cortex	De Souza et al, 2015
↑ GFAP	Early maternal deprivation in rats	Inner granular layer, white matter	Llorente et al, 2009
↑ GFAP	Gunn rats	Hippocampus	Limoa et al, 2016
↑ GFAP protein and mRNA	Schizophrenic patients	ACC	Rao et al, 2013
↑ GFAP	Schizophrenic patients	DLPFC	Feresten et al, 2013
↑ GFAP	Schizophrenic patients	Brodmann area 9	Toro et al, 2006
↑ Astrocyte clustering	Schizophrenic patients	DLPFC	Hercher et al, 2014
↑ Volume fraction, areal density of astrocytes	Schizophrenic patients	Hippocampus	Kolomeets, 2008
↑ EAAT1 mRNA	Schizophrenic patients	DLPFC, ACC	Bauer et al, 2008
↑ DAO	Schizophrenic patients	Cortex	Madeira et al, 2008
↑ DAO mRNA	Schizophrenic patients	Cerebellum	Verrall et al, 2007
↑ DAO activity	Schizophrenic patients	Cerebellum	Burnet et al, 2009
↑ DAO mRNA	Schizophrenic patients	Cerebellum	Burnet et al, 2009
↑ DAO mRNA	Rats treated with sub chronic administration of ketamine	Midbrain	Watanabe et al, 2010
↑ Serine racemase	Schizophrenic patients	DLPFC	Verrall et al, 2007
↑ Serine racemase	Schizophrenic patients	Hippocampus	Steffek et al, 2006

Astrocyte Marker	Study design	Brain Region	Reference
↓GFAP	Sub-chronic MK-801 treatment in rats	PFC	Rahati et al, 2016
↓ GFAP	Schizophrenic patients	Brodmann area 11/47	Toro et al, 2006
↓ GFAP	Schizophrenic patients	ACC	Steffek et al, 2008
↓ GFAP	Schizophrenic patients	Susbtantia Nigra	Williams et al, 2014
↓ GFAP	Schizophrenic patients	Frontal Cortex	Johnston-Williams et al, 2000
↓ GFAP	Schizophrenic patients	Brodmann area 9	Rajkowska et al, 2002
↓ GFAP density	Schizophrenic patients	Cingulate cortex, corpus callosum	Williams et al, 2013
↓ Glial cell density	Schizophrenic patients	PFC, ACC, primary motor cortex	Benes et al, 1986
↓ Glial cell density	Schizophrenic patients	Layer 6	Cotter et al, 2001
↓ EAAT1 protein	Schizophrenic patients	DLPFC, ACC	Bauer et al, 2008
↓ EAAT2 mRNA	Schizophrenic patients	PFC	Ohnuma et al, 1998
↓ EAAT1 and EAAT2 protein	Schizophrenic patients	Superior temporal gyrus, hippocampus	Shan et al, 2013
↓ Serine racemase	Schizophrenic patients	Frontal cortex, hippocampus	Bendikov et al, 2007
↓ Serine racemase mRNA	Rats treated with sub chronic administration of ketamine	Forebrain	Watanabe et al, 2010

Table III

Astrocyte related changes after cocaine exposure

Astrocyte Marker	Study Design	Brain Region	Reference
↑ GFAP	Acute and repeated cocaine administration (20 mg/kg body weight/day for 4 d; i.p in rats)	Hippocampus	Blanco-Calvo, E., et al., 2014
↑ GFAP	Cocaine treatment (10 uM)	Primary human astrocytes	Periyasamy, P., M.L. Guo, and S. Buch, 2016)
↑ GFAP	Chronic cocaine exposure (20 mg/kg body weight/day for 7days; i.p.; in mice)	Striatum	Periyasamy, P., M.L. Guo, and S. Buch, 2016
↑ GFAP	24 hrs after acute (1 × 20 mg/kg; i.p.) and chronic cocaine exposure (7 days/20 mg/kg; i.p. in mice)	Hippocampus	Fattore, L., et al., 2002
↑ GFAP	3 weeks after acute cocaine exposure (30 mg/kg; i.p; in rats)	NAc shell	Bowers, M.S. and P.W. Kalivas, 2003
↑ GFAP	3 weeks after 7 days of cocaine exposure (15 mg/kg (day 1 and 7) and 30 mg/kg (day 2–6); i.p.; in rats)	PFC, NAc core and shell	Bowers, M.S. and P.W. Kalivas, 2003
↑ GFAP	5 weeks after chronic cocaine exposure (15 mg/kg; i.p./15 days; in rats)	Hippocampus	Zhu, W., et al., 2016
No change GFAP	Acute cocaine exposure (20 mg/kg body weight/day; i.p. in rats)	Striatum	Blanco-Calvo, E., et al., 2014
No change GFAP	2 hrs after acute cocaine exposure (30 mg/kg; i.p.; in rats)	NAc core and shell, PFC	Bowers, M.S. and P.W. Kalivas, 2003
No change GFAP	24 hrs after chronic cocaine exposure (14 days/20 mg/kg; i.p; in mice.)	Hippocampus	Fattore, L., et al.,2002
No change GFAP	24 hrs or 1 weeks after chronic cocaine exposure (15 mg/kg (day 1 and 7) and 30mg/kg (day 2–6); i.p.; in rats)	Striatum, NAc core and shell, PFC	Bowers, M.S. and P.W. Kalivas, 2003
No change GFAP	2 days after chronic cocaine exposure (20 mg/kg/14 days; i.p; in rats)	PFC, Anterior cingulate	El Hage et al., 2012)
No change GFAP	3 days after acute cocaine exposure (4 × 15 or 25 mg/kg/1 day; s.c; in rats)	Striatum	Cappon, G.D., L.L. Morford, and C.V. Vorhees, 1998
No change GFAP	Following extinction (2 weeks) from contingent short-access cocaine (0.2 mg per infusion/2 hr per day/10 days; i.v.; in rats)	PFC	Scofield, M.D., et al., 2016
No change GFAP	3 weeks after 7 days of cocaine exposure (15 mg/kg (day 1 and 7) and 30mg/kg (day 2–6); i.p.; in rats)	Striatum	Bowers, M.S. and P.W. Kalivas, 2003
No change GFAP	3 weeks after acute cocaine exposure (30mg/kg; i.p.; in rats)	NAc core and PFC	Bowers, M.S. and P.W. Kalivas, 2003
↓ GFAP	Repeated cocaine administration (20 mg/kg/day for 4 d; in rats)	Striatum	Blanco-Calvo, E., et al., 2014
↓ GFAP	Following extinction (2 weeks) from contingent short-access cocaine (0.2 mg per infusion/2 hrs per day/10 days; in rats)	NAc core	Scofield, M.D., et al., 2016
No change GLT-1	Following short withdrawal (1 day) from short-access cocaine (0.25 mg/0.1 ml; i.v. infusion/11 days; in rats)	NAc shell	Fischer-Smith, K.D., A.C. Houston, and G.V. Rebec, 2012
No change GLT-1	Following extinction (2 weeks) from contingent short-access cocaine (0.20 mg/0.05 ml infusion/2 weeks days; in rats)	PFC	Reissner, K.J., et al., 2014
No change GLT-1	Following extinction (3 weeks) of contingent short-access cocaine (0.20 mg/0.05 ml infusion/2 weeks days; in rats)	PFC	Knackstedt, L.A., R.I. Melendez, and P.W. Kalivas, 2010

Astrocyte Marker	Study Design	Brain Region	Reference
No change GLT-1	10 days of withdrawal after non-contingent cocaine exposure (20mg/kg/7 days; i.p.; in rats)	Dorsal striatum	Parikh, V., et al., 2014
↓ GLT-1	Following short withdrawal (1 day) from short- and long-access cocaine (0.25 mg; i.v. infusion/11 days; in rats)	NAc core	Fischer-Smith, K.D., A.C. Houston, and G.V. Rebec, 2012
↓ GLT-1	Following short withdrawal (1 day) from long-access cocaine (0.25 mg; i.v. infusion/11 days; in rats)	NAc shell	Fischer-Smith, K.D., A.C. Houston, and G.V. Rebec, 2012
↓ GLT-1	Following extinction (2 weeks) of contingent short-access cocaine (0.25 mg/infusion/2hrs/day; 10 days i.v.; in rats)	NAc	Sondheimer, I. and L.A. Knackstedt, 2011
↓ GLT-1	Following extinction (2 weeks) of contingent short-access cocaine (0.20 mg/0.05 ml infusion/2 weeks days; in rats)	NAc core	Reissner, K.J., et al., 2014; Reissner, K.J., et al., 2015
↓ GLT-1	Following extinction (3 weeks) of contingent short-access cocaine (0.20 mg/0.05 ml infusion/2 weeks days; in rats)	NAc	Knackstedt, L.A., R.I. Melendez, and P.W. Kalivas, 2010
↓ GLT-1	Following long withdrawal (40–45 days) from short- and long-access cocaine (0.25 mg; i.v. infusion/11 days; in rats)	NAc core and shell	Fischer-Smith, K.D., A.C. Houston, and G.V. Rebec, 2012
No change xCT	Following extinction (2 weeks) of contingent short-access cocaine (0.25 mg/infusion/2hrs/day; 10 days i.v.; in rats)	NAc	Sondheimer, I. and L.A. Knackstedt, 2011
No change xCT	Following extinction (3 weeks) of contingent short-access cocaine (0.20 mg/0.05 ml infusion/2 weeks days; in rats)	PFC	Knackstedt, L.A., R.I. Melendez, and P.W. Kalivas, 2010
↓ xCT	Following extinction (12 to 20 days) of contingent short-access cocaine (0.25 mg/infusion/2hrs/day; 10–20 days i.v.; in rats)	NAc core	Baker, D.A., et al., 2003
↓ xCT	Following extinction (2 weeks) of contingent short-access cocaine (0.20 mg/infusion/12 days; in rats)	NAc	LaCrosse, A.L., et al., 2017
↓ xCT	Following extinction (3 weeks) of contingent short-access cocaine (0.20 mg/0.05 ml infusion/2 weeks days; in rats)	NAc	Knackstedt, L.A., R.I. Melendez, and P.W. Kalivas, 2010
↓ xCT	Following extinction (2–3 weeks) of contingent short-access cocaine (0.25 mg/infusion/12 days; in rats)	NAc	Trantham-Davidson, H., et al., 2012

Table IV

Astrocyte related changes after opiate exposure

Astrocyte Marker	Study Design	Brain Region	Reference
↑ GFAP	morphine-tolerant rat spinal cord (15 μg/hrs/5days; intrathecal (i.t., in rats)	Spinal cord	Wen, Z.H., et al., 2008
↑ GFAP	Chronic morphine administration (10 mg/kg/5 days; s.c., in rats)	Spinal cord	Takemoto, M., et al., 2016
↑ GFAP	Chronic morphine administration (50 mg/kg/9 days; i.p., in rats)	Hippocampus, Posterior cingulate cortex, Spinal cord	Song, P. and Z.Q. Zhao, 2001
↑ GFAP	2 hrs after acute morphine administration (10 mg/kg; s.c., in mice	Dorsal root ganglia	Berta, T., et al., 2012
↑ GFAP	24 hrs after 1 or 3 days of morphine administration (10mg/kg/day; s.c. in mice)	Midbrain	Harada, S., K. Nakamoto, and S. Tokuyama, 2013
↑ GFAP	16 hrs after 5 days morphine treatment (2 × 10 to 40mg/kg/dose; i.p., in rats)	Striatum	Marie-Claire, C., et al., 2004
↑ GFAP	12 hrs after chronic morphine treatment (10 mg/kg every 12 hrs per 13 days; i.p., in rats)	NAc shell, VTA, Frontal cortex	Garrido, E., et al., 2005
↑ GFAP	12 hrs after chronic morphine treatment (10 mg/kg/ every 12 hrs/14 days, in rats)	Locus coeruleus and nucleus of the Solitary Tract	Alonso, E., et al., 2007
↑ GFAP	1 day after chronic morphine (10 mg/kg/9 days; i.p., in rats)	NAc	Amaral, G.F., et al., 2016
↑ GFAP	Following naloxone-induced withdrawal of chronic morphine treatment (2× 20 mg/kg/9 days, in mice)	Mouse brain	Pajohanfar, N.S., et al., 2017
↑ GFAP	Naloxone-induced withdrawal of chronic morphine (7 days escalating every 8 hrs/20, 40, 60, 80, 100, 100, and 100mg/kg, i.p.)	Spinal Cord	Liu, W.T., et al., 2010
No change GFAP	Chronic morphine administration (50 mg/kg/9 days; i.p., in rats)	Thalamus	Song, P. and Z.Q. Zhao, 2001
No change GFAP	2 hrs after acute morphine administration (10 mg/kg; s.c., in mice)	Spinal cord	Berta, T., et al., 2012
No change GFAP	12 hrs after acute morphine treatment (30 mg/kg; i.p., in rats)	NAc shell, VTA, Frontal cortex	Garrido, E., et al., 2005
No change GFAP	24 hrs after 5 days of morphine administration (10mg/kg/day; s.c., in mice)	Midbrain	Harada, S., K. Nakamoto, and S. Tokuyama, 2013
No change GFAP	Following reinstatement of morphine-induced CPP (10mg/kg/5 days; i.p., in rats)	Amygdala	Lin, X., et al., 2011
↓ GFAP	1 day after chronic morphine (10 mg/kg/9 days; i.p., in rats)	Mesencephalon	Amaral, G.F., et al., 2016
↓ GFAP	Following extinction of morphine-induced CPP (10mg/kg/5 days; i.p., in rats)	Amygdala	Lin, X., et al., 2011
↓ GLT-1	Following repeated morphine treatment in mice (3 × 30mg/kg daily for 5 days s.c.)	Cerebrum	Wu, N., et al., 2008
↓ GLT-1	After morphine treatment (1 μM/72h, in rats)	Primary astrocyte cultures	Wang, H., et al., 2017
↓ GLT-1	Following extinction (2 weeks) from contingent heroin access (days 1–2, 100μg/4 s infusion, days 3–4, 50 μg/ infusion, days 5–14 25 μg/infusion /3 h/14 days, in rats)	NAc core	Shen, H.W., et al., 2014
No change GLT-1	Following repeated morphine treatment in mice (3 × 30mg/kg daily for 5 days s.c.)	Cerebrum	Wu, N., et al., 2008
↑ xCT	Following extinction (2 weeks) from contingent heroin access (days 1–2, 100μg/4 s infusion, days 3–4, 50 μg/ infusion, days 5–14 25 μg /infusion/3 h/14 days, in rats)	NAc core	Shen, H.W., et al., 2014

Table V

Astrocyte-related changes after alcohol exposure

Astrocyte Marker	Study design	Brain Region	Reference
No change GFAP	Intermittent ethanol access in rats	Infralimbic cortex and OFC	Bull et al, 2015
No change in GLAST	48-hour withdrawal from ethanol (4 g/kg every 6 hours for 3 days via oral gavage) in alcohol-preferring P rats	Striatum, PFC	Das et al, 2016
↑ GFAP	Offspring of rats that received 5.8 g/kg ethanol via intragastric intubation	Layer V	Fakoya, 2005
↑ GFAP	6 weeks of ethanol exposure in rats	Hippocampus, striatum, cortex	Evrard et al, 2006
↑ GFAP	Chronic ethanol treatment with increasing concentrations (2.4–7.2%) in rats	Hippocampus, globus pallidus, cortex, internal capsule, corpus callosum	Dalcik et al, 2009
↑ GFAP	Intermittent ethanol access in rats	Prelimbic cortex and ACC	Bull et al, 2015
↑ GFAP	36 weeks of exposure to 5% ethanol in rats	Hippocampus	Franke, 1995
↑ GFAP	4 or 12 weeks of exposure to 10% ethanol in rats	Hippocampus	Franke, 1995
↑ GFAP	Offspring of rats exposed to chronic ethanol	Hippocampus and striatum	Ramos et al, 2002
↑ GFAP	Short term alcohol exposure in mice	Hippocampus	Satriotomo et al, 2000
↑ GFAP	Short term alcohol exposure in mice	Suprachiasmatic nucleus	Satriotomo et al, 2000
↑ GFAP	6 weeks of exposure to 6% ethanol in rats	CA1	Tagliaferro et al, 2002
↑ GFAP	Low (20%) or high (40%) dose of ethanol for 3 weeks, 3 months or 6 months in rats	Hippocampus and cingulate cortex	Vongvatcharanon et al, 2010
↑ EAAT2	Alcoholics in early (1 day) and late (28 days) withdrawal	White blood cells	Ozsoy et al, 2016
↑ EAAT1	Post mortem tissue from human alcoholics	Prefrontal cortex	Flatscher-Bader et al, 2008
↓ GFAP	Post mortem tissue from alcoholics	Superior frontal gyrus, primary motor cortex	Lewohl et al, 2005
↓ Glial density	Post mortem tissue from alcoholics	DLPFC	Miguel-Hidalgo et al, 2002
↓ GFAP	3 weeks of abstinence from continuous ethanol exposure in rats	Prelimbic cortex and OFC	Bull et al, 2015
↓ GFAP	3 weeks of abstinence from access to ethanol in rats	OFC	Bull et al, 2015
↓ GFAP	Oral gavage 6.5 g/kg/day in rats	Cortex	Teixeira et al, 2014
↓ Density of GFAP + astrocytes	Alcohol preferring P rats	Prelimbic cortex	Miguel-Hidalgo et al, 2005
No change GLT-1	Adolescent intermittent ethanol exposure in rats	Nucleus accumbens core	Madayag et al, 2017
No change GLT-1	Chronic intermittent ethanol exposure in rats	Nucleus accumbens core	Griffin et al, 2015
No change GLT-1	Intermittent alcohol consumption in rats	Nucleus accumbens	Pati et al, 2016
↓ GLT-1	48-hour withdrawal from ethanol in rats	Striatum, PFC	Abulseoud et al, 2014
↓ GLT-1	48-hour withdrawal from ethanol in alcohol-preferring P rats	Striatum, PFC	Das et al, 2016
↓ GLT-1	5 weeks free choice ethanol (15 and 30%) in alcohol-preferring P rats	Nucleus accumbens	Das et al, 2015

Table VI

Changes in GFAP and GLT-1 expression in the hippocampus in stress/depression and schizophrenia

Disorder	Changes in GFAP or GLT-1	Study design	Reference
Stress/Depression	↓ GFAP	Chronic unpredictable mild stress in mice	Yang et al, 2014
		CUS in rodents	Liu et al, 2011
		Chronically stressed mice	Ding et al, 2017
		Chronic unpredictable mild stress in rats	Ye et al, 2011
		Chronic immobilization stress in rats	Shilpa et al, 2017
		Restraint stress in rats	Santha et al, 2015
		Chronic psychosocial stress in male tree shrews	Czeh et al, 2005
		Early life deprivation in rats	Leventopoulos et al, 2007
		Inescapable shock protocol in rats (PTSD model)	Saur et al, 2016
			Han et al, 2015
		Single prolong stress in rats (PTSD model)	Gosselin et al, 2009
		Rat model of depression	Cobb et al, 2016
		MDD patients	
	↓ GLT-1	Chronic unpredictable mild stress	Zhu et al, 2017
		Chronic Unpredictable Stress in rats	Chen et al, 2014
		Chronic Unpredictable Stress for 42 days in rats	Liu et al, 2016
		Chronic post-natal stress in rats	Odeon et al, 2015
		Prenatal stress in rats	Zhang et al, 2013
		Learned helplessness in rats	Zink et al, 2010
		MDD patients	Medina et al, 2016
	↑ GLT-1	Chronic unpredictable stress	Raudensky and Yamamoto, 2007
		Maternal separation in rats	Martisova et al, 2012
Schizophrenia	No change in GFAP	DISC-1 mutant mice	Abazyan et al, 2014
		Schizophrenic patients	Steffek et al, 2008
	↑ GFAP	MK-801 treatment in rats	Yu et al, 2015
		Cultured astrocytes bathed in MK-801	Yu et al, 2015
		Gunn rats	Limoa et al, 2016
	↓ GLT-1	Schizophrenic patients	Shan et al, 2013