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REVIEW ARTICLE

Stress-induced structural and functional modifications of astrocytes—Further implicating glia in the central response to stress

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Abstract

An organism's response to stress requires activation of multiple brain regions. This can have long-lasting effects on synaptic transmission and plasticity that likely provide adaptive benefits. Recent evidence implicates not only neurones, but also glial cells in the regulation of the central response to stress. Intense, repeated or uncontrolled stress has been implicated in the emergence of multiple neuropsychiatric conditions. Human studies have consistently observed glial dysfunction in mood and stress disorders such as major depression. Interestingly animal models of stress have recapitulated glial abnormalities that are comparable to the human condition, validating the use of rodent models for the study of stress disorders. In this review we will focus upon one family of glia, the astrocytes, and describe the evidence to date that links astrocytes to possible stress-related disorders.

1 | INTRODUCTION

All organisms experience stress. How the brain responds to stress is critical for survival; how it adapts to stress ensures that individuals learn from experiences and respond more effectively in the future. Although crucial for survival, the response to stress can also have negative consequences on brain health. For example, acute, intense stress, or trauma can produce deficits in learning and memory recall. Repeated severe bouts of stress or trauma can have consequences for behavior and physiology that persist for a lifetime. Furthermore, stress has been linked to the emergence of psychopathologies such as anxiety disorders and depression (Dienes, Hazel, & Hammen, 2013; Hammen, 2005; Monroe, Kupfer, & Frank, 1992; Muscatell, Slavich, Monroe, & Gotlib, 2009). The prevalence of stress-related disorders has driven work on understanding the mechanistic underpinnings ranging from genetic predisposition to synaptic, network, and behavioral dysfunction. Only recently has this search turned toward the investigation of glial cells.

Clinically in humans, stress pertains to quantifiable mood and stress disorders such as anxiety and depression, often based on the Diagnostic and Statistical Manual of Mental Disorders. Although animal models of stress serve as a powerful research tool, these models have been criticized due to their limited capacity to reproduce the broad spectrum of emotions and behaviors observed in humans. Animal models do, however, reproduce the physiological aspects of stress described in humans (autonomic and endocrine changes; classic fight or flight responses). These evolutionarily conserved and easily quantifiable traits allow investigators to (a) distinguish the effects of acute from chronic stress, (b) determine the impact on the underlying cellular function, (c) correlate these data to behavior, and (d) carry out preclinical drug testing. Examples of stress paradigms used in rodent models include, footshock, forced swimming, immobilization, dehydration, chronic social defeat, chronic unpredictable stressors, breeding animals for anxiety and depressive behaviors, and corticosterone treatment. Despite the wide variety of protocols, there is a high-level of convergence in the data (Figure 1), implicating similar signaling pathways and neural circuits across varied stress paradigms. Although there has been extensive consolidation of information on neuronal elements and stress (Bains, Cusulin, & Inoue, 2015; Joëls & Baram, 2009; Lupien, McEwen, Gunnar, & Heim, 2009; Ulrich-Lai & Herman, 2009), there is limited information on the role of glia in the response to stress. Here we set out to review the literature on the impact of stress as it pertains to astroglial morphology and function in human mental illness and rodent stress models.

1.1 | Part I—Glial dysregulation in mood and stress disorders

Glial cells play multiple roles in regulating neuronal activity, synaptic plasticity, blood flow and behavior. Although this is still a nascent field, there is accumulating evidence implicating astrocytes in acute

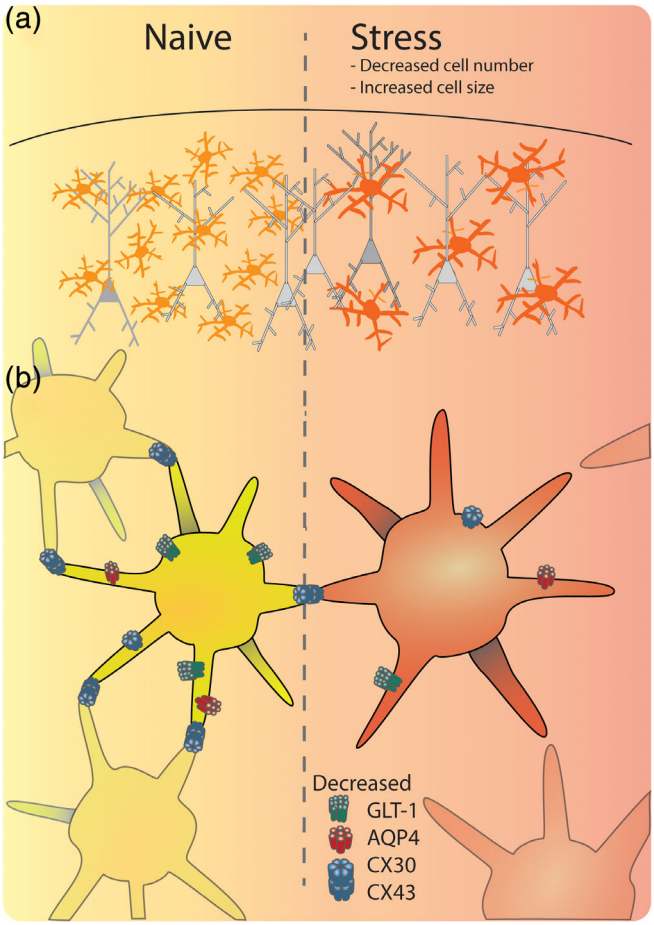

FIGURE 1 Effects of stress on astrocytic structure and function. (a) Schematic of astrocytes tiling the brain in naïve (nonstressed) conditions (left) compared to stress (right) with decreased astrocyte cell number and size. (b) In naïve conditions, individual astrocytes are tightly coupled to their neighboring astrocytes. They express high levels of astrocyte-specific proteins such as GLT-1, AQP4, Cx30, and Cx43. Following stress astrocyte function is impaired as denoted by decreased expression of the example proteins

and chronic stress effects in animal models, as well as stress disorders in humans.

1.1.1 | Stress is associated with changes in glial density and morphology

Human brain imaging studies demonstrate that decreases in brain tissue volume across multiple brain areas correlate with stress-related disorders such as major depressive disorder (MDD; Grieve, Korgaonkar, Koslow, Gordon, & Williams, 2013; Sheline, Wang, Gado, Csernansky, & Vannier, 1996; Zavorotnyy et al., 2018). It was initially proposed that neuronal loss was responsible for this observation in the hippocampus (Sheline et al., 1996). An independent study using histological staining of postmortem brain tissue revealed a similar reduction in brain volume in the prefrontal cortex associated with depression; these changes were not a consequence of decreases in the size or number of neuronal cells, but rather due to reduced numbers of glial cells (Ongür, Drevets, & Price, 1998). This depression-associated reduction in glial cell density was exacerbated in patients who had a family history of mental health issues, suggesting that genetic predisposition may be a contributing factor (Ongür et al., 1998). The effect of MDD on glial cell density and neuron: glia ratio has also been demonstrated in the amygdala (Bowley, Drevets, Öngür, & Price, 2002), but intriguingly, these effects were observed primarily in the left amygdala (Bowley et al., 2002). Lateralization of the amygdala is a well-described phenomenon and it has been suggested that grey matter volume changes in the left amygdala can be correlated with severity of depression (Zavorotnyy et al., 2018). In the hippocampus, data have been mixed. Some reports showing a decrease in hippocampal volume and increased pyramidal cell density in the CA1 region indicate no change in glial cell number, as observed with Nissl's staining, in MDD (Cobb et al., 2013). But when an astrocyte-specific marker is used, the same group reports a decrease in GFAP-positive (i.e., astrocytic) cell numbers in individuals with MDD who were not administered antidepressants (Cobb et al., 2016). No effect on glial cell numbers was found in brain tissue from patients with bipolar disorder (Bowley et al., 2002); this observation may be confounded by mood-stabilising medication (lithium or valproate) as separating patients based on treatment revealed a significant decrease in glial cell density in those not taking medication (Bowley et al., 2002). This evidence suggests that first, glial cell density is correlated with distinct mental health disorders, specifically major depression across multiple brain regions (Bowley et al., 2002; Ongür et al., 1998), and second, psychoactive drugs prescribed for mood disorders potentially mediate their effects through a rescue of glial cell number. Indeed, a recent study investigated the effects of lithium on cell proliferation in the prefrontal cortex compared to the hippocampus and observed increases in both neuronal and glial number in the hippocampus but not the cortex following lithium treatment in naïve (nonstressed animals) (Rajkowska et al., 2016). Furthermore, this study used GFAP staining to estimate astrocyte proliferation and observed a 15% increase in cell density in the dentate gyrus with no effect in the medial prefrontal cortex (Rajkowska et al., 2016). In agreement, it has been observed that the decrease number of hippocampal astrocytes associated with MDD was not observed in brain tissue from patients taking antidepressants (Cobb et al., 2016), again suggesting antidepressants limit depression-associated decline in glial cell number. Interestingly, these studies provide evidence of glial heterogeneity in their response to antidepressants. Further investigation into the underlying mechanism would be of great interest in the field. Although these papers were pivotal in the development of a more "gliocentric" hypothesis for stress disorders, one drawback is that many of them did not distinguish glial cell types. Nissl staining was used to differentiate neurons to glia, mainly based on soma size, but no further analysis was carried to distinguish the macroglia (astrocytes, oligodendrocytes and oligodendrocyte precursor cells) from microglia.

In addition to changes in glial cell density, studies have also reported structural modifications specifically in astrocytes in MDD (Miguel-Hidalgo et al., 2000; Torres-Platas et al., 2011). Initial evidence using anti-GFAP antibodies suggested an increase in astrocyte volume in postmortem tissue for MDD patients (Miguel-Hidalgo et al., 2000). Interestingly, this study revealed that astrocyte size was correlated with age, with younger depressed patients exhibiting smaller astrocyte size compared to healthy age-matched controls, whereas older depressed patients had larger astrocytes compared to controls (Miguel-Hidalgo et al., 2000). Detailed single-cell analysis demonstrated that both the

total length of astrocyte processes as well as astrocyte cell body volume were increased in MDD compared to healthy controls (Torres-Platas et al., 2011). These findings are reminiscent of the astrocytic hypertrophy and remodeling that occurs in a number of disease models including epilepsy (Castiglioni, Peterson, Sanabria, & Tiffany-Castiglioni, 1990; Oberheim et al., 2008), and following nerve injury (Butt & Colquhoun, 1996; Sun, Lye-Barthel, Masland, & Jakobs, 2010), which is believed to promote brain repair (Anderson et al., 2016). As astrocyte morphology is known to be intimately linked with synaptic function (Henneberger et al., 2018; Oliet, Piet, & Poulain, 2001; Ostroff, Manzur, Cain, & Ledoux, 2014; Pannasch et al., 2014), the astrocytic morphology changes observed in MDD brain tissue indicate that this disease could be affecting neuron–glia interactions at the level of the synapse.

Together, this evidence suggests brain region-specific alterations in astrocyte density and morphology in mood and stress disorders. Interestingly, antidepressants impact these structural changes, suggesting these drugs may rely on a glial mechanism to improve mental health. The variability between studies and the effects in different brain regions could reflect astrocyte heterogeneity across the brain. This is a rapidly developing field, as more tools to investigate detailed astrocyte function appear, we are able to distinguish discrete populations of cells. This heterogeneity appears to be associated with surrounding neurons and the co-dependent relationship between neurons and glia during development (Chai et al., 2017; Xin et al., 2019). Indeed, this could underlie the differential effects on glial cell number and structure in mood disorders. Other factors that may underlie this variability include the age, sex, ethnicity, environment, severity and duration of disease. One could imagine that alterations in astrocyte cell number would only occur in the most severe cases of mood and stress disorders as losing these glia is likely to have a profound impact on brain physiology.

1.1.2 | Stress is associated with changes in astrocyte gene expression profiles

Strong evidence of astrocyte dysfunction as a result of stress disorders has been generated using nonbiased transcriptome analyses. These analyses, which do not consider a priori assumptions, generate large data sets and are great resources when attempting to understand the mechanisms underlying pathology. These approaches have shown that the gene expression profiles of astrocytes are sensitive to depression, an indication that these cells may react and respond to the demands of stress (Ernst et al., 2011; Klempan et al., 2009; Nagy et al., 2015; Nagy, Torres-Platas, Mechawar, Turecki, & Blvd, 2017; Torres-Platas, Nagy, Wakid, Turecki, & Mechawar, 2016). In particular it has been shown that both connexin (Cx) 30 and 43 are downregulated in MDD (Ernst et al., 2011; Nagy et al., 2017). These two proteins are the major gap-junction channel forming proteins, responsible for intercellular communication between astrocytes, as well as for shuttling of energy substrates and metabolites between astrocytes (Giaume, Koulakoff, Roux, Holcman, & Rouach, 2010). Gap-junction coupling proteins Cx30 and 43 are known to have profound impact on neuronal signaling and plasticity (Pannasch et al., 2011, 2014; Rouach, Koulakoff, Abudara, Willecke, & Giaume, 2008; Sibille, Pannasch, & Rouach, 2014). Furthermore, it has been demonstrated that Cx30 controls astrocyte morphology, limiting synapse invasion by astrocyte processes (Pannasch et al., 2014). As such, these data demonstrating astrocyte hypertrophy (Torres-Platas et al., 2011) could be a consequence of reduced gap-junction channel expression and/or function in stress disorders (Ernst et al., 2011; Nagy et al., 2017). Also noteworthy, in the context of stress disorders where sleep becomes an issue, it has been shown that Cx43-mediated GJ coupling between astrocytes plays a crucial role in the regulation of the sleep–wake cycle (Clasadonte, Scemes, Wang, Boison, & Haydon, 2017). Whether stress-induced reduction in Cx43 expression contributes to the sleep dysregulation associated with depression remains unknown. Astrocytes are also known to influence sleep pressure through release of gliotransmitters acting on neuronal adenosine A1 receptors (Florian, Vecsey, Halassa, Haydon, & Abel, 2011; Halassa et al., 2009). This information is clinically relevant as the antidepressant effects of deep-brain stimulation appear to be dependent on astrocyte function, specifically relating to gliotransmitter release acting on A1 receptors (Etiévant et al., 2015).

The transcription factor sox-9, which is specific to astrocytes and has been used as a marker to label these cells (Sun et al., 2017), has been demonstrated to be downregulated in MDD (Ernst et al., 2011). The authors took this finding, which was acquired from human tissue, back to the bench to determine the relevance of sox-9 on astrocyte function. Using a rodent model to knock down sox-9 resulted in a strong decrease in Cx30 protein, as observed by western blots (Ernst et al., 2011). These data suggest depression can dramatically impact astrocyte network function, which may play a role in the synaptic deficits and cognitive decline associated with the disease. The mechanism by which sox-9 regulates specifically Cx30 expression is unknown and, to our knowledge, has not been investigated further. Sox9 is known to be involved in the Wnt/β-catenin signaling pathway, which can regulate expression of other gap-junction proteins such as Cx43 (Ai, Fischer, Spray, Brown, & Fishman, 2000). The mechanism by which sox-9 regulates Cx30 expression remains elusive.

The dysregulation of astrocyte gap-junction channel protein expression in the prefrontal cortex of individuals with MDD may be due to epigenetic mechanisms, including DNA methylation (Nagy et al., 2015). These data show that deficiency in GJA1 or GJB3 genes, which code for Cx30 and 43 respectively, does not underpin the major depression phenotype, but rather that the expression of these genes is reduced as a result of the disease. Evidence suggestive of reduced gap junction expression in astrocytes was also observed in hippocampal tissue from depressed patients (Medina et al., 2016), suggesting that the down regulation of Cx30 and Cx43 could be a brain-wide phenomenon and a general maladaptation of this disease.

Astrocytes are pivotal for efficient glutamate uptake and conversion to glutamine, which can then be recycled back to neurons. GLT-1, GLAST, and glutamine synthetase are all essential for glutamate uptake and recycling and are specifically expressed in astrocytes. Decreases in mRNA for all three proteins have been detected in the locus coeruleus (which provides significant noradrenergic input to the forebrain) of patients with MDD (Bernard et al., 2011). Interestingly, this study also revealed depression-induced reduction in transcripts for GFAP, S100 calcium-binding protein B (S100B), Cx30, and 43, as well as aquaporin 4 (AQP4) but not in bipolar patients (Bernard et al., 2011). Decreases in GFAP expression in hindbrain regions such as the

cerebellum have been described in patients with MDD (Fatemi et al., 2004). This is particularly relevant in light of recent data demonstrating the role for the cerebellum in reward circuitry and social behavior (Carta, Chen, Schott, Dorizan, & Khodakhah, 2019). One could speculate that astrocyte dysfunction in the cerebellum, and other hindbrain regions, in mood and stress disorders impact projections from these regions to forebrain areas such as the ventral tegmental area (VTA; Carta et al., 2019), influencing the salience of reward and social behaviors.

These data suggest significant astrocyte dysfunction in major depression, but not in other mood disorders. Furthermore, the specific mRNA transcripts affected by MDD are all highly relevant to astrocytic control of synaptic function. For example, astrocytic glutamate uptake, as well as conversion to glutamine, is pivotal to proper synaptic function at both excitatory and inhibitory synapses (Battaglioli & Martin, 1991; Norenberg & Martinez-Hernandez, 1979). As such, dysregulation of these genes could have dramatic effects on synaptic transmission, as well as modifying excitatory-inhibitory balance in the brain. Another astrocytic gene of interest impacted by depression is S100B (Bernard et al., 2011), a calcium binding protein commonly used as a marker for astrocytes. This protein is released by astrocytes to control neuronal firing and subsequently rhythm generation (Morquette et al., 2015). The reduction in S100B mRNA observed by Bernard et al. (2011), however, is in contrast to another study reporting an increase in S100B in patients with MDD (Schroeter, Abdul-Khaliq, Diefenbacher, & Blasig, 2002). This discrepancy may be due to measurement approaches (brain vs. serum) or it may reflect heterogeneity in MDD patient populations including the age of patients and the duration of disease.

Major depression can also result in modifications of protein expression in specific astrocyte compartments such as the astrocyte endfoot (Rajkowska, Hughes, Stockmeier, Javier Miguel-Hidalgo, & Maciag, 2013), which line the parenchymal cerebral vasculature (Mathiisen, Lehre, Danbolt, & Ottersen, 2010) and can modulate arteriole tone (Rosenegger, Tran, Wamsteeker Cusulin, & Gordon, 2015). Using antibodies against AQP4, an astrocyte specific water-permeable channel, a decrease was detected in AQP4 from MDD brain tissue compared to healthy controls (Rajkowska et al., 2013). There was, however, no evidence to support structural remodeling of the astrocyte endfoot, indicating that the stress-induced remodeling of astrocytes at the blood vessel was selective for specific proteins (Rajkowska et al., 2013). No changes to the fine astrocyte arbour, which interacts with synaptic elements, were detected using light microscopy. Given the small size of astrocyte processes, which can be below 100 nm (Henneberger et al., 2018), these studies likely did not have the subcellular resolution necessary to detect any fine structural modifications. The consequences of AQP4 dysregulation in MDD are unknown, but downregulation of this water channel leads to impaired signaling of volume regulated anion channels (Benfenati et al., 2007). Volume changes in astrocytes are also involved in many different aspects of astrocyte function, including the control of osmotic homeostasis (Ciura et al., 2018).

Together these data suggest possible links between structural dysregulation as well as gene expression changes in astrocytes to chronic pathological stress phenotypes. Considering what we have learned about astrocyte structure and function in the regulation of synaptic transmission and plasticity, it is highly likely that these broad changes in some of the most vital astrocyte-specific proteins contribute to the cognitive impairments associated with mood and stress disorders. These gene expression profile changes in astrocytes are likely to differ with severity of disease, following and potentially compensating for underlying synaptic alterations known to be associated with these disorders. For example, it is known that synaptic proteins and dendritic spines are dramatically reduced in major depression (Kang et al., 2012). Considering the intimate relationship between astrocyte fine processes and synaptic elements, it would be more surprising if this change was not mirrored by a decrease in astrocyte-specific proteins known to localise at the synapse such as glutamate transporters. What we do not know, is whether these changes in astrocyte gene expression profiles contribute to, or are a consequence of, the reduction in synaptic density and associated cognitive impairments. It is possible that stress directly affects astrocytes, as these cells highly express glucocorticoid receptors (Zhang et al. 2014), leading to dysregulation of many genes and ultimately neuronal dysfunction.

Human data, while being the gold standard for understanding disease, can prove difficult to interpret with many different genetic and lifestyle factors playing a role in disease phenotypes. The data presented above can only indicate astrocyte dysfunction in mood and stress disorders, as it is very challenging to make causal connections between astrocytes and human disease. However, we do know that astrocytes strongly regulate glutamate levels in the brain, and altered glutamate homeostasis has been repeatedly observed in depression. Increased glutamate levels have been measured in the plasma (Mauri et al., 1998), serum (Mitani et al., 2006), CSF (Frye, Tsai, Huggins, Coyle, & Post, 2007) and with magnetic resonance spectrometry (Frye et al., 2007). A meta-analysis of MRS data revealed decreased glutamate levels across multiple studies in the cortex (Luykx et al., 2012). Nevertheless, the locus of glutamate mishandling is difficult to pinpoint as this could be a combination of neuronal and/or astrocyte dysfunction. As such animal models are vital to better understand the mechanistic underpinnings of different aspects of stress disorders.

1.2 | Part II—Animal models linking astrocyte dysfunction in mood and stress disorder

Animal models used to study mood and stress disorders have delivered great insight into the effects of stress on astrocytes. These models enable the quantification of distinct aspects of stress on cellular function, and allow for the correlation with behavior. We will discuss the effects of stress on several aspects of astrocyte structure and function. It is important to note that astrocytes do not exist in isolation and dynamically interact with surrounding neurons and glia. As such, it can be difficult to ascertain whether stress directly impacts astrocyte function, or whether any changes in astrocyte structure and function is in response to effects on neighboring cell types. Furthermore, until recently it has been difficult to specifically target astrocytes, manipulate their function and observe the impact on network function and behavior.

1.2.1 | Effects of chronic stress paradigms on astrocyte structure and function

Glial fibrillary acidic protein

Early investigation revealed that corticosterone down-regulates GFAP expression brain-wide, in response to both acute and chronic CORT

delivery (Nichols, Osterburg, Masters, Millar, & Finch, 1990; O'Callaghan, Brinton, & McEwen, 1991). This reduction in GFAP has been more recently validated using a chronic unpredictable stress protocol (Banasr et al., 2010). The roles of the intermediate filament protein GFAP are many (Hol & Pekny, 2015), including the anchoring of astrocytic glutamate transporters in the membrane (Sullivan et al., 2007). Reduced GFAP expression has also been demonstrated to negatively affect cell process growth toward neurons in vitro (Weinstein, Shelanski, & Liem, 1991). This suggests that reduced GFAP levels observed after stress in rodent models, as well as in human brain tissue from major depressive patients (Bernard et al., 2011; Fatemi et al., 2004; Torres-Platas et al., 2016), could influence astrocytic interactions at the synapse. Neuron–glia interactions at the synapse are highly dynamic and have been shown to remodel in response to homeostatic stress such as dehydration (Chapman, Theodosis, Montagnese, Poulain, & Morris, 1986), following fear conditioning paradigms (Ostroff et al., 2014), and in response to physiological levels of neuronal activity (Bernardinelli et al., 2014; Henneberger et al., 2018). However, the precise mechanism by which prolonged CORT exposure leads to decreased GFAP protein expression, and whether this impacts neuron–glia interactions under these conditions remains unknown. As mentioned above, gene expression analysis revealed dysregulation of not only GFAP but also AQP4, S100B, and gap-junction channel proteins Cx30 and 43 in human MDD patients (Bernard et al., 2011). This demonstrates the complexity of chronic stress in the human compared to the rodent models, some of which rely on exogenous CORT exposure. It is likely that CORT treatment alone is mimicking one aspect of stress disorders, as high cortisol levels in humans is but one hallmark associated with stress disorders (Dienes et al., 2013). High blood cortisol is not unique to stress disorder but is also found in Cushing's disease, a rare metabolic disorder characterised by excessive secretion of adrenocorticotropic hormone (ACTH) from the pituitary. Interestingly, there is a strong co-morbidity of mental health disorders and depression in Cushing's disease (Pivonello et al., 2015; Sonino, Fava, Raffi, Boscaro, & Fallo, 1998), which may be due to the central effects of chronically elevated cortisol. To our knowledge astrocyte dysfunction underlying the depressive symptoms in Cushing's disease remains unexplored.

Neurovascular coupling

The chronic psychosocial stress rodent model of depression results in a reduction in individual astrocyte volume and decreased total number of astrocytes in the hippocampus (Czéh, Simon, Schmelting, Hiemke, & Fuchs, 2006). Furthermore, animals treated with an antidepressant during the chronic stress protocol were resistant to the stress-induced modifications in astrocyte number and structure (Czéh et al., 2006). Similar data were obtained by selectively breeding rats for depressive phenotypes, demonstrating that depression induces distinct changes in astrocyte morphology (Di Benedetto et al., 2016). These stress-induced morphological modifications which largely impacted the association of astrocyte endfeet at the blood vessel, could be completely reversed with selective serotonin reuptake inhibitor (SSRI) antidepressant (fluoxetine) treatment, in a mechanism requiring AQP4 (Di Benedetto et al., 2016). To date, despite the indication that astrocyte endfeet lining the cerebrovasculature are modified as a result of stress disorder in humans (Rajkowska et al., 2013) as well as in rodent models (Di Benedetto et al., 2016), evidence for dysfunction at the vascular interface is sparse. Under physiological conditions astrocytes integrate synaptic, behavioral and vascular information to mediate an appropriate blood vessel response (Tran, Peringod, & Gordon, 2018). As there is strong evidence for stress influencing both synaptic transmission and behavioral state (Füzesi, Daviu, Wamsteeker Cusulin, Bonin, & Bains, 2016; Sterley et al., 2018), stress-induced modification of neurovascular coupling is expected. One study, carried out in the amygdala, observed that 7 days of heterotypical stress lead to deficiency in the response of vascular cells to vasodilatory signals released by astrocytes (Longden, Dabertrand, Hill-Eubanks, Hammack, & Nelson, 2014). This suggests that as well as affecting astrocyte function, stress also appears to impair vascular contractile cells in a glucocorticoid-dependent manner (Longden et al., 2014). Whether stress affects astrocytic integration of synaptic and behavioral states, to influence blood vessel dynamics remains unknown. Regarding direct effects of stress on the vasculature, chronic stress has been shown to decrease blood–brain barrier stability (Menard et al., 2017) and increase vascular stiffness in a systemic manner (Goodson et al., 2017).

Glutamate uptake and transmission

Glutamate uptake and metabolism by astrocytes is impaired by chronic unpredictable stress in the cortex (Banasr et al., 2010). As mentioned above, glutamate metabolism to glutamine is carried out solely by astrocytes (Norenberg & Martinez-Hernandez, 1979) and glutamine is a precursor for both GABA and glutamate (Battaglioli & Martin, 1991). Importantly, it was demonstrated that manipulation of astrocyte function using Riluzole, a drug known to increase astrocytic glutamate transporter expression (Carbone, Duty, & Rattray, 2012), was sufficient to alleviate the effects of stress in this model (Banasr et al., 2010). These data suggest a link between astrocyte glutamate uptake and metabolism in stress-induced behavioral phenotypes. However, other studies have provided opposing data, with increased GLT-1 mRNA and protein expression in the hippocampus (Reagan et al., 2004; Wood, Young, Reagan, Chen, & McEwen, 2004). Interestingly, both the antidepressant Tianeptine (Reagan et al., 2004) and the antipsychotic Lithium (Wood et al., 2004) can restore GLT-1 expression to naïve levels. These seemingly opposing data could reflect the different stress paradigms used by the two groups. Banasr et al. (2010) used 35 days of unpredictable stress compared to 21 days of restraint stress used by Reagan et al. (2004) and Wood et al. (2004). Unfortunately, none of these studies measured glutamate transporter currents in astrocytes from these models. As such there is a possibility that despite the increased expression observed in Reagan et al. (2004) and Wood et al. (2004), there may still be functional deficits in glutamate uptake. Nevertheless, there was a common observation demonstrating modifications in glutamate transporter expression which was rescued—no matter whether it was pathologically increased or decreased—with antidepressants. Another study, using the Flinders sensitive line of rats, a strain which expresses a depressive-like phenotype (Overstreet & Wegener, 2013), found no modification in hippocampal GLT-1 expression assessed using western blots (Gómez-Galán, De Bundel, Van Eeckhaut, Smolders, & Lindskog, 2013). They did, however, observe

decreased GLAST expression. Furthermore, the study reports LTP impairments, which could be rescued with exogenous D-serine application. Validation of this finding using liquid chromatography revealed decreased levels of D-serine in this rodent model of depression (Gómez-Galán et al., 2013). Although there is no clear link between GLAST downregulation and D-serine production, this suggests astrocytic dysfunction in distinct aspects of glutamatergic transmission in the hippocampus. Furthermore, this study highlights the differences between models used for depression. The Flinders sensitive line of rats was developed specifically for its hypersensitivity to cholinergic agonists, similar to human depressive patients, and depressive-like phenotypes (Overstreet, 1993). As such, direct comparisons between this genetic rodent model and stress-induced models of depressive-like disorders are challenging. Distinct animal models likely reproduce specific aspects of disease. The Flinders sensitive model may be more suited for the study of genetic forms of human depression, as this depressive-like phenotype is genetic, whereas stress-induced models may relate more to depression following extreme, stressful life events.

It has been demonstrated that depressive phenotypes can be driven by inducing astrocyte dysfunction alone. It was found long-term NMDA receptor antagonism by memantine, which acts as an open channel blocker (Lipton, 2004), induced a reduction astrocytic glutamate transport that correlated with a depressive phenotype (Zimmer et al., 2015). The link between NMDA receptor antagonism and glutamate transporter function in this model of stress is unclear. It is possible that the reduction in neuronal activity induced by NMDA receptor antagonism was matched by reduced glutamate transporter expression on astrocytes. Dynamic feedback between neuronal activity and astrocytic glutamate uptake has been widely observed and thus this is a probable explanation (Al Awabdh et al., 2016; Armbruster, Hanson, & Dulla, 2016; Murphy-Royal et al., 2015; Yang et al., 2009). There is evidence, however, for the expression of functional NMDA receptors on astrocytes in upper layers of the cortex (Mehina, Murphy-Royal, & Gordon, 2017). As such the effects of prolonged NMDA receptor antagonism on glutamate transporter function used in Zimmer et al. (2015) could be mediated by direct effects of memantine on astrocytic NMDA receptors. In agreement with the data from Zimmer et al. (2015), injection of a dihydrokainate into the prefrontal cortex of rats, to block glutamate uptake, was found to be sufficient to drive anhedonia-like behaviors in multiple studies (Bechtholt-Gompf et al., 2010; Cui et al., 2014; John et al., 2012; Lee, Gaskins, Anand, & Shekhar, 2007).

In contrast to long-term NMDA receptor antagonism which appears to be able to drive a depressive phenotype (Zimmer et al., 2015), acute treatment with the NMDA receptor antagonist ketamine has been shown to reduce symptoms of depression (McGirr et al., 2015) and depressive-like phenotypes (McGirr, LeDue, Chan, Xie, & Murphy, 2017). One study investigated the effects of stress on cortical connectivity in situ using mesoscale cortical imaging of glutamatergic transmission in rodent model of depression. Following chronic stress the authors found aberrant cortical connectivity associated with alterations in glutamatergic signaling, which could be rapidly reversed with brief, low-dose ketamine exposure (McGirr et al., 2017). This data mimics the rapid antidepressant effects of ketamine in human patients (McGirr et al., 2015). The underlying mechanism by which this occurs remains to be resolved; however it does appear to involve increased neuronal activity (Carreno et al., 2016; Fuchikami et al., 2015), increased release and cycling of glutamate (Chowdhury et al., 2012, 2017; Moghaddam, Adams, Verma, & Daly, 1997), and release of neurotrophic factors (Autry et al., 2011). Despite the knowledge that astrocytes can regulate neuronal activity, are directly involved in glutamate homeostasis, and can readily release neurotrophic factors, their implication in the antidepressant effects of ketamine has yet to be determined.

Metabolic dysfunction

In addition to stress-induced metabolic deficiencies in glutamate handling (Banasr et al., 2010), recent reports demonstrate that peripheral infusion of L-lactate alleviates certain aspects of depression-like behavior in rodents (Carrard et al., 2018). This hints at a role for more global astrocytic metabolic deficiencies in stress-related disorders. These data suggest that L-lactate production and/or release from astrocytes is impaired in chronically stressed mice. Consistent with this idea, 5 weeks of chronic unpredictable stress have a severe impact on glycogen synthesis and glycogenolysis in the brain (Zhao et al., 2017). Unlike the periphery where glycogen synthesis decreases, stress is associated with an increase expression and function of glycogen synthase in the brain (Zhao et al., 2017). Despite the seemingly compensatory mechanism of upregulating glycogen synthesis during glycogenolysis, chronically stressed animals exhibited glycogen deficiency and a depressive-like phenotype (Zhao et al., 2017). These data are strongly suggestive of astrocytic metabolic dysfunction in chronic stress, as astrocytes are the only brain cells which can store energy in the form of glycogen.

In vivo evidence suggests that there is a gradient of lactate with high levels present in astrocytes and lower levels in neurons, predicting lactate movement down its concentration gradient (Mächler et al., 2016). As such, stress-induced impairment of astrocytic energy reserves, in the form of glycogen (Zhao et al., 2017), is likely to directly impact lactate production and shuttling to neurons. The idea that astrocytes support neuronal activity with lactate in an activity-dependent manner was originally proposed by Pellerin and Magistretti (1994), and forms the basis of what is now known as the astrocyte-neuron lactate shuttle (ANLS) hypothesis (Magistretti & Allaman, 2018). Metabolic networks formed by gap-junction channel connected astrocytes are necessary for sustained synaptic transmission (Rouach et al., 2008), for certain forms of synaptic plasticity such as long-term potentiation, and for memory formation in vivo (Gibbs et al., 2006, b; Suzuki et al., 2011). These data indicate that astrocytic networks function as an energy reservoir, permitting diffusion of energy substrates between individual cells to areas with high energetic demand. The fact that multiple studies link dysfunction of astrocyte metabolism with depression-like phenotypes is intuitive, as a breakdown in the ANLS would likely limit synaptic bioenergetics, and could underlie impaired synaptic plasticity has been reported to occur at glutamatergic synapses following stress in the hippocampus and surrounding brain regions (Baker & Kim, 2002; MacDougall & Howland, 2013).

Gap-junction coupling

Chronic unpredictable stress, which is sufficient to drive behavioral abnormalities, including decreased sucrose preference and novelty

suppressed feeding, is correlated with a downregulation in the astrocyte specific gap-junction channel Cx43 (Sun, Liu, Yuan, Li, & Chen, 2012). Intriguingly, in vivo treatment with SSRIs (fluoxetine and duloxetine) increased the expression of Cx43 protein (Sun et al., 2012). These data further support the hypothesis that clinical anti-depressants may relieve behavioral symptoms by modifying the expression of astrocytic proteins which are known to be affected by stress in rodents (Carter, Hamilton, & Thompson, 2013; Ernst et al., 2011; Sun et al., 2012) and in clinically depressed patients (Bernard et al., 2011; Ernst et al., 2011; Nagy et al., 2017). Furthermore, treatment with SSRIs or with the glucocorticoid receptor antagonist mifepristone fully rescues the effects of chronic stress on astrocytic Cx43 expression and reverses behavioral phenotypes associated with chronic unpredictable stress (Sun et al., 2012). An independent study made similar observations using chronic glucocorticoid treatment as their stress paradigm (Quesseveur et al., 2015). Specifically, chronic CORT reduced astrocytic Cx43 expression levels and this decrease was blocked when animals were treated with fluoxetine. Furthermore, knocking out Cx43 induced behavioral deficits similar to stress (Quesseveur et al., 2015). The fact that these two independent studies, using different stress protocols, revealed a conserved mechanism supports the robustness of the findings. Furthermore, noradrenaline, which is necessary for the effects of SSRIs to induce their antidepressant effects (Cryan et al., 2004), can also induce astrocytic release of ATP (Gordon et al., 2005), suggesting a potential role for astrocyte-derived ATP in stress disorders. Indeed, reduced gliotransmission can lead to a depressive-like phenotype (Cao et al., 2013). It was demonstrated that manipulating astrocyte calcium signaling, or blocking gliotransmitter release using the dominant-negative SNARE transgenic mouse line, was sufficient to prevent or mimic stress phenotypes (Cao et al., 2013). This was suggested to be a consequence of reduced ATP release from astrocytes (Cao et al., 2013). Although the data from this specific study are compelling, there are likely concomitant decreases in the release of other astrocytic gliotransmitters, as the dn-SNARE mouse is not selective for ATP. Furthermore, there could be a reduction in ATP production by astrocytes which limits ATP availability for gliotransmission.

Wnt/β-catenin signaling

There is an extensive literature regarding wnt/β-catenin signaling. This pathway is pivotal during development for both neurons and glia, specifically during angiogenesis and oligodendrocyte maturation (Fancy et al., 2009). Dysregulation of neuronal and/or astrocytic β-catenin may underlie stress-induced structural reorganisation of cortical dendrites and loss of dendritic spines (Liston et al., 2006; Radley et al., 2006). Endogenous levels of β-catenin can be used to predict stress resilience in a rodent model of chronic social defeat stress (Dias et al., 2014). Using a viral approach, Dias et al. (2014) increased or decreased β-catenin levels to influence stress resilience and susceptibility, respectively (Dias et al., 2014). The viral approach did not distinguish cell-type, and as such both neurons and glia were likely impacted by this manipulation. An independent study investigated the effects of targeting β-catenin overexpression specifically in GLAST-expressing cells (i.e., astrocytes; Vidal et al., 2018), which was sufficient to reduce anxiety-like behaviors (Vidal et al., 2018). These data implicate astrocytic wnt/β-catenin signaling in the central response to stress. Manipulation of wnt/β-catenin signaling impacts LTP (Ivanova et al., 2017). As mentioned above, canonical Wnt/β-catenin signaling can affect gap-junction channel expression (Ai et al., 2000). Linking these data together, it has been demonstrated that dysregulation of the astrocyte gap-junction channel Cx30, disrupts long-term potentiation of synaptic transmission (Pannasch et al., 2014). This speculative link between β-catenin and the expression of gap-junction proteins impacting plasticity in the context of stress requires further validation. Although the role of β-catenin in synapse formation has been well-described at the presynaptic active zone (Bamji et al., 2003), and in pre- and postsynaptic PDZ domain-recruiting proteins (Brigidi & Bamji, 2011), evidence for a role of astrocytic β-catenin in astrocyte–synapse interactions is limited. It appears that β-catenin positively regulates GLT-1 expression through an unidentified mechanism (Lutgen, Narasipura, Sharma, Min, & Al-Harthi, 2016), but whether β-catenin also functions as a scaffold element in glia to either form, or maintain the integrity of the tripartite synapse is not known.

Another tentative link between these distinct findings may be that wnt signaling can inhibit glycogen synthetase kinase 3β (Chen, Ding, & McCormick, 2000). Inhibition of GSK3β stimulates activation of glycogen synthase and glucose transport (Oreña, Torchia, & Garofalo, 2000) in nonbrain cells. As such altered wnt/β-catenin signaling could affect the metabolic function of astrocytes by impairing astrocyte network connectivity and/or directly manipulating metabolism in these cells. Finally, the effects of GSK3β can be replicated with lithium treatment, a common mood stabilizing drug used to treat bipolar disorder, suggesting that the benefits of lithium for mood disorders (Chen et al., 2000; Klein & Melton, 1996; Stambolic, Ruel, & Woodgett, 1996) may rely on astrocytes.

1.2.2 | Effects of acute stress on astrocyte structure and function

Although studies investigating the effects of acute stress on astrocytes are limited, the data published to date indicate profound effects on behavior. A single bout of acute stress provokes astrocytic release of fibroblast growth factor 2 (FGF2), promoting maturation of hippocampal neural stem/progenitor cells (NPCs) and conferring enhanced retainment of fear extinction memory (Kirby et al., 2013). Prior to this study, FGF2 had been identified as being necessary for the antidepressant-mediated rescue of depressive behaviors, as inhibition of FGF2 activity was shown to block the effect of antidepressants (Elsayed et al., 2012). Targeting the FGF system is a clinically relevant target as it has the FGF system is downregulated in MDD and modulated by SSRIs (Evans et al., 2004). Interestingly, FGF2 has also been implicated in a rodent model of post-traumatic stress disorder (PTSD), where a single prolonged stress protocol, which induces behavioral impairments lasting up to 14-days poststress, was rescued with FGF2 treatment (Xia et al., 2013). The study reports decreased GFAP and structural alterations in hippocampal astrocytes which were rescued with FGF2, suggesting astrocytic impairments could underlie the behavioral deficit in this model (Xia et al., 2013). Similar findings regarding GFAP expression and morphological alterations in astrocytes have been reported using a single inescapable foot shock protocol (Saur et al., 2016), indicating a conserved response by astrocytes to acute stress. We do not yet understand the impact of these structural modifications

on astrocytic function at the level of the synapse. The role for these long-lasting, late-onset adaptations to acute stress are unclear. This may indicate that even single bouts of acute stress may have long lasting impacts on brain function and could potentially influence future stress susceptibility or resistance.

Transcriptomic analyses of potential astrocyte-specific changes following both acute and chronic glucocorticoid treatment of rodents in vivo has been performed (Carter et al., 2013). Modifications in genes coding for gap-junction channels Cx30 and 43, glutamate transporters, glutamine synthetase, and many others were reported (Carter et al., 2013). These data are in line with human data from MDD patients (Bernard et al., 2011; Ernst et al., 2011; Nagy et al., 2017), and indicate that glucocorticoid signaling in stress pathology may be a primary driver of astrocyte dysfunction. Many of these genes are also differentially regulated by acute versus chronic CORT, displaying strong variability between the cortex and hippocampus which could reflect astrocyte heterogeneity across the brain (Carter et al., 2013). Although the functional outcome of altered gene expression could not be assessed using this approach, the data provide insight into the potential impact of acute and chronic glucocorticoid action on astrocyte function.

Despite the data noted above, acute glucocorticoid treatment cannot fully replicate the synaptic deficits induced by acute stress in vivo (MacDougall & Howland, 2013). Although acute stress induced significant impairments of synaptic plasticity in the rat dorsal subiculum through a glucocorticoid receptor-mediated process, glucocorticoid treatment alone was insufficient to reproduce this synaptic phenomenon (MacDougall & Howland, 2013). These data suggest potential synergistic effects of additional neurochemical cascades induced by stress, for example, catecholamines (Roebuck, Liu, Lins, Scott, & Howland, 2018), which may act in concert with glucocorticoids to drive modifications in synaptic function. Nevertheless, MacDougall and Howland (2013) neither quantified nor speculated upon the effects of CORT on astrocytes. Perhaps acute CORT actions on astrocytes maintain neuronal homeostasis, despite the stress, in this circuit. An independent study using an acute CORT administration protocol found a decrease in astrocytic gap-junction channel expression (Quesseveur et al., 2015), indicating that there are measurable effects of CORT treatment on astrocytes. Considering the strong role of astrocytes in tuning synaptic transmission and plasticity through various mechanisms (Gordon et al., 2009; Henneberger, Papouin, Oliet, & Rusakov, 2010; Matos et al., 2018; Morquette et al., 2015; Murphy-Royal, Dupuis, Groc, & Oliet, 2017; Panatier et al., 2011), it is possible that CORT along with neuromodulators released during the central stress response such as corticotropin releasing hormone or noradrenaline can act synergistically on astrocytes to induce the release of gliotransmitters, impacting synaptic plasticity. Evidence for the synergistic action of neuromodulators alongside classical neurotransmitters (such as glutamate) acting on astrocytes to modulate synaptic plasticity was recently demonstrated (Crosby et al., 2018).

1.2.3 | Effects of antidepressants on astrocyte function

Many independent laboratories have now investigated the effects of antidepressants on astrocytes. In order to isolate the effects of specific drugs on astrocytes, many of these studies have been carried out in purified cell culture models, which removes the interaction between other brain cell types. There appears to be an overall consensus that treating astrocytes with SSRIs, such as fluoxetine, leads to increased expression of gap-junction channel proteins in cultures (Jeanson et al., 2015; Mostafavi et al., 2014) as well as in vivo with chronic fluoxetine treatment (Fatemi et al., 2008). This has also been shown in cultured astrocytes treated with amitriptyline, a tricyclic antidepressant (Morioka et al., 2014). Antidepressants can also induce astrocytic release of neurotrophic factors such as VEFF (Allaman, Fiumelli, Magistretti, & Martin, 2011), and BDNF (Allaman et al., 2011; Hisaoka-Nakashima et al., 2016; Kittel-Schneider et al., 2012; Quesseveur et al., 2013). Fluoxetine induces metabolic modifications in astrocytes, which stimulate increased glucose uptake and lactate release in cell culture conditions (Allaman et al., 2011). This has also been demonstrated for another SSRI, paroxetine, but not the tricyclic antidepressants (TCAs) imipramine and desipramine (Allaman et al., 2011). Lithium has been shown to increase astrocyte proliferation in basal conditions (Rajkowska et al., 2016), providing a potential mechanism through which antidepressants rescue glial cell density in human depression (Cobb et al., 2016). Together, these studies suggest that antidepressants have dramatic effects on astrocytic protein expression profiles and induce the release of neuroactive factors. These observations warrant further investigation to delve into the mechanisms by which antidepressants alone, that is, without stress, induce such dramatic modifications in astrocytes. Furthermore, this suggests that a significant therapeutic contribution for a wide variety of antidepressants may be a consequence of direct actions on astrocytes.

Given the above literature, it is clear that there is a growing body of evidence suggesting that astrocyte dysfunction plays a role in driving depressive phenotypes. In the absence of correlative data from human stress disorders, these studies should be interpreted with caution. Manipulating astrocyte function in preclinical models to reveal anxiety- or depression-like phenotypes does not necessarily mean that such mechanisms are shared with the human condition. Impairment of even one aspect of astrocyte function could have dramatic consequences on a multitude of brain functions resulting in an array of behavioral phenotypes. Insights gleaned from animal models of stress are in line with many human studies regarding the stress-induced modification of astrocyte structure and function. This convergence is important for the validation that rodent models of stress-disorders might indeed prove useful in revealing the biological underpinnings in disease. Furthermore, these studies indicate that antidepressants have measurable effects on astrocyte structure and function. The mechanism by which antidepressants affected astrocytes in these studies remains unresolved and will undoubtedly require further investigation of astrocyte function and dysfunction in rodent models of disease.

1.3 | Part III—Conclusions and future directions

We have described many of the specific experiments and gaps in our knowledge regarding astrocytes and stress. The accumulating evidence is strongly suggestive of a role for astrocytes in mood and stress disorders. This family of glia appear to be highly-sensitive to stress and likely participate in multiple aspects of stress disorders.

One of the major questions remaining in the field is where these cells lie in disease development and progression. Could genetic dysregulation of these cells underlie mood disorders, leading to higher susceptibility for depression, anxiety, and PTSD? There is strong evidence for epigenetic regulation of astrocytes by depression, which contradicts a purely genetic origin and suggests that astrocytes are key players in mood and stress disorders (Nagy et al., 2015). Are astrocytes responding to neuronal dysfunction in depression, attempting to limit stress-induced effects on normal synaptic transmission and plasticity? These questions remain unanswered. The hope is that revealing underlying mechanism will dictate the therapeutic strategy to be taken. For example, if glia exacerbate the central effects of stress then we should attempt to limit astrocyte dysfunctions at specific therapeutic windows. However, if astrocytes are neuroprotective in the context of stress, as may be the case during brain injury (Anderson et al., 2016), we should attempt to upregulate specific functions of these cells in order to boost their neuroprotective (anti-stress) capacity.

It is clear that while the evidence for astrocyte dysregulation in the context of mood and stress disorders is convincing, our understanding of the (mal-)adaptations is limited. There are multiple animal models for the study of stress disorders, each reproducing many physiological aspects observed in human brain studies. As the burden of mental health disorders increases worldwide, with little development of novel therapeutic strategies, we must target glial cells in order to further understand the biological underpinnings of these diseases and potentially reveal novel therapeutic avenues. Currently prescribed antidepressants, including SSRIs, seem to target astrocytes reversing gene and protein expression changes associated with mood and stress disorders. This appears to be a direct effect on these cells, as similar changes are observed in isolated astrocytes in culture conditions. Further investigation into the mechanism by which SSRIs and other antidepressants induce these astrocyte-specific effects may lead to the generation of a new class of antidepressants directed toward these cells.

Astrocytes have also been implicated in early-life stress. Early life stress models in which mothers and pups are given access to limited amounts of bedding, result in impaired glutamate uptake by hypothalamic astrocytes (Gunn et al., 2013). Maternal separation, another early-life stress, impacts the number of astrocytes in the hippocampus (Saavedra, Fenton Navarro, & Torner, 2017). Considering the role for astrocytes in synapse formation and maturation (Allen et al., 2012; Blanco-Suarez, Liu, Kopelevich, & Allen, 2018; Stogsdill et al., 2017), impairment of astrocyte function at early stages of postnatal development should have dramatic consequences on neuronal function. This is one area that has the potential to expand immensely as we further our understanding of astrocytic-mediated dysregulation of synaptogenesis during development when animals are under duress.

The adoption of novel techniques and tools to investigate astrocyte function is critical if we are to further our understanding of the roles of these cells in mood and stress disorders. This will occur when current experts in the field begin to adopt these techniques or when glial-focused researchers turn their attention to stress disorders. There are now multiple tools available to control the activity of astrocytes in a precise spatial and temporal manner; this includes the chemogenetic and optogenetic manipulation of astrocytic signaling (Adamsky et al., 2018; Agulhon et al., 2013; Jones, Paniccia, Lebonville, Reissner, & Lysle, 2018; Mederos et al., 2019; Wang et al., 2012), as well as a novel approach to decrease endogenous astrocyte calcium activity by expressing a human plasma membrane calcium pump, which extrudes calcium from the cell (Yu et al., 2018). The use of these tools will greatly facilitate studies designed to better understand the role of astrocytes in the initiation, development, maintenance, or progression of stress disorders. Furthermore, we now have the capacity to investigate this in a brain region specific manner, isolating astrocytes embedded in specific "stress circuits." This will yield further information regarding astrocyte heterogeneity with respect to stress sensitivity. Genetic targeting and deletion of astrocytic hormone receptors will allow us to study the role played by these glia in stress and depressive pathologies. Some candidates of great interest are glucocorticoid receptors which are highly enriched in astrocytes (Zhang et al. 2014) but information regarding the functional relevance is lacking. Could activation of glucocorticoid receptors on astrocytes induce depressive-like phenotypes?

This is a rapidly developing and exciting field of research to explore. The role of glia in mood and stress disorders is beginning to pick up traction as the tools available to study these cells in detail become more numerous. Future research is likely to implicate astrocytes in the molecular deficits contributing to behavioral phenotypes associated with depression.

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