

Inflammation, Glutamate, and Glia: A Trio of Trouble in Mood Disorders

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Increasing data indicate that inflammation and alterations in glutamate neurotransmission are two novel pathways to pathophysiology in mood disorders. The primary goal of this review is to illustrate how these two pathways may converge at the level of the glia to contribute to neuropsychiatric disease. We propose that a combination of failed clearance and exaggerated release of glutamate by glial cells during immune activation leads to glutamate increases and promotes aberrant extrasynaptic signaling through ionotropic and metabotropic glutamate receptors, ultimately resulting in synaptic dysfunction and loss. Furthermore, glutamate diffusion outside the synapse can lead to the loss of synaptic fidelity and specificity of neurotransmission, contributing to circuit dysfunction and behavioral pathology. This review examines the fundamental role of glia in the regulation of glutamate, followed by a description of the impact of inflammation on glial glutamate regulation at the cellular, molecular, and metabolic level. In addition, the role of these effects of inflammation on glia and glutamate in mood disorders will be discussed along with their translational implications.

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INTRODUCTION

Two emerging theories regarding the development of mood disorders involve excessive activation of inflammatory pathways and alterations in glutamate metabolism (Dantzer *et al*, 2008; Haroon *et al*, 2012, 2016; Sanacora and Banasr, 2013; Sanacora *et al*, 2012). Recent evidence indicates that these two pathways converge at the level of the glia to result in behavioral alterations in patients with mood disorders. Indeed, data indicate that inflammatory mediators might regulate extracellular glutamate concentrations by exerting profound effects on the functioning of glial cells including astrocytes, oligodendrocytes, and microglia that regulate glutamate levels under both physiological and pathological conditions.

In this review, we propose the hypothesis that the effects of inflammation on glia initially lead to an increased release and ‘spillover’ of glutamate into the extrasynaptic space by decreasing the capacity of glial transporters to buffer and clear glutamate (McCullumsmith and Sanacora, 2015; Figure 1). This glutamate spillover in combination with glutamate

released by activated or primed glial and immune cells can activate extrasynaptic *N*-methyl-D-aspartate (NMDA) receptors and lead to atrophy and regression of dendritic spines and processes and loss of synaptic integrity, ultimately resulting in neuronal loss (Hardingham and Bading, 2010; Malarkey and Parpura, 2008). Moreover, increases in extrasynaptic glutamate can also stimulate presynaptic metabotropic glutamate receptors (mGluR2/3) leading to reductions in synaptic glutamate transmission (Duman, 2014; McEwen *et al*, 2016). In addition, alterations in the ratio between synaptic and extrasynaptic activation of ionotropic receptors by glutamate can result in the loss of synaptic fidelity and specificity of neurotransmission, contributing to circuit dysfunction (Allam *et al*, 2015; Allam *et al*, 2012; Figure 1). This process might however be reversed if treatments or spontaneous recovery processes engage astroglial repair and plasticity promoting mechanisms. Taken together, these effects of inflammation on glial cells can have a profound effect on glutamate neurotransmission, which may ultimately serve as a fundamental mechanism by which inflammation influences behavior in patients with mood disorders.

This review will examine the impact of inflammation on glutamate neurotransmission by first describing the role of glia in the regulation of glutamate, followed by a description of the impact of inflammation on glial glutamate regulation at the cellular, molecular, and metabolic level. In addition, a working model will be presented and the impact

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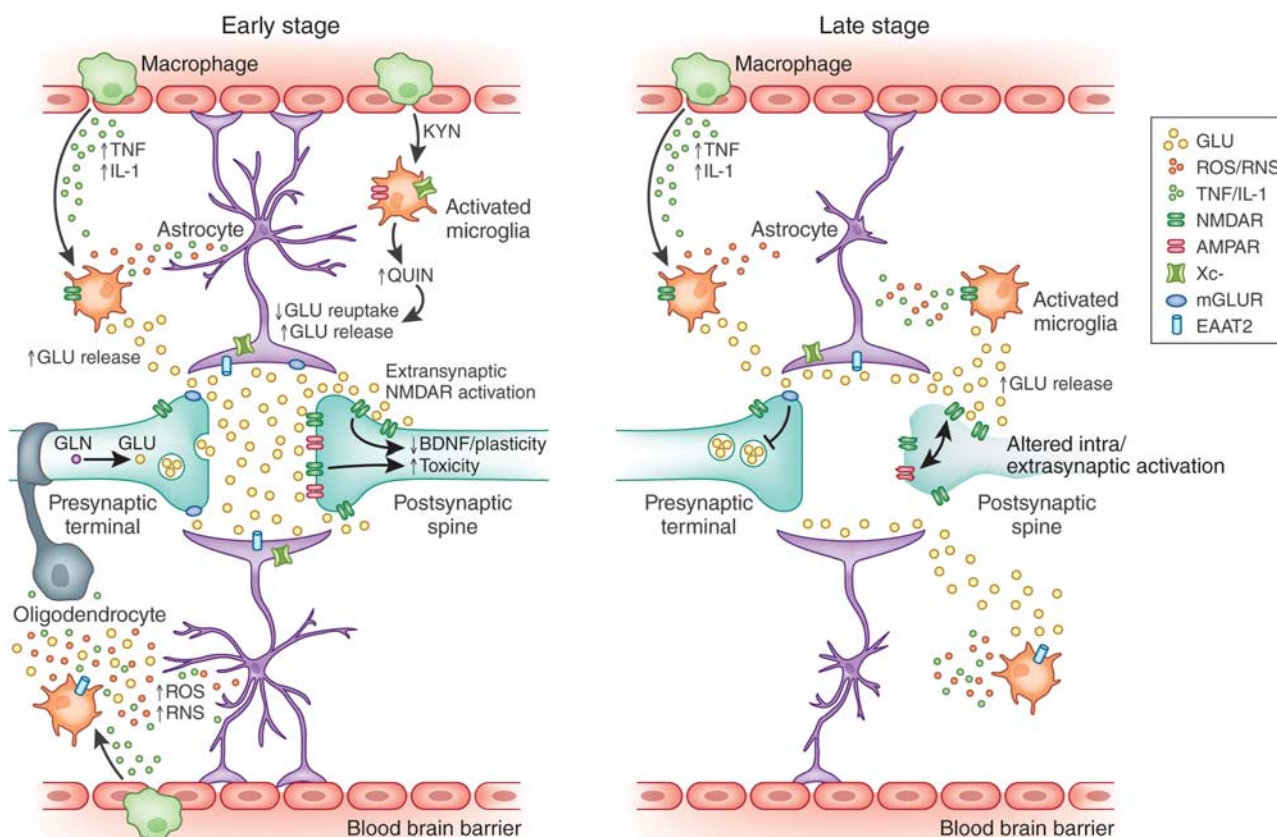


Figure 1. Impact of inflammation on glutamate neurotransmission and synaptic integrity. Left panel depicts the glutamatergic synapse at an early stage of inflammation. High levels of inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-1 β released by activated inflammatory cells including microglia, astroglial, and macrophages lead to increases in the concentration of synaptic glutamate (GLU), toxic kynurenine molecules with glutamate-like effects such as quinolinic acid (QUIN), and reactive oxygen (ROS)/nitrogen (RNS) species leading to oxidative stress. Effects of inflammatory molecules upon astrocytic cell morphology leads to decreased ability to ‘cradle’, sequester, and contain glutamate within the synapse resulting in a spillover of the glutamate into the extrasynaptic space. Concurrent decreases in the number and functioning of excitatory amino-acid transporters (EAAT) 2-induced by inflammation further limits the ability of astrocytes to buffer and clear the spillover glutamate. Additional release of glutamate by increased xC-activity alone or in combination with reverse effluxive release via EAATs by immune-activated glial cells further adds to the concentrations of extrasynaptic glutamate available to diffuse and bind to extrasynaptic binding sites. Increases in synaptic glutamate resulting from early inflammatory changes are shown as leading to the overactivation of intrasynaptic ionotropic receptors such as α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate receptors (NMDA) potentially contributing to excitotoxicity. The spillover glutamate is also shown as binding to the extrasynaptic NMDA receptors leading to suppression of neurotrophic support from factors such as brain-derived neurotrophic factor (BDNF). Some of the excess glutamate is also seen binding to presynaptic metabotropic glutamate receptors (mGluR2/3), which provides negative feedback to block further glutamate release as shown in the right panel. Right panel depicts the glutamate synapse at a late stage of chronic inflammation. The progression of glutamatergic dysfunction has resulted in an overall loss of glutamate neurotransmission. Sustained stimulation of presynaptic mGluR2/3 systems by glutamate diffusing through extrasynaptic space leads to inhibition of excitatory neurotransmission and increased trapping of glutamate in the vesicles within the presynaptic membrane. The toxic effect of overstimulation of intrasynaptic AMPA during early immune activation has led to a downregulation, desensitization, and atrophic loss of intrasynaptic AMPA receptors. Decreasing intrasynaptic glutamatergic activity also leads to the loss of intrasynaptic NMDA signaling even while the extrasynaptic NMDA signaling continues to remain high. This altered ratio of intrasynaptic to extrasynaptic signaling leads to atrophy and regional loss of neurons seen in patients with mood disorders as seen in the shrinking postsynaptic neuron. Finally, the persistently increased extrasynaptic glutamate, increased ROS/RNS, and QUIN also contribute to astrocytic and oligodendrocyte toxicity leading to atrophic changes in these cells as well.

of inflammation on glial glutamate regulation will be discussed in the context of its translational relevance.

to first describe the glial elements that serve as the point of convergence of these interactions.

CELLULAR BASIS OF INTERACTIONS BETWEEN THE IMMUNE SYSTEM AND GLUTAMATE NEUROTRANSMISSION

To fully understand the intersection between glutamate and inflammation as they relate to mood disorders, it is essential

ASTROCYTES

Historically, astrocytes were viewed as merely supporting cells providing structural support to the neuronal network much like the connective tissue in the periphery. However, it is now well established that astrocytes carry out a myriad of

functions including providing neurotrophic support, maintaining synaptic homeostasis, regulating synaptic pruning, participating in neuron–glia signaling, coordinating neuro-metabolic coupling, mitigating oxidative stress, and the most relevant to the purpose of this review, modulating glutamate metabolism (Kimelberg and Nedergaard, 2010; Verkhratsky *et al*, 2015a). A brief overview of these functions is presented here, although the reader is referred to other, more comprehensive texts for a more detailed description of the various functions of astrocytes (Kettenmann and Ransom, 2012; Nedergaard *et al*, 2002; Verkharatsky and Butt, 2013; Verkhratsky *et al*, 2015a; Verkhratsky *et al*, 2014; Volterra and Meldolesi, 2005).

In stark contrast to the myeloid/bone marrow origins of microglia, astrocytes (and oligodendrocytes) are derived from neural stem cells belonging to the embryonic, ectodermal plate, and neural crest. As part of the tripartite synapse that includes the synaptic regions of the pre- and postsynaptic neurons and associated astrocytic processes, the primary role of astrocytes is to maintain synaptic integrity (Haydon and Carmignoto, 2006; Nedergaard *et al*, 2002). Indeed, although astrocytic dysfunction and resulting synaptic loss might define the pathology of several neuropsychiatric and neurodegenerative disorders (such as depression and dementia), aberrant synapse formation has also been implicated in a number of neurodevelopmental disorders including schizophrenia, autism, and Fragile-X syndrome (Duman *et al*, 2016; Mateo *et al*, 2011).

Astrocytes are multi-branched stellate cells, whose morphology and functions tend to change with varying degrees of specialization and differentiation, often in response to physiological and pathological demands including immune activation. At least three morphological subtypes of astrocytes are recognized in the brain including protoplasmic, fibrous, and radial astrocytes (Liddelow and Barres, 2015; Sofroniew and Vinters, 2010).

Protoplasmic astrocytes are found throughout all gray matter and exhibit a branching morphology with several stem-like processes that give rise to branches and further divide into progressively finer processes, which at one end encase blood vessels through their endfeet and at the other end ensheath several thousand synapses forming ‘astrocytic cradles’ (Bushong *et al*, 2002; Sofroniew and Vinters, 2010). The ‘astrocytic cradles’ that encircle the synaptic region are densely enriched with glutamate transporters and have a primary role in glutamate clearance under physiological conditions (Khakh and Sofroniew, 2015; Liddelow and Barres, 2015; Sofroniew and Vinters, 2010). The glutamate is cleared primarily through highly efficient excitatory amino-acid transporters (EAAT1–2) located on astrocytes in the ‘cradles’ (Nedergaard *et al*, 2002; Verkhratsky *et al*, 2015a). Once taken up into the astrocytes, glutamate is rapidly converted into the ‘inert’ intermediate glutamine, which is then released and absorbed by neurons, where it is converted back into glutamate and packaged into synaptic vesicles through vesicular glutamate transporters (VGLUT1–3), completing the glutamate/glutamine metabolic cycle

(Danbolt, 2001; Zhou and Danbolt, 2014). The recycled glutamate serves as the principle source of synaptically released glutamate for neurotransmission. In addition to providing a mechanism of efficiently recycling extracellular glutamate, the ‘astrocytic cradle’ creates an anatomical and functional barrier that blocks the ‘spillover’ of glutamate into the extrasynaptic space (Dorsett *et al*, 2016; McCullumsmith and Sanacora, 2015). Although glutamate binds to EAATs with high affinity, not all the bound glutamate is immediately transported across the plasma membrane of astrocytes (Dorsett *et al*, 2016). EAAT-bound glutamate may become ‘unbound’, released, and rebound to neighboring glutamate transporters, thus bouncing from one transporter to the other until it is eventually transported across the plasma membrane (Tzingounis and Wadiche, 2007). This process of the temporary holding of glutamate before transport is referred to as ‘buffering’ and it helps limit its spillover outside the cradle (Dorsett *et al*, 2016). Finally, through their podocytic endfeet, astrocytes come in close proximity to blood vessels and vascular pericytes, leaving an empty space—a ‘no man’s land’ of extracellular space that forms an integral part of the blood–brain barrier (BBB) and brain lymphatic systems (Iliff and Nedergaard, 2013; Louveau *et al*, 2015). In summary, functions of the protoplasmic astrocytes and their astrocytic cradles are critical in maintaining amino-acid metabolic homeostasis, preventing excessive glutamate spillover and preserving the BBB.

Fibrous astrocytes are found throughout white matter regions and exhibit many elongated fiber-like processes, which encircle the nodes of Ranvier (Barres, 2008; Sofroniew and Vinters, 2010). These fibrous astrocytic processes protect and nurture the unmyelinated nodal regions as opposed to the oligodendrocytes that protect and nurture the myelin sheath and myelin cells (Khakh and Sofroniew, 2015; Sofroniew and Vinters, 2010). This unique spatial arrangement of astrocytes and oligodendrocytes enables them to interact and promote axonal and dendritic plasticity. In addition to performing all functions of protoplasmic astrocytes that are the most common form of astrocytes, the fibrous astrocytes also have a prominent role in repair of damaged neurons and lead to scar formation (Sofroniew and Vinters, 2010). A final type of astrocyte is the ‘radial’ astrocyte, which develops from neural stem cells during early embryogenesis to assist in neuronal migration and in the development of neural plate. The radial astrocyte is known to persist in the adult retina and cerebellum as Müller and Berger cells respectively (Khakh and Sofroniew, 2015; Liddelow and Barres, 2015).

Immune Regulation

Astrocyte function is modulated by a variety of immune processes. Astrocytes express receptors for multiple immune-derived molecules including cytokines, chemokines, complement, and acute-phase proteins, and respond to immune signals generated by microglia or peripheral macrophages recruited to into the brain during innate immune activation.

In addition, astrocytes express receptors for adipokines such as the leptin receptors (LepR), which can be upregulated in obesity and inflammation and may have a role in appetite regulation (Hsuchou *et al*, 2009; Pan *et al*, 2012). By regulating the BBB, astrocytes also act as ‘gate keepers’ to control peripheral immune cell trafficking to the brain (Abbott *et al*, 2006).

Acute activation. During pathologic conditions associated with large-scale cell death such as ischemia, oxidative stress, or neural trauma, astrocytes themselves can become inflammatory cells and demonstrate phagocytic activity (Fontana *et al*, 1984; Soos *et al*, 1998). Transformation of astrocytes into phagocytic and antigen-presenting cells (as evidenced by local increases of surface markers of inflammatory activation including major histocompatibility complex (MHC) class II receptors, toll-like receptors (TLRs), and intracellular immune receptor systems including the NOD-like protein 3 (NLRP3) or Rig-1-protein complex of the inflammasome) is triggered by local increases in concentrations of inflammatory cytokines such as interferon (IFN)- γ (de Rivero Vaccari *et al*, 2014, 2016b; Farina *et al*, 2005, 2007). The inflammasome is an intracellular complex that senses danger-associated molecular patterns (DAMPs) such as ATP that are released during cellular stress. DAMP signaling then leads to the activation of caspase 1, which in turn cleaves pro-IL-1 into active IL-1 β (Walsh *et al*, 2014a). Upon activation by IL-1 β , astrocytes can release large amounts of innate immune inflammatory mediators including several complement cascade proteins; cytokines including tumor necrosis factor (TNF), IL-1 β , IL-6; and chemokines with CC (cysteine–cysteine) and CXC (cysteine–other amino acids–cysteine) motifs including CCL2, CXCL1, CXCL10, and CXCL12 (Bezzi *et al*, 2001; Fischer *et al*, 2014; Johnstone *et al*, 1999; Marz *et al*, 1999; Olmos and Llado, 2014; Santello and Volterra, 2012; Takahashi *et al*, 2003a; Torres-Platas *et al*, 2014b; Xie *et al*, 2003). This state is also associated with impaired glutamate clearance and oxidative stress, both of which contribute to excitotoxicity (Matute *et al*, 2006; Tilleux and Hermans, 2007; Zou and Crews, 2005).

Chronic activation (reactive astrogliosis). Astrocytes respond to chronic CNS injuries and diseases by differentiating and proliferating into hypertrophic and/or migrating cell types—a term referred to as reactive astrogliosis (Khakh and Sofroniew, 2015; Liddelw and Barres, 2015; Sofroniew and Vinters, 2010). Reactive astrogliosis may have both reparative functions that preserve synaptic homeostasis (eg, increasing the secretion of neurotrophic factors such as nerve growth factor, brain-derived neurotrophic factor [BDNF], and activity-dependent neurotrophic growth factor, and increasing glutamate clearance through cradling and reuptake mechanisms) or toxic functions resulting in neuronal loss (Friedman *et al*, 1990; Liberto *et al*, 2004; Marz *et al*, 1999; Spranger *et al*, 1990). Accordingly, reactive

astrocytes can be classified into A1 and A2 astrocytes (Karpuk *et al*, 2012).

A2 reactive astrocytes were demonstrated to promote reparative healing after following ischemic injury induced by an experimental stroke lesion in a beneficial manner (Zamanian *et al*, 2012). Following ischemic injury, A2 reactive astrogliosis was associated with a rapid but quickly attenuated induction of the expression of two genetic markers—Lcn2 and Serpina3n—both of which were co-localized with the glutamate transporter gene (Zamanian *et al*, 2012). On the other hand, A1 phenotype was induced by inflammatory stimuli including experimental administration of endotoxin and was more pathological in nature (Zamanian *et al*, 2012). A1 astrocyte pathology falls into two general categories: loss-of-function type, in which astrocytes fail to perform normal functions (decrease glutamate clearance and/or decrease synaptogenesis) or gain-of-function type in which astrocytes exhibit new, potentially deleterious, functions (increased synaptic destruction) not seen in resting astrocytes (Khakh and Sofroniew, 2015; Sofroniew and Vinters, 2010). The neurotoxic effects of A1 reactive astrocytes were mediated by the upregulation of complement cascade components, glutamate-mediated excitotoxicity, and induction of oxidative stress (Zamanian *et al*, 2012). Of note, increases in genetic markers of reactive astrogliosis, namely, glial fibrillary acidic protein (GFAP) and aldehyde dehydrogenase 1 family member L1 (ALDH1L1), have been reported in multiple brain regions of patients with bipolar disorder (Barley *et al*, 2009).

Senescence-associated secretory phenotype. Astrocytes undergo phenotypic conversion during aging and can develop into the senescence-associated secretory phenotype (Salminen *et al*, 2011). This senescent phenotype exhibits exaggerated reactivity to immune activation and is associated with reduced glutamate clearance as well as the production of inflammatory cytokines (Haroon *et al*, 2015; Norden and Godbout, 2013).

Synaptogenesis, Gliotransmission, and Circuit Integration

Synaptogenesis. Synapses are formed by synapse-forming proteins secreted by astrocytes such as glypicans (Liddelw and Barres, 2015). Glypicans amplify the intensity of neurotransmission by increasing the expression and activity of postsynaptic AMPA receptors. Thus, the voltage of the postsynaptic current is amplified to a level sufficient enough to open the magnesium-gated NMDA receptors resulting in the establishment of synaptic connections (Liddelw and Barres, 2015). Once established, the synapse is maintained through a coordinated program of immune-glutamate signaling involving mGluRs, chemokines, and TNF. Some of the glutamate released during neurotransmission diffuses and binds to surface mGluRs on astrocytes and trigger release of the chemokine CXCL12/stromal cell-derived factor (CXCL12/SDF1), which in turn signals the microglia to

release small, physiologic (non-inflammatory) quantities of TNF (Heinisch and Kirby, 2010; Santello and Volterra, 2012). The released TNF binds to TNF receptors on astrocytes and enables regulated buffering and clearance of glutamate, thereby maintaining controlled neuronal excitation. This process of immune-to-glutamate signaling ensures that EAAT uptake is not an all or none phenomenon, but a more nuanced, synapse-strengthening process. Recently, direct evidence implicating CXCL12/SDF1 in preclinical models of anxiety and other neuropsychiatric disorders have been published (Guyon, 2014; Yang *et al*, 2016). Astrocytes have recently been implicated to have a role in synaptic elimination during brain development in a manner similar to the role played by the microglia in developmental pruning (Chung *et al*, 2013).

Postsynaptic density proteins (PSD95) are scaffolding proteins that cluster, hold, and connect AMPA and NMDA receptor proteins to their downstream signaling molecules such as stargazin and D-serine (Ma *et al*, 2014; Sheng and Hoogenraad, 2007). The clustering and location of ionotropic receptors within the postsynaptic membrane varies across contexts and time points, and regulates the balance between activation and desensitization of AMPA and NMDA receptors, and thus has the potential to decrease neuroplasticity and increase signaling disarray (Allam *et al*, 2015; Allam *et al*, 2012; Ma *et al*, 2014). PSD95 function is controlled by immune activity in the glial cells such as astrocytes and microglial cells (Torres-Platas *et al*, 2014b; Torres-Platas *et al*, 2011) during physiological (normal development) and pathological contexts (Estes and McAllister, 2015). For example, prenatal immune activation using poly(I:C), a preclinical model of prenatal viral exposure implicated in schizophrenia and autism spectrum disorders resulted in pronounced decreases of PSD95 in hippocampal regions associated with prominent behavioral changes (Giovanoli *et al*, 2016). Rapid antidepressant effect of ketamine has been linked with increases in PSD95 (Duman and Voleti, 2012). Postmortem studies using brain specimens from depressed suicide victims have revealed epigenetic modifications (methylation abnormalities) in the promoter region of *BEGAIN*, a gene associated with PSD95 expression (Nagy *et al*, 2015). In addition, PSD95 engulfment by microglia can lead to excessive complement activation and pruning (Estes and McAllister, 2015). Although specific information is still lacking, it would be tempting to speculate that the movement and clustering of AMPA and NMDA proteins and their binding to stargazin or nitric oxide synthase within the PSD95 complex might be altered during inflammatory activation in mood disorders.

Gliotransmission. Signaling between glial cells also known as gliotransmission is known to have a role in maintaining synaptic tone, guiding neuronal development, and engage in constructive pruning (Kielian and Esen, 2004; Petrelli and Bezzi, 2016). Glial signaling is facilitated by direct transfer of neurotransmitters (such as glutamate) and ions (such as

Ca⁺ and Na⁺) from one glial cell to another through gap junctions, which are essentially intracellular channels encircled by six transmembrane proteins known as connexins (Cx; Kielian and Esen, 2004). Thus, connections between distal process of neighboring astrocytes and oligodendrocytes and even microglia signal each other to convey useful information about the microenvironment. Large numbers of astrocytes connect with one another through such gap junctions to form connected astroglial syncytia capable of transmitting signaling information transsynaptically through large regions of the brain, thus placing astrocytes as hubs or intense brain activity (Volterra and Meldolesi, 2005). Neuronal presynaptic glutamate release triggers waves of intracellular Ca⁺ and Na⁺ oscillatory activity and inwardly rectifying currents in neighboring astrocytes, which is then propagated throughout the syncytium leading to glutamate release and reuptake changes in distant sites (Innocenti *et al*, 2000; Parri *et al*, 2001). Of note, immune signals are also propagated through gap junction communication between microglia and astrocytes (Kielian *et al*, 2004; Kielian and Esen, 2004). Immune mediators such as TNF modulate functioning and vitality of gap junctions (Santello and Volterra, 2012; Takeuchi and Suzumura, 2014). The role of the immune-related gap junction pathology in propagating neural activity through rapid transfer of glutamate has been blamed for the rapid dissemination of seizure discharges and the resulting kindling effects seen seizure disorder (Iori *et al*, 2016; Vezzani and Viviani, 2015; Viviani and Boraso, 2011). Mood disorders are known to be associated with Cx pathology and this remains an ongoing area of investigation (Miguel-Hidalgo *et al*, 2014).

Circuit integration. Recent work suggests the current concept of brain networks, as intelligent contacts between several neurons should be expanded to include communications occurring between neurons and glial cells (Rossi, 2015; Santello *et al*, 2011; Volterra and Meldolesi, 2005). Astrocytes are best viewed as local 'hubs' that can receive and integrate information from thousands of synapses, other glial cells and blood vessels (Bushong *et al*, 2002; Rossi, 2015; Santello *et al*, 2011; Volterra and Meldolesi, 2005). In contrast to neural circuits, astrocytic networks establish connections among unrelated and functionally segregated circuits (Bushong *et al*, 2002; Sofroniew and Vinters, 2010; Volterra and Meldolesi, 2005). Furthermore, astrocytes accomplish this integrative function using a combination of gliotransmitters such as glutamate and physiological concentrations of cytokines such as TNF as described above.

There is increasing evidence suggesting that the integrated function of these glial networks can become pathological in disease states. For instance, glutamate (along with dopamine) has been implicated in regulation of physiological reward-seeking behaviors and pathological anhedonic states (Bechtholt-Gompf *et al*, 2010; Whitton *et al*, 2015). A circuit level competition between midbrain dopaminergic circuits (mediating reward experience) and medial prefrontal cortex-

based glutamatergic circuits (mediating reward suppression) for the control of a third circuit (ventral striatum) to guide hedonic responses and stimulus salience in physiology and anhedonic responses in depression has been proposed (Ferenczi *et al*, 2016). Intriguingly, disruption of astrocytic glutamate uptake/clearance using EAAT2 inhibitor dihydrokainic acid in rodents was associated with reduced sensitivity to reward in intracranial self-stimulation paradigms implicating the role of glutamate increases in disrupting reward pathways (Bechtholt-Gompf *et al*, 2010). Further evidence suggesting that abnormal function of glia networks can contribute to mood disorder pathophysiology comes from a study demonstrating that dysfunction of the orbitofrontal cortex in MDD and alcohol abuse is associated with a reduction in the levels of gap junction protein Cx43, implicating gap junction in the pathophysiology of circuit dysfunction. Thus, using a dimensional perspective based on the RDOC initiative (Insel *et al*, 2010), it is possible to hypothesize a balance between glutamatergic and dopaminergic systems representing opposing polarities of salience, ie, ‘negatively valent/reward suppressive’ vs ‘positively valent/reward experience’ states. Given the impact of inflammation on both of these polarities, it is likely that inflammation-induced circuit pathologies will be an important area of future investigation (Felger *et al*, 2016; Haroon *et al*, 2016).

Astrocytic Dysfunction and Mood Disorders

A robust literature exists supporting the association between astrocytic dysfunction and mood disorders in general, and has been extensively reviewed elsewhere (Ongur *et al*, 2014;

Popoli *et al*, 2012; Rajkowska and Miguel-Hidalgo, 2007; Rajkowska and Stockmeier, 2013; Sanacora and Banasr, 2013; Verkhatsky *et al*, 2014). Major highlights of this literature are provided in Box 1.

OLIGODENDROCYTES

Oligodendrocytes form an integral part of the brain white matter and have critical roles in maintaining the convergence of excitatory neurotransmission, glutamate homeostasis, and immune dysregulation at the level of the white matter tissue. Oligodendrocytes produce myelin that provides critical insulation to enable faster conduction speeds compared with unmyelinated axons of the same diameter (Bartzokis, 2004; Edgar and Sibille, 2012). Oligodendrocytes have small round cell bodies surrounded by four to six branching processes that are the myelinating regions and can myelinate (or remyelinate following injury) up to 60 axons (Edgar and Sibille, 2012). Based on their location, two distinct types of oligodendrocytes have been described as follows: (1) perineural oligodendrocytes found primarily in the gray matter in close proximity to neuronal cell bodies; and (2) interfascicular oligodendrocytes that are found in the white matter, which ensheath axonal fibers (Edgar and Sibille, 2012). Myelin is synthesized by myelin-related genes in the oligodendrocytes using a combination of lipids (70%) and proteins (30%) including myelin basic protein throughout most of adult life (Chen *et al*, 2013). The declining trajectory of myelination has been correlated with decreases in cerebral function as happens during aging (Bartzokis, 2004).

BOX 1 Examples of Evidence Suggesting a Role for Astrocyte Pathology in Mood Disorders

Animal studies

- Experimental poisoning of glial EAATs in the medial prefrontal cortex generates depressive-like behaviors in laboratory animals (Banasr and Duman, 2008; Banasr *et al*, 2007; Sanacora and Banasr, 2013).
- Animals expressing learned helplessness showed a significantly suppressed expression of the glial glutamate transporter GLT1 (rodent nomenclature for EAAT2) in hippocampus and cerebral cortex compared with non-helpless animals and littermates with low levels of helplessness (Zink *et al*, 2010).
- Reduced glial fibrillary acidic protein (GFAP) expression is observed following chronic unpredictable stress (CUS) is associated with depressive-like behaviors in rodent models, and pharmacological treatments that attenuate the effects of CUS on GFAP expression and/or facilitate EAAT function can reverse the cellular and behavioral effects of CUS (Banasr *et al*, 2010; Czeh *et al*, 2006; Gourley *et al*, 2012; Mineur *et al*, 2007; Sanacora and Banasr, 2013)
- Induction of anhedonia in laboratory animals by inhibition of astroglial surface (plasmalemmal) glutamate transporters (Bechtholt-Gompf *et al*, 2010; Ongur *et al*, 2014).
- Reduced coupling between gap junctions of astroglial cells in prefrontal cortex associated with reduced expression of connexin-43 (gap junction) proteins leading to anhedonia following pharmacological inhibition of gap junctional conductance or chronic stress in laboratory animals (Sun *et al*, 2012).

Human

- Decreased astrocyte numbers and packing density in histopathological and morphometric analyses of multiple brain regions including prefrontal, orbitofrontal, anterior, subgenual frontal, entorhinal, and amygdalar cortices in postmortem brain specimens from depressed suicide victims (Bowley *et al*, 2002; Cotter *et al*, 2002; Cotter *et al*, 2001; Ongur *et al*, 1998; Rajkowska *et al*, 1999).
- Decreased astrocyte mRNA and/or protein expression of GFAP (Braun *et al*, 2009), aquaporin 4 (Rajkowska and Stockmeier, 2013), connexins (Miguel-Hidalgo *et al*, 2014; Rajkowska and Stockmeier, 2013; Verkhatsky *et al*, 2015b), plasmalemmal glutamate transporters (Bernard *et al*, 2011; Ernst *et al*, 2009), and glutamine synthetase (Barley *et al*, 2009; Bernard *et al*, 2011; Rajkowska *et al*, 1999; Sequeira *et al*, 2009) in postmortem brain samples from depressed suicides.
- Evidence of astroglial dysfunction and immune activation in postmortem brain samples from depressed suicide victims (Nagy *et al*, 2015; Torres-Platas *et al*, 2014; Torres-Platas *et al*, 2011).
- Hippocampal mRNA transcripts involved in glial syncytial function, including potassium and water channels (KCNJ10 and AQP4), gap junction proteins (GJA1), and glutamate transporters (SLC1A2 and SLC1A3), are downregulated in MDD subjects compared with controls (Medina *et al*, 2016).
- Association between inflammatory markers (in the plasma and CSF) and MRS-based evidence of astroglial activation—increased glutamate and myo-inositol in depressed patients (Haroon *et al*, 2016).

Oligodendrocytes Promote Excitatory Neurotransmission

Oligodendrocytes have an impact on excitatory neurotransmission and promote neural and circuit plasticity in concert with astrocytes (Gautier *et al*, 2015; Jebelli *et al*, 2015). Myelination of axons is dependent on neuronal activity and continues well into older adult life, underlining a role for oligodendrocytes in homeostatic (aging) and pathological contexts (demyelination and neural injury; Gautier *et al*, 2015; Jebelli *et al*, 2015). Oligodendrocytes control myelinated regions of the axon, whereas nodal astrocytes regulate the intervening nodes of Ranvier, which are spaces of bare axon enriched with ion channels, amino-acid transporters and their receptors (Edgar and Sibille, 2012). Together the oligodendrocytes and nodal astrocytes regulate and control the speed of 'saltatory conduction', thus maintaining optimal speed of information transfer across neurons and their networks. Activity-dependent axonal plasticity involves communication between myelinating oligodendrocytes and nodal astrocytes using glia–glia signaling probably through gap junctions (Ishibashi *et al*, 2006). These activity-dependent increases in myelination and plasticity seen among older individuals and points to the utility of neural entraining and stimulation techniques to reverse age-associated declines (Merzenich *et al*, 2014).

Oligodendrocytes and Glutamate

Similar to neurons, oligodendrocytes are highly vulnerable to glutamate toxicity. Glutamate toxicity to oligodendrocytes may be precipitated by oxidative stress or direct ionotropic receptor-mediated excitotoxicity (Oka *et al*, 1993; Takahashi *et al*, 2003b). Oligodendrocyte cell toxicity might be mediated by the overstimulation of AMPA and kainate receptors located on the oligodendrocyte cell body, whereas impaired myelin synthesis might result from toxic activation of NMDA receptors densely represented in the branching processes (Matute *et al*, 2006; Verkharatsky and Butt, 2013). Although cell death from glutamate overactivation of AMPA/kainate receptors is of interest in the study of demyelinating disorders, toxicity from oligodendrocytic NMDA receptors might be of interest to psychiatry, as these receptors are located on the oligodendrocyte branches that are active myelin-synthesizing regions (Matute, 2006). Similar to astrocytes, increases in inflammatory cytokines such as TNF and IL-1 β are known to impair glutamate buffering and clearance by oligodendrocyte EAATs, and trigger glutamate toxicity (Takahashi *et al*, 2003a; Takahashi *et al*, 2003b). Indeed, inhibition of the expression and functioning of glutamate transporters such as EAATs and xC-transporters in axonal tracts is sufficient to induce oligodendrocyte loss and demyelination, which undermines brain connectivity (Domercq *et al*, 2007; Evonuk *et al*, 2015).

Oligodendrocytes and Mood and Other Disorders

Varying degrees of myelin loss and decreasing function and/or numbers of oligodendrocytes have been reported among

patients with mood disorders and schizophrenia (Edgar and Sibille, 2012; Rajkowska *et al*, 2015; Tavares *et al*, 2002). Oligodendrocyte cells contain substantial quantities of iron, which make them highly vulnerable to oxidative stress through the generation of reactive oxygen species. Transferrin—an iron binding, mobilization, and detoxification protein—was underexpressed in the oligodendrocyte cells in the internal capsule of patients with bipolar disorder (Barley *et al*, 2009). Of note, transferrin is also an acute-phase protein, which is depleted during immune activation (Ritchie *et al*, 1999). Oligodendrocyte loss accounts for a high proportion of the cell loss in the amygdala in major depression (Hamidi *et al*, 2004).

NG2+ Glial Cells

NG2+ cells are a specific subtype of oligodendrocyte precursor cells that continue to exist and function in the adult brain (Woodbury-Farina, 2014). NG2+ glia cells connect with axons using primitive glutamatergic synapses and probably direct the formation of both glutamatergic and GABAergic synapses during the brain development before myelination (Dimou and Gallo, 2015). Exposure to preclinical stress paradigms led to decreases in number and density of NG2+ cells among lab animals (Birey *et al*, 2015) and loss of NG2+ was associated with decreased astrocytic EAATs activity and glutamate increases in prefrontal and hippocampal regions (Banasr *et al*, 2010; Birey *et al*, 2015). The depression-like symptoms associated with NG2+ loss responded to antidepressant medications and electroconvulsive treatments, both of which are known to alter glutamatergic neurotransmission in addition to other neurotransmitters (Banasr and Duman, 2008; Banasr *et al*, 2007; Sanacora and Banasr, 2013). Under conditions of immune activation, NG2+ cells are known to transform into both astrocytes and oligodendrocytes (Dimou and Gallo, 2015). The role of NG2+ cells in maintaining neural plasticity and promoting behavioral resilience warrants further study.

MICROGLIA

Microglia are the resident immune cells of the brain. Similar to macrophages in the peripheral blood, microglia arise from primitive myeloid cells in the embryonic mesoderm of the yolk sac, but migrate into the neural plate during a narrow time window before vascularization or definitive hematopoiesis (Ginhoux *et al*, 2010). However, unlike macrophages, microglia reside and function within the brain parenchyma outside the limits of peripheral circulation. Once established in the brain parenchyma, microglial cell lines are sustained by the proliferation of resident microglial progenitor cells. Microglial activity and its morphology is highly context-sensitive and depends on the spatial and temporal distribution of the physiological or pathogenic influences (Fenn *et al*, 2014; Figuera-Losada *et al*, 2014; Kettenmann and Ransom, 2012; Reus *et al*, 2015; Torres-Platas *et al*, 2014a; Torres-Platas *et al*, 2014b). However, defining and staging microglial

activation states have been complicated by the lack of unbiased insights into the contextual factors driving authentic microglial reaction states (Ransohoff, 2016). The contextual challenges may include a varying combination of neurological and immunological stimuli. In addition to their macrophage-like immune-surveillance functions, microglia also exhibit glial/trophic functions and actively respond to the changes in neural activity (Gras *et al*, 2012). Consequently, for the purpose of this review, it becomes necessary to define the stages of microglial activation despite the arbitrariness surrounding this discussion. Thus, the staging of microglial activation used in this discussion should be viewed as an oversimplification to facilitate the data interpretation, whereas a more comprehensive staging encompassing immunological and neurotrophic functions is awaited (Figure 1).

Surveillance State

Microglia are mobile cells, which possess motile ramified processes enriched with immune receptors that continually protrude and withdraw to scan their microenvironment for immune signals (Eggen *et al*, 2013; Nimmerjahn *et al*, 2005). Microglia in this 'surveillance state' can move around and scan the entirety of the brain parenchyma within a matter of hours and hence the name 'resting' state has been discarded.

Classic Activation State

Upon activation, microglia exhibit varying morphologies and activation patterns ranging from the classical pro-inflammatory and neurotoxic to the alternative anti-inflammatory and neuroprotective profiles (Kettenmann *et al*, 2011; Pocock and Kettenmann, 2007; Ransohoff, 2016). Inflammatory or 'classical activation' results from binding of microbial pathogen-associated molecular patterns to microglial TLRs and activation of inflammasome NLRP3 by DAMPs (eg, binding of ATP to the purinergic receptor P2X₇) released by stressed, damaged or dead cells. The 'classical activation' state is associated with high levels of inflammatory gene expression and secretion of inflammatory cytokines such as IL-1 β , TNF, IL-6, IL-12, and IFN- γ as well as chemokines such as CCL2 that attract peripheral monocytes into the brain and are increased in perivascular regions of postmortem brain specimens from depressed suicide victims (D'Mello *et al*, 2009; Torres-Platas *et al*, 2014b; Wohleb *et al*, 2014). Morphologically, these cells adopt a deramified (reactive) or amoeboid appearance (with one or less process) and move toward regions of injury (Torres-Platas *et al*, 2014a). Upon activation, microglial cells also express phagocytic profile characterized by the surface expression of antigen-presenting markers such as MHC class II. Of note, increased or *de novo* surface expression of glutamate receptors and transporters is seen exclusively during this phase of activation. Microglia and trafficking macrophages can be release large quantities of glutamate in the

extrasynaptic space along with glutamate-like toxic kynurenes (KYNS) such as quinolinic acid (QUIN; Table 1).

Alternative Activation and Acquired Deactivation States

A putative 'alternative activation' state has also been proposed as a predominantly anti-inflammatory phenotype seen in response to IL-4 or IL-13 (Wei and Jonakait, 1999). However, these microglia are still phagocytic but limited to clearing damaged tissue, misfolded proteins (such as β -amyloid), and other debris (Graeber and Streit, 2010; Miller and Streit, 2007; Streit and Xue, 2013), and do not possess antigen-presenting characteristics such as the surface expression of activation markers (MHC class II and cluster of differentiation (CD)40 (Town *et al*, 2005). In addition to producing anti-inflammatory cytokines such as IL-4, IL-10, and IL-13, these cells are also capable of producing growth factors such as transforming growth factor (TGF)- β and can serve a neuroprotective role (Town *et al*, 2005). A subtype known as 'acquired deactivation' state during which the cells show combined features of both 'surveillance' and muted but persisting activation states characterized by phagocytic and immune responses has also been described (Town *et al*, 2005). Taken together, the above data indicate that microglial cells form the backbone of innate immunity signaling and are often seen in varying levels of activation and rest. As will be seen later, these cells also engage in both glutamate clearance and release but only during activated states.

Microglia priming and chronic activation. Recent evidence suggests that activated microglia can reside in an in-between state of partial activation known as priming characterized both by increased responsivity to immune stimulation and persistent, chronic elevations of baseline cytokine secretion during unstimulated conditions (Dilger and Johnson, 2008; Godbout and Johnson, 2009; Godbout *et al*, 2008). This phenomenon of priming requires both a priming stimulus (such as chronic activation by IFN- γ) and a secondary but acute triggering stimulus such as TLR binding by bacterial antitoxins (Eggen *et al*, 2013; Fenn *et al*, 2014). The priming stimulus appears to cause a phenotypic shift towards a more sensitized state characterized by the increased expression of MHC class II and increased glutamate release. The primed cell will then mount a more exaggerated and rapid response to the triggering stimulus than a non-primed cell. Several conditions of priming exist. For instance, aged rodents demonstrate increased expression of mRNA and protein markers of inflammation following LPS challenge (Kumar *et al*, 2013; Norden and Godbout, 2013; Norden *et al*, 2015a, 2015b). In addition to aging, similar priming effects have been reported in microglia from patients with neuropsychiatric disorders including traumatic brain injury (Fenn *et al*, 2014) and neurodegeneration (Norden *et al*, 2015a). Of note, primed microglia were less responsive to the effects of glutamate reuptake enhancing agent riluzole compared with unprimed microglia from younger individuals (Brothers

et al, 2013). Accumulating data indicate that priming effects on microglia might represent a key pathway to pathophysiology of depression in general and glutamatergic dysfunction, and thus have been included into our working model (Reus *et al*, 2015; Torres-Platas *et al*, 2014a, b). Microglial cells are in constant communication with astrocytes as evidenced by the dynamic interactions between these cells demonstrated *in vivo* (Norden *et al*, 2015b). Under homeostatic conditions, astrocytes respond to microglia-induced inflammatory stimulation by producing anti-inflammatory cytokines such as IL-10 and TGF- β , which act as a feedback loop to decrease microglial activation (Norden *et al*, 2015b, 2016). Aged astrocytes fail to restrain microglial activation probably due to a loss of or decreased surface expression IL-10 receptors in older compared with younger astrocytes (Norden *et al*, 2015b, 2016).

Microglial pruning. Microglia engage in constructive pruning to maintain synaptic and functional specialization during critical developmental phases and in neurogenesis (Matcovitch-Natan *et al*, 2016; Schafer and Stevens, 2015). In contrast, toxic pruning by microglia results from excessive immune activation and aggressive neural signaling (eg, during prenatal infections and severe stress) and appears to move the trajectory toward synaptic destruction or aberrant synaptic construction (Brites and Fernandes, 2015). Physiological synaptic pruning by microglia appear to be triggered by the expression of lipopolysaccharide-binding protein and the synaptic marker protein PSD-95 in the microglia. Decreases in the availability of these two key proteins in the microglia were noticed both in animals exposed to early life stress and prenatal infections, and the loss of these proteins was associated with aberrant synaptogenesis, deficient glutamate neurotransmission, and impaired cognitive performance (Durieux *et al*, 2015; Wei *et al*, 2012).

Microglia and glutamate. During surveillance state, microglia do not express glutamate receptors or transporters. However, upon activation, microglia express both glutamate transporters (EAAT and xC) and glutamate receptors on their surface. Glutamate binding to AMPA and kainate subtypes of ionotropic receptors located on microglia stimulates the production and release of cytokines such as TNF (Noda *et al*, 2000; Verkharsky and Butt, 2013). mGluR2/3/5 is also expressed on microglia with varying modulatory effects. Glutamate binding to microglial mGluR2 promotes neurotoxicity via further release of inflammatory cytokines, glutamate, and nitric oxide (NO), whereas mGluR5 is neuroprotective through the opposing effects on same systems (Piers *et al*, 2011; Taylor *et al*, 2005). Considerable recent data implicate TNF in increasing microglial glutamate release. TNF increases extracellular glutamate levels by inducing glutamate release from microglia (Takeuchi *et al*, 2006) and astrocytes (Bezzi *et al*, 2001; Petrelli and Bezzi, 2016). The mechanism of glutamate release by microglia is linked to increased expression of the enzyme glutaminase that converts glutamine to glutamate,

indicating that immune-activated glial cells actively synthesize glutamate in a manner similar to neurons (Takeuchi *et al*, 2008). In addition, glutamate absorbed by surface transporters of activated microglia is also trafficked into the astrocytic cytoplasm through connexin gap junctions between microglial and astrocytic cells, further leading to the decreased functioning and expression of astrocytic EAATs (Takeuchi *et al*, 2008; Takeuchi *et al*, 2006).

Microglia and mood disorders. Postmortem studies have indicated evidence of activated and primed microglia in some brain regions of depressed suicide victims including the anterior cingulate cortical regions (Torres-Platas *et al*, 2014a, 2014b). Recently, *in vivo* activation of microglia in the brains of patients with mood disorders has been imaged using positron emission tomography and a radio-labeled tracer for the translocator protein (TSPO), which is overexpressed in these cells upon activation. Using this ligand in patients with major depressive disorder, one study found increased microglial activation (Setiawan *et al*, 2015), whereas another did not (Hannestad *et al*, 2013), a discrepancy that may be related to the severity of depression, medication status, and other demographic features. Nevertheless, TSPO ligand binding reliably labeled activated glial cells following endotoxin administration in healthy human subjects (Sandiego *et al*, 2015). Thus, current evidence of microglial activation is variable in patients with depression; however, more work is needed in this area.

MACROPHAGES

Macrophages are recruited into the brain parenchyma through the BBB by activated resident microglia using chemokine signals including CCL2 (D'Mello *et al*, 2009; Le *et al*, 2004). In fact, many of these cells reside in perivascular regions and upon activation express glutamate transporters (EAATs and xC) and receptors (ionotropic and metabotropic). In addition, they also secrete copious amounts of glutamate into the extrasynaptic space, thus adding to the excitotoxic environment of the brain during inflammation (Figure 1; Piani and Fontana, 1994; Piani *et al*, 1991).

T CELLS

T cells traffic into the brain through the choroid plexus and might have an important role in and confer neuroprotection by regulating glutamate and GABA neurotransmission while functioning as the cornerstone of brain's adaptive immune system (Kipnis *et al*, 2012; Walsh *et al*, 2014b). T cells are known to decrease excitotoxicity from glutamate, modulate astroglial activity, and promote growth factor expression (Kipnis *et al*, 2012). Several neurotransmitters including glutamate have cognate receptors expressed on the T-cell surface that might regulate at least some of their functions including the integrin-mediated adhesion and migration in response to chemotactic signals (Ganor *et al*, 2003).

Resting T cells also express NMDA receptors and exhibit a dose-dependent functional response to glutamate exposure (Levite, 2014). Low physiological concentrations (in nanomolar range) of glutamate appear to increase T-cell adhesion and facilitate chemotactic migration (Ganor *et al*, 2003). Moderately higher physiological concentrations (micromolar range) of glutamate promote T-cell proliferation via ionotropic receptors (AMPA and NMDA) and decreased apoptosis via mGluRs. High concentrations (millimolar range) in a variety of pathological conditions can activate mGluR5 to decrease T-cell proliferation and mGluR1 to increase inflammatory (eg, IFN- γ) cytokine release (Ganor *et al*, 2003). T-cell dysfunction is one of the least explored areas in neuropsychiatry and represents a gap in our current knowledge regarding cellular regulation of glutamate neurotransmission (Ellwardt *et al*, 2016; Walsh *et al*, 2014b).

MOLECULAR MECHANISMS OF GLUTAMATE RELEASE

Synaptic release of glutamate is the primary mechanism of glutamate under physiologic conditions (Danbolt, 2001). Nevertheless, there are several important non-vesicular (non-exocytotic) mechanisms responsible for glutamate release in pathological contexts (Malarkey and Parpura, 2008; Zhou and Danbolt, 2014) including: (1) release through anion channels (Wang *et al*, 2013a); (2) reverse efflux through EAATs (Ye and Sontheimer, 1996), (3) release by xC transporters as part of the cystine–glutamate exchange process (Lewerenz *et al*, 2013), (4) astrocytic vesicular glutamate release during gliotransmission (Petrelli and Bezzi, 2016) and release through hemi-channels on astrocytes and microglia (Malarkey and Parpura, 2008). A detailed review of the functioning of these release mechanisms is beyond the scope of this review, and the reader is directed elsewhere (Dantzer and Walker, 2014; Malarkey and Parpura, 2008; Najjar *et al*, 2013; Tilleux and Hermans, 2007). A brief overview is presented below.

Anion Channel Glutamate Release

This mechanism of glutamate release through anion channels occurs during states of astrocytic swelling such as seen in hepatic encephalopathy and stroke. Under such conditions, glutamate is expelled by astrocytes through anion channels into the extra- and intrasynaptic spaces leading to profound excitotoxicity (Wang *et al*, 2013a).

Reverse Efflux of Glutamate

Astrocytes release glutamate through reverse efflux via EAATs (Malarkey and Parpura, 2008; Zhou and Danbolt, 2014). The mechanism underlying reverse release appear to involve downstream inflammatory molecules such as cyclooxygenase (COX)-2 and prostaglandin E2 both of which are known to trigger release of calcium from intracellular stores (Bezzi *et al*, 2001; Petrelli and Bezzi, 2016). Glutamate

release by astrocytes can lead to marked ‘spillover’ effects and increase its binding to extra synaptic-NMDA receptors (Figure 1).

Glutamate Release through the Cystine–Glutamate Exchange system (xC-System)

Once thought to be exclusively astrocytic in location, now xC-transporters are known to be located on other glial cells including microglia (Lewerenz *et al*, 2013; Lewerenz and Maher, 2015). As described earlier, the xC-system exchanges cystine for glutamate in a 1:1 ratio where glutamate is extruded in exchange for intake of cystine, which is used for the synthesis of glutathione (GSH). GSH is the most abundant anti-oxidant molecule in the brain and its absence is usually fatal (Lewerenz *et al*, 2013; Lewerenz and Maher, 2015). Although *in vitro* functional ablation of the xC-system leads to fatal oxidative stress from depletion of GSH, *in vivo* genetic deletion of the system does not lead to oxidative stress or death, possibly due to GSH supplies from alternate cellular systems (Lewerenz *et al*, 2013; Lewerenz and Maher, 2015). Although the source of oxidative stress has been assumed to be due to immune stimulation, states of intense neural activity such as stress can also increase demand for GSH—which is met through an NMDA-mediated hyperactivation of GSH biosynthesis within in the neurons (Baxter *et al*, 2015; Nathan and Cunningham-Bussel, 2013). The glutamate that is extruded by the xC-system further adds to the extrasynaptic glutamatergic load. In several brain regions, the xC-system is a major source of both intracellular GSH and extracellular glutamate, and its enhanced transcription following induction can have widely varying effects ranging from intracellular protective effects to toxic increases in extracellular glutamate (Lewerenz *et al*, 2013). Excessive extracellular glutamate can bind to the xC-transporters and lead to their toxic paralysis resulting in GSH depletion and cell death—a process referred to as ‘oxidative glutamate toxicity’—in contrast to excitotoxic glutamate toxicity resulting from overstimulation of ionotropic receptors (Lewerenz *et al*, 2013). Thus, the combined effect of oxidative and excitotoxic glutamate toxicity has been associated with the neurotoxic effects and neurodegeneration under conditions of inflammation and possibly stress (Lewerenz and Maher, 2015).

Probably owing to their spatial proximity, glutamate released by the xC-system has preferential access to extrasynaptic NMDA receptors in a paracrine manner leading to neuronal toxicity as described earlier (Camacho and Massieu, 2006; Hardingham and Bading, 2010). Inflammatory cytokines including TNF and LPS administration upregulate the xC-system and induce glutamate release from cultured and primary microglia (Figuera-Losada *et al*, 2014; Mesci *et al*, 2015; Piani and Fontana, 1994). Similarly, IL-1 β has been implicated in increasing the xC-system expression on the surface of astrocytes (but not on microglia or macrophages)—an effect that is mediated through the activation of nuclear factor kappa B (NF- κ B) signaling (Jackman *et al*, 2010). LPS-induced activation of TLR3 and 4 increases surface expression

of the xC-system and thus co-administration of LPS and the xC-system stimulator cystine can potentially lead to enhanced glutamate toxicity (Kigerl *et al*, 2012). Increases in xC-system function have been implicated in multiple medical disorders (Massie *et al*, 2015), but more intriguingly is being actively targeted for new drug development for the treatment of substance dependence (Baker *et al*, 2003).

Vesicular Glutamate Release

Astrocytes and oligodendrocytes sense synaptic glutamate activity through their surface glutamate receptors or transporters and respond by triggering internal Ca²⁺ fluxes of their own as part of the gliotransmission processes described earlier (Nedergaard *et al*, 2002). Oscillations in intracellular Ca²⁺ are known to precipitate further release of glutamate through gap junctions with other glial cells or by release into synaptic or extrasynaptic spaces (Parpura and Verkhratsky, 2013). Binding of immune stimulating molecules such as ATP and TNF to astrocytic immune receptors can amplify and alter the magnitude and propagation of intracellular Ca²⁺ oscillations across glial networks (Volterra and Meldolesi, 2005). Thus, exaggeration of vesicular glutamate release by glial cells by immune activation might be an important part of glutamate increases seen in mood and other disorders, although direct evidence for this is just beginning to emerge.

MOLECULAR MECHANISMS OF GLUTAMATE CLEARANCE

EAATs

EAATs are specialized transport proteins expressed on the synaptic surface of neurons and glial cells that remove and detoxify glutamate from the synaptic (and to a lesser extent extrasynaptic) space in a matter of milliseconds into the glial cells (Nedergaard *et al*, 2002). There are at least five different types of EAATs described with specific patterns of cellular localization. EAAT2 and EAAT1 have primarily been localized to astrocytes and oligodendrocytes, respectively, and EAAT3–4 and EAAT5 are primarily localized to neurons (Arriza *et al*, 1997; Danbolt, 2001). It has been estimated that almost 80% of the glutamate released by presynaptic neurons under homeostatic conditions is cleared by EAAT2 reuptake into astrocytes and up to 20% by EAAT3 into neurons (Danbolt, 2001). EAAT1 expression in oligodendrocytes suggests that EAAT1 might have a role in myelination and CNS connectivity in addition to its role in glutamate removal (Regan *et al*, 2007). EAATs can transport glutamate against a 10 000-fold difference in concentration gradient between intra- and extracellular compartments (Milton *et al*, 1997). EAATs accomplish this seemingly impossible task by pairing glutamate intake with inward transfer of three Na⁺ ions and one H⁺ ion, and outward transfer of one K⁺ ion from the cell, resulting in a net inward movement of positive charge (Levy *et al*, 1998; Zerangue and Kavanaugh, 1996).

Immune molecules act at many levels of EAAT synthesis leading to a decrease in EAAT synthesis, expression, and functionality. Most importantly, the EAAT genes have promoter regions that are responsive to immune regulation through intracellular immune signaling molecules such as the transcription factor NF- κ B (Zou and Crews, 2005). EAAT proteins are synthesized in the endoplasmic reticulum and appear to undergo extensive posttranslational modification in the Golgi apparatus (Kalandadze *et al*, 2004) before being trafficked onto the plasma membrane for surface expression (Conradt and Stoffel, 1997; Figiel and Dzwonek, 2007; Figiel *et al*, 2007; Gamboa and Ortega, 2002; Schluter *et al*, 2002; Shan *et al*, 2013). The surface EAATs are periodically removed from the plasma membrane via endocytosis, and are then either shuttled back to the cell surface (via recycling endosomes) or targeted for degradation in lysosomes (Nakagawa *et al*, 2008). The entire process is regulated by protein–protein interactions and phosphorylation, and is highly responsive to immune influences. Immune mediators (such as TNF) regulate membrane trafficking and recycling of EAATs either alone or in association with several neurohumoral influences, including growth factors and neuropeptides (Gras *et al*, 2012; Takahashi *et al*, 2015). As mentioned previously, EAATs are expressed on astrocytes and oligodendrocyte cells both in resting and during activation states, whereas microglia express these transporters only when activated by immune factors such as LPS (Persson *et al*, 2005). Inflammatory molecules such as IL-1 β and TNF released during immune activation suppress astrocytic expression of GLT-1 and GLAST glutamate transporters (similar to EAAT2 and EAAT1 in humans) in cell culture experiments (Korn *et al*, 2005; Szymocha *et al*, 2000; Wang *et al*, 2013a; Ye and Sontheimer, 1996), and EAAT2 expression is diminished in inflammatory CNS lesions of both laboratory animals and humans (Ohgoh *et al*, 2002; Vercellino *et al*, 2007). Several excellent reviews on this topic are available for further reference (Malarkey and Parpura, 2008; Ohgoh *et al*, 2002; Tavares *et al*, 2002; Tilleux and Hermans, 2007; Vercellino *et al*, 2007). Although glutamate removal from the extracellular space by EAATs is sufficient to prevent excitotoxicity from physiological levels of glutamate release (Bergles and Jahr, 1997; Rothstein, 1996), it is often inadequate in pathological contexts such as during immune activation (Danbolt, 2001; Dantzer and Walker, 2014; Zhou and Danbolt, 2014).

BBB Glutamate Scavenging

Brain extracellular levels of glutamate are normally maintained in the micromolar range by EAATs but can rapidly increase 100-fold during microglial and macrophage release (Dantzer and Walker, 2014; Leibowitz *et al*, 2012). However, when glutamate concentrations become excessive through contributions from activated microglia and macrophages, the EAAT uptake mechanism may be insufficient to clear the entire glutamate load with further impairment of glutamate clearance (Gras *et al*, 2012; Takaki *et al*, 2012). Glutamate is

also removed by passive diffusion from the brain through the BBB into the systemic circulation. Extracellular glutamate effluxes through astrocytes into the perivascular space and then through the endothelium into the peripheral blood. It is now known that much of extracellular glutamate is removed by EAATs expressed on the abluminal (brain side) of the endothelium of the cerebral blood vessels, crosses the blood vessel wall, and is released into the blood by glutamate transporters present on the luminal or blood side of the endothelium (Helms *et al*, 2012). Thus, rapid reduction in the concentrations of plasma glutamate leads to an aggressive mobilization of glutamate from the brain into the plasma and can result in rapid reduction of brain glutamate. This in turn can be clinically accomplished by administering agents such as oxaloacetate and pyruvate that stimulate glutamate-metabolizing enzymes such as glutamate oxaloacetate and pyruvate transaminase (SGOT and SGPT) in the blood and lead to rapid depletion of blood glutamate. This strategy has met with some success in reducing glutamate-induced excitotoxicity following experimental induction of stroke (Leibowitz *et al*, 2012). More recently, this strategy of glutamate ‘scavenging’ has been proposed as a possible means to reduce excessive glutamate activity as a result of increased inflammation (Dantzer and Walker, 2014).

CYTOKINE EFFECTS ON GLUTAMATE NEUROTRANSMISSION

There is a rich literature on the impact of multiple cytokines on glia and glutamate neurotransmission including the cellular expression of glutamate receptors, and glutamate release and reuptake (Vezzani and Viviani, 2015). Selected effects of several inflammatory cytokines are reviewed below and are summarized in Table 1.

TNF

In vitro studies of primary hippocampal neurons have shown that TNF signaling controls synaptic scaling by increasing trafficking of AMPA glutamate receptors and decreasing the numbers of surface GABA receptors (Wohleb *et al*, 2016). Experimental application of TNF to hippocampal slices induced a rapid increase in excitatory postsynaptic electrical activity mediated by increased expression of overactive surface AMPA receptors (Beattie *et al*, 2002) associated with an overrepresentation of GluA1 compared with GluA2 subunits (Vezzani and Viviani, 2015). The hyperactive AMPA subtype is known to be extra-permeable to Ca²⁺ leading to acute enhancement of Ca²⁺ rises and has been associated with neuroinflammation-induced disease progression in epilepsy (Vezzani and Viviani, 2015). Effects of TNF on NMDA receptors is not yet well defined, although NMDA receptor blockers are known to confer neuroprotection against glutamate toxicity resulting from TNF-mediated EAAT inhibition (Zou and Crews, 2005). Thus, at physiological concentrations, TNF might promote synaptogenesis by stimulating postsynaptic AMPA activity (Pribrag and Stellwagen, 2014), synaptic maintenance by optimally stimulating pre- and postsynaptic NMDA through the TNFR1 system (Santello *et al*, 2011), regulate EAAT function to promote controlled clearance of glutamate (Volterra and Meldolesi, 2005), and increase neuroprotection through TNFR2 activity. (Cheng *et al*, 1994) However, during immune activation, TNF levels can rapidly increase from picomolar and micromolar levels to as high as 100 nM levels leading to sustained NF- κ B activation and neurotoxicity (Santello and Volterra, 2012).

IL-1 β

Hippocampal cell culture studies suggest that the activation of NMDA receptors promote membrane insertion of new IL-1 β receptors, whereas IL-1 β enriches the NMDA receptor

TABLE 1 Effects of Inflammatory Cytokines and Kynurenine Metabolites on Glutamate Neurotransmission

Mediator	Release				Re-uptake		Receptors			
	Release ^a		x _C		EAAT2		NMDA		AMPA	
	Neuron	Astrocytes	Expression	Function	Expression	Function	Expression	Function	Expression	Function
TNF	↑	↑	↑	↑	↓	↓	U	↑	↑↑	↑↑
IL-1 β	↑	↑	↑ ^b	↑ ^b	↓	↓	↑↑	↑↑	↑	IN
IFN- γ					↑/↓ ^c		↑		↑	
IL-6	↓						↓	↓	↑/↓ ^d	
QUIN	↑	↑	↑ ^e				↑			
KYNA	↓						↓			

Abbreviations: AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EAAT2, excitatory amino-acid transporter type 2; IN, insufficient data; NMDA, N-methyl-D-aspartate receptors; x_C, cystine–glutamate exchange transporter; U, unchanged.

^aPresynaptic neuronal and astrocytic release, reverse efflux, anionic release, or P2X7-related release.

^bMediated through IL-1 receptor in astrocytes only.

^cIncreased in low concentrations and decreased at high concentrations.

^dEarly-phase increase followed by late-phase decrease.

^eIndirect through promotion of oxidative stress.

pool and enhances its activity at the postsynaptic membrane (Vezzani and Viviani, 2015). By preferentially targeting the NMDA receptor complex, IL-1 β is hypothesized to lead to neuroprogression, kindling, and enhanced risk of excitotoxicity by promoting downstream consequences including tyrosine-kinase (TrK)-mediated phosphorylation of NMDA receptor proteins and progressively increasing Ca²⁺ permeability with repeated activation (Vezzani and Viviani, 2015). IL-1 β release may be mediated by the activation of NLRP3-inflammasome systems by DAMPs (such as high-mobility box group (HMGB)-1) and ATP; Vezzani and Viviani, 2015) and it is activated by stress (Iwata *et al*, 2013; Iwata *et al*, 2016). Taken together, the data indicate the marked engagement of progressive NMDA activation by IL-1 β signaling continues to represent a target for neuroprogressive changes in mood disorders.

IFN- γ

IFN- γ activation can lead to profound changes in the functioning of astrocytes, thus leading to changes in their ability to clear glutamate. Unlike other cytokines, T lymphocytes are the primary producers of IFN- γ (Kipnis *et al*, 2012) and once released at high concentrations, IFN- γ can transform astrocytes into phagocytic, antigen-presenting cells (Fontana *et al*, 1984; Shrikant and Benveniste, 1996; Soos *et al*, 1998). In concert with the anti-inflammatory cytokine IL-4 (which is also produced by T cells), IFN- γ controls the transition of the astroglial phenotype from neuroprotective (A2) to neurotoxic (A1) with the drastic reduction in the ability of these cells to clear glutamate (Garg *et al*, 2008; Garg *et al*, 2009; Kipnis *et al*, 2012). However, at lower concentrations, IFN- γ increases glutamate buffering and clearance by stimulating EAATs with the opposite effects at higher concentrations (Hu *et al*, 2000; Ye and Sontheimer, 1996). It also serves as a potent inducer of the tryptophan-catabolizing enzyme indoleamine-2,3-dioxygenase (IDO) in microglia ultimately leading to the generation of glutamate-like compounds such as QUIN further altering glutamate neurotransmission (Oxenkrug, 2011; Oxenkrug, 2010). IFN- γ may induce neuronal dysfunction by the enhancement of AMPA (but not NMDA)-mediated glutamate neurotoxicity (Mizuno *et al*, 2008).

IL-6

IL-6 is a key component of the inflammatory response in the brain, a profound stimulator of acute phase proteins from the liver and has been implicated in the etiology of neuropsychiatric disorders such as depression (Dowlati *et al*, 2010; Howren *et al*, 2009; Miller and Raison, 2016; Valkanova *et al*, 2013) and schizophrenia (Goldsmith *et al*, 2016). IL-6 has mixed effects on the glutamate system attributable to the more chronic and nuanced nature of its effects. Unlike IL-1 β and TNF, IL-6 is secreted mostly by astrocytes and its effects are mediated through its soluble receptor (sIL-6R), which acts on cells expressing gp130 on

their surface (Arisi, 2014). IL-6 leads to decreases in presynaptic glutamate release, immediate but transient enhancement of AMPA activity followed by its later decline and downregulation of NMDA receptor expression and activity (Pribrag and Stellwagen, 2014). In sum, IL-6 effects on glutamate metabolism and turnover is varied but more study is warranted.

DUAL ACTIVATION OF INFLAMMATION AND GLUTAMATE RELEASE: P2X7 RECEPTORS

So far, we have reviewed mechanisms by which the immune system and inflammation might lead to increases in glutamate concentrations. However, both the immune system and astrocytic glutamate release can be activated in concert by purinergic mechanisms stimulated by extracellular release of ATP (Li *et al*, 1999; Longuemare and Swanson, 1995; Rossi *et al*, 2000; Zeevalk *et al*, 1998). ATP is released into the extracellular space by apoptotic dead tissue or stress-induced neuronal firing and can rapidly activate the inflammasome, leading to the release of cytokines such as IL-1 β and IL-18 (de Rivero Vaccari *et al*, 2014, 2016a, 2016b). In addition to immune effects, binding of ATP to purinergic P2X7 cation channel receptors on glial cells is also known to trigger direct release of glutamate through these channels (Malarkey and Parpura, 2008). In contrast to other astrocytic ion hemichannels, P2X7 channels are insensitive to voltage changes and quickly become conduits for the reverse release of glutamate from astrocytes in a calcium-independent manner (Malarkey and Parpura, 2008). The leakage of glutamate through P2X7 ion channels can lead to drastic increases in glutamate. Intriguingly, a recent *in vivo* study using immobilization stress (a preclinical model of mood disorder) reported that concurrent stress-induced increases in the release of both glutamate (from neurons) and ATP (from astrocytes) was followed by the stimulation of the microglial inflammasome apparatus leading to release of IL-1 β (Iwata *et al*, 2016). Based on this data, the acute neurotoxic effects of ATP might be mediated through P2X7 channel release of glutamate, with more chronic effects being mediated through activation of inflammasome.

METABOLIC MECHANISMS OF GLUTAMATE PATHWAY ACTIVATION

KYN Pathway

Tryptophan is an essential amino-acid available primarily through dietary intake and has multiple biological roles such as being a substrate in the synthetic pathway of the mood regulating monoamine serotonin. During inflammatory conditions, tryptophan is shunted away from serotonin synthesis into the KYN pathway, which is an alternative catabolic pathway for tryptophan resulting in the generation of multiple glutamate-like metabolites that can trigger neurotoxicity and oxidative stress (Dantzer and Walker, 2014;

Schwarcz, 2016). The metabolism of tryptophan through the KYN pathway is initiated by activation of tryptophan-catabolizing enzymes IDO-1 and 2, and tryptophan-2,3-dioxygenase (TDO) (Schwarcz, 2004, 2016; Schwarcz *et al*, 2012; Schwarcz and Pellicciari, 2002). TDO is found in the liver and is regulated by glucocorticoids, whereas IDO is found both in the periphery and in the brain immune cells, and it is responsive to inflammatory cytokines including IFN- γ and TNF (Dantzer *et al*, 2008; Schwarcz *et al*, 2012). Once activated, the IDO system leads to a sequence of multi-step, enzyme-substrate reactions, which culminate in the generation of a wide range of glutamate-like and free radical-generating metabolites (Stone *et al*, 2012). Robust evidence has linked IDO activation to symptoms of depression following administration of IFN- α for the treatment of cancer and hepatitis C (Capuron *et al*, 2003; Raison *et al*, 2010). Taken together, the KYN pathway involves metabolites whose primary effects may be mediated through glutamatergic systems and hence might represent pharmacological targets to modulate glutamatergic neurotransmission. Given the vast number of review articles available on this subject (Dantzer *et al*, 2011; Myint *et al*, 2007; Oxenkrug, 2010; Schwarcz, 2016; Schwarcz *et al*, 2012; Stone *et al*, 2012; Vecsei *et al*, 2013), only topics essential to glutamate activity will be discussed in the ensuing paragraphs.

KYN Pathway and its Downstream Metabolites

The KYN pathway is initiated by the transformation of tryptophan to *N*-formylkynurenine by IDO, which in turn is converted into KYN by formamidase (Schwarcz *et al*, 2012). Approximately 60% of KYN in the brain are synthesized in the peripheral tissues and enters the brain through amino-acid uptake transporters in the BBB and the remaining 40% are synthesized *de novo* in the brain by IDO in activated immune and glial cells (Vecsei *et al*, 2013). Generation of KYN is a key step in the initiation of the KYN pathway (Schwarcz *et al*, 2012). Irreversible transamination of KYN by action of the enzyme kynurenine aminotransferase II results in the generation of an NMDA antagonist kynurenic acid (KYNA) with putative neuroprotective properties. Indeed, KYNA is a robust antagonist of α -7 nicotinic acetylcholine receptors (α 7nAChR), which leads to secondary decreases in presynaptic glutamate release (Schwarcz *et al*, 2012). Sequential activation by the enzymes kynurenine monooxygenase (KMO) and kynureninase results in the formation of the neurotoxic molecules 3-hydroxy kynurenine (3HK), anthranilic acid (AA), 3-hydroxy anthranilic acid (HANA), and QUIN that are ultimately converted to nicotinic acid adenine dinucleotide (NAD). 3HK, AA and, HANA all are known to trigger profound oxidative stress and precipitate cell death (Chiarugi *et al*, 2001a; Chiarugi *et al*, 2001b; Guidetti and Schwarcz, 1999). They also indirectly contribute to glutamate increases by increasing the need for GSH and activating the xC-system. QUIN is a direct-acting NMDA receptor agonist and powerful neurotoxin (Guillemin, 2012).

The balance between the concentrations of the various KYN byproducts depends on the activation status of the cells that host the synthetic enzyme systems for these molecules. The KYNA-synthesizing enzyme KAT is only present in astrocytes. Hence, the quantity of KYNA is dependent on astrocytic health and functioning (Schwarcz *et al*, 2012). In stark contrast, the enzyme KMO is present only in microglia, and its activation leads to increases in concentrations of neurotoxic metabolites including 3HK, AA, HANA, and QUIN (Schwarcz *et al*, 2012). Dysregulation of either of these systems or a loss of the balanced function of these systems is hypothesized to contribute to the pathogenesis and pathophysiology of several neuropsychiatric disorders. For example, increases in KYNA activation are associated with schizophrenia, whereas QUIN increases are associated with depression, suicidality, and neurodegeneration (Brundin *et al*, 2015; Erhardt *et al*, 2013; Guillemin, 2012; Savitz *et al*, 2015; Schwarcz *et al*, 2012).

QUIN Effects on Glutamate

QUIN is a powerful and potent excitotoxin, and the prolonged presence of even physiological concentrations (mid-to-high nanomolar range) of QUIN is sufficient to cause excitotoxicity (Guillemin, 2012; Schwarcz, 2016). Short-term exposure of neurons to QUIN can cause rapid neuronal excitation by activating NMDA receptors (Guillemin, 2012). QUIN selectively induces greater activation of NMDA receptors in neurons located in hippocampus, striatum, and neocortex, leading to a higher excitotoxic burden in these brain regions (Guillemin, 2012; Tavares *et al*, 2002). Mechanistically, it is proposed that differences in NMDA receptor configuration in these regions might mediate their hyper-responsiveness to QUIN toxicity (Dantzer *et al*, 2008; Guillemin, 2012; Schwarcz, 2004, 2016; Schwarcz *et al*, 2012). QUIN toxicity is often additive or synergistic with concurrently present neurotoxic processes including immune activation, oxidative stress, and excitotoxicity (Guillemin, 2012).

QUIN Effects on Glia

QUIN is also able to cause gliotoxicity (Guillemin, 2012). At low concentrations, QUIN treatment induced astrocytic activation, decreased EAAT activity, and produced a dose-dependent reduction in glutamine synthetase activity resulting in a net increase in tissue glutamate concentrations (Schwarcz, 2016). The mechanism of action of QUIN on astrocytes is likely to be mediated via activation of astrocytic NMDA receptors, which may be preferentially sensitive to the NMDA receptor ion channel blockers MK801 and memantine offering some hope for protection from QUIN toxicity in diseases such as Huntington's disease (Guillemin, 2012; Schwarcz, 2016), as well as other disorders of increased inflammation and behavioral dysregulation.

CONCEPTUAL CONVERGENCE: A WORKING MODEL

So far, we have reviewed the rich literature describing how activated immune mechanisms impact and alter cellular, molecular, and metabolic mechanisms that regulate glutamate in both physiological and pathological contexts. Based on the above data, we propose a working model that implicates dysregulation of glutamate processing by glial and neuronal cells resulting from inflammatory activation as a causal factor mediating behavioral changes in some patients with mood disorders (Figure 1). The model also proposes to incorporate early and late effects of inflammatory activation on glutamate processing by neurons, astrocytes, oligodendrocytes, and microglia leading to neuroprogressive changes often seen in mood disorders (Moylan *et al*, 2013).

Immune-induced changes in astrocytes leading to both defective cradling and impaired buffering by EAATs are proposed to result in defective containment and spillover of neuronal glutamate into the extrasynaptic regions (Haydon and Carmignoto, 2006; Parpura and Verkhratsky, 2013; Volterra and Meldolesi, 2005). Non-neuronal release of glutamate by activated and/or primed microglia, macrophages and astrocytes through xC system, hemichannel, reverse EAAT, anion channel and vesicular release mechanisms further contribute to increased glutamate available for diffusion into the extrasynaptic space (Ida *et al*, 2008; Malarkey and Parpura, 2008; Tilleux and Hermans, 2007). Of note, the effects of priming might have profound impact on the release of glutamate by microglial cells and might also impact the antidepressant effects of glutamatergic modulating agents.

The increased extrasynaptic diffusion of glutamate resulting from the combined effects of spillover and glial release further exerts downstream effects on extrasynaptic glutamate receptors. The extent and effects of glutamate diffusion will depend upon the spatial arrangement of extrasynaptic glutamate receptors, glutamate synapses, and their glutamate transporter buffering zones (Dorsett *et al*, 2016; McCullumsmith and Sanacora, 2015; Tzingounis and Wadiche, 2007). In physiological conditions, the buffering and release of glutamate is tightly regulated by EAATs and glutamate is not allowed to diffuse beyond 0.5 μm from its point of origin, thus restricting access to extrasynaptic glutamate receptors (Tzingounis and Wadiche, 2007). It is possible that decreases in number and functioning of EAATs by immune molecules drastically decreases buffering zones, increases the radius of spillover, and increases availability of freely diffusing glutamate to engage and over activate extrasynaptic binding sites in a paracrine manner (Tzingounis and Wadiche, 2007).

Extrasynaptic NMDA receptor stimulation has been implicated as one of the primary culprits mediating the early and late effects of glutamate toxicity by blocking the synthesis and release of nerve growth factors such as BDNF and other synaptic proteins resulting in synaptic loss (Hardingham, 2009; Hardingham and Bading, 2010;

Hardingham *et al*, 2002). Extracellular diffusion of glutamate can lead to the loss of synaptic fidelity, decreased specificity of neurotransmission, and lead to ‘noisy’, non-specific, and disruptive neural activity experienced by patients as cognitive and affective symptoms (Dorsett *et al*, 2016). Although precise data are lacking, we speculate that inflammatory activation in mood disorders might lead to increased AMPA activity during early phases followed by desensitization and decreased AMPA activity in later stages resulting in synaptic depression, decreased transmission efficiency, and impaired synaptic plasticity (Choquet and Triller, 2013; Popoli *et al*, 2012; Pribrag and Stellwagen, 2014; Pribrag and Stellwagen, 2013).

Increased extrasynaptic glutamate can also bind to presynaptic neuronal metabotropic mGluR2/3 autoreceptors inhibiting glutamate release leading to chronic reductions in intrasynaptic glutamate, loss of excitatory synaptic activity, and ultimately result in synaptic loss (Duman, 2014; Duman *et al*, 2016; McEwen *et al*, 2016). Of note, mGluR2/3 antagonists have demonstrated ketamine-like antidepressant effects (Duman, 2014; McEwen *et al*, 2016). Finally, we propose that the decrease in intrasynaptic glutamate also leads to further atrophy and loss of intrasynaptic NMDA receptors. The resulting imbalance between decreases in intrasynaptic vs increases in extrasynaptic NMDA signaling is hypothesized to lead to neurotoxicity, neuronal loss, and decreased regional brain volumes seen in patients with mood disorders (Sanacora and Banasr, 2013; Wang *et al*, 2013b). During gliotransmission, the astrocytes release small amounts of glutamate that binds to extrasynaptically located presynaptic glutamate receptors that can increase or decrease synaptic release—thus tuning synaptic activity up or down (De Pitta and Brunel, 2016). We speculate that processes mediating successful treatments or spontaneous remission in mood disorders engage these astroglia-mediated plasticity and repair mechanisms to reverse synaptic dysfunction. In accordance with the previously published literature, we propose that this model implicates the role played by glial cells in mediating the convergence between inflammation and glutamate seen among a number of intermediate behavioral phenotypes, including positive (reward learning and reward valuation) and negative (fear, anxiety and loss) valence systems, cognition, arousal, and socialization (Haroon *et al*, 2012, 2016; McCullumsmith and Sanacora, 2015).

PRECLINICAL AND CLINICAL STUDIES: TRANSLATIONAL RELEVANCE

Based on the multitude of interactions among the immune system, glia, and glutamate metabolism as noted in our working model, several recent preclinical and clinical studies have examined the association between inflammation and glutamate dysregulation. For example, blockade of glutamate by pre-administration of ketamine abrogated depressive symptoms following LPS without altering underlying

inflammatory responses in the brain (Walker *et al*, 2013). Moreover, in an animal model of treatment refractory depression using chronic administration of ACTH, animals that responded to ketamine exhibited higher baseline plasma concentrations of CRP and TNF (Walker *et al*, 2015). Elevated peripheral blood TNF, IL-1 β , and IL-6 predicted favorable antidepressant response to ketamine administration in a small sample of depressed patients (Hashimoto, 2015). Other studies report that increased body mass index (BMI) and plasma adipokine concentrations (both of which are associated with inflammation) correlated with ketamine response (Jaso *et al*, 2016; Machado-Vieira *et al*, 2016; Machado-Vieira *et al*, 2009). Intriguingly, as noted above, astrocytes express adipokine receptors such as the leptin receptors (LepR) and LepRs are increased in number in the astrocytes of obese animals and in C6 astrocytoma cells treated with LPS and TNF (Hsuchou *et al*, 2009; Pan *et al*, 2012).

More directly, addressing the impact of inflammation on glutamate, creatine-normalized glutamate (Glu/Cr) concentrations in the basal ganglia and anterior cingulate cortex (dACC) were measured using proton magnetic resonance spectroscopy (MRS) before and after administration of IFN- α (Haroon *et al*, 2014). IFN- α led to significant increases in Glu/Cr in the left basal ganglia and the dACC, which in turn correlated with depressive symptoms (Haroon *et al*, 2014). Of relevance to the potential role of the KYN pathway in these findings, is that IFN- α increases QUIN in the CSF of IFN- α -treated patients in association with depressive symptoms (Raison *et al*, 2010). Another study showed that IFN- α -induced Glu/Cr increases were seen more robustly among older compared to younger individuals and these Glu/Cr increases were associated with greater plasma TNF concentrations, increased psychomotor slowing and decreased motivation (Haroon *et al*, 2015). In sum, these findings indicate a greater susceptibility of glutamate metabolism to the effect of inflammation among older individuals (Haroon *et al*, 2015). These findings may be related to the alterations in glia function as a result of priming effects of aging described above.

Further substantiating the relationship between increased inflammation (as reflected by CRP) and glutamate, chronically depressed patients with varying levels of inflammatory activation underwent MRS to evaluate absolute glutamate concentrations in the left basal ganglia and the dACC (Haroon *et al*, 2016). Patients with major depression and high inflammatory activity (plasma CRP > 3 mg/l) showed significantly higher concentrations of glutamate in the left basal ganglia region compared to patients with low inflammation (CRP < 1 mg/l; Haroon *et al*, 2016). In addition, a significant correlation was found between plasma and CSF CRP, and basal ganglia glutamate. No glutamate changes as a function of inflammation were seen in the dACC of these depressed patients (Haroon *et al*, 2016). Of note, inflammation-induced basal ganglia glutamate changes were associated with behavioral changes including anhedonia and psychomotor slowing (Haroon *et al*, 2016).

Interestingly, aside from glutamate, the only other neuro-metabolite associated with inflammation both in the peripheral blood and CSF was myo-inositol (Haroon *et al*, 2016). Myo-inositol is believed to be an astroglial marker, suggesting an involvement of astrocytes in these findings (Brand *et al*, 1993; Haroon *et al*, 2009; Kim *et al*, 2005; Plitman *et al*, 2016). Taken together, these data indicate an association between inflammation and glutamate dysregulation in mood disorders including depression. Moreover, these findings are consistent with the rich basic science data demonstrating the impact of inflammation on the cellular, molecular, and metabolic constituents involved in the regulation of glutamate metabolism. Finally, these data identify potentially relevant biomarkers of inflammation effects on glutamate metabolism in mood disorders including peripheral blood inflammatory measures such as CRP, TNF, and IL-6; KYN metabolites such as QUIN; adipokines; and other markers of altered metabolic function including BMI, and central markers of altered glial function such as increased myo-inositol.

Regarding treatment considerations, as discussed above, the NMDA antagonist ketamine has received the most attention regarding glutamate alterations in mood disorders and may have special efficacy in patients with increased inflammation. Nevertheless, other glutamate active drugs warrant consideration. For example, memantine—a non-competitive but weak NMDA receptor antagonist—administered at doses ranging from 5 to 20 mg per day was not associated with antidepressant efficacy in controlled trials (Niciu *et al*, 2014a). All studies used doses of memantine approved for the treatment of dementia and it is unclear whether higher doses of memantine might have yielded better results. However, no study has used inflammatory biomarkers to predict memantine response, as with ketamine. Riluzole, a glutamate-stabilizing agent that acts by increasing uptake of glutamate into the glial cell and by modulating release of presynaptic glutamate has proven effective in reducing the physiological, cellular, and behavioral effects of chronic stress in rodent models (Banasr *et al*, 2010). Several small open-label clinical studies have also shown some promise for the drug in the treatment of mood and anxiety disorders (Pittenger *et al*, 2008). However, data from randomized placebo-controlled trials have been mixed, although none of these studies examined inflammatory biomarkers as potential predictors of response. A single parallel, randomized, controlled trial, study of 64 inpatients with diagnosis of moderate-to-severe major depressive disorder from Iran found that the patients receiving 6 weeks of treatment with riluzole (50 mg/bid) plus citalopram (40 mg per day) had a significantly greater response with greater speed to treatment was observed in the riluzole group than the placebo plus citalopram (40 mg per day) group (Salardini *et al*, 2016), but other studies have failed to show any clear evidence to support the efficacy of the drug in the treatment of major depressive disorder (Mathew *et al*, 2015; Niciu *et al*, 2014b). Similar to memantine, no study has taken into consideration the inflammatory status of the sample

population. Several proprietary drugs with effects on NMDA systems are under varying stages of development and evaluation, and the reader is referred to other more in depth articles focusing on this topic (Niciu *et al*, 2014a; Sanacora *et al*, 2012; Zarate *et al*, 2010).

CONCLUSIONS AND FUTURE DIRECTIONS

Extensive data indicate that the immune system has multiple roles in the regulation of glutamate neurotransmission and the maintenance of synaptic integrity. In addition, glutamate can profoundly influence the function of immune cells in the brain including microglia. Relevant to pathology, increased activation of the immune response in the periphery and CNS can lead to marked alterations in glial function and glutamate regulation, and through the activation of multiple avenues of excitotoxicity can lead to synaptic dysfunction and death, and ultimately behavioral and cognitive impairments. Much interest has focused on the role of these interactions among inflammation, glutamate metabolism, and glial function in mood disorders. However, studies have failed to fully establish whether inhibition of inflammation can reverse CNS glutamate changes as assessed by neuroimaging strategies such as MRS. Moreover, it remains unclear whether and which markers of inflammation might identify those patients who are most likely to respond to glutamate-targeted therapies. In addition, the contribution of inflammation-induced changes in glutamate to white matter pathology remains unclear. Finally, further examination of how treatments that target inflammation and glutamate can be combined or sequenced to achieve lasting response or disease prevention is warranted. In summary, it has become increasingly clear that there are many more pathways to pathology in mood and other neuropsychiatric disorders that go beyond the monoamines. Inflammation and its effect on glia and glutamate are two of these pathways, and data indicate that there is an important convergence that if recognized and studied may greatly enhance the further development of therapeutics that target these pathways.

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