




# Neuroprotective astroglial response to neural damage and its relevance to affective disorders

José Javier Miguel-Hidalgo\* 

Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS 39216, USA

**\*Correspondence:** José Javier Miguel-Hidalgo, Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, USA. [jmiguel-hidalgo@umc.edu](mailto:jmiguel-hidalgo@umc.edu)

**Academic Editor:** Rafael Franco, Universidad de Barcelona, Spain

**Received:** May 11, 2023 **Accepted:** August 3, 2023 **Published:** October 31, 2023

**Cite this article:** Miguel-Hidalgo JJ. Neuroprotective astroglial response to neural damage and its relevance to affective disorders. *Explor Neuroprot Ther.* 2023;3:328–45. <https://doi.org/10.37349/ent.2023.00054>

## Abstract

Astrocytes not only support neuronal function with essential roles in synaptic neurotransmission, action potential propagation, metabolic support, or neuroplastic and developmental adaptations. They also respond to damage or dysfunction in surrounding neurons and oligodendrocytes by releasing neurotrophic factors and other molecules that increase the survival of the supported cells or contribute to mechanisms of structural and molecular restoration. The neuroprotective responsiveness of astrocytes is based on their ability to sense signals of degeneration, metabolic jeopardy, and structural damage, and on their aptitude to locally deliver specific molecules to remedy threats to the molecular and structural features of their cellular partners. To the extent that neuronal and other glial cell disturbances are known to occur in affective disorders, astrocyte responsiveness to those disturbances may help to better understand the roles astrocytes play in affective disorders. The astrocytic sensing apparatus supporting those responses involves receptors for neurotransmitters, purines, cell adhesion molecules, and growth factors. Astrocytes also share with the immune system the capacity to respond to cytokines released upon neuronal damage. In addition, in response to specific signals, astrocytes release unique factors such as clusterin or humanin that have been shown to exert potent neuroprotective effects. Astrocytes integrate the signals above to further deliver structural lipids, remove toxic metabolites, stabilize the osmotic environment, normalize neurotransmitters, provide antioxidant protection, facilitate synaptogenesis, and act as barriers to contain varied deleterious signals, some of which have been described in brain regions relevant to affective disorders and related animal models. Since various injurious signals that activate astrocytes have been implicated in different aspects of the etiopathology of affective disorders, particularly in relation to the diagnosis of depression, potentiating the corresponding astrocyte neuroprotective responses may provide additional opportunities to improve or complement available pharmacological and behavioral therapies for affective disorders.

## Keywords

Astrocytes, neuroprotection, glutamatergic, neurotrophins, synaptic, antioxidant, oligodendrocytes



## Introduction

Astrocytes are now acknowledged not only for being general providers of metabolic and structural support to neurons and for their role in responses to gross central nervous system (CNS) injury, but also due to their more specific, and no less critical, roles in locally regulating neurotransmitter actions around synapses, buffering cations during action potential propagation, stabilizing myelin maintenance and contributing to action potential regeneration in the white matter (WM) [1]. Unregulated or persistent interruption of some of those homeostatic roles can surely lead to neural dysfunction and in specific cases to neuronal damage or death [2]. Accordingly, some of these essential properties of astrocytes have been shown to be substantially disrupted or deficient in various neuropsychiatric and neurological disorders, very likely providing a major contribution to their etiology and/or pathophysiology [3, 4]. In the same vein, a case has been made for targeting the restoration of pathologically changed astrocytes or mitigating the effects of their dysfunction as indirect neuroprotective approaches in the treatment of neuropsychiatric and neurological disorders, including affective disorders [5]. In the case of affective disorders, abundant evidence has accumulated showing that, mostly in major depressive disorder, the morphology of astrocytes and the expression of several proteins crucial to their function are reduced in various areas of the prefrontal cortex [3, 4, 6–12]. In human subjects diagnosed with depression, specific alterations involve lower levels in the glutamate transporters expressed by astrocytes [4, 13], which are crucial for the regulation of neuronal excitability and synaptic transmission. In the homologous brain region of rodent models of chronic stress and other animal models with depressive-like behaviors, there is also a decrease in those astrocytic transporters [14–16] or glutamate reuptake [17, 18]. In addition, animals chronically stressed and humans with major depression also show significantly lowered levels of astrocyte-expressed gap junction proteins connexin 43 (Cx43) and connexin 30 (Cx30), also in the prefrontal cortex [19–23], proteins that are crucial in the regulation of extracellular potassium as well as in the interaction of astrocytes with blood vessels and oligodendrocytes. The contributions of these alterations of astrocytes to the pathophysiology of depression and to behavioral changes in animal models of stress (as a major risk factor for depression) have been the subject of focused attention by many researchers [6], while some experimental approaches for the treatment of depression based on normalizing the decreased levels of the disturbed astrocytes components have been also proposed and explored in animal models of stress and clinical trials [24–30].

In addition to those critical roles played by dysregulation of astrocyte neurophysiology in affective disorders, knowledge is starting to rapidly accumulate showing that astrocytes themselves can respond to dysfunction and/or damage undergone by neurons or oligodendrocytes to mount responses that protect these cell types from further damage, mitigate deleterious functional effects and ultimately contribute to the restoration of normal neural function [31]. These neurorestorative properties of astrocytes would exist together with well-known responses of astrocytes that appear to result in variably temporary and localized impairment of neuronal or glial function and growth. The responsive abilities of astrocytes in the face of neural damage, although varied in nature, appear to lead to changes in astrocyte morphology and physiology that convert them into what, starting early in CNS damage studies, has been termed reactive astrocytes. Subtypes of reactive astrocytes as well as reactivity states have been distinguished that betray more or less permanent adaptations to specific environments or stages as they respond to damage or to significant alteration of the neuronal, metabolic, or extracellular environment [32]. Astrocytes may also respond to surrounding anomalies in neuronal function/metabolism or to degenerative signals without turning into reactive astrocytes as classically described, but still participating in neuroprotective activity by limiting damage or enhancing restoration of function. Whether characteristically reactive or not, astrocytes would perform neuroprotective tasks by adapting their metabolism and morphology to the altered environment and by releasing metabolites and growth factors that would protect surrounding cells such as neurons, oligodendrocytes, and microglia [33]. Thus, putative glia-based neuroprotective enhancements to treat affective and other psychiatric disorders may depend not only on facilitating the recovery of astrocytes from their own dysfunctional pathology [34], but also on exploiting the ability of astrocytes to protect against the decline or disruption of neuronal and oligodendrocyte morphology and physiology. The

ability to profit from or enhance these astrocytic capabilities to improve overall neural function in depression may provide additional avenues to treat or palliate psychiatric or neurological disorders. The present review, rather than discussing normal physiological and structural features of astrocytes that are compromised in affective disorders to disturb normal neuronal function, will discuss available knowledge on some important properties of astrocytes that activate after or positively contribute to the recovery from pathological disturbances occurring in neurons and oligodendrocytes in those disorders, and that could be leveraged in the treatment of major affective disorders such as major depression.

## Neuroprotection and structural changes of astrocytes after neuronal and synaptic damage

The severity of damage to the nervous tissue varies with the type of injury, but when it is extensive or clearly localized as in trauma, infection, blood-brain barrier disruption, or direct exposure to toxins it often leads to the appearance of reactive astrocytes that proliferate and form a border limitans separating the bulk of the damaged tissue from the less affected surrounding regions [35, 36]. This subtype of reactive, proliferative astrocytes has been distinguished from non-proliferative reactive astrocytes, which will rather respond to less extensively or recognizably damaged pathological tissue and would not form a scar surrounding or within the damaged tissue. Some of these astrocytes have been described as undergoing hypertrophy without proliferations, mostly preserving the extent of tissue reached by the extent of their processes [37]. Since in neuropsychiatric disorders there is very little, if any, macroscopic or overt damage to neurons and myelin (although clearly some forms and localizations of neurological injuries lead to psychiatric symptoms), it seems reasonable to think that astrocytes in psychiatric disorders may behave to some extent as that type of non-proliferating astrocytes that appears in some forms of brain trauma, and in fact, some studies in depression have observed that, together with some decreased population density of glial cells, there could be hypertrophy in the cell bodies of astrocytes in the prefrontal cortex, although the actual significance of this finding is yet to be determined. This type of reactive astrocyte may be involved in responses to neuronal or oligodendrocyte-related dysfunction.

As hinted above, after severe neuronal damage, a barrier or structure is formed by enlarged astrocyte processes with or without cell proliferation that was termed “glial scar” since early in CNS injury research, although it is not necessarily a scar in the same sense as scars formed after lesions or damage to tissues with a large connective tissue component, and in fact some researchers dispute that accumulation of reactive astrocytes and their processes should be rightly called a “glial scar” as astrocytes are part of the normal structure of the brain parenchyma [32]. Regardless of the actual pathophysiology and terminology assigned to accretions of reactive astrocytes near damaged CNS tissue, the morphological changes undergone by astrocytes are in response to neuronal and glial damage in the surrounding tissue. An interpretation of the “scar” as a passive limitans zone has led to proposing that the neuroprotective properties of astrocyte-based accretions depend mainly on their ability to physically isolate the damaged tissue from healthier tissue around it, so contributing to avoiding the spread of the damage [35–37]. On the other hand, the “scar” has been considered a negative reactive feature because, particularly in the CNS of some vertebrates, the scar appears to impair to some extent axon and neurite growth, and thus would contribute to reducing the plasticity and perpetuating local damage [36]. This concept of passive and/or negative functions of reactive astrocytes has progressively changed to ascribe them an important positive neuroprotective role [31, 32, 37, 38] in responses to neuronal damage as researchers have found, for instance, that removal of intermediate filaments formed by glial fibrillary acidic protein (GFAP) and vimentin, which are at the foundation of the enlargement and motility of astrocyte processes, results in a spread of the region of neuronal damage with only minor effects in facilitating neuroplasticity [39], although some studies show that in particular sites or environments, such as the hippocampus, absence of the cytoskeletal proteins may rather stimulate synaptogenesis [40, 41]. In fact, restrictive actions that contain and isolate damage, and the release/expression of factors that favor neuronal survival, neurite growth, and synaptogenesis, may be just two sides of the same coin that protects the function and structure of standing neurons from damaged tissue, and promotes their plasticity to effectively recover function [41].

Mitigation of neuronal damage by astrocytes after neuronal or synaptic disturbance may be triggered by astrocyte purinergic G-protein-coupled receptor 1 (P2Y1) downregulation in response to signals provided by surrounding microglia. Agonist binding to those receptors activates phospholipase C-activating guanine nucleotide-binding protein ( $G_q$ ) proteins leading to inositol-triphosphate receptor-dependent stimulation and increases in astrocyte intracellular calcium that eventually may lead to increased neuronal damage [42], while reduced P2Y1 receptors would lead to neuroprotective activity of astrocytes [43]. However, in other conditions, inositol 1,4,5 trisphosphate (IP3) receptor-dependent calcium increases in astrocytes may lead to increased astrocyte-derived production of cell adhesion molecule N-cadherin which would favor neuronal and synaptic neuroprotection [44], of importance since N-cadherin alterations have been implicated in major psychiatric disorders and the effects of stress [45]. Additionally, activation of guanine nucleotide-binding protein-coupled receptor (GPCR) receptors of astrocytes associated with stimulatory guanine nucleotide-binding protein ( $G_s$ )-type subunits may also result from surrounding disrupted circuits, and lead to increased intracellular cyclic adenosine monophosphate (cAMP) as, for instance, activation of dopamine receptors of astrocytes have been demonstrated to increase their production of glia-derived neurotrophic factor (GDNF) and fibroblast growth factor 2 (FGF2), increases that would elicit neuroprotective responses [46].

Astrocytes have been found to release a variety of small molecules that act on neurotransmitter receptors of neurons and other glial cells. These molecules, some of them the same as neuronal transmitters, have been then called “gliotransmitters”. For instance, evidence is available that upon injury or distress, the release of some gliotransmitters such as taurine, mainly produced by astrocytes, increased in the CNS [47], which may be of importance since various studies have shown that upregulation of taurine in the CNS results in neuroprotection through a variety of mechanisms [48–50], while increases in blood taurine are found in subjects with major depression [51] and taurine itself has been found to show antidepressant-like effects in animal models [52–54].

Furthermore, when damage to the tissue is mild or does not cause a typical glial scar, experimentally impairing astrocytes actually leads to increased neuronal death and higher tissue damage [55]. These neuroprotective responses may depend at least partly on the activity of transcription factors such as signal transducer and activator of transcription 3 (STAT3) in astrocytes, as its deletion increases damage and demyelination after CNS injury [56]. A major pathway for astrocytes to detect neuronal injury may depend on the regulation of ciliary neurotrophic factor (CNTF) production by astrocytes. In non-injured brain astrocytes are the main producers of CNTF, although at very low levels [57]. After injury, they significantly increase CNTF expression [58, 59]. There is evidence that interaction of neuronal surface molecules such as thymocyte antigen-1 (Thy-1) with integrins in the astrocyte cell membrane keeps the astrocytic expression of CNTF in check, but in the presence of damaged or dying neurons reduced binding to integrins results in an upregulation of astrocyte-produced CNTF to favor CNTF's neurotrophic and neuroprotective actions on surrounding neurons [58] and oligodendrocytes.

Responses of astrocytes to neural damage may also include the regulation of excess potassium in the synaptic environment since astrocytes have been found to increase potassium transporter following ischemia *in vitro* [60]. Increased glucose supply by astrocytes may also be a mechanism for neuronal protection at least in neurological disorders [60]. Both  $K^+$  control and glucose supply management may be implicated in depression mechanisms, and astrocytes could participate in regulating them to protect neuronal activity to prevent or mitigate the effects of depression mechanisms or their triggering factors. However, further studies are clearly needed to assess if aspects of extracellular ion regulation and metabolic mechanisms are actually relevant to neuroprotective mechanisms of astrocytes in psychiatric disorders [5, 41].

## Neuroimmune activation and the neuroprotective role of astrocytes

When neurons or other glial cells that surround astrocytes are damaged or dysfunctional, abnormal changes in neurotransmitters, ions, metabolites, or specific proteins may act as signals for astrocytes to engage their neuroprotective capabilities. In addition, some cells such as microglia, which rapidly activate

upon brain trauma, emit signals capable of downregulating astrocyte purinergic P2Y1 receptors and transform astrocytes into a neuroprotective phenotype that undergoes astrogliosis and protects neurons immediately outside of the damaged area from further damage while encircling and isolating damaged neurons [43]. Astrocytes can also exert neuroprotection by producing molecules such as transforming growth factor (TGF)- $\beta$  or orosomucoid which result in attenuated microglial activation [61, 62]. Despite the neuroprotective responses of astrocytes in response to microglia-derived information, it must be stressed that (as in other instances of astrocyte responses during damage) in some circumstances the interaction with microglial cells or cytokines such as tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)1- $\beta$  released by them, rather triggers pathways that locally impair or reduce neuronal function [63], the specific direction of the astrocyte's responses depending on the magnitude, nature, and location of the damage [64, 65].

Responses of astrocytes to microglia and cytokine signaling upon cell neuronal damage are of great relevance to understanding the roles of astrocytes in regulating neuronal function and structure in affective and stress-related disorders since depressive symptoms are known to be greatly influenced by alterations in both pro-and anti-inflammatory cytokines, and elevations or decreases of those cytokines are described in those disorders and their corresponding animal models [66, 67]. For example, IL6 is heavily released by astrocytes in response to neuronal or oligodendrocyte degeneration and may play a role in limiting the release of proinflammatory cytokines by astrocytes themselves and by microglial cells [68] and thus prevent further neuronal damage. However, in depression the available evidence suggests that increased plasma and brain IL6 is due at least partly to astrocytes and may contribute to the activation of amygdalar neurons, which is correlated with enhanced depressive symptoms [68]. Thus, due to the complexity and versatility of astrocytes in immune activation, leveraging the responses of astrocytes for neuroprotective ends will require specific knowledge of the triggers and intracellular pathway engaged in particular instances of damage.

In addition to the role of astrocytes in detecting and controlling cytokine and microglial disturbances in depression, astrocytes can also lead to neuroprotective responses to neuroinflammation due to their role in the metabolism of neuroinflammation-induced quinolinic acid (QA) and kynurenic acid (KYNA) and their intermediaries, which in turn would participate in the alterations of glutamatergic signaling in the brain of subjects with affective disorders [26, 69]. QA and KYNA result from the metabolism of tryptophan (central to affective disorders by being the precursor for serotonin in raphe nuclei cells). Astrocytes hold a complex relationship to the metabolism of those endogenous compounds but the available evidence supports that the production of KYNA by astrocytes is neuroprotective because KYNA is an inhibitor of *N*-methyl-*D*-aspartate (NMDA) receptors [70], which would be overstimulated by excess extracellular glutamate in depression [71, 72]. Since some cytokines acting on microglia and lymphocytic cells stimulate the production of QA (agonist of NMDA receptors), astrocytes would play another important role by limiting the actions on microglia and protecting neuronal circuits from excess NMDA activation that would happen because of augmented extracellular glutamate signaling in affective disorders.

## **Role of astrocytes in synaptic plasticity and reinnervation of neurons deprived of their synaptic inputs**

Astrocytes also play an important role in facilitating positive reactivation of postsynaptic neurons in extreme cases of synaptic loss and plasticity. For example, their role in facilitating synapse formation to repurposing brain areas fully deprived of their normal afferents as it happens in neurons of the visual cortex deprived of their synaptic input after monocular eye enucleation in rodents. In these conditions, the synaptic space vacated by the absent visual inputs is repopulated by neighboring synaptic terminals representing adjacent parts of the visual field or by terminals that are routed from axons of completely different sensory modality that eventually take over the vacated synapses [73, 74]. Remarkably, local astrocytes are not only necessary to the establishment of new contacts as shown by inducing their disappearance, but their experimental activation through inhibitory guanine nucleotide-binding protein (G<sub>i</sub>)-type GPCRs located on their membranes enhances the process of synaptic plasticity [75]. To the extent



that synaptic loss or malfunction is observed in the frontal cortex of subjects with depression or in animal models of stress-induced depression-like behaviors [25, 76–79], as well as in other psychopathologies [80–82], it is then possible that targeting specific astrocyte cellular pathways leading to synaptic plasticity contributes to neuroprotection through synapse normalization and restoration of synaptic function.

## **Role of astrocytes in neuroprotective regulation of the molecular environment of degenerating neurons**

As stated above, some functions and activities of astrocytes are required in supporting neuronal activity in normal conditions, and thus their deficit is deleterious to neurons. However, those functions take on a positive neuroprotective role in the presence of direct damage to neurons as in the case of stroke or more generally hypoxia. For instance, damage to neurites or neuronal death leads to increasing glutamate levels in the extracellular space, which further increases neuronal damage and death. Furthermore, in these conditions, neural tissue injury results in the release of factors such as FGF and nerve growth factor (NGF), which promote the conversion of glutamate taken up by astrocytes into glutamine, effectively reinforcing the ability of astrocytes to remove extracellular glutamate and redirecting glutamine to neurons to eventually replenishing glutamate in synaptic vesicles [83]. Other neurotrophic factors such as epidermal growth factor (EGF), basic FGF, insulin-like growth factor 1 (IGF1), and CNTF, which are released during neuronal injury, also signal astrocytes to increase the levels or membrane localization of glutamate transporters [84, 85], positively protecting neurons from further harmful stimulation. After cerebral ischemia, this neuroprotective ability of astrocytes can be removed upon knockdown of their expression of glutamate transporter glutamate transporter 1 (GLT1) with antisense technology [86].

These neuroprotective functions based on glutamate regulation are relevant to the mechanisms and treatment of affective disorders because studies of functional neuroimaging and genetic polymorphisms have shown that levels of some glutamate transporters are reduced in depression and other psychiatric disorders [14, 87–90], and though in normal circumstances the available glutamate transport capabilities of astrocytes may be sufficient in the face of an increased demand for glutamate removal, their transporting capabilities in depression may be insufficient to protect neuronal function from excess glutamate, thus contributing to an aggravation of depression symptoms. Accordingly, molecules that enhance glutamate reuptake such as riluzole have been shown to mitigate some forms of depression [24, 91, 92].

Another example of a specific neuroprotective role of astrocytes is the production of the antioxidant tripeptide glutathione. Astrocytes contain very high concentrations of glutathione as compared to other CNS cells. In stroke or other forms of damage that dramatically increase reactive oxygen species (and thus the risk for fast toxicity to neurons), glutathione released by astrocytes greatly limits neuronal damage due to its potent antioxidant properties [41] as demonstrated in models of hypoxia ischemia or in astrocytes from rodents lacking an enzyme necessary for the formation glutathione [93]. Likewise, several lines of evidence have demonstrated that oxidative mechanisms are increased in the brains of subjects with depression and other psychiatric diagnosis [94–96], making it possible that astrocyte-related antioxidant mechanisms such as glutathione activity limit the extent of the damage that could be reached without those mechanisms. In fact, some long-term antidepressant treatments have been found to enhance or increase the levels of antioxidant chemical species in animal models and in successfully medicated patients [97–99], while antioxidant treatments themselves have been proposed to exert desirable antidepressant effects [100, 101].

The hypothesis that monoaminergic deficits are central to depression or other psychopathologies has been significantly modified over the years, to recognize that changes in other neurotransmitter systems and the circuits that use them are also an important, if not essential, component of dysfunctional mechanisms in depression [102, 103]. In addition, it has become increasingly documented that some physiological mechanisms, such as those mediated by the stress response, normally trigger the involvement of various neurotrophic factors and other molecules that support neuronal growth and survival, but that, in some patients, the ability to recruit those neurotrophic mechanisms may be substantially diminished,

contributing to an eventual diagnosis of depression [103]. In such circumstances, stimulation of the astrocyte's capability to produce and deliver neurotrophic factors may prevent further deterioration, effectively providing a neuroprotective mechanism. Some antidepressant treatments, originally deemed to simply act through actions on serotonin or norepinephrine transporters, have been lately found to promote increases in neurotrophic factors, and glutamate transport and even favor antioxidant mechanisms in animal models, suggesting that independent potentiation of neurotrophic mechanisms supported by astrocytes may be a major source of more specific treatments for depression and other psychopathologies with shared mechanisms [104].

In various pathological conditions that jeopardize the function or structure of neurons and their synapses, a role has been described for sex steroids in ensuring the protection of neurons from further damage [105]. In these conditions too, the growth-limiting properties of reactive astrocytes appear to be modulated by sex steroids [106]. However, in neuroinflammatory pathology and other types of neuronal damage, some responsive astrocytes undergo induction of aromatase expression and consequently stimulation of estradiol production and release, allowing for the mitigation of cell death and the enhancement of neurogenesis brought about by those steroids [107–110]. This protective ability of astrocytes may substitute for the role of neurons in normal and non-injurious physiological conditions when neurons are the main cells in the CNS expressing aromatase to provide physiological levels of estradiol intrinsic to the CNS [111, 112]. There are also sex differences in astrocytes, microglia, oligodendrocytes, and myelin between males and females [106], which may contribute to explaining sex-dependent differences in behavioral and metabolic responses and may be leveraged for new avenues of treatment.

Accordingly, progesterone increases during brain damage tend to limit the expression of astrocyte features that impair neuron growth such as increased water transport through aquaporins, inflammatory cytokine release, increase in free radicals, or excitatory cell death [113], while estradiol overexpression by astrocytes would rather have the opposing effects of enhancing the production by astrocytes of factors that favor neuronal survival and neurite growth [106]. For instance, estradiol is capable not only of reducing astroglial reactivity but also of inducing astrocytes to release neuroglobin and other neurotrophic factors, some of them with neuroprotective and anti-inflammatory properties [114–121]. Actions of estradiol produced by astrocytes in response to synaptic loss or dysfunction may also result in an increase in synapse formation or maturation as has been shown in neuronal cultures supplemented with astrocyte conditioning medium or estradiol itself, while in those conditions tamoxifen, an estrogen receptor modulator, prevents synapse formation induced by astrocyte medium [122].

Astrocytes are well-known for their ability to release metabolites, neurotransmitters and their derivatives, as well as some cofactors through a vesicular release mechanism that involves fusion to the cell membrane [123, 124]. In addition, more recent research also shows that astrocytes are capable of forming and dispensing extracellular vesicles or exosomes to their immediate environment [125, 126]. These vesicles are of interest to the theme of this article because evidence is accumulating that the contents of these expelled vesicles may exert powerful neuroprotective action on the neurons exposed to them. For example, Xu et al. [127] have described that microRNA miR-92b-3p contained in exosomes generated by preconditioned astrocytes protects neurons from oxygen/glucose deprivation. It is also possible that another microRNA contained in astrocyte-derived exosomes, miR-34c, plays a role in increasing the survival of neurons after ischemia/reperfusion as shown *in vitro* and *in vivo* rodent models [128]. Small extracellular vesicles derived from astrocytes also may play more specific roles in synaptic plasticity by facilitating synapse formation by using their fibulin-2 cargo, which leads to activation of TGF- $\beta$  signaling and enhancement of synapse formation at cortical spines [129]. This recent knowledge on extracellular vesicles complements previous findings that several cell membrane-linked cell adhesion molecules of astrocytes, and their associated extracellular matrix proteins, are necessary for the formation and maturation of functional synapses [130]. Given recent findings that the cargo of extracellular vesicles in subjects with depression may play specific roles in the disease process and contain markers of

neuropathological changes [131], greater attention may have to be given to the ability of astrocytes to produce vesicles with contents that regulate the function or structure of neurons and other glial cells.

## Astrocytes in the protection of oligodendrocytes and myelin

Astrocytes not only mount responses that protect the structure and function of neurons and synapses but also are involved in or are capable of ensuring the maintenance of oligodendrocytes and their myelin [132–134] through a variety of released factors in normal and pathological conditions, as well as of supporting oligodendrocyte precursor cells [nerve/glial antigen 2 (NG2)] in the face of several types of damage [135, 136]. Accordingly, despite the neurite growth inhibitory properties of fully declared “glial scars” in severe injury, reactive astrocytes in milder forms of injury, whether scarring or non-scarring, actually can promote remyelination and *de novo* formation of oligodendrocytes [137–139]. This protective function can include enhancing the survival of NG2 cells against oxidative stress, starvation, or oxygen-glucose deprivation through mechanisms mediated by the mitogen-activated protein kinase (MAPK) kinase (MEK)/extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K)/Akt strain transforming factor (Akt) intracellular pathways [140], while other studies *in vitro* have shown that erythropoietin (EPO) released by astrocytes can protect NG2 cells subjected to hypoxia, by acting on EPO receptors expressed by NG2 cells [141]. The ability to detect damage to oligodendrocytes or their myelin and react to promote myelination and survival may be of importance in advancing new treatments for depression, because studies in prefrontal regions of the human brain have shown that, even in the absence of patent demyelination, the expression of some oligodendrocyte-related proteins and/or their corresponding mRNAs as well as microRNAs such as miR21 (abundant in oligodendrocytes) are significantly changed in depression and in animal models of chronic stress [142]. Nevertheless, any enthusiasm derived from evidence pointing to the protection of NG2 cells by astrocyte activation in experimental models may have to be moderated by a possible involvement of subcortical WM astrocytes in limiting NG2 cell proliferation and myelination after subcortical WM stroke by releasing inhibin A, which blocks the stimulating actions of matrilin-2 on NG2 cell proliferation and may delay motor recovery [143].

Another pathway that may be relevant to the promotion of axon growth and myelination is the binding of TGF- $\alpha$  to EGF receptor (EGFR) in astrocytes, which leads to increased invasiveness of these cells while increasing penetration and axon outgrowth in the lesion [137–139]. Another factor which is also upregulated in dysfunctional or injured states CNTF, has been shown to promote myelination *in vitro* [144].

## Other astrocytic factors with depression-relevant neuroprotective properties

In addition to neurotrophic factors, neurotransmitter-related metabolites, antioxidant compounds, steroids, proteins or factors that don't easily fall within those categories have more recently been shown to be significantly upregulated after neuronal and synaptic losses in specific degenerative processes. For instance, the astrocyte-produced humanin, a peptide encoded in the mitochondrial genome, has been suggested to play a protective role for synapses in the hippocampus, and also to be involved in preventing further synaptic dysfunction and cognitive deficits that at times are associated with menopause [145]. Interestingly, it seems that the expression of an isoform of humanin, humanin-like 8, is increased in the prefrontal cortex in major depression [146] and that humanin genes are differentially methylated in subjects with obsessive-compulsive disorder [147], further suggesting a role of these astrocyte-generated humanins in promoting neuronal integrity despite cellular stress in psychiatric disorders, because humanin has been found to exert neuroprotective and antiapoptotic actions in various other conditions [148–151].

Clusterin, an antiapoptotic protein, also known as apolipoprotein J (apoJ), though expressed in both astrocytes and neurons, is increased greatly in astrocytes after different types of injury and in neurological disorders [152–154], likely limiting ongoing neuronal damage. What is relevant to the present discussion is that clusterin expression in astrocytes has been shown to be neuroprotective in *in vivo* rodent models of ischemia and Alzheimer-like pathology [155, 156], although some *in vitro* experiments have provided



conflicting results [157, 158]. Since the bulk of the evidence rather suggests that clusterin potentiates neuroprotection [159], it is possible that its increased expression in astrocytes may contribute to limiting neuronal damage, and that this role may limit the consequences of stress in subjects with major depression and other psychiatric disorders. For instance, significant elevations of extracellular clusterin have been detected in the dorsolateral prefrontal cortex of subjects with schizophrenia, being interpreted as a neuroprotective response to continuing neuronal dysfunction and damage in that disorder [160], while in animal models of stress-related behaviors caused by social defeat, there appears to be an increase in levels of serum clusterin [161]. In subjects diagnosed with depression in remission, clusterin is also elevated in plasma [162]. Elevated concentrations of corticosteroids, which occur in some forms of depression and are a feature of stress (in itself a major risk factor for depression) can result in significant increases of clusterin expression by astrocytes [163]. These alterations of clusterin in the brain may remain rather local and not necessarily correlate with clusterin changes in the peripheral circulation [164–167], pointing to specific and localized neuroprotective actions on brain circuits.

## Conclusions

Depression and other affective disorders involve a plethora of pathological alterations at cellular and molecular levels in several brain regions dedicated to emotional and cognitive processing. The ubiquity of astrocytes, their activation following neural damage and dysfunction, and the variety of sensing mechanisms, metabolites, hormones, neurotransmitter transporters, growth factors, and specific proteins upregulated in astrocytes after damage suggest a complexity of pathways that would be involved in positively protecting injured or threatened neurons and oligodendrocytes. This putative ability of astrocytes to provide neuroprotection coexists with other actions that may aggravate damage in particular circumstances and brain areas. Thus, leveraging the neuroprotective activity of astrocytes to develop or complement new therapeutic approaches for affective disorders will require specific targeting of brain regions and astrocytic pathways that maximize neuroprotective responses while minimizing actions that block neural plasticity.

## Abbreviations

CNS: central nervous system

CNTF: ciliary neurotrophic factor

FGF: fibroblast growth factor

IL: interleukin

KYNA: kynurenic acid

NG2: nerve/glial antigen 2

NMDA: *N*-methyl-*D*-aspartate

P2Y1: purinergic G-protein-coupled receptor 1

QA: quinolinic acid

TGF: transforming growth factor

WM: white matter

## Declarations

### Author contributions

JJM: Conceptualization, Writing—original draft, Writing—review & editing.

### Conflicts of interest

The author declares that he has no conflicts of interest.

### Ethical approval

Not applicable.

### Consent to participate

Not applicable.

### Consent to publication

Not applicable.

### Availability of data and materials

Not applicable.

### Funding

Research reported in this article was partly supported by National Institute of Health grants [R21MH118675, R56MH113828]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### Copyright

© The Authors 2023.

## References

1. Chai H, Diaz-Castro B, Shigetomi E, Monte E, Oceau JC, Yu X, et al. Neural circuit-specialized astrocytes: transcriptomic, proteomic, morphological, and functional evidence. *Neuron*. 2017;95: 531–49, e1–9.
2. Verkhratsky A, Zorec R, Parpura V. Stratification of astrocytes in healthy and diseased brain. *Brain Pathol*. 2017;27:629–44.
3. Verkhratsky A, Rodriguez JJ, Steardo L. Astroglipathology: a central element of neuropsychiatric diseases? *Neuroscientist*. 2014;20:576–88.
4. Nagy C, Suderman M, Yang J, Szyf M, Mechawar N, Ernst C, et al. Astrocytic abnormalities and global DNA methylation patterns in depression and suicide. *Mol Psychiatry*. 2015;20:320–8.
5. Liu B, Teschemacher AG, Kasparov S. Astroglia as a cellular target for neuroprotection and treatment of neuro-psychiatric disorders. *Glia*. 2017;65:1205–26.
6. Miguel-Hidalgo JJ. Astroglia in the vulnerability to and maintenance of stress-mediated neuropathology and depression. *Front Cell Neurosci*. 2022;16:869779.
7. Joshi PC, Benerjee S. Effects of glucocorticoids in depression: role of astrocytes. *AIMS Neurosci*. 2018; 5:200–10.
8. Jeanson T, Pondaven A, Ezan P, Mouthon F, Charveriat M, Giaume C. Antidepressants impact connexin 43 channel functions in astrocytes. *Front Cell Neurosci*. 2016;9:495.
9. Lima A, Sardinha VM, Oliveira AF, Reis M, Mota C, Silva MA, et al. Astrocyte pathology in the prefrontal cortex impairs the cognitive function of rats. *Mol Psychiatry*. 2014;19:834–41.
10. Rajkowska G, Hughes J, Stockmeier CA, Javier Miguel-Hidalgo J, Maciag D. Coverage of blood vessels by astrocytic endfeet is reduced in major depressive disorder. *Biol Psychiatry*. 2013;73:613–21.
11. Rajkowska G, Miguel-Hidalgo JJ. Gliogenesis and glial pathology in depression. *CNS Neurol Disord Drug Targets*. 2007;6:219–33.
12. Cotter D, Mackay D, Landau S, Kerwin R, Everall I. Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch Gen Psychiatry*. 2001;58:545–53.
13. Miguel-Hidalgo JJ, Waltzer R, Whittom AA, Austin MC, Rajkowska G, Stockmeier CA. Glial and glutamatergic markers in depression, alcoholism, and their comorbidity. *J Affect Disord*. 2010;127: 230–40.

14. Piao CS, Holloway AL, Hong-Routson S, Wainwright MS. Depression following traumatic brain injury in mice is associated with down-regulation of hippocampal astrocyte glutamate transporters by thrombin. *J Cereb Blood Flow Metab.* 2019;39:58–73.
15. Gómez-Galán M, De Bundel D, Van Eeckhaut A, Smolders I, Lindskog M. Dysfunctional astrocytic regulation of glutamate transmission in a rat model of depression. *Mol Psychiatry.* 2013;18:582–94.
16. Zink M, Vollmayr B, Gebicke-Haerter PJ, Henn FA. Reduced expression of glutamate transporters vGluT1, EAAT2 and EAAT4 in learned helpless rats, an animal model of depression. *Neuropharmacology.* 2010;58:465–73.
17. Almeida RF, Thomazi AP, Godinho GF, Saute JA, Wofchuk ST, Souza DO, et al. Effects of depressive-like behavior of rats on brain glutamate uptake. *Neurochem Res.* 2010;35:1164–71.
18. de Vasconcellos-Bittencourt AP, Vendite DA, Nassif M, Crema LM, Frozza R, Thomazi AP, et al. Chronic stress and lithium treatments alter hippocampal glutamate uptake and release in the rat and potentiate necrotic cellular death after oxygen and glucose deprivation. *Neurochem Res.* 2011;36:793–800.
19. Miguel-Hidalgo JJ, Wilson BA, Hussain S, Meshram A, Rajkowska G, Stockmeier CA. Reduced connexin 43 immunolabeling in the orbitofrontal cortex in alcohol dependence and depression. *J Psychiatr Res.* 2014;55:101–9.
20. Nagy C, Torres-Platas SG, Mechawar N, Turecki G. Repression of astrocytic connexins in cortical and subcortical brain regions and prefrontal enrichment of H3K9me3 in depression and suicide. *Int J Neuropsychopharmacol.* 2017;20:50–7.
21. Ernst C, Nagy C, Kim S, Yang JP, Deng X, Hellstrom IC, et al. Dysfunction of astrocyte connexins 30 and 43 in dorsal lateral prefrontal cortex of suicide completers. *Biol Psychiatry.* 2011;70:312–9.
22. Miguel-Hidalgo JJ, Moulana M, Deloach PH, Rajkowska G. Chronic unpredictable stress reduces immunostaining for connexins 43 and 30 and myelin basic protein in the rat prelimbic and orbitofrontal cortices. *Chronic Stress (Thousand Oaks).* 2018;2:2470547018814186.
23. Sun JD, Liu Y, Yuan YH, Li J, Chen NH. Gap junction dysfunction in the prefrontal cortex induces depressive-like behaviors in rats. *Neuropsychopharmacology.* 2012;37:1305–20.
24. Pittenger C, Coric V, Banasr M, Bloch M, Krystal JH, Sanacora G. Riluzole in the treatment of mood and anxiety disorders. *CNS Drugs.* 2008;22:761–86.
25. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med.* 2016;22:238–49.
26. Müller N, Myint AM, Schwarz MJ. The impact of neuroimmune dysregulation on neuroprotection and neurotoxicity in psychiatric disorders - relation to drug treatment. *Dialogues Clin Neurosci.* 2009;11:319–32.
27. Czéh B, Simon M, Schmelting B, Hiemke C, Fuchs E. Astroglial plasticity in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment. *Neuropsychopharmacology.* 2006;31:1616–26.
28. Morioka N, Suekama K, Zhang FF, Kajitani N, Hisaoka-Nakashima K, Takebayashi M, et al. Amitriptyline up-regulates connexin43-gap junction in rat cultured cortical astrocytes via activation of the p38 and c-Fos/AP-1 signalling pathway. *Br J Pharmacol.* 2014;171:2854–67.
29. Patil CR, Gawli CS, Bhatt S. Targeting inflammatory pathways for treatment of major depressive disorder. *Drug Discov Today.* 2023;28:103697.
30. Frizzo ME, Ohno Y. Perisynaptic astrocytes as a potential target for novel antidepressant drugs. *J Pharmacol Sci.* 2021;145:60–8.
31. Bylicky MA, Mueller GP, Day RM. Mechanisms of endogenous neuroprotective effects of astrocytes in brain injury. *Oxid Med Cell Longev.* 2018;2018:6501031.
32. Sofroniew MV. Astrocyte reactivity: subtypes, states, and functions in CNS innate immunity. *Trends Immunol.* 2020;41:758–70.

33. Allaman I, Bélanger M, Magistretti PJ. Astrocyte–neuron metabolic relationships: for better and for worse. *Trends Neurosci.* 2011;34:76–87.
34. Belanger M, Magistretti PJ. The role of astroglia in neuroprotection. *Dialogues Clin Neurosci.* 2009; 11:281–95.
35. Sofroniew MV. Molecular dissection of reactive astrogliosis and glial scar formation. *Trends Neurosci.* 2009;32:638–47.
36. McGraw J, Hiebert GW, Steeves JD. Modulating astrogliosis after neurotrauma. *J Neurosci Res.* 2001; 63:109–15.
37. Escartin C, Galea E, Lakatos A, O’Callaghan JP, Petzold GC, Serrano-Pozo A, et al. Reactive astrocyte nomenclature, definitions, and future directions. *Nat Neurosci.* 2021;24:312–25.
38. Filous AR, Silver J. “Targeting astrocytes in CNS injury and disease: a translational research approach”. *Prog Neurobiol.* 2016;144:173–87.
39. Escartin C, Bonvento G. Targeted activation of astrocytes: a potential neuroprotective strategy. *Mol Neurobiol.* 2008;38:231–41.
40. Wilhelmsson U, Li L, Pekna M, Berthold CH, Blom S, Eliasson C, et al. Absence of glial fibrillary acidic protein and vimentin prevents hypertrophy of astrocytic processes and improves post-traumatic regeneration. *J Neurosci.* 2004;24:5016–21.
41. Liu Z, Chopp M. Astrocytes, therapeutic targets for neuroprotection and neurorestoration in ischemic stroke. *Prog Neurobiol.* 2016;144:103–20.
42. Zheng W, Talley Watts L, Holstein DM, Wewer J, Lechleiter JD. P2Y1R-initiated, IP3R-dependent stimulation of astrocyte mitochondrial metabolism reduces and partially reverses ischemic neuronal damage in mouse. *J Cereb Blood Flow Metab.* 2013;33:600–11.
43. Shinozaki Y, Shibata K, Yoshida K, Shigetomi E, Gachet C, Ikenaka K, et al. Transformation of astrocytes to a neuroprotective phenotype by microglia via P2Y1 receptor downregulation. *Cell Rep.* 2017;19:1151–64.
44. Kanemaru K, Kubota J, Sekiya H, Hirose K, Okubo Y, Iino M. Calcium-dependent N-cadherin up-regulation mediates reactive astrogliosis and neuroprotection after brain injury. *Proc Natl Acad Sci U S A.* 2013;110:11612–7.
45. Tohyama M, Miyata S, Hattori T, Shimizu S, Matsuzaki S. Molecular basis of major psychiatric diseases such as schizophrenia and depression. *Anat Sci Int.* 2015;90:137–43.
46. Zhang X, Zhou Z, Wang D, Li A, Yin Y, Gu X, et al. Activation of phosphatidylinositol-linked D1-like receptor modulates FGF-2 expression in astrocytes via IP3-dependent Ca<sup>2+</sup> signaling. *J Neurosci.* 2009;29:7766–75.
47. Saransaari P, Oja SS. Enhanced taurine release in cell-damaging conditions in the developing and ageing mouse hippocampus. *Neuroscience.* 1997;79:847–54.
48. Schaffer S, Azuma J, Takahashi K, Mozaffari M. Why is taurine cytoprotective? In: Lombardini JB, Schaffer SW, Azuma J, editors. *Taurine 5*. Boston (MA): Springer; 2003. pp. 307–21.
49. Tu DG, Chang YL, Chou CH, Lin YL, Chiang CC, Chang YY, et al. Preventive effects of taurine against d-galactose-induced cognitive dysfunction and brain damage. *Food Funct.* 2018;9:124–33.
50. Ramírez-Guerrero S, Guardo-Maya S, Medina-Rincón GJ, Orrego-González EE, Cabezas-Pérez R, González-Reyes RE. Taurine and astrocytes: a homeostatic and neuroprotective relationship. *Front Mol Neurosci.* 2022;15:937789.
51. Altamura C, Maes M, Dai J, Meltzer HY. Plasma concentrations of excitatory amino acids, serine, glycine, taurine and histidine in major depression. *Eur Neuropsychopharmacol.* 1995;5:71–5.
52. Zhu Y, Wang R, Fan Z, Luo D, Cai G, Li X, et al. Taurine alleviates chronic social defeat stress-induced depression by protecting cortical neurons from dendritic spine loss. *Cell Mol Neurobiol.* 2023;43: 827–40.

53. Murakami T, Furuse M. The impact of taurine- and beta-alanine-supplemented diets on behavioral and neurochemical parameters in mice: antidepressant versus anxiolytic-like effects. *Amino Acids*. 2010;39:427–34.
54. Wu GF, Ren S, Tang RY, Xu C, Zhou JQ, Lin SM, et al. Antidepressant effect of taurine in chronic unpredictable mild stress-induced depressive rats. *Sci Rep*. 2017;7:4989.
55. Myer DJ, Gurkoff GG, Lee SM, Hovda DA, Sofroniew MV. Essential protective roles of reactive astrocytes in traumatic brain injury. *Brain*. 2006;129:2761–72.
56. Okada S, Nakamura M, Katoh H, Miyao T, Shimazaki T, Ishii K, et al. Conditional ablation of Stat3 or Socs3 discloses a dual role for reactive astrocytes after spinal cord injury. *Nat Med*. 2006;12:829–34.
57. Stöckli KA, Lottspeich F, Sendtner M, Masiakowski P, Carroll P, Götz R, et al. Molecular cloning, expression and regional distribution of rat ciliary neurotrophic factor. *Nature*. 1989;342:920–3.
58. Keasey MP, Kang SS, Lovins C, Hagg T. Inhibition of a novel specific neuroglial integrin signaling pathway increases STAT3-mediated CNTF expression. *Cell Commun Signal*. 2013;11:35.
59. Kang SS, Keasey MP, Arnold SA, Reid R, Gerald J, Hagg T. Endogenous CNTF mediates stroke-induced adult CNS neurogenesis in mice. *Neurobiol Dis*. 2013;49:68–78.
60. Barreto G, White RE, Ouyang Y, Xu L, Giffard RG. Astrocytes: targets for neuroprotection in stroke. *Cent Nerv Syst Agents Med Chem*. 2011;11:164–73.
61. Norden DM, Fenn AM, Dugan A, Godbout JP. TGFβ produced by IL-10 redirected astrocytes attenuates microglial activation. *Glia*. 2014;62:881–95.
62. Jo M, Kim JH, Song GJ, Seo M, Hwang EM, Suk K. Astrocytic orosomucoid-2 modulates microglial activation and neuroinflammation. *J Neurosci*. 2017;37:2878–94.
63. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. 2017;541:481–7.
64. Liddelow SA, Marsh SE, Stevens B. Microglia and astrocytes in disease: dynamic duo or partners in crime? *Trends Immunol*. 2020;41:820–35.
65. Froger N, Orellana JA, Calvo CF, Amigou E, Kozoriz MG, Naus CC, et al. Inhibition of cytokine-induced connexin43 hemichannel activity in astrocytes is neuroprotective. *Mol Cell Neurosci*. 2010;45:37–46.
66. Licinio J, Wong ML. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. *Mol Psychiatry*. 1999;4:317–27.
67. Yang L, Zhou Y, Jia H, Qi Y, Tu S, Shao A. Affective immunology: The crosstalk between microglia and astrocytes plays key role? *Front Immunol*. 2020;11:1818.
68. García-Juárez M, Camacho-Morales A. Defining the role of anti- and pro-inflammatory outcomes of interleukin-6 in mental health. *Neuroscience*. 2022;492:32–46.
69. Müller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. *Mol Psychiatry*. 2007;12:988–1000.
70. Guillemin GJ, Kerr SJ, Smythe GA, Smith DG, Kapoor V, Armati PJ, et al. Kynurenine pathway metabolism in human astrocytes: a paradox for neuronal protection. *J Neurochem*. 2001;78:842–53.
71. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology*. 2012;62:63–77.
72. Sanacora G, Gueorguieva R, Epperson CN, Wu YT, Appel M, Rothman DL, et al. Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. *Arch Gen Psychiatry*. 2004;61:705–13.
73. Van Brussel L, Gerits A, Arckens L. Evidence for cross-modal plasticity in adult mouse visual cortex following monocular enucleation. *Cereb Cortex*. 2011;21:2133–46.



74. Nys J, Aerts J, Ytebrouck E, Vreysen S, Laeremans A, Arckens L. The cross-modal aspect of mouse visual cortex plasticity induced by monocular enucleation is age dependent. *J Comp Neurol*. 2014; 522:950–70.
75. Hennes M, Lombaert N, Wahis J, Van den Haute C, Holt MG, Arckens L. Astrocytes shape the plastic response of adult cortical neurons to vision loss. *Glia*. 2020;68:2102–18.
76. Moda-Sava RN, Murdock MH, Parekh PK, Fetcho RN, Huang BS, Huynh TN, et al. Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. *Science*. 2019;364: eaat8078.
77. Csabai D, Wiborg O, Czéh B. Reduced synapse and axon numbers in the prefrontal cortex of rats subjected to a chronic stress model for depression. *Front Cell Neurosci*. 2018;12:24.
78. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. *Science*. 2012;338:68–72.
79. Kang HJ, Voleti B, Hajsan T, Rajkowska G, Stockmeier CA, Licznarski P, et al. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. *Nat Med*. 2012;18:1413–7.
80. Honer WG, Falkai P, Chen C, Arango V, Mann JJ, Dwork AJ. Synaptic and plasticity-associated proteins in anterior frontal cortex in severe mental illness. *Neuroscience*. 1999;91:1247–55.
81. Eastwood SL, Harrison PJ. Synaptic pathology in the anterior cingulate cortex in schizophrenia and mood disorders. A review and a Western blot study of synaptophysin, GAP-43 and the complexins. *Brain Res Bull*. 2001;55:569–78.
82. Volk DW, Pierri JN, Fritschy JM, Auh S, Sampson AR, Lewis DA. Reciprocal alterations in pre- and postsynaptic inhibitory markers at chandelier cell inputs to pyramidal neurons in schizophrenia. *Cereb Cortex*. 2002;12:1063–70.
83. Buffo A, Rolando C, Ceruti S. Astrocytes in the damaged brain: molecular and cellular insights into their reactive response and healing potential. *Biochem Pharmacol*. 2010;79:77–89.
84. Li L. Protective role of reactive astrocytes in brain ischemia. *J Cereb Blood Flow Metab*. 2008;28: 468–81.
85. Escartin C, Brouillet E, Gubellini P, Trioulier Y, Jacquard C, Smadja C, et al. Ciliary neurotrophic factor activates astrocytes, redistributes their glutamate transporters GLAST and GLT-1 to raft microdomains, and improves glutamate handling *in vivo*. *J Neurosci*. 2006;26:5978–89.
86. Rao VL, Dogan A, Todd KG, Bowen KK, Kim BT, Rothstein JD, et al. Antisense knockdown of the glial glutamate transporter GLT-1, but not the neuronal glutamate transporter EAAC1, exacerbates transient focal cerebral ischemia-induced neuronal damage in rat brain. *J Neurosci*. 2001;21: 1876–83.
87. Zhao J, Verwer RW, van Wamelen DJ, Qi XR, Gao SF, Lucassen PJ, et al. Prefrontal changes in the glutamate-glutamine cycle and neuronal/glial glutamate transporters in depression with and without suicide. *J Psychiatr Res*. 2016;82:8–15.
88. Miguel-Hidalgo JJ, Waltzer R, Wanzo V, Lo V, Rajkowska G, Stockmeier CA. Differential prefrontal alterations of glial glutamatergic components in depression, alcoholism and comorbid depression/ alcoholism. *Biol Psychiatry*. 2008;63:60S.
89. McKlveen JM, Morano RL, Fitzgerald M, Zoubovsky S, Cassella SN, Scheimann JR, et al. Chronic stress increases prefrontal inhibition: a mechanism for stress-induced prefrontal dysfunction. *Biol Psychiatry*. 2016;80:754–64.
90. Yoshino K, Oda Y, Kimura M, Kimura H, Nangaku M, Shirayama Y, et al. The alterations of glutamate transporter 1 and glutamine synthetase in the rat brain of a learned helplessness model of depression. *Psychopharmacology (Berl)*. 2020;237:2547–53.
91. Sanacora G, Kendell SF, Levin Y, Simen AA, Fenton LR, Coric V, et al. Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. *Biol Psychiatry*. 2007;61:822–5.

92. Banasr M, Chowdhury GM, Terwilliger R, Newton SS, Duman RS, Behar KL, et al. Glial pathology in an animal model of depression: reversal of stress-induced cellular, metabolic and behavioral deficits by the glutamate-modulating drug riluzole. *Mol Psychiatry*. 2010;15:501–11.
93. Giordano G, Kavanagh TJ, Costa LG. Mouse cerebellar astrocytes protect cerebellar granule neurons against toxicity of the polybrominated diphenyl ether (PBDE) mixture DE-71. *Neurotoxicology*. 2009;30:326–9.
94. Hayley S, Poulter MO, Merali Z, Anisman H. The pathogenesis of clinical depression: stressor- and cytokine-induced alterations of neuroplasticity. *Neuroscience*. 2005;135:659–78.
95. Chiuccariello L, Houle S, Miler L, Cooke RG, Rusjan PM, Rajkowska G, et al. Elevated monoamine oxidase a binding during major depressive episodes is associated with greater severity and reversed neurovegetative symptoms. *Neuropsychopharmacology*. 2014;39:973–80.
96. Kim YK, Na KS, Myint AM, Leonard BE. The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2016;64:277–84.
97. Schmidt AJ, Heiser P, Hemmeter UM, Krieg JC, Vedder H. Effects of antidepressants on mRNA levels of antioxidant enzymes in human monocytic U-937 cells. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:1567–73.
98. Cumurcu BE, Ozyurt H, Etikan I, Demir S, Karlidag R. Total antioxidant capacity and total oxidant status in patients with major depression: impact of antidepressant treatment. *Psychiatry Clin Neurosci*. 2009;63:639–45.
99. Bharti V, Tan H, Deol J, Wu Z, Wang JF. Upregulation of antioxidant thioredoxin by antidepressants fluoxetine and venlafaxine. *Psychopharmacology*. 2020;237:127–36.
100. Lee SY, Lee SJ, Han C, Patkar AA, Masand PS, Pae CU. Oxidative/nitrosative stress and antidepressants: targets for novel antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;46:224–35.
101. Riveros ME, Ávila A, Schruers K, Ezquer F. Antioxidant biomolecules and their potential for the treatment of difficult-to-treat depression and conventional treatment-resistant depression. *Antioxidants (Basel)*. 2022;11:540.
102. Massart R, Mongeau R, Lanfumey L. Beyond the monoaminergic hypothesis: neuroplasticity and epigenetic changes in a transgenic mouse model of depression. *Philos Trans R Soc Lond B Biol Sci*. 2012;367:2485–94.
103. Duman RS. Neurotrophic factors in etiology and treatment of mood disorders. In: Sibley DR, Kuhar M, Hanin I, Skolnick P, editors. *Handbook of contemporary neuropharmacology*. Hoboken (NJ): John Wiley & Sons; 2007. pp. 789–815.
104. Tamási V, Petschner P, Adori C, Kirilly E, Ando RD, Tothfalusi L, et al. Transcriptional evidence for the role of chronic venlafaxine treatment in neurotrophic signaling and neuroplasticity including also glutamatergic- and insulin-mediated neuronal processes. *PLoS One*. 2014;9:e113662.
105. Garcia-Segura LM, Balthazart J. Steroids and neuroprotection: new advances. *Front Neuroendocrinol*. 2009;30:v–ix.
106. Acaz-Fonseca E, Avila-Rodriguez M, Garcia-Segura LM, Barreto GE. Regulation of astroglia by gonadal steroid hormones under physiological and pathological conditions. *Prog Neurobiol*. 2016;144:5–26.
107. Saldanha CJ, Duncan KA, Walters BJ. Neuroprotective actions of brain aromatase. *Front Neuroendocrinol*. 2009;30:106–18.
108. Saldanha CJ, Rohmann KN, Coomaringam L, Wynne RD. Estrogen provision by reactive glia decreases apoptosis in the zebra finch (*Taeniopygia guttata*). *J Neurobiol*. 2005;64:192–201.
109. Duncan KA, Walters BJ, Saldanha CJ. Traumatized and inflamed — but resilient: glial aromatization and the avian brain. *Horm Behav*. 2013;63:208–15.

110. Garcia-Segura LM, Veiga S, Sierra A, Melcangi RC, Azcoitia I. Aromatase: a neuroprotective enzyme. *Prog Neurobiol.* 2003;71:31–41.
111. Azcoitia I, Yague JG, Garcia-Segura LM. Estradiol synthesis within the human brain. *Neuroscience.* 2011;191:139–47.
112. Stanić D, Dubois S, Chua HK, Tonge B, Rinehart N, Horne MK, et al. Characterization of aromatase expression in the adult male and female mouse brain. I. Coexistence with oestrogen receptors  $\alpha$  and  $\beta$ , and androgen receptors. *PLoS One.* 2014;9:e90451.
113. Arbo BD, Bennetti F, Ribeiro MF. Astrocytes as a target for neuroprotection: modulation by progesterone and dehydroepiandrosterone. *Prog Neurobiol.* 2016;144:27–47.
114. Sortino MA, Chisari M, Merlo S, Vancheri C, Caruso M, Nicoletti F, et al. Glia mediates the neuroprotective action of estradiol on  $\beta$ -amyloid-induced neuronal death. *Endocrinology.* 2004;145:5080–6.
115. Platania P, Seminara G, Aronica E, Troost D, Vincenza Catania M, Angela Sortino M. 17 $\beta$ -estradiol rescues spinal motoneurons from AMPA-induced toxicity: a role for glial cells. *Neurobiol Dis.* 2005;20:461–70.
116. Dhandapani KM, Brann DW. Protective effects of estrogen and selective estrogen receptor modulators in the brain. *Biol Reprod.* 2002;67:1379–85.
117. Barouk S, Hintz T, Li P, Duffy AM, MacLusky NJ, Scharfman HE. 17 $\beta$ -estradiol increases astrocytic vascular endothelial growth factor (VEGF) in adult female rat hippocampus. *Endocrinology.* 2011;152:1745–51.
118. De Marinis E, Acáz-Fonseca E, Arevalo MA, Ascenzi P, Fiocchetti M, Marino M, et al. 17 $\beta$ -oestradiol anti-inflammatory effects in primary astrocytes require oestrogen receptor  $\beta$ -mediated neuroglobin up-regulation. *J Neuroendocrinol.* 2013;25:260–70.
119. De Marinis E, Marino M, Ascenzi P. Neuroglobin, estrogens, and neuroprotection. *IUBMB Life.* 2011;63:140–5.
120. DellaValle B, Hempel C, Kurtzhals JAL, Penkowa M. *In vivo* expression of neuroglobin in reactive astrocytes during neuropathology in murine models of traumatic brain injury, cerebral malaria, and autoimmune encephalitis. *Glia.* 2010;58:1220–7.
121. Acáz-Fonseca E, Sanchez-Gonzalez R, Azcoitia I, Arevalo MA, Garcia-Segura LM. Role of astrocytes in the neuroprotective actions of 17 $\beta$ -estradiol and selective estrogen receptor modulators. *Mol Cell Endocrinol.* 2014;389:48–57.
122. Hu R, Cai WQ, Wu XG, Yang Z. Astrocyte-derived estrogen enhances synapse formation and synaptic transmission between cultured neonatal rat cortical neurons. *Neuroscience.* 2007;144:1229–40.
123. Bohmbach K, Schwarz MK, Schoch S, Henneberger C. The structural and functional evidence for vesicular release from astrocytes *in situ*. *Brain Res Bull.* 2018;136:65–75.
124. Verkhratsky A, Matteoli M, Parpura V, Mothet JP, Zorec R. Astrocytes as secretory cells of the central nervous system: idiosyncrasies of vesicular secretion. *EMBO J.* 2016;35:239–57.
125. Gharbi T, Zhang Z, Yang GY. The function of astrocyte mediated extracellular vesicles in central nervous system diseases. *Front Cell Dev Biol.* 2020;8:568889.
126. Venturini A, Passalacqua M, Pelassa S, Pastorino F, Tedesco M, Cortese K, et al. Exosomes from astrocyte processes: signaling to neurons. *Front Pharmacol.* 2019;10:1452.
127. Xu L, Cao H, Xie Y, Zhang Y, Du M, Xu X, et al. Exosome-shuttled miR-92b-3p from ischemic preconditioned astrocytes protects neurons against oxygen and glucose deprivation. *Brain Res.* 2019;1717:66–73.
128. Wu W, Liu J, Yang C, Xu Z, Huang J, Lin J. Astrocyte-derived exosome-transported microRNA-34c is neuroprotective against cerebral ischemia/reperfusion injury via TLR7 and the NF- $\kappa$ B/MAPK pathways. *Brain Res Bull.* 2020;163:84–94.

129. Patel MR, Weaver AM. Astrocyte-derived small extracellular vesicles promote synapse formation via fibulin-2-mediated TGF- $\beta$  signaling. *Cell Rep.* 2021;34:108829.
130. Kim NS, Chung WS. Astrocytes regulate neuronal network activity by mediating synapse remodeling. *Neurosci Res.* 2023;187:3–13.
131. Li Y, Gui Y, Zhao M, Chen X, Li H, Tian C, et al. The roles of extracellular vesicles in major depressive disorder. *Front Psychiatry.* 2023;14:1138110.
132. Corley SM, Ladiwala U, Besson A, Yong VW. Astrocytes attenuate oligodendrocyte death *in vitro* through an  $\alpha_6$  integrin-laminin-dependent mechanism. *Glia.* 2001;36:281–94.
133. Modi KK, Sendtner M, Pahan K. Up-regulation of ciliary neurotrophic factor in astrocytes by aspirin: implications for remyelination in multiple sclerosis. *J Biol Chem.* 2013;288:18533–45.
134. Pang Y, Fan LW, Tien LT, Dai X, Zheng B, Cai Z, et al. Differential roles of astrocyte and microglia in supporting oligodendrocyte development and myelination *in vitro*. *Brain Behav.* 2013;3:503–14.
135. Domingues HS, Portugal CC, Socodato R, Relvas JB. Oligodendrocyte, astrocyte, and microglia crosstalk in myelin development, damage, and repair. *Front Cell Dev Biol.* 2016;4:71.
136. Traiffort E, Kassoussi A, Zahaf A, Laouarem Y. Astrocytes and microglia as major players of myelin production in normal and pathological conditions. *Front Cell Neurosci.* 2020;14:79.
137. White RE, Jakeman LB. Don't fence me in: harnessing the beneficial roles of astrocytes for spinal cord repair. *Restor Neurol Neurosci.* 2008;26:197–214.
138. White RE, Yin FQ, Jakeman LB. TGF- $\alpha$  increases astrocyte invasion and promotes axonal growth into the lesion following spinal cord injury in mice. *Exp Neurol.* 2008;214:10–24.
139. White RE, Rao M, Gensel JC, McTigue DM, Kaspar BK, Jakeman LB. Transforming growth factor alpha transforms astrocytes to a growth-supportive phenotype after spinal cord injury. *J Neurosci.* 2011;31:15173–87.
140. Arai K, Lo EH. Astrocytes protect oligodendrocyte precursor cells via MEK/ERK and PI3K/Akt signaling. *J Neurosci Res.* 2010;88:758–63.
141. Kato S, Aoyama M, Kakita H, Hida H, Kato I, Ito T, et al. Endogenous erythropoietin from astrocyte protects the oligodendrocyte precursor cell against hypoxic and reoxygenation injury. *J Neurosci Res.* 2011;89:1566–74.
142. Miguel-Hidalgo JJ, Hall KO, Bonner H, Roller AM, Syed M, Park CJ, et al. MicroRNA-21: expression in oligodendrocytes and correlation with low myelin mRNAs in depression and alcoholism. *Prog Neuropsychopharmacol Biol Psychiatry.* 2017;79:503–14.
143. Elif GS, David JD, Shira R, Jason DH, Sam PB, Miguel Alejandro M, et al. White matter stroke induces a unique oligo-astrocyte niche that inhibits recovery. *J Neurosci.* 2019;39:9343–59.
144. Nash B, Thomson CE, Linington C, Arthur AT, McClure JD, McBride MW, et al. Functional duality of astrocytes in myelination. *J Neurosci.* 2011;31:13028–38.
145. Zárate SC, Traetta ME, Codagnone MG, Seilicovich A, Reinés AG. Humanin, a mitochondrial-derived peptide released by astrocytes, prevents synapse loss in hippocampal neurons. *Front Aging Neurosci.* 2019;11:123.
146. Pantazatos SP, Huang YY, Rosoklija GB, Dwork AJ, Arango V, Mann JJ. Whole-transcriptome brain expression and exon-usage profiling in major depression and suicide: evidence for altered glial, endothelial and ATPase activity. *Mol Psychiatry.* 2017;22:760–73.
147. Schiele MA, Lipovsek J, Schlosser P, Soutschek M, Schrott G, Zaudig M, et al. Epigenome-wide DNA methylation in obsessive-compulsive disorder. *Transl Psychiatry.* 2022;12:221.
148. Lee C, Yen K, Cohen P. Humanin: a harbinger of mitochondrial-derived peptides? *Trends Endocrinol Metab.* 2013;24:222–8.
149. Nishimoto I, Matsuoka M, Niikura T. Unravelling the role of humanin. *Trends Mol Med.* 2004;10:102–5.

150. Bodzioch M, Lapicka-Bodzioch K, Zapala B, Kamysz W, Kiec-Wilk B, Dembinska-Kiec A. Evidence for potential functionality of nuclearly-encoded humanin isoforms. *Genomics*. 2009;94:247–56.
151. Thiankhaw K, Chattipakorn K, Chattipakorn SC, Chattipakorn N. Roles of humanin and derivatives on the pathology of neurodegenerative diseases and cognition. *Biochim Biophys Acta Gen Subj*. 2022; 1866:130097.
152. Troakes C, Smyth R, Noor F, Maekawa S, Killick R, King A, et al. Clusterin expression is upregulated following acute head injury and localizes to astrocytes in old head injury. *Neuropathology*. 2017;37: 12–24.
153. Pasinetti GM, Johnson SA, Oda T, Rozovsky I, Finch CE. Clusterin (SGP-2): a multifunctional glycoprotein with regional expression in astrocytes and neurons of the adult rat brain. *J Comp Neurol*. 1994;339:387–400.
154. Charnay Y, Imhof A, Vallet PG, Kovari E, Bouras C, Giannakopoulos P. Clusterin in neurological disorders: molecular perspectives and clinical relevance. *Brain Res Bull*. 2012;88:434–43.
155. Imhof A, Charnay Y, Vallet PG, Aronow B, Kovari E, French LE, et al. Sustained astrocytic clusterin expression improves remodeling after brain ischemia. *Neurobiol Dis*. 2006;22:274–83.
156. Chen F, Swartzlander DB, Ghosh A, Fryer JD, Wang B, Zheng H. Clusterin secreted from astrocyte promotes excitatory synaptic transmission and ameliorates Alzheimer's disease neuropathology. *Mol Neurodegener*. 2021;16:5.
157. Hakkoum D, Imhof A, Vallet PG, Boze H, Moulin G, Charnay Y, et al. Clusterin increases post-ischemic damages in organotypic hippocampal slice cultures. *J Neurochem*. 2008;106:1791–803.
158. Han BH, DeMattos RB, Dugan LL, Kim-Han JS, Brendza RP, Fryer JD, et al. Clusterin contributes to caspase-3-independent brain injury following neonatal hypoxia-ischemia. *Nat Med*. 2001;7:338–43.
159. Rodríguez-Rivera C, Garcia MM, Molina-Álvarez M, González-Martín C, Goicoechea C. Clusterin: always protecting. Synthesis, function and potential issues. *Biomed Pharmacother*. 2021;134: 111174.
160. Athanas KM, Mauney SL, Woo TUW. Increased extracellular clusterin in the prefrontal cortex in schizophrenia. *Schizophr Res*. 2015;169:381–5.
161. Stelzhammer V, Ozcan S, Gottschalk MG, Steeb H, Hodes GE, Guest PC, et al. Central and peripheral changes underlying susceptibility and resistance to social defeat stress – a proteomic profiling study. *Diagn Neuropsychiatry*. 2015;1:1–7.
162. Kosten T, Ye A, Nielsen D, Patriquin M, Palat A, Rezaei H, et al. Specific miRNAs associated with treatment response during hospitalization for suicidal ideation. *Res Square [Preprint]*. 2022 [cited 2023 May 11]. Available from: <https://www.researchsquare.com/article/rs-2100363/v1>
163. Nichols NR. Glial responses to steroids as markers of brain aging. *J Neurobiol*. 1999;40:585–601.
164. Mukaetova-Ladinska EB, Abdel-All Z, Andrade J, Alves da Silva J, O'Brien JT, Kalaria RN. Plasma and platelet clusterin ratio is altered in Alzheimer's disease patients with distinct neuropsychiatric symptoms: findings from a pilot study. *Int J Geriatr Psychiatry*. 2015;30:368–75.
165. Mukaetova-Ladinska EB, Abdel-All Z, Dodds S, Andrade J, Alves da Silva J, Kalaria RN, et al. Platelet immunoglobulin and amyloid precursor protein as potential peripheral biomarkers for Alzheimer's disease: findings from a pilot study. *Age Ageing*. 2012;41:408–12.
166. Silajdžić E, Minthon L, Björkqvist M, Hansson O. No diagnostic value of plasma clusterin in Alzheimer's disease. *PLoS One*. 2012;7:e50237.
167. Dukic L, Simundic AM, Martinic-Popovic I, Kackov S, Diamandis A, Begcevic I, et al. The role of human kallikrein 6, clusterin and adiponectin as potential blood biomarkers of dementia. *Clin Biochem*. 2016;49:213–8.