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Assessing the Potential Role of Astrocytes in Modulating the Neuroplastic Effects of Psychedelic Drugs

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ABSTRACT

The neuroplastic effects of classical psychedelics have been studied mostly through neuronal mechanisms. However, astrocytes may also be involved in the long-lasting neuroplastic effects of psychedelics because of their role in synaptic function and plasticity. This review examines if astrocytes could mediate or modulate psychedelic-induced neuroplasticity and evaluates the evidence supporting this possibility. Classical psychedelics produce different forms of neuronal plasticity at molecular, functional, and structural levels, including dendritic remodeling and synaptic changes. However, it is still not completely understood how these changes are regulated and maintained. Astrocytes regulate several of these processes, including neurotransmitter homeostasis, Ca^{2+} signaling, synaptic organization, metabolic support, and neuroimmune processes.

Experimental evidence outside of psychedelic models showed that astrocytic signaling may influence serotonin-dependent synaptic plasticity and N-methyl-D-aspartate receptor-dependent long-term potentiation. Recent evidence shows that psilocin alters astrocytic proliferation, mitochondrial function, ATP, lactate, and glutamate release, while partial depletion of prefrontal astrocytes attenuates some behavioral responses to psilocybin. Psychedelics have also been shown to influence astrocyte-associated neuroimmune processes involved in stress-related fear. All together, these findings suggest that astrocytes may function alongside established neuronal mechanisms to influence the development, stabilization, or persistence of psychedelic-induced plasticity.

However, current evidence does not establish astrocytes as necessary mediators of psychedelic-induced plasticity. There is a lack of direct experimental evidence showing that psychedelic exposure produces a defined astrocytic response that then leads to neuronal plasticity and, ultimately, to persistent behavioral or therapeutic effects. Future studies that selectively manipulate astrocytic pathways during psychedelic exposure while directly measuring neuronal plasticity and longer-term outcomes are needed to establish this causal relationship. Current evidence is therefore more consistent with a potential modulatory role for astrocytes than with an established mediating role in psychedelic-induced neuroplasticity.

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INTRODUCTION

There has been a renewed clinical interest in classical psychedelic compounds for the treatment of mood and substance use disorders due to their rapid and long-lasting effects. For instance, while conventional antidepressants take 4-6 weeks to take effect, psychedelics such as psilocybin have shown significant depressive symptom reduction within 24 hours of administration (Acero et al., 2025). Additionally, studies have shown 1-2 doses of psilocybin can produce reductions in depressive symptoms for up to 12 months (Acero et al., 2025). Moreover, psychedelic-assisted therapy has been shown to produce similarly large, rapid, and long-lasting benefits in several psychiatric conditions, including major depressive disorder (MDD), substance use disorders, and post-traumatic stress disorder (PTSD) (Acero et al., 2023). Given the potential therapeutic effects of psychedelic compounds, research is currently focused on unraveling the cellular and molecular mechanisms that drive psychedelic treatment outcomes.

Neuroplasticity is the brain's ability to structurally and functionally adapt by forming new synaptic connections in response to internal or external stimuli. This function is essential for normal brain function, aiding in cognitive learning, memory, and environmental adaptation. Impairments in functional plasticity, conversely, contribute to neuropsychiatric disorders, particularly depression, because of altered synaptic connections and reduced brain-derived neurotrophic factor (BDNF) signaling (Acero et al., 2025). Neuroplasticity is one of the most promising explanations for the rapid and long-lasting effects of psychedelic compounds (Acero et al., 2025). Psychedelics start signaling pathways that result in structural and functional changes that persist beyond the acute drug effects. As such, specific psychedelic compounds that induce enduring and robust changes in neuroplasticity at the cellular level, are increasingly described as psychoplastogens (Acero et al., 2023).

Serotonergic psychedelics seem to be capable of promoting neuroplasticity through neurogenesis, dendritic spine growth, and synapse formation, largely through activation of serotonin receptors, primarily the 5-HT2A receptor. This receptor activation initiates neuronal intercellular signaling pathways, leading to increased BDNF expression and tropomyosin receptor kinase B (TrkB) activation (Acero et al., 2025). Given that preclinical and clinical studies have indicated that neuroplasticity may be one of the main mechanisms for psychedelic-induced therapeutic effects, further research towards learning more about the underlying mechanisms would lead to clearer understanding and, in turn, more effective treatments.

Increasing evidence suggests that neuroplasticity should no longer be viewed as only a neuronal phenomenon but as an interlinked system between neurons and astrocytes, a type of glial cell in the central nervous system (CNS). Astrocytes influence synaptic function and plasticity through involvement in a tripartite functional synapse where astrocytes regulate calcium signaling, glutamate homeostasis, and metabolic support within the synaptic gap between neurons (Robertson, 2013; Yamamoto & Takano, 2025). These astrocytic functions aid in synaptic efficacy, neuronal communication, neurotransmitter homeostasis, and circuit remodeling, ultimately supporting long-term synaptic plasticity. Additionally, classical psychedelics have been shown to modulate astrocytic mechanisms. For instance, in a Chronic Restraint Stress Mouse Model, in vivo psilocybin was associated with a reversal of astrocyte loss, while

in vitro psilocin exposure increased astrocyte proliferation and improved astrocyte mitochondrial function. Partial astrocyte depletion attenuated some antidepressant-like effects of psilocybin (Qiao et al., 2026). Psilocybin is a prodrug that is converted to its active metabolite, psilocin, after administration. Experimental studies have found that disrupted astrocyte function, including reduced calcium signaling and impaired glutamate uptake, contribute to depressive-like behaviors and diminished neuroplasticity. However, in stressed mice, increasing astrocyte Ca^{2+} signaling has been shown to improve depressive-like behaviors (González-Arias et al., 2023).

Research has been predominantly focused on neural mechanisms, and little is known about whether astrocytes mediate or modulate psychedelic-induced neuroplasticity. Despite the growth in research regarding the astrocytic involvement in the modulation of synaptic plasticity, this gap in knowledge limits progress towards fully understanding how psychedelics produce potent therapeutic effects. If astrocytes are involved in the process of psychedelic-induced neuroplastic effects, identifying the relevant astrocytic mechanisms could provide potential targets for future therapeutic development. Although multiple biological mechanisms may be involved in psychedelics' therapeutic effects, this review will focus specifically on neuroplasticity because it is one of the most supported mechanisms and is only partially understood.

This review will focus on classical serotonergic psychedelics such as psilocybin, lysergic acid diethylamide (LSD), N,N-dimethyltryptamine (DMT), ayahuasca, and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) because they primarily act through 5-HT2A receptor signaling and have strong research evidence relevant to their mechanisms. Limiting the scope to classical psychedelics allows for a more focused evaluation of potential astrocytic mechanisms (Acero et al., 2025). Classical and non-classical psychedelics can be distinguished by their predominant pharmacological mechanisms. Classical psychedelics are serotonergic compounds that act as agonists at the 5-HT2A serotonin receptor. On the other hand, non-classical psychedelics produce their effects through different mechanisms, such as NMDA receptor antagonism or increased neurotransmitter release. This distinction between classical and non-classical psychedelics is made to clarify the scope of this review rather than to suggest that the therapeutic value of classical and non-classical psychedelics differs.

This review aims to address the importance of understanding the cellular process of psychedelic-induced neuroplasticity, in particular how astrocytes may be involved in this process. Towards this, we first give background on psychedelics and their therapeutic effects. Next, we will evaluate current evidence and address the importance of neuroplasticity in these effects and how astrocytes may be involved through related cellular processes. Finally, we will discuss future research directions and the potential therapeutic implications of targeting astrocytic mechanisms.

METHODS

Literature Search Strategy

A literature search was conducted on PubMed, Google Scholar, Google, and the National Institutes of Health (NIH). The Search included the terms "psychedelics and astrocytes," "astrocytes and neuroplasticity," and "psychedelic-induced neuroplasticity and astrocytes." Additional search terms were used such as classical psychedelics, including psilocybin, psilocin, LSD, DMT, ayahuasca, 5-MeO-DMT, and mescaline, combined with the terms "astrocytes," and "neuroplasticity." The search was limited to articles published from 2010 through September 2026 to emphasize recent evidence. The reference lists of relevant articles were also reviewed for additional studies related to the topics.

Study Selection

Relevant studies or peer-reviewed articles regarding classical psychedelics, astrocytes, and neuroplasticity were identified. They were included if they addressed at least two of these three areas or provided supporting background information relevant to classical psychedelics, astrocyte function, or possible astrocyte involvement in psychedelic-induced neuroplasticity. Studies that did not cover these areas, papers focused exclusively on non-classical psychedelics, and abstracts without full text were excluded. Books and general websites were not included as sources.

Classification of Evidence

For this review, the selected studies were classified according to their relationship to the main research question. Direct psychedelic–astrocyte evidence included studies that directly evaluated classical psychedelic exposure together with astrocytic outcomes. Indirect astrocyte/plasticity evidence included studies evaluating astrocyte mechanisms involved in neuroplasticity or serotonergic signaling without direct psychedelic exposure. Hypothesis/perspective evidence included proposed psychedelic–astrocyte mechanisms lacking direct experimental support. Background/context evidence included studies and reviews providing supporting information on psychedelic-induced neuroplasticity, antidepressant mechanisms, or astrocyte functions in other neurological conditions. The goal of this classification was to distinguish between direct experimental, indirect, proposed, and background evidence. These categories are summarized in Table 1.

Table 1: Evidence Categories Used in the Literature Review

Evidence category	Definition
Direct psychedelic–astrocyte evidence	Studies that directly expose animals or cells to a classical psychedelic and evaluate astrocytic outcomes
Indirect astrocyte/plasticity evidence	Studies that examine astrocyte mechanisms involved in neuroplasticity or serotonergic signaling without the direct testing of psychedelic exposure
Hypothesis/perspective	Papers that propose psychedelic–astrocyte mechanisms without direct experimental support
Background/context	Papers that provide supporting information about psychedelic neuroplasticity, clinical or antidepressant mechanisms, or astrocyte functions in other neurological conditions but do not directly test the central psychedelic–astrocyte question

The studies included in this review provide different levels of evidence for the involvement of astrocytes in psychedelic-induced neuroplasticity. Table 2 summarizes the selected studies according to evidence category, experimental model, astrocytic outcome, main findings, and limitations.

Table 2: Summary and Classification of Evidence Relevant to Astrocyte Involvement in Psychedelic-Induced Plasticity

Reference	Evidence category	Model / exposure / Location	Astrocyte endpoint	Main finding / What it adds	Key limitation
Martin & Nichols, 2016	Direct psychedelic–astrocyte evidence	Mice exposed to (R)-DOI; cortical regions	Astrocyte-specific transcriptional responses, including c-fos and per1	(R)-DOI produced cell-type-specific transcriptional responses involving astrocytes, showing direct astrocyte recruitment by a classical psychedelic.	Neuronal plasticity was not directly measured; astrocyte transcriptional responses were not shown to cause lasting plasticity.
Zandonadi et al., 2023	Direct psychedelic–astrocyte evidence	Primary astrocytes; exposed in vitro to ayahuasca/DMT-containing preparations	metabolic changes including pathways involving B vitamin and branched-chain amino acids	Ayahuasca exposure altered astrocyte metabolic pathways, providing direct evidence of psychedelic-related effects on astrocyte metabolism.	In vitro study; no direct neuronal plasticity measurement, effects cannot be attributed to DMT alone because ayahuasca contains multiple active components
Chung et al., 2025	Direct psychedelic–astrocyte evidence	Mice; exposed to psilocybin and MDMA; the relevant component is psilocybin; amygdala/neuroimmune system	Astrocytic EGFR-centered neuroimmune signaling in amygdala	Identified an astrocyte-centered EGFR pathway involved in stress-induced fear and showed that psychedelic treatment influenced the associated neuroimmune system.	Focused on neuroimmune regulation and fear rather than directly testing astrocyte-mediated neuronal plasticity.
Qiao et al., 2026	Direct psychedelic–astrocyte evidence	CRS mice plus primary astrocyte in vitro; psilocybin in vivo and psilocin in vitro; PFC	Astrocyte loss/proliferation, gliotransmitter release and mitochondrial function	Psilocybin/psilocin affected multiple astrocytic processes, and astrocyte manipulation influenced some antidepressant-like effects.	Neuronal plasticity was not directly measured; also psilocin-induced Ca++ signaling was not directly examined, therefore no causal pathway established
González-Arias et al., 2023	Indirect astrocyte/plasticity evidence	Chronic corticosterone-treated mice; serotonin signaling; mPFC	Astrocytic Ca^{2+} signaling	Links astrocytic Ca^{2+} signaling with serotonin-dependent synaptic plasticity, supporting a connection among serotonin, astrocytes and plasticity.	No psychedelic was administered; relevance to psychedelic-induced plasticity remains indirect.
Henneberger et al., 2010	Indirect astrocyte/plasticity evidence	Hippocampal preparations; no psychedelic; CA1	Ca^{2+}-dependent D-serine release	Manipulating individual astrocytes affected nearby NMDAR-dependent LTP, demonstrating local astrocytic regulation of synaptic plasticity.	No psychedelic exposure; whether the same mechanism occurs during psychedelic-induced plasticity is unknown.
Yamamoto & Takano, 2025	Indirect astrocyte/plasticity evidence	Review of experimental literature; multiple experimental models	Ca^{2+} signaling, gliotransmission and astrocyte–synapse interactions	Synthesizes evidence that astrocytes contribute to synaptic efficacy and formation and stabilization of plasticity.	Review rather than primary experimental evidence and does not specifically examine psychedelic exposure.
Robertson, 2013	Hypothesis/perspective	Hypothesis article; no psychedelic	Astrocyte domains and tripartite synaptic interactions	Provides a conceptual framework in which astrocytes are active components of synaptic information processing rather than passive support cells.	Hypothesis article; proposed functions are not direct experimental evidence and psychedelics were not examined.
Ke et al., 2026	Hypothesis/perspective	Review/perspective; psilocybin, LSD and related compounds	Proposed Ca^{2+} signaling, glutamate regulation, metabolic and neuroimmune functions	Proposes that astrocytes may shape, consolidate or stabilize psychedelic-induced changes and identifies mechanisms for future testing.	Hypothesis-driven perspective; proposed mechanisms are synthesized largely, direct evidence that astrocytes mediate psychedelic-induced neuroplasticity remains limited.
de Vos et al., 2021	Background/context	Systematic review; preclinical and clinical psychedelic studies	Astrocytes not a primary endpoint	Summarizes broader evidence for psychedelic-induced molecular, cellular, synaptic and structural neuroplasticity.	Astrocyte involvement was not directly examined; much of the underlying evidence was preclinical.
Grieco et al., 2022	Background/context	Review; preclinical and clinical psychedelic literature	Astrocytes not a primary endpoint	Summarizes psychedelic-induced molecular, synaptic and structural plasticity, providing the neuronal framework for the astrocyte question.	Primarily neuron-centered review; does not establish an astrocytic mechanism.
Acero et al., 2023	Background/context	Review; multiple psychedelic compounds	Glial mechanisms discussed within broader psychedelic effects	Provides background on neuroplasticity and possible glial contributions to psychedelic mechanisms.	Broad review; does not experimentally test a psychedelic–astrocyte–plasticity pathway.
Acero et al., 2025	Background/context	Review; clinical and mechanistic psychedelic evidence	Astrocytes not a primary endpoint	Connects proposed molecular and cellular psychedelic mechanisms with antidepressant and therapeutic effects.	Review rather than primary astrocyte evidence; does not establish astrocyte-mediated psychedelic plasticity.
Abedin & Kastanenka, 2026	Background/context	Review; Alzheimer's disease	Reactive astrocytes, Ca^{2+} signaling, metabolism and neuroinflammation	Demonstrates the broader importance of astrocyte dysfunction and astrocyte-targeted mechanisms in neurological disease.	No psychedelic exposure; relevance to psychedelic-induced neuroplasticity is peripheral.

Burda et al., 2016	Background/context	Review; traumatic brain injury	Reactive astrogliosis and astrocyte functions	Shows active, context-dependent astrocyte roles in injury, inflammation, tissue repair and synaptic remodeling.	TBI-specific and no psychedelic exposure; doesn't directly inform psychedelic-induced plasticity.

NEURAL PLASTICITY IN HEALTH AND PSYCHIATRIC DISEASE

Neuroplasticity physiology

Neuroplasticity is the ability of the nervous system to undergo structural and functional changes in response to activity of neurons, environmental experiences, learning, trauma, and disease. Rather than representing a single biological process, neuroplasticity occurs across multiple levels, ranging from molecular changes within individual synapses to structural remodeling of the entire neuronal circuit. Functional plasticity includes changes in synaptic strength, such as long-term potentiation (LTP) and long-term depression (LTD), whereas structural plasticity involves physical changes including neurite growth, dendritic remodeling, dendritic spine formation and elimination, synaptogenesis, and neurogenesis in selected brain areas (de Vos et al., 2021; Grieco et al., 2022). These processes allow neural circuits to continuously adjust their connectivity and function rather than remaining anatomically or physiologically fixed.

At the synaptic level, plasticity enables communication between neurons to change in an activity-dependent manner. LTP produces a sustained increase in synaptic efficacy and is strongly associated with learning and memory, whereas LTD reduces synaptic strength and contributes to refinement and reorganization of neural circuits (de Vos et al., 2021). Structural changes often occur alongside these functional adaptations. Dendritic spines, which contain the postsynaptic components of most excitatory synapses, can form, enlarge, shrink, or be eliminated in response to neuronal activity. Formation and stabilization of new spines can establish new synaptic connections, whereas removal of existing spines allows circuits to reorganize. Dendritic remodeling and neurite extension can further modify the connectivity available to individual neurons. Together, these processes provide a cellular mechanism through which experience can produce persistent alterations in circuit function (Grieco et al., 2022).

Neuroplasticity in Psychiatric Disease

Plasticity is vital for normal learning, memory, adaptation to environmental changes, and recovery following neural injury. However, this capacity for remodeling can become impaired or maladaptive in psychiatric disease. Major depressive disorder (MDD), for example, is increasingly understood as involving more than abnormalities in monoamine concentrations. Chronic stress and depression are associated with altered neuronal connectivity, reduced synaptic density, dendritic atrophy, and impaired plasticity in brain regions involved in mood and cognition, particularly the prefrontal cortex and hippocampus. Alterations in neurotrophic signaling, including reduced brain-derived neurotrophic factor (BDNF)-related signaling, may further limit the ability of affected neural circuits to adapt (Acero et al., 2025). The reduction in neural circuit plasticity may contribute to the persistence of maladaptive patterns

of cognition and behavior by limiting the ability of neural networks to reorganize in response to new experiences.

Evidence from astrocyte research further suggests that impaired plasticity in depression is not exclusively neuronal. González-Arias et al. (2023) demonstrated abnormalities in astrocytic signaling in a chronic corticosterone model of depressive-like behavior. Astrocytes in the medial prefrontal cortex exhibited enhanced oscillatory activity while having reduced amplitude of Ca^{2+} events and diminished Ca^{2+} responses to serotonin. Importantly, these abnormalities were accompanied by altered serotonin-driven synaptic plasticity in excitatory neurons. Experimentally reducing astrocytic Ca^{2+} signaling in control animals reproduced aspects of the synaptic abnormality; however, behavioral deficits were improved in stressed animals when astrocytic signaling was manipulated chemogenetically (González-Arias et al., 2023). These findings demonstrate that impaired plasticity in depression may be related to altered interactions between neurons and surrounding glial cells rather than neuronal dysfunction alone.

The relationship between neuroplasticity and psychiatric disease has therapeutic importance. Conventional antidepressants were originally conceptualized mainly through their effects on monoamine availability. However, increasing serotonin alone may not completely explain the therapeutic effects of selective serotonin reuptake inhibitors because clinical improvement generally requires repeated administration and takes several weeks to occur (Acero et al., 2025). Additionally, repeated antidepressant treatment can influence neurotrophic signaling and gradually create conditions that allow neuronal remodeling. Given that neuroplasticity may be impaired in depression, restoring plasticity within these affected neural circuits may also be involved in the therapeutic effects of antidepressants.

Classical psychedelics have received increasing interest because of their rapid effects on plasticity-related processes. Preclinical studies reviewed by de Vos et al. (2021) have shown psychedelic-induced changes at molecular, cellular, and structural levels, including changes in neurotrophic signaling, neuritogenesis, dendritic morphology, and synaptic plasticity. Grieco et al. (2022) similarly described evidence that serotonergic psychedelics can produce structural remodeling of cortical neurons, including alterations in dendritic spines that may persist after the acute pharmacological effects have resolved. Thus, psychedelic-induced plasticity is not limited to transient changes in neuronal firing but may involve longer-lasting modification of the physical and functional organization of synapses.

At the molecular level, classical psychedelics are expected to initiate these effects through serotonergic signaling, particularly 5-HT2A receptor activation, with subsequent involvement of glutamatergic signaling, and the activation of intracellular signaling pathways associated with neuronal growth and synaptic remodeling. BDNF and its receptor tropomyosin receptor kinase B (TrkB), together with downstream mammalian target of rapamycin (mTOR) signaling, have been implicated in these plasticity-related effects (Acero et al., 2023; Acero et al., 2025). Rather than repeating the acute pharmacology described above, the important point for neuroplasticity is that these pathways regulate protein synthesis, dendritic structure, and synaptic organization and therefore provide a mechanism by which brief receptor activation could initiate changes that persist beyond drug exposure.

Nevertheless, several limitations prevent psychedelic-induced neuroplasticity from being treated as a complete explanation for sustained clinical benefit. de Vos et al. (2021) emphasized that much of the mechanistic evidence comes from preclinical experiments, and the methods and time points used to define plasticity vary considerably among studies. Grieco et al. (2022) similarly highlighted the difficulty of directly connecting molecular or structural changes observed in experimental models with long-lasting therapeutic responses in humans. An increase in dendritic spines, for example, demonstrates structural remodeling but does not by itself establish that the new connections are functionally beneficial, appropriately integrated into existing circuits, or responsible for improvement in psychiatric symptoms. Therefore, the quality, localization, timing, and stabilization of newly induced plasticity are likely as important as its magnitude.

This distinction raises an important question for understanding psychedelic action. Initiating neuronal growth may be only one component of sustained neuroplasticity. Newly modified synapses must also be supplied metabolically, exposed to appropriately regulated extracellular neurotransmitter concentrations, supported by local trophic signals, and maintained within an environment that permits stable circuit remodeling. All these processes suggest that sustained plasticity may not be understood solely by examining intracellular signaling within neurons. Astrocytes are positioned at the interface of many of these processes and can regulate synaptic efficacy, neurotransmitter homeostasis, metabolic support, and the local environment surrounding remodeling synapses.

ASTROCYTES AS POTENTIAL MODULATORS OF PSYCHEDELIC-INDUCED PLASTICITY

Classical Psychedelics and Psychiatric Disease

Psychedelic compounds are a form of hallucinogenic drugs that induce a dream-like state through altered consciousness, mood, and perception primarily by activation of the 5-HT2A receptor. There is renewed scientific interest in these compounds due to evidence that they not only provide acute psychedelic experiences but also contribute to sustained changes in neuronal structure and processes (Acero et al., 2025). The clinical relevance of classical psychedelics has become increasingly apparent as psychedelic-assisted therapies have been investigated for neuropsychiatric disorders. Psilocybin has been shown to have rapid and long-lasting antidepressant effects in humans, including in MDD (major depressive disorder) and TRD (treatment resistant depression), and further research is being conducted to discover the mechanisms underlying these therapeutic effects.

Preclinical evidence indicates that classical psychedelics can promote structural neuroplasticity including increased neurite outgrowth, dendritic remodeling, spine formation, and synaptogenesis beyond the acute psychedelic state (Acero et al., 2023; Grieco et al., 2022; de Vos et al., 2021). These effects primarily involve increased agonist activity at neuronal serotonin 5-HT2A receptors and downstream activation of intracellular pathways involving BDNF, TrkB, and mTOR (Acero et al., 2023; Acero et al., 2025). However, because the surrounding synaptic environment is continuously regulated by astrocytes, it is

important to address whether these cells are involved in the development or persistence of psychedelic-induced remodeling (Figure 1).

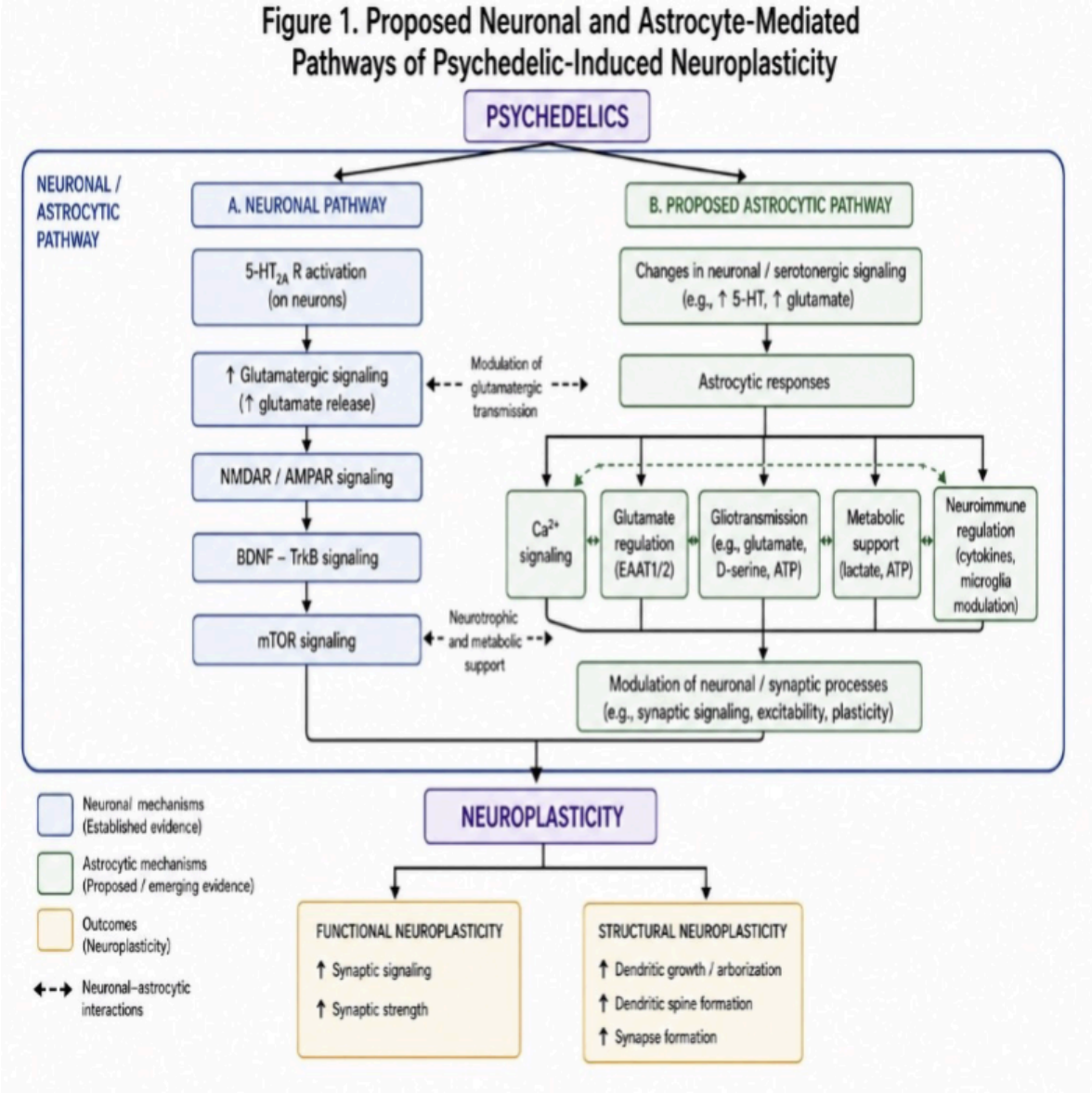


Figure 1. Proposed Neuronal and Astrocyte-Mediated Pathways of Psychedelic-Induced Neuroplasticity. This figure shows neuronal mechanisms with potential astrocytic involvement in psychedelic-induced neuroplasticity. **(A) Neuronal pathway:** Activation of 5-HT2A receptors drives glutamatergic signaling and downstream pathways, including BDNF–TrkB and mTOR signaling, resulting in functional and structural neuronal plasticity (de Vos et al., 2021; Grieco et al., 2022). **(B) Astrocyte pathway:** The astrocytic pathway is a proposed mechanism. Psychedelics may affect astrocytic

processes involving Ca^{2+} signaling, gliotransmission, metabolic support, and neuroimmune regulation. These processes might modify the synaptic environment and potentially affect the stabilization or persistence of neuronal plasticity (Henneberger et al., 2010; González-Arias et al., 2023; Qiao et al., 2026; Ke et al., 2026). However, current evidence does not establish astrocytes as necessary mediators of psychedelic-induced neuroplasticity. Author-created figure based on the literature reviewed in this article.

More direct evidence for astrocyte involvement comes from the preclinical study by Qiao et al. (2026). In a chronic restraint stress mouse model, psilocybin reversed stress-associated astrocyte loss, while experiments with primary astrocytes showed that psilocin affected astrocyte proliferation, ATP, lactate, and glutamate release, and mitochondrial function. Partial depletion of astrocytes in the prelimbic medial prefrontal cortex also attenuated some behavioral effects of psilocybin. The authors discussed astrocytic 5-HT2A-related Ca^{2+} signaling as a potential mechanism, although the effect of psilocin on astrocytic Ca^{2+} signaling was not directly examined. However, the study did not directly measure structural or functional neuronal plasticity. Therefore, these findings support an astrocytic response to psychedelic exposure and a possible contribution to behavioral effects but do not establish that astrocytes mediate psychedelic-induced neuronal plasticity.

When classical psychedelics modify serotonergic and glutamatergic activity, nearby astrocytes may detect and respond to changes within their local synaptic environment. The important question is whether these responses actively affect the onset, stabilization, or persistence of psychedelic-induced plasticity or only occur alongside changes in neuronal activity.

Astrocyte Morphology

Neuroplasticity does not occur through neuronal activity alone but depends on continuous interactions between neurons and surrounding glial cells. Among these cells, astrocytes are particularly important because their processes are positioned in proximity to synapses, allowing them to detect neuronal activity and regulate the extracellular conditions in which synaptic modification occurs. This positioning has contributed to a shift from the traditional view of astrocytes as passive support cells toward a model in which neurons and astrocytes operate as interconnected components of neural circuits. Astrocytes can influence both functional changes in synaptic strength and the structural remodeling required for longer-lasting plasticity (Yamamoto & Takano, 2025).

An important characteristic of this relationship is the spatial arrangement of astrocytes in neural tissue. Each astrocyte occupies a relatively defined region and interacts with large numbers of synapses. In these areas, fine astrocytic processes extend to the neuronal synaptic structures and form functional associations with presynaptic and postsynaptic neuronal elements, commonly described as the tripartite synapse (Acero et al., 2023; Acero et al., 2025). This arrangement enables an astrocyte to monitor activity occurring within its local synaptic territory and respond to changes in neuronal signaling. Importantly, astrocytic regulation is not necessarily uniform throughout an entire cell. Local signaling events within fine astrocytic processes can permit relatively specific responses to activity at nearby synapses, while

broader intracellular signals may coordinate responses across larger portions of an astrocytic territory (Yamamoto & Takano, 2025).

Astrocyte Gliotransmitters

Astrocytes may affect synaptic activity through the release of signaling molecules that are referred to as gliotransmitters including glutamate, D-serine, and ATP. Astrocyte Ca^{2+} signaling has been associated with the release of these molecules, providing a potential mechanism for converting changes in neurotransmitter signaling to modulation of nearby synapses (González-Arias et al., 2023). D-serine is a co-agonist at NMDA receptors and can contribute to activation, long-term potentiation, and stabilization of NMDA receptor-dependent plasticity (Henneberger et al., 2010; Figure 2).

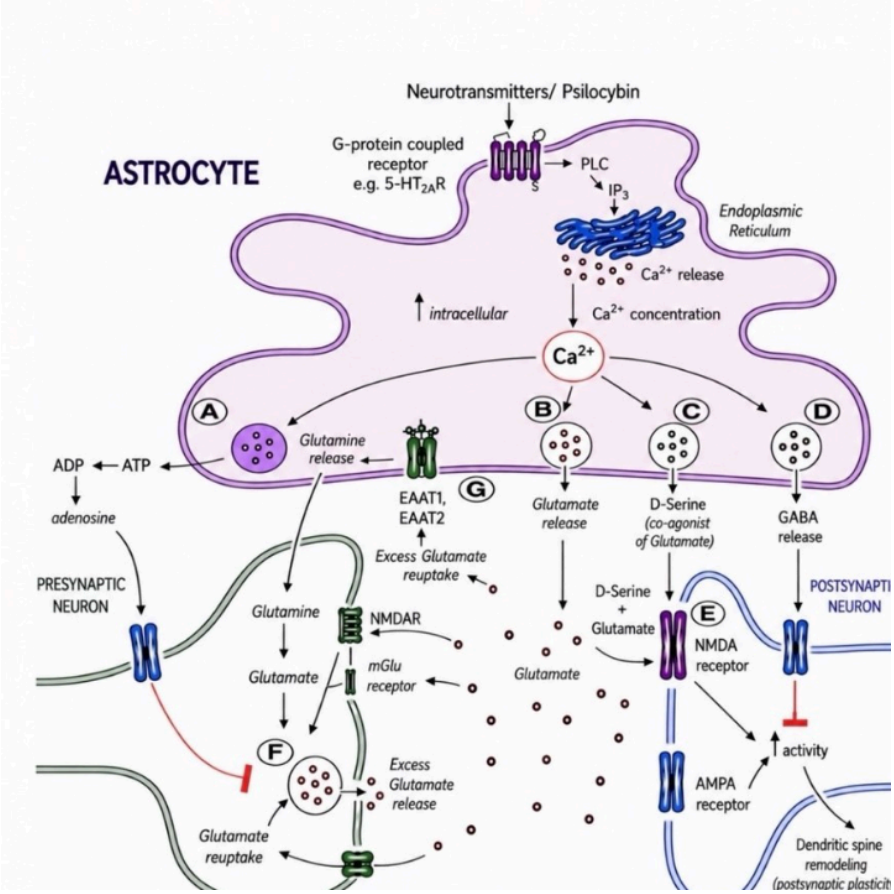


Figure 2. Proposed astrocyte-mediated regulation of synaptic signaling. Neurotransmitter- or psychedelic-associated G-protein-coupled receptor signaling may activate the PLC/IP_3 signaling pathway and increase intracellular Ca^{2+} in astrocytes which might affect several Ca^{2+}-associated signaling processes. **(A)** Astrocytic ATP release may contribute to extracellular adenosine signaling that regulates presynaptic signaling. **(B)** Astrocytic glutamate release may modulate nearby neuronal receptors and synaptic signaling. **(C)** D-serine can act as a co-agonist at NMDA receptors and might affect NMDA

receptor-dependent synaptic signaling. **(D)** Astrocytic GABA release may modulate postsynaptic neuronal activity through inhibitory GABA signaling. **(E)** Activation of postsynaptic NMDA and AMPA receptors may affect postsynaptic plasticity. **(F)** Recycled glutamate can contribute to presynaptic glutamate availability and release. **(G)** EAAT1/EAAT2-mediated uptake of excess extracellular glutamate regulates glutamate homeostasis and recycling through the glutamate–glutamine cycle. Author-created figure based on the literature reviewed in this article.

Another potential astrocytic signaling pathway relevant to psychedelic-induced plasticity is ATP. Astrocytes release ATP into the extracellular space, which can be converted to adenosine and can therefore help regulate neuronal excitability and synaptic transmission. Psilocin modifies astrocytic release of ATP, glutamate and lactate, and alters astrocytic mitochondrial function (Qiao et al., 2026). This indicates that psychedelic exposure can modify astrocytic signaling pathways associated with neuron-glia communication but does not establish that ATP or its conversion to adenosine mediates psychedelic-induced neuronal plasticity.

Astrocytic Regulation of Glutamate Homeostasis

One of the fundamental contributions of astrocytes to plasticity is maintaining an extracellular environment in which synaptic signaling can remain appropriately regulated. Excitatory neuronal activity releases glutamate into the synaptic space, where the concentration and duration of the signal must be tightly controlled. Astrocytes remove extracellular glutamate through high-affinity transport systems and participate in its recycling through the glutamate–glutamine cycle (Yamamoto & Takano, 2025). This process supports continued neuronal communication while limiting excessive accumulation and diffusion of glutamate beyond active synapses. Since glutamatergic transmission is involved in both strengthening and weakening synapses, changes in how extracellular glutamate is regulated may also change the conditions where synaptic plasticity occurs.

This homeostatic function illustrates an important principle: astrocytes do not necessarily promote neuroplasticity simply by increasing neuronal activity. Instead, they can regulate the balance and spatial specificity of activity. Effective plasticity requires sufficient excitatory signaling to modify synapses while avoiding excessive or poorly localized excitation that could interfere with normal circuit organization. Astrocytes may therefore regulate which signals remain within the active synapse and which signals spread to neighboring connections. During increased remodeling, this regulation may become especially important because neuronal circuits require the ability to change and the capacity for keeping these changes appropriately controlled.

Experimental studies provide evidence that astrocytes may determine whether neuronal activity develops into persistent synaptic modification. Henneberger et al. (2010) found that clamping the internal Ca^{2+} of individual astrocytes in hippocampal areas decreased the occupancy of an NMDAR co-agonist site and blocked LTP induction at nearby excitatory synapses, while synapses associated with a neighboring control astrocyte were still able to undergo LTP normally. When D-serine was added, the blocked LTP was restored. Therefore, Ca^{2+}-dependent release of D-serine from individual astrocytes can locally

regulate NMDAR-dependent plasticity at nearby excitatory synapses rather than acting as a generalized support for neuronal function.

Astrocytes also participate in the structural organization of synapses. Formation of a new neuronal protrusion does not necessarily produce a mature and functional synaptic connection. New synapses require appropriate presynaptic and postsynaptic structures, functional receptor organization, and enough stability to become integrated into existing circuits. Astrocytes can influence several stages of this process through cell–cell interactions and extracellular factors involved in synapse formation and maturation. For instance, astrocyte-derived proteins, including thrombospondins and glypicans, have been associated with different components of synaptic development and organization (Yamamoto & Takano, 2025). Thus, astrocytes may be involved not only in acute changes in synaptic transmission but also in whether newly formed neuronal structures develop into stable synaptic connections.

This distinction between induction and stabilization of plasticity is important. Many molecular pathways can initiate neuronal growth or change synaptic strength, but persistent neuroplasticity also requires these changes to be maintained. Newly remodeled synapses require appropriate extracellular neurotransmitter concentrations, continued metabolic resources, protein synthesis, membrane remodeling, and maintenance of local ionic conditions. Astrocytes contribute to the regulation of several of these processes. Therefore, the contribution of astrocytes may not always involve starting the neuronal change. Instead, astrocytes may be involved in whether an initially temporary neuronal change is maintained, modified, or eventually removed.

Astrocyte-Mediated Metabolic Support

Metabolic coupling between astrocytes and neurons provides another mechanism through which this stabilization may occur. Neuronal activity and structural remodeling impose substantial energetic demands associated with restoration of ionic gradients, neurotransmitter cycling, protein synthesis, and maintenance of newly formed cellular structures. Astrocytes participate in glucose metabolism, contain glycogen reserves, and provide neurons with metabolic substrates such as lactate. Direct evidence that psychedelic exposure can affect astrocyte metabolism was reported by Zandonadi et al. (2023). They exposed primary astrocytes in vitro to ayahuasca preparations at concentrations defined according to DMT concentration and found changes in intracellular and secreted metabolites. These changes involved several metabolic pathways, including B-vitamin and branched-chain amino-acid metabolism. However, because the study was performed in isolated astrocytes, it did not determine whether these metabolic changes contributed to neuronal plasticity. These functions place astrocytes in a position to match local metabolic support with changes in neuronal activity. Astrocytic metabolism may therefore become particularly relevant during prolonged periods of circuit remodeling, when the energetic requirements of maintaining newly modified synapses extend beyond the signaling events that initially produced them (Ke et al., 2026).

Astrocytes also play a role in regulating the larger extracellular and tissue environment. These functions include extracellular ion regulation, water balance, blood–brain barrier function, interactions with the

cerebral blood vessels, and communication with immune cells (Ke et al., 2026). Many of these functions are also associated with synaptic activity. For instance, increased neuronal signaling changes local metabolic and ionic requirements, while inflammatory conditions can alter neurotransmitter regulation and synaptic function. Therefore, astrocytes are considered to participate in the regulation of both synaptic activity and the surrounding tissue environment. This may allow astrocytes to influence not only individual synapses but also the local extracellular environment that impacts structural remodeling of neurons.

Astrocyte Functional Heterogenicity

Astrocyte function is heterogeneous rather than uniform. Astrocytes differ in morphology, gene expression, receptor profiles, and their interactions with surrounding neuronal circuits. Even within a single astrocyte, signaling may differ between the soma and fine peripheral processes. Yamamoto and Takano (2025) describe this organization at different levels, in which astrocytic activity ranges from local microdomain events to broader cellular and network-level responses. Therefore, describing an astrocyte simply as either "active" or "inactive" may overlook the spatial complexity of their contribution to plasticity. The effect of astrocytic signaling may depend on where the response occurs, which neuronal population is involved, and the physiological or pathological condition of the surrounding circuit.

Astrocyte heterogeneity is also relevant to psychiatric disease. Chronic stress and other pathological conditions can modify astrocyte morphology, signaling, metabolic function, and interactions with synapses. These changes may impair the capacity of astrocytes to sustain the extracellular environment required for adaptive remodeling. In psychiatric disease, impaired neuroplasticity may be due to disruption of the larger neuron-glia system rather than a single neuronal abnormality. This framework complements the neuronal changes described in the previous section and provides a broader explanation for why restoration of neuronal signaling alone may not fully account for the persistence or effectiveness of therapeutic plasticity.

The importance of astrocytic functions in neuroplasticity is not that astrocytes replace neurons as the principal site of synaptic plasticity, but that neuronal remodeling occurs within an environment that astrocytes continuously regulate. Neuroplasticity may therefore be better understood as a coordinated cellular process in which neuronal changes and astrocytic support mechanisms interact over both spatial and temporal scales. Establishing the normal role of astrocytes in this process therefore provides the necessary foundation for examining the more specific question addressed in the following section: do classical psychedelics recruit astrocytic functions as part of psychedelic-induced neuroplasticity?

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

There is growing evidence regarding the rapid and long-lasting effects of classical psychedelics on neuroplasticity. However, it is still not completely understood how acute psychedelic exposure can result in long-lasting changes in synaptic and circuit function. Systematic reviews support psychedelic-induced changes at different levels of plasticity, but most of this evidence is preclinical and is derived from

cultured cells and animal models (de Vos et al., 2021; Grieco et al., 2022). Astrocytes also regulate multiple processes involved in neuroplasticity, including glutamate homeostasis, Ca^{2+} signaling, gliotransmission, metabolic support, synaptic stabilization, and neuroimmune regulation. This raises a major question of how astrocytes are involved in these effects: whether astrocytes only respond to neuronal changes caused by psychedelics or whether they could also be involved in producing, shaping, or maintaining psychedelic-induced neuroplasticity.

Establishing a Casual Psychedelic-Astrocyte-Plasticity Pathway

One of the main gaps is the lack of direct experimental evidence establishing the complete pathway between psychedelics, astrocytes, and neuronal plasticity. Studies have not yet demonstrated that psychedelic exposure results in a specific astrocytic response that leads to neuronal plasticity and, eventually, to long-lasting behavioral or therapeutic effects. Direct psychedelic–astrocyte evidence has now been reported across four studies involving transcriptional, metabolic, neuroimmune, and other astrocytic responses (Martin & Nichols, 2016; Zandonadi et al., 2023; Chung et al., 2025; Qiao et al., 2026). However, none of these studies directly demonstrated that the observed astrocytic changes caused structural or functional neuronal plasticity.

There is strong evidence supporting individual components of the proposed psychedelic–astrocyte–plasticity pathway. Psychedelics can promote dendritic growth, spine remodeling, synaptic changes, and molecular pathways related to plasticity (de Vos et al., 2021; Grieco et al., 2022). Astrocytes, independently, can regulate synaptic plasticity through Ca^{2+} signaling, neurotransmitter regulation, gliotransmission, and metabolic coupling (Yamamoto & Takano, 2025). Henneberger et al. (2010) found that clamping intracellular Ca^{2+} signaling in individual astrocyte impaired nearby hippocampal long-term potentiation (LTP), whereas supplying D-serine restored LTP. Thus, astrocytic signaling may have an important role in NMDAR-dependent synaptic plasticity.

There are other factors to consider before astrocytes can be considered necessary for psychedelic-induced neuroplasticity. Showing that astrocytes regulate neuroplasticity generally does not establish that they are necessary for psychedelic-induced neuroplasticity. Similarly, changes in astrocyte function after psychedelic exposure do not establish that these changes cause neuronal remodeling. Future studies need to manipulate astrocytes during psychedelic exposure while directly measuring plasticity. For instance, astrocyte-specific inhibition could be combined with dendritic spine imaging, electrophysiological measurements of LTP/LTD, and behavioral testing. If psychedelic-induced spine formation or synaptic strengthening is reduced when a specific astrocytic pathway is blocked and returns after restoring that pathway, then this would provide considerably stronger evidence for causal involvement.

Direct Versus Indirect Astrocytic Effects

Another major question is whether psychedelics directly act on astrocytes or whether the changes in astrocytes happen in response to neuronal activation. Classical psychedelics mainly exhibit their pharmacological effects through serotonergic receptors, particularly 5-HT2ARs. Astrocytes also possess serotonergic signaling mechanisms and can respond to serotonin with changes in intracellular Ca^{2+}.

However, expression and function of these receptors can vary between cultured and mature astrocytes, between different regions of the brain, and depending on the physiological or pathological state (Ke et al., 2026).

This difference becomes important given evidence that the cellular location of 5-HT2ARs may influence psychedelic-induced plasticity. Intracellular neuronal 5-HT2ARs have been implicated in psychoplastogenic effects. However, it is still unknown whether functionally relevant intracellular 5-HT2AR populations are also present in astrocytes. For instance, 5-HT2B receptors may have a larger role than 5-HT2ARs in some astrocytic responses. In the case of DMT, sigma-1 receptor signaling may provide another potential mechanism (Ke et al., 2026).

Future studies could use astrocyte-specific receptor deletion rather than systemic receptor antagonists alone. For example, 5-HT2ARs could be deleted specifically from astrocytes while leaving the neuronal receptors intact. This could help determine whether direct activation of astrocytic 5-HT2ARs contributes to psychedelic-induced neuroplasticity. Similar studies involving 5-HT2B and sigma-1 receptors could help determine whether different classical psychedelics recruit distinct astrocytic pathways. This would help determine whether astrocytes are directly affected by psychedelics or whether they are responding to changes that occur first in neurons.

Astrocytic Ca^{2+} Signaling as a Potential Mechanism

Astrocytic Ca^{2+} signaling may also be involved in the connection between serotonergic signaling and neuroplasticity. In stressed mice, exposure to chronic corticosterone, altered astrocytic Ca^{2+} signaling in the medial prefrontal cortex and reduced serotonin-evoked astrocytic Ca^{2+} responses (González-Arias et al., 2023). These changes were also associated with altered serotonin-dependent synaptic plasticity. Furthermore, increasing astrocytic Ca^{2+} signaling through chemogenetic manipulation of astrocytic Gq signaling restored cognitive and mood-related abnormalities in stressed mice (González-Arias et al., 2023).

These findings provide indirect evidence connecting serotonin, astrocytic Ca^{2+} signaling, synaptic plasticity, and behavior, despite the lack of direct psychedelic evidence. In addition, increasing astrocytic activity in healthy animals could produce behavioral impairments. This indicates that the effects of increasing astrocytic Ca^{2+} signaling are not uniformly beneficial, suggesting that these effects may depend on neural circuit location and the physiological condition in which it occurs.

More directly related to psychedelic pharmacology, Qiao et al. (2026) found that psilocin affected astrocytic proliferation, mitochondrial function, and enhanced ATP, lactate, and glutamate release. Partial depletion of astrocytes in the prelimbic medial prefrontal cortex also reduced some antidepressant-like behavioral effects of psilocybin (Qiao et al., 2026). However, they did not directly measure psilocin-induced astrocyte Ca^{2+} signaling or neuronal plasticity. Future studies could manipulate Ca^{2+} signaling during psilocybin exposure while changes in neuronal dendritic spines are measured using longitudinal two-photon imaging. This could help determine whether astrocytic Ca^{2+} signaling is

necessary for structural neuronal remodeling. Simultaneous astrocytic Ca^{2+} imaging and neuronal electrophysiology might further establish the temporal relationship between glial and neuronal responses.

Identifying the Appropriate Astrocytic Functions Involved

There are several astrocytic functions that could be involved in psychedelic-induced neuroplasticity. Even if astrocytes are eventually shown to be necessary for this process, their relevant downstream mechanism remains uncertain. Candidate astrocytic functions may include glutamate uptake, D-serine availability, ATP/adenosine signaling, extracellular K^+ regulation, metabolic support and lactate delivery, trophic factors, extracellular matrix composition, and neuroimmune regulation.

D-serine is one of the possible mechanisms because it acts as a co-agonist at NMDARs and can influence NMDAR-dependent plasticity. Astrocytic D-serine has played a functional role in NMDAR-dependent LTP under experimental conditions (Henneberger et al., 2010). Based on this, cortical excitation caused by psychedelics could interact with astrocytic D-serine availability and determine whether temporary neuronal activity develops into long-lasting synaptic strengthening. However, there is currently no direct evidence for such a mechanism following psychedelic administration.

Glutamate homeostasis is another mechanism to consider. Classical psychedelics can alter cortical glutamatergic signaling, while astrocytes regulate extracellular glutamate through transporters such as EAAT1/GLAST and EAAT2/GLT-1. Therefore, astrocytes might affect the magnitude, distribution, and duration of glutamatergic signaling after psychedelic exposure. Future studies could selectively manipulate astrocytic glutamate transporters during psychedelic treatment and measure the changes in neuronal plasticity. This could help determine whether appropriate glutamate clearance is required for adaptive remodeling or mainly protects against excessive excitation.

ATP and adenosine are potentially involved in another regulatory mechanism. Extracellular astrocyte-derived ATP can be converted into adenosine, which can reduce excessive presynaptic glutamate release. This process could be involved in controlling excessive excitation and regulating synaptic transmission. However, it is still debated which cells are responsible for extracellular adenosine and how large their contributions are. Therefore, future studies need to identify the cellular source of ATP and adenosine rather than assuming that these adenosine-mediated effects originate from astrocytic ATP.

Metabolic Support and Stabilization of New Plasticity

Since neuronal remodeling is energetically demanding, metabolic support is essential for neuroplasticity. Dendritic growth, protein synthesis, receptor trafficking, synapse formation, and maintenance of altered neuronal activity all depend on metabolic support. Astrocytes are important in cerebral energy metabolism through glycogen storage, glucose utilization, mitochondrial function, and lactate delivery to neurons. This raises the possibility that psychedelics may initiate signaling pathways required for neuronal growth, while astrocytes provide the metabolic support needed for those newly remodeled synapses to become stable and persistent.

Direct studies with psychedelics also support changes in astrocyte metabolism. Zandonadi et al. (2023) found that exposure of primary astrocytes to ayahuasca preparations produced changes in intracellular and secreted metabolites, providing direct evidence that psychedelic exposure can alter astrocytic metabolic processes. Qiao et al. (2026) also found that psilocin altered astrocytic ATP and lactate release and improved mitochondrial function. However, neither study directly established whether these metabolic changes are needed for the formation or stabilization of psychedelic-induced neuroplasticity. Future pharmacologic or genetic manipulation of the astrocyte–neuron lactate shuttle could then determine whether altering metabolic support reduces the persistence of psychedelic-induced synaptic changes without blocking their initial formation. This experiment would directly test the possibility that neurons initiate remodeling while astrocytes provide metabolic support.

Regional and Cellular Heterogeneity

Astrocytes vary considerably in morphology, transcriptional profile, receptor expression, metabolic function, and interaction with surrounding neurons. Astrocyte signaling also occurs at different levels, from individual perisynaptic processes to larger interconnected astrocyte networks (Yamamoto & Takano, 2025). Therefore, the function of astrocytes in one brain region may not be the same in another region.

Current psychedelic-related findings suggest regional specificity. González-Arias et al. (2023) found serotonergic astrocyte dysfunction in the medial prefrontal cortex, while Qiao et al. (2026) implicated prelimbic prefrontal astrocytes in the behavioral response to psilocybin. In contrast, Chung et al. (2025) discovered an astrocyte-centered neuroimmune mechanism in the amygdala that regulates stress-associated fear. Thus, the astrocytes in the prefrontal cortex may contribute differently to psychedelic-induced plasticity than astrocytes in the amygdala, hippocampus, or other regions. However, it is not known whether these differences reflect true region-specific functions. To prevent generalizations, future studies should therefore avoid extrapolating findings from one brain region to the entire brain.

Timing Sequence

Another factor to consider is the timing of astrocyte involvement. Psychedelics activate receptors and change neuronal signaling within minutes to hours, while structural plasticity and behavioral effects can continue for days or longer. de Vos et al. (2021) note that the acute, subacute, and long-term plasticity outcomes should be considered separately instead of considering neuroplasticity as a single event.

It is unknown when astrocytes become involved in this process. Astrocytes may be involved early through glutamatergic signaling and Ca^{2+} activity. On the other hand, they may become more important later by supplying metabolic and trophic support. It is also possible that astrocytes are involved at multiple stages. Ke et al. (2026), in a hypothesis-driven perspective, proposed a model in which neuronal signaling may initiate psychedelic-induced plasticity while astrocytes contribute to its consolidation and tissue-level integration. The proposed mechanisms include astrocytic regulation of glutamate, Ca^{2+} signaling, metabolic support, and neuroimmune processes. However, these mechanisms were synthesized primarily

from indirect evidence rather than demonstrated experimentally during psychedelic-induced neuronal plasticity. Therefore, this model remains hypothetical and requires direct experimental testing.

To understand the timing, future studies could measure neuronal and astrocytic responses together after psychedelic administration. Measurements could be made at minutes and hours for the acute changes and then at days and weeks for the longer-lasting changes. This would help distinguish mechanisms involved in initiating plasticity from those that occur during the maintenance or stabilization of plasticity.

Neuroimmune Regulation

Astrocytes are also involved in neuroimmune regulation and may change the cellular environment in which neuronal plasticity occurs. Neuroinflammation can disrupt glutamate regulation, metabolism, synaptic function, and neuronal survival. Therefore, reactive astrocytes may alter how neuronal plasticity develops following a plasticity-inducing stimulus.

More directly related to psychedelics, Chung et al. (2025) found that astrocytic EGFR signaling in the amygdala regulates stress-associated neuroimmune interactions and fear behavior. Psilocybin and MDMA also reduced meningeal inflammatory monocyte accumulation and fear-related responses. However, the molecular mechanisms that caused these changes in immune populations are still unknown, and the study did not establish whether immune changes are necessary for psychedelic-induced plasticity.

In addition, Qiao et al. (2026) showed that psilocin improved several abnormalities in experimentally induced A1-like reactive astrocytes. These studies raise the possibility that psychedelic effects may modify the surrounding glial and immune environment to make plasticity more adaptive or sustainable and not only initiate neuronal plasticity. Future studies should measure inflammatory signaling, astrocyte state, neuronal spine remodeling, electrophysiological plasticity, and behavior simultaneously. This could determine whether normalization of astrocyte reactivity precedes structural remodeling and whether blocking these changes reduces psychedelic-induced plasticity.

Experimental Methods to Advance Understanding

Most evidence regarding psychedelic-induced neuroplasticity is still preclinical (de Vos et al., 2021). Also, direct evidence regarding astrocyte involvement mainly comes from experimental models (Qiao et al., 2026). Discovering whether astrocytes are actively involved in psychedelic-induced neuroplasticity will require models in which astrocytic and neuronal responses can be studied separately to determine how interactions between these cells affect plasticity. In vitro and in vivo models along with single-cell and spatial techniques can provide information about which cells are changing and where these changes occur.

In vitro models allow for more specific evaluation of cellular mechanisms. For instance, human induced pluripotent stem cell (iPSC)-derived neurons and astrocytes could be used in neuron-astrocyte co-cultures. Psychedelic exposure could then be used to study changes in each cell type and their interactions. Cerebral organoids provide another model with more complex neuronal and glial interactions in

human-derived tissue. These models could be employed to study whether astrocytic Ca^{2+} signaling, metabolism, and neurotransmitter release affect neuronal plasticity.

Animal models are still useful because they permit astrocytic mechanisms to be studied within an intact neural circuit and linked to behavioral outcomes. Astrocyte-specific genetic or chemogenetic manipulation during psychedelic administration could determine whether changing a specific astrocyte function also changes neuronal plasticity or behavioral responses. Longitudinal two-photon imaging could be used to examine astrocytic Ca^{2+} activity and dendritic spine remodeling simultaneously. In addition, electrophysiology can reveal whether astrocytic manipulation changes LTP or other functional forms of plasticity.

Single-cell and spatial techniques can identify which astrocyte populations respond to psychedelic exposure. Single-cell RNA sequencing could show which populations of astrocytes have transcriptional changes after psychedelic exposure, while spatial transcriptomics could show where these changes occur in the brain. When combined with metabolic studies, these techniques may show whether particular astrocyte states are associated with neuronal remodeling and whether similar responses occur in different experimental models.

Therapeutic Implications

Understanding astrocytic involvement in psychedelic-induced neuroplasticity may also have therapeutic importance. Most current research has focused on neuronal 5-HT2AR signaling. However, astrocytes regulate several mechanisms involved in neuronal plasticity including glutamate homeostasis, Ca^{2+} signaling, metabolic support, synaptic regulation, and neuroimmune activity. If future studies show that a specific astrocytic mechanism is involved in psychedelic-induced plasticity, this could provide another therapeutic target in addition to neuronal mechanisms.

Astrocytes are already being studied in other neurological conditions as possible therapeutic targets. In Alzheimer's disease, astrocytes undergo morphological and functional changes including altered Ca^{2+} signaling, impaired gliotransmission, and changes in inflammatory and homeostatic pathways. Reactive astrocytes can have both beneficial and harmful effects during disease progression (Abedin & Kastanenka, 2026). Following traumatic brain injury (TBI), astrocytes also undergo changes in gene expression, morphology, proliferation, and function. These changes are involved in inflammation, tissue repair, and synaptic remodeling that may contribute to recovery or secondary injury depending on the surrounding conditions (Burda et al., 2016). These examples illustrate that changes in astrocyte function can affect the environment in which neuronal damage, repair, and remodeling occur, demonstrating that the effect of astrocytes is not always unidirectional.

Therefore, targeting astrocytes would not simply mean increasing or decreasing their activity. The specific astrocyte function that contributes to beneficial plasticity would need to be identified, and then that pathway could be targeted. For instance, this could include a receptor, glutamate transporter, Ca^{2+}-dependent pathway, metabolic pathway, or inflammatory mechanism. These studies in Alzheimer's

disease and TBI highlight why this specificity is crucial. Astrocyte responses can have different effects depending on the involved brain area and the cellular environment. In psychedelic research, no specific astrocytic pathway has yet been shown to be necessary for psychedelic-induced neuronal plasticity. Thus, astrocyte-targeted treatment is still a possible direction and not an established treatment.

The development of non-hallucinogenic psychoplastogens provides another example of how more selective approaches to neuroplasticity could be explored. These compounds are being studied to determine whether plasticity-promoting effects can be maintained while reducing the acute perceptual effects of psychedelics (Grieco et al., 2022). It is still not known if these effects can be completely separated. These more selective compounds could also be useful for finding which pathways are involved in persistent plasticity and whether astrocytic pathways are part of these effects.

Ke et al. (2026) similarly proposed that slower astrocyte-associated processes, including metabolic support, extracellular matrix remodeling, and inflammatory resolution, could contribute to sustained outcomes beyond the acute psychedelic state. If future studies show that these astrocytic processes are required for sustained neuronal plasticity, then specific astrocyte pathways could be investigated as targets for future research rather than as established treatment.

Future Perspective

There is increasing evidence that astrocytes may be involved in psychedelic-induced neuroplasticity. Psychedelics produce structural and functional neuronal plasticity, while astrocytes regulate several mechanisms involved in synaptic plasticity. For instance, astrocytic D-serine can control NMDAR-dependent LTP, and serotonergic signaling can influence astrocytic Ca^{2+} signaling and synaptic plasticity. More directly related to psychedelics, psilocin has been shown to change astrocyte proliferation, metabolism, and transmitter release. Partial depletion of prefrontal astrocytes also attenuated some behavioral effects of psilocybin. In addition, psychedelics have been shown to affect astrocyte-related neuroimmune pathways. However, these findings still do not show that astrocytes mediate psychedelic-induced neuroplasticity.

There are several steps that still need to be studied beyond simply observing that psychedelics affect astrocytes. First, it is important to determine which astrocyte populations respond to psychedelic exposure, which receptors or signaling pathways are involved, and which downstream astrocytic function is changed. It then needs to be shown how this astrocytic change affects neuronal plasticity and whether the resulting neuronal plasticity contributes to persistent behavioral or therapeutic effects. Different methods such as astrocyte-specific genetic manipulation, simultaneous neuronal and astrocytic imaging, electrophysiology, metabolic tracing, single-cell and spatial techniques, and human neuron-astrocyte models could be used to study these different steps.

There are still limitations in considering astrocytes as proven mediators of psychedelic-induced neuroplasticity. Current studies increasingly support that astrocytes may regulate or modulate this process, but the complete causal relationship has not been established. Astrocytes may be involved in determining

where neuronal remodeling occurs, providing metabolic support to new synapses, regulating the inflammatory environment, and how long the neuronal changes are maintained. Therefore, establishing these effects would expand the predominant neuron-centered model to a more integrated view in which neurons initiate rapid responses to psychedelics while astrocytes are involved in shaping whether those responses develop into stable, adaptive, and meaningful therapeutic changes.

CONCLUSION

Classical psychedelics have received increasing attention because of their rapid and long-lasting effects that persist beyond the acute psychedelic state. One of the main mechanisms proposed to explain these effects is neuroplasticity. Studies have shown that psychedelic exposure produces changes in neuronal signaling, dendritic structure, spine formation, and synaptic organization (de Vos et al., 2021; Grieco et al., 2022; Acero et al., 2025). Most research regarding these changes has focused on neuronal mechanisms, particularly 5-HT2AR signaling and downstream pathways involved in neuronal growth and plasticity. However, neuronal plasticity may not be limited to neurons, and the surrounding cellular environment may be involved.

Current evidence supports expanding the neuron-centered view of psychedelic-induced neuroplasticity to include astrocytes. However, studies have not yet shown a complete pathway in which psychedelic exposure causes a specific astrocytic response, followed by structural or functional neuronal plasticity, and eventually long-lasting behavioral or therapeutic effects. Astrocytes may have a role in psychedelic-induced neuroplasticity, but current evidence supports a possible modulatory role rather than a proven mediating role.

This raises a major question of how astrocytes are involved in psychedelic-induced neuronal plasticity. Future studies need to manipulate specific astrocytic pathways during psychedelic exposure while also measuring neuronal plasticity and longer-term behavioral outcomes. This would help determine whether astrocytes respond to neuronal changes that are already produced by psychedelics or whether astrocytes are actively involved in the development, stabilization, or persistence of plasticity. It is still unknown to what extent astrocytes are involved in the persistence of neuroplasticity after the acute psychedelic state. Finding the astrocytic mechanisms involved in this process may help to better understand how these changes persist and may provide additional areas for future research and possible therapeutic development.

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