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► **To cite this version:**

Daniel Barnett, Kirsten Bohmbach, Valentin Grelot, Alexandre Charlet, Glenn Dallérac, et al.. Astrocytes as Drivers and Disruptors of Behavior: New Advances in Basic Mechanisms and Therapeutic Targeting. *Journal of Neuroscience*, 2023, 43 (45), pp.7463-7471. 10.1523/JNEUROSCI.1376-23.2023 . hal-04281520

**HAL Id: hal-04281520**

**<https://hal.science/hal-04281520>**

Submitted on 23 May 2024

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## Symposium

# Astrocytes as Drivers and Disruptors of Behavior: New Advances in Basic Mechanisms and Therapeutic Targeting

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Astrocytes are emerging as key regulators of cognitive function and behavior. This review highlights some of the latest advances in the understanding of astrocyte roles in different behavioral domains across lifespan and in disease. We address specific molecular and circuit mechanisms by which astrocytes modulate behavior, discuss their functional diversity and versatility, and highlight emerging astrocyte-targeted treatment strategies that might alleviate behavioral and cognitive dysfunction in pathologic conditions. Converging evidence across different model systems and manipulations is revealing that astrocytes regulate behavioral processes in a precise and context-dependent manner. Improved understanding of these astrocytic functions may generate new therapeutic strategies for various conditions with cognitive and behavioral impairments.

## Introduction

Astrocytes regulate diverse brain functions, including information processing and storage (Santello et al., 2019; Kofuji and Araque, 2021). The exact roles of astrocytes in higher cognitive function and behavior are a growing area of neuroscience spurred by new and improved experimental tools and better understanding of astrocyte biology, astrocytic–neuronal interactions, and neural circuit activities underlying cognition and behavior. Accumulating evidence suggests that astrocytes play key roles in cognitive and behavioral processes (Han et al., 2012; H. S. Lee et al., 2014; Habbas et al., 2015; Orr et al., 2015; Gao et al., 2016; Papouin et al., 2017; Adamsky et al., 2018; Curreli et al., 2022; Doron et al., 2022) and that these roles are precise and context-dependent, and vulnerable to perturbation in injury and disease (Rusakov et al., 2014; Chung et al., 2015; Verkhratsky and Nedergaard, 2018). Alterations in astrocyte function have been implicated in various disorders of cognition

and behavior (Tong et al., 2014; De Strooper and Karran, 2016; Windrem et al., 2017; Brandebura et al., 2023). In this focused review, we highlight recent studies mainly in mice on the effects of astrocytes on visual processing, learning and memory, emotion, attention, and motor activity in health and disease. These studies suggest that diverse astrocytic factors and molecular pathways regulate normal behavior and can contribute to disease-associated behavioral and cognitive deficits. These insights enhance our understanding of astrocyte function and may facilitate therapeutic advancement for neurocognitive disorders.

## Astrocytes regulate cortical maturation and hippocampal activities underlying normal behavior

Astrocytes are crucial for synaptic development and maturation, and changes to astrocytes in critical periods (CPs) of brain development are implicated in neurodevelopmental disorders (Molofsky et al., 2012; Allen and Eroglu, 2017). Astrocytes are considered crucial elements of brain circuitry that enable synapse formation, maturation, activity, and elimination (Clarke and Barres, 2013). Although how exactly they exert such control is a topic of intense research, it is well known that astrocytes participate in critical developmental periods and affect brain disorders involving synaptic alterations. Unraveling how astrocytes control synaptic circuit formation and maturation is crucial not only for the understanding of normal brain development, but also for identifying effective therapeutics for neurodevelopmental disorders, such as autism spectrum disorder, attention-deficit/hyperactivity disorder, and epilepsy.

In the immature brain, both neurons and astrocytes develop in parallel during the early postnatal period characterized by enhanced

Received July 19, 2023; revised Aug. 13, 2023; accepted Aug. 22, 2023.

This work was supported by the following: National Institutes of Health/National Institute on Aging F31 AG084165 to D.B.; German Research Foundation (Deutsche Forschungsgemeinschaft) SFB1089 to K.B.; Center National de la Recherche Scientifique Contract UPR3212, Université de Strasbourg Contract UPR3212, and Agence Nationale de la Recherche, Jeune Chercheuse Jeune Chercheur Grant 19-CE16-0011-0 to A.C.; European Research Council, UNADEV-Aviesan, Fondation pour la Recherche Médicale, and the French Research Ministry to G.D.; Japan Society for the Promotion of Science KAKENHI JP21H00220, JP21H02588, JP23H04179, JST FOREST JPMJFR2249, and AMED JP22dk0207063 to J.N.; and National Institutes of Health/National Institute of Neurological Disorders and Stroke R01NS118569, National Institutes of Health/National Institute on Aging R00AG048222, Alzheimer's Association Research Grant, and Leon Levy Foundation Fellowship in Neuroscience to A.G.O.

The authors declare no competing financial interests.

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<https://doi.org/10.1523/JNEUROSCI.1376-23.2023>

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plasticity-related processes. In the first weeks of life, there is a period of massive synaptogenesis followed by selective pruning of synapses and sculpting of synaptic connections. These processes result in sensitive periods, known as CPs, involving enhanced neuroplasticity during which synaptic networks are shaped by experience in postnatal development. Synapse elimination may occur through engulfing mechanisms involving astrocytic MEGF10 and MERTK-dependent phagocytic pathways, which are strongly influenced by local neuronal activities (Chung et al., 2013). Conversely, astrocytes may also control CP by releasing various synaptogenic factors. For instance, at thalamocortical synapses, astrocytes can secrete the glycoprotein hevin, which facilitates the development of glutamatergic synapses between the thalamus and neocortex. The effects of hevin involve the bridging of presynaptic factor neurexin-1 $\alpha$  with the postsynaptic factor neuroligin-1 (Singh et al., 2016).

The exact time windows for CP and neural network formation vary between cerebral areas and their functions (Hensch, 2005). Importantly, closure of the CP and stabilization of neural circuits rely on activity-dependent maturation of local inhibitory networks, in particular parvalbumin-expressing GABAergic interneurons. The visual cortex is well known to undergo experience-dependent developmental shaping of synaptic circuits during its CP with enhanced plasticity that follows eye opening. Primary visual areas in the cortex are typically activated more by contralateral compared with ipsilateral eye stimulation, which is termed ocular dominance. The start and end of visual cortex CP is classically defined according to the development of ocular dominance.

Ocular dominance can be manipulated experimentally by occlusion of the contralateral eye for several days, which abolishes dominance or switches it to the ipsilateral eye. Pioneering studies have revealed a key role of astrocytes in the timing of the visual CP by showing that implantation of immature astrocytes into the visual cortex is sufficient to reopen a period of enhanced plasticity (Muller and Best, 1989). More recently, Ribot et al. (2021) unveiled the mechanisms by which astrocytes modulate the wiring of visual circuits. Astrocytes in the visual cortex were shown to regulate the extracellular matrix that promotes maturation of interneurons, and this process involves unconventional connexin signaling in astrocytes. In particular, the timing of CP closure was controlled by marked developmental upregulation of astrocytic connexin-30, which inhibited the expression of matrix-degrading enzyme matrix metalloproteinase 9 through the RhoA-GTPase pathway. These findings suggest that astrocytes control experience-dependent wiring of neuronal circuits in neurodevelopment that enable visual processing. Interestingly, in parallel work using *Drosophila melanogaster*, studies have also uncovered astrocyte roles in the closure of a newly discovered CP for motor behavior (Ackerman et al., 2021). Here, astrocytes appear to promote the end of CP by disrupting the balance between excitation and inhibition through astrocyte-derived neuroligins and their neuronal target neurexin-1. This work and other studies suggest that astrocytes in insects and mammals regulate early neuroplasticity and that astrocytes have determinant roles in early sculpting of synaptic connections and maturation of neural circuits involved in perception and behavior.

Astrocytes also modulate synaptic function and neural circuits in the hippocampus of young and adult animals. For instance, astrocytes influence dendritic computations essential for spatial learning and memory and other processes. The understanding of microcircuit computations underlying spatial learning has grown

steadily (Geiller et al., 2023) since the discovery of place cells in the hippocampus by O'Keefe and Dostrovsky (1971). While the initial focus was centered on somatic neuronal activities, recent studies have identified a crucial role for active dendritic computations in shaping place field firing patterns and spatial learning (Sheffield and Dombeck, 2019). Similarly, the roles of astrocytes in spatial learning has gained increased attention (Akther and Hirase, 2022; Bohmbach et al., 2023). In particular, astrocytic Ca<sup>2+</sup> signaling in the hippocampus has been shown to modulate synaptic transmission and plasticity underlying spatial learning (Perea and Araque, 2005, 2007; Shigetomi et al., 2008; Di Castro et al., 2011; Panatier et al., 2011), and can predict the location of an expected reward (Doron et al., 2022). However, exactly when astrocytic Ca<sup>2+</sup> signaling pathways are recruited and whether they modulate dendritic computation remained unknown until recently.

In the stratum radiatum of the CA1 region in the hippocampus, active dendritic integration can amplify simultaneous clustered inputs through the generation of dendritic spikes (Losonczy and Magee, 2006; Stuart and Spruston, 2015). This nonlinear dendritic computation has been shown to modulate long-term plasticity (Remy and Spruston, 2007), complex burst firing (Grienberger et al., 2014), and the formation of place cells (Sheffield and Dombeck, 2015; Sheffield et al., 2017). As NMDAR signaling is crucial for dendritic spikes (Losonczy and Magee, 2006; Grienberger et al., 2014; Harnett et al., 2015; Bohmbach et al., 2022) and astrocytes are known to modulate NMDARs through the supply of the co-agonist D-serine (Henneberger et al., 2010; Papouin et al., 2017; Robin et al., 2018), it was hypothesized that astrocytes modulate dendritic computations. Through a series of *ex vivo* electrophysiological experiments, Bohmbach et al. (2022) revealed that the co-agonist binding site of NMDARs allows the modulation of dendritic spikes and that this effect was mediated by an increase in the NMDAR co-agonist D-serine. However, important questions remain. How do neurons engage astrocytes to enhance D-serine release and what is the exact mechanism regulating astrocytic D-serine release?

Neuronal firing can increase endocannabinoid levels, which are lipophilic substances with short-range neuromodulatory actions (Di Marzo et al., 1998; Wilson and Nicoll, 2002; Chevaleyre and Castillo, 2003; Fortin et al., 2004; Dubruc et al., 2013; Albarran et al., 2023). Astrocytes express endocannabinoid receptors, including Type 1 cannabinoid receptors (CB1R), which regulate astrocytic Ca<sup>2+</sup> levels (Navarrete and Araque, 2008), synaptic plasticity and memory (Han et al., 2012; Min and Nevian, 2012), and metabolic processes (Jimenez-Blasco et al., 2020; Covelo et al., 2021). In addition, CB1R is involved in Ca<sup>2+</sup>-dependent release of gliotransmitters, including D-serine (Gomez-Gonzalo et al., 2015; Robin et al., 2018; Bohmbach et al., 2022). Bohmbach et al. (2022) demonstrated that astrocytes respond to neural activity via the activation of endocannabinoid receptors, which are recruited for D-serine release. In turn, astrocyte-derived D-serine modulated neurotransmission by lowering the threshold and increasing the amplitude of dendritic spikes. Overall, these results suggest that hippocampal astrocytes control dendritic computations through endocannabinoid receptor activation and Ca<sup>2+</sup>-dependent release of D-serine that enhances dendritic NMDAR activation.

Bohmbach et al. (2022) also investigated when and how this astrocytic modulation is recruited. Importantly, the recruitment of astrocytic Ca<sup>2+</sup> and subsequent modulation of dendritic

integration by D-serine exhibited a distinct activity-dependent pattern. While low (4 Hz) and high (40 Hz) frequency neuronal firing did not recruit astrocytic modulation, firing rates in the theta band (~10 Hz) recruited reciprocal signaling between astrocytes and neurons. This activity-based engagement of astrocytes is likely mediated by dendrites themselves, as blockade of hyperpolarization-activated cyclic nucleotide-gated channels impaired feedback signaling. Moreover, Bohmbach et al. (2022) showed that this positive feedback exerted by astrocytes is required for spatial learning and memory. Decreasing intracellular  $\text{Ca}^{2+}$  levels through the expression of hPMCA2, a  $\text{Ca}^{2+}$  ATPase (also known as CalEx), or ablating the cannabinoid receptor CB1R specifically in astrocytes disrupted this astrocytic–neuronal cross-talk and impaired memory.

These findings and related work illustrate that astrocytes modulate spatial learning-related processes in the hippocampus and are engaged by specific types of neuronal activity patterns to modulate dendritic input computations. Further studies are needed to determine whether additional neuronal factors act on astrocytes to control these mechanisms and whether specific patterns of neural activities in other brain regions similarly recruit astrocytic feedforward mechanisms.

### Astrocytes modulate neural circuits in the amygdala and striatum to affect various behavioral domains

Astrocytes in different brain regions have distinct transcriptomic, structural, and functional properties (Chai et al., 2017; Morel et al., 2017; Endo et al., 2022), and these regional differences are also evident in aging and disease (Clarke et al., 2018; Hasel et al., 2021; Burda et al., 2022; Endo et al., 2022). Throughout the brain, astrocytes are responsive to various factors, including neurotransmitters and neuropeptides, that likely promote distinct astrocytic functions among different brain regions and circuits. In particular, recent studies have explored the roles of astrocytes in the effects of oxytocin (OT), a neuropeptide known for its regulation of various behavioral functions ranging from social interactions to pain and anxiety (Eliava et al., 2016; Jurek and Neumann, 2018; Hasan et al., 2019; Tang et al., 2020; Wahis et al., 2021; Iwasaki et al., 2023). Mainly synthesized in the hypothalamus, OT reaches distant brain nuclei through long-range axonal projections of OT-synthesizing neurons (Zhang et al., 2021). Once locally released, OT binds to its transmembrane receptor (OTR). While in the past, the effects of OT were mostly attributed to neuronal OTR and its direct effects on neuronal activities, new findings have uncovered a crucial role for astrocytes in OT-induced neuromodulation in the amygdala (Wahis et al., 2021; Baudon et al., 2022).

The central amygdala (CeA) is a key nucleus in the brain involved in the regulation of emotion. Wahis et al. (2021) found that a specific subpopulation of CeA astrocytes expresses OTR. Strikingly, these astrocytes appeared to be larger, more complex, and more likely to be connected to neighboring astrocytes compared with astrocytes lacking OTR expression. In *ex vivo* slice preparations, evoked OT release using optogenetics or direct OTR activation using TGOT, a selective OTR agonist, led to the appearance or significant increases in astrocytic  $\text{Ca}^{2+}$  transients. Targeted genetic deletion of the OTR-encoding gene specifically in CeA astrocytes revealed that CeA astrocytes express functional OTR. The authors evaluated the functional impact of OTR-induced astrocytic  $\text{Ca}^{2+}$  transients on the CeA neuronal network. To this end, patch-clamp recordings of electrical activities and currents in CeA neurons revealed strong modulation of CeA

neuronal activity by astrocytic OTRs. These effects were mediated by neuronal NMDARs at least in part through astrocytic release of D-serine. Given the crucial roles of CeA in emotional behavior, Wahis et al. (2021) also explored the behavioral effects of astrocytic OTR using a neuropathic pain model and measuring nociceptive thresholds, and assessing anxiety-like behavior and place preferences. Although there was not a strong involvement of OTR in nociception, activation of OTR reduced anxiety-like behavior and increased place preference; and these effects were dependent on CeA astrocytes.

These findings suggest that astrocytic OTR activation in the CeA induces astrocytic  $\text{Ca}^{2+}$  transients and transmitter release that modulate neuronal activity and emotion-related behaviors (Wahis et al., 2021). However, many important questions remain. Do astrocyte-mediated effects by OT differ according to brain region and pathophysiological state? Which intracellular pathways does astrocytic OTR recruit, and are there long-term effects of astrocytic OTR activation on astrocyte–neuronal interactions and behavioral functions (Baudon et al., 2022)? Further research is necessary to unravel the exact mechanisms and roles of astrocytes in emotion-linked circuits and behaviors and their changes in pathologic conditions that involve emotional dysregulation.

Astrocytes also regulate neural circuits involved in movement and attentional behaviors. Recent studies have explored the importance of astrocytes in cognitive processes related to how organisms exploit external stimuli for action selection. This process is heavily influenced by the striatum, a major input region of the basal ganglia, an area of the brain that coordinates voluntary movements directed by the cerebral cortex and regulates motor functions, innate behaviors, and cognitive processes, such as reinforcement learning (Graybiel, 2008; Markowitz et al., 2018). Intricate intercellular signaling plays pivotal roles in striatal microcircuits, and impairments in these mechanisms are implicated in neurodegenerative disorders, such as Parkinson's disease and Huntington's disease, and in drug addiction (Burguiere et al., 2015; Graybiel and Grafton, 2015; Khakh, 2019).

Astrocytes tile the striatum, where ~95% of neurons are GABAergic medium spiny neurons (MSNs). Striatal astrocytes respond to MSN activities through  $\text{G}_i$ -coupled  $\text{GABA}_B$  receptors, leading to increases in intracellular  $\text{Ca}^{2+}$  levels (Nagai et al., 2019). Accumulating evidence suggests that striatal astrocytes regulate behavior. In particular, recent studies have manipulated  $\text{Ca}^{2+}$  signaling and metabotropic receptor activation in striatal astrocytes using membrane-targeted expression of  $\text{Ca}^{2+}$  ATPase (CalEx) (Yu et al., 2018, 2021) or chemogenetic stimulation of  $\text{G}_i$ -coupled DREADDs. Silencing astrocytic  $\text{Ca}^{2+}$  signaling with CalEx caused an increase in astrocytic expression of GABA transporter GAT3, which induced repetitive self-grooming behavior in mice that is reminiscent of obsessive-compulsive disorder (Yu et al., 2018). Furthermore, Nagai et al. (2019) revealed that chemogenetic activation of astrocytic  $\text{G}_i$ -coupled receptors using hM4Di enhanced cortico-striatal excitatory synaptic transmission through aberrant induction of a synaptogenic molecule, thrombospondin-1, which induced behavioral hyperactivity and disrupted attention. These findings suggest that re-activation of astrocytic factors required in neurodevelopment can cause behavioral impairments in adulthood.

Striatal astrocytes are also instrumental in modulating reward-seeking behavior and behavioral flexibility. In particular, chemogenetic activation of  $\text{G}_q$ -coupled receptors in astrocytes located in the dorsomedial striatum modulates synaptic transmission in direct and indirect pathway MSNs in distinct ways,

promoting a shift from habitual behavior to goal-directed behavior (Kang et al., 2020). Astrocytic  $G_q$ -coupled signaling can also preserve behavioral flexibility and action switching by decreasing the expression of the glutamate transporter GLT-1, which prevents excessive glutamate clearance (Boender et al., 2021). Ventrostriatal astrocytes also respond to increases in extracellular dopamine, which can be induced by blocking dopamine transporters with psychostimulants. The increases in dopamine augment astrocytic  $Ca^{2+}$  levels and influence synaptic depression and addiction behavior (Corkrum et al., 2020; J. Wang et al., 2021). Beyond GPCRs, astrocytic GluN2C-containing NMDARs can also mediate  $Ca^{2+}$  signaling (Chipman et al., 2021), and this mechanism is suggested to maintain cocaine preference memory (Shelkar et al., 2022). The diverse array of astrocytic mechanisms and effects on striatum-dependent behaviors highlight the engagement of astrocytes in diverse neural processing and the functional variation observed within brain regions (Khakh and Deneen, 2019; Endo et al., 2022) in terms of intercellular signaling (Akther and Hirase, 2022), behavioral modulation (Nagai et al., 2021a, 2021b), and disease type and progression (Escartin et al., 2021; Burda et al., 2022).

Further understanding the specific contributions of striatal astrocytes to behavioral functions may reveal new therapeutic targets for conditions, such as Huntington's disease (H. G. Lee et al., 2022). Striatal astrocytes have highly context-specific molecular responses in disease, as evidenced by differential changes in gene expression patterns across 14 experimental perturbations (Yu et al., 2020). Chemogenetic stimulation of astrocytic  $G_i$ -coupled signaling in models of Huntington's disease pathology led to improvements in some, but not all, behavioral symptoms through increased expression of thrombospondin-1. Thus, stimulating  $G_i$ -coupled receptors in astrocytes could promote synapse formation and may offer a potential therapeutic approach for conditions characterized by synaptic loss (Yu et al., 2020). Future studies should address the complex interactions of astrocytes with neurons and other cell types within the striatum and throughout the cortico-basal ganglia circuits to better understand localized and broader effects of astrocytes in this region.

In summary, astrocytes have essential roles in synaptic transmission, plasticity, and behavioral control in the striatum and amygdala, highlighting the potential importance of astrocytes in the broader landscape of neurologic and neuropsychiatric disorders.

### **Astrocytes have context-dependent and multifactorial roles in neurocognitive disorders**

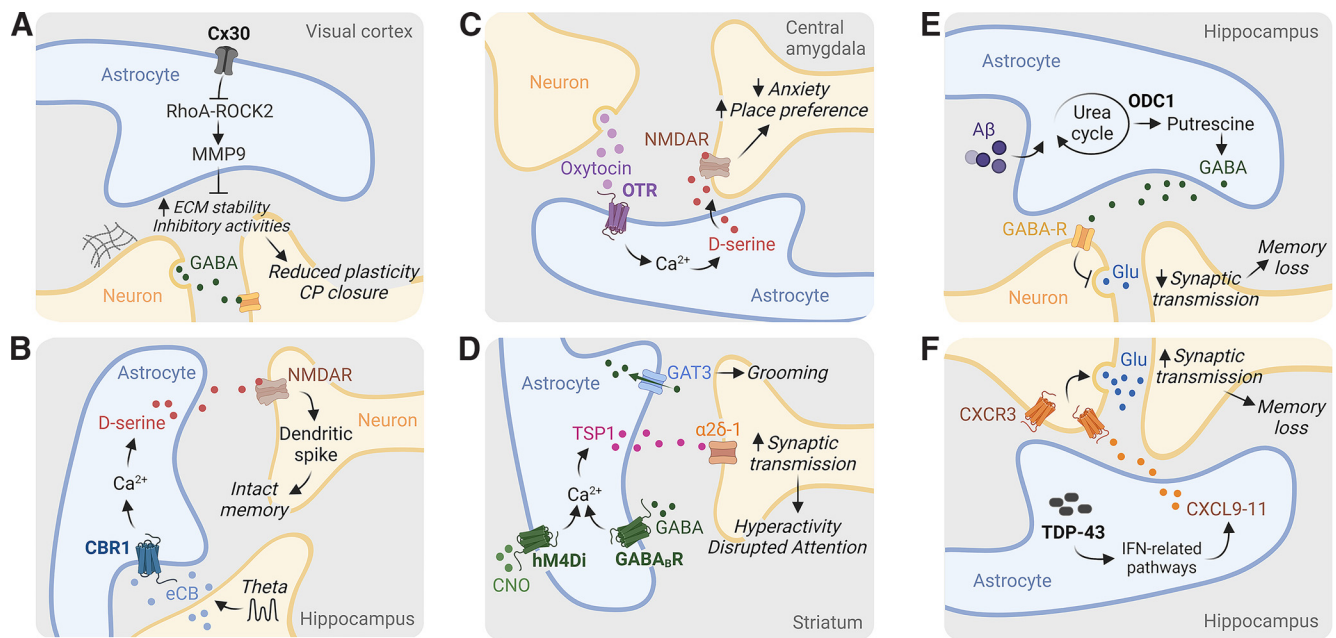
Astrocytes are increasingly recognized as having phenotypic diversity and functional versatility (Haustein et al., 2014; Khakh and Sofroniew, 2015; Ben Haim and Rowitch, 2017; Chai et al., 2017; John Lin et al., 2017; Morel et al., 2017; Patani et al., 2023; Soto et al., 2023). As mentioned above, astrocytic features and effects can vary across brain regions and neural circuits. Astrocytes are also affected by brain maturation and aging (Sun et al., 2013; Boisvert et al., 2018; Clarke et al., 2018; Lattke et al., 2021; E. Lee et al., 2022), sex (Bracchi-Ricard et al., 2008; Baier et al., 2022; Krawczyk et al., 2022; Meadows et al., 2022), and genetic variations (Messing et al., 2012; Arnaud et al., 2022), and they are sensitive to sensory processing (Schummers et al., 2008), locomotion (Paukert et al., 2014), arousal (Rasmussen et al., 2023; Reitman et al., 2023; F. Wang et al., 2023), metabolic and dietary cues (Camandola, 2018; Jimenez-Blasco et al., 2020; Nampoothiri et al., 2022; Morant-Ferrando et al., 2023), and stressors, such as sleep deprivation

(Bellesi et al., 2017), social isolation (Cheng et al., 2023), and viral infections (Soung and Klein, 2018; Jorgacevski and Potokar, 2023). It is possible that astrocytes play precise and context-dependent roles as a result of their integrated processing of diverse cues inherent to different biological and environmental contexts.

In brain injury and disease, astrocytic responses are emerging as highly context-dependent. These dynamics are becoming particularly evident in neurodegenerative disorders, including Alzheimer's disease (AD) and related dementias. Astrocytes express or respond to most, if not all, dementia-associated factors (Bruijn et al., 1997; Gu et al., 2010; Serio et al., 2013; Sun et al., 2015; di Domenico et al., 2019; Sadick and Liddel, 2019; Patani et al., 2023) and show extensive changes in gene expression patterns and functional characteristics depending on age (Soreq et al., 2017; Boisvert et al., 2018; Clarke et al., 2018), type of pathology (Delekate et al., 2014; Orr et al., 2015; Jiang et al., 2016; Liddel et al., 2017; Giovannoni and Quintana, 2020), and exact brain region (Boisvert et al., 2018; Clarke et al., 2018; Itoh et al., 2018). Indeed, astrocytes have highly diversified transcriptional signatures in different pathologic contexts at least in part because of the combinatorial effects of various transcriptional regulators (Burda et al., 2022).

Astrocytic context specificity is further evident in the cell-autonomous effects of dementia-related proteinopathy on astrocytic gene expression and astrocytic regulation of specific neuronal functions. One of the central pathogenic proteins implicated in neurodegenerative disorders is transactivating response region DNA-binding protein 43 (TDP-43), a multifunctional and ubiquitous DNA/RNA-binding factor that localizes primarily in the nucleus and regulates RNA processing and trafficking, among other functions. In disease, TDP-43 accumulates in the cytoplasm and other subcellular compartments, and is a major component of protein inclusions in amyotrophic lateral sclerosis and frontotemporal dementia (Arai et al., 2006; Neumann et al., 2006; T. J. Cohen et al., 2011). Notably, TDP-43 is also implicated in AD and other conditions that cause behavioral impairments (Amador-Ortiz et al., 2007; Uryu et al., 2008; Davidson et al., 2011; Nag et al., 2015). In addition to its effects in neurons, TDP-43 also affects glial cells and likely promotes disease by multiple mechanisms (Uryu et al., 2008; Diaper et al., 2013; Serio et al., 2013; Uchino et al., 2015; Takeuchi et al., 2016; Paolicelli et al., 2017; Weskamp et al., 2020). In support, aberrant astrocytic cleavage or accumulation of TDP-43 has been detected in amyotrophic lateral sclerosis, frontotemporal dementia, and AD (Serio et al., 2013; Takeuchi et al., 2016; Weskamp et al., 2020; Licht-Murava et al., 2023), but exactly how astrocytic TDP-43 dysregulation affects astrocyte function, astrocytic-neuronal interactions, and behavior was not clear.

New findings by Licht-Murava et al. (2023) indicate that aberrant buildup of TDP-43 in astrocytes is sufficient to cause progressive memory loss, but not other types of behavioral impairments, suggesting that hippocampal astrocytes are more vulnerable to TDP-43 pathology compared with astrocytes in other brain regions. Although hippocampal pathology and dysfunction are prevalent in aging and dementia, exact causes are uncertain and treatment options for neurocognitive decline in dementia are limited. In the context of TDP-43 pathology, Licht-Murava et al. (2023) uncovered abnormal increases in antiviral gene activities in hippocampal astrocytes and excessive production of interferon-inducible chemokines. These chemokines are known to activate  $G_i$ -coupled CXCR3 receptors, which are typically enriched in



**Figure 1.** Newly uncovered astrocytic mechanisms and behavioral effects in health and disease. Simplified summaries of select studies. Refer to the corresponding text and original reports for details. **A**, Ribot et al. (2021). **B**, Bohmbach et al. (2022). **C**, Wahis et al. (2021). **D**, Yu et al. (2018); Nagai et al. (2019). **E**, Ju et al. (2022). **F**, Licht-Murava et al. (2023).

immune cells. However, in TDP-43 pathology, the increases in hippocampal CXCR3 levels were localized to excitatory presynaptic terminals. Chronic stimulation of presynaptic CXCR3 caused aberrant increases in neuronal activities, and genetic ablation of CXCR3 prevented memory loss. Together, these findings reveal that TDP-43-linked increases in astrocytic antiviral signaling and chemokine production can trigger selective neuronal dysregulation and progressive cognitive decline.

Intriguingly, viral infections and other immune challenges can cause changes in memory, mood, and behavior, including sickness behavior and post-acute sequelae of SARS-CoV-2 infection (D’Mello and Swain, 2017; Becker et al., 2021; Damiano et al., 2022; Devlin et al., 2022; Hampshire et al., 2022; Takao and Ohira, 2023). Astrocytic antiviral pathways might contribute to these symptoms in part through increased release of chemokines and other immune response factors (Habbas et al., 2015) that disrupt specific synaptic activities. Of note, CXCR3 blockers have been developed and tested in clinical trials for arthritis and other peripheral inflammatory conditions but have not been assessed in behavioral disorders.

In addition to neuroimmune signaling, metabolic pathways may underlie astrocytic context-specific modulation of neurotransmission and behavior in disease. Astrocytes are crucial for maintaining brain homeostasis and neuronal health in part through astrocytic uptake, processing, and release of various metabolic factors (Belanger et al., 2011; Siracusa et al., 2019). These mechanisms modulate the extracellular environment, control neurotransmitter levels, and regulate energy metabolism. An important component of astrocytic metabolism is the urea cycle, a pathway associated with detoxification of ammonia, a byproduct of amino acid metabolism (P. P. Cohen, 1981; Meijer et al., 1990; Morris, 2002; Gropman et al., 2007).

Recent findings by Ju et al. (2022) have shed new light on the intricate relationship between the urea cycle in astrocytes and their roles in neurotransmission, and reveal how altered astrocyte metabolism can contribute to neurocognitive deficits in disease. In AD patients, astrocytes were found to have increased expression of urea cycle enzymes, including carbamoyl phosphate synthetase-1

and ornithine transcarbamylase, enabling astrocytes to convert toxic ammonia into less harmful byproducts (Ju et al., 2022). Because amyloid- $\beta$  ( $A\beta$ ) catabolism results in the production of ammonia, the upregulation of the urea cycle enzymes in AD suggests an adaptive response to the elevated ammonia levels. Ju et al. (2022) found that, although the urea cycle is relatively inactive in healthy astrocytes, it is engaged in AD and linked to the clearance of toxic  $A\beta$  aggregates. However, excessive activation of the astrocytic urea cycle was found to disrupt the delicate balance of neurotransmitters, including glutamate and GABA, leading to synaptic dysfunction and memory impairments. In particular, increased urea cycle metabolism led to the production of putrescine via ornithine decarboxylase 1 (ODC1). Subsequently, excessive conversion of putrescine to GABA, an inhibitory neurotransmitter, and hydrogen peroxide ( $H_2O_2$ ), a toxic byproduct of GABA production in astrocytes, was found to disrupt neurotransmission and impair hippocampal synaptic plasticity, thereby contributing to cognitive decline (Chun et al., 2020).

Targeting astrocytic urea cycle-related mechanisms may hold therapeutic potential for mitigating cognitive deficits in AD. Ju et al. (2022) targeted ODC1 to avoid disrupting the urea cycle, an essential detoxification pathway that promotes  $A\beta$  clearance. ODC1 inhibition prevented GABA overproduction and restored memory in mice with AD-linked pathology. Activation of the urea cycle in AD illustrates a context-dependent shift in astrocytic metabolism that also alters neurotransmission and cognition. Furthermore, the duality of the beneficial removal of  $A\beta$  with the subsequent detrimental effects of excess putrescine on neurotransmitter balance and memory emphasizes the complexity of astrocytic roles in disease. Understanding the precise mechanisms underlying the interplay between astrocytic urea cycle activity and cognitive decline in AD may inform therapeutic strategies aimed at preserving cognitive function while maintaining ammonia detoxification.

The relationship between astrocytes and the urea cycle represents a fascinating area of research with significant implications for brain metabolism and neurologic health. Elucidating the

precise mechanisms and regulation of these interactions may open new avenues for therapeutic interventions. Dysregulation of astrocyte–urea cycle axis has been implicated in several neurologic conditions, including hepatic encephalopathy, a neuropsychiatric disorder associated with liver dysfunction. Notably, metabolic activities in astrocytes and the expression of astrocytic metabolic and mitochondrial genes can be region-specific (Hasel et al., 2021), but it is not clear whether astrocyte metabolism in distinct brain regions responds differently to AD pathology.

Together, these studies suggest that astrocytes can disrupt cognitive function in disease and affect pathology in a context-dependent and dynamic manner through specific changes in neuroimmune and metabolic pathways that influence neurotransmission. There is a strong bidirectional relationship between immune responses and metabolism (Tannahill et al., 2013; O'Neill et al., 2016), which may converge on neural mechanisms underlying neurotransmission and cognitive processes. Further unraveling these glial-neuronal molecular networks may be crucial for better understanding and effectively treating neurocognitive disorders that involve neuroimmune and metabolic alterations.

In conclusion, astrocytes are increasingly recognized as active contributors to behavior and cognitive processes. As summarized in Figure 1, new studies have revealed how astrocytes regulate synaptic maturation in the visual cortex and dendritic integration in the hippocampus through context-dependent engagement of astrocytic connexins and endocannabinoid pathways, respectively, that affect visual perception and spatial memory (Fig. 1A,B). Moreover, in the amygdala, a subset of astrocytes were found to express OT receptors and selectively modulate anxiety-like behaviors and place preference, and astrocytes in the striatum were found to control synaptic activities through G<sub>i</sub>-coupled signaling and modulate attention, hyperactivity, and repetitive behaviors through multiple molecular mechanisms (Fig. 1C,D). In neuropathological conditions, changes in astrocyte functions can contribute to neurocognitive decline in a pathology-specific and context-dependent manner. In particular, dementia-associated A $\beta$  and TDP-43 proteinopathies were found to alter specific metabolic and neuroimmune pathways in hippocampal astrocytes that disrupted select aspects of neurotransmission (Fig. 1E,F). Future studies should continue to make use of advanced experimental approaches to gain further insights into the complex and diverse mechanisms by which astrocytes modulate neural signaling, plasticity, network activities, and behavior. Growing evidence points to astrocyte dysfunction in cognitive and behavioral impairments in a wide range of neurologic and neuropsychiatric disorders, suggesting that new therapeutic strategies that target astrocytes may be useful in the treatment of these disorders.

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