Symposium

Neuron–Glial Interactions: Implications for Plasticity, Behavior, and Cognition

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The traditional view of glial cells as mere supportive tissue has shifted, due to advances in technology and theoretical conceptualization, to include a diversity of other functions, such as regulation of complex behaviors. Astrocytes, the most abundant glial cells in the central nervous system (CNS), have been shown to modulate synaptic functions through gliotransmitter-mediated neurotransmitter reuptake, influencing neuronal signaling and behavioral functions. Contemporary studies further highlight astrocytes' involvement in complex cognitive functions. For instance, inhibiting astrocytes in the hippocampus can lead to memory deficits, suggesting their integral role in memory processes. Moreover, astrocytic calcium activity and astrocyte–neuron metabolic coupling have been linked to changes in synaptic strength and learning. Microglia, another type of glial cell, also extend beyond their supportive roles, contributing to learning and memory processes, with microglial reductions impacting these functions in a developmentally dependent manner. Oligodendrocytes, traditionally thought to have limited roles postdevelopment, are now recognized for their activity-dependent modulation of myelination and plasticity, thus influencing behavioral responses. Recent advancements in technology and computational modeling have expanded our understanding of glial functions, particularly how astrocytes influence neuronal circuits and behaviors. This review underscores the importance of glial cells in CNS functions and the need for further research to unravel the complexities of neuron–glia interactions, the impact of these interactions on brain functions, and potential implications for neurological diseases.

Introduction

In 1846, Rudolf Virchow used the term "Nervenkitt," or neuroglia, to describe nerve-glue–like connective substance where the nervous elements are embedded (Somjen, 1988). This conceptualization of glia as support tissue remained the prevalent view for over 100 years. Research studies in the past two decades have dramatically shifted this view providing growing evidence implicating glia in diverse metabolic and neurophysiological functions including regulation of neuronal cell numbers and migration, axon specification and growth, circuit-wide neuronal differentiation, synapse formation and pruning, synaptic communication and plasticity, ion homeostasis and neuro-glial-vascular coupling, and behavior (H. S. Lee et al., 2014; Perea et al., 2014b; Allen and Lyons, 2018). Drawing upon this knowledge, a broader role of glia in the central nervous system (CNS) has begun to emerge, pointing out these cells' regulatory role in complex, higher-order brain functions and behaviors (Wyart and Prendergast, 2019).

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Glia reconceptualized

The role of astrocytes

Among the different subtypes of glial cells, astrocytes are the most numerous glial cells in the CNS (Augusto-Oliveira et al., 2020). These star-shaped cells have received considerably more attention due to the advent of novel technologies for their manipulation and recording, which has facilitated a reconceptualization of their role in the brain (Halassa and Haydon, 2010; Oliveira et al., 2015). Astrocytes are directly connected to neuronal synapses, where they participate in modulation of synaptic functions through the release of gliotransmitters (Kofuji and Araque, 2021) and the reuptake of neurotransmitters. Astrocytes are thought to contact every synapse in the brain, with a single astrocyte contacting perhaps 100,000 synapses. Increases in astrocyte calcium reflect their ability to take up glutamate and GABA at excitatory and inhibitory synapses via transporters, which also shapes neurotransmitter availability in space and time at these synapses. Astrocyte calcium signaling may promote the release of gliotransmitters, which are reported to have a wide range of effects on neurons, including modifying information processing in neural circuits (Araque et al., 2014; Harada et al., 2015). Furthermore, astrocyte calcium dynamics range from hundreds

of milliseconds to several seconds (Winship et al., 2007; X. Wang et al., 2009; Stobart et al., 2018), suggesting that these signals can reflect as well as influence neuronal activity and behavior on a wide range of timescales. These mechanisms have been postulated to underlie astrocytes' ability to modulate neuronal signaling (Allen, 2013; Perea et al., 2014a; Stogsdill and Eroglu, 2017), information processing across the brain, and behavioral functions (Durkee and Araque, 2019; Hwang et al., 2021); however, how they interact with neurons during cognition and specifically shape the activity of neuronal circuits is poorly understood.

An important mechanism implicated in astrocyte involvement in brain function is through their responses to neuromodulators, which act as key regulators of global brain states (S. H. Lee and Dan, 2012) in addition to having distinct signaling roles in goal-directed behaviors (Breton-Provencher et al., 2022). Astrocytes respond strongly to norepinephrine (NE; Bekar et al., 2008; Ding et al., 2013; Paukert et al., 2014; Horvat et al., 2016; Slezak et al., 2019), suggesting a specific role for astrocytes in NE-dependent learning and behavior. Furthermore, astrocytes are responsive to sensory stimuli (D. O. Wang et al., 2006; Stobart et al., 2018), motor activity (Paukert et al., 2014; Mu et al., 2019), and changes in brain state (Poskanzer and Yuste, 2016; Bojarskaite et al., 2020; Vaidyanathan et al., 2021), which are often critical features of learned behaviors.

However, despite the astrocyte involvement in diverse brain functions (Khakh and Deneen, 2019), it is unknown whether astrocytes exhibit the same forms of adaptive plasticity in response to sensory, learning, and social experiences. If they do, how do we measure it?

Because of astrocytes' complexity, there is no clear measurement for their activity or function. They are electrically inert, which prevents direct physiological readout. Calcium is used as a proxy for astrocyte activity, but unlike in neurons, the role of calcium in astrocytes is enigmatic. At the molecular level, the field only has a superficial understanding of how astrocytes respond to neuronal activity or even changes in brain states or experiences. Accordingly, there are no clear markers that signify a state of plasticity. Furthermore, astrocytes do not have a hallmark characteristic that can be readily measured like myelin in oligodendrocytes. Their one hallmark feature is their complex morphology, characterized by thousands of processes, but measuring astrocyte complexity can be challenging and, in many cases, it is difficult to interpret what altered morphology might mean. Despite these challenges, several recent studies have investigated how astrocytes respond to experiences. In the sections that follow the Introduction, the way astrocytes respond to sensory, social, and learning experiences will be described.

The role of microglia

Another type of glial cells, the microglia, has also been linked to complex roles that extend beyond being supportive tissue for neurons. Although the role of microglia in the modulation of behavior has been much less explored compared to astrocytes, microglia reductions can produce marked effects on learning and memory, depending on the developmental stage of the organism (Augusto-Oliveira et al., 2019). In a recent study that investigated microglial contribution to short-term memory processes in adult rat brains, ablation and subsequent repopulation of microglia in the hippocampus led to improvements in memory performance (De Luca et al., 2020). Furthermore, entrainment of gamma-frequency activity, which has been strongly linked to improvements in memory performance, altered gene expression in microglia. These findings demonstrate that microglial dynamics have an important role in selective enhancement of memory processes (Adaikkan and Tsai, 2020).

The role of the oligodendrocytes

For a long time, oligodendrocytes have been thought to have a limited role after the initial stages of development. However, oligodendrocytes can modulate plasticity in an activity-dependent manner (Noori et al., 2020), and activity-dependent myelination mediated by oligodendrocytes has been associated with the sustained perception of stimuli in complex behavioral paradigms (Moore et al., 2020). The interplay between de- and remyelination that occurs during the process of learning a motor task further hints at the involvement of oligodendrocytes in complex behaviors (Bacmeister et al., 2020).

Neuronal–glial interactions

The interaction between neurons and glia at the homeostatic and functional levels has been documented for decades (Kettenmann and Ransom, 1988). Early studies indicated that membrane-potential oscillations in glial cells and neurons tend to synchronize in brain regions related to states of arousal, such as the locus ceruleus (Alvarez-Maubecin et al., 2000). The oscillatory dynamics resulting from neuron–glia interactions might be integral to plasticity processes and the mechanisms by which neuron–glia interactions participate in modulation of complex behaviors (Araque and Navarrete, 2010).

Given the expanding knowledge about the distinct roles of different types of glial cells in the brain (Fields et al., 2014; Jebelli et al., 2015), this review aims to highlight the recent advances in our understanding how neuron–glia interactions shape neuronal plasticity, diverse brain functions, and behaviors. The topics covered in the review coincide with those presented at a symposium at the 2024 meeting of the Society for Neuroscience. This symposium will showcase the latest research that uses state-of-the-art tools and technologies to manipulate and record neuronal and glial activity and computational modeling to expand our understanding on how neuron–glia interaction may influence cognitive functions and other complex behaviors. Although the focus of this review is on the role of astrocytes in neuron interactions and complex behaviors, we briefly reference other types of glial cells to recognize their importance.

Neuron–Astrocyte Interactions in Sensory Processing

Research has revealed that bidirectional interactions between neurons and glia are critical for the maturation of neural circuits (Kim et al., 2017; Allen and Lyons, 2018; Benfey et al., 2022). Early studies of visual cortex development using cats reared in the dark reported that mature appearance of the visual cortex (i.e., its circuitry and neuronal morphology) develops during a limited postnatal period under the influence of visual experience. Subsequent studies reported that compared with light-experienced animals, dark-reared animals show compromised glial cell proliferation (Gabbott et al., 1986) resulting in a reduced presence of the astroglial marker glial fibrillary acidic protein (GFAP; Stewart et al., 1986; Müller, 1990). These findings provided some of the first evidence suggesting that neuronal activity can influence astrocytic maturation in the visual cortex.

Additional studies of experience-dependent plasticity (EDP)-like changes in astrocytes have examined mouse somatosensory barrel cortex, which expresses a number of different EDP forms. For example, all-whisker deprivation in wild-type mice induced experience-dependent Hebbian depression accompanied by

homeostatic upregulation in layer 2/3 barrel cortex that was not observed in mutant mice (IP3R2−/−) lacking the astrocyte-expressed IP3 receptor subtypes (Butcher et al., 2022). Using a whisker deflection protocol and novel calcium indicators for simultaneous two-photon calcium imaging of cortical astrocytes and neurons in awake mice, (Stobart et al., 2018) described fast astrocytic responses that were independent of IP3R2-mediated signaling. This led to conclusions that rapid astrocyte-mediated signals actively participate in synaptic modulation and neurovascular coupling (Stobart et al., 2018).

Indeed, astrocytes have been shown to be responsive to sensory stimuli in multiple different brain regions and are often activated on the timescales similar to those of neighboring neurons. In vivo studies in the visual cortex have shown that astrocytes, like neurons, respond to visual stimuli with distinct spatial receptive fields and tuning to visual features (Schummers et al., 2008). Using two-photon calcium imaging of astrocyte and neuronal responses to visual stimuli in the ferret primary visual cortex, Schummers et al. (2008) showed that astrocytes exhibited stimulus-locked responses to visual gratings with receptive fields similar to those of neighboring neurons (Schummers et al., 2008). Additionally, astrocytes exhibited clear orientation selectivity, with the same preferred orientation as nearby neurons. Finally, blocking astrocyte glutamate transporters affected visually evoked activity in nearby neurons, indicating that astrocytes influence synaptic responses to visual stimuli and hence neuronal stimulus processing. Together, these data were the first to demonstrate that astrocytes can modulate neuronal responses and play an active role in neuronal information representation.

To further probe how astrocyte activity in visual cortex affects neuronal processing, Perea et al. (2014b) optogenetically photostimulated astrocytes in the primary visual cortex while recording nearby neurons. PV+ interneurons exhibited an increase in firing rate in response to astrocyte stimulation, while SOM+ and excitatory neurons had more variable changes in firing rate. PV+ neurons also showed increased visual responses and decreased orientation selectivity, while SOM+ and excitatory neurons again showed both increased and decreased visual responses and corresponding changes in orientation selectivity. Together these studies indicate that astrocyte signaling in the visual cortex influences neuronal integration during sensory information processing, with effects dependent on neuronal subtype. Interestingly, later studies showed that the strength of astrocyte responses to visual stimuli appears to be dependent on brain state, in that astrocyte response amplitude and pupil size were highly correlated (Slezak et al., 2019). Depleting NE inputs to the cortex using the toxin DSP-4 resulted in reduced amplitude of visual responses but did not affect the temporal dynamics of astrocyte responses to visual stimuli, suggesting that NE modulates astrocyte stimulus encoding (Slezak et al., 2019).

In studies investigating the role of astrocytes in olfactory sensory processing and mapping the lines of communication between olfactory neurons and astrocytes, mice were exposed to novel odors. This produced widespread changes in astrocyte transcriptomes, highlighted by a complete shift in the patterns of DNA binding by the Sox9 transcription factor. This shift in Sox9 DNA binding led to the identification of Slc22a3 as an odor-experience-dependent target gene of Sox9 that is induced in astrocytes after exposure to novel odors. Expanding upon these results, the authors reported that astrocytic Slc22a3 is required for olfactory detection and that Slc22a3 functions in part by enabling serotonin to be transported into the nucleus, where it binds histones and serves as an activating epigenetic mark to regulate astrocytic gene expression (Sardar et al., 2023). Among the genes and pathways that are subject to epigenetic regulation by histone serotonylation in astrocytes are key enzymes in the GABA synthesis pathway. Further analysis of these changes revealed the key roles for GABA release from olfactory bulb astrocytes in mediating adaptive responses to sensory input (Sardar et al., 2023). Taken together, these findings suggest that increased neuronal activity in response to sensory experiences can induce EDP-like responses in astrocytes which in turn integrate neural signaling necessary for sensory information processing.

Neuron–Astrocyte Interaction in Learning, Goal-Directed Behaviors, and Social Experiences

In addition to their role in sensory processing, recent work has demonstrated a critical role for astrocytes in learning and other complex behaviors (Padmashri et al., 2015; Delepine et al., 2023). Mice with attenuated astrocyte calcium signaling in motor cortical area M1 show deficits in a motor learning task (Padmashri et al., 2015). Furthermore, astrocytes show hypertrophy in rats that learn motor skills (Anderson et al., 1994). Using a lever push task that requires coordinated neuronal ensemble activity in the primary motor cortex (Peters et al., 2014), Delepine et al. (2023) investigated the contributions of astrocytes to motor learning and the corresponding neuronal ensemble activity in the primary motor cortex. Using astrocyte-specific knockdown of glucagon-like peptide-1 (GLT1) in the motor cortex, they showed that astrocyte uptake of extracellular glutamate is important for developing a stereotyped movement trajectory in a lever push task, but not for learning the cue–lever push association. However, expressing Gq protein-designer receptors exclusively activated by designer drugs (Gq-DREADDs) selectively in primary motor cortex astrocytes to disrupt astrocyte calcium signaling, affected the associatively conditioned hit rate response and response time, in addition to movement stereotypy. These data suggest that astrocytes play a role in motor learning through multiple distinct mechanisms. To evaluate how astrocyte signaling during motor learning influences neuronal activity, Delepine et al. (2023) recorded neuronal calcium activity during the task. During both astrocyte GLT1 inhibition and astrocyte Gq protein activation, neuronal population encoding of movement trajectory was decreased, indicating that astrocyte signaling mediates neuronal ensemble formation during motor learning.

Astrocytes respond to nearby neuronal activity but may also themselves integrate behaviorally relevant information. Astrocytes mediate switches in cortical state by regulating extracellular glutamate (Poskanzer and Yuste, 2016), and recent work indicates that astrocytes respond directly to NE to modulate cortical state (Reitman et al., 2023). Studies in zebrafish have shown that NE–astrocyte signaling modulates behavior as well (Mu et al., 2019). Zebrafish were put in a virtual environment with visual cues to mimic swimming forward. When the visual cues stopped, and swim attempts repeatedly failed to generate perceived movement, the zebrafish eventually stopped swimming. NE neurons encoded the mismatch between motor output and visual input and signaled to radial astrocytes. Radial astrocytes then accumulated the NE failure signals and eventually triggered a change in strategy (Mu et al., 2019). These data suggest that, through regulation of behavioral state, astrocytes themselves play a critical role in integrating neuromodulatory signals to motor learning relevant behaviors.

Astrocyte responses to neuromodulators may be a critical mechanism underlying their integrative function. Indeed, astrocytes

in the nucleus accumbens of the ventral striatum respond robustly to dopamine, and, remarkably, may activate a specific adenosine tri-phospahate (ATP) signaling pathway to depress presynaptic transmission at excitatory synapses (Corkrum et al., 2020). Recent work from the Sur lab has highlighted a critical role for NE signaling in reinforcement learning, such that high levels of NE release after a surprising outcome facilitates behavioral optimization (Breton-Provencher et al., 2022). Specifically, mice were trained in a go/no-go task to press a lever on go tones to receive a water reward and to refrain from pressing on no-go tones to avoid a mild air-puff punishment. When mice received the air-puff on false-alarm trials, they changed their behavior on the subsequent trial, so they performed more hits and fewer false alarms. This behavioral updating was mediated by NE signaling. When mice were presented with a surprising water reward, they changed their behavior on the next trial and performed more false alarms, suggesting that NE release modulates behavior in a context-specific manner (Breton-Provencher et al., 2022). The phasic NE activity following a surprising outcome lasts only milliseconds, while the effect of a trial outcome on the next trial requires that the signal persists for several seconds. Since astrocytes have been shown to respond strongly to NE to mediate cortical and behavioral state changes, we propose that astrocytes integrate and alter neuronal signals over longer timescales to facilitate behavioral optimization during reinforcement learning (Drummond et al., 2023). In line with this hypothesis, a recent review has suggested that astrocytes reconfigure neuronal circuits in a context-dependent manner (Murphy-Royal et al., 2023).

Further investigations of whether NE influences memory formation through its corresponding receptors expressed on astrocytes used a combination of virus-mediated, cell-specific knockdown approaches (Gao et al., 2016). These investigators have shown that hippocampal beta-2 noradrenergic receptors (β2Ars), specifically expressed on astrocytes, but not β1ARs, are required for hippocampal-mediated contextual fear memory consolidation—the process required to stabilize the initially fragile long-term memory (Gao et al., 2016). The β2Ars subtypes were also shown to be necessary for the learning-evoked release of lactate from astrocytes, which is necessary to support the neuronal molecular changes essential for long-term memory formation. In sum, from these studies, it emerged that critical mechanisms of long-term memory previously believed to directly act on neurons act instead on astrocytes and that astrocytic functions are necessary for the consolidation and long-term storage of memories (Alberini et al., 2018).

Furthermore, astrocytes have well-established roles in regulating hippocampal circuit function and its associated learning and memory processes (Adamsky et al., 2018; Huang et al., 2020). Learning experiences have been shown to activate ensembles of neurons called engrams (Goode et al., 2020; Josselyn and Tonegawa, 2020) and reactivation of these engrams can elicit memory recall (Tonegawa et al., 2015; Frankland et al., 2019; Luft et al., 2024). However, whether learning experiences activate ensembles of astrocytes that participate in memory recall is unknown. Using fear conditioning as an associative learning paradigm, a not-yet-published study by Williamson et al. showed that in a small subset of astrocytes, c-Fos is induced after fear conditioning. Conditional knock-out of c-Fos in astrocytes resulted in impaired learning and memory and circuit activity. In subsequent experiments, these authors created a suite of viral-based tools that enabled conditional tagging of c-Fos-expressing astrocytes after fear conditioning. Using these tools, a subset of astrocytes, termed learning-associated astrocytes (LAAs), was labeled. These LAAs were near engram neurons that exhibit elevated numbers of synapses. Using DREADD-based chemogenetics, it was found that reactivation of LAAs promotes memory recall in a novel context, suggesting that astrocytes themselves store memories. Additional experiments addressing the mechanisms of this phenomenon have found that knock-out of the astrocytes' transcription factor NFIA abolishes the capacity of LAAs to stimulate recall (Williamson et al., 2024). Altogether, these results implicate LAAs as a new form of plasticity that is sufficient to provoke memory recall.

Expanding efforts to unravel the role of glia in complex behaviors suggest that neuron–glia interaction also contributes to social experiences. Environmental manipulation studies using social deprivation and environmental enrichment paradigms show widespread effects on glia, neuronal activity, brain function, and cognitive ability (Robinson et al., 2008; Ferle et al., 2020; Curley and Champagne, 2023). For glia, evidence suggest that environmental enrichment promotes myelination (Forbes et al., 2020) while social deprivation impairs oligodendrocyte differentiation and myelination in the prefrontal cortex and leads to aberrant social interactions and working memory (Makinodan et al., 2012). However, how astrocytes respond and adapt to social experiences is not well understood. In a recent study by Cheng et al. (2023), juvenile social deprivation was shown to produce minor increases in calcium activity with no changes in astrocyte morphology. Subsequent experiments using single-cell RNA-Seq on the hippocampus revealed widespread molecular changes in astrocyte transcriptomes, highlighted by an increase in TRPA1 expression (Cheng et al., 2023). TRPA1 is a calcium channel that has previously been implicated in astrocyte roles in hippocampal circuit function (Shigetomi et al., 2011), though its role in astrocyte adaptation to social experience remains unknown. Pharmacological and genetic deletion of TRPA1 from astrocytes after social deprivation reversed cognitive deficits and hippocampal circuit impairment. Further studies revealed that hippocampal astrocytes in socially deprived mice release GABA via a TRPA1-dependent mechanism and that genetic inhibition of GABA production in astrocytes also restores cognitive function and hippocampal circuit activities after social deprivation. Together, the results of this study demonstrated that astrocyte function is tuned to social experience, where social deprivation provokes astrocytes to release GABA and thereby suppress hippocampal circuit function.

While the importance of astrocytes and neuron–glia interaction in complex behaviors is becoming increasingly evident, future studies are needed to evaluate the strong possibility that astrocytes act as integrators of stimulus and environmental information to facilitate complex learning processes, goal-directed behaviors, and social experiences.

The Active Cooperation between Astrocytes and Neurons in Long-Term Memory via Metabolic Coupling

Long-term memory formation, the ability to retain information over time about an experience, is a complex function that affects multiple behaviors and is an integral part of an individual's identity (Wilson and Ross, 2003). The understanding of the biological mechanisms underlying memory formation and processes has focused most extensively on neuronal mechanisms. However, neurons and glia have been documented to cooperate to mediate learning and memory.

Studies have provided evidence that the breakdown of astrocytic glycogen (in the adult brain glycogen is stored mainly in astrocytes), i.e., glycogenolysis, is an important mechanism involved in the formation of memories (O'Dowd et al., 1994; Gibbs et al., 2006; Alberini et al., 2018). Furthermore, astrocytic–neuronal metabolic coupling via the glycolysis product lactate was found to be critical in the hippocampus for the formation of episodic-like long-term memories in rats (Suzuki et al., 2011). Using an inhibitory avoidance learning task, it was observed that learning leads to an increase in the extracellular lactate levels in the rat hippocampus, hinting on the involvement of astrocytes in learning and memory. Further investigations showed that astrocytic glycogen breakdown in the hippocampus and lactate release from astrocytes are essential for long-term memory and for the maintenance of long-term potentiation of synaptic strength elicited in vivo but dispensable for short-term memory formation. Disrupting the expression of the astrocytic lactate monocarboxylate transporters 4 (MCT4) or MCT1 led to amnesia, which was rescued by L-lactate but not equicaloric concentration of glucose. Disrupting the expression of the neuronal lactate transporter MCT2 also led to memory impairment, which however was not affected by the administration of either L-lactate or glucose, suggesting that lactate import into neurons is necessary for long-term memory. Subsequent examination of molecular mechanisms of plasticity revealed that glycogenolysis and astrocytic lactate transporters are also critical for the induction of molecular changes accompanying memory consolidation, including the induction of phospho-CREB, ARC, and phospho-cofilin. Similar conclusions were reached by Newman et al. (2011) who provided evidence for a critical role of astrocyte–neuron lactate transport in a spatial working memory task.

Following up on these findings, Descalzi et al. (2019) investigated the nature of the function(s) supported by lactate in neurons. The Krebs cycle substrates pyruvate and ketone body B3HB were shown to be able to functionally replace lactate in rescuing memory impairment caused by inhibition of glycogenolysis or expression knockdown of glia MCTs 1 and 4 in the dorsal hippocampus of rats. In contrast, neither metabolite was able to rescue memory impairment produced by expression knockdown of the neuronal MCT2, suggesting that a critical role of astrocytic lactate is to provide energy for neuronal responses required for long-term memory (Descalzi et al., 2019). Given that de novo protein synthesis—one of the hallmark mechanisms required for long-term memory formation, is an energy-intensive cellular process (Buttgereit and Brand, 1995; Sutton and Schuman, 2006; Costa-Mattioli et al., 2009; D. O. Wang et al., 2009; Richter and Klann, 2009; Topisirovic and Sonenberg, 2011), Descalzi et al. (2019) subsequently asked whether lactate fuels energy required to support learning-induced de novo protein synthesis. They found that lactate or pyruvate is important for learning-induced de novo mRNA translation in both excitatory and inhibitory neurons and for the induced expression of neuronal ARC/ARG3.1. However, these findings did not exclude the possibility that astrocytic–neuronal lactate coupling plays additional critical roles in long-term memory formation, e.g., by regulating redox or cellular signaling through direct activation of the G-protein-coupled lactate receptor GPR81/HCAR1, prostaglandin modulation, cerebral vasoconstriction and vasodilation, or other mechanisms. Altogether, these studies suggested that cooperative molecular mechanisms, working across multiple cell types, i.e., astrocytes and neurons, might server as key biological substrates for complex behavioral responses such as memory formation.

In light of the role of neuron–glia interaction in memory formation, an open question was how the astrocytic and neuronal metabolism changes over development, influence memory processes when the consumption of energy and glucose in the brain is remarkably higher compared with adult. The extremely high energy requirement during development (Kuzawa et al., 2014) likely reflects the energetic costs associated with developmental structural changes, including cell proliferation, migration, differentiation, axonal growth, and refinement of connections (Agathocleous and Harris, 2009; Magistretti and Allaman, 2015; Agostini et al., 2016; Vaarmann et al., 2016) which all can influence learning and memory. Yet, whether and how the increased energy needs of the young brain reflect experience-dependent processes and astrocyte-mediated metabolic changes in response to learning and in memory formation in the juvenile brain was unknown.

Given that formation of episodic-like memories in adult animals requires glycogenolysis and the delivery of astrocytic-derived lactate into neurons in the hippocampus, Cruz et al. (2022) investigated whether similar mechanisms underlie learning and memory in the hippocampus of juvenile rats. Using an inhibitory avoidance learning paradigm, they showed that the juvenile rats, as compared with adult rats, have significantly higher mRNA levels of several glucose metabolism enzymes, higher levels of the monocarboxylate transporters MCT1 and MCT4, and higher levels of the glucose transporters endothelial-GLUT1 and GLUT3 proteins. Furthermore, relative to adults, long-term episodic memory formation in juvenile animals needed significantly higher rates of aerobic glycolysis and astrocytic–neuronal lactate coupling in the hippocampus. Only juvenile but not adult long-term memory formation recruited GLUT3 and neuronal 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3)—a powerful stimulator of glycolysis. In addition, the juvenile hippocampus was found to differentially engage the direct transport of glucose into neurons (Cruz et al., 2022). In sum, these results indicated that glucose metabolism regulation greatly shifts as the brain matures, and, while the adult hippocampus preferentially employed glycogenolysis and astrocyte–neuronal lactate-mediated coupling, the juvenile hippocampus selectively required higher astrocyte–neuronal lactate transport and the direct neuronal glucose transport relying upon glycolytic enzyme PFKFB3 in neurons (Cruz et al., 2022).

These studies provided important evidence addressing the long debated on how the brain regulates the use of glucose to fuel its functions, and particularly whether glucose is directly consumed by all brain cell types, as classically it has been thought, or whether the variety of brain cell types differentially regulate glucose metabolism pathways and the use of different energy substrates including glycogen and lactate (Chih and Roberts, 2003; Aubert et al., 2005; Dienel and Hertz, 2005; Dienel, 2012, 2013; Pellerin and Magistretti, 2012; Alberini and Travaglia, 2017; Rich et al., 2019). Altogether these findings underscore the importance of further research about experience-induced metabolic regulation and investigating underlying mechanisms by which glia–neuron interactions regulate behavioral functions in health and in diseases.

Computational Modeling of Neuron–Astrocyte Interactions Predicts Astrocytic Calcium Involvement in Spike-Timing–Dependent Plasticity

In recent years, computational modeling of astrocytic activity has increasingly been used to study the various roles of astrocytes in brain functions (Manninen et al., 2018a,b, 2023; Linne et al.,

2022). Models of astrocytic function have mainly been of four types. Initially, single-astrocyte and astrocyte network models were developed, but lately, the focus has shifted to neuron–astrocyte interaction models, including single-synapse and network models (Fig. 1*A*). These models have helped us understand the combined aspects of various mechanisms underlying different brain functions and dysfunctions, test hypotheses easily, and guide experimental studies. Despite the development of almost 150 models for astrocytic calcium signaling by 2020, the advancement of astrocyte models still lags that of neuron models. Much work is needed to make these in silico models more biologically relevant by incorporating additional mechanisms beyond the typically modeled ones. Ideally, these models should incorporate the multiple mechanisms that regulate calcium transport through the plasma membrane, and the mechanisms through which cytosolic calcium levels are regulated intracellularly.

Among the intracellular calcium mechanisms, almost all the astrocyte models focus primarily on modeling astrocytic IP3-dependent calcium-induced calcium release (CICR) via IP_3 receptors from the endoplasmic reticulum (ER), Sarco/ER calcium-ATPase (SERCA), and leakage from the ER to the cytosol (Fig. 1*B*). Other intracellular calcium mechanisms in astrocytes, such as calcium buffers, calcium diffusion, ryanodine receptors (RyRs), intracellular diacylglycerol (DAG), and protein kinase C (PKC)-related pathways, and mitochondrial calcium mechanisms, including mitochondrial calcium uniporter (MCU) and sodium-calcium exchanger (NCX), are less frequently incorporated in astrocyte models (Fig. 1*B*). Each of these calcium mechanisms is included in similar proportions of models across the four classes (Fig. 1*B*).

Various mechanisms for transporting calcium through the astrocyte plasma membrane are considered in some models across the four types described, but they are included in fewer than 40% of the models, and significantly less frequently than the most commonly used intracellular calcium mechanisms (Fig. 1*B*,*C*). On the other hand, a greater variety of plasma membrane mechanisms than intracellular mechanisms are included in the models. The modeled plasma-membrane calcium mechanisms include efflux, influx, capacitive calcium entry (CCE), gap junctions, neuronal membrane potential (V_m)-dependent

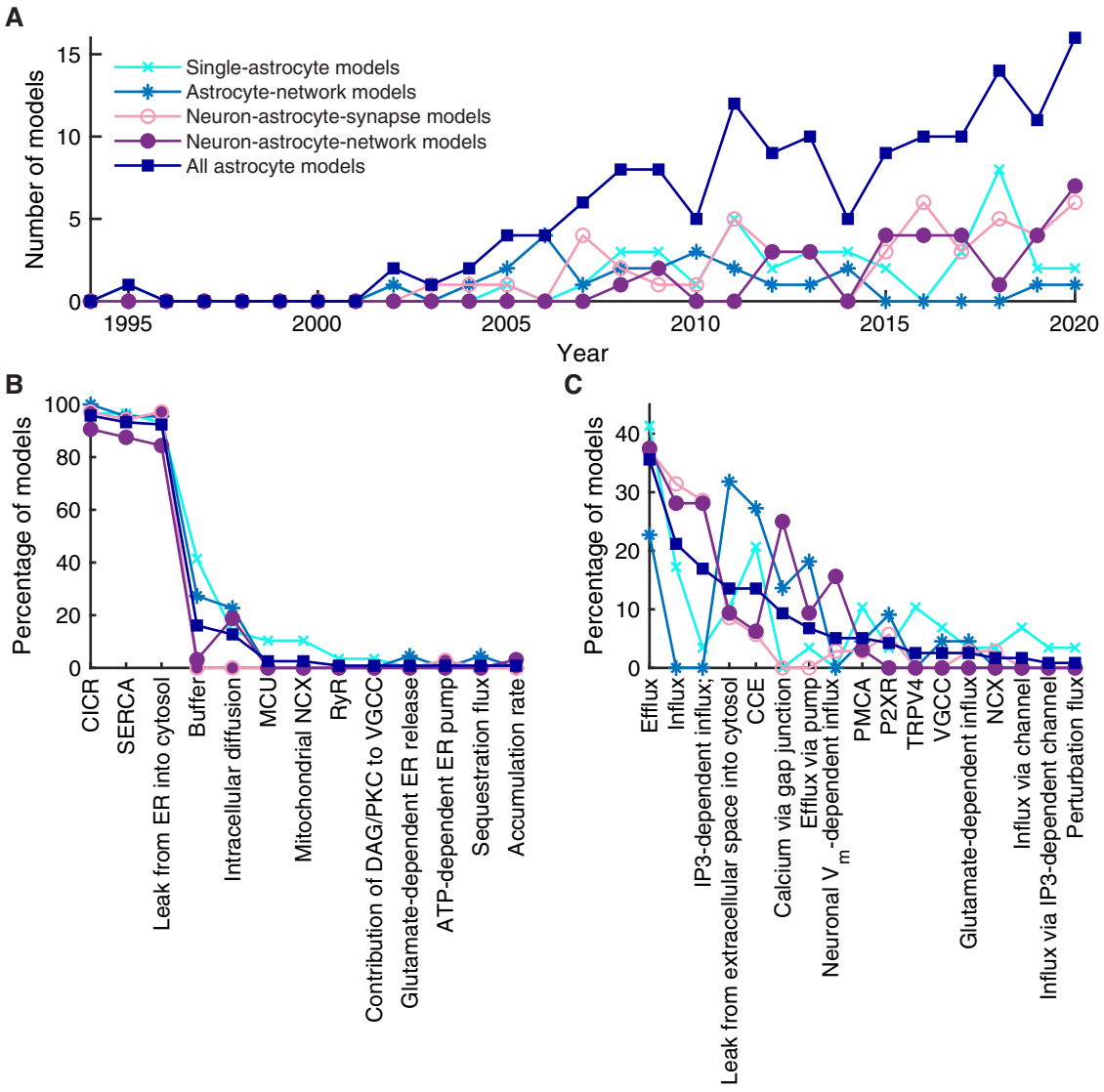

Figure 1. Computational astrocyte models developed for calcium signaling. ***A***, 147 models for astrocytes developed by 2020 can be divided into four groups: 41 single-astrocyte models, 24 astrocyte network models, 49 neuron–astrocyte-synapse models, and 33 neuron–astrocyte network models. ***B***, Percentage of models considering different intracellular calcium mechanisms in astrocytes. ***C***, Percentage of models considering different calcium mechanisms on the plasma membrane of astrocytes. Data gathered from the work by Manninen et al. (2018b, 2023).

influx, plasma membrane calcium-ATPase (PMCA), ionotropic purinergic ATP receptor (P2XR), transient receptor potential vanilloid 4 channel (TRPV4), and voltage-gated calcium channel (VGCC). Various combinations of plasma membrane calcium mechanisms are used in the models, indicating that single-astrocyte and astrocyte network models often focus on similar mechanisms. The same applies to neuron–astrocyte synapse and network models (Fig. 1C).

Specific examples of astrocyte models

To demonstrate the use of astrocyte models, we will focus on two synapse models specifically designed to understand spike-timing-dependent plasticity (STDP), which is sensitive to the temporal order and temporal difference between pre- and postsynaptic firing. The two synapse models developed to study STDP presented here are the models developed by De Pittà and Brunel (2016) and Manninen et al. (2020). Both models include three cells: two neurons and an astrocyte. Details for each model can be found in the studies by De Pittà and Brunel (2016), Manninen et al. (2018b, 2020), and Linne et al. (2022). Importantly, these models incorporate elements of astrocyte activation and astrocytic activation of neurons.

In the model by De Pittà and Brunel (2016), synaptic glutamate activates the astrocyte, while in the model by Manninen et al. (2020), the astrocyte is activated by the postsynaptic endocannabinoid 2-arachidonoylglycerol (2-AG). Both models incorporate similar astrocytic calcium mechanisms on the endoplasmic reticulum (ER) membrane, including IP3 receptors (CICR), SERCA, and leakage from the ER into the cytosol, of which De Pittà and Brunel (2016) use a more biologically detailed IP_3 equation than Manninen et al. (2020) by taking into account phospholipase Cβ- and Cδ-mediated production of IP3 and IP3 3-kinase- and inositol polyphosphatase 5-phosphatase-mediated degradation of IP3. Both models utilize the model by Tsodyks et al. (1998) for gliotransmitter glutamate release, where an increase in astrocytic calcium concentration beyond a certain threshold triggers the release of glutamate into the extrasynaptic space. This gliotransmitter glutamate can activate extrasynaptically located receptors: both the pre- and postsynaptic receptors in the model by De Pittà and Brunel (2016) and only presynaptic receptors in the model by Manninen et al. (2020). De Pittà and Brunel (2016) study the role of astrocyte-mediated presynaptic glutamate release and postsynaptic slow inward currents, while Manninen et al. (2020) focus on astrocyte-mediated presynaptic glutamate release.

The model by De Pittà and Brunel (2016) examines both short- and long-term forms of STDP in the hippocampus. The model behavior is validated against multiple experimental data, including recordings from cultures of dissociated rat hippocampal neurons by Bi and Poo (1998) and brain slices of rodent hippocampus by Wittenberg and Wang (2006). The model predicts that astrocyte-mediated presynaptic glutamate release and postsynaptic slow inward currents both influence STDP. Notably, gliotransmitter glutamate can switch potentiation into depression with the same stimulus protocol and vice versa.

The model by Manninen et al. (2020) investigates spike-timing-dependent long-term depression (t-LTD) at a L4 to L2/3 synapse in the developing somatosensory cortex. The model behavior is also validated against experimental data, such as recordings from rodent somatosensory cortex brain slices by Min and Nevian (2012) and Banerjee et al. (2014). This synapse model predicts how the dynamics of molecular mechanisms related to postsynaptic endocannabinoids, astrocytic calcium signaling, and presynaptic *N*-methyl-D-aspartate (NMDA) receptors and calcineurin signaling induce t-LTD. It confirms the wide time window of t-LTD induction shown by Banerjee et al. (2014). Additionally, the model verifies that astrocytic calcium signaling and presynaptic NMDA receptors are necessary for t-LTD induction, while postsynaptic NMDA receptors are not, as demonstrated by Min and Nevian (2012) and Banerjee et al. (2014) in their experimental studies.

These two models (De Pittà and Brunel, 2016; Manninen et al., 2020) suggest that astrocytes play a critical role in synaptic computation, guiding the development of brain circuits. However, there is a need for more reproducible, data-based in silico models at all levels—from morphologically detailed reaction-diffusion models (e.g., the model by Denizot et al., 2022) to neuron–astrocyte network models (e.g., the model by De Pittà and Brunel, 2022 for working memory) across different brain areas to better understand

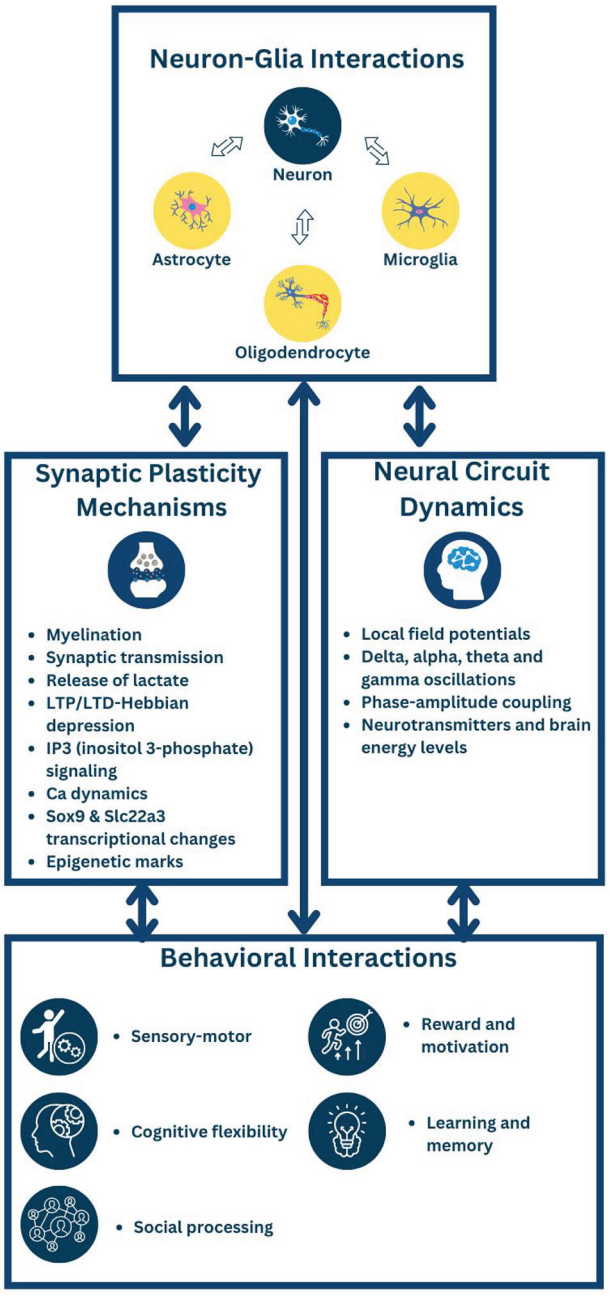

Figure 2. Summary figure that presents the contents included in this review paper.

astrocytic contributions in both health and disease. When developing astrocyte models, the latest experimental data, particularly from in vivo studies, should be used for testing and validation. Additionally, these models should be implemented using open-access simulation tools or with clearly written and commented code, and they should be properly documented. In the future, integrating morphological and biophysicochemical wet-lab data with computational models will enhance our understanding of the mechanisms underlying brain diseases. For this purpose, new tools are needed, such as the tool developed by Keto and Manninen (2023) to prepare astrocyte morphologies for reaction-diffusion simulations in different environments.

Conclusion

Recent advances in technologies and computational approaches in cellular and circuit-level neuroscience have transformed the historical view of glial cells as a supportive matrix for the other cell types within the CNS. The past two decades of research describe glia involvement in a diversity of brain functions, from modulation of neurotransmitter release to synaptic remodeling to regulation of neural circuits, functions, and behavior (Knowles et al., 2022; Bataveljic et al., 2024; Bollinger et al., 2024). In particular, it appears that astrocytes significantly contribute synaptogenesis, synaptic transmission, neuronal excitability, and angiogenesis and vascularization (Allen, 2014; Khakh and Deneen, 2019).

Despite significant strides in understanding the role of astrocytes, several questions remain open. One of them concerns the mechanisms by which astrocytes modulate local neurotransmission and behaviors, given that they do not necessitate rapid transmission of electrical signals as a form of communication with other cells. Thus far, assessments of astrocyte activity have been limited to indirect measurements, such as the intracellular calcium levels and the diffusion of second messengers like inositol 1,2,5-triphosphate (IP3), ATP, and diacylglycerol (Paniccia et al., 2022). Although these indirect readouts have implicated astrocytes in sensory processes (Schummers et al., 2008; Butcher et al., 2022), social behaviors (Cheng et al., 2023), goal-directed behaviors (Delepine et al., 2023), and learning (Kol et al., 2020), the exact neurophysiological mechanisms underlying astrocytic modulation of these behaviors await further investigation.

An additional open question is whether other glial cells use similar or different neurobiological mechanisms to modulate neuronal functions. Recent studies have suggested that these diverse mechanisms of interaction between astrocytes, neurons, and other cell types depend on coordinated activity patterns that support the regulation of brain functions and behaviors (Suzuki et al., 2011; Ung et al., 2020). Further studies interrogating how glia interacts with diverse cellular players across the brain may yield novel insights into how alterations in glia–neuron interactions might have an important role in pathogenesis of brain diseases (Khakh and Sofroniew, 2015).

Computational modeling approaches hold promise for addressing complex questions regarding the mechanisms of astrocytic signaling (Manninen et al., 2018b, 2023) in their interactions with neurons. Although there are currently >150 models of astrocytic calcium signaling, further refinement of the existing models and the development of new computational models will facilitate better understanding of the mechanisms by which astrocytes modulate synaptic functions, neural circuit activity, and different behaviors (De Pittà and Brunel, 2016; Manninen et al., 2020).

In summary, future research on the role of glia in the brain could help address challenges such as the following: (1) the complexity of the glia interactions with other cell subtypes, (2) the mechanisms that underlie glia–neuron interactions in brain functions and behavior, (3) the heterogeneity of glial cells and their functional roles throughout development, (4) further development of the existing technologies to image and manipulate glial cell interactions in vivo, (5) refinement of computational models of glia functional roles in the brain, and (6) the translation of basic neuroscience findings (see Fig. 2 for a summary schematic).

In conclusion, ongoing research on glial cells and their interaction with neuronal cells in regulation of complex behavior is transforming previously accepted conceptions of their role in the brain. Continuing advances in experimental and computational approaches are poised to provide better understanding of the complexity of glial cells and their involvement in complex brain function in health and diseases.

References

Adaikkan C, Tsai LH (2020) Gamma entrainment: impact on neurocircuits, glia, and therapeutic opportunities. Trends Neurosci 43:24–41.
Adamsky A, et al. (2018) Astrocytic activation generates de novo neuronal potentiation and memory enhancement. Cell 174:59–71.e14.
Agathocleous M, Harris WA (2009) From progenitors to differentiated cells in the vertebrate retina. Annu Rev Cell Dev Biol 25:45–69.
Agostini M, Romeo F, Inoue S, Niklison-Chirou MV, Elia AJ, Dinsdale D, Morone N, Knight RA, Mak TW, Melino G (2016) Metabolic reprogramming during neuronal differentiation. Cell Death Differ 23:1502–1514.
Alberini CM, Cruz E, Descalzi G, Bessières B, Gao V (2018) Astrocyte glycogen and lactate: new insights into learning and memory mechanisms. Glia 66:1244–1262.
Alberini CM, Travaglia A (2017) Infantile amnesia: a critical period of learning to learn and remember. J Neurosci 37:5783–5795.
Allen NJ (2013) Role of glia in developmental synapse formation. Curr Opin Neurobiol 23:1027–1033.
Allen NJ (2014) Astrocyte regulation of synaptic behavior. Annu Rev Cell Dev Biol 30:439–463.
Allen NJ, Lyons DA (2018) Glia as architects of central nervous system formation and function. Science 362:181–185.
Alvarez-Maubecin V, Garcia-Hernandez F, Williams JT, Van Bockstaele EJ (2000) Functional coupling between neurons and glia. J Neurosci 20: 4091–4098.
Anderson BJ, Li X, Alcantara AA, Isaacs KR, Black JE, Greenough WT (1994) Glial hypertrophy is associated with synaptogenesis following motor-skill learning, but not with angiogenesis following exercise. Glia 11:73–80.
Araque A, Carmignoto G, Haydon PG, Oliet SH, Robitaille R, Volterra A (2014) Gliotransmitters travel in time and space. Neuron 81:728–739.
Araque A, Navarrete M (2010) Glial cells in neuronal network function. Philos Trans R Soc Lond B Biol Sci 365:2375–2381.
Aubert A, Costalat R, Magistretti PJ, Pellerin L (2005) Brain lactate kinetics: modeling evidence for neuronal lactate uptake upon activation. Proc Natl Acad Sci U S A 102:16448–16453.
Augusto-Oliveira M, Arrifano GP, Lopes-Araújo A, Santos-Sacramento L, Takeda PY, Anthony DC, Malva JO, Crespo-Lopez ME (2019) What do microglia really do in healthy adult brain? Cells 8:1293.
Augusto-Oliveira M, Arrifano GP, Takeda PY, Lopes-Araújo A, Santos-Sacramento L, Anthony DC, Verkhratsky A, Crespo-Lopez ME (2020) Astroglia-specific contributions to the regulation of synapses, cognition and behaviour. Neurosci Biobehav Rev 118:331–357.
Bacmeister CM, Barr HJ, McClain CR, Thornton MA, Nettles D, Welle CG, Hughes EG (2020) Motor learning promotes remyelination via new and surviving oligodendrocytes. Nat Neurosci 23:819–831.
Banerjee A, González-Rueda A, Sampaio-Baptista C, Paulsen O, Rodríguez-Moreno A (2014) Distinct mechanisms of spike timing-dependent LTD at vertical and horizontal inputs onto L2/3 pyramidal neurons in mouse barrel cortex. Physiol Rep 2:e00271.
Bataveljic D, Pivonkova H, de Concini V, Hebert B, Ezan P, Briault S, Bemelmans AP, Pichon J, Menuet A, Rouach N (2024) Astroglial Kir4.1

potassium channel deficit drives neuronal hyperexcitability and behavioral defects in Fragile X syndrome mouse model. Nat Commun 15:3583.
Bekar LK, He W, Nedergaard M (2008) Locus coeruleus alpha-adrenergic-mediated activation of cortical astrocytes in vivo. Cereb Cortex 18: 2789–2795.
Benfey N, Foubert D, Ruthazer ES (2022) Glia regulate the development, function, and plasticity of the visual system from retina to cortex. Front Neural Circuits 16:826664.
Bi GQ, Poo MM (1998) Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. J Neurosci 18:10464–10472.
Bojarskaite L, et al. (2020) Astrocytic Ca(2+) signaling is reduced during sleep and is involved in the regulation of slow wave sleep. Nat Commun 11: 3240.
Bollinger JL, Johnsamuel S, Vollmer LL, Kuhn AM, Wohleb ES (2024) Stress-induced dysfunction of neurovascular astrocytes contributes to sex-specific behavioral deficits. bioRxiv.
Breton-Provencher V, Drummond GT, Feng J, Li Y, Sur M (2022) Spatiotemporal dynamics of noradrenaline during learned behaviour. Nature 606:732–738.
Butcher JB, et al. (2022) A requirement for astrocyte IP(3)R2 signaling for whisker experience-dependent depression and homeostatic upregulation in the mouse barrel cortex. Front Cell Neurosci 16:905285.
Buttgereit F, Brand MD (1995) A hierarchy of ATP-consuming processes in mammalian cells. Biochem J 312:163–167.
Cheng YT, Woo J, Luna-Figueroa E, Maleki E, Harmanci AS, Deneen B (2023) Social deprivation induces astrocytic TRPA1-GABA suppression of hippocampal circuits. Neuron 111:1301–1315.e5.
Chih CP, Roberts EL Jr (2003) Energy substrates for neurons during neural activity: a critical review of the astrocyte-neuron lactate shuttle hypothesis. J Cereb Blood Flow Metab 23:1263–1281.
Corkrum M, et al. (2020) Dopamine-evoked synaptic regulation in the nucleus accumbens requires astrocyte activity. Neuron 105:1036–1047.e5.
Costa-Mattioli M, Sossin WS, Klann E, Sonenberg N (2009) Translational control of long-lasting synaptic plasticity and memory. Neuron 61: 10–26.
Cruz E, Bessières B, Magistretti P, Alberini CM (2022) Differential role of neuronal glucose and PFKFB3 in memory formation during development. Glia 70:2207–2231.
Curley JP, Champagne FA (2023) Shaping the development of complex social behavior. Ann N Y Acad Sci 1530:46–63.
Delepine C, Shih J, Li K, Gaudeaux P, Sur M (2023) Differential effects of astrocyte manipulations on learned motor behavior and neuronal ensembles in the motor cortex. J Neurosci 43:2696–2713.
De Luca SN, Soch A, Sominsky L, Nguyen TX, Bosakhar A, Spencer SJ (2020) Glial remodeling enhances short-term memory performance in Wistar rats. J Neuroinflammation 17:52.
Denizot A, Arizono M, Nägerl UV, Berry H, De Schutter E (2022) Control of Ca(2+) signals by astrocyte nanoscale morphology at tripartite synapses. Glia 70:2378–2391.
De Pittà M, Brunel N (2016) Modulation of synaptic plasticity by glutamatergic gliotransmission: a modeling study. Neural Plast 2016:7607924.
De Pittà M, Brunel N (2022) Multiple forms of working memory emerge from synapse-astrocyte interactions in a neuron-glia network model. Proc Natl Acad Sci U S A 119:e2207912119.
Descalzi G, Gao V, Steinman MQ, Suzuki A, Alberini CM (2019) Lactate from astrocytes fuels learning-induced mRNA translation in excitatory and inhibitory neurons. Commun Biol 2:247.
Dienel GA (2012) Brain lactate metabolism: the discoveries and the controversies. J Cereb Blood Flow Metab 32:1107–1138.
Dienel GA (2013) Astrocytic energetics during excitatory neurotransmission: what are contributions of glutamate oxidation and glycolysis? Neurochem Int 63:244–258.
Dienel GA, Hertz L (2005) Astrocytic contributions to bioenergetics of cerebral ischemia. Glia 50:362–388.
Ding F, O'Donnell J, Thrane AS, Zeppenfeld D, Kang H, Xie L, Wang F, Nedergaard M (2013) α1-Adrenergic receptors mediate coordinated Ca2+ signaling of cortical astrocytes in awake, behaving mice. Cell Calcium 54:387–394.
Drummond GT, Shih J, Celotto M, Osako Y, Leow Y-N, Park J, Breton-Provencher V, Panzeri S, Sur M (2023) Effects of locus coeruleus norepinephrine signaling on cortical neurons, neuronal populations, and astrocytes during reinforcement learning. Society for Neuroscience, Washington D.C.
Durkee CA, Araque A (2019) Diversity and specificity of astrocyte-neuron communication. Neuroscience 396:73–78.
Ferle V, Repouskou A, Aspiotis G, Raftogianni A, Chrousos G, Stylianopoulou F, Stamatakis A (2020) Synergistic effects of early life mild adversity and chronic social defeat on rat brain microglia and cytokines. Physiol Behav 215:112791.
Fields RD, Araque A, Johansen-Berg H, Lim SS, Lynch G, Nave KA, Nedergaard M, Perez R, Sejnowski T, Wake H (2014) Glial biology in learning and cognition. Neuroscientist 20:426–431.
Forbes TA, Goldstein EZ, Dupree JL, Jablonska B, Scafidi J, Adams KL, Imamura Y, Hashimoto-Torii K, Gallo V (2020) Environmental enrichment ameliorates perinatal brain injury and promotes functional white matter recovery. Nat Commun 11:964.
Frankland PW, Josselyn SA, Kohler S (2019) The neurobiological foundation of memory retrieval. Nat Neurosci 22:1576–1585.
Gabbott PL, Stewart MG, Rose SP (1986) The quantitative effects of dark-rearing and light exposure on the laminar composition and depth distribution of neurons and glia in the visual cortex (area 17) of the rat. Exp Brain Res 64:225–232.
Gao V, Suzuki A, Magistretti PJ, Lengacher S, Pollonini G, Steinman MQ, Alberini CM (2016) Astrocytic β2-adrenergic receptors mediate hippocampal long-term memory consolidation. Proc Natl Acad Sci U S A 113:8526–8531.
Gibbs ME, Anderson DG, Hertz L (2006) Inhibition of glycogenolysis in astrocytes interrupts memory consolidation in young chickens. Glia 54: 214–222.
Goode TD, Tanaka KZ, Sahay A, McHugh TJ (2020) An integrated index: engrams, place cells, and hippocampal memory. Neuron 107:805–820.
Halassa MM, Haydon PG (2010) Integrated brain circuits: astrocytic networks modulate neuronal activity and behavior. Annu Rev Physiol 72: 335–355.
Harada K, Kamiya T, Tsuboi T (2015) Gliotransmitter release from astrocytes: functional, developmental, and pathological implications in the brain. Front Neurosci 9:499.
Horvat A, Zorec R, Vardjan N (2016) Adrenergic stimulation of single rat astrocytes results in distinct temporal changes in intracellular Ca(2+) and cAMP-dependent PKA responses. Cell Calcium 59:156–163.
Huang AY, Woo J, Sardar D, Lozzi B, Bosquez Huerta NA, Lin CJ, Felice D, Jain A, Paulucci-Holthauzen A, Deneen B (2020) Region-specific transcriptional control of astrocyte function oversees local circuit activities. Neuron 106:992–1008.e9.
Hwang SN, Lee JS, Seo K, Lee H (2021) Astrocytic regulation of neural circuits underlying behaviors. Cells 10:296.
Jebelli J, Su W, Hopkins S, Pocock J, Garden GA (2015) Glia: guardians, gluttons, or guides for the maintenance of neuronal connectivity? Ann N Y Acad Sci 1351:1–10.
Josselyn SA, Tonegawa S (2020) Memory engrams: recalling the past and imagining the future. Science 367:eaaw4325.
Keto L, Manninen T (2023) Cellremorph: a toolkit for transforming, selecting, and slicing 3D cell structures on the road to morphologically detailed astrocyte simulations. Neuroinformatics 21:483–500.
Kettenmann H, Ransom BR (1988) Electrical coupling between astrocytes and between oligodendrocytes studied in mammalian cell cultures. Glia 1:64–73.
Khakh BS, Deneen B (2019) The emerging nature of astrocyte diversity. Annu Rev Neurosci 42:187–207.
Khakh BS, Sofroniew MV (2015) Diversity of astrocyte functions and phenotypes in neural circuits. Nat Neurosci 18:942–952.
Kim SK, Nabekura J, Koizumi S (2017) Astrocyte-mediated synapse remodeling in the pathological brain. Glia 65:1719–1727.
Knowles JK, et al. (2022) Maladaptive myelination promotes generalized epilepsy progression. Nat Neurosci 25:596–606.
Kofuji P, Araque A (2021) Astrocytes and behavior. Annu Rev Neurosci 44: 49–67.
Kol A, Adamsky A, Groysman M, Kreisel T, London M, Goshen I (2020) Astrocytes contribute to remote memory formation by modulating hippocampal-cortical communication during learning. Nat Neurosci 23: 1229–1239.
Kuzawa CW, Chugani HT, Grossman LI, Lipovich L, Muzik O, Hof PR, Wildman DE, Sherwood CC, Leonard WR, Lange N (2014) Metabolic

costs and evolutionary implications of human brain development. Proc Natl Acad Sci U S A 111:13010–13015.
Lee HS, et al. (2014) Astrocytes contribute to gamma oscillations and recognition memory. Proc Natl Acad Sci U S A 111:E3343–E3352.
Lee SH, Dan Y (2012) Neuromodulation of brain states. Neuron 76:209–222.
Linne ML, Aćimović J, Saudargiene A, Manninen T (2022) Neuron-glia interactions and brain circuits. Adv Exp Med Biol 1359:87–103.
Luft JG, Popik B, Gonçalves DA, Cruz FC, de Oliveira Alvares L (2024) Distinct engrams control fear and extinction memory. Hippocampus 34:230–240.
Magistretti PJ, Allaman I (2015) A cellular perspective on brain energy metabolism and functional imaging. Neuron 86:883–901.
Makinodan M, Rosen KM, Ito S, Corfas G (2012) A critical period for social experience-dependent oligodendrocyte maturation and myelination. Science 337:1357–1360.
Manninen T, Aćimović J, Havela R, Teppola H, Linne ML (2018a) Challenges in reproducibility, replicability, and comparability of computational models and tools for neuronal and glial networks, cells, and subcellular structures. Front Neuroinform 12:20.
Manninen T, Aćimović J, Linne ML (2023) Analysis of network models with neuron-astrocyte interactions. Neuroinformatics 21:375–406.
Manninen T, Havela R, Linne ML (2018b) Computational models for calcium-mediated astrocyte functions. Front Comput Neurosci 12:14.
Manninen T, Saudargiene A, Linne ML (2020) Astrocyte-mediated spike-timing-dependent long-term depression modulates synaptic properties in the developing cortex. PLoS Comput Biol 16:e1008360.
Min R, Nevian T (2012) Astrocyte signaling controls spike timing-dependent depression at neocortical synapses. Nat Neurosci 15:746–753.
Moore S, et al. (2020) A role of oligodendrocytes in information processing. Nat Commun 11:5497.
Mu Y, Bennett DV, Rubinov M, Narayan S, Yang CT, Tanimoto M, Mensh BD, Looger LL, Ahrens MB (2019) Glia accumulate evidence that actions are futile and suppress unsuccessful behavior. Cell 178:27–43.e19.
Müller CM (1990) Dark-rearing retards the maturation of astrocytes in restricted layers of cat visual cortex. Glia 3:487–494.
Murphy-Royal C, Ching S, Papouin T (2023) A conceptual framework for astrocyte function. Nat Neurosci 26:1848–1856.
Newman LA, Korol DL, Gold PE (2011) Lactate produced by glycogenolysis in astrocytes regulates memory processing. PLoS One 6:e28427.
Noori R, Park D, Griffiths JD, Bells S, Frankland PW, Mabbott D, Lefebvre J (2020) Activity-dependent myelination: a glial mechanism of oscillatory self-organization in large-scale brain networks. Proc Natl Acad Sci U S A 117:13227–13237.
O'Dowd BS, Gibbs ME, Sedman GL, Ng KT (1994) Astrocytes implicated in the energizing of intermediate memory processes in neonate chicks. Brain Res Cogn Brain Res 2:93–102.
Oliveira JF, Sardinha VM, Guerra-Gomes S, Araque A, Sousa N (2015) Do stars govern our actions? Astrocyte involvement in rodent behavior. Trends Neurosci 38:535–549.
Padmashri R, Suresh A, Boska MD, Dunaevsky A (2015) Motor-skill learning is dependent on astrocytic activity. Neural Plast 2015:938023.
Paniccia JE, Otis JM, Scofield MD (2022) Looking to the stars for answers: strategies for determining how astrocytes influence neuronal activity. Comput Struct Biotechnol J 20:4146–4156.
Paukert M, Agarwal A, Cha J, Doze VA, Kang JU, Bergles DE (2014) Norepinephrine controls astroglial responsiveness to local circuit activity. Neuron 82:1263–1270.
Pellerin L, Magistretti PJ (2012) Sweet sixteen for ANLS. J Cereb Blood Flow Metab 32:1152–1166.
Perea G, Sur M, Araque A (2014a) Neuron-glia networks: integral gear of brain function. Front Cell Neurosci 8:378.
Perea G, Yang A, Boyden ES, Sur M (2014b) Optogenetic astrocyte activation modulates response selectivity of visual cortex neurons in vivo. Nat Commun 5:3262.
Peters AJ, Chen SX, Komiyama T (2014) Emergence of reproducible spatiotemporal activity during motor learning. Nature 510:263–267.
Poskanzer KE, Yuste R (2016) Astrocytes regulate cortical state switching in vivo. Proc Natl Acad Sci U S A 113:E2675–E2684.
Reitman ME, et al. (2023) Norepinephrine links astrocytic activity to regulation of cortical state. Nat Neurosci 26:579–593.
Rich LR, Harris W, Brown AM (2019) The role of brain glycogen in supporting physiological function. Front Neurosci 13:1176.
Richter JD, Klann E (2009) Making synaptic plasticity and memory last: mechanisms of translational regulation. Genes Dev 23:1–11.
Robinson GE, Fernald RD, Clayton DF (2008) Genes and social behavior. Science 322:896–900.
Sardar D, et al. (2023) Induction of astrocytic Slc22a3 regulates sensory processing through histone serotonylation. Science 380:eade0027.
Schummers J, Yu H, Sur M (2008) Tuned responses of astrocytes and their influence on hemodynamic signals in the visual cortex. Science 320:1638–1643.
Shigetomi E, Tong X, Kwan KY, Corey DP, Khakh BS (2011) TRPA1 channels regulate astrocyte resting calcium and inhibitory synapse efficacy through GAT-3. Nat Neurosci 15:70–80.
Slezak M, Kandler S, Van Veldhoven PP, Van den Haute C, Bonin V, Holt MG (2019) Distinct mechanisms for visual and motor-related astrocyte responses in mouse visual cortex. Curr Biol 29:3120–3127.e5.
Somjen GG (1988) Nervenkitt: notes on the history of the concept of neuroglia. Glia 1:2–9.
Stewart MG, Bourne RC, Gabbott PL (1986) Decreased levels of an astrocytic marker, glial fibrillary acidic protein, in the visual cortex of dark-reared rats: measurement by enzyme-linked immunosorbent assay. Neurosci Lett 63:147–152.
Stobart JL, Ferrari KD, Barrett MJP, Glück C, Stobart MJ, Zuend M, Weber B (2018) Cortical circuit activity evokes rapid astrocyte calcium signals on a similar timescale to neurons. Neuron 98:726–735.e4.
Stogsdill JA, Eroglu C (2017) The interplay between neurons and glia in synapse development and plasticity. Curr Opin Neurobiol 42:1–8.
Sutton MA, Schuman EM (2006) Dendritic protein synthesis, synaptic plasticity, and memory. Cell 127:49–58.
Suzuki A, Stern SA, Bozdagi O, Huntley GW, Walker RH, Magistretti PJ, Alberini CM (2011) Astrocyte-neuron lactate transport is required for long-term memory formation. Cell 144:810–823.
Tonegawa S, Pignatelli M, Roy DS, Ryan TJ (2015) Memory engram storage and retrieval. Curr Opin Neurobiol 35:101–109.
Topisirovic I, Sonenberg N (2011) mRNA translation and energy metabolism in cancer: the role of the MAPK and mTORC1 pathways. Cold Spring Harb Symp Quant Biol 76:355–367.
Tsodyks M, Pawelzik K, Markram H (1998) Neural networks with dynamic synapses. Neural Comput 10:821–835.
Ung K, Tepe B, Pekarek B, Arenkiel BR, Deneen B (2020) Parallel astrocyte calcium signaling modulates olfactory bulb responses. J Neurosci Res 98:1605–1618.
Vaarmann A, et al. (2016) Mitochondrial biogenesis is required for axonal growth. Development 143:1981–1992.
Vaidyanathan TV, Collard M, Yokoyama S, Reitman ME, Poskanzer KE (2021) Cortical astrocytes independently regulate sleep depth and duration via separate GPCR pathways. Elife 10:e63329.
Wang DO, Kim SM, Zhao Y, Hwang H, Miura SK, Sossin WS, Martin KC (2009) Synapse- and stimulus-specific local translation during long-term neuronal plasticity. Science 324:1536–1540.
Wang X, Lou N, Xu Q, Tian GF, Peng WG, Han X, Kang J, Takano T, Nedergaard M (2006) Astrocytic Ca2+ signaling evoked by sensory stimulation in vivo. Nat Neurosci 9:816–823.
Wang X, Takano T, Nedergaard M (2009) Astrocytic calcium signaling: mechanism and implications for functional brain imaging. Methods Mol Biol 489:93–109.
Williamson MR, Kwon W, Woo J, Ko Y, Maleki E, Yu K, Murali S, Sardar D, Deneen B (2024) Learning-associated astrocyte ensembles regulate memory recall. Under review.
Wilson AE, Ross M (2003) The identity function of autobiographical memory: time is on our side. Memory 11:137–149.
Winship IR, Plaa N, Murphy TH (2007) Rapid astrocyte calcium signals correlate with neuronal activity and onset of the hemodynamic response in vivo. J Neurosci 27:6268–6272.
Wittenberg GM, Wang SS (2006) Malleability of spike-timing-dependent plasticity at the CA3-CA1 synapse. J Neurosci 26:6610–6617.
Wyart C, Prendergast A (2019) Glia: a gate controlling animal behavior? Curr Biol 29:R847–R850.