HHS Public Access

Author manuscript

Trends Neurosci. Author manuscript; available in PMC 2024 June 01.

Published in final edited form as:

Trends Neurosci. 2023 June ; 46(6): 418–425. doi:10.1016/j.tins.2023.03.003.

Astrocytes: integrators of arousal state and sensory context

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Abstract

The integration of external information with the internal state of the body is central to the survival of virtually every multicellular organism. Yet, a complete picture of the mechanisms that govern this process is lacking. In this article, we synthesize evidence demonstrating that astrocytes sense the momentary arousal state – through neuromodulator release – as well as the sensory inputs – through local synaptic activity – and respond to them with changes in Ca^{2+} signaling. We hypothesize that astrocytes integrate sensory signals with the internal state, and that this process is necessary for securing optimal behavior. Finally, we argue that dysfunctional astrocytic Ca^{2+} signaling could be an underlying factor in disorders characterized by disrupted sensory processing.

Keywords

Glial cells; calcium signaling; internal state; sensory processing; neuromodulation

How are external signals and internal state information merged in the brain?

The brain is constantly integrating signals conveying information about the inner states of the body with external sensory inputs from the outside world to produce appropriate, context-dependent behaviors [1–4]. This process ensures both efficient behavioral shifts when conditions change and selecting relevant information for memory consolidation to guide future behavior.

The current model for this integration process implicates that sensory information is encoded by fast and spatially constricted neuronal synaptic transmission, while internal state

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Declaration of Interests

The author declares no competing interests.

information is relayed brain-wide by slowly acting neuromodulators. In this Opinion article, we argue that astrocytes, an often-overlooked type of brain cell in systems neuroscience, also contribute to the integration of these two information sources, adding a new dimension to our understanding of how external and internal information is merged in the brain.

We first provide a short overview of the nature and characteristics of astrocytic calcium (Ca^{2+}) signals. Second, we present evidence, mainly from rodent models demonstrating that astrocytes respond to both arousal and sensory inputs with changes in their Ca^{2+} signaling. Next, we formulate a general hypothesis about the integration of arousal and sensory information in astrocytes. Finally, we discuss this hypothesis in light of recent data and outline outstanding questions and future experiments which can extend our knowledge about the role of astrocytes in cognitive functions.

Astrocytic Ca^{2+} signals

Astrocytic Ca^{2+} signaling has been characterized in a wide range of species and preparations, including human tissue [5], ferrets [6], rodents [7–15], zebrafish [16], and flies [17,18]. Surges in intracellular Ca^{2+} concentration are predominantly caused by Ca^{2+} release from internal stores, triggered by G-protein-coupled receptor-mediated activation of the inositol triphosphate (IP_3) pathway. However, other IP_3-independent mechanisms such as Ca^{2+}-permeable ion channels, exchangers, and transporters are likely also involved (reviewed in [19,20]). The spatiotemporal organization of Ca^{2+} signals in astrocytes is diverse (reviewed in [20–22]): Spatially, events range from local responses in fine astrocytic processes to responses extending throughout the cell, with the latter often occurring in many astrocytes in parallel [8–10,23] or spreading from one astrocyte to another [12,24]. Similarly, the time course of responses varies notably, from hundreds of milliseconds to minutes. Unfortunately, understanding of the underlying mechanisms and functional role of this diversity is still very limited. A growing body of literature suggests that astrocytic Ca^{2+} signaling regulates neuronal activity and behavior, and the phylogenetic conservation of Ca^{2+} signaling in astrocytes suggests that this signaling has important functions. However, the question of when and why astrocytic Ca^{2+} signals are evoked remains to be answered. Interestingly, astrocytes express receptors for both neuromodulators and neurotransmitters [25], indicating they are able to sense changes in arousal state as well as sensory input.

Astrocytes signal arousal state

The ability of animals to interact with external events highly depends on their body's internal state, including their momentary arousal level [1–4] (Box 1).

In mammals, periods of heightened arousal correlate with increased noradrenaline (NA) and acetylcholine (ACh) signaling [26–28]. Recent *in vivo* experiments in awake mice have reignited research into NA-mediated astrocytic Ca^{2+} signaling [8,9], and there is strong evidence now supporting the notion that astrocytes reflect arousal changes by NA-driven global Ca^{2+} signaling [19–22,29], confirming early *ex vivo* data [30–32] and further evidenced by the cellular expression pattern of noradrenergic receptors [33,34]. Indeed, electrical or optogenetic stimulation of NA-producing locus coeruleus neurons leads to a

sharp increase in astrocytic Ca^{2+} in the somatosensory cortex of awake and anesthetized mice [23,35].

Astrocytic Ca^{2+} signaling has been investigated in both externally triggered (e.g., air-puff whisker stimulation, tail stimulation, or forced locomotion) and internally generated (e.g., spontaneous locomotion bouts) arousal-increasing contexts. Concretely, salient sensory stimulation [7–9,36–38] and self-initiated locomotion bouts [10,11,39,40] elicit NA-mediated Ca^{2+} signaling in large cortical astrocytic networks, through activation of the $alpha_1$ noradrenergic receptor. Although most studies on NA and astrocytic signaling have been done in rodents, there is evidence from zebrafish and drosophila to support that this type of signaling is evolutionarily conserved [16,18].

The close association between arousal and astrocytic signaling is corroborated by experiments showing that astrocytic Ca^{2+} signaling is notably reduced during natural sleep and anesthesia compared to wakefulness [41–45]. Interestingly, large synchronized astrocytic Ca^{2+} events, extending across the soma and processes, are consistently associated with awakening from sleep [41–43], and these Ca^{2+} events are most likely induced by NA release [46]. While most research on astrocytes and arousal has focused on NA, another important regulator of arousal, ACh, can also elicit astrocytic Ca^{2+} signaling [47,48]. Collectively, the literature strongly supports the idea that astrocytes respond to state-related neuromodulators and that astrocytic Ca^{2+} signaling is a general correlate of arousal.

Astrocytes respond to sensory input

Mounting evidence indicates that astrocytes can respond to sensory inputs *in vivo* [6,9,12–15,24,39,48–51] and local synaptic transmission *ex vivo* [13–15,20,50,52–55]. Curiously, astrocytic responses to sensory stimulation *in vivo* appear to depend on the arousal state of animals. For instance, astrocytes in the visual cortex of mice exhibit robust visual-evoked Ca^{2+} signals during locomotion (i.e., increased arousal) [9,37,39]. Interestingly, these Ca^{2+} signals are larger than signals triggered by arousal alone, suggesting an interaction between sensory inputs and arousal in astrocytes [9, 34]. By contrast, during periods of quiescence, visual-evoked Ca^{2+} is weak or non-existent [9,37,39]. These findings suggest that high arousal is necessary for sensory-activated astrocytes, yet sensory inputs still trigger astrocytic Ca^{2+} signals during anesthesia, a state characterized by low arousal [6,12–14,24,45–47]. Furthermore, after pharmacologically blocking arousal-related astrocytic Ca^{2+} signals in awake mice, visual input-driven Ca^{2+} transients in the soma [51] and whisker stimulation-induced Ca^{2+} events in the processes [15] are still observed. This aligns with the idea that local sensory-evoked synaptic activity is adequate to drive astrocytic Ca^{2+} signaling independent of the arousal state. Together, these results suggest that astrocytic signaling reflects both sensory signals and arousal levels.

Astrocytes may integrate arousal state and sensory information

We hypothesize that astrocytes integrate external sensory signals (carried as synaptic activity in neuronal circuits) and internal arousal state information (relayed by neuromodulators such as NA and ACh) through differential Ca^{2+} signaling (Figure 1). We postulate that

arousal-related signaling shifts astrocytes into a distinct activity mode, which increases the probability of exhibiting Ca^{2+} signals in response to sensory inputs. Hence, if the sensory input-driven synaptic activity is insufficient to elicit measurable Ca^{2+} signaling alone, neuromodulators such as NA and ACh can push astrocytes above a theorized activation threshold. Conversely, if sensory input is strong enough, it can trigger astrocytic Ca^{2+} signaling without notable arousal. Intriguingly, our proposal is in congruence with recent preliminary work showing that the probability that astrocytic Ca^{2+} signals originating in the processes will propagate to the soma increases during states of higher arousal [56], suggesting that arousal primes astrocytes to be more responsive to sensory input.

While the precise mechanism of the proposed integration is currently unresolved, it is tempting to speculate that global arousal signaling is primarily mediated by Ca^{2+} release from internal stores through the IP_3 pathway, and local sensory signaling is initially mediated by IP_3-independent Ca^{2+} transients, such as via activation of Ca^{2+}-permeable ion channels. It is plausible that these two different signaling pathways converge; arousal-related intracellular Ca^{2+} released from internal stores can increase the conductance of Ca^{2+}-permeable ion channels and thereby amplify sensory-related signaling, while local Ca^{2+} transients mediated by ion channels can stimulate Ca^{2+} release from internal stores through Ca^{2+}-induced Ca^{2+} release [57]. Although this mechanistic explanation is likely overly simplified, it captures the core elements of our proposed hypothesis and thus seems a reasonable starting point for guiding future experiments aiming to decipher the subcellular mechanisms of the integrated astrocytic Ca^{2+} signal.

Finally, we propose that downstream of the integrated Ca^{2+} signal, astrocytes can feed back to neural circuits to modulate sensory processing and, ultimately, behavior. Astrocyte-to-neuron signaling remains largely enigmatic, but we propose that it can occur as a result of direct gliotransmitter release (such as ATP [53]) and/or through indirect regulation of glutamate and GABA uptake [58,59] or extracellular potassium ion levels [60]. Through these mechanisms, astrocytes can both enhance and dampen synaptic activity, and future experiments are needed to determine if and when this occurs (see Outstanding Questions).

Predictions and evidence for the behavioral role of astrocytic Ca^{2+} signaling

The most direct support for our hypothesis that astrocyte Ca^{2+} serves as a molecular substrate for integrating arousal and sensory information comes from studies manipulating astrocytic Ca^{2+} signaling in behaving animals. Here, we interpret the results of such studies through the lens of our hypothesis by discussing how they align with specific predictions.

Prediction 1:

Attenuating astrocytic Ca^{2+} signaling will result in impaired integration of information conveyed by sensory-evoked neuronal and arousal states (i.e., necessity).

A novel tool that allows astrocytic Ca^{2+} signaling manipulation is iβARK, an inhibitory peptide that attenuates G_q G-protein-coupled receptor-dependent Ca^{2+} elevations [36]. Interestingly, mice with brain-wide expression of iβARK in astrocytes exhibit deficient sensory adaptation to repeated obnoxious stimuli [36]. In this experimental context,

sensory input remains unchanged, while the arousal level of animals likely diminishes as they habituate to repeated stimulation [61,62]. Thus, the deficient behavioral adaptation of iβARK-expressing mice suggests that astrocytic Ca^{2+} signaling secures a behavioral response that matches the subjects' arousal state with incoming sensory information. Furthermore, attenuation of Ca^{2+} signaling led to impaired memory performance in tasks that relies on consolidating sensory information [36]. Specifically, this deficit was obvious in a subtle object exploration task (i.e., object-location recognition), while performance in a task with salient novelty (i.e., object recognition) remained unaffected. Similarly, although using different tests, memory processes are affected in another mouse model with reduced Ca^{2+} signals in astrocytes: namely mice lacking the IP_3 type 2 receptor (IP_3R_2 KO) [7,63]. These mice exhibit subtle memory impairments for newly acquired sensory information and deficient long-term plasticity in the hippocampus and somatosensory cortex [64–69].

Notably, the findings from iβARK and IP_3R_2 KO manipulations are in congruence with results from mice expressing an artificial Ca^{2+} pump that dampens Ca^{2+} signaling in both the soma and processes of astrocytes [59,70,71]. Such manipulation in the striatum leads to reduced neuronal excitability and excessive self-grooming [59]. Interestingly, NA-deficient mice also exhibit increased self-grooming [72]. A parsimonious interpretation of these results is that astrocytic Ca^{2+} signaling in response to arousal, signaled by NA release, and accumulation of sensory information from the periphery (e.g., orofacial area) is important for the termination of self-grooming [73]. Similar evidence comes from zebrafish, where astrocytic Ca^{2+} signaling increases after repeated bouts of futile swimming to control when an animal ultimately gives up [16]. These studies suggest that normal astrocytic Ca^{2+} signaling is necessary to ensure context-dependent sensory-guided behaviors.

It is important to note that none of the currently available astrocytic Ca^{2+} loss-of-function tools permit specific attenuation of either arousal-related or synaptic activity-induced astrocytic Ca^{2+} transients. Therefore, there are no straightforward means to currently dissociate between the two sources of Ca^{2+} signaling in astrocytes and establish a causal description of their roles.

Prediction 2:

Artificial induction of astrocytic Ca^{2+} signaling that resembles naturally occurring dynamics will facilitate sensory information accumulation, leading to improved behavioral performance (i.e., sufficiency).

Studies have shown that artificial enhancement of astrocytic Ca^{2+} signaling during sensory-guided learning promotes memory formation and retention [74–76]. These findings support the prediction that elevating Ca^{2+} signaling will prime astrocytes to sense local synaptic activity and enhance sensory information accumulation, causing improved behavioral performance. However, an important limitation of these studies is the inherently artificial nature of the evoked Ca^{2+} signal. The highly complex spatiotemporal dynamics of astrocytic Ca^{2+} signals cannot currently be replicated with optogenetic or chemogenetic manipulations [77]. Finally, while currently available data appears to confirm specific predictions derived from our hypothesis, the multifaceted role of astrocytic Ca^{2+} signaling is undoubtedly

more complex than outlined here, and many open questions remain to be addressed (see **Outstanding Questions**).

Astrocytic Ca^{2+} signaling and pathophysiological conditions

Abnormal astrocytic Ca^{2+} signaling appears to be a pathophysiology component of various conditions, including disorders associated with disrupted sensory processing and arousal [78,79]. Sensory hypersensitivity and hyperarousal are hallmarks of autism spectrum disorders, Fragile X, and Rett syndromes [80–82]. Conversely, sensory hyposensitivity and hypovigilance are associated with major depression and dementia [83–86]. Interestingly, astrocytes derived from individuals with autism spectrum disorders, Rett or Fragile X syndrome exhibit exacerbated Ca^{2+} signaling *ex vivo* [87–89], and mice deficient in astrocytic Ca^{2+} signaling exhibit long-range functional connectivity changes *in vivo* consistent with those seen in patients with major depressive disorder [90]. Moreover, recent reports suggest that astrocytic Ca^{2+} signaling is less responsive to NA and sensory inputs in two different models of Alzheimer's disease [91,92]. Interestingly, some antidepressant medications, such as ketamine, could act through astrocytes [93]. It is, therefore, tempting to speculate that distorted astrocytic Ca^{2+} signaling is a key component of the cellular pathophysiology underlying sensory and arousal-related deficits in various brain disorders, and astrocytes could be a valid treatment target.

Concluding remarks and future perspectives

Considering astrocytes as integral players in cognitive function adds a new layer to the mechanistic understanding of information processing in the brain. While neurons can deliver fast and precise information, and neuromodulators provide long-lasting and long-ranging signals to tune brain activity, astrocytic Ca^{2+} signaling is somewhere in the middle: slow yet sufficiently fast for regulating behavior, diffused yet defined, and gradual yet punctual. It is these properties that enable astrocytes to partake in the integration of external sensory information, carried as synaptic activity in sensory neuronal circuits, with momentary internal arousal state relayed by neuromodulators. According to our hypothesis, astrocytic Ca^{2+} signaling is central in fine-tuning the dynamic range of sensory processing: permitting the integration of subtle sensory inputs during aroused states while also responding to strong sensory inputs in the absence of notable arousal. This optimum sensory dynamic range facilitates appropriate behavioral responses and drives memory formation.

Astrocytes are increasingly appreciated as a vastly heterogeneous cell-type population between and within brain areas [94–97]. Astrocytic Ca^{2+} signaling likely depends on the specific astrocyte subtype and is adapted to respond to local neuronal activity patterns and neuromodulation. While most studies in this context have focused on astrocytic Ca^{2+} signaling in the neocortex, technological progress now allows for the investigation of astrocyte activity in subcortical areas, such as the hippocampus [98,99] and the striatum [59]. Furthermore, microglia, the resident immune cells of the central nervous system, interact with astrocytes and neurons [100] and can regulate neuronal activity in an arousal-dependent manner [101,102]. Future work will undoubtedly widen current knowledge of the diversity and function of state-dependent glial cell signaling.

There is growing recognition that tackling some of the fundamental questions neuroscience is grappling with requires large datasets collected using advanced tools in a streamlined manner. In view of this perspective, there has been a move towards centralized brain observatories and large collaborations (e.g., the Allen Brain Observatory[i], the International Brain Laboratory[ii], and the BRAIN Initiative[iii]) [103]. While glial cells are yet to be part of the focus of such large-scale initiatives, placing astrocytes and other glial cells within their remit, would allow uncovering these cells' roles in brain function and behavior. Crucially, well-defined hypotheses – for instance the proposed roles of astrocytic Ca^{2+} dynamics in controlling behavior, as presented here – are essential to make the most out of the new age of neuroscience research.

Much remains to be learned about how astrocytic Ca^{2+} signaling is regulated by, and in turn influences, neuronal activity. However, two things are certain: one, communication between neurons and astrocytes is vastly more complicated than previously thought, and two, continuing technological progress is allowing detailed dissection of this communication. It is our hope that future work, guided by specific hypotheses, will significantly expand current understanding of how astrocytes regulate internal state-dependent sensory processing.

Acknowledgments

We want to thank members of the Center for Translational Neuromedicine and the Del Monte Institute for Neuroscience for discussions on the ideas presented in this manuscript. This work was supported by the National Institutes of Health Grant K01NS110981 to N.A.S., the National Science Foundation NSF1926781 to N.A.S., European Union under Marie Skłodowska-Curie Fellowship (ANCoDy, #101064009) to A.A., an ONO Rising Star Fellowship to A.A., a Lundbeck Foundation, Experiment Grant to R.N.R. (R370-2021-764), and the Novo Nordisk Foundation (NNF20OC0066419) to C.K.

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Resources

i. https://portal.brain-map.org/

ii. https://www.internationalbrainlab.com/

iii. https://braininitiative.nih.gov/

Box 1:

The internal state of arousal

In psychology and related fields, arousal is defined as a state of physiological activation associated with sensory stimulation or a state of excitement linked to an emotion. While arousal is sometimes conceptualized as a distinct state, in reality, arousal comprises a spectrum ranging from states of lower to higher arousal. Arousal level is indexed by biological measures such as pupil diameter, heart and breathing rate, and shifts in brain activity patterns. Essential regulators of arousal in the nervous system are neuromodulators, such as noradrenaline (NA) and acetylcholine (ACh), which are increased in the aroused brain [1–4]. An inherent challenge when evaluating sensory input-related astrocytic Ca^{2+} responses in awake-behaving animals is, therefore, the potential influence of concomitant arousal. In this article, as a simplification, we differentiate between non-arousing sensory stimulation, such as the display of visual gratings and subtle whisker stimulation, and arousal-inducing salient sensory stimulation, such as startle-related air-puff stimulation and forced locomotion. In future experiments, monitoring arousal fluctuations during sensory experiences are essential and will allow researchers to disentangle the contribution of arousal and sensation and provide important new insight into the interaction between the two.

Outstanding Questions

- What are the specific molecular and cellular events downstream of astrocytic Ca^{2+} surges that facilitate interaction with neural circuits and regulation of sensory processing? While some clues to the mechanisms exist, a full and definitive picture is currently lacking, and would require a multitude of carefully planned *in vitro*, *ex vivo* and *in vivo* studies.
- How does arousal affect astrocytic Ca^{2+} signaling in subcortical sensory areas (e.g., the lateral geniculate nucleus or superior colliculus)? How do other internal states (e.g., hunger, anxiety, aggression) induce astrocytic Ca^{2+} signaling to affect sensory input integration? What neuromodulators and hormones might mediate such effects? Carefully designed experiments in freely moving animals will allow addressing these questions. Advances in deep-tissue imaging, genetically encoded biosensors, and miniaturized microscopy are bound to offer insights into these processes.
- What is the relation between the temporal dynamics of the astrocytic Ca^{2+} signal and the temporal window of sensory information integration? Systematic testing of the temporal organization of sensory inputs and the transitions between internal states is needed to tackle this question.
- How does attenuation, or facilitation, of astrocytic Ca^{2+} signaling affect sensory discrimination performance in the healthy and diseased brain? How do changes in arousal regulate this? Leveraging psychophysical experiments with careful titration of sensory information salience and real-time monitoring of neuromodulation can offer insights into these unknowns.

Highlights

- A growing body of literature suggests that astrocytic Ca^{2+} signaling regulates various aspects of neuronal activity and behavior.
- We propose that astrocytes are in a unique position to integrate internal and external signals via astrocytic Ca^{2+} signaling.
- Astrocytes respond to internal arousal signals by detecting neuromodulator release such as noradrenaline and acetylcholine and elevating their intracellular Ca^{2+} concentration.
- Astrocytes also respond to external sensory inputs by sensing local synaptic activity that leads to Ca^{2+} transients.
- Manipulation of astrocytic Ca^{2+} signaling results in altered acquisition of sensory information.
- We hypothesize that arousal can amplify weak sensory input at the level of astrocytes.

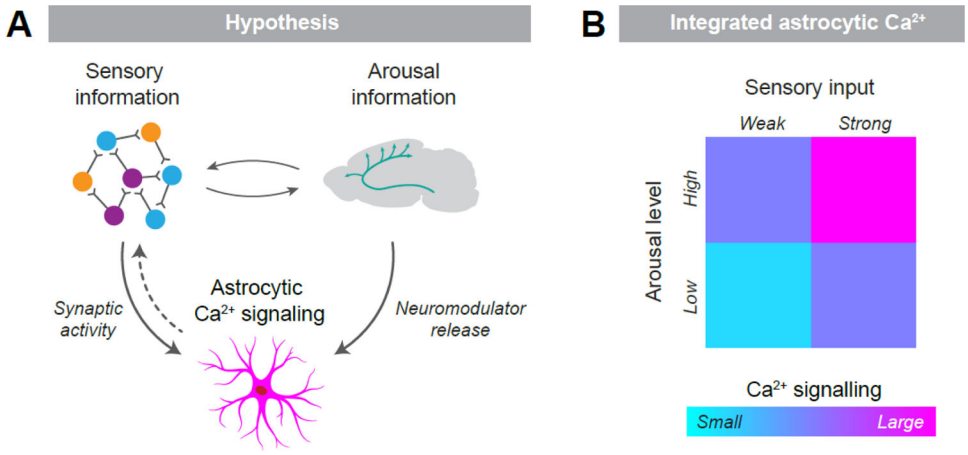

Figure 1. Astrocytic Ca^{2+} signaling as an integrator of external and internal information.

(A) Visualization of the proposed concept: astrocytes integrate sensory information, conveyed by synaptic activity in neuronal circuits, and arousal information, conveyed by neuromodulator release, by means of differential Ca^{2+} signaling. Salient sensory stimulation can increase arousal levels, and in turn, arousal-related neuromodulators affect sensory processing in neuronal circuits. While not discussed in detail here, the signaling events downstream of astrocytic Ca^{2+} that facilitate interactions with neuronal activity and modulate sensory experiences remain elusive (dotted arrow; see Outstanding questions). (B) Heat map illustrating the anticipated magnitude of astrocytic Ca^{2+} signaling due to the integration of arousal level and sensory input.