A conceptual framework for astrocyte function

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The participation of astrocytes in brain computation was hypothesized in 1992, coinciding with the discovery that these cells display a form of intracellular Ca^{2+} signaling sensitive to neuroactive molecules. This finding fostered conceptual leaps crystalized around the idea that astrocytes, once thought to be passive, participate actively in brain signaling and outputs. A multitude of disparate roles of astrocytes has since emerged, but their meaningful integration has been muddied by the lack of consensus and models of how we conceive the functional position of these cells in brain circuitry. In this Perspective, we propose an intuitive, data-driven and transferable conceptual framework we coin 'contextual guidance'. It describes astrocytes as 'contextual gates' that shape neural circuitry in an adaptive, state-dependent fashion. This paradigm provides fresh perspectives on principles of astrocyte signaling and its relevance to brain function, which could spur new experimental avenues, including in computational space.

Following the discovery that astrocytes, a type of glia, possess a form of intracellular Ca^{2+} 'excitability' strikingly slower than that of neurons[1], Stephen Smith hypothesized that "astrocyte networks might mediate slow modulations of neuronal function," citing arousal, selective attention, mood and learning as examples[2]. These early predictions, shown to be true over the subsequent decades, embraced the slowness of astrocyte signaling as a distinctive feature. Noting that "brain function, in all its complexity and glory, requires many different kinds of computation—some discrete, fast and specific; others slow and diffuse," Smith de facto positioned astrocytes as a slow computing unit of the brain[2].
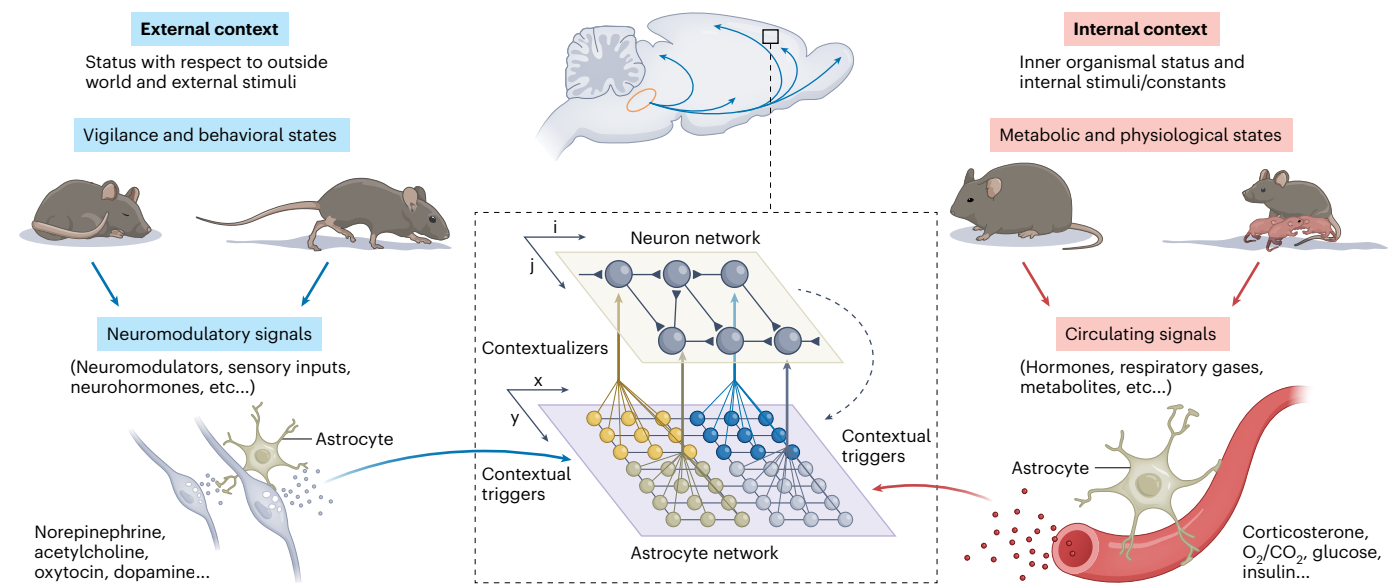
Yet, three decades later, the question 'what do astrocytes do in the brain?' still has no simple answer. Instead, it prompts a list of seemingly unconnected functions fulfilled by these cells in the developing and adult CNS, from ion homeostasis to synapse regulation, energy supply and blood flow control[3]. This lack of general and communicable agreement on why astrocytes fundamentally exist in the brain highlights the need for a unified and broadly applicable framework that could portray the role of astrocytes in the CNS across scales and species, in transferable and useful terms. In the past, several such models have been formulated, primarily the lactate shuttle hypothesis[4], in which astrocytes are depicted as an energetic intermediate between neuronal activity and blood flow, and the tripartite synapse hypothesis, in which astrocytes

are thought to monitor and influence activity at individual synapses[5,6]. Both permitted great strides in dissecting the roles of astrocytes in synaptic function, hemodynamics and circuit activity[3]. But, while they count many supporters, these traditional perspectives are not broadly accepted, in part because they are limited to a single scale or locus and do not articulate, together or separately, a comprehensive view of astrocyte function. This has become particularly apparent amidst a recent wave of discoveries that are not captured by these standard views and appear to challenge the conceptual horizon of the field (Supplementary Table 1). To address this rising disconnect between a rapidly evolving field and the lack of adequate models guiding its inquiry, it would be useful to agree on what we truly consider the core function of astrocytes in neural systems, irrespective of organisms, regions or loci. This could shed light on existing debates, help articulate the many facets of astrocytes in a way that logically accounts for their interplay with high-speed neuronal processing and account for the combined contribution of both cell types to cognition and behavior[7].

In search of a consensual framework for astrocyte biology

We reason that, to be valid, a framework for astrocyte biology should satisfy the following criteria. (1) Reliability: it should reflect

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Fig. 1 | Astrocyte networks are cued by contextual signals to guide neural circuits. In contextual guidance, neuronal networks operate rapid point-to-point transfer and integration of information, while astrocytic networks transduce slower modulatory information over large spatial scales. In this proposed framework, astrocytes act as the primary receiver of slow contextual signals, such as neuromodulators, sensory inputs and neurohormones, that carry information about the status of the animal with respect to the outside world (left). Owing to their interactions with blood vessels, they are also the first responders to circulating signals, such as corticosterone, glucose, oxygen and CO$_2$, that carry information about the animal's bodily status (right). In response, astrocytes signal onto neuronal elements to alter circuit connectivity and/or activity (middle). The net result is a context-specific reconfiguration of the neural network's topology and functional output. The large spheres represent neurons (in the neuron network), along with their synaptic connections. The small spheres represent astrocytes (in the astrocyte network), with the lines illustrating the gap-junction coupling of astrocytes into functional networks. The dashed arrow from the neuron network represents the influence of local neuron network activity on the astrocyte contextualizing response.

unanimously accepted or validated empirical evidence and remain agnostic to dogmas. (2) Causality and parsimony: it should provide, through inner causality, simple explanations for observed phenomena with few theoretical parts. (3) Usefulness: it should alleviate existing controversies or inconsistencies by providing new perspectives. (4) Robustness: it should yield correct predictions and continue to satisfy the first three criteria as new discoveries are made.

As a foundation for such a framework, we thus sought out general and reductionist principles that have remained unwavering during the last three decades, rather than individual observations. This is in part to avoid the caveat of subjectivity but also because the field of astrocyte biology has undergone a rigorous transformation with regards to technical developments and experimental standards, such that once-accepted observations might not all pass muster nowadays. A first defining principle of astrocytes is that they present the characteristics of a sentinel of the interstitial space: high surface-to-volume ratio, extensive morphology, intricate integration in the neuropil and rich molecular makeup[3,8–12]. A second is that astrocytes also dynamically shape the physical and biochemical properties of the extracellular milieu (or 'active milieu'[13]), from diffusivity of signaling molecules to energy availability, ion concentration and functional connectivity[7,14–18]. An additional, important realization is that the interstitial space is not static; it is a constantly regulated medium and its properties dictate the behavior of the cellular elements it bathes[19,20]. Combined, these premises portray astrocytes as sensors and orchestrators of the extracellular environment in which brain cells reside.
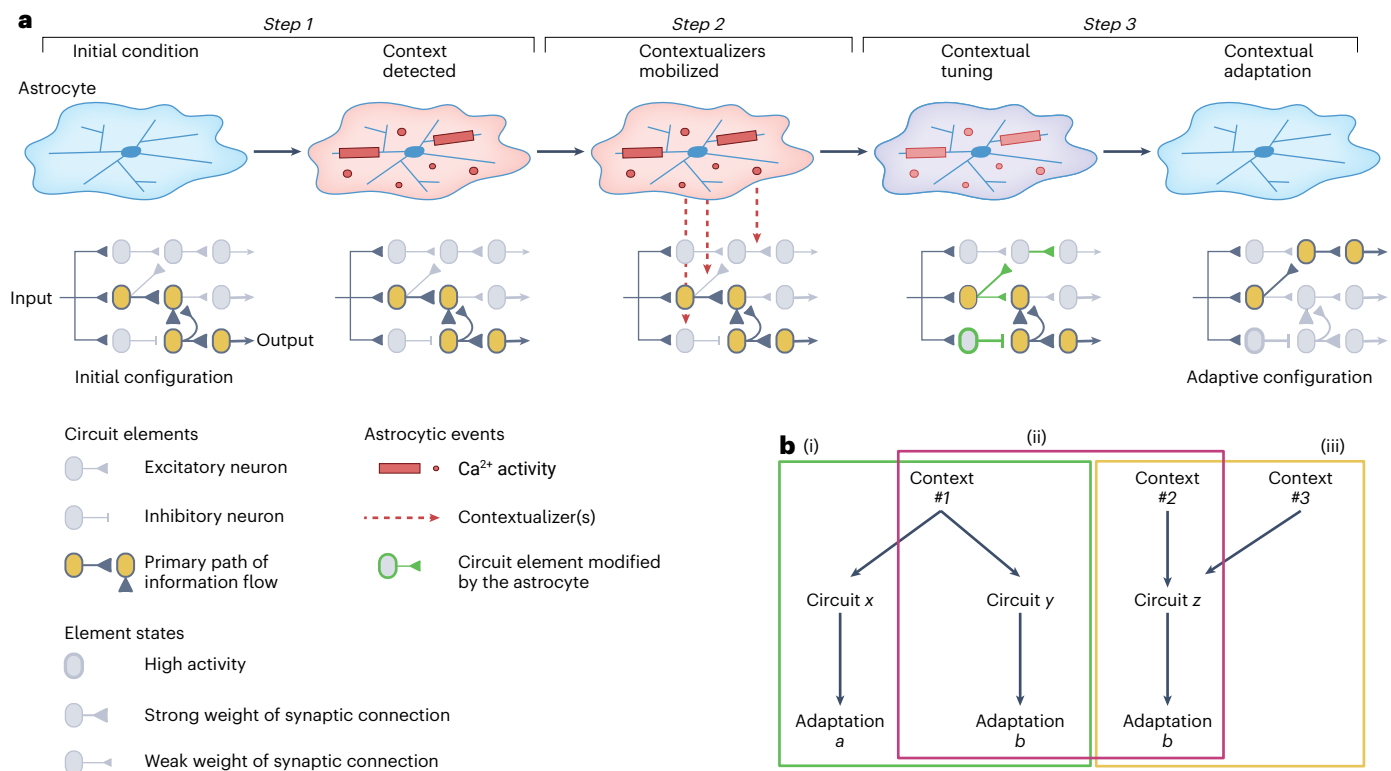
Context-dependent configuration of neural circuits by astrocytes

With these guidelines, we here introduce 'contextual guidance', an intuitive framework for astrocyte biology that depicts these cells as state-dependent orchestrators of neural circuitry (Fig. 1). In brief, we propose that: (1) astrocytes are tuned to circuit-relevant organismal contexts, by sensing state-dependent cues; (2) these cues mobilize astrocytic outputs that alter the activity and/or topology of the underlying neuropil; and (3) these modifications produce a context-specific adaptation of associated neural networks.

In this three-step framework, astrocytes are stimulated by diffusive signals that are relevant to the function of the local circuit[15] and encode a change in the animal's state[21] (Fig. 2a; step 1). We term these signals 'contextual triggers' (Box 1) because they convey information on the organism's status and mobilize astrocyte signaling. We give examples of such signals from the literature in Supplementary Table 2. By definition, contextual triggers are specific to the circuit and vary greatly in nature, prevalence and origin, across the CNS, yielding a seemingly heterogeneous repertoire of signals to which astrocytes respond—some shared across the brain (for example, norepinephrine) and others unique to select nuclei (for example, pCO$_2$; ref. 22). This aligns with the molecular diversity of astrocytes[12,23–27] and captures the nonuniformity of astrocytes' responsiveness to many types of signaling molecule and conditions[28] (Supplementary Table 1).

In response to contextual triggers, astrocytes mobilize effectors that influence the local circuitry (step 2) and can take many forms, including synapse-bound transmitters[29], glutamate uptake[30], lactate supply[31], hemodynamic control[32], regulation of extracellular Ca^{2+} and K^{+}[17,33], synapse elimination[34] and retraction or extension of peri-synaptic astrocytic processes[35], to name a few. We coin these astrocytic outputs 'contextualizers' because they alter neural properties in response to a context (Box 1 and Fig. 2a). Contextualizers are thus defined on the basis of their circuit-modifying competence, rather than their nature, mode of mobilization or mechanism of action, unifying the plethora of astrocyte outputs onto a multitude of cellular targets that abound in the literature.

Fig. 2 | Astrocytes reconfigure circuits in a context-dependent fashion. a, Stepwise illustration of the contextual guidance proposal, showing an individual astrocyte and embedded neuronal circuit over time. The astrocyte responds to the emergence of a context (shown as Ca²⁺ transients). This leads to the mobilization of circuit-modifying contextualizer(s), which act on select elements (here presynaptic strength as in ref. 77 and interneuron firing as in ref. 48). These modifications reconfigure the network, illustrated as a change in the path of least resistance and resulting output[78]. **b**, Putative scenarios in which (i) a context 1 yields circuit adaptations *a* and *b* in circuits *x* and *y*, respectively; (ii) two contexts 1 and 2 yield the same adaptation *b* in circuits *y* and *z*; and (iii) adaptation *b* is achieved in circuit *z* in response to contexts 2 or 3.

BOX 1

Definitions

Context: ensemble of conditions that relates to an internal or external status, such as a physiological, metabolic, biochemical, behavioral or vigilance state

Contextual trigger: a signal that (i) diffuses through the interstitial space, (ii) is relevant to the function of the local circuit, (iii) encodes a change in internal or external state and (iv) can mobilize astrocyte signaling

Contextualizer: astrocytic output, mobilized in response to a contextual trigger, that is consequential to the underlying neural circuitry
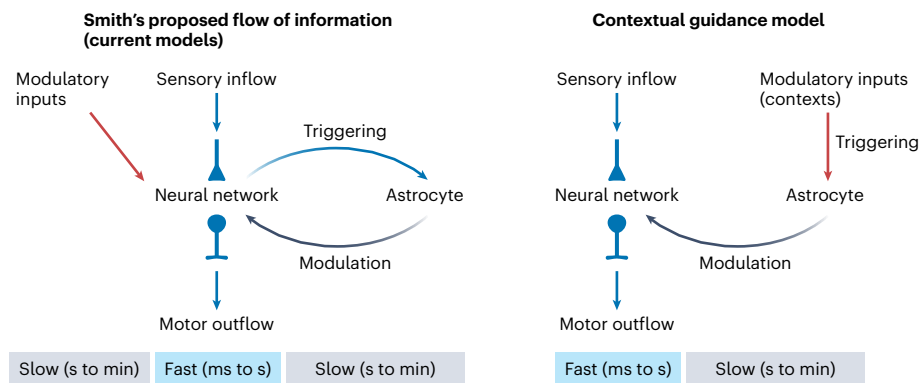
Contextual tuning: effects of a contextualizer on the activity and/or functional topology of a neural circuit

Contextual adaptation: adaptive value of the circuit reconfiguration produced under contextual tuning, regarding the context that triggered it

Contextualizing rules: association of the specific instances of the elemental parts described above into a unique 'context→contextual trigger→contextualizer→contextual tuning and adaptation' sequence

Finally (step 3), the net effect of contextualizers is to shape the activity (excitability, firing mode and synchrony) or functional topology (synaptic wiring, fidelity, potency, efficacy and plasticity) of the neuropil, as abundantly evident from the literature of the past 30 years. We call these circuit modifications 'contextual tuning' because, importantly, we postulate that they amount to a functional adaptation to the context (Box 1). Many instances of the full contextual guidance flow and its adaptive nature already exist in the literature, some of which are summarized in Supplementary Table 2. For example, during high-vigilance states (context), cholinergic signaling (contextual trigger) drives astrocytic release of D-serine (contextualizer) to augment NMDA receptor readiness at CA3–CA1 synapses (contextual tuning), which enhances the potential for hippocampal learning during periods of spatial exploration (adaptation)[29].

Importantly, we refer to 'context' as the conditions that arise during a physiological[35], metabolic[30], biochemical[15], behavioral[36], vigilance[37] or pathological state[38], in alignment with mounting evidence that astrocytes are attuned to brain states (Supplementary Table 1). An essential commonality of 'contexts', therefore, is that they relate to an internal or environmental status of the animal. Together, this forms a logical and minimalist framework in which astrocytes are a hub for circumstantial inputs into relevant specialized circuits that permits adaptive behaviors at the network and organism levels (Fig. 1). This view is consistent with the features of early astrocyte homologs, CEPsh glia in the nerve ring of *Caenorhabditis elegans*, which extend processes that associate with sensory neuron-receptive endings of the animal's nose, forming postsynaptic-like structures sensitive to environmental cues[39].

Smith's proposed flow of information (current models)

Contextual guidance model

Fast (ms to s)

Fig. 3 | In contextual guidance, astrocytes are a gate for modulatory inputs. In current concepts of astrocyte function (left), which are based on ref. 5, the contribution of astrocytes to neuronal networks is constrained in a feedback loop: synaptic or neuronal signaling is the driver of astrocyte activity, which outputs back onto synapse or neuron activity. Modulatory inputs are assumed to act directly on synapses or neurons. Contextual guidance (right) comprises the same fundamental parts. However, it makes astrocytes a gateway for modulatory signals at large, which are not synaptic by default, de facto describing astrocytes as circuit effectors in a feedforward mechanism. This hierarchical architecture reconciles the slowness of astrocytes and modulatory signaling with the fast timescale of neuronal and synaptic activity. The modulatory contextual inputs that drive astrocyte activity may also comprise, or be influenced by, direct signaling from local neuronal networks.

New views on past conundrums through the lens of contextual guidance

A growing body of work has implicated astrocytes in brain signaling and behavior, and fueled the hypothesis that, analogous to neurons, astrocytes possess input–output rules with which they process information—that is, a set of predictable relationships between signals astrocytes receive, pathways engaged in response to them and downstream effects on circuits. While it is acknowledged that these rules might not resemble the ones known in neurons, their very existence is still uncertain. Relatedly, the organizing principles of signal processing by astrocytes are largely obscure, in part because the Ca^{2+} responses of astrocytes are of unknown reliability. In this section, we discuss how contextual guidance sheds light on these conundrums.

What signals do astrocytes really respond to?

Elucidating whether and how astrocytes process information has been hindered by the lack of clarity on what signals stimulate them in the first place[28]. A culprit is our reliance on Ca^{2+} transients as the sole proxy for astrocyte responsiveness, which we discuss below. Another is the heterogeneous and seemingly unreliable range of cues to which astrocytes react (Supplementary Table 1), and traditional perspectives have offered limited insights into how these disparate observations fit together and what they tell us about the conditions that recruit astrocytes[4,6]. Contextual guidance, by contrast, is modeled after these very reports of astrocytes' responsiveness to a vast repertoire of signaling molecules. By virtue of generalization across circuits, regions and states, it provides a framework that accounts for such a diversity of stimuli in the form of contextual triggers. In doing so, it allows the hypothesis that astrocytes are tuned not to signals of a specific nature but to circuit-relevant conditions, that is, state-dependent cues.

Because information about context (that is, the state of the animal) is often not relayed by local synapses but by cocktails of circulating signals or far-reaching afferents, contextual guidance shifts the focus away from the notion that astrocytes are mainly entrained by the unitary activity of synapses in their domains. This is a departure from the tripartite synapse concept[6], in which baseline synaptic activity is considered the primary driver of astrocyte signaling. In that model, astrocytes perform a "re-encoding of fast synaptic information that feeds back onto neurons for retransmission of that information"[2], but the evolutionary and computational advantages of this feedback have remained unclear. Additionally, the relative slowness of astrocyte signaling compared to synapses[40,41] puts into question the functional relevance of synapse-triggered astrocytic outputs (Fig. 3) and, anecdotally, blocking neuronal activity has, in some cases, little to no effect on astrocyte Ca^{2+} dynamics[27,42]. Hence, contextual guidance aligns with observations questioning the idea that synaptic transmission is the driver of astrocyte function.
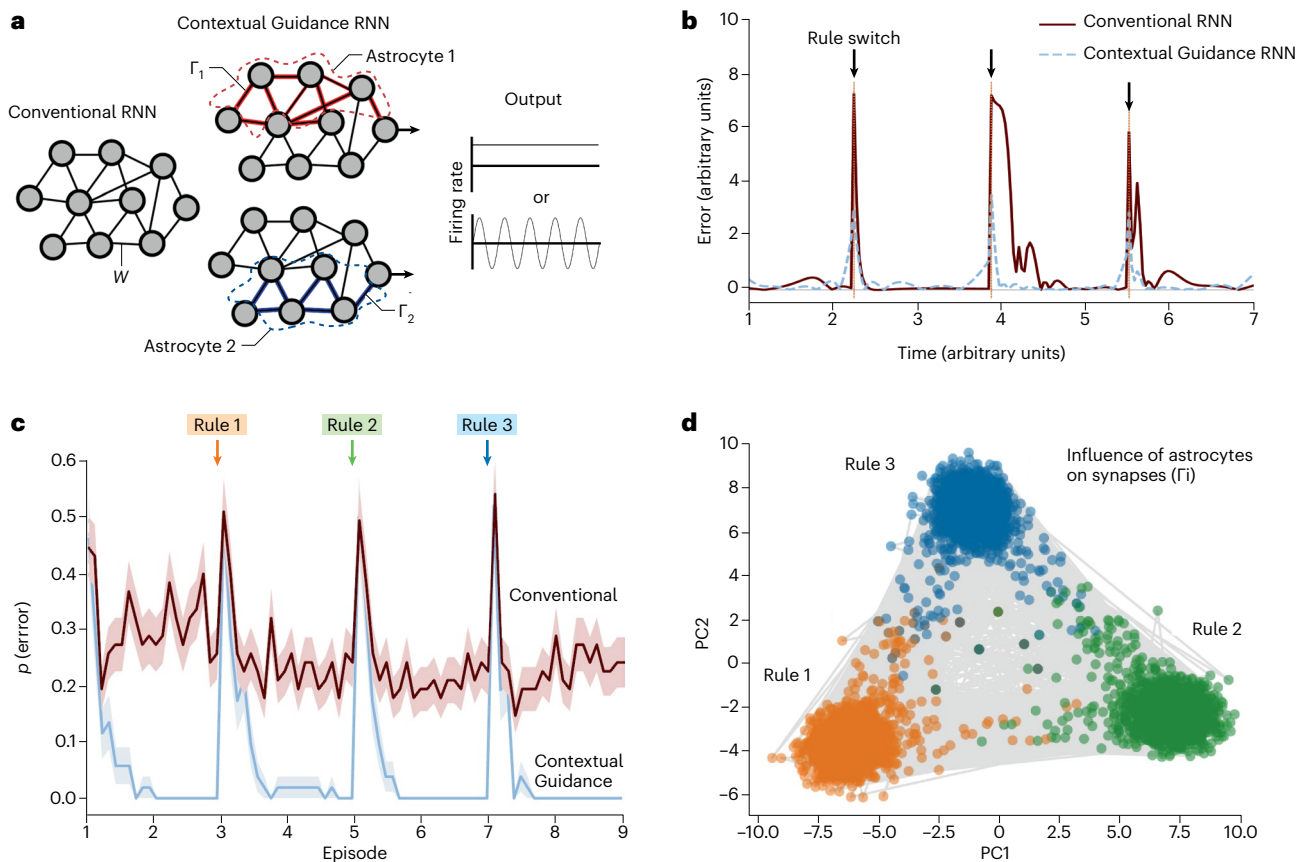
However, the contextual guidance and tripartite synapse models coalesce under certain conditions. Functionally salient or coordinated synaptic inputs could act as contextual triggers. They might inform astrocytes of circuit-relevant sensory saliencies or high local activity and energy demand, respectively, and tune astrocytes' responses to the network state[43]. Indeed, evidence suggests that recruitment of astrocytes by synapses often requires strong or synchronized activity[44]. Such conditions favor transmitter spillover and diffusive retrograde signaling[44–46] (for example, endocannabinoids), both of which fulfill the contextual trigger criteria (Box 1). Similarly, there is a growing appreciation that astrocytes are sensitive to discrete populations of inhibitory contacts that play salient roles in reshaping the activity of neuronal ensembles and orchestrating network outputs, and which entrain astrocytes to influence circuit activity[47–51].

Combined, these considerations underscore the usefulness of contextual guidance in untangling what signals stimulate astrocytes and when.

Are there input–output rules in astrocytes?

A potential lesson from contextual guidance is that a quest for broadly applicable principles of astrocyte input–output rules is bound to fail, because the answer may lie at a highly circuit-specific level. Contextual guidance puts no constraints a priori on the combinations of astrocyte inputs and outputs, as it allows a contextual trigger to mobilize distinct contextualizers in different circuits, and vice versa. For instance, norepinephrine signaling elicits the release of astrocytic D-serine in the mouse spinal cord[52] but has been linked to ATP release in the cortex[53], highlighting that a context may yield different adaptations in different circuits (for example, Fig. 2b(i)). Conversely, astrocytic secretion of D-serine is gated by norepinephrine in the spinal cord[52], oxytocin in the amygdala[54], and acetylcholine in the cortex[29,55], indicating that distinct contextual triggers can yield the same adaptation in separate circuits (Fig. 2b(ii)). Finally, D-serine availability in the CA1 is also governed by other pathways, such as endocannabinoid signaling[45], denoting that,

Fig. 4 | Astrocytes provide context adaptation and stability to recurrent neural networks: proof of principle. a, In a conventional recurrent artificial neural network (RNN), synaptic weights are given by a matrix W (left). In a 'contextual guidance RNN' (center), synaptic weights are given by the sum $W + \Gamma i$, where Γi reflects astrocyte-mediated modulation of synaptic strength over two ensembles of connections (red and blue), enacting tiled astrocytic domains (dashed areas). Both RNNs are tasked with producing a specific output (right): bursting activity (harmonic oscillation) or tonic firing, as in ref. 33. **b**, RNNs must change their output at the occurrence of a contextual signal (arrow), with error measured as a deviation from the expected output frequency. In this abstraction, where the context is known to the RNNs, a conventional RNN 're-learns' W at each context switch, resulting in high error transients. The 'contextual guidance RNN' can change its regime rapidly. In effect, a single W is learned and the network adapts to the context by rapidly modulating synaptic weights through astrocytes (Γi). **c**, Two LSTM RNNs were built as in **a**, and trained on an abstraction of the Wisconsin card-sorting task, in which agents receive a set of cards, each with different numbers, shapes and colors, and are tasked with picking one card to match a hidden rule (for example, select the card with triangles). In this task, the rule (that is, context), can be learned only by trial and error, and changes during the task. The RNNs are trained to maximize future rewards by determining and exploiting each new rule. We used 64 neurons and 16 astrocytes, and numerically optimized all free parameters using episodes of 80 trials. Solid traces show the mean error probability, and shading shows the s.e.m. The 'contextual guidance' LSTM RNN outperforms a conventional network by adapting to the new context and performing optimally until the next context switch. **d**, Dimensionality reduction across trials in **c** shows that the astrocytic modifications of synaptic weights (Γi) are highly context dependent, reminiscent of the contextualizing rules described in the text. Simulations were run on MATLAB (**b**) and Python (**c** and **d**).

within a circuit, more than one context can produce the same tuning (Fig. 2b(iii)). These seemingly inconsistent results, when put in the contextual guidance framework, reflect that 'contextualizing rules' (what context yields what adaptation; Box 1) are circuit specific. This allows the important hypothesis that input–output rules exist in astrocytes but that, unlike rules in neurons, they are specified on a circuit basis and influenced by astrocytes' local identity, rather than generated in a cell-intrinsic manner. Interestingly, this fits the general notion that astrocytes' genetic and epigenetic identity is a function of its context in the brain, being both state-dependent and circuit-dependent[56].

Do astrocytes integrate inputs?

A central tenet of contextual guidance is the ability of astrocytes to integrate information from multiple sources and types of signal about the animal's internal state and external environmental conditions, to produce the appropriate contextualizing response. Strikingly, a growing collection of published findings and emerging research lends strong support to this idea. In the area of neurovascular coupling, for instance, it has been shown that the influence of astrocytes over blood vessels is contextually defined by synaptic, behavioral and vascular states[32]. Similarly, unpublished work indicates that internal states and behavioral contexts profoundly modulate astrocytes' Ca^{2+} responsiveness to neuromodulatory cues and local circuit activity. For instance, the detection of food or water elicits strong activation of astrocytes in food-restricted or water-restricted animals, respectively, whereas the detection of these nutritional cues yields no Ca^{2+} responses in metabolically satiated animals with unlimited access to food and water[57]. Similarly, astrocytes' responses to fear-associated cues in the amygdala[58] are disrupted by stress[59]. However, we acknowledge that the body of evidence corroborating the notion of signal integration by astrocytes remains very limited at this time. Mapping the effects of individual neuromodulators, hormones and other contextual cues on astrocytes across brain regions will allow researchers to investigate the permissive, synergetic or antagonist nature of these signals in combinatorial studies and provide insights into this question. In vivo recordings of astrocyte

activity with micro-domain resolution across changing behavioral states or contexts will be instrumental as well.

Signal integration may take place at many levels of transduction. For example, changes in surface expression of receptors via local translation[60] is a likely mechanism, tuning the ability of astrocytes to respond to other cues once conditioned in a given state. Ca^{2+} is another mechanistic candidate because it is prone to modulation by G-protein-coupled receptor pathways, transmembrane fluxes or other signals that affect endoplasmic reticulum actuators, pumps and cytoplasmic buffers[28].

What are the mechanisms of astrocyte signaling?

The above considerations bring the more complex and multifaceted question of astrocyte signaling, and its mechanism. In particular, how multiple inputs can converge on one integrator (that is, Ca^{2+}) yet still generate diverse cellular outputs is unknown. While Ca^{2+} is an important second messenger, we advocate that it should only be seen as one of many that are potentially relevant to the question of information processing, and that interactions between multiple second messenger pathways might be equally important. Indeed, our knowledge of astrocytes responsiveness was obtained almost exclusively through the lens of Ca^{2+} transients. This is because, historically, inspiration was drawn from neurons to understand astrocytes. But astrocytes are, resolutely, not neurons, and one should refrain from this natural inclination. For instance, the notion that Ca^{2+} excitability governs the Ca^{2+}-dependent release of chemicals stored in vesicles, even though evidence suggests that such signaling mechanisms exist in astrocytes[8,18,61], might be an exception we relentlessly looked for, obscuring other possibilities. This is why contextual guidance makes no assumptions regarding the mechanisms that drive input–output coupling and signal integration in astrocytes. There is a need to look beyond Ca^{2+} and explore other modes of signaling and metrics of astrocyte responsiveness, such as cAMP and PKA signaling[62], astrocyte membrane depolarization[63] or even the ability of signals to alter existing Ca^{2+} dynamics rather than triggering events of their own. Contextual guidance offers a platform to investigate these alternative mechanisms by suggesting the existence of a circuit-specific 'astrocyte code' but putting no limitations on the molecular processes underlying it.

Additionally, these considerations focus on single cells, but it is likely that the notion of networks plays an important part in signal detection and integration[64]. For example, studies in the amygdala suggest that a subset of morphologically distinct oxytocin receptor-positive astrocytes interspersed in the network act as primary sensors of oxytocin and entrain the rest of the network in the contextualizing response[54].

Are astrocytes slow?

In contextual guidance, astrocyte activity is closely linked to signals that fluctuate over the course of seconds to hours. This echoes Smith's original proposal and is consistent with the kinetics of astrocyte Ca^{2+} dynamics and observations that astrocytes are slow secretory cells compared to neurons[41]. A corollary is that the bulk of spontaneous Ca^{2+} transients in astrocytes may reflect the ambient neuromodulatory state or tone. Interestingly, this could be permissive to incidence detection of other inputs at faster timescales, including integration of fast synaptic activity. It is known that while ~90% of astrocyte Ca^{2+} events are an order of magnitude slower than neuron Ca^{2+} events, astrocytes can also sense signals on fast timescales[40], and this sensitivity might be tuned in a state-dependent fashion. Perhaps it could be useful to agree on a nomenclature of Ca^{2+} signals based on their temporal kinetics, rather than spatial properties, akin to the one used for capillary endothelial cells where a hierarchy of Ca^{2+} events coexist, ranging from small, sub-second proto-events reflecting Ca^{2+} release through a small number of channels, to high-amplitude, sustained compound events mediated by large clusters of channels[65].

Predictions and new questions

Embracing the contextual guidance perspective allows new predictions that could help propel the field in new areas of investigation. In this last section, we focus on three examples.

The tiling of astrocyte domains is a compartmentalization mechanism

Contextual guidance implies that only one set of contextualizing rules (or 'astrocyte code') should apply at a given location for a context-bearing signal to produce consistent outcomes. A possible mechanism to guarantee this fidelity would be one ensuring that an element of the neuropil is contacted by only a single astrocyte, which might be achieved if each astrocyte occupies a dedicated volume of neuropil. Astrocytes, in effect, tile the brain in individual nonoverlapping domains, a hallmark preserved from nematodes to primates and humans[7–10] that is unexplained at the functional level and unaccounted for in models of astrocyte biology. Insights from the contextual guidance notion allow the hypothesis that astrocyte tiling is a functional compartmentalization mechanism. A subsequent prediction would be that altering tiling will have severe consequences on synaptic, circuit and behavior adaptation across states and contexts with no or limited impact on individual astrocyte input processing and Ca^{2+} dynamics.

A related conundrum is that an astrocyte domain includes a mixture of synapses from a multitude of afferents onto different target neurons. It is unknown whether these synapses, and neuronal elements more generally, are contacted and influenced by astrocytes homogeneously, at random, or following a logic related to micro-circuitry. The view we outlined here predicts that astrocytic outputs affect neuronal elements according to their functional value within the underlying micro-circuitry, rather than in bulk. If this is true, molecular, morphological and functional signatures of this organization must exist. Remarkably, recent work points to the existence of astrocyte-defined synaptic clusters within astrocyte domains, fueling the idea of a specified functional architecture for astrocyte–synapse interactions[10]. Interestingly, the idea that astrocytes shape neural circuitry with some degree of precision, in a state-dependent fashion, allows the hypothesis that there may exist a context-specific astrocyte imprint of circuit configuration (for example, weight distribution) that can be re-implemented upon context reoccurrence (Fig. 2). This raises the question of a potential astrocytic memory.

Neuromodulators and hormones signal through astrocytes to affect neural circuits

Neuromodulators and hormones have potent effects at many scales of neural signaling, including synaptic function and neuronal firing. This has been known for decades, but how compartment-specific effects are achieved besides the volume-transmitted nature of neuromodulatory signaling remains obscure. How such effects, in turn, tune large-scale network activity in a coordinated fashion to guide behavior is equally unclear. Evidence now shows that neuromodulatory systems are sensed by astrocytes and elicit astrocyte responses. Astrocytic endfeet that ensheathe blood vessels, in addition, are optimally positioned to sense hormones and other metabolically active molecules, including glucocorticoids, insulin, leptin, ghrelin and cholecystokinin, and subsequently to shape circuits and behavior[21,66–69]. In line with these notions, contextual guidance allows the prediction that well-known effects of neuromodulators and hormones, especially as they relate to the reconfiguration of circuit connectivity and activity[70], are achieved not by acting on neurons directly but by leveraging astrocyte signaling[71,72] (Fig. 3). This can be systematically tested and, if true, would have rippling consequences throughout neuroscience. A direct implication is that astrocyte research should pay increasing attention to the effect of sex and gender, as astrocytes might be highly sensitive to the balance of sex hormones[73].

Contextual guidance in computational neuroscience

Efforts to emulate neural computation have focused on circuit mechanisms at the level of neurons and synapses, with information coded in spiking patterns. Here, we conceptualize astrocytes as state-dependent transformers of neuronal topology and dynamics, which could easily overthrow simplistic and neuron-dominated views that prevail in computational neuroscience. For instance, this approach could improve computational theories of learning and adaptation by animals and humans in dynamic contexts, and over multiple timescales. Specifically, in the field of artificial intelligence, artificial neural networks (ANNs) that rely only on neuronal rules of learning are prone to catastrophic forgetting[74,75] because previous memory traces are overwritten as new memories are formed. This prevents agents from accruing knowledge spanning long timescales. To mitigate this issue, ANNs are often endowed with slow memory elements to allow stable representations of prior experience and contexts[76]. But such long short-term memory networks (LSTMs)[76] are difficult to reconcile with any known neurobiological mechanisms, and they often struggle to capture contextual dependencies. Astrocytes, which are active in a context-dependent fashion and reconfigure neural circuits on demand, are a natural biological substrate for context representations in artificial networks such as those implemented in LSTMs or transformer architecture. A prediction, therefore, is that contextual guidance will overcome current limitations of ANNs by introducing astrocytes as a biologically relevant element whose outputs can be modeled to permit context sensitivity and network stability (Fig. 4). This will enable more accurate and robust modeling of complex tasks in ANNs and open new avenues for glia-inspired artificial intelligence in computational neuroscience and machine learning.

Concluding remarks

Astrocytes have garnered growing interest in the neuroscience community, perhaps because they appear more diverse, complex and active than previously thought, and because a series of discoveries has placed them at the center of signaling pathways across brain regions and animal models. However, a lack of consensus on their core function has limited our understanding of how these cells contribute to information processing and behavior, hindering a wider 'glia adoption'. Here, we propose a view whereby astrocytes integrate environmental factors to fine-tune neural circuits in a context-specific, feedforward and adaptive fashion. We think it provides a foothold for exploring the manifold nature of astrocytes, probing their role in network functions and investigating their contribution to behavior. To fully capture the environmental conditions that mobilize astrocytes, the adoption of in vivo studies in behaving animals seems inevitable, and such studies should systematically consider sex as a biological variable. We hope that contextual guidance will be useful in guiding these future inquiries in the rapidly growing field of astrocyte biology, to help achieve a multicellular understanding of brain function.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon request.

Code availability

Codes and mathematical algorithms used in Fig. 4 will be made available upon publication.

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The authors declare no competing interests.

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