Acta Pharmaceutica Sinica B 2026;16(4):2595−2597

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com

COMMENTARY

# Astrocytes in predictive processing of emotion: Kir4.1 as precision modulator of social interaction

**KEY WORDS**

Astrocytes;
Emotion;
Kir4.1;
Social interaction

Astrocytes are non-neuronal (glia) cells in the brain which respond to and regulate neuronal synaptic function. Named for their star-like projections, astrocytes physically sense glutamate at the synaptic cleft and undergo waves of calcium which causes them to release neurotransmitters onto neurons. Thus, astrocytes are structured to provide feedback in response to ongoing neural activity. While neuronal release of neurotransmitters is regulated by electrical spikes, astrocytic gliotransmitter release (*e.g.*, ATP) is caused by calcium increase rather than action potentials. Thus, recent appreciation for astrocytes owes in part to the development of optical imaging of calcium and neurochemical release which have enabled the characterization of astrocytic responses *in vivo*.

With those tools, recent systems neuroscience studies of astrocytes have shown that they respond to environmental stimuli, including higher order associations, in a rich way previously associated with neurons. Recent decades have seen an explosion of interest in glia, first beginning with microglia and now with astrocytes emerging as critical regulators of fundamental CNS functions like learning and memory[1,2].

Yet many circuit mechanisms exist for the regulation of synaptic plasticity: what makes astrocytes a key focus for translational neuroscience and drug discovery? One answer may lie in the slowness of astrocytic regulation of neuronal activity. Neuronal synapses drive spikes with millisecond precision, but the processes underlying emotions and social behaviors are much slower. Astrocyte calcium responses to stimuli can last for minutes, and in turn this drives the release of slow regulatory gliotransmitters which could regulate synapses for days or longer. Thus, astrocytes might integrate information from ongoing neuronal activity to predict and enable adaptation to ongoing demands which are persistent[3].

A major puzzle in modeling emotions in neuroscience is how to derive the level of precision we have in our understanding of sensory circuits. In the visual system, the predictive coding hypothesis holds that higher order visual areas send top-down predictions about what lower level areas will sense. We do not currently have this hierarchy for emotional brain circuits, but one theoretical model suggests that the slowest varying circuits could be at the top of the hierarchy of control of emotions[4]. Seen in this context, the slowness of astrocytic response and control appears as a beneficial feature rather than a drawback. In turn, cortical astrocytic responsivity to neuronal activity is modulated by higher order predictions from neuromodulators[5].

Recent evidence supports this view: norepinephrine sends aversive signals to frontal cortex to guide behavior, but the critical receptors belong to astrocytes. Norepinephrine signaling unexpected outcomes triggers calcium increases in astrocytes lasting for minutes, which in turn cause release of ATP[6]. Astrocytes thus selectively amplify the most important signals to alter further functioning on longer timescales. Parallel work in amygdala recently found that astrocytes participate in retrieval of fear memories[2]. One recent study further underscored the long timescale persistence of astrocytic state changes, finding that they stabilize long term memory connections across days[1]. These data provide a window into how long timescales of emotional processing can interact with astrocytic state changes to predict and influence neuronal activity.

Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2026.03.043

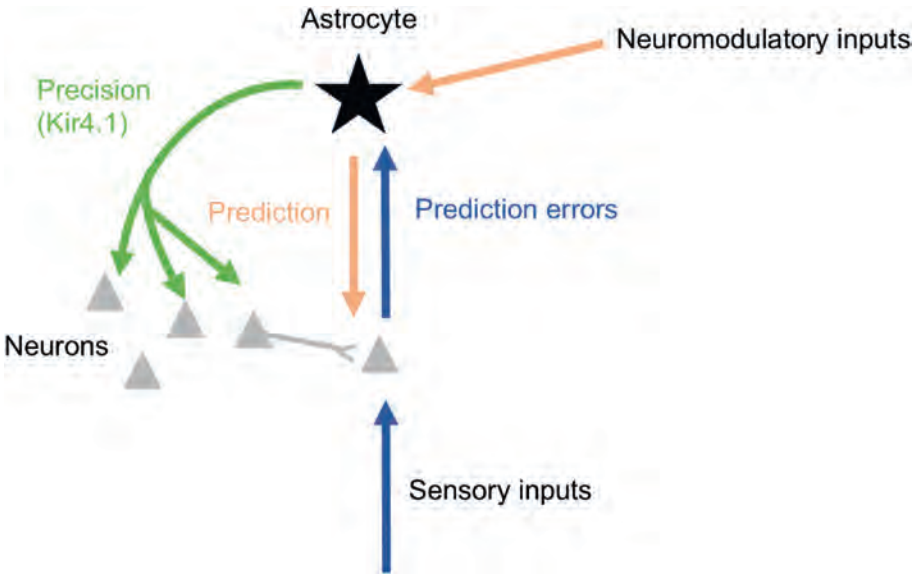


**Figure 1** Predictive coding model of astrocyte interactions with neurons relevant to social behavior. Astrocytes sample synaptic cleft (tripartite synapse), thus receiving prediction error signals (glutamate) from neurons. Astrocytes return two types of signals to neurons: precision modulation signals that globally affect excitability (Kir4.1 buffering of extracellular potassium), and predictions to affect plasticity at synapses (gliotransmitters).

In this issue, the work of Li and colleagues[7] presents new insight into how astrocytes in anterior cingulate cortex (ACC) affect social behavior through the potassium channel Kir4.1. Kir4.1 is a characteristic ion channel of astrocytes that regulates extracellular potassium, and thus neuronal excitability. Astrocytes can, in a sense, use Kir4.1 to absorb potassium produced by local neuronal activity, thus buffering against destabilizing neuronal activity which would reduce the precision of neural encoding (Fig. 1).

Li and colleagues focused on ACC Kir4.1 to understand social deficits, given its emerging role of ACC in mediating social behaviors[8]. In an herbicide toxicity model of autism, the authors found that Kir4.1 was differentially expressed (as it was in human autism samples). Both knockdown and pharmacological inhibition of Kir4.1, an exclusively glial potassium channel[9], was sufficient to rescue both ACC hypoexcitability and social deficits in offspring of GLA-exposed parents. Thus, the present study determines astrocytic Kir4.1 as causative of ACC hypoexcitability and social deficits in offspring of herbicide-exposed parents.

The present study underscores the importance of astrocytes towards mediating complex behavior, and suggests a model of how drug development may target astrocytes in neuropsychiatric disorders. The identified mechanism of social deficit, Kir4.1, is an exclusively glial ion channel, suggesting that future therapeutic interventions for developmental disorders should consider glial targets as well as neural targets. A conceptual predictive processing model[4] (Fig. 1) suggests why astrocytes might be a useful target for drug discovery. Since astrocytes integrate rapidly varying neuronal signals with a larger context over time, they could serve as top-down regulators of behaviorally relevant neuronal plasticity and precision. Recent evidence revealing the importance of astrocytes in regulating both neuronal activity and behavior[1,2,6] supports this direction.

Drug development seeks cell-types with specific protein targets; astrocytes contain differentiated proteins such as Kir4.1 that may directly modulate neuronal activity to influence social behavior. Support for this direction also comes from a recent study where astrocytes were recently identified as a critical mediator of emotional plasticity from psychedelic drugs[10]. Further research is needed to understand how Kir4.1 modulates neuronal activity during complex emotional and social behaviors. Computational modeling of the function of astrocyte−neuron crosstalk in the formation of emotional predictions may guide the development of more precise astrocyte-based treatments. Given the emerging importance of astrocytes in behavior, identifying the most druggable targets for modulating astrocytic computation may yield improved treatments for neuropsychiatric disorders.

## References

1. Dewa KI, Kaseda K, Kuwahara A, Kubotera H, Yamasaki A, Awata N, et al. The astrocytic ensemble acts as a multiday trace to stabilize memory. *Nature* 2025;**648**:146−56.
2. Bukalo O, O'Sullivan R, Tanisumi Y, Mendez A, Weinholtz C, Zimmerman S, et al. Astrocytes enable amygdala neural representations supporting memory. *Nature* 2026. Available from: https://doi.org/10.1038/s41586-025-10068-0.
3. Murphy-Royal C, Ching S, Papouin T. A conceptual framework for astrocyte function. *Nat Neurosci* 2023;**26**:1848−56.
4. Kaye AP, Krystal JH. Predictive processing in mental illness: hierarchical circuitry for perception and trauma. *J Abnorm Psychol* 2020; **129**:629−32.
5. Reitman ME, Tse V, Mi X, Willoughby DD, Peinado A, Aivazidis A, et al. Norepinephrine links astrocytic activity to regulation of cortical state. *Nat Neurosci* 2023;**26**:579−93.
6. Drummond GT, Natesan A, Celotto M, Shih J, Ojha P, Osako Y, et al. Cortical norepinephrine-astrocyte signaling critically mediates learned behavior. *bioRxiv* 2024. Available from: https://doi.org/10.1101/2024.10.24.620009.
7. Li Z, Zhang Y, Chen Y, Lu Y, et al. Aberrant astroglial Kir4.1 activation in the anterior cingulate cortex disrupts neuronal excitability and social behavior. *Acta Pharm Sin B* 2026. Available from: https://doi.org/10.1016/j.apsb.2026.01.029.
8. Kitagawa K, Takemoto T, Seiriki K, Kasai A, Hashimoto H, Nakazawa T. Socially activated neurons in the anterior cingulate cortex are essential for social behavior in mice. *Biochem Biophys Res Commun* 2024;**726**:150251.

9. Nwaobi SE, Cuddapah VA, Patterson KC, Randolph AC, Olsen ML. The role of glial-specific Kir4.1 in normal and pathological states of the CNS. *Acta Neuropathol* 2016;**132**:1−21.
10. Chung EN, Lee J, Polonio CM, Choi J, Akl CF, Kilian M, et al. Psychedelic control of neuroimmune interactions governing fear. *Nature* 2025;**641**:1276−86.

Aakash Basu[a,b], Alfred P. Kaye[b,c,d,e,*]
[a]*Interdepartmental Neuroscience Program, Yale University, New Haven, CT 06511, USA*
[b]*Department of Psychiatry, Yale University, New Haven, CT 06511, USA*
[c]*Department of Comparative Medicine, Yale University, New Haven, CT 06511, USA*
[d]*Wu Tsai Institute, Yale University, New Haven, CT 06511, USA*
[e]*Center for Brain Mind Health, Yale University, New Haven, CT 06511, USA*

*Corresponding authors.
*E-mail address:* alfred.kaye@yale.edu (Alfred P. Kaye)