Social behavior

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Control of social hierarchy beyond neurons

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Noh et al. show that the regulation of social behavior extends beyond neurons. Astrocytes, a major type of glial cell in the CNS, can influence social dominance behavior by modulating excitatory and inhibitory neural activities in the dorsomedial prefrontal cortex of adult male mice. This work highlights the importance of neuron–astrocyte interplay in controlling ethologically relevant behaviors.

Spanning across species from the stag in the wild to humans in the corporate world, social dominance[1,2] crucially determines who gets access to the best resources, the best chances for survival, and even the best opportunities for reproductive success. Extensive research has focused on unraveling the neural circuits and computations that underlie social dominance, with the dorsomedial prefrontal cortex (dmPFC) emerging as a key region[3–6]. The activity of neurons in the dmPFC modulates social ranks in mice during competitive social interaction, and this effect is mediated by disinhibitory microcircuits between pyramidal neurons, vasoactive intestinal peptide (VIP)-expressing neurons and parvalbumin-expressing neurons in the dmPFC[3,4]. However, the role of non-neuronal cells in this process remains largely unexplored. In this issue of *Nature Neuroscience*, Noh et al.[7] describe an important role for astrocytes in modulating social dominance behavior in male mice (Fig. 1).

Astrocytes, a major type of glial cell in the CNS, have garnered attention as active regulators of neural circuits that drive complex behaviors[8]. Recent findings have revealed transcriptomic, proteomic, and anatomical diversity of astrocytes across multiple brain regions and identified various routes taken by astrocytes to regulate their communications with neurons[9]. Moreover, regulatory roles of astrocytes have been shown to be developmentally controlled and neural circuit- and behavior-specific. A key mechanism of such regulation is proposed to be mediated via astrocytic intracellular calcium signaling[10], which is dynamic and spatiotemporally complex.

In line with this notion, Noh et al.[7] provide compelling evidence supporting the involvement of astrocytes in the dmPFC in controlling social hierarchy in adult male mice. The authors used fiber photometry and two-photon imaging to establish a positive correlation between in vivo astrocytic calcium activity in the dmPFC and specific dominance behaviors observed during competitive interactions with other animals. Notably, astrocytic activity varied according to the relative social rank of the opponent male mouse, suggesting a link between astrocytic calcium signaling and social dominance behavior.

To investigate the causal role of astrocytes in social dominance, Noh et al.[7] used chemogenetics and calcium silencing approaches (that is, hM3Dq and CalEx) to enhance or suppress dmPFC astrocytic calcium signaling, respectively. The results revealed that chemogenetic activation of astrocytes led to an increase in social rank in initially lower-ranked male mice, characterized by increased time resisting and approaching opponents and a decrease in retreats. Conversely, silencing of astrocytes resulted in a decrease in social rank in previously highly ranked male mice. Importantly, these effects were specific to social dominance behaviors and did not influence other factors such as muscle power, aggressive behavior, or locomotion. To gain deeper insights into the behavioral components of displayed social dominance, the authors also conducted force tests on the pushing and resisting behaviors elicited by the chemogenetic activation of dmPFC

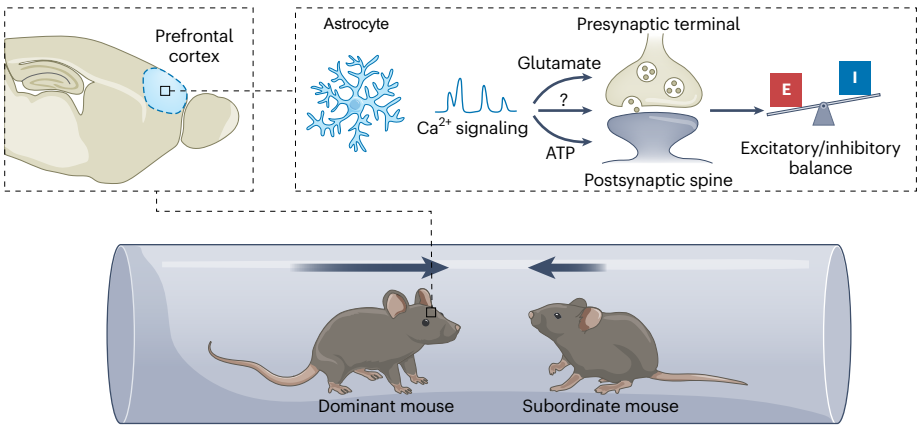

Fig. 1 | Astrocytes in the dmPFC modulate social rank and dominance in male mice through bidirectional modulation of synaptic excitatory/inhibitory balance. Noh et al. used various techniques to investigate the contribution of dmPFC astrocytes to the regulation of social dominance behavior in a tube test. They propose that astrocytes modulate the balance of excitatory and inhibitory synaptic activity through calcium signaling-dependent release of glutamate and ATP, resulting in changes in social rank.

astrocytes (which resulted in the elevation of social rank in low-ranked animals). Interestingly, neuron- and astrocyte-specific optogenetic manipulations appeared to be associated with distinct behavioral phenotypes – activation of neurons increased both pushing and resisting behaviors, whereas activation of astrocytes specifically enhanced resisting behaviors during a tube test.

Complementing the behavioral analysis, electrophysiological recordings of brain slices revealed that the effects of altered dmPFC astrocyte signaling on dominance behavior could be achieved by tuning the excitatory/inhibitory (E/I) balance of dmPFC neurons[7] (Fig. 1). Higher excitatory and lower inhibitory synaptic currents are observed in brain slices from dominant compared to subordinate male mice, indicating a positive correlation between E/I values and hierarchical ranks. Moreover, activating or silencing astrocytic calcium signaling shifted the E/I balance in opposing directions. Indeed, activation of dmPFC astrocytes with hM3Dq increased the E/I ratio by reducing the amplitude of inhibitory postsynaptic currents (IPSCs), whereas expression of CalEx decreased the E/I ratio by increasing the amplitude of IPSCs.

The findings presented by Noh et al. shed light on the previously unrecognized role of dmPFC astrocytes in the regulation of social dominance. By modulating the balance of excitatory and inhibitory synaptic activities, astrocytes directly influence social rank and dominance in adult male mice. These findings are likely to prompt further investigations into the broader role of astrocytes in the neural circuitry underlying social dominance behavior – for instance, whether and how astrocytes modulate specific dmPFC neuronal subpopulations that have been implicated in such behavior. These may include pyramidal neurons that project to the lateral hypothalamus[6] or VIP interneurons[4]. Investigating the intricate interplay among astrocytes, neurons, and other cell types as part of the social dominance circuit across brain regions and social contexts will deepen our understanding of this complex behavior and its underlying neural processes.

In this study[7], the authors further suggested that this bidirectional astrocytic modulation of E/I balance presumably occurs through astrocytic release of glutamate and ATP, on the basis of experiments using pharmacological manipulations and a light-inducible vesicle-trapping method (Fig. 1). Considering the lack of cell-type specificity and neurotransmitter selectivity in these approaches, an intriguing future direction could be to explore the use of genetic sensors for glutamate and ATP. Such a strategy would offer more direct evidence for astrocytic release of neuroactive substances. In addition, activation of G_q G-protein-coupled receptors and attenuation of calcium signaling in astrocytes may trigger downstream changes on the transcriptional and translational levels, given the substantial transcriptomic changes induced by hM3Dq activation and CalEx expression in astrocytes[11]. These changes may contribute to circuit function and behavioral changes on longer timescales and may account for the delayed change in social rank change upon hM3Dq activation of dmPFC astrocytes, in contrast to the rapid increase in intracellular calcium[7].

From a behavioral neuroscience perspective, the findings reported by Noh et al.[7] also raise an important question about how astrocytes may exert a behavior-specific function and differentially regulate diverse types of behavior. Although activation of neurons in the dmPFC elicited both pushing and resisting behavior, activation of astrocytes increased only resisting but not pushing behavior. Moreover, although the dmPFC is traditionally known as the executive hub for higher cognitive functions and exerts top-down control over various behaviors in addition to social dominance[12], manipulating astrocytes in this region does not seem to uniformly affect all dmPFC-mediated behaviors[7]. This suggests potential specificity of astrocytes in differentially regulating different behaviors. Indeed, recent studies using chemogenetic and genetic manipulations of astrocyte signaling have started to unravel the contributions of astrocytes in various brain regions to distinct behavioral functions[8]. For instance, hM3Dq activation in astrocytes in the central amygdala depressed excitatory synaptic transmission and enhanced inhibitory synaptic transmission in a synapse-specific manner, leading to altered conditioned fear expression[13]. hM3Dq activation in hippocampal CA1 astrocytes, however, enhanced excitatory synaptic transmission and promoted memory acquisition[14]. On the other hand, silencing astrocyte calcium signaling with CalEx in the dorsolateral striatum changed tonic GABA currents without altering fast synaptic transmission, causing an excessive self-grooming phenotype[15]. Together, these findings highlight a functional heterogeneity of astrocyte physiological roles[9] and open up exciting avenues for future research to explore the mechanisms that allow astrocytes to exert behavior-specific functions in the dmPFC and other brain regions.

This current work, together with decades of pioneering studies, underscores the physiological importance of the interplay between neurons and astrocytes in ethologically relevant behaviors. Importantly, there is mounting evidence that disruption of key astrocyte mechanisms alters brain function and contributes to the pathogenesis of many neurological and psychiatric disorders, including those characterized by social behavioral deficits (for example, major depressive disorder and autism spectrum disorder). Thus, a comprehensive, mechanistic understanding of this intercellular interaction will be not only instrumental for deciphering neural and behavioral functions in the normal brain but also crucial for developing effective therapeutic interventions for complex mental disorders.

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Competing interests

The authors declare no competing interests.