Trends in
Cognitive Sciences

CellPress

Spotlight

How is helping behavior regulated in the brain?

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In humans and other animals, individuals can actively respond to the specific needs of others. However, the neural circuits supporting helping behaviors are underspecified. In recent work, Zhang, Wu, and colleagues identified a new role for the anterior cingulate cortex (ACC) in the encoding and regulation of targeted helping behavior (allolicking) in mice.

The proverb 'a friend in need is a friend indeed' illustrates that a true friend will provide support and help in a time of hardship. Indeed, both humans and animals display various forms of helping behaviors towards others in need, which are crucial for the survival and health of social species [1,2]. The occurrence of helping behavior involves two fundamental processes: perceiving the emotional states of others and taking actions to fulfil the needs of others [1,2]. Numerous studies have investigated how the brain perceives the states of others [1–3]. However, the neural mechanisms that underlie helping behavior towards others in need remain unclear.

Recently, Zhang, Wu, and colleagues (henceforth Zhang *et al*.) provided a comprehensive characterization of targeted helping behavior towards others in pain and insights into the mechanistic basis of this behavior. In the study, the authors first characterized how mice respond to conspecifics experiencing pain [4]. To do this, they injected melittin, a major component in bee venom that can induce tonic pain, into one hind paw of one mouse ('demonstrator') in a pair of co-housed mice to induce localized pain. As expected, demonstrator mice showed sustained self-licking towards their melittin-injected paws. They next examined how a cage mate ('observer') responded to the melittin-injected demonstrator. Consistent with previous findings demonstrating that animals socially respond to emotionally distressed partners [5,6], observer mice exhibited an increase in general allogrooming (social grooming) broadly directed to the head, neck, and dorsal flank of the melittin-injected demonstrator, as compared with the saline-injected controls [4]. In addition, they observed robust allolicking in observers, specifically targeted to the melittin-injected paw of the demonstrator. Moreover, they demonstrated that these behaviors co-occur when demonstrator mice are in ongoing pain but not in stress. Together, these data suggest that allogrooming and allolicking are two separable behaviors that naturally co-occur in response to others in pain.

As self-licking and allolicking share similar licking patterns, specifically directed towards the injury site [1,2,7], Zhang *et al*. hypothesized that allolicking might serve a similar function to self-licking. When observers interacted with demonstrators in pain, the authors observed a marked overall decrease in the duration of self-licking by demonstrators [4]. More importantly, this decrease was positively correlated with the total duration of allolicking and general allogrooming and allolicking can temporarily suppress the self-licking of demonstrators. These findings indicated that allolicking can benefit the demonstrator by partially replacing the need for self-licking [4]. To further test what factors are involved in the regulation of allolicking, Zhang *et al*. carried out several additional behavioral experiments, demonstrating that several sensory modalities contribute to inducing allolicking [4]. Collectively, these findings reveal that targeted allolicking behavior is a form of proactive helping behavior and is critically regulated by various sensory cues.

How does the brain encode the pain and stress of others in promoting prosocial behaviors? To address this, the authors performed *in vivo* miniscope calcium imaging in the ACC, a brain node implicated in prosocial behaviors [1,2,7,8]. Consistent with the findings that distinct behaviors in observers are elicited when interacting with others in pain or stress, they observed differential neural representations of the emotional states of others in the ACC [4]. Moreover, the authors found that self- and other-related pain exhibit both differential and shared neuronal encoding in the ACC of observers. This differential neural encoding of self- and other-related pain might contribute to behavioral flexibility, whereas the shared encoding might play a role in generating a negative emotional state in oneself in response to the pain of others.

To investigate whether the ACC is required for helping behaviors towards others in pain, Zhang *et al*. chemogenetically suppressed ACC neurons by expressing the inhibitory designer receptor exclusively activated by designer drug (DREADD) hM4Di [4]. Clozapine-N-oxide (CNO) injection in hM4Di-expressing observers led to a substantial decrease in the total duration of both allolicking and general allogrooming to the injured paw of the demonstrator. The authors then examined whether activation of the ACC can enhance prosocial behaviors. They expressed Channelrhodopsin-2 (ChR2) in ACC pyramidal neurons of observer mice and found that optogenetic activation of these neurons in ChR2-expressing mice, but not the controls, resulted in a significant increase in the total duration of both allolicking and general allogrooming [4]. Together, these results identify a previously uncharacterized role

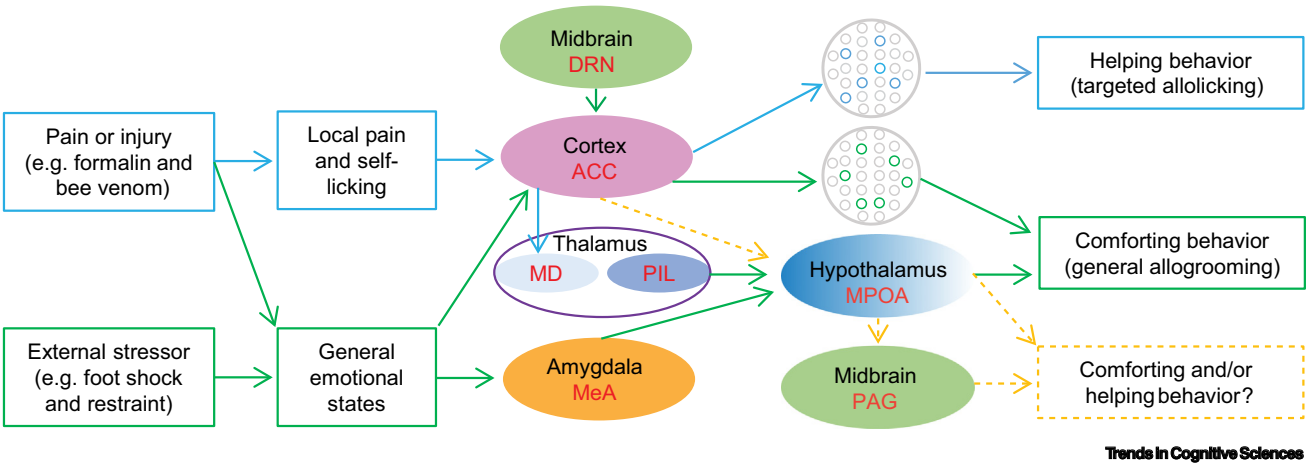

Figure 1. Neural circuits for prosocial comforting and helping behaviors. Several recent studies ([4–6,8,9], among others) have identified key brain regions and circuits for prosocial behaviors, as summarized in the schematic. In a recent study by Zhang *et al*. [4], the anterior cingulate cortex (ACC) has been identified as an important brain node for the encoding and coregulation of targeted helping behavior and comforting behavior towards others in pain. Blue arrows: helping behavior; green arrows: comforting behavior; and broken orange arrows: to be fully characterized behavioral types. Abbreviations: DRN, dorsal raphe nucleus; MD, medial-dorsal thalamus; MeA, medial amygdala; MPOA, medial preoptic area; PAG, periaqueductal gray; PIL, posterior intralaminar nucleus.

for the ACC in the bidirectional coregulation of allolicking and general allogrooming towards others in pain.

Finally, Zhang *et al*. examined how allolicking and general allogrooming are represented by ACC neurons. They showed that individual ACC neurons activated during allolicking and allogrooming towards conspecifics in pain are largely nonoverlapping, suggesting that these behaviors are differentially represented by separable ACC neuronal populations [4]. The authors next examined how allolicking and self-licking in observers are encoded. Similarly, allolicking and self-licking also activated distinct subpopulations of ACC neurons [4], indicating that different subtypes of ACC neurons may distinguish the pain-coping behaviors in others versus oneself. Together, these results suggest that allolicking and allogrooming are separably encoded in the ACC and are differentially represented from self-pain coping behavior.

Overall, Zhang *et al*. provide two major contributions to the field [4]. First, they provide a comprehensive characterization of allolicking as a relatively rapid and easy-to-use assay for studying innate helping behavior in rodents [1,2,4]. Second, the ACC is identified as a key brain node in the encoding and regulation of both helping and comforting behaviors [4]. These findings also highlight many exciting open questions. For instance, are allolicking and general allogrooming in observer mice separably regulated via distinct ACC projections? Moreover, whether other brain areas associated with comforting behaviors, such as the medial amygdala and the posterior intralaminar nucleus, similarly encode and regulate these separable behaviors remains to be clarified (Figure 1) [5,9]. Finally, given the existence of various forms of both helping behaviors and prosocial behaviors, an in-depth characterization of ACC circuitry and other related brain circuits at the molecular, cellular, and circuit levels represents an important future research direction. Addressing these questions will greatly advance our current mechanistic understanding of the neural mechanisms of prosocial behaviors.

Acknowledgments

The authors are supported by the National Science and Technology Innovation 2030 Major Projects of China (STI2030-Major Projects-2022ZD0207300), Fudan University (No: JIF2641002), and National Natural Science Foundation of China (No: 82301395). We also thank Dr Mingmin Zhang for critical comments on the manuscript.

Declaration of interests

The authors declare no competing interests.

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https://doi.org/10.1016/j.tics.2024.02.009

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