

Neural mechanisms of comforting: Prosocial touch and stress buffering

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ABSTRACT

Comforting is a crucial form of prosocial behavior that is important for maintaining social unity and improving the physical and emotional well-being of social species. It is often expressed through affiliative social touch toward someone in distress, providing relief for their distressed state. In the face of increasing global distress, these actions are paramount to the continued improvement of individual welfare and the collective good. Understanding the neural mechanisms responsible for promoting actions focused on benefitting others is particularly important and timely. Here, we review prosocial comforting behavior, emphasizing synthesizing recent studies carried out using rodent models. We discuss its underlying behavioral expression and motivations, and then explore both the neurobiology of prosocial comforting in a helper animal and the neurobiology of stress relief following social touch in a recipient as part of a feedback loop interaction.

1. Prosocial comforting across species

A pat on the shoulder, a gentle embrace; comforting behavior can have a profound impact on mitigating an individual's negative emotional state. Comforting, or consolation, is commonly characterized by affiliative social touch aimed at relieving the distress of others, and is an important form of prosocial behavior that is essential for fostering social cohesion and improving the physical and emotional health of social species (de Waal and Preston, 2017; Dunfield, 2014; Mussen and Eisenberg-Berg, 1977; Rault, 2019; Wu and Hong, 2022). In today's society, we are facing increasing levels of stress, anxiety, and other forms of emotional distress (Almeida et al., 2020). Prosocial actions that can provide comfort and support for alleviating distress to promote a happier, healthier community are therefore of utmost significance.

Across cultures and species, extensive research has shown that offering comfort through physical contact is a powerful form of social support (Eckstein et al., 2020; Korisky et al., 2020; Suvilehto et al., 2015). In humans, comforting behavior appears early in childhood (Dunfield and Kuhlmeier, 2013; Fujisawa et al., 2006; Zahn-Waxler

et al., 1992) and may involve various forms of gentle social touch, such as patting, caressing and hugging. These forms of gentle touch are often seen as an expression of empathic or sympathetic concern for the other (Eisenberg, 2003; Zahn-Waxler et al., 1985) and may serve to reduce stress in the recipient (Jakubiak and Feeney, 2017).

In non-human animals, comforting behavior involves related forms of social touch such as allogrooming in mammals or allopreening in birds. Allogrooming (or allopreening) is typically characterized by scratching, stroking, licking or nibbling and is directed toward the outer body surface (fur, feathers, or bare skin) (Dunbar, 2010; Pellis and Pellis, 2010; Spruijt et al., 1992). Affiliative allogrooming plays a crucial role in the formation and maintenance of social relationships across diverse social species (Morrison, 2016; Pellis and Pellis, 2010; Rault, 2019). While a baseline amount of allogrooming occurs between animals as part of general affiliation, a significant increase in allogrooming can be observed in a prosocial context when a helper responds to another distressed animal—we refer to the former as *affiliative allogrooming* and the latter as *prosocial allogrooming*.

First described in great apes (Clay and de Waal, 2013; de Waal and

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van Roosmalen, 1979), prosocial allogrooming has been studied extensively in several non-human primate species, where it is one of the primary mechanisms of conflict resolution for maintaining peace and providing social comfort in groups (Dunbar, 2010; Jablonski, 2021; Newton-Fisher and Kaburu, 2017; Schino and Aureli, 2010). Other field studies have also observed affiliative allogrooming as important for social cohesion and improving the welfare of distressed conspecifics in other mammals, including elephants (Plotnik and de Waal, 2014), cattle (de Freslon et al., 2020; Wood, 1975), horses (Normando et al., 2002; Shimada and Suzuki, 2020; VanDierendonck and Spruijt, 2012), bats (Narizano and Carter, 2020), and felines (Bradshaw, 2016; Matoba et al., 2013; van den Bos, 1998). Several highly social avian species have also been observed to display post-conflict bystander affiliation through allopreening (Fraser and Bugnyar, 2010; Kenny et al., 2017; Lewis et al., 2007; Radford and Du Plessis, 2006; Seed et al., 2007).

In rodents, prosocial allogrooming was only first experimentally demonstrated less than a decade ago in the socially monogamous prairie vole (Burkett et al., 2016). This behavior has a comforting effect on the recipient and occurs more frequently toward familiar partners, which is consistent with the familiarity bias in human and non-human primate consolation literature (de Waal and Preston, 2017). Similarly, laboratory mice were recently shown to exhibit prosocial allogrooming behavior toward distressed conspecifics subjected to acute stressors such as footshock and physical restraint (Wu et al., 2021), offering opportunities for employing the versatile genetic tools available in mice to dissect the neural mechanisms underlying this behavior. Since then, the phenomenon of prosocial allogrooming has been consistently observed in mice in subsequent studies (Carneiro de Oliveira et al., 2022; Phillips et al., 2023). Other rodent species including mandarin voles and rats also show increased allogrooming towards a distressed other, although their stress buffering effects have not been formally demonstrated yet (Li et al., 2019a; Lu et al., 2018). In addition to allogrooming, animals sometimes engage in prolonged close contact when interacting with a distressed conspecific (Li et al., 2019b; Matsumoto et al., 2021; Muroy et al., 2016). Whether these prolonged affiliative body contacts may serve independently as a comforting behavior is an open question for future study.

2. Behavioral motivations

In order to engage in comforting behavior, a helper must first perceive the distress signals that an animal in distress produces. The distressed state, which is characterized by experiencing anxiety and emotional or physical discomfort, activates the neuroendocrine sympatho-adrenomedullary and hypothalamic-pituitary-adrenal systems and produces physiological and behavioral changes in response to stress (Atrooz et al., 2021). These changes may then be sensed by the helper through multiple sensory modalities. For example, stress information can be transmitted through volatile chemical signals in rats and mice through feces, urine, saliva, tear, and other bodily fluids largely produced by facial or anogenital glands (Brechtbühl et al., 2013; Inagaki et al., 2009; Kiyokawa et al., 2004; Novotny, 2003). Chemical signals released by a distressed animal are sufficient to trigger an increase in comforting behavior (Wu et al., 2021). In addition to olfactory cues, visual inputs may also contribute to observational contagious pain and consolation behavior (Geng et al., 2020). In humans, others' stress is largely communicated by visual and auditory cues, where negative emotional facial expressions can elicit a prosocial response (Marsh and Ambady, 2007) and watching other people experience pain increased the helper's effort to alleviate their partner's pain through hand holding (Peled-Avron et al., 2018).

After perceiving distress signals, this perception of another's distressed state may elicit a behavioral and physiological affective state-matching between the helper and distressed target (emotional contagion), then potentially followed by other-oriented empathic concern (de Waal and Preston, 2017; Eisenberg et al., 2010; Pérez-Manrique and

Gomila, 2018). Indeed, helpers exposed to a distressed conspecific show more anxiety-like behaviors and elevated plasma corticosterone that match the recipient's responses (Burkett et al., 2016; Carneiro de Oliveira et al., 2022; Li et al., 2019a). Similarly, helpers exposed to a surgerized conspecific exhibit more anxiety-like behaviors and increased serum and brain pro-inflammatory cytokines matching the recipient's responses (Zeng et al., 2021).

Although the phenomenon of emotional contagion has been well-documented in animal studies, it can be difficult to distinguish an other-oriented empathic motivation to relieve others' distress, from a self-serving motivation (e.g., self-soothing) aimed at alleviating the personal unpleasantness of sharing the distress of the other (Fig. 1, helper). Instead, considering prosocial comforting from a consequentialist perspective may allow us to assess comforting without imposing assumptions of intentions. Specifically, a behavioral action can be defined as prosocial comforting as long as 1) the action is induced by another's distress and 2) helps to alleviate stress or improve the negative state of the recipient individual, regardless of the motivations or intentions behind it. In rodents, the fact that prosocial allogrooming reduces behavioral measures of anxiety (Burkett et al., 2016; Wu et al., 2021; Zeng et al., 2021) suggests that the behavior is indeed beneficial to the recipient. In multiple non-human primate and ungulate species, receiving allogrooming induces behavioral and physiological changes indicative of stress reduction. Being groomed reduces heart rates (Aureli et al., 1999; Boccia et al., 1989; Normando et al., 2002; Sato and Tarumizu, 1993) and behavioral measures of stress (Fraser et al., 2008). In monkeys, receiving allogrooming can also release beta-endorphins in cerebrospinal fluid that in humans are reported to be pleasurable and released during social touch activities such as massage (Kaada and Torsteinbø, 1989; Keverne et al., 1989; Russell and Phelps, 2013). In fact, even experimental imitation of allogrooming can similarly reduce heart rate (Feh and de Mazières, 1993) and promotes behavioral cues and facial expressions reflective of a positive emotional state (Coulon et al., 2015).

It is important to note that although empathy and prosocial behavior are inter-connected, they are distinct concepts and should not be conflated. Empathy broadly refers to the process of feeling, recognizing,

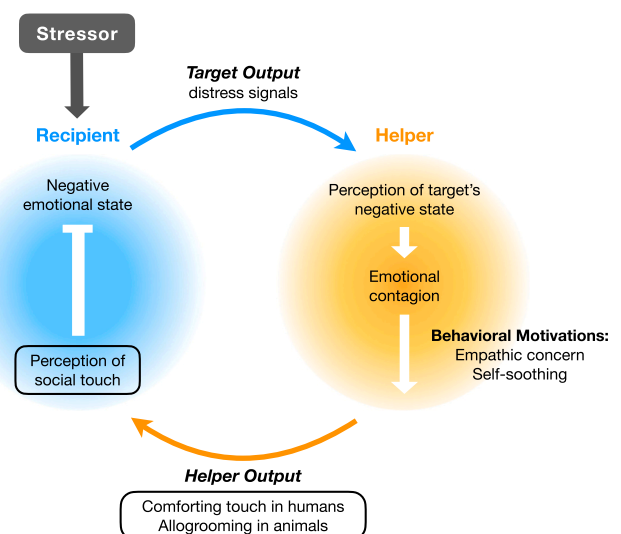


Fig. 1. Comforting touch feedback loop. A stressor commences the loop, activating distress circuits and stress responses in the recipient. This triggers perception of distress signals by the helper, leading to emotional contagion driving behavioral motivations like empathic concern or self-soothing for a behavioral decision. The helper initiates social touch/allogrooming, which is perceived by the recipient and reducing its distress. This cycle may continue as the helper detects changes in the recipient's distress levels, adapting behavioral responses based on feedback from the recipient.

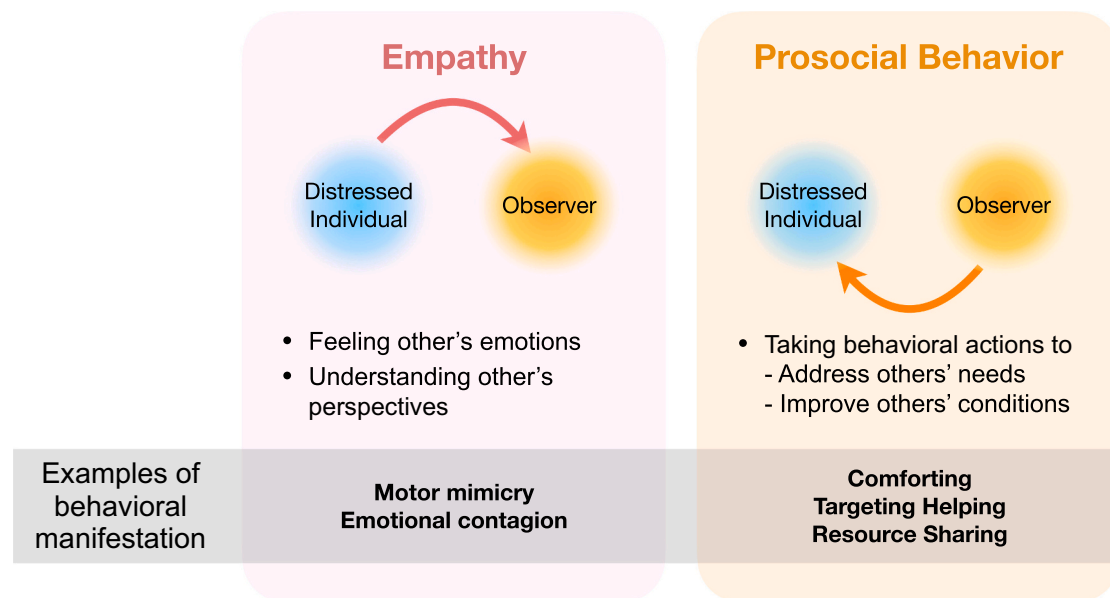


Fig. 2. Conceptual differences between empathy and prosocial behavior. Empathy involves feeling, recognizing, and understanding others' emotional states and perspectives, while prosocial behavior encompasses the crucial step of taking actions to address their needs and improve their conditions.

and understanding others' emotional states and perspectives, whereas prosocial behavior refers to the behavioral actions that address others' needs and improve their conditions (Fig. 2). Prosocial behavior is an essential step beyond feeling and understanding others—simply experiencing and understanding other's emotional states provides limited value to those in need if the observers do not take action to provide assistance and address the needs. Given the limited attention to prosocial comforting behavior in previous reviews, we focus on the expression and mechanisms of comforting behavior in the following sections, with a primary emphasis on recent advances in rodent studies. For more comprehensive discussions of the process of empathy, including the perception and social transfer of negative states, we recommend referring to other reviews (de Waal and Preston, 2017; Ferretti and Papaleo, 2019; Meyza et al., 2017; Panksepp and Lahvis, 2011; Paradiso et al., 2021; Sivaselvachandran et al., 2018).

3. Functions of allogrooming behavior in rodents

3.1. Prosocial allogrooming

Although providing comfort through allogrooming is widely observed in a variety of social species, recent studies of prosocial allogrooming in rodents enable us to gain new insights into the neural mechanisms underlying comforting. As discussed above, a primary effect of allogrooming toward a distressed other is the social buffering of stress (Burkett et al., 2016; Lee et al., 2021; Phillips et al., 2023; Wu et al., 2021). In both prairie voles and mice, distressed animals exhibited reduced anxiety-like behaviors after receiving increased allogrooming compared to animals that did not receive any allogrooming (Burkett et al., 2016; Phillips et al., 2023; Wu et al., 2021), suggesting that allogrooming behavior produces a comforting effect on other individuals.

In rodents, additional social contexts like social hierarchy can modulate the effect of prosocial allogrooming. For example, the display and effects of prosocial allogrooming may differ depending on an individual's place in a social hierarchy. Interestingly, subordinate mice engaged in less prosocial allogrooming than dominant mice toward their respective stressed partners (Lee et al., 2021). Additionally, the stress buffering effect is observed when naïve subordinate helper mice allogroom their stressed dominant partners, and not when dominant helpers

allogroom stressed subordinate partners.

Although animals display increased allogrooming during prosocial interactions, increased social approach has also been commonly observed as a potential way to seek information about the other animal's negative state (Keysers et al., 2022). As stress information is largely transmitted through volatile chemical signals in rats and mice produced by facial or anogenital glands, these investigative behaviors (particularly those involving direct contact towards the anogenital region) allow helpers to obtain information about potential environmental threats, which is a vital component of survival (Brechtbühl et al., 2013; Inagaki et al., 2009; Kiyokawa et al., 2004; Novotny, 2003; Sterley et al., 2018). By contrast, allogrooming typically occurs following investigative behavior and is largely directed toward the dorsal flank, neck and head regions (Burkett et al., 2016; Carneiro de Oliveira et al., 2022; Wu et al., 2021). Allogrooming is thus unlikely to serve as a risk assessment behavior, but rather primarily a comforting behavior.

3.2. Allogrooming in other social contexts

While allogrooming functions as a comforting behavior in prosocial interactions, it may also serve additional purposes depending on the social context (Arakawa et al., 2007; Kalueff et al., 2006). Allogrooming is commonly associated with its role in general affiliation, where multiple rodent species, including pine voles, rats, and mice, have been observed to engage in social grooming in both observational field studies and laboratory studies (Barnett, 1963; Geyer and Kornet, n.d.; Happold, 1976; Mondragón et al., 1987). Several characteristics like body language, reciprocity, mutual care, and familiarity bias support the general affiliative role of allogrooming. Amongst naïve rats, recipients of affiliative allogrooming typically adopt droopy eyelids characteristic of a relaxed body tone and may solicit grooming by nudging and pushing its head under the potential groomer (Pellis and Pellis, 2010). In mice and rats, allogrooming within a group tends to be reciprocated, suggesting that perhaps this behavior may serve some mutually affiliative function between individuals (Schweinfurth et al., 2017a, 2017b; Schweinfurth and Taborsky, 2018; So et al., 2015). Additionally, allogrooming can help maintain group hygiene by removing ectoparasites and improving hygienic benefits, as an extension of the hygienic benefits of self-grooming. In domesticated and wild-derived rats, animals directly groom localized difficult-to-reach regions for the groomee including the

body trunk, shoulder region and back of head (Hart, 1990; Murray, 1987; Schweinfurth, 2020; Weisbroth et al., 1974).

Moreover, allogrooming may serve multiple roles in social hierarchical structure depending on its directionality and specific temporal sequence. Allogrooming occurring between dominant and subordinate mice may support the social hierarchy through opposing approaches of maintaining dominance (dominant toward subordinate) and ameliorating aggression (subordinate toward dominant) (Lee et al., 2019), while allogrooming between mutually subordinate mice may provide social buffering after being attacked (Mondragón et al., 1987; So et al., 2015). However, other studies have shown that allogrooming is not predictive of social rank or dominance hierarchy in males (Barabas et al., 2021a; So et al., 2015).

Finally, across male-female dyads in wood mice, herb-field mice, and singing short-tailed singing mice, males allogroom females more than vice versa, which is likely driven by males obtaining information on female reproductive receptivity and establishing mating access (Fernández-Vargas et al., 2011; Polechová and Stopka, 2002; Stopka and Gracíasová, 2001; Stopka and Macdonald, 1999). These distinct functions may be distinguished by dynamics of the allogrooming interaction and social context (e.g. vocalizations and receptivity of recipient), but are still largely ill-defined.

4. Neurobiology of providing comforting in rodents

4.1. Neural circuits underlying allogrooming

Until recently, the direct physical interactions between bystanders and distressed individuals have rarely been studied, despite evidence of rodents demonstrating social transmission of emotions such as fear and stress (Keysers et al., 2022; Kim et al., 2021; Wu and Hong, 2022). While multiple brain regions have emerged from studies of perception and transfer of others' emotional states like observational fear and emotional contagion in rodents (Allsop et al., 2018; Andraka et al., 2021; Jeon et al., 2010; Rogers-Carter et al., 2018), only recently have regions specifically linked to prosocial comforting behavior been identified. Below, we discuss studies that directly examined the biological mechanisms of providing and/or receiving comforting.

In rodents, olfactory cues play a potent role in communicating emotional states and mediating social behaviors (Ryan et al., 2008; Sterley and Bains, 2021). The odor of a distressed conspecific via an anogenital swab transfer to a naive conspecific is sufficient to elicit increased allogrooming (Wu et al., 2021). Additionally, specific olfactory compounds from sweat, saliva, and urine are associated with allogrooming behavior in laboratory mice in a strain-specific manner (Barabas et al., 2021b, 2022). The medial amygdala (MeA) is an important hub that receives chemosensory inputs from the olfactory system (Chen et al., 2019; Imamura et al., 2020; Raam and Hong, 2021), and is a key node in bridging the perception of distress in others and the expression of comforting behavior (Wu et al., 2021). *In vivo* calcium imaging show that MeA neurons exhibit distinct responses to stressed versus unstressed animals, suggesting that the MeA is involved in the detection of conspecific stress. Additionally, MeA neurons responded to distressed animals partially overlap with neurons activated during allogrooming, implying a potential direct link between the perception of another's stress state and the regulation of allogrooming.

Interestingly, an intersectional genetic approach identified a molecularly defined neuronal population in the MeA—tachykinin-1-expressing (Tac1⁺) GABAergic neurons—in regulating allogrooming behavior (Wu et al., 2021). Optogenetic activation of these neurons directly evokes allogrooming, whereas silencing this population acutely suppresses this behavior. Moreover, activation of the axonal projections of these neurons to the medial preoptic area (MPOA) in the hypothalamus directly elicits allogrooming. These findings provide the first evidence that allogrooming behavior can be evoked by modulating a precise molecularly and anatomically defined neural circuit.

In addition, neurons in the posterior intralaminar thalamic nucleus (PIL) were recently identified as critical for allogrooming behavior in female rats through their projections to the MPOA (Keller et al., 2022), although it is unclear if they also function in a prosocial comforting context. While both the MeA and PIL appear to directly control allogrooming behavior through their projections to the MPOA, the functional relationship between these pathways and other brain regions in driving comforting remains to be characterized. In rats, the PIL acts as an information processing center, receiving multiple modalities of ascending sensory input (primarily auditory and somatosensory), with strong efferents to multiple subcortical and cortical regions (Barsy et al., 2020; Dobolyi et al., 2018; Motomura and Kosaka, 2011). Given that PIL neurons have yet to be well characterized in mice, whether or not the circuits underlying this allogrooming is the same in rats and mice also remains an open question. Another thalamic nucleus, the paraventricular thalamus (PVT), has also been implicated in increased allogrooming towards surgerized mice (Zeng et al., 2021). The PVT is involved in both arousal and valence during affective behavior (Kirouac, 2021; Penzo and Gao, 2021). In a prosocial context, the PVT shows increased cFos expression in response to surgerized mice and chemogenetic silencing of PVT neurons reduces allogrooming behavior (Zeng et al., 2021). Future experiments activating PVT neurons will allow us to gain better insight into whether it plays an instructive role in driving comforting behavior.

Beyond the subcortical regions, the anterior cingulate cortex (ACC) is a hub for emotion processing sharing, social transfer of affect, and the integration of emotional and cognitive processes (Burgos-Robles et al., 2019). Several studies have indicated that ACC neurons play an important role for prosocial allogrooming in prairie voles and mandarin voles (Burkett et al., 2016; Li et al., 2019a), largely based on the evidence of immediate early gene activation. Consistent with this role, infusion of an oxytocin receptor antagonist into the ACC reduces allogrooming behavior in voles (Burkett et al., 2016; Li et al., 2019b). Interestingly, allogrooming behavior is impaired in a transgenic mouse model of frontotemporal dementia. Chemogenetically activating neurons in rostral ACC and PL could rescue behavioral deficits in general affiliative behavior (Phillips et al., 2023), although the extent to which this manipulation rescued allogrooming in this mouse model is unclear. It also remains to be determined if activating ACC/PL neurons may drive consolation behavior similarly in wild-type animals. Given that the ACC is a large brain structure, it is noteworthy that studies linking ACC to prosocial allogrooming behavior range across rostral ACC (Li et al., 2021; Li et al., 2019b; Phillips et al., 2023) and caudal ACC (Burkett et al., 2016) across several rodent species. This necessitates more comprehensive analyses of how each subregion contributes to various stages of the prosocial process.

Whether these brain regions play a role in detecting and sharing other's negative state, empathetic motivations, modulating prosocial behavior responses, or multiple of these roles—have yet to be disambiguated. For example, MeA neurons not only respond to conspecific stress, but also control allogrooming behavior (Wu et al., 2021). How might the MeA orchestrate both stress perception and comforting behavior? Are there discrete neural computations for these processes? Moreover, specific subpopulations of MeA neurons have been found to regulate different behaviors—while Tac1-expressing GABAergic neurons evoke allogrooming, glutamatergic Tac1 neurons promote self-grooming. These findings emphasize the complexity of the MeA's role in regulating multiple types of behavior, and highlight the broader question of how a single brain region can regulate such a range of behaviors. Similarly, PVT neurons are crucial for both allogrooming and anxiety-like behaviors in the helper (Zeng et al., 2021) and the ACC has been implicated in both emotional contagion (Allsop et al., 2018) and prosocial comforting (Burkett et al., 2016; Phillips et al., 2023). Given the evidence for these regions multiplexed roles, this raises multiple questions for they facilitate prosocial comforting behavior. For example, do the PVT and ACC only mediate the initial stage of affective empathy

(emotional contagion), or do they play a role in directly regulating affiliative allogrooming, or both? Are PVT or ACC neurons and circuits involved in each process discrete or overlapping? Additionally, allogrooming across social contexts may have similar motor patterns but differing motivations, thus raising the question of where the circuits diverge and converge in their dynamics.

4.2. Neuroendocrinological mechanisms underlying allogrooming

Prosocial affiliative allogrooming is orchestrated by a complex interplay of neuroendocrine mechanisms. Of the neuropeptidergic systems implicated, the one that has received the most attention is oxytocin. Oxytocin signaling is thought to play a major role in promoting a variety of affiliative social interactions and empathy-related phenomena (Ferretti et al., 2019; Peen et al., 2021; Pisansky et al., 2017), and has been implicated in comforting behavior. Oxytocin neurons in the PVN show increased cFos activity when interacting with a distressed conspecific (Li et al., 2019a). Moreover, infusion of OT receptor antagonists in the brain or deletion of OT receptor appears to be necessary for prosocial allogrooming behavior in voles and mice (Burkett et al., 2016; Li et al., 2020; Matsumoto et al., 2021). Evidence from other mammalian species including vampire bats, pigs, and non-human primates, where intranasal oxytocin delivery increases allogrooming, suggests that oxytocin signaling within the brain indeed supports a conserved role in comforting across species (Arias del Razo et al., 2020; Camerlink et al., 2016; Carter and Wilkinson, 2015; Marsh et al., 2021). However, given the diversity in oxytocinergic effects and marked differences in OTR distribution across rodent species and across sex (Freeman et al., 2020; Sharma et al., 2019), the precise roles of the oxytocin system in detecting and responding to the distress of others remain to be determined. Since OTR are also expressed in multiple regions involved in comforting like the MeA and PVT and are important for processing social cues in mice (Barrett et al., 2021; Gur et al., 2014; Yao et al., 2017), it is also possible that oxytocin may also exert its influence there to regulate comforting.

Serotonergic modulation may also regulate prosocial comforting behavior. The dorsal raphe nucleus is one of the major sources of serotonin (5-HT) in the brain (Ishimura et al., 1988). Both serotonergic dorsal raphe neurons that project to the rostral ACC and serotonergic receptors within the ACC are required for prosocial allogrooming in mandarin voles (Li et al., 2021). Additionally, infusions of 5HT1A receptor agonist into the rostral ACC increases allogrooming behavior (Li et al., 2020, 2021). Furthermore, fiber photometry evidence of increased neuronal activity of dorsal raphe serotonergic neurons and endogenous release of 5-HT in the ACC during natural allogrooming, social approach and investigation suggest that this circuit's role facilitates both general sociability and prosocial allogrooming (Li et al., 2021). By contrast, in mice, experimentally inducing 5-HT increase in the ACC reduces observational fear responses (Kim et al., 2014) and systemic 5-HT3 receptor activation attenuates observational contagious pain (Rodrigues Tavares et al., 2021). The counterintuitive observation that 5-HT can both promote sociability and allogrooming, and also suppress emotional contagion, necessitates further investigation. The diversity of distribution, signaling pathways, and functions of 5-HT receptor subtypes in the brain make it essential to further explore the complex role of serotonin in regulating prosocial comforting behavior.

The vertebrate-specific parathyroid hormone 2 (PTH2) has also been implicated in allogrooming behavior (Keller et al., 2022), although it is unclear if it also plays a role in a prosocial comforting context. Interestingly, PTH2-expressing PIL neurons also innervate PVN oxytocin (Cservenák et al., 2017) and corticotropin-releasing hormone neurons (Dimitrov and Usdin, 2010), presenting an appealing intersection for how PTH2-PTH2R signaling may interact with other neuropeptide systems in modulating affiliative allogrooming behavior. Additionally, D2 receptors in the ACC are important for allogrooming (Li et al., 2020) and are required for observational fear learning (Kim et al., 2014),

suggesting that dopamine signaling might play a role in emotional contagion to promote comforting behavior.

What role do these neuropeptides play in distress perception versus expression of comforting behavior and how do they act in concert? As neuropeptides can modulate the activity of co-released neurotransmitters to increase or decrease postsynaptic responses and can also exert influence over other peptidergic systems (Nusbaum et al., 2017), the regulation of such complex social behavior likely requires the coordinated actions of multiple neuromodulators and neurotransmitters in an intertwined manner. Furthermore, given that physiological responses involved in emotional contagion may affect the expression of comforting behavior, neuropeptidergic action on peripheral systems should also be considered. Recent tool development for measuring endogenous peptide signaling (Wu et al., 2022) may allow us to begin building a more comprehensive understanding of the neuroendocrinology underlying prosocial comforting behavior.

5. Neural mechanisms mediating the social buffering effect of comforting behavior

A key attribute of comforting behavior is the other-benefitting feature of prosocial allogrooming. How and why is affiliative allogrooming comforting for the recipient? The neurophysiology of affiliative social touch may provide some insight into how receiving allogrooming can modulate a recipient's stress-buffering pathways in rodents.

5.1. Peripheral circuits of gentle touch perception

The peripheral pathways transmitting gentle touch signals starting with cutaneous sensory low-threshold mechanoreceptors (LTMRs) are classified based on their action potential conduction velocities (Abraira and Ginty, 2013; Horch et al., 1977). In rodents and other non-human mammals, gentle, pleasant touch information are primarily conveyed by a class of slow unmyelinated low-threshold mechanosensitive afferents called unmyelinated C-tactile LTMRs (C-LTMRs) (Abraira and Ginty, 2013). C-LTMRs are attuned to low-velocity gentle touch and are found exclusively in the hairy skin, which are the predominant areas involved in social touch behaviors like allogrooming (Pitcher et al., 2016). They are also thought to convey information about affiliative social touch. While there is currently no universal molecular marker for the overall C-LTMR population, several genetically-defined subtypes have been identified that are activated specifically to innocuous social-like touch stimuli mimicking stroking and allogrooming (Abraira and Ginty, 2013; Elias and Abdus-Saboor, 2022; Zimmerman et al., 2014). These neuronal subtypes include those expressing tyrosine hydroxylase (Li et al., 2011), MrgprB4 (Liu et al., 2007; Vrontou et al., 2013), TAFA4 (Delfini et al., 2013), Cav3.3 (Reynders et al., 2015), and VGLUT3 (Seal et al., 2009). Experiments characterizing these peripheral pathways have largely been performed with gentle somatosensory stimuli mimicking social touch, like gentle brushing or stroking stimuli presented by experimenters (McGlone et al., 2014).

There is increasing evidence that gentle social touch can be anxiolytic and rewarding across species (Mortazavi et al., 2012; Nummenmaa et al., 2016; Perini et al., 2015; Tang et al., 2020; Weze et al., 2007). Endogenous activation of C-LTMRs through gentle stroking stimuli produces soothing and stress-buffering effects. Receiving massage-like gentle stroking is sufficient to lower heart rate (Liu et al., 2022), decrease anxiety behaviors and reduce plasma corticosterone levels following stress (Walker et al., 2020). Chemogenetically activating C-LTMRs similarly reduces physiological markers of stress (Schaffler et al., 2022) and has been found to be rewarding (Huzard et al., 2022; Vrontou et al., 2013) and can trigger dopamine release in the nucleus accumbens in female mice (Elias et al., 2023).

5.2. Convergence of gentle touch and stress circuits in the brain

One potential mechanism to explain the stress buffering effects of allogrooming is the convergence of gentle touch signals onto stress circuits in the brain. Peripheral inputs of gentle touch travel through a spinothalamic tract that transmits signals from the dorsal horn of the spinal cord to the brain (Choi et al., 2020; Liu et al., 2022). Several subcortical structures involved in touch-related responses also regulate autonomic stress responses. For example, hypothalamic nuclei (PVN, arcuate nucleus) which are implicated in beta-endorphin/mu-opioid- and oxytocin-mediated responses to gentle social touch stimulation, also regulate stress responses. The nucleus of the solitary tract (NTS) in the brainstem receives signals from these nuclei as well as touch-related signaling reflecting thermoreceptive and skin stimulation (Herman, 2018), influencing peripheral heart and vascular responses through the vagal nerve and sympathetic ganglia respectively (Zoccal et al., 2014). Additionally, noradrenergic inputs to the PVN from the NTS and the ventral lateral medulla modulate the activity of corticotropin-releasing factor producing neurons, thereby regulating the expression of stress-associated behaviors and activating the HPA axis (Daviu and Bains, 2021; Füzesi et al., 2016; Kim and Iremonger, 2019).

The anxiolytic effects of social touch are commonly attributed to oxytocin, a neuropeptide associated with general affiliative and prosocial behaviors (Marlin and Froemke, 2017; Onaka and Takayanagi, 2019; Walker et al., 2017; Yoshida et al., 2009). Dynamic stroking cutaneous stimulation activates oxytocin neurons in the PVN and SON (Okabe et al., 2015, 2020; Tang et al., 2020; Yu et al., 2022) and triggers oxytocin release and elevated plasma oxytocin levels (Stock and Uvnäs-Moberg, 1988). Exogenous infusion of oxytocin into the brain has been linked with decreased anxiety, reduced blood pressure and stress-induced tachycardia, reduced stress-induced rises of circulating corticosterone and anxiety-like behavior (Heinrichs et al., 2003; Morris et al., 1995; Ring et al., 2006; Smith and Wang, 2012, 2014; Tops et al., 2007). This aligns with evidence from human research that receiving a massage is a pleasant and de-stressing experience that is associated with increased oxytocin release and a dampening of HPA response (Li et al., 2019b; Morhenn et al., 2012). Given oxytocin's ability to increase the salience of both positive and negative social contexts, it is important to also consider the diversity in oxytocinergic effects. Although the mechanisms underlying both gentle touch and distress are complex with interactions between multiple neuropeptide systems, the shared components between the two provide some insight into how comforting behavior can provide stress-relief and comfort to an individual (Uvnäs-Moberg and Petersson, 2022).

Comforting behavior via allogrooming is likely to be effective in generating calming effects to buffer the recipient's stress through these gentle touch neural circuits and endocrinological mechanisms, though many open questions remain. It has been previously shown that the mere presence of a conspecific can reduce stress (Kiyokawa and Hennessy, 2018). However, there is evidence that that allogrooming provides additional stress buffering beyond just physical proximity (Wu et al., 2021). How do comforting social touch signals compound and integrate with olfactory communication-induced social buffering? Across species, gentle touch perception is modulated by additional available multisensory information/cues (Bieler et al., 2018; Croy et al., 2014; Imschloss and Kuehnl, 2019; Jousmäki and Hari, 1998) – how are these signals integrated during comforting to attenuate stress? And how is receiving grooming from another more stress-relieving than self-grooming? Despite its explanatory potential, the neurophysiology of affiliative touch has been largely overlooked in studies of comforting behavior thus far. Future studies integrating prosocial behavior assays with experiments probing stress-buffering effects resulting specifically from social touch will begin to deepen our understanding of comforting. Additionally, the real-time physiological effects of prosocial allogrooming in a recipient mouse such as changes in respiratory and cardiovascular autonomic responses can be measured through wireless telemetry

systems, allowing assessment of the temporal dynamics and sequence of comforting behavior and the resultant stress buffering.

6. Concluding remarks

In this review, we examined prosocial comforting behavior, particularly in rodent studies, and its associated behavioral expression and motivations. Herein we also discussed recent advancements in the neural circuits and neuroendocrinology of the integrated process of performing comforting behavior in a helper and the stress-buffering effects of social touch in the recipient. Since the neurobiology of empathy and prosocial actions have largely been considered in isolation from the mechanisms underlying the positive effects in the recipient, we encourage examining helper and recipient as a dynamic system where distress precipitates comforting that then reduces distress (Kingsbury and Hong, 2020). Advancements in rodent studies have provided foundational discoveries and insights into this complex process, which coupled with emerging techniques such as simultaneous long-term physiological measurements or neuronal recordings of stress signals across animals, will provide a more comprehensive understanding of the neurobiology and dynamics of comforting touch. Despite these advances, there is still much to learn about individual and species differences in both expression of comforting behavior and its stress-buffering effects, and how their neural mechanisms might be shared with other prosocial interactions. While many questions remain, gaining a deeper understanding of the neural mechanisms of both promoting comforting touch and its beneficial stress-buffering properties is increasingly pertinent to the field of social neuroscience.

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