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Brain circuits that regulate social behavior

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Social interactions are essential for the survival of individuals and the reproduction of populations. Social stressors, such as social defeat and isolation, can lead to emotional disorders and cognitive impairments. Furthermore, dysfunctional social behaviors are hallmark symptoms of various neuropsychiatric disorders, including autism spectrum disorder (ASD) and post-traumatic stress disorder (PTSD). Consequently, understanding the neural circuit mechanisms underlying social behaviors has become a major focus in neuroscience. Social behaviors, which encompass a wide range of expressions and phases, are regulated by complex neural networks. In this review, we summarize recent progress in identifying the circuits involved in different types of social behaviors, including general social investigation, social preference, mating, aggression, parenting, prosocial behaviors, and dominance behaviors. We also outline the circuit mechanisms associated with social deficits in neuropsychiatric disorders, such as ASD, schizophrenia, and PTSD. Given the pivotal role of rodents in social behavior research, our review primarily focuses on neural circuits in these animals. Finally, we propose future research directions, including the development of specific behavioral paradigms, the identification of circuits involved in motor output, the integration of activity, transcriptome, and connectome data, the multifunctional roles of neurons with multiple targets, and the interactions among multiple brain regions.

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INTRODUCTION

Social behaviors encompass a complex array of actions essential for survival, reproduction, offspring nurturing, and the overall well-being. These behaviors include any form of communication or interaction between two conspecifics and are observed across a wide range of organisms, from single-celled microorganisms to complex humans [1, 2]. Social need, similar to food and sleep, is maintained in a homeostasis [3]. Chronic social deprivation (isolation) induces multisystem dysregulation in rodents, including metabolic dysfunction, affective disorders, cognitive impairment, and social behavior deficits [4]. Clinical epidemiology further confirms social isolation as a risk factor for several human pathologies including diabetes, cancer, neuropsychiatric disorders, and cardiovascular disease in humans [5].

In addition, social behaviors, whether cooperative or competitive, have been evolutionarily selected due to their necessary roles in adapting the complex environment. However, when expressed inappropriately in terms of timing, context, or intensity, they can have harmful effects [6]. Chronic and repeated social stress can lead to anxiety, depression, and cognitive impairments. For example, chronic social defeat and forced loss of social rank have been shown to induce significant depressive states [7], while conditioned fear based on social cues can result in persistent social fear [8]. Early-life maternal separation differentially affects stress resilience, where predictable separation enhances adaptive capacity while unpredictable separation reduces it [9]. Similarly, human studies highlight social stress as a key risk factor for neuropsychiatric disorders, including depression and anxiety. Together, these findings emphasize the importance of social homeostasis, requiring neither deficiency nor excessively stressful expression.

Social deficits also represent core symptoms of multiple neurological disorders. For example, patients with autism spectrum disorder (ASD) show deficits in social-emotional reciprocity and nonverbal communicative behaviors used for social interaction [10]. Patients with post-traumatic stress disorder (PTSD) show reduced prosocial behaviors, social avoidance, and heightened irritability [11]. Despite their diagnostic centrality, social deficits remain therapeutically challenging, partially due to incomplete understanding of the neural mechanisms governing social behavior regulation. Therefore, decoding neural mechanisms underlying social behaviors is essential for unraveling the intricacies of species-specific interactions and advancing effective treatments for brain disorders associated with social deficits.

Previous studies have extensively explored the foundations of social behaviors across multiple levels, including genetic, cellular, circuit, and behavioral dimensions. The emergence of chemogenetics in the 1990s and optogenetics in 2005 have enabled neuroscientists to establish causal relationships between neural circuits and social behaviors [12, 13]. As a result, significant progress has been made in deciphering the circuit-level mechanisms that regulate social behaviors, marking a transformative advancement in the field.

In this review, we summarize recent advances in understanding the neural circuits that regulate various social behaviors, including general social investigation, social preference, mating, aggression, parenting, prosocial behaviors, and dominance behaviors. We also discuss circuit mechanisms underlying social

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deficits in neuropsychiatric disorders. Together, these insights contribute to a comprehensive understanding of the brain nuclei and neural circuits involved in social behaviors. It should be noted that our discussion mainly focuses on rodent models, given their central role in research on social behaviors and the neural mechanisms underlying them.

NEURAL CIRCUIT BASIS OF SOCIAL BEHAVIOR

Circuit mechanisms underlying general social investigation

Social investigation is characterized by the close examination of social stimuli, a process that relies on the integration of multiple sensory cues to gather sufficient information before transitioning to the appropriate consummatory phase. During this investigatory phase, motor output includes orienting toward the stimulus and inspecting specific body parts.

In many mammals, such investigation is primarily conducted through sniffing, often directed toward facial and anogenital regions, where pheromones are concentrated [14]. Consequently, the neural circuits involved in general social investigation are centered around interactions within the olfactory system. During nasal contact, pheromones carrying identity-related information are drawn into the vomeronasal organ (VNO), where they bind to specific receptors on vomeronasal sensory neurons (VSNs). These neurons then relay the information to the accessory olfactory bulb (AOB), a key structure in shaping appropriate social behavioral responses. The AOB projects to the medial amygdala (MeA), the bed nucleus of the stria terminalis (BNST), and the posteromedial cortical amygdala (COApm) [15]. From there, pheromone signals are further transmitted to a series of medial hypothalamic nuclei, which are critical for generating social behaviors.

Notably, social investigation involves pheromone detection by both the vomeronasal and main olfactory systems. The main olfactory epithelium (MOE) transmits signals via the main olfactory bulb (MOB), which converge with vomeronasal inputs in the MeA —either directly or through the posterolateral cortical amygdala (COApl) [16]. While traditionally regarded as distinct pathways (the MOE-MOB pathway for general odorant detection; whereas the VNO-AOB pathway for pheromones), recent studies demonstrate that MOE is indispensable for social behaviors. For example, MOE dysfunction eliminates aggression and sexual behaviors in both sexes in mice [17–19], underscoring the essential role of the main olfactory system in social chemosensing.

Social investigation also provides tactile stimulation through close physical interaction. Although social tactile cues remain understudied compared to other sensory modalities, they constitute essential components of social behavior. Physical contact serves fundamental homeostatic functions, where disrupted tactile input impairs social motivation during isolation [3]. Early-life social touch, such as maternal grooming, critically shapes neurodevelopmental trajectories [20]. In adults, non-noxious affective touch engages cutaneous low-threshold mechanoreceptors (LTMRs), with subsequent signal transmission occurring via Aβ afferents and C tactile fibers to spinal pathways. From there, tactile cues are relayed to brains through different ascending pathway including dorsal column pathway and spinocervical tract pathway. In the brain, the ventral posterior nuclear complex of the thalamus receives the information from spinal cord-medulla pathway and send it to the somatosensory cortex [21]. Recent study found that social contact activates the parabrachial nucleus, mediating spinal-to-forebrain transmission of social touch signals, and reunion-related neurons in the medial preoptic nucleus (MPN), which regulate social satiety [3]. Nevertheless, precise mechanistic understanding of tactile processing circuits in specific social behaviors remains limited.

Circuit mechanisms underlying general social preference

Social interactions are highly complex and involve a balance between approach and avoidance behaviors, leading to an individual's preference for specific subjects. The social preference test, which measures the relative time a test animal spends investigating two targets (Fig. 1A) [22], is widely used paradigm to assess social interest. In mammals, individuals typically exhibit a preference for social over non-social stimuli and for novel over familiar conspecifics [23].

The generation of social preference. The internal drive behind social preference is thought to be rooted in the brain's reward system, where preference can be understood as the reinforcement of social rewards. This process involves several reward-related brain regions, including the basal forebrain (BF) [24], the paraventricular thalamus (PVT) [25], ventral tegmental area (VTA) [24, 26, 27], and nucleus accumbens (NAc) [28, 29]. Additionally, social preference is closely linked to memory and recognition abilities, which interact with the reward system. Rewards create motivation that facilitates rapid learning, while memory and recognition are necessary to identify and remember more rewarding subjects. Thus, social preference can be viewed as an associative learning process driven by social reward (Fig. 1B).

The mPFC as the center of sociability. Preference for social over non-social targets, often referred to as sociability, has been extensively studied, with the medial prefrontal cortex (mPFC) playing a central role (Fig. 1C). The mPFC bidirectionally modulates sociability through distinct subregions and circuits. For example, the circuit from the infralimbic cortex (IL) to the basolateral amygdala (BLA) promotes social interaction, while the circuit from the prelimbic cortex (PrL) to the BLA or NAc suppresses it [28, 30]. Early-life social experiences are also critical for the development of sociability in adulthood, mediated by the mPFC-PVT circuit [25]. Given the importance of PVT in reward system, one possible explanation is that prior social experiences help individuals learn that social interactions are rewarding. As a central hub, the mPFC integrates inputs from various regions, including the BLA and the ventromedial thalamus (VMT), which transmits cerebellar signaling to the mPFC. Activation of these circuits has been shown to impair social interactions [31, 32].

Circuits regulating social novelty preference. The mPFC serves as a central hub for social cognition and critically regulates social novelty preference. Unlike circuits governing general sociability, those mediating social novelty preference involve greater hippocampal engagement—particularly the ventral hippocampus and CA2/CA3 subregions (Fig. 1D). These regions are essential for encoding and recognizing social memory. The hippocampus facilitates memory- and recognition-dependent novelty preference through extensive connections with other "social" brain areas, especially those processing novel stimuli [33–39].

Social novelty preference is also strongly regulated by the reward system. The VTA-NAc circuit, a central component of the reward system, is robustly activated by novel social stimuli [27]. The NAc receives inputs from the mPFC and hippocampus, both of which are necessary for mediating social novelty preference [29, 40]. Additionally, the lateral septum (LS), another key component of the reward system, receives inputs from corticotropin-releasing hormone (CRH)-expressing neurons in the IL. The IL^{CRH}-LS circuit suppress social interaction with familiar individuals, and inhibition of this circuit impairs social novelty preference [41].

Neuromodulation of social preference. Neuromodulatory systems also play a significant role in social preference. Oxytocin (OXT), for instance, is essential for social preference and acts through projections from the paraventricular nucleus (PVN) to various regions, including the hippocampus [33], VTA [26], and supramammillary nucleus (SuM) [42]. Additionally, OXT signaling converges with serotonin signaling in NAc and contributes to social reward [43, 44]. Neuropeptide B/W activates the central amygdala (CeA), which regulates social

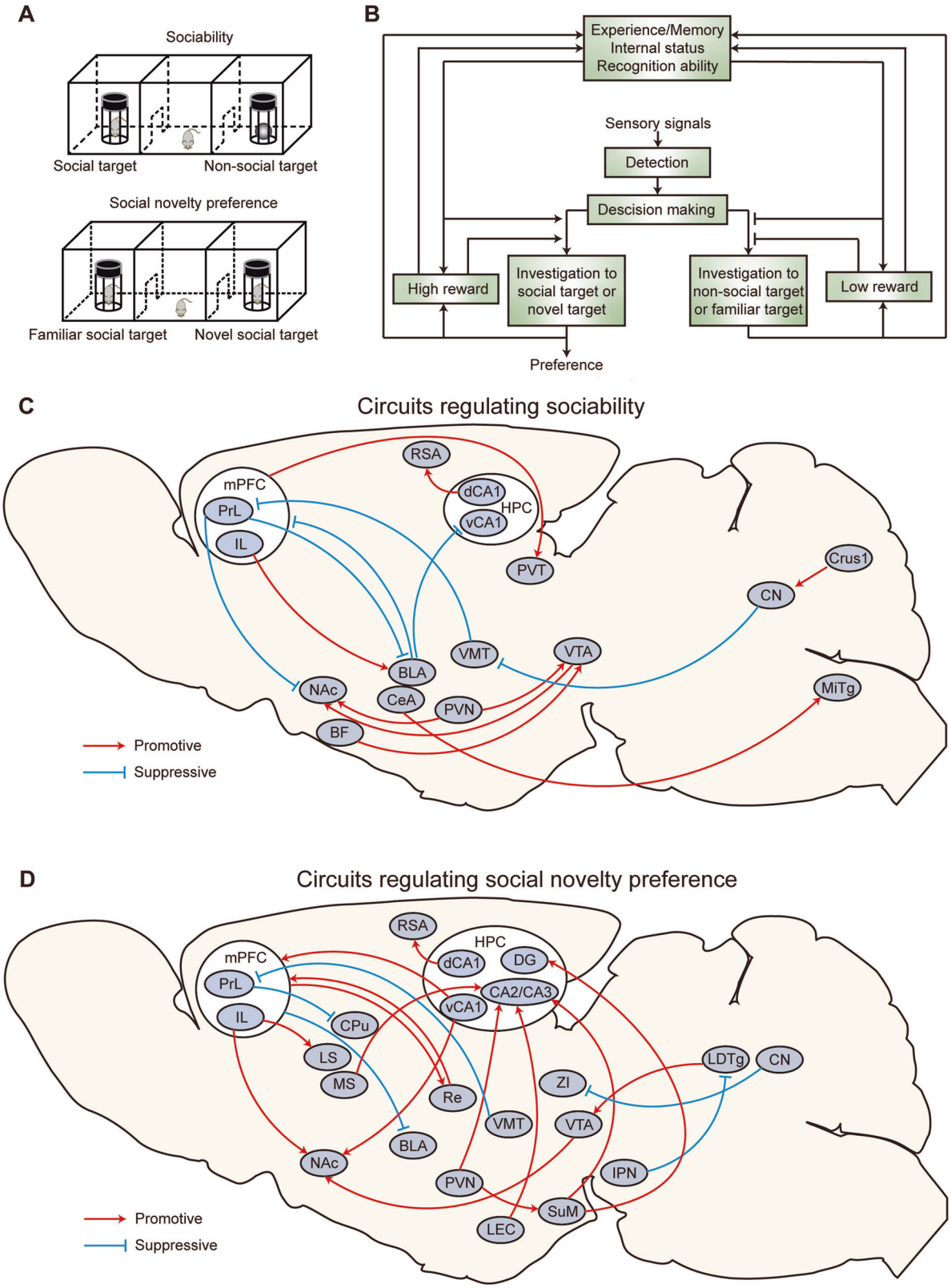
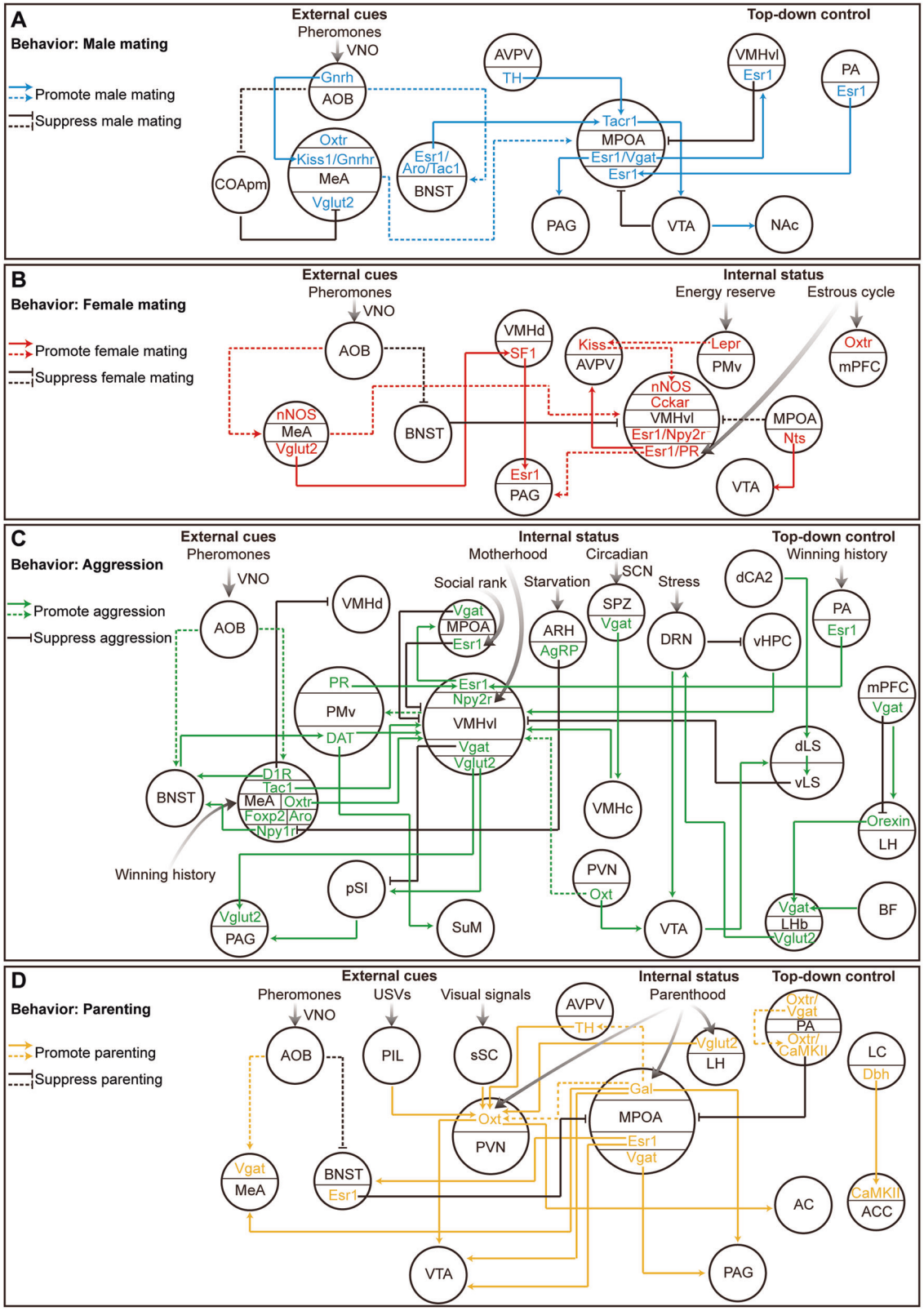


Fig. 1 The generation and circuit mechanism of general social preference. A Schematics of the social preference test. **B** Schematic illustrating the generation of social preference. **C** Representative neural circuits underlying sociability. **D** Representative neural circuits underlying social novelty preference. BF basal forebrain, BLA basolateral amygdala, CeA central amygdala, CPu caudate putamen, HPC hippocampus, IL infralimbic cortex, IPN interpeduncular nucleus, LDTg lateral dorsal tegmentum, LEC lateral entorhinal cortical, LS lateral septum, MiTg microcellular tegmentum, mPFC medial prefrontal cortex, MS medial septum, NAc nucleus accumbens, PrL prelimbic cortex, PVN hypothalamic paraventricular nucleus, PVT paraventricular thalamus, Re thalamic nucleus reuniens, RSA retrosplenial agranular cortex, SuM hypothalamic supramammillary nucleus, VMT ventromedial thalamus, VTA ventral tegmental area.



preference by inhibiting the microcellular tegmentum, thereby promoting physical contact with unfamiliar individuals [45].

It is important to note that social preference can also be directed toward specific subjects, such as a male's preference for females. These behaviors will be discussed in subsequent sections.

Circuit mechanisms underlying mating

Mating behavior exhibits distinct sexual dimorphism in its behavioral expressions. In rodents, male copulation consists of three stages: mounting, intromission, and ejaculation. In contrast, females adjust their postures to either allow or reject males. The

Fig. 2 Circuits regulating innate social behaviors. A–D Representative brain regions, molecules, and circuits involved in **A** male copulation, **B** female copulation, **C** aggression, and **D** parenting. Dotted lines represent behavior-related circuits that have not yet been validated using advanced manipulation techniques. Molecular markers are indicated within the corresponding circles of brain regions. If a circuit terminates inside a circle, it has been confirmed to originate from or target a specific neuronal population within that region. If a circuit terminates outside a circle, it has been confirmed to involve the region, but the specific neuronal population remains unidentified. For example, in Fig. 2A, $MPOA^{Esr1/Vgat}$ neurons project to VMHvl to promote male copulation; however, it remains unclear whether this circuit targets $VMHvl^{Esr1}$ neurons. AC auditory cortex, ACC anterior cingulate cortex, AOB accessory olfactory bulb, ARH arcuate nucleus of the hypothalamus, AVPV. anteroventral periventricular nucleus, BF basal forebrain, BNST bed nucleus of the stria terminalis, COApm posteromedial cortical amygdala, dCA2 dorsal CA2, dLS dorsolateral septum, DRN dorsal raphe nucleus, LC locus coeruleus, LH lateral hypothalamus, LHb lateral habenula, MeA medial amygdala, mPFC medial prefrontal cortex, MPOA medial preoptic area, NAc nucleus accumbens, PA posterior amygdala, PAG periaqueductal gray, PIL posterior intralaminar nucleus of the thalamus, PMv ventral premammillary nucleus, pSI posterior substantia innominate, PVN hypothalamic paraventricular nucleus, SCN suprachiasmatic nucleus, SPZ subparaventricular zone, sSC medial superficial layers of ipsilateral superior colliculus, SuM hypothalamic supramammillary nucleus, vHPC ventral hippocampus, vLS ventrolateral septum, VMH ventromedial hypothalamus, VMHc central VMH, VMHd dorsal VMH, VMHvl ventrolateral VMH, VNO vomeronasal organ, VTA ventral tegmental area.

typical posture indicating female sexual receptivity is known as lordosis [46].

The control center and motor output of mating processes. The hypothalamus serves as the central hub for regulating mating behavior, with notable differences between the sexes (Fig. 2A, B). In males, the medial preoptic area (MPOA) plays a primary role in controlling copulation, whereas the ventrolateral part of the ventromedial hypothalamus (VMHvl) is more critical for female mating behavior [47]. In males, a subset of MPOA neurons co-expressing estrogen receptor type 1 (Esr1) and vesicular γ-aminobutyric acid transporter (Vgat) has been identified as essential for initiating copulation [48, 49]. Additionally, activation of neurons expressing tachykinin receptor 1 (Tacr1) can drive male mice to mount even inanimate objects [50]. In females, $VMHvl^{Esr1}$ neurons that are positive for progesterone receptor (PR) and negative for neuropeptide Y receptor Y2 (Npy2r) are necessary for lordosis [51, 52]. However, not all $VMHvl^{Esr1/Npy2r-}$ neurons are involved in female sexual behaviors due to their functional heterogeneity. Recent studies have further subdivided the VMHvl into medial (VMHvlm) and lateral (VMHvll) regions [53, 54]. Activation of VMHvll neurons expressing cholecystokinin A receptor (Cckar) has been shown to reduce rejection and enhance receptivity in females [54].

The MPOA also plays a central role in mating-related reward. $MPOA^{Tacr1}$ neurons enhance male mating motivation through both anteroventral periventricular nucleus (AVPV)-dependent and AVPV-independent pathways [50, 55], although the differences between these pathways remain unclear. Additionally, $MPOA^{Tacr1}$ neurons project directly to the VTA, a key reward center, to promote mating [50]. Interestingly, the MPOA also appears to be essential for female mating reward. Activation of neurotensin (Nts)-expressing MPOA neurons or the $MPOA^{Nts}$-VTA circuit generates rewarding effects and promotes social approach behaviors in females [56]. VTA appears crucial for mediating mating reward in both sexes, with its canonical VTA-NAc circuit potentially enhancing mating-related motivational states [50]. Furthermore, the VTA establishes reciprocal connectivity with the periaqueductal gray (PAG) [57], which may coordinate behavioral initiation and termination processes.

Following hypothalamic processing, decision-making signals are transmitted to the PAG [50, 58]. PAG constitutes a core component of the emotional motor system, which is considered the principal mediator of social actions [59]. In the context of female sexual behaviors, PAG projects to spinal motoneurons controlling lordosis-related musculature (such as iliopsoas and adductor) via the nucleus retroambiguus, and sacral spinal cord innervating uterus through the pelvic organ stimulating center [60]. These innervations enable postural adjustments and cervical dilation to facilitate successful mating. In males, both PAG and PVN project to the paragigantocellularis nucleus (nPGi) which provides tonic descending inhibition on penile reflexes and pudendal motoneurons. During copulation, PAG and PVN signaling disinhibit nPGi-mediated suppression, enabling erectile responses and mating behavior execution [61]. While these findings establish the functional significance of PVN in motor output, the central neural circuits mediating its role in male mating remain poorly characterized.

Sensory inputs that modulate mating. The MPOA and VMHvl primarily function as control centers that integrate external cues, internal status, and top-down regulatory signals to guide appropriate social decisions. Although the expression of mating behaviors requires integration of multimodal sensory inputs (olfactory, visual, auditory, tactile), pheromonal signals represent the most extensively characterized class of social signals. These chemical cues exert bidirectional regulatory effects on reproductive behaviors, with both stimulatory and inhibitory subtypes identified such as the exocrine gland-secreting peptide 1 (ESP1) enhancing female receptivity and ESP22 suppressing mating in both sexes [58, 62].

Correspondingly, both MPOA and VMHvl receive dense inputs from olfactory-processing areas, including the MeA and BNST, as mating behavior in both sexes is largely driven by opposite-sex pheromones [58]. Traditionally, the MeA and BNST were thought to recognize sex-specific information and relay it to the hypothalamus, as they exhibit distinct neural encoding patterns in response to male and female intruders [63–65]. However, recent evidence suggests that this information processing may not follow a strictly hierarchical pathway [65]. For instance, $MPOA^{Esr1}$ and $VMHvl^{Esr1}$ neurons can still exhibit sex-specific representations even after the inhibition of $BNST^{Esr1}$ neurons, indicating that $BNST^{Esr1}$ neurons may be necessary for sex preference but not for sex identification [65].

Nevertheless, the BNST and MeA remain critical for mating behavior. In males, inhibition of $MPOA^{Tacr1}$-projecting $BNST^{Esr1}$ neurons, which preferentially respond to females, suppresses mating [50, 63], while distinct MeA neuronal populations are involved in sex discrimination and mounting [66, 67]. Additionally, the COApm, another key component of the olfactory system, mediates male avoidance of unhealthy females via its projections to MeA^{Vglut2} neurons [68]. In females, the MeA promotes sexual behaviors in response to ESP1 and darcin—chemosignals secreted by males in lacrimal fluid and urine, respectively [58, 69]. In contrast, the BNST suppresses mating behavior when activated by ESP22, a juvenile mouse lacrimal protein [62, 70]. However, direct evidence for the regulatory roles of MeA-MPOA and MeA-VMHvl circuits remains limited. Instead, vesicular glutamate transporter 2 (Vglut2)-expressing MeA neurons have been shown to enhance female receptivity through their projections to the dorsal VMH (VMHd) [58].

Beyond pheromonal cues, acoustic communication plays a crucial role in mating interactions. Males emit ultrasonic vocalizations (USVs) upon encountering novel females and dynamically

adjust their vocal output in response to female auditory feedback. Females produce two distinct vocalizations : USVs during male approach and broadband vocalizations (or audible squeaks) signaling sexual rejection [71]. However, the precise neural mechanisms by which auditory cues influence mating behavior remain unclear. Somatosensory inputs also shape female reproductive behavior. Vaginal-cervical stimulation triggers hormone-dependent neural activation in key nodes of the mating circuit, including the MPOA, VMH, MeA, BNST, and PAG [72]. Together, while pheromonal cues drive core mating sequences, auditory and tactile inputs likely provide modulatory influences through incompletely understood circuit mechanisms.

Mating behavior is also influenced by environmental stimuli. A recent study found that mice exposed to predator odors, such as those from foxes, exhibit preference shift from females to males, which might partly explain the suppression of male copulation by external threats. This shift in sex preference is regulated by the VTA in both males and females, albeit through distinct circuit-dependent and activity-dependent mechanisms. In males, the VTA-MPOA circuit promotes preference for males, while the VTA-NAc circuit drives preference for females. In females, the VTA-NAc circuit controls preference for both sexes, with phasic firing mediating preference for females and tonic firing mediating preference for males [73].

Internal status and top-down control that regulate mating behaviors. Beyond external cues, male copulation is also regulated by the posterior amygdala (PA), which may provide top-down facilitation [74]. Female copulation, on the other hand, is influenced by the ventral premammillary nucleus (PMv) and AVPV, which mediate the effects of internal energy status and the estrous cycle, respectively [51, 75–78]. Female sexual receptivity is strictly gated by the estrous cycle, occurring exclusively during estrus—a phase marked by ovulation and regulated by ovarian hormones, including estrogen and progesterone [51]. Neural circuit analyses reveal that this hormonal control induces estrogen-dependent plasticity. For instance, VMHvl^{PR} neurons (particularly the VMHvl^{Cckar} subset) exhibit increased axonal terminal density in the AVPV of hormonally primed females compared to unprimed controls, a process dependent on estrogen signaling [51, 54].

The AVPV, a key hub sensitive to estrous cycle fluctuations, produces kisspeptin—a critical upstream regulator of gonadotropin-releasing hormone (GnRH) secretion [79]. This forms a positive feedback loop: from VMHvl$^{Esr1/PR}$-AVPV to kisspeptin-GnRH-gonadotropin-ovary, which amplifies mating behavior. However, the VMHvl^{PR}-AVPV circuit is necessary but insufficient for receptivity [51]. Recent work identifies additional subsets (VMHvl$^{Esr1/Npy2r-}$ and VMHvll^{Cckar}) that can induce receptivity independent of estrous phase [52, 54]. Notably, VMHvll^{Cckar} neurons show estrous-cycle-dependent responses to male cues, with heightened activity during estrus [54].

Estrogen also regulates OXT and its receptor (OXTR) [80], enabling OXT-mediated control of reproductive behavior. For example, OXT signaling in mPFC somatostatin (SST) interneurons selectively enhances male preference during estrus (but not diestrus) [81]. Though the mPFC likely exerts top-down modulation of mating, its integration with VMHvl-centered circuits remains unclear.

Finally, motherhood overrides mating behavior: lactating females shift from receptivity to aggression toward adult males —a mechanism detailed in the following section on aggression.

Circuit mechanisms underlying aggression

The control center and motor output of aggression. Aggression, a behavior essential for competing over resources and protecting oneself or family, is a universal and survival-critical trait. VMHvl and PMv serve as the central hub for aggression in both sexes (Fig. 2C). Although the VMHvl appears to play seemingly contradictory roles in female copulation and aggression, recent studies have revealed that these behaviors are regulated by distinct neuronal populations in a reproductive-state-dependent manner.

Aggression is expressed in both sexes, albeit with quantitative differences. Consequently, some neural circuits may be shared, although direct evidence in females remains relatively limited [47, 82]. The heterogeneity of VMHvl^{Esr1} neurons contributes to sex-specific differences in aggression [82]. A common pathway for various aggressive behaviors involves the circuit from the posterior substantia innominata (pSI) to the PAG, which encodes aggressive actions [83, 84]. VMHvl^{Esr1} neurons, located upstream of the pSI, exhibit sexual dimorphism in glutamatergic and GABAergic synaptic strength. Male VMHvl^{Esr1} neurons send stronger excitatory projections to the pSI, promoting aggression, whereas female VMHvl^{Esr1} neurons send stronger inhibitory projections, suppressing aggression [82].

The PAG plays a critical role in aggression motor output, mirroring its function in mating behavior. Notably, PAG activation occurs selectively during the action phase rather than the sensory phase of aggression. It orchestrates aggression-specific motor patterns through projections to effector systems: (1) polysynaptic connections to jaw muscles essential for bite attacks [84], and (2) brainstem-mediated pathways to spinal α-motoneurons that regulate chasing locomotion [85]. Additionally, aggressive encounters also require coordinated autonomic activation (tachypnea, mydriasis, tachycardia). While the PVN directly connects with sympathetic pathways, the PAG influences autonomic output indirectly via rostral ventrolateral medulla (RVLM) relays [86], enabling synchronized physiological and behavioral responses.

Although the PAG-centered emotional motor system primarily mediates instinctive aggression, emerging evidence suggests involvement of voluntary motor systems in action refinement. For instance, male mounting behavior occurs in both mating (female-directed) and aggression (male-directed) contexts, with distinct postural variations [49]. This raises several key mechanistic questions: (1) How does neural coding distinguish these nuanced motor patterns? (2) Are discrete PAG neuronal populations recruited by specific upstream control centers? (3) Alternatively, does the PAG generate core motor sequences that are contextually modulated by voluntary systems (e.g., motor cortex)?

Sensory inputs that modulate aggression. Olfactory cues serve as the predominant sensory drivers of aggressive behavior, typically promoting this response through a dedicated neural pathway. In this circuit, the MeA and BNST relay pheromonal information from AOB to key aggression control centers, including both the VMHvl and PMv [74, 86, 87]. Several MeA neuronal populations have been identified as critical regulators of aggression [64, 87, 88]. Among these, only MeA^{Oxtr} and MeA^{Tac1} neurons have been proven to project directly to VMHvl neurons [87, 89]. Surprisingly, a posteroventral MeA population expressing dopamine D1 receptor (D1R) bidirectionally regulates aggression through distinct projections to VMHd or BNST. Glutamatergic MeA^{D1R} neurons suppress aggression via projections to the VMHd, while GABAergic MeA^{D1R} neurons promote aggression via projections to the BNST [90]. Although the BNST, another key role in relaying pheromone information, is also involved in aggression and sends strong inputs to the VMHvl, direct experimental evidence for the BNST-VMHvl circuit remains limited.

Given the critical role of olfactory cues in both mating and aggression, a key question arises: how does the olfactory processing system coordinate these distinct behaviors? Although these behaviors engage overlapping olfactory regions (e.g., MeA and BNST), they recruit sexually dimorphic neuronal populations and downstream targets [49, 64, 65]. This functional segregation is particularly evident in pheromone signal interpretation, where identical chemosignals can elicit opposing, sex-specific responses. A striking example is ESP1, which enhances female receptivity while

promoting male aggression. This behavioral dichotomy likely stems from sexually dimorphic processing in the MeApv: ESP1 mainly activates MPA-projecting neurons in males while VMHd-projecting neurons in females [58]. This sex-specific routing of chemosensory information may underlie the divergent behavioral responses to identical pheromonal cues.

Adaptive aggression requires dynamic behavioral modulation in response to social cues. In rodents, submissive signals from defeated opponents actively suppress further attacks - for instance, a subordinate rat's cessation of sniffing significantly reduces the likelihood of renewed aggression from the dominant individual [91]. However, the specific sensory modalities mediating this inhibition remain unclear, with potential candidates including visual assessment of submissive postures or tactile feedback during social interaction.

Notably, auditory cues appear to play a minimal role in murine aggression regulation. Unlike mating behaviors which involve ultrasonic vocalizations (USVs), aggressive mounting in male mice occurs independently of USV production [49], suggesting distinct sensory processing requirements for these competing social behaviors.

Top-down regulation and internal status that modulate aggression. PA is the major excitatory inputs of VMHvl to promote aggression, which is thought to provide top-down regulation [74]. Additionally, this network also involves the mPFC and hippocampus. The hippocampus promotes aggression through direct projections to the VMHvl and a disinhibitory motif in the lateral septum [92–94]. In contrast, the mPFC plays a more complex role. Glutamatergic mPFC neurons projecting to lateral hypothalamus (LH) can trigger violent biting behaviors [95]. However, the PrL, a subregion of the mPFC, suppress aggression via GABAergic projections to Orexin-expressing neurons in the LH, which in turn increases aggression through the lateral habenula (LHb) [96, 97].

Compared to mating, more studies have elucidated the circuits mediating the influence of internal states on aggression. The VMHvl indirectly connects with the suprachiasmatic nucleus (SCN) regulating circadian rhythms and the DRN mediating stress responses. These connections underlie increased aggression during early evening (zeitgeber times 13) or after social isolation stress [94, 98, 99]. Additionally, the MeA and BNST are involved in the reduction of aggression induced by starvation, mediated by their connections with agouti-related peptide (AgRP)-expressing neurons in the arcuate nucleus [100]. Finally, subordinate mice tend to avoid conflict with dominant conspecifics. The social state is reflected in caudal MPOA^{Esr1} neurons projecting to the VMHvl. Inhibition of this circuit overrides the suppression of aggression towards stronger opponents [101].

Maternal status profoundly shapes female aggression, with lactating dams exhibiting robust offspring-protective aggression toward intruders, while virgin females show minimal aggressive responses. This behavioral dichotomy is particularly striking in male encounters: virgins display mating behaviors, whereas lactating dams initiate attacks [52]. The behavioral switch reflects reproductive state-dependent neural activity in VMHvl subpopulations. Particularly, mating-related VMHvll^{Cckar} neurons respond robustly to male cues in estrous virgins (but not lactating dams), while aggression-related VMHvl^{Npy2r} neurons specifically activate in lactating dams (but not virgins) [52, 54]. Moreover, oxytocin further modulates aggression in a sexually dimorphic manner, enhancing mild aggression in females compared to severe aggression in males [102]. Given its prepartum surge and essential role in lactation [103], oxytocin represents a likely mediator of the maternal aggression switch, though direct mechanistic evidence remains to be established.

Circuits mediating the experience-dependent aggression. Aggression exhibits intrinsic rewarding properties, as demonstrated by conditioned place preference tests in which mice preferentially spend time in environments previously paired with aggressive experiences. This reward value implicates a broad neural network involving key reward-processing regions, including: the VTA, dorsal raphe nucleus (DRN), LHb, and BF [98, 102, 104, 105]. Notably, dopamine transporter (DAT)-expressing PMv neurons contribute to aggression reward through their projections to the SuM [106], revealing a specialized circuit component for aggressive behavior reinforcement.

The "winning effect" refers to experience-dependent aggression potentiation, where prior victories enhance subsequent aggression. Notably, short-term and long-term winning produce distinct behavioral outcomes: short-term winning (1st-5th encounters) progressively strengthens aggression, while long-term winning (5th-10th encounters) promotes attacks even against stronger opponents [107]. This behavioral shift reflects a multi-stage plasticity cascade in the VMHvl (Fig. 3): Initial victories (1st-5th encounters) induce progressive strengthening of long-range inputs and local microcircuits, which further lead to heightened intrinsic excitability of VMHvl neurons. Meanwhile, sustained dominance (5th-10th encounters) stabilizes long-range input strength and enhances neuronal excitability, while reduces local synaptic efficacy [107]. Key circuits mediating this plasticity include: the PA-VMHvl circuit, which is crucial for the multi-stage cascade [107], and the posteroventral MeA (MeApv)-VMH circuit, showing rapid synaptic strengthening after initial wins, although its long-term role remains unclear [108].

Defeat experience induces context-specific behavioral adaptation, characterized by social avoidance toward prior attackers but heightened aggression against less aggressive conspecifics [109, 110]. Mechanistically, the activation of MeApv may underlie defeat-induced aggression enhancement towards less aggressive intruders, as chemogenetic inhibition of MeApv during losing experiences suppresses the enhancement of aggression post-defeat [109]. Current evidence suggests that both winning and losing experiences activate excitatory MeApv neurons, which mediate experience-dependent aggression. However, it remains unclear whether winning and losing involve distinct neural mechanisms, or separate neuronal populations within MeApv. Furthermore, while VMHvl^{Esr1} neurons are known central mediators of aggression, their specific role in defeat-induced aggression modifications requires further investigation.

Neuromodulatory systems critically regulate experience-dependent aggression through plasticity modulation. For example, testosterone, which promotes aggression, increases following repeated winning [107]. Testosterone treatment enhances aggression in non-aggressive mice and induces stronger long-term potentiation (LTP) in ex vivo brain slices [111]. More importantly, testosterone-treated non-aggressive mice show enhanced synaptic strength in the PA-VMHvl circuit following winning experiences. Although the precise mechanism remains unresolved, this synaptic enhancement may result from either testosterone's direct neuromodulatory effects or secondary effects mediated by testosterone-facilitated winning experiences [111].

Conversely, OXT mediates defeat-induced social avoidance through the retrochiasmatic supraoptic nucleus (SOR)-anterior VMHvl (aVMHvl) circuit. Activation of the SOR^{Oxt}-aVMHvl^{Oxtr} circuit facilitates synaptic potentiation, driving aVMHvl neuronal hyperactivation upon re-exposure to attackers [110].

Circuit mechanisms underlying parenting

The control center and motor output of parenting behaviors. In rodents, maternal and paternal behaviors share similar behavioral expressions, with the exception of nursing, though they differ in frequency. Parenting and infanticide are both critical for resource optimization and the survival of social groups. The balance between these behaviors is finely regulated by a network of circuits centered on MPOA, which plays diverse roles in a cell type-

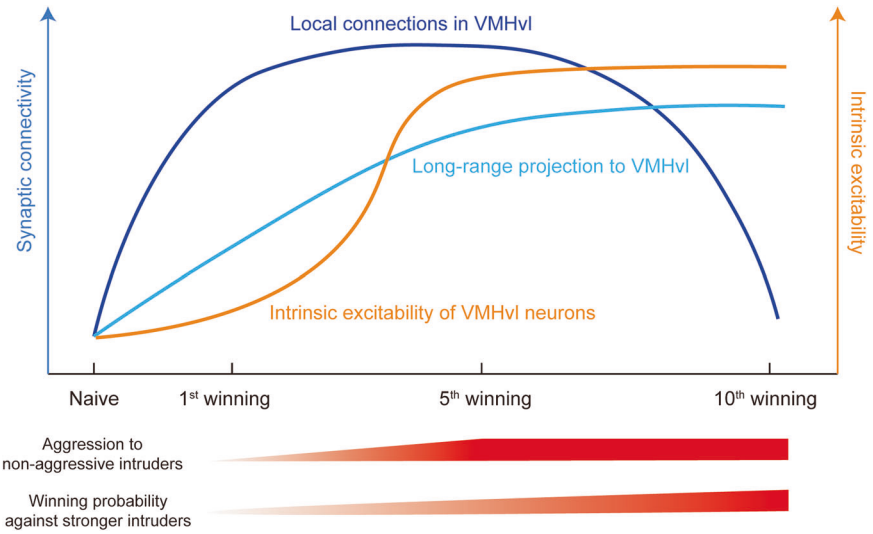


Fig. 3 Neural mechanisms underlying winning-dependent aggression enhancement. This figure is modified from [107]. VMHvl the ventrolateral part of the ventromedial hypothalamus.

and circuit-specific manner (Fig. 2D) [112, 113]. For instance, activation of galanin (Gal)-expressing MPOA neurons projecting to the PAG, VTA, and MeA elicits grooming, pup-seeking, and suppression of infanticide, respectively [112]. Similarly, activation of $MPOA^{Esr1}$ neurons projecting to the VTA promotes pup retrieval [114]. Additionally, Calcitonin receptor (Calcr)-expressing MPOA neurons both promote parenting and suppress infanticide [115, 116]. Conversely, MPOA receives inputs from glutamatergic PA neurons, which increase infanticide and decrease parenting [117].

Parenting behaviors primarily comprise pup retrieval and grooming, with retrieval involving a sequential action cascade from exploratory seeking to motor execution. The manipulation of MPOA-VTA circuit significantly influence pup seeking and retrieval quantity [112, 114], while damaging PAG suppresses pup grooming and prolongs retrieval duration without affecting total retrieved pup count [112, 118]. This functional dissociation suggests stage-specific neural control: Initial exploratory phases predominantly engage VTA-mediated motivational circuits, while execution phases recruit PAG-dependent motor coordination. Notably, both parenting and aggression involve orofacial motor patterns such as bite-related actions, though with differences in intensity. The PAG's indirect connectivity to jaw muscle may mediate this shared motor output, yet the neural mechanisms enabling context-dependent modulation of bite force (gentle pup carrying versus aggressive biting) remain a critical knowledge gap.

Sensory inputs that regulate parenting behaviors. Unlike mating and aggression, the role of pheromone and olfactory cues in the context of parenting is indeterminate [47]. Correspondingly, the positive regulators upstream of the MPOA remain relatively unclear. VNO signaling has been shown to suppress parenting, while the MeA bidirectionally regulates parenting in an activity-dependent manner [115, 119]. Similarly, BNST also bidirectionally regulates parenting, while in a subregion-dependent way [46]. Furthermore, recent studies found that $BNST^{Esr1}$ neurons and $MPOA^{Esr1}$ neurons antagonize each other to regulate both infanticide and maternal care through reciprocal projections [120]. However, whether MeA and BNST function as transmitter of olfactory cues or other roles in the regulation of parenting is unclear.

Pup-related cues that drive parenting are mainly transmitted through USVs. The PVN, another key center for parenting, plays a significant role in USVs-induced parenting behaviors. PVN^{Oxt} neurons are both necessary and sufficient to suppress infanticide and elicit pup retrieval [121]. These neurons receive inputs from the posterior intralaminar nucleus of the thalamus, which transmits USVs information [122], and send oxytocinergic axons to regions involved in parenting, such as the VTA [54] and auditory cortex (AC) [123, 124]. Additionally, the AVPV, located upstream of PVN^{Oxt} neurons, is necessary for maternal behaviors [125]. Interestingly, both the PVN and AVPV are downstream of $MPOA^{Gal}$ neurons [112], linking these two parenting centers.

Visual signals seem mainly mediate the influence of environment. For example, maternal behaviors can be transmitted through social interaction, with virgins co-housed with dams developing the ability to respond to pup USVs and performing pup retrievals. This transmission requires the visual inputs for virgins to observed the parenting behaviors of dams, which is mediated by the medial superficial layers of the ipsilateral superior colliculus (sSC)- PVN^{Oxt}-AC circuit [124, 126]. In addition, a recent study found that the visual signals of intruder mice significantly influence the pup retrieval order. When seeing male (but not female) intruders, dams preferentially retrieve pups positioned closest to the intruders [127]. However, the circuit mechanisms are unclear.

Parenting is also robustly influenced by tactile stimuli. Orofacial tactile stimulation via nasal contact with pups initiates trigeminal nerve-dependent jaw-opening reflexes essential for retrieval initiation [128]. Furthermore, suckling stimuli is necessary to induce the kyphosis posture, which facilitates nursing. Once sufficient pups begin to suck, the previously active dams become quiescent and adopt kyphosis [128]. This suckling-induced postural adaptation involves caudal PAG [118], though the neural circuit mechanisms underlying this transition remain poorly characterized.

Internal physiological states modulate parenting behaviors. Although parenting is an innate behavior, its expression depends on the appropriate internal state, such as parenthood. Parenting is primarily exhibited by parents rather than virgins, and this behavioral shift is mediated by $MPOA^{Gal}$ and PVN^{Oxt} neurons. $MPOA^{Gal}$ neurons are involved in the pregnancy-induced onset of parenting through Esr1 and PR signaling [129]. PVN^{Oxt} neurons, on the other hand, have more complex functions. In females, OXT levels rise rapidly and acutely before parturition, followed by a gradual decline [103]. This surge is necessary for the development of subsequent maternal behaviors, such as responding to pup

calls [123]. Accordingly, PVN^{Oxt} neurons are activated by pup USVs in mothers but not in virgins [122, 124]. Similarly, the switch to paternal behavior depends on the OXT system, mediated by a strengthened LH^{Vglut2}-PVN^{Oxt} circuit in fathers [121].

Parenting is closely associated with emotional regulation and shares some circuits involved in modulating negative affect. Generally, parenting and negative affect are antagonistic. For example, neonatal distress can induce parental anxiety, which is alleviated by paternal care [130]. The MPOA, as the central hub for parenting, bidirectionally regulates parenting and anxiety through distinct neuronal populations, with enhanced parenting often accompanied by reduced anxiety [131]. Additionally, the anterior cingulate cortex (ACC), which is important for empathy, is activated during pup retrievals, likely due to empathy for distressed pups. Inactivation of the locus coeruleus (LC)-ACC circuit disrupts pup retrieval behaviors [132].

Circuit mechanisms underlying prosocial behaviors

In research on humans and non-human primates, prosocial behaviors are typically defined as affiliative social behaviors aimed at benefiting others. However, in rodent studies, the concept of "prosocial behaviors" has broadened to encompass general non-antagonistic behaviors [133]. In this review, we confine the discussion to a narrower definition. The expression of prosocial behaviors involves a complex process, from perception to consummation, with the consummation phase comprising distinct forms such as comforting, helping, and resource sharing, which respectively support others' emotional states, goals, and material needs [133].

Perception of others' states. The perception of others' states is a prerequisite for the subsequent decision-making and consummation steps, which include the perception of both mental states and physical states. The former is often assessed using the affective state discrimination task, which reflects emotional recognition and discrimination. In this paradigm, observer animals choose between naïve animals and demonstrator animals exhibiting specific emotional states. In rodents, state information is primarily relayed through olfactory cues, as is the case with many other social behaviors [133]. Some studies have also found that emotional information can be transmitted through auditory cues via the BLA [134]. Additionally, the CeA [135], PVN [136], insular cortex (IC) [137], piriform cortex [138], and mPFC [139] are all implicated in emotional perception and discrimination. In addition, affective states can also be reflected by facial expressions or body posture [91], which suggests visual cues may be involved in the initiation of prosocial behaviors.

The physical states contain physiological conditions such as pain and anesthesia and environmental constraints such as physical entrapment. Although the sensory cues relaying physical states remain poorly understood, it should depend on multisensory integration rather than discrete sensory modalities. Emerging evidence demonstrates murine capacity to distinguish anesthetized from sleeping conspecifics [140]. Given that behavioral expressions rapidly change following anesthesia induction [140], olfactory or pheromonal signaling (requiring sustained metabolic processes) appears insufficient for state discrimination. Instead, the perception may involve an interactive model, in which individuals execute social investigation while assessing partner feedback to infer states.

Empathy and emotional contagion. Perception of others' states can elicit corresponding emotional and behavioral responses in observers, such as empathy and helping behaviors. The circuits involved in empathy—the ability to share the experiences of others—vary depending on the form of shared experience, the familiarity between observers and demonstrators, and prior experiences.

Observational fear and pain are the most common forms of shared experience. The BLA and NAc appear to be common downstream regions that receive empathic information and elicit emotional and behavioral responses, given their direct roles in regulating fear and pain [141]. However, distinct upstream regions are involved in different forms of empathy. For example, circuits from the DRN and ACC to the NAc, as well as the circuit from the IC (but not the ACC) to the BLA, regulate the social contagion of pain and analgesia [142–144]. Conversely, circuits from the hippocampus, LS, and ACC to the BLA, as well as the circuit from the hippocampus (but not the ACC) to the NAc, regulate observational fear [141, 142, 145]. Further studies are needed to clarify the specific roles of the BLA and NAc, as well as their various inputs, and to determine whether there is functional redundancy. Additionally, the lateral basolateral amygdala-MeA and ACC-lateral mediodorsal thalamus (MDT) circuits are also involved in fear contagion [146, 147]. While appropriate empathy helps prevent potential threats, overexpression of empathic fear can lead to emotional disorders. The mPFC circuit projecting to the l/vlPAG is activated during observational fear and suppresses vicarious freezing, suggesting a regulatory role in controlling empathic responses [148].

In this complex network, the ACC has been identified as a core regulator of empathy, integrating local microcircuits and various neuromodulator systems (Fig. 4A) [149–153]. Both SST and parvalbumin (PV) interneurons in the ACC suppress observational fear by inhibiting pyramidal neurons [151, 152]. Vasopressin (AVP), OXT, and dopamine signaling in the ACC are all necessary for empathy, while increased serotonin (5-HT) levels can impair empathic responses [149, 150, 154]. Notably, although most circuit-based studies use bilateral manipulations, one study found that the ACC's role in observational fear is lateralized, with the right ACC (but not the left) being involved [155]. Further research is needed to explore the lateralized circuitry mechanisms.

The ACC is often implicated in experience-independent empathy, while the hippocampus mediates the influence of prior experience and familiarity. In experience-dependent empathic fear, the dorsal hippocampus activates BLA fear memory engram cells during prior experiences, and these engram cells are reactivated by the ventral hippocampus during observational fear [145]. In experience-independent empathy, the ventral hippocampus regulates fear contagion between familiar (but not unfamiliar) observers and demonstrators through its projections to the NAc [141, 145].

Prosocial actions: comforting and helping. Prosocial actions in rodents include comforting (often expressed as allogrooming) and targeted helping [133]. Both behaviors are regulated by the ACC, albeit through distinct neuronal populations [156]. The ACC's role in prosocial actions requires the integration of several neuromodulatory signals, including OXT [157, 158], dopamine, and 5-HT [159, 160]. Interestingly, 5-HT circuits promote consolation but suppress empathy [149, 160], likely due to the involvement of distinct 5-HT receptor subtypes. Another important but unresolved question is how sensory cues are transmitted to the ACC to elicit different behavioral expressions.

The MeA is another critical hub for comforting, promoting allogrooming through its projections to the MPOA and IC [89, 161]. Additionally, the MPOA-posterior intralaminar thalamus (PIL) circuit has been found to regulate social grooming in natural social contexts [162]. Whether this circuit regulates consolation-directed allogrooming and whether it functions downstream of the MeA-MPOA circuit to encode action-specific information requires further experimental evidence.

The neural circuits involved in helping behaviors vary depending on the context. The ACC primarily mediates actions such as liberating a trapped conspecific [158], while the PVT-NAc circuit is activated to drive rescue-like behaviors toward anesthetized conspecifics in bystander mice [163]. In social decision-making task, where a "dictator" decides whether to help a recipient obtain

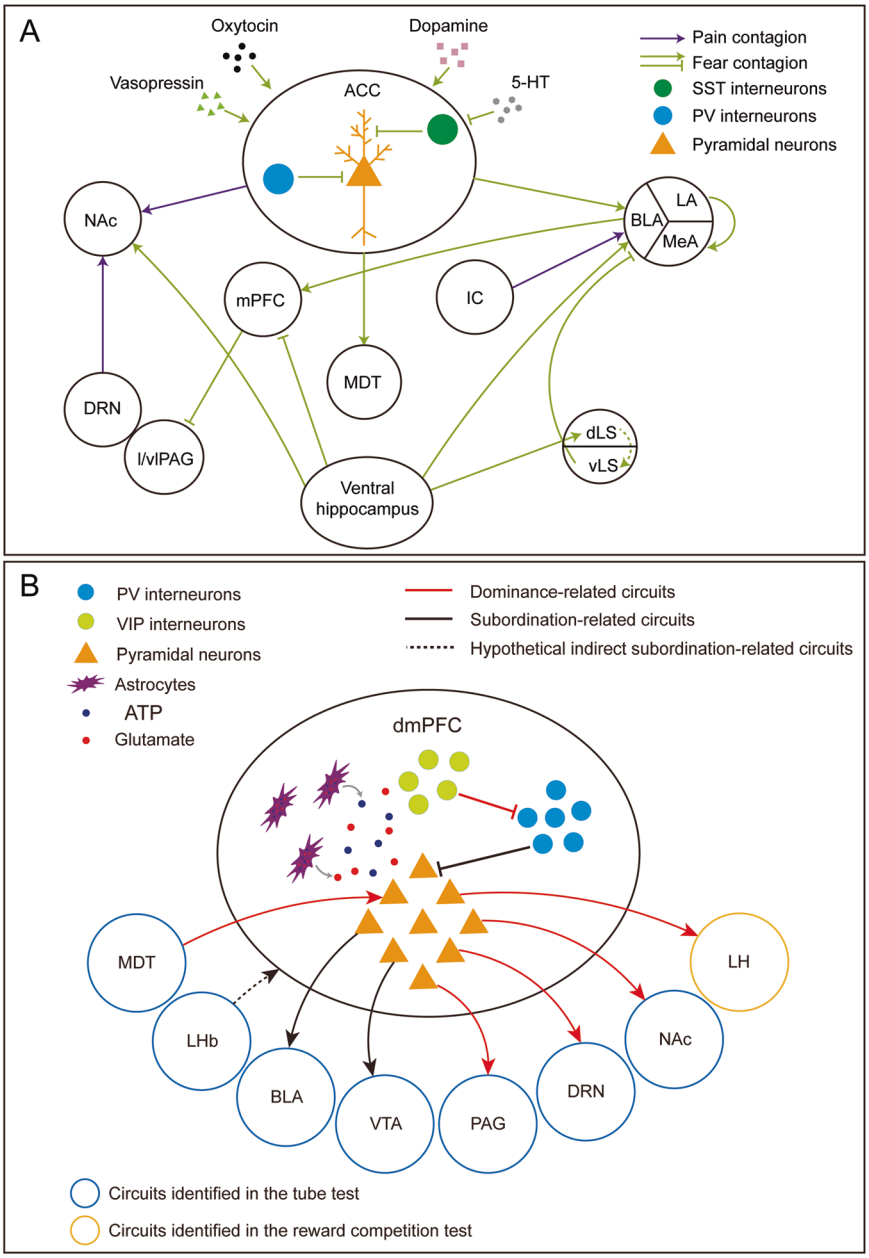


Fig. 4 Circuits regulating empathy and social hierarchy. A ACC-centered circuits involved in empathy. Dotted lines represent circuits that have not yet been validated using manipulation-based techniques. **B** mPFC-centered circuits involved in the establishment of social hierarchy. ACC anterior cingulate cortex, BLA basolateral amygdala, dmPFC dorsomedial prefrontal cortex, DRN dorsal raphe nucleus, IC insular cortex, LA lateral part of basolateral amygdala, LH lateral hypothalamus, LHb lateral habenula, LS lateral septum, MeA medial amygdala, MDT mediodorsal thalamus, NAc nucleus accumbens, PAG periaqueductal gray, VTA ventral tegmental area.

a food reward, the BLA plays a critical role in promoting altruistic choices over selfish ones through its reciprocal connections with the PrL. Inhibition of the BLA-PrL circuit abolishes this altruistic preference, and inhibition of the PrL-BLA circuit can even reverse the preference toward selfish choices [164].

Prosocial behaviors exhibit greater motor complexity compared to other social interactions, primarily due to their requirement for goal-directed motor planning in experimental paradigms. This heightened complexity likely engages corticostriatal motor learning circuits. Nevertheless, conserved emotional motor pathways may co-mediate these behaviors, as evidenced by innate behavioral expression like reviving-like behaviors toward anesthetized conspecifics [140]. The motor patterns underlying such prosocial actions including specific orofacial movements (such as eye licking and tongue manipulation) demonstrate notable homology with parenting behaviors, suggesting their potential overlap in conserved caregiving-related circuits.

Circuit mechanisms underlying dominant behaviors

Social competition for limited resources is essential for the survival of individuals and leads to the formation of hierarchical structures. Such hierarchies are conserved across species, from insects to primates, and serve to reduce intense conflicts, conserve energy, and promote social stability [165]. Although social ranks, as internal states, can influence other forms of social behaviors, dominant and subordinate behaviors themselves have specific expressions [165, 166]. In laboratory rodents, the tube test is a widely used paradigm to study social hierarchies. Notably,

dominant behaviors and aggression are distinct, even though aggression is initially necessary for establishing social hierarchies [165]. Aggression is instinctive and can be exhibited by all individuals, whereas social hierarchies are gradually established through long-term social interactions, and dominance behaviors are expressed only by specific individuals [167].

Perception of social hierarchy. Social hierarchy maintenance requires continuous perception of conspecific social status, enabling context-appropriate behavioral responses such as competitive engagement and social withdrawal. Given that social ranks are gradually established through long-term social interactions, the perception may represent an associative learning process which links one's identification with its social ranks. However, rank-specific sensory signatures may permit direct social state recognition. In rodents, dominant state can be recognized by sniffing. For example, the major urinary protein (MUP), a conserved pheromone, increases in the urine of winning mice [107]. In addition, in the courtship context, dominant males produce more USVs compared to the subordinate [71]. However, the circuit mechanisms underlying direct perception of social states remain poorly understood.

The mPFC as the center of social hierarchy. The mPFC is the central hub for regulating social hierarchy (Fig. 4B) [168, 169]. Specifically, the dorsal mPFC (dmPFC) has been extensively regarded as a fundamental regulator in both dominant and subordinate individuals across various behavioral paradigms including the tube test [169], the warm spot competition [169], and the reward competition test [170]. The activity patterns of dmPFC are influenced by both innate characteristics, such as AMPA receptor currents which can be modulated to bidirectionally shift social ranks in the tube test [171], and external factors, including astrocytes, microcircuits, and long-range inputs. Astrocytes in the dmPFC bidirectionally modulate dominance behaviors by regulating the excitatory/inhibitory (E/I) balance, with chemogenetically activated astrocytes inducing elevated E/I ratio and higher social ranks in the tube test [167]. Within mPFC microcircuits, a "vasoactive intestinal peptide (VIP)-PV-pyramidal neuron" motif plays a critical role. In the tube test, PV interneurons suppress winning by inhibiting pyramidal neurons, while VIP interneurons promote winning through disinhibitory circuits [168].

The established hierarchies are maintained by a series of reinforcing mechanisms such as "winner effect", by which winner mice exhibit more effortful behaviors including pushes and resistances in the later tube test. This maintenance of existing hierarchies relies on consistently strengthened synapses, which are regulated by a thalamic circuit. After six consecutive winning, field excitatory postsynaptic potentials (fEPSPs) which reflect the mediodorsal thalamus (MDT)-dmPFC synaptic efficacy are increased. Modulating the plasticity of MDT-dmPFC circuit can effectively induce sustained changes in social hierarchy in the tube test [169]. Additionally, the activation of LHb, a neural hub encoding negative valence, decrease social ranks of dominant individuals in the tube test [7]. However, a recent study reveals comparable activation of LHb among dominant, subordinate, and control mice after the tube test [172], suggesting its hierarchical modulation may be pathology-specific (such as depressive states) rather than physiologically constitutive. Although how LHb transmits depressive internal status to dmPFC remains unclear. Similarly, another key unanswered question is which sensory signals carry social rank information and how they are transmitted to the dmPFC. The MPOA has been identified as a region that senses resource-holding potential [101], but whether it bridges the gap between external cues and the dmPFC remains unknown.

Downstream circuits regulating dominant and subordinate behaviors. The mPFC organizes several downstream regions to regulate dominant and subordinate behaviors. Reward competition tests, in which multiple mice compete for limited reward, are often used to study social hierarchy. LH-projecting mPFC neurons are activated during competition and mediate winning behaviors [170]. However, the activity of this circuit does not significantly differ between dominant and subordinate animals in the tube test, which may be due to the functional heterogeneity of these circuits in distinct paradigms. Instead, mPFC neurons projecting to the DRN and PAG are activated in winners [172], while those projecting to the BLA and VTA are activated in losers [166, 172]. These findings raise important questions: Do specific mPFC circuits directly encode specific actions, or do these circuits process information hierarchically, with the mPFC responsible for decision-making and sorting information to downstream regions that encode corresponding actions?

Additionally, while Choi et al. reported that the mPFC-NAc circuit mediates social winning in the tube test [166], a recent study found that optogenetic inhibition of this circuit does not modulate social ranks [172]. One possible explanation for this discrepancy is the requirement for chronic metabolic changes in social rank switches. Previous studies have shown that mitochondrial function in the NAc is associated with social hierarchy in the reward competition test [173], suggesting that acute inhibition may be insufficient to alter social ranks. Another possibility is the subdivision-specific heterogeneity of the NAc. For instance, D1R-expressing medium spiny neurons (MSNs) in the NAc shell mediate decreases in social rank, while dopamine D2 receptor (D2R)-expressing MSNs in the NAc core mediate increases in social rank in the tube test [174].

Aggression-related circuits in dominance behaviors. Given the initial role of aggression in establishing social hierarchies, aggression-related circuits may also contribute to dominance behaviors. For example, DAT-expressing PMv neurons (PMv^{DAT}), which regulate intermale aggression, are also involved in the establishment of social hierarchies. Manipulation of PMv^{DAT} neurons can induce long-lasting switches in intermale hierarchy [106].

NEURAL CIRCUIT DYSFUNCTION UNDERLYING SOCIAL DEFICITS OF DISEASES

Circuit dysfunction in autism spectrum disorder

ASD is a neurodevelopmental disorder characterized by impairments in social communication and the presence of restricted, repetitive behaviors or interests [10]. Previous studies have attempted to manipulate various neural circuits to restore social deficits in ASD animal models. However, whether these circuits directly mediate behavioral abnormalities remains unclear. Therefore, this section focuses on summarizing circuits that exhibit abnormal activity in ASD models and can be manipulated to rescue social impairment (Fig. 5).

Given that the social preference test is the most commonly used paradigm to assess autistic-like social deficits in existing studies, many identified ASD-related circuits are implicated in social preference, as reviewed above. Although the circuit mechanisms are complex and genetically heterogeneous, the mPFC appears to be a common node frequently found to be functionally impaired in individuals with ASD. Abnormalities in mPFC microcircuits have been observed in various models [175]. Hyperactivation of the mPFC is associated with social deficits in many ASD models, which may result from abnormal inputs in some cases. For example, decreased inputs from cerebellar Purkinje cells and increased inputs from the ventral hippocampus have been observed in *Tsc1* conditional knockout and maternal immune activation (MIA)-induced ASD models, respectively. Activation of the cerebellum-mPFC circuit and inhibition of the hippocampus-mPFC circuit have both been shown to rescue social

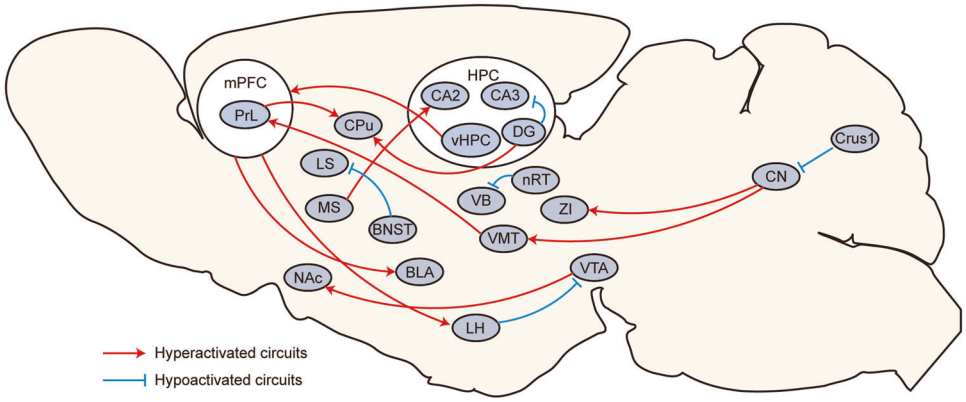


Fig. 5 Circuits mediating social deficit in autism. BLA basolateral amygdala, BNST bed nucleus of the stria terminalis, CPu caudate putamen, CN cerebellar nuclei, DG dentate gyrus, LH lateral hypothalamus, LS lateral septum, mPFC medial prefrontal cortex, MS medial septum, NAc nucleus accumbens, nRT thalamic reticular nucleus, VB ventrobasal thalamus, VMT ventromedial thalamus, VTA ventral tegmental area, ZI zona incerta.

impairment [32, 176]. The hyperactivated mPFC also forms atypical connections with various downstream regions, including striatum in the *Tmem74*$^{-/-}$ mice and BLA in *Pten*$^{-/-}$, MIA, or *Shank3* conditional knockout ASD models. Inhibition of these circuits restores social deficits [177–180]. In *Irsp53*^{Emx1} conditional knockout mice, hyperactivation of the mPFC induces a compensatory decrease in the excitability of the downstream LH-VTA circuit, leading to reduced disinhibition of VTA dopaminergic neurons and impaired social behaviors [181].

The hippocampus, another central regulator of social preference, has also been extensively reported to exhibit abnormal functional connectivity in ASD. Abnormalities in hippocampal microcircuits have been observed in *Fmr1*$^{-/-}$ and valproic acid induced ASD models [182, 183]. The regulatory effects of the hippocampus are subregion-specific and model-specific. For instance, in mice with *Auts2*^{Emx1} conditional knockout, atypical development of the dentate gyrus (DG) results in hypoactivation of the DG-CA3 intra-hippocampal circuit [184]. In mice with *Nlg3* conditional knockout in the medial septum (MS), the activity of CA2-projecting MS GABAergic neurons is increased [185]. Both scenarios lead to impaired hippocampal function. However, in *Dcf1*$^{-/-}$ and MIA models, DG-innervated striatum neurons and ventral hippocampus-innervated mPFC neurons are hyperactivated, respectively [176, 186]. An interesting contradiction arises in that the MS-CA2 circuit appears to be both necessary and detrimental to social preference. These findings may reflect neuronal heterogeneity, with glutamatergic and cholinergic projections being indispensable for social behaviors, while GABAergic projections contribute to social deficits [34, 35, 185].

Neuroimaging studies in humans have indicated that autism involves abnormal structure and functional connectivity in the cerebellum and thalamus [187]. Correspondingly, in rodent models, cerebellar nuclei (CN) send increased innervation to the zona incerta (ZI) in *Nlg3*^{R451C} mice [188], and the ventrobasal thalamus (VB) exhibits impaired GABAergic transmission in *Nlg2* knockout mice [189]. Both inhibition of the CN-ZI circuit and activation of the thalamic reticular nucleus-VB circuit have been shown to rescue social deficits.

Additionally, dysfunction in neuromodulatory systems has been widely accepted as a potential mechanism underlying social deficits in ASD. The VTA, a major component of the dopamine system, shows abnormal connectivity between VTA dopaminergic neurons and the NAc in both ASD patients and rodent models [190, 191]. Several important questions arise: How does the VTA-NAc circuit encode and elicit distinct behaviors, such as social novelty preference and sex preference [27, 73]? Why is VTA-NAc circuit both necessary and detrimental to social behaviors [191, 192]? One possibility is that distinct neuronal populations respond to specific, and sometimes contradictory, behavioral effects. Furthermore, in *Magel2* mutant mice, AVP axons are reduced in the LS, leading to hyperactivation of SST^{+} GABAergic neurons. Activation of the circuit from the BNST to the LS, but not from the PVN to the LS, rescues social impairment [193]. The OXT system has also been extensively associated with social deficits in ASD, and OXT is considered a potential therapeutic target [194]. Although OXT may restore social behaviors by normalizing altered circuits [195], direct evidence of dysfunction in oxytocinergic circuits remains limited.

Circuit dysfunction in schizophrenia

Patients with schizophrenia experience not only psychotic symptoms, such as delusions and hallucinations, but also significant social deficits [196]. Disturbances in neural activity and connectivity have been identified across nearly all regions of the "social brain" in schizophrenia [196]. Key regions implicated include the amygdala, mPFC, paracingulate cortex, ACC, temporal lobe, temporo-parietal junction, and ventral striatum [196].

Corresponding circuit dysfunctions have also been observed in rodent models. In the chromosome 16p11.2 duplication mouse model, impaired connections are found across the hippocampus, basal ganglia, amygdala, and prefrontal cortex [197]. In MK-801-induced schizophrenia mice, the activity of the ACC and BLA is inhibited, and activation of the BLA-ACC circuit alleviates social deficits [198]. Conditional knockout of *synaptotagmin-11*, a schizophrenia risk gene, in dopaminergic neurons during early adolescence leads to sustained social deficits accompanied by overactive dopaminergic synapses. Specifically, hyperactivation of the VTA-mPFC circuit, but not the VTA-NAc circuit, is associated with social withdrawal. In particular, local treatment with D2R antagonists in the mPFC restores social impairment [199].

Circuit dysfunction in post-traumatic stress disorder

PTSD following traumatic events is characterized by hyperarousal, social avoidance, and re-experiencing the trauma, indicative of memory abnormalities [11]. Recent studies have shown that patients with PTSD exhibit impairments in prosocial behaviors [200], including deficits in both emotional empathy and cognitive empathy [201]. Neuroimaging studies have revealed altered activity in multiple brain regions involved in prosocial behaviors, such as the amygdala, mPFC, ACC, hippocampus, and insular cortex, in PTSD patients [202]. Additionally, the OXT system, a major neuromodulatory system involved in prosocial behaviors, may function abnormally in PTSD. Intranasal OXT is considered a potential pharmacological intervention for alleviating PTSD

symptoms [203]. Furthermore, social cognition is disrupted in PTSD [204], which may be linked to dysfunction in the brain's default network, including the PFC, posterior cingulate/precuneus, temporoparietal junction, lateral temporal cortex, and temporal poles [205].

In rodent models, however, studies on PTSD have primarily focused on fear generalization, with limited research on social deficits. A recent study established a social defeat-induced PTSD mouse model and found that the circuit from dopaminergic neurons in the VTA to the BLA mediates the alleviative effects of ketamine. Activation of this circuit restores post-traumatic social avoidance [206]. Additionally, social fear conditioning, which pairs social investigation with traumatic stimuli, induces significant social fear in mice. This process involves the LS, a key hub for reward processing, and the LHb, a center associated with negative emotions. OXT and AVP signaling within the LS are crucial for both fear conditioning and extinction [207, 208]. However, distinct inputs are involved: the PVN-LS circuit mediates fear conditioning, while the SON-LS circuit mediates fear extinction [207]. During social fear, LHb neurons exhibit hyperactivation, partly due to increased activity of upstream inputs, including the mPFC and BF. Inhibition of either the mPFC-LHb or BF-LHb circuits reduces social fear responses [8, 209]. Given the critical roles of these regions in regulating negative learning, reinforcement, and social reward or preference, it is plausible that these nuclei work in concert to establish a framework that links emotional arousal with the reduction in social motivation induced by negative affect in PTSD.

CONCLUSION AND PERSPECTIVES

This review highlights recent progress in elucidating the neural mechanisms that regulate social behaviors. Despite significant progress, social deficits—a common symptom in neuropsychiatric disorders—remain poorly understood and lack effective treatments. Advanced neuronal manipulation and observation techniques, combined with high-resolution behavioral analysis, have greatly enhanced our ability to study the neural circuits governing social behaviors. These tools enable researchers to explore nuanced aspects of social interactions, such as perception, motivation, and recognition, in complex scenarios. A critical question arises: Can distinct behavioral paradigms effectively capture and differentiate these interrelated stages, or do they require continuous, high-temporal-resolution observation? Addressing this challenge is essential for unraveling the complexity of social behavior and its underlying neural mechanisms.

One of the understudied behavioral aspects is the execution phase. As discussed above, a critical unresolved question is whether nuanced behavioral outputs are governed by discrete emotional motor circuits or emerge through integrated emotional-voluntary motor system interactions. Anatomically, the motor cortex and cerebellum directly connect with PAG, circuits implicated in fine-scale behavioral modulation such as vocalization dynamics [85, 210]. Whether these connections analogously regulate other social motor sequences requires systematic investigation. In addition, the motor cortex and cerebellum also directly connect with VTA. These connections may enable VTA-mediated reinforcement of action initiation through motor network engagement. VTA also reciprocally connect with PAG, which may establish positive feedback loops to sustain behavioral persistence. Collectively, these observations highlight critical knowledge gaps in understanding how neural systems orchestrate motor circuitry to execute context-appropriate social behaviors.

Neuronal heterogeneity is increasingly recognized as a key factor in social behavior regulation. Previous studies have classified neurons into distinct clusters based on activity patterns, transcriptional profiles, or projective connectivity to identify specific populations or circuits mediating social behaviors. However, research integrating these characteristics remains limited. Whether activity-defined, transcriptome-defined, and connectome-defined neuronal populations can converge into a unified framework is still unclear. Resolving this question is crucial for understanding how diverse neuronal features collectively contribute to social behavior. Additionally, individual neurons often project to multiple brain regions, allowing a single neuron to influence various circuits simultaneously. While most studies on multi-target neurons focus on microcircuits, their broader projective patterns likely play a critical role in integrating and balancing multiple aspects of social behaviors. Investigating the functions of long-range, multi-target neurons will provide deeper insights into how brain networks coordinate complex social behaviors.

Finally, social behaviors cannot be attributed to isolated circuits but emerge from the interplay of multiple networks. As our understanding of brain connectivity and function advances, studying circuits from a network perspective becomes increasingly important, particularly for social deficits in neuropsychiatric disorders, which often involve widespread circuit dysfunctions. Recent studies have also challenged the traditional hierarchical view of information processing, suggesting a more dynamic and distributed computational framework [211–213]. Rethinking the roles of individual nodes and circuits within this broader network context will help reveal how the brain processes social information and coordinates behavior. Future research should focus on integrating multi-omics data, advanced imaging, and computational modeling to build a comprehensive understanding of social behavior regulation in health and disease.

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AUTHOR CONTRIBUTIONS

HL: conceptualization, visualization, writing—original draft; ZZ: visualization, writing—original draft; SJ: writing—review and editing; HW: conceptualization, writing—review and editing, supervision.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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