REVIEW

Hypothalamic control of innate social behaviors

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Sexual, parental, and aggressive behaviors are central to the reproductive success of individuals and species survival and thus are supported by hardwired neural circuits. The reproductive behavior control column (RBCC), which comprises the medial preoptic nucleus (MPN), the ventrolateral part of the ventromedial hypothalamus (VMHvl), and the ventral premammillary nucleus (PMv), is essential for all social behaviors. The RBCC integrates diverse hormonal and metabolic cues and adjusts an animal's physical activity, hence the chance of social encounters. The RBCC further engages the mesolimbic dopamine system to maintain social interest and reinforces cues and actions that are time-locked with social behaviors. We propose that the RBCC and brainstem form a dual-control system for generating moment-to-moment social actions. This Review summarizes recent progress regarding the identities of RBCC cells and their pathways that drive different aspects of social behaviors.

The medial hypothalamus houses three heavily interconnected nuclei—the medial preoptic nucleus (MPN), the ventrolateral part of the ventromedial hypothalamus (VMHvl), and the ventral premammillary nucleus (PMv)—that constitute the reproductive behavior control column (RBCC) (*1*). The RBCC is indispensable for all social behaviors that subserve reproduction, including mating, parenting, and fighting. It is part of the larger social behavior network (SBN) that was initially proposed by S. Newman in 1999 on the basis of rodent studies (*2*) and was later extended by J. L. Goodson to other vertebrate species (*3*). Anatomically, the RBCC is highly evolutionarily conserved and recognizable in mammals, birds, reptiles, amphibians, and fish (*3*, *4*). Immediate early gene mapping suggests similar response patterns during social behaviors across species (*3*, *5*). In this Review, we summarize recent studies, mainly in rodents, regarding the molecular identity, functions, and responses of RBCC cells. RBCC function in nonrodent species has been reviewed in other work (*4*, *6*).

This Review will be separated into two parts. The first part summarizes recent studies regarding the functions and responses of molecularly defined RBCC cells during each social behavior. We will also offer our views about the general principles of RBCC organization and the relationship among different social circuits. The second part of the Review discusses how the RBCC controls each stage of social behaviors, from increasing social exploration and maintaining social interest to promoting consummatory social actions. In particular, we propose that the RBCC acts as a "permissive gate" to allow specific brainstem and/or spinal cord motor circuits to respond to immediate and simple sensory inputs to drive moment-to-moment social actions.

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The role of the RBCC in sexual, parental, and aggressive behaviors

Male sexual behaviors

Sexual behaviors differ qualitatively between the sexes. Thus, the male and female sexual behavior circuits have little in common. For males, the medial preoptic area (MPOA), which includes the MPN and its surrounding region, has been recognized as a site of paramount importance since the early 1960s (*7*, *8*). Recently, single-cell and nucleus RNA sequencing have revealed a high molecular heterogeneity of MPOA cells, leading to a series of studies to refine the molecular identities of mating-related MPOA subpopulations (*9*, *10*). In 2018, Wei *et al.* showed that optogenetic activation of MPOA *estrogen receptor alpha* (*Esr1*)–expressing cells ($MPOA^{Esr1}$) can elicit male mounting, albeit with relatively low efficiency (50% of animals) (*11*). In 2021, Karigo *et al.* reported that activating γ-aminobutyric acid–expressing (GABAergic) $MPOA^{Esr1}$ ($MPOA^{Esr1\cap VGAT}$) cells can induce male mounting with 100% efficiency (*12*). Most recently, Bayless *et al.* pinpointed *tachykinin receptor 1* (*Tacr1*)–expressing cells ($MPOA^{Tacr1}$), likely a subset of $MPOA^{Esr1\cap VGAT}$ cells (*10*), as the key population for male sexual behaviors (*13*). Optogenetic activation of $MPOA^{Tacr1}$ cells was able to induce intromission-like behaviors toward a toy mouse (*13*). Importantly, Tacr1 is itself functionally critical for the behavior because antagonizing MPOA Tacr1 suppressed male mounting (*13*).

The role of the VMHvl in male sexual behaviors appears to be relatively minor. Optogenetic activation of $VMHvl^{Esr1}$ cells at a low intensity induced mounting in male mice, but this behavior was not coupled with ultrasonic vocalization, which typically accompanies male-female interaction, and hence was interpreted as a dominance behavior instead of a sexual behavior (*12*, *14*). Although ablating VMHvl *progesterone receptor* (*PR*)–expressing cells ($VMHvl^{PR}$) or chemogenetically inhibiting $VMHvl^{Esr1}$ cells (*Esr1* and *PR* overlap nearly 100% at the VMHvl) suppressed male mounting (*12*, *15*), optogenetic inhibition of $VMHvl^{Esr1}$ cells did not disrupt ongoing copulation, suggesting that the role of the VMHvl in male sexual behavior is likely limited to the initiation phase (*14*). This functional result is supported by the response pattern of VMHvl cells: Whereas the cells increase activity during mounting, they decrease activity during intromission (*16*, *17*).

The PMv receives dense inputs from the medial amygdala, a social odor and pheromone processing region, and thus has been considered the sensory relay of the RBCC (*18*). Indeed, the PMv expresses abundant c-Fos after conspecific odor presentation and shows a moderate activity increase during the male-female investigation (*17*, *19*). However, PMv cells do not respond during any phases of male copulation, and PMv deficits fail to impair male reproduction (*17*, *20*, *21*).

Thus, the MPOA is likely the primary site that mediates male mating, whereas the VMHvl and PMv seem to play minor roles in the early phase of male-female interaction (Fig. 1). $MPOA^{Tacr1}$ cells represent the most refined population for male sexual behaviors (Fig. 2).

Female sexual behaviors

Female sexual behavior, in comparison, is notably simple in its motor output. As males mount, females stay stationary with their back arching downward to facilitate penile insertion, a posture known as lordosis (*22*). Since the 1970s, many lesion and stimulation experiments have demonstrated a critical role of the VMHvl in female sexual behaviors (*22*). Similar to studies in males, recent efforts focused on refining the molecular identity of VMHvl cells relevant to female sexual behaviors. Toward this goal, $VMHvl^{PR}$ cells were identified as necessary for female sexual receptivity in mice (*15*, *23*). However, activating $VMHvl^{PR}$ cells failed to facilitate lordosis (*23*). This negative result is likely due to the fact that the female VMHvl contains two subdivisions, which both express abundant *PR* and *Esr1*, but only the lateral subdivision (VMHvll) is strongly activated during female sexual behaviors (*24*). When the VMHvl cells that express *Cholecystokinin A receptor* (*Cckar*), a lateral subdivision–specific gene, are chemogenetically or optogenetically activated, female sexual receptivity rapidly increases (*10*, *25*). In mice, female sexual receptivity is tightly coupled with ovulation, that is, the estrus cycle. The in vivo responses and physiological properties of $VMHvll^{Cckar}$ cells, including intrinsic excitability and synaptic inputs, vary over the estrus cycle, suggesting that these cells probably support the cyclic changes in female sexual behaviors (*25*).

The PMv is also critical for female reproduction, but its role differs from that of the VMHvl. Specifically, the PMv enables metabolic signals to modulate the reproductive neuroendocrine axis. Leptin, an adipocyte-derived hormone, signals energy reserve levels and triggers sexual

maturation by acting on PMv leptin receptors (Lepr) (*26*). Upon sensing leptin, PMv^{Lepr} cells activate *kisspeptin*-expressing cells to release gonadotropin-releasing hormone and trigger the onset of puberty (*20*, *26*). In adults, PMv impairment decreases ovulation frequency, an abnormality that could occur naturally during leptin deficiency caused by food deprivation (*20*, *27*). Thus, PMv modulates sexual readiness based on the energy reserve level. During food shortages, the PMv signals the hypothalamic-pituitary-ovarian axis to slow down female reproduction.

The MPOA has been consistently found to suppress female receptivity, possibly through its strong inhibitory inputs to the VMHvl (*12*, *28*). MPOA lesion or site-specific *Esr1* knockdown increases lordosis, whereas electric stimulation of the MPOA has the opposite effect (*29*–*33*).

Thus, contrary to the male mating circuit, female sexual behaviors are mainly mediated by the VMHvl and PMv, whereas the MPOA likely plays a negative role (Fig. 1). VMHvll^{Cckar} and PMv^{Lepr} cells represent the most refined populations for female sexual behavior thus far (Fig. 2).

Parental behaviors

In rodents, all parental behaviors, except nursing, can be exhibited by both males and females with some quantitative differences (*34*). Thus, perhaps unsurprisingly, the hypothalamic regions that control parental behaviors are largely similar between the sexes. Since 1974, the MPOA has been recognized as a crucial region for controlling maternal behaviors (*35*, *36*). More recently, Wu *et al.* identified MPOA cells that express *galanin* (MPOA^{Gal}) as a critical population for regulating parental behaviors, especially grooming, in male and female mice (*37*). Subsequently, Wei *et al.* and our study collectively found that both male and female MPOA^{Esr1} cells in mice are necessary, sufficient, and naturally active during pup approach and retrieval (*11*, *38*). Later, multiplexed error robust fluorescence in situ hybridization (MERFISH) revealed that *calcitonin receptor* (*Calcr*), which is expressed in a subset of *Esr1*-positive cells, preferentially marks MPOA cells that are activated by parental behaviors (*9*). Following this finding, Yoshihara *et al.* reported that silencing MPOA^{Calcr} neurons or knocking down *Calcr* in the MPOA suppresses maternal behaviors (*39*). *Gal*, *Esr1*, and *Calcr* are expressed in both GABAergic and glutamatergic MPOA cells. However, the glutamatergic MPOA cells likely do not promote parental behaviors because optogenetic silencing of MPOA glutamatergic cells increases, not decreases, pup retrieval in female mice (*40*). Lastly, MPOA cells not only drive parental behaviors but also suppress hostile behaviors toward the pups. During lactation, MPOA^{Esr1} cell excitability increases, causing stronger inhibition of infanticide-driving cells in the principal nucleus of the bed nucleus of stria terminalis (BNSTpr) and enabling the drastic switch from hostile to caring behaviors toward the young (*41*).

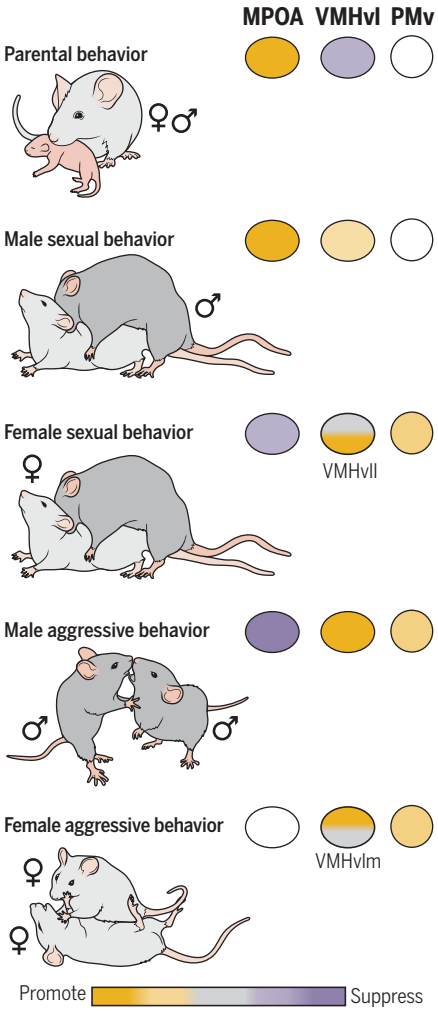

Fig. 1. The role of RBCC regions in various social behaviors. White indicates that the function of the region is to be determined. Gray indicates the region has no function. Purple indicates that the region suppresses the behavior. Yellow indicates that the region promotes the behavior. Note that the MPOA and the VMHvl and PMv generally play opposite roles in each social behavior.

In contrast to the pivotal role of the MPOA in parental care, the VMHvl and PMv appear to be dispensable. VMHvl inactivation or PMv lesion did not cause any deficit in maternal care (*24*, *42*). In vivo recordings found no activity changes of VMHvl^{Esr1} cells during maternal behaviors (*24*). Recent studies further suggest a negative role of the VMHvl in parental behaviors. Activating VMHvl cells that are connected with the MPOA suppressed pup investigation in virgin female mice (*41*). Similarly, when the projection from *urocortin-3* (*Ucn3*)–expressing cells in the perifornical region (PeFA^{Ucn3}) to the VMH was activated, the female mice spent less time investigating pups (*43*).

Altogether, present data support the idea that the MPOA, but not the VMHvl and PMv, is the key RBCC region that drives parental behaviors in both sexes (Fig. 1). MPOA^{Calcr} cells represent the most refined population for parental behaviors (Fig. 2).

Aggressive behaviors

Although the tendency to attack differs between the sexes, its motor pattern, at least in rodents, seems to be similar (*44*). Thus, the neural substrates of aggression are qualitatively similar in males and females. Studies from the past decade firmly established the central role of the VMHvl in male and female aggression (*45*). Inactivating or ablating VMHvl cells abolishes natural intermale aggression and maternal aggression in mice (*14*–*16*, *24*). Conversely, activating VMHvl cells, especially those expressing *Esr1* or *PR*, promotes attack toward both natural and suboptimal targets (*14*, *16*, *24*), regardless of the subject's social status, housing condition, or testing context (*46*). Simultaneous recording of 13 limbic regions, including five in the hypothalamus, revealed the VMHvl as the region with the largest and fastest activity increase during attack onset, highlighting its crucial role in the behavior (*17*). Furthermore, recent works revealed the flexibility of VMHvl cell responses. For example, with sexual experience, the male- and female-induced activation patterns in the VMHvl become more distinct (*47*). With winning experience, the VMHvl cells show long-term potentiation of excitatory synaptic inputs (*48*). When an arbitrary motor action, for example, a nose poke, is associated with future opportunities to attack, VMHvl cells increase activity before poking (*49*). Lastly, Yang *et al.* recently reported increased VMHvl cell activity when animals witness fights between others (*50*). Thus, the VMHvl cells carry diverse aggression-related information, including aggressive motivation, aggression-provoking sensory cues, the motor execution of attacks, and one's own fighting experiences and those of others. Notably, only the posterior VMHvl is related to aggression; the anterior VMHvl mediates conspecific self-defense and social fear (*51*, *52*).

In female mice, only the medial VMHvl (VMHvlm) is relevant for aggression (*24*). Using activity-dependent single-cell RNA sequencing (Act-seq), Liu *et al.* identified *neuropeptide Y receptor Y2* (*Npy2r*), a VMHvlm-biased gene, as a genetic marker for the female aggression population (*53*). When *Npy2r*$^{+}$, but not *Npy2r*$^{-}$ *Esr1*$^{+}$, VMHvl cells were optogenetically activated, virgin female mice attacked various social targets, including adult males (*53*). VMHvl^{Npy2r} cells show reproductive state–dependent activity changes, with the highest response occurring during lactation, when the level of female aggression peaks (*53*).

The PMv is also a critical site for both male and female aggression. Several recent studies targeted *dopamine transporter* (*DAT*)–expressing cells in the PMv (PMv^{DAT}) and showed that

aggression can be bidirectionally modulated in male and female mice (*21*, *54*, *55*). In vivo recordings show that PMv cells, like VMHvl cells, respond preferentially to aggression-provoking social cues (*17*, *21*, *56*). However, the PMv differs from the VMHvl in that it responds more during social investigation than attack (*17*, *21*). Lesioning the PMv reduces aggression-induced c-Fos in the VMHvl substantially, suggesting that the PMv is likely to be upstream of the VMHvl, relaying conspecific cues (*42*). Of note, regardless of sex, PMv^{DAT} cells are quiescent and hyperpolarized in non-aggressive mice and become spontaneously active and depolarized in aggressive mice (*54*, *55*), suggesting that the aggressiveness of an animal could be encoded by the biophysical properties of PMv cells. It is worth mentioning that although *DAT* is a good marker for PMv because it is distinctively expressed in the PMv among neighboring regions, PMv^{DAT} cells do not appear to synthesize dopamine, and it remains unclear whether *DAT*$^{+}$ cells are more involved in aggression than *DAT*$^{-}$ cells in the PMv (*56*).

Recent studies support an aggression-suppressing role of MPOA^{Esr1} cells through their inhibition of VMHvl glutamatergic cells (*12*, *28*). Rostral MPOA^{Esr1} cells in males are activated by females, whereas caudal MPOA^{Esr1} cells preferentially respond to superior male opponents (*28*). Thus, the MPOA could suppress aggression toward inappropriate targets in various contexts. Indeed, when MPOA^{Esr1}-to-VMHvl terminals are optogenetically inactivated, male mice attack social targets indiscriminately, including superior males, and end up inflicting more defeat (*28*).

Present data suggest that the VMHvl and PMv are central for male and female aggression, whereas the MPOA suppresses this behavior (Fig. 1). In terms of cell populations, VMHvl^{Esr1} cells in males, which are equivalent to VMHvl^{PR} cells, and VMHvl^{Npy2r} cells in females are, at present, the best-defined populations for aggression (Fig. 2).

General organization of RBCC cells

Several general conclusions emerge when considering the circuits for all social behaviors together. First, the VMHvl and PMv have similar social functions that are opposite to those of the MPOA (Fig. 1). For example, the VMHvl and PMv promote aggression in both sexes and sexual behaviors in females, whereas MPOA activation suppresses these behaviors (*12*, *14*–*16*, *24*, *25*, *28*, *53*). The MPOA promotes parental behaviors, whereas the VMHvl reduces them (*11*, *37*–*39*, *41*, *57*). The only exception is male sexual behavior, the initiation of which is promoted by both the MPOA and VMHvl, although the MPOA increases, whereas the VMHvl decreases, activity during intromission (*12*, *14*, *17*). The functional relationship between the MPOA, PMv, and VMHvl is probably rooted in the neurotransmitter expressed by the cells. Cells in the PMv and VMHvl are overwhelmingly glutamatergic, whereas socially relevant cells in the MPOA are likely GABAergic (*12*, *40*). Because these three regions are heavily reciprocally connected, activating MPOA social cells should suppress PMv and VMHvl cells, whereas PMv and VMHvl cells should facilitate activation of each other (*28*, *56*).

Second, cells supporting distinct social behaviors often occupy different subregions within the VMHvl or MPOA (Fig. 2). For example, the lateral and medial VMHvl mediate female sexual and aggressive behaviors, respectively (*24*, *25*, *53*). Rostral and caudal MPOA cells in males are activated during female and dominant male interactions, respectively (*28*). *Fos* catFISH (compartment analysis of temporal activity by fluorescence in situ hybridization) suggests that mating- and parental care–induced *c-Fos* expression is largely distinct in the MPOA, and the former could be more medially located [see figure 2 in (*37*)]. At the single-cell level, most cells show biased, though not necessarily exclusive, responses during one social behavior (*16*, *38*, *47*, *58*). Thus, individual MPOA and VMHvl cells are likely preferentially involved in one social behavior, and cells with similar response patterns tend to cluster. Whether such topographic organization of social behaviors also exists in the PMv remains to be elucidated.

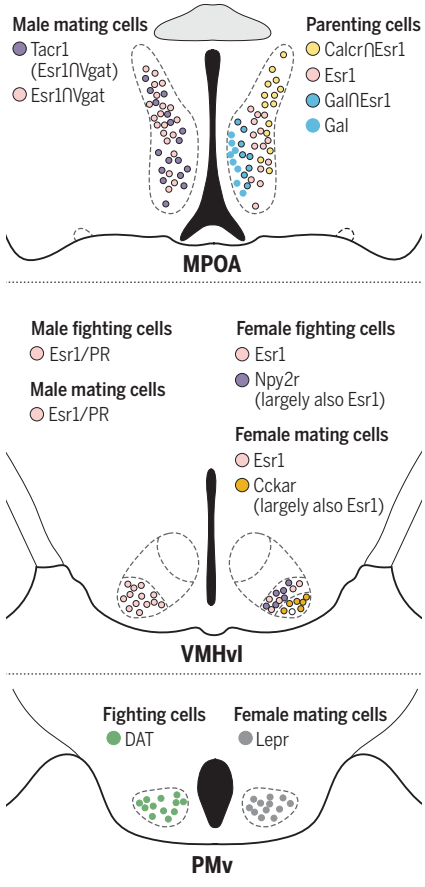

Fig. 2. The known molecular markers for social behavior–relevant cells in the RBCC.

Third, fighting- and mating-related cells in the RBCC antagonize each other in both sexes. In males, activating mating-related MPOA^{Esr1} cells suppresses intermale aggression, whereas activating fighting-related VMHvl^{Esr1} cells suppresses male-female mounting and female urine-elicited ultrasonic vocalization (*12*, *28*). In females, activating fighting-related VMHvl^{Npy2r} cells suppresses sexual receptivity (because the female attacks the male), whereas activating mating-related VMHvll^{Cckar} cells suppresses female aggression (*25*, *53*). This relationship is not simply due to motor incompatibility. In lactating females, VMHvll^{Cckar} cell activation could not increase female sexual receptivity, possibly because of changes in the downstream circuit, but remained effective in suppressing maternal aggression (*25*).

The relationship between parenting-related cells and mating- and fighting-related cells is less understood because these three behaviors are rarely examined together. Limited evidence suggests that these cells could operate independently. For example, after VMHvll^{Cckar} cells are inactivated, there is no change in maternal behaviors (*25*). Rather than counteracting with mating- and fighting-related cells, parenting-related cells form strong mutual inhibition with infanticide-related cells: Activating infanticide-related cells suppresses parenting-related cells and vice versa (*41*). These circuit relationships make sense when considering the social target of each behavior. Because mating and fighting are both directed to adult conspecifics with similar physical features, the mutual inhibition between these circuits ensures one behavior output dominates. By contrast, parenting behaviors and mating and fighting behaviors are activated by highly distinct social targets, making cross-activation unlikely and, hence, mutual inhibition unnecessary.

Lastly, as the number of studies increases, the "molecularly defined populations" for each behavior will keep growing. *Gal*-, *Esr1*-, and *Calcr*-expressing cells in the MPOA have all been found to be essential for driving parental behaviors on the basis of recording and functional studies (*37*–*39*) (Fig. 2). These cells are neither distinct nor identical. MPOA^{Gal} cells partially overlap with MPOA^{Esr1} cells but largely differ from MPOA^{Calcr} cells, whereas *Calcr* is expressed in a subset of MPOA^{Esr1} cells (*9*). How is it determined whether a gene truly marks the social behavior population or a random population containing some social behavior–relevant cells just by chance? Indeed, if a behavior is the dominant output of a brain region, activating a random subset of cells in the region, marked by any of thousands of expressed genes, may drive the behavior. We think two criteria should be met for a gene to be considered a relevant maker. First, the cells expressing the gene should show a higher activity change during the behavior than the gene-negative cells. Second, functional manipulation of the gene-positive cells should influence the behavior more

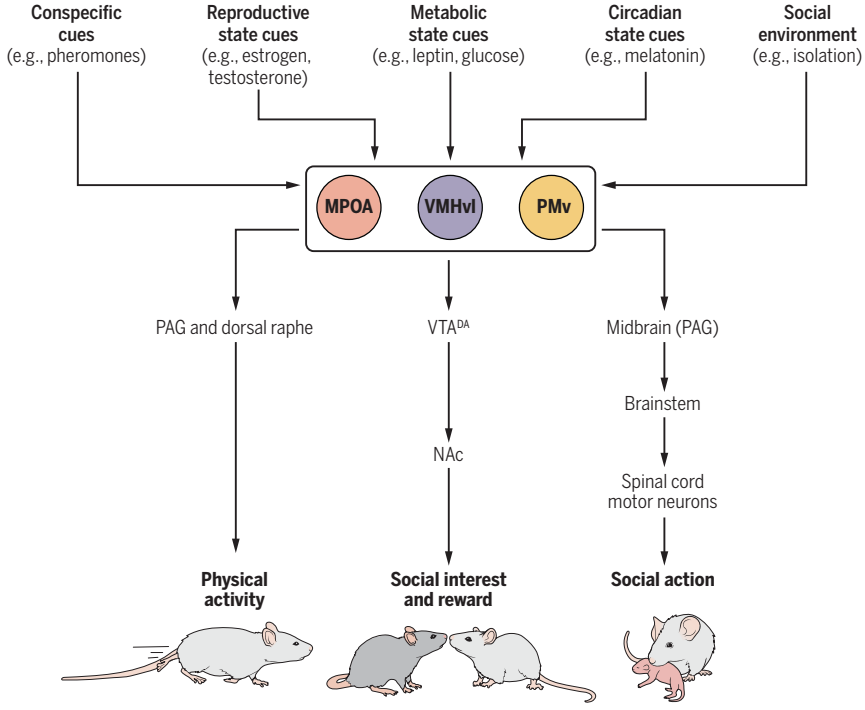

Fig. 3. Pathways extended from the RBCC that mediate various aspects of social behaviors.

profoundly than the cells that lack the expression. For example, *Esr1*-positive MPOA cells show higher responses than *Esr1*-negative cells during parental care (*38*). Activating *Esr1*-positive, but not *Esr1*-negative, cells in the VMHvl can drive male aggression (*14*). Additionally, it is unlikely, although not impossible, that a gene is distinctively expressed in the social behavior population coincidently. More plausibly, it is expressed for a reason, for example, to modulate the behavior output. Thus, a good gene marker is probably also functionally important for the behavior. Indeed, *Esr1* or *Calcr* knockout in the MPOA impairs parental behaviors, whereas antagonizing MPOA Tacr1 impairs male mating (*13*, *39*, *59*). Based on these rationales, receptors of neuropeptides or hormones that specifically modulate a social behavior could be the top candidates for marking specific social behavior populations.

The RBCC coordinates multiple aspects of social behaviors

We propose that the RBCC achieves social behavior control by (i) promoting exploration to increase the probability of social encounters, (ii) maintaining social interest when a social target is encountered, and (iii) permitting consummatory social actions at the appropriate times. In this section, we review the neural pathways downstream of the RBCC that mediate each aspect of these behavioral controls.

Social encounter probability

Animals must physically encounter each other to engage in social behaviors. We consider the first role of the RBCC to be to modulate an animal's physical activity, hence the likelihood of social encounters, based on an animal's internal state. In support of this idea, previous work has shown that animals increase locomotion when GABAergic MPOA cells (MPOA^{VGAT}), VMHvl^{Esr1} cells, or *NK2 homeobox 1* (*Nkx2-1*)–expressing VMHvl cells (VMHvl$^{Nkx2\text{-}1}$) are artificially activated (*60*–*63*). Conversely, loss of *Esr1* or *Nkx2-1* in the VMHvl reduces physical activity and causes obesity in female mice (*61*, *64*). VMHvl^{Esr1} projection to the dorsal raphe and MPOA^{VGAT} projection to the periaqueductal gray (PAG) appear important for RBCC control of physical activity (*62*, *63*) (Fig. 3).

The RBCC expresses abundant neuromodulator, neuropeptide, and hormone receptors, which allows various small molecules that are indicative of an animal's reproductive, metabolic, circadian, and other internal states to adjust the ongoing cell activity and, consequently, an animal's physical activity (Fig. 3). For the reproductive state, estrogen is a crucial hormone that signals ovarian activity. Estrogen supplementation substantially increases the excitability of MPOA and VMHvl cells (*65*, *66*). This estrogenic modulation likely underlies the increased spontaneous activity of VMHvl cells during estrus (*25*, *67*) and the increased activity of MPOA cells during motherhood (*38*, *41*). In addition to sex hormones, metabolic cues also modulate VMHvl^{Esr1} cell activity. For example, 24-hour fasting decreases the excitability of VMHvl^{Esr1} cells, which can be reversed with refeeding (*63*). Glucose may mediate these changes, because nearly all VMHvl cells are responsive to glucose in vitro (*68*). The circadian clock could also modulate the ongoing VMHvl activity. *Melanocortin receptor 4* (*MCR4*), a female VMHvl enriched gene, increases expression when estrogen levels are high, enabling nighttime melatonin to increase VMHvl cell activity and promote exploration during proestrus when the female is getting ready to mate (*69*, *70*). Beyond the internal cues, the social environment could also influence the ongoing activity of RBCC cells. Recently, Fukumitsu *et al.* found that prolonged social isolation decreases amylin and its receptor expression in the MPOA and reduces social-seeking behaviors (*71*). Thus, the ongoing RBCC cell activity is dynamically modulated by the internal state and external environment, which in turn adjusts an animal's physical activity level and the probability of social encounters.

Social interest level

Once the animals encounter each other, the next step is to recognize the identity of the social target. Although VMHvl and MPOA lesion or inhibition consistently change social preference, this likely does not reflect a deficit in sex discrimination, given that the manipulated animals often show reversed preference instead of no preference, which suggests that they remain capable of discriminating between males and females (*25*, *72*, *73*). Indeed, sex identity information is widely distributed in the limbic system, including regions upstream of the medial hypothalamus (*17*, *58*, *74*, *75*). Thus, the male- and female-induced neural activation patterns should remain different even without the RBCC. On the basis of these data, we reason that the RBCC deficit–caused changes in social preference likely reflect a decreased interest in certain social targets instead of an inability to discriminate between the sexes.

The RBCC likely promotes and maintains social interest by engaging the mesolimbic dopaminergic pathway (Fig. 3). Dopamine release in the nucleus accumbens (NAc) during initial social encounters has been shown to positively correlate with the total interaction time (*76*). Inhibiting ventral tegmental area (VTA) dopamine neurons decreases social interaction with an unfamiliar social target and the number of nose pokes an animal is willing to emit in order to access a conspecific (*77*–*79*). Conversely, optogenetic activation of the VTA dopaminergic projection to the NAc notably increases social interaction time (*76*, *78*).

The RBCC, especially the MPOA, likely engages the mesolimbic dopaminergic pathway by direct projection to the VTA. Indeed, optogenetic activation of the MPOA-to-VTA terminals evokes dopamine release in the NAc and promotes interaction with pups or potential mates (*38*, *65*). Additionally, activating medial amygdala GABAergic projection to the MPOA increases NAc dopamine release and promotes nose poking to access social targets (*80*). Channelrhodopsin (ChR2)–

assisted circuit mapping revealed that MPOA^{Esr1} cells preferentially target VTA GABAergic cells, suggesting that a disinhibition mechanism underlies the increased dopamine release (*38*). Similar to the MPOA, the VMHvl also promotes social seeking and approach. In male mice, optogenetic activation of VMHvl cells shortens the latency to nose poke for a weaker male intruder, whereas inhibiting the cells has the opposite effect (*49*). Activating female VMHvll^{Cckar} cells promotes social interest in males (*25*). VMHvl activation may evoke dopamine release directly through its glutamatergic projection to VTA dopaminergic cells (VTA^{DA}) or indirectly through its projection to the MPOA (*81*); additional studies are required to identify the exact circuit mechanism.

It is worth noting that the RBCC-VTA^{DA}-NAc circuit is also essential for the reinforcing property of consummatory social actions (Fig. 3). During social behaviors, the level of dopamine increases in the NAc, and animals subsequently develop a preference for the contexts, actions, or specific conspecific cues associated with these experiences (*76*, *82*–*84*). When VTA dopamine release or NAc dopamine receptors are blocked, the social experience-induced reinforcement diminishes (*83*–*86*). Conversely, optogenetically activating the socially relevant cells in the MPOA and VMHvl rapidly enhances the preference of the stimulation-coupled contexts and reinforces the actions that precede the stimulation (*25*, *40*, *65*). Taken together, these results suggest that the increased RBCC activity that is observed during consummatory social actions leads to NAc dopamine increase and reinforces sensory cues and motor actions that are time-locked to the behavior.

Consummatory social actions

Sexual, aggressive, and parental behaviors are recognized on the basis of their stereotyped and distinctive motor patterns. RBCC output to the midbrain, especially the PAG, has been established as a key pathway for the motor execution of social actions (*87*–*90*) (Fig. 3). The VMHvl mainly targets the dorsomedial and lateral PAG, matching the male aggression-induced c-Fos pattern. By contrast, the MPOA mainly targets the ventrolateral PAG, consistent with male mating-induced c-Fos (*81*, *87*, *88*, *90*, *91*). PMv projection to the PAG is relatively sparse (*89*, *90*). Interestingly, the RBCC largely avoids the dorsolateral PAG, a region that is important for defense (*90*). The PAG then relays the hypothalamic signal to spinal cord motor neurons directly or indirectly through the pons and medulla (*92*).

The role of the PAG in female sexual behavior and aggression, which are two VMHvl-mediated social behaviors, has been well established. PAG lesion in rats reduces both behaviors, whereas electric stimulation of the PAG has the opposite effect (*22*, *93*, *94*). More recently, we found that activating the VMHvl to the PAG pathway induces attack in male mice, whereas inactivating the PAG blocks VMHvl stimulation–induced attack (*95*). Interestingly, after PAG inactivation, animals remain highly engaged with the intruder and show attack-like behavior, for example, lunging, but fail to complete the attack sequence (*95*). Consequently, the opponent walks away unharmed. Thus, PAG lesion impairs the motor execution of attack but not the underlying aggressive motivation.

The role of the PAG in male sexual and parental behaviors, which are two MPOA-mediated social behaviors, is less clear. For male mating, c-Fos increased in the PAG (*91*), but large lesions in the PAG accelerated rather than suppressed mounting behaviors (*96*). For parental behaviors, caudal PAG lesion reduces kyphosis, a supine posture during nursing, but does not affect active parental behaviors, such as pup retrieval (*97*). Rostral PAG–lesioned animals still initiate retrieval of pups but have trouble releasing them when held in the mouth (*98*). Optogenetic manipulation of MPOA^{Gal} to PAG projection specifically affects pup grooming (*57*). Thus, different subregions of the PAG are likely involved in different aspects of parental behaviors, and midbrain regions outside of the PAG may drive active parental actions. Indeed, early lesion studies and recent pathway-specific optogenetic activation experiments have suggested that the MPOA engages the ventral pallidum through its projection to the VTA to mediate pup retrieval (*38*, *99*).

How does the RBCC control social actions in broader terms (Fig. 4)? Electrophysiological recordings have shown that medial hypothalamic cells do not carry information regarding specific movements during social behaviors. For example, individual VMHvl cells increase activity during the entire attack sequence regardless of whether the animal is lunging, biting, or tumbling (*100*). Thus, RBCC cells could not instruct moment-to-moment movement; instead, the cells likely serve as a "permissive gate" that allows motor neurons to drive an action based on immediate sensory cues. We speculate that a brainstem–spinal cord reflex circuit exists for each social action, such as biting, retrieving, or mounting, that takes in sensory inputs and activates the local motor neurons to drive coordinated muscle movements (Fig. 4). Visual inputs may enter the circuit at the brainstem level, for example, through the superior colliculus (*101*), whereas spinal cord sensory neurons presumably receive somatosensory inputs. The brainstem–spinal cord circuits, however, are likely unable to operate on their own, either because the motor neurons are under tonic suppression or the inputs from sensory neurons are not sufficiently robust. We suggest that only when the RBCC is activated to remove the inhibition or boost the excitatory drive can the motor neurons respond to the acute sensory inputs. During social encounters, the increased activity from specific cells in the RBCC determines which brainstem–spinal cord circuits are permitted to operate. However, the final release of the action should be triggered by the acute sensory inputs to the brainstem or spinal cord. We speculate that the sensing cells in the brainstem–spinal cord circuits have a limited ability to integrate information from various sensory modalities and thus are activated promiscuously if ungated. Therefore, when the medial hypothalamic cells are artificially activated, the animals initiate social actions toward improper targets (*12*, *13*, *16*). For example, VMHvl activation can induce attacks toward an inflated glove (*16*). Although the glove has no resemblance to a mouse in its smell, sound, or shape, its soft and bouncy surface provides sufficient somatosensory input to trigger the brainstem–spinal cord biting circuit once its gate is opened by artificial VMHvl activation.

A similar conceptual framework for generating lordosis was proposed by Donald Pfaff and

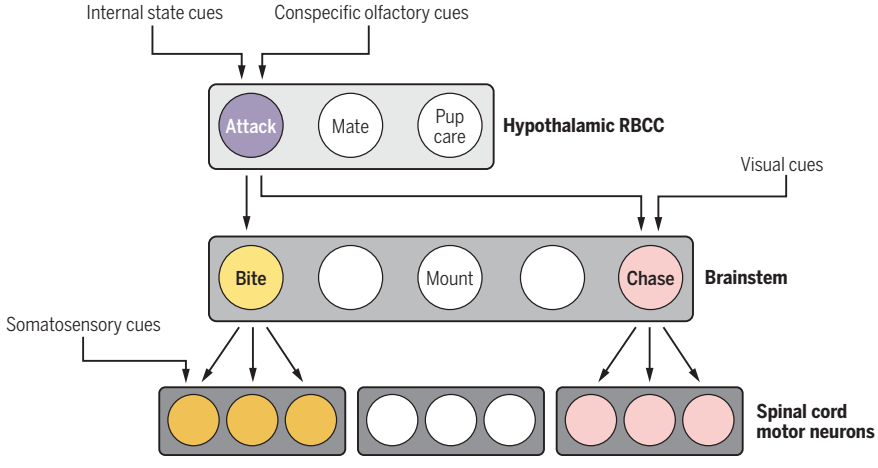

Fig. 4. The RBCC and brainstem–spinal cord dual control of social behaviors. In rodents, the RBCC receives many internal state and conspecific olfactory cues to determine the type of social behaviors to be executed. The RBCC provides permission to specific brainstem–spinal cord cell groups so that those cells can respond to acute sensory visual and somatosensory inputs and generate motor outputs.

co-workers (*22*). They suggested that a series of brain modules mediates lordosis. The spinal cord modules, coordinated by the brainstem module, control the muscle movements in response to the somatosensory inputs to the spinal cord during male mounting, whereas the output of the hypothalamus module to the brainstem might be essential for ensuring that lordosis only occurs during estrus (*22*). We now know that female VMHvl activity increases during estrus and with the proximity of a male (*23*–*25*, *67*). Thus, the increased VMHvl output provides a window of opportunity for the brainstem–spinal cord circuit to drive lordosis upon receiving the somatosensory cues during male mounting. The dual hypothalamic and brainstem control system ensures that the social action is supported by the animal's physical and reproductive states, is directed toward the right social target (based on hypothalamus input), and happens at the right moment (based on the acute sensory inputs to the brainstem and spinal cord). We speculate that this dual-control system is a common feature in generating innate social actions, and the same principle may apply to learned social actions that vary rapidly with the opponent's behaviors (Fig. 4). As we gain a better understanding of the connectivity between the RBCC and the brainstem–spinal cord circuit that is relevant for each social action, this dual-control system will be further tested and specified in future studies.

Concluding remarks

The RBCC orchestrates all innate social behaviors that subserve reproduction. The MPOA drives male sexual, paternal, and maternal behaviors, whereas the VMHvl and PMv promote female sexual behavior and aggression in both sexes. The MPOA and the VMHvl and PMv may have an antagonistic relationship, as indicated by their opposing roles in multiple social behaviors. At the baseline, the RBCC adjusts an animal's physical activity, hence the chance of social encounters, on the basis of hormonal and metabolic signals. Upon encountering a social target, the RBCC engages the dopamine system to sustain the social interest and reinforce the actions and contexts that lead to the successful completion of social behaviors. The PAG has emerged as a critical midbrain relay for executing VMHvl-driven social behaviors, but the midbrain region that transforms MPOA signals into motor actions remains elusive. Regardless of the exact circuit, we propose a hypothalamic and brainstem–spinal cord dual-control system for the motor execution of each social action. In this model, medial hypothalamus activity determines the broad behavior category based on the animal's internal state and opponent's social identity and opens the gates to allow specific brainstem–spinal cord circuits to respond to the immediate sensory cues and drive moment-to-moment motor output. Though not discussed here, the RBCC also drives a suite of autonomic responses to prepare the body for social actions and triggers neuropeptide and hormone releases that are essential for reproduction after mating (*102*). Lastly, it is worth mentioning that although the RBCC circuit is hardwired developmentally, it remains plastic. The input-output relationship of the circuit can be shaped through experience during development and adulthood, enabling widely different tendencies in the expression social behaviors across individuals (*103*).

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Hypothalamic control of innate social behaviors

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