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Review

Neural circuits of social behaviors: Innate yet flexible

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SUMMARY

Social behaviors, such as mating, fighting, and parenting, are fundamental for survival of any vertebrate species. All members of a species express social behaviors in a stereotypical and species-specific way without training because of developmentally hardwired neural circuits dedicated to these behaviors. Despite being innate, social behaviors are flexible. The readiness to interact with a social target or engage in specific social acts can vary widely based on reproductive state, social experience, and many other internal and external factors. Such high flexibility gives vertebrates the ability to release the relevant behavior at the right moment and toward the right target. This maximizes reproductive success while minimizing the cost and risk associated with behavioral expression. Decades of research have revealed the basic neural circuits underlying each innate social behavior. The neural mechanisms that support behavioral plasticity have also started to emerge. Here we provide an overview of these social behaviors and their underlying neural circuits and then discuss in detail recent findings regarding the neural processes that support the flexibility of innate social behaviors.

Innate social behaviors

Throughout its lifetime, an organism is exposed to a plethora of internal and external stimuli. It responds to such stimuli to survive and thrive. At times, the organism must respond in a social context via multimodal forms of communication with conspecifics. For instance, as an infant, it may derive food from its parents to satiate its hunger. As a juvenile, it may indulge in play behavior with its siblings. As an adult, it may mate with conspecifics, defend its territory and resources from conspecific intruders, and take care of its young to ensure continuation of its line. Such social behaviors are instinctive, can be initiated without being explicitly taught, and consist of a series of robust stereotypical action progressions. Their implementation is driven by developmentally hardwired neural circuits and constrained by anatomical and morphological features that evolve simultaneously. These behavioral solutions are retained through generations because of their contribution to ensuring the continuation of the species (Kappeler et al., 2013).

Much thought has been put into characterizing the components of innate social behaviors. The famed ethologists Konrad Lorenz and Nikolaas Tinbergen proposed that instinctive behaviors start with an appetitive phase (Hashikawa et al., 2016; Hogan and Bolhuis, 2009; Lorenz, 1981). The initial component of the appetitive phase is detecting and subsequently approaching the social stimulus or, conversely, soliciting a conspecific. A subsequent component of the appetitive phase involves investigation or exploration of the social stimulus. The appetitive phase is followed by a stereotyped consummatory phase that consists of a series of fixed motor patterns (Hashikawa et al., 2016; Hogan and Bolhuis, 2009; Lorenz, 1981). In this review, we divide innate social behaviors into four instead of two phases to better describe the points of change observed in progression of a particular social behavior. These four phases are detection, approach, investigation, and consummation or action (Figure 1). The first three phases can be considered together as an identification phase that brings the animal into close proximity of the target to determine its identity so that appropriate actions can be taken.

Below we describe common innate social behaviors seen in vertebrates. We particularly focus on rodents because they are at the center of biological research and display a complex array of innate social behaviors.

Detection phase

In this phase, an individual aims to identify the presence and location of a distant social target via unique sensory cues emitted by the target. In rodents, such cues are mainly olfactory in nature, such as vaginal secretions of females or urine markings of males. Chemical cues are particularly useful for species that live in relative isolation because of their long-lasting nature. Animals can also locate a social target using species-specific acoustic or visual cues; for instance, rodent pups emit ultrasonic vocalizations when they are out of their nest and cold (Hofer et al., 2002). These pup calls trigger approach in dams and stop when pups are in contact with their mother or litter, an effect known as contact quieting (Hofer et al., 2002).

Upon sensing conspecific olfactory cues, a rodent decreases its velocity, twitches its nose rhythmically, whiskers, and bobs its

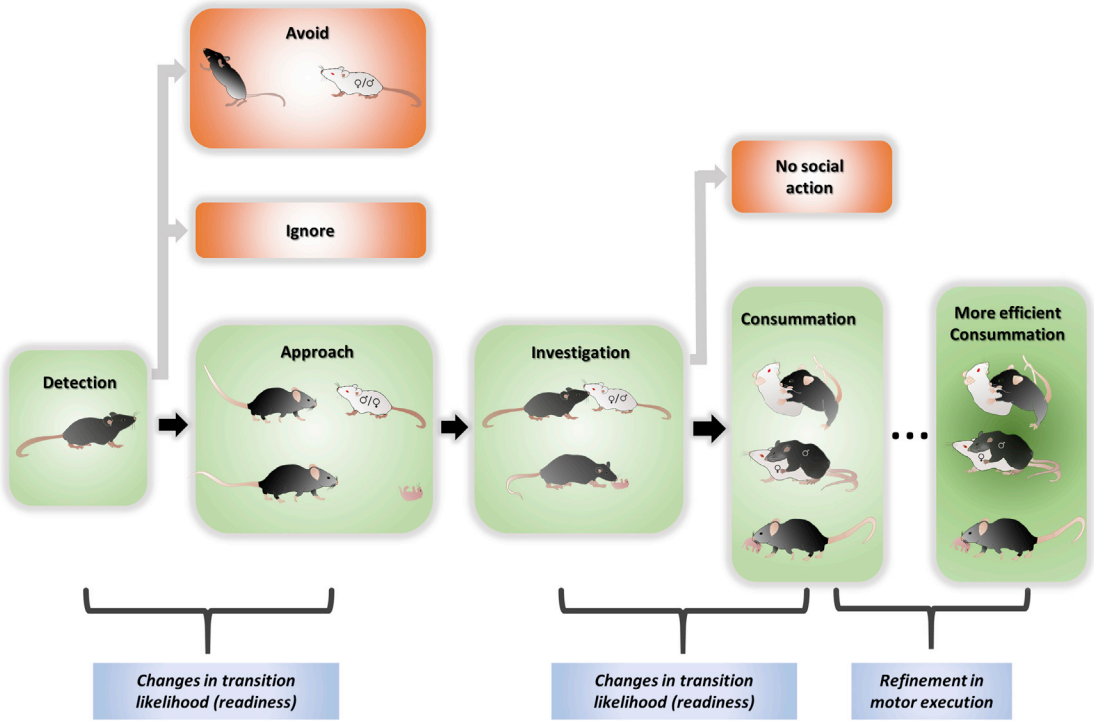

Figure 1. The four proposed phases of innate social behaviors
The four phases—detection, approach, investigation, and consummation—are illustrated in green. The readiness to transition from detection to approach and from investigation to consummation is subject to change based on the animal's experience, internal state, and external factors. The motor execution of the consummatory phase can also be refined with experience.

head, all phase-locked with the respiratory cycle, while slowly changing its orientation (Kurnikova et al., 2017). During this process, the breathing rate increases from a basal level of 1–3 Hz to 4–12 Hz (Deschênes et al., 2016). These well-coordinated actions allow the rodent to maximally sample the odor and determine the direction of its source before making a move toward or, in some cases, away from it.

Approach phase

The purpose of the approach phase is to reduce the distance between an individual and a distal social stimulus. It is a prerequisite of social investigation and consummatory actions.

The motor outputs that define approach are similar for different types of innate social behaviors, which could involve walking, running, flying, or swimming toward the social stimulus.

Approach toward a social target is a consequence of an individual's internal readiness to engage with conspecifics. Most vertebrates and invertebrates are socially inclined. For some, the mere proximal presence of a conspecific or the presence of a conspecific cue is rewarding. For instance, dams are willing to give up food or cocaine to be close to pups, specifically early postpartum (Fleming et al., 1994; Trezza et al., 2011). Naive female mice develop a preference for the chamber where they were exposed to male-soiled bedding (Martínez-García et al., 2009). More importantly, approach provides a gateway for the individual to carry out rewarding consummatory actions endemic to innate social behaviors such as sexual intercourse, aggression, parenting, and social play (Golden et al., 2016; Tenk et al., 2009; Trezza et al., 2011). The opportunity for a two-fold reward, companion of a conspecific and the subsequent consummatory act, is what drives an individual to approach a conspecific.

Investigation phase

The investigation phase is defined as close exploration of the social stimulus, aiming to gather information about the conspecific. This phase helps the individual collect enough evidence to proceed to the appropriate, potentially rewarding consummatory phase.

The motor output during the investigatory phase involves orienting toward the stimulus and examining a part of its body. In many mammals, including rodents and primates, such examination is carried out via sniffing (Jänig et al., 2018; Kepecs et al., 2006). Sniffing is often directed toward facial and anogenital areas, where pheromones are enriched (Liberles, 2014). In addition to sampling chemical cues, the action of sniffing itself could signal the social status of the two animals involved. Specifically, subordinate male rats reliably reduce their sniffing frequency upon being investigated by the dominant rats, and failure to do so shortens the latency of the dominant rat to initiate attacks (Wesson, 2013).

The approach and investigation phases precede the consummatory phase of innate social behaviors and are therefore independent of it. The expression of approach and investigation can thus reflect an individual's internal readiness to engage with a social stimulus even when the subsequent consummatory phase

is blocked. The social preference test (conducted mostly in rodents; Kim et al., 2019a) measures the relative time a test animal spends approaching and investigating two social targets or a social and non-social target under a cup. This assesses the animal's internal readiness to engage with the stimulus, commonly referred to as social interest. When consummatory behaviors are not blocked, however, the animal investigates and then carries out the appropriate actions toward the social stimulus. A quick transition from the investigation to the consummation phase reflects a high level of internal readiness to release the consummatory actions.

Consummation (action) phase

The consummation phases of different social behaviors differ because different innate social behaviors aim to accomplish different goals. Below we describe the consummation phases seen in goal-directed innate social behaviors such as sexual behavior, aggression, and infant and parental behavior.

Sexual behavior. Sexual behaviors are necessary for species survival. The vast majority of vertebrates reproduce sexually. The consummation phase of mating in male rodents consists of three stages (Hull and Dominguez, 2007). The first stage is mounting, where the male pushes his forepaws against the female's flanks and gives her several shallow thrusts. During the second stage, or intromission, he detects the female's vagina with his penis and gives several deeper thrusts. The third stage, or ejaculation, is expulsion of sperm into the vagina following rounds of intromission. Males emit ultrasonic vocalization in conjunction with copulation to facilitate sexual responsiveness of the female (McIntosh et al., 1978). The female, typically in the proestrus or estrus stage of her reproductive cycle ("receptive"), solicits sexual behavior from the male (Beach, 1976). She then allows the male to mount her with relative ease and assumes a position known as lordosis. Lordosis is characterized by an arched back, allowing vaginal penetration by the male. Despite being thought of as relatively quiescent during mating, female rodents play an active role in copulation. This could be by pacing the male's mounts or by adjusting position to allow more efficient intromissions (McClintock and Adler, 1978).

Aggressive behavior. Aggression is an important and ubiquitous method to defend or compete for territory, resources, and mates and to protect oneself and one's family against potential threats. For rodents, biting is one of the main strategies to inflict pain upon their opponents. A series of motor actions, such as aggressive grooming, chasing, lunging, and sideway threats, are employed to gain access to a favorable target of attack (e.g., the back of an opponent) before a bite is delivered (Blanchard and Blanchard, 1977; Takahashi and Miczek, 2014). Male rodents are typically more aggressive than females, although the motor patterns of attack are largely similar between sexes (Hashikawa et al., 2018). Upon being attacked, the other animal employs a different set of defensive actions, such as jumping, dashing, standing upright, and pushing to fend off the bites and escape from the aggressor (Blanchard et al., 1979; Wang et al., 2019).

Infant and parental behavior. Infants depend on their parents for food, shelter, and protection. Accordingly, a set of innate behaviors has evolved in the young and in the parents to ensure that the needs of the young are met. Most infant mammals show suckling behaviors upon birth to derive milk from their mother (German et al., 2006), and initiation of suckling depends on the olfactory cues around the nipples (Logan et al., 2012). With regard to parenting, starting from early pregnancy, females increase their nest-building behavior (Auclair et al., 2014). After giving birth, female mice spend an average of 10–15 h a day in the nest to care for the young (Auclair et al., 2014). Dams assume a crouching posture over the pups, with all four limbs supported and a slightly arched back, so that the pups can access the ventral surface to suckle the milk. Dams also lick and groom the pups extensively to keep them clean and retrieve the pups when they accidently wander out of the nest. Although females are the main caregivers, fathers, especially those of monogamous species, express many of the same parental behaviors as mothers (Dulac et al., 2014; Kohl et al., 2017).

Circuitry of innate social behaviors

Below we describe the circuitry that underlies the detection, approach, investigation, and consummation phases of social behaviors. Our focus is on subcortical circuitries involved in generating sexual, aggressive, and parental behaviors. Much of our knowledge is obtained from rodents, although these circuitries are likely highly conserved across vertebrate species (Goodson, 2005; O'Connell and Hofmann, 2011). Cortical regions, such as the prefrontal cortex, encode complex social information that could be used to modulate social behaviors (Behrens et al., 2008; Kingsbury et al., 2019, 2020; Nelson et al., 2019; Wang et al., 2011; Zhou et al., 2017). Readers interested in this topic should refer to several excellent reviews (Gangopadhyay et al., 2021; Krueger et al., 2009; Watanabe, 2017).

Circuitry underlying the detection phase

In rodents, olfaction is the most crucial sensory modality of communication, although they also use auditory and visual cues to facilitate localization of the social target (Ryan et al., 2008; Smotherman et al., 1974; Strasser and Dixon, 1986). Volatiles emitted from distant animals are detected by olfactory sensory neurons (OSNs) in the main olfactory epithelium (MOE) and are transferred to the main olfactory bulb (MOB), where the signal is distributed to multiple regions, including the olfactory tubercle (OT), anterior olfactory nucleus (AON), cortical amygdala (anterior and posterolateral part; CoAa and CoApl, respectively), piriform cortex (Pir), and entorhinal cortex (EC) (Spehr et al., 2006; Figure 2). During sniffing, a process by which an individual actively acquires olfactory cues, the animal performs a series of micromovements, including faster breathing, recurrent protraction and retraction of mystacial vibrissae, repeated retraction and protraction of the tip of the snout, and up-and-down head movements (Deschênes et al., 2016). These movements are generated by a medullary circuit, including the preBotzinger complex (preBotC), the core respiratory generator (Feldman and Kam, 2015). How the odor cues reach the preBotC to accelerate respiration and generate coordinated micromovements remains largely unknown (Deschênes et al., 2016). Along with these nose and head micromovements, the animals gradually orient toward the odor source based on the small difference of the odor inputs to the left versus right nostril (Rajan et al., 2006). The neural circuit that supports odor orientation is also

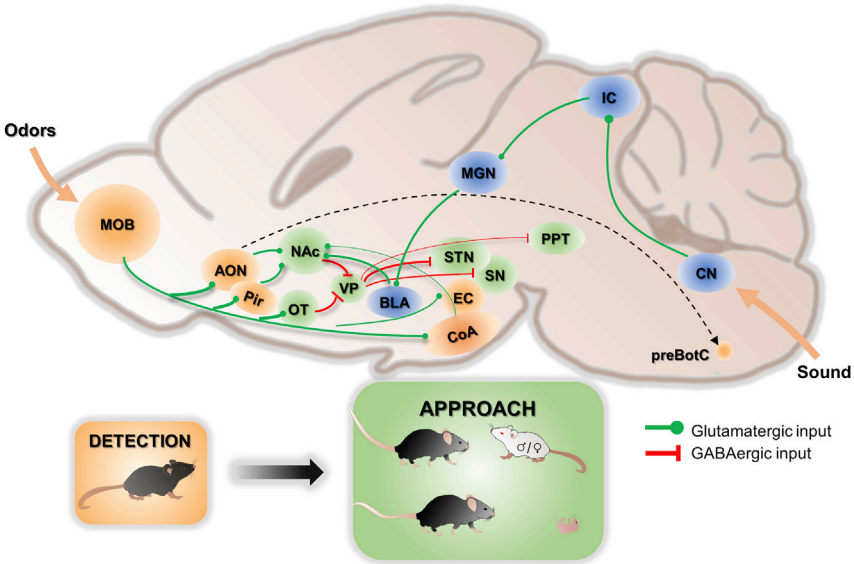

Figure 2. The circuitry underlying detection of olfactory and auditory cues and approach
Schematics show the brain regions involved in detecting olfactory (orange) and auditory (blue) social cues and approaching the cues (green) and the relevant connections. The dotted line represents a putative connection that could be indirect. The widths of the lines indicate the connection strength. AON, anterior olfactory nucleus; BLA, basolateral amygdala; CN, cochlear nucleus; CoA, cortical amygdala; EC, entorhinal cortex; IC, inferior colliculus; MGN, medial geniculate nucleus; MOB, main olfactory bulb; NAc, *nucleus accumbens*; OT, olfactory tubercle; Pir, piriform cortex; PPT, pedunculopontine nucleus; preBotC, pre-Botzinger complex; SN, *substantia nigra*; STN, subthalamic nucleus; VP, ventral pallidum.

poorly understood but likely involves inputs from the AON (Kikuta et al., 2010).

Circuitry underlying the approach phase

The *nucleus accumbens* (NAc) has been firmly established as a key region in mediating goal-directed approach behaviors, including approach toward social targets (Blaiss and Janak, 2009; Floresco, 2015; Hamel et al., 2017). Bilateral inactivation of the NAc impairs preferential social approach toward stressed juveniles in rats (Rogers-Carter et al., 2019). Administration of an oxytocin receptor antagonist into the NAc decreases social approach in monogamous California mice and mandarin voles (Williams et al., 2020; Yu et al., 2016). Conversely, enhancing serotonin release in the NAc rescues a social approach deficit in mouse autism models (Walsh et al., 2018). Recently, Scribner et al. (2020) performed *in vivo* miniscope imaging and revealed that distinct ensembles of NAc cells are activated during approach toward partners and novel conspecifics in prairie voles. Importantly, NAc cells become active prior to approach, supporting its potential function in driving the behavior (Scribner et al., 2020). Dopaminergic cells in the ventral tegmental area (VTA) project densely to the NAc and are known to modulate synaptic transmission onto striatal medial spiny neurons (MSN) (Tritsch and Sabatini, 2012). Consistent with a role of VTA-NAc dopaminergic cells in social approach, the cells increase activity during the behavior, and optogenetic activation of the cells facilitates social approach (Gunaydin et al., 2014). The NAc likely connects to the motor system through its GABAergic efferent to the ventral pallidum (VP) (Mogenson and Yang, 1991; Richard et al., 2016). The VP, in turn, projects to the brain stem motor output, such as the pedunculopontine tegmentum (PPT), *substantia nigra* (SN), and subthalamic nucleus (STN), to direct locomotion (Smith et al., 2009; Figure 2).

Multiple regions along the main olfactory pathway can potentially send conspecific olfactory information to the NAc (Figure 2). Tracing studies revealed that the AON and Pir provide strong inputs to the NAc, especially its core regio (Li et al., 2018). The Pir is the primary olfactory cortex with broad functions in odor recognition and discrimination (Bekkers and Suzuki, 2013). Very little is known regarding the function of the AON. Two studies involving electrophysiological recordings of AON cells in anesthetized mice and rats showed that AON cells integrate inputs from diverse chemical classes and that some cells are tuned specifically to socially relevant olfactory cues (e.g., soiled bedding) (Lei et al., 2006; Tsuji et al., 2019). The CoApl also sends weak projections to the NAc and is activated preferentially by innately attractive odors. Reactivation of CoApl cells that are responsive to attractive odors recapitulates the approach behavior (Root et al., 2014).

One additional region along the main olfactory pathway that is worth mentioning is the OT. The OT is primarily composed of GABAergic cells and is considered a part of the ventral striatum, just like the NAc (Yamaguchi, 2017). The OT receives projections mainly from the ventral side of the MOB, where social information is encoded (Martel and Baum, 2007; Scott et al., 1980), and projects strongly to the VP (Wesson and Wilson, 2011). Thus, the OT is well positioned to form a circuit parallel to the NAc to drive approach based on conspecific olfactory inputs. Consistent with this possibility, recent functional studies showed that lesion or pharmacogenetic inactivation of the OT abolished the attraction of male cues to female mice (Agustín-Pavón et al., 2014; DiBenedictis et al., 2015).

Prosocial ultrasonic vocalizations (USVs) also activate NAc cells and increase dopamine levels in the area (Sadananda et al., 2008; Willuhn et al., 2014). The precise pathway that passes USVs to the NAc remains incompletely understood, but the basolateral amygdala (BLA), a region that receives extensive auditory inputs and projects heavily to the NAc, is likely a key relay. Electrophysiological recordings found that the majority of BLA cells are responsive to social USVs (Parsana et al., 2012).

Circuitry underlying the investigation phase

With rodents, when the social target is in close proximity, the approaching animal closely investigates the target to acquire additional information regarding the latter's social identity. During nasal contact with a conspecific, nonvolatile pheromones are actively pumped into the vomeronasal organ (VNO) and then bind to highly specific receptors on vomeronasal sensory

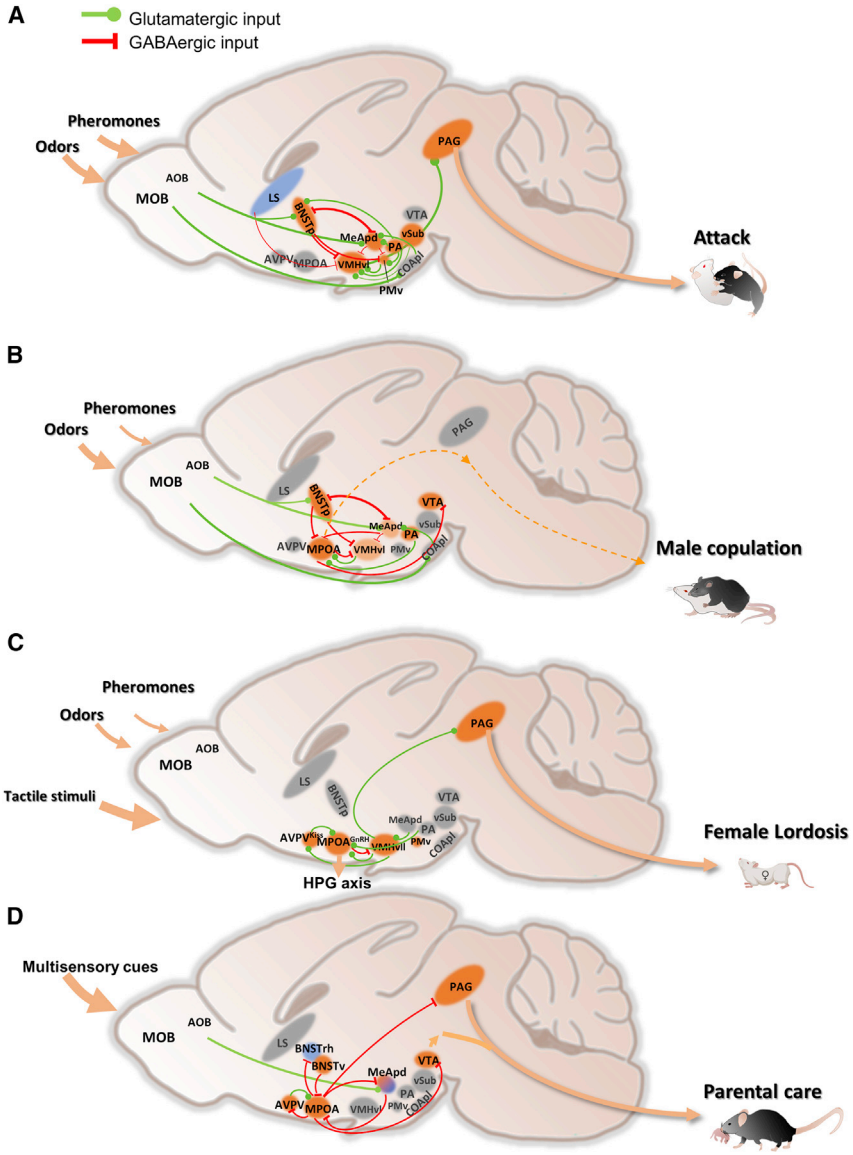

Figure 3. Schematics showing neural circuits of social behaviors

(A) Aggression circuit.
(B) Male sexual behavior circuit.
(C) Female sexual behavior circuit.
(D) Parental care circuit.

Solid lines denote known pathways that are involved in mediating the behaviors. Dashed lines denote potential pathways to be explored further. Blue regions suppress the behavior, whereas orange regions promote the behaviors. Light orange marks regions that play minor roles in the behavior. Gray regions are not essential for the behaviors or have not yet been studied. Arrow size indicates the importance of the sensory input. Line width indicates connection strength. Not all known connections are shown. AOB, accessory olfactory bulb; AVPV, anteroventral periventricular nucleus; BNSTp, posterior part of the bed nucleus of the *stria terminalis*; BNSTrh, rhomboid nucleus of the bed nucleus of the *stria terminalis*; BNSTv, ventral part of the bed nucleus of the *stria terminalis*; CoApl, posterolateral cortical amygdala; LS, lateral septum; MeA, medial amygdala; MPOA, medial preoptic area; PA, posterior amygdala; PAG, periaqueductal gray; PMv, ventral premammillary nucleus; VMHvl, ventrolateral part of the ventromedial hypothalamus; VMHvll, lateral subdivision of the VMHvl; vSUB, ventral subiculum; VTA: ventral tegmental area.

neurons (VSNs). VSNs then pass the information to the accessory olfactory bulb (AOB), which, in turn, projects to the medial amygdala (MeA), the posterior part of the bed nucleus of the *stria terminalis* (BNSTp), and the posteromedial cortical amygdala (CoApm) (Spehr et al., 2006). From there, pheromone information is delivered to a series of medial hypothalamic nuclei that are essential for generating social behaviors (Figure 3).

Unique to the VNO is its ability to accumulate sensory cues. With each bout of sniffing, the pheromone concentration in the VNO increases, and more VSNs and their downstream cells are activated (He et al., 2010). The information conveyed by the VNO is essential for precise social identification (Pankevich et al., 2006), although its exact role in behavior initiation varies based on the nature of social behaviors. VNO inputs appear to be indispensable for aggression initiation. Blocking or genetically impairing the VNO severely suppresses aggressive behaviors in male and female mice in nearly all studies (Chamero et al., 2011; Kimchi et al., 2007; Leypold et al., 2002; Stowers et al., 2002). In contrast, the effects of VNO deficits on male sexual behavior are variable. VNO ablation diminishes mating in some males but not others (Clancy et al., 1984; Powers and Winans, 1975; Winans and Powers, 1977). A careful survey revealed that sexually experienced males are less prone to mating deficits after VNO removal (Meredith, 1986; Saito and Moltz, 1986). Transgenic mice with deficits in subsets of VNO cells showed differential changes in sexual behaviors based on the mutated genes (Yu, 2015). Male and female mice that are deficient for Trpc2, an ion channel essential for VNO sensory transduction, mount intruder males and females excessively and indiscriminately (Kimchi et al., 2007; Leypold et al., 2002; Stowers et al., 2002). Deletion of a cluster of V1R genes causes reduced mounting in males (Del Punta et al., 2002), whereas disruption of a signal molecule, Gαi2, did not alter male sexual behaviors (Norlin et al., 2003). Thus, VNO inputs appear to facilitate male sexual behaviors but are not absolutely required, and inputs from some VNO cells are likely more important than others. In females, VNO ablation experiments support a facilitating role of VNO inputs in female sexual receptivity, although *Trpc2*$^{-/-}$ females show no decrease in lordosis (Kimchi et al., 2007; Lepri and Wysocki, 1987; Mackay-Sim and Rose, 1986; Rajendren et al., 1990).

It is worth noting that, during investigation, olfactory signals continue to be detected by the MOE, pass through the MOB,

and converge with vomeronasal inputs onto MeA cells directly or via the CoApl (Figure 3; Martinez-Marcos, 2009). Genetically or chemically disabling MOE cells completely abolishes aggression in both sexes and sexual behaviors in male mice (Mandiyan et al., 2005; Wang et al., 2006). The manipulation also reduces lordosis in sex hormone-primed females by approximately 50% (Keller et al., 2006). These deficits are unlikely to be solely caused by a lack of close interaction because MOE-defective males failed to copulate with females even after 10 days of co-housing in a standard shoebox-sized cage. Instead, it suggests that olfactory inputs are indispensable for the transition from investigation to consummatory actions related to aggression and mating.

Circuitry underlying the consummation phase

Decades of research have established the medial hypothalamus as a key region where social behavior-promoting cells reside. For nearly 100 years, neuroscientists have been captivated by the strikingly natural-looking social behaviors elicited by artificial activation of medial hypothalamic cells (Hashikawa et al., 2017b; Kohl and Dulac, 2018; Siegel et al., 1999; Sternson, 2013). Conversely, blocking activity of this area by permanent lesions or transient inactivation impairs those behaviors (Falkner and Lin, 2014; Kohl and Dulac, 2018; Sternson, 2013). Studies in the last decade further elaborated the hypothalamic regions and their related circuits underlying social behaviors, and those findings were covered extensively in several recent reviews (Chen and Hong, 2018; Hashikawa et al., 2016; Ishii and Touhara, 2019; Kohl et al., 2017; Lenschow and Lima, 2020; Micevych and Meisel, 2017; Sternson, 2013). Here we attempt to provide a synthesized overview of these results, highlighting the differences among those circuits.

The neural circuitry of attack. The ventrolateral part of the ventromedial hypothalamus (VMHvl) and the ventral premammillary nucleus (PMv), two hypothalamic nuclei with cells that are almost exclusively glutamatergic, have emerged as the key neural substrates for generating attack (Falkner et al., 2014, 2016; Hashikawa et al., 2017a; Lee et al., 2014; Lin et al., 2011; Motta et al., 2013; Stagkourakis et al., 2018; Yang et al., 2013, 2017; Figure 3A). The VMHvl and PMv receive inputs from the MeA and BNSTp, with more dense inputs to the PMv than the VMHvl (Canteras et al., 1995; Dong and Swanson, 2004).The projections from the MeA and BNSTp to the VMHvl and PMv are primarily GABAergic. Nevertheless, these connections promote aggression, presumably by increasing activity in the VMHvl and PMv through a disinhibition mechanism. Another major area upstream of the PMv and VMHvl is the posterior amygdala (PA). The PA is largely glutamatergic, and PA cells that project to the VMHvl are essential for generating male aggression (Canteras et al., 1992b). Unlike the MeA and BNSTp, the PA receives inputs mainly from the ventral hippocampus (Yamaguchi et al., 2020; Zha et al., 2020). The lateral septum (LS) receives massive and topographically arranged inputs from the hippocampus and provides GABAergic inputs to the VMHvl (Leroy et al., 2018; Swanson and Cowan, 1977; Wong et al., 2016). Inactivation of the LS causes an increase in aggression, "septal rage," suggesting that the LS exerts tonic inhibition on the aggression circuit (Albert and Chew, 1980). Last, the ventral hippocampus also directly provides a moderate projection to the VMHvl, and pharmacogenetic activation of this pathway promotes attack in male mice (Chang and Gean, 2019). Within the hypothalamus, the VMHvl and PMv densely and reciprocally connect with the medial preoptic nucleus (MPN), forming the "medial hypothalamic reproductive system" (Canteras, 2002), although the functional importance of the MPN in aggression remains unclear. Between the VMHvl and PMv, the PMv provides more inputs to the VMHvl than vice versa (Canteras et al., 1992a, 1994; Lo et al., 2019).

At the output level, the PMv primarily targets regions in the hypothalamus, whereas the VMHvl projects densely to the midbrain, especially the periaqueductal gray (PAG), a premotor region essential for the final execution of attack (Falkner et al., 2020). Thus, the sensory information roughly flows from the early olfactory relays to the MeA, PMv, and VMHvl and then to the PAG to generate an attack. Regions that are essential for male aggression play similarly important roles in female aggression, although quantitative differences of aggression cells between males and females clearly exist (Hashikawa et al., 2018; Motta et al., 2013; Yang et al., 2013). In females, aggression-related cells are mostly concentrated in the medial subdivision of the VMHvl (VMHvlm), whereas the cells are distributed throughout the VMHvl in males (Hashikawa et al., 2017a, 2018).

The neural circuitry of male copulation. The consummation phase of sexual behaviors differs qualitatively between sexes and, not surprisingly, is supported by sex-specific neural circuits. In males, the medial preoptic area (MPOA) has long been recognized as a key region for sexual behaviors based on numerous lesion, activation, and recording experiments (Hull and Dominguez, 2007; Figure 3B). The MPOA is a heterogeneous region that includes the MPN, several other nuclei, and unnamed regions between the anterior commission and nuclei (https://portal.brain-map.org/). In this review, we use the MPOA unless the original study mapped the target precisely to the MPN. The VMHvl also plays a role in male sexual behaviors but likely a minor one (Yang et al., 2013). *In vivo* recordings reveal clear differences between VMHvl and MPOA cell responses during sexual behaviors; MPOA cells increase activity as the sexual behaviors advance, and VMHvl cells are only activated transiently during the initial mounting and then are suppressed for the rest of the behavior (Lin et al., 2011; Shimura et al., 1994). Interestingly, cells that drive male-style mounting appear to exist in the female MPOA and VMHvl; optogenetic activation of estrogen receptor alpha-positive (Esr1+) cells in these regions can elicit time-locked mounting in mice of both sexes (Hashikawa et al., 2017a; Wei et al., 2018). However, male-style mounting in females is generally considered a dominance behavior for maintaining social status instead of being a form of female sexual behavior (Fang and Clemens, 1999).

Surprisingly, little is known regarding the outputs from the MPOA and VMHvl that drive motor actions during male copulation. One early study that systematically lesioned midbrain regions downstream of the MPOA suggested the dorsolateral tegmentum (DLT) as a key region for male sexual behaviors (Brackett et al., 1986), but a later study failed to confirm this result (Romero-Carbente et al., 2006). Instead, the central tegmental field, a region adjacent to the DLT, appears to impair sexual behaviors after lesion, but the effect is incomplete and transient (Romero-Carbente et al., 2007). The projection from

the MPOA to the VTA has received some attention, but it is not essential for copulation (Hull and Dominguez, 2007; Iyilikci et al., 2017). The MPOA-VTA pathway is likely to be responsible for dopamine release in the NAc during sexual behaviors, which may reinforce the preference toward female cues in sexually experienced males (Fujiwara and Chiba, 2018; Iyilikci et al., 2017; Sun et al., 2018; Wang et al., 1995).

The MeA, BNST, and PA are three major regions upstream of the MPOA and VMHvl. The MeA contains an abundance of cells responsive to female pheromone cues (Li et al., 2017), but, surprisingly, recent cell-type-specific inactivation and ablation experiments found a relatively small functional role of the MeA in male sexual behaviors (Hong et al., 2014; Unger et al., 2015). In contrast, PA cells that project to the MPN are indispensable for male sexual behaviors. Inactivation of PA^{Esr1} to MPN-projecting cells abolished nearly all aspects of male sexual behaviors (Yamaguchi et al., 2020). Similarly, inactivation of BNSTp cells that express aromatase caused clear deficits in male sexual behaviors (Bayless et al., 2019).

The neural circuitry of female copulation. In contrast to males, the VMHvl plays a pivotal role in mediating female sexual behaviors (Lenschow and Lima, 2020; Micevych and Meisel, 2017; Figure 3C). The VMHvl is sexually dimorphic. The female VMHvl contains a lateral subdivision (VMHvll) that mediates sexual behaviors (Hashikawa et al., 2017a), which likely does not exist in males, based on the lack of many VMHvll-specific genes in the male VMHvl (Kim et al., 2019b). The female VMHvll, but not the VMHvlm, projects densely to the anteroventral periventricular nucleus (AVPV), a region enriched in kisspeptin (Kiss)-expressing cells (Hashikawa et al., 2017a), which, in turn, are important for regulating gonadotropin-releasing hormone (GnRH) secretion from MPOA cells (Gottsch et al., 2004). Although the $VMHvll\text{-}AVPV^{Kiss}\text{-}MPOA^{GnRH}$ circuit likely controls neuroendocrine responses associated with mating, VMHvll-PAG projection has been suggested to mediate lordosis (Lonstein et al., 1998; Sakuma and Pfaff, 1979; Yamada and Kawata, 2014). The PMv, the third component of the medial hypothalamic reproductive system, is positioned as an interface between the metabolic state, environmental cues, and the female reproductive circuit. Specifically, leptin, a hormone released from fat cells, can activate PMv leptin receptor-expressing cells to promote activity of GnRH-expressing cells in females (Donato and Elias, 2011). In birds, the PMv contains a population of light-sensitive cells that can detect the day length change and activate the hypothalamus-pituitary-gonad (HPG) axis in preparation for seasonal reproduction (Kang et al., 2007).

BNSTp and MeA aromatase cells are nonessential for female sexual receptivity; i.e., lordosis (Kim et al., 2019b; Unger et al., 2015). Although it remains possible that other cells in the BNSTp and MeA, especially those receiving information from the MOB, contribute to the behavior, it is worth noting that tactile cues (e.g., palpation of the flanks and perineal contact) appear to be key sensory triggers of the action phase of female behavior. In female rats, manual vaginal cervical stimulation (VSC) is sufficient to elicit lordosis and induces strong c-Fos expression in the PAG, VMHvl, and MPOA (Auger et al., 1996; Pfaus et al., 1996). Future studies are needed to delineate the pathway that delivers tactile information to the hypothalamus.

The neural circuitry of parental care. Although the readiness to show parental behaviors could differ between sexes, the motor outputs of the behaviors, except nursing, are largely the same in males and females. Correspondingly, the neural circuits underlying parental behaviors are qualitatively similar between sexes (Figure 3D; Dulac et al., 2014). Starting from a lesion study that was performed nearly half a century ago, numerous studies have demonstrated a central role of the MPOA in parental care (Numan, 2006). More recently, studies that focus on genetically identified subpopulations revealed that galanin-expressing cells in the MPOA ($MPOA^{Gal}$) mediate pup grooming, whereas Esr1-expressing cells in the MPOA ($MPOA^{Esr1}$), which partially overlap with galanin-expressing cells, are essential for pup retrieval in both sexes (Bloch et al., 1992; Fang et al., 2018; Kohl et al., 2018; Wu et al., 2014). *In vivo* electrophysiological recordings have revealed important features of MPOA cell responses (Fang et al., 2018). First, many MPOA cells are activated during pup investigation, suggesting that pup sensory cues are key inputs that drive MPOA cells. Second, MPOA cells that respond to adults and pups are largely non-overlapping, suggesting that the MPOA contains subpopulations with distinct social functions. Consistent with the recording data, single-cell RNA sequencing (RNA-seq) of MPOA cells revealed that cells activated during different social behaviors are genetically distinguishable (Moffitt et al., 2018).Third, some MPOA cells are activated exclusively during pup retrieval but not pup investigation, and the increase in cell activity precedes retrieval, which is consistent with the response patterns of premotor cells. Fourth, MPOA cells that are activated during pup retrieval, grooming, and nest building are largely distinct, giving credence to the hypothesis that there are multiple MPOA populations, each of which drives one aspect of parental behavior. Consistent with this, activating $MPOA^{Gal}$ projection to the PAG, VTA, and MeA elicits grooming, pup seeking, and suppression of infanticide, respectively, whereas activating $MPOA^{Esr1+}$ projection to the VTA elicits pup approach and retrieval (Fang et al., 2018; Kohl et al., 2018). In addition to direct behavioral control, the MPOA also modulates neuroendocrine responses related to parental behaviors through its projection to vasopressin-, oxytocin-, and corticotropin-releasing hormone (CRH)-expressing cells in the paraventricular nucleus (PVN) (Kohl et al., 2018; Scott et al., 2015) as well as neuroendocrine dopaminergic (NEDA) neurons in the arcuate nucleus (ARC) (Esteves et al., 2019). NEDA cells are essential for parental behaviors because it controls release of prolactin, which directly activates MPOA cells and promotes parental behaviors (Brown et al., 2017; Gudelsky, 1981; Stagkourakis et al., 2020a). Interestingly, a recent study found that differential NEDA cell activity caused species differences in paternal behaviors. In male rats, NEDA cells are synchronized, resulting in a high level of dopamine, a low level of prolactin, and poor paternal behaviors, whereas NEDA cells in male mice fire asynchronously, leading to low dopamine, high prolactin, and high $MPOA^{Gal}$ cell activity and paternal care (Stagkourakis et al., 2020a). In contrast to a pivotal role of the MPOA in parental care behaviors, the VMHvl appears to be completely dispensable. Inactivation of the VMHvl did not cause any deficit in maternal care, and *in vivo* recordings found no activity change of VMHvl cells during maternal care (Hashikawa et al., 2017a).

Although much progress has been made regarding the circuit downstream of the MPOA, the parental circuit upstream of the MPOA remains elusive. Although VNO input that relays through the MeA has been traditionally considered a negative regulator of parental behaviors based on many lesion and inactivation studies (Fleming et al., 1979, 1980; Numan et al., 1993; Sheehan et al., 2001; Tachikawa et al., 2013), a recent study showed that optogenetic activation of MeA GABAergic cells (the major population in the MeA) can elicit parental (i.e., grooming) and infanticidal behavior depending on the stimulation intensity (Chen et al., 2019). Similarly, disruption of specific subregions of the BNST can facilitate or suppress parental behaviors (Numan and Numan, 1996; Tsuneoka et al., 2015). Thus, it is likely that the MeA and BNST contain cell groups that play opposite roles in parental behaviors, and their precise molecular identities await identification in future studies.

An alternative strategy to identify the parental circuit upstream of the MPOA is to understand the sensory trigger of the behavior. In studies that systematically alter the females' senses or physical properties of pups (e.g., temperature, smell, skin texture, shape, etc.), it was found that none of the sensory modalities are indispensable (Beach and Jaynes, 1956). Anosmic, blind, deaf, or anaptic lactating females retrieved the pups indistinguishably from intact females (Beach and Jaynes, 1956). The abnormality of pup cues in any sensory modality (e.g., painting the pup with a foreign odor) reduces the efficiency of the pup to elicit parental behaviors but rarely abolishes the behaviors. This multisensory strategy may be in place to ensure that parental behaviors are released readily and robustly, or it may simply be due to a lack of pup-specific pheromones (Isogai et al., 2018). Nevertheless, the diverse sensory cues that can trigger the parental behaviors suggest that the circuitry underlying pup cue processing is likely to be complex. Future studies will be needed to further understand how this multi-modal sensory information reaches the MPOA and ultimately releases parental behaviors.

Summary of the neural circuits underlying the consummation phase. By examining various social behavioral circuits all at once, some general principles emerge. First, social behaviors that differ qualitatively in motor patterns between sexes (e.g., sexual behaviors) are mediated by sex-specific circuits, whereas social behaviors that only differ quantitatively in their motor patterns between sexes (e.g., aggressive behavior) are mediated largely by the same circuit in both sexes.

Second, in rodents, the sensory modality of proximate cues that trigger the consummation phase of social behaviors differs across the behaviors. Although aggression relies heavily on olfactory cues and pheromones, tactile cues likely play a bigger role in female copulation. Therefore, the MeA and BNST, two important relays in the accessory olfactory system, are essential for aggression but dispensable for female sexual behaviors.

Third, the medial hypothalamus is essential for all innate social behaviors examined so far, and each behavior is likely to be mediated by a distinct neural population in the region. Specifically, the VMHvl is essential for aggression and female sexual behaviors, whereas the MPOA is essential for parental behaviors and male sexual behavior.

Fourth, the VMHvl and MPOA recruit motor-action pathways, at least partly through the PAG, and neuroendocrine pathways. The neuroendocrine pathway is developed particularly for the female reproductive circuit, likely because of the significant physical changes required for pregnancy as a result of copulation.

Innate social behaviors are flexible

Social behaviors are innate and are expressed with a stereotypical set of movements; however, they are far from fixed. All animals navigate a dynamic world. Therefore, the ability to adjust their social behaviors accordingly, in the short and long term, is crucial for survival and reproductive success. In this section, we will provide an overview of the plasticity seen in social behaviors. Later, we will delve deeper into the mechanisms that make the plasticity of innate social behavior possible.

Plasticity in the readiness to express innate social behaviors

The readiness or tendency to express a social behavior is highly plastic and is the biggest source of variability in social behaviors across individuals. For example, in a classic resident-intruder assay, where a single-housed resident male mouse encounters a male intruder, some resident mice initiate attack within seconds, whereas others never do. However, when the VMHvl is activated artificially in non-aggressive mice, they attack the intruder in a way that is indistinguishable from a naturally occurring attack, suggesting a fully developed motor circuit for executing the behavior (Yang et al., 2017). Thus, the lack of attack in non-aggressive males is primarily a result of low readiness to engage in the behavior.

Why does readiness to express a social behavior vary so widely? In short, it is because innate social behaviors are costly. Although social stimuli and social behaviors are intrinsically rewarding, the individual must balance these payoffs with a potentially substantial trade-off: cost.

The basic costs of innate social behaviors are opportunity cost and metabolic cost. Metabolic cost refers to the energy spent on performing a certain task. The energy level and health of an individual determines whether it can afford the associated metabolic cost. Opportunity cost refers to the loss of potential gain from carrying out alternative behaviors. For instance, an individual carrying out a social behavior could have competing needs in life, such as feeding, and must adjust its behavior accordingly after a cost-benefit evaluation. Additionally, engaging in agonistic social behaviors (i.e., aggression) could be particularly costly; i.e., have a risk cost. It could inflict physical damage and, in extreme cases, lead to death. Thus, the risk to engage in aggressive behaviors needs to be calculated, and one should only take on such a risk when there is a reasonable chance of winning. Because the experience is a good predictor of the future outcome, the willingness to engage in a fight adjusts based on the previous fighting experience (Rutte et al., 2006). In addition to costs incurred in the immediate context, social behaviors often have a long-term cost. For example, sexual behavior could result in pregnancy and birth, which requires abundant food and energy to be sustained. Thus, in this case, the frequency of sexual behavior needs to be adjusted to suit the organisms' environment.

Many factors influence the weights of trade-off and pay-off and, subsequently, the individual's readiness to exhibit innate social behaviors. These factors include

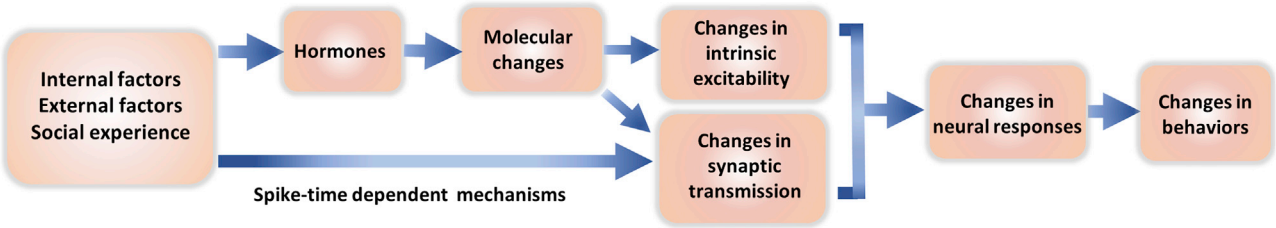

Figure 4. An overview of the neural mechanisms underlying the plasticity of innate social behaviors
Internal factors (e.g., reproductive state), external factors (e.g., population density), and social experience (e.g., winning) can lead to changes in hormonal levels or Hebbian spike timing-dependent plasticity. Hormones induce changes in the molecular composition of cells and lead to changes in cell morphology, excitability, and synaptic strength. Hebbian mechanisms can lead to potentiation or depression of specific synapses. Together, these physiological changes alter the cell's responses to conspecific sensory inputs and the readiness to express social behaviors.

(1) internal factors that are defined as scalable and persistent factors internal to an individual, such as sex, age, metabolic level, circadian state, and reproductive state;
(2) external factors that are associated with the environment, such as food availability, territory, and population density; and
(3) experiential factors, such as sexual experiences and winning or losing experiences.

These factors collectively determine an individual's readiness to express social behaviors by modulating the probability of sensory-motor transition at two time points (Figure 1). The first point is when the animal initiates a reaction to a distal social stimulus; i.e., transition from the detection to the approach phase. Internal factors, external factors, and the individual's experience collectively determine whether and how quickly an individual approaches, avoids, or ignores the social cue upon its detection. The second point is when the animal initiates a reaction to a proximal conspecific; i.e., transition from the investigation to the consummation phase. Similar to a perceptual decision-making process, the sensory information is gathered and accumulated during investigation. When a specific internal threshold is reached, the relevant consummation (e.g., attack) is initiated. The external, internal, and experiential factors can influence the set point of the threshold that triggers the action.

Plasticity in the motor performance of consummatory actions

Although the consummation phase of social behaviors is highly stereotyped, there is room for improvement to make the actions more efficient. The consummation aspects of social behaviors follow the same "practice makes perfect" rule that applies to complex learned motor actions (Papale and Hooks, 2018; Figure 1).

The winner effect, found in rodents, humans, and fish among others, states that the probability of winning a fight increases after repeated winning experiences (Beaugrand et al., 1991; Hsu and Wolf, 2001; Oyegbile and Marler, 2005; Zilioli and Watson, 2014). This increase in winning probability is likely not only due to an increase in willingness to fight but also in the actual fighting ability, meaning fighting with high efficiency (minimum movement to strike), high accuracy (accurate targeting of the vulnerable body parts of the opponent), and high precision (consistency of the behavior) (Briffa and Lane, 2017). As a result, experienced winners can defeat opponents that are bigger in size even though size is a strong predictor of the outcome (Oyegbile and Marler, 2005). To date, detailed and quantitative measures of attacking movements remain lacking. Future studies combining high-speed video recordings, wireless electromyogram (EMG) recordings, and machine learning-based fine movement characterization will allow quantitative assessment of motor actions during attack and its potential refinement with experience (Wiltschko et al., 2015).

Repeated sexual experience also quickens and refines actions performed during mating. Sexually experienced male mice and rats show a shorter latency to mount and intromit and a higher chance to achieve ejaculation (Sulain et al., 2011; Swaney et al., 2012). On the other hand, sexually inexperienced male hamsters often orient themselves incorrectly, resulting in ectopic mounts of the female's head (Miller et al., 1977). Sexual experience in females also contributes to a higher success of mating. When naive male hamsters mount sexually experienced female hamsters, they have a higher chance to turn mounts to intromissions (hit rate, 70%) in comparison with mounting naive female hamsters (hit rate, 50%) (Bradley et al., 2005).

Neural mechanism mediating the plasticity of social behaviors

The plasticity in social behaviors must be supported by changes in the underlying circuits. The circuit changes could occur at the level of individual cells or communication between cells (i.e., synapses) and, ultimately, the input-output relationship of the circuit (Figure 4). As mentioned earlier, changes in innate social behaviors mainly occur at two sensory-motor transformation points: the first is when the animal responds to a distant social cue and approaches it, and the second is when the animal responds to proximate cues and initiates specific consummatory actions. Here we discuss the neural mechanisms underlying the social behavioral changes at these two time points with specific examples. Sex hormones, neuromodulators, and spike-timing dependent plasticity all contribute to the changes. Although the efficiency and precision of actions endemic to social behaviors can change with experience (another form of plasticity), its underlying mechanisms remain unexplored and are not discussed in this review.

Changes in females' readiness to approach males with the estrus cycle

Female sexual motivation is synchronized with the ovulation period in most species. In rodents, females show low interest

toward male cues during diestrus, when the progesterone level is high and the estrogen level is low. In contrast, females' interest toward males increases during proestrus and estrus, when the estrogen level surges and the progesterone level is low. Sex hormones play a pivotal role in changing female sexual interest by acting on multiple nodes in the circuit (Erskine, 1989; Mhaouty-Kodja et al., 2018; Figure 5A).

In an elegant study, Dey et al. (2015) found that VNO cells lost their responses to male mouse pheromones—major urinary proteins (MUPs) during diestrus because of the high progesterone level. Progesterone suppresses VNO cell responsiveness by acting on the non-canonical progesterone receptor, which then recruits phospholipase C β2 (PLCβ2), which is expressed abundantly in MUP-responsive but not MUP-nonresponsive VNO cells (Dey et al., 2015). Thus, the rise of progesterone in diestrus causes females to become selectively "anosmic" to male pheromones.

Sex hormones, especially estradiol, also act centrally (e.g., in the NAc) to increase females' readiness to approach males (Figure 5A). First, estradiol can directly modulate the activity of NAc MSNs through estrogen receptors (Almey et al., 2015). Application of estradiol can rapidly change the intrinsic excitability and miniature excitatory postsynaptic current (mEPSC) of NAc MSNs and is essential for estrus cycle-dependent fluctuation of the intrinsic properties of MSNs (Krentzel et al., 2019; Proaño et al., 2018). Second, estradiol can also modulate MSNs through its influence on dopamine transmission. For example, during estrus, when the estradiol level is high, VTA dopamine cells show a higher firing rate, and stimulation of VTA dopaminergic terminals elicits a higher dopamine release in the NAc in comparison with diestrus females (Calipari et al., 2017). The enhanced VTA-NAc dopamine level, in turn, promotes activation of D1R MSN cells and favors social approach (Gunaydin et al., 2014; Tritsch and Sabatini, 2012; Yoest et al., 2014). Third, estradiol can act on hypothalamic neurons to enhance dopamine release specifically in response to social cues. Estradiol has been found to increase excitability of neurotensin-expressing MPOA cells ($MPOA^{Nts}$) in ovariectomized (OVX) female mice (McHenry et al., 2017). Because $MPOA^{Nts}$ cells are preferentially responsive to male cues, project to the VTA, and directly induce dopamine release in the NAc, an increase in excitability of these cells during proestrus is expected to increase dopamine release in the NAc to male odors (McHenry et al., 2017).

Sex hormone fluctuation during the estrus cycle changes the female's sensitivity and interest to male cues by modulating cell responsiveness at multiple regions along the detection, approach, and investigation circuits.

Changes in partner preference with sexual experience

The experience of positive consummatory social behaviors could lead to changes in preference to the cues associated with the experience; i.e., the readiness to approach the cue. In rats and mice, naive males show no preference for cues of males, estrous females, and diestrous females, whereas sexually experienced males strongly prefer estrous female cues (Fujiwara and Chiba, 2018; Hayashi and Kimura, 1974; Hosokawa and Chiba, 2005; Landauer et al., 1977). In the case of monogamous prairie voles, mating induces a strong and enduring preference toward the mated partner, a phenomenon known as pair bonding (Young et al., 2011). Several lines of evidence suggest that, just like other forms of reward-associated learning, VTA dopaminergic neurons and the NAc play important roles in mating-induced partner preference. *In vivo* microdialysis, fast-cyclic voltammetry, and optical recordings using genetically encoded dopamine sensors revealed an increase in dopamine in the NAc during sexual behaviors (Pleim et al., 1990; Sun et al., 2018). The dopamine release is locked to individual mating episodes and reaches its maximum during ejaculation (Sun et al., 2018). Blocking dopamine action in the NAc by injecting a D2 receptor antagonist prior to the mating period blocks partner preference induced by mating in prairie voles (Aragona et al., 2006; Aragona and Wang, 2009; Gingrich et al., 2000), whereas activation of D2 receptors within the rostral NAc shell facilitates partner preference, supporting an important role of dopamine in mating-induced partner preference (Aragona et al., 2006).

Dopamine is not the only neuromodulator essential for social reward learning. Oxytocin, a neuropeptide hormone involved widely in social behaviors, is released abundantly during mating in rodents and humans (Borrow and Cameron, 2012). Blockade of oxytocin receptor (OXTR) in the NAc prevents partner preference induced by mating, whereas administration of oxytocin in the NAc is sufficient to induce partner preference in female prairie voles (Liu and Wang, 2003). The facilitating effect of oxytocin and dopamine on partner preference is interdependent because a D2 antagonist in the NAc abolished partner preference induced by oxytocin and vice versa, although the precise mechanisms remain unclear (Liu and Wang, 2003; Young et al., 2001). In addition to dopamine, oxytocin also interacts with serotonin to induce plasticity in the NAc. Dölen et al. (2013) found that oxytocin release at the NAc core during social interaction is indispensable for social interaction-induced conditioned preference. Oxytocin acts on the presynaptic terminals of serotonin axon terminals from the dorsal raphe, causing an increase in serotonin release, which, in turn, induces long-term depression (LTD) of glutamatergic synaptic inputs onto MSNs. Knocking down OXTR or antagonizing 5HT1B in the NAc abolished the preference to the social interaction conditioned chamber (Dölen et al., 2013).

Thus, mating-induced partner preference, either to a specific animal or ones alike, could be considered an associative learning process supported by synaptic plasticity and resulting from combined actions of various neuromodulators, including dopamine, oxytocin, and perhaps many more.

Social defeat-induced social avoidance

Although social stimuli are intrinsically attractive, negative social experiences can completely override this attraction (Figure 5B). When a male mouse is defeated by another male conspecific for as short as 10 min, the defeated animal shows avoidance toward the aggressor for at least 3 days (Qi et al., 2018). The avoidance behavior is not simply a lack of social approach, although it is often quantified in such a way; instead, it is an active behavior that involves freezing, defensive crouching, stretched approaches (risk assessment), and running away from the defeater (Toth and Neumann, 2013). The one-time defeat-induced avoidance is target specific. The defeated animals only avoid the defeater but not unknown conspecifics (Toth and Neumann, 2013).

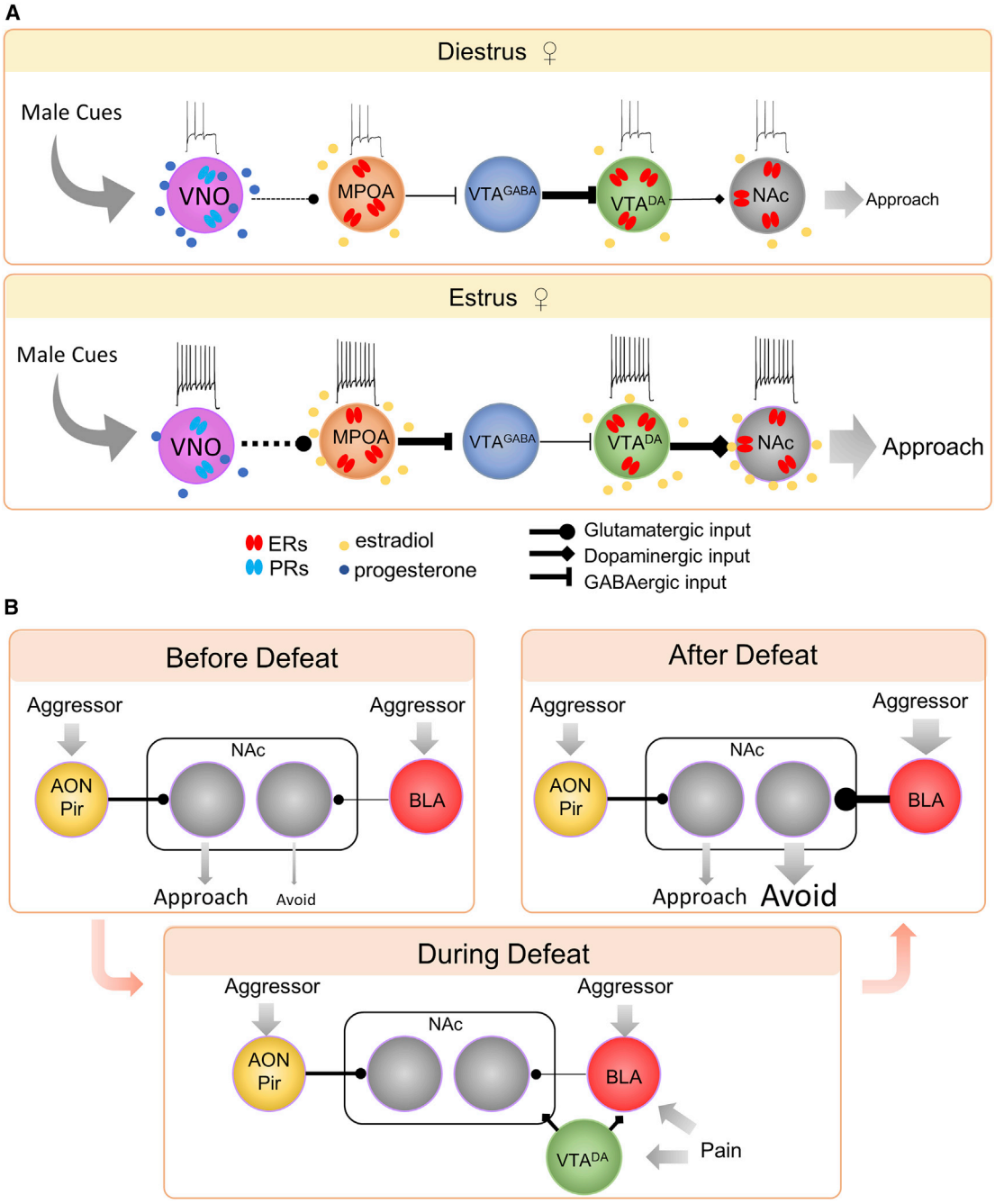

Figure 5. Neural mechanisms underlying the reproductive state and experience-induced changes in social approach

(A) Schematics showing how females' readiness to approach males changes with the estrus cycle. The progesterone level during diestrus is high, causing a decrease in VNO cell responses to males cues. In contrast, during estrus, the estradiol level is high, causing an increase in intrinsic excitability of MPN^{Nts} cells, which leads to decreased inhibitory tone within the VTA and increased dopamine (DA) transmission to the NAc. Estradiol also acts on VTA DA neurons and NAc MSN cells to increase dopamine release from the VTA and the overall responses of NAc MSNs.

(B) A proposed circuit underlying defeat-induced social avoidance. Before defeat, male cues, including cues of the aggressor, dominantly activate the AON/Pir-NAc circuit and drive approach. During acute defeat, pairing of the sensory cues of the aggressor and pain cause potentiation of the aggressor input to the BLA. Pairing of DA release in the NAc and BLA inputs causes potentiation of BLA synaptic inputs to NAc cells. Collectively, the aggressor cues activate the BLA-NAc circuit after defeat to drive social avoidance, whereas other male cues continue to primarily activate the AON/Pir-NAc circuit to drive approach.

The size of the arrows and line width indicate the strength of the inputs and outputs, and font size indicates readiness of approach. Dashed lines indicate multi-synaptic connections.

The specificity of the avoidance behavior suggests that the behavioral change is likely a result of the associative learning process, during which the cues of a specific conspecific become tightly associated with the painful experience of defeat (Diaz and Lin, 2020). The BLA, a region that is well studied for its role in fear conditioning, has been found to be essential for acute defeat-induced social avoidance. Inactivation, blocking protein synthesis, or blocking NMDA receptors into the BLA before defeat reduced social avoidance 24 h later (Day et al., 2011; Jasnow and Huhman, 2001; Markham and Huhman, 2008; Markham et al., 2010). Conversely, increasing cyclic AMP (cAMP)-responsive element binding protein (CREB), a transcription factor essential for memory formation, in the BLA enhanced social avoidance (Jasnow et al., 2005). Inhibiting the BLA immediately before the post-defeat social avoidance test also reduced the avoidance behavior, supporting a role of the BLA in social avoidance acquisition and expression (Jasnow and Huhman, 2001).

Although the NAc is essential for driving social approach, paradoxically, it is also a region essential for social avoidance. Pharmacological inhibition of the NAc 24 h after defeat reverses social avoidance (Luckett et al., 2012). Injecting a dopamine receptor antagonist, flupenthixol, into the NAc before defeat also blocks social avoidance in defeated hamsters 24 h later, suggesting that defeat-induced avoidance is dependent on DA signaling in the NAc (Gray et al., 2015; Luckett et al., 2012). Microdialysis revealed an increase in dopamine level in the NAc during defeat (Holly et al., 2015). The NAc is a major area downstream of the BLA. A recent study reported that direct optogenetic activation of the BLA-NAc pathway increases social avoidance in undefeated mice (Folkes et al., 2020). These data support a model where repeated association between aggressor cues and the painful experience during defeat causes an increased response of BLA cells to the aggressor, whereas repeated pairing of BLA glutamatergic inputs and dopamine release in the NAc potentiates the BLA-NAc pathway and leads to social avoidance of the defeater (Figure 5B).

How NAc cells drive social approach and social avoidance remains incompletely understood, but it is likely that the NAc contains subpopulations of cells with distinct functions. The responses and functions of NAc cells vary with their anatomical location in the NAc as well as with MSN type (D1R versus D2R) (Al-Hasani et al., 2015; de Jong et al., 2019; Hikida et al., 2010; Kravitz et al., 2012; Peciña and Berridge, 2005; Yang et al., 2018). Generally, NAc D1R cells are approach-promoting and essential for reward learning, whereas NAc D2R cells are aversion promoting and essential for aversive learning (Hikida et al., 2010, 2013; Kravitz et al., 2012; Zalocusky et al., 2016). Thus, it is possible that the relative activity of approach-driving and avoidance-driving cells in the NAc determines the final behavior output. It is worth noting that the BLA-NAc pathway is likely not the only pathway to drive defeat-induced social avoidance; other pathways involving the BNST and hypothalamus may also play a role (Diaz and Lin, 2020; Duque-Wilckens et al., 2020; Steinman et al., 2019).

Unlike acute defeat, chronic social defeat (10 continuous days) leads to generalized social avoidance as well as a suite of depression-like behaviors, including decreased preference for attractants (e.g., sucrose), in a subset of animals (called susceptible animals) (Kudryavtseva et al., 1991; Rygula et al., 2005; Toth and Neumann, 2013; Wells et al., 2017). These profound behavioral changes appear to be critically dependent on an increase in brain-derived neurotrophic factor (BDNF), but not DA, in the NAc that originates from VTA terminals (Berton et al., 2006; Wook Koo et al., 2016). Specifically, after chronic defeat, VTA dopamine cells that project to the NAc show enhancement of tonic firing while the corticotropin-releasing factor (CRF) level in the NAc is increased, resulting in activity-dependent and CRF-gated upregulation of BDNF secretion in the NAc (Krishnan et al., 2007; Walsh et al., 2014). BDNF appears to preferentially act on TrkB receptors of MSN D1 cells, causing phosphorylation of extracellular signal-regulated kinase (ERK), which is linked to a reduction in MSN D1 cell activity (Koo et al., 2019; Lobo et al., 2010; Wook Koo et al., 2016). Furthermore, chronic defeat reduces excitatory synaptic inputs to MSN D1 cells, leading to reduced activity of MSN D1 cells (Francis et al., 2015). These results suggest a model where chronic defeat dampens NAc MSN D1 cell responses by increasing the BDNF level in the NAc and decreasing the excitatory synaptic drive of the cells. The blunted MSN D1 responses cause suppression of approaching behaviors toward various hedonic stimuli. Consistent with this model, artificial activation of MSN D1 cells, but not D2 cells, reverses social avoidance and restores sucrose preference in susceptible mice (Francis et al., 2015).

Changes in the animals' readiness to execute consummatory social behaviors with reproductive state

The reproductive state profoundly influences readiness to express social behaviors. Perhaps the most extreme example comes from behavioral changes during parenthood. In mothers, sexual behavior and infanticide are virtually abolished, whereas maternal behavior and aggression toward intruders increase dramatically. These behavioral changes are a result of orchestrated hormonal changes during pregnancy, starting with surges of ovarian hormones, such as estrogen and progesterone, before parturition and followed by an increase in pituitary hormones, such as prolactin and oxytocin, after parturition to elicit fast onset of behavioral changes (Bridges et al., 1985; Rosenblatt et al., 1988). All key brain regions in the social behavior circuit (see above) are enriched in receptors that sense estrogen, progesterone, oxytocin, prolactin, and many others. Thus, the hormone waves during pregnancy induce a suite of "pre-programmed" changes in these areas to support the behavioral changes. Indeed, emerging evidence supports plasticity in core social regions at the molecular, morphological, and physiological levels during parenthood. Here we discuss these changes, highlighting results in the MPOA, an essential region for parental behaviors. At the morphological level, Keyser-Marcus et al. (2001) showed that rat MPOA cells increase in neuronal soma size by 50% as parturition approaches. During the postpartum period, the neuronal soma returns to the pre-pregnancy level, but the basal dendritic length and branching number remain increased. At the molecular level, systematic comparison of gene expression patterns at the MPOA has identified differences in the expression of hundreds of genes (Akbari et al., 2013; Gammie et al., 2005). More specifically, receptors for estrogen, progesterone, prolactin, oxytocin, and neurotensin are upregulated toward the end of pregnancy and during the early

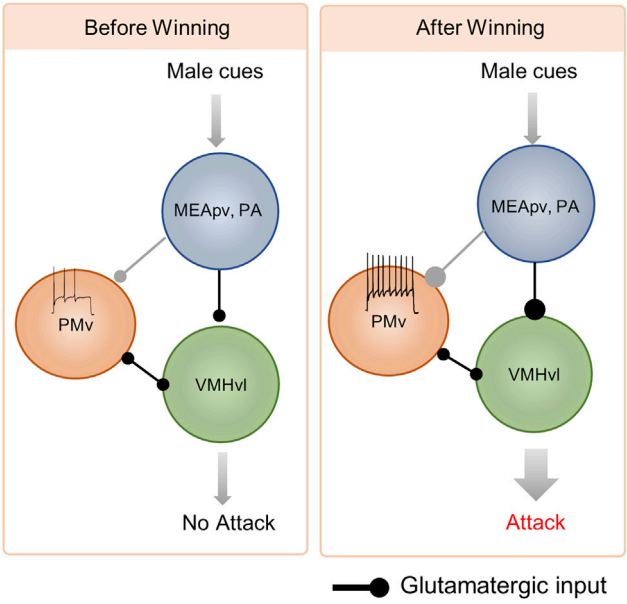

Figure 6. Neural mechanisms underlying winning cause and increase in readiness to attack

After winning, the synaptic connection between the MEApv/PA and VMHvl increases, and PMv excitability also increases, causing an overall enhanced response of VMHvl cells to male cues and, thus, an increase in readiness to attack. The MEApv/PA-to-PMv pathway may also be potentiated after winning. The size of the lines and heads indicates the strength of the inputs and outputs.

postpartum period (Driessen et al., 2014; Francis et al., 2002; Grattan et al., 2001; Meddle et al., 2007; Numan et al., 1999; Wagner and Morrell, 1996; Young et al., 1997). A recent comprehensive study using single-cell RNA-seq revealed that molecularly distinct clusters of cells in the preoptic area are activated in mothers and fathers, in comparison with virgin females, during pup interaction (Moffitt et al., 2018). At the physiological level, our recent *in vivo* optical recordings revealed increased Ca^{2+} responses (ΔF/F) of $MPOA^{Esr1+}$ cells during pup approach and retrieval in lactating females in comparison with prepartum female mice (Fang et al., 2018). Interestingly, *in vivo* electrophysiological recording showed that the spiking activity during pup-directed behaviors did not increase in mothers; instead, the basal firing rate of MPOA cells decreased by 50%, resulting in an effective increase in the signal-to-noise ratio (Fang et al., 2018). How do the electrophysiological changes link to the hormonal and molecular changes during parenthood? A direct answer to this question at the level of the MPOA remains unavailable, but some clues have been provided by studies of other brain regions. *In vitro* slice recordings in the hippocampal and auditory cortex showed that oxytocin increased the signal-to-noise ratio of pyramidal neurons by elevating the basal firing of GABAergic interneurons (Marlin et al., 2015; Owen et al., 2013). Because of the enhanced inhibitory tone, pyramidal neurons in the auditory cortex show a decrease in spontaneous firing but an increase in evoked response to pup ultrasonic vocalization, possibly because of use-dependent fatigue of interneurons (Marlin et al., 2015). Future studies will elucidate whether a similar mechanism is responsible for an enhanced response to pup cues in the MPOA and other brain regions during parenthood. Nevertheless, given the large array of molecular changes, multiple signaling pathways likely work in concert to change MPOA cell responses and cause the suite of behavioral changes during parenthood.

As a second example, the readiness to engage in female sexual behaviors varies with the estrus cycle. Female rats in estrus solicit males by ear wiggling and hopping and readily show lordosis upon being mounted, whereas female rats in diestrus actively avoid male rats and rebuff their mounting attempts by kicking them and rolling on their backs (Hardy, 1972). These behavioral changes are causally linked to the cyclic change of estrogen and progesterone; applying estrogen and progesterone in a pattern similar to the hormone changes during proestrus and estrus is sufficient to enhance female sexual receptivity in OVX female rats (Powers, 1970). The VMHvl, the essential region for female sexual behavior, shows striking plasticity in morphology and electrophysiological responses with estrus cycle or sex hormone injections. Specifically, during proestrus, when the estrogen level is high, VMHvl cells in female rats increase in somatic size, dendritic length, and spine density (Madeira et al., 2001; Sá and Madeira, 2005). Application of estrogen to OVX females induces a similar set of morphology changes in the VMHvl (Calizo and Flanagan-Cato, 2000). The increases in spine density during estrus suggests an increase in inputs from upstream regions. Electrophysiological recordings found a higher firing rate increase in VMHvl cells during male investigation in estrous females than in diestrus females (Hashikawa et al., 2017a; Nomoto and Lima, 2015). A recent study further revealed changes in axon morphology of VMHvl cells with estrus cycle. Inoue et al. (2019) found that the terminal density of progesterone-expressing VMHvl ($VMHvl^{PR}$) cells in the AVPV increases by approximately 3-fold during estrus in comparison with diestrus in female mice. This morphological change is functional, as supported by a 3-fold increase in the EPSC magnitude of AVPV cells upon optogenetic activation of $VMHvl^{PR}$ axon terminals *in vitro* (Inoue et al., 2019). The rise of sex hormones during proestrus enhances the synaptic inputs and outputs of VMHvl cells, which leads to an increase in the probability to express female sexual behaviors in response to male cues.

Increase in the readiness to attack with winning experience

Social experience can change an animal's readiness to engage in social behaviors in the short and long term. In the short term, for example, a single attack or even brief exposure to a same-sex conspecific causes a transient increase in the readiness to attack, manifesting as a decreased latency to attack, a phenomenon known as "aggression priming" (Miczek et al., 2013; Potegal, 1992; Potegal et al., 1996). In the long term, repeated winning permanently increases an animal's readiness to engage in a fight; i.e., the winner effect (Hsu et al., 2006). Although the neuroendocrine events that are relevant for the winner effect (e.g., a post-winning testosterone surge) have been studied widely (Hsu et al., 2006), the neural mechanisms underlying the winner effect are only beginning to be elucidated (Figure 6).

Nordman et al. (2020) recently reported that the pathway from the MeA to the VMHvl and BNST can undergo long-term potentiation (LTP) and is essential for aggression priming. They found that, after a short period of attack, MeA stimulation evoked field excitatory postsynaptic potentials (fEPSPs) at the VMHvl and BNST increases. This increase is blocked by an NMDA receptor antagonist or a low-frequency stimulation protocol known to induce LTD. Importantly, when LTP is blocked, so is aggression priming. Conversely, when the MeA is stimulated at high frequency (100 Hz), the MeA-VMHvl pathway is potentiated, and the aggression level increases.

The synaptic potentiation between the amygdala and VMHvl could also be an essential mechanism for the winner effect. In a recent study, Stagkourakis et al. (2020b) reported a significant increase in spontaneous EPSCs (sEPSCs) and the spine density of VMHvl cells in experienced winners in comparison with naive animals. The authors then focused on the projection from the PA—a major source of excitatory input to the VMHvl. Strikingly, the AMPA/NMDA ratio (EPSCs mediated by AMPA receptors versus NMDA receptors) of VMHvl cells in response to optogenetic stimulation of the PA is over 3 times higher in experienced winners than in naive or non-aggressive animals, indicating insertion of AMPA receptors into the postsynaptic membrane after winning. Additionally, winning animals showed facilitated synaptic integration, whereas naive animals showed depressed synaptic integration. These results suggest that communication from the PA to the VMHvl becomes much more efficient after repeated winning. PA aggression-responsive cells also project extensively to the PMv, another aggression-promoting medial hypothalamic region, and it remains to be investigated whether the synapse between PA and PMv is also potentiated after winning (Yamaguchi et al., 2020; Figure 6).

The winner effect likely also involves changes in the intrinsic properties of cells in the aggression circuit. PMv dopamine transporter (DAT)-expressing cells in winners are more excitable than those in non-aggressive animals, as reflected by a higher percentage of spontaneously active cells and a higher resting membrane potential (Stagkourakis et al., 2018). As PMv DAT cells form strong connections with each other and cells in VMHvl, an increase in excitability of PMv cells can lead to an overall higher activity in the circuit in response to an excitatory input. In this study, however, the authors did not examine PMv cell property in naive animals; thus, it remains unclear whether the winning experience increases PMv cell excitability or whether the excitability difference exists prior to winning, and animals with higher PMv cell excitability are predisposed to become aggressive.

The testosterone surge after winning has been shown to be essential for the post-winning behavioral change (Oyegbile and Marler, 2005; Trainor et al., 2004). Is the testosterone increase also causally linked to changes in the neural circuit? This remains incompletely understood, but the answer is likely to be yes, at least partially. Stagkourakis et al. (2020b) found that the testosterone level in non-aggressive males was low, and VMHvl cells in those animals failed to show LTP. When non-aggressive males were supplemented with testosterone, LTP was induced reliably, suggesting a permissive role of testosterone in synaptic potentiation at the VMHvl. Additionally, testosterone is expected to change the aggression circuit through non-Hebbian spike timing-dependent mechanisms, given that testosterone supplementation alone is sufficient to increase aggression without winning experience. Perhaps such a mechanism involves a series of genomic events triggered by sex hormones that causes changes in the molecular composition and physiological properties of cells. This non-Hebbian plasticity might explain the "cross-talk" of social experience. For example, sexual experience, which also induces a testosterone surge, can lead to an increase in aggression (Gleason et al., 2009). Future studies will be needed to understand the full effect of testosterone on the neural circuit of aggression.

The experience-dependent change of social behavior likely involves changes in synaptic transmission and intrinsic biophysical properties of cells in the relevant circuit. These changes could be mediated by Hebbian mechanisms as well as pre-programmed hormonal actions. Although here we focused on reproductive state- and social experience-induced changes, other internal and external factors, such as hunger state, stress, phases of the circadian clock, and population density, could modulate social behaviors, presumably through their influence on the relevant social circuit. Although the ventral striatum, amygdala, and hypothalamus are likely key sites for plasticity, similar social experience-induced physiological changes have been reported in the thalamus-prefrontal cortex pathway (Nelson et al., 2019; Zhou et al., 2017) as well as the accessory olfactory bulb microcircuit (Gao et al., 2017) and are likely wide-spread phenomena in the central nervous system.

Concluding remarks and future directions

All animals possess a repertoire of social behaviors that can be initiated without being taught. These behaviors are central for survival and continuation of any species. They are triggered by a set of species-specific cues and are expressed by all members of a species in a stereotypical way. It is important to recognize that different social behaviors rely on cues of a certain sensory modality to different extents. For example, although olfactory cues and pheromones are indispensable for aggression, they are dispensable for parental behaviors in rodents. Future studies should carefully determine the contributions of each cue to a given social behavior. Such an understanding will be instructive in identifying the brain regions relevant for the behavior.

Social behaviors can be roughly separated into four phases: detection, approach, investigation, and action. The first three phases could be collectively considered as a process to determine the identity of a target. Decades of research have identified key neural substrates for each stage of social behavior, with the NAc and medial hypothalamus emerging as essential areas to drive approach and specific consummatory actions, respectively. Despite our fast-growing knowledge, many nodes in each of the behavior circuit remain missing. For example, what are the upstream regions of the VMHvl essential for female sexual behaviors? What are the pathways that carry auditory or somatosensory information to the hypothalamus? Is the PAG the only key premotor region downstream of the hypothalamus essential for motor execution of social behaviors? Additionally, different social behaviors often involve the same brain region. For example, female sexual behaviors, aggression, and social

defense are critically dependent on VMHvl activity. How do cells in the same region drive different and often incompatible behaviors? Does this involve the same set of cells or distinct cells with different molecular identities and connectivities? As our knowledge of the circuit grows, it becomes clear that the same behavior, e.g., aggression, can be triggered from multiple regions. How does the information transform among those regions? Many regions in the circuit are connected reciprocally, indicating that the information is likely distributed instead of flowing unidirectionally.

Although social behaviors are innate, they are flexible; the same social cues could evoke vastly different or even opposite social responses from the same individual at different time points in life. This behavioral flexibility is accomplished by changes in two sensory-motor transition points: one from detecting a distant cue to approaching a conspecific and the other from sampling proximal cues to undertaking consummatory actions. Our understanding of how the social behavior circuit changes as a function of various factors is just starting to emerge, and many studies will follow in the near future. It is becoming increasingly clear that social behavior circuits are plastic and that changes are likely to occur in various nodes along the circuit. They undergo not only spike timing-dependent plasticity but are also subject to preprogrammed hormonal actions. The combination of learning-dependent and -independent modulatory mechanisms makes seemingly stereotypical social behaviors incredibly flexible and adaptive, ensuring the continuation of life.

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AUTHOR CONTRIBUTIONS

D.W. and V.T. co-wrote the first draft of the paper and made the figures. D.L. conceptualized the content of the review, wrote following drafts, and finalized the figures.

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