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Review

Neural Circuit Mechanisms of Social Behavior

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We live in a world that is largely socially constructed, and we are constantly involved in and fundamentally influenced by a broad array of complex social interactions. Social behaviors among conspecifics, either conflictive or cooperative, are exhibited by all sexually reproducing animal species and are essential for the health, survival, and reproduction of animals. Conversely, impairment in social function is a prominent feature of several neuropsychiatric disorders, such as autism spectrum disorders and schizophrenia. Despite the importance of social behaviors, many fundamental questions remain unanswered. How is social sensory information processed and integrated in the nervous system? How are different social behavioral decisions selected and modulated in brain circuits? Here we discuss conceptual issues and recent advances in our understanding of brain regions and neural circuit mechanisms underlying the regulation of social behaviors.

Introduction

In a broad sense, social behaviors can be defined as any modality of communication and/or interaction between two conspecifics of a given species and are observed in species as simple as single-celled microorganisms to species as complex as humans (Crespi, 2001; Ebstein et al., 2010). Why is social behavior important? Like other types of behaviors, social behaviors, no matter cooperative or competitive, have been selected for and have persisted throughout evolutionary history due to their contributions toward increasing survival and reproductive fitness. Social behaviors displayed at the inappropriate time or place or of inappropriate intensity can have detrimental effects on both the individuals and a social group as a whole. Mating, or sexual reproduction, is a clear example of an absolutely required social behavior for reproductive fitness, as it is the substrate for genetic heritability across generations. Parenting, including uniparental or biparental investment of energy and resources into prenatal care like nesting and brooding and postnatal care like nursing and defense, works toward ensuring that offspring are able to survive until reproductive maturity. Aggression is an example of a competitive social behavior where the winner of an aggressive encounter is provided greater access to resources, including territories or mating opportunities, resulting in a greater chance of survival and reproductive success. Social group living, termed sociality, also increases reproductive fitness due to group association offering greater capabilities for threat defense, resource acquisition, and opportunities for mating (Silk, 2007). Finally, eusocial species such as ants and naked mole-rats have a high degree of social organization, displaying communal cooperative rearing of offspring across generations with clear divisions of non-reproductive and reproductive castes (Wilson and Hölldobler, 2005).

Social interactions involve active detection and response to cues from multiple sensory modalities and are instantaneously shaped by dynamic, mutual feedback between participants (Figure 1A). Given the complexity of social interactions, does the brain process social information and make social behavioral decisions in a special manner? One possibility is that there are unique "social" brain regions or social behavioral circuits that are dedicated to the sensorimotor transformation of socially encoded information. Ultimately, however, the brain is a highly interconnected structure and thus social circuits, if they exist, clearly interface with other nonsocial circuits (such as those involved in feeding and homeostasis). Are there dedicated "social" brain structures or social behavioral circuits? Are there distinct principles that govern social information processing? How does social processing interface with processing of nonsocial behavior?

Addressing the above questions requires a thorough understanding of the brain regions and neural circuits involved in the spectrum of social behaviors. In this Review, we discuss conceptual issues underlying the regulation of social behavior. Social behaviors and the underlying brain circuit mechanisms have been an area of active research for a long time (Newman, 1999; Numan and Sheehan, 1997; Swanson, 2000). We will primarily summarize recent literature that has elucidated the role of defined brain regions and neural circuits in regulating social behaviors, with a focus on rodent model systems. For social behavior in other organisms including humans, see reviews by Anderson (2016), Chang et al. (2013), Sokolowski (2010), Stanley and Adolphs (2013), and Yamamoto and Koganezawa (2013).

Unique Qualities of Social Behavior

What are the unique qualities of social behavior that set it apart from other, nonsocial behaviors? Social interactions among conspecifics often involve (1) a high-level complexity of possible behavioral communication avenues, (2) sensory cues that are specific or unique to social behaviors, (3) dynamic information from a conspecific that is also making its own decisions simultaneously, and (4) modulation by changes of internal states resulting from past social experiences.

Communication through multiple sensory modalities is a common feature of social interactions, and the possible kinds of communication through each of these modalities (termed

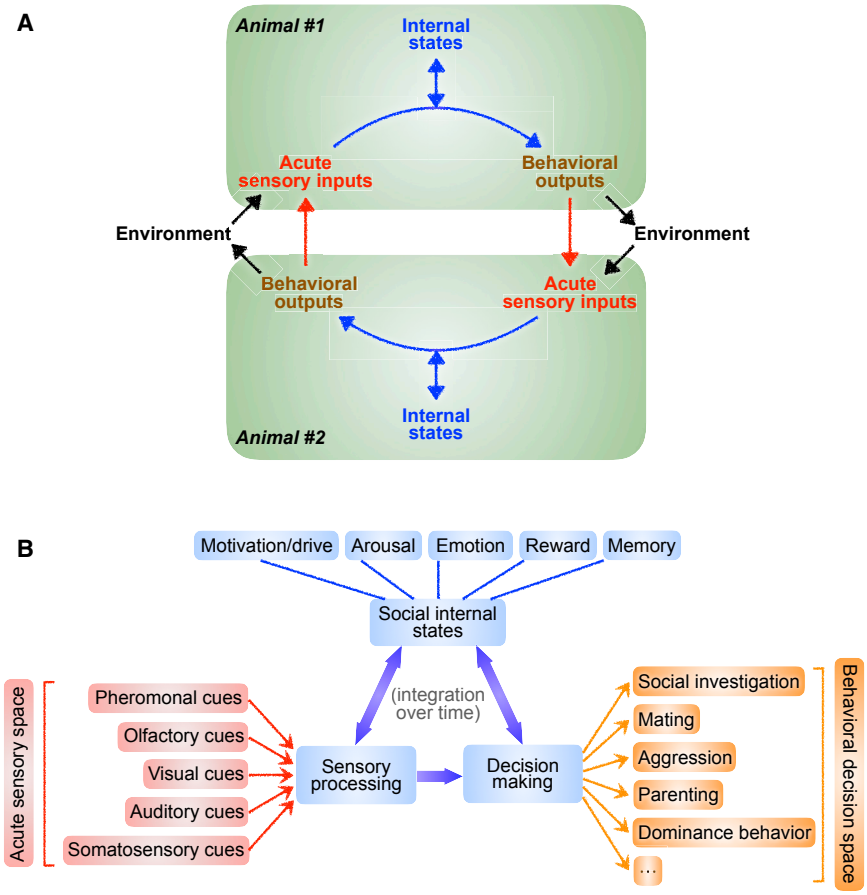

Figure 1. Transformation of Sensory Inputs to Social Behavioral Decisions in Social Contexts

(A) Schematic depicting social interaction between two individuals. Information from acute sensory inputs detected from the other individual (and the environment) is transformed into a behavioral output. The behavioral output in turn will provide sensory cues to the other individual, forming a reciprocal feedback loop for the duration of social interaction between the two individuals.

(B) Examples of sensory inputs, internal states, and behavioral outputs that are involved in the sensory processing to behavioral decision transformation.

communication space) are vast. Using mating in rodents as an example, early stages require both visual recognition of a conspecific and chemosensory investigation of the anogenital region. Sensory communication expands to involve ultrasonic vocalization (USV), followed by somatosensory inputs at copulation. Each sex has a large repertoire of cues that leads to a diverse array of downstream behavioral responses. Since the complexity of behavioral interactions scales with the complexity of potential communication space between two individuals, social behaviors are among the most complex behaviors.

Moreover, these complex communication avenues often involve integration of sensory cues that are specific or unique to social behaviors. Specific pheromones are produced only by conspecifics of specific sexes; post-pubertal males produce the pheromone ESP1, which enhances female sexual receptivity (Haga et al., 2010). Specific frequencies of USVs are produced in social (i.e., mating) but not nonsocial contexts (Kimchi et al., 2007; Portfors, 2007). All of these specific forms of communication are indispensable for the corresponding social behaviors, which contributes to the overall complexity of social behavioral decisions.

Social behavioral decisions also depend on dynamic information from a conspecific that is also making its own decisions simultaneously (Figure 1A). In other words, social interactions could be viewed as interactions between two decision-making brains. A male animal may seek to copulate with a female but his success depends on the receptivity of the female, who may or may not actively cooperate with the male's efforts. Acute sensory inputs from one conspecific are recognized by another individual and are transformed into a behavioral decision; the decision of this second individual may in turn generate new sensory cues for the original individual, who will consequently exhibit a behavioral decision based on these cues. This reciprocal interaction between two decision-making individuals, which occurs at a fast temporal scale (as short as milliseconds), essentially forms a continual feedback loop. The behavioral decision of an individual is also influenced by a high level of uncertainty due to the inability to reliably predict the behavioral response from the other individual (Dayan, 2012). This uncertainty in turn broadly expands the possible social behavioral decisions, or decision space, relative to a nonsocial behavioral decision. This feedback loop underscores the dynamic, reciprocal, and complex nature of social interactions.

Lastly, to complicate matters, the same individual exposed to the same sensory cues at different time points often does not make the same behavioral decisions. For example, if a male is exposed to a male intruder, it may initially engage in sniffing or close investigation and subsequently decide to attack the intruder, or, alternatively, simply ignore it. Differences in behavioral progression and action selection can be shown by the same animal, despite the fact that the exact same sensory cues are present. Thus, factors that are internal to the individual, which we loosely and broadly refer to as internal states (discussed further later), may directly modulate the sensorimotor transformation into behavioral decisions (Figures 1A and 1B) (Anderson, 2016). A critical component of internal states is dynamic integration of past sensorimotor experience across time that modulates any steps of the transformation from sensory inputs to behavioral decisions (Figure 1). This integration may occur over both short and long time frames and reciprocally influences

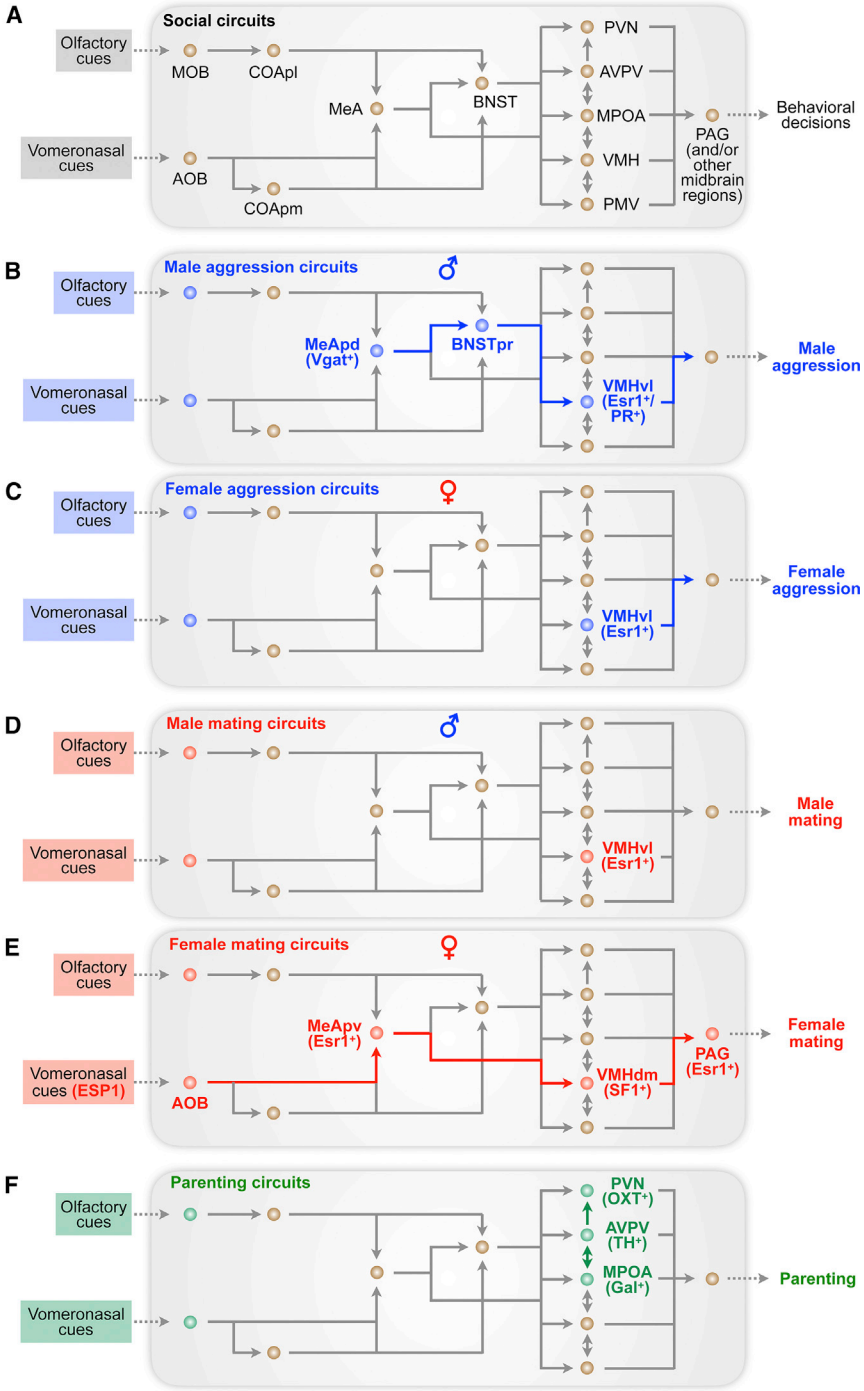

Figure 2. Current Understanding of Circuits and Brain Regions in Males and Females Implicated in Different Social Behaviors

(A) Overview of key social behavioral circuits and regions.

(B and C) Circuits involved in male (B) and female (C) aggression.

(D and E) Circuits involved in male (D) and female (E) mating.

(F) Circuits involved in parenting in males and females.

MOB, main olfactory bulb; AOB, accessory olfactory bulb; COApl/pm, posterolateral and posteromedial cortical amygdala; MeApd/pv, posterodorsal and posteroventral medial amygdala; BNSTpr, principal nucleus of the bed nucleus of the stria terminalis; PVN, paraventricular hypothalamic nucleus; AVPV, anteroventral periventricular hypothalamic nucleus; MPOA, medial preoptic area; VMHvl/dm, ventrolateral and dorsomedial subregions of the ventromedial hypothalamic nucleus; PMV, ventral premammillary hypothalamic nucleus; PAG, periaqueductal gray. In (B)–(F), some of the nodes and connections are hypothetical. Colored nodes and connections represent circuits with direct experimental evidence for the corresponding behavior.

and is influenced by sensory processing and behavioral decisions (Figure 1B).

To discuss the circuits underlying social behavioral decisions, in the next three sections, we discuss three loosely defined, general stages of social decision making: (1) recognition and integration of sensory cues from a conspecific, (2) further processing of sensory information to generate a behavioral decision, and (3) influence of experience-dependent internal state changes on the selection of behavioral choices. Note that these three loosely defined stages do not occur sequentially and are instead highly intertwined—they may overlap with one another, may occur at the same time or in different sequences, and may be processed in different or the same brain structures or circuits (Figure 2).

Perception of Social Cues

As mentioned previously, the diversity and social specificity of sensory cues (such as specific pheromones, frequencies of USVs, and grooming patterns) make social behaviors uniquely complex. The exact combinations of cues shape the behavioral output. A classic example is that a male mouse exposed to female cues may initiate behavioral programs related to mating, while exposure to male cues may lead to displays of aggression (Figure 3A).

In rodents, one of the most critical upstream sensory pathways mediating the choice of nearly all social behaviors is olfaction. The main olfactory system detects odorants through the main olfactory epithelium (MOE) and is critical in both males and females for establishing appropriate social behavioral patterns, since MOE ablation results in decreased sexual behaviors in both sexes (Keller et al., 2006a, 2006b). Male CNGA2 knockout (KO) mice, where a critical main olfactory signaling transduction protein is removed, show a loss of sex-specific behavior including loss of preference for female cues, equal numbers of USVs toward male and female cues,

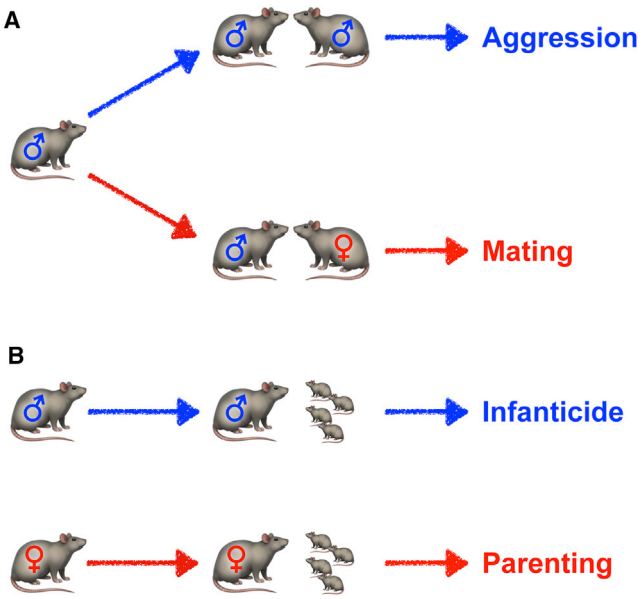

Figure 3. Examples of Different or Similar Sensory Inputs Leading to Different Behaviors

(A) The same individual experiencing different sensory inputs can lead to different behavioral outputs.

(B) Different individuals experiencing the same sensory inputs can lead to different behavioral outputs.

and decreased aggression toward male intruders (Mandiyan et al., 2005; Matsuo et al., 2015). In contrast, female KO mice show decreased parenting-related behaviors such as pup retrieval, which results in decreased pup survival (Matsuo et al., 2015).

Pheromones are chemical signals released by an individual that modulate the behavior or physiology of a conspecific (Karlson and Luscher, 1959; Liberles, 2014) and are detected by both the main olfactory system through the MOE and the vomeronasal system (or the accessory olfactory system) through the vomeronasal organ (VNO). The VNO is anatomically separate from the MOE; the sensory neurons in the VNO versus MOE express almost completely different sets of olfactory receptors and respond to different classes of ligands (Stowers and Kuo, 2015). Ablation or surgical removal of the VNO leads to deficits in conspecific aggression and copulatory behavior in both sexes (Clancy et al., 1984; Keller et al., 2006c). In agreement with these results, removal of a protein critical for pheromonal sensory transduction, TRPC2, renders the animals unable to discriminate between male and female mice. TRPC2 KO males show no sign of aggression toward other males, and an equal degree of sexual behavior toward both males and females; TRPC2 KO females show a reduction of female-specific behaviors like maternal aggression and lactating behavior, and an appearance of male sexual behaviors (Kimchi et al., 2007; Leypold et al., 2002; Stowers et al., 2002). Lastly, pheromonal sensing through the VNO in virgin males is required for their normal infanticidal behavior and the suppression of parental behaviors (Tachikawa et al., 2013; Wu et al., 2014). Thus, like the main olfactory system, the vomeronasal system is necessary for sex-specific behavioral outputs and other social decisions.

Auditory cues have also been shown to be involved in a number of different social behaviors including mating and parenting. Female mice have an innate preference for male USVs, and USVs emitted by males lead to enhanced sexual receptivity in females (Asaba et al., 2014; Pomerantz et al., 1983). Qualities of male courtship songs in mice are correlated with mate choice (Asaba et al., 2014); adult females are known to vocalize in the presence of novel conspecifics and vocally interact with males during courtship and parenting (Hammerschmidt et al., 2012; Liu et al., 2013; Neunuebel et al., 2015). The exact role(s) of adult-produced vocalizations on social behaviors remain to be further studied. Pups emit USVs in response to maternal separation and other environmental stressors like changes in temperature, and these are lessened when interacting with the mother (Hofer, 1996). Indeed, pup calls activate neurons in the auditory cortex of mothers but not virgin females, and inactivation of the left primary auditory cortex leads to reductions in pup retrieval in mothers (Marlin et al., 2015).

Less is known about the function of visual or somatosensory circuits in rodent social behaviors. There are conflicting reports about the necessity and role of visual stimuli on social behaviors like mating and fighting (Strasser and Dixon, 1986). Nevertheless, when ventromedial hypothalamus (VMH) is optogenetically activated (discussed later), aggression can be triggered toward an inflated glove but does not occur when there is no attackable object (Lin et al., 2011). Moreover, stronger aggression is seen toward a moving glove than toward a non-moving one, suggesting that detection of visual objects and their movements is critical for aggressive behavior. Somatosensory stimulation is critical for both parenting and mating, as somatosensory feedback from the penis is critical for penile thrusting during copulation and tactile stimulation of pups is important for normal behavioral development (Champagne and Curley, 2005; Contreras and Agmo, 1993).

As mentioned previously, social behaviors require integration of multiple sensory cues. An example of a brain region that receives direct convergent sensory inputs is the medial amygdala (MeA); both main olfactory and vomeronasal pathways synapse onto individual cells in the posteroventral MeA (MeApv), with these cells responding differently to the two inputs (Figure 2A) (Keshavarzi et al., 2015). As both main olfactory and vomeronasal systems detect chemosensory cues, how is chemosensory information integrated with other sensory modalities in the brain? The visual presence of an attackable object needs to be integrated with olfactory and pheromonal signaling for aggressive behavior to occur. USVs emitted from males, together with olfactory and pheromonal cues, promote female receptivity and progression of male-female mating behavior (Shepard and Liu, 2011). These examples suggest that integration of both chemosensory and non-chemosensory social cues is critical for the control of specific social behaviors. The underlying neural mechanisms for this and other examples of multisensory integration in social behaviors are unclear. One possibility is that a small number of defined brain circuits like the MeA serve as hubs to receive direct convergent sensory inputs from multiple modalities. Alternatively, sensory integration could occur in broadly distributed regions or circuits. Further research should distinguish between these possibilities.

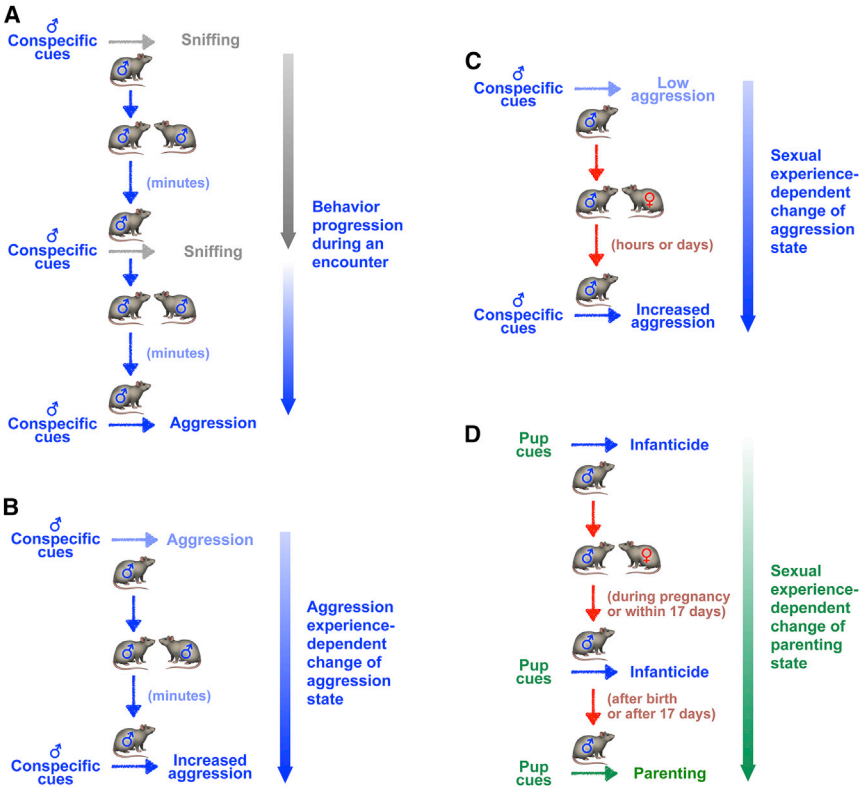

Figure 4. Examples of Experience-Dependent Changes of Social Behavioral Decisions on Different Timescales

(A) A experience-dependent change in social internal state during a same-sex interaction leads to a change in behavior from investigation to aggression on the scale of minutes.

(B) A heightened aggression state (i.e., higher probability for aggression) following an aggressive interaction on the scale of minutes.

(C) A heightened aggression state following sexual experience on the scale of hours to days.

(D) A change of an infanticidal to parenting state following sexual experience on the scale of weeks.

Transformation of Sensory Cues into Behavioral Decisions

In this section, we discuss how sensory cues are transformed into social behavioral decisions and focus on three relatively well-characterized behaviors—aggression, mating, and parenting. Recent studies have identified specific nuclei in the amygdala and hypothalamus that receive inputs from sensory regions and send outputs to midbrain and motor systems (Figure 2A). Below, we discuss the key circuit components that mediate specific behavioral decisions.

Circuits for Aggression Behavior

Aggression is an "overt behavior that has the intention of inflicting physical damage on another individual" (Nelson and Trainor, 2007). Engaging in aggressive behaviors is risky for the organism, as it must weigh the potential benefits of winning (usually access to mates, protection, and resources) against the potential costs of fighting (injury, death, and in some cases loss of social status). In rodents, aggressive behavior usually progresses from an appetitive phase that involves close investigation, to a consummatory phase that involves intense attack behaviors like biting and tussling (Figure 4A). Aggression commonly occurs between two unfamiliar male mice, or a lactating female mouse caring for pups toward an intruder.

A series of classic electric stimulation studies identified a "hypothalamic attack area" or "HAA" as a critical region that could elicit attack behavior in rats, cats, and other animals (Hess and Brugger, 1943; Kruk, 2014). This region includes part of the VMH and its adjacent brain areas. More recent studies using genetically defined functional manipulations were able to pinpoint the VMH and the MeA as critical sites for eliciting aggression (Figure 2B).

The MeA receives inputs from both main olfactory and vomeronasal systems (Figure 2B). GABAergic (*Vgat*$^+$) neurons, but not glutamatergic (*Vglut2*$^+$) neurons, in the posterodorsal portion of the MeA (MeApd) are highly activated by aggressive inter-male social interactions (Hong et al., 2014). Optogenetic activation of MeApd GABAergic neurons results in aggression, while silencing of this population results in termination of ongoing attack (Hong et al., 2014). A subpopulation of MeApd GABAergic neurons, which expresses aromatase, is required for aggression, although chemogenetic activation of this population is unable to promote aggression (Unger et al., 2015). MeApd regulates aggression through one of its downstream projection targets, the posterior portion of the bed nucleus of the stria terminalis (BNST); stimulation of MeApd-BNST projections results in increased aggression (Padilla et al., 2016).

The VMH receives both direct and indirect inputs from the MeA as well as inputs from BNSTpr and other brain structures involved in aggressive behavior (Figure 2B). Neurons in the ventrolateral area of the VMH (VMHvl) are activated during both investigation and attack of a male intruder, and they are more strongly activated by social stimuli compared to nonsocial ones (Lin et al., 2011). Activation of *Esr1*$^+$/*PR*$^+$ neurons in male VMHvl leads to attack behavior toward males, castrated males, females, and even toward a mirror, while silencing of these neurons results in decreased aggressive behaviors (Lee et al., 2014; Lin et al., 2011; Yang et al., 2013, 2017). The involvement of *Esr1*$^+$/*PR*$^+$ neurons in aggression is likely specific, as stimulation of non-*Esr1* neurons within the VMHvl is not sufficient to drive aggression (Lee et al., 2014).

Recent work has indicated that the VMHvl mediates aggression in females as well (Figure 2C). Female aggression depends on a number of factors including strain background, reproductive state, and conspecific type (juvenile versus adult) (Crawley et al., 1997; Hurst and Barnard, 1995). Like in males, *Esr1*$^+$ neurons in females are activated during aggression (Hashikawa et al., 2017a). Although a previous study suggested that this population was not essential for female aggression (Lee et al., 2014),

the use of a more naturalistic female aggression induction paradigm demonstrated that activation of this population is sufficient to drive aggression, and silencing results in a significant decrease in aggression (Hashikawa et al., 2017a).

In addition to regions that directly promote aggression, several other brain regions have been shown to modulate aggressive behavior. For example, the probability of inter-male aggression is decreased by stimulation of excitatory neurons of the medial prefrontal cortex (mPFC) and silencing of these neurons results in increased intensity of aggressive behaviors (Takahashi et al., 2014). Activation of inputs from the lateral septum onto the VMHvl during episodes of attack leads to attenuation of attack and decreased likelihood of attack re-initiation (Wong et al., 2016). Many brain regions that have been implicated in aggression through lesion studies or measures of activity, like the BNST, lateral septum, medial preoptic area of the hypothalamus (MPOA), periaqueductal gray (PAG), and anterior hypothalamic area (AHA), are connected with the MeApd and VMHvl either indirectly or directly (Hashikawa et al., 2016; Nelson and Trainor, 2007), sometimes with reciprocal connections. The PAG is thought to be a critical node for connecting the VMHvl to motor output in the spinal cord (Hashikawa et al., 2017b); lesions of subregions of the PAG result in increased female aggression (Lonstein and Stern, 1997). The exact nature and role of these brain regions and connections in regulating aggression remains to be clarified.

How Do MeApd and VMHvl Control Aggression?

Under normal conditions, males do not attack females, but optogenetic activation of MeApd or VMHvl neurons causes males to attack not only males but also females and even an inanimate object (Hong et al., 2014; Lin et al., 2011). This suggests that the optogenetic activation of MeApd or VMHvl bypasses most, if not all, requirements of the olfactory and/or phenomenal inputs for the initiation of the behavior. Indeed, removal of TRPC2 or CNG2 does not affect the ability of chemogenetic activation of VMHvl neurons to trigger attack (Yang et al., 2017). Thus, the MeApd or VMHvl neurons either directly encode the representation of the olfactory and phenomenal inputs that are needed for normal aggression or encode social information that is sufficient to replace sensory representation.

Do neurons in MeApd or VMHvl purely encode a representation of aggression-specific sensory signals, do they purely encode specific aggression-related motor commands, and/or do they directly contribute to the selection of behaviors, such as encoding an aggressive state? Both electrophysiological recordings and calcium imaging experiments showed that neurons in the VMHvl are activated not only by sex-specific sensory cues but also during specific aggressive actions (Lin et al., 2011; Remedios et al., 2017). Moreover, VMHvl activity predicts several parameters of future aggressive action, including the latency to and duration of the next attack (Falkner et al., 2014). These findings indicate that the VMHvl encodes both sensory- and motor-specific representations. In addition, VMHvl neurons are able to promote self-reinforcing aggressive behavior (or aggression-seeking behavior), in which the animal learns to nosepoke to retrieve a submissive animal to attack, suggesting that the VMHvl promotes a drive to attack a conspecific (Falkner et al., 2016). Lastly, electrophysiological recording identified a population of VMHvl neurons that are activated during the nosepoke and waiting phase of the task, whereas the MOB is not active during nosepoking (Falkner et al., 2016). Together, these observations argue against the possibility that the VMHvl purely encodes motor commands of aggressive behavior itself, but instead suggest that the VHMvl is involved in some form of transformation of sensory cues into behavioral decisions and may encode a general aggressive state. Since the MeApd functions upstream of the VMHvl, whether and how MeApd neurons encode different information than VMHvl neurons remains to be investigated.

Circuits for Mating Behavior

For sexually reproducing species, mating is a fundamental social behavior that requires coordinated activity between two conspecifics of the opposite sex. Male and female behavioral patterns differ in both precopulatory and copulatory stages. In male mice, mating involves approach and investigation of the female's face and anogenital region, emission of USVs, mounting, intromission, and ejaculation (Hull and Dominguez, 2007). On the other hand, female mice display solicitation behavior such as pacing, and undergo postural changes like lordosis behavior (Angoa-Pérez and Kuhn, 2015). In a mating behavioral sequence, both precopulatory and copulatory behaviors are temporally intermixed with constant switching between the two, so the phase distinction is context and time dependent (Angoa-Pérez and Kuhn, 2015).

Olfactory and pheromonal signals are critical for normal mating behavior of both sexes (Figures 2D and 2E). Activation of the VNO and its downstream projections in adult males through pheromones produced by sexually immature juvenile females results in inhibition of mounting toward these sexually immature conspecifics (Ferrero et al., 2013), providing evidence for one mechanism for assessing sexual receptivity.

Many downstream targets of the main and accessory olfactory systems have been implicated in mating (Hashikawa et al., 2016). Although the VMHvl has been traditionally implicated in female mating behavior (Pfaff and Sakuma, 1979), recent work has shown that VMHvl neurons are activated in both males and females during their encounters with animals of the opposite sex (Figure 2D) (Hashikawa et al., 2017a; Lin et al., 2011). In addition to attack, activation of *Esr1*$^{+}$ neurons is sufficient to drive mounting behavior in males (and occasionally in females) (Lee et al., 2014). Although it is unclear whether VHMvl neurons promote other elements of mating behavior, mounting is one key behavioral element of mating. Moreover, genetic ablation of VMHvl *PR*$^{+}$ neurons, or RNAi-mediated knockdown of *Esr1* in the VMHvl, causes a partial reduction in male mating behavior (Yang et al., 2013).

Surprisingly, the MeApv was recently found to be involved in lordosis behavior, a female behavior indicating sexual receptivity (Figure 2E). While previous studies have implicated this subregion of the MeA predominantly in predator defensive behaviors (Choi et al., 2005), this study identified a MeApv to VMHdm to dorsal PAG pathway that is critical for pheromone-mediated lordosis behavior (Ishii et al., 2017). Silencing of *Vglut2*$^{+}$ neurons in the MeApv and *Sf1*$^{+}$ or ESP1-responding neurons in the VMHdm leads to decreases in ESP1-induced lordosis, while activation of ESP1-responding neurons in the VMHdm is

sufficient to increase lordosis. Silencing of the *Sf1*$^+$ VMHdm to *Esr1*$^+$ dPAG pathway also results in decreased lordosis.

Other brain regions implicated in mating include the MPOA and BNST. Lesioning or silencing the MPOA in males results in deficits in sexual behaviors (Hull and Dominguez, 2007), while ablation of Galanin-positive (*Gal*$^+$) MPOA neurons results in decreased mounting duration and increased latency to mount (Wu et al., 2014). Similarly, cells within the BNST in males are activated during mating, while lesions in the BNST result in decreased preference for opposite-sex odors (Veening and Coolen, 2014). Projection-specific and cell-type-specific manipulations of these regions in the context of mating remain to be examined.

Mating versus Aggression

A brain-wide neuronal activation mapping study showed that male- versus female-specific cues activate both distinct and shared brain regions or subregions (Kim et al., 2015), raising the question of whether mating and aggression are regulated by the same or different circuits. Interestingly, low-intensity stimulation of VMHvl *Esr1*$^+$ or MeApd *Vgat*$^+$ neurons leads to mounting, whereas high-intensity stimulation leads to attack, suggesting the possibility that mounting and attack could be controlled either by different subpopulations of neurons with different activation thresholds, or by the amount of neurons that are being recruited. Within the MeApd and VMHvl, the representation of male- versus female-specific cues appears to be partially distinct, both at the level of individual neurons and at the level of populations (Bergan et al., 2014; Hashikawa et al., 2017a; Li et al., 2017; Lin et al., 2011; Remedios et al., 2017). This separation of the male- and female-specific representations can be promoted by social interactions. Moreover, single-unit recording in the male and female VHMvl showed that certain neurons are selectively tuned for either aggression or mating (Hashikawa et al., 2017a; Lin et al., 2011). Interestingly, the VMHvl in females could be divided into two anatomically distinct subregions that are differentially activated in mating and aggression and display different gene expression and axonal projection patterns (Hashikawa et al., 2017a). These lines of evidence suggest that the circuits for mating and attack are at least partially distinct.

Circuits for Parenting and Infanticidal Behavior

Parenting behavior is seen between adult and juvenile conspecifics to ensure the survival of young offspring and occurs in both a pup-directed (i.e., pup grooming) and non-pup-directed (i.e., defense against intruders) manner. Investment in parental care is often higher by females compared to males owing to differences in optimal reproductive strategies for each sex (Figure 3B), although this is highly species and context dependent (Clutton-Brock and Parker, 1992). Conversely, infanticidal behavior is intended to kill offspring and is usually committed by adult virgin males and virgin females (though not exclusively) (Dulac et al., 2014). Multiple explanations have been proposed for the reproductive benefits of infanticidal behavior, including elimination of unhealthy litters that have a decreased chance of survival, ensuring the paternity of the offspring, and elimination of offspring of potential competitors (Hrdy, 1979).

The MPOA is a large hypothalamic structure that has been heavily implicated in parenting (Figure 2F). Lesions within the MPOA result in altered parental behavior (Lee et al., 1999). *Gal*$^+$ neurons in the MPOA have been shown to be critical for parental behaviors in both males and females (Wu et al., 2014). Activity mapping following parental behavior in both father and virgin females showed increased activity in *Gal*$^+$ cells, and ablation of *Gal*$^+$ cells in virgin females, nursing females, and fathers results in decreased parental behavior. Optogenetic activation of *Gal*$^+$ neurons in virgin males both suppresses pup-directed aggression and increases grooming time, while activation in fathers also leads to increases in grooming time (Wu et al., 2014). Projection mapping of MPOA *Gal*$^+$ neurons revealed extensive projections to the cortical amygdala (CoA), with deceased activity in CoA in parenting females compared to infanticidal males (Renier et al., 2016), revealing a potential target of the MPOA involved in parenting.

One brain structure upstream to the MPOA is the anteroventral periventricular nucleus of the hypothalamus (AVPV), which is highly sexually dimorphic for tyrosine hydroxylase (*Th*)-expressing neurons (Figure 2F) (Scott et al., 2015). Numbers of AVPV *Th*$^+$ neurons in females are greater than males and are greatly increased in postpartum females relative to virgin females. Ablation of *Th*$^+$ neurons in virgin and postpartum females reduces maternal behavior, while activation of *Th*$^+$ neurons increases maternal behavior. Activation of AVPV *Th*$^+$ cells also leads to an increase in oxytocin release from the paraventricular hypothalamic nucleus (PVH), pointing to regulation of neuropeptides as one potential mechanism for how this circuit influences maternal behaviors (Dulac et al., 2014).

As discussed earlier, USVs emitted by pups are important for normal parenting behavior, and oxytocin activity in the auditory cortex was shown to promote pup retrieval in females (Marlin et al., 2015). Lastly, like the other social behaviors discussed here, the PAG has also been implicated in parenting behavior, since it is a projection target of parenting centers such as the MPOA and silencing or lesioning subregions of the PAG results in decreased parenting behaviors (Numan, 2012; Salzberg et al., 2002).

Experience-Dependent Changes of Internal States in Social Behavioral Decisions

A given set of sensory cues may result in a different behavioral response in the same individual at different time points, due to experience-dependent changes of an individual's internal state (Figure 4). Broadly speaking, internal states are factors internal to an individual that act in addition to (and separately from) the acute sensory inputs to influence the behavioral decision (Figure 1A). Internal states may be conceptualized in different ways (Anderson, 2016). One hypothesis is that an internal state is represented by or equivalent to a circuit state (or neural representation) that (1) acts in addition to acute sensory inputs, (2) is shaped by past sensory experiences and their integration over time, (3) may persist for an extended period of time, and (4) may collectively affect a set of multiple different behavioral actions that are associated with a shared goal. Changes of internal states could be thought of as learning- or experience-dependent plastic changes of circuit state or neural representation that give rise to different behavioral decisions even when the acute sensory inputs are the same. In a broad sense, many different properties can be considered internal states, including classic

examples like motivation, arousal, emotion, physiological states like hunger and sickness, and extending to concepts like memory and reward (Anderson, 2016). These properties are not mutually exclusive but instead should be thought of as different components all contributing to a social behavioral output.

Internal states are involved in and influence most, if not all, behavioral decisions. Some examples of time- or experience-dependent changes of nonsocial behavioral selection include temporary predator odor exposure resulting in greater propensities for freezing or satiety changing feeding behavior in response to food cue exposure. Integration of social sensory cues (as a social internal state) is particularly important for social behavioral decisions, because of the dynamic and complex nature of the sensory and behavioral decision space. Using aggression as an example, an individual allowed to attack an initial intruder will subsequently have a heightened aggressive state (Figure 4B), which leads to a higher probability and decreased latency of attacking a second intruder and collectively influences multiple behavioral actions including chasing, tussling, and biting the other animals (Potegal et al., 1996). Another example is parenting, where the activity of an animal following sexual activity and pregnancy will change from an infanticidal state to a parenting state consisting of retrieval, grooming, crouching over pups, and nest building (Figure 4D) (Dulac et al., 2014). Both examples indicate that the initial social experience does indeed change the subsequent action selection in a similar sensory context. We further discuss below how changes of internal state that result from past social experiences can lead to changes of social behavioral decisions.

Experience-Dependent Changes in Action Selection

On short timescales, experience-dependent changes in internal state underlie the transition from appetitive phases to consummatory phases (Figure 4A). The initial appetitive phase involves the accumulation of sensory cues. At a certain threshold, when the cues have produced enough of an effect on the internal state to affect action selection, the subsequent sensory cue exposures result in a change from investigation to "attack."

This change in internal state is presumably dependent on some form of plasticity. One example at a sensory level is activity in the AOB in response to pheromonal signaling. Activity of AOB cells increases over time following initial investigation of a conspecific and is maintained for a short period of time after the conspecific has been removed (Hashikawa et al., 2016; Luo et al., 2003), suggesting that activity in the AOB changes with duration of investigation, and is not strictly correlated with the presence of sensory cues. Whether AOB activity is a direct representation of internal state, or is modulated by the changes of internal state that is encoded elsewhere, is unclear.

Evidence in the VMHvl suggests that activity in the region may serve as one representation of an aggressive internal state. Increased activity in the VMHvl is initiated following introduction of an intruder and sustained for minutes even after removal of the intruder (Falkner et al., 2014). Specifically, increases in the average spike rate during sniffing are able to predict both duration of attack and latency to attack, suggesting that activity in the VMHvl represents distinct behavioral decisions. Furthermore, during a paradigm that tests whether aggression-seeking tendencies are separate from the behavioral attack sequence itself, activation or silencing of the VMHvl is capable of respectively increasing or decreasing the aggression-seeking component independently of aggression, suggesting that at least a component of the aggressive internal state may be encoded within the VMHvl (Falkner et al., 2016).

Experience-Dependent Changes of Longer-Term Behavioral Decisions

Changes of internal states resulting from past social experiences can influence behavioral decisions in both the short term, like in the transition from investigatory to aggressive behaviors in a single interaction, and in the longer term, like in an overall heightened aggressive state for hours, days, or longer. For example, repeated exposure to submissive conspecifics in an aggression-seeking training paradigm will increase an individual's aggression-seeking tendencies over the course of days (Figure 4B) (Falkner et al., 2016).

A change in the neural representation of conspecific sex occurs following social interactions, which is correlated with changes in behaviors. Over the course of days of repeated exposure to both males and females, the fraction of female-tuned and male-tuned cells in the VMHvl increases; the degree of separation between male and female neural ensembles is correlated with the time spent on sex-specific behaviors like mating (Figure 4C) (Remedios et al., 2017). Strikingly, this change in ensemble representations also increases following a short, 30-min mating episode and is correlated with a subsequent increase in male-directed aggression. A similar change in neural representation occurs in the MeA as well, with the separation of neural representations for different sexes increasing following sexual experience that is maintained even after 5 days following isolation (Li et al., 2017). Therefore, learning and experience-dependent plasticity are involved in repeated sexual experience and serve as a mechanism underlying the changes of neural representation following social experience.

Another consequence of mating is that males transition from an infanticidal state to a parental state (Figure 4D) (vom Saal, 1985). The same pup cues before and during a parenting state will elicit completely different behavioral responses from males, and this can last for weeks (Kohl et al., 2017). As mentioned previously, activation of the MPOA leads to a switch from infanticide to parenting in virgin males (Wu et al., 2014). Surgical ablation or genetic silencing of the VNO in virgin males is also sufficient to suppress infanticidal behavior and increase parental behaviors (Tachikawa et al., 2013; Wu et al., 2014). However, unlike in females, where sex hormones following mating and during pregnancy have been implicated in the switch to maternal behaviors, the effect of sex hormones on male parenting behavior remains largely unclear (Kohl et al., 2017). Moreover, the long-term changes in specific neural circuits or neural representation that may account for this change in social internal state also remain largely unclear.

Social Rank as a Social Internal State

On longer timescales, certain forms of social internal states can end up being relatively stable and result in long-lasting changes in behavioral decisions. In many socially interacting species, some form of intrasexual social structure or hierarchy—that is, a stable representation of social rank (which is a stable expression of social internal state)—can be observed (Rowell, 1974).

Higher social rank, or dominance, in males is associated with greater access to resources and reproductive success (although in primates this association is complicated; Ellis, 1995), with individuals of different ranks experiencing different kinds of physical and psychosocial stressors (Sapolsky, 2005). Formation of social ranks arises from repeated social interactions between individuals and is influenced by environmental pressures such as crowding (Beery and Kaufer, 2015; Rowell, 1974), highlighting the time integration component of internal states. A potential qualitative difference between social rank and other internal states previously discussed is that social ranks tend to be longer-lasting (i.e., for weeks or months) and relatively stable for a given group size over a longer period of time than internal states influencing aggression, mating, and parenting (Dewsbury, 1982).

Recent work utilizing rodent model systems, which also show stable rank status, have strongly implicated the mPFC as a key region for social rank. Whole-cell recordings of excitatory neurons in the dorsal mPFC revealed that synaptic strength is positively correlated with rank status, and activity mapping showed greater activation in this region for higher ranked individuals relative to lower ranked individuals following a dominance test (the tube test) (Wang et al., 2011). Single-unit recording further confirmed that dmPFC neurons are active during effortful behaviors during the dominance test, such as pushing and resistance to being pushed (Zhou et al., 2017). Acute optogenetic activation of excitatory neurons during the tube test results in an immediate increase in rank status and effortful behaviors, with stimulation intensity positively correlated with amount of rank increase, while chemogenetic inhibition of dmPFC neurons results in the lowering of rank status and certain effortful behaviors (Zhou et al., 2017). Interestingly, the elevated rank status attained by repeat winners through optogenetic activation persists even in trials without optogenetic activation and is transferrable to another dominance test; this persistence requires NMDA receptor-mediated long-term potentiation of the mediodorsal thalamus to dmPFC projection. Taken together, these results demonstrate that the dmPFC both encodes and is functionally critical for social rank status and that learning and experience-dependent synaptic plasticity are critical for changes in social internal states.

Neural Mechanisms of Internal State Representation

A number of fundamental concepts concerning the circuit representation and mechanisms of social internal states are important to raise for discussion. One possibility is that different social behaviors (such as aggression versus mating versus parenting) could be separately regulated by distinct internal states. Alternatively, they could be synergistically regulated by a single, "master" social internal state. This distinction would point toward potential differences in the neural circuit mechanisms or representation of social internal states in the brain. For example, arousal and aggression states may be highly integrated and therefore may overlap and share similarities in their representation, while parenting and dominance states may be distinctly represented from each other and contribute to behavioral decisions separately.

Furthermore, where are social internal states represented at an anatomical level? One possibility is that a social internal state is encoded discretely within a single or very few hub region(s), which in turn modulate neural processing in other brain regions. Alternatively, internal states could be encoded independently in multiple brain regions in a distributed manner. Along this line of thought, is the VMHvl a key hub or one of the many distributed brain centers for encoding aggression state? Examining these possibilities requires further dissecting the representation of social internal states across various brain regions.

Lastly, how are social internal states represented, encoded, and/or modulated at a circuit or physiology level? In classic nonsocial internal states that involve homeostasis, such as hunger and sleep, neuromodulators and hormones have been implicated in regulating the circuits underlying these states (Waterson and Horvath, 2015; Weber and Dan, 2016). These effectors are capable of changing the neural circuits through both direct action on neuronal physiology, such as increasing excitability, as well as changes in gene expression, which may have longer-lasting effects on circuit function (van den Pol, 2012). Similar mechanisms involving neuromodulators and neuropeptides may also regulate social internal states. Recent work on social internal state representation has focused on excitability and spontaneous activity of key brain regions in aggression (e.g., VMHvl). Oxytocin, serotonin, and other neuromodulators are known to be involved in social behaviors and have been shown to influence the activity of VMHvl and MeApd neurons (Hashikawa et al., 2017b; Li et al., 2017). Whether this effect is directly relevant to aggression states, and whether these neuromodulators act through directly changing intrinsic neuronal physiological properties, or through other mechanisms like alterations in gene expression, is unclear. Similarly, hormones and neuropeptides like oxytocin and estrogen are both elevated during and following pregnancy, and their activity in parenting circuits is sufficient to induce a maternal state in females (Kohl et al., 2017). Oxytocin activity in the auditory cortex alters the plasticity of excitatory/inhibitory activity in response to pup calls (Marlin et al., 2015), but whether there is a similar effect of these neuropeptides on other parenting centers like the MPOA remains to be addressed. Future studies of the neuromodulatory systems and their impacts on modulating circuit plasticity will greatly expand our understanding of the underlying circuit mechanisms.

Other Factors Influencing Internal States

Different social housing conditions (single versus group housing) lead to marked differences in baseline aggressive state when tested in the home cage (Wongwitdecha and Marsden, 1996) as well as the ability to chemogenetically induce attack behavior when tested in a novel environment (Yang et al., 2017). In addition to sensory experiences during adulthood, early life experiences such as early developmental stress (e.g., prenatal stress, maternal separation, early social deprivation) have a profound impact on selection of social behavioral decisions later in life (Sandi and Haller, 2015). Moreover, a given set of sensory cues may also result in a different behavioral response in different individuals of the same species (Figure 3B). This could be due to differences of internal states between individuals (such as different sensory experiences) and/or other factors, such as genetic backgrounds and experience-independent developmental events. Certain inbred mouse strains such as NZB/BINJ and outbred mouse strains such as Swiss Webster

are substantially more aggressive than C57BL/6J (Hashikawa et al., 2017a), underscoring the importance of genetic factors. Puberty is an example of a dramatic developmental event that occurs largely independently of social experience and has a profound effect on social internal states. Pre-pubertal male mice do not show aggression, but during and after puberty, testosterone levels increase in male mice and this increase underlies aggression in post-pubertal males (Sisk and Zehr, 2005; Vetter-O'Hagen and Spear, 2012). How these factors shape the internal state at a neural circuit level remains an active area of research (Robinson et al., 2008; Sano et al., 2016).

Social Preference and Reward

In mammals, individuals prefer to interact with a conspecific over a nonsocial object (Moy et al., 2004). This suggests that the experience of interacting with a conspecific is more rewarding than the alternative choices. This preference or reinforcement of social interactions is therefore defined as "social reward" and plays a critical role in social interactions (Insel, 2003). Dysfunction of the social reward system has been implicated in neuropsychiatric disorders such as autism spectrum disorders (Young and Barrett, 2015). In addition to general social interactions, specific social behavioral choices can also be rewarding. One example is seen in aggression; animals can be trained to voluntarily seek out a submissive conspecific to attack by initiating a nosepoke to gain access, with learners increasing the number of pokes for access over successive training days (Falkner et al., 2016). Additionally, when interacting with an intruder animal, aggressive animals develop a conditioned place preference, whereas non-aggressive animals develop a conditioned place aversion, suggesting that positive versus negative valence are associated with responses of aggressors versus non-aggressors to intruders, respectively (Golden et al., 2016).

How do social cues generate social reward? Several classic reward centers of the brain previously known to encode general reward, such as the NAc, the ventral tegmental area (VTA), the dorsal raphe nucleus (DRN), and the lateral habenula (LHb), have been implicated in modulating social reward (Dölen et al., 2013; Golden et al., 2016; Gunaydin et al., 2014; Hung et al., 2017; Li et al., 2016). For example, oxytocin neurons in the paraventricular nucleus of the hypothalamus (PVN) are activated during social interaction; the release of oxytocin modulates the neurons in the VTA and NAc to generate social reward (Dölen et al., 2013; Gunaydin et al., 2014; Hung et al., 2017). In addition, basal forebrain projections to the LHb modulate aggression reward (Golden et al., 2016).

Where and how do these reward centers receive social information? A recent study revealed that *Neurotensin* (*Nts*)-expressing MPOA neurons generate social reward via projections to the VTA (McHenry et al., 2017). *In vivo* two-photon imaging demonstrated that MPOA Nts^+ neurons in females preferentially respond to attractive male stimuli over nonsocial appetitive cues and that the dynamics of neuronal response can be regulated by ovarian hormone signals. Activation of MPOA Nts^+ neurons and MPOA-to-VTA circuitry generates the rewarding effect and promotes social approach. Since the MPOA is directly involved in several social behaviors, it may be one of the social brain regions that provides social information to the reward centers.

Many fundamental questions regarding the circuitry underlying social reward still need to be addressed. Where is the reward signal first encoded? Are social versus nonsocial reward stimuli encoded in the same or different ways? One possibility is that "social" brain regions, such as MeApd, VMHvl, BNST, AVPV, and PMV, directly encode the reward signals; alternatively, these social circuits may purely provide social sensory cues to be transmitted to the classic reward centers. In either scenario, how does the reward circuit interact with other aspects of social internal state? Moreover, do different social behaviors correspond to different reward values? Future studies should be directed at answering some of these questions.

Relationship to Nonsocial Behaviors

Many "social" brain regions, such as the MPOA, PMV, and VMH, are also involved in diverse sets of important nonsocial functions, such as regulation of body temperature, sleep, feeding, energy balance, and metabolism (Morrison and Nakamura, 2011; Xu et al., 2011). How are social and nonsocial behaviors regulated in the same brain areas? Are social and nonsocial behaviors regulated by the same or different neuronal subpopulations? Recent studies have dissected specific neuronal subpopulations in these social brain regions in regulating nonsocial behaviors. The MPOA is a highly anatomically and molecularly heterogeneous structure. In the MPOA, Gal^+ neurons are involved in maternal behavior, and Nts^+ neurons are involved in social reward (McHenry et al., 2017; Wu et al., 2014), while BDNF/PACAP-expressing neurons control body temperature (Tan et al., 2016) and a subset of tuberomammillary nucleus-projecting GABAergic neurons promotes sleep (Chung et al., 2017). Interestingly, a subset of Nts^+ neurons are activated by peanut oil, which are a distinct subset from Nts^+ neurons responding to social cues, demonstrating that social and nonsocial cues are encoded in non-overlapping subsets of neurons and that subpopulations defined by single genetic markers may be further refined through functional, genetic, and/or projection dissection. In the VMH, $Esr1^+$ neurons not only regulate social behavior but also modulate physical activity, food intake, thermogenesis, and metabolism (Choi et al., 2013; Correa et al., 2015). Lastly, in the MeA, GABAergic neurons promote several social behaviors including aggression, mounting, and social grooming, whereas glutamatergic neurons promote self-grooming behavior (Hong et al., 2014). A subset of GABAergic neurons that expresses the *Npy1r* have also been linked to feeding behavior (Padilla et al., 2016). These examples illustrate the heterogeneity of neuronal function and potential crosstalk between social and nonsocial circuits. Whether and how different functional populations overlap with and influence each other in local and downstream circuits remain to be further studied.

Future Directions

Functional Mapping of Social Circuits

Although studies have identified some key brain regions involved in social behaviors, there are still many more that have not been identified or studied. In addition, some types of social behaviors, such as social play, social grooming, and social foraging, have not been extensively studied at a functional circuit level. With known brain regions critical for social behaviors like the VMHvl,

MeApd, and MPOA, the upstream and downstream targets have not been fully identified (Figure 2). Understanding these targets would help move our understanding beyond brain regions and into circuit connectivity. For example, if the MeApd, VMHvl, and MPOA all control some forms of aggression, how are they all functionally linked together? How are different social behavioral decisions regulated in closely linked circuits? Identifying and comparing the functions of different circuit components will be critical for our understanding of how each component contributes to the encoding of the sensory integration, social internal states, and social reward. Finally, a completely understudied area with respect to the neural circuits underlying social behaviors concerns the role of non-neuronal cell types in shaping or regulating these circuits. Previous studies have identified a functional role for astrocytes in other nonsocial behaviors (Martin-Fernandez et al., 2017; Suzuki et al., 2011), raising the possibility that they may participate in social behavioral regulation.

Understanding the Functional Units in Circuits

Brain regions, projections of a brain region, cell types of a brain region, and cell-type-specific projections of a brain region have all been shown to be functionally relevant for a social behavioral circuit. One open area of investigation involves understanding the composition of cell types and heterogeneous projection patterns of individual cells within brain regions. Recent advances in single-cell RNA sequencing and multiplexed fluorescent *in situ* hybridization have significantly improved our understanding of cell-type compositions in many brain regions such as subregions of the hypothalamus and the amygdala as well as their activation states in behaviors (Romanov et al., 2017; Wu et al., 2017; Zeng and Sanes, 2017). Other techniques that allow for identifying projection patterns of individual neurons or synapse-specific projections of brain regions hold great potential in understanding the projection composition of cells that comprise a circuit (Callaway and Luo, 2015; Kebschull et al., 2016; Tervo et al., 2016; Zingg et al., 2017). With the ever-growing usage of single-cell approaches to study the nervous system, a fundamental question has arisen concerning the definition of a cell type. A recent discussion has proposed a number of key components to the definition of a neuronal subtype, including molecular signature, physiology, morphology, and connectivity (Zeng and Sanes, 2017). With this context in mind, a fundamental, open question concerns what the minimal functional unit for a social circuit (or for any neuronal circuit) is.

In vivo imaging in freely behaving animals allows for examination of activity patterns at the population level during social behaviors. This has traditionally been challenging due to the depth of social brain structures and the need to record from freely behaving animals, but recent advances of miniature microendoscopy allows deep brain structures to be imaged in freely behaving animals (Grewe et al., 2017). A few studies mentioned in this Review have begun to use this approach to study the activity of neural ensembles during social behaviors and found that sensory cues and behavioral decisions are represented not only at the level of individual neurons but also at the population level (Li et al., 2017; Remedios et al., 2017). Continuing to study the population encoding of socially relevant information and behaviors in other brain regions or contexts will greatly contribute to our understanding of the encoding of social behaviors.

New Technology for Advanced Behavioral Analysis

Studying two or more interacting individuals simultaneously is challenging, as the complexity of their behavioral decision space is likely to be substantially higher than that of only one individual. An additional hurdle lies in the variability in interpretation and scoring of behavioral data between different studies or research groups, which could in turn influence the conclusions when examining the neural circuits underlying these behaviors. Sophisticated tools capable of sensitive, objective, efficient, and quantitative behavioral measurement and characterization are much needed and represent one of the major challenges in behavioral neuroscience in general (Anderson and Perona, 2014). Recent advances include the use of automated video tracking, three-dimensional depth sensing, and machine learning to record and analyze the behavior of two or more interacting individuals (Hong et al., 2015; Kabra et al., 2013; Weissbrod et al., 2013; Wiltschko et al., 2015), although the complexity and specificity of the behavioral phenotyping remains an active area of study. Furthermore, behavioral analysis systems that can incorporate multiple modalities of information, such as USVs and pheromonal or olfactory composition, will further contribute to our understanding of the integration of social cues and behaviors. Future efforts in this area could significantly transform the study of social behavior.

Concluding Remarks

In this Review, we have discussed many exciting findings that have identified key social behavioral circuits and basic mechanisms underlying different aspects of social behavioral regulation, including sensory perception, social decision making, social internal states, and social reward. Providing a conceptual framework incorporating the contributions of individual aspects of social circuits will hopefully help future studies focus on the numerous unanswered questions in the field. For example, how are different sensory modalities integrated? How do feedback loops shape the dynamic progression of social behavior? How is internal state encoded and how does it influence behavioral decisions? Are different social behaviors (such as aggression versus mating) encoded in the same or different circuits? How are social hubs and reward hubs linked with each other? How do social behaviors interact with nonsocial behaviors? How are emotional components of social behavior encoded? In addition to circuits, what are the underlying cellular, molecular, and/or synaptic mechanisms?

One important goal of studying social behavioral circuits in mice as a model system is to identify fundamental biological principles that can be extended to other species and can be applied to our understanding of human social interactions and the related disorders. Humans are uniquely advanced in our degree of social communication with each other and in our interactions with other species, making our social behaviors remarkably malleable (Blakemore, 2010; Ebstein et al., 2010). Disruption of normal social behavioral function has been observed in many mental disorders and is being actively studied in mouse models that are of both construct and face validity (de la Torre-Ubieta et al., 2016; Nestler and Hyman, 2010). Accumulating evidence in mouse models suggests that the disruption of social behaviors in mental disorders may occur at many different levels, from sensory perception and integration to social reward and to

communication between individuals (de la Torre-Ubieta et al., 2016; Young and Barrett, 2015).

Understanding social behaviors in animals (including human) could also potentially help us understand "social" interactions between human and artificial intelligence or artificial general intelligence (Lemaignan et al., 2017) and among artificial intelligence systems themselves (Oh et al., 2017). The research of artificial intelligence benefits from the studies of the biological brain, and the progress has been remarkable (Hassabis et al., 2017). Collective interactions of decentralized, self-organized artificial intelligence systems have been used in swarm robotics (Brambilla et al., 2013). AlphaGo Zero, an algorithm utilizing artificial neural networks, has played against itself (which can be considered as another AlphaGo Zero) without human inputs and achieved superhuman levels in the game of Go (Silver et al., 2017), suggesting that interactions between machines can evolve with astronomically high speed and complexity. Moreover, the influence of artificial intelligence in our species' communication has already been changing and will continue to change the way we socially interact with one another. We can only begin to speculate where the future will go on this new frontier.

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