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Bespoke behavior: mechanisms that modulate pheromone-triggered behavior

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Abstract

What is good for others, may not be in my best interest. Individuals should not, and do not, respond identically in the same environment. Personalized social behavior is particularly important to ultimately ensure reproductive fitness. How and where neural activity is modulated to customize behavior has remained largely unknown. The robust response to pheromones provides a platform to identify the logic of how the brain initiates social behavior. Mouse pheromones engage innate motor actions that underlie social behavior yet are plastic to suit individual needs. Recent study of mouse pheromone behavior, neurocircuit activity, and functional manipulations is beginning to paint a complex, dynamic, and diverse picture of the mechanism that enable flexible modulation of social behavior.

Introduction

Social behavior requires the coordination of many complex brain computations to ensure that the action is appropriate. For example, in the same environment a stressed, socially subordinate, and pregnant brain will react differently than a hungry, socially dominant, tired brain. The internal environment and previous experience inform the brain to initiate an appropriate motor output. How and where neural activity is modulated to generate behavior that fits one's needs has remained largely unknown. Pheromones are chemosignals that are emitted and detected between members of the same species to trigger innate social behavior. However, pheromone-evoked behavior output is not stereotyped across individuals - it can vary depending on the sex, experience, and internal state of the receiver (Figure 1). Focused study on brain regions that generate pheromone-mediated behavior is beginning to reveal a variety of neural mechanisms that personalize output behavior to suit the needs and experience of the individual.

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Sex-state modulates behavior

Males and females often display different social behavior in the same sensory context. In order to maintain reproductive fitness, it is essential that the perceiver's neural and behavioral response to the environment matches the needs of their specific sex-state. Sexually-dimorphic responses occur to male- emitted mouse cues such as MUP urine pheromones and ESP1 tear pheromones [1–5]. When a male detects another male's MUPs or ESP1 pheromones he responds with territorial aggression which establishes dominance and reduces mating competition [1–6]. If male pheromones evoked the same aggression behavior when detected by females, it would decrease both sexes' reproductive fitness. Instead, male pheromones promote sexual attraction and receptivity when detected by females [3–5,7]. While the display of attraction and aggression both share an increase in arousal, they are strikingly different in the muscle activity that produces the behavioral response, the associated internal valence, and the overall social outcome.

How do male and female brains produce such different behavioral responses to the same pheromone cues (Figure 2)? Pheromones such as MUP and ESP ligands are detected by sensory neurons located in a specialized olfactory subsystem, the vomeronasal organ (VNO). The VNO expresses approximately, 350 different sensory receptors that detect a variety of specialized chemosensory cues (eg. MUPs or ESPs) known to evoke social and emotional behaviors. Perhaps behavioral differences, stem from sex-specific expression of pheromone receptors - subsets of female-specific receptors that activate mating circuits and male-specific receptors that trigger aggression circuits could provide a straight-forward solution. However, recent transcriptional profiling has discounted this idea, as sensory receptor expression is largely identical between males and females [8,9]. It is interesting to note that social experience maintained over many months can alter the baseline expression frequency of several receptors that detect male specific cues [10,11], but this timescale is unlikely to serve as a fundamental mechanism underlying gender-specific behavior. However, functional sexual dimorphisms arise downstream of immediate sensory processing. VNO sensory neurons project to the accessory olfactory bulb (AOB), which in turn target third order nodes including the medial amygdala (MeA, Figure 2). The VNO to AOB to MeA circuit is a primary route for information processing of pheromone signals that promote social behavior. The first evidence of sexual dimorphism occurs in the MeA where male pheromone-evoked activity is overrepresented in females while female pheromone-evoked activity is overrepresented in males [12]. The action of puberty sex hormones are essential to functionally sculpt male- and female- specific responses [12], but the mechanism that generate these developmental differences remain unknown.

When a female detects male odor she is aroused to display mating behavior. How are pheromone- evoked circuits modulated to suit the needs of a female (Figure 2, red)? Recently, the Touhara group has leveraged ESP1 to specifically identify pheromone-activated central circuits. Female sexual receptivity depends on a single VNO receptor, V2Rp5, that is equally expressed in both males and females. Surprisingly, the extent of activation of V2Rp5's targets in the AOB and downstream in the MeA(pv) does not appear to quantitatively differ between males and females [7]. Moreover, male and female MeApv neurons that are activated by ESP1 develop similar axon projections to two hypothalamic

nodes; the dorsal ventromedial hypothalamus (VMHd) and the medial preoptic area (MPOA). Though the circuits are similar, functional analysis indicates that use of these nodes is sexually dimorphic. In the female brain ESP1 preferentially stimulates the VMHd^{SF1+} node, while in the male brain it drives MPOA activity [7]. In the brains of both sexes, pheromones in male urine also activate neurons in the VMH(vl) which co-express estrogen (ESR1) and progesterone (PR) receptors (referred to here as VMH^{Esr1+}), and additionally express an additional GPCR, Cckar in females [13]. The functional significance of this female-specific molecular sexual dimorphism remains unknown. Both the VMHd^{SF1+} and VMHvl^{ESR1+} neurons project to the dorsal periaqueductal gray (dPAG) to drive female motor behavior (such as the receptive mating posture, lordosis) [7,13].

VMH^{ESR1+} neurons also project to Kisspeptin expressing neurons in the anteroventral periventricular nucleus (AVPV)[14], which are silent during diestrus, most active immediately before estrus, and trigger ovulation by activating GnRH neurons to surge luteinizing hormone (Figure 2). This arm of the circuit is anatomically sex-differentiated, consisting of seven times the amount of projections in the female compared to the male brain [13,15]. In addition to orchestrating ovulation, AVPV^{Kiss+} neurons influence female mating behavior - they are activated by male odor, ablation eliminates male preference, and optogenetic activation triggers lordosis [16] (Figures 2–3). AVPV neurons send reciprocal connections back to the VMH which may serve as the circuit route to initiate mating behaviors and coordinate their display with ovarian physiology [16]. Another pheromone (ESP22) that is only emitted by juveniles [17] activates a parallel circuit from the VNO to AOB to GABAergic neurons in the bed nucleus of the stria terminalis (BNST), which inhibit the VMH^{ESR1+} neurons [18]. Together, these studies describe the primary sensory to motor circuit arrangement that promotes female sexual behavior towards males and may decrease female mate receptivity during infant care.

In contrast, male detection of MUPs, ESP1, and other currently unknown male urine pheromones triggers rage [1,6]. How are pheromone-evoked circuits modulated to suit the needs of a male? The aggression circuit relies on the same nodes as the female brain uses to generate mating behavior (VNO to MeA to VMH; Figure 2, blue) but the cellular identity within each brain node is different. Pheromone detection activates a subpopulation of GABAergic neurons in the MeA which project to the excitatory VMH^{ESR1+} neurons (largely lacking Cckar) [19,20]. Photomanipulation of these inhibitory MeA neurons reveal their necessity and sufficiency to drive aggression, indicating that they must directly synapse on local VMH inhibitory neurons that have not yet been described [19,20]. The VMH is part of a hypothalamic region that has been identified through classic electric stimulation studies as a “hypothalamic attack area” [21]. In the male, low intensity photostimulation of VMH^{ESR1+} or MeA^{VGAT+} cells elicits sexual mounting while high intensity stimulation promotes attack [19,22]. This was originally interpreted to indicate that the VMH^{ESR1+} neurons use a scalable activity code to generate either aggression or mating [22], but subsequent studies in the female alternately suggest that scaling activity may trigger different thresholds in two distinct VMH^{ESR1+} populations, with the Cckar negative cells predominating in males and driving aggression [15]. Recently, the anatomy of neurons that project to and from VMH^{ESR1+} has been systematically mapped to reveal a complex network of over 30 targets [14]. Individual VMH^{ESR1+} neurons collateralize onto multiple

targets and can be binned into two classes; those that project anteriorly, with an abundance of reciprocal connections into the hypothalamus and amygdala, and, those that project posteriorly into motor regions [14]. The Lin lab has studied one of these projection arms from VMH^{ESR1+} neurons posterior to the (l)PAG and found their activity to coincide with a single element of aggression; jaw movements associated with biting during male-male attacks [23]. This ‘fan out’ of multiple, parallel circuits from an organizing node to generate specific actions of motor behavior has also been seen in other pheromone-driven neural circuits including the MPOA’s role in parenting and across the hypothalamus regulating social stress [24,25]. Such an arrangement provides a mechanism to link motor actions that support innate behavior and flexibly reroute information flow to initiate variable motor action as the individual gains experience.

Despite these dimorphic findings, mutant and photostimulation analysis has revealed that much of the basic circuit organization is present and similar in the male and female brain [26,27] (Figure 2). How small differences between male and female development alter brain structure to generate sex-specific function and use of these circuits is still largely unknown. Identification of the primary circuits and their sexually dimorphic differences now provides a solid platform to understand how the brain generate sex-specific social behavior.

Hormonal state modulates behavior

Within a sex, hormones that rise in response to stress or basic physiology such as hunger modulate behavior over hours and days. Similarly, cycling female sex-hormone state modulates social behavior in response to pheromones (Figure 3). In order to reproduce, female mice must first be attracted to male-emitted pheromones. Though this attraction is assumed, female response to male pheromones is not fixed - male pheromones can evoke a variety of different female behaviors depending on females’ circulating levels of reproductive hormones. When estrogen surges during estrus female mice respond to male pheromones with sexual receptivity, such as lordosis, yet are indifferent to male pheromones during diestrus when progesterone levels are high [28], and respond with actual aggression when progesterone surges in motherhood [15,29]. Estrogen and progesterone are we know for entraining aspects of female reproductive physiology including ovulation and pregnancy. The use of one system to regulate and modulate both physiology and behavior ensures that she set out males during ovulation, but not when she is unable to conceive or when young pups requires complete attention. The mechanisms that enable female hormones to modulate physiology are largely well understood, and how they act to trigger appropriate behavior is now beginning to be revealed (Figure 3).

Surprisingly, internal hormones can exert their effects on behavior before information is even sent to the brain, through modulation of VNO sensory neurons themselves. While most sensory systems passively detect stimuli, the ability of the female VNO to detect male MUPs is abolished by progesterone during diestrus [28]. PGRMC1, a non-canonical progesterone receptor, is expressed on MUP-detecting VNO sensory neurons and directly responds to the female hormone state. During diestrus, progesterone triggers a kinase cascade that silences neuronal activation in MUP-sensing sensory neurons [28]. This indicates that internal hormone state can render females “blind” to male pheromones, allowing them to enact state-

specific behaviors. Similarly VNO expression of the calcium-activated TrpM4 channel is regulated by estrogen and aromatase, an enzyme that converts testosterone to estrogen. TrpM4 is highly expressed in male and estrus females' VNOs, yet is undetectable during diestrus when estrogen levels fall [30]. While TrpM4's broad expression in most VNO neurons suggests a key role in sensation, it is not necessary for primary sensory signaling and the function of sex hormone-driven modulation remains unknown [30]. Nonetheless, the ability of sex hormones to alter VNO sensory neuron expression and function provides an efficient means of modulating social behavior.

In the brain, the mechanistic significance and role of hormones in the function of adult behavioral circuits remains largely unknown. However, key hormone receptors are expressed in many pheromone-responsive nodes that contribute to sexually-dimorphic social behavior. The estrogen receptor ESR1 is expressed extensively in areas linked to social behavior, including the MeA, MPOA, BNST, VMH, and PAG [7,22,31,32] (Figure 3), yet region-specific deletion of ESR1 has inconsistent effects on mating and aggression [33]. The Shah lab recently found that aromatase is expressed in a subset of BNST neurons that allow male mice to perceive and be attracted to females, and also promote male-male aggression [31]. Surprisingly, despite these behavior-linked neurons' expression of aromatase, testosterone removal in males does not impact their response to social signals [31]. Even so, greater mechanistic understanding of sex hormone effects has been achieved in a subpopulation of neurotensin-expressing, estrogen-sensitive cells in the MPOA that mediate attraction to male cues in female mice [34,35]. Priming these neurons with estradiol enhanced their excitability and increased the proportion of male pheromone-responsive MPOA cells during in vivo imaging of neuronal activity [34]. Further study of how sex hormones affect neural activity across sexual behavior circuits will be of great benefit to the ultimate understanding of pheromone-mediated social behavior.

Other brain features change during the estrus cycle. In addition to effects on neural activity, sex hormone changes can result in periodic remodeling of functional connections between nodes controlling sexual behavior. During pregnancy, MUP pheromones activate AOB neurons, yet, unknown mechanisms prevent transmission of this information to the MeApv and attraction behavior is not initiated [4]. VMH^{ESR1+} cells are required for and show endogenous activity during female sexual behavior [13], yet chemogenetic activation of VMH^{ESR1+} cells does not induce female receptivity in diestrus females [36]. Surprisingly, VMH^{ESR1+} neurons increase their axonal projections to the AVPV by 3-fold during estrus (Figure 3). While circuit remodeling cycles with female sex hormones, priming with estrogen in males did not induce a similar effect, suggesting a developmental hardwiring to enable regular changes in connectivity in females [36]. The mouse estrus cycle lasts only 4–6 days in lab strains, so circuit remodeling is very rapid. This form of modulation seems unintuitive, as, it is an energetically costly way to regulate behavior compared to hormonal modulation of existing circuits.

These recent studies have identified at least three different mechanisms that hormones use to modulate behavior: directly silencing or sensitizing neural activity, re-routing neural activity, and changing neural anatomy. One of these strategies is utilized at almost every node of pheromone behavioral circuits and it is likely that understanding is still incomplete, perhaps

engaging currently unknown mechanisms (Figure 3). This implies an extreme level of redundancy perhaps to ensure fitness and/or flexibility that can be utilized modularly even for brain function beyond social behavior.

Experience driven states modulates behavior

In addition to the hardwired and intrinsically constrained effects of sex-development and sex hormones to modulate the effects of pheromones, there is mounting evidence that an individual's past behavioral circumstances modulate future neural activity and behavior. For example, the experience of social isolation or copulation with a female dramatically promotes subsequent male-male aggression. In the lab, these changes are long lasting, and re-grouping sexually-experienced males can result in lethal aggression among previously amicable brothers. Within established social groups, memory of wins and losses from past fights results in the formation of a dominance hierarchy which decreases further injurious aggression between cage mates. Recent studies have begun to uncover how social experience modulate pheromone-promoted aggressive behavior (Figure 4).

Social behavior experiences can fine tune neuronal ensembles to enhance both the signal-to-noise ratio of pheromone-evoked signals and the probability of ensuing motor output. The Dulac lab chronically imaged single cell activity in the MeA of sexually-inexperienced males and found neural ensembles encoding various social stimuli, such as the presence of other males, females, pups, or predators [12,37]. To study neural correlates of experience, they co-housed these virgin males with females and found that the experience enhanced differences in activity patterns displayed by the female-tuned neurons, increasing the ability of the male to discriminate females for weeks afterward [37]. The Anderson lab has also recently investigated the effect of experience using single cell imaging of VMH^{ESR1+} neurons. As was observed in the MeA [37], ensembles of VMH neurons that represent male or female cues overlap in socially-naïve, seldom-aggressive males [38]. However, as little as thirty minutes of sexual experience produces divergent VMH^{ESR1+} activity patterns in response to female stimuli, and this neural activity change correlates with the robust display of male-male rage [38]. How social experience tunes activity in the MeA and VMH is not yet clear, but there is some evidence to suggest that neuropeptides are involved. Relevant MeA neurons express oxytocin receptor, and oxytocin antagonists or oxytocin receptor deletion blocked males' experience-induced changes in female discrimination and female preference [37,39]. It is also possible that signal sharpening could occur anterograde to the MeA and VMH rather than within these exact nodes.

Olfactory memory of conspecific partners can also influence the expression of aggression (Figure 4). VMH^{ESR1+} neurons are sufficient to generate male aggression in socially isolated males, however chemoactivation of these neurons fails to elicit similar rage in males that remain group housed [40]. As the VMH is one of the last nodes in the canonical VNO-MeA-VMH pheromone processing circuit, this effect is likely to occur at outlying nodes that intersect the primary circuit. This is seen from lateral septum (LS) which provides major inhibitory input to the VMH. LS lesions generate extreme aggression known as "septal rage" [41]. Activation of LS-VMH projections terminated ongoing aggression immediately [42], illustrating the importance of these projections for suppression of aggressive behavior. How

the LS becomes engaged remained elusive until a recent study discovered a major input to the LS from the hippocampal CA2, a region essential for memory [43]. Inactivation of CA2 pyramidal neurons impairs social recognition but does not reduce soda preference [44]. Interestingly, it was found that CA2 provides a net inhibitory input to the LS. In-vivo imaging of neural activity of CA2-LS projections showed that they were highly activated during aggression but not during social exploration, and chemogenetic silencing of these projections inhibited aggression [43]. Thus, olfactory memory of past experiences associated with pheromonal cues can trigger aggression by relieving LS inhibition. It suggests however that there should also be a yet unidentified parallel circuit to downregulate aggression upon olfactory recognition of partners where aggression would be inappropriate.

Repeated experience of losing fights (social defeat) induces social avoidance, decreases aggression, and increases defensive and submissive postures in encounters with novel individuals [45]. Recent studies have uncovered how history of social winning and defeats is stored and processed in cortical circuits and how that modulates aggression in dominant compared to subordinate states. Dominant mice showed higher synaptic inputs in the medial prefrontal cortex (mPFC) [46], a region important for processing social dominance and social hierarchy information [47]. The mPFC receives prominent projections from the mediodorsal thalamus (MDT) and social defeat weakened synaptic strength of MDT-mPFC projections [48,49]. How this modulating effect comes about is not clear, but it is likely to be key to altering behavior. The mPFC makes direct glutamatergic projections to the PAG, a brainstem area that encodes motor outputs for aggressive behavior [23], and directly inhibiting mPFC-PAG projections increased retreats from an aggressive intruder and social avoidance [49].

These recent studies have identified at least three different methods that experience modulates aggression circuits: tuning neuronal ensembles, engaging memory circuitry and changing circuit connectivity. How experience engages these circuits, and the cellular and molecular mechanisms underlying such changes, is still unknown.

Conclusion

Pheromones are powerful sensory cues that promote social behavior. Their detection generates behavior that is personalized to suit the state of the receiver which can vary based on gender, social status, and experience. The brain uses sex hormone signaling to cement the development and cyclic regulation of gender dimorphic circuits as well as neuropeptides and other unknown mechanisms to allow more flexibly-initiated modulations to occur from experience. Mechanisms generating flexible or dimorphic behavior occur at almost all known nodes of pheromone activated circuits, from sensation to motor command, and can additionally be initiated by other circuits that impact the edges of primary pheromone-response circuits. While progress has been made to understand how the brain selects a behavior to meet individual state needs, much understanding is still correlative. Systematic study of pheromones, social behavior, and neural information coding is now poised to uncover the mechanisms that underlie state modulation of behavior.

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Highlights

- Pheromones promote behavior that is personalized to match one's needs
- Sexual development, internal state, and experience modulate pheromone action
- Modulation targets most primary pheromone-circuit nodes via diverse mechanisms

Figure 1. Pheromone-mediated behavior is modulated to suit the needs of the receiver. Response to pheromone sensory cues can vary depending on one's sex-state, hormone-state or past experiences. This modulation enables flexible, personalized social behavior.

Figure 2. Gender-development generates male and female differences in pheromone response circuits.

Male pheromones including MUPs/ESP1 (light blue circles) promote behavior that suits the sex of the recipient (red = female; blue = male). Grey nodes are important for pheromone-mediated social behavior but are not known to play a role in sex-modulation. VNO - vomeronasal organ, AOB - accessory olfactory bulb, MEA - medial amygdala, MPOA - medial preoptic area, BNST - bed nucleus of the stria terminalis, VMH - ventromedial hypothalamus, AVPV - anteroventral periventricular nucleus, PAG - periaqueductal gray. Width of lines symbolizes strength of connections.

Figure 3. Hormones dynamically modulate pheromone response.

In the female brain, estrus cycle hormones estrogen (blue balls) and progesterone (green balls) regulate the activity of pheromone response circuits. A) Estrogen is high during estrus when females are attracted to males while progesterone peaks during diestrus when females do not display sexual receptivity. B) Female circuits activated by male pheromones (light blue circles) coordinate the display of ovulation and mating behavior. Node outlines indicates cells expressing progesterone (green) and estrogen (blue) receptors. A role for progesterone at the VNO and estrogen at the MPOA and VMH have been mechanistically identified, however, the functional significance of hormonal receptors at other regions remains to be determined. Grey nodes are important for pheromone-mediated social behavior, but are not known to play a role in hormonal-modulation of female mating. VNO - vomeronasal organ, AOB - accessory olfactory bulb, MEA - medial amygdala, MPOA - medial preoptic area, BNST - bed nucleus of the stria terminalis, VMH - ventromedial hypothalamus, AVPV - anteroventral periventricular nucleus, PAG - periaqueductal gray. Width of lines symbolizes strength of connections.

Figure 4. Experience modulates activity and behavior of pheromone response circuits.

The response to male pheromones including MUPs/ESP1 (light blue circles) changes with social experience. Primary pheromone response circuit that promotes aggression in the male brain following detection of male pheromones (light orange). Other circuits intersect at the edges of the primary pheromone response to modulate behavior in response to social dominance (brown) or olfactory memory (dark orange) experiences. Dashed lines indicate unknown route for transfer of pheromonal information into those regions. Stripes indicate nodes that are implicated in experience-driven modulation. Grey nodes are important for pheromone-mediated social behavior but are not known to play a role in experience-modulation. VNO - vomeronasal organ, AOB - accessory olfactory bulb, MEA - medial amygdala, BNST - bed nucleus of the stria terminalis, VMH - ventromedial hypothalamus, PAG - periaqueductal gray, CA2 - hippocampal CA2, LS - lateral septum, MDT - mediodorsal thalamus, PFC - prefrontal cortex. Greyed out nodes are not important for this modulation.