Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

State-dependent responses to sex pheromones in mouse

Lisa Stowers[1] and Stephen D Liberles[2]

A single sensory cue can evoke different behaviors that vary by recipient. Responses may be influenced by sex, internal state, experience, genotype, and coincident environmental stimuli. Pheromones are powerful inducers of mouse behavior, yet pheromone responses are not always stereotyped. For example, male and female mice respond differently to sex pheromones while mothers and virgin females respond differently to pup cues. Here, we review the origins of variability in responses to reproductive pheromones. Recent advances have indicated how response variability may arise through modulation at different levels of pheromone-processing circuitry, from sensory neurons in the periphery to central neurons in the vomeronasal amygdala. Understanding mechanisms underlying conditional pheromone responses should reveal how neural circuits can be flexibly sculpted to alter behavior.

Addresses
[1] Department of Molecular and Cellular Neuroscience, The Scripps Research Institute, La Jolla, CA 02037, United States
[2] Department of Cell Biology, Harvard Medical School, Boston, MA 02115, United States

Corresponding author: Stowers, Lisa (stowers@scripps.edu)

Current Opinion in Neurobiology 2016, **38**:74–79

This review comes from a themed issue on **Neurobiology of sex**

Edited by **Barry J Dickson** and **Catherine Dulac**

For a complete overview see the Issue and the Editorial

Available online 16th April 2016

http://dx.doi.org/10.1016/j.conb.2016.04.001

Pheromones provide a way for animals to communicate socially, and can strongly induce or suppress sexual behavior [1,2]. Responses to pheromones occur in both the main olfactory epithelium (MOE) and vomeronasal organ (VNO), with downstream neural circuits providing streamlined connectivity to limbic system nuclei that orchestrate behavioral responses. Destroying MOE and/or VNO function through surgical ablation or genetic deletion of key signaling molecules impacts a variety of social behaviors, including mating [3–9], social attraction [8,10•,11–13], territorial aggression [6,7,9,12,14,15], maternal aggression [6,14], dominance hierarchies [16], scent marking [6,16], parenting [17,18,19••], suckling [20,21], and sick animal recognition [22]. Other sensory systems like vision and hearing remain intact in these models; therefore, olfaction features prominently in control of many social behaviors in mouse. Although pheromones robustly promote innate behavior, the type of behavioral response can vary depending on the receiver's gender, reproductive physiology, and experience (Figure 1). That responsive neural circuits are flexibly molded to tailor behavioral outcome to the receiver's social needs. For example, male odors evoke scent-marking or aggressive behavior when detected by other males yet promote sexual receptivity when detected by females. Pheromone responses in females can vary across the ovulation cycle, and in males, can depend on position in the social dominance hierarchy [16]. Furthermore parents and sexually naive mice display different responses to pup odors, and mothers display aggression rather than sexual attraction to foreign males [23,24]. Recent studies have begun to shed light on how changes in internal state modify both the dynamic production of pheromones, and recipient neural circuits that dictate behavioral outcomes.

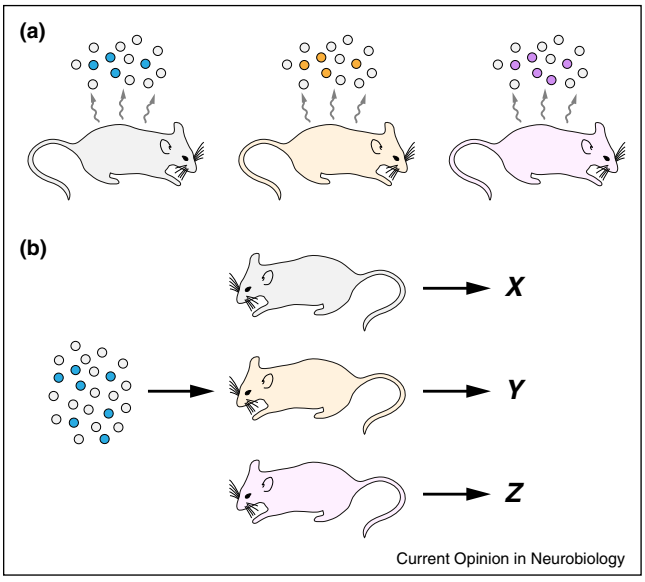
Pheromone production varies with internal state

Mice emit odors and pheromones that broadcast their internal state. Some pheromones are produced at near-constant levels throughout life without influence of internal state, such as those that signal individual identity (genotype or kinship) [25]. Production of other pheromones is strikingly altered at puberty: for example, levels of male and female pheromones increase while levels of a juvenile pheromone decrease [2,3,26,27••,28••,29]. Yet others are rapidly induced, such as those indicating alarm or illness [22,30].

Sex pheromones are emitted as complex chemical blends that include volatile odors, steroids, and proteins (Table 1). Single pheromones have not been described to indicate 'maleness' or 'femaleness'; instead these perceptions are thought to arise from the gestalt of detected olfactory cues. Perhaps by emitting multiple cues, male mice maximize the chance that sensory receptors in a receptive female will be stimulated. Release of multiple cues may also allow for simultaneous evaluation of gender, genotype, species, and perhaps other aspects of internal state.

How does internal state influence pheromone production? Some pheromones are derived by direct chemical transformation of internal state-regulating hormones into

Figure 1



State-dependent pheromone signaling. **(a)** Individuals emit pheromones and odors that reflect their state of development, internal physiology, and experience. **(b)** Given pheromones and odors can initiate a variety of responses (X, Y, and Z) depending on the receiver's state of development, internal physiology, and experience. The combination of state-dependent signals and state-dependent reception allows the receiver to tailor an appropriate behavioral response.

externally broadcast pheromones. Circulating steroid and internal state hormones such as testosterone, estradiol, and pregnanolone can be directly transformed into externally emitted chemosensory ligands [27••]. Some steroids are sulfated to promote excretion into the environment. Once emitted, sulfated steroids potently activate VNO sensory neurons of receiving individuals and serve as faithful indicators of the emitter's internal state [27••,28••,31,32]. For example, one sulfated estrogen is emitted by ovulating females as a byproduct of the reproductive cycle, and then functions secondarily as part of a pheromone blend that promotes male courtship behavior [28••]. Other pheromones including lacrimal peptides and urinary proteins are more indirectly controlled by sex hormones [29,33]. Sexually dimorphic expression of major urinary proteins occurs in the liver, and is regulated by testosterone-dependent patterns of pulsatile growth hormone secretion [33]. Similar pathways control sexually dimorphic expression of a liver enzyme flavin monooxygenase 3 (FMO3), which catabolizes trimethylamine, a male mouse odor found in urine [11]. Male-specific *Fmo3* gene repression evolved recently in male mice, causing abundant, species-dependent, and sexually dimorphic emission of trimethylamine odor [11].

State-dependent responses in sensory neurons

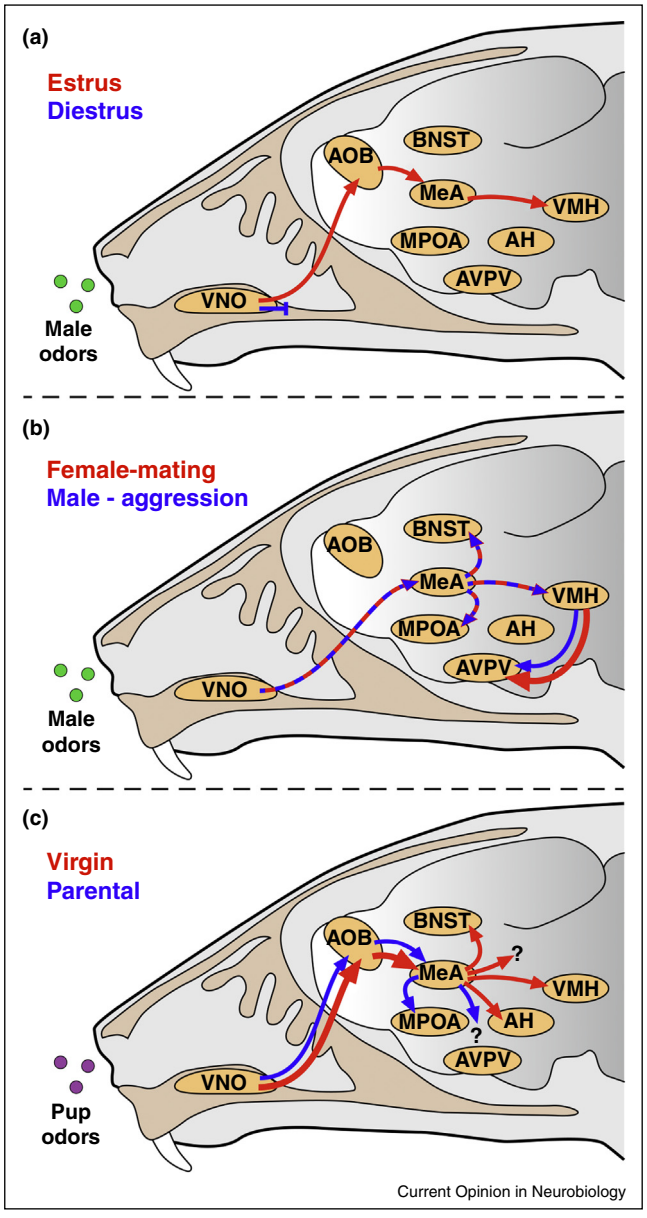
Peripheral sensory neurons are thought to detect stimuli in the environment and faithfully transmit that information to the brain, while the brain is thought to make appropriate behavioral decisions based on internal state and experience. However, contrary to this expected division of labor, some sensory information undergoes state-dependent filtering directly in peripheral sensory neurons. For example, females are attracted to males prior to ovulation, but are behaviorally indifferent during the opposing phase of the reproductive cycle [10•]. This change in female attraction behavior occurs through sex hormone-mediated silencing of certain VNO sensory neurons responsive to male pheromones (Figure 2a) [10•,34]. Silencing of sensory neurons does not enable the brain to receive maximal information from the external environment, but may provide a way to discard irrelevant signals.

Table 1

Sexually dimorphic odors and pheromones of mice

Chemical	Biosynthesis	Behavior	Detection pathway
Trimethylamine	Male urine	Scent attraction	MOE; response lost in TAAR5 knockout mice
(Methylthio)-methanethiol	Male urine	Scent attraction	MOE
(*Z*)-5-Tetradecen-1-ol	Male urine	Scent attraction	MOE, includes Olfr288
2-*sec*-Butyl-4,5-dihydrothiazole	Male urine	Aggression	Activates OE and VNO
2,3-Dehydro-*exo*-brevicomin	Male urine	Aggression	Activates OE and VNO
Major urinary proteins	Male urine	Aggression, scent countermarking, attraction	VNO neurons containing V2Rs
Exocrine-gland secreting peptides	Male tears (ESP1, ESP24)	Lordosis behavior (ESP1)	VNO neurons containing V2Rs; ESP1 response lost in V2Rp5 knockout mice
Modified steroids	Female urine (estrogen derivatives) Male urine (androgen derivatives)	Courtship behavior	VNO neurons containing V1Rs

Figure 2



Different coding solutions to create accessory olfactory state-dependent circuits. **(a)** Variable processing of male pheromones by females in estrus (red) or diestrus (blue). Silencing of specific male-pheromone responsive VNO sensory neurons can occur during diestrus, contributing to state-dependent responses. **(b)** Variable processing of male odors by females (red) and males (blue) results in differential mating and aggression behaviors. While the overall circuit logic is similar, sexual dimorphisms within each nucleus or hormonal differences during development may account for behavioral differences. **(c)** Variable processing of pup odors by virgins (red) and parents (blue). Experience and pregnancy hormones can gate changes in information flow, contributing to the development of parental behavior.

Pheromone processing in higher order olfactory circuits

Inputs from the MOE and VNO diverge centrally, and variable responses to pheromones can involve neuromodulation within any of several downstream brain regions. MOE-derived signals access the main olfactory bulb and then third-order recipient nuclei that include the piriform cortex and cortical amygdala. Innate odor aversion and attraction responses involve the cortical amygdala [35], while the piriform cortex likely contributes to experience-dependent modulation of odor responses [36,37]. One example where experience guides a pheromone response is odor-driven suckling behavior in newborn mice, which involves learning of maternal cues through main olfactory pathways [20,21].

VNO-derived inputs instead target the accessory olfactory bulb, and then third-order limbic system nuclei including the medial amygdala and posteromedial cortical nucleus (which together comprise the vomeronasal amygdala). The medial amygdala is one major hub in pheromone-processing circuitry, and recent advances revealed it to be a key site for state-dependent modulation of vomeronasal inputs [38]. Sex hormone receptors and aromatase are abundant in the medial amygdala, which has striking sexual dimorphisms in anatomy, responses, and functions [38].

The medial amygdala receives direct excitatory input from accessory bulb mitral cells, and in turn routes information to several brain regions, with prominent connections to the ventromedial hypothalamus (VMH). The medial amygdala and VMH can be partitioned into discrete anatomical subnuclei, with discrete information processing streams distinguishable at a gross morphological level [39,40]. Defensive responses to predator odors primarily involve the ventral medial amygdala and the dorsomedial VMH, while reproductive and aggressive responses to pheromones instead primarily involve the posterior dorsal medial amygala and ventrolateral VMH. Integration of VNO-derived information into a small number of behaviorally relevant channels would indicate different organizational principles from the main olfactory system, which instead is wired for diversity recognition. Interestingly, intermingled and perhaps identical VMH neurons respond to male and female odors and are relevant for mating and aggression [41,42], suggesting that a functional topography is not absolute.

Several classes of excitatory and inhibitory projection neurons in the medial amygdala have been defined by gene expression patterns and electrophysiological characteristics. Different VNO-activating stimuli from predators, competitors, mates, and juveniles activate subsets of medial amygdala neurons [3,39,43••,44]. *In vivo* electrophysiology revealed that medial amygdala neurons generally display enhanced selectivity related to the

behavioral salience of odor mixtures than upstream accessory olfactory bulb mitral cells [43••]. Moreover, responses in medial amygdala neurons are strikingly sexually dimorphic: most female neurons respond to male odors, and most male neurons respond to female odors [43••]. Preferential responses to opposite-sex odors are maximal after puberty, and require sex hormone signaling during development [43••].

Obtaining genetic control of molecularly distinct neuron types within the limbic system would provide an important foundation for understanding how pheromones control different behaviors. In the medial amygdala, selective stimulation of inhibitory GABAergic or excitatory glutamatergic neurons evokes antagonistic social (mating, fighting) or asocial (grooming) behaviors respectively [45]. Furthermore, genetic tools have enabled targeting of neurons in the medial amygdala and VMH that express key regulators of nervous system sexual differentiation [41,46,47••]. About 10–20% of neurons in the medial amygdala contain aromatase, an enzyme that converts testosterone into estrogen and is essential for brain masculinization. Genetically guided ablation of medial amygdala aromatase neurons impairs aspects of aggression without impacting sexual behavior [46]. Moreover, some neurons in the ventrolateral VMH contain receptors for estrogen and progesterone, and these neurons regulate sexually dimorphic mating and aggression behaviors [41,47••]. It is possible that limbic system neuron types can be further subdivided into discrete populations that specify behavioral outcomes related to reproduction, aggression, or predator defense. An alternative model intriguingly posits that the same population of VMH neurons can evoke mating and aggression depending on the scalable intensity of their activation [41]. Understanding the cellular logic of limbic system structures will provide a needed framework for understanding how inputs from pheromone-responsive sensory neurons are appropriately routed.

So how do male pheromones evoke sexually dimorphic responses? One possibility is that peripheral processing of male pheromones by males and females is similar. Once pheromonal inputs reach the limbic system, they are received by higher-order neurons whose connectivity and signaling properties have already been shaped during development by sex hormone signaling (Figure 2b). Perhaps at this point in the circuitry, signals in female and male mice diverge, differentially resulting in sex and aggression. Progesterone receptor-containing neurons in the VMH guide sexual behavior in females and aggression in males [47••] — it would be exciting if these neurons are initially indistinguishable in both sexes, deriving from a common progenitor and being shaped by sex hormone signaling to alter behavioral outcomes. Future studies are needed to see if these or other sexually dimorphic neurons mediate pheromone responses, and if so, how sexual differentiation of the brain during the perinatal critical period and puberty mechanistically impacts their form and function.

The development of parental behavior and variable responses to young

Rodents display several stereotyped parental behaviors, such as building nests, nursing, and retrieving wayward pups [23]. The medial preoptic area (MPOA) of the hypothalamus and adjacent ventral regions of the bed nucleus of stria terminalis (vBST) form a brain region critical for development of parental behavior [24]. Lesions of the MPOA/vBST impair parental behavior in rodents without impacting other survival functions of the hypothalamus, and electrical stimulation of the MPOA/vBST conversely promotes parental behavior [24]. Behavioral interaction with pups, or their odors alone, activates subsets of MPOA neurons [19••,24], and genetic approaches revealed that galanin-containing MPOA neurons and other tyrosine hydroxylase-containing hypothalamic neurons govern parental behavior [19••,48].

In rats, a complex re-wiring of the maternal brain occurs late in pregnancy to enable development of parental behavior [24]. Virgin female rats are not maternal, but can learn to care for foster pups. However, mothers display parental behavior due to a series of pregnancy-associated surges in levels of hormones such as prolactin, oxytocin, estrogen, and progesterone, and receptors for these hormones are expressed in the MPOA. Hormone-induced changes in neural circuitry can impact responses to pup pheromones, which are more attractive to lactating mothers [24]. Outputs from the medial amygdala are modified during pregnancy: in sexually naive females, pup pheromones stimulate the VMH and periaqueductal grey, while in mothers, pup pheromones stimulate the MPOA and ventral tegmental area (Figure 2c) [24]. Cellular mechanisms by which pregnancy hormones reroute olfactory circuits are unknown.

Rats and lab mice display several differences in maternal behavior [23,24]. First, sexually naive female mice display maternal behavior to foster pups, suggesting that pregnancy hormone-induced switches in amygdala outputs may be less pronounced. Second, rats use any of several senses to identify pups, with olfaction sufficient but not independently required. Lab mice instead rely heavily on olfactory cues, as impairment or silencing of main olfactory pathways in mice induces severe maternal behavior deficits [18,49,50]. Interestingly, male mice display a range of behaviors from infanticide to parental behavior that varies with personal experience [17,19••]. Virgin males often kill foreign pups while recently mated males display parental behavior. Genetic or surgical removal of the vomeronasal organ disrupts infanticide in virgin males and promotes parental behavior [17,19••]. Perhaps the choice between infanticide and parental behavior

involves the relative strength of sensory signals from main and accessory olfactory pathways, with relative pathway weights shaped by mating experience in males.

Conclusions

Pheromone processing by the mouse brain is highly streamlined, providing a powerful opportunity to study how variable behaviors arise to controlled sensory stimuli. Responses to males and pups, and the odors they emit, vary by recipient. State-dependent odor processing is not restricted to social cues; for example, processing of food odors varies between hungry and sated individuals. Olfactory circuits are flexibly sculpted by hormone signaling and experience to cause different responses. Modulation occurs at multiple levels within responding neural circuits, including directly in peripheral sensory neurons and in higher order olfactory nuclei. Future research is needed to understand the essential cellular changes that occur in neurons to allow for conditional behavioral responses. Understanding mechanisms by which pheromone responses vary should help explain how behavioral diversity arises across animal populations.

Conflict of interest statement

Nothing declared.

Acknowledgments

This work was supported by grants to SDL (NIH: RO1DC013289) and LS (NIH: RO1 DC006885 and Ellison Medical Foundation: NR-SS-0107-12).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Liberles SD: **Mammalian pheromones**. *Annu Rev Physiol* 2014, **76**:151-175.
2. Stowers L, Kuo TH: **Mammalian pheromones: emerging properties and mechanisms of detection**. *Curr Opin Neurobiol* 2015, **34**:103-109.
3. Ferrero DM, Moeller LM, Osakada T, Horio N, Li Q, Roy DS, Cichy A, Spehr M, Touhara K, Liberles SD: **A juvenile mouse pheromone inhibits sexual behaviour through the vomeronasal system**. *Nature* 2013, **502**:368-371.
4. Haga S, Hattori T, Sato T, Sato K, Matsuda S, Kobayakawa R, Sakano H, Yoshihara Y, Kikusui T, Touhara K: **The male mouse pheromone esp1 enhances female sexual receptive behaviour through a specific vomeronasal receptor**. *Nature* 2010, **466**:118-122.
5. Kimchi T, Xu J, Dulac C: **A functional circuit underlying male sexual behaviour in the female mouse brain**. *Nature* 2007, **448**:1009-1014.
6. Leypold BG, Yu CR, Leinders-Zufall T, Kim MM, Zufall F, Axel R: **Altered sexual and social behaviors in trp2 mutant mice**. *Proc Natl Acad Sci U S A* 2002, **99**:6376-6381.
7. Mandiyan VS, Coats JK, Shah NM: **Deficits in sexual and aggressive behaviors in cnga2 mutant mice**. *Nat Neurosci* 2005, **8**:1660-1662.
8. Oboti L, Perez-Gomez A, Keller M, Jacobi E, Birnbaumer L, Leinders-Zufall T, Zufall F, Chamero P: **A wide range of pheromone-stimulated sexual and reproductive behaviors in female mice depend on g protein galphao**. *BMC Biol* 2014, **12**:31.
9. Stowers L, Holy TE, Meister M, Dulac C, Koentges G: **Loss of sex discrimination and male-male aggression in mice deficient for trp2**. *Science (New York, NY)* 2002, **295**:1493-1500.
10. • Dey S, Chamero P, Pru JK, Chien MS, Ibarra-Soria X, Spencer KR, Logan DW, Matsunami H, Peluso JJ, Stowers L: **Cyclic regulation of sensory perception by a female hormone alters behavior**. *Cell* 2015, **161**:1334-1344.

VNO sensory neurons display state-dependent responses to pheromones.

11. Li Q, Korzan WJ, Ferrero DM, Chang RB, Roy DS, Buchi M, Lemon JK, Kaur AW, Stowers L, Fendt M, Liberles SD: **Synchronous evolution of an odor biosynthesis pathway and behavioral response**. *Curr Biol* 2013, **23**:11-20.
12. Matsuo T, Hattori T, Asaba A, Inoue N, Kanomata N, Kikusui T, Kobayakawa R, Kobayakawa K: **Genetic dissection of pheromone processing reveals main olfactory system-mediated social behaviors in mice**. *Proc Natl Acad Sci U S A* 2015, **112**:E311-E320.
13. Roberts SA, Simpson DM, Armstrong SD, Davidson AJ, Robertson DH, McLean L, Beynon RJ, Hurst JL: **Darcin: A male pheromone that stimulates female memory and sexual attraction to an individual male's odour**. *BMC Biol* 2010, **8**:75.
14. Chamero P, Katsoulidou V, Hendrix P, Bufe B, Roberts R, Matsunami H, Abramowitz J, Birnbaumer L, Zufall F, Leinders-Zufall T: **G protein g(alpha)o is essential for vomeronasal function and aggressive behavior in mice**. *Proc Natl Acad Sci U S A* 2011, **108**:12898-12903.
15. Chamero P, Marton TF, Logan DW, Flanagan K, Cruz JR, Saghatelian A, Cravatt BF, Stowers L: **Identification of protein pheromones that promote aggressive behaviour**. *Nature* 2007, **450**:899-902.
16. Kaur AW, Ackels T, Kuo TH, Cichy A, Dey S, Hays C, Kateri M, Logan DW, Marton TF, Spehr M, Stowers L: **Murine pheromone proteins constitute a context-dependent combinatorial code governing multiple social behaviors**. *Cell* 2014, **157**:676-688.
17. Tachikawa KS, Yoshihara Y, Kuroda KO: **Behavioral transition from attack to parenting in male mice: a crucial role of the vomeronasal system**. *J Neurosci* 2013, **33**:5120-5126.
18. Wang Z, Storm DR: **Maternal behavior is impaired in female mice lacking type 3 adenylyl cyclase**. *Neuropsychopharmacology* 2011, **36**:772-781.
19. •• Wu Z, Autry AE, Bergan JF, Watabe-Uchida M, Dulac CG: **Galanin neurons in the medial preoptic area govern parental behaviour**. *Nature* 2014, **509**:325-330.

Hypothalamic galanin neurons govern parental behavior.

20. Brunet LJ, Gold GH, Ngai J: **General anosmia caused by a targeted disruption of the mouse olfactory cyclic nucleotide-gated cation channel**. *Neuron* 1996, **17**:681-693.
21. Logan DW, Brunet LJ, Webb WR, Cutforth T, Ngai J, Stowers L: **Learned recognition of maternal signature odors mediates the first suckling episode in mice**. *Curr Biol* 2012, **22**:1998-2007.
22. Boillat M, Challet L, Rossier D, Kan C, Carleton A, Rodriguez I: **The vomeronasal system mediates sick conspecific avoidance**. *Curr Biol* 2015, **25**:251-255.
23. Dulac C, O'Connell LA, Wu Z: **Neural control of maternal and paternal behaviors**. *Science* 2014, **345**:765-770 New York, NY.
24. Numan M, Fleming AS, Levy F: **Maternal behavior**. In *Knobil and Neill's Physiology of Reproduction*, vol 2. Edited by Neill JD. St. Louis, MO: Elsevier Academic Press; 2006:1921-1993.
25. Boehm T, Zufall F: **Mhc peptides and the sensory evaluation of genotype**. *Trends Neurosci* 2006, **29**:100-107.
26. Ferrero DM, Liberles SD: **The secret codes of mammalian scents**. *Wiley Interdiscip Rev Syst Biol Med* 2010, **2**:23-33.

27. •• Fu X, Yan Y, Xu PS, Geerlof-Vidavsky I, Chong W, Gross ML, Holy TE: **A molecular code for identity in the vomeronasal system**. *Cell* 2015, **163**:313-323.
Circulating female hormones are emitted into the environment, where they serve as chemosensory cues that evoke sex-specific behaviors.

28. •• Haga-Yamanaka S, Ma L, He J, Qiu Q, Lavis LD, Looger LL, Yu CR: **Integrated action of pheromone signals in promoting courtship behavior in male mice**. *Elife* 2014, **3**:e03025.
Sulfated estrogens activate a clade of V1Rs and control courtship behaviour.

29. Kimoto H, Sato K, Nodari F, Haga S, Holy TE, Touhara K: **Sex- and strain-specific expression and vomeronasal activity of mouse esp family peptides**. *Curr Biol* 2007, **17**:1879-1884.

30. Brechbuhl J, Moine F, Klaey M, Nenniger-Tosato M, Hurni N, Sporkert F, Giroud C, Broillet MC: **Mouse alarm pheromone shares structural similarity with predator scents**. *Proc Natl Acad Sci U S A* 2013, **110**:4762-4767.

31. Isogai Y, Si S, Pont-Lezica L, Tan T, Kapoor V, Murthy VN, Dulac C: **Molecular organization of vomeronasal chemoreception**. *Nature* 2011, **478**:241-245.

32. Nodari F, Hsu FF, Fu X, Holekamp TF, Kao LF, Turk J, Holy TE: **Sulfated steroids as natural ligands of mouse pheromone-sensing neurons**. *J Neurosci* 2008, **28**:6407-6418.

33. Clodfelter KH, Holloway MG, Hodor P, Park SH, Ray WJ, Waxman DJ: **Sex-dependent liver gene expression is extensive and largely dependent upon signal transducer and activator of transcription 5b (stat5b): Stat5b-dependent activation of male genes and repression of female genes revealed by microarray analysis**. *Mol Endocrinol* 2006, **20**:1333-1351.

34. Cherian S, Wai Lam Y, McDaniels I, Struziak M, Delay RJ: **Estradiol rapidly modulates odor responses in mouse vomeronasal sensory neurons**. *Neuroscience* 2014, **269**:43-58.

35. Root CM, Denny CA, Hen R, Axel R: **The participation of cortical amygdala in innate, odour-driven behaviour**. *Nature* 2014, **515**:269-273.

36. Choe HK, Reed MD, Benavidez N, Montgomery D, Soares N, Yim YS, Choi GB: **Oxytocin mediates entrainment of sensory stimuli to social cues of opposing valence**. *Neuron* 2015, **87**:152-163.

37. Wilson DA, Sullivan RM: **Cortical processing of odor objects**. *Neuron* 2011, **72**:506-519.

38. Yang CF, Shah NM: **Representing sex in the brain, one module at a time**. *Neuron* 2014, **82**:261-278.

39. Samuelsen CL, Meredith M: **Categorization of biologically relevant chemical signals in the medial amygdala**. *Brain Res* 2009, **1263**:33-42.

40. Swanson LW: **Cerebral hemisphere regulation of motivated behavior**. *Brain Res* 2000, **886**:113-164.

41. Lee H, Kim DW, Remedios R, Anthony TE, Chang A, Madisen L, Zeng H, Anderson DJ: **Scalable control of mounting and attack by esr1+ neurons in the ventromedial hypothalamus**. *Nature* 2014, **509**:627-632.

42. Lin D, Boyle MP, Dollar P, Lee H, Lein ES, Perona P, Anderson DJ: **Functional identification of an aggression locus in the mouse hypothalamus**. *Nature* 2011, **470**:221-226.

43. •• Bergan JF, Ben-Shaul Y, Dulac C: **Sex-specific processing of social cues in the medial amygdala**. *Elife* 2014, **3**:e02743.
In vivo recordings in the medial amygdala reveal sex-dependent pheromone processing.

44. Choi GB, Dong HW, Murphy AJ, Valenzuela DM, Yancopoulos GD, Swanson LW, Anderson DJ: **Lhx6 delineates a pathway mediating innate reproductive behaviors from the amygdala to the hypothalamus**. *Neuron* 2005, **46**:647-660.

45. Hong W, Kim DW, Anderson DJ: **Antagonistic control of social versus repetitive self-grooming behaviors by separable amygdala neuronal subsets**. *Cell* 2014, **158**:1348-1361.

46. Unger EK, Burke KJ Jr, Yang CF, Bender KJ, Fuller PM, Shah NM: **Medial amygdalar aromatase neurons regulate aggression in both sexes**. *Cell Rep* 2015, **10**:453-462.

47. •• Yang CF, Chiang MC, Gray DC, Prabhakaran M, Alvarado M, Juntti SA, Unger EK, Wells JA, Shah NM: **Sexually dimorphic neurons in the ventromedial hypothalamus govern mating in both sexes and aggression in males**. *Cell* 2013, **153**:896-909.
Progesterone receptor-expressing neurons in the hypothalamus control different behaviors in males and females.

48. Scott N, Prigge M, Yizhar O, Kimchi T: **A sexually dimorphic hypothalamic circuit controls maternal care and oxytocin secretion**. *Nature* 2015, **525**:519-522.

49. Gandelman R, Zarrow MX, Denenberg VH, Myers M: **Olfactory bulb removal eliminates maternal behavior in the mouse**. *Science* 1971, **171**:210-211 (New York, NY).

50. Weiss J, Pyrski M, Jacobi E, Bufe B, Willnecker V, Schick B, Zizzari P, Gossage SJ, Greer CA, Leinders-Zufall T, Woods CG *et al.*: **Loss-of-function mutations in sodium channel nav1.7 cause anosmia**. *Nature* 2011, **472**:186-190.