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The neural circuits of mating and fighting in male mice

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Tinbergen proposed that instinctive behaviors can be divided into appetitive and consummatory phases. During mating and aggression, the appetitive phase contains various actions to bring an animal to a social target and the consummatory phase allows stereotyped actions to take place. Here, we summarize recent advances in elucidating the neural circuits underlying the appetitive and consummatory phases of sexual and aggressive behaviors with a focus on male mice. We outline the role of the main olfactory inputs in the initiation of social approach; the engagement of the accessory olfactory system during social investigation, and the role of the hypothalamus and its downstream pathways in orchestrating social behaviors through a suite of motor actions.

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Mating and aggression are innate social behaviors prevalent across mammalian and non-mammalian species. Pursuit of the underlying neural circuitry responsible for these behaviors has been a goal of neuroscientists for nearly a century. Here we will provide an updated view regarding the neural circuits of mating and aggression with a special focus on mice — a genetically tractable model organism widely used in the laboratory. Sexual and aggressive behaviors are highly sexually dimorphic and thus the underlying neural circuits for these behaviors are likely to be different between sexes. In this review we will focus on male neural circuits, given that this has been the subject of choice for most recent studies. The lack of studies in females is possibly due to concerns about confounding contributions from the estrous cycles and maternal states, the relatively low level of aggression in females or simply out of convention. Fortunately, with NIH's new emphasis on sex balance in animal studies [1], research using female subjects is likely to increase, which will provide a better understating of sex differences in neural circuits of mating and aggression.

Lorenz and Tinbergen proposed that each sequence of instinctive behavior can be divided into a variable appetitive phase and a more rigid consummatory phase [2]. The appetitive phase contains variable seeking actions that bring an organism into contact with a certain stimulus, which would then elicit relatively stereotypic consummatory actions. In rodents, the appetitive phase of both mating and aggression involves approach and investigation of a social stimulus. The subsequent consummatory phase for mating includes mounting, intromission and ejaculation whereas attack is the major consummatory action of aggression. Generally speaking, as mating and aggression advance from the appetitive phase to consummatory phase, the behavioral expression as well as the involved brain regions become increasingly different.

The main olfactory pathway relays information for social approach

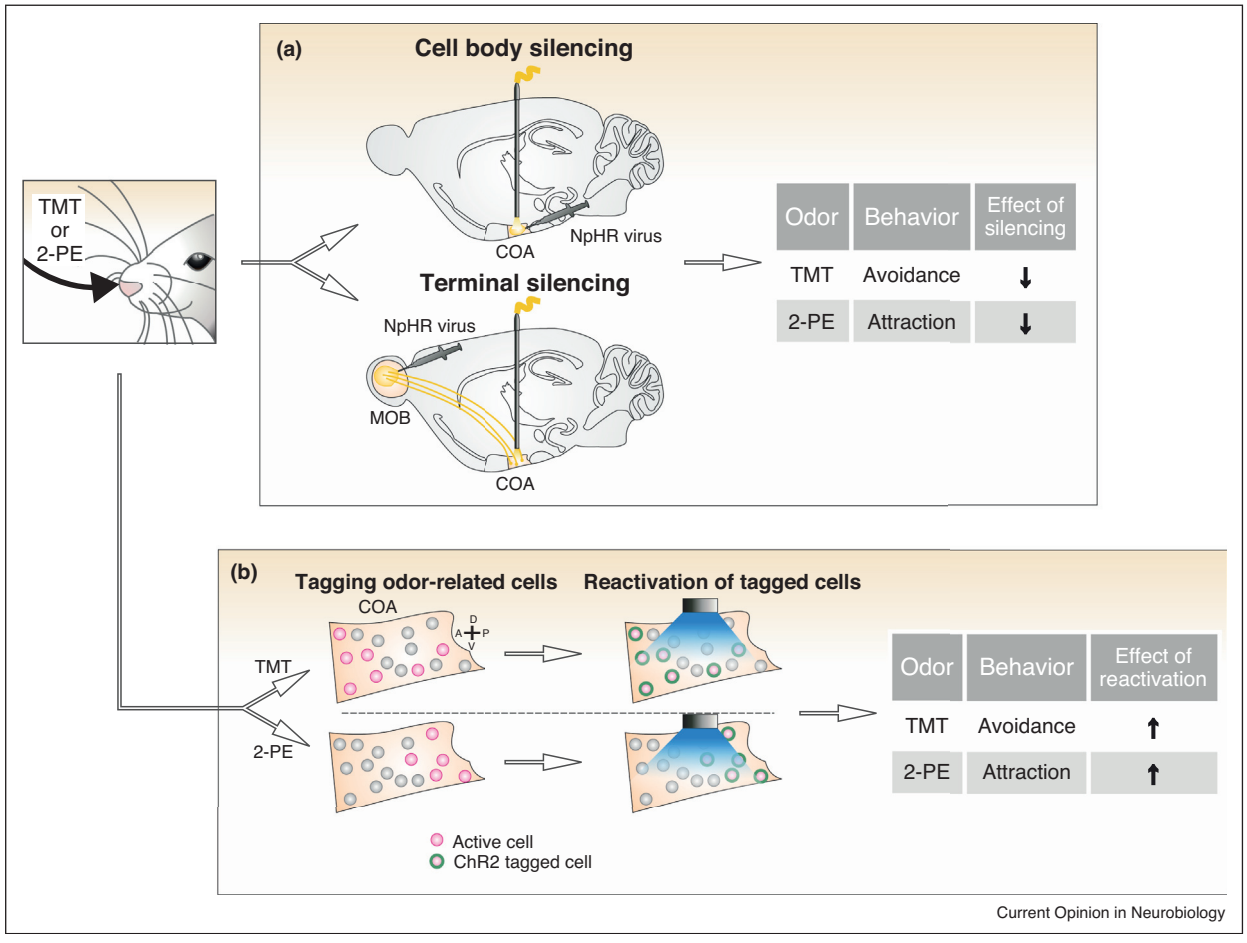
Approach, as a critical appetitive step of mating and aggression, can potentially be triggered by sensory cues that are detectable from a distance, such as auditory, visual and olfactory cues. For rodents, olfactory volatiles play an especially important role relative to other sensory modalities. For example, male mice preferentially approach soiled bedding which is enriched in volatiles from a stranger male over clean bedding but show no preference towards the conspecific in a solid plexi-glass cylinder that blocks the olfactory cues [3].

Which brain regions are involved in detecting a distant conspecific odor before initiating approach? In mice, odors can be detected through either accessory olfactory system (AOS) or the main olfactory system (MOS) [4]. The AOS detects mostly non-volatile odorants including major urinary proteins [5] and steroids [6] through close contact with the source of odor [7,8] and probably contributes minimally to the initial approach. For the MOS, the odor recognition starts from the binding of small volatile molecules to the over ~1000 olfactory receptors in the main olfactory epithelium [9]. Neurons expressing the same olfactory receptor converge onto a pair of glomeruli in the main olfactory bulb (MOB) and thus transform the conspecific odor to a distinctive glomerular

activity map [10–13]. Interestingly, not all components in the conspecific odor contribute equally to the activation map. *In vivo* recording revealed that certain biologically salient cues (e.g. MTMT-a female attractant specifically present in male urine) are overrepresented in the main olfactory bulb [14•].

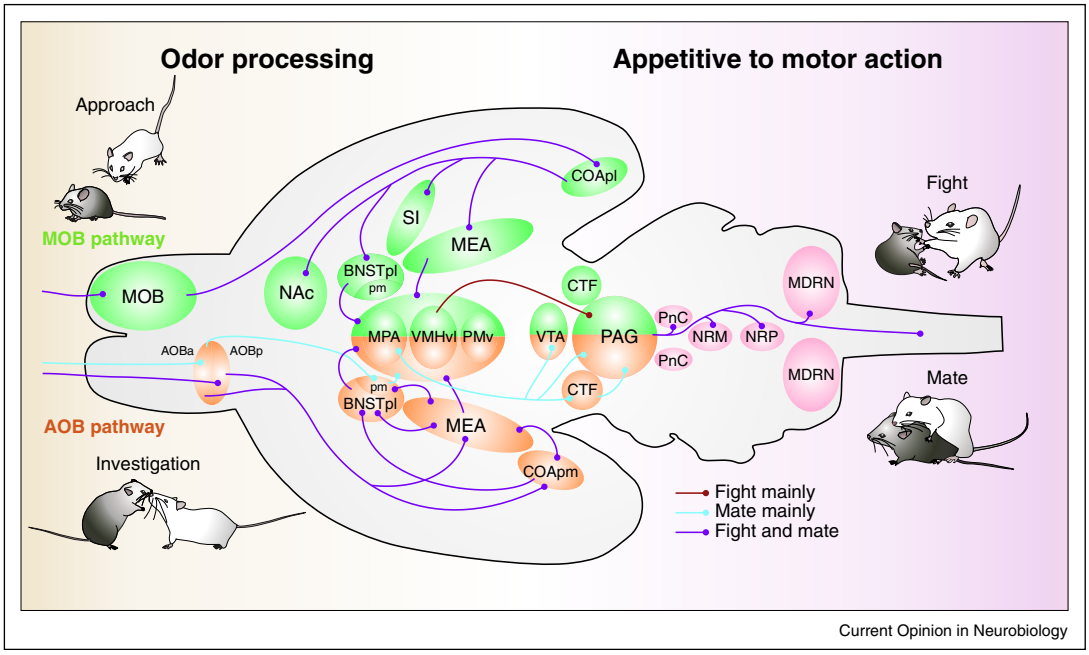
From the main olfactory bulb, the odor information is relayed to five main downstream areas, including the anterior olfactory nucleus, piriform cortex, olfactory tubercle, anterior and posterolateral cortical amygdala (COAa and COApl) and lateral entorhinal cortex [15,16]. Among those regions, the cortical amygdala has been recently suggested to be essential for mediating approach and avoidance behaviors towards innately attractive or aversive odors. This region, unlike the piriform cortex, retains the topographic organization pattern present in the MOB [17,18]. This topographic specificity suggests that if innately attractive or aversive odors evoke distinct glomerular activation patterns in the MOB, this segregation in patterns will be preserved in the COA and could be used to activate innate pathways for approach and avoidance. Indeed, aversive odors, such as TMT (a component of fox feces) activate mainly the anterior COA [19] whereas attractive odors, such as 2-phenylethanol (a component of male mouse feces [20]) activate mainly the posterior COA [21••] (Figure 1). When Root *et al.* optogenetically inhibited either the MOB to COA pathway or cells in the COA, they eliminated the attraction towards 2-phenylethanol and avoidance towards TMT [21••]. Conversely, optogenetic reactivation of the COA population activated by the 2-phenylethanol is appetitive whereas reactivation of the TMT responsive cells is aversive [21••] (Figure 1). Thus, activity in the COApl is essential for the innate approach response towards an attractive odor (Figure 2). One interesting

Figure 1



COApl neurons are essential for innate odor driven avoidance and attraction (Root *et al.* [21••]).
(a) Optogenetic inhibition of cells in the COA (upper) or axonal terminals from the MOB to the COA (lower) eliminated TMT induced avoidance and 2-PE induced attraction. **(b)** Reactivation of odor responsive neurons in COA recapitulates the odor-induced behavioral responses. Using ArcCreERT2 mice, ChR2 is selectively expressed in neural ensembles activated by TMT or 2-PE in COA (left). Light activation of the ChR2 expressing cells recapitulates the avoidance and attraction behaviors elicited by TMT and 2-PE, respectively (middle and right). COA: cortical amygdala; MOB: main olfactory bulb; TMT: 2,3,5-trimethyl-3-thiazoline; 2-PE: 2-Phenylethanol.

Figure 2



Neuronal circuits implicated in different phases of aggression and sexual behaviors in rodents. Red, blue and purple lines indicate pathways mainly involved in fighting, mating or both. AOBa: anterior accessory olfactory bulb; AOBp: posterior AOB; BNSTpl/pm: posterolateral/posteromedial bed nucleus of the stria terminalis; COApl/pm: posterolateral/posteromedial cortical amygdala; CTF: central tegmental field; MDRN: medullary reticular nucleus; MEA: medial amygdala; MOB: main olfactory bulb; MPA: medial preoptic area; NAc: nucleus of accumbens; NRM: nucleus of raphe magnus; NRP: nucleus of raphe pallidus; PAG: periaqueductal gray; PnC: caudal Pontine; SI: substantia innominate; VTA: ventral tegmental area.

feature of the COApl cells that receives little attention is its abundant expression of estrogen receptor alpha (ERα) and androgen receptor (AR) [22]. The highly enriched hormone receptors suggest that the responsiveness of the COApl cells and correspondingly the attractiveness of odors may be under the regulation of the circulating sex hormones. The levels of these sex hormones can change drastically during development, aging and after various social experience (e.g. winning a fight) and could modify the role of the COApl in approach behavior [23].

Although the neural activity in the COApl during social approach remains unknown, high levels of expression of Fos, a surrogate molecular marker for neural activity, are observed after episodes of male or female chemo-investigation [24•]. One interesting question is whether the approach-promoting conspecific volatiles detected by the COA provide sufficient information to identify the social target as an opponent or a potential mate. Our previous Fos Catfish mapping (a method that allows the comparison of neural activity after two separable behaviors within a single animal) revealed that a relatively large percentage of mating-activated and fighting-activated cells overlap in the COApl [25••], suggesting that male and female odor may recruit similar COA cells that carry little information regarding the sex identity of the targeted animal.

Major targets of the COApl include the bed nucleus of stria terminalis (anterior, posterolateral and transverse nuclei), medial (posterodorsal and anterior) and central amygdala, ventral subiculum (SUBv), ventral part of the lateral septum (LSv), substantia innominate (SI), nucleus accumbens (NAc) and infralimibic area [26] (Figure 2). Among those downstream areas, the NAc and SI have been identified as potential regions for regulating social interest. Mice that experience repeated defeat develop a long-lasting aversion to social contact. This change in behavior is accompanied by increased brain-derived neurotrophic factor (BDNF) in the dopaminergic cells in the ventral tegmental area (VTA), and increased dopamine release as well as dramatic changes in the gene expression pattern in the NAc, a major downstream area of the VTA [27,28]. Blockage of BDNF activity in the VTA reverses changes in gene expression pattern in the NAc and restores the social approach in defeated male mice [27]. In addition, comparison of the Prairie and montane vole, two species that are closely related but exhibit opposite social phenotypes, has implicated the SI in promoting social interest. Prairie voles are monogamous, seek out social contact, and form long-lasting social bonds. In contrast, montane voles are promiscuous and avoid social contact, except for the purpose of mating. In monogamous social voles, the vasopressin receptor 1a

(VR1a) is expressed at much higher levels in the ventral pallidum (which contains a large part of SI) [29]. Strikingly, increasing the VR1a expression in the ventral pallidum significantly enhances social interaction in the promiscuous voles [30]. Future pathway specific functional manipulations will help address whether the COApl initiates approaching behavior through its projections to these two areas.

Social investigation activates the accessory olfactory system

Once the animal reaches a conspecific target, it often closely investigates the target. The length of investigation depends on the familiarity of the intruder [31] and the experience of the animal [32] and can range from a few seconds to several minutes. Most of the investigation is directed towards the anal and facial regions of the intruder which are rich sources of chemical signals that convey information about sex and strain, namely pheromones [33,34]. Pheromones are actively pumped into a liquid filled lumen of the vomeronasal organ (VNO) lined up with specialized receptors [35]. With each bout of investigation, the concentration of pheromone cues increases in the VNO [36]. Within a bout of investigation, the activity of mitral cells in the AOB gradually increases over the course of 20 s after initial contact and remains active for 10–30 s after cessation of direct interaction [8].

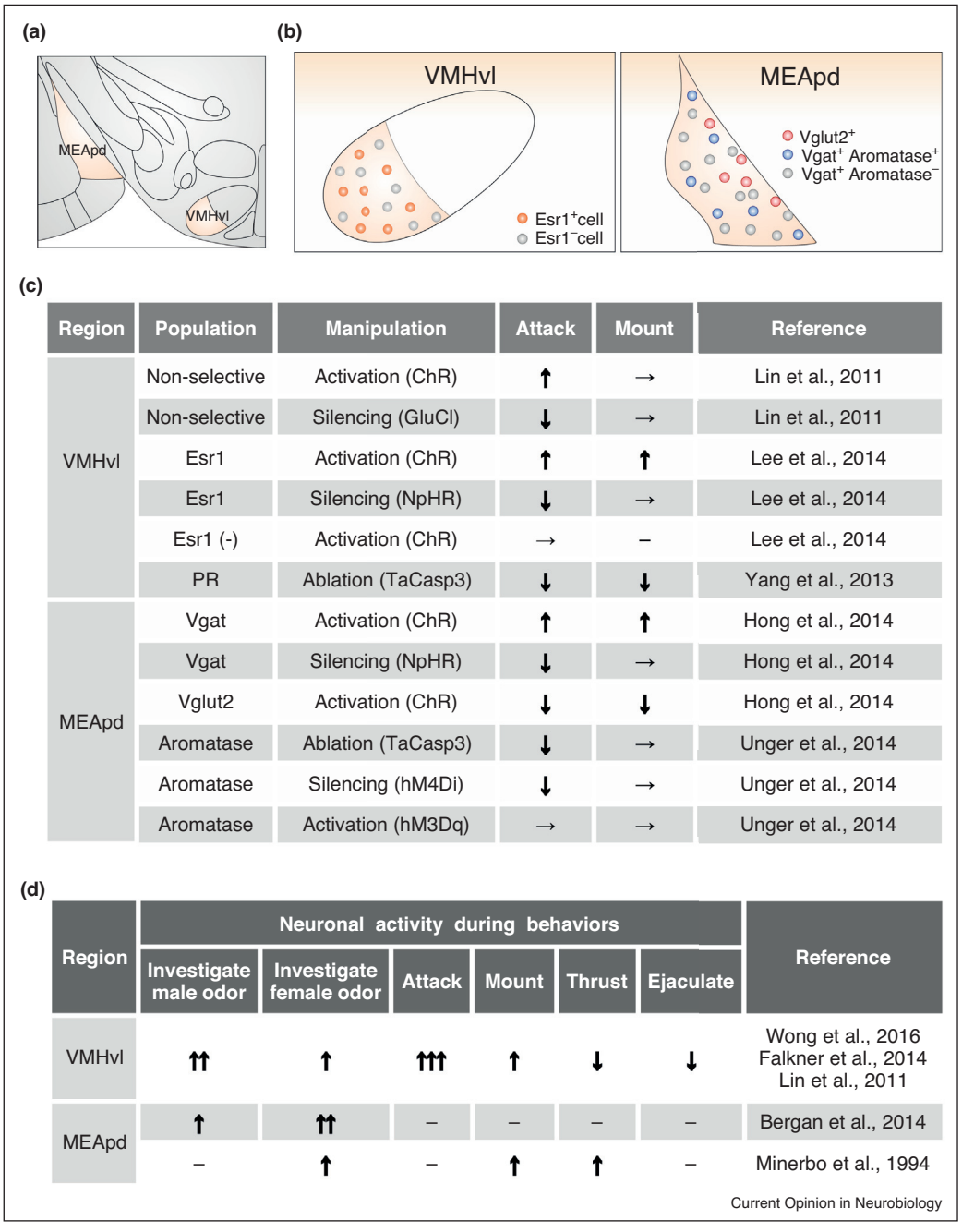
Investigation of male and female pheromones results differential activation patterns in the AOB: male mice exposed to female urine showed a strong Fos induction in the rostral AOB whereas male urine induced a bias distribution of Fos in the posterior AOB [37•]. This differential activation pattern is likely to result in differential activation patterns in the central brain. Whereas both rostral and caudal AOB project heavily to the medial amygdala (MEA), posteromedial COA (COApm) and bed nucleus of the accessory olfactory tract (BOAT), only rostral AOB projects to the BNST, posteromedial part (BNSTpm) [38•] (Figure 2). Thus, BNSTpm may be preferentially activated during female but not male investigation. Consistent with this, a significant increase in Fos expression was only observed in the BNSTpm after female investigation but not male investigation [24•]. In line with these data, large electrical lesions encompassing both BNSTpm and its lateral part significantly reduced chemoinvestigation of females in male hamsters [39]. It is worth noting that posterodorsal part of the MEA, the other major target of the AOB, also projects heavily to the BNSTpm [40]. Thus, male pheromones could still have indirect access to the BNSTpm (Figure 2). However, MEApd projection cells are largely GABAergic [41] whereas AOB mitral cells are exclusively glutamatergic [42]. Thus, these two pathways likely influence the activity of BNSTpm cells in opposite directions. Future studies using more precise functional manipulation and recording techniques will help understand any potentially differential involvement of the BNSTpm in male and female investigation.

MEApd is arguably the most studied downstream targets of the AOB [43]. Indeed, multiple lines of evidence suggest the activation of the MEApd during social behaviors. Immediate early gene mapping studies consistently reported increased Fos expression in the MEApd after mating, fighting or conspecific investigation [25••,39,44,45]. Electrophysiological recordings in anaesthetized animals showed that MEA cells respond robustly to conspecific pheromones especially from the opposite sex [46•]. Recordings made in freely moving male rats revealed elevated MEA cell activity during both investigation of females and during discrete copulatory events [47]. Consistent with this, lesioning the MEA in several species robustly impaired male sexual behaviors but resulted in minor or inconsistent effects on male aggression [48–55]. However, recent data from cell type specific functional manipulations of the MEA suggest a more dominant role of the MEApd in aggression in comparison to mating [56••,57•] (Figure 3). Ablation of aromatase expressing cells in the MEApd significantly increased the latency to attack and the total number of attack events but did not affect male sexual behaviors [57•]. Optogenetic inhibition of the GABAergic cells in the MEApd instantaneously halted ongoing attack but failed to disrupt ongoing intromission ([56••] and personal communication with Weizhe Hong, UCLA). Although mounting can be induced by optogenetic activation of GABAergic cells in the MEApd, it is relatively rare in comparison to aggression which can be elicited in 100% of test animals [56••] (Figure 3). The discrepancy between the results from recent cell-type specific manipulations and previous non-selective lesion studies could suggest the existence of additional subpopulations in the MEA that are more critically involved in mating or that other AOB targets such as the BNSTpm may play a more essential role in male sexual behavior than previously appreciated.

Other AOB targets, such as the BOAT, MEAa, MEApv and COApm are less well studied although all these areas show strong Fos induction after encounter with conspecific stimulus [39,58,59]. Do they play redundant, distinct or counter-acting roles in mediating social behaviors? Functional manipulation and recordings in each of these areas will be needed to address this question and provide a more comprehensive understanding of how pheromonal information is processed during social investigation.

The role of the main olfactory input is not limited to the approach phase of social behaviors. In fact, MOB inputs during social investigation are probably as critical as AOB inputs and may also be required to promote consummatory actions. Unconditional disruption of genes that encode signal transduction proteins that are required for

Figure 3



(c)

Region	Population	Manipulation	Attack	Mount	Reference
VMHvl	Non-selective	Activation (ChR)	↑	→	Lin et al., 2011
	Non-selective	Silencing (GluCl)	↓	→	Lin et al., 2011
	Esr1	Activation (ChR)	↑	↑	Lee et al., 2014
	Esr1	Silencing (NpHR)	↓	→	Lee et al., 2014
	Esr1 (-)	Activation (ChR)	→	–	Lee et al., 2014
	PR	Ablation (TaCasp3)	↓	↓	Yang et al., 2013
MEApd	Vgat	Activation (ChR)	↑	↑	Hong et al., 2014
	Vgat	Silencing (NpHR)	↓	→	Hong et al., 2014
	Vglut2	Activation (ChR)	↓	↓	Hong et al., 2014
	Aromatase	Ablation (TaCasp3)	↓	→	Unger et al., 2014
	Aromatase	Silencing (hM4Di)	↓	→	Unger et al., 2014
	Aromatase	Activation (hM3Dq)	→	→	Unger et al., 2014

(d)

Region	Neuronal activity during behaviors						Reference
	Investigate male odor	Investigate female odor	Attack	Mount	Thrust	Ejaculate	
VMHvl	↑↑	↑	↑↑↑	↑	↓	↓	Wong et al., 2016 Falkner et al., 2014 Lin et al., 2011
MEApd	↑	↑↑	–	–	–	–	Bergan et al., 2014
	–	↑	–	↑	↑	–	Minerbo et al., 1994

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The roles of the MEApd and VMHvl in male mouse aggression and mating.
(a) Coronal atlas illustrating the MEApd and VMHvl. **(b)** Molecularly defined subpopulations in the VMHvl (left) and MEApd (right). **(c)** Summary of behavioral effects induced by functional manipulations in the MEApd and VMHvl on aggression and mounting. ↑: increase behavior; ↓: decease behavior; →: no change in behavior. -: not reported. **(d)** Summary of *in vivo* electrophysiological responses of cells in the VMHvl and MEApd during sampling of male and female conspecific odors or various phases of aggression and mating. ↑: activation, ↓: inhibition. Number of Arrows indicates the magnitude of the responses across the population.

activating olfactory neurons resulted in the impairment of several social behaviors [60–62]. More recently, Mastuo *et al.* selectively deleted the dorsal part of the MOB and found that the manipulation reduced aggression towards males and also ultrasonic vocalization towards females, whereas copulatory behavior remained relatively unchanged [63••]. However, these mutant mice lacking the dorsal MOB showed mostly normal investigation

towards a conspecific and the activity in the AOB was unchanged. These data suggest that MOB input is required for the initiation of certain aspects of consummatory social actions even after the contact with the stimulus animal was successfully established.

The hypothalamus plays an essential role in aggressive and sexual behaviors

The medial hypothalamus is the most prominent downstream target of both the medial and cortical amygdaloid areas. Not surprisingly, this region has been identified as the most critical site for expression of innate social behaviors based on decades of lesion, stimulation, hormone implantation and electrophysiological recording experiments. Here, we review some recent progress regarding the role of the medial preoptic area (MPA) and the ventrolateral part of the ventromedial hypothalamus (VMHvl) in mating and aggression. Both of these areas express high level of hormone receptors and integrate inputs from the main and accessory olfactory systems.

A series of classic electric stimulation studies mapped out a 'hypothalamic attack area (HAA)' from which attack can be induced in rats. This region includes a part of the VMHvl and its anterior and lateral structures [64,65]. More recently, our lab and others pinpointed the VMHvl as a critical site for eliciting male mouse aggression. The VMHvl spans approximately 700 μm along the anterior-posterior axis, 400 μm medial-laterally and 200–400 μm dorsal-ventrally depending on the anterior-posterior position. We estimate that it contains approximately 10,000 neurons, most of which (>90%) are glutamatergic [41]. Non-cell type specific pharmacogenetic inhibition, optogenetic inhibition of the Esr1 expressing cells or killing the progesterone receptor (PR) expressing cells in the VMHvl all effectively suppressed natural inter-male attack [25••,66,67••]. Conversely, optogenetic activation of the VMHvl cells, either non-selectively or selectively in the Esr1 population induced attack towards castrated males, females and even inanimate objects [25••,67••]. Electrophysiological recording showed that a quarter to a half of VMHvl cells respond maximally during attack and also carry information regarding the imminence and intensity of future attacks [25••,68,69•]. During interaction with a female, a subset of VMHvl cells are also activated (but to a much lesser extent) and the majority of the female-excited cells overlap with male excited cells [25••,68]. Female-excited VMHvl cells were most active during female investigation and initial mounting. During intromission and ejaculation, the female-excited cells gradually decreased activity and as a population the VMHvl activity decreases [25••]. Consistent with the low level of activity increase in the VMHvl during sexual behaviors, no change in mating was observed during optogenetic inhibition of Esr1 cells or non-selective pharmacogenetic inhibition of VMHvl cells although ablation of the PR expressing cells reduced mounting and intromission events [25••,66,67••] (Figure 3). Thus, whereas the VMHvl is indispensable for male aggression, it may play a subsidiary role in promoting male sexual behavior. This role may possibly include facilitating mount initiation and the transition to intromission.

Unlike the VMHvl, the MPA appears to be indispensable for male sexual behavior based on numerous classical lesion, stimulation, hormone implantation and pharmacological studies (Reviewed in [70]). Unfortunately, research effort along this direction has diminished in recent years despite the fact that our understanding of the MPA function is far from complete. MPA is a large structure, spanning approximately 1.2 mm along the anterior-posterior axis. It converges both olfactory inputs from the amygdala and bed nucleus of stria terminalis and the somatosensory inputs from the genital area via the central tegmental field [71,72], a region that becomes highly active during penile stimulation and ejaculation [73–76]. The MPA is heterogeneous, containing a variety of neuropeptides (e.g. calbindin, galanin, neurotensin and enkephalin), neurotransmitters (GABA and glutamate), hormone receptors (Esr1 and AR) and receiving a variety of neuromodulatory and neuropeptergic inputs (e.g. neuropeptide Y, oxytocin, serotonin) (www.brain-map.org) [77,78]. Further complicating this heterogeneity, tracing studies revealed distinct input and output patterns from each subdivisions of the MPA [79]. Thus, the MPA contains a cluster of subregions, each with different molecular features, projection patterns and possibly non-overlapping roles in sexual behaviors. For example, a specific subregion of the MPA (posterodorsal preoptic nucleus, a small cluster of cells situated in the posterior dorsal part the MPA) was only found active after repeated ejaculations [80]. While the role of the MPA in male sexual behavior is well established, many details remain to be filled in.

The role of the MPA in aggression remains unclear. Some studies reported that the MPA is active during aggression [81], but others failed to find such an involvement of the MPA [60,82]. This discrepancy in results could be partly due to the different MPA subregions targeted in each study. Veening *et al.* noticed that whereas the anterior MPOA was activated only after mating, the posterior MPA was activated after both male and fighting [81], suggesting that the posterior MPA may be more relevant for aggression. Future studies using refined cell type specific manipulation and recording tools will be especially useful in teasing apart the functions of individual MOPA cell groups in social behaviors (e.g. [82]).

Although the review focuses on results from rodents, the functions of the VMHvl and MPA are evolutionarily conserved. In visually dominant animals, such as birds and primates, the MPA and VMH remain the key sites for mating and aggression [83–86]. How socially relevant

information from other sensory systems, such as vision, reaches and informs those hypothalamic areas is largely unknown and represents an important knowledge gap.

The motor output of social behaviors beyond the hypothalamus

The activity in the hypothalamus ultimately needs to propagate to motoneurons to initiate discrete mating and aggression related movements, such as mount, chase, circle, lunge and bite. The precise pathway information from the hypothalamus to the motoneurons is not completely understood. In 1990, Holstege *et al.* proposed two parallel pathways governing the motor outputs. One is the well-known voluntary motor system involving the motor cortex, the other is so-called 'emotional motor system' involving direct projections from the limbic system (including hypothalamus, amygdala, bed nucleus of stria terminalis and prefrontal cortex) to the brainstem and spinal cord [87,88]. The existence of the emotional motor pathway is evident from hemiplegic patients with damage to corticobulbar fibers. Although those patients suffer from paresis of the lower face on one side, they are able to smile symmetrically when they, for instance, enjoy a joke. This example and many others illustrate that there exists a complete dissociation between the voluntary and emotional routes to control motor neurons. In rodents, lesion and tracing studies suggest that most of innate social behavior related movements depend little on the motor cortex. In extreme cases, neonatally decorticated rats fight and copulate nearly indistinguishably from their intact counterparts [89–91].

The periaqueductal gray (PAG) represents one of the most important relays between the hypothalamus and the motor neurons in the spinal cord. It is the major midbrain target of the MPA and the VMHvl as well as other hypothalamic nuclei [79,92–94]. Tracing studies reveal that PAG neurons project to the nucleus raphe magnus (NRM) and pallidus (NRP), the ventral part of the caudal pontine, the medullary reticular formation and directly to the spinal cord [95–98]. The PAG projecting brainstem areas in turn project diffusely, but very strongly to all parts of the gray matter throughout the length of the spinal cord [99–101]. Thus, the PAG provides a potential access point for the hypothalamus to directly control the spinal cord motor neurons. To illustrate this, when the pathway between the dorsomedial part of the VMH, a region essential for predator defense, and the PAG was optogenetically activated, the animal showed instantaneous immobility [102•]. Although pathway specific activation between the hypothalamus and PAG has not yet been reported in the context of aggression, the VMHvl, including the $Esr1^{+}/PR^{+}$ subpopulation, projects heavily to the dorsomedial and lateral columns of the PAG [66,92]. These PAG columns also express high level of Fos after aggressive behaviors [44,103]. Limited electrophysiological recordings revealed that cells related to fighting exist in the PAG [104]. Electric stimulation of the PAG could elicit attack though it was often accompanied by motor disturbance [105]. Electric lesion in the PAG decreased natural aggression and increased the current threshold required to induce attack from the hypothalamus [106].

Several lines of evidence suggest a role of the PAG in sexual behavior although it remains unclear whether the role is behavior-promoting or suppressing. Increased Fos expression was found in the dorsal and ventral PAG after mating [74] (but see [44]). Medial preoptic cells that are active during mating project to the lateral PAG [107]. However, lesioning a large part of the PAG accelerated instead of suppressing mounting behaviors [108], suggesting that PAG may play an inhibitory role in sexual behavior. Consistent with this hypothesis, recent tracing studies show that projection from the MPA to PAG may be originated largely from GABAergic cells rather than glutamatergic cells (www.brain-map.org experiment ID: 305270515 and 292123352). Thus, during natural sexual behaviors, MPA inputs to the PAG may facilitate the sexual behaviors by inhibiting cells in the PAG.

In contrast to PAG mediated motor actions, many other types of actions are mediated through striatal circuits. Do the striatal motor circuits play any role in mating and fighting? In a widely cited paper, Mogenson *et al.* proposed that the ventral tegmental area (VTA) may link hypothalamic output to the striatum [109]. In this model, the hypothalamus specifies the goal of the future actions and then relays this information through the VTA to the striatum which then initiates the appropriate motor actions to achieve the goal. Anatomical tracing supports the existence of a projection from the medial preoptic area to VTA dopaminergic cells which in turn project heavily to the NAc, a major component of the ventral striatum [110,111]. The dopaminergic projection from the VTA to NAc appears to be functionally relevant for social behaviors since changing the activity level of the VTA-NAc projection can bi-directionally modulate the time spent in social interaction [112•]. Microdialysis studies further demonstrated that dramatic increases of dopamine level in the NAc emerge during mating or fighting [47,113]. This increase can be sensed by the downstream dopamine receptor expressing cells and reflected in the activity level of protein kinase A in those cells [114•]. Despite a clear involvement of the NAc during social behavior, a close look at the dynamics of the dopamine activity suggests that the role of the NAc is less likely to be motor related but more likely to be motivation and/or reward associated. For examples, the dopamine increases not only during fighting but also when the animal anticipates a fight and is sustained after a fight [47]. Antagonizing dopamine receptors in the NAc nearly abolished an appetitive operant response for the opportunity to attack but only partially reduced attack during a resident-intruder assay [115]. Whereas dopamine levels in the NAc

increased during repeated copulation with sexually receptive females, no concurrent dopamine increase was detected during interaction with non-receptive females even when the test animal attempted to mount the female for a few times [113]. Thus, the non-striatal emotional motor circuit may be indeed sufficient for the initiation and full execution of fighting and mating while the VTA to NAc pathway may modulate the likelihood and intensity of the behavior at the moment and in the future.

Concluding marks

Through nearly a century of research, key brain regions have been identified as critical nodes for the appetitive and consummatory phases of sexual and aggressive behavior. However, the circuit diagram underlying these behaviors remains incomplete. First, while some headway has been made in a few areas in identifying relevant molecularly defined populations, we still have far to go. Each known relevant regions likely contains heterogeneous subpopulations that may play distinct yet unknown roles in social behaviors. Second, the functional roles and physiological responses of many brain regions that are directly connected to the known aggression/mating loci have not been investigated. Third, basic principles regarding how information is relayed or transformed between brain regions are unclear. Lastly, how circuits are modified with social experience is largely unknown. Future studies can fill these knowledge gaps by taking advantage of the various cell-type and pathway specific manipulation, recoding and tracing tools that are becoming increasingly available in mice and other species. Given that fighting and mating are innate behaviors universal among vertebrate animal species, the basic brain mechanisms underlying those behaviors are likely evolutionarily conserved and principles learned from study in experimental organisms will likely be applicable to humans.

Conflict of interest statement

All authors declare no conflict of interest.

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

- • of special interest
- •• of outstanding interest

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