

# Estrogen Receptor Alpha–Expressing Neurons in Bed Nucleus of the Stria Terminalis and Hypothalamus Encoding Aggression and Mating

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## Abstract

Aggression and mating of male mice are strongly associated with *Esr1*-expressing neurons in the bed nucleus of the stria terminalis (BNSTpr) and hypothalamus in the vomeronasal pathway. By projecting to the downstream hypothalamus, the upstream BNSTpr<sup>Esr1</sup> gates mating and aggression of male mice and maternal behavior of female mice. The medial preoptic area (MPOA) and ventrolateral subdivision of the ventromedial hypothalamus (VMHvl) are two subdivisions of the hypothalamus downstream. In addition to receiving projections from upstream BNSTpr, there is also a mutual projection between MPOA and VMHvl. In the process of transforming sex information into mating and aggression, *Esr1*-expressing neurons in BNSTpr, MPOA, and VMHvl act as messengers of information, finally producing inhibitory or excitatory projection. These projections are different in direction, but they all work together to control the behavior selection that is most conducive to defense and reproduction when male mice encounter female or male mice. Here, we summarized the property and the function of connections between these *Esr1*-expressing neurons in BNSTpr, MPOA, and VMHvl that encode mating and aggression and highlight the importance and benefits of inhibitory projection of *Esr1*-expressing cells in mating and aggression.

**Key words:** aggression; estrogen receptor alpha–expressing neurons; mating; medial preoptic area; the principal nucleus of the bed nucleus of stria terminalis; ventrolateral subdivision of the ventromedial hypothalamus

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## Significance Statement

Neural networks that control mating and aggression have been studied with particular attention to the activity of *Esr1*-expressing cells in recent years. It is highly expressed in regions that regulate social behavior and is critical for aggression and mating behavior in male mice. More and more studies have been conducted on the function of *Esr1*-expressing cells, and further studies on the subtypes of *Esr1*-expressing cells have gradually clarified the molecular mechanism regulating mating and aggression. Here, the opinion deepens our understanding of the function and significance of *Esr1*-expressing cells and underscores the need for continued research on them.

## Introduction

Social behavior can be divided into two stages: the appetitive stage and the consummatory stage. For defense and reproduction, social behavior typically transitions from the appetitive stage to the consummatory stage (Hashikawa et al., 2016). While mating and

aggression take place during the consummatory stage, sniffing is a behavior that happens during the appetitive stage (B. Yang et al., 2022). In order to ensure that animals can respond appropriately to their living environment, external pheromones and internal sex steroid hormones generated by the gonads strictly regulate the neural circuits of mating and aggression (C. F. Yang and Shah, 2014).

On the one hand, sex steroid hormones, including testosterone, estrogen, and progesterone, induce selective expression of genes in neurons that express corresponding receptors including androgen receptor (AR), estrogen receptor alpha (Esr1), estrogen receptor beta (Esr2), and progesterone receptor (PR). Thus, the connection, activity, and state of the neural network may all be impacted by this dynamic regulation (Gegenhuber et al., 2022; Yu et al., 2023). Testosterone attaches to AR and can be aromatized to become estrogen, which then binds to Esr1 and Esr2. Without an efficient aromatase, male mice cannot engage in mating and aggression (Matsumoto et al., 2003). However, testosterone is more important to increase the intensity of male behavior (Juntti et al., 2010). Esr1 mediates the main effect of estrogen on behavior, whereas Esr2 has a more regulatory function (C. F. Yang and Shah, 2014). Additionally, progesterone influences female mating through PR. Both PR and Esr1 are required for female sexual receptivity (Blaustein, 2008).

On the other hand, chemical cues with external pheromones have two forms, i.e., volatile and nonvolatile; the latter is processed by the vomeronasal organ (VNO) pathway (Bergan et al., 2014; Xiao et al., 2022). Sex cues in urine are transmitted by VNO to the accessory olfactory bulb (AOB; Wagner et al., 2006; Bergan et al., 2014; Leroy et al., 2018; Li and Dulac, 2018), which in turn is further transmitted to the medial amygdala (MeA), the principal nucleus of the bed nucleus of stria terminalis (BNSTpr), and two subdivisions of hypothalamus, medial preoptic area (MPOA) and ventrolateral subdivision of the ventromedial hypothalamus (VMHvl; Dong et al., 2001; Bergan et al., 2014; B. Yang et al., 2022; Itakura et al., 2022). Years of study have improved our understanding of social behavior neural network. Attacking and sexual behavior of male mice was disrupted by damage to the VNO, AOB, MeA, BNST, or suppression-specific neurons in these nuclei, and activation of these neurons can lead to mating and aggression (Ropartz, 1968; Rowe and Edwards, 1972; Dominguez et al., 2001; Lin et al., 2011; Hong et al., 2014; Unger et al., 2015; Leroy et al., 2018; B. Yang et al., 2022).

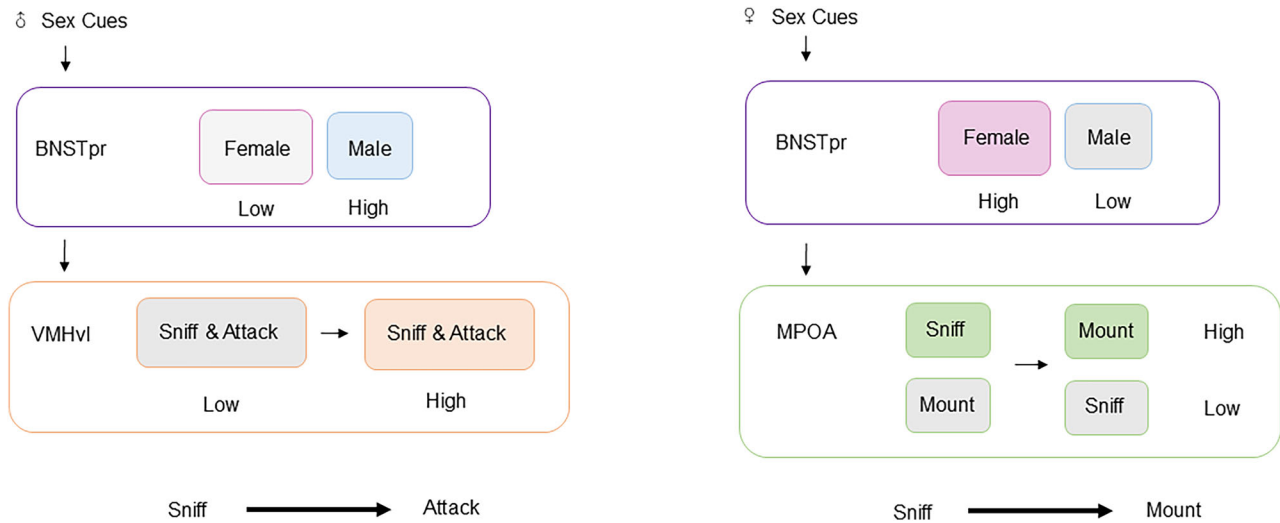
In order to better understand how sex cues are transformed from convergence to divergence, we focused on the neural circuits from BNSTpr to MPOA and VMHvl in the vomeronasal pathway. Recent research has focused on the manifestation of neurons expressing estrogen receptor alpha (Esr1) in response to sex cues and behavior selection (Fig. 1). This has provided insights into the neuronal representation in response to sex and behavior selection in BNSTpr and hypothalamus, as well as the transformation of both regions and the connections between heterogeneous neuron populations in hypothalamus.

Sex hormone receptor-expressing neurons are involved in sex-dependent social behaviors to a large extent (Wu et al., 2009; C. F. Yang and Shah, 2014; B. Yang et al., 2022). In male mice, the distribution and function of Esr1- and aromatase-expressing cells significantly overlap, but the distribution of Esr1-expressing cells is larger than aromatase-expressing cells (Stanić et al., 2014). In BNST, Esr1 is primarily expressed in BNSTpr (BNSTpr<sup>Esr1</sup>; Mei et al., 2023). In the study of the sex-specific neural representation of BNSTpr in male mice, the researchers suspended mice of different sexes in male mice cages. During this time, the male mice in cage are not allowed to mount or attack, only to sniff. At this time, the neurons that were only activated while sniffing female or male mice were classified as female-preferring neurons and male-preferring neurons, respectively (B. Yang et al., 2022). They used single-cell resolution imaging BNSTpr<sup>Esr1</sup> during mating and aggression of male mice to distinguish between male- and female-preferring neurons in BNSTpr and discovered that the ratio of female-preferring to male-preferring neurons in BNSTpr is 2:1 (B. Yang et al., 2022). Furthermore, the sex selection in BNSTpr of male mice was shown to have a greater difference compared with behavior selection. This suggests that BNSTpr plays a significant role in proceeding the sex cues rather than behavior selection, which is supported by the sex-specific responses in two overlapping subsets of BNSTpr<sup>Esr1</sup>, i.e., BNSTpr<sup>Tac1</sup> (Tac1, tachykinin 1, a subset of BNSTpr<sup>Aro</sup> neurons) and BNSTpr<sup>Aro</sup> (aromatase-expressing BNSTpr<sup>Esr1</sup>), although BNSTpr<sup>Esr1</sup> alone does not represent sex in the same way as these subsets do (Bayless et al., 2019, 2023; B. Yang et al., 2022). When the activity of upstream BNSTpr<sup>Esr1</sup> is

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**Figure 1.** Sex cues are translated into social behavior. Male-preferring neurons in BNSTpr transmit male sex cues to VMHvl and realize the behavior transition from sniffing to aggression. Projection from BNSTpr triggers sniff- and attack-selective neurons overlapped in VMHvl during this phase. In order to realize the behavior shift from sniffing to mounting, female-preferring neurons in BNSTpr send female sex cues to MPOA. In this phase, mount-selective neurons, which are distributed independently of sniff-selective neurons, are activated while the projection from BNSTpr inhibits the sniff-selective neurons in MPOA.

inhibited, the sex bias in downstream VMHvl is completely reversed, further highlighting the importance of BNSTpr<sup>Esr1</sup> for sex recognition in male mice. It is the sexually dimorphic processing of social cues that enables BNSTpr<sup>Esr1</sup> to encode mating and aggression in male mice.

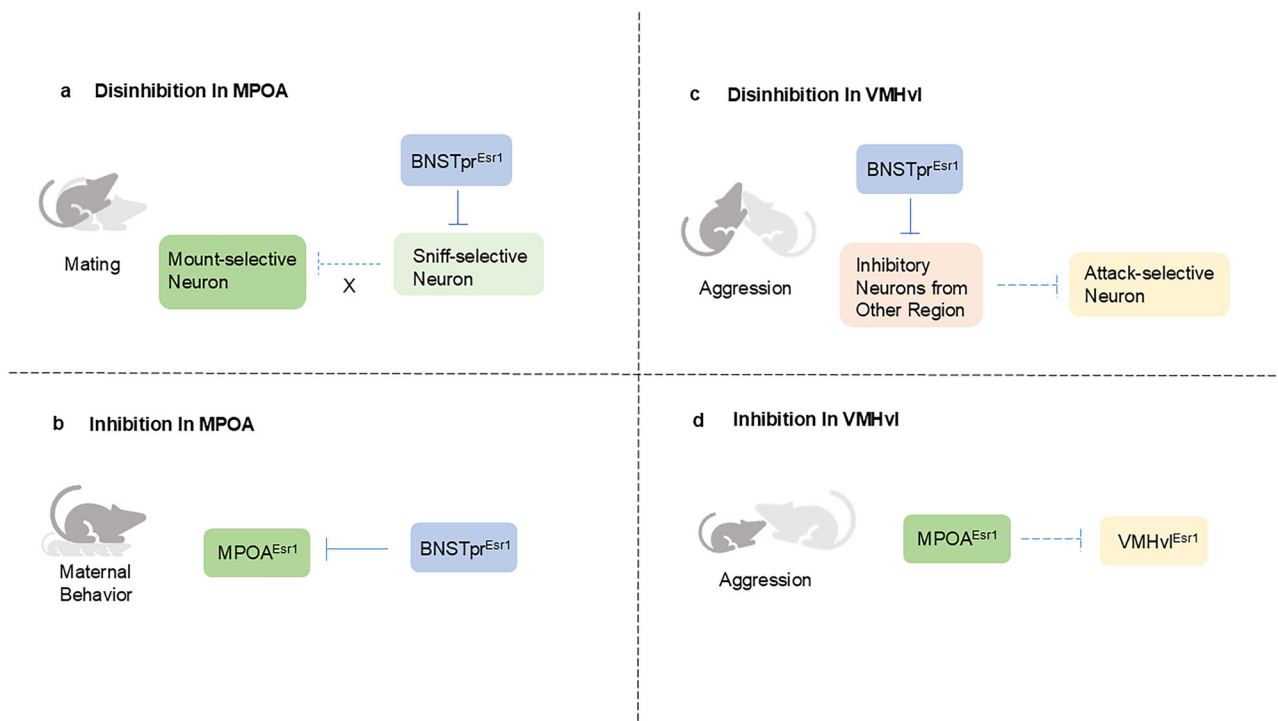
Mating and aggression in male mice can be suppressed by optogenetically and chemogenetically silencing BNSTpr<sup>Esr1</sup> (B. Yang et al., 2022). In addition to this, inhibition of BNSTpr<sup>Tac1</sup>, a subset of BNSTpr<sup>Esr1</sup> but smaller than BNSTpr<sup>Aro</sup> (Knoedler et al., 2022; Bayless et al., 2023), greatly reduces mating and aggression of male mice. It works on POA<sup>Tac1</sup> to foster mating through the release of substance P. Furthermore, BNSTpr<sup>Esr1</sup> neurons also contribute to aggressive behavior in female mice. Mei et al. employed optogenetic activation of BNSTpr<sup>Esr1</sup> in noninfanticidal female mice, which projected onto MPOA and markedly triggered infanticide and suppressed maternal behavior during lactation. Maternal behavior of female mice returned to normal once light stimulation ceased (Mei et al., 2023; Fig. 2b). Infanticide can be considered a manifestation of aggressive behavior in female mice (Zhu et al., 2021). Thus, BNSTpr plays a gating role in mating and aggression (Fig. 1). However, the impact of BNSTpr on the hypothalamus in relation to these behaviors remains unknown.

Given that Joseff et al. identified a derepression mode of gene regulation in *Esr1* neurons (Knoedler et al., 2022), and that Jiang and Pan summarized the necessary derepression in several behavior selection models in male mice and flies (Jiang and Pan, 2022), it is reasonable to assume that the repressive inputs from other regions modulate the activity of the behavior-selective cells in these two nuclei. In order to better understand how mating and aggression move from the appetitive stage to the consummatory stage, researchers identified the neurons active during appetitive behavior (sniffing) as appetitive (sniff)-selective neurons and the neurons active during consummatory behavior (mating and aggression) as consummatory behavior (mount and attack)-selective neurons (B. Yang et al., 2022). Additionally, sniff- and mount-selective neurons are separated in MPOA, and sniff- and attack-selective neurons are mixed in VMHvl. During mating or aggression of male mice, the activity of mount-selective neurons or the attack-selective neurons was significantly higher than that of sniff-selective neurons. However, the situation was reversed during sniffing. And silencing of BNSTpr<sup>Esr1</sup> neurons in male mice leads to a decrease in activity of mount-selective neurons in MPOA and sniff- and attack-selective neurons in VMHvl.

The dynamic and reversible shift in male mice's behavior from appetitive to consummatory behavior is intimately associated with the activity of certain selective neurons. To

control the activity of these neurons, various nuclei from the social behavior neural network transfer neurotransmitters with various characteristics. For this reason, it appears that the restriction from sniff-selective neurons to mount-selective neurons is blocked by inhibitory input from BNSTpr (Fig. 2a). Similarly, inhibitory inputs from other regions simultaneously suppress sniff-selective neurons and attack-selective neurons in VMHvl, which have overlapping distribution (B. Yang et al., 2022). It is possible that inhibitory input from BNSTpr counteracts this suppression (Fig. 2c). This was greatly supported by the discovery that optogenetic activation of GABAergic BNSTpr<sup>Tacr1</sup> neurons in male mice initially induced inhibition and followed by Tacr1-dependent excitatory long-term potentiation in MPOA (Bayless et al., 2023).

The majority of cell types in BNSTpr and MPOA are GABAergic, while in VMHvl they are predominantly glutamatergic (Nair et al., 2023). Cells in MPOA and VMHvl can respond to excitatory or inhibitory inputs from other regions (Mei et al., 2023). In addition to the inhibitory input of BNSTpr<sup>Esr1</sup> mentioned previously, there is also a reciprocal inhibitory projection between MPOA and VMHvl at the hypothalamic level. Activation of this inhibitory projection leads to corresponding behavior effects. Specifically, activation of projection from MPOA to VMHvl decreases aggression, while activation of VMHvl to MPOA projection leads to female-directed ultrasonic vocalization emission and suppression of mating in male mice. Recent breakthroughs have shed light on the effects and significance of these projections. Some studies have shown that VMHvl receives inhibitory inputs from other regions, including MPOA in male mice (Wei et al., 2023; Minakuchi et al., 2024). Wei et al. found that by constraining VMHvl<sup>Esr1</sup>, cMPOA<sup>Esr1</sup> (the caudal part of MPOA) can suppress male aggression (Wei et al., 2023; Fig. 2d). Patch clamp in conjunction with optogenetic activation, which recorded the inhibitory input from cMPOA<sup>Esr1</sup> to VMHvl<sup>Esr1</sup>, provides evidence for this. Similar to this, Minakuchi et al. displayed that all VMHvl core neurons receive functional long-range GABAergic input from MPOA after optogenetic activation of GABAergic neurons in MPOA, resulting in optical inhibitory post-synaptic current (Minakuchi et al., 2024).



**Figure 2.** Disinhibition and inhibition in MPOA and VMHvl. In the mating context, BNSTpr<sup>Esr1</sup> inhibits sniff-selective neurons in male mice MPOA, unblocking the inhibition of mount-selective neurons (a). BNSTpr<sup>Esr1</sup> functions as a brake on maternal behavior by inhibiting MPOA<sup>Esr1</sup> in female mice (b). In the context of the attack, BNSTpr<sup>Esr1</sup> relieves the inhibitory effect of other areas on attack-selective neurons in VMHvl in male mice (c). To reduce aggression in male mice, MPOA<sup>Esr1</sup> from the caudal part of MPOA arrests VMHvl<sup>Esr1</sup> (d).

Although the sources of GABAergic input are different, all of these inhibitory inputs have varying effects on mating and aggression and are designed to facilitate defense and reproduction in mice. At the hypothalamic level, MPOA and VMHvl control the mating and aggression of male mice in distinct ways. The neurons in VMHvl are predominantly glutaminergic, and the connections between excitatory neurons generally exhibit sustained activity. In contrast, neurons in MPOA are mostly GABAergic neurons, and a subset of inhibitory neurons cannot achieve similar sustained activity (Nair et al., 2023). This distinction is closely related to the interplay between behavior selection and defense mechanisms. The all-or-nothing nature of ejaculation serves as a stage in mating to guarantee that reproduction is carried out under the proper conditions. While an attack is a periodic event, the intensity of the attack is different, in order to “bully the soft and fear the hard.” However, interestingly, during mating and aggression of male mice, certain subsets of *Esr1*-expressing neurons in both clusters show comparable activation (Nair et al., 2023). This nonsex-specific neuron activity suggests that their function extends beyond behavior regulation and may be involved in motivation that results in behavior to keep the neural system in a stable and continuous state conducive to defense and reproduction.

## Discussion

Overall, the analysis of *Esr1*-expressing neurons in the social behavior network has gradually revealed the transmission of sex cues (Fig. 1), and these findings indicate the importance of *Esr1*-expressing neurons in the BNSTpr and hypothalamus in encoding mating and aggression. Even though they perform differently, the modifications in neural representation specific to sex and behavior within each nucleus are closely linked to promoting defense and reproduction. Further research is necessary to refine the map of neuronal circuits that control aggression and mating at the cellular level. BNSTpr, MPOA, and VMHvl exhibit significant divergence and convergence in the process of mating and aggression, and the antagonistic or promoting properties among them require refinement. The current study focuses on the subsets of BNSTpr<sup>*Esr1*</sup> neurons that control social behavior, providing new insights into the molecular mechanisms (Bayless et al., 2023).

Nevertheless, the majority of earlier research were obtained using mice and a single social object. In actuality, mice live in intricate social environments in their typical habitats. Improving social complexity and even simulating the natural environment are crucial for the validity and richness of the experimental results, since they bring the outcomes closer to the natural state. To go one step further, we can even release mice with implanted devices into the wild to track the brain activity of genuinely wild male mice during mating and aggression. It would be more complicated but also valuable.

However, the explanation above is restricted to mouse models. In fact, several studies have been conducted on the neural circuit associated with aggression and mating in various species. It is surprising that pC1 (posterior cell 1) neurons and VMHvl<sup>*Esr1*</sup> neurons regulate the sexual behavior and aggression of male mice in comparable ways (Anderson, 2016). Sniffing, mating, and aggression in male mice can be gradually elicited by progressively increasing the intensity of optogenetic stimulation of VMHvl<sup>*Esr1*</sup>, and this regulating impact is dependent on neuronal population activity of VMHvl<sup>*Esr1*</sup> (Lee et al., 2014; Nair et al., 2023). Interestingly, mating and aggression in flies are also regulated by the activity level of pC1 neurons, but the threshold dependency of aggression and mating in flies and mice is reversed (Anderson, 2016; Jiang and Pan, 2022). Additionally, VMHvl<sup>*Esr1*</sup> neurons express tachykinin 1 that is concerned with aggression in several mammals, including humans (Shaikh et al., 1993; De Felipe et al., 1998; Coccaro et al., 2012). It is also expressed in flies and promotes aggressive motivational states of them. This shows that there may be some conservation in the neuromodulation of aggression (Lee et al., 2014; Anderson, 2016).

As more conserved molecular mechanisms and functions of neuronal activity are discovered, it is possible for us to find new targets or strategies to treat or ameliorate psychiatric disorders associated with pathological mating and aggression. In other words, research on the neural circuits governing mating and aggression can improve our comprehension of the fundamental mechanisms underlying innate behavior network and possibly provide new therapeutic avenues for the regulation of social function.



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