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Estrogen Control of Social Behaviors

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Abstract

Social behaviors, including parental care, mating, and fighting, all depend on the hormonal milieu of an organism. Decades of work highlighted estrogen as a key hormonal controller of social behaviors, exerting its influence primarily through binding to estrogen receptor alpha (ERα). Recent technological advances in chemogenetics, optogenetics, gene editing, and transgenic model organisms have allowed for a detailed understanding of the neuronal subpopulations and circuits for estrogen action across *Esr1*-expressing interconnected brain regions. Focusing on rodent studies, in this review we examine classical and contemporary research demonstrating the multifaceted role of estrogen and ERα in regulating social behaviors in a sex-specific and context-dependent manner. We highlight gaps in knowledge, particularly a missing link in the molecular cascade that allows estrogen to exert such a diverse behavioral repertoire through the coordination of gene expression changes. Understanding the molecular and cellular basis of ERα's action in social behaviors provides insights into the broader mechanisms of hormone-driven behavior modulation across the lifespan.

Contents

INTRODUCTION

Going through puberty, experiencing pregnancy, parenting a child, undergoing menopause or andropause, we experience hormonal changes throughout our lives. Some of these changes have longer timescales, such as giving birth and caring for a child, while others, such as ovulatory cycles, show plastic changes in shorter timescales. Hormones are chemical substances synthesized and released from endocrine glands into the bloodstream. They play crucial roles in aligning physiological responses with behaviors, such as increasing sexual receptivity during ovulation. Hormones readily pass the blood-brain barrier and exert their actions in the brain. Estrogens, progestogens, and androgens are three sex steroid hormones released from the gonads and adrenal glands and are involved in the organization and activation of social behaviors. Estrogen is perhaps the best studied, with 17β-estradiol (E2) being its most common active form, exerting its effect through binding to estrogen receptors, resulting in both genomic and nongenomic downstream effects. Although it is generally considered a female sex hormone produced by the ovaries, estrogen is also abundantly present in the male brain by aromatizing androgen, a process mediated by brain-synthesized aromatase. There are three classes of estrogen receptors: estrogen receptor α (*Esr1*, protein: ERα), estrogen receptor β (*Esr2*, protein: ERβ), and G protein–coupled estrogen receptor 1 (GPR30/GPER1). ERα is the most broadly expressed form in the central nervous system (Ehret & Buckenmaier 1994, Mitra et al. 2003, Morishita et al. 2023, Perez et al. 2003). How does ERα regulate each social behavior circuit to ensure that the proper behavior is expressed at the appropriate time in a sex-specific manner? Here, we discuss the ERα mechanisms of action, including the role of *Esr1* and the *Esr1*-expressing cells. We focus on the rodent literature due to vast technical advances in the last few decades, which enable the precise targeting and manipulation of *Esr1*-expressing neurons and profiling of ERα activation–induced genomic and transcriptomic changes.

THE PROFOUND IMPACT OF ESTROGEN ON SOCIAL BEHAVIORS

Classic studies over 50 years ago provided the groundwork for the role of gonadal hormones in the organization and activation of social behaviors. These early studies examined changes in social behaviors in rodents after removing their gonads (**Supplemental Table 1**). When adult male mice were castrated, they no longer showed territorial aggression, which could be restored by

Supplemental Material >

testosterone or estrogen supplementation (Barfield et al. 1972, Christie & Barfield 1979, Edwards & Burge 1971, Gandelman 1980, Luttge 1972, Simon & Whalen 1986, Uhrich 1938). Chronic exposure to testosterone increased aggression in less aggressive male and female mice (Barkley & Goldman 1977, Martínez-Sanchis et al. 2003). Estrogen administration in adult male rodents resulted in increased aggression in mice housed in short photoperiods (winter-like) but not in mice housed in long photoperiods (spring-like), most likely through fast nongenomic effects (Silva et al. 2010; Trainor et al. 2007, 2008). Interestingly, preventing the aromatization of testosterone to estrogen or administering testosterone with antiestrogen, an estrogen receptor antagonist, prevented the recovery of aggression in castrated male mice, suggesting the aggression-promoting effect is mediated by estrogen instead of testosterone (Bowden & Brain 1978, Clark & Nowell 1979, Luttge 1979).

The critical role of estrogen in aggression starts during early development through its involvement in masculinizing the brain. After birth, the ovaries are quiescent, whereas neonatal testes are active and produce testosterone. Due to the minimal expression of androgen receptors in the neonatal rodent brain, testosterone exerts its action mainly through its conversion to estrogen and binding to estrogen receptors (Juntti et al. 2010; MacLusky et al. 1985, 1987; Naftolin et al. 1972; Reddy et al. 1974; Ryan et al. 1972). Neonatal testosterone or estrogen exposure was sufficient to induce male-like aggression in females, highlighting the critical role of estrogen in the development of male-typical aggression (Edwards 1971, Wu et al. 2009).

Gonadal hormones also profoundly affect sexual behaviors. Castrated male mice rarely mounted females, which could be rescued by either testosterone or estrogen administration (Edwards 1969, Edwards & Burge 1971). Similarly, ovariectomized females rarely became sexually receptive, measured as the probability of expressing lordosis—a back arched-down posture to facilitate male mounting—and instead, rejected the male mounting attempts, which could be later recovered by administration of estrogen and progesterone (Martini et al. 2011, Ring 1944, Thompson & Edwards 1971). Administration of testosterone in adult intact male rodents that were slow to ejaculate did not decrease ejaculation latency (Antonio-Cabrera & Paredes 2012). However, neonatal testosterone administration decreased the age to first ejaculation (Campbell & McGill 1970), indicating the importance of timing in the gonadal hormone's effect on sexual behaviors. Estrogen administration in intact adult male rodents either decreased sexual behaviors or caused no change, depending on the sexual experience of the subjects (Antonio-Cabrera & Paredes 2012, Davidson & Allinson 1969, Södersten 1973). Aromatase knockout (ArKO) male mice, which are unable to synthesize endogenous estrogen from testosterone, were mostly infertile and showed major deficits in sexual behaviors (Matsumoto et al. 2003). ArKO female mice showed reduced receptivity (Bakker et al. 2002). Importantly, the sexual receptivity deficit in ArKO females could only be rescued if estrogen was applied between postnatal day (P)15 and P25, suggesting a critical role of estrogen during the development of the female sexual behavior circuit (Bakker et al. 2002, Brock et al. 2011).

The role of sex steroid hormones in parental behaviors is less clear. Castrated adult male mice and ovariectomized females retrieved significantly more pups than intact virgin males and females, but these effects appear strain dependent (Okabe et al. 2010). Others reported no change in parental behaviors in gonadectomized male mice (Gatewood et al. 2006). Nonetheless, an injection of estradiol benzoate (EB) in ovariectomized and hysterectomized virgin female rats was sufficient to promote pup retrieval and lactating postures over foster pups (Siegel & Rosenblatt 1975a,b; Siegel et al. 1978). Similar to the organizational role of estrogen in aggression and sexual behavior circuits during development, the parental behavior circuit also depends on prepubertal sex hormones. Male and female mice gonadectomized at P25 showed reduced pup retrieval and parental behaviors regardless of treatment with EB in adulthood (Kercmar et al. 2014).

ESTROGEN MODULATES SOCIAL BEHAVIORS MAINLY THROUGH ERα

The two primary estrogen receptors, ERα and ERβ, are both nuclear receptors composed of a ligand-independent transactivation domain, a hormone-dependent transactivation domain, and a DNA binding domain and function as transcription factors upon activation (Kumar et al. 2011). Consistent with castration-induced behavior changes, *Esr1* knockout (KO) male mice exhibit significantly reduced levels of aggression compared to wild-type and heterozygous mice (Ogawa et al. 1998b). *Esr1* KO mice carry male-typical pheromones as they can elicit attack from resident wild-type mice (Ogawa et al. 1997). Furthermore, daily testosterone propionate injections, which restore aggression in wild-type gonadectomized mice, fail to induce aggressive behaviors in gonadectomized *Esr1* KO mice, suggesting that ERα is crucial for testosterone's effect on male aggression (Ogawa et al. 1998b).

Global *Esr1* deletion also revealed the role of ERα in sexual behaviors. Although *Esr1* KO male mice showed normal motivation to mount females, they achieved fewer intromissions, virtually never ejaculated, and were infertile (Ogawa et al. 1997, 1998b). *Esr1* deletion, exclusively in the brain, did not result in infertility but drastically reduced sexual behaviors in male mice (Trouillet et al. 2022). These findings suggest that ERα is not essential for the initiation but is necessary for the continuation and completion of sexual behaviors. Both *Esr1* KO and central nervous system *Esr1* deletion in female mice showed profoundly impaired sexual behaviors and increased rejection toward males (Ogawa et al. 1998a, Trouillet et al. 2022). They did not exhibit lordosis even when treated with estrogen or a combination of estrogen and progesterone (Kudwa & Rissman 2003; Ogawa et al. 1996, 1998a; Trouillet et al. 2022). *Esr1* KO females are often vigorously attacked by the males as if they are male intruders, suggesting the crucial role of ERα in facilitating sexual behaviors and the production of appropriate pheromones for mate recognition by males (Ogawa et al. 1996).

ERα also plays a role in parental behaviors. Male mice lacking *Esr1* retrieved pups with similar latency to wild-type males but exhibited a significantly higher rate of infanticide (Ogawa et al. 1998b). *Esr1* KO females also showed infanticide, which is extremely rare in their wild-type counterparts. Additionally, the noninfanticidal *Esr1* KO females retrieved significantly fewer pups and had longer latencies to retrieve pups compared to wild-type females (Ogawa et al. 1996, 1998a).

Social behavior deficits caused by *Esr1* KO appear mostly due to the loss of *Esr1* in GABAergic but not glutamatergic neurons (Wu & Tollkuhn 2017). Deletion of *Esr1* in GABAergic neurons expressing the vesicular GABA transporter (*Vgat*+) led to marked deficits in mating and territorial marking behaviors, including a significant reduction in the percentage of males that achieve ejaculation and a decrease in territorial urine marking (Wu & Tollkuhn 2017). In contrast, the deletion of *Esr1* in glutamatergic neurons expressing the vesicular glutamate transporter 2 (*Vglut2*+) did not significantly alter male-typical behaviors.

Unlike *Esr1* KO mice, *Esr2* KO males exhibit normal intermale aggression and even attack more than wild-type males in initial aggression tests (Ogawa et al. 1999). *Esr2* KO mice also show no deficiencies in sexual behaviors in males and sexual receptivity and lordosis in females (Ogawa et al. 1999). These results suggest that ERβ likely plays a relatively minor role in mediating the effect of estrogen on social behaviors.

ESTROGEN MODULATES SOCIAL BEHAVIOR THROUGH ERα IN THE SOCIAL BEHAVIOR NETWORK

The earlier castration and gene KO experiments demonstrated the critical roles of estrogen and its receptors in enabling the proper expression of social behaviors. In parallel, a series of lesioning,

electric stimulation, and pharmacological experiments revealed critical brain regions essential for social behaviors, which include the medial preoptic area (MPOA), ventromedial hypothalamus (VMH), medial amygdala (MeA), bed nucleus of the stria terminalis (BNST), and lateral septum (LS) (Helmy et al. 2020, Wei et al. 2021, Yu et al. 2020). Based on functional and immediate early gene studies of these regions, Newman (1999) proposed the social behavior network (SBN) for mediating social behaviors in mammals. The SBN comprises six interconnected regions, including the MeA, BNST, MPOA, anterior hypothalamus (AHN), LS, VMH, and midbrain [including periaqueductal gray (PAG) and tegmentum]. This framework was later expanded to other vertebrates, including birds and fish, by Goodson (2005). Interestingly, a common feature of these social behavior–activated regions is the abundant expression of ERα (Ehret & Buckenmaier 1994). In recent years, additional brain regions that are functionally important for social behaviors have been identified (see below), and high ERα expression levels remain a common feature of these newly identified social regions.

Given the abundant expression of ERα in the SBN, one natural question is whether SBN ERα expression is important for social behaviors. To address this, researchers employed RNA interference or small hairpin RNA to knock down ERα in specific brain regions (**Figure 1**). Sano et al. (2013) knocked down ERα in the male VMH and found that both aggression and sexual behaviors were reduced. Interestingly, although knocking down ERα in the VMH of female mice diminished sexual receptivity (Musatov et al. 2006), it increased, instead of decreased, aggression in female rats (Spiteri et al. 2010). Knocking down ERα in the MPOA of male mice reduced male sexual behaviors (Sano et al. 2013), while a similar manipulation in the female MPOA impaired parental behaviors (Ribeiro et al. 2012). ERα knockdown in the MeA during adulthood did not impair male aggression or sexual behaviors (Sano et al. 2013). However, prepubertal MeA ERα knockdown reduced both behaviors later in adulthood, suggesting ERα mainly plays an organizational role in the MeA (Sano et al. 2016). In the LS of male mice, knockdown of ERα did not result in changes in social interactions with other males (neither aggression nor sexual

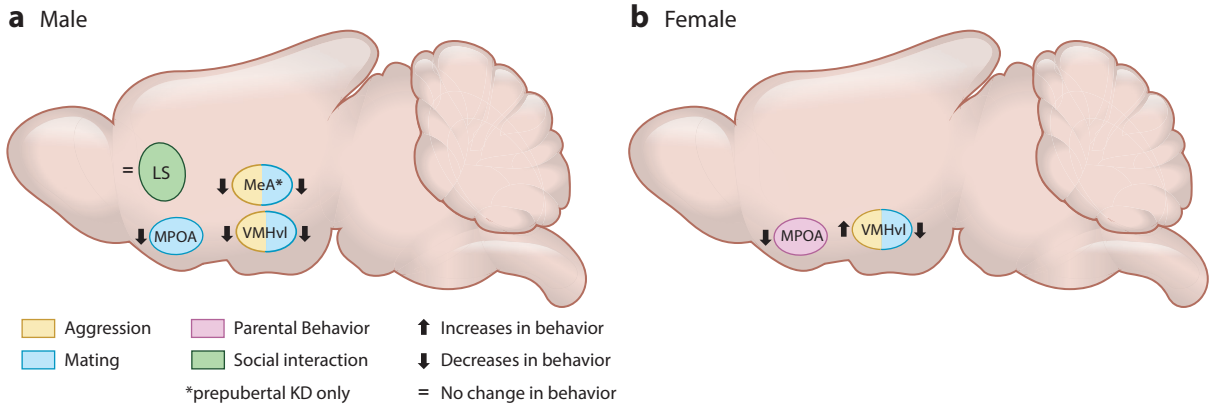


Figure 1

Functional role of ERα in the SBN during social behaviors in male and female rodents. To determine whether ERα was necessary for distinct social behaviors in a region-specific manner, studies performed RNA interference or small hairpin RNA ERα KD during social behaviors in a subset of SBN regions in males (*a*) and females (*b*). Some regions exhibited deficits in multiple social behaviors during unique developmental stages (i.e., MeA), while other regions showed sexually dimorphic differences (i.e., VMHvl and MPOA), and not all resulted in behavioral changes (i.e., LS). These findings highlight how ERα function during social behaviors is sex-, region-, and developmental stage–specific. Abbreviations: ERα, estrogen receptor α; KD, knockdown; LS, lateral septum; MeA, medial amygdala; MPOA, medial preoptic area; SBN, social behavior network; VMHvl, ventrolateral part of the ventromedial hypothalamus.

behaviors were assessed), but instead, deficits in social interactions were present after ERβ knockdown (Hasunuma et al. 2024). Thus, ERα modulates social behaviors in a region-, sex-, and developmental stage–specific way (**Figure 1**).

ESR1-EXPRESSING CELLS DRIVE SOCIAL BEHAVIORS

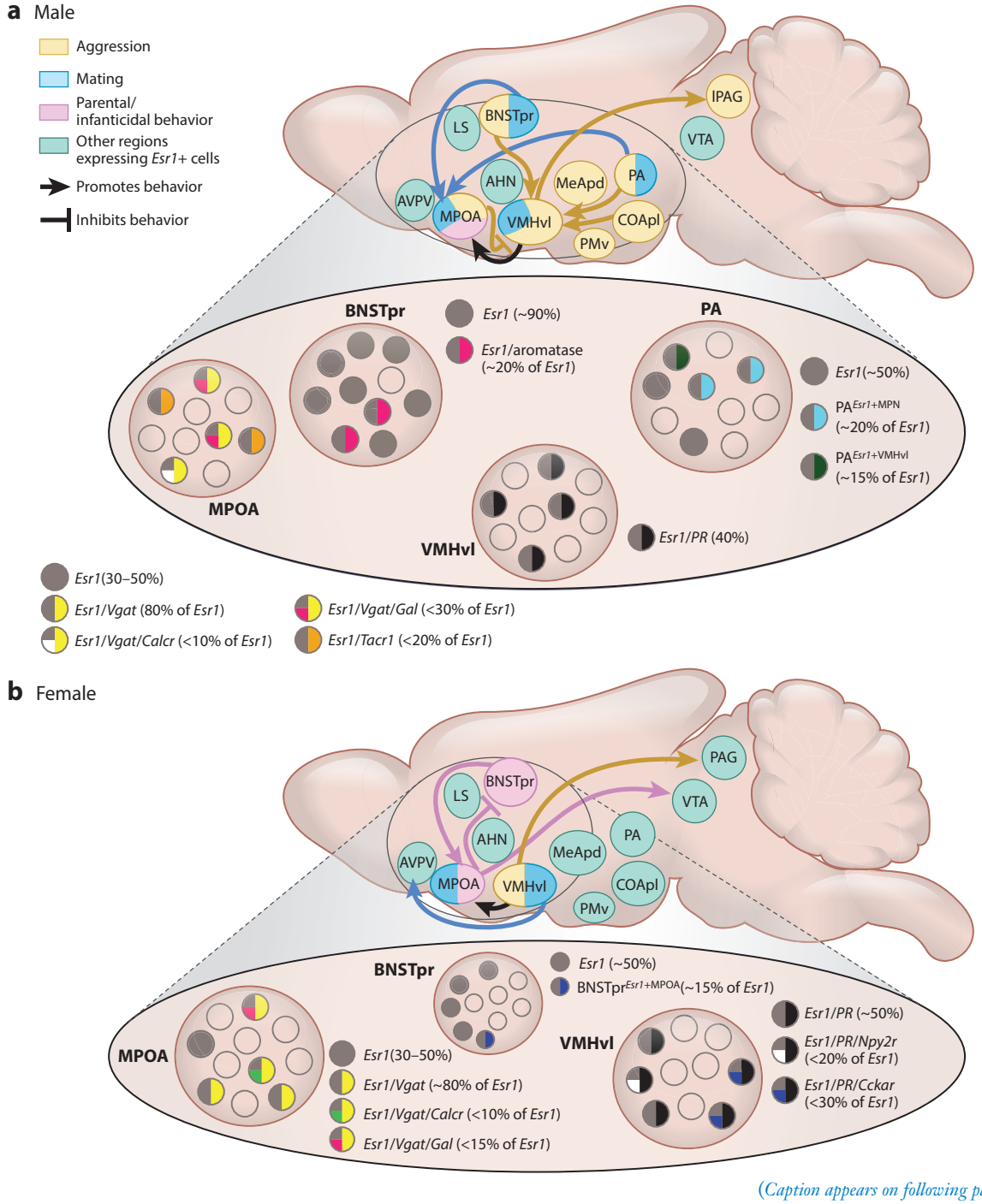
Estrogen acts on ERα to modulate cell responses and, ultimately, behavior output. Hence, cells expressing ERα must be critical in mediating social behaviors. Based on this rationale, recent works have focused on investigating *Esr1*-expressing cells in social behaviors. Advances in genetic tools for manipulating and recording specific cell types paired with computational models have allowed for precise and detailed characterization of the function, circuit, and neural computation of ERα+ cells (**Figure 2**).

Aggression

Esr1+ cells broadly increase activity during aggressive encounters. We recently recorded calcium signals of *Esr1*-expressing cells in 13 brain regions of the limbic system and found that 12 out of 13 significantly increased activity during attack (Guo et al. 2023). Based on the relative response patterns during mating and fighting, we proposed an aggression-biased network (ABN) and a mating-biased network (MBN). The ABN includes the ventrolateral part of the ventromedial hypothalamus (VMHvl), ventral premammillary nucleus, the posterior dorsal subdivision of MeA (MeApd), dorsomedial hypothalamus, AHN, and lateral periaqueductal gray, which are preferentially activated during male aggression. The ABN is an expansion of the core aggression circuit we previously proposed (Lischinsky & Lin 2020). Some regions in the MBN, such as the posterior amygdala (PA, also termed amygdalohippocampal area) and BNST, are also activated during attack, although their responses are higher during male sexual behaviors.

The VMHvl is a core region for aggression and aggression-seeking behavior (Falkner et al. 2014, 2016; Lin et al. 2011). We initially found that unselective optogenetic stimulation of the VMHvl cells could trigger immediate and robust attacks in male mice, even toward suboptimal targets, such as females and inanimate objects (Lin et al. 2011). Conversely, chemogenetic silencing of VMHvl neurons significantly reduced aggressive behaviors (Lin et al. 2011). VMHvl cells expressing *Esr1* (VMHvl^{Esr1}), which comprise half of the cells in the region, show a preferential overlap with aggression-induced c-Fos in both males and females, prompting the investigation of their roles in aggression (Hashikawa et al. 2017, Lee et al. 2014). Interestingly, VMHvl^{Esr1} neurons control both sexual and aggressive behaviors in an intensity-dependent manner. Weak optogenetic activation of VMHvl^{Esr1} cells ($\leq$1.4 mW/mm^2) induced sniffing, close investigation, and mounting toward both male and female mice, whereas strong activation (>3 mW/mm^2) prompted male mice to attack (Lee et al. 2014). Conversely, optogenetic inhibition of *Esr1*+ cells rapidly halted ongoing attacks and prevented the initiation of new attacks, although it did not terminate mating (Lee et al. 2014). This finding suggests that these neurons are required to initiate and sustain aggressive actions. To better understand the neuronal dynamics of these cells at the population level, Nair et al. (2023) employed an unsupervised dynamical systems method to analyze the activity of VMHvl^{Esr1} cells during social interactions. They revealed that VMHvl^{Esr1} cells encoded aggression through an approximate line attractor, by which an aggressive internal state escalates as the neural activity progresses along the attractor and as neurons integrate inputs over time to maintain an aggressive state. This model is unique to the VMHvl and does not apply to MPOA during either aggression or mating, where behaviors are represented via a cell identity code instead.

In a separate study, Yang et al. (2013) found that selective ablation of VMHvl progesterone receptor (VMHvl^{PR}) cells, the majority (>92%) coexpressing *Esr1*, in male mice decreased



(Caption appears on following page)

Figure 2 (*Figure appears on preceding page*)

Function, circuit, and molecular cytoarchitecture of *Esr1*-expressing regions across sexes. All regions of the SBN as well as additional regions recently implicated in social behaviors express *Esr1* in both males (*a*) and females (*b*). These regions can be further classified based on *Esr1*-expressing cell function and neuronal activity during aggression, mating, and parental/infanticidal behaviors, establishing behavioral-specific networks by which *Esr1*-expressing cells can promote or inhibit specific behaviors. Interestingly, several regions in the network, such as the MPOA and VMHvl in both males and females, have dual functions by which activation of *Esr1*-expressing cells can result in distinct social behaviors that are dependent on their circuit connectivity and the *Esr1* subpopulation being targeted. Despite a clear function of *Esr1*-expressing cells in males during social behaviors, the role of *Esr1*-expressing cells in multiple regions of the female brain, such as the PA, PMv, and COApl, remains understudied. Other regions expressing ERα, such as the VTA and LS in males and PMv in females, play a role in social behaviors, but whether the *Esr1*+ cells are driving those behaviors needs to be further investigated. Additionally, we present zoomed-in schematics of several SBN regions that have been studied in depth and highlight their vast molecular diversity, which is sexually dimorphic, with some regions, such as the VMHvl, possessing additional anatomical differences in cell distribution. Abbreviations: AHN, anterior hypothalamic nucleus; AVPV, anteroventral periventricular nucleus; BNSTpr, principal nucleus of the bed nucleus of the stria terminalis; *Calcr*, calcitonin receptor; *Cckar*, cholecystokinin A receptor; COApl, posterolateral cortical amygdala; *Esr1*, estrogen receptor 1; *Gal*, galanin; lPAG, lateral periaqueductal gray; LS, lateral septum; MeApd, posterodorsal part of the medial amygdala; MPOA, medial preoptic area; *Npy2r*, neuropeptide Y receptor type 2; PA, posterior amygdala; PMv, ventral premammillary nucleus; *PR*, progesterone receptor; SBN, social behavior network; *Tacr1*, tachykinin receptor 1; *Vgat*, vesicular GABA transporter; VMHvl, ventrolateral part of the ventromedial hypothalamus; VTA, ventral tegmental area.

aggression toward intruder males (**Figure 2*a***). Interestingly, the VMHvl^{PR} cell control of aggression varies with the social context but not the hormonal state of the animal. Chemogenetic activation of these cells induced attack more efficiently in solitary animals than group-housed animals but was similarly effective in intact and castrated males (Yang et al. 2017). One potential explanation for this result is that social context may modulate the aggression circuit downstream of the VMHvl, whereas estrogen modulates aggression mainly through VMHvl and its upstream regions, which could thus be overridden when VMHvl cells are artificially activated. Additionally, VMHvl^{PR} neurons were activated when a mouse observed others fighting, suggesting their potential roles in not only driving but also perceiving aggression, which may enable the animals to learn from observation and facilitate more nuanced social interactions (Yang et al. 2023).

The responses of VMHvl^{Esr1} cells are not fixed. Miniature endoscopic imaging revealed overlapping response patterns of VMHvl cells to male and female conspecifics in inexperienced adult male mice (Remedios et al. 2017). Interestingly, VMHvl^{Esr1} responses became sex-specific after experiencing a 30-min interaction with a female and led to increases in aggressiveness toward a male intruder. Stagkourakis et al. (2020) investigated how fighting experience alters the synaptic strength of VMHvl^{Esr1} neurons. They found that repeated fighting increased aggression levels in male mice as well as the frequency and amplitude of spontaneous excitatory postsynaptic currents of VMHvl^{Esr1} neurons. Recently, we further discovered that VMHvl^{Esr1} cells undergo three-phase plasticity over 10 days of repeated winning, including a monotonic synaptic potentiation between long-range input and VMHvl cells, a transient enhancement of VMHvl cell local connection, and a delayed increase in excitability (Yan et al. 2024). These plasticity events are causally linked, increasing the VMHvl responses to aggression-provoking cues and the animal's aggressiveness (Yan et al. 2024). Therefore, social experience modifies aggression by inducing multiple forms of plasticity in the aggression circuit.

VMHvl^{Esr1} cells also play an important role in female aggression. Although initial optogenetic activation of VMHvl^{Esr1} cells in C57BL/6 virgin female mice only induced social investigation and occasionally mounting behaviors (Lee et al. 2014), our later studies found that activating VMHvl^{Esr1} neurons in virgin Swiss Webster (SW) female, lactating C57BL6 female, and lactating SW female mice induced attacks toward juvenile intruders (Hashikawa et al. 2017). This behavioral difference likely lies in endogenous differences in the aggression circuit between virgin C57 and SW females, with the former showing nearly no aggression naturally, suggesting a likely

hypoactive circuit due to domestication. Additionally, chemogenetic inhibition of VMHvl^{Esr1} cells in female mice, regardless of the animal's genetic background or reproductive stage, significantly reduced and sometimes abolished aggression against intruders (Hashikawa et al. 2017). However, female VMHvl aggression cells differed from those of males in that aggression-activated cells in females (based on c-Fos) are concentrated in the medial part of the VMHvl, while those in males spread throughout the VMHvl. Bulk transcriptomic analysis revealed differential gene expression patterns in the medial and lateral parts of the VMHvl (Hashikawa et al. 2017). For example, cholecystokinin A receptor (*Cckar*) is uniquely expressed in the lateral VMHvl. At the output level, while the lateral VMHvl projects to areas involved in female reproductive behavior, such as the anteroventral periventricular nucleus (AVPV), medial VMHvl cells project preferentially to regions associated with aggression, such as the PAG (Hashikawa et al. 2017). Later, detailed single-cell RNA sequencing revealed over a dozen molecularly distinct clusters within VMHvl^{Esr1} cells (Kim et al. 2019). Interestingly, the cluster marked by *Cckar* is found exclusively in females, not males, suggesting that the lateral VMHvl could be a female-specific structure. In a follow-up study, Liu et al. (2022) identified VMHvl neuropeptide Y receptor type 2 (VMHvl^{Npy2r}) cells, a subset of the VMHvl^{Esr1} cells, as the aggression-activated VMHvl cells in females. Optogenetic activation of VMHvl^{Npy2r} in both virgin and lactating females evoked time-locked attacks toward male and female intruders (Liu et al. 2022). In contrast, activation of VMHvl^{Esr1} neurons that do not express Npy2r suppressed maternal aggression in lactating females (Liu et al. 2022). Thus, VMHvl^{Npy2r} cells, a subset of VMHvl^{Esr1} cells concentrated in the medial VMHvl, are the critical population for mediating female aggression (**Figure 2*b***).

PA cells expressing *Esr1* (PA^{Esr1}) are a major excitatory input to the VMHvl (Yamaguchi et al. 2020). The PA^{Esr1} to VMHvl–projecting (PA$^{Esr1\rightarrow VMHvl}$) neurons were active during aggressive interactions, and pharmacogenetic or optogenetic activation of these neurons induced attack, while their inhibition reduced aggression (Yamaguchi et al. 2020). PA$^{Esr1\rightarrow VMHvl}$ neurons receive excitatory inputs from various brain regions, including the hippocampus and cortical areas involved in olfactory processing, making them well-positioned to integrate sensory and contextual information to modulate social behaviors (Yamaguchi et al. 2020) (**Figure 2*a***).

Posterior cortical amygdala *Esr1*-expressing cells (COApl^{Esr1}) represent another excitability input to the VMHvl and also play a role in aggression. COApl^{Esr1} cells in male mice showed increased activity during social investigation before attacks (Scott et al. 2023). Inhibiting COApl^{Esr1} projections to the VMHvl and central amygdala decreased aggression and increased social investigation. The COApl^{Esr1}-VMHvl modulation on aggression appears male-specific, as similar manipulations did not affect aggressive behavior in female mice (Scott et al. 2023).

The principal component of the bed nucleus of the stria terminalis (BNSTpr) provides dense GABAergic inputs to the VMHvl. Nonetheless, ablation of BNSTpr aromatase-expressing cells, a subset of *Esr1*+ cells, suppressed male aggression but not maternal aggression (Bayless et al. 2019). The male-specific role of BNSTpr in aggression may not be surprising given that this is a sexually dimorphic region, twice bigger in male than female rodents (Hines et al. 1992). Consistent with the ablation results, optogenetic silencing of BNSTpr *Esr1*-expressing neurons (BNSTpr^{Esr1}) during sniffing blocked the transition from investigation to attack in male mice, whereas silencing the cells during attack terminated ongoing attacks (Yang et al. 2022). Miniscope calcium imaging of BNSTpr^{Esr1} cells revealed their largely distinct responses to female and male conspecifics, with a higher proportion of cells responding to females (Yang et al. 2022). Interestingly, silencing BNSTpr^{Esr1} neurons altered the sex-tuning bias of VMHvl^{Esr1} cells from male dominant to female dominant (Yang et al. 2022). The circuit mechanism through which BNSTpr^{Esr1} cells alter VMHvl^{Esr1} cell responses to social cues remains to be investigated.

MPOA reciprocally connects with the VMHvl and similarly expresses ERα densely (Fang et al. 2018, Karigo et al. 2021, Wei et al. 2018, Wei et al. 2023). While females preferentially activated the rostral MPOA^{Esr1} cells in male mice, caudal MPOA *Esr1*+ (cMPOA^{Esr1}) cells showed higher responses to males (Wei et al. 2023). Interestingly, cMPOA^{Esr1} cells inhibited instead of promoted aggression. Chemogenetic inhibition of these cells increased aggression toward both male and female intruders, while their activation suppressed intermale aggression. Thus, the MPOA^{Esr1} cells bidirectionally modulate aggression via direct inhibitory projections to the VMHvl. Interestingly, cMPOA^{Esr1} cells increased their response specifically to a stronger male opponent after defeat, suggesting that the cells can evaluate the fighting capability of the opponent and put a break on the aggression circuit to prevent conflict with a superior conspecific (Wei et al. 2023). When the cMPOA^{Esr1} cells were optogenetically inhibited, the defeated animal attacked the winners and ended up suffering more attacks.

A relevant *Esr1*-expressing region in the ABN is the MeApd. *Esr1*+ cells in the MeApd are highly responsive during intermale attack in male mice (Guo et al. 2023). However, whether these cells are required for territorial aggression has yet to be tested. The GABAergic cells in this region (Hong et al. 2014), as well as subpopulations expressing aromatase (Unger et al. 2015), and recently the transcription factor Foxp2 (Lischinsky et al. 2023) have been shown to play a functional role in territorial aggression. Interestingly, the MeApd Foxp2+ cells comprise only approximately 10% of the total *Esr1*-expressing subpopulation and have limited coexpression with aromatase-expressing cells (Lischinsky et al. 2017). Furthermore, MeA subpopulations projecting to the BNST, including those expressing the dopamine D1 receptor (Miller et al. 2019), neuropeptide Y receptor type 1 (Padilla et al. 2016), and calcium/calmodulin-dependent protein kinase 2 (Nordman et al. 2020), can promote aggression. Therefore, both *Esr1*+ and *Esr1*− subpopulations in the MeA could be required for aggression. Whether *Esr1*+ cells are directly or indirectly regulating the function of *Esr1*− cells for aggressive behaviors remains to be studied.

Male Sexual Behaviors

Sexual behaviors are composed of mounting, intromission, and ejaculation in male mice and lordosis in female mice. Thus, they fundamentally differ between the sexes and, unsurprisingly, are supported by distinct neural circuits in males and females. Nevertheless, *Esr1*+ cells are essential for both male and female sexual behaviors. Our recent recording of *Esr1*+ cells throughout the limbic system in male mice revealed their robust and dynamic activity changes during mating. The MPOA, BNSTpr, PA, and anterior MeA show preferential activation during mating versus fighting and constitute the MBN (Guo et al. 2023) (**Figure 2*a***).

The MPOA is the best-known region for driving male sexual behaviors based on lesion studies from decades ago. Wei et al. (2018) first reported the responses of male MPOA^{Esr1} cells using bulk calcium recording and showed that these cells increase their activity during female investigation and mounting. Ablating or inhibiting MPOA^{Esr1} cells reduced mounting and intromission by male mice, while optogenetic activation of MPOA^{Esr1} neurons induced male-typical mounting in male and female mice. The induction of mounting in females suggests that the male-typical mounting circuit is also present in females but is likely inactive under normal conditions (Wei et al. 2018). Although mounting can be induced by activating MPOA^{Esr1} cells, the efficiency is relatively low (<50%). Later, Karigo et al. (2021) found that optogenetic stimulation of GABAergic MPOA^{Esr1} (MPOA$^{Esr1\cap Vgat}$) cells promoted mounting with nearly 100% efficiency. Furthermore, stimulating MPOA$^{Esr1\cap Vgat}$ cells evoked ultrasound vocalizations (USVs), which typically accompany natural male sexual behaviors, and these cells show increased activity during female-directed USVs accompanied by mounting. These results established a critical role of MPOA$^{Esr1\cap Vgat}$ cells in male sexual behaviors.

Unlike the MPOA$^{Esr1\cap Vgat}$ stimulation–induced mounting, no USVs were emitted when male mice mounted other conspecifics upon VMHvl^{Esr1} stimulation (Karigo et al. 2021, Lee et al. 2014). Consistent with the functional results, VMHvl^{Esr1} cells increased activity during USV-free mounting toward a male (Karigo et al. 2021). Thus, the VMHvl^{Esr1} activation–induced mounting was proposed to be a dominant instead of sexual behavior (Karigo et al. 2021). Nevertheless, it remains possible that VMHvl^{Esr1} cells also play a role in male sexual behaviors as ablating or inhibiting VMHvl$^{Esr1+PR+}$ neurons in male mice significantly reduced the frequency and duration of mounting and intromission of a female mouse (Karigo et al. 2021, Yang et al. 2013) (**Figure 2*a***).

BNSTpr^{Esr1} cells densely project to the MPOA and are necessary for male mating behaviors. Silencing of these projections in male mice attenuated the transition from sniffing to mounting (Yang et al. 2022). Directly silencing aromatase-expressing BNSTpr cells eliminated a preference for female pheromones and abrogated mating success (Bayless et al. 2019). Our multisite *Esr1*+ cell recording revealed a unique response pattern of BNSTpr^{Esr1} cells during mating, featuring a gradual increase in activity as mating advanced and a strikingly high response during ejaculation (Guo et al. 2023). Recently, Zhou et al. (2023) showed that ejaculation, but not intromission, caused a long-lasting activation of BNSTpr *Esr2*-expressing (BNSTpr^{Esr2}) neurons, which largely overlap with *Esr1*-expressing cells (Knoedler et al. 2022). Furthermore, after a series of activation and silencing experiments, Zhou et al. (2023) determined that BNST^{Esr2} cells are important for maintaining sexual satiety, referring to a diminished interest in females after the male ejaculates. Therefore, BNSTpr cells could be involved in multiple stages of male sexual behaviors. While BNSTpr^{Esr2} cells promote sexual satiety, *Esr1*+ cells (potentially St18-expressing cells) are critical for promoting mounting and intromission (Knoedler et al. 2022).

The MPOA also receives dense projections from PA, which plays an indispensable role in the initiation and execution of sexual behaviors. PA^{Esr1} to MPOA–projecting cells were primarily active during mating in males and could bidirectionally modulate mounting toward females (Yamaguchi et al. 2020). Most strikingly, when PA^{Esr1}-MPOA cells were inhibited, males nearly lost their ability to initiate mounting and never achieved intromission (Yamaguchi et al. 2020).

Altogether, PA^{Esr1}, BNSTpr^{Esr1}, and MPOA^{Esr1} cells form the core circuit mediating male sexual behaviors (Guo et al. 2023) (**Figure 2*a***). Interestingly, during advanced sexual behaviors, *Esr1*+ cells outside of the core mating circuit are broadly inhibited, possibly to ensure the uninterrupted completion of sexual intercourse (Guo et al. 2023).

Female Sexual Behaviors

Esr1+ cells in the VMHvl, instead of the MPOA, are the most important and well-studied population for female sexual behaviors. Ablating VMHvl^{PR} cells, which are virtually the same population as VMHvl^{Esr1} cells, decreased sexual receptivity and increased rejection of male mounting attempts in female mice (Yang et al. 2013). Female sexual receptivity varies with the estrous cycle. It is high during estrus and low during diestrus. VMHvl^{PR} cells show estrous cycle–dependent structure variation. During estrus, there is a multifold increase in presynaptic termini between VMHvl^{PR} neurons and AVPV (Inoue et al. 2019, Knoedler et al. 2022). AVPV houses kisspeptin neurons, which also express ERα and are critical for activating gonadotropin-releasing hormone neurons to initiate a luteinizing hormone surge and, ultimately, the estrous cycle (Adachi et al. 2007, Smith et al. 2005, Yin & Lin 2023). Inhibiting these projections resulted in a significant reduction in female sexual receptivity; however, activating these cells failed to promote female receptivity (Inoue et al. 2019). Later, Liu et al. (2022) found that when the VMHvl^{Esr1} cells that do not express *Npy2r* (recall that *Npy2r* marks the VMHvl female aggression-related cells) were activated, the sexual receptivity in virgin females significantly increased regardless of the estrous state. Our group and

Knoedler et al. (2022) further demonstrated that lateral VMHvl *Cckar* (VMHvll^{Cckar}) cells, a subset of *Esr1*+ cells that are largely distinct from *Npy2r*+ cells, can bidirectionally modulate female sexual receptivity (Yin et al. 2022) (**Figure 2*b***). Activating these cells promoted female sexual proceptivity and receptivity acutely, even in ovariectomized females (Yin et al. 2022). Inactivating the VMHvll^{Cckar} cells optogenetically or chemogenetically suppressed females' interest in males and dampened sexual receptivity. VMHvll^{Cckar} cells are specifically activated by male cues, with the highest response during estrus (Yin et al. 2022). The VMHvl to AVPV projection likely mainly originates from the *Cckar*+ cells, as 70% of AVPV retrogradely labeled VMHvl cells express Cckar (Yin et al. 2022). These results established the central role of VMHvll^{Cckar} cells as a key population for female sexual behaviors. Interestingly, similar to the persistent activity increase of VMHvl^{Esr1} cells in male mice during aggression, VMHvl$^{Esr1+/Npy2r-}$ cells in female mice showed similar ramping activity during male interaction, likely reflecting a sexually motivated internal state as mating progresses (Liu et al. 2024, Nair et al. 2023). These neural dynamics were unique to a receptive and hormonal state and were no longer observed when the females were nonreceptive (Liu et al. 2024).

Additional *Esr1*-expressing regions in the SBN have also been implicated in female sexual behaviors. Silencing olfactory inputs to the MeA or the MeA itself resulted in a reduction in male pheromone preference and decreases in lordosis in female mice (Johnson et al. 2021, McCarthy et al. 2017), suggesting the MeA as a possible input to VMHvl^{Esr1} cells for female sexual behaviors. BNST^{St18} cells showed increased activity during female lordosis (Zhou et al. 2023). Whether *Esr1*-expressing cells in these regions are the functionally important population for female sexual behaviors remains to be determined.

Parental and Infanticidal Behaviors

In addition to male sexual behaviors, MPOA^{Esr1} cells also play a critical role in driving parental behaviors in both males and females (Fang et al. 2018, Wei et al. 2018). Bulk calcium and electrophysiological recordings revealed preferential activity increases of MPOA^{Esr1} cells during pup retrieval, among various pup-directed behaviors (Fang et al. 2018, Wei et al. 2018). Ablation or acute optogenetic inhibition of MPOA^{Esr1} cells reduced pup retrieval in virgin females, mothers, and fathers (Fang et al. 2018, Wei et al. 2018). Conversely, optogenetic activation of MPOA^{Esr1} cells promoted pup approach and retrieval in both male and female mice (Fang et al. 2018). MPOA^{Esr1} cells drive parental behaviors at least partly through their projections to the VTA, as MPOA^{Esr1} to VTA–projecting cells showed increases in activity during pup retrieval, and optogenetic activation of this pathway quickly promoted the female to walk out of the nest in a large arena and retrieve a distant pup (Fang et al. 2018). If the stimulation terminated before reaching the pup, the female would often abort the retrieval attempt, suggesting that activity of this pathway is essential for motivating the animal to initiate and complete retrieval. Further experiments demonstrated that MPOA^{Esr1} cells provide strong inhibitory inputs to nondopaminergic neurons in the VTA, resulting in the disinhibition of dopaminergic cells (Fang et al. 2018). MPOA^{Esr1} cell activity changes across reproductive states, with higher excitability, higher in vivo responses to pups, and lower baseline firing in lactating animals, effectively increasing the signal-to-noise ratio to pup cues during motherhood (Fang et al. 2018, Mei et al. 2023) (**Figure 2*b***).

MPOA^{Esr1} cells are not a homogeneous population (**Figure 2**). As discussed above, MPOA^{Esr1} cells can drive both parental and male sexual behaviors. Our single-unit recordings of MPOA cells suggest that adult and pup-responsive cells are largely distinct (Fang et al. 2018). Later, detailed RNA sequencing and multiplexed error-robust fluorescence in situ hybridization revealed that calcitonin receptor (*Calcr*)-expressing cells, which comprise less than 10% of *Esr1*+ cells, are

preferentially activated during parental but not sexual behaviors (Moffitt et al. 2018, Yoshihara et al. 2021). Yoshihara et al. (2021) found that silencing MPOA^{Calcr} cells disrupted maternal behaviors, while activating the cells suppressed infanticide in males. Knocking down Calcr in females reduced pup retrieval, especially in a risky environment. However, whether MPOA^{Calcr} cells are functionally relevant to only parental behaviors and not sexual behaviors remains to be addressed.

Galanin-expressing MPOA (MPOA^{Gal}) cells have also been suggested as a key population for mediating parental behaviors in both males and females (Wei et al. 2018, Wu et al. 2014). MPOA^{Gal} and MPOA^{Esr1} cells only partially overlap (Ammari et al. 2023, Moffitt et al. 2018). Ablating MPOA^{Gal} cells in nursing females, virgin females, and male parents impaired all parental behaviors and, in extreme cases, led to pup-directed aggression (Wu et al. 2014). Optogenetic activation of male MPOA^{Gal} neurons increased pup grooming but did not induce pup retrieval like MPOA^{Esr1} cells (Wu et al. 2014). A follow-up study further suggests that MPOA^{Gal} cells mediate different aspects of parental behaviors, such as grooming and pup interaction, through projections to different downstream regions, including PAG, VTA, and MeA (Kohl et al. 2018). Although it was not directly addressed whether *Esr1*+ or *Esr1*− MPOA^{Gal} cells are responsible for driving parental behaviors, Ammari et al. (2023) recently showed that estrogen and progesterone change the excitability and synapses, respectively, of MPOA^{Gal} cells during pregnancy and cause more robust and selective responses to pup stimuli during lactation, suggesting that the parental behavior–relevant MPOA^{Gal} cells likely express sex hormone receptors and can alter their responses based on the animal's hormonal state.

Contrary to MPOA^{Esr1} cell function, BNSTpr^{Esr1} cells promote negative pup-directed behaviors. Population calcium recording revealed that BNSTpr^{Esr1} cells respond more strongly during infanticide in hostile virgin female mice compared to maternal behaviors in mothers (Mei et al. 2023). Optogenetically activating BNSTpr^{Esr1} inputs to the MPOA in noninfanticidal mice suppressed maternal behaviors and induced infanticide (Mei et al. 2023). In contrast, optogenetically inhibiting this pathway reduced pup attack and promoted maternal care in infanticidal female mice. Channelrhodopsin-assisted circuit mapping revealed that BNSTpr^{Esr1} and MPOA^{Esr1} neurons are strongly reciprocally connected mainly through GABAergic synapses. Thus, BNSTpr^{Esr1} and MPOA^{Esr1} cells mediate negative and positive pup-directed behaviors, respectively, and have a seesaw relationship (Mei et al. 2023). Interestingly, BNSTpr^{Esr1} cell excitability decreases during motherhood, whereas MPOA^{Esr1} cell excitability increases, shifting the output balance toward the positive pup-directed behaviors (Mei et al. 2023).

The rhomboid nucleus of the bed nucleus of the stria terminalis (BNSTrh) has also been indicated in mediating infanticide behavior, although ERα expression is weak in this area (Tsuneoka et al. 2015). Fukui et al. (2022) recently found that BNSTrh cells receive increased excitatory synaptic inputs after E2 treatment in castrated males, most likely from the PA^{Esr1} cells. This increase coincides with increased infanticide, hinting at the potential relevance of synaptic changes leading to behavioral change. Although the functional importance of the PA^{Esr1}-BNSTrh pathway remains to be confirmed, estrogen-mediated potentiation of this pathway may be responsible for the increased infanticide from juveniles to adults (Amano et al. 2017).

MeA cells projecting to MPOA also promote infanticide (Mei et al. 2023). Chemogenetic activation of MeA-MPOA cells increased infanticide in virgin female mice (Mei et al. 2023). However, MeA likely also contains cells that are important for parental care as activating GABAergic MeA cells, the main MeA population, induced pup grooming and infanticide in an intensity-dependent manner in male mice (Chen et al. 2019). MeA expresses abundant ERα, although the roles of *Esr1*-expressing MeA cells in infanticide or parental behaviors remain to be tested.

Altogether, a subset of MPOA^{Esr1} cells, likely expressing *Calcr*, are critical for mediating parental behaviors in both males and females. However, upstream regions of MPOA^{Esr1} cells,

including *Esr1*-enriched BNSTpr, PA, and MeA, are mainly important for infanticide (Chen et al. 2019, Mei et al. 2023, Sato et al. 2020). Functions of *Esr1*+ cells in the MPOA^{Esr1} downstream regions are not yet clear. Thus, it remains to be investigated whether a parental care circuit composed of *Esr1*+ cells exists, like the case of sexual and aggressive behavior circuits (**Figure 2**).

THE INTRACELLULAR ACTIONS OF ESTROGEN

How do sex hormones modulate cells in the social behavior circuits to ultimately modulate social behaviors? ERα can exert its intracellular actions through both genomic (long-term: hours to days) (**Figure 3*a***) and nongenomic (short-term: milliseconds to minutes) mechanisms (**Figure 3*b***). Estrogen binding to ERα results in its entrance to the nucleus to modulate gene expression and chromatin accessibility. Recent work by Gegenhuber et al. (2022) identified 1,930 ERα binding sites in BNSTpr, MPOA, and posterior MeA collectively. ERα mainly binds the estrogen-responsive elements, the canonical ERα binding site. Among the genes targeted by ERα, gene ontology analysis uncovered that many are in the categories of synaptic and neurodevelopmental disease, including neurotransmitter receptors, ion channels, and extracellular matrix genes. Additionally, ERα binds to loci encoding neurotrophin receptors (*Ntrk2* and *Ntrk3*) and other sex hormone receptors (androgen and progesterone receptors). The study also revealed over 7,000 chromatin regions that increase accessibility (E2-open) and 123 regions that decrease accessibility (E2-close) with EB treatment. Thus, ERα activation can drastically change the genomic landscape and potentially alter the expression level of thousands of genes.

How does estrogen exactly change gene expression patterns? Given the different estrogen levels in males and females, comparing gene expression patterns between sexes could provide some clues. A more controlled approach involves eliminating the endogenous sex hormones through castration and then comparing the gene expression patterns in castrated versus intact or castrated + hormone-supplemented animals. Early work utilizing microarrays identified dozens of genes that are differentially expressed between sexes and between intact and castrated animals in several *Esr1*-enriched hypothalamic and amygdala regions (Xu et al. 2012). Recent work leveraged novel sequencing tools to reveal many more genes that are under the regulation of estrogen. Bulk sequencing of *Esr1*-expressing cells identified over 300 genes that are up- or downregulated by EB in the BNSTpr (Gegenhuber et al. 2022). Single-nucleus RNA sequencing of *Esr1*+ cells identified an impressive array of 1,415 genes that are differentially expressed across sexes and hormonal states in the BNSTpr, MeA, POA, and VMHvl. A significant portion of identified genes are involved in synaptic transmission, steroid-hormone and reproductive organ processes, and gene expression regulation.

Given that many genes, including those that contribute to neuron wiring (*Brinp2*, *Unc5b*, and *Enah*), synaptic plasticity (*Rcn1* and *Irs2*), and cell excitability (ion channels), are regulated by estrogen, it is not surprising that *Esr1*-expressing cells show sex hormone state-dependent changes in physiological properties, morphology, and connectivity. As mentioned above, maternal behavior–related MPOA$^{Esr1/Gal}$ cells increase excitability and spine density during late pregnancy and motherhood due to the combined action of estrogen and progesterone (Ammari et al. 2023, Mei et al. 2023). Infanticide-related BNST^{Esr1} cells decrease excitability in lactating females (Mei et al. 2023). VMHvll^{Cckar} cells increase excitability and decrease spontaneous inhibitory postsynaptic current frequency during estrus (Yin et al. 2022). VMHvl^{PR} cells, likely the *Cckar*-expressing subpopulation, increase axon density in the AVPV during estrus (Inoue et al. 2019). These changes in synaptic connectivity and cell excitability could collectively alter the input-output relationship of the social behavior circuits and, ultimately, the readiness to express specific social behaviors.

Though less studied, estrogen can induce rapid morphological and electrophysiological changes in a shorter timescale through nongenomic mechanisms (Brann et al. 2022;

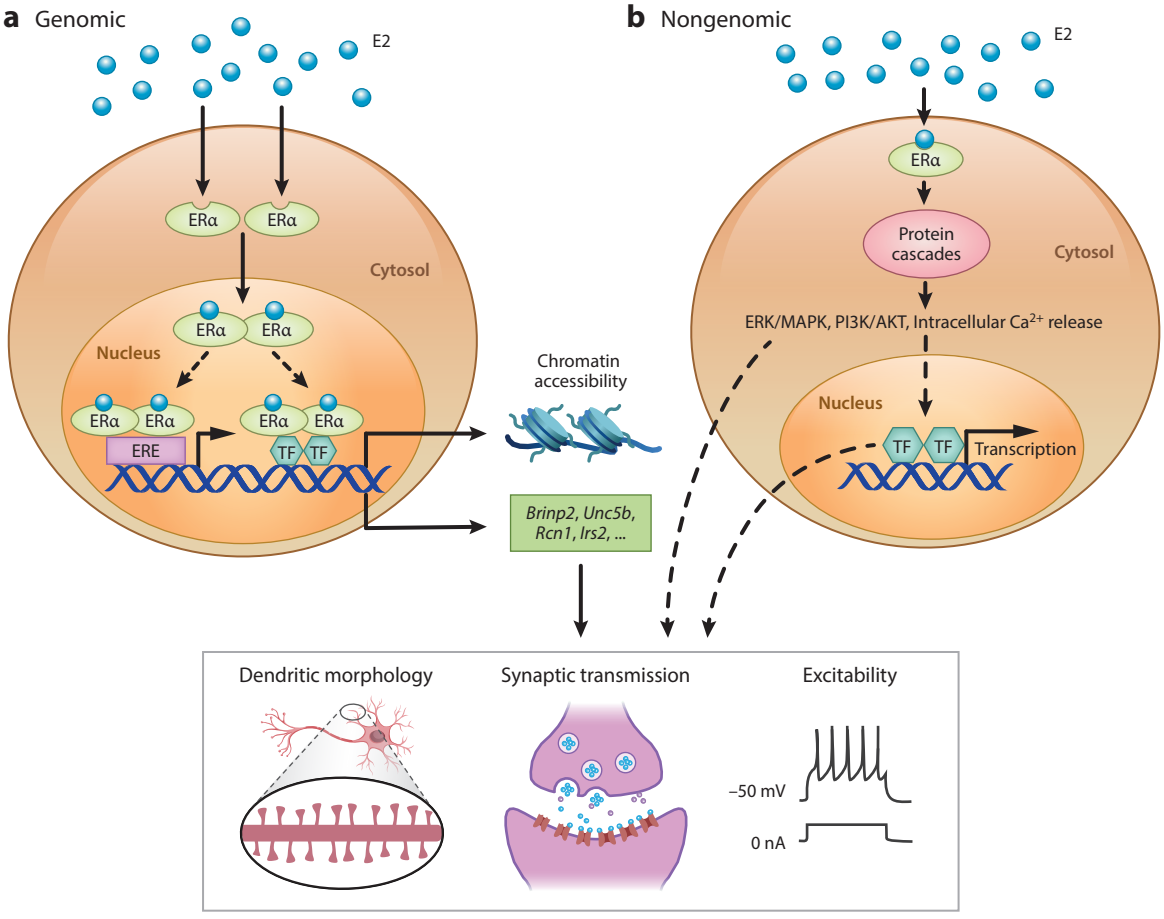


Figure 3

Estrogen-dependent genomic and nongenomic effects. Estrogen binding to ERα results in an intracellular cascade leading to short-term nongenomic and/or long-term genomic transcriptional, molecular, and electrophysiological changes. (*a*) Estrogen's genomic effects result after estrogen binds to ERα, which enters the nucleus, dimerizes, and binds to the ERE, resulting in differential gene expression of a wide array of genes in a region-specific manner. Dimerized ERα can also bind to other transcription factors and sex hormone receptors to lead to additional transcriptional regulation, including increases in chromatin accessibility. These changes in gene expression result in changes in dendritic morphology and synaptic transmission, as well as intrinsic increases in cell excitability, which can lead to long-term potentiation and strengthening of circuits. (*b*) However, estrogen can also result in short-term nongenomic changes by its binding to cytosolic ERα, leading to a protein kinase cascade and activation of the ERK/MAPK and PI3K/AKT pathways, as well as increases in intracellular calcium release, which can directly lead to synaptic changes and excitability increases. These pathways can also indirectly result in the transcription of relevant genes to exert longer-lasting effects. Abbreviations: *Brinp2*, BMP/retinoic acid inducible neural specific 2; E2, 17β-estradiol; ERE, estrogen-responsive element; ERK/MAPK, extracellular signal–regulated kinase 1 and 2/mitogen-activated protein kinase; ERα, estrogen receptor 1; *Irs2*, insulin receptor substrate 2; PI3K/AKT, phosphatidylinositol 3-kinase; *Rcn1*, reticulocalbin 1; TF, transcription factor; *Unc5b*, unc-5 netrin receptor B.

Bueno & Pfaff 1976; Gould et al. 1990; Kelly et al. 1976, 1992; Laredo et al. 2014; McEwen 2002; McEwen et al. 2012) (**Figure 3*b***). Estrogen binds to ERα in the cytoplasm, activating a protein kinase cascade that increases intracellular cAMP (Beyer & Karolczak 2000, Vasudevan & Pfaff 2008, Zheng et al. 1996). The increased cAMP then triggers synaptic and cellular changes through mechanisms that remain incompletely understood (Beyer & Karolczak 2000, Laredo et al. 2014,

Murphy & Segal 1997). In the dorsal hippocampus, in vivo infusion of E2 could increase spine density, which critically depends on the activation of extracellular signal–regulated kinase 1/2 (ERK) and mammalian target of rapamycin (mTOR) (Tuscher et al. 2016). Estrogen can also increase spine density by upregulating brain-derived neurotrophic factor (Singh et al. 1995, Sohrabji et al. 1995) and its receptors, tyrosine kinase receptors A and B (TrKA and TrKB) (Luine & Frankfurt 2013), which promote synaptogenesis (Santos et al. 2010). Slice recording in the VMH showed that bath application of EB could increase cell excitability through regulation of NMDA and histamine receptors, which could represent a potential mechanism for changing VMHvll^{Cckar} cell excitability over the estrous cycle (Kow et al. 2005, Yin et al. 2022). It is likely that estrogen modulates the cell activity in the SBN through both genomic and nongenomic actions, and the exact action may vary from cell to cell.

CONCLUDING REMARKS AND OPEN QUESTIONS

From manipulating sex hormones (gonadectomy and estrogen supplementation) of the whole animal to manipulating estrogen receptors and their expressing cells in specific brain regions and pathways, the critical role of estrogen in orchestrating social behaviors has been firmly established. Hours after birth, the surge of testosterone in males, which is then converted to estrogen, is responsible for the structural differences in social behavior circuits between sexes (McCarthy 2008). During puberty and continuing in adult life, sex hormones are indispensable for keeping the social behavior circuits active and sex-specific. While thousands of genes are differentially expressed between males and females in the limbic system, removing sex steroid hormones nearly eliminates these gene expression differences between sexes (Gegenhuber et al. 2022). In adult females, estrogen, together with progesterone, fine tunes the social behavior circuits during the estrous cycle, pregnancy, lactation, and menopause to ensure the appropriate and timely expression of specific social behaviors for the continuation of the species. In adult males, estrogen (or testosterone, the main source of estrogen) does not vary in an autonomous fashion. However, it surges during or after social behaviors, such as copulation and aggression, and likely plays important roles in reinforcing the behavior circuit to facilitate future behavior expression (Hirschenhauser & Oliveira 2006, Wingfield et al. 1990). Thus, sex hormones, especially estrogen, are the master controllers of nearly all aspects of social behaviors, from their emergence to their maintenance.

Estrogen appears to mainly act through ERα to control social behaviors. Fewer studies have focused on ERβ, possibly due to a lack of strong social behavior deficits after *Esr2* KO, although some studies have revealed the potentially complementary roles of ERβ and ERα (Naulé et al. 2016, Nomura et al. 2006, Ogawa et al. 1999, Zhou et al. 2023). ERα ultimately modulates social behaviors via *Esr1*-expressing cells, which are proven to be critical mediators for all social behaviors. Thus, if a brain region is involved in multiple social behaviors, for example, VMHvl in females or MPOA in males, ERα likely marks multiple functionally heterogeneous populations. Additional molecular markers likely exist to label subsets of *Esr1*+ cells, each involved in one social behavior, for example, VMHvl^{Cckar} cells for female sexual behaviors and VMHvl^{Npy2r} cells for female aggression. These refined markers could provide more precise access to the social behavior circuit of interest.

Despite the tremendous progress made in recent years regarding estrogen control of social behaviors, many questions remain. First, how does ERα activation result in changes in neural circuits? More specifically, what are the molecular events that link estrogen to the physiological, morphological, and connectivity changes? ERα can change the accessibility of thousands of chromatin regions and regulate over 1,000 genes (Gegenhuber et al. 2022, Knoedler et al. 2022). Some of the ERα-targeted genes are transcription factors themselves and could further change

the expression of many other genes. Thus, the possible intracellular effects caused by ERα activation seem endless and are likely cell-specific. Are there some general principles underlying the differential effects of estrogen on *Esr1*-expressing cells? Although we have considered ERα expression as binary (negative or positive), this is far from the reality. ERα expression levels could differ significantly in the same brain region between sexes (e.g., male and female BNST) or between subpopulations in the same region (e.g., female lateral VMHvl versus medial VMHvl). How estrogen modulation varies with ERα expression level is an important question for future investigation.

Second, how do different sex hormone receptors interact to change the properties of a cell? Cells in the limbic system often coexpress multiple sex hormone receptors. For example, PR and androgen receptor are abundantly expressed in most *Esr1*-expressing VMHvl, MPOA, BNST, and MeA cells, although their relative levels vary across clusters of cells (Knoedler et al. 2022). In particular, male estrogen is largely converted from testosterone by aromatase in the brain. How the estrogen level is controlled and how it is coordinated with testosterone action remain unclear.

Lastly, although ERα is a key feature of the SBN, it is conceivable that *Esr1*− cells that receive inputs from *Esr1*-expressing cells could change their output based on estrogen level and participate in social behaviors (Fukui et al. 2022).

In summary, estrogen binds to ERα to induce diverse cell-specific changes in electrophysiological properties, gene expression, morphology, and circuit connectivity. These changes collectively ensure that the social behavior circuit is optimally prepared to respond to the right social target for the ultimate purpose of reproduction. Recent advancements in genetic and circuit tools give us a glimpse of the vast molecular space estrogen can access. We are entering an exciting new era to uncover the molecular milieu via which sex hormones powerfully coordinate diverse social behaviors throughout the lifespan.

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