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## Genetic, Epigenetic and Environmental Impact on Sex Differences in Social Behavior

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### Abstract

The field of behavioral neuroendocrinology has generated thousands of studies that indicate differences in brain structure and reactivity to gonadal steroids produce sex-specific patterns of social behavior. However, rapidly emerging evidence shows that genetic polymorphisms and resulting differences in the expression of neuroactive peptides and receptors as well as early life experience and epigenetic changes are important modifiers of social behavior. Furthermore, due to its inherent complexity, the neurochemical mechanisms underlying sex differences in social behavior are usually studied in a tightly regulated laboratory setting rather than in complex environments. Importantly, specific hormones may elicit a range of different behaviors depending on the cues present in these environments. For example, individuals exposed to a psychosocial stressor may respond differently to the effects of a gonadal steroid than those not exposed to chronic stress. The objective of this review is not to re-examine the activational effects of hormones on sex differences in social behavior but rather to consider how genetic and environmental factors modify the effects of hormones on behavior. We will focus on estrogen and its receptors but consideration is also given to the role of androgens. Furthermore, we have limited our discussions to the importance of oxytocin and vasopressin as targets of gonadal steroids and how these effects are modified by genetic and experiential situations. Taken together, the data clearly underscore the need to expand research initiatives to consider gene-environment interactions for better understanding the neurobiology of sex differences in social behavior.

### Keywords

social behavior; sex differences; epigenetics; gene polymorphisms; social environment

### Introduction

Many facets of behavior are thought to be governed by the activational effects of gonadal hormones acting on neurochemical circuits within cortico-limbic-hypothalamic regions of the brain [1,2]. Moreover, studies indicate that gender differences in brain structure and in reactivity to gonadal steroids produce sex-specific manifestations of social behavior. It is known, for example, that exposure to androgens during critical periods of pre- and postnatal

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brain maturation organizes the brain to produce a range of sex differences in brain structure, the distribution of steroid receptors, and neuropeptide gene expression that ultimately regulates behavior [3,4]. However, gender differences in behavior are not limited to the effect of perinatal gonadal hormone exposure alone as recent studies of mutant mice reveal that the presence of the *Sry* gene on the Y chromosome accounts for sex differences in some behaviors independent of testis formation and secretion of androgen during prenatal development [5–7]. These topics have been well studied, as a PubMed search yields over 10,000 citations for sex differences in brain organization and over 30,000 citations for sex differences in behavior.

The field of behavioral neuroendocrinology has historically designed experiments to dissect behavior and identify the hormonal - neural interactions that produce specific behaviors and, when appropriate, to see how these differ between males and females [8,9]. However, the expression of social behavior is more complex than simply the result of a particular pattern of gonadal steroid stimulation of a sex-specific brain organization. Due to its inherent complexity, the physical and biochemical mechanisms underlying social behavior are usually studied in a tightly regulated laboratory setting rather than within a natural environment. Nevertheless, it is well appreciated that social behavior does not occur in a vacuum but rather is the reciprocal response to the action of a conspecific. Thus, a critically important variable is the socio-environmental context in which the behavior occurs. Consequently, hormones elicit specific behaviors when appropriate cues are present in the social environment [10]. For instance, while increased estradiol concentrations clearly elicit proceptive and receptive behaviors in female macaques in response to the presence of a male [11], these behaviors typically occur coincident with increased aggression as a consequence of competition for mates and a decrease in interaction with kin [12,13]. Hence, a specific social context and exposure to a particular pattern of hormones elicits multiple behaviors in an individual. In addition, other behaviors that do not involve interactions with conspecifics may also be important in understanding factors that modify the hormonal regulation of behavior. For example, in the absence of an available male, what behavior is elicited by estradiol in a female macaque? While ethologists would predict that displacement behaviors [14] signifying increased rates of anxiety would occur [15], the crucial point is that social context changes the behavior elicited by a specific hormonal milieu.

In addition to the presence or absence of appropriate cues, several other factors may alter the action of hormones on social behavior. A number of studies now show that genetic polymorphisms and resulting constitutive differences in neuroactive peptides and receptors [16,17] as well as early life experience and epigenetic changes [18,19] may modify the activational effects of hormones on social behavior. In addition, exposure to stressors, especially those of a psychosocial nature, may affect the ability of hormones to elicit specific social behaviors [20]. Because males and females generally respond and thus adapt differently to psychosocial stress exposure [21–26], one might assume that stressor exposure leads to different outcomes with regard to the activational effects of steroids on behavior. Despite an extensive history of investigating the importance of hormones for the expression of social behavior in males and females using a wide range of animal models and experimental approaches [27], the importance of the stress background to reduce or alter the hormone-induced expression of social behavior has received little attention.

The objective of this review is not to re-examine the well-researched activational effects of hormones on social behavior, but to delve into relatively new or poorly understood topics relevant to the control of social behavior. Included in these topics is the effect of polymorphisms in the gene encoding the estrogen receptor, and within neurotransmitter systems that are modulated by estrogen. In addition, the effect of psychosocial stress on the expression of social behavior is reviewed. Finally, the effect of early environment modulation of gene expression on social behaviors is discussed.

## Neural substrates for social behavior

A neural circuitry involving limbic and hypothalamic areas has been described as the target for steroid hormone regulation of social behavior, including the medial amygdala (MeA), bed nucleus of the stria terminalis (BNST), medial preoptic area (mPOA), anterior hypothalamus (AH), ventromedial hypothalamus (VMH), lateral septum, and midbrain [28]. In addition to expressing androgen (AR) and estrogen receptors (ER) in a sexually dimorphic pattern, these regions receive input from and send projections to cortical areas for processing information from the environment [29,30].

Isoforms of the estrogen receptor, designated as ER $\alpha$  and ER $\beta$ , have a distinct and overlapping distribution in the mammalian brain [31–34]. The existence of one or both receptor subtypes in several limbic system nuclei as well as in hypothalamic and brain stem regions critical for emotional expression and memory formation, strongly suggests that these two ER subtypes participate in the control of other types of behaviors in addition to those modulating reproductive function. Indeed, recent studies in rodents using selective ER agonists indicate that the anti-anxiety effects of estradiol are mediated through activation of the  $\beta$  receptor [35, 36]. Activation of ER $\alpha$ , on the other hand, seems to be necessary for reproductive behavior and, interestingly, is shown to be anxiogenic in some paradigms [35]. Thus, the simultaneous activation of ER $\alpha$  and ER $\beta$  by application of exogenous estradiol to brain regions that have both receptor subtypes like the BNST, the basolateral nucleus of the amygdala, and the hippocampus may somewhat obscure the effects of estradiol on measures like fear and anxiety.

As noted above, there is a vast literature on the sex differences in the activational effects of sex steroids on social behavior, e.g., the importance of estradiol [37] and specific ER subtypes [38] for female sexually motivated behavior females; the importance of both androgens and estrogen in male sexual behavior [39,40]; the role of androgens in eliciting aggressive behavior [41,42]. The neurochemical targets of these steroids are many. For example, a role for estradiol-induced changes in striatal dopamine in sexually motivated behavior is established [43] as is the importance of androgen regulation of serotonin for inter-male aggressive behavior [44, 45].

The central action of estrogen and androgen in the regulation of social behavior is also mediated by oxytocin (OT) and arginine vasopressin (AVP) [46]. Although data suggest that AVP is more prominent in the expression of male social behaviors while OT is essential for the expression of many female social behaviors [47,48], clearly these neuropeptides influence social behavior in both sexes. Although peripheral AVP has an antidiuretic function, central AVP activity has been linked to scent marking behaviors, aggression, parental behavior, pair bonding, and social recognition in males from a range of mammalian species (reviewed in [47]). Likewise, OT has peripheral effects on contraction during labor and lactation after birth, but its central action influences maternal care, pair bond formation, social recognition, and social motivation in females from a number of species (reviewed in [49]). It is important to note, however, that while the sexes may require different neuropeptides for the expression of social behavior, activity of both systems can influence social behavior. Often, the neuropeptides govern the same behavior in different sexes. For example, OT is necessary for formation of pair bonds in female prairie voles [50], whereas AVP is necessary for this behavior to occur in males of the same species [51]. The importance of OT and AVP for social behavior in lower animals has led to an interest in their functions in humans. Studies in people have found links between neuropeptide activity in the amygdala and the expression of more complex emotions like love, fear, and trust [52].

The extended amygdala, including the BNST and the MeA are the primary source of AVP-immunoreactive fibers to the forebrain [53], with male mammals generally having more

innervation than females. AVP neurons in the extended amygdala express both ER and AR [54]. Consequently, the expression of AVP in the extended amygdala of males is dependent upon both androgens and testosterone, as dihydrotestosterone (DHT) and estradiol replacement more closely normalizes AVP expression than either steroid alone [55].

Neuronal populations of OT and AVP within limbic-hypothalamic areas are targets of estradiol; ER $\beta$  is colocalized with AVP and OT neurons in parvocellular regions of the hypothalamus [56]. The oxytocin/vasopressin family of peptides is highly conserved, with homologs present in a range of vertebrate and non-vertebrate species. While the behaviors influenced by OT and AVP are species specific [57] due largely to the species-typical expression of the peptide and receptors [47], the actions of these neuropeptides are generally prosocial, stimulating interactions between conspecifics [49]. In addition to a species typical pattern of expression, the receptor distribution shows a sexually dimorphic pattern within species [58]. Finally, polymorphisms in genes encoding these receptors account for individual variation in behavior within species [59].

Like AVP, OT released from the posterior pituitary has a number of peripheral effects such as uterine contractions and milk let down during lactation [60]. Importantly, OT has long been implicated as a key neuropeptide in establishing social bonding in mammals [61], but its precise role in facilitating social behaviors may be dependent upon the species specific distribution of OT receptors [62]. Social recognition in mice is disrupted if the genes for ER $\alpha$ , ER $\beta$ , or OT are deleted [63]. Because this behavior is dependent upon OT binding to OT receptors in the amygdala [64], these data suggest that estradiol acts through ER $\beta$  to increase OT in the paraventricular nucleus (PVN) of the hypothalamus and through ER $\alpha$  to increase the oxytocin receptor (OTR) expression in the amygdala [63,65]. Obviously, disruption of the specific ER subtype or OT synthesis could negate any behavioral effects of estradiol.

Any number of neurochemicals may mediate the effects of steroid-induced changes in AVP and OT in the regulation of sex differences in social behavior of males and females (e.g. [66–68]). However, this review will focus how gene polymorphisms, social context, and experientially-mediated epigenetic changes in gene expression may modify the role of steroids, OT and AVP, and their interactions on social behavior.

## Gene polymorphisms regulating social behavior

One cause of variability in behavior that is receiving more attention is the possibility that particular predispositions may be conferred on an individual due to specific modifications in genotype [69,70]. Changes in the DNA sequence encoding hormones, neuropeptides, or associated proteins can affect the social behaviors regulated by these factors. For example, single nucleotide polymorphisms (SNP), which are small changes in DNA coding mutations that result in the substitution of one amino acid for another in the final protein product, and variations in regions upstream to an exon have been found to differentially influence social behavior [71,72]. Importantly, polymorphic loci within the DNA of genes encoding vasopressin and oxytocin and its receptors as well as those encoding estrogen receptors, may account for variability in social behavior. The neuropeptide AVP is implicated in a wide array of social behaviors [47]. The expression of one of its receptors (V<sub>1a</sub>) correlates with variation in social behavior across and between species [73], suggesting that polymorphisms in regulatory regions may underlie differential expression of this receptor. Indeed, it has been shown that a microsatellite repeat within the 5' regulatory region of the gene encoding the V<sub>1a</sub> receptor (*AVPR1a*) is responsible for region-specific regulation of V<sub>1a</sub>R expression as well as increased paternal behavior [59] and affiliative behavior toward a female conspecific [74] in male voles. The influence of this polymorphism on social behavior in rodents and the

description of SNPs within *AVPR1a* [75] have since led to an increase in the number of studies looking at *AVPR1a* SNPs and associations with social behavior in humans.

Indeed, human behaviors analogous to those studied in rodents have been linked to *AVPR1a* polymorphisms. One such polymorphism is associated with marital status and perceived marital problems in males but not females, and in the study that showed this, genotype was even linked to the carrier's spouse's perception of the relationship [76]. Reproductive behavior has also been linked to *AVPR1a* polymorphisms, as both men and women carrying the long allele of one such SNP tend to have first sexual intercourse at an early age [75]. A behavior as unique to humans as creative dance is also linked to a specific *AVPR1a* polymorphism [77]. Eating behavior, specifically dietary restriction for weight loss purposes, also has a strong association with the RS3 microsatellite located in the *AVPR1a* promoter region [78]. More recently, the association of this same RS3 microsatellite has been linked to altruism, assessed by individual play of a dictator game, as individuals carrying the long allele of RS3 allocated more money to other players than individuals carrying the short allele at this locus [79]. The same study showed that the long variant of RS3 was associated with higher levels of  $V_{1a}R$  mRNA in the hippocampus in postmortem human tissue, further suggesting that variability in behavior could be due to natural variation in the genome. The *AVPR1a* RS3 polymorphism has been described in multiple non-human primates, including chimpanzees, bonobos, and macaques, allowing for future assessment of differences in social behavior between species that correlated with these SNPs [80]. Finally, it is important to note that dysfunction of social cognition, as observed in autism spectrum disorders, has also been associated with specific SNPs in *AVPR1a* [81,82].

OT is also implicated in social cognition, as it has been linked to social recognition and motivation, maternal behavior, and sexual behavior [83–85]. Expression levels and innervation of OT itself are similar between species, whereas distribution of OTR is highly variable between species and may explain species differences in social behaviors such as parental care [86] and formation of pair bonds [48]. Variability in site-specific expression levels of the oxytocin receptor gene (*OXTR*) is associated with variation in maternal care [87,88] as OTR densities in the nucleus accumbens, caudate-putamen, and lateral septum correlate with parental care across rodent species (voles, rats, and mice) and between individuals of the same species [86,89]. Unlike the *AVPR1a* SNP that has an ample literature, accounts of behavioral associations with polymorphisms within the *OXTR* sequence are sparse. One report associates an *OXTR* SNP with a higher tendency for females to parent children at an earlier age [90]. As OT is critical to social cognition, it is not surprising that polymorphisms in *OXTR* are also associated with autism in multiple cultural populations [91,92].

Because both the  $V_{1a}R$  and the OTR are inherited on autosomes, it is unlikely that there is any gender specificity in the polymorphisms associated with AVP or OT. Indeed, the presence of sex differences within these polymorphic neuropeptide systems has not been pursued as no studies have specifically looked for such differences. However, because both AVP, OT and their receptor systems are modulated by gonadal steroids, it is important to examine whether transcriptional control of these peptides by gonadal hormones is affected by these polymorphisms, and whether this occurs in a sex-specific fashion. The AVP system is one of the most sexually dimorphic systems within the central nervous system, showing sex-specific receptor distributions in the amygdala, BNST, periaqueductal grey, septum, and mPOA across a number of mammalian species [47], as well as a sexual dimorphism in AVP projections from the BNST to the amygdala [53]. Sex differences in AVP activity are not surprising considering that androgens and estrogen regulate release of AVP and expression of AVP receptors [53]. Likewise, the importance of estradiol in regulating the OT system is well documented. Estradiol administration increases OT and OTR expression within the PVN of the hypothalamus [93–95] through the activity of estrogen receptors alpha and beta respectively [38]. It is also well

established that the effects of estradiol on OT facilitate the expression of female sexual behavior in lower mammals [94].

The interaction between the activation of ERs and up-regulation of the OT system implicates a possible role of ER polymorphisms in affecting social behavior. Most reports of associations between specific ER SNPs and behavior revolve around emotional behavior and personality types, both important determinants of social behavior. Several studies have looked at anxiety behavior and polymorphism in the human estrogen receptor alpha gene (*ESR1*) and have found associations between polymorphisms and anxiety in both males and females [96–98]. One such study showed that the PvuII and XbaI polymorphisms in *ESR1* correlated with increased anxiety in postmenopausal women but not in men [99]. Studies looking for associations between *ESR1* SNPs and depressive behavior have reported mixed results as both PvuII and XbaI polymorphisms in *ESR1* correlate with major depressive disorder in women and not men [100], but not with suicidal behavior or aggression-related traits [101]. Furthermore, personality traits such as non-conformity, including indirect aggression, irritability and psychoticism, are associated with a repeat sequence SNP in *ESR1* in women [102].

Not all *ESR1* polymorphisms are associated with increased vulnerability to emotional regulation disruptions, as even the comparatively rare variants of *ESR1* SNPs are not associated with psychiatric disorders [103]. To date, only one study has reported correlations between *ESR1* polymorphisms and reproductive fecundity. Italian men carrying a specific allele had a higher number of children whereas Italian women showed a lower rate of abortion [104]. This same study correlated an *ESR1* SNP with increased number of offspring in African-Ecuadorian women. Overall, there is a lack of data surrounding polymorphisms of *ESR1* and correlations with more traditional social behaviors like those discussed with OT and AVP systems. This disparity is due to minimal accounts of how this polymorphic locus associates with more basic social behaviors in lower order animals as well as humans.

Importantly, estradiol is not only crucial in the mediation of neuropeptide systems mediating social behavior, but also vital in the regulation of neurotransmitter and neurochemical signals, including serotonin (5HT), that are involved in social behavior. Estradiol is not only capable of changing levels of 5HT [105–110], but also of modulating expression levels of critical serotonergic proteins, including 5HT receptors and the serotonin reuptake transporter (5HTT) [111–116]. Variations in these proteins are known to influence mood regulation and social behavior. Of particular interest is 5HTT and the gene encoding it (*Slc6a4*), as polymorphisms in *Slc6a4* have been linked to distinct behavioral phenotypes in a number of species. The short variant polymorphism in the promoter region of the gene encoding 5HTT diminishes transcriptional activity compared to the long allele [117] and is associated with a higher incidence of anxiety and depression in response to life stressors [118–121]. It is likely that these emotional predispositions can influence the expression of social behavior, as female rhesus macaques carrying the short variant of 5HTT initiate more aggressive and submissive behavior towards run-mates than females carrying the long allele [122].

The polymorphisms described above confer predispositions upon their carriers that influence, but do not solely determine, the resulting behavioral phenotype. These genotypes ultimately interact with the environment to impact the expression of behavior. A particularly striking example of this phenomenon can be seen in the study of the 5HTT polymorphism, where the short allele is associated with a potentiation of the effects of adverse early social experience on behavior [123,124] as well as an increased response to psychosocial stress in adults [125]. The next section will focus on environmental control of behavior and the roles of stress and reproductive hormones as mediators of this relationship.

## Social context and the hormone regulation of behavior

The notion that socio-environmental factors can modify the expression of hormone-dependent behaviors implies information from the environment is encoded into neural connections that act on targets of hormones regulating prosocial behaviors. Activation of stress hormone pathways likely represents one such circuit that can modify behavior. The stress response is integrated through limbic and forebrain circuits coordinating the release of corticotropin-releasing hormone (CRH) and AVP from the hypothalamic PVN, which act synergistically through specific receptors in the pituitary to release ACTH that, in turn, stimulates adrenal glucocorticoid release [126]. This response is terminated by glucocorticoid negative feedback through glucocorticoid receptors (GR) in the pituitary, PVN, and noradrenergic neurons in the locus coeruleus (LC) as well as mineralocorticoid receptors (MR) in the hippocampus [127–129]. During prolonged exposure to stressors, however, CRH is up-regulated in the CeA and the BNST [130–132] and acts through CRH<sub>1</sub> receptors to down-regulate GRs in the PVN and LC, subsequently diminishing glucocorticoid negative feedback and increasing CRH and AVP in the PVN [133–135]. The result is continuous, unchecked activation of the stress axis, leading to alterations in physiology and behavior.

Ample evidence indicates that estrogens, as well as several other types of gonadal steroids, actively control the function of the LHPA axis. Studies on rats have found higher ACTH levels subsequent to acute stress at proestrus or following treatment with proestrus levels of estrogen, and longer lasting post-stress elevations of corticosterone in female rats treated with estradiol or estradiol and progesterone [136]. Estradiol increases ACTH secretion in female baboons [137] and increases ACTH and cortisol by decreasing glucocorticoid negative feedback in female monkeys [138]. In women, exercise stress enhances ACTH and AVP only in the mid-luteal stage when ovarian hormones are rising [139]. These studies suggest that estradiol stimulates the LHPA axis across several species and that this may be exaggerated when estradiol levels are increasing. Indeed, chronic low estradiol replacement reduces LHPA activation in female rats [140]. Importantly, the stimulation of the LHPA by rising levels of the estradiol concomitantly induces a range of behaviors, including proceptive and affiliative behaviors. Thus, the reduction of estradiol, or perhaps the addition of progesterone, may reverse the stimulatory effect of estradiol. For example, estradiol enhances the increase in *c-fos*, CRF, and AVP expression in the PVN [141] and directly stimulates the gene for CRH [142], but reduces biosynthetic enzymes for brain stem catecholamines if given daily for 16 days prior to immobilization stress [143]. In another study, *in situ* hybridization for CRH in the PVN of rhesus monkey following the maintenance of artificial menstrual cycles found that CRH was significantly higher in the simulated follicular phase than in the simulated luteal phase [144]. Moreover, these differential effects may be mediated by opposing activation of ER $\alpha$  versus ER $\beta$ . For instance, ER $\alpha$  induces and ER $\beta$  represses activity in the promoter region of the human CRH-binding protein gene [145], and ER $\alpha$  enhances and ER $\beta$  inhibits transcription of the urocortin gene [146]. ER $\beta$  in the PVN is increased by corticosterone treatment [147], and ER $\alpha$  co-localization is increased in the PVN in brains from people suffering from major depressive and bi-polar disorder [148]. Together these studies suggest that estradiol is modulating LHPA activity through the specific activity of each particular intracellular receptor subtype. Further, these data suggest that stress can modify ER $\alpha$  and ER $\beta$  densities hypothalamic regions, potentially modifying estradiol action on prosocial behaviors.

Sex differences in LHPA axis activation can be attributed in part to differential responses to sex hormones. In the same way that estrogen can stimulate CRH expression by acting on estrogen response elements (EREs) adjacent to the CRH gene [149], androgens act on androgen response elements (AREs) in the promoter of the CRH gene to repress its expression [150]. The same study that reported on these AREs found colocalization of AR in CRH-producing neurons in the PVN of the hypothalamus, suggesting that androgen exposure here can attenuate

CRH expression at the top of the axis. However, other research has shown that the non-aromatizable androgen DHT influences CRH expression primarily via ER $\beta$ , rather than AR [151]. Support for the notion that androgens have an inhibitory effect on LHPA axis activation is evident [152–155], although the precise mechanisms of androgenic control remain uncertain. One study found that GR expression in the PVN was decreased in castrated males compared to gonadally intact or androgen-replaced rats [155], and this implicates sensitivity to negative feedback as the mechanism of androgen activity on the axis. These findings, however, conflict with research that found that LHPA responsivity in male rats is not mediated by changes in glucocorticoid receptor binding in hypothalamic or limbic areas [153]. Importantly, the sex difference in LHPA responsivity may be mediated through glucocorticoid negative feedback as differences in ACTH between males and females are absent following adrenalectomy [156]. On a more organismic level, the inhibitory effect of androgens on the stress axis is corroborated by the observation that aging males experience an increase basal cortisol levels during a time when circulating testosterone levels are decreasing [157]. This relationship could also explain why older men with lower levels of circulating testosterone experienced greater incidence of depressed mood in one study [158]. Taken together, the studies discussed above underscore the importance of sex hormone interactions with the LHPA axis and provide a substrate for the sexual dimorphism in LHPA reactivity. Signals resulting from this sex specific activation of the LHPA axis could target cortico-limbic-hypothalamic circuits regulating social behavior and may explain why males and females respond differently to aversive social experiences life.

While chronic activation of the LHPA axis can broadly affect physical and emotional health [159,160], the adverse effects of chronic stress on the reproductive axis have been studied extensively. A direct role of stress hormones in the etiology of reproductive suppression is suggested by a number of pharmacological studies. Exogenous cortisol reduces luteinizing hormone (LH) pulse frequency during the follicular phase in normal women [161]. Furthermore, CRH administered centrally inhibits LH secretion in female rats [162] and monkeys [163]. This inhibition was not attributed to CRH-induced increases in glucocorticoids, as administration of ACTH which produced a comparable increase in serum cortisol as did CRH, failed to affect LH secretion [164]. However, a recent series of studies with ewes indicate that cortisol inhibits pulsatile LH by reducing pituitary responsiveness to gonadotropin-releasing hormone (GnRH) [165,166]. The effect of all these factors in suppressing the effects of estradiol is thought to underlie the amenorrhea of stress observed during psychopathologies associated with long-term disruption of the LHPA axis. However, the important question for this review is whether exposure to stressors attenuates the activational effects of gonadal steroids on social behavior.

### **Behavioral consequences of stressor exposure**

The central role of CRH and AVP in mood disorders in humans is supported by studies in animals [167]. The over-expression of CRH in mice is anxiogenic [168] and rats bred for high anxiety have reduced glucocorticoid negative feedback, increased sensitivity to CRH, and more AVP in the PVN [169–171]. Similarly, CRH given centrally increases anxiety and depression in monkeys [172]. Antagonism of the AVP V<sub>1a</sub> and V<sub>1b</sub> receptors [170,173,174] or CRH<sub>1</sub> or CRH<sub>2</sub> receptors [175–181] reduce anxiety in both rodent and nonhuman primate models, indicating these neuropeptides are involved in stress-induced anxiety and depression [170, 182,183]. The same is implicated in anxiety, depression, post-traumatic stress disorder and anorexia [142,184,185].

These data imply that stress-induced up-regulation of CRH/AVP circuits in cortico-limbic-hypothalamic circuits that produces anxiety and depression may also affect prosocial behavior in part by altering the behavioral efficacy of estradiol. For instance, a meta analysis of double-



blind controlled studies indicates that estradiol replacement improves general well-being in some women but it is unclear what accounts for differences in sensitivity [186]. The observation that affective disorders, including major depression and anxiety, occur with greater frequency in women and emerge predominately during a women's reproductive years, especially during times of hormonal flux, implies that estradiol plays a key role in the neurobiology of emotional well being [187–193]. Data from animal models also show the importance of estradiol in the regulation of emotional behavior. Female rats often exhibit less fear or anxiety-like behavior than do their male conspecifics [194,195]. However, this tendency is observed during the afternoon of proestrus, when the ovarian hormones estradiol and progesterone are at their peak. Proestrus females show reduced periods of immobility in the Porsolt forced swim tests, increased latencies in burying an electrified prod, and more time spent in the open arms of the elevated plus maze than do diestrous females or males [196,197]. These data suggest an attenuation of fear and anxiety in females at the time of proestrus (or behavioral estrus) due to high endogenous levels of ovarian hormones. Accordingly, long periods of anovulation and associated hypoestrogenism are characteristic of female macaques that exhibit behavioral indices of depression analogous to those seen in women [198,199]. Although the hormonal effects discussed above all concern mood, it is important to keep in mind that emotion is an important modulator of social behavior. For instance, a primary symptom of depression in humans is the withdrawal from social interaction [200].

Most studies looking at the effect of estradiol on mood focus on reductions in anxiety in women and anxiety-like behavior in animal models. However, it is rare that any type of psychopathology is unitary, and although anxiety is indeed a component of many psychiatric illnesses several other emotional states are usually also associated with depression. Indeed, one of the most universal symptoms in depression is a severe drop in motivation to engage in social interactions [200]. People suffering from depression are often anhedonic, in that they eat too little or too much and lose interests in sex and other activities that they had previously experienced as pleasurable [200]. These symptoms have lead a growing number of investigators to suggest that dysfunctions in brain systems governing motivation and reward may be involved in the etiology of these diseases (for a review see [201]). It is well established that estradiol is motivational with respect to the induction of sexual behavior [202]. In addition, estradiol enhances cocaine seeking behavior [203], produces conditioned place preference [204] in rats, and induces increased rates of intracranial self-stimulation in female rats [205]. The involvement of estradiol in systems involved with reward and motivation has thus far been largely ignored when considering the mechanism whereby estradiol exerts its beneficial effects on emotion. Thus, it seems that both the activational and the anxiolytic effects of estradiol take part in mediating active social behavior, and that both of these effects are disrupted by psychosocial stress.

The data discussed above, as well as the notion that estradiol may improve depressive symptoms associated with the perimenopause [206,207] and post partum depression [208, 209], may suggest that hypoestrogenism precipitates mood disorders. Clearly, this is not the case as individuals show a differential behavioral sensitivity to estradiol depletion. Socioeconomic and life style factors interact with neuroendocrine status to determine social – emotional wellbeing [193,210,211]. In addition, certain individuals may be more susceptible to the deleterious effects of hypoestrogenism [212,213] as the severity of depressive scores during premenopause predicts mood disturbances during perimenopause [214]. Contextual cues, likely reflecting differential activation of the LHPA axis, are also important since estradiol is anxiogenic and enhances fear learning when anxiety tests are performed in novel environments. In contrast, estradiol is anxiolytic when tests are done in the less stressful, home cage [215–217]. In addition, estradiol is anxiolytic when females are tested in standard open field test but anxiogenic when tested in a social interaction test [218]. A similar context also modifies the response to estradiol in female monkeys, as mate competition results in an increase

in female aggression coincident with rising follicular phase levels of estradiol [13,219]. Furthermore, in this situation, estradiol increases anxiety measures in dominant animals whereas these behaviors are elevated in subordinate females regardless of estradiol concentrations [220]. Yet other studies using rodent models show that estradiol reduces measures of anxiety in females exposed to repeated restraint compared to acute stress [221]. Studies by Wallen [11] demonstrate a correlation between social status position and serum estradiol in the number of sexual solicitations made by female rhesus macaques. In this study, the expression of sexual behavior in more subordinate females is only evident at high levels of estradiol whereas more dominant females can show the same degree of sexual solicitations at lower levels of estradiol. Stated another way, it takes higher levels of estradiol to overcome the social inhibition of sexual behavior in subordinate females. Indeed, restraint stress in rats attenuates the ability of estradiol and progesterone to stimulate the expression of female sexual behavior [222,223] and the continuous expression of CRH in the CeA significantly attenuates the expression of proceptive behavior in ovariectomized, steroid primed rats [224]. Supporting these observations, women suffering from depression and anxiety show reduced libido [225–227]. Thus, context and an experiential background may influence an individual's behavioral response to estradiol.

Unfortunately, additional data systematically evaluating how context or an individual's experiential background alters the anxiolytic action of estradiol are difficult to identify as most studies have used male rodents. Indeed, there is limited data to evaluate how exposure to stress hormones differentially affects the hormonal regulation of social behavior in males and females. Corticosterone facilitates pair bonding in male prairie voles but attenuates the behavior in females [228]. Furthermore, laboratory male but not female rats form dominance hierarchies when housed in a visual burrow system and subordinate males show altered food intake and metabolic dysregulation [229].

The unanswered question is how chronic activation of the LHPA axis can disrupt the behavioral efficacy of gonadal steroids on prosocial behavior. Studies of African cichlid fish show dominant males have greater expression of AR and ER $\beta$  in the brain, which also correlates with testis size [230]. Because sex steroids can regulate the expression of their own receptors [231] and, as noted above, chronic stressor exposure attenuates gonadal hormone secretion, it is possible that the reduction in sex steroid receptors is secondary to a reduction in circulating hormones. However, glucocorticoids render the target tissues resistant to the effect of estradiol [184], presumably by affected expression of ER or posttranslational processing. Furthermore, stress hormones could act to affect targets of sex steroids mediating the regulation of social behavior. For example, glucocorticoids diminish the translation of AVP but not OT in the human hypothalamus [232]. Glucocorticoid or stress exposure increases OT receptor binding in limbic regions [233], but the functional significance of these findings are not known.

Although stressors in the environment can disrupt the activational effects of gonadal steroids with respect to social behavior, the social environment may also serve as a buffer to confer resistance to stress. Understanding the neurobiology of stress resilience is important to treating and preventing psychopathology. The presence of social support has long been known to minimize the adverse effects of exposure to stressors [17,234–236]. A series of recent reviews [17,234] indicate that the presence of a conspecific that engages positive social behaviors (e.g., verbal statements in humans, maintaining proximity, engaging in grooming or contact) attenuates the physiological measures and behavioral indices that typically result from stressor exposure, including cardiovascular responses, glucocorticoid elevation, and anxiety. It is not known how LHPA activation is reduced in individuals receiving prosocial behaviors, but OT release from limbic regions may be involved [61]. Importantly, these effects of OT may be influenced by the stress background of the individual as chronic stressor exposure mediated through GR activation can down-regulate the OT system [237]. The hypothesis is that receiving

affiliative behavior from a conspecific may prevent or override the stress-induced deficits in central OT action. Indeed, OT administered centrally reduces stress-induced glucocorticoid release and anxiety behavior in rats [238,239] and attenuates CRH expression in PVN [240]. Correspondingly, OT knock out mice show increased anxiety and exaggerated corticosterone responses to stressors [241]. Furthermore, the hyposensitivity to stressors in lactating females has also been attributed to the central action of OT [234]. Exposing rabbits to familiar conspecifics increases peripheral measures of OT but not hypothalamic levels and was associated with more affiliative interactions [242]. In women, partner contact increases peripheral concentrations of OT and reduces blood pressure and heart rate [243]. Taken together, these data suggest that the adverse behavioral effects of chronic stress exposure could be attenuated by socially-induced elevations in central OT. If behavior-induced increases in OT account for individual resilience to stress, it would seem that stress-induced attenuation of the behavioral efficacy of estradiol and other gonadal steroids on the regulation of prosocial behavior are due to the stress-induced disruption of OT expression.

In addition to oxytocin, other neurochemicals may also be important but it is unclear whether these mediate gonadal steroid effects on behavior. Neuropeptide Y (NPY) is anxiolytic [17] and when administered to limbic areas, specifically the basolateral nucleus of the amygdala (BLA), in rats reduces the behavioral and sympathetic but not the LHPA activation response to stressors [244]. However, it is not clear whether receiving social support from conspecifics also increases NPY release to amygdala targets as it possibly does with OT. Other studies using a conditioned defeat model in hamsters found that glutamate receptor antagonists and GABA receptor antagonists injected into the BLA prevent the development a depressive phenotype [245]. Furthermore, activation of brain-derived neurotrophic factor (BDNF) and tyrosine kinase receptors (TRK) in the BLA, BNST, and mesolimbic reward pathways mediates the acquisition of behaviors characteristic of conditioned defeat and the absence of motivation to engage in prosocial behaviors [245,246]. While these data do not specifically show how social support attenuates the adverse consequences of psychosocial stressors on prosocial behavior, the data do show how downstream targets of LHPA activation change brain neurochemistry to affect the motivation of individuals to engage in social behaviors [158]. Virtually no studies have examined differences in brain neurochemistry between males and females in response to socially stressful situations. Given that the behavioral response to psychosocial stressors can differ between males and females [247–252], one can assume that the neurochemical changes that occur in response to stressor in the presence and absence of social support may also show a sex difference.

Environmental influence over social behavior as discussed above lasts only as long as the individual's exposure to that environment. For instance, an individual will only benefit from the effects of social support as a buffer so long as he or she is in the presence of supportive conspecifics. Furthermore, it is likely that these environmentally dependent changes are mediated through temporary changes in gene expression, translations of proteins, or post-translational processing. However, a growing body of research suggests that the social environment may induce permanent changes in gene expression during the perinatal period, and the resulting expression profile can have long-term implications for the individual's behavior and social interactions. The next section will discuss the environmental influence over the genome achieved through epigenetic modification.

## Epigenetic Effects

Although negative experience can lead to stress responses throughout life, evidence suggests that the adverse experience that occurs early in development has a particularly lasting impact on subsequent behavior. Recent research has found that this effect results from long-term changes in gene expression mediated by epigenetic modification. In both animals and humans,

experiences in childhood create a template for future behavioral patterns. Because the majority of an individual's early-life social interactions occur between child and mother, studies involving animal models of maternal care are especially useful in elucidating influences on social behavior that last into adulthood.

Hundreds of studies show correlations between adverse childhood treatment and maladaptive adult behavior or psychopathology in humans. Children who are abused are more likely to experience psychoses such as hallucinations and delusional ideation, and this effect has a dose-response relationship, with more severe abuse producing more psychotic symptoms in adulthood [253]. Survivors of childhood abuse are also more likely to have problems with addiction [254]. Sexual abuse in childhood is especially traumatic, with a history of this type of abuse increasing a child's likelihood of becoming depressive and suicidal eightfold according to one study [255]. A survey of incarcerated child molesters and rapists found that they were significantly more likely to have been sexually abused themselves, demonstrating that abuse often begets abuse [256]. These later-life effects are not limited to the affective: survivors of childhood abuse have also been found to have deficits in verbal memory that mirror those exhibited by patients with posttraumatic stress disorder [257].

Research in a variety of species has shown that the negative effects caused by an abusive or neglectful upbringing are not unique to humans. Rat and macaque models have been particularly useful in studying the effects of maltreatment in early childhood. Familial patterns of poor maternal behavior and infant neglect occur naturally in a small percentage of macaques [258], and neglected infant monkeys show abnormal behavioral phenotypes early in life [259]. These infants emit more vocalizations and initiate social interactions more often than do infants from non-neglectful mothers in the first three months of life, and this pattern of behavior continues even after the infants have matured and are not dependent on their mothers. As adults, a subset of these offspring become poor mothers themselves [260], and these individuals have elevated cerebrospinal fluid (CSF) levels of CRH, indicating chronic activation of the stress axis [261]. Indeed, these offspring show a flattened profile of diurnal cortisol, similar to humans with depression or other affective disorders [262]. Furthermore, there is a sex difference in the response to poor maternal behavior in macaques, with neglected females showing a greater response to an acute stressor than neglected males or control juveniles of either sex, as well as a flatter diurnal cortisol profile in response to chronic stressor exposure [262]. This is consistent with the previously discussed sex differences in LHPA activity. Behaviorally, female offspring of poor mothers seek out interaction with other monkeys more often than do males, and this may be a compensatory measure to ease greater LHPA reactivity [259]. Because many neglectful mothers begin life as abused offspring, the elevation of CRH levels may be caused by their mistreatment and could contribute to maltreatment of their own infants.

In the same way that macaque populations have natural variability in quality of maternal care, maternal behavior in rats is characterized by a range of mothering styles based on the type of attention they give their offspring during the postpartum period. The more time a mother spends licking and grooming her offspring, the lower her pups' levels of stress axis hormones are after a period of acute stress and the more sensitive the axis will be to negative feedback, presumably due to increased expression of the GR in the hippocampus [263]. These effects are independent of total time spent with offspring and time spent nursing, because these values were roughly equal regardless of whether the mother spent a lot of time licking and grooming (high LG) or less time performing these activities (low LG) [264]. This model is of particular importance because it examines the effects of maternal care that varies within a normal range of behavior. In the rat model, the individuals examined have not been subject to traumatic levels of abuse or neglect, but rather a more normalized sample that receives a standard of maternal care that better represents the subtle parenting differences represented in a human population.

Because a legacy of abuse can be attributed to experience or genetic effects, cross-fostering designs can separate nature from nurture. When offspring of low LG mothers are fostered to high LG mothers and vice versa, the pups reared by low LG mothers are more fearful than offspring reared by high LG mothers regardless of the phenotype of their biological mother [265]. When they mature and rear their own pups, they adopt the mothering style of the parent that raised them. Their choice of mothering style can be reversed when their own pups are subjected to human handling and a brief removal from their home cage. This is a manipulation known to artificially stimulate mothering behaviors - essentially making low LG mothers act like high LG mothers - and decrease the stress level of the pups themselves [266]. After this manipulation, the handled offspring of low LG mothers behave like the natural offspring of high LG mothers: they are less fearful and express less CRH mRNA in the PVN than low LG offspring that have not been handled [265]. This suggests that transmission of maternal care habits does not occur through the genome but is rather mediated by experience. Although it is more difficult to execute [267], the cross-fostering procedure has been used to the same effect in primate populations to show that maternal care habits are transmitted by experience from the rearing mother rather than by genetics from the biological mother [260,268]. The body of research using the cross-fostering technique suggests that maltreated offspring could learn patterns of abusive behavior through their relationships with their caregivers. Alternatively, the process of incurring abuse may generate neurobiological changes that guide behavior in the long term. These neurobiological changes are likely to include changes in receptor expression that alter sensitivity to hormones that guide social behavior.

A major question concerns the reversibility of these effects. Will adverse treatment in childhood inevitably lead to dysfunction in adulthood? Although a definitive answer will require more research, there is some evidence that despite early childhood maltreatment, negative outcomes in adulthood can be avoided. When rats who have been chronically stressed as pups are housed in an enriched environment with numerous conspecifics, LHPA axis reactivity and anxiety are decreased [269]. Their hormonal and behavioral profiles become similar to rats raised by high LG mothers. This may be caused by increased GR expression, which increases LHPA sensitivity to negative feedback. Similarly, a study by Bredy and colleagues [270] demonstrated that housing rats in an enriched environment during their peripubescent years improved scores on cognitive tasks that had been hindered by poor maternal care. The improvement in cognition was associated with an increase in expression of an NMDA receptor subunit. These studies indicate that while maternal behavior can guide the establishment of behavioral patterns, experience can change the behavioral phenotype. The mechanism of these changes likely involves changes in gene expression and subsequently, protein activity. A newly researched but nevertheless powerful mode through which gene expression can be regulated is through epigenetic modification.

The mechanism underlying epigenetics as we understand it to date involves the structure of chromatin and DNA, specifically changes that do not modify the DNA sequence itself but do modify which genes are transcribed [271]. These modifications include histone proteins mediating DNA accessibility through chromatin structure and methylation patterns on DNA [272,273]. Active DNA is generally hypomethylated whereas inactive DNA is generally hypermethylated [271]. Conversely, regions near acetylated histones are more likely to be expressed than regions that are deacetylated [271]. The importance of these states resides in the ability of transcriptional machinery to access gene promoter sequences to initiate their transcription, as active chromatin is more loosely wrapped around histones and inactive chromatin is tightly packed to them. Histone organization is primarily dependent on acetylation through the actions histone acetyltransferases (HATs) and deacetylases (HDACs) [274]. Likewise, DNA methylation is dependent upon DNA methyltransferases (HMTs) and demethylases (HDMs). The extent of methylation and acetylation in a cell is dependent upon the balance of these enzymes' activity. The purpose of this review is not to review epigenetic

mechanisms, as this has been done [18], but we will address these concepts within the context of our discussion.

Much of the existing research on epigenetics and social behavior concerns the differential methylation patterns on the GR promoter in the offspring of high LG and low LG rat mothers. As mentioned previously, rat pups raised by high LG mothers express more GRs in their hippocampi than those raised by low LG mothers. High LG offspring have lower LHPA axis reactivity, presumably because of the increased sensitivity to negative feedback conferred by a greater concentration of GR [264,275]. Correlational evidence shows that the exon 1<sub>7</sub> promoter of the GR is methylated in the offspring of low LG mothers, but unmethylated in the offspring of high LG mothers [276]. Cross-fostered offspring in the same study showed that the dam that reared the pup, not the biological mother, determined this methylation pattern. Although the precise mechanism by which maternal licking and grooming affects DNA methylation is unknown, Weaver and colleagues proposed that maternal behavior influences GR expression via 5HT action on the 5HT<sub>7</sub> receptor subtype [271]. This receptor increases intracellular levels of cAMP, which activates protein kinase A (PKA) and cAMP response element binding protein (CREB). CREB increases expression of nerve-growth-factor-inducible-protein A (NGFI-A), a transcription factor that can ultimately increase expression of GR. The increase in NGFI-A concentration increases the chance that the low-affinity protein will bind to the GR promoter region, thus increasing the amount of GR mRNA transcripts and, therefore, proteins. However, this mechanism can only explain differences in pup behavior early in life, as expression of NGFI-A is equalized in adulthood [277]. NGFI-A expression may actually influence methylation and histone deacetylation, as NGFI-A binding to the GR exon 1<sub>7</sub> promoter discourages methylation and promotes acetylation, thus favoring transcription [277]. These findings provide an explanation for the low level of GR expression in low LG offspring compared to high LG offspring, first through expression of NGFI-A, and later through epigenetic changes to the GR gene.

The potential for epigenetic programming in neurons is dependent on the presence of the enzymatic machinery discussed above. This machinery is not, however, thought to be present in post-mitotic cells [271]. Because neurons don't reproduce throughout the lifespan, it has been assumed that epigenetic modification cannot occur in the nervous system in adult animals. There is one important exception to this generalization: neurogenesis is known to occur in the hippocampus, an area which is involved in the stress response [278]. But overall, by the existing logic, the epigenetic marks laid down in early life will persist through adulthood regardless of how the adult's environment changes. However, there is a growing body of evidence that suggests that epigenetic modification is a result of dynamic activity of acetylating and methylating enzymes rather than static inheritance from the parent cell. Although it remains to be seen whether reversal of epigenetic modification occurs spontaneously *in vivo*, pharmacological manipulations have been successful in altering epigenetic status at specific loci. An *in vitro* experiment showed that artificially methylated genes were demethylated by the cell if they resided downstream from promoters that are relatively active in that particular cell type [279]. In other words, the cell could detect which genes "should" be expressed and therefore demethylated that specific segment of DNA, and thus made changes accordingly. In the same study, addition of trichostatin-A (TSA, a histone deacetylase inhibitor) to the preparation resulted in a dose-dependent increase in demethylation. Simply by altering the concentration of a relevant enzyme, researchers were able to change the methylation status of a cell's DNA. This effect carries over *in vivo*, where central infusion of L-methionine, a precursor to the compound that donates methyl groups during DNA methylation, selectively increases methylation of exon 1<sub>7</sub> of the GR promoter [280]. This manipulation is also sufficient to increase cortisol profiles of high LG offspring to levels seen in low LG offspring after an acute stress. Similarly, intraventricular administration of TSA erases the differences in methylation, GR expression, and stress response between the adult offspring of high LG and

low LG mothers [276]. Central administration of TSA changes expression profiles of a suite of genes in addition to GR, but these alterations are not as global as one may think, considering methylation and acetylation are found throughout the genome [281]. Although pharmacological manipulations do not necessarily represent what happens naturally *in vivo*, they hold promise as therapeutic treatments. In fact, there is some evidence to suggest that treatments that act via epigenetics have been in use for years. One study found that imipramine, a commonly used antidepressant, selectively downregulates HDACs in the hippocampi of mice subjected to chronic social defeat, but not control mice [282]. Because the antidepressant effects of imipramine were reversed by HDAC overexpression, epigenetic modification is presumed to be the main route by which chronic administration of imipramine alleviates depression. In addition to pharmacological treatments, dietary changes may be sufficient to induce changes in DNA methylation. As mentioned above, methionine administration increases methylation on the GR promoter. Because intracellular methionine levels are controlled in part by dietary intake of the amino acid, increased consumption of methionine may lead to higher levels of DNA methylation [280].

For the purposes of this review, we will focus on the small but intriguing body of evidence that examines epigenetic control of the relationship between sex hormones and social behavior. Like GR, ER $\alpha$  is over-expressed in the offspring of high LG dams compared to low LG dams, though this effect is found in the mPOA of the hypothalamus rather than the hippocampus [283]. Cross-fostering designs show that the difference in ER $\alpha$  expression between the offspring of high and low LG mothers is dependent upon rearing, not genetic inheritance [284]. This disparity is likely due to differential methylation of an ER $\alpha$  promoter, as the offspring of low LG mothers show elevated methylation of the ER $\alpha$ 1b promoter compared to the high LG offspring [284]. As a consequence of this methylation pattern, transcription factors will be less likely to bind to the promoter and induce transcription of the receptor in the offspring of low LG dams. Research on the mechanism by which maternal care affects ER $\alpha$  expression has not yet been performed, but we can infer what the consequences of impaired ER expression would be. When ovariectomized, virgin females are injected with estradiol, the result is higher levels of OTR binding in the mPOA, but only if the females were raised by high LG mothers [285]. From this, we can reason that though estradiol is needed to induce OTR expression, it cannot act if its receptors are not being produced. As noted above, OT is necessary for the production of a number of social behaviors, but its action in the mPOA is related specifically to maternal behavior [286]. Greater ER $\alpha$  expression, and subsequently OTR expression in pups of high LG mothers can explain why high LG offspring become high LG dams. Because licking and grooming increase ER $\alpha$  and OTR expression, which themselves are associated with the production of maternal care (i.e., licking and grooming behaviors), a cycle is created. Obviously, this relationship is found only between rat mothers and their female offspring. Comparatively little is known about how maternal care influences androgen or neuropeptide receptor distributions in males.

Although nearly all of the studies discussed above use animals of both sexes, virtually none of them report on sex differences in their findings. While the enzymatic processes that produce epigenetic modification are likely the same in both sexes, the epigenetic response to maternal care and even the interactions of the mother with her offspring may differ between the sexes. Indeed, one study found that V<sub>1a</sub> receptor binding in the amygdala is increased in males, but not females, reared by high LG dams. Conversely, OTR binding in the BNST and central amygdala is greater in females, but not males, reared by high LG dams [88]. Although these results imply sexually dimorphic neuropeptide activity, the differences in receptor expression ultimately lead to the same behavioral phenotype, as high LG offspring demonstrate lower levels of stress axis reactivity regardless of sex [264]. It is plausible to think that sex differences in the epigenetic response to maternal care underlie the disparities in neuropeptide receptor distribution. Furthermore, it has long been established that rat dams spend more time licking

their male pups than their female offspring [287,288]. This effect can be manipulated by treating pups with hormones: females given androgens or estradiol are licked at rates equal to untreated males [289], and administration of progestins increases maternal licking all around [290]. As we have seen above, the amount of licking and grooming a pup receives has a profound influence on its LHPA activity later in life. We have already seen that males tend to have lower overall stress axis activation than females. Although this can partially be explained by the LHPA activity of the gonadal hormones, the observation that rats spend more time licking their male offspring could also contribute to this effect. It is important to note, however, that because the studies finding sex differences in maternal treatment of offspring were done in rats, it is unclear how this would carry over to primate species. The licking and grooming paradigm is so specific to rodents, it does not necessarily follow that human or primate mothers exhibit uniformly biased treatment toward their offspring, or that these differences can account for the dimorphism in LHPA activity.

## Summary and conclusions

As one recent review stated, the nature vs. nurture debate has become increasingly irrelevant [271]. It is now appreciated that social behaviors are not simply hormonally mediated interactions elicited by the immediate environment. The evidence presented here emphasizes several predisposing influences that guide behavioral patterns and may persist throughout the lifespan, including gene polymorphisms that may influence the expression of behavior from birth and epigenetic modifications that arise in early childhood and have lasting effects on hormone profiles and subsequently, future behavior. While these differences in genotype and experience contribute to normal variability between individuals, they have also been implicated in antisocial behavior [291] and psychopathology [253]. Consequently, there is much current interest in gaining a greater understanding of the extent to which a particular genotype or childhood experience can be overcome.

It should now be evident that the importance of gene polymorphisms and epigenetic effects, as well as socio-environmental context in understanding sex differences in social behavior, is poorly understood. Although sex differences in behavior arise from differential activity of the neuropeptides on varying receptor distributions, or from the activational effects of the gonadal hormones on neurotransmitter systems or the stress axis, very few studies look into sex differences in the effects of gene polymorphisms implicated in social behavior or susceptibility to epigenetic modification. It stands to be mentioned, however, that at least with respect to the latter, promising research has begun in this direction [292]. But overall, most studies that examine these phenomena do not look for the influence of sex on effect size and therefore sex differences may be lost in the data. Although the sex differences in social behavior are well documented, the mechanisms underlying them will only be understood when sex is taken into account by all research examining the neural substrates of social phenomena.

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