CHAPTER 4

Sex Differences in the Social Behavior Network and Mesolimbic Dopamine System

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1 INTRODUCTION TO SEX DIFFERENCES IN SOCIAL BEHAVIOR AND THE IMPORTANCE OF SEX-SPECIFIC RESPONSES IN NEURAL CIRCUITRY

Social interactions are a critical component of life for most species of vertebrates. Although there is considerable diversity in social behavior across species, certain features of social behavior are strongly conserved. This may explain why there is an evolutionarily conserved network of hypothalamic and limbic nuclei that regulate social behaviors. Based on lesion and immediate early gene expression studies, Sarah Winans Newman (1999) proposed that these nuclei form a "social behavior network" that controls social behaviors such as mating, parental behavior, and aggression. Over time this hypothesis has been supported with results from a variety of perspectives ranging from the comparative method (Goodson, 2005; O'Connell and Hofmann, 2012) to optogenetics (Lin et al., 2011). There is a growing appreciation for the importance of sex differences in social behaviors. Sex differences can range from subtle to more extreme (Shuster and Wade, 2003). In many fish, the actual act of spawning consists of motor patterns that are more similar in males and females whereas mating in rodents is mediated by motor patterns that typically are relatively unique to either males or females. The presence of sex differences in behavior has sparked an interest in identifying the underlying mechanisms. As might be expected, important neuroanatomical and neurochemical sex differences have been identified at several nodes within the social behavior network. Intriguingly, data also indicate that motivational systems, particularly the mesolimbic dopamine system, can also generate important sex differences in behavior (Becker, 2009).

Motivational systems play a key role in determining how individuals engage in social interactions. Dopamine neurons in the ventral tegmental area (VTA) project to forebrain areas such as the nucleus accumbens (NAc) and the frontal cortex. In the VTA, similar patterns of gene expression are observed in fish, amphibians, birds, and mammals suggesting that this small collection of neurons has a highly conserved function (O'Connell

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and Hofmann, 2012). Although anatomical sexual dimorphism in the mesolimbic dopamine system is either subtle (Forlano and Woolley, 2010; Wissman et al., 2012) or absent (Campi et al., 2013), there is growing evidence for sex differences in how activity in this circuit contributes to sex differences in behavior. Furthermore, the mesolimbic dopamine system has direct and indirect connections with the social behavior network (O'Connell and Hofmann, 2011). The bed nucleus of the stria terminalis (BNST) in particular has emerged as a particularly important integrative node facilitating cross-talk between the social behavior network and mesolimbic dopamine system.

In this chapter, we review sex differences in structure and function across both the social behavior network and mesolimbic dopamine system. In some cases structures that are not obviously sexually dimorphic mediate very important sex differences in behavior. Context is also a key factor influencing behavior. Factors such as using more naturalistic behavior testing conditions can reveal key sex differences in brain function and behavior. Here, studying species with different social organizations can provide key insights into context-dependent function of brain circuits regulating social behavior. Compared with the social behavior network, the mesolimbic dopamine system is not particularly sexually dimorphic. However, at a functional level, dopaminergic signaling in this pathway is an important mediator of sex differences in behavior in both appetitive and aversive contexts. Finally, we review evidence for connectivity between the social behavior network and the mesolimbic dopamine system. The use of new optogenetic tools has provided novel insights into how connections between the BNST and VTA modulate affective states. Progress in understanding how these networks control behavior should continue to expand, increasing its focus on including both males and females in neuroscience research (Cahill, 2006; Beery and Zucker, 2011).

2 THE SOCIAL BEHAVIOR NETWORK AND SEX DIFFERENCES IN SOCIAL BEHAVIOR

The social behavior network consists of an interconnected network of hypothalamic and limbic nuclei that modulate social behaviors, such as reproduction, aggression, and affiliative behavior (Newman, 1999; Goodson, 2005; Goodson and Kingsbury, 2013). Most of these nuclei contain sex steroid hormone receptors such as androgen and estrogen receptors (ARs and ERs, respectively). These receptors have important effects on behavior both during development and in the adult brain (i.e., organizational versus activational effects (Pak and Handa, 2007). Steroid hormones can play a crucial role for organizing sexual dimorphisms in neuroanatomy (Arnold and Breedlove, 1985), but they can also influence more subtle sex differences in chemoarchitecture (Patisaul et al., 2003). Steroid hormones can also induce important patterns of sex- and region-specific gene expression (Xu et al., 2012). Steroid hormone levels are dynamic and are affected by interactions with the physical and social environment. Long-term changes in photoperiod (Prendergast et al., 2009) or rapid responses to social challenges (Gleason et al., 2009) have important effects on the levels of gonadal hormones that activate the social behavior network. We will discuss influences of

steroid hormones within sexually dimorphic social behavior network nodes over various social behaviors, beginning with the most anatomically dimorphic regions and moving through its connections to less anatomically dimorphic structures. When discussing each region, we will emphasize the importance of connectivity between nodes that can allow for nonanatomically dimorphic subdivisions to have sex-specific effects on behavior. Finally, we will address how each node has direct or indirect connections to the mesolimbic dopamine system that regulate sex differences in motivation to engage in social behaviors.

2.1 Sexual dimorphism in the medial preoptic area (MPOA)

The sexually dimorphic nucleus of the preoptic area (SDN-POA) was discovered in rats (Gorski et al., 1978), and has been found to be larger in males in at least nine different species including humans (Hofman and Swaab, 1989), quail (Viglietti-Panzica et al., 1986), and the monogamous California mouse (Figure 4.1; Campi et al., 2013). The mechanisms for this sex difference are largely driven by the effects of estradiol early during the postnatal period (Gorski, 1986). In males, aromatase expressed in the SDN-POA converts circulating testosterone to estradiol, which in turn inhibits apoptosis in the SDN-POA resulting in a larger volume in the adult (Arai et al., 1996). Indeed, regulation of apoptosis during development, rather than neurogenesis, is observed in other sexually dimorphic regions of brain as well (Forger and de Vries, 2010). Effects of steroid hormones on the SDN-POA are not limited to development. Gonadectomy in the adult also reduces the size of the SDN-POA and this effect is blocked if testosterone replacement is added (Commins and Yahr, 1984a; Bloch and Gorski, 1988).

Sex differences in the MPOA are also observed outside of the SDN-POA. Across the entire MPOA, aromatase expression and aromatase activity (the rate at which androgens are converted to estrogens) is increased via androgen receptors (Roselli et al., 1997; Resko et al., 2000). Not surprisingly, aromatase activity in the MPOA is much higher in males than in females in many species (Roselli et al., 1985; Schumacher and Balthazart, 1986). In contrast, there is little evidence for sex differences in estrogen receptor expression

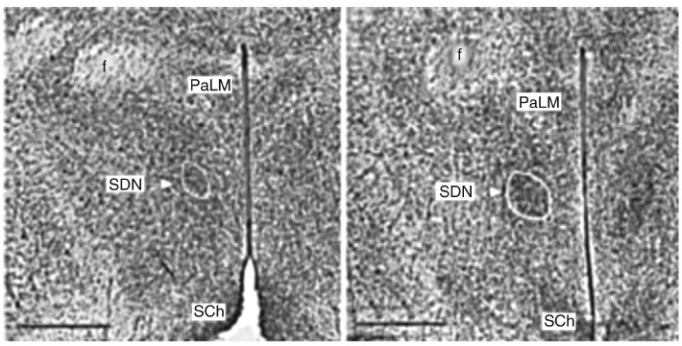

Figure 4.1 ***Sexually dimorphic nucleus in female (a) and male (b) California mice.*** Thin solid lines indicate the boundary of the SDN-POA. Scale bars = 500 μm. *(From Campi et al. (2013).)*

in the MPOA (Cintra et al., 1986; Scott et al., 2000), although there do appear to be subtle differences in the cell types that express estrogen receptors (Herbison and Theodosis, 1992).

2.2 Sex differences in the MPOA on social behavior

Curiously, the region of the brain that is consistently larger in males versus females, the SDN-POA, has an uncertain role in behavior. In quail, testosterone implants placed in the preoptic area increased male sexual behavior and lesions reduced sexual behavior (Balthazart and Surlemont, 1990). However, in rodents, the SDN-MPOA in particular does not appear necessary for the performance of male sexual behavior (Hart and Leedy, 1985; Cherry et al., 1990). There is some evidence in mammals that the SDN-MPOA modulates mating preferences (reviewed by Campi et al., 2013). For example, rams that preferred to mount other rams had smaller SDN-POA volumes than rams that preferred to mount ewes (Roselli et al., 2004). Another intriguing case is the parthenogenic whiptail lizard *Cnemidophorus uniparens*. In this all-female species, some females engage in male-like courtship behavior directed at other females (Crews and Fitzgerald, 1980). The anterior hypothalamus-preoptic area (AH-POA), which includes the SDN-POA in mammals, is larger in males versus females in the sexually reproducing species *Cnemidophorus inoratus*. However, the size of the AH-POA in female *C. uniparens* is more similar to female *C. inoratus* rather than male (Grassman and Crews, 1990; Wade et al., 1993). It is possible that more subtle differences in the structure or function of the AH-POA may impact mating preferences in *C. uniparens*. However, it is clear that there is a great deal of diversity in how sexual dimorphism in the SDN impacts behavior.

In males, inactivation of the MPOA induces major deficits in male reproductive behavior (Hull and Dominguez, 2007). Initial lesion studies found that removing the entire MPOA inhibited copulatory behavior in male rats (Heimer and Larsson, 1967), while electrical stimulation of the MPOA facilitates mating behavior (Malsbury, 1971; Van Dis and Larsson, 1971). Indeed, the MPOA has been found to be a critical region for the modulation of sexual behavior in males of almost all mammalian species studied (Hart and Leedy, 1985), including mice (Bean et al., 1981), ferrets (Panzica et al., 1995), guinea pigs (Phoenix, 1961), and gerbils (Commins and Yahr, 1984b). Both androgens and estrogens act in the MPOA to facilitate male sexual behavior (Cornil et al., 2012). In adult rats aromatase activity in these nuclei is elevated in males compared with females (Roselli et al., 1996), and estrogens facilitate male sexual behavior (Scordalakes et al., 2002). Interestingly, careful study has shown that the motivation to engage in sexual behavior can be separated from mating itself, and that different neural circuits are involved. Although inactivation of the MPOA greatly reduces male copulatory behavior, sexual motivation appears to be less severely impacted (Everitt, 1990, but see Hull and Dominguez, 2007).

In females, the role of the MPOA is less clear with some studies reporting no effect of MPOA inactivation on lordosis (Malsbury et al., 1977; Gray et al., 1978) and other studies reporting evidence for an inhibitory effect of the MPOA on lordosis (Powers and Valenstein, 1972; Takeo et al., 1993). It appears that the MPOA has more important effects on proceptive behaviors that occur before mating, and can only be observed if investigators use more complex testing arenas (Pfaus, 1999). Under these conditions, lesions of the MPOA reduce hopping and darting (Whitney, 1986). This effect can also be induced by increased D1 dopamine receptor signaling or reduced D2 receptor signaling in the MPOA (Graham and Pfaus, 2010). Whereas the MPOA appears to have sex-specific roles for mating behaviors, its role appears to be more similar for males and females in the context of parental behaviors.

In many species reproduction is associated with an extended period of parental care, and the MPOA has been shown to play a very important role in this behavior. In most species of mammals, only females provide parental care. Thus, parental care frequently represents an extreme case of a sexually differentiated behavior. The MPOA is one of the most important nodes in the social behavior network controlling parental behavior (Stolzenberg and Numan, 2011). Lesions of the MPOA induce severe disruptions in maternal behavior (Numan, 1974, 1988). The MPOA also is an important mediator of parental motivation, as MPOA lesions will decrease operant bar pressing to gain access to pups (Lee et al., 1999). Intriguingly, the MPOA is the only brain region that shows a greater increase in c-fos immunoreactivity to pup-associated cues compared with cues associated with cocaine (Mattson and Morrell, 2005). Both hormones and experience have important effects on the MPOA.

Estradiol acts directly in the MPOA to prime virgin female rats to exhibit maternal care (Numan et al., 1977). Maternal behavior can also be induced by exposure to pups (Fleming and Rosenblatt, 1974). Virgin female mice exposed to pups have fewer neurons expressing c-fos in the MPOA compared with females with prior pup experience (Tsuneoka et al., 2013). However, virgin females exposed to pups over a 4-day period show significant increases in cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), ERβ, and oxytocin within the MPOA (Stolzenberg et al., 2012, 2014). Intriguingly, these changes can be mimicked in half the time if females are cotreated with a histone deactylase inhibitor, sodium butyrate. These results suggest that experience with pups induces epigenetic changes in the MPOA that facilitate maternal behavior (Dobolyi et al., 2014). Although almost all of our knowledge of the mechanisms controlling parental care is derived from females, a handful of studies from monogamous species have provided insights into neural mechanisms of paternal behavior. Overall it appears that some mechanisms of parental care are similar in males and females. For example, electrolytic lesions of the MPOA reduce male parental behavior in the monogamous California mouse (Lee and Brown, 2002, 2007). In California mice, estradiol promotes male parental care (Trainor

and Marler, 2002) and California mouse fathers have more aromatase activity than virgin males (Trainor et al., 2003). Intriguingly, c-fos expression in the MPOA following a resident-intruder aggression test is significantly higher in parental males compared with virgin males (Trainor et al., 2008a). In general, the MPOA is considered less important for male-male aggression (Newman, 1999; Delville et al., 2000). However, the MPOA appears to play a much more important role in facilitating maternal aggression (Gammie, 2005; Arrati et al., 2006). Thus, in contrast to sexual behavior, the MPOA appears to have more similar effects on parental behavior in males and females.

2.3 Anatomical dimorphism in the medial amygdala

The medial amygdala (MeA) is an important node for processing social stimuli, especially social odor cues. Like the SDN-POA, the MeA is sexually dimorphic at an anatomical level. The volume of the posterior dorsal subdivision of the medial amygdala (MeAPD) in rats is larger in males than females (Hines et al., 1992), and this difference is associated with greater neuronal soma size in males than in females (Cooke et al., 1999; Morris et al., 2008). The difference in MeAPD size has been attributed to high concentrations of ARs and ERs in MeA neurons (Sheridan, 1979; Simerly et al., 1990), because the enlarged volumes and cell sizes are absent in androgen-insensitive rats (Cooke et al., 1999). The developmental mechanisms controlling sexual dimorphism in the MeA, such as cell size and chemoarchitecture, have interesting parallels with the MPOA. Like the MPOA, hormones during the perinatal period have crucial organizational influences on synaptic connectivity and cellular differentiation in the MeAPD (Cooke and Woolley, 2005). However, the maintenance of this sexual dimorphism appears to be more complicated. Interestingly, in adults, sex differences in MeAPD volume and neuronal soma size appear to be more dependent on circulating androgens (Cooke et al., 1999), whereas sex differences in total neuron number is independent of circulating androgens (Morris et al., 2008). Similar to the MPOA, more subtle sex differences derived from sex steroids are observed in MeA chemoarchitecture. The MeAPD contains some of the densest concentrations of the neuropeptide cholecystokinin in the male rat forebrain, and castration reduces cholecystokinin immunoreactivity (Simerly and Swanson, 1987). Intriguingly, sex differences in MeA chemoarchitecture are also observed in eusocial animals, such as the naked mole-rat. Males have more AR-positive nuclei than females, even though there are no sex differences in region size or cell numbers (Holmes et al., 2008). The importance of these differences in AR expression in MeA for behavior is still being studied.

Sex differences in chemoarchitecture of the MeA have been linked to sex differences in social behavior, particularly mating and aggression. Male mice have more aromatase-positive cells in the MeA and BNST compared with female mice, and the fibers from these neurons are more dense in males compared to females (Wu et al., 2009). In addition, both mating and the presentation of conspecific olfactory stimuli increase fos expression in AR-immunoreactive (ir) cells in the MeA of male Syrian and golden

hamsters, respectively (Wood and Newman, 1993; Blake and Meredith, 2011). In other species, there is evidence that this relationship is not sex-specific. AR expression in the avian medial amygdala is positively associated with aggressive behavior in male and female juncos (Rosvall et al., 2012). However, it is important to note that within the MeA, there are discrete subpopulations of neurons that respond to different components of sexual behavior (Heeb and Yahr, 1996; Coolen et al., 1997; Kollack-Walker and Newman, 1997), and androgens and estrogens appear to work differently in different subdivisions of MeA.

The effect of prenatal androgen exposure on amygdala function in humans was tested using positron emission tomography of women diagnosed with congenital adrenal hyperplasia (CAH). Women diagnosed with CAH are exposed to elevated androgen levels during fetal development (Merke and Bornstein, 2005). This condition is typically diagnosed at birth and treatment normalizes androgen levels. However, girls with CAH typically engage in more male-typical play than their unaffected sister (Berenbaum, 1999). Although functional connectivity in amygdala and hypothalamus differed between unaffected men and women, women diagnosed with CAH did not differ from unaffected women (Ciumas et al., 2009). Although it is possible that prenatal androgen exposure may not affect brain function to the same extent in humans versus rodents, an alternative possibility is that androgens may need to be present in the adult to induce sex differences in connectivity.

2.4 Sex differences in effects of MeA on social behavior

As would be expected based on neuroanatomical sex differences in the MeA, there is also evidence for sex differences in the effects of the MeA on behavior. Infusion of testosterone into the MeAPD can restore sexual behavior in castrated male rats (Wood and Newman, 1995). In contrast, estradiol, but not dihydrotestosterone, implants placed in the MeAPD increased sexual behavior (Wood, 1996). Many neurons in the MeAPD project primarily to posterior-medial subregions of the BNST (Canteras et al., 1995; Coolen and Wood, 1998), including the principal nucleus of the BNST. In contrast, neurons in more anterior subregions of the MeA project to more lateral subregions of the posterior BNST. This differential circuitry may contribute to the different effects of the anterior MeA on behavior. Selective lesions to anterior MeA abolish both appetitive and consummatory components of male sexual behavior in hamsters (Lehman et al., 1980; Lehman and Winans, 1982). In contrast, male hamsters with lesions including the MeAPD still display mating behavior, but have deficits in their timing of appetitive sexual behavior (i.e., anogenital sniffing) (Lehman et al., 1983). In female rodents, the MeA appears to have a less important role in mediating sexual behaviors. Male but not female hamsters exposed to opposite sex olfactory cues had increased fos expression specifically in the MeAPD (Newman, 1999). Consistent with this observation MeA lesions did not block lordosis behavior, although it did reduce preferences for odors of

intact males versus castrated males (Kondo and Sakuma, 2005). Studies using functional magnetic resonance imaging on humans are largely consistent with these data. Sexually arousing images increased activity in the left amygdala to a greater extent in men versus women (Hamann et al., 2004).

The MeA also modulates aggressive behavior, as lesions reduce aggression in male rodents (Shibata et al., 1982; Wang et al., 2013). Interestingly the impact of the MeA on aggression is stronger in animals with prior experience winning aggressive encounters (Vochteloo and Koolhaas, 1987). Winning aggressive encounters increases androgen receptor expression in the MeA of male California mice (Fuxjager et al., 2010). The experience of winning also increases the probability that an individual will win in the future, independently of intrinsic competitive ability (Oyegible and Marler, 2005; Hsu et al., 2007). Long-lasting changes in androgen sensitivity in the MeA may contribute to this effect. Future studies should further characterize which cell types in the MeA express ARs. For example, selective activation of gamma-aminobutyric acid (GABA) neurons within the MeA was found to increase aggressive behavior whereas activation of glutamate neurons in the MeA had the opposite effect (Hong et al., 2014).

Less is known about the effects of the MeA on female aggression, largely because female-female aggression levels in most rodent species are relatively low. However, Syrian hamsters are solitary (Gattermann et al., 2001) and females are extremely aggressive toward both males and females (Wise, 1974). Similarly, in the monogamous California mouse, females defend territories with males (Ribble and Salvioni, 1990) and are aggressive toward other females (Davis and Marler, 2003). In Syrian hamsters MeA lesions reduced female-female aggression (Takahashi and Gladstone, 1988) and female-female aggressive encounters in California mice induce increased c-fos (Davis and Marler, 2004) and phosphorylated extracellular signal regulated kinase (pERK) in the MeA (Silva et al., 2010). Strong increases in immediate early gene expression such as c-fos (Hasen and Gammie, 2005) and Egr-1 (Hasen and Gammie, 2006) are observed in the MeA following maternal aggression as well. In general, there has been little investigation of the neuroendocrine mechanisms in the MeA controlling aggression in males and females. In males, estrogens generally increase aggression (Laredo et al., 2014), and ERα cell counts in the MeA are positively correlated with aggression in males (Trainor et al., 2006). In contrast, experimental knockdown of ERα in the MeA of female rats increased agonistic behaviors directed toward juveniles (Spiteri et al., 2010). However, without a direct comparison to males it is unclear whether the inhibitor effects of ERα on aggression are context-dependent (e.g., aggression toward juveniles) or a genuine sex difference in how ERα in the MEA regulates aggression.

2.5 Sexual dimorphism in the bed nucleus of the stria terminalis

The BNST is a highly complex nucleus extending just posterior from the NAc and extending through to the hypothalamus (Moga et al., 1989). The posterior subregions of

the BNST have been studied more intensely as they exhibit strong sexual dimorphism on both anatomical and neurochemical levels. Posterior divisions of BNST, including the principal nucleus of the BNST, are larger in males than females in a diverse group of species (Hines et al., 1985; del Abril et al., 1987; Allen and Gorski 1990; Campi et al., 2013). As in the MPOA, inhibition of apoptosis through aromatization of androgens during fetal development is an important process contributing to the masculinization of posterior BNST subregions (Chung et al., 2000). The posterior subdivisions of the BNST have dense concentrations of gonadal steroid receptors (Commins and Yahr, 1985; Simerly et al., 1990; Chen and Tu, 1992; Shah et al., 2004). Neuroanatomical tracers have revealed substantial sex differences in projections originating from the oval nucleus of the BNST (Gu et al., 2003). Most terminal fields had stronger projection in males versus females, and these differences were particularly strong in the MPOA and MEA.

In contrast to the posterior BNST, anterior subregions of the BNST (which includes the anteromedial BNST, BNSTam) generally lack anatomical sexual dimorphism (del Abril et al., 1987; Campi et al., 2013). Likewise, the concentration of estrogen and androgen receptors is quite low compared to posterior subregions of the BNST. Despite the lack of obvious sex differences in anatomy, evidence suggests that anterior subregions of the BNST respond to stressors in a sex-specific manner.

2.6 Sex differences in effects of anterior BNST on social behavior

The anterior BNST is highly responsive to social stress, as increased c-fos is observed in this area in male hamsters that lose aggressive encounters (Kollack-Walker et al., 1997). A series of experiments on California mice determined that the anterior BNST has an important role in mediating sex-specific responses to social defeat stress (Greenberg et al., 2014b). As the California mouse is one of the few species in which females are aggressive toward other females, this provides a unique opportunity to study both males and females exposed to an equivalent intensity of defeat stress (Trainor et al., 2013). The long-term effects of defeat stress are sex-specific and generally consistent with reactive and proactive coping strategies described by Koolhaas and colleagues (Koolhaas et al., 1999). In females, the long-term effects of social defeat are more consistent with reactive coping strategies such as social withdrawal (Greenberg et al., 2014b), reduced aggression (Steinman et al., 2015), and behavioral flexibility (Laredo et al., 2015). In contrast, stressed males adopt more proactive coping strategies such as social approach, aggressive behavior, and behavioral inflexibility. Sex differences in social withdrawal are mediated in part by sex differences in neurotrophin function in anterior subregions of the BNST.

First, immunoblot studies demonstrated that defeat stress increased protein expression of brain derived neurotrophic factor (BDNF) in anterior, but not posterior, micropunch samples of the BNST (Figure 4.2a; Greenberg et al., 2014b). Although BDNF is often considered to exert antidepressant effects (Duman and Monteggia, 2006), these effects appear to be mediated by tyrosine-related kinase B receptor (TrkB) activation in

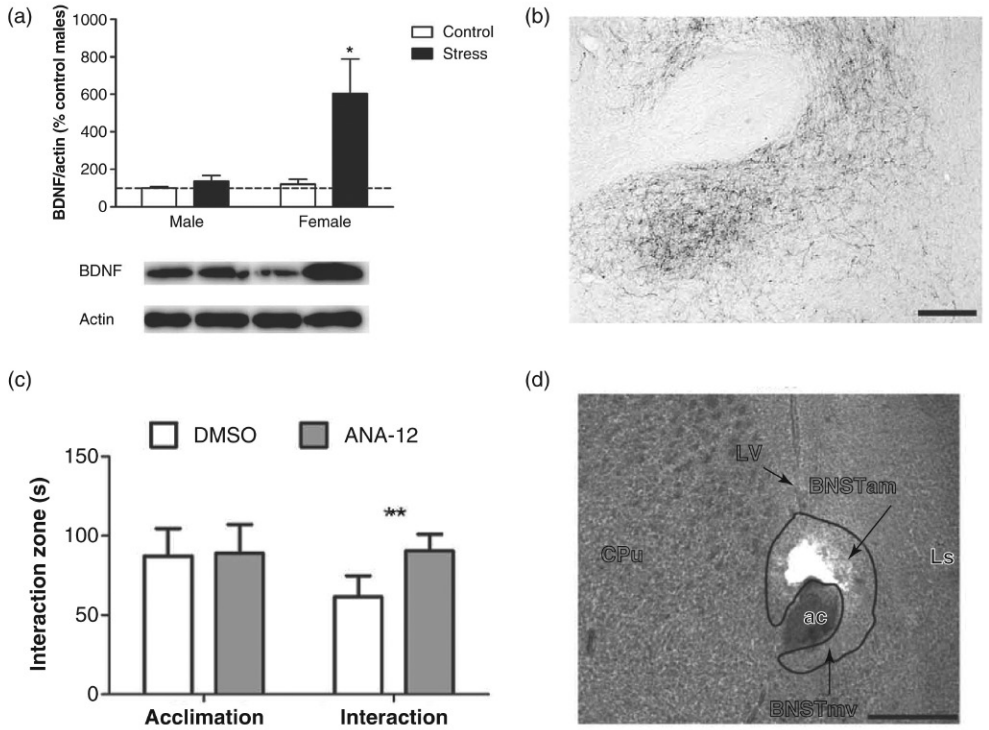

Figure 4.2 ***Brain derived neurotrophic factor (BDNF) mediates sex differences in stress-induced social withdrawal.*** In punch samples of the anterior BNST, defeat stress increased BDNF protein expression in females but not males (a). Immunohistochemistry showed increased BDNF immunoreactivity in ventromedial subregions of the anterior BNST (b, scale bar = 200 μm). Infusion of a TrkB antagonist into the anterior BNST blocked stress-induced social withdrawal in females (c). Photomicrograph showing needle track in anterior BNST (d, scale bar = 500 μm). Structures caudate-putamen (CPu), anterior commissure (ac), anterior-medial bed nucleus of the stria terminalis (BNSTam), ventromedial bed nucleus of the stria terminalis (BNSTmv), and lateral septum (LS) shown for reference. *$p < 0.05$, **$p < 0.01$ versus control. *(From Greenberg et al. (2014b).)*

the hippocampus (Malberg and Duman, 2003). Successful antidepressant treatment increases expression of BDNF in the hippocampus (Nibuya et al., 1995; Autry et al., 2011) and bilateral infusion of mature BDNF into the dentate gyrus has antidepressant effects (Shirayama et al., 2002). However, BDNF action in the NAc had prodepressive effects (Krishnan, 2007). Results from female California mice indicate that BDNF acting in the anterior BNST also exerts prodepressive effects.

Immunohistochemistry was used to more accurately identify specific subregions of BNST expressing BDNF protein in California mice exposed to defeat stress (Figure 4.2b). Females but not males exposed to defeat had increased BDNF-ir within the ventral portion of the anterior BNST. Analyses of BDNF in the adjacent NAc

revealed no sex differences or effects of stress on expression. Increased BDNF expression was reversed with chronic administration of a low dose of the selective serotonin reuptake inhibitor sertraline, which also blocked defeat-induced social withdrawal. Anterior-ventral BNST neurons receive serotonergic input (Phelix et al., 1992), which is one possible mechanism that could directly mediate the inhibitory effects of sertraline on BDNF. While the mechanism through which sertraline normalized BDNF levels is unresolved, another study demonstrated that the depressive-like effects of BDNF in the anterior BNST on social interaction are mediated by activation of TrkB.

Site-specific infusions of a TrkB selective antagonist into the anterior BNST blocked the expression of social aversion in stressed female mice (Figure 4.2c) while infusions of the TrkB antagonist that missed the anterior BNST had no effect on behavior (Greenberg et al., 2014b). Furthermore, TrkB antagonist infusions into the anterior BNST had no effect on behavior in females naïve to defeat. Intriguingly, the Val66Met point mutation in the human *Bdnf* gene impairs release of mature BDNF in the brain (Egan et al., 2003; Chen et al., 2006), yet this mutation is linked to reduced risk of depression (Frustaci et al., 2008; Matsuo et al., 2009; Grabe et al., 2012). This suggests that BDNF action in the NAc and BNST may have an underappreciated role in governing the effects of stress on psychological health.

To this point we have considered the impact of experience in the adult on BDNF expression. However, developmental experience also exerts critical effects on brain function and behavior (Lu et al., 2005). The developing brain is considerably plastic and influenced by environmental experience, and, interestingly, the social environment also has important effects on BDNF expression in the BNST. In prairie voles, juveniles that are raised with younger siblings have increased anxiety-like behavior as adults (Greenberg et al., 2012). Intriguingly, this increased anxiety-like behavior corresponds with increased BDNF expression in the BNST. In this study, anterior and posterior subregions of BNST were not examined individually. However, it seems likely that effects of early life experience on behavior and BDNF are mediated by anterior subregions of BNST.

2.7 Sex differences in effects of posterior BNST on social behavior

Some subcircuits from the posterior BNST are responsive to both sexual and aggressive behavior, and this activity is not selective to males. The anterior-dorsal MeA and posterior BNST have coordinated fos production both following mating and intermale aggression in Syrian hamsters (Kollack-Walker and Newman, 1995). Interestingly, similar patterns of fos expression in these nodes was observed in female hamsters after aggression (Potegal et al., 1996) or mating (Joppa et al., 1995). Syrian hamster females are as aggressive (and sometimes more aggressive) as males. Thus, even though anterior-dorsal MeA and BNST circuits are sexually dimorphic, they respond similarly in the context of aggression, and a similar phenotype is observed. These observations support

the hypothesis that in some cases sexually dimorphic brain circuits counter-intuitively facilitate similar behavior patterns in males and females (De Vries and Boyle, 1998).

Posterior subdivisions of the BNST also have important effects on reproductive behaviors. Lesions of posterior BNST severely disrupt male copulatory behavior (Powers et al., 1987). Selective lesions of the oval nucleus of the BNST also disrupt mating, but only in virgin males (Claro et al., 1995). Testosterone implants placed directly into the posterior BNST of castrated male hamsters greatly increased sexual behavior (Wood and Newman, 1995). This is consistent with the high concentrations of androgen and estrogen receptors in the posterior BNST. In female hamsters, electrolytic lesions of the BNST and lateral septum reduced ultrasonic vocalization but had no effect on lordosis (Kirn and Floody, 1985). In rats, not only did excitotoxic BNST lesions have no effect on lordosis, they did not interfere with paced mating either (Guarraci et al., 2004). These data indicate that the posterior BNST has a much stronger effect on mating behaviors in males versus females.

Despite the strong sex differences in how the posterior BNST regulates mating behavior, a consistent observation is that engaging in sexual behavior induces a strong increase in c-fos expression in the posterior BNST. Intriguingly, this effect is not dependent on steroid hormones. Although castration also reduces mating behavior in male rats, this behavior is not completely eliminated. When mating-induced c-fos immunoreactivity in the posterior BNST was examined in castrated rats implanted with testosterone, dihydrotestosterone, or estradiol capsules, there were no differences between these groups (Baum and Wesinger, 1993). Similar results have been observed in females (Flanagan-Cato and McEwen, 1995). In females, mating also induces increased c-fos immunoreactivity in the posterior BNST. Although gonadal hormones play an important role in promoting lordosis, the c-fos response in the posterior BNST appears less dependent on hormones and more dependent on vaginal-cervical stimulation (Tetel et al., 1993). Vaginal-cervical stimulation in ovariectomized females induced an equivalent c-fos response in posterior BNST to that observed in hormone primed rats that mated with a male (Pfaus et al., 1993). Curiously, although mating-induced c-fos in males and females is not dependent on gonadal hormones, it is clear that the affected cells are hormone sensitive. In male hamsters, nearly half of the neurons in posterior-medial BNST expressing mating-induced c-fos were also positive for androgen receptors (Wood and Newman, 1993). Similar results were observed in male rats with about 50% of mating-induced c-fos positive cells coexpressing ERα and 90% coexpressing androgen receptor (Greco et al., 1998). This organization of neural circuitry within the BNST may explain why mated males are more aggressive than virgin males (Flannelly and Lore, 1977). It would be interesting to determine whether mating-induced activation of hormone-sensitive neurons in the posterior BNST results in long-term changes in aggression. In females mating-induced c-fos in the MPOA is observed in ERα expressing cells in the MPOA and MeA (Greco et al., 2003); however, the BNST was not

quantified in this study. Estrogen receptors in the BNST are closely associated with male aggressive behavior.

In several species, the number of ERα-ir positive cells in the BNST is positively correlated with aggressive behavior (Trainor et al., 2006, 2007a). This relationship extends beyond the standard resident-intruder aggression test, as ERα gene expression is positively correlated with aggressive behavior even in the home cage of *Mus musculus* (Greenberg et al., 2014a). Photoperiod appears to regulate aggression by modulating the mechanisms through which estrogens control behavior. During long, summer-like days, estrogens modulate aggression via slower, probably genomic mechanisms, whereas during short, winter-like days, estrogens act rapidly to modulate aggression via nongenomic mechanisms (Trainor et al., 2007b, 2008b; Laredo et al., 2014). Currently, it is unclear whether estrogens modulate seasonal variation in aggressive behavior in females. One of the pathways that can mediate rapid effects of estrogens on behavior is extracellular signal regulated kinase (ERK). Both male and female California mice display increased protein expression of another indirect marker of neural activity, phosphorylated ERK (pERK), in the posterior BNST following aggressive interactions (Silva et al., 2010; Trainor et al., 2010). Similar results in female California mice were observed using c-fos immunohistochemistry (Davis and Marler, 2004). Interestingly, there can be more subtle sex-specific environmental interactions that influence the aggression/pERK relationship in California mice. Increased pERK expression in posterior BNST occurs only during short day photoperiods in male mice, but it is observed in females regardless of photoperiod. While neural activity in the posterior BNST is activated in the context of aggressive behavior in both males and females, it is also linked to sex-specific reproductive behaviors.

3 THE MESOLIMBIC DOPAMINE SYSTEM

For a system that has been studied so intensively, there is still considerable debate over the exact function of the dopamine neurons within the VTA (Hyman et al., 2006; Niv and Schoenbaum, 2008; Berridge, 2012). However, it is clear that dopamine released within the mesolimbic dopamine system has important effects outside the context of reward. For example, both electric shocks and social stressors induce increased dopamine release in the mesolimbic system (reviewed in Miczek et al., 2008; Trainor, 2011). Similar to anterior subregions of the BNST, components of the mesolimbic dopamine system are characterized by a lack of striking sexual dimorphism in vertebrates. However, important differences in mesolimbic dopamine function are observed in males and females.

3.1 Sex differences in the neuroanatomy of the mesolimbic dopamine system

Although there are some reports in rats that the VTA volume is larger in females than in males (McArthur et al., 2007), this difference is not always found (Creutz and

Kritzer, 2002; Campi et al., 2013). This may be due to ambiguity in the boundaries of the VTA, as well as technical factors. For example, VTA dopamine neurons have an anterior to posterior orientation, so horizontal sections of the brain maximize the visibility of these cells (Margolis et al., 2006). Similarly, there is little evidence for sexual dimorphism in the size of the NAc. However, females have a higher density of dendritic spines on medium spiny neurons in the NAc than male rats (Forlano and Woolley, 2010; Wissman et al., 2012). The size of the prefrontal cortex (PFC) also does not appear to exhibit consistent sex differences, but has been linked instead to social organization. Females had larger PFC size in two species of voles but not two species of field mice (*Peromyscus*) (Kingsbury et al., 2012). However, socially monogamous prairie voles and California mice had significantly smaller PFC volumes than polygamous montane voles and white-footed mice. Examination of steroid receptor expression in the mesolimbic dopamine system has revealed some interesting differences between males and females.

Within the mesolimbic dopamine system, only the VTA shows abundant nuclear expression of estrogen receptors and androgen receptors. Nuclear localization of steroid receptors reflects the long-term action of these receptors on gene expression (Laredo et al., 2014). In rats, a greater percentage of VTA dopamine neurons coexpress androgen receptors in males versus females, and are expressed on dopamine neurons projecting to the PFC (Kritzer and Creutz, 2008). This may explain why castration reduces dopamine release in the PFC (Aubele and Kritzer, 2012) and inhibits performance in behavioral tasks dependent upon PFC function, such as working memory (Kritzer et al., 2007). In contrast, ERα immunoreactivity was limited primarily to nondopaminergic cells and was more abundant in females than males (Kritzer and Creutz, 2008). Within the NAc and PFC, nuclear expression of estrogen and androgen receptors is generally absent. However, estrogens infused into the NAc act rapidly to increase dopamine release (Thompson and Moss, 1994). Estrogens also modulate PFC function during fear extinction learning. During proestrus, when estradiol levels are high, c-fos expression in PFC neurons projecting to the basolateral amygdala is positively associated with extinction learning (Rey et al., 2014). However, when estradiol levels are low, this relationship is reversed. There is growing evidence that posttranslational modifications of estrogen receptors can allow for insertion into the plasma membrane (Levin and Pietras, 2008), which can facilitate rapid action of estrogens independent from direct regulation of gene expression. Intriguingly, ERβ messenger RNA is detectable in the NAc (Shughrue et al., 1998) raising the possibility that ERβ expressed in the membrane could mediate rapid effects of estrogens in the NAc. The lack of a reliable ERβ antibody (Snyder et al., 2010) has hindered empirical evaluation of this hypothesis.

3.2 Sex differences in the mesolimbic dopamine system: appetitive social contexts

While sexual dimorphism at the anatomical levels is relatively subtle in the mesolimbic dopamine system, functional sex differences can be similar in magnitude as observed

in the BNST and MPOA. For example, the extent to which appetitive stimuli induce dopamine release is much stronger in females versus males. This has been best described for psychostimulants such as amphetamine and cocaine, which induce stronger release of dopamine in females versus males (Becker, 2009; Gilles et al., 2014) and are more likely to be abused by women than men (Anker and Carroll, 2011). In anesthetized rats electrical stimulation of the medial forebrain bundle, which includes axons traveling from the VTA to the NAc, leads to greater release of dopamine in the ventral striatum and faster reuptake rate in females in males (Walker et al., 1999). Sex differences in dopamine function are observed in social contexts as well.

During reproductive behavior, dopamine can be released in the NAc in both males and females. However, there are important differences between males and females in the exact conditions required to induce dopamine release. For male rats, dopamine release is induced both by a sexually receptive female behind a screen and by mating with a female (Pfaus et al., 1990; Damsma et al., 1992). Functionally, dopaminergic neurotransmission in the NAc appears to be especially important in the anticipation of mating opportunities in male rats (Pfaus and Phillips, 1991). In contrast, dopamine release in the NAc in female rats is only observed in specific contexts. Under more naturalistic conditions, female rats control the pace of mating through solicitation displays such as hopping or darting (Erskine, 1989). If the testing arena has insufficient space for these proceptive behaviors to be expressed, dopamine release in the NAc is not observed during mating. However, if the female is able to control the pace of copulations large increases in dopamine release are observed (Mermelstein and Becker, 1995; Becker et al., 2001).

In rats, mating behavior is a short-term social interaction. In contrast, in socially monogamous prairie voles it can mark the beginning of a long-term social relationship known as a pair bond (Carter et al., 1995). In female prairie voles, activation of D2 dopamine receptors in the NAc contributes to the formation of pair bonds (Gingrich et al., 2000; Liu and Wang, 2003). In males, activation of D2 receptors in the NAc is also necessary for pair bond formation (Aragona et al., 2006). Interestingly, after mating there is a substantial upregulation of D1 receptor expression in the NAc of male prairie voles, which in turn stimulates aggression toward unfamiliar females. This pattern of behavior is very different in rats, in which D1 receptors in the NAc increase male sexual motivation (Everitt et al., 1989; Bialy et al., 2010).

Outside the context of mating, evidence from several sources suggests that dopamine neurons in the VTA are more reactive during social contexts in females versus males. A study in California mice used c-fos/tyrosine hydroxylase (TH) immunohistochemistry to examine the activity of dopamine neurons following a social interaction test (Greenberg et al., in review). Tyrosine hydroxylase is an essential enzyme for the synthesis of dopamine and the use of TH immunohistochemistry is considered a "gold standard" for identifying dopamine neurons in the VTA (Margolis et al., 2006). Females tested in a social interaction test had more c-fos/TH positive neurons across the entire VTA compared with males. There were no sex differences in c-fos/TH positive neurons in mice

that were not exposed to a social context, suggesting that the sex difference was specific to social contexts. Consistent with this finding, a study on juvenile rats engaging in social play induced significant increases in TH/c-fos cells in the VTA of females but not males (Northcutt and Nhuyen, 2014). Interestingly, a study used *in vivo* calcium imaging to demonstrate increased activity of VTA dopamine neurons in female mice during social interactions with unfamiliar females (Gunaydin et al., 2014). Although these studies suggest that VTA dopamine neurons are more sensitive to social interactions in female, only a few species have been considered. It will be important in the future to determine whether this pattern generalizes to species with different social systems.

3.3 Sex differences in the mesolimbic dopamine system: aversive social contexts

Similar to appetitive social contexts, there is growing evidence that there are important sex differences in how the mesolimbic dopamine system responds to aversive social contexts. Here, too, the California mouse has proved to be a useful species for examining the effects of social stressors in both males and females. Results from these studies indicate that the mesolimbic dopamine system is more sensitive to social defeat in females compared with males. Intriguingly, after a single episode of defeat, no changes in c-fos/TH immunoreactivity are observed within the VTA in either males or females (Greenberg et al., in review). However, after a third episode of defeat an increase in c-fos/TH expressing cells was observed within the ventral subregion of the VTA of females but not males. This observation is interesting from two perspectives. First, an electrophysiology study on anesthetized rats found that footshocks preferentially activated ventral VTA neurons (Brischoux et al., 2009). This suggests that there is topographical organization to the VTA and that aversive contexts preferentially activate ventral dopamine neurons. Second, increased fos/TH activation was only observed in animals experiencing a third episode of defeat. Behavioral observations show that anxiety-like behaviors are elevated in the minutes immediately preceding a third episode of defeat (Greenberg et al., in review), indicating a level of anticipation that is not present after an initial episode of defeat. This result is consistent with the hypothesis that VTA dopamine neurons do not respond to rewards or punishment per se, but are activated by highly salient stimuli (Berridge, 2007).

Sex differences in the long-term effects of defeat stress have been identified in the NAc. An initial study used immunohistochemistry for phosphorylated CREB (pCREB) as an indirect marker for cellular activity (Trainor et al., 2011). Females exposed to social defeat had more pCREB positive cells in the NAc shell and core than control females (Figure 4.3a). While there was no effect of defeat on pCREB immunoreactivity in males, control males had more pCREB positive cells than control females in both NAc shell and core. Activation of D1 receptors increases cAMP production (Kebabian et al., 1972), which in turn increases phosphorylation of CREB. These results suggested that defeat stress might increase the activity of D1 receptors to a greater extent in females versus males. Total

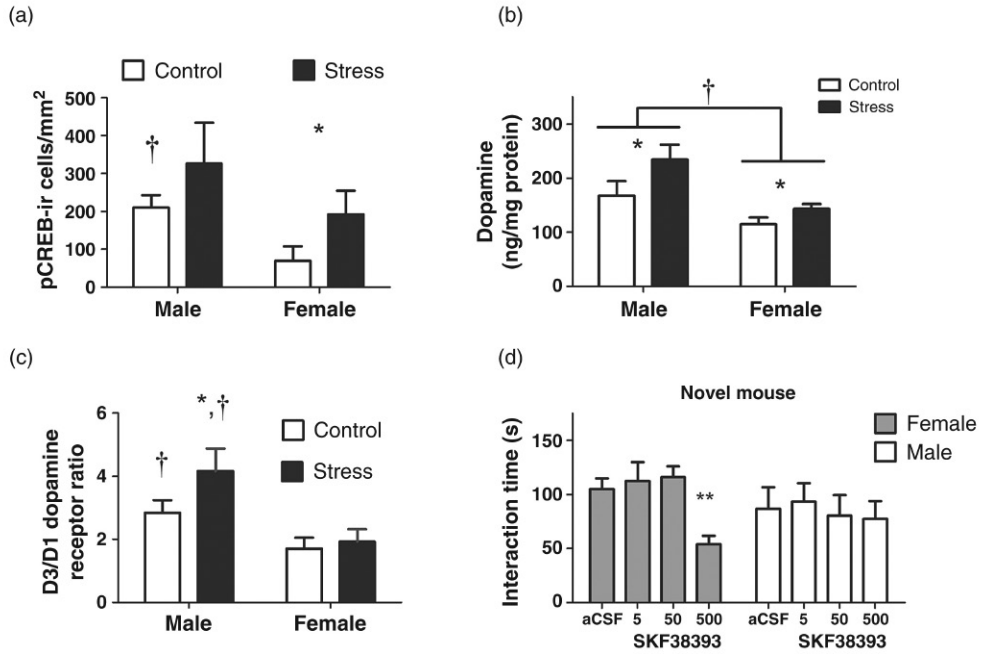

Figure 4.3 ***Effects of defeat stress on the nucleus accumbens in male and female California mice.*** Defeat stress increases the number of pCREB positive neurons in the NAc shell in females but not males (a). In contrast, defeat stress increases total dopamine content of the NAc in both males and females (b). Control males have a higher ratio of D3/D1 receptors than control females and defeat stress increases this ratio further in males (c). This may explain increased sensitivity to D1 receptors in females. Infusion of 500 ng of the D1 agonist SKF3839 infused into the NAc shell reduced social interaction in females (d) but not males. $^{\dagger}p < 0.05$ sex difference, $^{*}p < 0.05$ effect of defeat, $^{**}p < 0.01$ versus aCSF. *(From Trainor et al. (2011); Campi et al. (2014).)*

dopamine (Figure 4.3b), dihydroxyphenylacetic acid, and homovanilic acid were measured in NAc punch samples collected during the inactive phase to assess baseline dopaminergic activity (Campi et al., 2014). Social defeat stress increased expression of both dopamine and its metabolites in both males and females. Although this result is consistent with previous studies in male mice and rats exposed to defeat (Krishnan et al., 2007; Razzoli et al., 2011), it does not explain sex differences in the effect of defeat on pCREB immunoreactivity or behavior. When real-time polymerase chain reaction was used to measure the expression of D1, D2, D3, and D5 receptors in the NAc, no effects of defeat stress were observed (Campi et al., 2014). However, defeat stress did have a more subtle effect on the ratio of the two most abundant receptor subtypes: D1 and D3. The D3 receptor is in the D2-like family of receptors and its activation decreases cAMP production. Intriguingly, control males had a higher ratio of D3/D1 receptors than females and defeat stress further increased this ratio of D3/D1 receptors in males but not females (Figure 4.3c). This result suggested that males

might be less sensitive than females to D1 activation and that males exposed to defeat may compensate for increased dopaminergic activity by adjusting the expression of different receptor subtypes in the NAc. This hypothesis is supported by observations that a dose of the D1 agonist SKF38393 infused into the NAc, which induces social withdrawal in females, has no effect in males (Campi et al., 2014). Consistent with these data, infusion of the D1 antagonist SCH23390 into the NAc shell increased social interaction behavior in stressed females but not females naïve to defeat (Figure 4.3d). The results in California mice correspond well with the effects of chronic mild stress on behavior and NAc gene expression in male and female mice (LaPlant et al., 2009). Chronic mild stress induced more behavioral despair in the forced swim test in females versus males. However, males exposed to stress showed more changes in gene expression in the NAc than females, suggesting that some of the gene expression changes in males may confer resilience to stress. Overall, these data show that sex differences in the effects of defeat stress on dopaminergic signaling in the NAc have important effects on behavior.

4 CONNECTIVITY BETWEEN SOCIAL BEHAVIOR NETWORK AND THE MESOLIMBIC DOPAMINE SYSTEM

So far, the effects of the social behavior network and mesolimbic dopamine system have been considered in isolation. However, there are several nodes through which these two networks can communicate. One of the most important nodes appears to be the BNST (O'Connell and Hofmann, 2012). Posterior subregions of the BNST, which include the sexually dimorphic oval nucleus, receive dopaminergic input from the VTA (Swanson, 1982; Hasue and Shammah-Lagnado, 2002). The strongest evidence for functional connections between the BNST and VTA comes from research programs considering the behavioral processes that contribute to drug addiction (Jalabert et al., 2009). Electrodes implanted into the posterior mesencephalon (PM) support self-administered electrical stimulation (Rompré and Boye, 1989), similar to the medial forebrain bundle. Self-stimulation of the PM increased fos-ir in the VTA, NAc shell, and posterior BNST (Marcangione and Rompré, 2008). This coordinated activity between BNST and VTA plays an especially important role in animal models of drug relapse. A primary animal model of relapse is reinstatement of drug seeking behavior (Shaham et al., 2003), which is the recovery of a previously learned response after a period of extinction (Epstein et al., 2006). Reinstatement of drug seeking can be induced by psychosocial stress, and BNST-VTA connectivity plays a key role. Inactivation of the posterior BNST using sodium channel blockers (Erb and Stewart, 1999), GABA receptor agonists (McFarland et al., 2004), or norepinephrine receptor antagonists (Leri et al., 2002) can prevent footshock stress from reinstating cocaine self-administration. When a retrograde tracer was used to identify BNST neurons projecting to the VTA, swim stress induced a significant increase in the number of VTA projecting neurons coexpressing c-fos in the BNST (Briand et al., 2010). Anterior subregions of the

BNST also impact the VTA. Electrical stimulation of the anterior ventral BNST increased the activity of VTA neurons (Georges and Aston-Jones, 2001). The BNST-VTA circuit also appears to impact other aspects of reinforcement, as pharmacological disconnection of this circuit disrupts the formation of place preferences for cocaine (Sartor and Aston-Jones, 2012). A study using optogenetic tools provided insights into how BNST-VTA connectivity could impact behavior in different contexts.

Both excitatory and inhibitory projections from the anterior ventral BNST to the VTA were identified using a combination of optogenetic stimulation and electrophysiology (Jennings et al., 2013). Mice exposed to footshocks induced activation of the excitatory BNST-VTA pathway and inhibition of the inhibitory pathway. Experimental activation of excitatory neurons in the ventral BNST produced excitatory currents in the VTA, induced aversion, and reduced reward seeking. In contrast, activation of inhibitory neurons in the ventral BNST produced inhibitory currents in the VTA, induced place preferences, and enhanced reward seeking. Optogenetic stimulation of excitatory neurons in the BNST suppressed the activity of VTA GABA neurons, which in turn released dopamine neurons from inhibition. A different group, also using optogenetic approaches, reported slightly different results (Kim et al., 2013). Here activation of a projection from the oval nucleus of the BNST (which is sexually dimorphic) to the VTA was found to be anxiogenic whereas activating a projection from the anterodorsal BNST (which is not sexually dimorphic) was found to be anxiolytic. Clearly, knowledge of how BNST-VTA interactions impact behavioral states is moving quickly. A notable gap in this literature is that all of the studies reviewed in this section have been conducted on male rodents. This is surprising given the importance of posterior subregions of the BNST, which has some of the strongest and most evolutionarily conserved sexual dimorphisms in the brain.

There are also important interactions between the MPOA and mesolimbic dopamine circuitry for the motivation to engage in sex-typical social behaviors. These interactions have been extensively studied for maternal behavior in particular, which has been reviewed previously (Numan and Stolzenberg, 2009; Stolzenberg and Numan, 2011). The MPOA sends dense projections to the VTA, and these MPOA neurons are primed by the hormonal events of pregnancy to activate the VTA. Lesion studies show that the MPOA and mesolimbic structures are functionally associated. MPOA lesions, pharmacological inhibition of VTA neurons, and D1 receptor blockade in NAc all have similar effects on maternal behavior

Direct connections between the MeA and mesolimbic nodes are lacking. Tracer studies indicate few MeA neurons project to either the NAc (McDonald, 1991; Canteras et al., 1995) or the VTA (Geisler and Zahm, 2005). However, the MeA sends strong projections to the BNST. Interestingly, dorsal anterior MeA projects to both anterior and posterior subregions of the BNST, but more posterior subregions of the MEA project primarily to posterior subregions of the BNST but not anterior subregions of the BNST

(Gomez and Newman, 1992; Canteras et al., 1995; Coolen and Wood, 1998). This pathway is significant because there is growing evidence that the BNST acts as a critical node connecting the social behavior network with the mesolimbic dopamine system. This suggests that interactions between the MeA and mesolimbic dopamine system are likely mediated by the BNST.

5 CONCLUSIONS

In this chapter, we examined how sex differences in structure and function of the social behavior network and mesolimbic dopamine system impact social behavior in both males and females. Interestingly, sexual dimorphism within the social behavior network is strongly conserved across a diverse range mammalian species with different social systems. In some cases, such as the SDN-POA, we still do not fully understand the impact of these sex differences on behavior. Other nodes such as the BNST exert very different effects on behavior in males and females. An important observation is that sex differences in how the BNST impacts behavior are not limited to the sexually dimorphic posterior subregions. This theme carries over to the mesolimbic dopamine system, which also lacks sexual dimorphism at an anatomical level. Focus on connectivity between the BNST and VTA has provided insights into how these two systems communicate with one another. However, this circuit has not been studied in females and so it is unclear exactly how results identified in males will translate to females. Finally, we reviewed evidence that social experiences such as social stress or parental experience induce long-term changes in the function of both the social behavior network and mesolimbic dopamine system. Further study of how experience impacts the effects that these networks have in both males and females will be critical for understanding the neurobiological control of social behaviors.

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