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Chapter 27

Functional anatomy of the bed nucleus of the stria terminalis–hypothalamus neural circuitry: Implications for valence surveillance, addiction, feeding, and social behaviors

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Abstract

The bed nucleus of the stria terminalis (BNST) is a medial basal forebrain structure that modulates the hypothalamo–pituitary–adrenal (HPA) axis. The heterogeneous subnuclei of the BNST integrate inputs from mood and reward-related areas and send direct inhibitory projections to the hypothalamus. The connections between the BNST and hypothalamus are conserved across species, promote activation of the HPA axis, and can increase avoidance of aversive environments, which is historically associated with anxiety behaviors. However, BNST–hypothalamus circuitry is also implicated in motivated behaviors, drug seeking, feeding, and sexual behavior. These complex and diverse roles, as well its sexual dimorphism, indicate that the BNST–hypothalamus circuitry is an essential component of the neural circuitry that may underlie various psychiatric diseases, ranging from anorexia to anxiety to addiction. The following review is a cross-species exploration of BNST–hypothalamus circuitry. First, we describe the BNST subnuclei, microcircuitry and complex reciprocal connections with the hypothalamus. We will then discuss the behavioral functions of BNST–hypothalamus circuitry, including valence surveillance, addiction, feeding, and social behavior. Finally, we will address sex differences in morphology and function of the BNST and hypothalamus.

INTRODUCTION

The bed nucleus of the stria terminalis (BNST) is a highly heterogeneous structure that is implicated in many homeostatic and behavioral functions. Sometimes referred to as the extended amygdala, the BNST is located just ventral and anterior to the amygdala proper in rodents. In humans, the BNST is a medial basal forebrain structure approximately the size of a sunflower seed at 190 mm^3 (Avery et al., 2016). The BNST is bordered laterally by the internal capsule, supracapsular pallidal tissue, and the basal forebrain region and bordered ventromedially by the preoptic area. It lies posterior to the nucleus accumbens, and anterior to the thalamus. Like the BNST of rodents, the human BNST is inferior to the lateral ventricles and mainly superior to the anterior commissure, though it extends below the anterior commissure in lateral regions. The structural and functional connectivity of the BNST is thought to be similar in humans, nonhuman primates, and rodents (Avery et al., 2016).

In rodents, amygdalar projections to the BNST originate in both the central amygdala (CeA) and the medial amygdala (MeA). The BNST is also directly connected

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to several other limbic areas, including the hypothalamus, hippocampus, lateral septum, ventral tegmental area, and nucleus accumbens. Sensory inputs, like those from the olfactory bulbs, also project directly to the BNST. BNST nuclei are mostly populated by GABAergic neurons that disinhibit the BNST itself and its hypothalamic connections (Gungor and Pare, 2016), including those to the lateral hypothalamus (LH), paraventricular nucleus (PVN), and preoptic area. Human imaging studies have found anatomic and functional connectivity that is similar to rodents and nonhuman primates. The human BNST has dense connections to the central amygdala (Oler et al., 2012; Avery et al., 2014; Torrisi et al., 2015) and other limbic areas, including the hippocampus, and subcallosal cortex. The structural connections between the human BNST and the thalamus, the insula, and basal ganglia areas, including the accumbens, caudate, putamen, and pallidum, are similar to those found in rodents (Avery et al., 2014; Flook et al., 2020). The evolutionarily conserved connections between the BNST and the hypothalamus, limbic area, basal ganglia, and forebrain areas permit the BNST to play an integratory and regulatory role in diverse processes including osmotic regulation, appetite, sleep, arousal, sustained fear states, sexual behavior, addiction, and the stress response.

The BNST itself is a complex heterogeneous structure consisting of several subnuclei, as well as a few lesser defined regions. Characterization of the BNST subnuclei remains a work in progress, and there are a variety of designations and terms used to describe the divisions of the BNST. In humans, lateral, central, and medial subdivisions can be identified by chemoarchitectural differences (Walter et al., 1991) that correlate with rodent subnuclei. In rodents, 12–18 subnuclei were mainly defined by anatomical experiments with rats. However, the anatomy in mice is somewhat more dispersed and heterogeneous. Therefore, most work on the mouse BNST mainly uses conservative language to appropriately describe the discordant designations of BNST regions and subnuclei. Studies often target the "anterodorsolateral" subgroups (Giardino et al., 2018) or the "dorsal region that includes the oval nucleus" (Russell et al., 2020) rather than specific subnuclei. Here we will use subnuclei terminology as defined by the seminal tracing experiments of Dong et al. (2001), Dong and Swanson (2006), but acknowledge that these demarcations are insufficient to fully encompass BNST heterogeneity.

Cytoarchitectural and functional differences segregate the anterior BNST and posterior BNST in rodents. The anterior BNST (Fig. 27.1) is responsible for

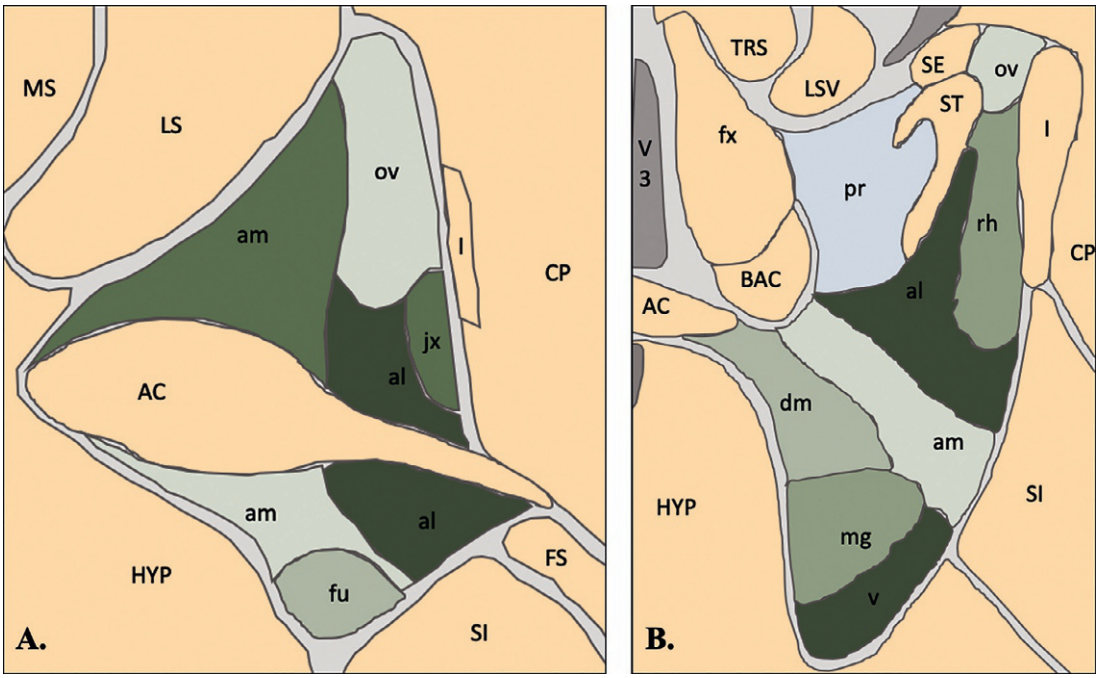


Fig. 27.1. Coronal diagram of the mouse anterior BNST and its subnuclei, shown in green, and surrounding regions, based on the Allen Brain Atlas. Anterior subnuclei of the BNST consist of (A) the oval (ov), rhomboid (rh), anterolateral (al), anteromedial (am), dorsomedial (dm), magnocellular (mg), ventral (v) (B) juxtacapsular (jx), and fusiform (fu) nuclei. *AC*, anterior commissure; *BAC*, bed nucleus of the anterior commissure; *CP*, caudoputamen; *FS*, fundus of striatum; *fx*, fornix; *HYP*, hypothalamus; *I*, internal capsule; *LS*, lateral septum; *LSV*, lateral septal nucleus; *MS*, medial septal nucleus; *SE*, strial extension; *SI*, substantia innominata; *ST*, stria terminalis; *TRS*, triangular nucleus of septum; *V3*, third ventricle.

Hypothalamo–Pituitary–Adrenal (HPA) axis activation and includes the oval, anteromedial, dorsomedial, magnocellular, anterolateral, anteroventral/ventral, rhomboid, juxtacapsular, and fusiform nuclei (Allen Mouse Brain Atlas, 2004). The posterior BNST (Fig. 27.2) is implicated in regulation of reproductive and social defensive behaviors, along with indirect inhibition of the HPA axis (Choi et al., 2007, 2008b), and consists of the principal, intrafascicular, and transverse nuclei (Allen Mouse Brain Atlas, 2004). The human BNST is less divided and includes the lateral, medial, central, and ventral divisions (Fig. 27.3) (Walter et al., 1991; Swaab, 2003). Complexity in the BNST is a product of both diversity in the cell types within BNST nuclei and diversity in nuclei connectivity. Tracing studies in rodents have illuminated the heterogeneity in the anterior and posterior regions, and the microcircuitry of the BNST; however, less research has been conducted in humans because neuroimaging methods lack sufficient resolution to study BNST subnuclei.

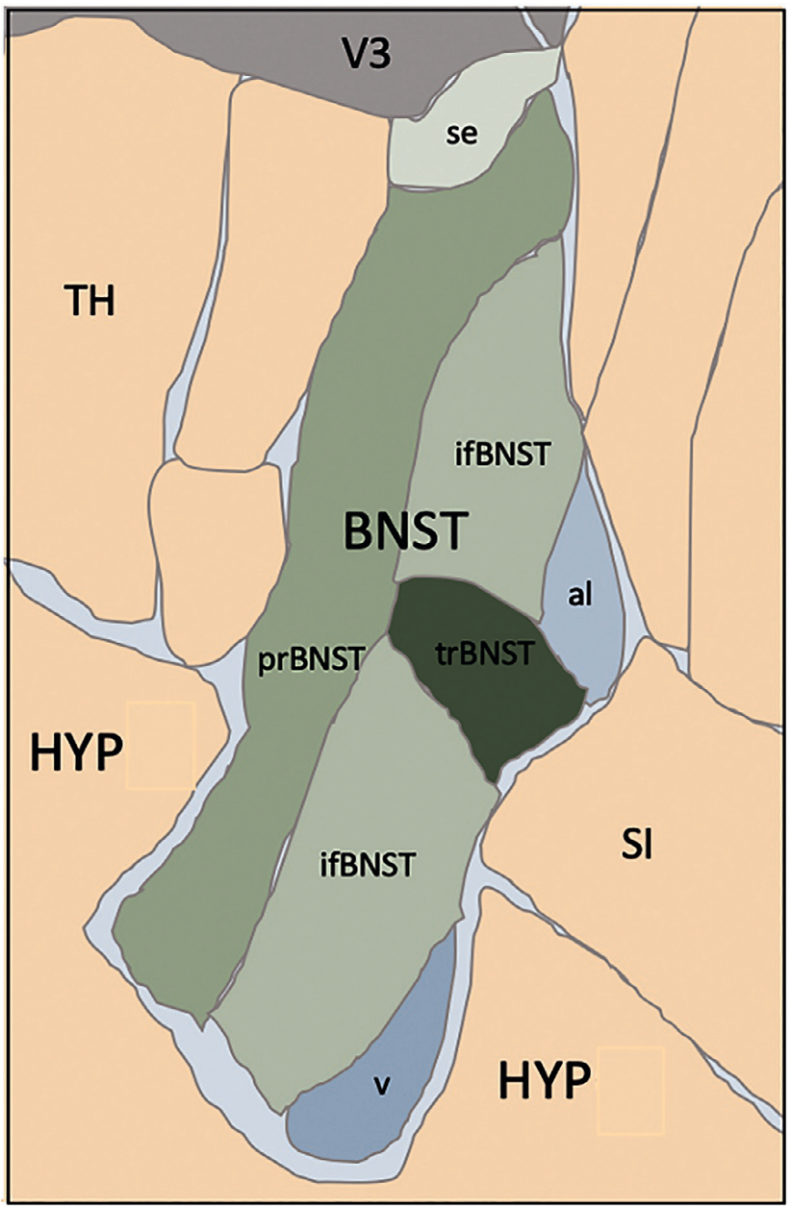


Fig. 27.2. Coronal diagram of the posterior bed nucleus of the stria terminalis and surrounding regions, based on the Allen Brain Atlas. The posterior regions are depicted in shades of *green*: the principal nucleus (prBNST), interfascicular nucleus (ifBNST), transverse nucleus (trBNST), and strial extension (se). The anterior regions are depicted in *blue*: anterolateral nucleus (al) and ventral nucleus (v). *HYP*, hypothalamus; *TH*, thalamus; *V3*, third ventricle; *SI*, substantia innominata.

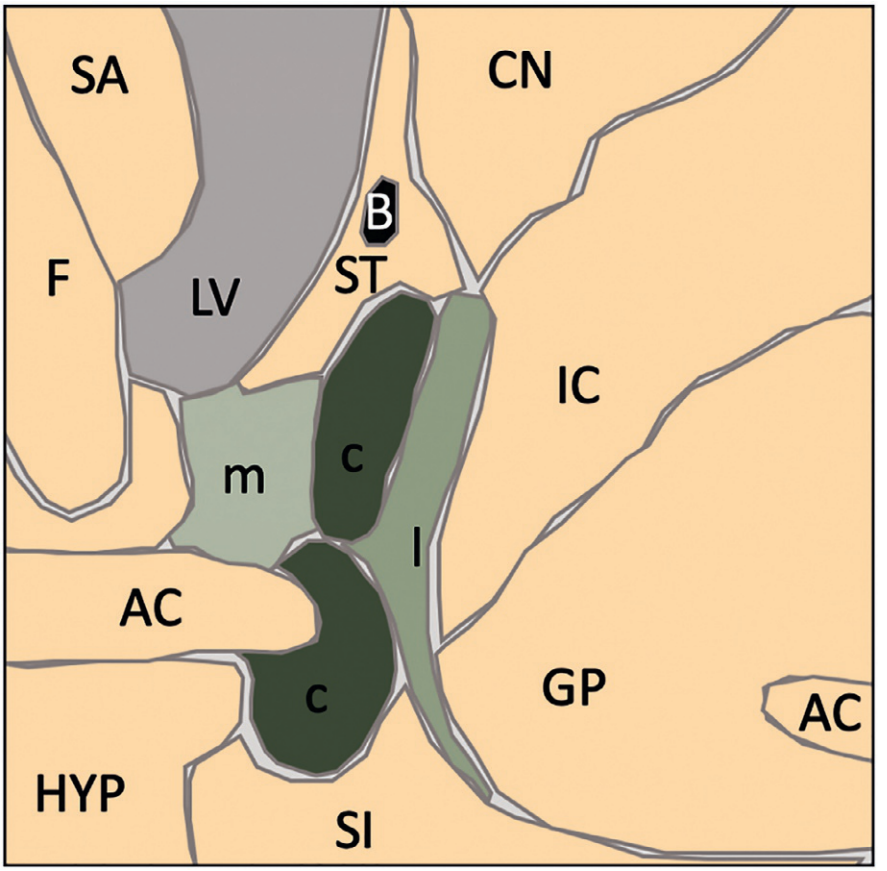


Fig. 27.3. Coronal diagram of the human BNST and its subdivisions, shown in shades of *green*, and surrounding areas. The human BNST can be divided into the central (c), lateral (l), and medial (m) divisions. *AC*, anterior commissure; *B*, blood vessel; *CN*, caudate nucleus; *F*, fornix; *GP*, globus pallidus; *HYP*, hypothalamus; *IC*, internal capsule; *LV*, lateral ventricle; *SA*, septal area; *ST*, stria terminalis; *SI*, substantia innominata.

ANTERIOR BNST CIRCUITRY

The most thoroughly studied BNST subnucleus is the *oval nucleus* (ovBNST) because of its important role in the stress response and more homogeneous cell population relative to other subnuclei. The ovBNST is marked by a majority-population of corticotropin releasing factor (CRF, or corticotropin releasing hormone, CRH)-expressing GABAergic neurons. CRF+ neurons are activated by viscerosensory inputs from the insula and brainstem, as well as periaqueductal gray (PAG) dopaminergic and glutamatergic neurons. CRF inputs also come from both the CeA and PVN. The ovBNST is a major output subnucleus, and CRF neurons in the ovBNST project to and inhibit areas involved in avoidance, reward behaviors, and the stress response, including the hypothalamus, ventral tegmental area, and nucleus accumbens (Taha and Fields, 2005; Gungor and Pare, 2016). GABAergic ovBNST neurons are mainly CRF+ (Forray and Gysling, 2004), but some neurons also express either protein kinase C delta (PKCδ) or somatostatin (SOM). PKCδ+ neurons receive most of the projections into the ovBNST, while SOM+ neurons function as outputs to the lateral parabrachial nucleus and periaqueductal gray (Ye and Veinante, 2019). These neurons project reciprocally to GABAergic CeA neurons and to the lateral hypothalamus and act as inhibitory interneurons for other ovBNST neurons expressing CRF receptor 1 (CRF1R). OvBNST projections seem to act in a positive feedback system, in which CeA neurons disinhibit ovBNST projections to the hypothalamus, which ultimately increases glucocorticoid release (Dong et al., 2001). The presence of CRF amplifies GABA-A receptor conducted inhibitory postsynaptic currents (Gungor et al., 2018).

For the most part, like the ovBNST, other BNST subnuclei are populated by GABAergic neurons that disinhibit one another and their hypothalamic connections. However, the *anteroventral BNST* (avBNST) has a minority population of glutamatergic neurons projecting to the paraventricular nucleus and ventral tegmental area (Gungor and Pare, 2016). This relatively small number of glutamatergic neurons have a disproportionately large influence on the avBNST's role in mood regulation. Along with noradrenergic inputs, the avBNST is controlled by GABAergic and glutamatergic inputs. Central amygdalar

GABAergic inputs into avBNST induce inhibitory postsynaptic potentials that are amplified by CRF. Glutamatergic inputs arrive at the avBNST from the mPFC and subiculum (Gungor and Pare, 2016). The avBNST plays a major role in HPA axis activation through projections to the amygdala, hypothalamus, and brainstem areas that regulate cardiovascular stress response (Choi et al., 2008a).

The anteromedial BNST (amBNST) receives most of the inputs into the BNST, including those from the basomedial amygdala (BMA). Glutamatergic inputs from the hippocampus and BMA, and GABAergic inputs from the MeA, are implicated in fear conditioning (Haufler et al., 2013). Most amBNST projections are within the BNST, synapsing on the *anterolateral BNST* (alBNST) and ovBNST.

The dorsomedial BNST (dmBNST) receives inputs from several amygdalar areas, including the BMA, MeA, and CeA. Importantly, the dmBNST is the main connection between the BNST and PVN, with a massive GABAergic output (Dong and Swanson, 2006). *The magnocellular BNST* is spatially and functionally similar to the dmBNST, with massive outputs to the PVN. Both the magnocellular BNST and dmBNST act as interneurons, receiving GABAergic input from the principal BNST.

The *anterolateral BNST* receives a variety of inputs, including glutamatergic projections from the ventral subiculum, serotonergic inputs from the dorsal raphe, and GABAergic inputs from the CeL, vagus nerve, and BL (Dong et al., 2001; Gungor and Pare, 2016). AlBNST neurons project to a variety of regions, including regions within the somatomotor system, the central autonomic system, the thalamocortical feedback system, and neuroendocrine system, including the hypothalamus. Some neurons express CRF1R receptors and receive CRF inputs from other BNST subnuclei including the ovBNST (Dong and Swanson, 2004a,b). Opposing circuitry in the alBNST helps regulate the stress response (Gungor and Pare, 2016).

Several less well-defined areas are also present in the anterior BNST. Some researchers group the *rhomboid BNST*, *juxtacapsular BNST*, and *fusiform BNST* subnuclei with larger, more understood nuclei. For example, the rhomboid BNST is located within the anterolateral BNST but varies from other subnuclei in receptor expression and circuitry. The rhomboid BNST and juxtacapsular BNST neurons are GABAergic and act as interneurons within the BNST, mainly projecting to ovBNST and to CeA neurons containing CRF-1 receptors. The fusiform BNST projects to other subnuclei and several extra-BNST areas and is cellularly similar to the ovBNST, with high expression of CRF mRNA. CRF is released from the fusiform BNST into the CeA, PVN, nucleus accumbens, and PAG. The inputs that activate this release are different from the ovBNST, with mainly noradrenergic fibers from the brain stem and LC, which are activated in response to immediate stressors (Daniel and Rainnie, 2015).

POSTERIOR BNST CIRCUITRY

The *principal nucleus* (prBNST) is the largest region of the posterior BNST. It receives input from the accessory olfactory system via the posterodorsal medial amygdala and receives GABAergic input from the lateral septum and central amygdala (Gu et al., 2003; Dong and Swanson, 2004a,b; Myers et al., 2014). The prBNST is primarily GABAergic (Bota et al., 2012) and projects to the lateral septum, medial amygdala, posterior amygdala, medial lateral hypothalamus, medial preoptic area, periventricular hypothalamus, ventromedial hypothalamus, ventral premamillary nucleus of the hypothalamus, periaqueductal gray, and the pontine micronutrition center (Barrington's nucleus) (Gu et al., 2003). The prBNST also projects to the ventral, magnocellular, dorsomedial, anterodorsal, and anteroventral nuclei of the BNST (Dong and Swanson, 2004a,b; Myers et al., 2014). It has a large population of GABAergic CRFR2-expressing neurons that project to the medial amygdala, paraventricular hypothalamus, periaqueductal gray, and locus coeruleus (Bota et al., 2012; Henckens et al., 2017). Approximately one-fifth of prBNST neurons express enkephalin and are glutamatergic, although the importance of this cell population is unknown (Poulin et al., 2009). The prBNST further has a high expression of androgen receptors and distinct alpha and beta estrogen receptors and may be the most sexually dimorphic nucleus (Gu et al., 2003).

The *intrafascicular subnucleus* (ifBNST) receives input from the accessory olfactory system via the posteromedial medial amygdala. GABAergic inputs also come from the lateral septum, central amygdala, and medial amygdala. The ifBNST has high expression of kainate receptors and is also strongly regulated by glutamatergic input from the CA1 of the hippocampus, ventral subiculum, paraventricular thalamus, and basomedial amygdala (Bota et al., 2012; Myers et al., 2014). The ifBNST sends projections to the lateral septum, substantia innominata, ventral tegmental area, medial amygdala, basomedial amygdala, posterior amygdala, medial preoptic nucleus of the hypothalamus, anterior hypothalamus, lateral medial hypothalamus, ventromedial nucleus (VMH), ventral premamillary nucleus of the hypothalamus, nucleus reuniens of the thalamus, and periaqueductal gray. It also projects to the ventral, magnocellular, anteroventral, and anterodorsal nuclei of the BNST (Dong and Swanson, 2004a,b). Similar to the prBNST, the ifBNST has high expression of enkephalin, but the majority of these cells are GABAergic (Poulin et al., 2009). The ifBNST also has high expression of androgen receptors, but not of estrogen receptors (Bota et al., 2012), and there is less data available about possible sexual dimorphism of this region compared to the prBNST.

Like the ifBNST, the *transverse subnucleus* (trBNST) receives input from the accessory olfactory system via the

posteromedial cortical nucleus and the medial amygdala. It has similar GABAergic and glutamatergic inputs and has high expression of kainite receptors (Bota et al., 2012; Myers et al., 2014). The trBNST sends primarily GABAergic projections to the lateral septum, nucleus accumbens, ventral tegmental area, substantia innominata, central amygdala, medial amygdala, basomedial amygdala, lateral medial preoptic nucleus of the hypothalamus, anterior hypothalamus, dorsomedial lateral hypothalamus, dorsal premamillary nucleus, ventral posterior hypothalamus, thalamus, and pontine central gray. It also projects within the BNST to the anterolateral, anteroventral, anterodorsal, ventral, magnocellular, rhomboid, and fusiform nuclei (Dong and Swanson, 2004a,b).

BNST–HYPOTHALAMUS CIRCUITRY

The BNST projects to several regions of the hypothalamus, including the paraventricular nucleus, ventromedial nucleus, lateral hypothalamus, supraoptic region, and medial preoptic area (MPOA) (Fig. 27.4). The densest BNST projections to the hypothalamus are via inhibitory projections from the BNST to the PVN and VMH, which regulate the stress-induced endocrine response (Kash et al., 2015). The greatest number of hypothalamic projections comes from the dmBNST, which inhibits the magnocellular and parvocellular neurons in the PVN and also inhibits the supraoptic region and MPOA (Dong and Swanson, 2006). Other inputs to the PVN include GABAergic inputs from the fusiform BNST, rhomboid BNST, alBNST, amBNST, and CRF+ ovBNST neurons. Posterior subnuclei, including the principal and transverse BNST, also inhibit the parvocellular neurons of the PVN (Dong and Swanson, 2004a,b). The hypothalamus connects reciprocally to the BNST: the PVN projects to BNST neurons expressing oxytocin and CRF receptor 2 (CRF2R) (Dong and Swanson, 2006).

In addition to the dmBNST, the MPOA also receives GABAergic inputs from the rhomboid BNST and principal BNST (Dong and Swanson, 2004a,b). In turn, the amBNST receives inputs from the MPOA (Dong and Swanson, 2006). The VMH is inhibited by the principal BNST. GABAergic amBNST neurons project to the VMH shell and contribute to an opposing circuit described later (Yamamoto et al., 2018). Projections to the LH are mainly GABAergic, originating from CRF+ ovBNST (Dong et al., 2001; Dong and Swanson, 2004a,b), fuBNST (Dong et al., 2001), and adBNST neurons (Kim et al., 2013; Giardino et al., 2018), though the avBNST sends some glutamatergic projections (Gungor et al., 2018). GABAergic adBNST neurons express either CRF or cholecystokinin (CCK), and these distinct neuronal subtypes have opposing effects on target hypocretin/orexin-expressing LH neurons, as described later

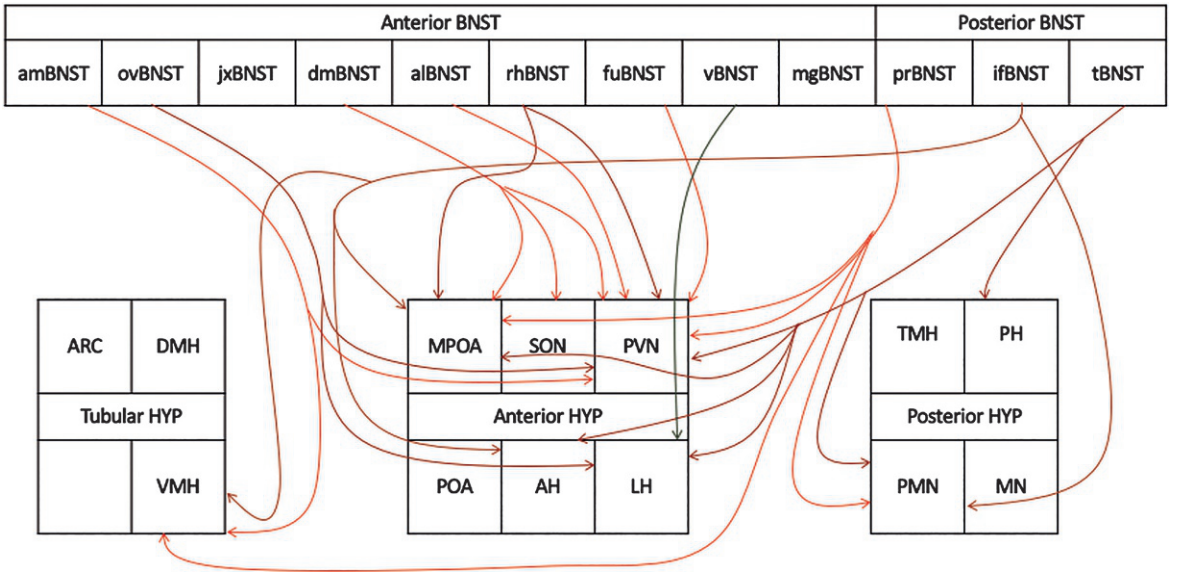


Fig. 27.4. The BNST is highly interconnected with the hypothalamus. *Red arrows* represent afferent, GABAergic projections. *Green arrows* represent afferent, glutamatergic projections. *AH*, anterior hypothalamus; *alBNST*, anterolateral BNST; *amBNST*, anteromedial BNST; *ARC*, arcuate nucleus; *dmBNST*, dorsomedial BNST; *DMH*, dorsomedial nucleus of hypothalamus *fuBNST*, fusiform BNST; *HYP*, hypothalamus; *ifBNST*, intrafascicular BNST; *jxBNST*, juxtacapsular BNST; *LH*, lateral hypothalamus; *mgBNST*, magnocellular BNST; *MN*, mamillary nucleus; *MPOA*, medial preoptic area; *ovBNST*, oval BNST; *PH*, posterior hypothalamus; *PMN*, premamillary nucleus; *POA*, preoptic nucleus; *prBNST*, principal BNST; *PVN*, paraventricular nucleus; *rhBNST*, rhomboid BNST; *SON*, supraoptic nucleus; *tBNST*, transverse BNST; *TMH*, tuberomamillary nucleus; *vBNST*, ventral BNST; *VMH*, ventromedial nucleus; *MN*, mamillary nucleus.

(Giardino et al., 2018). Furthermore, the supraoptic nuclei receive inputs from the alBNST while fusiform nuclei neurons project to the dorsomedial nucleus of the hypothalamus.

The BNST circuitry appears to be well conserved across species. Imaging in nonhuman primates repeats findings from rodent studies, with strong structural and functional connectivity between the BNST and the amygdala (Oler et al., 2017). BNST connectivity is evolutionarily conserved in humans, with functional connections including amygdalar, basal ganglia, and prefrontal areas, as well as the thalamus, anterior hippocampus, periaqueductal gray, and midcingulate cortex (Avery et al., 2014; Tillman et al., 2018). Imaging studies also demonstrate that the BNST has functional connectivity with the hypothalamus (Torrisi et al., 2015), but not at the level of specificity in rodent tracing studies. In rodents and humans, activation of the BNST–hypothalamus circuitry is thought to mainly disinhibit the hypothalamus, promoting activation of the HPA axis. BNST–hypothalamic projections are implicated in several behaviors, including valence surveillance, addiction, feeding, and social behaviors.

BNST–HYPOTHALAMUS CIRCUITRY IN VALENCE SURVEILLANCE

The majority of BNST research has focused on how it regulates the HPA axis to mediate sustained fear states, fear learning, and the stress response. HPA axis activation results in what is commonly known as the stress response: a fast rise in adrenaline production is followed by glucocorticoid release, increased heart rate, and increased blood pressure. Until the early 2000s, BNST–hypothalamus connections were thought to mainly promote negative affective responses mediated by glucocorticoid release (Dong et al., 2001). However, the BNST also regulates avoidance behaviors (Kim et al., 2013; Yamamoto et al., 2018) and visceral sensitivity (Song et al., 2020). While the amygdala regulates the short-term, acute stress response, the BNST is implicated in long-term, sustained threat responses in rodents (Walker et al., 2009; Avery et al., 2016; Lebow and Chen, 2016; Goode et al., 2019; Goode and Maren, 2019). A "valence surveillance role" has now emerged, which suggests that opposing circuitry in the BNST regulate both positive and negative affective responses (Kim et al., 2013; Jennings et al., 2013b; Gungor and Pare, 2016). Most behavioral studies focus on the BNST and avoidance, but the BNST also regulates approach, reward, and motivation.

Rodent experiments demonstrate that opposing neural connections to the hypothalamus can activate and terminate stress responsivity. More specifically, the basomedial amygdala regulates the stress response via direct and indirect connections to the hypothalamus. Direct glutamatergic neurons connect the BMA and VMH core, activating an endocrine response to stress. The BMA also projects indirectly to the VMH: glutamatergic BMA inputs excite amBNST interneurons that project to and inhibit the VMH shell, which in turn inhibits the VMH core. Excitation of BMA-VMH or BMA-amBNST results in amplification or inhibition, respectively, of a stress response (Yamamoto et al., 2018). The dual projections from the BMA allow a tight regulation of the HPA axis response, allowing either precise amplification of HPA axis activation or a return to homeostasis.

Differential projections, including those to the hypothalamus, define the functions of several BNST subnuclei. The ovBNST drives avoidance via differential circuits and inhibition of the surrounding anterodorsal region of the BNST, which in turn decreases avoidance. Neural firing in the anterodorsal BNST is correlated with safety. Activation of anterodorsal BNST circuitry increases avoidance behaviors, decreases respiratory rate, and decreases motivated behaviors via connections to the LH, PBN, and VTA, respectively (Kim et al., 2013). Neuromodulators add another layer of complexity to BNST circuits. Parallel GABAergic circuits to the orexin-expressing lateral hypothalamus play opposing roles. Stimulation of projections to the LH from the CRF-expressing anterodorsolateral BNST neurons is aversive, while those from the CCK-expressing posterior principal nucleus are rewarding (Giardino et al., 2018). Neurons expressing CRF are located near those expressing enkephalin, which blocks the action of CRF, cytoarchitecture that may permit the BNST to control approach and avoidance response (Lebow and Chen, 2016).

The BNST itself, especially the CRF circuitry, undergoes neuroplasticity in response to chronic or early life stress, including increased dendritic arborization, postsynaptic receptor expression (Hu et al., 2020a,b), CRF signaling (Forray and Gysling, 2004; Hu et al., 2020a,b), and firing rates (Conrad et al., 2011; Glangetas and Georges, 2016; Hu et al., 2020a,b). The BNST is a major source of stress-induced neural plasticity and changes to BNST sensitivity have repercussions in the hypothalamus. There is some evidence that stress alters sensitivity of the BNST–hypothalamus circuitry: adrenalectomized rats exhibit decreased total and CRF+ projection density from the BNST to the PVN (Mulders et al., 1997). However, the close, direct, and reciprocal relationship between the BNST and PVN suggests that changes to the BNST are sufficient to alter the hypothalamus. For example, glutamate-dependent high-frequency stimulation of the BNST invokes long-lasting suppression of evoked field potentials in the PVN (Tartar et al., 2006).

The functional role of the BNST in sustained threat response is conserved in humans. Unpredictable long-term (40 s) (Alvare et al., 2011) and short-term

(1.75–5.75 s) threats (Choi et al., 2012; Klumpers et al., 2015) elicit increased human BNST activity, though middle (10–20 s) phases of cued anticipation elicit the greatest BNST response (McMenamin et al., 2014). BNST activity correlates with increasing risk of shock, skin conductance (anxiety), and temporal (Somerville et al., 2010) and spatial (Mobbs et al., 2010) proximity to physical threat, imagined threat (Coaster et al., 2011), and aversive images (Grupe et al., 2013). The valence surveillance role of the BNST implicates it in maladaptive mood, including anxiety, posttraumatic stress disorder (PTSD), and both negative and positive valence aspects of depression. Recent studies provide emerging evidence for heightened BNST responses to unpredictable threat in individuals with anxiety disorders (Straube et al., 2007; Brinkmann et al., 2017; Figel et al., 2019) or with higher levels of anxiety symptoms (Somerville et al., 2010, 2013; Brinkman et al., 2018). Furthermore, studies of BNST connectivity show correlations with anxiety symptoms (Andreescu et al., 2015; Brinkmann et al., 2018; Clauss et al., 2019) and altered in anxiety disorders (Torrisi et al., 2019). Recently, the BNST has emerged as a therapeutic target against mood disorders. Long-term deep brain stimulation in the BNST improves severe obsessive–compulsive disorder symptoms (Winter et al., 2018), treatment resistant anorexia nervosa, and major depressive disorder (Blomstedt et al., 2017).

THE BNST IN ADDICTION

Circuitry between the BNST and reward and mood-related areas contribute to drug-associated behaviors, including drug-seeking and the affective symptoms of withdrawal and intoxication (Vranjkovic et al., 2017). For an in-depth analysis of the role of BNST circuitry in addiction-related behaviors, see reviews by Koob and Volkow (2010), Stamatakis et al. (2014), and Vranjkovic et al. (2017). Importantly, rodent experiments indicate that the valence surveillance capabilities of the BNST play an integratory role for stress and addiction.

Inactivation of the BNST reduces drug-seeking behavior (Buffalari and See, 2011). Several distinct neurotransmitters and neuromodulators are implicated in this role of the BNST in drug-related behavior (Vranjkovic et al., 2017). First, CRF is important for addiction and drug-related behavior (Sarnyai et al., 2001). CRF inputs to the BNST, like those from BNST interneurons, the PVN, and the CeA, promote drug-seeking behaviors in rodents, especially after exposure to stress (Silberman et al., 2013). CRF signaling in the BNST is necessary (Vranjkovic et al., 2014) and sufficient for stress-induced reinstatement of cocaine-seeking behavior (Erb and Stewart, 1999). The CRF upstream regulator pituitary adenylate cyclase activating polypeptide (PACAP), and its receptor protease activating compound (PAC1), also drive drug reinstatement (Miles et al., 2019). Similarly, alcohol binging is both driven by and induces neuroplasticity in CRF signaling in the BNST (Francesconi et al., 2009; Silberman et al., 2013; Pleil et al., 2015). The effects of CRF on drug-motivated behavior can be attributed to BNST-VTA signaling. CRF1R binding in VTA-projecting BNST neurons increases BNST-VTA signaling, which may drive drug-seeking behavior. Alcohol withdrawal reduces CRF-induced excitation in the BNST, suggesting that withdrawal induces neuroplasticity in BNST-VTA circuitry (Silberman et al., 2013). The link between CRF and drug use has potent translational implications, suggesting that neuroplasticity induced by both stress and drugs promote a vicious cycle of mood disorder and substance abuse.

Alcohol exposure also induces neuroplasticity in glutamatergic BNST signaling. Chronic and acute alcohol consumption in rodents increase glutamate sensitivity and LTP in the BNST (Weitlauf et al., 2004), an effect that is dependent on NMDA receptor subunit GluN2B (Kash et al., 2008, 2009; Wills et al., 2012). Kash et al. (2009) hypothesized that alcohol-induced plasticity in the BNST promotes alcoholism, when they observed that intermittent, but not chronic, exposure to ethanol vapor led to upregulation of NMDA receptors with GluN2B, driving alcohol consumption. Interestingly, in a study of the adult human brain, gene expression of GRIN2B, which encodes for GluN2B, was upregulated in the hippocampus of alcoholics and cocaine addicts (Enoch et al., 2014).

The BNST regulates dopaminergic neurons in the VTA (Jalabert et al., 2009), which plays a major role in reward behaviors. However, the role of dopamine within the BNST is not fully understood. Exposure to addictive drugs including morphine, nicotine, cocaine, and ethanol increases dopamine in the BNST (Carboni et al., 2000). Alcohol self-administration in rats is dependent on D1 dopamine receptors (Eiler et al., 2003; Krawczyk et al., 2011). Dopaminergic inputs to the BNST may arise from the VTA and periaqueductal gray.

Noradrenergic signaling drives affective symptoms of cocaine intoxication. Adrenergic receptor antagonism in the rodent vBNST decreases the anxiogenic effects of cocaine (Wenzel et al., 2014) and stress-induced drug reinstatement (Leri et al., 2002; Vranjkovic et al., 2014). In humans, pharmacologic intervention of noradrenaline signaling has therapeutic effects against cocaine addiction. Propranolol, a nonspecific beta-adrenergic receptor antagonist, reduces withdrawal and guanfacine, an alpha 2a agonist, decreases craving (Kampman et al., 2001; Fox et al., 2012; Fox and Sinha, 2014). The BNST, especially in the CRF and noradrenaline signaling pathways, is a potential therapeutic target for addiction.

BNST–HYPOTHALAMUS CIRCUITRY IN FEEDING

The ovBNST (and BNST on the whole) is heavily involved in regulation of feeding. CRF+ ovBNST neurons send dense projections to the lateral hypothalamus, which functions as an interface between motivation and the control of feeding behavior (Dong and Swanson, 2004a,b; Jennings et al., 2013a; Nieh et al., 2015; O'Connor et al., 2015). CRF activates GABAergic LH neurons (Petrovich, 2018) and can induce anorexic feeding behavior (Ciccocioppo et al., 2003). PKCδ+ ovBNST neurons also inhibit LH-projecting neurons from the ventrolateral region of the BNST, attenuating inflammation-induced anorexia (Wang et al., 2019). The intersection of CRF, PKCδ, and feeding behavior suggests that stress-induced changes to feeding may arise from BNST–hypothalamus connectivity.

BNST–hypothalamic connections also affect the digestive tract in ways other than feeding. Visceral hypersensitivity, like that seen in Irritable Bowel Syndrome, has been linked to stress (Holschneider et al., 2016; Fuentes and Christianson, 2018) and excitation of CRF+ neurons in the PVN. Colorectal distension (CRD)-induced visceral hypersensitivity and early life stress increased neural sensitivity and firing of CRF+ parvalbumin neurons in the PVN. Inhibition of PVN neurons via GABAergic avBNST inputs in turn reduces CRD-induced visceral hypersensitivity (Song et al., 2020). Though further research is needed, the BNST and hypothalamus are potential therapeutic targets for maladaptive feeding behaviors, from anorexia (Blomstedt et al., 2017) to obesity (Baldermann et al., 2019).

BNST–HYPOTHALAMUS CIRCUITRY IN SOCIAL BEHAVIOR

The posterior BNST, particularly the prBNST, is part of a neural circuit implicated in reproductive behavior. Reproductive behavior is often described in two stages: appetitive behaviors (the approach and investigation of a social stimulus) and consummatory behaviors (the elicited response typically referring to mounting, intromission, and ejaculation). The prBNST is implicated in appetitive rather than consummatory behaviors. Exposure to opposite-sex odors results in activation of the rostral accessory bulb, while exposure to same sex odors results in activation of the posterior olfactory bulb. However, only the rostral olfactory bulb projects to the prBNST, suggesting that it is activated preferentially during the investigation of potential mates (Hashikawa et al., 2016). Both the medial preoptic area and the ventrolateral part of the ventromedial hypothalamus express high levels of ERα and progesterone receptors and integrate information from both the main and accessory olfactory systems to play important roles in mediating copulatory behaviors. Both nuclei receive dense projections from the prBNST (Gu et al., 2003; Hashikawa et al., 2016).

Interestingly, while prBNST provides dense input to the medial preoptic area, these nuclei are implicated in different aspects of reproductive behavior. Lesions to the medial preoptic area terminate consummatory behaviors but not appetitive behaviors, whereas lesions to the posterior BNST decrease chemoinvestigation of opposite-sex odors but only delay, or do not effect, copulatory behaviors (Powers et al., 1987; Been and Petrulis, 2010). Within the prBNST, there is a significant increase in cell activity after investigation of an opposite-sex odor (Kim et al., 2015). Specifically, inhibition of aromatase-expressing neurons in the prBNST of males eliminates preference for female odors, while activation promotes male–male mating. These neurons do not appear to control sex recognition or mating behaviors in females. While there are fewer studies of reproductive behavior in females, the posterior BNST is necessary for solicitation behaviors in response to male odor stimuli (Martinez and Petrulis, 2011; Bayless et al., 2019). While the medial amygdala plays a prominent role carrying sex-specific odor information, more research is necessary to determine the exact role of the posterior BNST in reproductive behaviors. It is possible that the BNST plays an integrative role in rodent chemoinvestigation (genital sniffing), by receiving olfactory and pheromonal signals, and then relaying that information to the periaqueductal gray, and eventually, motor neurons in the spinal cord (Been and Petrulis, 2011; Hashikawa et al., 2016).

Reproductive and social defense behaviors activate similar but different neural pathways in the brain. In rodents, both behaviors depend upon chemosensory cues and gonadal steroids that activate both the main olfactory system and the accessory olfactory system. The posterior BNST receives dense projections from both of these systems via the medial and central amygdala and send projections to nuclei in the hypothalamus that regulate aggression and social defense behaviors (Kollack-Walker and Newman, 1995; Nelson and Trainor, 2007; Coria-Avila et al., 2014). Specifically, the anterior hypothalamic nucleus, the ventromedial nucleus, and the dorsal premamillary nucleus comprise a circuit implicated in innate defensive behaviors. In particular, the ventromedial hypothalamus expresses ERα receptors and integrates information from the main and accessory olfactory systems. The ifBNST sends dense projections to all three of the hypothalamic nuclei implicated in this aggression circuit (Canteras et al., 1997; Canteras, 2002; Dong and Swanson, 2004a,b; Hashikawa et al., 2016). The ventromedial hypothalamus is implicated in male aggression, and while some argue it is not essential for female aggression, inactivation of populations of estrogen receptor alpha-expressing cells in the

ventromedial hypothalamus reduces female aggression, while activation of these cells elicits attack (Hashikawa et al., 2017).

The posterior BNST sends dense projections to many subnuclei in the anterior BNST, but the purpose of these neurons remains poorly understood. The posterior BNST may indirectly regulate the HPA axis via inhibitory microcircuitry. Posterior BNST lesions elevate plasma ACTH, CRH mRNA, and corticosterone, while anterior BNST lesions weaken the plasma corticosterone response and cause a decrease of CRH mRNA (Herman et al., 1994; Choi et al., 2007). This suggests that the posterior BNST inhibits the HPA axis, while the anterior BNST activates it. The posterior BNST, specifically the prBNST and trBNST, sends moderate to low projections to the paraventricular hypothalamus, with the densest projections sent to the anterior parvocellular part of the paraventricular hypothalamus (Gu et al., 2003; Dong and Swanson, 2004a,b). However, CRH and AVP are released from the medial parvocellular part of the paraventricular hypothalamus to trigger ACTH secretion from the anterior pituitary (Herman et al., 1994; Choi et al., 2007, 2008b). The dorsomedial and fusiform subnuclei of the anterior BNST, which receive input from the prBNST and trBNST, respectively, express CRF and send dense projections to the medial parvocellular part of the paraventricular hypothalamus (Dong et al., 2001; Dong and Swanson, 2004a,b, 2006). While it is possible that posterior BNST inhibition of the HPA axis is due to direct projections to the paraventricular hypothalamus, different BNST subregions differentially regulate the HPA axis and the posterior BNST sends dense projections to the anterior BNST, but only moderate to weak projections to the region of the paraventricular hypothalamus that mediates CRH release. Taken together, this suggests the possibility of an inhibitory microcircuit within the BNST that differentially mediates the HPA axis.

While there is substantial research into the role of the posterior BNST in reproductive behavior, the specific projections from the posterior BNST to hypothalamic regions implicated in these behaviors, such as the medial preoptic area, ventromedial, and ventral premamillary nucleus, are not well studied. Lesions disconnecting the ventral posterior BNST from the medial preoptic area of the hypothalamus eliminates mating in sexually experienced male gerbils (Sayag et al., 1994). It is clear from tracing studies that the posterior BNST, particularly the prBNST, sends dense projections to hypothalamic regions involved in reproductive behavior (Gu et al., 2003; Dong and Swanson, 2004a,b; Hashikawa et al., 2016), but more research is necessary in order to determine the exact role these projections play in the mediation of these behaviors.

SEX DIFFERENCES IN THE BNST

Both the BNST and hypothalamus differ in mammalian males and females, by functionality and morphology. The human hypothalamus (Madeira and Lieberman, 1995) and BNST (Hines et al., 1985, 1992; Segovia and Guillamón, 1993; Chung et al., 2002; Swaab, 2007; Forger, 2009) are larger in males. Specifically, the central nucleus of the BNST is larger in males and contains twice the number of neurons as is found in females. Most interestingly, transgender women (assigned male at birth) have a female-typical, smaller central nucleus with less somatostatin neurons, and transgender men (assigned female at birth) have male-typical BNSTs (Zhou et al., 1995; Kruijver et al., 2000; Swaab, 2007). These sex differences occur early in development and are at least in part due to differences in hormone exposure in early developmental stages (Chung et al., 2002). This notion is supported by rodent studies where sex differences in the BNST were suppressed via alteration of gonadal hormones during development, through orchiectomy or androgynization (Segovia and Guillamón, 1993).

Increased BNST size might suggest that males are more prone to a stress response, but HPA axis activation is more intense and longer lasting in female rats after stress (Critchlow et al., 1963; Kant et al., 1983; Williams et al., 1985; Brett et al., 1986; Heinsbroek et al., 1988). In rodents, corticosteroid release during acute stress is greater in male rats relative to females. However, corticosteroids may have a greater impact in females due to a less sensitive negative feedback system. In females, CRF1R couples to a greater extent with the Gsα subunit of G proteins than in males. Therefore, CRF1R binding in females induces a greater neuronal response (Bangasser et al., 2010). Binding of CRF2R, thought to have opposite effects relative to CRF1R, is greater in males in some subregions of the BNST (Weathington et al., 2014).

There are also sex differences in expression of a variety of receptors in BNST. Males have more muscarinic receptors in the hypothalamus (Avissar et al., 1981; Egozi et al., 1982). High-affinity binding sites on muscarinic receptors decrease in aging male rates at a greater number than female rats (Gurwitz et al., 1987). Gonadal steroid-dependent sex differences in the vasopressin and vasotocin pathways are highly conserved between species, especially those in the BNST (De Vries and Panzica, 2006). Gonadal hormone pathways themselves are sexually divergent within BNST and hypothalamus structures. Estrogen receptor ERα and aromatase are more densely expressed in the BNST of male rats (Wu et al., 2009; Tabatadze et al., 2014). However, ERα immunoreactivity is higher in the MPOA and BNST of females (Brock et al., 2015). Androgen receptors are

found in somatostatin PVN, VMH, arcuate nucleus, and posterior BNST neurons in males but are sparsely expressed in these regions in females (Herbison, 1995; Brock et al., 2015). Testosterone action is limited in the BNST, VMH, and preoptic area in females, not only due to differences in receptor density but due to decreased velocity of cytochrome P-450 aromatase conversion of testosterone to estrogen (Roselli et al., 1996). Morphologic sexual dimorphism of ERα and aromatase in BNST–hypothalamus circuitry have been well established (Handa and Weiser, 2014), but the behavioral implications of these differences on stress and addiction is a neglected area of research.

The BNST–hypothalamus neural circuitry is sexually dimorphic, as well. Perhaps the most sexually dimorphic nucleus, the prBNST sends dense projections to areas such as the anteroventral periventricular nucleus of the hypothalamus, and the ventral premamillary nucleus is significantly denser in male rats than in females (Gu et al., 2003). The periventricular nucleus appears to play a critical role in controlling the estrous cycle in females, though sex differences in prBNST connectivity likely affects more than hormonal cycling. Conserved circuitry between the BNST and anterior regions of the insula, which may be implicated in anxiogenic effects of alcohol withdrawal, are also sexually dimorphic, wherein human male BNST–insula projections are denser in the left hemisphere, but females lack a hemisphere difference (Flook et al., 2020). Females have a stronger anatomic connectivity between the BNST and several areas implicated in mood disorder, reward, and addiction, including the nucleus accumbens, amygdala, hippocampus, pallidum, caudate, putamen, and subgenual cingulate cortex (Avery et al., 2014).

Sexual dimorphism in the BNST may have functional ramifications, as well. Females are twice as likely to develop stress-induced mood disorders (Kessler et al., 1994), including posttraumatic stress disorder (Breslau, 2001). Female PTSD patients show a stronger correlation between the risk and severity of PTSD and two key single-nucleotide polypeptides (SNPs): the SNPs for CRF2R and protease activating compound receptor. Binding at PAC1, the specific G-protein coupled receptor for pituitary adenylate cyclase activating polypeptide, increases avoidance in rodents (Hammack et al., 2009). Chronic stress increases both PACAP and PAC1 expression in the anterolateral BNST (Hammack et al., 2009; Hu et al., 2020a). This sex-specific link between PTSD and CRF signaling may be associated with the makeup of the PAC1 gene, which hosts a single SNP in a putative estrogen response element that predicts PTSD diagnosis and symptoms in females (Ressler et al., 2011).

Rodent approaches to studying psychiatric diseases, including depression, anxiety, PTSD, and addiction, usually exhibit sexually dimorphic behavioral responses. However, the directionality of these differences is not consistent. Some paradigms, behavioral tests, and genetic models suggest that males are more susceptible to stress and mood disorders, while others suggest the opposite. Even similar stressors can result in behavioral sex differences (Kokras and Dalla, 2014). This variability indicates a need for validating stress paradigms in both males and female rodents (Yohn et al., 2019) and in postmortem tissue of human patients.

CONCLUDING COMMENTS

The BNST is a hub for positive and negative valence information, and its tight regulation of areas like the hypothalamus and VTA drives behavioral responses to ever-changing environmental conditions. The integratory role of the BNST makes it a key player in a wide variety of typical functions in mammals, including mood, feeding, and social behavior. It also makes it an investigatory target for maladaptation in these functions, including mood disorder, eating disorder, and addiction. Though rodent studies have promoted it as a prospective therapeutic target, the BNST has proven difficult to study in vivo in humans due to its minute size and indiscernibility from bordering structures. Further molecular analysis of human postmortem material, as well as recent developments in 3T and 7T MRI, will help improve the scope of human BNST research (Avery et al., 2014; Torrisi et al., 2015; Theiss et al., 2017). In recent years, the BNST has been used as a therapeutic target, including deep brain stimulation and manipulation of key BNST signaling pathways. These recent developments foster optimism for the future of the BNST as a potential therapeutic target, and as a window into the sexual dimorphism of mood disorder.

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