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Maternally responsive neurons in the bed nucleus of the stria terminalis and medial preoptic area: putative circuits for regulating anxiety and reward

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Abstract

Postpartum neuropsychiatric disorders are a major source of morbidity and mortality and affect at least 10% of childbearing women. Affective dysregulation within this context has been identified in association with changes in reproductive steroids. Steroids promote maternal actions and modulate affect, but can also destabilize mood in some but not all women. Potential brain regions that mediate these effects include the medial preoptic area (mPOA) and ventral bed nucleus of the stria terminalis (vBNST). Herein, we review the regulation of neural activity in the mPOA/vBNST by environmental and hormonal concomitants in puerperal females. Such activity may influence maternal anxiety and motivation and have significant implications for postpartum affective disorders. Future directions for research are also explored, including physiological circuit-level approaches to gain insight into the functional connectivity of hormone-responsive maternal circuits that modulate affect.

Keywords

maternal behavior; anxiety; motivation; medial preoptic area; bed nucleus of the stria terminalis; postpartum mood

1. Introduction

Changes in reproductive steroids, such as those that occur during the puerperium, are associated with increased vulnerability for affective dysregulation[1]. In fact, an estimated 10–

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20% of perinatal women are afflicted by a mood disorder, such as anxiety or depression[2]. Further, perinatal depression is the leading cause of maternal mortality, resulting from suicide[3]. The sequelae of these disorders entails not only elevated anxiety and disrupted mood for the mother, but also aversive outcomes for the developing infant[4,5]. The symptomology of postpartum affective disorders, such as anhedonia, anxiousness, and agitation[6], implies a dysregulation of neural circuitry that regulates emotion and motivation. However, the neurobiological etiology of postpartum affective disorders remains unclear, perhaps due to the complexity of hormonal and environmental contributors that influence maternal affect and the lack of previous tools to disentangle the functional elements of these neural circuits.

Throughout pregnancy, the brain organizes adaptations that prepare the mother for a timely parturition and the rapid onset of maternal care following parturition. Pregnancy hormones drive these adaptations before parturition, but afterward maternal actions are maintained by external infant stimuli[7]. Ordinarily, maternal brain adaptations reduce anxiety and promote maternal actions that facilitate infant-associated motivation and reward[8–10]. However, neural maladaptation and hormone withdrawal during the puerperium may precipitate anxiety and depressive behavior. While environmental and hormonal correlates of maternal anxiety and mood[7,9–11], as well as relationships between the brain, endocrine systems, and maternal care[8,12–16] have been reviewed elsewhere, no review to date has focused on the precise hormone-responsive brain regions central to both maternal behavior and affective regulation. The most prominent candidates include the medial preoptic area (mPOA) and ventral bed nucleus of the stria terminalis (vBNST), two sexually dimorphic steroid-sensitive nuclei[17,18] essential for maternal behavior[19,20]. In addition, the BNST regulates anxiety[21–23] and motivated behavior[21,23,24]. Further, we have recently demonstrated that vBNST sub-circuits have opposing roles in divergent anxiety and reward states in male mice. It is unclear whether similar circuit processing occurs in females or is influenced by reproductive steroids, parturition, or infant stimuli.

In this review, we examine the regulation of neural activity in the mPOA and vBNST by environmental and hormonal concomitants in the puerperal female. Since the vBNST and mPOA control similar maternal functions but lack clear anatomical demarcations and most tools used to date have been limited in their capacity to delineate between their functions, we will refer to them as an adjoining region (mPOA/vBNST). Herein, we discuss mPOA/vBNST inputs engaged by hormonal or infant stimuli and their potential outputs that orchestrate maternal actions, anxiety, and motivated behavior. We also identify candidate steroid and peptide hormones that could prepare the phenotype of mPOA/vBNST neurons late in pregnancy, allowing for altered reactivity to infant, emotional, or rewarding stimuli. Lastly, we identify gaps within the current literature that require further investigation, especially pertaining to the functional connectivity of circuits that influence anxiety and reward processing in response to hormones and maternal experience.

2. Maternal vBNST/MPOA circuitry

In mammalian females, external infant cues stimulate multiple sensory modalities to trigger maternal responses. In rodents, low frequency ultrasonic vocalization pup calls promote

licking and nursing behavior by the mother[25] and high frequency distress calls induce search and retrieval behavior by the mother when pups are separated from the nest[26]. Multisensory infant cues are processed by mPOA/vBNST circuits that receive hormonal and infant input and orchestrate complex maternal actions essential for offspring survival[8,15,27]. The mPOA/vBNST receives widely distributed inputs from forebrain, hypothalamic, and brainstem regions and has reciprocal interactions with many of these structures, allowing for bidirectional control (illustrated in Figure 1). Preoptic inputs that regulate maternal responsiveness have been reviewed in greater detail elsewhere [15,28]. The mPOA/vBNST are functional nodes within these circuits, as mPOA/vBNST lesions impair maternal behavior [29–32] and pup-associated motivation [33–35] in female rodents.

In rodents, chemosensory input originates from olfactory and vomeronasal systems and is relayed to the mPOA/vBNST through the medial amygdala (MeA)[36–38]. The vomeronasal organ and main olfactory epithelium are both important for retrieval of pups that stray from the nest[39]. Olfactory bulbectomy eliminates neuronal Fos activity in the MeA following mother-pup interactions and slightly decreases but does not eliminate Fos expression in the mPOA/vBNST[40,41]. However, these females still display relatively normal maternal behavior. Thus, other sensory stimuli are likely critical for the expression of maternal care[39]. Somatosensory infant input is provided during nursing, although nipple removal does not affect maternal behavior (except crouched nursing), maternal anxiety[42], or pup-induced Fos expression in the mPOA/vBNST[40,43]. However, when olfactory bulbectomy is coupled with nipple removal a significant reduction in Fos expression in the mPOA/vBNST is observed, although maternal care is still present[40]. Therefore, infant generated neural activity in the mPOA/vBNST and the expression of maternal behavior is likely the result of combined afferent inputs. Further, olfactory pup cues and playback of pup ultrasonic vocalizations are most effective in producing maternal search behavior when presented together rather than separately[44]. However, a better functional dissection of maternally responsive mPOA/vBNST neurons is necessary to explain the ostensible discordance between neural activation and behavioral effects in this region.

Regulation of maternal behavior and modulation of affect both involve reward circuits. Models suggest that mPOA/vBNST efferent projections to the midbrain stimulate mesolimbic activity for infant-related reward processing and motivated behavior[8,15,20]. Specifically, mPOA/vBNST projections innervate midbrain neurons in the ventral tegmental area (VTA)[19,45–50] and are stimulated by maternal[50], aversive, and rewarding experiences[51–53]. Further, mPOA/vBNST to VTA projecting neurons directly or indirectly activate dopaminergic neurons in the VTA[48,54] and inactivation of the VTA disrupts maternal motivation[55] and preference for infant-associated cues[56]. Further, damage to the dorsolateral POA disrupts maternal behavior and likely severs the axons that project from the mPOA/vBNST to the VTA via the lateral hypothalamus[57]. Dopaminergic cell bodies in the VTA project to a number of regions, including the ventral striatum, to mediate goal-directed behavior[58–60] and are stimulated by infant-associated cues[35,61,62]. Studies utilizing voltammetry and microdialysis associate dopamine release in the ventral striatum with mother-infant interactions[63,64]. In addition, ablation of dopamine neurons in the VTA or striatum disrupts maternal motivation[35,65]. Functional magnetic resonance imaging studies reveal that infant stimuli are associated with increased activity in mesolimbic regions in

postpartum dams, which is suppressed by presentation of cocaine rather than pup stimuli[66]. Neural activity in the mPOA/vBNST may contribute an infant-specific bias to motivational circuitry in the VTA in postpartum females[67]. Together, these studies suggest that dopaminergic midbrain activity is enhanced by infant stimuli under normal puerperal conditions. Conversely, postpartum depression is correlated with reduced responsivity to rewarding stimuli. Functional MRI studies reveal that women with postpartum depression have rapid attenuation of ventral striatum activity following presentation of a reward, compared to healthy mothers[68]. It is unclear whether postpartum depression results in deficits in reward processing that affect both infant care and general motivation. However, genetic rodent models of depression display reduced maternal care[69] and lack elevated dopamine levels in response to infant interactions[70], compared to normal rodents.

Projections from the mPOA/vBNST to the VTA also have the capacity to control divergent motivational and anxiety states. Recently, we demonstrated that glutamatergic and GABAergic vBNST projection neurons synapse onto VTA GABA neurons[54]. Further, we found that optogenetic stimulation of vBNST GABAergic terminals in the VTA is anxiolytic and rewarding, while activation of glutamatergic terminals in the VTA is anxiogenic and aversive. However, these data are based on findings in male mice and it is unknown whether sex differences occur in the functioning of this circuit or if infant-dependent anxiety and reward states are under similar circuit control. The majority of the maternally responsive mPOA/vBNST neurons appear to be GABAergic[71,72], however the subset that project to the midbrain remain uncharacterized within this behavioral context. The potential genetic phenotypes and receptor expression profile of mPOA/vBNST neurons that respond to hormones or infant stimuli for complex circuit regulation of motivation and maternal behavior are discussed below.

3. Maternally responsive mPOA/vBNST neurons

Pregnancy hormones and infant stimuli appear to recruit and maintain mPOA/vBNST circuits that regulate maternal actions and motivated behavior in puerperal females. Approach-avoidance models of maternal behavior suggest that maternal behavior occurs when the inclination to approach infant stimuli is greater than the tendency to avoid such stimuli. Then, recurrent infant exposure reinforces infant care through sustained activation of maternal circuits that promote maternal actions. Infant stimuli have anxiolytic and rewarding effects that may also act as reinforcing properties. Postpartum dams readily engage in operant responding tasks for pup reinforcement[33,73–75] and develop a strong place preference for pup-associated cues[8,76–78]. Further, lactating dams exhibit less anxiety-like behavior in a battery of assays following mother-pup interactions[9,11,79–81]. Such anxiolytic effects appear to depend on the presence of the pups, as separation often has opposite and anxiogenic effects. Further, infant exposure has anxiolytic effects in virgin females after recurrent exposure[79,81]. This implies that infant experience imparts changes in anxiety and reward related systems. Hormones and infant stimuli appear to act synergistically to promote maternal actions, in part by stimulating neural activity in the mPOA/vBNST, as discussed below.

3.1 Infant stimuli

Infant stimuli generate neuronal Fos expression, a marker of neural activity, within the mPOA/vBNST of postpartum rodents[71,82,83], even after prolonged infant exposure[84] and ovariectomy[85]. Such induction likely serves a function role, since genetic knock out of FosB abolishes maternal behavior in postpartum mice[83,86,87]. Further, similar effects of infant exposure are observed in virgin females, including expression of maternal-like behavior[88] and Fos expression in the mPOA/vBNST[89]. This suggests that infant stimuli alone are a potent activator of maternal circuits, even in the absence of hormones and pregnancy. Studies suggest that experience-induced effects of infant exposure may occur through epigenetic modifications within the mPOA[88]. In addition, neural activation patterns are influenced by the anxiety state of the mother and the presence of her offspring. Dams separated from their pups display higher Fos expression in the dorsal mPOA but less Fos expression in the vBNST, compared to those that remained unseparated from their pups [82]. It is unknown whether disparate maternal affective states result in distinct patterns of neural activity or target similar genetic populations within the mPOA/vBNST.

3.2 Steroid hormones

Hormonal priming late in pregnancy, characterized by a rise in estrogen, prolactin, and oxytocin, and decline in progesterone, is required for the rapid induction of maternal care. Functionally, estrogen appears to enhance and progesterone inhibits, respectively, maternal behavior. Further, intra-mPOA estradiol facilitates maternal behavior[90,91]; thus, this is one site of estrogen's maternal effects. Estradiol administration in conjunction with progesterone withdrawal or pregnancy termination also enhances Fos expression in mPOA/vBNST neurons[92]. Conversely, progesterone administration alone impairs maternal care and lowers Fos expression within the mPOA/vBNST[92]. It is less clear whether pregnancy termination and steroid hormones activate similar or distinct genetic populations in this region. However, hormonal profiles that occur around parturition likely promote expression patterns that act to facilitate maternal responsiveness. For instance, a pregnancy-like regimen of steroids alters prolactin receptor expression in the mPOA, with estrogens increasing and progesterone decreasing its expression[93]. As discussed below, prolactin helps to enhance maternal care through actions in the mPOA. Consistent with this, there are greater estrogen receptor concentrations[94] and fewer progesterone receptors[95] within the mPOA in rodents during late pregnancy. These steroid receptor changes may enhance the physiological effects of estrogen in the mPOA/vBNST and diminish those of progesterone, thereby promoting maternal actions in puerperal females.

While steroids often promote maternal behavior, they also predispose some mothers to disruptions in mood. Estrogens in particular are potent mediators of maternal behavior that may underpin altered postpartum affective states[96–98]. In female rodents, estradiol withdrawal enhances anhedonia, such as reduced operant responding for electrical self-stimulation [99] and sucrose consumption [98], compared to non-steroid deprived females. While, the brain regions involved remain undefined, estrogenic actions in the mPOA may contribute to postpartum changes in mood. Late in pregnancy, rodents express higher levels of Fos expression in the mPOA than non-pregnant females, and approximately 25–45% of these neurons co-express estrogen receptor α (ERα)[100]. ERα expression in the mPOA is

linked with individual differences in maternal care and anxiety behavior. Specifically, females with higher ERα expression are more maternal and less anxious, opposite from those with lower ERα expression in the mPOA[101]. Moreover, administration of an ERα agonist reduces postpartum anxiety and depressive-like behaviors[102]. However, knock down of ERα in the mPOA similarly reduces postpartum anxiety[103]. Thus, estrogenic actions within the mPOA may act through disparate routes and modulate affect in complex ways in response to fluctuating estrogen levels. Further, estrogens often interact with other steroid and peptide hormones to modulate maternal activity, as discussed below. In addition, estrogen-responsive mPOA/vBNST circuits, including those that influence mood and maternal actions, remain unmapped. Neuroanatomical tracing studies indicate that mPOA/vBNST to VTA projections are estrogenic[104,105]. However, it is unknown whether estrogenic actions in the mPOA/vBNST stimulate midbrain projections that control anxiety and divergent motivational states.

Apart from estrogen, progesterone could influence maternal affect, directly or through the progesterone metabolite and neurosteroid, allopregnanolone. Allopregnanolone can alter inhibitory functions through its actions at ionotropic $GABA_A$ receptors[106]. Such effects could alter neuronal excitability within maternal circuits. For instance, application of allopregnanolone in mPOA brain slices enhances GABAergic transmission[107–109]. Changes in inhibitory tone within the mPOA could have ramifications for downstream targets that regulate motivated behavior or anxiety state, such as those that project to the midbrain.

3.3 Peptide hormones and neurotransmitters

The mPOA/vBNST is a heterogeneous structure with the capacity to integrate a variety of hormonal, neurochemical, and environmental signals that collectively modify maternal anxiety and reward states. These neuronal and hormonal substrates have distinct expression patterns within the mPOA/vBNST, as exemplified in Figure 2. This information was originally derived from the Allen Brain Atlas in situ mouse brain database[110]. Recently, a web-based tool has become available by the Allen Brain Atlas to visual gene expression within specified structures of the mouse brain[111]. In Figure 2B, we have created a heat map of relative gene expression levels within the POA and BNST. Microarray studies have recently shown that parity and maternal behavior can alter gene expression patterns in the mPOA[112]. Molecular studies by Shah have also found that adult sex hormones regulate gene expression in a sex- and site- specific manner[18]. Further, mice with disruptions of these target genes show functional deficits in an array of reproductive behaviors, including parenting and mating. Thus, additional studies, such as those that incorporate Cre-driver tools and transgenic mouse lines, are necessary to further dissect the functional properties of genetically defined cells and circuits within the mPOA/vBNST and their role not only in reproductive behaviors, but also in regulation of divergent motivational and emotional states.

Studies have begun to phenotype select neuronal populations within the mPOA/vBNST that are maternally and hormonally responsive. Neurochemical investigation of Fos-expressing neurons in the mPOA/vBNST of maternal mice indicate that most are inhibitory GABAergic neurons (~75%, glutamate decarboxylase 67), while very few appear to be glutamatergic (~6%, Vglut2)[72]. The majority of Fos positive GABAergic cells are located primarily in the

dorsal central MPOA and ventral lateral BNST[71]. Many of the Fos activated subset co-express galanin (~47%), neurotensin (~49%), or tachykin2 (~29%)[71]. Studies have started to examine the functional role of these cell types and other steroid and peptide hormones within the context of infant care and maternal anxiety or reward. Recently, a study found that a sub-set of galanin neurons in the mPOA are activated by parental experience in male mice[50]. Optogenetic activation of mPOA galanin neurons in male mice enhances parental care, whereas genetic ablation results in impairments in both male and female mice. This demonstrates a functional role for galanin neurons in paternal behavior. However, the projection targets of these neurons remain uncharacterized, as well as the function of maternally activated mPOA/vBNST neurons within the context of maternal affect and emotion. Apart from galanin, neurotensin-containing neurons in the mPOA may also promote maternal functions. Neurotensin mRNA is elevated within the mPOA and dorsal BNST of postpartum mice, but lowered in other regions, compared to virgins[114]. Neurotensin administration enhances Fos expression in the mPOA and dorsal BNST and suppresses maternal aggression[115]. Neurotensinergic neurons in the mPOA project to the VTA and appear to convey distinct reward information[116,117], although no studies have examined these projections within the context of maternal specific motivation or infant reward.

One commonality among maternally engaged peptides is that reproductive steroids, such as estrogen, often modulate their activity. For instance, approximately half of neurotensin neurons in the mPOA contain estrogen receptors[118] and estrogens enhance galanin expression in the mPOA[113]. Further, estrogen interacts with oxytocin to promote maternal actions[119,120] and estrogen enhances oxytocin receptor binding in the mPOA[101]. *In vitro* electrophysiological slice recordings in the BNST reveal that oxytocin sensitivity is higher during lactation compared to late pregnancy and is enhanced by concomitant application of estradiol[105]. Also, oxytocin has potent anxiolytic effects[123] that are enhanced by estrogens[124].

3.3.1 Oxytocin—Oxytocin subserves a number diverse maternal functions, including the regulation of maternal care, infant reward, social attachment, and anxiolysis[62,125,126]. Oxytocin acts as a peripheral hormone for peripartum functions, including milk ejection and labor. Suckling discharges bursts of spikes that release oxytocin into circulation, acting as an infant-mediated positive feedback loop[127]. Oxytocin also acts as a neuropeptide in the mPOA to promote maternal functions around parturition. Oxytocin administration induces the spontaneous onset of maternal care in steroid-primed virgin females[128]. In contrast, oxytocin antagonists disrupt this natural onset of maternal behavior through actions within the mPOA[129,130]. Additionally, oxytocin receptor expression is upregulated in the mPOA late in pregnancy and in the mPOA/vBNST after parturition[131,132]. Changes in oxytocin receptor expression affect not only maternal behavior, but also anxious states. In lactating dams, central oxytocin infusions enhance Fos within the mPOA/vBNST[133] and reduce anxiety-related behavior, compared to virgin females[134]. The target projections of oxytocin containing neurons remain unmapped, although. neuroanatomical tracing studies suggest that oxytocin containing cells in the mPOA project to the VTA[61] and promote anxiolytic and

rewarding maternal states[61]. Oxytocin interacts with the mesolimbic dopamine system here to facilitate aspects of maternal motivation and infant reward states[62].

3.1.2. Prolactin—Prolactin has been implicated in maternal care and peripartum adaptations, as extensively reviewed elsewhere[11,16,135–137]. Prolactin systems undergo changes that facilitate maternal behavior under the presence of gonadal steroids, in part through actions in the mPOA[136,138,139]. For instance, exogenous prolactin stimulates maternal-like behavior in nulliparous females, but only when administered centrally rather than systemically, and only in steroid-primed females[140,141]. Further, a similar effect is observed when prolactin is infused directly into the mPOA. Prolactin is released within the mPOA of lactating rats during suckling[142], and prolactin receptors are upregulated peripartum[133]. In addition, treatment with prolactin increases prolactin receptors in the mPOA[144]. Steroid-induced changes around parturition likely promote prolactin receptor alterations that enhance maternal responsiveness, since estrogen increases prolactin receptor expression, whereas progesterone decreases it[93]. Further, actions at the prolactin receptor likely play a functional role in maternal care, since prolactin receptor knock out results in maternal deficits[145,146]. While prolactin is clearly involved in the regulation of maternal behavior, it is less clear whether it affects maternal anxiety or mood, although, maternal hypoprolactinemia around the end of lactation is associated with increased anxiety[147].

3.1.3. Corticotrophin releasing factor—In contrast to the peptides discussed thus far, corticotrophin releasing factor (CRF) enhances anxiety and impairs maternal care. Central administration of CRF impairs maternal behavior in lactating dams[148] and results in pup killing in steroid-primed ovariectomized females[149]. Administration of a CRF agonist in the BNST reduces pup care and enhances maternal anxiety in virgin and lactating dams[150]. In contrast, administration of a CRF antagonists in the BNST reduces anxiety in virgin and lactating females[150]. Further, CRF enhances Fos expression in the BNST to a greater extent in virgin females compared to lactating dams[151]. Since CRF in the BNST inhibits maternal functions, reduced sensitivity here may protect against maternal deficits. Neuroanatomical and electrophysiological studies indicate that BNST to VTA projecting CRF neurons influence reward processing[143–145], although none have examined BNST-VTA circuit processing in maternal females.

4. Concluding remarks

Collectively, these findings indicate that infant stimuli and reproductive steroids regulate motivated behavior and maternal affect. Such changes appear to be modulated through neural and hormonal actions in the mPOA/vBNST. However, most studies to date are based on behavioral pharmacology and immunohistochemical analyses, and functional circuit-level relationships are lacking. Dulac and colleagues have begun to examine the functional role of mPOA neurons in parenting with the use of *in vivo* behavioral optogenetics. Future studies should expand upon these findings and target other genetically defined and maternally responsive cell populations. Also, studies should establish the function of mPOA/vBNST input and output circuits not only in relation to maternal care, but also in the context of general affective and motivational states. In particular, a more detailed dissection of mPOA/vBNST to midbrain circuits is necessary to determine similarities between infant-specific

and general motivational processing. The influence of steroids and reproductive experience on mPOA/vBNST circuits that modulate anxiety and affect may have significant implications for the understanding and treatment of reproductive subsets of affective disorders.

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Highlights

- Postpartum neuropsychiatric disorders are a major source of morbidity and mortality.
- The neurobiological etiology of postpartum affective disorders remains unclear.
- The mPOA and vBNST regulate maternal actions and motivated behavior.
- Adaptations in the mPOA and vBNST may be involved in modulation of postpartum affect.
- Future studies should examine the functional connectivity of maternal circuits that regulate anxiety and reward.

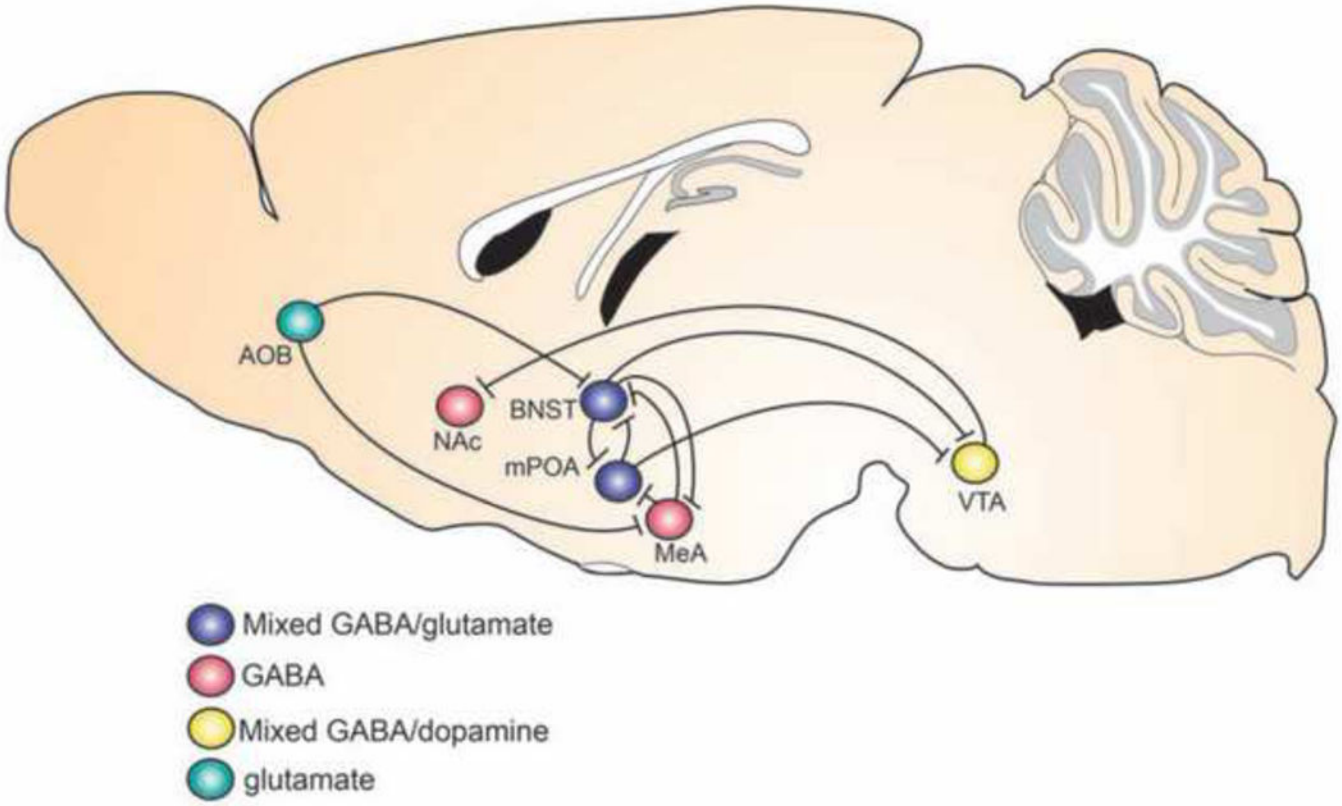

Figure 1.

Schematic detailing medial preoptic (mPOA) and bed nucleus of the stria terminalis (BNST) afferent and efferent connectivity implicated in maternal functions. (A) The BNST receives inputs from the accessory olfactory bulb (AOB), medial amygdala (MeA), and medial preoptic area (mPOA) and ventral tegmental area (VTA, projection not shown). The BNST sends projections to the VTA, MeA, and mPOA. The mPOA receives inputs from the AOB, MeA and BNST and sends outputs to the VTA. The VTA has reciprocal connections with the nucleus accumbens (NAc). Cellular phenotypes are indicated by color; mixed GABAergic/glutamatergic populations shown in purple, GABAergic shown in pink, mixed GABAergic/dopaminergic shown in blue, and glutamatergic shown in green.

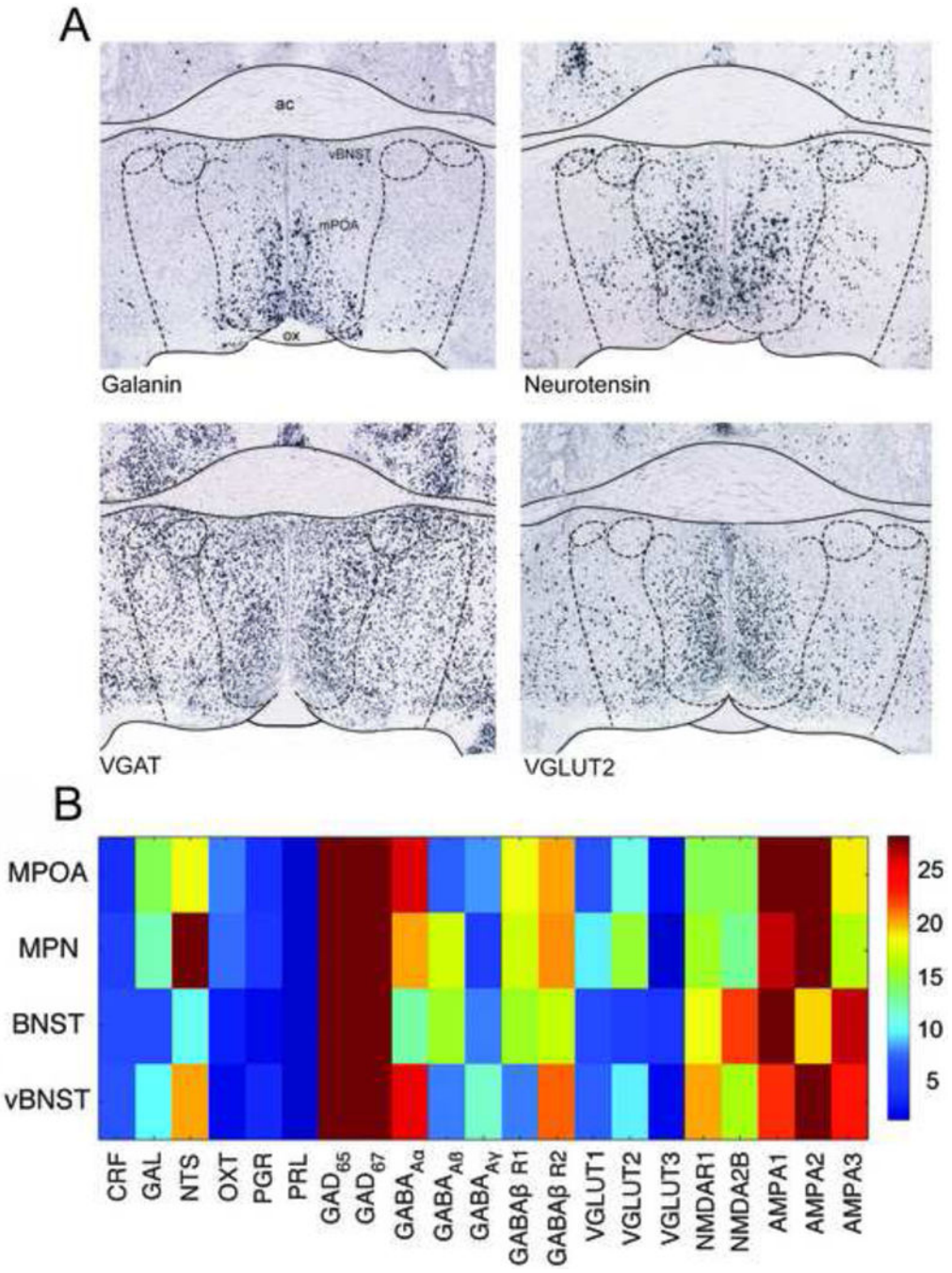

Figure 2.

Allen Brain Atlas–Driven Visualizations: A) Photomicrographs represent mRNA expression for galanin, neurotensin, VGAT (GABA vesicular transporter), and VLGUT2 (vesicular glutamate transporter) in the mPOA and vBNST. Derived from Allen Brain Atlas In situ hybridization data. B) Heatmap illustrates gene expression within the medial preoptic area (MPOA), medial preoptic nucleus (MPN), bed nucleus of the stria terminalis (BNST), and

ventral (vBNST). Values were derived from energy expression; see Zaldivar & Krichmar, 2014. Gene symbols are labeled according to Allen Brain Atlas.