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Lateral habenula neurocircuits mediate the maternal disruptive effect of maternal stress: A hypothesis

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ABSTRACT

Up to 20% of women experience stress-related disorders during the postpartum period; however, little is known about the specific neural circuitry by which maternal stress exerts its negative impacts on mental health and maternal caregiving behavior. Theoretically, such a circuitry should serve as an interface between the stress response system and maternal neural network, transmitting stress signals to the neural circuitry that mediates maternal behavior. In this paper, I propose that the lateral habenula (LHb) serves this interface function. Evidence shows that the LHb plays a key role in encoding stress-induced effects and in the pathophysiology of major depression and stress-related anxiety, and thus may play a role in maternal behavior as part of the maternal brain network. I hypothesize that maternal stress acts upon the LHb and two of its major downstream targets, i.e., ventral tegmental area (VTA) and dorsal raphe nucleus (DRN), compromising the maternal care and contributing to postpartum mental disorders. This hypothesis makes three predictions: (1) maternal stress enhances LHb neuronal activity; (2) activation of DRN- and VTA-projecting neurons in the LHb mimics the detrimental effects of maternal stress on maternal behavior; and (3) suppression of DRN- and VTA-projecting neurons in the LHb attenuates the detrimental effects of maternal stress on maternal care in stressed mothers. Confirmation of this hypothesis is expected to enhance our understanding of the neurocircuit mechanisms mediating stress effects on maternal behavior.

Keywords: Maternal behavior; Lateral habenula (LHb); Ventral tegmental area; Dorsal raphe; Maternal stress; Postpartum depression; Postpartum anxiety

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INTRODUCTION

Pregnancy, parturition, and lactation induce numerous changes in a female's brain, body, and behavior, which are essential for the survival and health of offspring and necessary for the female to successfully respond to new demands in her changing environment (Hillerer et al., 2012). Various adaptive changes, from the molecular to behavioral level, are well documented in laboratory animals, including increased chronic basal hypercorticism, decreased hypothalamic pituitary adrenal (HPA) axis responsiveness to stressors, decreased corticotropin-releasing hormone (CRH, a stress hormone) mRNA and hypothalamic paraventricular nucleus (PVN) binding, increased oxytocin and receptor mRNA expression in the PVN, increased adult neuroplasticity (e.g., adult neurogenesis), reduced sensorimotor gating (an attentional filtering function) as measured in prepulse inhibition (PPI), reduced acoustic startle response, increased pup-directed maternal responses (pup retrieval and nursing), increased maternal aggression, decreased anxiety, and enhanced memory function (Byrnes et al., 2007; Hård & Hansen, 1985; Hillerer et al., 2012; Kask et al., 2008; Kinsley & Lambert,

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2008). Magnetic resonance imaging (MRI) studies on the brains of human mothers have also documented structural and functional changes in certain corticolimbic circuits involved in emotional processing, volitional attention and executive function, reward and motivation, and sensorimotor functions (Kim et al., 2010, 2016; Pawluski et al., 2021). These areas include the prefrontal cortex (PFC), cingulate cortex, parietal cortex, amygdala, striatum, hypothalamus, and substantia nigra (SN). These normal adaptations can easily be disrupted by various individual, environmental, and societal factors, which contribute to the occurrence of postpartum mood, anxiety, and memory disorders (Lonstein, 2007). It is estimated that approximately 5%–12% of mothers display postpartum anxiety (Andersson et al., 2006), 5%–25% experience postpartum depression (Beck, 2006), and 0.1% suffer postpartum psychosis (Jones et al., 2008). Some individuals also show impairments in prospective memory (Henry & Rendell, 2007). Of the risk factors identified, exposure to chronic stress before and/or during pregnancy is among the most studied for these disorders (Bifulco et al., 1998). Indeed, exposure to chronic stress during pregnancy or shortly after giving birth is cited as a preceding factor for depression (Parker et al., 2003). It also constitutes one of the most convincing and translational risk factors employed to develop animal models of postpartum depression (Li & Chou, 2016). Accumulating evidence suggests that maternal stress (i.e., occurring during pregnancy or after birth) contributes to postpartum mental disorders by preventing or inhibiting behavioral, neuroendocrine, and neuronal adaptations specific to the reproductive status of females (Hillerer et al., 2012).

MATERNAL STRESS ALTERS BEHAVIOR IN MOTHERS AND NEGATIVELY INFLUENCES OFFSPRING

Human maternal stress is known to have long-term detrimental impacts on both mothers and their offspring. As a common risk factor for postpartum mental disorders (e.g., depression, anxiety, and psychosis), maternal stress may also impair the quality of maternal care. Depressed mothers can exhibit greater hostility, with increased negative and/or disengaged (withdrawn) parenting and decreased positive (warmth) parenting (National Research Council et al., 2009 ; Paris et al., 2009), which can, in turn, adversely affect the physical, psychosocial, and neurobiological development of their children. Increasing studies have documented the maladaptive effects of maternal depression on children (Goodman et al., 2011; National Research Council et al., 2009), including deficits in affective functioning (e.g., increased negative affect and dysregulated aggression), lower cognitive functioning (e.g., lower academic/intellectual performance), poorer interpersonal functioning, and impaired stress response (neuroendocrine and autonomic) and cortical activity (O'Hara & McCabe, 2013). Preclinical rodent studies on the effects of maternal stress, including prenatal and postpartum stress and stress hormone exposure, generally support the findings reported in humans (Brummelte & Galea, 2010, 2016; Brummelte et al., 2006; Pawluski et al., 2017). Notably, maternal stress significantly changes maternal behavior in rats and recapitulates some of the behavioral abnormalities observed in human offspring. Deficits in maternal care include changes in time spent on arched-back nursing and pup contact, greater time spent away from nest and pups, longer latency to initiate nursing, and lower durations of pup grooming/nursing (Haim et al., 2016; Leuner et al., 2014; Nephew & Bridges, 2011; Smith et al., 2004). Stressed mothers also show increased anxiety, impaired learning and memory, reduced sensitivity to anxiolytic or antidepressant treatment, and increased depressive-like behaviors (e.g., forced swim test and sucrose preference test) (Boccia et al., 2007; Bowman et al., 2003; Nephew & Bridges, 2011; Rayen et al., 2011; Smith et al., 2004). Offspring of stressed mother rats commonly show elevated anxiety and deficits in attention, spatial learning and memory, and executive functions (Maccari et al., 2014; Weinstock, 2001a, 2001b, 2017). Despite the prevalence and high costs of maternal stress for both the mother and developing child, our understanding of the neurocircuit mechanisms of stress-induced postpartum emotional and mood disorders remains limited (Pawluski et al., 2017). Thus, it is imperative to clarify how maternal stress induces deficits in maternal care at the neurocircuitry level, and how it contributes to the psychopathology of postpartum mental disorders. Such knowledge is critical for improving the well-being of mothers and their offspring.

MATERNAL STRESS ALTERS BRAIN STRUCTURE AND FUNCTION

Maternal stress and stress-related disorders can affect the brains of mothers. Functional magnetic resonance imaging (fMRI) of the human brain has shown activity and connectivity changes in the cortical and subcortical areas of women with affective symptoms and postpartum depression, especially in PFC areas, insular cortex, limbic system (e.g., anterior cingulate cortex, hippocampus, and amygdala), ventral tegmental area (VTA), SN, and periaqueductal gray (PAG) (Pawluski et al., 2017). For example, at rest, women with postpartum depression exhibit disrupted posterior cingulate cortex-right amygdala connectivity compared to non-depressed postpartum women (Chase et al., 2014). A recent study identified an area in the dorsomedial PFC (DMPFC) with enhanced connectivity to the rest of the default mode network in depressed mothers and showed significant positive correlation between depression severity and resting-state functional connectivity within the DMPFC (Deligiannidis et al., 2019). When tested with infant and non-infant cues, mothers with postpartum depression show an overall increased response in the amygdala compared to non-depressed mothers. They also show an enhanced response in the right amygdala to positive infant photos and positive non-infant photos and decreased bilateral amygdala-right insular cortex connectivity when viewing infant photos (Wonch et al., 2016). Although these correlational neuroimaging studies undoubtedly identified several brain regions correlated with postpartum mental disorders, they do not explain how postpartum mental disorders develop or disclose the cause-effect relationship between symptoms of postpartum mental disorders and alterations in brain functions.

Research using animal models of maternal stress is more appropriate for studying the neural basis of postpartum stress disorders. In line with clinical work, animal studies also point to the central role of maternal stress in postpartum mental disorders and associated remodeling effects on the brain. Documented changes include reduced adult neurogenesis in the hippocampus and alterations in dendritic morphology in the ventral striatum and medial PFC (Haim et al., 2016; Leuner et al., 2014; Pawluski et al., 2016). Chronic stress can impact various maternal adaptations, including basal plasma hypercorticism, hypothalamic oxytocin mRNA expression, and anxiolysis (Hillerer et al., 2011). Importantly, none of these parameters are affected in stressed nulliparous females, indicating that these stress-induced changes are specific to the maternal period (Hillerer et al., 2011). However, how these changes in brain structure and function are involved in the mediation of stress-induced alterations in maternal behavior is not known. This may be because changes in the brain due to stress do not always represent the neural substrates that mediate stress signals and cause stress-induced maternal alterations. For example, maternal stress is known to cause plastic changes in the hippocampus; however, hippocampal lesions can have minimal effects on maternal behavior (Kimble et al., 1967; Terlecki & Sainsbury, 1978). Consequently, identifying broad stress-induced changes in the brain is not sufficient, making it imperative to pinpoint the specific neural circuitry that stress acts upon to disrupt maternal behavior.

HYPOTHESIS: LATERAL HABENULA (LHb)-CENTERED NEURAL CIRCUITS MEDIATE MATERNAL STRESS EFFECTS

In the current paper, I propose a novel hypothesis regarding the neural circuitry by which maternal stress exerts negative impacts on maternal behavior and postpartum mental disorders. Theoretically, such neural circuitry should serve as an interface between the stress response system and maternal caregiving neural system, thereby transmitting stress effects to the maternal neural circuitry. After a careful review of the literature, I propose that the LHb is a likely candidate serving this interface function. The central idea is that the LHb and its downstream projections to the VTA and dorsal raphe nucleus (DRN) mediate the disruptive effects of maternal stress on maternal behavior (Figure 1). Clinically, maternal stress-induced dysfunction in the LHb-centered neurocircuits may eventually contribute to the psychopathology of postpartum mental disorders (e.g., postpartum depression, anxiety, and psychosis). This hypothesis is based on the following observations. First, the LHb plays a critical role in stress-related behaviors, such as encoding negative-valence signals and promoting behavioral aversion. Hyperactivity of the LHb is also implicated in the pathophysiology of major depression and stress-related anxiety. Second, the LHb is an essential brain region involved in the mediation of maternal behavior onset in rats. Lesions of the LHb produce deficits in all components of rat maternal behavior and the LHb is interconnected with several brain nuclei implicated in the mediation of emotional and motivational aspects of maternal behavior (VTA and raphe nuclei). In the following, I present evidence that the LHb is well positioned for transmitting stressful signals to alter the function of maternal neural circuitry.

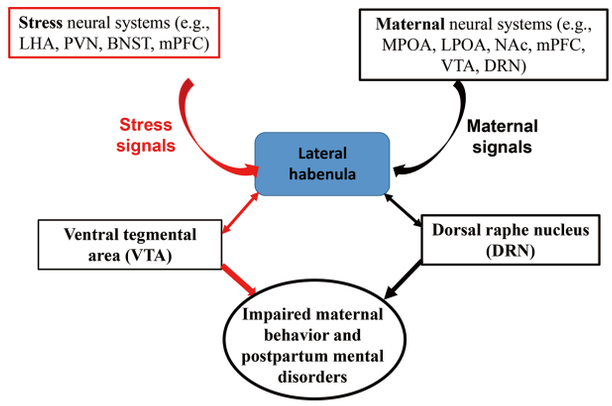

Figure 1 Hypothesized neurocircuit mechanism underlying stress-induced maternal impairment and postpartum mental disorders

Central component of the system is the lateral habenula (LHb), which receives "stress" and "maternal" signals from the brain response stress system (e.g., LHA, PVN, BNST, mPFC) and maternal response system (e.g., MPOA, NAc, mPFC, VTA, DRN). LHb interacts with downstream projection sites (VTA and DRN) to mediate the disruptive effects of maternal stress on maternal behavior, thereby contributing to the psychopathology of postpartum mental disorders. BNST: Bed nucleus of the stria terminalis; DRN: Dorsal raphe nucleus; MPOA: Medial preoptic area; mPFC: Medial prefrontal cortex; LHA: Lateral hypothalamic area; LPO: Lateral preoptic area; NAc: Nucleus accumbens; PVN: Paraventricular nucleus; VTA: Ventral tegmental area.

LHb PLAYS A CRITICAL ROLE IN STRESS-INDUCED BEHAVIORAL CHANGES

The LHb is a bilateral epithalamic structure connecting the forebrain (e.g., PFC and nucleus accumbens (NAc)) with monoaminergic systems in the midbrain and hindbrain (e.g., VTA, SN, and raphe nuclei) (Aizawa et al., 2011; Sutherland, 1982; Zahm & Root, 2017). The LHb receives major afferent inputs from the basal nuclei and limbic forebrain, and it primarily projects to the rostromedial tegmental nucleus (RMTg) and midbrain aminergic centers (Figure 2). Forebrain inputs to the LHb mostly come from the hypothalamic nuclei (e.g., lateral hypothalamic area (LHA), lateral preoptic area, (LPO), and PVN) basal forebrain structures (e.g., entopeduncular nucleus, NAc, ventral pallidum, lateral and medial septum, and bed nucleus of the stria terminalis (BNST)). In addition, the LHb also receives direct cortical inputs from the medial PFC (mPFC) and reciprocal feedback inputs from the monoaminergic centers, including the VTA and raphe nuclei (see recent reviews (Hu et al., 2020; Metzger et al., 2021)). Interestingly, the LHb receives input from the medial preoptic nucleus (Yetnikoff et al., 2015), one of the most critical brain regions for maternal behavior (Stack et al., 2002). I speculate that this input, together with that from the NAc, mPFC, VTA, and raphe nuclei, may send "maternal

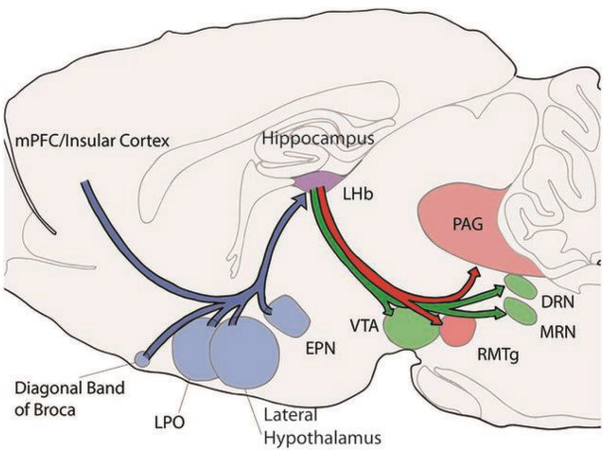

Figure 2 Schematic of selected afferent and efferent connections of the lateral habenula (LHb; shown in purple)

Afferent connections/structures are shown in blue, efferent connections are shown in red, and bidirectional connections are shown in green. LHb: Lateral habenula; PAG: Periaqueductal gray; DRN: Dorsal raphe nucleus; MRN: Median raphe; RMTg: Rostromedial tegmental nucleus; VTA: Ventral tegmental area; LPO: Lateral preoptic area; EPN: Entopeduncular nucleus; mPFC: Medial prefrontal cortex. Copyright © 2015 Baker, Oh, Kidder and Mizumori (Baker et al., 2015).

signals" to the LHb, as they are all part of the maternal brain neural network (Li, 2020; Numan, 2007). These afferents to the LHb may modulate LHb-mediated stress functions and contribute to the reduced stress response and anxiety often observed in postpartum females (Agrati & Lonstein, 2016; Lonstein, 2005, 2014; Ragan & Lonstein, 2014). This hypothesis merits further exploration in the future.

Through the fasciculus retroflexus, the LHb mainly projects to the RMTg, which, in turn, projects to the dopaminergic neurons in the VTA and serotonergic neurons in the DRN to suppress their activity (Gonçalves et al., 2012; Jhou et al., 2009; Kaufling & Aston-Jones, 2015; Metzger et al., 2021; Sego et al., 2014). The LHb is now recognized as a key region in the pathophysiology of depression and stress-related anxiety, as is critically involved in encoding negative-valence signals, expectations of punishment, and behavioral aversion (Matsumoto & Hikosaka, 2007, 2009; Proulx et al., 2014). The LHb is activated by various stressors and negative emotional stimuli, such as inescapable foot or tail shock, physical restraint, lithium chloride-induced illness, maternal deprivation, and social defeat (Langlois et al., 2021; Wirtshafter et al., 1994). The LHb also shows higher metabolic activity in animal models of depression (Caldecott-Hazard et al., 1988; Shumake et al., 2003; Shumake & Gonzalez-Lima, 2003, 2013). Lesions of the LHb improve depressive-like responses in depressed rats via increasing the serotonin (5-HT) levels in the DRN (Yang et al., 2008). Similarly, inhibiting habenular hyperactivity ameliorates maternal separation-driven depressive-like symptoms in mice (Tchenio et al., 2017), and blocks the anxiety-like behaviors produced by inescapable tail shock in male rats (Dolzani et al., 2016). Suppression of VTA-projecting habenula neuronal activity can even reduce learned helplessness behavior in rats (Li et al., 2011). Circuitry-level analysis suggests that the LHb mediates the aversive effects of stress by suppressing dopaminergic neurons in the VTA and 5-HT neurons in the raphe via the LHb-RMTg pathway (Brown et al., 2017; Brown & Shepard, 2016; Metzger et al., 2017; Yang et al., 2018), as activation of this pathway promotes avoidance behaviors and facilitates depressive-like behaviors in animals. Studies also show that in volunteer human patients experiencing a profound mood change following serotonergic challenge, there is an enhanced modulation of the projections from the habenula to the DRN (Morris et al., 1999). Overall evidence is consistent with the concept that the LHb is a critical node in the network of subcortical nuclei that regulate stress-induced behavioral changes, such as helplessness, anhedonia, and lack of motivation (Nair et al., 2013; Yang et al., 2018). Therefore, in the context of maternal behavior, maternal stress is very likely to induce a hyperactive habenular state in mothers, which could, in turn, cause deficits in maternal behavior and presentation of postpartum stress disorders. Thus, the LHb may transmit stress into maternal behavior due to its participation in the maternal caregiving neural system (see below).

LHb FORMS PART OF THE MATERNAL BRAIN NEURAL NETWORK THAT MEDIATES MATERNAL BEHAVIOR

Various studies have reported on the core neural circuit that mediates rat maternal behavior, which includes the medial preoptic area (MPOA), lateral preoptic area (LPOA), ventral bed nucleus of the stria terminalis (VBST), and their downstream projections to the VTA and PAG (Kohl & Dulac, 2018; Kohl et al., 2018; Numan, 2015; Numan & Insel, 2003b). This circuit is essential for the onset and early expression of all aspects of maternal behavior (i.e., pup retrieval, licking, and nursing) and maternal motivation in rodents (Pereira & Ferreira, 2016). It is also the primary site where parturitional hormones act to drive maternal behavior via hormonal receptor-mediated mechanisms, as the MPOA contains receptors for all hormones involved in the rapid onset of maternal behavior, including receptors for estradiol, prolactin, and oxytocin (Numan, 2020). Communication between MPOA neurons and the mesolimbic dopaminergic (DA) system is particularly important for maternal motivation, consistent with the well-documented role of DA in reward processing and incentive motivation (Berridge, 2007; Berridge & Robinson, 1998). Functional disturbance of the mesolimbic system, either enhancing or suppressing DA neurotransmission, disrupts maternal behavior, especially the active components of maternal behavior, such as pup retrieval and licking, but not passive ones, such as high-arched-back nursing (Fang et al., 2018; Hansen, 1994; Li, 2015; Li & Fleming, 2003; Olazábal et al., 2013; Pereira & Ferreira, 2006; Pereira et al., 2005; Stern & Keer, 1999; Stolzenberg & Numan, 2011; Zhao & Li, 2009).

Another monoaminergic system that plays an important role in maternal behavior is the raphe serotonergic system as cell body-specific DRN serotonergic lesions significantly reduce pup licking and generate aberrant patterns of nursing behavior (Holschbach et al., 2018). The DRN projects to the VTA (McDevitt et al., 2014; Watabe-Uchida et al., 2012) and 5-HT_{2C} receptors have been detected in VTA neurons (Bubar &

Cunningham, 2007; Bubar et al., 2011). One well-documented effect of VTA 5-HT_{2C} activation is the inhibition of DA cell firing and consequent DA release into the NAc (Howell & Cunningham, 2015), which is primarily achieved by activating local GABA neurons (Bubar et al., 2011; Di Giovanni et al., 2000; Di Matteo et al., 2002; Howell & Cunningham, 2015). This supports the idea that activating VTA 5-HT_{2C} receptors suppresses incentive motivation (Fletcher et al., 2004; Valencia-Torres et al., 2017), consistent with the finding that intra-VTA infusion of MK212 (a 5-HT_{2C} receptor agonist) reduces pup retrieval and pup preference (Gao et al., 2020). Taken together, within the maternal brain network, the MPOA-VTA and DRN-VTA pathways appear to be critically involved in the mediation of maternal motivation.

How is the LHb configured into the maternal brain network? Anatomically, the LHb has widespread connections with various components of the network. The LHb receives multiple projections from brain regions critically involved in the mediation of maternal behavior, including the MPOA, LPOA, VTA, raphe, and PAG (Numan & Insel, 2003b; Zahm & Root, 2017). As the LHb exerts powerful inhibitory actions on VTA DA neurons and DRN 5-HT neurons (Metzger et al., 2021), it is conceivable that it may transmit diverse stress signals to the VTA and DRN to suppress maternal motivation. The LHb itself also plays a critical role in the onset of maternal behavior in rats (Corodimas et al., 1993; Corodimas et al., 1992; Matthews-Felton et al., 1995). LHb neurons, but not medial habenula (MHb) neurons, express estrogen receptors in cell nuclei and axon terminals (Wagner et al., 1998). Thus, estrogen may directly act on the LHb to stimulate maternal behavior by modulating the input and output signals of the LHb. Electrical or excitotoxic lesions of the LHb produce deficits in all components of maternal behavior, including pup retrieval, nest building, and nursing behavior, as demonstrated in naturally parturient rat mothers as well as in hysterectomized-ovariectomized pregnant females (Corodimas et al., 1992, 1993; Matthews-Felton et al., 1995). Cytotoxic lesions of the LHb also induce significant deficits in pup retrieval and nest building in pup-sensitized virgin females, indicating that the LHb is also involved in non-hormonal-dependent onset of maternal behavior (Felton et al., 1998). However, the nature of maternal behavior deficits induced by LHb lesions is not well clarified. As habenula lesions are known to cause anxiety-like hyperactivity (Lee & Huang, 1988) and attention deficits (Lecourtier & Kelly, 2005), it is possible that LHb-lesioned mother rats may become anxious and inattentive, and thus provide inadequate maternal care. My speculation is that adverse factors (e.g., stress, abnormal hormonal changes) cause maternal behavior deficits by altering LHb functions, resulting in increased anxiety and decreased attention. This conceptualization of the role of the LHb in maternal behavior is elaborated in the following section.

PREDICTIONS BASED ON HYPOTHESIZED ROLE OF LHb IN MEDIATION OF MATERNAL DISRUPTIVE EFFECTS

My proposed hypothesis is that distinct LHb neurocircuits, such as the LHb-VTA and LHb-DRN pathways, play critical roles in the mediation of maternal stress effects. This hypothesis leads to three testable predictions in animal research.

First, maternal stress increases LHb neuronal activity. If the LHb is involved in stress effects on maternal behavior, it should exhibit a hyperactive state in stressed dams. This hyperactive state could be detected using various techniques (e.g., c-Fos immunohistochemistry and electrophysiological recording). Concurrently, functional changes induced by maternal stress should also be found in the two major downstream targets of the LHb (VTA and raphe), given that stress activates the LHb, which inhibits VTA DA neurons and DRN 5-HT neurons to achieve its behavioral effects (Brown & Shepard, 2016; Brown et al., 2017; Metzger et al., 2017; Yang et al., 2018), and both regions are implicated in the regulation of emotional and motivational aspects of maternal behavior (Barofsky et al., 1983a, 1983b; De Almeida & Lucion, 1997; Gao et al., 2018; Numan & Smith, 1984; Shahrokh et al., 2010; Zhao & Li, 2012). By extrapolation, LHb hyperactivity should also be found in animal models of postpartum mental disorders (Li & Chou, 2016) that encompass a stress component, such as the estradiol withdrawal model (Galea et al., 2001), chronic corticosterone treatment model (Brummelte & Galea, 2010; Brummelte et al., 2006), and repeated maternal separation model (Boccia et al., 2007). Behaviorally, I predict that maternal stress impairs behavior by increasing maternal anxiety and decreasing maternal motivation. Maternal stress could disrupt maternal behavior via multiple mechanisms, for example, reducing the rewarding value of pups, increasing maternal anxiety, causing a depression-like state, or reducing attention sensitivity to pups. Although several studies have used standard anxiety and depression tests (e.g., elevated plus maze (EPM) or forced swim test (FST)), they were not conducted within the maternal behavior context (Haim et al., 2016; Leuner et al., 2014). Thus, the direct implications of anxiety and depression on maternal impairment are at best correlational. To verify this element of the hypothesis, two maternally dependent tests could be applied to assess maternal anxiety and motivation. The first is pup retrieval on an EPM, which can assess maternal anxiety and maternal motivation while dams are engaged in pup retrieval (Yang et al., 2015). The second is the pup preference test, which can examine the relative strength of a mother's maternal motivation or affective response towards pups versus her motivation to seek novelty (a novel object) (Gao et al., 2019, 2020; Li et al., 2018; Wu et al., 2018).

Second, activation of the LHb and its projections to the VTA and DRN should mimic the effects of maternal stress on the maternal brain and behavior. If LHb activation is sufficient to drive aversion and induce a depressive-like state through inhibition of VTA DA and DRN 5-HT neurons (Baker et al., 2016), one would expect that activation of LHb neurons could cause a depressive-like or anxiety-like state in dams and mimic the disruptive effects of stress on maternal behavior (Leuner et al., 2014). LHb neurons can be activated by pharmacological tools, while the LHb-VTA and LHb-DRN pathways can be specifically activated using an intersectional approach with optogenetic or chemogenetic manipulation (Fenno et al., 2020). For example, we could use dual-viral

chemogenetics (Designer Receptors Exclusively Activated by Designer Drugs (DREADDs)) to activate DRN- and/or VTA-projecting LHb neurons in normal dams and compare their maternal behavior and stress-like responses with those receiving a control adeno-associated virus (AAV). In brief, a retrograde AAV can be injected into the DRN or VTA, while a Cre-recombinase-dependent excitatory DREADD AAV (hM3Dq) can be injected into the LHb to selectively activate each neurocircuit under clozapine N-oxide (CNO). Maternal behavior can be tested in the home cage and LHb activation-induced stress-like effects can be assessed using a battery of physiological and behavioral assessments (i.e., body temperature, open field, and EPM), as activation of the LHb can increase body temperature (emotional hyperthermia) and cause stress-like behaviors in these tests (Fu et al., 2020; Jakobs et al., 2019; Ootsuka & Mohammed, 2015). Finding such evidence would provide strong support for the hypothesis that the LHb is involved in the mediation of stress effects on maternal behavior.

Third, inhibition of the LHb and its projections to the VTA and DRN should reduce the effects of maternal stress on the maternal brain and behavior. If, as hypothesized, maternal stress causes a hyperactive state in the LHb, and such a change mediates the maternal disruptive effects of maternal stress, limiting hyperactivity of the LHb and its projections to the VTA and DRN could reverse this effect. In this case, inhibitory DREADD hM4Di, in combination with retrograde AAV, could be used to selectively suppress the LHb-VTA and/or LHb-DRN neurocircuit. This finding would complement those above in support of the LHb as a critical brain region involved in maternal stress effects.

CONCLUSIONS

Maternal stress is a known risk factor that negatively influences maternal caregiving behaviors, and stressed mothers often respond more negatively to their infants compared with healthy mothers. Determining the neurocircuitry basis of maternal stress on the expression of maternal behavior should enhance our understanding of the behavioral and neuronal changes caused by stress and how these changes impact the quality of maternal care. This will, in turn, improve our understanding of the psychopathology of postpartum mental disorders and contribute to the foundational knowledge needed to develop novel strategies for their treatment.

This paper proposes a brain mechanism mediating stress effects on maternal care, with a focus on LHb-related neurocircuits. One limitation with this hypothesis is that the exact role of the LHb in maternal behavior is not clear. Evidence supporting its maternal involvement is also inadequate and sometimes mixed. For example, although some studies have reported maternal behavior-induced c-Fos expression in the LHb (Kalinichev et al., 2000; Lonstein et al., 1998), others have reported negative results (Sheehan et al., 2000; Stack & Numan, 2000; Stack et al., 2002). It is possible that those dams that exhibited an increase in c-Fos expression in the LHb had relatively higher stress levels than those that did not. As stated by (Numan & Insel, 2003a), the exact way in which the LHb fits into the overall neural circuitry of maternal behavior and its functional role still require careful examination. Once we decipher the exact role of the LHb in maternal behavior, we can better understand how it regulates "maternal"-related signals and stress signals.

However, it should be emphasized that the LHb-related neurocircuits should not be viewed as the sole system that mediates maternal stress effects. Other brain systems, such as those involved in maternal motivation (e.g., striatum), negative-emotion processing (e.g., amygdala, insula, and orbitofrontal cortex), and emotion regulation (e.g., dorsolateral PFC and anterior cingulate cortex) are certainly involved (Kim et al., 2016). In addition to the DA and 5-HT systems, norepinephrine and oxytocin also likely play roles in maternal stress, given their roles in stress response and maternal behavior (Kim & Strathearn, 2016; Lonstein, 2007; Neumann et al., 2001; Thomas & Palmiter, 1997).

One promising field of future research is the functional interactions among various LHb neurocircuits (LHb-VTA, LHb-DRN, or LHb-median raphe nucleus (MRN)) in the mediation of maternal stress effects. Additionally, the relative impacts of the LHb-VTA and LHb-DRN pathways in maternal stress mediation need to be determined. Both the VTA and DRN are implicated in the regulation of emotional and motivational aspects of maternal behavior (Barofsky et al., 1983a, Barofsky et al., 1983b; De Almeida & Lucion, 1997; Gao et al., 2018; Numan & Smith, 1984; Shahrokh et al., 2010; Zhao & Li, 2012). The vast majority (98%) of LHb-projecting neurons target either the VTA or DRN (also MRN) only, with very few heterogeneously distributed LHb neurons projecting to both dopaminergic and serotonergic nuclei (Bernard & Veh, 2012). This suggests that the LHb forms segregated connections with one of the three major monoaminergic target nuclei (VTA, DRN, and MRN) and each LHb output may mediate distinct aspects of maternal stress effects. Future research should also examine the neurochemical basis of the maternal stress effects. Thus, the role of dopamine D_2 receptors and serotonin 5-HT_{2A} and 5-HT_{2C} receptors in these neurocircuits merits further examination (Gao et al., 2019; Nie et al., 2018).

COMPETING INTERESTS

The author declares that he has no competing interests.

AUTHORS' CONTRIBUTIONS

The author wrote, read, and approved the final version of the manuscript.

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