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Effects of opioids on the parental brain in health and disease

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Abstract

The epidemic of opioid use disorder (OUD) directly affects millions of women of child-bearing age. Unfortunately, parenting behaviors – among the most important processes for human survival – are vulnerable to the effects of OUD. The standard of care for pregnant women with OUD is opioid maintenance therapy (OMT), of which the primary objective is to mitigate addiction-related stress. The aim of this review is to synthesize current information specific to pregnancy and parenting that may be affected by OUD. We first summarize a model of the parental brain supported by animal research and human neuroimaging. We then review animal models of exogenous opioid effects on parental brain and behavior. We also present preliminary data for a unifying hypothesis that may link different effects of exogenous opioids on parenting across species and in the context of OMT. Finally, we discuss future directions that may inform research and clinical decision making for peripartum women with OUD.

Keywords

Opioid; Maternal brain; Neuroimaging; Hypothalamus; Periaqueductal gray; Animal models

1. Introduction to the parental brain

It has been established in animal (Numan and Young, 2016) and human (Swain and Ho, 2017) brain research that parenting involves an evolutionarily conserved **Maternal**

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Appendix A. Supplementary material

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Behavior Neurocircuit (MBN) under neuroendocrine control and opioid influence (Numan and Young, 2016; Brunton et al., 2008) (see Fig. 1).

1.1. Parental brain in health

Healthy parenting is governed by the MBN with two reciprocally modulating subsystems that either activate maternal caregiving behaviors solicited by the offspring **(care processing)** or defensive and aggressive behaviors when the mother or offspring is threatened **(defense processing)**. The former "care" subsystem consists of the medial preoptic area (mPOA) in hypothalamus (HYP), ventral tegmental area (VTA), nucleus accumbens (NAc) and ventral pallidum (VP), which activate sensitive maternal care behaviors across species (Lonstein et al., 2015). Examples of maternal **care processing** behaviors for rats include nursing, licking, grooming and characteristic vocalizations (Bayerl and Bosch, 2019). Among humans, sensitive parenting includes attuned interactions with appropriate tone of voice and resourcefulness in dealing with infant negative states in order to sustain infant life and optimize development (Swain and Ho, 2017; Bornstein et al., 2017). In the latter **defense processing** subsystem, which includes the periaqueductal gray (PAG), regulation of different opioid receptors in rodents can activate maternal "defense" or aggressive behaviors, such as hostility towards intruders or predatory behaviors in rats (Klein et al., 2014). The PAG is less-well studied in humans (preliminary data presented below in Section 4.3). These opposing care and defense behaviors must be reciprocally modulated to regulate sensitive maternal behavior according to contextual demands. The brain orchestrates these behaviors with the amygdala (AMY), insular cortex (IC), and orbitofrontal cortex (OFC) (Stolzenberg and Numan, 2011) and neuromodulators such as oxytocin and cortisol (Klampfl and Bosch, 2019).

Indeed, the healthy maternal brain undergoes tremendous neuroendocrinological adaptations in response to peripartum circumstances, including rising levels of progesterone, estrogens and modulation of oxytocin, endogenous opioids and stress-regulation hormones such as cortisol (Brunton et al., 2008; Feldman and Bakermans-Kranenburg, 2017; Swain et al., 2011; Brunton and Russell, 2008). For example, for virgin rodents, pups usually constitute an aversive stimulus that does not immediately induce care-giving behaviors. This aversion, particularly to the neonate's odor, is mediated by olfactory bulb projections to the amygdala and from there to the anterior hypothalamus and PAG. In fact, maternal care-giving behaviors are not commonly present until late-pregnancy hormones induce changes in the MBN, including downregulation of pup-aversion projections to the amygdala and upregulating reward processing of pup cues. Rising levels and receptor densities of estrogens, progesterone, prolactin and oxytocin activate the hypothalamic mPOA and the adjacent ventral bed nucleus of stria terminalis (vBNST), overriding aversive reactions to pups and their odor that is present during early gestation. With this activation, glutamatergic projection from the mPOA and vBNST start to stimulate dopaminergic neurons in the VTA, which in turn increases release of dopamine in the NAc such that pup-specific stimuli (their odor, suckling behavior and touch) become rewarding and thus promote maternal care behaviors during the postpartum.

Among healthy human mothers, differential activation of the MBN has been shown to be a function of maternal sensitivity - the specific ability to perceive and respond to their infant's behavioral signals (Elmadih et al., 2016). In this study, brain activation to infant cues was studied in 15 mothers with high sensitivity (HSMs) and 15 mothers with low sensitivity (LSMs). Mothers were selectively recruited from a pool based on mother–infant play interaction at 4–6 months postpartum. Brain responses to viewing silent videos of their "own" versus an "unknown" infant in 3 affective states (neutral, happy, and sad) were measured at 7–9 months postpartum. The participants' plasma oxytocin was measured immediately following free-play interactions with their infant. HSMs versus LSMs showed significantly greater brain activation in right superior temporal gyrus (STG) in response to own versus unknown neutral infant and to own-happy vs. own-neutral. Activation in the right STG in the latter contrast was negatively correlated with post-free-play oxytocin responses in HSMs mothers. By way of interpretation, the enhanced activation of STG for HSM mothers may indicate increased emotion regulation processing for HSM mothers – in accord with another report of STG activation to videos of own versus unknown infants among healthy mothers (Wan et al., 2014) and among synchronous vs. intrusive mothers (Atzil et al., 2011). Indeed, the STG has been widely implicated in the regulation of emotion, particularly facial emotion processing, and in empathizing with others "Theory of Mind" (Rizzolatti and Fabbri-Destro, 2008) – both facilities key for a mother to differentially express sensitivity to her infant's needs over other demands on her resources (Strathearn et al., 2012). Other studies have also reported greater activation of STG in mothers who delivered vaginally compared with Caesarean section (Swain et al., 2008), for breastfeeding compared with bottle feeding mothers (Kim et al., 2011), and finally in accord with STG role in the intention to move and provide maternal care (Bornstein et al., 2017; Zebardast et al., 2013). The inversed correlation of post-free-play oxytocin and brain responses in HSMs mothers hints at the complex role for oxytocin – which may increase parent-child prosocial interaction under normal conditions, yet may also interfere through anxiety or erroneous recollection of maternal closeness and care during childhood with early life adversity (Szymanska et al., 2017; Bakermans-Kranenburg and Van, 2013). In sum, these data suggest that there are variations in MBN activation that correlate with hormone levels and different parenting phenotypes among healthy populations according to stress (Kim et al., 2016; Mayes et al., 2005; Leckman et al., 2004). We proceed with consideration of early life adversity and frank psychopathology in the parental brain.

1.2. Parental brain in psychopathology

Unsurprisingly, activation of the MBN in humans is highly sensitive to severe environmental stress, psychopathology, and early life adversity. For instance, the chronic stress of childhood poverty, well established to interfere with normal brain physiology for emotion response and executive function (Duval et al., 2017; Evans et al., 2016; Javanbakht et al., 2016; Javanbakht et al., 2015; Liberzon et al., 2015; Sripada et al., 2014; Sripada et al., 2014), has also been shown to impact parental MBN function – interestingly, in a sex-specific way (Kim et al., 2015). Among females' activations to salient own infant cry (Swain et al., 2004) with childhood poverty was associated with increased neural in the posterior insula, striatum, calcarine sulcus, hippocampus and fusiform gyrus, but with decreased neural responses to own infant cry in the same regions in males. Furthermore, neural

activation in these regions was associated with higher levels of perceived annoyance elicited by infant cries and reduced motivation to approach crying infants regardless of the gender of the participants (Kim et al., 2015). These results are surprising given that the striatum is associated positively with motivation and reward (Lee and Reeve, 2017). It may be that chronic poverty has adverse effects yet also induces compensatory changes – essentially reprogramming some circuits – especially for these non-parent participants without the experience of becoming a parent. Indeed, in a related study on mothers (Kim et al., 2016), lower income was associated with reduced responses to infant cry only in cortical brain circuits, including those that evaluate emotional valence (medial prefrontal gyrus), regulate affect (middle prefrontal gyrus) and process sensory information (superior temporal gyrus). Furthermore, lower positive perceptions of parenting were associated with reductions in infant-cry response in the right middle frontal gyrus and superior temporal gyrus. Perhaps some poverty effects are themselves a function of the adaptation to becoming a parent.

Maternal depression is a serious mental disorder that affects approximately 12–20% of new mothers. From a recent review (Pawluski et al., 2017), brain activation patterns that are affected by depression and anxiety include cortical (dmPFC, dlPFC, IFG, SFG, OFC, STG), ACC, PCC) and subcortical regions (striatum, thalamus, hippocampus, SN, VTA, PAG) – highlighting the amygdala which is differentially active according to critically important experimental specifics. For example, it has been shown that depressed mother's amygdala may be hypo-responsive to certain standard cognitive neuroimaging challenges (Moses-Kolko et al., 2014) and that mothers with chronic unresolved attachment trauma exhibit dampened amygdala responses to viewing their own (but not unknown) infant's crying faces (Kim et al., 2014). Amygdala responses have also been positively correlated with maternal attribution of intentionality to their infant in response to own versus other infant cry (Hipwell et al., 2015). On the other hand, depressed compared to healthy mothers displayed greater reactivity of the right amygdala using a child face empathy task (Lenzi et al., 2016) – perhaps indicating emotional dysregulation in this task. Amygdala reactivity was also increased in a self-focused baby-cry task designed to provoke brain responses in participants with a history of adverse early life experiences sometimes described as a malevolent background "shark music" (Ho and Swain, 2017). This study demonstrated depression effects on amygdala connectivity, which also seem to change with anxiety (Guo et al., 2018). Variance in the properties of infant stimuli and context of presentation, along with research using hormone challenges will be helpful to clarify the role of the amygdala in depression – especially given that often-used depression measures may not perfectly capture real-life parental dysfunction. For example, intranasal oxytocin effects on amygdala response to infant crying were moderated by attachment security of the mothers, with oxytocin decreasing emotional and amygdala reactivity only in mothers with insecure attachment representations (Riem et al., 2016). Thus, parents with insecure attachment – perhaps different from other attachment classifications, may have different brain mechanisms that render them amenable to oxytocin interventions. Such future interventions may apply to many stress-related syndromes. However, more work using both animal and human models is needed to confirm findings over the complete range of hormone physiology and neuroanatomy that relate to sensitive parenting behaviors and mentalizing for applications to better understand and safely treat parental psychopathology.

2. Opioids use disorder and treatment during pregnancy

Opioid use disorder (OUD) has reached epidemic proportions in the United States recently and opioid dependence among pregnant women has more than doubled in the last 10 years. Approximately one-third of all women of reproductive age have filled a prescription for an opioid medication in the previous year, suggesting that affected women may be on opioid medication when they conceive. Indeed, the opioid epidemic in the U.S. affects millions of women – with about 20% of all pregnant women prescribed opioids and 2.5% chronically using (Krans and Patrick, 2016), and the number of pregnant women with OUD more than quadrupled from 1999 to 2014 (from 1.5 per 1000 delivery hospitalizations to 6.5) (Haight et al., 2018). In addition, many pregnant women with OUD are among those estimated to also use other drugs, licit drugs that are known to be harmful during pregnancy, alcohol and tobacco (Substance Abuse and Mental Health Services Administration, 2014; Hayes and Brown, 2012; Forray, 2016). Finally, neonatal abstinence syndrome (NAS), the signs and symptoms from the cessation of prenatal exposure (via placental transfer) to various substances – especially if untreated – can be associated with infant morbidity and unclear long-term consequences of opioid exposure – currently a subject of ongoing study (Coyle et al., 2018; Johnson and Jones, 2018; Kaltenbach et al., 2018).

Since the publication of the NIDA-funded Maternal Opioid Treatment: Human Experimental Research (MOTHER) study in 2010 (Jones et al., 2010) the use of Buprenorphine Treatment (BT) as a way of alleviating withdrawal symptoms has become the gold standard opioid maintenance therapy (OMT) (Jones et al., 2017; Nanda et al., 2015; Krans et al., 2016; Zedler et al., 2016) – partly due to reports of milder and more treatable withdrawal and NAS (Jones et al., 2010; Zedler et al., 2016; Cleary et al., 2011; Unger et al., 2011; Fischer et al., 2006; Kayemba-Kay's and Laclyde, 2003; Schindler et al., 2003; Jones et al., 2005; Laslo et al., 2017). For minimizing fetal stress, there are clear advantages to BT compared with detoxification (Whitten, 2012; Kakko et al., 2008), and for BT compared with methadone treatment (Johnson and Martin, 2017; Meyer et al., 2015; Gaalema et al., 2012; Hall et al., 2016; Mucke et al., 2017; Lemon et al., 2017; Brogly et al., 2014) although findings are controversial (Brogly et al., 2014; Lund et al., 2012; Jones et al., 2012) and BT is not without risks. For example, recent findings maintain that BT maternal buprenorphine dose is indeed associated with NAS symptoms (Velez et al., 2018) as well as lower birth weight and length over and above substance use severity (Jansson et al., 2017). Findings from our own research indicated that 89% of infants prenatally exposed to buprenorphine were diagnosed with NAS and 36% were admitted to the NICU.

Despite increased levels of stress due to parenthood-related psychosocial, physiological and economical demands (Barclay et al., 1997), parents typically find themselves highly motivated to take care of their offspring’s needs and find the interactions with their infants to be rewarding (Mercer, 1985; Goodman, 2002). Notably, the adaptation of brain stress systems is integral to such parenting behaviors. While the first few months postpartum are especially stressful for mothers affected by OUD, very little is known about the effects of BT on postpartum women with OUD. BT does help to break the repetitive cycle of quit attempts and hence, to some extent, desensitize core stress systems. Nevertheless, at least one in three mothers receiving BT still suffer relapse to illicit opioids and other harmful

substances (Jones et al., 2012). Further, aspects of buprenorphine exposure, including dosing parameters, withdrawal stress pertaining to induction as well as pre- and post-natal effects (Jones et al., 2008) are also not as well understood compared with methadone treatment (Kaltenbach et al., 2012). In addition, there are theoretical concerns regarding the unique pharmacokinetic and dynamic properties of buprenorphine that may predispose higher occurrence of NAS (Kennedy-Hendricks et al., 2016) due to elevated dosing needed to offset higher clearance rates (Kacinko et al., 2009) and accelerated maternal metabolism during pregnancy (Welsh and Valadez-Meltzer, 2005). Although BT should reduce the risks of exposing fetus to repeated cycles of acute withdrawal (World Health Organization, 2014), a systematic risk/benefit assessment of BT is still required in order to accurately inform optimal parameters of use in treating pregnant women with OUD. To date, a central challenge pertaining to risk/benefit assessment has arisen from the fact that buprenorphine maintenance exposure has been difficult to quantify, because variables commonly affecting intra-uterine stability and postnatal environment have been difficult to account for. These include, but are not limited to, severity and pattern of maternal licit, illicit and prescription drug use, as well as maternal socio-economic and environmental factors. These problems have made it challenging to fully determine the extent to which neurodevelopmental risk from greater NAS severity is offset by the more stable intrauterine environment.

There is also a dearth of knowledge about the optimal timing for switching to a maintenance opioid during pregnancy and whether the switch or opioid withdrawal during certain sensitive periods may have a negative impact for the mother and/or her offspring. Finally, the prevalence of relapse with BT may be even higher during the first few months postpartum when additional parenting stresses of childcare are salient, such as having an infant go through NAS. As such, it is essential to better understand how BT may mediate stress system adaptations and motivation for opioid use during early postpartum periods for mothers with OUD.

In the current paper we propose that the MBN provides an effective mechanistic model which is applicable to early postpartum parental adaptation and accounts for the common neural circuitry underlying maternal behavior, stress system dysregulation and relapse to illicit opioids in BT mothers. Given that the motivation for opioid use and relapse have been linked to dysregulated stress system neurocircuits (Koob and Volkow, 2016), which are also integral to parenting behavior, the utility of this model may help to identify overlapping mechanisms relating to the impact of BT upon parenting. The importance of addressing this knowledge gap is magnified by risks to the infants of BT mothers who relapse to illicit drug use.

Addressing this gap is challenging because of the common co-morbidities of depression (Conway et al., 2006; Davis et al., 2017) and polysubstance use (Substance Abuse and Mental Health Services Administration, 2009) that may mask the effects of BT in OUD discussed above. Postpartum depression has a prevalence of 15–20% in general population (Gavin et al., 2005; Gaynes et al., 2005; O'Hara and McCabe, 2013), adversely affecting infants – even for subthreshold symptoms (Murray and Cooper, 1997; Righetti-Veltema et al., 2003; McLearn et al., 2006) – with long-term adverse effects on emotion and behavior regulation (Hay et al., 2008; Grace et al., 2003; Halligan et al., 2007; Goodman et al., 2011).

Furthermore, maternal substance use places their infants at fourfold increased risk for abuse or neglect, contributing to as much as 80% of child maltreatment cases (Barth, 2009) and 60% of infant out-of-home placements (Child Welfare Information Gateway, 2014). Indeed, even during intermittent periods of sobriety, mothers with addiction are observed to be less keenly attentive and contingently responsive, while more intrusive and hostile toward their infants (Strathearn and Mayes, 2010) and may find infant cues to be less gratifying and more stressful, as compared to non-addicted mothers (Rutherford et al., 2011; Rutherford and Mayes, 2017; Kim et al., 2017). Additionally, maternal behaviors can be adversely influenced by infantile NAS that can still occur with BT (Jones and Fielder, 2015).

Relapse in BT mothers to illicit drug use is another significant concern. For women through pregnancy and the postpartum with OUD, co-occurring anxiety, mood and other substance use disorders, guilt, poor nutrition, impaired health, homelessness, violence, confusion regarding available medical options, and a lack of social support are more prevalent (Johnson and Jones, 2018; Young and Martin, 2012; McCarthy et al., 2017; Bishop et al., 2017; Jansson et al., 1996). From a neuroendocrine perspective, such chronic stressors alongside the cyclical use of short-term opioids and other drugs, reciprocally sensitize neurohormonal stress systems (Rutherford et al., 2011; Landi et al., 2011). This, in turn, may lead to further use of opioids and other drugs, worsening dysphoria, negative affect, anxiety and the relapse cycle (Koob, 2017a, 2017b; Hyman et al., 2007). Research on non-pregnant substance abusers has shown that stress system sensitivity is a key predictor of stress response dysregulation, elevated anxiety and depressive symptomatology as well as craving and relapse to various drugs of abuse during attempts at abstinence (Fox et al., 2008; Fox et al., 2007; Sinha et al., 2011; Sinha et al., 2006). Given a stress-sensitized and negatively reinforcing environment, the additional parenting stress (Suchman and Luthar, 2001) and the frequently rapid metabolism of opioids that characterize pregnancy (McCarthy et al., 2017), it is not surprising that OUD in peripartum women is characterized by numerous failed quit attempts (Guille et al., 2017). Indeed, In the MOTHER Study (Maternal Opioid Treatment: Human Experimental Research) (Jones et al., 2012), 33% of BT mothers relapsed to illicit opioids (Jones et al., 2012). This is likely driven by stress system pathophysiology and repeated cycles of opioid intoxication and acute withdrawal.

BT improves both maternal and fetal outcomes by limiting psychobiological changes associated with withdrawal (Klaman et al., 2017). The first few months postpartum for BT mothers are nevertheless fraught with depressive stress symptoms commonly comorbid with drug dependency (Oei et al., 2009). Indeed, pilot data from our study site suggest ~50% prevalence of significant depression in BT mothers (EPDS > 10). Finally, the children of affected mothers are vulnerable to long-term effects of early maternal depressive stress (Murray and Cooper, 1997; Righetti-Veltema et al., 2003; McLearn et al., 2006; Hay et al., 2008; Grace et al., 2003; Halligan et al., 2007; Goodman et al., 2011). Thus, early postpartum comorbid maternal opioid use and stress disorders can exert transgenerational consequences – likely through maladaptive maternal parenting behaviors (Stanley et al., 2004; Feldman et al., 2009; Field et al., 1988; Murray and Cooper, 1997; Weissman et al., 2004). For mothers with OUD, adaptative parenting behaviors depend on their perceived parenting stress (Suchman and Luthar, 2001), which depends on how well they can emotional attune to the child’s psychological needs (Borelli et al., 2012).

3. Animal research on the parental brain and opioids

3.1. Effects of opioids on the maternal brain and behavior

It is well known that gestational opioid exposure results in alterations in opioid receptor binding and functionality in dams during pregnancy and the early postpartum (Hou et al., 2004; Darmani et al., 1992), however only a few comparative studies have investigated the effects of opioids on a parental brain compared to a virgin or non-postpartum brain. Though changes in pharmacokinetics and thus plasma and tissue distribution of opioids are well established during pregnancy (Shah et al., 1976), the effects of these changes on the maternal brain are not well documented. In one study, pregnant mice had 96% lower brain-to plasma ratios of methadone after a single dose compared to non-pregnant mice, but levels of buprenorphine in brain or plasma were no different between pregnant and non-pregnant animals (Coles et al., 2009). To further complicate our understanding of the effects of opioids on the maternal brain, many of the early toxicology studies were performed in male animals only and there is accumulating evidence of substantial sex difference in opioid pharmacology (Rasakham and Liu-Chen, 2011; Dahan et al., 2008).

Additionally, opioids are well established to be involved in the healthy regulation of maternal behavior and to play an essential role in mediating some of the processes involved in the initiation of maternal care through the activation of the MBN (Brunton and Russell, 2008; Bridges and Grimm, 1982; Felicio et al., 1991; Grimm and Bridges, 1983; Moura et al., 2010). Endorphins exhibit an inhibitory effect on oxytocin and prolactin-releasing neurons in preparation for parturition, that allows an accumulation and then surge of these hormones during birth. This withdrawal of the inhibitory control of the opioid system is believed to be crucial for facilitating rapid initiation of maternal behaviors at birth (Byrnes et al., 2000). Further; this system is also involved in opioid-regulated switching from maternal to predatory behaviors for lactating rats (Klein et al., 2014). This regulation involves activation of different subtypes of opioid receptors in the PAG, as evidenced by the elegant demonstration that μ opioid receptor activation inhibits maternal behaviors, while blocking κ receptor increases predatory and hunting behaviors (Klein et al., 2014). Fast switching between caring and predation behaviors are essential for dams to increase the chances of survival for her pups and herself. The complex interaction of multiple opioid receptor systems in the regulation of these maternal behaviors suggests that endogenous opioids play crucial roles in this essential behavioral selection process.

Studies using the opioid antagonist naloxone have confirmed the importance of the opioid system in the activation of the maternal networks, as treatment with naloxone increases prolactin as well as oxytocin levels in the maternal brain (Brunton and Russell, 2008; Brunton, 2018; Brunton et al., 2005). Further, naloxone treatment after the birth of the first pup can increase oxytocin levels as well as adrenocorticotropic hormone and corticosterone, demonstrating that endogenous opioids usually inhibit the release of these hormones during parturition (Wigger et al., 1999). However, less is known as to whether exposure to opioid agonists (such as morphine, heroin or methadone), or partial agonists (such as buprenorphine) during gestation and throughout parturition can alter normal hormonal regulations during birth. Many animal models of gestational opioid exposure have focused

on the outcome of the offspring, and not on the effects on the maternal brain or processes during labor (Byrnes and Vassoler, 2018). In line with this, many animal models cross-fostered pups after birth and have thus not monitored the initiation of maternal care behaviors. However, opioid-induced deficits in maternal behaviors have been documented in animal models (Bridges and Grimm, 1982; Slamberova et al., 2001) and there is evidence that the decrease in maternal care behaviors due to morphine and other μ-opioid receptor agonists is mediated through the activating of μ-opioid receptors in the mPOA, PAG and other brain areas (Mann et al., 1991; Rubin and Bridges, 1984; Stafisso-Sandoz et al., 1998). Additionally, more recent findings implicate the activation of select opioid receptor subtypes within the PAG in regulating select maternal behavior. Interestingly, μ-opioid receptor agonists infused into the PAG disrupts the balance of maternal care and aggression, while as mentioned above, κ-opioid receptor antagonism can shift maternal behaviors from caring to predatory behaviors in rodents (Klein et al., 2014). In accord with our central hypothesis, these findings are particularly relevant to the potential effects of buprenorphine given its antagonistic effects on κ receptors. Accordingly, preliminary data from the Brummelte lab (Wallin et al., 2018) has shown that low (0.3 mg/kg) but especially high (1 mg/kg) doses of buprenorphine given prior to and throughout gestation and continued in the postpartum in rat dams significantly impairs maternal care-giving behaviors. In fact, high dose buprenorphine resulted in complete neglect of the offspring in some dams. This supports the idea that exogenous opioids can interfere with the crucial role of endorphins in neural adaptation in the transition to motherhood. Opioid levels right at the time of parturition or during the very early postpartum period may be particularly important for determining the effect on maternal behaviors, given a report on buprenorphine exposure from 7 to 21 days of pregnancy (Hung et al., 2013). In this study, there were no significant neurobehavioral or physical (body/brain mass) alterations in dams that received buprenorphine (0.3 or 1 mg/kg) but there were depression-like neurobehaviors for pups at 1 mg/kg. It appears that these behaviors are regulated by protein phosphorylation and dephosphorylation mechanisms that are emerging in the regulation of animal neurotransmitter release that have consistently been shown to play roles in depression and addiction (Swain et al., 1991; Wu et al., 2017; Liu et al., 2016; Xu et al., 2006).

Endogenous opioids in offspring are released during social contact and low levels have been shown to induce behaviors to seek out contact from a caregiver (Nelson and Panksepp, 1998). Indeed, it has long been known, that proper attachment and maternal care have a tremendous impact on infant development and the adult phenotype (Denenberg, 1999; Denenberg and Bell, 1960; Denenberg et al., 1962; Rosenberg et al., 1970; Bayart et al., 1990; Hennessy et al., 1980; Joffe et al., 1972; Levine, 1967; Levine et al., 1988). However, we are far from fully understanding the underlying mechanisms of how responsive and sensitive parenting is initiated and how it can affect the offspring in the long-term (Kentner et al., 2018). Inhibitory effects of opioids on oxytocin secretion in postpartum females have been reported in numerous mammalian species (Tancin et al., 2000; Russell et al., 1991; Haldar and Sawyer, 1978; Haldar et al., 1982; Wright et al., 1983), including humans (Lindow et al., 1999). Furthermore, the role of endogenous opioids in attenuating the prosocial effects of oxytocin has been supported by data from both animals and humans (Dal Monte et al., 2017). While buprenorphine and other opioids clearly impinge upon the MBN,

the precise nature of these relationships and effects on parenting remain unclear given the complex effects of BT and opioids on receptor occupancy, buffering postpartum stress and depression, and ultimately breaking the relapse cycle. It is clear though, that maternal behaviors are crucial in mediating offspring outcome, suggesting that infants from mothers with OUD may be suffering from a 'double-hit' of early adversity with gestational drug exposure as well as altered maternal care due to maternal opioid use.

3.2. Gestational opioid animal models: Need for better translational value

Although numerous animal studies have investigated the effects of gestational opioid exposure on the offspring, there is considerable variation in reported outcomes probably due to several factors, including species used, type and dose of drug and time of exposure (preconceptional, start during pregnancy, continued through postpartum or not). For instance, endogenous opioids and prescription opioids have been associated with normal maturational processes and can upregulate brain-derived neurotrophic factor as well as oligodendrocyte maturation and myelination through activation of opioid receptors (Zhang et al., 2006; Vestal-Laborde et al., 2014). Therefore, it is conceivable that prenatal exposure to exogenous opioids may interfere with proper brain development. In fact, recent data suggests that early opioid exposure may lead to accelerated brain development that could disrupt the complex sequence of synchronized neurochemical events leading to normal connectivity in the developing brain (Vestal-Laborde et al., 2014).

It has also been suggested that some of the variability in offspring outcome after gestational opioid exposure could be explained by the distinctive role that endogenous opioids play in regulating hypothalamic and pituitary outflow during pregnancy and the postpartum period (Byrnes and Vassoler, 2018). In other words, the physiological reaction of the mother to the drug is a crucial factor in determining the effects on the offspring. Unfortunately, many previous animal models, which typically began opioid exposure during pregnancy, failed to account for the fact that most women will already be taking opioids by the time of conception (either abusing, prescription or maintenance opioids) rather than starting to use them during pregnancy. As a woman's body develops tolerance to a set opioid level and goes through withdrawal once that opioid level drops, the effect on the fetus could be very different in an 'established' user compared to a 'new' user. This crucial aspect of drug use patterns has previously been mostly ignored in animal studies that commonly start exposure after gestational day 7 when the opioid system started to develop in the fetus (Zhu et al., 1998; Khachaturian et al., 1983). Thus, there is a lack of research on the effects of pre-conceptional drug use and drug withdrawal, in addition to relapse or switching opioids during pregnancy. Importantly, there is also a lack of data concerning the short and long-term effects of opioids during these critical developmental periods on the dam's brain, behavior and physiology – critical to determine the long-term consequences for the dam and her offspring.

Although perinatal exposure to buprenorphine has not been shown to produce severe maternal and fetal or neonatal mortality, it was associated with significant perinatal mortality and perturbations of pup development in the rat (Robinson and Wallace, 2001). These effects included increases in maternal and fetal mortality and morbidity, in addition to the

perturbations in the acquisition of several pup developmental milestones, weight gain, precipitated withdrawal, and the antinociceptive effect of morphine. Specifically, it was shown that 1 and 3 mg/kg/day of buprenorphine suppressed food intake over the first few days after minipump implantation on gestational day 7, but then the rats seemed to develop a tolerance for that effect. The resulting reduction in maternal weight gain during those first days again highlights the importance of considering the timing of exposure since a nutrition deficit during pregnancy has long been known to have its own detrimental effects on maternal behavior and offspring (Wiener et al., 1976; Connor et al., 2012). Similar concerns come from rat research showing that the relative amount of morphine in placental and fetal tissue was reduced significantly following continuous administration compared to a single administration (DeVane et al., 1999). Taken together, future animal and human research must address critical issues of exposure timing and duration in addition to amount, since opioids are associated with many adaptive responses and many co-morbidities, such as stress, that could contribute to offspring outcome.

4. Research on the parental brain and opioids

4.1. Opioid-mediated regulation of stress during pregnancy

Endogenous opioids are well known to have a robust effect on extended amygdala morphology, which contributes to Hypothalamic-Pituitary-Adrenal/Sympathetic-Adrenal-Medullary (HPA/SAM) axis regulation. Interestingly, chronic opioid use seems to suppress HPA axis function in humans (Delitala et al., 1983), but rodents often show activation and increased cortisol levels after opioid treatment (Buckingham and Cooper, 1984). This paradox produces a challenge for translational studies of opioid effects, especially during stressful periods such as pregnancy and the postpartum. Despite this, experimental animal studies have been essential in determining how endogenous opioids suppress HPA axis function during gestation (Brunton and Russell, 2008). Briefly, increased inhibition of noradrenergic terminals in the hypothalamus by endogenous opioids prevents CRH neuron activation. In turn, decreased CRH neuron activity results in less CRH release which eventually translates into less corticosterone (rodents) or cortisol (humans) released from the adrenal glands and thus a reduced stress response to external stressors. This opioid-induced down-regulation of the HPA axis is believed to protect the fetus from maternal stress and negative effects of elevated glucocorticoid levels. Thus, in addition to regulating emotions and reward processes (Benarroch, 2012), opioids play a central role in regulating objective and subjective stress that women experience during pregnancy and lactation (Brunton, 2018). This further highlights the importance of assessing the behavioral effects of long-term opioid-related HPA-axis suppression, which may result in response dysregulation of the stress response system. This is particularly germane in terms of parenting behavior as appropriate response to stress may be key in the face of prenatal maternal stressors including fears regarding impending labor and delivery, health and welfare of the fetus, inactivity, concerns pertaining to child rearing and elevated levels of anxiety, obsessions and depressive symptomatology (Lobel et al., 2008; Lobel et al., 2016; Lobel and Ibrahim, 2018; Mahaffey et al., 2018; Alderdice et al., 2012; Feygin et al., 2006). Interestingly, several research studies have indicated that pregnancy-specific stress is a more robust indicator of fetal

activity and adverse developmental outcome than general stress (Lobel et al., 2008; Dunkel Schetter, 2011; Huizink et al., 2004) potentially due to its lack of parenting specificity.

Finally, maternal stress and cortisol levels are associated with brain activation patterns in response to emotional stimuli in the mother. For example, dispositional personal distress was associated with greater cortisol reactivity to social evaluation stress in mothers, and mother's ventral ACC response to positive versus negative child feedback to their parenting decisions was inversely related to parenting-related cortisol reactivity (Ho et al., 2014). This suggests that opioids and BT may impact the mother-infant dyad and infant development beyond gestation, via their effects on external stressors, pregnancy specific stress and HPA-axis function.

4.2. Assessing maternal stress in the context of opioid maintenance therapy

The severity of stress as a behavioral teratogen (Dipietro, 2012) is compounded in women with addictive disorders, including OUD. For examples, OUD has co-occurring anxiety and mood related disorders, guilt, poor nutrition, impaired health, homelessness, violence, confusion regarding available medical options, and a lack of social support (McCarthy et al., 2017; Bishop et al., 2017; Jansson et al., 1996). From a neuroendocrine perspective, such chronic stressors alongside the repeated use of short-term opioids reciprocally sensitize HPA/SAM system activity. This in turn contributes to further use of opioids and other drugs, which further worsens dysphoria, negative affect, anxiety and the “relapse cycle” (Koob, 2017a, 2017b; Hyman et al., 2007). Indeed, research on non-pregnant substance abusers has indicated stress system sensitivity to be a key predictor of stress response dysregulation, elevated anxiety and depressive symptomatology as well as craving and relapse to various drugs of abuse during early abstinence (Fox et al., 2008; Fox et al., 2007; Sinha et al., 2011, 2006). Given this sensitized and negatively reinforcing environment, and added to the fact that pregnancy is frequently characterized by a rapid metabolism of opioids (McCarthy et al., 2017), it is not surprising that OUD during pregnancy is characterized by numerous failed quit attempts (Guille et al., 2017) potentially driven by aberrations in stress system pathophysiology, exacerbating the repeating cycle of opioid intoxication and acute withdrawal.

OMT such as BT may attenuate prenatal maternal stress in several ways. First, extensive clinical and preclinical data have indicated that the analgesic effects of buprenorphine dampen stress and reduce central levels of cortisol and ACTH in laboratory animals, clinical populations and healthy humans (Bershad et al., 2016). In addition, buprenorphine demonstrates both anti-depressive and anxiolytic properties in patients with opioid dependence (Kosten et al., 1990), treatment-resistant depression disorders (Bodkin et al., 1995; Kosten, 2016; Karp et al., 2014), and suicidal ideation (Yovell et al., 2016; Norelli et al., 2013). Healthy volunteers also show attenuation of cortisol and social stress with low buprenorphine which attenuates anxiety, rejection stress and response to fearful faces (Bershad et al., 2016; Bershad et al., 2015). Second, as BT provides a constant level of maternal μ receptor occupancy (McCarthy et al., 2017), it may effectively “break” cyclic withdrawal and relapse-related behaviors, decreasing bio-psychological aspects of the allostatic withdrawal state including anxiety, negative affect and sensitized HPA/SAM

function – all shown to underpin relapse factors as well as negatively impact health outcomes in the mother-child dyad (Lobel et al., 2008, 2016; Lobel and Ibrahim, 2018; LeWinn et al., 2009; Entringer et al., 2009).

4.3. Toward a unifying hypothesis of opioids as treatment with side effects

In humans, MBN regions respond to ethologically pertinent own-baby cry in correlation with adaptive caregiving thoughts and behaviors during early postpartum (Swain et al., 2007; Barrett and Fleming, 2011; Swain, 2011). Many of these are same brain regions known to be regulated by endogenous opioids and dysregulated by stress and OUD. For example, in animal models, addiction affects reward processing in the OFC, VTA, and nucleus NAc (Rutherford et al., 2011). Furthermore, human neuroimaging has shown that amygdala, insula, ACC, and OFC are dysregulated in stress-related disorders like depression (Groenewold et al., 2012).

We previously presented preliminary data on the effects of BT on the response of human maternal brain systems to own baby-cry (Swain and Ho, 2017), which we update here: We studied 46 mothers in early postpartum who completed structural and functional magnetic resonance imaging (MRI) scans at two time-points: 1-month postpartum (T1) and 4-month postpartum (T2). The participants reported depressive symptoms using Beck Depression Inventory (BDI) (Beck et al., 1997) and parenting stress using Parenting Stress Index (PSI) (Abidin, 1995) T1 & T2. According to the BDI at T1 and prescription opioid usage, we divided the participants into three groups, including a group of 7 mothers who were on prescription buprenorphine treatment (BT) from the first trimester until the time of study (4–20 mg), a group of 7 non-OUD mothers who had elevated depressive symptoms similar to BT mothers (Depressed Controls, DC), and a group of 32 non-OUD mothers who were not depressed nor receiving BT (Healthy Controls, HC). At T1 and T2, the participants underwent functional magnetic resonance imaging (fMRI) scans during a baby-cry task, wherein they listened to own and other's baby cry and respective control sounds in a block design (30 s per block, 5 blocks per condition), and an 8-minute resting state task. The fMRI images were processed and analyzed in SPM 8 to examine the differential neural responses to Own vs. Other’s Baby Cry, functional connectivity during own vs. other baby cry and resting state functional connectivity (rsFC).

This preliminary data on mothers during the early postpartum shows that adaptation of maternal brain physiology and behaviors are influenced by opioid exposure. First, BT mothers with OUD showed greater PAG *and* hypothalamus responses related to Own vs. Other’s Baby-Cry as compared to healthy mothers. Second, Own vs. Other’s Baby-Cry responses in the hypothalamus were associated with greater parenting stress (PSI). Lastly, both differential functional connectivity in Own vs. Other’s Baby-Cry and rsFC between the PAG and hypothalamus were associated with PSI, suggesting a role of PAG in driving hypothalamus as a function of parenting stress. Although preliminary, these findings suggest that neuroimaging may reveal both mechanisms for therapeutic benefit from BT, as well as potential risks of parenting stress according to dysregulation in the MBN.

Based on our preliminary data and MBN model, we propose a unifying hypothesis to explain how BT may be helpful in the treatment of OUD, although also posing side-effect

risks to maternal behavior, consistent with preclinical research. In OUD, BT increases activity in both care (hypothalamus) and defense (PAG) subsystems of MBN – both potentially supporting maternal care behaviors. However, we also reveal potential dysregulation of the normal reciprocal inhibition between these subsystems by exogenous opioids. The latter effect may result in excessive infant-oriented defensive/aggressive thoughts and behaviors that may manifest as anxiety or aggression during maternal behavior and responding to their baby-cry. This compelling yet simple idea could explain how exogenous opioids such as BT may be therapeutic role, yet also risk side-effect of diminished care with intrusive or insensitive parental behaviors in the case of OUD with exogenous opioid treatment, and as a function of stress (Bridges and Grimm, 1982; Slamberova et al., 2001). Evaluation of this hypothesis requires a currently lacking characterization of maternal phenomenology for BT mothers as to whether they are overly focused on defense of the infant, lacking in caregiving motivation, or more stress-sensitive during maternal behaviors.

5. Summary and future directions

Opioid use has reached epidemic proportions in the United States. Besides the health consequences for the using mother, there is also a significant concern following the use of opioids in pregnancy for adverse infant outcomes (Broussard et al., 2011; CSAT, 2006), as evidenced by a 5-fold increase in the prevalence of NAS in recent years. The use of OMT is the highly recommended “gold standard” for treatment despite its own risks. In addition to mitigating withdrawal, physicians are currently more likely to prescribe buprenorphine because emerging data suggest that neonatal withdrawal symptomology appears to be less frequent and less severe with buprenorphine than methadone (Kakko et al., 2008; Jones et al., 2005, 2010; Hall et al., 2018). OMT is designed to prevent relapse to illicit opioid drug use (i.e., heroin or morphine) and to avoid the cycling of intoxication and withdrawal resulting in inconsistent blood opioid levels and high fetal stress (Fischer et al., 2000). However, there is still a lack of data on the long-term consequences of OMT exposure for the fetus as well as a lack of consensus about appropriate dosing regimens especially around the time of parturition. Further, the impact of stress as a co-morbidity with opioid abuse is not well studied and deserves further attention. Animal models also raise concerns for adverse parenting behavior effects. Considering the role of endogenous opioids in regulating maternal behaviors and the stress response in pregnant women (Swain et al., 2005), exogenous opioids may have a unique effect on maternal physiology by impacting the HPA axis functioning and brain circuits involved in maternal caregiving behaviors. It is possible that opioids disrupt the normal regulation (reciprocal inhibition) of caring and defensive/aggressive brain circuits in mothers suffering from OUDs and concurrent high levels of stress. More research is needed to better understand how we can administer opioids to help mothers reduce their withdrawal symptoms without affecting important MBN brain networks leading to negative consequences in maternal–infant interactions and parenting. Parental brain models of reward-stress dysregulation by addiction present opportunities to understand how caregiving may be compromised in addicted parents and assisted by opioids. Future studies should further investigate the impact of opioids on parenting behavior in

mothers and fathers (Swain et al., 2014) and test whether parenting interventions can alleviate some of the negative consequence for exposed children.

For example, the Mom Power (MP) parenting intervention, which aims to promote maternal empathy, reflective functioning, and stress reduction skills (Muzik et al., 2015, 2016) has been associated with decreased parenting stress and increased child-focused responses in social brain areas (Swain et al., 2017). This kind of parenting intervention may be optimized specifically to treat OUD or OUD-treatment related neurophysiological deficits for mothers affected.

Animal and human parental brain models may also lead to new and improved pharmacological and psychological interventions. For example, exogenous oxytocin may improve maternal caregiving motivation in OUD since opioids inhibit oxytocin – with due care for the timing and context of therapeutic administration of oxytocin to decrease maternal aggression (Szymanska et al., 2017; Bosch and Young, 2018). Although animal and human models can help disentangle the complex relationships between the direct and indirect effects of opioids on the maternal brain and behavior and the outcome of the offspring, we need better translational approaches that take these complexities into consideration and focus more on the dam and offspring. For example, it will be important to consider the fact that most women do not start abusing opioids during pregnancy but are rather already suffering from opioid abuse and likely related stress system dysregulation before conception. Given the opioid epidemic, there is also an urgent need to investigate the impact of switching during pregnancy – from drugs of abuse to therapeutic maintenance drugs such as buprenorphine. Indeed, the impact of experiencing recurring withdrawal during gestation and high levels of circulating opioids at the time of parturition is not well understood for maternal brain or behavior. Finally, brain-based models may help explore the underlying mechanisms of changes to maternal caregiving behaviors in women with OUD, as well as consequences of poly-drug use or frequent relapse for the mother and her offspring that may inform treatment.

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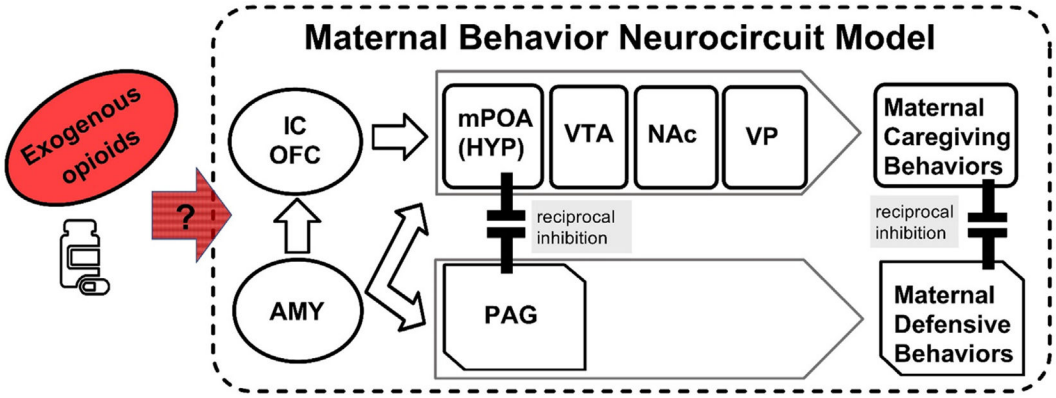

Fig. 1.

The maternal behavior neurocircuit - a framework to consider the effects of exogenous opioids. Maternal behaviors may be activated by the amygdala (AMY). Insular cortex (IC), orbitofrontal cortex (OFC), medial preoptic area (mPOA) of the hypothalamus (HYP), ventral tegmental area (VTA), nucleus accumbens (NAc) and ventral pallidum (VP) activate caregiving. behaviors. Periaqueductal gray (PAG) activates defensive/aggressive behaviors. Sensitive maternal behavior requires that caregiving and defense processing reciprocally inhibit each other. Exogenous opioids, which affect multiple parts of the maternal brain, require further study in animals. We present preliminary data.on the effects of exogenous opioids on human mothers below in 4.3.