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Co-occurrence of preconception maternal childhood adversity and opioid use during pregnancy: Implications for offspring brain development

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Abstract

Understanding of the effects of *in utero* opioid exposure on neurodevelopment is a priority given the recent dramatic increase in opioid use among pregnant individuals. However, opioid abuse does not occur in isolation—pregnant individuals abusing opioids often have a significant history of adverse experiences in childhood, among other co-occurring factors. Understanding the specific pathways in which these frequently co-occurring factors may interact and cumulatively influence offspring brain development *in utero* represents a priority for future research in this area. We highlight maternal history of childhood adversity (CA) as one such co-occurring factor that is

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more prevalent among individuals using opioids during pregnancy and which is increasingly shown to affect offspring neurodevelopment through mechanisms beginning *in utero*. Despite the high incidence of CA history in pregnant individuals using opioids, we understand very little about the effects of comorbid prenatal opioid exposure and maternal CA history on fetal brain development. Here, we first provide an overview of current knowledge regarding effects of opioid exposure and maternal CA on offspring neurodevelopment that may occur during gestation. We then outline potential mechanistic pathways through which these factors might have interactive and cumulative influences on offspring neurodevelopment as a foundation for future research in this area.

Keywords

maternal childhood adversity; prenatal opioid exposure; *in ntero* exposure; opioid epidemic; brain development; maternal-placental fetal biology

1 - Introduction

The marked increase in opioid misuse in recent decades (Cicero et al., 2014; Substance Abuse and Mental Health Services Administration (US) and Office of the Surgeon General (US), 2018), including high rates of usage among pregnant individuals (Desai et al., 2014; Maeda et al., 2014; Terplan et al., 2010), has raised concern regarding effects of *in utero* opioid exposure on offspring brain development. (Abdel-Latif et al., 2013; Camden et al., 2021; Maeda et al., 2014). Advancing understanding of how *in utero* opioid exposure influences fetal brain development is of critical importance—the prenatal period is the most rapid period of brain development across the lifespan, and biological signaling mechanisms guiding embryonic and fetal brain development are highly sensitive to cues from the extra-uterine environment (Entringer et al., 2015). Furthermore, alterations to brain development during gestation have implications for adaptive potential in response to the postnatal environment (Hartman and Belsky, 2018) and long-term risk for psychiatric disorders (O'Donnell and Meaney, 2016). While there is some empirical evidence in support of poorer physiological and neurodevelopmental outcomes soon after birth in infants exposed to opioids *in utero* versus non-exposed peers (Beckwith and Burke, 2015; de Cubas and Field, 1993; McGlone and Mactier, 2015; Moe, 2002; Nygaard et al., 2016, 2015; Ornoy et al., 2001), these observations have not been consistently replicated (Baldacchino et al., 2014), and long-term effects of prenatal opioid exposure on neurodevelopment remain poorly understood (Conradt et al., 2018).

A significant challenge in understanding the short- and long-term effects of prenatal opioid exposure lies in disentangling the potential influence of prenatal opioid exposure from the multiple, frequently co-occurring factors in the pre- and postnatal environment with potential to influence neurodevelopment. Previous literature in this area does not thoroughly account for the wide array of co-occurring factors prevalent in pregnant individuals using opioids (Conradt et al., 2019). Focusing on the potential mechanisms by which *in utero* opioid exposure and commonly co-occurring risk factors in the prenatal environment influence neurodevelopmental trajectories has potential to increase clarity into

the etiology of poor neurodevelopmental outcomes with implications for prevention and early intervention strategies.

Among pregnant individuals using opioids, there is an increased prevalence of exposure to childhood adversity (CA), which is a well-established risk factor for substance use (Brown and Shillington, 2017; Racine et al., 2020). Here we consider CA to include a range of negative experiences in childhood shown to have long-term consequences for psychiatric and other health outcomes. These include experiences involving threat (physical abuse, sexual abuse, exposure to domestic and community violence), deprivation (emotional or physical neglect), and instability (loss of a caregiver, caregiver transitions, family conflict and divorce) (Koss and Gunnar, 2018; McLaughlin et al., 2014). The number of CA exposures (also referred to as Adverse Childhood Experiences) proportionally increased the odds of opioid misuse in adulthood in a study of a large community sample while controlling for a variety of other sociodemographic factors (Merrick et al., 2020; Quinn et al., 2019). Additionally, childhood abuse and neglect were shown to increase the risk for adulthood prescription opioid misuse in a large nationally-representative sample (Austin and Shanahan, 2018). Among adults receiving treatment for opioid use disorder, CA is correlated with increased likelihood of relapse (Derefinko et al., 2019), younger age of opioid use initiation, more recent injection drug use, and increased likelihood of overdosing (Stein et al., 2017). The high co-occurrence of CA and opioid misuse is of particular relevance for advancing understanding of fetal brain development in the context of maternal opioid use given recent evidence for effects of maternal CA on maternal-placental-fetal (MPF) biology and fetal brain development (Buss et al., 2017; Hendrix et al., 2020; Lehrner and Yehuda, 2018; Moog et al., 2018, 2016a).

The current review aims to provide a foundation for examining the potential cumulative and interactive influences of maternal history of CA and opioid use during pregnancy on offspring neurodevelopment. We note that neonatal opioid withdrawal syndrome (NOWS) is a common focus both in clinical settings and in prior research on *in utero* opioid exposure (Bakhireva et al., 2019; Kelty and Preen, 2019; Kocherlakota, 2014). However, NOWS is not a primary focus of this manuscript given the lack of understanding of its role in neurodevelopment and long-term outcomes (Conradt et al., 2019). Further, NOWS diagnoses are variable, and a sizable portion of infants exposed to opioids *in utero* do not receive a NOWS diagnosis (Jones et al., 2018)—we aim to include all opioid-exposed neonates in this review to ensure a comprehensive examination of *in utero* opioid exposure. We first provide a brief review of current knowledge regarding the effects of prenatal opioid exposure and maternal CA on the developing brain *in utero*. We highlight research with potential to disentangle prenatal versus postnatal effects of prenatal opioid exposure and maternal CA, given that transmission of these risk factors may occur prenatally via alterations to MPF biology and epigenetic mechanisms, as well as through alterations to the postnatal environment. This literature is then contextualized with a discussion of the candidate mechanistic pathways by which opioids and sequelae related to maternal CA can influence offspring brain development *in utero*. Finally, we make recommendations for future research with the aim of increasing clarity regarding the implications of maternal opioid use during pregnancy on offspring neurodevelopment in the context of accompanying risk factors. We speak to the potential relevance of such research for eventually informing

public health messaging and the stigma related to opioid use during pregnancy, in addition to prevention and intervention efforts for individuals at risk for misusing opioids.

2 – Neurodevelopmental outcomes associated with *in utero* opioid exposure and preconception maternal CA

2.1 – Long-term neurodevelopmental outcomes associated with *in utero* opioid exposure and maternal preconception CA

Given the focus of this review on mechanistic pathways for the *in utero* effects of opioid exposure and maternal CA on human offspring neurodevelopment, clinical research examining the effects of both factors on neonatal human brain outcomes represent a primary interest due to enhancing capacity for distinguishing pre- versus postnatal effects. However, it is worth noting that research with animal models, which allows for experimental control to isolate effects of specific exposures during certain developmental windows, has identified long-term impacts of *in utero* opioid exposure and maternal CA on a range of outcomes beyond the neonatal period. While it is challenging to differentiate the role of the pre- versus post-natal environment in clinical studies investigating long-term neurodevelopmental outcomes of *in utero* opioid exposure and maternal CA, these studies suggest the potential for neurodevelopmental alterations related to these exposures to persist well beyond infancy into later childhood and adulthood. We therefore provide a brief review of literature examining long-term neurodevelopmental alterations in relation to these factors to contextualize the impetus for advancing understanding of the relevant mechanistic pathways leading to these alterations.

Pre-clinical studies suggest that long-term neurodevelopmental alterations in offspring exposed to opioids *in utero* include increased risk for behaviors analogous to symptoms of mood and anxiety disorders (Ahmadalipour et al., 2015; Hung et al., 2013; Wu et al., 2020), altered social and reward processing (Buisman-Pijlman et al., 2009b; Hol et al., 1996; Niesink et al., 1996; Vanderschuren et al., 1995; Vathy and Katay, 1992), cognitive differences (Ahmadalipour et al., 2015; Niu et al., 2009; Šlamberová et al., 2003; Wang et al., 2017; Wang and Han, 2009), in addition to increased seizure potential and alterations in endogenous opioid system and endocrinal stress-response functioning (Boggess and Risher, 2020; Byrnes and Vassoler, 2018). These studies primarily employ rodents (rats or mice), with the exception of one study which used chicks (Wang et al., 2017). Despite significant differences in brain morphology and the timing of neurodevelopment between rodents and humans (Ohmura and Kuniyoshi, 2017), there is some evidence to support potential translation to humans. This includes reports of emotional challenges and cognitive deficits in toddlers and school-aged children exposed to opioids during gestation (Levine and Woodward, 2018; Nelson et al., 2020; Nygaard et al., 2016, 2015; Yeoh et al., 2019), although these findings have not been consistently replicated (Bakhireva et al., 2019; Conradt et al., 2019).

Several factors require consideration in translating findings from animal models of prenatal opioid exposure. First, the role of the postnatal environment on offspring development can be challenging to model in animal studies. Animal models that include variation

in the postnatal environment indicate that the role of the postnatal environment plays a significant role in developmental trajectories of offspring exposed to opioids *in utero*. Some evidence suggests that effects of prenatal opioid exposure on offspring neurodevelopment may not persist in a beneficial postnatal environment—adult rodents exposed to opioids during pregnancy showed depressive-like behaviors that were prevented with postnatal environmental enrichment (Ahmadalipour et al., 2015) and exercise (Wu et al., 2017). These rodent models suggest an important modulatory role of the postnatal environment on neurodevelopment in offspring exposed to opioids *in utero*, although studies examining the role of the early postnatal environment on rodent development must be translated to human findings with caution. Rodents are born at the equivalent of about mid-gestation in human fetuses (Clancy et al., 2007), implying that early postnatal factors may have differential effects on brain development in rodents than in humans.

Evidence from clinical research also emphasizes the need to consider postnatal environmental influences on neurodevelopment in offspring exposed to opioids *in utero*. Compared to children without prenatal substance exposure, children exposed to opioids *in utero* are more likely to experience a range of adversities in the postnatal environment, including abuse, neglect, housing instability, low socioeconomic status (SES), poor nutrition, parental psychopathology, low access to healthcare, and caregiver disruptions (Conradt et al., 2018; Levine et al., 2021). While consideration of such co-occurring adversities is rare in studies examining the effects of prenatal opioid exposure on long-term neurodevelopment in humans (Conradt et al., 2018), those that attempt to control for factors such as low SES, maternal education level, and the quality of the home environment have found that the detrimental effects of prenatal opioid exposure on cognitive and psychomotor development were no longer evident (Hans and Jeremy, 2001; Messinger et al., 2004). A recent study by Levine et al. (2021) similarly reported that deficits in motor development, cognitive development, and emotional and behavioral dysregulation found in 2-year-old children with prenatal methadone exposure were mediated by gestational age at birth, and aspects of the postnatal environment, including, breastfeeding participation, maternal stress, and punitive parenting. They also found that the children exposed to methadone *in utero* demonstrated deficits in language development at 2 years old that did not remain significant after controlling for maternal education and polysubstance use during pregnancy (Levine et al., 2021). This work highlights the role of the postnatal environment in the developmental trajectories of offspring exposed to opioids *in utero*.

Similar to human studies of children exposed to opioids *in utero* (Boggess and Risher, 2020; Conradt et al., 2019; Kirkegaard et al., 2020; Skumlien et al., 2020; Winklbaur et al., 2009), offspring of mothers who experienced CA are at increased risk for a myriad of poor neurodevelopmental and physiological outcomes (Buss et al., 2017). In childhood, offspring with maternal CA exposure show increased physiological anxiety markers (Jovanovic et al., 2011), higher rates of obesity and smoking behaviors (Roberts et al., 2014), increased externalizing behaviors (Miranda et al., 2013; Myhre et al., 2014; Plant et al., 2017; Rijlaarsdam et al., 2014), increased negative emotionality (Bouvette-Turcot et al., 2015), and increased risk for autism (Roberts et al., 2013). While several of these studies identified postnatal mediators of the relationship between maternal CA and offspring outcomes (Collishaw et al., 2007; Miranda et al., 2013; Plant et al., 2017; Rijlaarsdam et al., 2014;

Roberts et al., 2014), others also indicated co-occurring factors in the prenatal environment that modulate the association between poorer long-term neurodevelopmental outcomes and maternal CA history, such as antenatal depression (Collishaw et al., 2007; Plant et al., 2017) and genetic variation (Bouvette-Turcot et al., 2015). Limited pre-clinical studies examining the effect of parental early life adversity on offspring neurodevelopment partially support findings from clinical studies, suggesting either maternal or paternal early life adversity may increase the risk for biological and behavioral stress phenotypes in mice and primate offspring (Cowan et al., 2016). These findings further emphasize the need to examine offspring neurodevelopmental alterations at birth in order to identify alterations related to prenatal opioid exposure and maternal CA that truly occur before exposure to the postnatal environment.

2.2 – Offspring neonatal brain outcomes associated with *in utero* opioid exposure and maternal preconception CA

2.2.1 – Whole-brain outcome measures—

In utero opioid exposure and maternal CA have both been associated with altered neonatal head circumference, which is thought to be associated with smaller intracranial, or brain, volume (Cheong et al., 2008; Lindley et al., 1999), suggesting that these exposures may impede or alter fetal brain growth during gestation. Head circumference at birth is often utilized as a predictor for later neurodevelopment—neonates with head circumferences at the top or bottom 2% are at significantly greater risk for neurodevelopmental disorder diagnosis later in life (Wright and Emond, 2015).

Prenatal opioid exposure has been associated with reduced neonatal head circumference (Craig et al., 2020; Monnelly et al., 2018; Peterson et al., 2020; Towers et al., 2019; Visconti et al., 2015). Additionally, two studies directly examining intracranial volume using MRI techniques identified global volumetric reductions in brains of neonates exposed to opioids *in utero* compared to unexposed controls (Peterson et al., 2020) and previous literature documenting normative neonatal brain development (Yuan et al., 2014). However, consideration of co-occurring factors has been limited in these studies. Additionally, the type of opioid exposure is likely to influence fetal head growth. Methadone and buprenorphine are two opioid maintenance treatments that are currently the frontline treatments for pregnant individuals with opioid dependence (World Health Organization, 2014). Both drugs have affinity for the μ-opioid receptor (MOR), and reduce mortality rates and risk of relapse associated with opioid misuse due to their long half-life (methadone) and partial agonist (buprenorphine) properties (Bonhomme et al., 2012). Of these two opioid maintenance treatments, only methadone appears to be associated with smaller neonatal head circumference (Jones et al., 2014, 2010; O'Connor et al., 2019; Pritham et al., 2012; Zedler et al., 2016). Poly-substance use during pregnancy, which is very common among opioid-using pregnant individuals, may exacerbate reductions in offspring head circumference associated with prenatal opioid exposure—among prenatally opioid-exposed infants, additional exposure to tobacco has been associated with further reduced head circumference (Winklbaur et al., 2009). Limited evidence from clinical literature suggests that reduction in neonatal head circumference related to prenatal opioid exposure does not appear to be dose-dependent (Gray et al., 2010; O'Connor et al., 2019), although this will

need to be replicated in future studies. Smaller cerebral size at birth is associated with poorer intellectual and executive functioning outcomes, particularly when subsequent postnatal head growth does not catch up to peers (Aagaard et al., 2018; Bilder et al., 2013; Ferrer et al., 2019; Gale et al., 2006; Heinonen et al., 2008; Kirkegaard et al., 2020; Langridge et al., 2013; Wright and Emond, 2015).

Maternal CA has also been associated with alterations in global cerebral development at birth, however interpretation of findings is limited by the sparsity of research in this area. One study reported an association between maternal CA history and a higher cephalization index (ratio of head circumference to body weight) at birth when adjusting statistically for factors related to maternal demographics, maternal health, delivery, infant sex assigned at birth, and infant gestational age at delivery (Appleton et al., 2019). These findings are consistent with reports of a higher offspring cephalization index linked to earlier age of maternal menarche (Holdsworth and Appleton, 2020), given that exposure to CA is associated with earlier pubertal onset (Colich et al., 2020; Holdsworth and Appleton, 2020; Lei et al., 2018; Noll et al., 2017). Another group demonstrated positive correlations between maternal CA and offspring head circumference and weight at birth, while accounting for multiple maternal psychosocial, health, and nutritional factors (Apanasewicz-Grzegorczyk et al., 2020). Additionally, maternal CA has been associated with reduced neonatal cortical gray matter, which contributed to an overall smaller intracranial volume (Moog et al., 2018). These results persisted after adjusting for multiple potential confounds frequently associated with maternal history of CA, including SES, complications during pregnancy, obesity, recent exposure to interpersonal violence, stress throughout pregnancy and in the early postpartum period, and length of gestation (Moog et al., 2018).

Overall, there appears to be potential for both prenatal opioid exposure and maternal CA to influence fetal cerebral growth, suggesting potential for cumulative or interactive influences to be examined in future studies. In addition, future research would benefit from examining trajectories of postnatal intracranial growth to see if differences persist over time, with consideration of additional moderating factors (including environmental risks and weight at birth).

2.2.2 – Outcomes in large-scale brain networks and global connectivity—

Examining connectivity both with resting state functional MRI and diffusion tensor imaging is of great interest for understanding the long-term effects of fetal neurodevelopment, as key aspects of adult brain organization, such as small worldness (component of brain network organization consisting of close and highly interconnected nodes) and nacent forms of large-scale brain networks, are detectable during the neonatal period and are predictive of neurodevelopment throughout childhood (De Asis-Cruz et al., 2020; Graham et al., 2021; Schneider et al., 2004; Smyser et al., 2010; van den Heuvel et al., 2015). Some evidence suggests that prenatal opioid exposure is related to altered maturation of white matter fiber tracts in the neonatal brain. Monnelly et al. (2018) reported decreased fractional anisotropy (FA), a measure of white matter integrity and connection orientation, in the neonatal white matter skeleton, which represents the center of each white matter tract common to the sample. Additionally, Walhovd et al., (2012) found increased mean diffusivity (MD), indicative of reduced white matter integrity, in the superior longitudinal fasciculi of neonates

exposed to opioids during pregnancy. Furthermore, Merhar et al., (2019) found preliminary evidence of increased risk of white matter lesions and abnormalities in neonates prenatally exposed to opioids. In contrast, while controlling for gestational age, offspring sex, tobacco and alcohol use, maternal age, SES, race/ethnicity, depression, anxiety, and prenatal stress, a small cohort study found that frontal and parietal white matter in prenatally opioid-exposed neonates showed increased FA and reduced MD (Peterson et al., 2020). These studies have attempted to account for key pre- and post-natal environmental covariates, but maternal CA history has not been considered either as a covariate or moderator. Moreover, small sample sizes (ranging from 20 to 60 participants) and lack of replication in independent datasets decrease confidence in these findings, particularly in light of the expected small effect sizes and recent literature highlighting the lack of reproducibility in neuroimaging studies (Boekel et al., 2015; Kharabian Masouleh et al., 2019; Ks et al., 2013; Marek et al., 2020).

Utilizing resting state functional connectivity MRI has become increasingly popular in neonatal brain development research, as it takes advantages of brain activity at rest and can reveal neonatal functional brain network activity with potential implications for long-term neurodevelopment. Recent work by Salzwedel et al. (2020) employing resting state functional connectivity included a larger sample size relative to prior studies (n=133), although only 18 infants in the study had *in utero* opioid exposure. However, examining the potential link between alterations in neonatal brain connectivity and subsequent cognitive development, and employing multivariate modeling to account for co-occurring prenatal influences (including polysubstance exposure and maternal depression, although not maternal CA history) represent significant strengths of the study. The findings indicate an association between prenatal opioid exposure and alterations in neonatal resting state functional connectivity of the left middle frontal and right angular gyrus, as well as the cingulo-opercular network. These alterations in the neonatal brain were not associated with cognitive, language, or motor composite scores at 3 months of age. Thus, while this study suggests that prenatal opioid exposure may be associated with alterations in developing brain systems involved in cognition and executive functioning, it is unclear if these effects persist long after birth.

Maternal CA has not been examined in relation to offspring neonatal global brain connectivity. Alterations in region-specific connectivity (Hendrix et al., 2020) and global gray matter differences (Moog et al., 2018) in neonates exposed to maternal CA, in addition to functional connectivity differences in school-aged children with maternal CA (Zhang et al., 2021), suggest that the effects of maternal CA on neonatal functional connectivity may be an area of interest for future research.

2.2.3 – Region-specific volume and connectivity outcomes—Additional findings from neonatal brain imaging reveal that prenatal opioid exposure is associated with volumetric alterations of multiple cortical and subcortical brain regions with potential implications for basic motor and sensory processing and integration, as well as higher-order cognitive and emotional processing. One pilot study demonstrated decreased volume of the basal ganglia and larger volume of the lateral ventricle in neonates exposed to buprenorphine or methadone during pregnancy (Yuan et al., 2014). Additionally, research employing mid-pregnancy ultrasounds (18-22 weeks gestation) identified increased thalamic diameters in

fetuses exposed to opioids *in utero* (Schulson et al., 2014). A pilot study utilized MRI in fetuses at approximately 33 weeks of gestation to identify reduced anteroposterior diameter of the cerebellar vermis in fetuses exposed to opioids *in utero* compared to unexposed fetuses (Radhakrishnan et al., 2021a). Peterson et al. (2020) also found alterations in brain volume across multiple cortical regions, with increases observed in the middle temporal and inferior frontal gyri, posterior cingulate cortex, and inferior medial prefrontal cortex (mPFC), and decreases in the middle frontal gyrus, orbitofrontal cortex, and some dorsal and lateral regions of the prefrontal cortex. A recent pilot study identified that prenatally opioid-exposed neonates showed increased right amygdala-mPFC connectivity and decreased amygdala connectivity to other regions within the medial temporal lobe while controlling for maternal depression and infant sex (Radhakrishnan et al., 2021b). These findings indicate potential alterations in the cerebellum, multiple subcortical brain regions involved in sensory processing, movement, arousal, stress and emotion processing and reactivity, and distributed cortical brain regions, including those involved in higher level cognitive processes. However, limitations in sample size and a lack of replication in independent samples again hamper the generalizability of these findings.

The literature examining maternal CA in relation to specific brain volumes and connectivity in the neonatal period is even more limited. However, one recent study observed an association between maternal childhood emotional neglect and stronger offspring neonatal functional connectivity between the amygdala and dorsal anterior cingulate cortex, as well as between the amygdala and ventromedial prefrontal cortex (Hendrix et al., 2020). Increasing sample sizes, testing for replication in independent data sets, and considering potential cumulative and interactive effects of maternal CA and opioid use, among other co-occurring factors, represent important next steps in advancing understanding of whether coordinated functioning of the amygdala with regions of the prefrontal cortex, and other early neural phenotypes, play a role in mediating effects of these prenatal exposures on subsequent development.

2.2.4 – Summary of neonatal brain outcomes associated with *in utero* opioid exposure and maternal preconception CA—The findings to date indicate that both maternal CA and opioid use during pregnancy have potential to influence offspring brain development *in utero*. Prenatal opioid exposure appears to be associated with several neurodevelopmental alterations at birth, including smaller cerebral size, white matter abnormalities, alterations to functional connectivity networks, and volumetric changes to various brain regions. However, there are substantial limitations to existing literature examining the neurodevelopmental effects of prenatal opioid exposure during the fetal and neonatal period, including small sample sizes and lack of replication of findings, making it particularly difficult to draw conclusions about specific functional connectivity or volume changes. A significant challenge in studying the effects of prenatal opioid exposure in humans is how varying dosages, timings, frequencies, and specific opioid compounds will alter fetal neurodevelopment, given the substantial variability of each of these factors in the population of pregnant individuals using opioids. Furthermore, we continue to lack understanding of long-term neurodevelopmental consequences of prenatal opioid exposure in humans, and our review did not identify evidence to support the commonly held belief

that alterations at birth associated with prenatal opioid exposure will persist into later childhood and adulthood.

Additionally, studies examining potential neonatal brain alterations associated with maternal CA are currently very rare. To our knowledge, only four studies examine how maternal CA influences offspring brain outcomes at birth: two studies indicating a higher cephalization index (Apanasewicz-Grzegorczyk et al., 2020; Appleton et al., 2019), one reporting smaller gray matter and overall intracranial volumes (Moog et al., 2018), and one showing altered frontoamygdala connectivity (Hendrix et al., 2020). While understanding the specific effects of maternal CA on fetal neurodevelopment will be challenging without replication of this work, the current evidence does suggest that maternal CA alters offspring neurodevelopmental trajectories during gestation, and this is a compelling area for further research. Beyond increasing sample sizes to increase likely reproducibility of findings, future investigations into the effects of both prenatal opioid exposure and maternal CA on offspring neurodevelopment would benefit from study designs which carefully balance major potential confounds and provide sufficient statistical power to model cumulative and interactive influences.

3 - Pathways by which *in utero* opioid exposure and maternal preconception CA influence fetal brain development

3.1 – Endogenous opioid system

The endogenous opioid system is a complex neuromodulatory system that consists of several families of peptides and receptors that influence a wide range of behavioral and biological processes, including pain, reward processing, stress responsivity, cell survival, respiratory depression, ionic homeostasis, digestion, euphoria, cardiovascular health, and sedation (Fricker et al., 2020; Shenoy and Lui, 2020). Opioid peptides, including enkephalins, endorphins, dynorphins, nociceptin and endomorphins, have distinct effects depending on the regional and developmental context, as well as their differential affinities for the opioid receptors, including the μ-opioid receptor (MOR), δ-opioid receptor (DOR), κ-opioid receptor (KOR), nociceptin receptor (NOR), and zeta opioid receptor (ZOR) (Dhaliwal and Gupta, 2021; Fricker et al., 2020). The endogenous opioid system is distributed throughout the body, although it is particularly active in the central and peripheral nervous systems (Fricker et al., 2020).

During the prenatal period, the endogenous opioid system is thought to play a unique modulatory role in fetal brain development. Rodent studies suggest that developing neural cells begin to produce opioid receptors and opioid peptides early in gestation (Farid et al., 2008; Hauser and Knapp, 2018), while limited studies in humans verify endogenous opioid system activity by 11 (Tripathi et al., 2008) and 20 (Kinney et al., 2008; Magnan and Tiberi, 1989; Wang et al., 2006) weeks of gestation. Endogenous opioids modulate a range of early fetal neurodevelopmental processes involved with neuronal and glial maturation, and some opioid peptide activity appears to be reserved for developmental processes alone (Farid et al., 2008; Hauser and Knapp, 2018). While there are exceptions, opioid receptor activation tends to suppress fetal brain growth via inhibition of neuronal and glial proliferation

and differentiation, in addition to increased neuronal cell death, although specific activity differs by brain region and type of opioid receptor involved (Hauser and Knapp, 2018). One significant exception is the association of endogenous opioid activity with growth of oligodendrocytes, glial cells responsible for myelination. MOR activation during the prenatal period leads to increased mitosis of immature oligodendrocytes, which do not yet produce myelin (Knapp et al., 1998; Knapp and Hauser, 1996), while KOR agonists promote embryonic myelin production and mature oligodendrocyte differentiation and proliferation (Knapp et al., 2009, 2001; Mei et al., 2016), at the cost of neuron and astrocyte genesis (Hahn et al., 2010).

Opioid drugs (also referred to as exogenous opioids) with addiction potential take effect by mimicking endogenous opioid peptides and acting on opioid receptors throughout the body, both prenatally via placental transfer (Hauser and Knapp, 2018) and postnatally (Davis and Pasternak, 2005). When used during pregnancy, exogenous opioids travel across the placenta in significant amounts, reaching drug equilibrium between the pregnant individual and the fetus (Gerdin and Lindberg, 1990; Griffiths and Campbell, 2015). While developing fetal brain cells often appear to transiently express opioid receptors at different concentrations throughout gestation (Hauser and Knapp, 2018), some evidence suggests that certain neural cells are more sensitive to exogenous opioids during parts of the prenatal period than in adulthood—rat fetal neurons have been found to bind to methadone at a rate 2-14 times higher than in adults (Pertschuk et al., 1977). The potential for exogenous opioids to exaggerate the differential endogenous opioid activity on the development of various neural cell types, including promotion of oligodendrocyte growth and inhibition of neuron and astrocyte growth, suggests a potential pathway for reduced overall head circumference (Craig et al., 2020; Monnelly et al., 2018; Peterson et al., 2020; Towers et al., 2019; Visconti et al., 2015) and intracranial volume (Peterson et al., 2020; Yuan et al., 2014), in addition to altered white matter structure in opioid-exposed neonates (Merhar et al., 2019; Monnelly et al., 2018; Peterson et al., 2020; Walhovd et al., 2012).

Additionally, animal models suggest that prenatal opioid exposure may have specific programing effects on the rapidly developing fetal endogenous opioid system (Byrnes and Vassoler, 2018). The effects of prenatal opioid exposure on postnatal endogenous opioid system functioning appear to vary depending on the brain region of interest, postnatal age, and hormonal factors (Byrnes and Vassoler, 2018). Overall, the majority of literature in this area suggests that rodent offspring chronically exposed to exogenous opioids during fetal development show reduced opioid receptor binding across specific brain regions in the early postnatal period, but increased receptor binding in the same regions in adulthood (Byrnes and Vassoler, 2018). However, this does not appear to be consistent across brain regions—adult animals prenatally exposed to morphine showed reduced MOR binding in the bilateral amygdala (Šlamberová et al., 2005) and the medial preoptic area (Vathy et al., 2003). Prenatal opioid exposure may also be associated with increased endogenous opioid release in brain regions important for reward processing (substantia nigra, piriform cortex, and septum) in adulthood (Buisman-Pijlman et al., 2009a). Additionally, whole-brain analyses in rats exposed to opioids *in utero* showed increased MOR expression and binding during the neonatal period, but not in adulthood (Bhat et al., 2006), further suggesting

that opioid receptor alterations induced by prenatal opioid exposure appear to vary across developmental periods.

Direct CA exposure has also been shown to permanently alter the endogenous opioid system, which may in turn alter offspring development during pregnancy (Vazquez et al., 2005). To our knowledge, there is only one study that examined the intergenerational effects of adversity on offspring endogenous opioid system functioning—non-stressed male offspring of female rats exposed to chronic stress (beginning post-weaning through adulthood) showed significantly decreased spinal cord MOR gene expression compared to non-stressed male rats without parental stress exposure (Hormozi et al., 2018). Spinal cord MOR gene expression in male offspring exposed to only paternal stress or both maternal and paternal stress did not significantly differ from unexposed male rats (Hormozi et al., 2018). These findings verify that maternal chronic stress, including stress over the course of development, does influence offspring endogenous opioid system functioning.

Direct exposure to early adversity in rodents is associated with alterations in mRNA expression of brain opioid receptors in a time-, region- and sex-specific manner (Nakamoto et al., 2020). In mice exposed to maternal separation and social isolation, an animal model of CA, expression of KOR, MOR and DOR mRNA in the periaqueductal gray area was reduced, but KOR mRNA in the amygdala was significantly increased (Nakamoto et al., 2020). Chronic lifetime stress was associated with decreased MOR mRNA in the spinal cord of adult male rats (Hormozi et al., 2018). Additionally, chronic stress in mice is associated with increased dynorphin release and subsequent increased KOR activation in the basolateral amygdala, nucleus accumbens (NAc), dorsal raphe, and hippocampus (Land et al., 2008). Increased KOR activation of serotonergic neurons in the dorsal raphe nucleus projecting to the NAc appear to mediate the aversive stress response (Land et al., 2009). A rat model of early life adversity reported alterations to KOR and dynorphin activity in the lateral habenula, a brain region associated with reward- and aversion-related learning and depression (Simmons et al., 2020). They reported that juvenile, adolescent, and adult rats exposed to early life adversity exhibited increased dynorphin levels and significantly decreased KOR mRNA expression in the lateral habenula compared to rats unexposed to early life adversity. Karkhanis et al. (2016) observed that compared to unexposed controls, adult rats exposed to chronic early life stress demonstrated differences in KOR and dynorphin activity in the NAc, including decreased dynorphin levels, increased KOR agonist-mediated inhibition of dopamine, and increased dopamine levels in response to a KOR antagonist. Chang et al. (2019) observed reductions in KOR and MOR mRNA in the NAc of neonatal female rats recently exposed to predator odor, but increased MOR and DOR mRNA in juvenile females exposed to predator odor during the neonatal period. In humans, postmortem brain tissue of individuals with a history of abuse who died by suicide revealed that KOR expression was significantly decreased in the anterior insula compared to controls—an effect that was not observed in suicide victims without CA exposure and that was associated with decreased DNA methylation in an intron of the KOR gene (Lovallo et al., 2018; Lutz et al., 2018).

Findings from both animal and human literature indicate that direct CA exposure appears to alter endogenous opioid system functioning, particularly KOR and dynorphin functioning

in brain regions associated with reward processing. If carried forward into pregnancy, these alterations have implications for fetal neurodevelopment via the mechanisms previously discussed. Moreover, among pregnant individuals using opioids, these alterations may interact with the dysregulating effects of exogenous opioids on the endogenous opioid system and thereby exacerbate effects on the developing fetal brain. Future research will need to examine how CA-induced alterations to endogenous opioid system functioning may alter offspring neurodevelopment during pregnancy, although preliminary evidence suggests that MOR gene expression in the spinal cord may be downregulated in offspring with maternal chronic lifetime stress exposure.

Alterations to the maternal endogenous opioid system related to preconception CA have potential to subsequently alter maternal hypothalamic-pituitary-adrenal (HPA) axis functioning (Areda et al., 2005; Bilkei-Gorzo et al., 2008; Brunton, 2019; Hale et al., 2003; Jaschke et al., 2021; Kudryavtseva et al., 2004; Marinelli et al., 2004; Yamamoto et al., 2003). In adults assigned female at birth (AFAB)[1] without CA exposure, administration of an opioid receptor antagonist, naltrexone, typically causes a strong increase in HPA axis activity; however this activation was suppressed in adults AFAB exposed to CA, suggesting that endogenous opioid modulation of the HPA axis is reduced in CA-exposed individuals AFAB (Lovallo et al., 2018). During pregnancy, the neurosteroid allopregnanolone, a metabolite of progesterone that increases in concentration during pregnancy, potentiates endogenous opioid inhibition of HPA axis reactivity (Brunton et al., 2009; Kammerer et al., 2002; Russell et al., 2008). Individuals that experienced CA show an exaggerated blunting of the HPA axis during pregnancy compared to pregnant individuals without preconception CA (Morrison et al., 2017), which can be mimicked in non-pregnant mice when they are administered allopregnanolone (Morrison et al., 2020). This provides further evidence that maternal CA alters endogenous opioid modulation of the HPA axis during pregnancy. Alterations in HPA axis functioning during pregnancy in turn have significant implications for fetal neurodevelopment, which is discussed further below.

3.2 – HPA axis

The HPA axis directs the body's physiological response to acute and chronic stress through the sequential release of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids (cortisol in humans). During pregnancy, maternal cortisol levels stimulate placental corticotropin releasing hormone (pCRH) (Rehman et al., 2007; Sandman et al., 2006), which acts on the fetal adrenal gland to stimulate cortisol synthesis *in utero* (Sandman et al., 2012). Maternal cortisol also passes through the placenta, particularly in adverse contexts (Benediktsson et al., 1997). Cortisol plays an obligatory role in fetal neurogenesis, gliogenesis, synaptogenesis, and growth of axons and dendrites, creating ample opportunity for alterations in cortisol levels during pregnancy to exert an influence on fetal neurodevelopment (Matthews, 2000).

[1]The terminology "assigned female at birth" (AFAB) and "assigned male at birth" (AMAB) are utilized in this review to acknowledge that human sex is a composite of many traits (i.e. chromosomes, genes, hormones, sex organs, and sex characteristics) that vary between individuals and may not align with sex assigned at birth (de Vries and Södersten, 2009; Keevil et al., 2017; Montañez, 2017). References may not have used these terms in their studies.

There has been increasing interest in the co-occurrence of opioid use and dysregulated HPA axis in pregnant individuals, as both factors may influence offspring development through overlapping and interacting pathways (Lester and Padbury, 2009; Pastor et al., 2017). Some evidence suggests that opioid use during pregnancy may increase glucocorticoid release—pregnant rats administered daily morphine had significantly elevated glucocorticoid levels compared to pregnant controls (Kazemi et al., 2011). A recent pilot study found that higher levels of hair cortisol concentrations in pregnant individuals using opioids were associated with less severe withdrawal symptoms in offspring at birth (Wachman et al., 2020). Given that chronic stress and extensive opioid use have been associated with blunted HPA axis activity, the authors hypothesized that lower maternal cortisol levels in this sample may correspond to increased chronic stress and adversity history, which may contribute to worse opioid withdrawal symptoms at birth (de Vries et al., 2020; Wachman et al., 2020; Zhou et al., 2010; Zhou and Leri, 2016). Additionally, if exogenous opioid use exaggerates endogenous opioid inhibition of the HPA axis during pregnancy, higher rates of opioid use would likely correspond to both decreased cortisol and worse offspring withdrawal symptoms at birth. Thus, while the evidence to date is relatively mixed, it suggests that opioid use during pregnancy impacts the maternal HPA axis with implications for programming the fetal brain and HPA-axis. Future studies will be needed to advance understanding of this topic.

CA is well-known to produce long-term alterations in endocrine stress physiology, including greater HPA axis reactivity as well as hypocortisolism, and current literature suggests that HPA alterations related to preconception CA carry forward into pregnancy (Heim et al., 2019). Pregnant individuals with CA history have been found to have lower baseline levels of cortisol immediately after waking, an elevated cortisol awakening response (the rapid increase in cortisol levels occurring shortly after waking), and a flattened diurnal slope (slope of decreasing cortisol levels throughout the day) (Bublitz et al., 2014; Bublitz and Stroud, 2012a; Shea et al., 2007; Thomas et al., 2018; Thomas-Argyriou et al., 2020), as well as increased concentrations of cortisol in hair during mid- to late-pregnancy compared to pregnant individuals without a history of CA (Schreier et al., 2015a; Swales et al., 2018). Additionally, childhood sexual abuse may have more pronounced effects on HPA axis alterations than other adversities—pregnant individuals with a history of childhood sexual abuse showed increasing cortisol awakening responses throughout pregnancy when compared to pregnant individuals with histories of non-sexual childhood abuse and neglect, but diurnal slope did not significantly differ between groups (Bublitz and Stroud, 2012a). Maternal exposure to CA has also been associated with a steeper increase of pCRH during the third trimester of pregnancy (Moog et al., 2016b; Steine et al., 2020).

HPA axis functioning alterations during pregnancy frequently observed in relation to CA and opioid use are likely to mediate offspring developmental alterations. Elevated cortisol levels early in pregnancy are associated with a greater increase in pCRH during the third trimester of pregnancy (Sandman et al., 2006), and high concentrations of pCRH during the third trimester of pregnancy are associated with preterm birth and a more difficult infant temperament (Davis et al., 2005; Wadhwa et al., 2004). Furthermore, infants exposed to elevated maternal cortisol in late pregnancy show increased behavioral challenges and negative temperament beginning at 1 week old (de Weerth et al., 2003) and increased parent-

reported infant negative reactivity at 2 months of age (Davis et al., 2007). Interestingly, elevated maternal cortisol levels early in gestation were associated with slower and poorer offspring cognitive development throughout the first year of life, while elevated maternal cortisol levels late in gestation were associated with accelerated and more advanced cognitive development over the first year of life (Davis and Sandman, 2010). In one recent study, a flatter diurnal slope during the first and second trimesters of pregnancy was predictive of internalizing behavior in children AFAB and externalizing behavior in children AMAB at 4 years of age (Thomas-Argyriou et al., 2020). Additionally, higher average cortisol awakening response in individuals at any point in pregnancy mediated the association of maternal CA history with offspring internalizing, but not externalizing, problems at 4 years of age. Alterations to HPA axis activity that are typically observed in pregnant individuals with CA histories, particularly elevated cortisol levels and high late-gestation pCRH, appear to alter offspring developmental trajectories. Some evidence suggests that elevated cortisol during early-, mid-, and late-gestation differentially alters offspring development, but further research in this area will be needed to clarify these findings.

While it is challenging to definitively predict how maternal CA and opioid use during pregnancy may interact to alter maternal HPA axis functioning and subsequent offspring outcomes, both factors do appear to independently and uniquely alter maternal HPA axis activity. Given that the maternal HPA axis plays a prominent role in offspring neurodevelopment during pregnancy (Matthews, 2000), it will be important to investigate how prenatal opioid exposure may differentially alter fetal brain development in combination with frequently co-occurring factors, such as maternal CA, through alterations to maternal HPA axis fetal programming.

3.3 - Inflammation

Both opioid use and CA have repeatedly been shown to influence immune system functioning, and specifically to contribute to a pro-inflammatory phenotype in adulthood (Baumeister et al., 2016; Buchanan et al., 2010; Hutchinson et al., 2011; Lacagnina et al., 2017; Wang et al., 2012; Zhang et al., 2020), which appears to persist during pregnancy (Boeck et al., 2016; Moog et al., 2016a). Emerging preclinical data have shown non-neuronal actions of opioids on glial cells that activate pro-inflammatory cascades, including: elevated tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin 1 beta (IL1-β), interleukin 6 (IL-6), chemokine ligand 4 (CCL4), chemokine ligand 16 (CCL16) (Buchanan et al., 2010; Hutchinson et al., 2007; Wang et al., 2012; Zhang et al., 2020). Furthermore, heightened systemic inflammation secondary to exogenous opioids may create a feedback loop with neuroinflammation leading to increased opioid-seeking behavior. Specifically, opioid-induced activation of glial cells appears to enhance the analgesic and rewarding effects of opioids, and contribute to opioid tolerance (Arezoomandan et al., 2016; Bachtell et al., 2015; Hutchinson et al., 2012; Narita et al., 2006; Song and Zhao, 2001; Zhang et al., 2012).

In pregnant individuals, CA is associated with higher IL-6 and of CRP concentrations (Finy and Christian, 2018; Mitchell et al., 2018). These associations are partially moderated

by nutritional factors (Hantsoo et al., 2019a; McCormack et al., 2020) and depressive symptoms (McCormack et al., 2020; Walsh et al., 2016) and may be mediated by pre-pregnancy body-mass index (BMI) (Finy and Christian, 2018; Mitchell et al., 2018). A small study in pregnant individuals with gestational diabetes observed elevated IL-15 levels in association with a history of CA (Bublitz et al., 2017).

The potential for opioid use and maternal CA to independently lead to heightened maternal inflammation both preconception and during pregnancy has significant implications for programming offspring neurodevelopment. A host of animal and increasingly human literature have demonstrated the effects of heightened maternal inflammation during pregnancy on the developing fetal brain (Graham et al., 2018; Hantsoo et al., 2019b; Jantzie et al., 2020; Rasmussen et al., 2019; Rudolph et al., 2018; Yoon et al., 1997), infant and toddler socioemotional and cognitive development (Graham et al., 2018; Gustafsson et al., 2018; Rudolph et al., 2018), and subsequent risk for higher rates of neuropsychiatric disorders including schizophrenia, autism, ADHD, and obsessive-compulsive disorder (Gustafsson et al., 2020; Hantsoo et al., 2019b). While direct transfer of pro-inflammatory cytokines across the placenta seems to be limited (Aaltonen et al., 2005), maternal immune activation may indirectly increase cytokine concentrations in the fetal compartment via placental cytokine production (Ashdown et al., 2006; Urakubo et al., 2001). Importantly, the same pro-inflammatory cytokines activated by exogenous opioids (IL-6 and TNF-α) and maternal CA (IL-6 and CRP) have been identified in studies linking maternal inflammation during pregnancy to offspring neurobehavioral development (Coelho et al., 2014; Graham et al., 2018; Gustafsson et al., 2018; Rudolph et al., 2018).

Beyond pathways involving maternal inflammation during pregnancy, exogenous opioid transfer across the placenta and the fetal blood-brain-barrier may influence fetal neuroinflammation through similar pathways as adults after the initial development of opioid receptors at 9-10 weeks of gestation (Byrnes and Vassoler, 2018; Farid et al., 2008; Gerdin and Lindberg, 1990; Griffiths and Campbell, 2015). In rodents, prenatal methadone exposure has been associated with heightened levels of systemic inflammation (TNF-α, IL-1β, IL-6, and chemokine CXC ligand 1 (CXCL1)) in pups at postnatal day 10 (roughly 40-42 weeks of postconceptional age in human neurodevelopment), but the majority of these markers returned to baseline at postnatal day 21 (roughly 9 months old in human neurodevelopment) (Jantzie et al., 2020). However, heightened inflammation specifically in 21-day-old offspring brains prenatally exposed to methadone was evidenced by elevated cytokine levels (TNF-α, IL-6, toll-like receptor 4 (TLR4), and myeloid differentiation primary response protein (Myd88)), reduced glial cell branching, and differences in structural tract formation (Jantzie et al., 2020). While further research is needed in animal models and humans to better understand the pathways through which opioid use may influence maternal inflammation, MPF biology and ultimately offspring brain and immune system functioning, findings to date indicate multiple potential pathways for such effects.

Overall, these findings indicate the potential for a history of CA combined with both pre-pregnancy and pregnancy opioid use to result in a significantly heightened inflammatory state during pregnancy (Table 1). Although evidence of inflammatory changes in fetuses with maternal CA and exposed to opioids *in utero* is limited, findings of heightened

maternal inflammation during pregnancy and heightened offspring inflammation postnatally may imply heightened offspring inflammation during gestation as well. If fetal offspring exhibit increased inflammation during gestation, neurodevelopment *in utero* may be altered, including increased oligodendrocyte proliferation and differentiation (Filipovic and Zecevic, 2008). Given the strong evidence for effects of heightened inflammation during pregnancy on offspring neurodevelopment and risk for psychiatric disorders, future research investigating the cumulative and interactive effects of maternal CA and opioid use on maternal inflammation during pregnancy represents a priority for future research.

3.4 - Oxidative stress

Given that oxidative stress and pro-inflammatory processes are highly interconnected mechanisms of pathology, it is not surprising that alterations in mitochondrial biology and increased oxidative stress markers have been observed in individuals exposed to CA and prenatal opioid exposure. Oxidative stress is a term used to describe a pronounced imbalance in oxidation-reduction homeostasis beyond normal redox signaling (Sies et al., 2017). Under typical physiological conditions, the mitochondrion produces a small amount of reactive oxygen species (ROS) which are counteracted by enzymatic defense mechanisms. Mitochondrial damage (e.g. fragmentation) may lead to an imbalance in ROS production and antioxidant defense capacity resulting in further cell-damaging oxidative stress (Gyllenhammer et al., 2020; Hoffmann and Spengler, 2018). The deleterious consequences of oxidative stress may include an increase in nucleic acid mutations, amino acid and protein damage, endoplasmic reticulum (ER) stress, and cell death, as well as numerous pathologies including cardiovascular disease, cancer, neurodegenerative disease, inflammatory disease, and viral infections (Sies et al., 2017). Individuals using opioids demonstrate evidence of oxidative stress (Awadalla and Salah-Eldin, 2016; Fan et al., 2015; Faria et al., 2016; Zhuo et al., 2012), likely resulting from mitochondrial impairment (Cunha-Oliveira et al., 2008; Faria et al., 2016; Mohamed et al., 2015; Zhuo et al., 2012).

Preclinical studies show a direct link between prenatal opioid exposure and elevated markers of oxidative stress in offspring brains throughout development (Aboulhoda and Hassan, 2018; Guzmán et al., 2006; Hung et al., 2013). Similarly, animals administered opioids were found to have increased ROS production, oxidative stress, and mitochondrial activity and density (Cunha-Oliveira et al., 2008; Faria et al., 2016; Mehdizadeh et al., 2017; Mohamed et al., 2015; Zhuo et al., 2012). Human adults AFAB with direct CA exposure showed increased ROS production, oxidative stress, and mitochondrial activity and density outside of the perinatal period (Boeck et al., 2016).

Similar signs of elevated oxidative stress were observed in association with preconception CA. The amount of mitochondrial DNA (mtDNA) in peripheral blood mononuclear cells or buccal cells is an indicator of the quality or health of mitochondria when considered with mitochondrial functional capacity, which has implications for oxidative stress (Picard et al., 2018). In two studies, mtDNA levels were observed to be increased in association with CA (Cai et al., 2015; Tyrka et al., 2016), but in one of these the alterations in mtDNA were contingent on presence of depressive state (Cai et al., 2015), and another study did not replicate these findings (Cai et al., 2020). During pregnancy, maternal stress and particularly

lifetime stress have been associated with reduced placental mtDNA content (Brunst et al., 2017) and differential expression of protein-coding mitochondrial genes in the placenta, which, in turn was associated with a more difficult infant temperament (Lambertini et al., 2015). However, the amount of mtDNA alone may not be a good indicator of mitochondrial quality or health without any information on mitochondrial functional capacity (Picard et al., 2018). Boeck et al. (2016) investigated mitochondrial functioning in individuals AFAB exposed to CA and observed a dose-response association with higher ROS production, higher oxidative stress and increased mitochondrial activity. Extending on this work, the same group demonstrated increased mitochondrial activity and density in individuals with CA shortly after parturition compared to controls (Gumpp et al., 2020), an association that was also observed 3 months postpartum, however, only in participants with high concentrations of cortisol (Boeck et al., 2018).

Animal studies demonstrate multiple deleterious brain outcomes associated with prenatal exposure to stress-induced oxidative stress, including cognitive impairment, dopamine D1 receptor dysfunction (D1DR), dysregulated N-Methyl-D-aspartate (NMDA) synaptic currents, neural apoptosis (especially in the hippocampus), and impaired long-term potentiation in CA1 (Cao et al., 2014; Giussani et al., 2012; Lu et al., 2013; Wang et al., 2014). Maternal oxidative stress appears to be indirectly associated with fetal oxidative stress through the reduction of placental perfusion and intrauterine increases in glucocorticoids and cytokines (Rakers et al., 2017). The increases in fetal oxidative stress, inflammation, and HPA axis activity all appear to contribute to the increased chances of offspring neurodevelopmental impairments associated with maternal oxidative stress and mitochondrial dysfunction (Buss, 2021; Graham et al., 2019, 2018). In addition to indirect effects of maternal mitochondrial biology on the developing fetus via alterations in placental function, stress hormone concentration, or pro-inflammatory processes, maternal mitochondria are physically passed from the oocyte to the zygote and thus directly influence offspring mitochondrial biology which may confer long-term effects on health and disease risk (Gyllenhammer et al., 2020). Thus elevations in oxidative stress during pregnancy, to which both maternal CA and opioid use may contribute, represent an important potential pathway for influencing offspring neurodevelopment.

3.5 – Epigenetics

Prenatal opioid exposure and maternal CA both have potential to influence offspring brain development via epigenetic mechanisms. Epigenetics refers to environmentally-induced alterations to gene expression through modification of DNA methylation and histone tails, chromatin structure, non-coding RNAs (i.e. microRNAs), and transposable elements (Jirtle and Skinner, 2007; Murrell et al., 2005; Slotkin and Martienssen, 2007, 2007; Wolffe and Matzke, 1999). While parental epigenetic marks are almost fully erased after fertilization (Seisenberger et al., 2012), some gene loci survive this methylation reprogramming, introducing the possibility of intergenerational and transgenerational transmission of epigenetic changes (Anway et al., 2005; Branco et al., 2016; Lane et al., 2003; Morgan et al., 1999; Radford, 2018; Rakyan et al., 2003; Sanchez-Delgado et al., 2016; Smallwood et al., 2011; Smith et al., 2012). As previously discussed, gestation represents a critical window in which developmental trajectories are more susceptible to changes in response to

environmental conditions through multiple pathways, including via epigenetic modifications (Jirtle and Skinner, 2007). Here we first discuss direct epigenetic alterations, which may occur in the fetus during gestation in response to biological cues from an MPF environment affected by opioid exposure and maternal CA. Second, we examine potential intergenerational inheritance of parental epigenetic changes in response to opioid use and preconception CA that may survive zygotic reprogramming and persist in offspring.

In utero opioid exposure is associated with offspring epigenetic modifications with implications for withdrawal symptoms shortly after birth (NOWS) and long-term development. Maternal exposure to morphine during the preconception, prenatal, and lactation periods in rats was associated with reduced hippocampal synaptic plasticity in rat offspring, with potential implications for offspring learning and memory abilities (Sarkaki et al., 2008). In humans, opioid-exposed neonates have increased methylation of adenosine triphosphate (ATP)-binding cassette sub-family B member 1 (ABCB1), cytochrome P450 family 2 subfamily D member 6 (CYP2D6), and the MOR gene in comparison to opioid-naïve neonates (McLaughlin et al., 2017). These genes are important for basic cellular and neurological function, in addition to the metabolism of opioids and other substances (Gaedigk, 2013; Hodges et al., 2011; Valentino and Volkow, 2018). Additionally, hypermethylation patterns on the MOR gene of human neonates exposed to opioids *in utero* were associated with greater severity of withdrawal symptoms at birth (Wachman et al., 2014), but this finding has not been consistently replicated (McLaughlin et al., 2017). These alterations reported in offspring with prenatal opioid exposure do demonstrate epigenetic modifications in this population. However, the exact mechanisms of these epigenetic alterations remain unclear. Additionally, the role of co-occurring prenatal environmental influences continues to complicate clinical studies in this area and will need to be considered in future research.

Telomeres, DNA-protein complexes which prevent chromosomal damage and maintain genomic stability (Blackburn, 2005), are of particular interest for tracking intrauterine epigenetic alterations and intergenerational epigenetic inheritance associated with offspring neurodevelopment. Telomere length is epigenetically altered throughout the lifespan in response to aging and environmental exposures, and shorter telomere length is associated with multiple psychiatric disorders (Lindqvist et al., 2015) and other health conditions (Zhu et al., 2011). The epigenetic regulation of fetal telomere length appears to begin *in utero* with input from stress-sensitive oxidative, immune, endocrine, and metabolic pathways in the MPF environment, and shorter telomere length at birth appears to increase risk for long-term adverse outcomes (Entringer et al., 2018). These findings suggest that both prenatal opioid exposure and maternal CA have potential to alter offspring telomere length *in utero* through several of the MPF pathways previously discussed.

Furthermore, epigenetically-altered parental telomere length appears to program zygote telomere length through both parental germ lines, suggesting that preconception parental exposures may alter offspring telomere length through intergenerational epigenetic inheritance (Bauch et al., 2019; Delgado et al., 2019; Factor-Litvak et al., 2016; Olsson et al., 2011). CA in particular is associated with shorter telomere length throughout the lifespan (Blaze et al., 2015; Kiecolt-Glaser et al., 2011; Li et al., 2017; Ridout et al., 2018), which

may be transmitted to offspring. Telomere length was shorter in 4-, 12-, and 18-month-old infants with maternal CA history, which corresponded to offspring externalizing problems at 18 months while controlling for prenatal stress and maternal depression (Esteves et al., 2019). While prenatal opioid exposure has not been examined in association with offspring telomere length, one study found that heroin use was associated with shorter telomere length in adults while controlling for psychiatric and physical comorbidities, stressful event exposures, age, sex, and smoking (Yang et al., 2013). This suggests a potential pathway through which preconception opioid use may alter offspring telomere length through intergenerational epigenetic inheritance. Future research will be needed to directly examine this pathway.

The majority of other studies investigating epigenetic inheritance through the germ line have been conducted in paternal germ cells. Limited evidence suggests that both adulthood opioid use and CA history may epigenetically alter human sperm (Chorbov et al., 2011; Roberts et al., 2018), but it is unclear if these alterations would survive post-fertilization methylation reprogramming. Additionally, several studies demonstrate that stress and fear may initiate epigenetic alterations to paternal germ cells in mice that are associated with offspring behavioral and physiological alterations (Dias and Ressler, 2014; Gapp et al., 2020; Rodgers et al., 2015, 2013).

While there is increasing evidence for true epigenetic inheritance via the paternal germ line, to our knowledge there is no study to date directly showing the inheritance of epigenetic marks of parental opioid use or CA via the maternal germ line. However, some animal studies provide indirect evidence for an epigenetic contribution to intergenerational effects of preconception maternal opioid use, demonstrating that offspring epigenetic alterations were associated with preconception maternal opioid administration (Byrnes et al., 2013; Vassoler et al., 2016). Several studies also indirectly suggest that epigenetic sequelae associated with maternal CA may be transmitted through oocyte alterations. Female rats that underwent chronic unpredictable stress in adulthood showed an increase in corticotropin releasing factor type 1 (CRF1) mRNA in the frontal cortex as well as in mature oocytes. The effects on brain CRF1 expression persisted into the next generation and were associated with behavioral abnormalities (Zaidan et al., 2013).

There does appear to be evidence that both prenatal opioid exposure and maternal (and paternal) CA have implications for epigenetic modifications in offspring, but much of the current evidence is not able to identify mechanisms for these modifications. Additionally, many of these findings lack a direct connection between epigenetic pathways of prenatal opioid exposure and maternal CA. However, epigenetic pathways of intergenerational CA appear to interact with other mechanisms influenced by prenatal opioid exposure, such as differential HPA axis functioning (Yehuda et al., 2014; Zaidan et al., 2013), highlighting the likelihood of complex, interactive effects with potential to influence offspring neurodevelopment. See Table 1 for a summary of findings related to pathways reviewed in Section 3.

4 – Conclusions and future directions

A substantial amount of research has been dedicated to understanding how *in utero* opioid exposure influences neurodevelopment due to the considerable increase in opioid use in recent decades. Our interpretation of the literature to date indicates some subtle alterations evident soon after birth following *in utero* opioid exposure, which may confer vulnerability to mood and anxiety disorders, differential social and reward processing, and learning and memory impairments. However, there is limited evidence that these behavioral and cognitive differences persist into early childhood or adulthood given that many of the findings appear to be completely or partially mitigated by differences in the postnatal environment (Ahmadalipour et al., 2015; Hartman and Belsky, 2018; O'Donnell and Meaney, 2016; Salzwedel et al., 2020). These findings are of particular interest because recent research in the area of prenatal programming has suggested that prenatal adversity does not program neurodevelopmental disorders, rather exposure to poorer circumstances during gestation may alter susceptibility to the influences of the postnatal environment, for better or for worse (Hartman and Belsky, 2018; O'Donnell and Meaney, 2016). However, much of our understanding comes from well-controlled animal research, which has acknowledged limitations, including cross-species differences in drug metabolism and gestational and neurodevelopmental timing, and challenges in approximating the multiple co-occurring risk factors typically accompanying opioid use during pregnancy in humans (Byrnes and Vassoler, 2018). Research in humans addressing effects of *in utero* opioid exposure on offspring neurodevelopment is limited due to small sample sizes and the challenges of addressing myriad commonly co-occurring pre- and postnatal factors with significant potential to influence offspring neurodevelopment.

Examining candidate mechanistic pathways by which opioids and commonly co-occurring factors may influence offspring brain development represents an important direction for future research in this area. We highlight maternal CA history as a common yet understudied potential influence on offspring neurodevelopment in the context of maternal opioid use during pregnancy. Our review identifies multiple overlapping mechanistic pathways for the influence of maternal opioid use during pregnancy and maternal CA history on offspring neurodevelopment. These are aspects of MPF biology with evidence supporting sensitivity to both exogenous opioids and maternal CA history, and potential for programming fetal neurodevelopmental processes. The identified mechanistic pathways include the endogenous opioid system, the HPA axis, the immune system, epigenetics, and oxidative stress (Table 1). We also note that this review is not exhaustive, and other shared candidate mechanisms for effects of prenatal opioid exposure and maternal CA history likely include metabolic and other endocrine pathways (Buss et al., 2017; de Vries et al., 2020). The existence of these overlapping mechanistic pathways has important implications for research and policy.

From a research perspective, the existence of multiple shared mechanistic pathways for effects of *in utero* opioid exposure and maternal CA history on neurodevelopment suggests strong potential for cumulative and interactive influences, which call into question the utility and meaning of research focusing exclusively on effects of opioid exposure on neurodevelopment. A more fruitful approach will likely involve assessment of opioid use during pregnancy along with maternal CA history and other historical, environmental, and

demographic factors. Examination of these factors in relation to candidate shared biological mechanisms for effects on fetal neurodevelopment represents an important first step in this research. Such work will require interdisciplinary expertise to facilitate assessment of maternal substance use, CA history, psychological and physical health, environment and demographics, as well as MPF biology. A second critical step in this work will involve use of neuroimaging tools that can be used to assess brain structure and function shortly after birth, including structural and functional MRI and electroencephalograms, to minimize confounding effects of postnatal environmental influences on neurodevelopment. More generally, but also particularly important in the case of multivariate analyses and neuroimaging research, larger sample sizes (up to several thousands (Marek et al., 2020)) will be needed to identify reproducible findings. Furthermore, longitudinal studies assessing a wide variety of potentially co-occurring factors during pregnancy that follow offspring into childhood and beyond will be important for better understanding the roles of co-occurring risk factors and predictive pathways to offspring outcomes in childhood.

Implications for future directions include the need to facilitate and support collaborative science, changing public policy for individuals using opioids, and improving the treatment and prevention of opioid use in this population. Bringing together the necessary resources and expertise to recruit large samples of high risk, frequently stigmatized populations, while thoroughly assessing complex environmental, psychological, and biological systems, will be important next steps in this area of research. The heterogeneity of factors affecting offspring brain development in pregnant individuals using opioids, and the difficulty of disentangling these factors with the current scientific literature, also has implications for public policy, treatment, and prevention in this population. Many individuals are still penalized for using opioids during pregnancy and face high levels of societal pressure and stigma (Krans and Patrick, 2016; Patrick et al., 2017). Further, we acknowledge that the opioid crisis has received increasing resources, attention, public sympathy, and decriminalization as its demographics have shifted toward a primarily white population (Cicero et al., 2014; Hansen et al., 2020; Santoro and Santoro, 2018). White individuals are overrepresented in the opioid-misusing population because of two primary factors: 1) opioid prescriptions have fueled increasing nationwide opioid use in recent decades (Volkow and Blanco, 2021), and 2) Black, Indigenous, and People of Color (BIPOC) are less likely to receive opioid prescriptions due to racial biases among prescribers and reduced access to healthcare (Hansen et al., 2020; Om, 2018; Santoro and Santoro, 2018). The opioid epidemic is a great public health concern deserving of the resources it has been given; however, we acknowledge that many other current and historical public health crises primarily affecting marginalized populations in the United States have not received appropriate public and legislative support (Hardeman et al., 2018; Montoya-Barthelemy et al., 2020; Tester, 2017).

This review highlights findings indicating that individuals with CA experience long-lasting consequences that not only increase their risk of opioid abuse (Austin and Shanahan, 2018; Derefinko et al., 2019; Merrick et al., 2020; Savulich et al., 2017), but have implications for offspring neurodevelopment, and potential to exacerbate effects of *in utero* opioid exposure through shared mechanistic pathways. Further research in this area has potential to inform policy focused on ameliorating the negative sequelae of the opioid epidemic for the next generation by elucidating the biological programming potential of factors

co-occurring with opioid use, which may frequently be conceptualized as less relevant for offspring neurodevelopment. Such work has important implications for determining the extent to which resources will be devoted to making evidence-based trauma treatment readily available and increasing accessibility of trauma-informed treatment for pregnant individuals using opioids (SAMHSA, 2016). Long-term goals include increasing community resources and access to appropriate care, while supporting the most vulnerable members of our population.

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Highlights

- Opioid-using pregnant individuals are often affected by many co-occurring risk factors
- Disentangling effects of prenatal opioid use from co-exposures is challenging
- Prenatal opioid use and maternal CA affect fetal brains through similar pathways

Table 1.

Common mechanistic pathways of influence for maternal opioid use during pregnancy and maternal CA on offspring brain development.

	Prenatal opioid exposure		Maternal CA	
Pathways	***Main Findings***	***Population studied***	***Main findings***	***Population studied***
Endogenous opioids	↓ MOR expression in midbrain	Rats on PND1 prenatally exposed to oxycodone (Vassoler et al., 2018)	↓ MOR expression in spinal cord and hyperalgesia	Non-stressed male offspring of female rats exposed to chronic stress post-weaning through adulthood (Hormozi et al.,2018)
	↓ MOR binding in spinal cord	Rats in early postnatal period prenatally exposed to opioids (Chiou et al., 2003; Kirby, 1983)	↓ MOR expression in spinal cord	Adult male rats exposed to chronic stress post-weaning through adulthood (Hormozi et al., 2018
			↓ MOR mRNA in NAc	Neonatal rats exposed to predator odor (Chang et al., 2019)
	↓ MOR density in striatum, thalamus, amygdala		↓ MOR mRNA in PAG	Adult mice exposed to CA (Nakamoto et al., 2020)
	↓ MOR binding and expression in whole brain		↑ MOR mRNA in NAc	Juvenile rats exposed to neonatal predator odor (Chang et al., 2019)
	↓ MOR binding in MPOA	Adult rats prenatally exposed to morphine (Vathy et al., 2003)	↓ expression of KOR in the PAG and lateral habenula	Adult rodents exposed to CA (Nakamoto et al., 2020; Simmons et al., 2020)
	↓ MOR binding in BLA	Adult male rats prenatally exposed to morphine (Šlamberová et al., 2005)		
	↑ MOR binding in spinal cord	Adult rats prenatally exposed to morphine (Bhat et al., 2006; Kirby, 1983; Vathy et al., 2003)	↓ expression of KOR in NAc	Neonatal rats exposed to predator odor (Chang et al., 2019)
	↑ MOR binding in CeA, PMCoA, and NAc		↑ expression of KOR in amygdala	Adult mice exposed to CA (Nakamoto et al., 2020)
	↑ MOR binding and expression in whole brain		↑ dynorphin-dependent KOR activation in the basolateral amygdala, NAc, dorsal raphe, and hippocampus	Adult mice exposed to chronic stress (Land et al., 2008)
	↑ MOR density in hippocampus	Female adult rats prenatally exposed to morphine (Šlamberová et al., 2003)	↑ inhibition of DA release (suggesting ↑ KOR sensitivity)	Adult rats exposed to CA (Karkhanis et al., 2016)
	↑ KOR binding in POA	Adult ovariectomized female rats prenatally exposed to morphine (Rimanóczy et al., 2001)	↓ DOR mRNA in PAG	Adult mice exposed to CA (Nakamoto et al., 2020)
	↑ endogenous opioid release (substantia nigra, piriform cortex, septum)	Adult rats exposed to morphine during gestation (Buisman-Pijlman et al., 2009b)	↑ DOR mRNA in NAc	Juvenile rats exposed to neonatal predator odor (Chang et al., 2019)
			↑ dynorphin levels in lateral habenula	Rats across development that were exposed to CA (Simmons et al., 2020)
			↓ cortisol increase in response to naltrexone (suggesting ↓ endogenous opioid signaling)	Adult individuals AFAB exposed to CA (Lovallo et al., 2018)

Pathways	Prenatal opioid exposure		Maternal CA	
	Main Findings	***Population studied***	***Main findings***	***Population studied***
			↓ morphine antinociception ↓ HPA axis response to naltrexone	Adult mice exposed to CA (Nakamoto et al., 2020) Humans AFAB with preconception CA compared to humans AFAB unexposed to CA (Lovallo et al., 2018)
HPA axis	↑ glucocorticoid levels	Pregnant rats administered daily morphine compared to opioid-naïve pregnant rats	↓ baseline cortisol immediately after waking	Pregnant humans with CA history (Bublitz et al., 2014;Bublitz and Stroud, 2012b; Shea et al., 2007; Thomas et al., 2018; Thomas-Argyriou et al., 2020)
			↑ cortisol awakening response	
			Flattened diurnal cortisol slope	
			↑ hair cortisol concentrations	Individuals in mid- to late-pregnancy (Schreier et al., 2015b; Swales et al., 2018)
	↑ maternal cortisol correlated with ↓ offspring NOWS	Pregnant humans using opioids (Wachman et al., 2020)	Steeper increase of pCRH during third trimester of pregnancy	Pregnant humans in third trimester (Moog et al., 2016a; Steine et al., 2020)
	Mixed effects of prenatal opioid exposure on offspring HPA axis activity	Animals prenatally exposed to opioids (Byrnes and Vassoler, 2018)		
Immune	↑ systemic TNF-α, IFN-γ, IL1-β, IL-6, IL-10, CCL4, CCL16 via opioid interaction with TLR4-MD2-LPS complex	Animals administered opioids (Buchanan et al., 2010; Hutchinson et al., 2007; Wang et al., 2012; Zhang et al., 2020)	↑ serum CRP	Pregnant individuals with CA (Finy and Christian, 2018; Mitchell et al., 2018)
	↑ opioid-seeking behavior after opioid activation of glial cells	Adult rodents administered opioids (Arezoomandan et al., 2016; Bachtell et al., 2015; Hutchinson et al., 2012; Narita et al., 2006; Song and Zhao, 2001; Zhang et al., 2012)	↑ serum IL-6	
	↑ systemic TNF-α, IL-1β, IL-6, CXCL1	10-day-old rats prenatally exposed to morphine (Jantzie et al., 2020)	↑ serum IL-15	Pregnant individuals with gestational diabetes and a history of CA (Bublitz et al., 2017)
	↑ systemic IL-1β, no difference in TNF-α, IL-6, CXCL1	21-day-old rats prenatally exposed to morphine (Jantzie et al., 2020)		
	↑ brain TNF-α, IL-6, TLR4, and Myd88			
	↓ glial cell branching			
Oxidative stress	↑ oxidative stress	Offspring prenatally exposed to opioids across development (Aboulhoda and Hassan, 2018; Guzmán et al., 2006; Hung et al., 2013)	↑ ROS production associated with ↑ oxidative stress and ↑ mitochondrial activity	Non-pregnant individuals with CA exposure compared to unexposed controls (Boeck et al., 2016)
	↑ oxidative stress and mitochondrial damage	Animals administered opioids (Cunha-Oliveira et al., 2008; Faria et al., 2016; Mehdizadeh et al., 2017; Mohamed et al., 2015; Zhuo et al., 2012)	↑ mitochondrial activity and density	Individuals with CA exposure shortly after parturition compared to unexposed controls (Gumpp et al., 2020)
			↓ reduced placental mtDNA content associated with ↑ stress	Pregnant individuals (Brunst et al., 2017)

Pathways	Prenatal opioid exposure		Maternal CA	
	Main Findings	***Population studied***	***Main findings***	***Population studied***
			during pregnancy and ↑ lifetime stress	
			No changes found in mitochondrial respiration or density	Neonates with maternal CA exposure compared to unexposed controls (Gumpp et al., 2020)
Epigenetics	↓ hippocampal synaptic plasticity	Rat offspring during puberty exposed to maternal preconception, prenatal, and lactation morphine (Sarkaki et al., 2008)	Epigenetic alterations to paternal germ lines (methylation and sncRNA)	Paternal germ lines of male mice exposed to chronic stress/ odor-paired fear conditioning (Dias and Ressler, 2014; Rodgers et al., 2013), and humans exposed to childhood abuse (Roberts et al., 2018)
	↑ methylation of ABCB1, CYP2D6, MOR mRNA	Human neonates prenatally exposed to opioids (McLaughlin et al., 2017)	Lower glucocorticoid receptor sensitivity	Adult offspring of AMAB Holocaust survivors (Yehuda et al., 2014)
			↑ methylation of the NR3C1 promotor region	
	↓ telomere length	Human adults with chronic heroin exposure (Yang et al., 2013)	↓ telomere length	4-, 12-, and 18-month-old infants with maternal CA history (Esteves et al., 2019)
			↑ CRF1 mRNA in the frontal cortex	Offspring of female rats that underwent chronic unpredictable stress in adulthood (Zaidan et al., 2013)
			↑ CRF1 expression	Female rats exposed to chronic unpredictable stress and their offspring (Zaidan et al., 2013)

Abbreviations: adenosine triphosphate (ATP)-binding cassette sub-family B member 1 (ABCB1), assigned male at birth (AMAB), assigned female at birth (AFAB), bilateral amygdala (BLA), childhood adversity (CA), chemokine ligand 4 (CCL4), chemokine ligand 16 (CCL16), central amygdaloid nuclei (CeA), corticotropin releasing factor type 1 (CRF1), corticotropin releasing hormone (CRH), chemokine CXC ligand 1 (CXCL1), cytochrome P450 family 2 subfamily D member 6 (CYP2D6), Dopamine (DA), δ-opioid receptor (DOR), early life stress (ELS), hypothalamic-pituitary-adrenal (HPA), interferon gamma (IFN-γ), interleukin 1 beta (IL1-β), interleukin 6 (IL-6), interleukin 10 (IL-10), interleukin 15 (IL-15), κ-opioid receptor (KOR), lipopolysaccharide (LPS), medial preoptic area (MPOA), mitochondrial DNA (mtDNA), μ-opioid receptor (MOR), myeloid differentiation protein 2 (MD2), myeloid differentiation primary response protein (Myd88), nucleus accumbens (NAc), nuclear-factor kappa-B (NF-κB), neonatal opioid withdrawal syndrome (NOWS), nuclear receptor subfamily 3 group C member 1 (NR3C1), periaqueductal gray (PAG), placental corticotropin releasing hormone (pCRH), posteromedial cortical amygdaloid nuclei (PMCoA), postnatal day (PND), preoptic area (POA), reactive oxygen species (ROS), tumor necrosis factor alpha (TNF-α), toll-like receptor 4 (TLR4).