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Neural, Hormonal, and Behavioral Development following Prenatal Stress Exposure

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Neural, Hormonal, and Behavioral Development Following Prenatal Stress Exposure

By

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M.A., Emory University, 2016

Advisor: Patricia A. Brennan, Ph.D.

An abstract of
a dissertation submitted to the Faculty of the
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Abstract

Neural, hormonal, and behavioral development following prenatal stress exposure

By Cassandra L. Hendrix

Exposure to adversity, such as childhood maltreatment and discrimination, as well as an individual's response to adversity (i.e., stress) increases risk for psychological illness, and may have intergenerational effects on an individual's offspring. The prenatal period has been identified as a sensitive time when the effects of maternal stress exposure may be transmitted to her fetus, having lifelong effects on development into the next generation. But what are the biobehavioral processes that are impacted by maternal stress exposure and how early in development can we identify these intergenerational effects? The present dissertation is composed of two studies that answer this question, focusing on behavioral and biological processes that underlie adaptive stress regulation. In Study 1, the influence of maternal adversity and psychological distress on infant behavioral adaptation to a stressor and infant diurnal cortisol is examined. Study 2 extends these findings by examining how neural circuitry that may underlie these regulatory processes is shaped by maternal stress in infants as young as 1 month old. Importantly, both studies consider stress during pregnancy as well as adversity from other sensitive times in the mother's life, such as her own childhood, in order to explore the novel hypothesis that a mother's early life stress exerts competing or additive effects on her child's development relative to prenatal stress. Moreover, these questions are examined in a sample of African American mother-infant dyads, a group that is disproportionately affected by intergenerational stress exposure. We found greater levels of late pregnancy maternal stress to predict less mature infant attention in the context of a mild stressor paradigm, which in turn predicted enhanced infant diurnal cortisol responsiveness (Study 1). Maternal experiences of discrimination and adversity from her own childhood also predicted heightened prenatal distress and conferred indirect influences on infant attention. The importance of maternal early life stress was further supported by Study 2 findings; maternal experiences of emotional neglect from her own childhood predicted stronger frontoamygdala neural connectivity in her 1-month-old infant, even after controlling for maternal reports of prenatal stress. Taken together, these findings indicate robust associations between maternal early life adversity and infant biobehavioral development and highlight the need to consider the intergenerational effects of maternal childhood adversity on the development of her child's stress regulation from the earliest stages of life.

Neural, hormonal, and behavioral development following prenatal stress exposure

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General Introduction

Exposure to stress is a transdiagnostic risk factor for a number of psychological and other health disorders, ranging from depression to cardiovascular disease. Stress can take many different forms, for instance poverty or interpersonal conflict, but can broadly be defined as the experience of being exposed to stimuli or situations (i.e., stressors) that are perceived as threatening and challenge one's ability to cope (Miller, Chen, & Zhou, 2007). It is important to differentiate stress, which is a response, from adversity, which is the stress-inducing experience (or the stressor). Stress may occur in the presence of an acute, short-term stressor or may be experienced for an extended period of time (the latter of which is known as chronic stress). Acute stress causes a number of transient biological changes, many of which are adaptive in the context of an imminent threat. Chronic stress, on the other hand, may lead to behavioral and neurobiological alterations which are less transient, and come with long-term health costs (McEwan, 2004). Chronic stress that occurs early in development may have particularly potent and long-lasting effects. It has been estimated that childhood adversity is associated with as many as 44% of all childhood-onset psychological disorders and 32% of all adult-onset psychological disorders, which highlights the important role early life stress plays in long-term healthy development (Green et al., 2010).

Stress may begin to shape development as early as *in utero*. Prenatal experiences program short as well as long-term adaptation to environmental deprivation or enrichment across multiple species (Kuzawa, 2008). Interest in similar fetal programming effects in humans began following observations that fetal growth (e.g., low birth weight) predicts adult disease over and above adult lifestyle factors such as exercise and diet (Barker, 1995; Godfrey & Barker, 2000). These initial findings and subsequent replications (Buss, Entringer, & Wadhwa, 2012; Hanson & Gluckman,

2008; Vickers, Breier, Cutfield, Hofman, & Gluckman, 2000) have led researchers to develop the developmental origins of health and disease (DOHaD) hypothesis (Barker, 1995), which posits that risk for certain diseases is at least partly programmed *in utero*. In the broader literature, this idea is often referred to as the fetal programming hypothesis.

Since the formal development of the DOHaD hypothesis, several other theoretical frameworks, and empirical evidence, have highlighted the prenatal period as a developmental stage during which the environment may have potent programming effects on offspring neurobiology (Charil, Laplante, Vaillancourt, & King, 2010; Harris & Seckl, 2011). For instance, maternal nutrition, immune functioning, and hormonal output during pregnancy can signal information to the fetus about the postnatal environment across multiple species, including mammals and amphibians (Kuzawa, 2008). Moreover, this information can sculpt offspring development, even after birth, to optimize likelihood of survival in the predicted environment. Indeed, there is growing evidence of prenatal influences playing a similar role in humans, though at times this adaptability may come at a cost (Sandman, Glynn, & Davis, 2013). Much research on this topic has focused on the shaping effects of maternal prenatal nutrition (Adair, Kuzawa, & Borja, 2001; McDade, Beck, Kuzawa, & Adair, 2001), but a growing body of evidence (e.g., Charil et al., 2010; Schechter et al., 2017; Scheinost et al., 2017; Schetter & Tanner, 2012) highlights prenatal stress as a defining factor that shapes offspring neurobiology and behavior. The present dissertation is composed of two studies that examine the influence of prenatal stress on infant stress functioning, a broad construct that is robustly tied to transdiagnostic psychological risk (Steinberg & Mann, 2020; Zorn et al., 2017). Moreover, the present studies additionally extend extant research by examining the intergenerational effects of maternal adversity that occurs outside of the perinatal period.

Potential mechanisms of prenatal stress programming

Among other mechanisms, maternal stress during pregnancy can impact fetal neurodevelopment by increasing exposures to circulating maternal stress hormones. Glucocorticoids such as cortisol readily cross the placental barrier (Howerton & Bale, 2012) and play a number of important roles in prenatal development, such as promoting lung maturation (Ward, 1994) and inhibiting cell proliferation in the fetus (Yehuda, Fairman, & Meyer, 1989). However, heightened or chronic exposure to cortisol can have deleterious effects (Charil et al., 2010). Cortisol not only decreases survival rates among newly formed synaptic connections, but also poses a risk to synaptic connections formed early in development (Hall, Moda, & Liston, 2015). For this reason, the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) converts a large amount of maternal cortisol to its inert form (cortisone) before it crosses the placenta, thereby protecting the fetus from excessive exposure to cortisol's damaging effects (Harris & Seckl, 2011). However, experimental nonhuman animal studies indicate that activity of 11β-HSD2 is inhibited by chronic maternal stress exposure, thus allowing greater levels of cortisol to cross the placenta and alter fetal development if the mother is stressed (Weinstock, 2008). The functional purpose of this stress-induced alteration in 11β-HSD2 is unknown, but one possibility is that increasing fetal exposure to glucocorticoids may prepare the fetus to survive or reproduce at a younger age in a stressful or unpredictable postnatal environment.

Other biological mechanisms additionally link maternal prenatal stress to fetal growth and neurodevelopment. First, increased stress may alter blood flow to the fetus, which may directly impact brain development (Bronson & Bale, 2016). Second, epigenetic changes may lead to differential expression of certain genes following prenatal stress exposure. In particular,

maternal perceived stress during pregnancy has been associated with increased methylation of the glucocorticoid receptor gene NR3CI, which decreases glucocorticoid receptor expression (Isgut, Smith, Reimann, Kucuk, & Ryan, 2017). This decreased expression of glucocorticoid receptors can desensitize the HPA axis to cortisol output, interrupting the negative feedback loop that regulates its activity. Third, heightened glucocorticoids following prenatal stress may interact with the GABA and dopaminergic neurotransmitter systems, which may then have downstream effects on fetal development (Braun et al., 2017). Together this growing body of research suggests multiple mechanisms by which prenatal stress can shape fetal development.

The fetal stage of development has also been proposed as a time when early life adversity *from the mother's childhood* may additionally be transmitted across generations (Buss et al., 2017; Keenan, Hipwell, Class, & Mbayiwa, 2018). Adversity during childhood puts mothers at heightened risk for depression, anxiety, and stress during pregnancy (Plant, Barker, Waters, Pawlby, & Pariante, 2013) which are in turn associated with altered stress reactivity in children (McGowan & Matthews, 2018). In addition to elevating mothers' risk for psychological illness or general distress during pregnancy, recent work suggests early life adversity may shape fetal development through other mechanisms as well. Maternal history of maltreatment has been linked to altered placental production of corticotrophin releasing hormone (Moog et al., 2016) and alterations in newborn brain morphology (Moog et al., 2018), above and beyond the effects of prenatal distress. This powerful link between adversity from the mother's own childhood with her infant's functioning is hypothesized to occur secondary to adversity-induced epigenetic, immune, and HPA axis alterations in the mother; each of these alterations impact the functioning and development of the intrauterine environment (Buss et al., 2017; Keenan et al., 2018). These findings raise the intriguing possibility that other experiences of maternal adversity *prior to the*

prenatal period may additionally program her infant's early development and potential psychological risk, both indirectly via increasing prenatal distress and directly by affecting the intrauterine environment. To-date, however, most research on the intergenerational impacts of maternal stress has focused exclusively on stress that occurs during pregnancy, and prospective longitudinal research is needed to clarify the relationships between maternal early childhood adversity, prenatal stress, and infant outcomes. The studies in this dissertation were designed to examine these associations, with a particular focus on infant stress functioning.

Neurobehavioral measures of stress functioning in infancy

Prenatal stress and infant HPA axis activity

Consistent with the DOHaD hypothesis and adaptive calibration model (Del Giudice, Ellis, & Shirtcliff, 2011), a number of studies have specifically linked prenatal stress exposure to future child stress responsivity. One of the most commonly examined measures of stress responsivity is activity of the hypothalamic pituitary adrenal (HPA) axis, whose end hormonal output is cortisol. Dysregulation of the HPA axis (most frequently measured via salivary cortisol levels) has been linked to a number of neuropsychiatric disorders, including depression (Burke, Davis, Otte, & Mohr, 2005) and schizophrenia (Walder, Walker, & Lewine, 2000), making it an outcome of particular interest to clinical scientists. Maternal prenatal stress (e.g., perceived stress, life events, cortisol output, anxiety) has been linked to altered offspring cortisol reactivity – or cortisol change in response to an acute stressor – at various developmental stages, from infancy (Pearson, Tarabulsy, & Bussières, 2015) to adulthood (Pluess & Belsky, 2011). In particular, prenatal stress exposure may sensitize the HPA axis to more readily respond to threat

in the postnatal environment in some individuals (Del Giudice et al., 2011) or to become more responsive to the postnatal environment more broadly, thereby increasing a child's susceptibility to environmental influences for better and for worse (Hartman & Belsky, 2018). Theoretically, such sensitivity may increase the likelihood of detecting potential threat, adapting to changing environmental demands, and surviving in a dangerous or unpredictable environment.

Cortisol can be used to assess varying HPA axis dynamics. Increases in cortisol following exposure to a stressor are believed to capture HPA axis reactivity while subsequent cortisol decreases tap into recovery of this system, or a return to homeostasis. The use of cortisol reactivity measures is controversial in infancy, with some researchers arguing that a hyporeponsive period (similar to that seen in rodents) prohibits the consistent activation of the HPA axis in early infancy, making it an unreliable measure at this stage of development (e.g., Martinez-Torteya et al., 2015). Yet other researchers have identified effects of acute stress on HPA axis reactivity in early infancy, usually in response to a vaccination or heel stick (Leung et al., 2010; Tollenaar, Beijers, Jansen, Riksen-Walraven, & de Weerth, 2011), so the presence of a hyporesponsive period in infancy remains controversial.

An alternative approach is to examine overall functioning or sensitivity of the HPA axis via examination of diurnal cortisol levels. Beginning in infancy and persisting through adulthood, cortisol output peaks early in the day (around 30 minutes after awakening) and follows a steady decline over the remainder of the day, which lowest levels of cortisol typically seen around bedtime (Adam et al., 2017). Diurnal variation in cortisol offers unique insight into the circadian rhythm and sensitivity of this system, and alterations in the circadian functioning of the HPA axis have been postulated to interfere with resilience of other physiological systems in the face of adversity (Rao & Androulakis, 2019). For example, flatter diurnal cortisol slopes are

linked to increased physiological aging, such as shorter telomere lengths (Tomiyama et al., 2012), and prospectively predict sleep problems into toddlerhood (Saridjan et al., 2017), which is a transdiagnostic risk factor for a wide array of psychological and health difficulties.

Although stress response systems are shaped over the course of a person's life and particularly across childhood (Engel & Gunnar, 2019), examining early markers of stress responsivity in infants may be helpful in understanding the beginning of developmental cascades that ultimately lead to psychological illness. Maternal prenatal distress (i.e., anxiety, depression, and perceived stress) has been linked to flatter diurnal cortisol slopes and a smaller cortisol awakening response (CAR) in adolescent offspring. Notably, this association is not present for paternal distress during the prenatal period, suggesting the intrauterine environment may be key in transmitting parental stress into the next generation (O'Donnell et al., 2013). Yet there remain significant gaps in our knowledge of the prenatal programming effects on HPA axis development. For instance, most of the work on prenatal stress and infant HPA axis activity to date has been completed in predominantly Caucasian samples. This is notable given that racial differences in diurnal cortisol output can be detected by middle childhood, with African American (AA) children demonstrating flatter diurnal slopes compared to Caucasian children, even after accounting for potential confounding variables like socioeconomic status (SES) and parenting (Martin, Bruce, & Fisher, 2012). Whether HPA axis activity shows similar race-based differences within the first year of life is unknown, and it is unclear whether the findings linking prenatal stress to diurnal HPA axis functioning – a finding consistently demonstrated in Caucasian, middle to high SES samples – can be replicated in AA samples (see section on "Stress and African American families" for additional discussion of this point).

Prenatal stress and infant behavior

Prenatal-stress induced offspring sensitivity may also be characterized by behavioral alterations. Carefully controlled animal work suggests a causal role for chronic maternal prenatal stress to lead to behavioral changes in offspring, including cognitive and learning deficits as well as increased anxiety and depressive-like behaviors (Glover & Hill, 2012). Correlational studies among humans generally suggest similar associations. Neonates born to women who experience chronic stress during pregnancy show an impaired ability to regulate their state (e.g., self-sooth) and have more difficulty orienting to and tracking objects compared to neonates who were prenatally exposed to low levels of maternal chronic stress (Rieger et al., 2004). Higher maternal cortisol during pregnancy has also been linked to heightened infant irritability (de Weerth, van Hees, & Buitelaar, 2003). A recent meta-analysis of 32 studies confirms these associations, revealing a small to moderate effect size of heightened maternal prenatal stress on impaired self-regulation and enhanced emotional reactivity in infants (Korja et al., 2017). Interestingly, there were few differences between types of stress exposure: that is, prenatal maternal depression, anxiety, perceived stress, and stressful life events all predicted greater reactivity and impaired regulation. Together these studies suggest that heightened maternal prenatal stress predicts more reactive infants who are less able to self-sooth. The impaired ability to track objects by these infants may also reflect decreased attentional control, which may interfere with subsequent cognitive and/or self-regulatory development.

Most studies on maternal prenatal stress and infant regulation include only one outcome measure (typically parent report or lab observation), and studies that use multiple measures do not necessarily find that different measures of regulation are correlated with one another (Korja, Nolvi, Grant, & McMahon, 2017). It is therefore necessary for future studies to combine multiple

measures of infant stress regulation, including both behavioral and neurobiological measures, in order to advance our understanding of converging and diverging effects of maternal prenatal stress across different levels of analysis.

A novel measure of stress functioning: neural connectivity

The brain undergoes rapid and dramatic changes across the prenatal period as neurogenesis, neural migration, axonal growth, dendritic branching, and synaptogenesis begin to lay the groundwork for complicated neural circuitry that will later be refined by postnatal experience (Weinstock, 2008). These dramatic and rapid changes render the brain particularly plastic, or susceptible, to environmental influence. Yet our knowledge of how prenatal stress shapes long-term brain development in humans remains limited (Lupien, McEwen, Gunnar, & Heim, 2009). Fortunately, recent advances in technology have now rendered it possible to study neural activity patterns following maternal prenatal stress exposure in human infant populations.

Magnetic resonance imaging (MRI) provides a safe, noninvasive method for examining brain development and can be conducted during natural sleep, making it an optimal technique to use with young populations who lack the cognitive and motor control required to stay still for prolonged periods of time, such as infants. Several infant neuroimaging studies have utilized structural MRI scans to understand the volumetric growth of specific brain regions with age (Thompson et al., 2008; Uematsu et al., 2012). Such studies are useful in understanding early development, but provide almost no knowledge about how brain regions may connect, or communicate, with one another. Importantly, animal and human neuroimaging studies have given rise to the hypothesis that neural connectivity (or the connections between brain regions) may be a sensitive measure of psychological risk (Drevets, Price, & Furey, 2008), and as such may be an important biological mechanism to assess early in development.

Resting-state functional MRI (rsfMRI) is therefore becoming an increasingly popular tool in the study of early development (Fox & Greicius, 2010). RsfMRI infers functional connectivity (FC) by correlating the spontaneous fluctuations in blood oxygen level dependent (BOLD) signals that occur over time. Regions whose BOLD signals co-vary positively or negatively together over time are believed to share functional connections with one another, with the strength of the correlation indicating the strength of the FC between regions. RsfMRI also provides the added benefit of being easily utilized with a wider array of populations, as it is absent of cognitive and physical task demands that may otherwise preclude very young or cognitively impaired populations from study participation. The absence of cognitive and physical task demands also makes rsfMRI a unique tool that can be used in comparative studies across species. This method further lends itself to multi-site collaborations and inclusion in large, publicly available datasets because rsfMRI data collected by independent research groups can more easily be combined (Fox & Greicius, 2010).

RsfMRI and task-based functional connectivity have also provided important insight into the neural circuitry that supports regulation in the face of acute stress as well as general emotion processing. In particular, these neuroimaging methods have repeatedly identified that frontoamygdala circuitry (i.e., the connection between the amygdala and prefrontal regions) plays a crucial role in emotional reactivity (Banks, Eddy, Angstadt, Nathan, & Phan, 2007), stress regulation (Veer et al., 2011, 2012), and psychological illness in childhood, adolescence, and adulthood (Hamilton et al., 2012; Kaiser et al., 2015; Kim, Gee, Loucks, Davis, & Whalen, 2011; Kim, Loucks, et al., 2011; Yoshimura et al., 2010). The medial prefrontal cortex (PFC) is well-known for its protracted development across childhood and adolescence as well as its role in top-down inhibitory processing (Casey, Tottenham, Liston, & Durston, 2005), while bottom

up neural projections from the amygdala to the mPFC underlie emotion and stress activation (Tottenham, 2019).

Moreover, the connection between these regions is sensitive to stress exposure that occurs during one's own life, with neurocircuitry involving the amygdala and mPFC being the most commonly studied target in neuroimaging studies on childhood adversity (McLaughlin, Weissman, & Bitrán, 2019). An abundance of studies clearly show an association between adversity and frontoamygdala structural and functional connectivity in childhood and adolescence, but the directionality of these effects are mixed, with childhood adversity being linked to both weakened *and* strengthened amygdala-mPFC connections (McLaughlin et al., 2019). Chronic stress, and particularly chronic experiences of deprivation, may lead to exaggerated pruning, which can lead to damaged, or impaired connections between brain regions (Hensch, 2005; McLaughlin, Sheridan, & Nelson, 2017). Yet there is also evidence that caregiver deprivation, a potent early life stressor, leads to accelerated development of frontoamygdala circuitry. Children who were previously institutionalized (and therefore lacking caregiver emotional support early in life) show a more mature connectivity pattern between the amygdala and mPFC that resembles that of adolescents (i.e., a negative instead of positive functional coupling, which is believed to represent more effective top-down control of amygdala activation) (Gee et al., 2013). Although this pattern may confer resilience in adulthood (Moreno-López et al., 2019), the premature development of this system during childhood may come with long-term psychological costs (Callaghan & Tottenham, 2016; Tottenham, 2019). Alterations of this circuitry in either direction (i.e., weakening or strengthening) may therefore confer risks during childhood. Alarmingly, there is growing evidence suggesting the negative effects of adversity can be transmitted across generations, with children of trauma-exposed mothers

showing increased risk for anxiety (Robinson, Hendrix, Krakovsky, Smith, & Brennan, 2019), a disorder that has been tied to altered frontoamygdala FC (Kim, Gee, et al., 2011). Yet the mechanisms for this intergenerational transmission remain unclear, and it is unknown whether adversity that occurred prior to a child's own life (i.e., during a parent's lifetime) exerts effects on frontoamygdala neural phenotypes.

Prenatal stress and neural connectivity

Despite the potential of these MRI methods and research linking childhood stress exposure to frontoamygdala development, surprisingly little research has examined the extent to which frontoamygdala circuitry is shaped by maternal stress during pregnancy. However, extensive research does suggest the amygdala and mPFC may individually be specific targets for the organizing effects of prenatal stress hormones. High numbers of glucocorticoid receptors in the amygdala increase its sensitivity to stress hormones during gestation (Weinstock, 2008), with animal models revealing that heightened prenatal stress (and subsequently heightened levels of stress hormones such as glucocorticoids) causally alters offspring amygdala structure (Hall et al., 2015). Similarly, chronic stress can impair mPFC functioning and structure (Henckens et al., 2015; McEwen & Morrison, 2013), and even milder forms of prenatal stress (i.e., placing a pregnant rodent on an elevated platform twice a day for 10 minutes) can yield similar effects on offspring mPFC development (Muhammad & Kolb, 2011). Although the extent to which carefully controlled animal studies generalize to human biobehavioral processes is often unclear, the extant research generally suggests that maternal prenatal stress in human samples yields neural effects on offspring that are similar to the alterations observed in model systems (Bock, Wainstock, Braun, & Segal, 2015). In humans, two studies in independent cohorts have found heightened maternal cortisol levels during pregnancy to predict larger amygdala volumes and

affective problems in preadolescent girls, but not boys (Buss, Davis, et al., 2012; Wen et al., 2017). Additionally, maternal usage of synthetic glucocorticoids during pregnancy and maternal depression during pregnancy both predict thinning of the prefrontal cortex in offspring during middle childhood (Davis, Sandman, Buss, Wing, & Head, 2013; Sandman, Buss, Head, & Davis, 2015).

It follows that these neuroanatomical alterations may impede their connectivity (Arnsten, 2009), but these effects are inconsistently reported. One study found the number of stressful life events endorsed by mothers during pregnancy to predict microstructural alterations in the uncinate fasciculus – a white matter tract that connects the amygdala to the prefrontal cortex – in 7-year-old children (Sarkar et al., 2014). Similarly, increased maternal cortisol across pregnancy has been linked to weaker resting-state FC between the amygdala and medial prefrontal cortex (mPFC) in 3-week-old neonates (Buss et al., 2015). However, research on maternal prenatal distress (which includes psychological illnesses like depression and anxiety as well as perceived stress) yields more mixed findings. One study found weakened amygdala-mPFC FC in neonates exposed to prenatal maternal depression (Soe et al., 2018), which is consistent with the aforementioned finding that heightened maternal prenatal cortisol is associated with weaker amygdala-mPFC connectivity (Buss et al., 2015). Other research suggests that maternal depression during pregnancy predicts *strengthened* amygdala-mPFC functional connectivity in neonates (Qiu et al., 2015). A third study found maternal depression to predict weaker amygdala resting-state FC with several areas, including the insula and hypothalamus, but did not find altered amygdala-mPFC connectivity in neonates (Scheinost et al., 2016). Given that cortisol dysregulation has consistently been identified in individuals with depression, these disparate

findings across studies are surprising and difficult to reconcile. Additional carefully conducted, prospective longitudinal studies are clearly needed.

One possibility is that these conflicting results are artefacts of the manner in which the mPFC was parcellated in analyses. The aforementioned studies all treat the mPFC as a unitary region despite research suggesting that different areas within the mPFC are functionally distinct (De La Vega, Chang, Banich, Wager, & Yarkoni, 2016) and may connect with the amygdala in different ways (Kim, Gee, et al., 2011). In neonates, at least one study suggests the amygdala shares negative FC with the dorsomedial PFC (dmPFC) but positive connectivity with the ventromedial PFC (vmPFC) while at rest, and that maternal prenatal depression is differentially associated with these circuits (Posner et al., 2016). Specifically, maternal depression predicted *increased* FC between the amygdala and dmPFC (i.e., the dorsal anterior cingulate cortex) and *decreased* FC between the amygdala and vmPFC in sleeping neonates (Posner et al., 2016). This pattern of results is consistent with the functional correlates of these circuits, as well as known behavioral correlates of maternal prenatal depression. Namely, amygdala-dmPFC connectivity and maternal depression are associated with heightened stress reactivity and child anxiety (Madigan et al., 2018; Posner et al., 2016; Rogers et al., 2016), while amygdala-vmPFC connectivity is linked to more effective emotion regulation (Etkin, Egner, & Kalisch, 2011; Moreno-López et al., 2019), a process impaired by exposure to maternal depression (Goodman, 2020). Averaging activity across these two regions – or using the same name for these regions in the absence of providing standard space coordinates – may obscure significant associations and lead to seemingly conflicting results across studies.

Another explanation for mixed findings regarding the impact of prenatal stress on frontoamygdala circuitry in the first few weeks of life is that different samples have differing

levels of stress exposure outside of the prenatal period, introducing a potentially important but unmeasured confound. Prenatal stress does not occur within a vacuum and many women who are stressed during pregnancy have likely experienced adversity at other times in their lives as well. Indeed, stress exposure prior to pregnancy may yield epigenetic alterations that impact the development of the intrauterine environment (Buss et al., 2017; Keenan et al., 2018). Yet none of the aforementioned studies assessed for or considered maternal stress prior to the prenatal period. Emerging evidence suggests that maternal experiences of maltreatment from her own childhood are linked to volumetric differences in her newborn's brain (Moog et al., 2016), even after controlling for prenatal stress. Such findings raise the intriguing question of whether certain experiences of maternal adversity – that are disproportionately experienced among certain groups of women – compound, or even override, the effects of prenatal stress on infant brain development. The present dissertation was designed to address this very question.

Stress among African American families

It is important to note that stress is often distributed in a manner that falls along socioeconomic, ethnic, and racial lines. Not only does stress contribute to an individual's health, it can also contribute to offspring health via developmental programming (as described above). AA infants are disproportionately at risk for infant mortality, low birth weight, and prematurity compared to European American infants (Austin & Leader, 2000; Giscombé & Lobel, 2005). Importantly, this difference is not explained by differences in SES (Alexander, Kogan, Himes, Mor, & Goldenberg, 1999; Berg, Wilcox, & d'Almada, 2001) or quality of prenatal care (Klerman et al., 2001). Instead, researchers have posited that differences in birth outcomes may

occur because AA fetuses are exposed to more stress (Hogue et al., 2013) and may be more sensitive to such stress (Simon et al., 2016) compared to Caucasians. Additionally, lifelong experiences of racial discrimination may increase accumulated physiological strain and stress sensitivity among AA women, which may impact the development of the intrauterine environment (Giscombé & Lobel, 2005). Despite social and health disparities experienced by this group, AA individuals are underrepresented in neuroscientific research on the effects of adversity. To date, only one published study has used MRI to examine infant brain development in an all AA sample (Betancourt et al., 2015).

Sample diversity and representativeness are integral to generalizing scientific findings to the broader population. In addition to the reasons stated above, examining brain development in ethnically and socioeconomically diverse samples is an important empirical pursuit because these factors may influence study findings (Falk et al., 2013). A recent study using analytical techniques from population science found that weighting a sample to better represent U.S. Census data changes associations between age and brain volumes, with a representative sample showing earlier brain maturation compared to the original convenience sample (which, among other differences, was of higher socioeconomic status and had a lower proportion of AA individuals than the general population; LeWinn, Sheridan, Keyes, Hamilton, & McLaughlin, 2017). Conducting developmental neuroimaging studies with diverse samples is essential in order to further advance our knowledge of early brain development.

The proposed project

An important area for growth in studies examining the intergenerational transmission of maternal stress is to examine whether adversity that occurs outside of the prenatal period also influences child development. Some research on maternal prenatal stress has controlled for maternal postnatal stress (Korja et al., 2017) or examined the interactive effects of prenatal and postnatal maternal stress on child stress functioning (Hartman & Belsky, 2018; Hartman, Freeman, Bales, & Belsky, 2018), and research is beginning to consider maternal stress that occurs during the preconception period, that is during the year leading up to pregnancy (Class et al., 2014; Class, Khashan, Lichtenstein, Långström, & D'Onofrio, 2013; Keenan et al., 2018). Yet there is a paucity of research that examines competing or additive effects of maternal prenatal stress and adversity that occurred earlier in a mother's life, for instance during her own childhood.

This dissertation project is composed of two studies that collectively examine the competing effects of maternal prenatal and early life stress (i.e., from her own childhood and from prior to pregnancy) on infant stress functioning across multiple levels of analysis. Both studies were conducted in AA samples using a prospective, longitudinal design. Study 1 examines competing, interactive, and mediational relationships between maternal early life adversity and prenatal stress on infant behavioral adaptation in the context of stress and infant diurnal cortisol. Study 2 expands this work by examining associations of maternal early life adversity and prenatal stress with neonatal frontoamygdala functional connectivity within 1 month of birth. Taken together, these multimodal studies provide novel insight into the intergenerational transmission of adversity from mothers to their children and the early development of biobehavioral processes that underlie stress regulation.

Prenatal distress mediates the association between maternal early life adversity and infant stress functioning

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Abstract

Maternal prenatal stress exerts powerful programming effects into the next generation. Yet it remains unclear whether and how prenatal stress interacts with adversity from other times in the mother's life to shape her children's stress functioning. In a sample of 217 African American mother-infant dyads, we examined whether different types of maternal stress were differentially related to her infant's stress functioning within the first few months after birth. We prospectively assessed maternal distress (perceived stress, depression, and anxiety) early and late in pregnancy, infant behavioral adaption in the context of a mild stressor at 2 weeks of age, and infant diurnal cortisol at 3-6 months of age as a marker of hormonal stress functioning. We additionally collected retrospective reports of maternal experiences of lifetime discrimination and childhood adversity. Maternal distress experienced late, but not early, in pregnancy predicted lower infant attention in the context of a stressor. Moreover, lifetime experiences of discrimination and experiences of adversity from the mother's own childhood indirectly impacted infant attention by increasing maternal distress late in pregnancy. These effects were specific to infant behavioral adaptation and were not related to infant diurnal cortisol levels. Our results highlight the specificity of late prenatal distress influencing infant stress functioning and underscore the cascading nature of stress across mothers' lifespan. Expanding our conceptualization of intergenerational stress effects to include maternal adversity that occurred prior to pregnancy is an important next step in understanding the impacts of maternal stress on both the developing stress response and long-term psychological risk in offspring.

Prenatal distress mediates the association between maternal early life adversity and infant stress functioning

Up to 30 percent of individuals meet criteria for at least one psychological illness over the course of their lifetime (Steel et al., 2014) and at least 45 percent of patients meet criteria for two or more disorders (Kessler, Wai, Demler, & Walters, 2005). Alarmingly, prospective research with a nationally representative sample (n>34,000) reveals almost all psychological disorders increase risk for unemployment, violence, and physical health problems (Blanco et al., 2019). This universal burden has increased interest in identifying *transdiagnostic* factors that influence risk for a wide range of psychological illnesses (Kessler et al., 2003). Identifying these transdiagnostic risk factors and understanding how they increase risk is an integral step in designing and implementing effective preventative interventions and ultimately decreasing the worldwide burden of psychological illness. Identifying these risk factors early in childhood may additionally facilitate interventions that can be implemented at younger ages when the developing brain is more sensitive to environmental influences.

The Developmental Origins of Health and Disease hypothesis (Barker, 1995), also known as fetal programming, postulates that transdiagnostic risk for negative health outcomes may begin as early as *in utero*, with certain prenatal factors programming postnatal development across the lifespan. Empirical research suggests that prenatal stress is one such factor that has long-term, clinically significant impacts on the development of psychological illness into adolescence and young adulthood (Glover, O'Donnell, O'Connor, & Fisher, 2018). Several mechanisms have been proposed to explain how prenatal stress shapes fetal brain development and ultimately psychological risk, including fetal exposure to cortisol – a glucocorticoid secreted by the hypothalamic pituitary adrenal (HPA) axis.

Activation of the HPA axis has been cited as one of the main biological mechanisms underlying the effects of prenatal stress on fetal development (Talge, Neal, & Glover, 2007). The HPA axis is stress-responsive, but under basal conditions, cortisol follows a diurnal pattern and is rhythmically released – with highest levels in the morning followed by steep decreases throughout the day. This diurnal profile has been cited as the best indicator of stress *regulation* (Liu, Rovine, Klein, & Almeida, 2013), as it captures both reactivity and recovery of the system. In healthy individuals with little stress exposure, the HPA axis follows a harmonious negative feedback loop, but when cortisol is chronically overproduced, the stress response system becomes dysregulated (Atkinson, Khoury, Ludmer, Jamieson, & Gonzalez, 2016; Kuras et al., 2017). A flatter diurnal slope can signify either a high (or exaggerated) awakening response that fails to recover over the course of the day or a less reactive (blunted) awakening response. In either case, this flattened slope represents restricted circadian variability and decreased sensitivity of this system. Flatter diurnal slope during pregnancy has been associated with more negative infant behavior shortly after birth (Braithwaite, Murphy, Ramchandani, & Hill, 2017), alterations in the child's biological stress systems during adolescence (Van Den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008), and differences in the development of brain regions that underscore psychological risk, such as the amygdala, by middle childhood (Buss, Davis, et al., 2012).

In addition, adversity during earlier periods of the mother's life may also impact offspring fetal development and confer transdiagnostic risk. More specifically, evidence suggests that adversity during childhood puts mothers at heightened risk for depression, anxiety, and stress during pregnancy (Plant, Barker, Waters, Pawlby, & Pariante, 2013) which are in turn associated with altered biological and behavioral stress responses in their children (McGowan &

Matthews, 2018). In fact, one recent study demonstrated the association between maternal childhood adversity and child psychological problems may be mediated by higher prenatal awakening cortisol levels (Thomas-Argyriou, Letourneau, Dewey, Campbell, & Giesbrecht, 2020). The totality of evidence therefore supports a process model by which early life adversity makes mothers more vulnerable to psychological distress during pregnancy, which has important implications for fetal and child development.

In addition to elevating mothers' risk for psychological illness or stress during pregnancy, recent evidence suggests early life adversity may shape offspring fetal development through other mechanisms as well. Maternal history of maltreatment has been linked to altered placental production of corticotrophin releasing hormone (Moog et al., 2016) and alterations in newborn brain morphology (Moog et al., 2018) and connectivity (Hendrix et al., in preparation), above and beyond the effects of maternal prenatal distress. This powerful link between adversity from the mother's own childhood and her infant's functioning is hypothesized to occur secondary to adversity-induced epigenetic, immune, and HPA axis alterations in the mother; each of these alterations impact the functioning and development of the intrauterine environment (Buss et al., 2017). These findings raise the intriguing possibility that other experiences of maternal adversity *prior to the prenatal period* may additionally program an infant's early development and potential psychological risk, both indirectly via increasing maternal prenatal distress and directly by affecting the intrauterine environment. To-date, however, most research on the intergenerational impact of maternal stress has focused exclusively on stress that occurs during pregnancy, and prospective longitudinal research is needed to clarify these relationships.

Perhaps unsurprisingly, maternal prenatal stress does not predict adverse outcomes in all children. This is partly attributable to the vast heterogeneity in the types of stress – for example,

acute versus chronic stressors (McEwen, 2004) – and in timing of stress. Within pregnancy, there may be certain sensitive periods in which maternal stress is especially likely to exert programming effects. For instance, stress during the late 2nd or early 3rd trimester is consistently linked to increased infant negative affective reactivity and impaired regulation abilities, while 1st trimester adversity is not (Korja et al., 2017). A prospective, population cohort study from Sweden also found that bereavement stress during the early 3rd trimester is linked to increased offspring risk for Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder, but there is no association with these outcomes when the same stressor occurred in the year leading up to pregnancy, early in pregnancy, or in the first two years postpartum (Class et al., 2014). Interestingly, during the late 2nd and early 3rd trimester is when brain regions that are involved in emotion regulation, such as the amygdala, are developing rapidly (Ulfig, Setzer, & Bohl, 2006) and therefore may be especially sensitive to the programming effects of maternal prenatal stress.

Inconsistencies in the intergenerational impacts of prenatal stress may additionally be explained by individual differences in maternal sensitivity to stress exposure. Certain mothers may be particularly sensitive to stress that occurs during pregnancy, and their fetuses may also be more likely to experience programming effects by extension. In addition to genetic predispositions, stress sensitivity can be altered over the course of an individual's life as a consequence of certain adverse experiences. Among the first to document this phenomenon was Hammen and colleagues (2000), who compared the association between stressful life events and subsequent depression in individuals with and without a history of childhood adversity. Among individuals who experienced significant childhood adversity, lower levels of stress were required to evoke a depressive episode compared to individuals who did not experience childhood adversity. The authors described this phenomenon as stress sensitization and posited that

experiencing traumatic and adverse events early in life can sensitize individuals such that they are more vulnerable to the effects of subsequent stress exposures (Hammen, Henry, & Daley, 2000). The sensitizing effects of early life adversity have been replicated in large population cohorts and across a number of psychological disorders (McLaughlin, Conron, Koenen, & Gilman, 2010). However, it is unclear whether stress sensitization contributes to the *intergenerational* transmission of risk for psychological illness. Given the dearth of studies in this area, research is needed to examine how child development is shaped by maternal experiences of adversity during childhood, preconception, and the prenatal period.

Research with under-studied, high risk groups is important for parsing apart the intergenerational transmission of adversity. Stress is often disproportionately distributed across socioeconomic and racial lines, with 40 percent of African American (AA) women experiencing significant adversity during childhood (Koenen, Roberts, Stone, & Dunn, 2010). Nearly 25 percent of AA women live in poverty (Proctor, Semega, & Kollar, 2016), an environmental circumstance that is closely linked with chronic stress exposure (Morrison Gutman, McLoyd, & Tokoyawa, 2005), compared to the 9 percent of European American women who live below the poverty line (Tucker & Lowell, 2015). Finally, AA women experience high levels of racial discrimination in the United States (Krieger, Smith, Naishadham, Hartman, & Barbeau, 2005), which is a uniquely potent stressor that is linked to heightened risk for a wide array of psychological and health disorders (Pieterse, Todd, Neville, & Carter, 2012), even after accounting for differences in health-related behaviors (e.g., diet, smoking) and socioeconomic status (Berger & Sarnyai, 2015). Like maternal childhood adversity, discrimination appears to have physiological consequences, as studies have demonstrated associations between perceived

discrimination and flatter diurnal cortisol slope (Busse, Yim, Campos, & Marshburn, 2017); once under the skin, discrimination may confer risk to future generations.

Taken together, it is clear that AA women are more likely to experience multiple types of adverse life experiences, and evidence suggests this elevated stress exposure can have intergenerational effects (Hogue et al., 2013). AA infants are more likely to be born preterm compared to European American infants (Giscombé & Lobel, 2005), which itself is a transdiagnostic risk factor for a number of psychological disorders (Johnson & Marlow, 2011). Maternal experiences of discrimination also predict heightened cortisol reactivity, an early marker of HPA axis sensitivity, among 1-year-old AA infants, but not among European American infants (Dismukes et al., 2018). These results suggest that discrimination-related experiences in mothers may become biologically embedded in their infants early in development via intergenerational processes. Moreover, lifelong experiences of discrimination may alter the way women perceive or are able to physically and psychologically cope with stress that occurs during pregnancy, resulting in higher levels of perceived stress prenatally and/or sensitizing women such that their infants are more likely to be impacted by prenatal stress (Hogue & Bremner, 2005).

The intergenerational transmission of stress sensitivity from mothers to their children is particularly relevant for identifying transdiagnostic risk factors and potential targets for intervention. Although stress response systems are shaped over the course of a person's life (Engel & Gunnar, 2019), examining early markers of stress regulation in infants may be helpful in understanding the beginning of developmental cascades that ultimately lead to psychological illness. In addition to examining infant diurnal cortisol patterns, behavioral measures of early stress responsiveness may offer additional insight into how maternal adversity becomes

embedded across generations to increase psychological risk. Specifically, the ability to adaptively respond to a changing or challenging environment may be a key process that underlies resilience in the context of adversity. Adaptation in the context of challenge can be assessed surprisingly early in development via neurobehavioral assessments such as the NICU Network Neurobehavioral Scale (NNNS). Scores on the NNNS representing greater state dysregulation and poorer adaptation in the context of a challenge prospectively predict greater internalizing symptoms in toddlerhood (Montirosso et al., 2018) as well as greater behavior problems and lower IQ by early childhood (Liu et al., 2010). These findings highlight the predictive utility of behavioral adaptation in the newborn period and suggest that it may be an early marker of psychological risk. Moreover, examining behavioral adaptation when postnatal exposure is inherently limited (i.e., in the newborn period) helps researchers parse apart the influence of maternal prenatal stress from confounding factors that continue into the postpartum period (e.g., postpartum stress, low social support, SES, poor nutrition, etc.).

We sought to integrate these different lines of research to examine how infant stress functioning is shaped by maternal experiences of adversity during childhood, prior to conception, and the prenatal period. Consistent with Research Domain Criteria (RDoC) framework (Insel et al., 2010), we prospectively examined infant outcomes across multiple levels of analysis, including both behavioral and hormonal measures of infant stress functioning. This is particularly important for examining converging and diverging effects of maternal stress exposure on infant behavior and physiology. We focused specifically on infant diurnal cortisol levels and on newborn behavioral adaptation in the context of a mild stressor paradigm in a sample of AA mother-infant dyads. The specific hypothesis for this study were:

(1) *Main effects:* Prenatal distress late in pregnancy will predict alterations in infant stress functioning, but prenatal distress early in pregnancy will not. We additionally explored whether this effect is specific to prenatal stress, or whether lifetime discrimination and adversity from the mother's childhood also predict infant stress functioning above and beyond prenatal stress.

(2) *Mediation:* Maternal childhood adversity and lifetime discrimination will indirectly predict infant stress functioning via increases in maternal prenatal distress late in gestation.

(3) *Moderation:* Maternal childhood adversity and lifetime discrimination will independently interact with maternal prenatal stress exposure to predict infant stress functioning in a manner consistent with the stress sensitization hypothesis. Specifically, maternal prenatal stress will show stronger associations with infant stress functioning if mothers report that they also experienced high levels of childhood adversity or racial discrimination.

Method

Participants. Mothers were recruited from an ongoing longitudinal study that follows AA women through pregnancy (R01NR014800; Corwin et al., 2017) and across the first 18 months postpartum (1R01MD009746; Brennan et al., 2019). Women were recruited for the larger ongoing study during the first trimester of pregnancy (M=11.5 estimated gestational age (EGA), SD=2.5) from two major hospitals in the Atlanta area: Grady Memorial Hospital (a public hospital) and Emory Midtown Hospital (a private hospital), resulting in a socioeconomically diverse sample (see Table 1). A majority of women (>85%) additionally completed a second prenatal visit during the late second/early third trimester (M=26.4, SD=2.7). Following birth, 217

women enrolled in our postpartum follow up study, which involved completing home visits at 2 weeks (M=15 days, SD=1.9), 3 months (M=3.6, SD=0.9), and 6 months postpartum (M=6.9, SD=1.0). At 3 and 6 months postpartum, mothers also collected saliva samples from their infant to be assayed for cortisol (see Figure 1). Due to missing data, our final sample size for analyses using the 2-week infant behavioral measure was 144 and our final sample size for analyses on infant cortisol was 88. There were no differences in demographics or in measures of maternal adversity between dyads who were and were not missing data (p's > 0.25).

Figure 1. Study Overview and Timeline

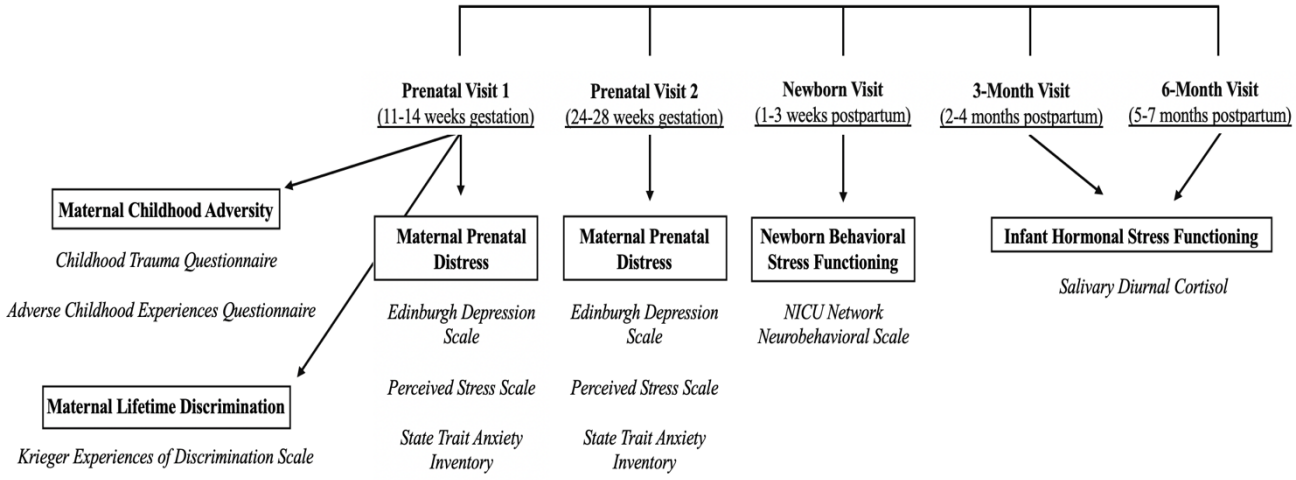


Table 1. Demographics of sample and differences between included and excluded dyads.

	Overall Sample (n=217)	NNNS Completed (n=143)	Cortisol Completed (n=88)
Gestational age at birth, M (SD)	38.58 (1.97) weeks	38.62 (1.98)	38.54 (2.29)
Preterm, N (%)	24 (11.00) yes	15 (10.50)	10 (11.40)
Mode of delivery, N (%)	44 (20.30) C-section	32 (22.40)	16 (18.20)
# previous pregnancies, M (SD)	2.82 (1.74)	2.80 (1.85)	2.43 (1.35)*
Infant age at 1-week visit, M (SD)	15.01 (1.90) days	24.65 (15.22)	17.26 (1.97)
Infant age at 3-month visit, M (SD)	3.64 (0.76) months	3.67 (0.72)	3.65 (0.70)
Infant age at 6-month visit, M (SD)	6.96 (1.03) months	6.96 (1.05)	6.89 (0.96)
Infant sex, N (%)	111 (50.90) female	73 (51.00)	41 (46.60)
Maternal age, M (SD)	25.39 (5.75) years	25.42 (5.71)	25.01 (5.99)
Cohabitating with partner, N (%)	100 (45.90) yes	62 (43.40)	39 (44.3)
Mom ethnicity, N (%)	217 (100) AA	143 (100)	88 (100)
Mom education, N (%)	93 (42.7) some college or more	83 (58.00)	50 (56.8)
Type of prenatal insurance, N (%)	65 (29.8) low-income Medicaid	44 (30.8)	25 (28.4)
# persons living in home, M (SD)	3.39 (1.48)	3.43 (1.52)	3.23 (1.54)
Childhood adversity, M (SD)	0.01 (0.87)	0.003 (0.86)	0.09 (0.93)
# discrimination situations, M(SD)	2.29 (2.53)	2.29 (2.64)	2.31 (2.70)
Early prenatal distress, M (SD)	0.001 (0.89)	-0.04 (0.87)	-0.01 (0.74)
Late prenatal distress, M (SD)	0.01 (0.88)	0.04 (0.92)	-0.01 (0.77)

Note. *Infants who were missing cortisol were born to mothers who had a higher number of prior pregnancies, but there were no other differences between infants who were and were not missing cortisol. There were no differences between infants who were and were not missing the *NICU Network Neurobehavioral Scale* (NNNS). The number of situations in which mothers reported being discriminated against was measured using the *Krieger Experiences of Discrimination Scale*. Childhood adversity was measured using the *Childhood Trauma Questionnaire* and the *Adverse Childhood Experiences Questionnaire.* Early and late prenatal distress were composite measures created using the *Edinburgh Depression Scale*, *Perceived Stress Scale*, and *State-Trait Anxiety Inventory*.

Measures.

Maternal prenatal distress. A composite maternal prenatal distress variable was created by combining multiple self-report measures that were completed early in pregnancy and again late in pregnancy. The *Perceived Stress Scale* (PSS; Cohen, Kamarck, & Mermelstein, 1983) assesses the degree of stress an individual perceives in their current life, and has demonstrated construct validity and good internal consistency (Roberti, Harrington, & Storch, 2006). Mothers also completed the Spielberger *State Trait Anxiety Inventory* (STAI; Gaudry, Vagg, & Spielberger, 1975; Spielberger, Gorsuch, & Lushene, 1970), a 20-item measure that assesses state and trait-like anxiety. Only the state scale of the STAI was used for the present study, with higher scores indicating greater anxiety. Finally, the *Edinburgh Depression Scale* (EDS; Cox, Holdenand, & Sagovsky, 1987) assessed depressive symptoms. This 10-item scale has been shown to have acceptable sensitivity and specificity in community samples and good construct validity when compared with structured clinical interviews (Murray & Cox, 1990).

A composite prenatal stress variable was created based on principle components analysis (PCA) completed with the full prenatal study cohort (n>500). PCA identified that the PSS, EDS, and STAI total scores formed one component, which was conceptualized as a maternal prenatal distress factor. Visual inspection of correlations between the PSS, EDS, and STAI in the current study also suggested these measures were moderately to strongly correlated (see Table 2), further supporting combining these measures into a single factor. The total score from each measure was therefore standardized, and these standardized scores were averaged to create two composite scores – one representing maternal distress early in pregnancy (which corresponded to the end of first/beginning of second trimester) and the other representing maternal distress late in pregnancy

(corresponding to the end of second/beginning of third trimester). Higher scores on these measures indicate greater maternal distress.

Discrimination-related lifetime stress. Mothers completed the Krieger Experiences of Discrimination Scale (Krieger et al., 2005) at the first prenatal visit, which assesses self-reported experiences of race-based discrimination across the lifespan. On this measure, individuals are asked whether, and how many times, they have been discriminated against in 9 different situations (e.g., "getting hired or getting a job" and "getting services in a store or restaurant"). Consistent with epidemiological research showing that experiencing discrimination across a greater number of different situations predicts psychological symptoms among AA women (Ertel et al., 2012), we measured the number of different situations in which women experienced discrimination. Our discrimination summary score therefore ranged from 0 to 9, with higher scores representing discrimination in more situations.

Maternal childhood adversity. A composite measure of retrospectively-reported adversity from the mother's childhood was created using the *Childhood Trauma Questionnaire-Short Form* (CTQ; Bernstein et al., 2003) and the *Adverse Childhood Experiences Questionnaire* (ACEs; Felitti et al., 1998), both of which were completed at the first prenatal visit. The CTQ is a 28-item self-report questionnaire assessing objective and subjective evaluations of childhood abuse and neglect. The CTQ is comprised of five subscales: Sexual Abuse, Physical Abuse, Emotional Abuse, Physical Neglect, and Emotional Neglect. High scores are indicative of more severe neglect and abuse. Nearly 40 percent (n=82) of women in the current sample reported experiencing at least one form of moderate to severe abuse or neglect during childhood, which is consistent with national prevalence rates of childhood trauma exposure among AA women (Koenen et al., 2010).

On the ACEs questionnaire, women indicate whether or not they were subjected to 10 different stressful life experiences during childhood. The specific stressful life experiences include living with a person who was addicted to alcohol or other drugs (1), parental separation (2) or divorce (3), living with a step parent (4), living in a foster home (5), running away from home for more than a day (6), living with a person who had a mental illness (7) or who attempted suicide (8), and living with a person who committed a serious crime (9) or who went to prison (10). Elevated scores on this measure have been associated with adverse outcomes in diverse samples (Dietz et al., 1999). Although the CTQ and ACEs have typically been examined as separate predictors in prior studies, in order to minimize the number of tests run and because they both represented maternal early life adversity and were moderately correlated with one another (see Table 2), we combined the CTQ and ACES into a single composite measure. To create this composite score of maternal childhood adversity, we standardized and averaged these two measures, with higher scores representing a higher number of adverse childhood experiences.

Table 2. Intercorrelations between primary measures of adversity.

	1.	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**	**11.**
1. # childhood MT categories	--	--	--	--	--	--	--	--	--	--	--
2. # ACEs	**r=0.38, p<0.001**	--	--	--	--	--	--	--	--	--	--
3. Childhood adversity composite	**r=0.75, p<0.001**	**r=0.86, p<0.001**	--	--	--	--	--	--	--	--	--
4. Lifetime discrimination	r=0.05, p=0.44	r=0.14, p=0.05	**r=0.17, p=0.01**	--	--	--	--	--	--	--	--
5. Early prenatal depression	**r=0.39, p<0.001**	**r=0.28, p<0.001**	**r=0.44, p<0.001**	**r=0.29, p<0.001**	--	--	--	--	--	--	--
6. Early prenatal stress	**r=0.30, p<0.001**	**r=0.18, p=0.01**	**r=0.30, p<0.001**	**r=0.16, p=0.03**	**r=0.69, p<0.001**	--	--	--	--	--	--
7. Early prenatal anxiety	**r=0.41, p<0.001**	**r=0.26, p<0.001**	**r=0.44, p<0.001**	**r=0.17, p=0.02**	**r=0.70, p<0.001**	**r=0.66, p<0.001**	--	--	--	--	--
8. Early prenatal distress composite	**r=0.41, p<0.001**	**r=0.28, p<0.001**	**r=0.45, p<0.001**	**r=0.23, p=0.001**	**r=0.90, p<0.001**	**r=0.88, p<0.001**	**0.89, p<0.001**	--	--	--	--
9. Late prenatal depression	**r=0.25, p<0.01**	**r=0.28, p<0.001**	**r=0.37, p<0.001**	**r=0.33, p<0.001**	**r=0.70, p<0.001**	**r=0.44, p<0.001**	**r=0.55, p<0.001**	**r=0.63, p<0.001**	--	--	--
10. Late prenatal stress	**r=0.24, p<0.01**	**r=0.16, p=0.03**	**r=0.28, p<0.001**	**r=0.25, p<0.01**	**r=0.48, p<0.001**	**r=0.59, p<0.001**	**r=0.53, p<0.001**	**r=0.58, p<0.001**	**r=0.63, p<0.001**	--	--
11. Late prenatal anxiety	**r=0.34, p<0.001**	**r=0.18, p=0.02**	**r=0.33, p<0.001**	r=0.13, p=0.07	**r=0.55, p<0.001**	**r=0.49, p<0.001**	**r=0.70, p<0.001**	**r=0.64, p<0.001**	**r=0.67, p<0.001**	**r=0.68, p<0.001**	--
12. Late prenatal distress composite	**r=0.31, p<0.001**	**r=0.24, p=0.001**	**r=0.38, p<0.001**	**r=0.27, p<0.001**	**r=0.65, p<0.001**	**r=0.57, p<0.001**	**r=0.66, p<0.001**	**r=0.70, p<0.001**	**r=0.88, p<0.001**	**r=0.88, p<0.001**	**r=0.89, p<0.001**

Note. Due to high correlations between the *EDS*, *PSS*, and *STAI* (denoted in the shaded boxes), these measures were combined to create a single composite measure of prenatal distress. One prenatal distress composite measure was created to capture early pregnancy distress (i.e., end of the 1st/beginning of the 2nd trimester) and another composite measure was created to capture late pregnancy distress (i.e., end of the 2nd/beginning of the 3rd trimester), allowing us to examine timing effects. We also combined our measure of childhood maltreatment (the *CTQ*) and *ACEs* into a single measure of maternal childhood adversity. MT=maltreatment. ACEs=adverse childhood experiences. Significant associations at p<0.05 are bolded.

Infant behavioral response to stress. At 2 weeks of age, the *NICU Network Neurobehavioral Scale* (NNNS; Lester & Tronick, 2004) was administered to newborns by certified, masters-level research specialists. The NNNS was developed to describe behavior of at-risk newborns, such as those born preterm or who were prenatally exposed to substances. This exam provides a comprehensive neurobehavioral profile for neonates, including state regulation, arousal, autonomic functioning, reflexes, motor maturity, attentional abilities, and signs of physiological stress. The NNNS is designed to challenge the newborn's neurobehavioral organization by placing demands on the newborn's motor functioning, attentional abilities, and state regulation (e.g., alerting to new stimuli, self-soothing when upset). The examiner administers 45 items that involve direct manipulation of the newborn and records observations across the course of the exam for an additional 69 items to assess the newborn's functioning and neurobehavioral organization in the context of a changing environment. Because infants are undressed, manipulated by a stranger, and often cry at some point during the exam, it is conceptualized as a mild stressor paradigm.

We created two composite scores based on previous research (Ostlund et al., 2019). The first composite measures newborn neurobehavioral arousal and includes summary scores tapping into newborn excitability, arousal, the number of handling strategies used by the examiner to keep the infant calm, physiological signs of stress (e.g., tremors, startles), and infant ability to self-regulate their state (reverse scored). Higher scores on this composite indicate greater newborn arousal. The second composite measure captures newborn ability to respond, attend to, and track environmental stimuli. This composite is comprised of the attention summary score and lethargy summary score (reverse scored), with higher scores representing greater newborn attention. Correlations between these summary scores in our sample are shown in Table 3. An

additional advantage of using these composites is their consistency with the RDoC constructs of arousal and attention, respectively. Finally, utilizing this measure allows us to examine these transdiagnostic constructs in the context of a mild stressor paradigm, which may offer particular insight into the intergenerational transmission of adversity and how it shapes the infant stress response.

Table 3. Correlations between NNNS summary scores.

	Arousal	Exc.	Ar.	Reg.	Hand.	Str./A.	**Attention**	Leth.
Arousal Composite	--	--	--	--	--	--	--	--
Excitability	**r=0.89, p<0.001**	--	--	--	--	--	--	--
Arousal	**r=0.82, p<0.001**	**r=0.81, p<0.001**	--	--	--	--	--	--
Regulation	**r=-0.78, p<0.001**	**r=-0.74, p<0.001**	**r=-0.52, p<0.001**	--	--	--	--	--
Handling	**r=0.68, p<0.001**	**r=0.44, p<0.001**	**r=0.47, p<0.001**	**r=-0.35, p<0.001**	--	--	--	--
Stress/Abstinence	**r=0.61, p<0.001**	**r=0.37, p<0.001**	**r=0.30, p<0.001**	**r=-0.32, p<0.001**	**r=0.31, p<0.001**	--	--	--
Attention Composite	r=-0.07, p=0.38	r=0.04, p=0.63	r=0.09, p=0.32	r=0.12, p=0.16	**r=-0.19, p=0.03**	r=-0.10, p=0.23	--	--
Lethargy	**r=-0.25, p<0.01**	**r=-0.37, p<0.001**	**r=-0.39, p<0.001**	r=0.11, p=0.20	r=-0.06, p=0.51	r=-0.03, p=0.75	**r=-0.87, p<0.001**	--
Attention	**r=-0.43, p<0.001**	**r=-0.37, p<0.001**	**r=-0.30, p<0.001**	**r=0.39, p<0.001**	**r=-0.40, p<0.001**	**r=-0.21, p=0.02**	**r=-0.85, p<0.001**	**r=-0.46, p<0.001**

Note. We created two composites from NNNS summary scores: Arousal and Attention. The Arousal composite was comprised of the NNNS summary scores of Excitability, Arousal, Regulation (reverse-scored), Handling, and Stress/Abstinence. The Attention composite was comprised of the NNNS summary scores of Lethargy and Attention. As shown above, the summary scores in each composite (shown in the shaded boxes) were moderately to highly correlated with one another in our sample (N=143), further supporting the creation of two overarching composite scores to measure neonatal neurobehavior.

Salivary cortisol. Mothers collected infant saliva at home using cotton swabs at three time points throughout the day when infants were 3 and 6 months of age: at awakening, 30 minutes after awakening, and at bedtime. Mothers were sent text reminders at each of these times on the day of saliva collection and were asked to record what time they collected each sample. Saliva samples were stored at room temperature until staff could pick up the samples, at which point they were frozen at -80 degrees. Samples were assayed at Salimetrics using the following methodology: after thawing samples to room temperature, they were vortexed and centrifuged for 15 minutes at approximately 3,000 RPM. Next, samples were assayed for cortisol using a high sensitivity enzyme immunoassay. This assay has a lower sensitivity limit of 0.007 μg/dL, standard curve range from 0.012-3.0 μg/dL, an average intra-assay coefficient of variation of 4.60 percent, and an average inter-assay coefficient of variation of 6.00 percent. Notably, these standards exceed the NIH guidelines for Enhancing Reproducibility through Rigor and Transparency.

Recent data suggests that a wide range of cortisol measures assess the same two underlying constructs: overall cortisol production and cortisol responsivity, and that each of these can each be adequately captured using AUCg and AUCi respectively (Khoury et al., 2015). We therefore calculated these AUC measures (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) from the 3 infant saliva samples collected at the 3- and 6-month visits. Given that infants provided saliva samples over the course of the day, we conceptualize AUCg as overall daily cortisol output, and AUCi as daily cortisol responsiveness, which captures both the cortisol awakening response and diurnal slope. In order to maximize our sample size, we combined participants across visits in the following way. If 3 infant saliva samples were available from either the 3-month or from the 6-month visit, we used the AUC measures from

that single timepoint in our analyses. If 3 saliva samples were available from *both* the 3- and the 6-month visit for a given infant, we used the average of the AUC measures from the 3- and 6-month timepoints in our analyses. There were no differences between AUCi at the 3-month visit (M=-99.11, SD=349.06) and AUCi at the 6-month visit (M=18.24, SD=389.07, *paired* $t(34)$=-1.41, p=0.17) further supporting their combination into a singular cortisol measure. AUCg was higher at the 6-month visit (M=470.22, SD=658.01) compared to the 3-month visit (M=269.70, SD=243.91, *paired* $t(47)$=-2.05, $p<0.05$). We therefore additionally repeated our analyses by randomly selecting either the 3- or 6-month AUC measure for these infants to ensure that averaging across visits did not impact our results. Our results were unchanged if we randomly selected cortisol AUC from one of the two visits or if we averaged across the visits. Because we combined cortisol data across the 3- and 6-month visits, we refer to our AUC measures as 3-6 month AUCg and AUCi (correlations between cortisol measures are shown in Table 4).

Data analysis plan. Descriptives and measures of variability were examined for all variables to examine skew, kurtosis, and acceptable range. Hierarchical linear regressions were used to test study hypotheses, with relevant covariates (i.e., variables correlated with newborn behavior or infant cortisol) entered in the first step, and the primary predictor variable entered in the second step. Linear regression assumptions were assessed in several ways. Unstandardized residuals were visually examined using histograms to determine normality and residuals were plotted against predicted values to ensure homoscedasticity. Finally, Cook's D was used to identify potential outliers since it considers both leverage and discrepancy, and we re-ran our analyses using bootstrapping with 5,000 samples to ensure our results were not driven by outliers. For analyses involving mediation and moderation, the PROCESS Macro Version 3.3 (Hayes, 2012) was used with 5,000 bootstrapped samples.

Table 4. Correlations between infant cortisol measures.

	AUCg	AUCi	3-mo T1	3-mo T2	3-mo T3	6-mo T1	6-mo T2
Cortisol Composites							
AUCg	--	--	--	--	--	--	--
AUCi	**r=0.21, p<0.05**	--	--	--	--	--	--
3-month cortisol							
T1	**r=0.48, p<0.001**	**r=-0.30, p=0.02**	--	--	--	--	--
T2	**r=0.70, p<0.001**	r=-0.16, p=0.21	**r=0.73, p<0.001**	--	--	--	--
T3	**r=0.60, p<0.001**	r=-0.20, p=0.11	**r=0.58, p<0.001**	**r=0.55, p<0.001**	--	--	--
6-month cortisol							
T1	**r=0.55, p<0.001**	**r=-0.38, p<0.01**	r=0.29, p=0.08	r=0.21, p=0.21	r=0.27, p=0.10	--	--
T2	**r=0.72, p<0.001**	r=0.22, p=0.08	r=-0.07, p=0.67	r<0.01, p=0.98	r=0.03, p=0.86	**r=0.63, p<0.001**	--
T3	**r=0.72, p<0.001**	r=0.24, p=0.06	r=0.15, p=0.36	r=0.19, p=0.27	r=0.27, p=0.09	**r=0.63, p<0.001**	**r=0.57, p<0.001**

Note. Salivary cortisol was collected from infants at 3 and 6 months of age. As shown in the above table, measures of cortisol from the same point correlated appropriately with each other. We calculated area under the curve with respect to ground (AUCg) and area under the curve with respect to increase (AUCi) to use in final analyses. To maximize our sample size, we combined these AUC measures across the 3- and 6-month visits. AUCg correlated positively with all individual measures of infant cortisol, and AUCi correlated negatively with baseline measures of cortisol from the 3- and 6-month visits.

Results

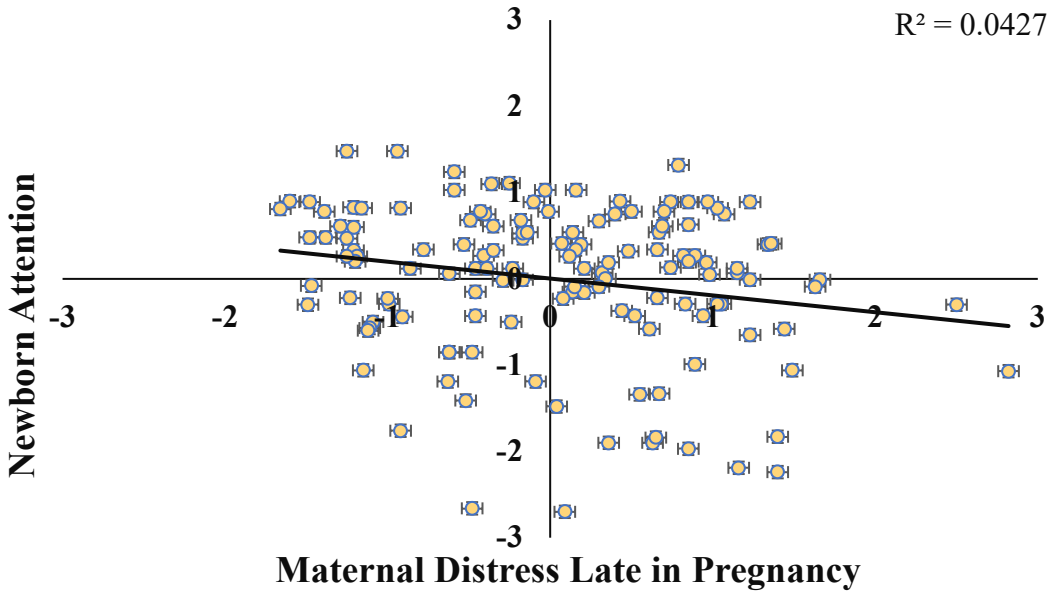
Are the effects of maternal stress on infant stress functioning detectable shortly after birth?

Newborn arousal and attention during stress. After controlling for relevant covariates, maternal prenatal distress did not predict newborn arousal at 2 weeks of age for either gestational timepoint (Tables 5 and 6). Maternal distress early in pregnancy was also not associated with newborn attention during the stressful exam, however, greater maternal distress late in pregnancy predicted lower newborn attention at 2 weeks of age (Figure 2). Moreover, the effect of late pregnancy maternal distress continued to predict newborn attention, even after controlling for

concurrent maternal distress at the 2-week visit (β=-0.25, ΔR^2=0.04, b=-0.23, SE=0.11, $95\%CI$[-0.45, -0.02], p=0.03).

Infant diurnal cortisol. Maternal prenatal distress did not predict infant daily cortisol output or infant daily cortisol responsiveness after controlling for relevant covariates (Tables 5 and 6).

Figure 2. Maternal distress late in pregnancy predicts lower infant attentional abilities in the context of a mild stressor paradigm.



Does a mother's stress from prior to pregnancy predict her infant's stress functioning?

There were no significant associations between maternal lifetime experiences of discrimination with newborn arousal, newborn attention, infant daily cortisol output, or infant daily cortisol responsiveness after controlling for covariates and prenatal stress exposure (Table 7). There was a trend for maternal childhood adversity to predict greater infant daily cortisol

output, but these associations did not reach significance after controlling for relevant covariates and prenatal stress. Maternal childhood adversity did not directly predict other infant outcomes (Table 8).

Table 5. Maternal distress from early in pregnancy and infant stress functioning.

	β	t	95% CI	p	R^2	ΔF	ΔR^2
Outcome: Newborn Arousal							
Step 1					0.13	5.90	0.13
Visit Location	0.23	2.49	0.07, 0.61	0.01			
Infant Age	-0.22	-2.57	-0.02, -0.003	0.01			
Prenatal Drug Use	0.13	1.46	-0.41, 2.66	0.15			
Step 2					0.13	0.70	<0.01
Early Preg. Distress	-0.07	-0.84	-0.22, 0.09	0.41			
Outcome: Newborn Attention							
Step 1					0.03	3.55	0.03
Infant Age	0.16	1.88	0.00, 0.02	0.06			
Step 2					0.05	2.93	0.02
Early Preg. Distress	-0.14	-1.71	-0.29, 0.02	0.09			
Outcome: Infant Daily Cortisol Output							
Step 1					0.22	6.32	0.22
Infant Age	0.18	1.64	-0.001, 0.01	0.11			
Preterm	0.26	2.34	0.05, 0.60	0.02			
Gestational Hypertension	0.27	2.53	0.04, 0.36	0.01			
Step 2					0.22	0.01	<0.001
Early Preg. Distress	-0.01	-0.08	-0.13, 0.12	0.93			
Outcome: Infant Daily Cortisol Responsiveness							
Step 1					0.14	3.88	0.14
Infant Age	0.29	2.58	0.99, 7.74	0.01			
Prenatal Marijuana Use	0.22	1.95	-5.00, 427.58	0.06			
Gravidity	0.03	0.24	-69.26, 88.55	0.81			
Step 2					0.14	0.04	<0.001
Early Preg. Distress	0.02	0.21	-112.68, 138.76	0.84			

Note. Consistent with predictions, prenatal distress early in pregnancy did not predict infant stress functioning. Infant age was assessed at the same visit as the outcome data (2 weeks for behavioral data and 3-6 months for cortisol data). Visit location reflects whether the 2-week postnatal visit occurred in the participant's home or in lab. Prenatal marijuana use was assessed during the first prenatal visit to reflect any use vs. no use. Prenatal drug use reflects any vs. no use of other illicit drugs aside from alcohol, tobacco, or marijuana. 95 % confidence intervals are for unstandardized beta values.

Table 6. Maternal distress from late in pregnancy and infant stress functioning.

	β	t	95% CI	p	R^2	ΔF	ΔR^2
Outcome: Newborn Arousal							
Step 1					0.12	5.68	0.12
Visit Location	0.21	2.31	0.05, 0.59	0.02			
Infant Age	-0.23	-2.64	-0.02, -0.003	0.01			
Prenatal Drug Use	0.13	1.47	-0.40, 2.67	0.15			
Step 2					0.12	0.06	<0.001
Late Preg. Distress	-0.02	-0.25	-0.16, 0.12	0.80			
Outcome: Newborn Attention							
Step 1					0.02	2.96	0.02
Infant Age	0.15	1.72	-0.001, 0.02	0.09			
Step 2					0.07	6.26	0.04
Late Preg. Distress	**-0.21**	**-2.50**	**-0.36, -0.04**	**0.01**			
Outcome: Infant Daily Cortisol Output							
Step 1					0.23	6.32	0.23
Infant Age	0.16	1.40	-0.001, 0.01	0.17			
Preterm	0.33	2.81	0.13, 0.78	0.01			
Gestational Hypertension	0.20	1.75	-0.02, 0.32	0.08			
Step 2					0.23	0.11	<0.01
Late Preg. Distress	-0.04	-0.33	-0.14, 0.10	0.74			
Outcome: Infant Daily Cortisol Responsiveness							
Step 1					0.08	1.86	0.08
Infant Age	0.22	1.78	-0.39, 6.78	0.08			
Prenatal Marijuana Use	0.15	1.25	-85.45, 368.33	0.22			
Gravidity	0.05	0.40	-65.16, 97.62	0.69			
Step 2					0.09	0.43	<0.01
Late Preg. Distress	0.08	0.66	-81.79, 161.52	0.52			

Note. Maternal distress late in pregnancy predicted lower infant attentional abilities in the context of a mild stressor paradigm. Maternal distress late in pregnancy did not predict other measures of infant stress functioning. Infant age was assessed at the same visit as the outcome data (2 weeks for behavioral data and 3-6 months for cortisol data). Visit location reflects whether the 2-week postnatal visit occurred in the participant's home or in lab. Prenatal marijuana use was assessed during the first prenatal visit to reflect any use vs. no use. Prenatal drug use reflects any vs. no use of other illicit drugs aside from alcohol, tobacco, or marijuana. 95 % confidence intervals are for unstandardized beta values.

Table 7. Maternal lifetime discrimination and infant stress functioning.

	b	SE	95% CI	p	R^2	ΔF	ΔR^2
Outcome: Newborn Arousal							
Step 1: Main Effects					0.13	2.87	0.13
Visit Location	0.33	0.14	0.05, 0.62	0.02			
Infant Age	-0.01	<0.01	-0.02, -0.003	0.01			
Prenatal Drug Use	1.08	0.80	-0.50, 2.65	0.18			
Prenatal Stress (PS)	-0.02	0.08	-0.17, 0.13	0.81			
Discrimination	-0.004	0.03	-0.06, 0.05	0.90			
Step 2: Interaction					0.13	0.33	<0.01
Discrimination*PS	-0.02	0.03	-0.08, 0.04	0.57			
Outcome: Newborn Attention							
Step 1: Main Effects					0.08	2.69	0.08
Infant Age	0.01	<0.01	-0.001, 0.02	0.07			
Prenatal Stress	-0.22	0.09	-0.38, -0.05	0.01			
Discrimination	0.02	0.03	-0.04, 0.09	0.46			
Step 2: Interaction					0.08	0.36	<0.01
Discrimination*PS	0.02	0.04	-0.05, 0.09	0.55			
Outcome: Infant Daily Cortisol Output							
Step 1: Main Effects					0.39	6.63	0.39
Infant Age	1.77	1.90	-2.04, 5.57	0.36			
Preterm	697.80	171.47	355.05, 1040.56	<0.01			
Gest. Hypertension	223.38	91.17	41.12, 405.64	0.02			
Prenatal Stress	-84.55	66.59	-217.66, 46.56	0.21			
Discrimination	36.40	22.16	-7.91, 80.70	0.11			
Step 2: Interaction					0.39	0.75	<0.01
Discrimination*PS	22.58	26.01	-29.41, 74.57	0.39			
Outcome: Infant Daily Cortisol Responsiveness							
Step 1: Main Effects					0.11	1.18	0.11
Infant Age	2.58	1.92	-1.26, 6.41	0.18			
Pre. Marijuana Use	139.16	115.13	-91.22, 369.55	0.23			
Gravidity	8.31	42.49	-76.72, 93.34	0.85			
Prenatal Stress	21.28	65.77	-110.32, 152.88	0.75			
Discrimination	15.63	22.57	-29.52, 60.79	0.49			
Step 2: Interaction					0.11	0.30	<0.01
Discrimination*PS	14.23	26.18	-38.17, 66.62	0.59			

Note. Maternal experiences of lifetime discrimination did not predict infant stress functioning after controlling for distress late in pregnancy. Results are similar when examining prenatal distress from early in pregnancy. Infant age was assessed at the same visit as the outcome data (2 weeks for behavioral data and 3-6 months for cortisol data). Visit location reflects whether the 2-week postnatal visit occurred in the participant's home or in lab. Prenatal marijuana use was assessed during the first prenatal visit to reflect any use vs. no use. Prenatal drug use reflects any vs. no use of other illicit drugs aside from alcohol, tobacco, or marijuana. 95 % confidence intervals are for unstandardized beta values. PS=Prenatal Stress.

Table 8. Effects of maternal childhood adversity on infant stress functioning.

	b	SE	95% CI	p	R^2	ΔF	ΔR^2
Outcome: Newborn Arousal							
Step 1: Main Effects					0.14	3.08	0.14
Visit Location	0.32	0.14	0.04, 0.60	0.02			
Infant Age	-0.01	<0.01	-0.02, -0.002	0.01			
Prenatal Drug Use	1.28	0.81	-0.31, 2.88	0.11			
Prenatal Stress	0.01	0.08	-0.14, 0.16	0.86			
Childhood Adversity	-0.04	0.09	-0.21, 0.13	0.66			
Step 2: Interaction					0.015	1.26	0.01
CA*PS	-0.09	0.08	-0.25, 0.07	0.26			
Outcome: Newborn Attention							
Step 1: Main Effects					0.05	1.55	0.05
Infant Age	0.01	<0.01	-0.003, 0.02	0.17			
Prenatal Stress	-0.16	0.08	-0.32, 0.001	0.05			
Childhood Adversity	-0.02	0.09	-0.19, 0.16	0.85			
Step 2: Interaction					0.03	0.14	<0.01
CA*PS	0.03	0.09	-0.14, 0.20	0.71			
Outcome: Infant Daily Cortisol Output							
Step 1: Main Effects					0.40	6.37	0.40
Infant Age	2.87	1.90	-0.93, 6.66	0.14			
Preterm	600.82	176.42	247.66, 953.97	<0.01			
Gest. Hypertension	230.52	93.69	42.98, 418.05	0.02			
Prenatal Stress	-41.67	67.93	-177.64, 94.31	0.54			
Childhood Adversity	107.48	58.92	-10.47, 225.42	0.07			
Step 2: Interaction					0.40	0.06	<0.01
CA*PS	15.59	62.92	-110.35, 141.54	0.81			
Outcome: Infant Daily Cortisol Responsiveness							
Step 1: Main Effects					0.15	1.65	0.15
Infant Age	3.22	1.84	-0.46, 6.90	0.08			
Pre. Marijuana Use	135.38	115.26	-95.52, 366.27	0.25			
Gravidity	7.39	44.02	-80.80, 95.59	0.87			
Prenatal Stress	43.68	67.13	-90.79, 178.15	0.52			
Childhood Adversity	81.92	57.52	-33.30, 197.14	0.16			
Step 2: Interaction					0.15	0.01	<0.01
CA*PS	-6.19	61.24	-128.87, 116.48	0.92			

Note. Maternal childhood adversity did not predict infant stress functioning after controlling for distress from late in pregnancy. Results are similar when examining prenatal distress from early in pregnancy. Infant age was assessed at the same visit as the outcome data (2 weeks for behavioral data and 3-6 months for cortisol data). Visit location reflects whether the 2-week postnatal visit occurred in the participant's home or in lab. Prenatal marijuana use was assessed during the first prenatal visit to reflect any use vs. no use. Prenatal drug use reflects any vs. no use of other illicit drugs aside from alcohol, tobacco, or marijuana. 95 % confidence intervals are for unstandardized beta values. PS=Prenatal Stress. CA=Childhood Adversity.

Do maternal experiences of lifetime discrimination and adversity from her own childhood indirectly impact newborn attention by increasing prenatal distress?

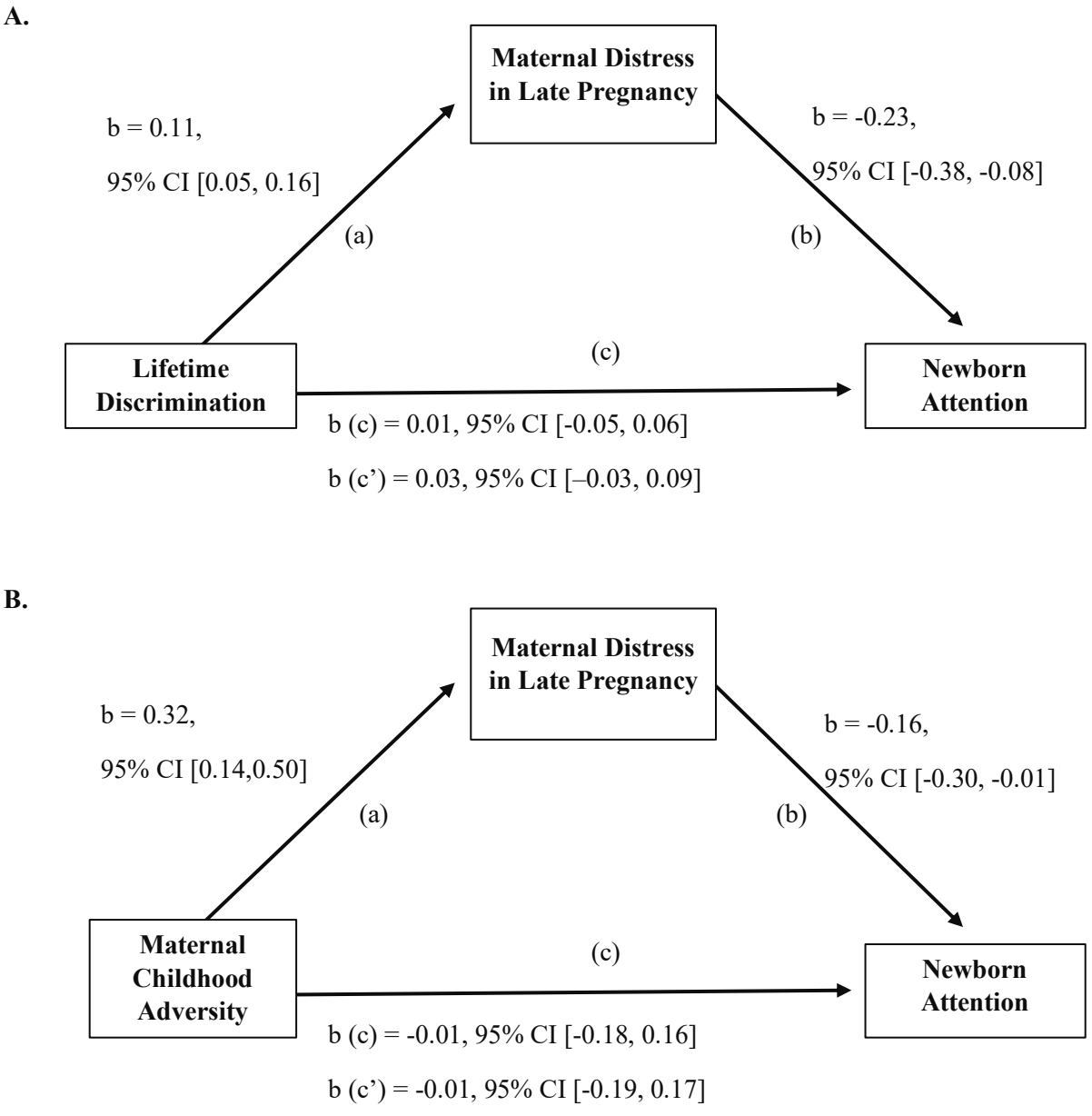
Next, we explored late pregnancy maternal distress as a mediator linking maternal lifetime discrimination and childhood adversity with infant attention. Experiencing greater lifetime discrimination predicted greater maternal distress in late pregnancy (β=0.31, b=0.11, SE=0.03, $95\%CI$[0.05, 0.17], p<0.001), which in turn predicted lower infant attention at 2 weeks of age (β=-0.24, b=-0.23, SE=0.08, $95\%CI$[-0.39, -0.06], p<0.01). Moreover, the indirect effect of discrimination on infant attention was significant (β=-0.07, SE=0.03, $95\%CI$[-0.15, -0.02]), indicating mediation via late pregnancy prenatal distress.

Similar to discrimination, experiencing greater adversity during childhood predicted greater maternal distress during late pregnancy (β=0.29, b=0.32, SE=0.09, $95\%CI$[0.14, 0.50], p<0.001), which in turn predicted worse infant attention (β=-0.18, b=-0.16, SE=0.08, $95\%CI$[-0.32, 0.00], p=0.05). The indirect effect of childhood adversity on infant attention via late pregnancy distress was also significant (β=-0.05, SE=0.03, $95\%CI$[-0.12, -0.002]), indicating mediation (see Figure 3).

Does maternal stress exposure prior to pregnancy sensitize fetuses to the effects of prenatal stress?

We did not find evidence that maternal experiences of discrimination or of childhood adversity sensitized fetuses to the influence of maternal prenatal stress. As shown in Table 7, discrimination did not interact with maternal distress early or late in gestation to predict infant outcomes. Maternal childhood adversity also did not interact with maternal prenatal distress (Table 8).

Figure 3. Mediational analyses with 5,000 bootstrapped samples revealed that maternal lifetime experiences of discrimination and maternal experiences of childhood adversity independently predicted increased prenatal distress late in pregnancy (a), which in turn predicted lower infant attentional abilities at 2 weeks postpartum (b). Moreover, the indirect effect of lifetime discrimination and adversity from the mother's childhood on newborn attentional abilities was significant, suggesting mediation via late gestation maternal distress.



Does newborn behavior predict later infant cortisol?

To aid interpretation of our finding that prenatal distress in late pregnancy predicted lower infant attentional abilities, we conducted exploratory analyses examining associations between infant behavior at 2 weeks of age and infant diurnal cortisol at 3-6 months of age (see Table 9). Lower newborn attention, but not newborn arousal, at 2 weeks predicted greater diurnal cortisol responsivity at 3-6 months of age, predicting 8 percent of the variance in this outcome (β=-0.29, ΔR^2=0.08, *b*=-189.94, *SE*=78.76, *95%CI*[-347.23, -32.66], *p*=0.02).

Table 9. Correlations between infant outcomes.

	Arousal	Attention	Cortisol AUCg
Behavioral Arousal	--	--	--
Attention	r(143)=-0.07, p=0.38	--	--
Cortisol AUCg	r(67)=-0.01, p=0.94	r(67)=-0.19, p=0.12	--
Cortisol AUCi	r(67)=-0.13, p=0.31	**r(67)=-0.29, p=0.02**	r(88)=0.21, p=0.05

Note. Behavioral arousal and attention were assessed using the NICU Network Neurobehavioral Scale at 2 weeks of age. Cortisol was measured from infant saliva at 3-6 months of age.

Discussion

This is the first study to examine how a mother's experiences of childhood, lifetime, and prenatal stress interact to shape early stress functioning in her infant. We examined these questions in a sample of AA mother-infant dyads, a group that is disproportionately exposed to adverse experiences. Our findings revealed that maternal distress (i.e., perceived stress, anxiety, and depression) late, but not early, in gestation predicted infant attentional abilities in the context of a mild stressor paradigm. We also found that adverse experiences from the mother's childhood and maternal lifetime experiences of discrimination indirectly predicted newborn

attention by increasing late pregnancy distress. Neither maternal childhood adversity nor lifetime discrimination moderated the association between maternal prenatal distress and infant outcomes, suggesting that these early life experiences in mothers did not sensitize fetuses to the influence of maternal prenatal distress, at least in terms of impacts on stress functioning in early infancy.

Our finding that maternal prenatal distress at the later gestational timepoint predicted infant stress functioning is consistent with experimental and correlational research that shows stress from later, versus earlier, in pregnancy is more likely to be associated with child socioemotional outcomes (Class et al., 2014; Korja et al., 2017; Rice et al., 2010). As such, our findings contribute to the growing evidence that late pregnancy is a sensitive time for the intergenerational transmission of adversity from mothers to their children. We specifically found effects on newborn attention, which may be an early marker of ability to respond in the context of stress. Laboratory-based assessments of infant attention at 10 months have been shown to prospectively predict more mature emotion regulation abilities by toddlerhood (Perry, Swingler, Calkins, & Bell, 2016) and attention-shifting is one way that infants effectively regulate their state (Ekas, Lickenbrock, & Braungart-Rieker, 2013). Early attentional abilities have therefore been postulated to be a precursor of self-regulation (Wilson, Gottman, & Gottman, 2014) or an early marker of temperamental reactivity (Calkins & Marcovitch, 2010). Our attention measure specifically captures the newborn's ability to alert and orient in the context of a changing environment, which may be an important early marker of how infants are able to organize their behavior in challenging circumstances. This possibility is further supported by early attention predicting future cortisol diurnal responsiveness, but not diurnal cortisol output, in our sample. Importantly, late gestation maternal distress predicted lower newborn attention even after

controlling for self-reported maternal distress at the 2-week postnatal visit, and stress from other developmental periods in the mother's life (i.e., lifetime discrimination and childhood adverse experiences) did not predict newborn attention. This pattern of results highlights gestation as a sensitive period for the intergenerational effects of stress exposure on developing attentional abilities.

Our results further suggest that maternal prenatal distress may be shaped by prior experiences of adversity in the mother's life. Although we did not find evidence for direct effects on infant outcomes, maternal experiences of childhood adversity as well as lifetime experiences of discrimination predicted increased maternal prenatal distress, which in turn predicted lower newborn attention. This mediational finding is consistent with work indirectly linking childhood maltreatment in mothers to child behavior problems via increases in perinatal depression (Plant, Jones, Pariante, & Pawlby, 2017), and with research that has linked discrimination to increased distress in pregnant women of minority status (Bécares & Atatoa-Carr, 2016). Our work extends this literature by identifying two specific types of stress exposure that increase AA women's perceived stress, anxiety, and depression during pregnancy, which in turn collectively shape newborn development. Additionally, these findings highlight the cascading nature of stress across the lifespan. Discrimination is a chronic, consistent experience across AAs' lifespan, and mothers who experience elevated stress during pregnancy have likely experienced elevated stress at other points of their lives as well (Brownlow et al., 2019). Yet most research to date exclusively examines stress that occurs during the prenatal period or early in the postpartum (Korja et al., 2017), and studies have only begun to examine preconception stress in recent years (Keenan et al., 2018). This narrow focus, rather than a broader lifespan approach, prohibits the researcher's ability to examine competing, additive, or cascading intergenerational effects of

maternal stress from different developmental timepoints. Although we saw relatively few effects of prenatal stress on its own in our sample, this remains a sensitive time for the transmission of adversity from mothers to their children and additional research on prenatal stress is needed to understand this transmission. However, prenatal stress does not occur within a vacuum. In order to interrupt the intergenerational cycle of maternal adversity leading to increased child psychological risk, it is important to additionally assess, and eventually intervene with, women prior to conception, and potentially early in their lives.

We expected to detect an effect of maternal prenatal stress on infant behavioral arousal and on infant cortisol. A recent meta-analysis across 14 different species confirms causal effects of prenatal stress on offspring cortisol reactivity, with few differences across species (Thayer, Wilson, Kim, & Jaeggi, 2018). The consistency of these results across species suggests the impact of maternal prenatal stress on offspring HPA axis functioning is an evolutionarily conserved phenomenon. However, our results did not replicate this effect. One notable difference is that the infants in our study were assessed very early in development (at 2 weeks and 3-6 months). It is possible the effects of prenatal stress on HPA axis functioning do not become detectable until diurnal HPA axis rhythms have fully settled, which occurs sometime between 1 month of age (Ivars et al., 2015) and 1 year of age (de Weerth & van Geert, 2002), with substantial inter-individual variability (de Weerth, Zijl, & Buitelaar, 2003). It is further possible that prenatal stress yields latent, or sleeper, effects specifically on diurnal HPA axis functioning and not on HPA axis reactivity to a stressor.

We hypothesized that discrimination may lead to epigenetic alterations that change placental functioning, making fetuses more likely to be affected by maternal stress that occurs during pregnancy. However, we did not find support for any sensitization effects in our sample,

perhaps because we failed to capture the most impactful aspects of discrimination and childhood adversity in our study design. First, we relied solely on self-reported experiences of racism, which are likely underreported. Our measure also focused specifically on the number of different situations in which a woman experienced race-based discrimination in her life. We consider this to be a measure of the pervasiveness of discrimination, but perhaps it is not the pervasiveness of discrimination that is most likely to have intergenerational effects. Indeed, it may not be mere exposure that confers risk across generations, but instead an individual's *response* to stressors that yields the most potent effects (Harkness & Monroe, 2016). Stress responsivity is multiply determined and there are significant individual differences in whether a given exposure yields sensitizing, desensitizing, or no effects on future stress reactivity (Korous, Causadias, & Casper, 2017). For instance, research shows that AA adolescents who receive emotional support show a weaker correlation between experiences of discrimination and physiological weathering (Brody et al., 2014) and AA youth who demonstrate higher levels of self-control in the context of race-related stress exhibit greater physiological weathering (Miller, Yu, Chen, & Brody, 2015). Emotional and behavioral responses to stress may therefore act as important moderators. Measuring an individual's physiological response to discrimination may be a more sensitive way to examine the impact of adversity across generations given that such responses will better capture individual differences in protective and exacerbating factors. Physiological weathering in particular may be important moderators of the extent to which the intrauterine environment is able to protect a fetus from the effects of maternal prenatal stress. This may be especially true in light of evidence that epigenetic alterations that impact the intrauterine environment – such as changes to 11beta-hydroxysteroid dehydrogenase-2 (11ß-HSD-2) and the glucocorticoid receptor

NR3C1, which regulate fetal exposure to glucocorticoids – have also been tied to physiological weathering (Lester, Marsit, Conradt, Bromer, & Padbury, 2012).

We also combined a variety of different types of adverse experiences together in our childhood adversity measure, including abuse, neglect, and parental divorce. These are very different experiences that may each shape development in unique ways, with certain types of experiences being especially likely to confer intergenerational effects on developing stress responses. For instance, emotional abuse and neglect are particularly prevalent and pervasive maltreatment experiences (Baker & Maiorino, 2010) that interfere with the development of secure attachment relationships and negatively impact socioemotional development (Shaffer, Yates, & Egeland, 2009) and psychological risk into adulthood (Wright, Crawford, & Del Castillo, 2009). Emotional maltreatment may therefore be especially likely to exert intergenerational influences on offspring (Hendrix et al., in preparation). Combining our measures of adversity did not allow us to examine these associations and may have obscured the sensitizing and intergenerational effects of specific types of childhood experiences.

It is also possible that other, more proximal factors may mediate or moderate the impact of maternal stress exposures on infant stress functioning. Race-based discrimination can lead to increased rumination, which in turn negatively impacts sleep (Brownlow et al., 2019). Chronic sleep disruption is further associated with depression (Conklin, Yao, & Richardson, 2018) and immune dysregulation (Tan, Kheirandish-Gozal, & Gozal, 2019), which exert their own fetal programming effects. It is also possible that maternal sleep disruption and immune functioning moderate the impact of prenatal distress on fetal and infant development and that stress only predicts infant stress functioning when these physiological systems are also dysregulated in the mother. Socioeconomic status may be an additional moderator of the impact of prenatal stress on

infant stress functioning given that the combination of race-based differences in income *and* interpersonal discrimination can prematurely age AA women (Hogue & Bremner, 2005). This premature aging, in turn, may render their fetuses more susceptible to stress-related pregnancy complications.

Limitations of our study included a relatively small sample size, particularly with regard to infant cortisol. Although this subsample was still representative of the larger sample of women and infants (as evidenced by no differences between mothers with and without missing data), a smaller sample size may have limited our power to detect effects. Moreover, given the young age of our infants, some infants may not have established diurnal patterns of cortisol yet, which could add noise to our analyses. Stress during late pregnancy is also likely to continue into the postpartum period and may have its own effects on development. We examined infant outcomes shortly after birth, which helps parse out the influence of continued stress into the postpartum period as well as other factors, like parenting, that can be influenced by stress and can shape child psychological risk. We also controlled for postnatal distress at the appropriate visits to more carefully isolate the effects of prenatal exposure. However, other postnatal factors, or potential interactions between pre and postnatal stress may still be important to examine.

Despite these limitations, the present study has a number of notable strengths. First, we examined infant outcomes at multiple levels of analysis, including both behavioral and hormonal measures of infant stress functioning. This is an important step towards understanding the converging and diverging effects of maternal stress exposure on the developing stress response into the next generation. Using composite measures of stress additionally aided in reducing measurement error (Epstein, 1983), and using a longitudinal, prospective design limited retrospective biases in reporting for our prenatal distress measures. We additionally examined

our research questions in a socioeconomically diverse sample of AA women and their infants, enabling us to better understand the intergenerational transmission of adversity in a population for whom these questions are particularly relevant.

In this novel study with AA mother-infant dyads, we found that prenatal maternal distress experienced late, but not early, in gestation predicted lower newborn attentional abilities, which in turn predicted future daily cortisol responsiveness in infants. We additionally found that maternal early life adversity and lifetime discrimination indirectly shape infant stress functioning by increasing maternal distress late in pregnancy. Such findings highlight the cascading nature of stress across the lifespan and the subsequent need to expand our conceptualization of the intergenerational transmission of maternal stress to include earlier life experiences. Enhancing our understanding of the cumulative, competing, and interactive effects of stress exposure and stress responses at varying developmental timepoints is integral in illuminating how adversity becomes biologically embedded and ultimately increases psychological risk across generations.

Moving beyond prenatal stress: Maternal childhood adversity predicts frontoamygdala connectivity in neonates

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Abstract

It is well established that exposure to adversity, especially during sensitive periods of development such as childhood, has both behavioral (e.g., increasing one's risk for psychiatric illnesses) and cortical consequences. But could these effects of early-life exposure to adversity also be transmitted across generations? Here we directly address this question, investigating the associations between maternal exposure to adversity during her own childhood and neural connectivity in her neonate. More specifically, a sample of African American (AA) mother-neonate dyads (n=41) – a group that is disproportionately affected by early life adversity – completed questionnaires assessing their current distress (i.e., a composite measure of anxiety, depression, and perceived stress) during the first and third trimesters of pregnancy and retrospectively reported on their own childhood experiences of abuse and neglect. At one-month postpartum, neonatal offspring of these women completed a resting-state fMRI scan during natural sleep. Strikingly, greater maternal exposure to emotional neglect during her own childhood predicted stronger functional connectivity (FC) of two different frontoamygdala circuits in these neonates, as early as one month after birth. This effect was specific to early experiences of emotional neglect and was not explained by maternal exposure to other forms of childhood maltreatment or maternal distress during pregnancy. Thus, these results provide novel evidence that the absence of emotional support early in a mother's life, and years before conception, are associated with neural changes – namely, in the connectivity between amygdala and medial prefrontal regions – in her offspring.

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Early life adversity is linked to a number of negative health outcomes in one's own life, including increased risk for neuropsychiatric illnesses such as depression and anxiety (Green et al., 2010). This risk may be conferred in part via adversity-induced alterations in the hypothalamic pituitary adrenal (HPA) axis, one of the body's main stress response systems. Although some of these alterations are adaptive in the context of an acute stressor (e.g., preparing the body to fight, flight, or freeze), persistent HPA axis alterations can have detrimental effects long-term, including increased risk for psychopathology (e.g., Raymond, Marin, Majeur, & Lupien, 2018). Moreover, HPA axis alterations may have particularly potent effects if they occur early in life, for instance as a consequence of exposure to adverse experiences or parental deprivation during childhood (see Engel & Gunnar, 2019 for a recent review).

Recent behavioral work suggests that such adversity-associated risk may additionally be transmitted across generations, even if the stress occurs years before a child is born (Flory, Bierer, & Yehuda, 2011). For example, maternal experiences of physical and sexual abuse during her own childhood has been shown to increase her *child's* risk for anxiety (Robinson et al., 2019). In addition, maternal exposure to adversity early in life further predicts altered HPA axis functioning both in abused mothers and in their infants (Brand et al., 2010). Together, this work suggests that adversity that occurs years before a child is born can influence that child's neuropsychiatric risk from very early in life. Thus, to create effective preventative interventions, it is of the utmost importance to understand how adversity becomes biologically embedded to increase risk for neuropsychiatric disorders across generations.

The fetal stage of development has been proposed as a time when the intergenerational effects of early life adversity in the mother may be particularly likely to occur (Buss et al., 2017; Keenan et al., 2018). Early life adversity may lead to long-term alterations in an individual's HPA axis, immune functioning, and epigenome, all of which may have cascading effects on the eventual uterine environment in which a fetus develops during gestation. These biological alterations may lead to increased fetal exposure to circulating glucocorticoids, the final hormonal output of the HPA axis. In turn, fetal brain development, which occurs rapidly across gestation, may be impacted, particularly in regions that are rich in glucocorticoid receptors (e.g., the amygdala and medial prefrontal cortex). Although this theoretical model clearly identifies the intrauterine environment as a development stage when early life adversity in mothers may influence offspring development, empirical work is needed to provide support for this model of transmission in humans and to identify the biological sequelae of inheriting maternal adversity.

Of particular importance, little work to date has been able to tease apart the influence of adversity that occurred during a mother's childhood from the effects of prenatal adversity or adversity that occurs during the *child's* lifetime. Preventative interventions depend upon our understanding of how timing and type of maternal stress exposure impact child risk; similarly, it is necessary to determine how early in development we can observe the effects of maternal adversity on child stress regulation and emotional development given that these are early precursors of neuropsychiatric health (VanTieghem & Tottenham, 2018). Fortunately, recent technological advances in functional magnetic resonance imaging (fMRI), such as resting-state fMRI (rsfMRI) can aid this effort by enabling us to noninvasively examine brain functioning very early in life. The use of this methodology with neonates who have limited postnatal

exposure to their mothers additionally allows us to better parse apart the respective roles of maternal preconception, prenatal, and postnatal stress in shaping child development.

At least one recent study found that maltreatment from a mother's childhood predicted global volumetric differences in the brains of newborn babies, even after controlling for prenatal experiences of stress and depression (Moog et al., 2018). This work raises the possibility that experiencing adversity during a sensitive period of development (i.e., a mother's own childhood) could have potent intergenerational effects that are not fully explained by continued stress into the perinatal period or by the child's postnatal exposure to maltreatment-induced parenting alterations. Additional studies are needed to replicate this effect and, importantly, to determine whether maternal early life adversity impacts brain *function* into the next generation, especially since certain disorders may result from impaired functional circuitry rather than gross volumetric differences (Drevets et al., 2008). It is further necessary to determine whether any observable effects are driven by particular types of childhood adversity (e.g., neglect versus abuse) in order to better understand potential moderators of risk transmission.

Here, using a prospective longitudinal design and rsfMRI in neonates as young as one-month old, we asked just these questions, examining whether and how different maternal experiences of adversity during childhood yield intergenerational effects on neonatal frontoamygdala connectivity, a circuit that is often disrupted in the context of depression and anxiety. Specifically, we examined amygdala connectivity with two distinct regions within the mPFC – the dorsal anterior cingulate cortex (dACC) and the ventromedial prefrontal cortex (vmPFC). We selected these regions because prior work suggests they are functionally distinct components of the mPFC (De La Vega et al., 2016) that share differential connections to the amygdala (Kim, Gee, et al., 2011) and may be differentially impacted by maternal prenatal

distress (Posner et al., 2016). Whether maternal *childhood* adversity similarly associates with this neural circuitry in neonates has not yet been tested – the very question asked here.

Furthermore, we examined this question in a sample of African American (AA) mother-neonate dyads. We selected AA women for this study because 40 percent of AA women report experiencing trauma during childhood (Koenen et al., 2010) and AA individuals are at heightened risk for living in poverty (Proctor et al., 2016), an environmental circumstance that tracks closely with more frequent adverse experiences (Evans & English, 2002; Evans & Kim, 2013). Moreover, lifelong experiences of racial discrimination and other forms of chronic stress may increase accumulated physiological strain and stress sensitivity among AA women (Giscombé & Lobel, 2005), making them particularly sensitive to the influence of childhood and prenatal adversity.

Methods

Participants. Mothers were recruited from an ongoing longitudinal study that follows AA women through pregnancy (R01NR014800; Corwin et al., 2017) and across the first 18 months postpartum (1R01MD009746; Brennan et al., 2019). Women were recruited for the larger ongoing study during the first trimester of pregnancy (M=11.5 EGA, SD=2.5) from two major hospitals in the Atlanta area: Grady Memorial Hospital (a public hospital) and Emory Midtown Hospital (a private hospital), resulting in a socioeconomically diverse sample (see Table 1). A majority of women (>85%) additionally completed a second prenatal visit during the third trimester (M=26.4, SD=2.7). Forty-eight mother-neonate dyads (n=27 female infants) enrolled in the present study, which involved the neonate completing a 30-minute MRI scan at approximately 1 month postpartum (M=40 days, SD=15). Seven enrolled dyads were excluded from final analyses due to unusable data (see Figure 1), resulting in a final sample size of 41

neonates. As shown in Table 1, there were no differences in demographics or in measures of maternal adversity between dyads who were and were not included in final analyses.

Figure 1. Recruitment flow chart.

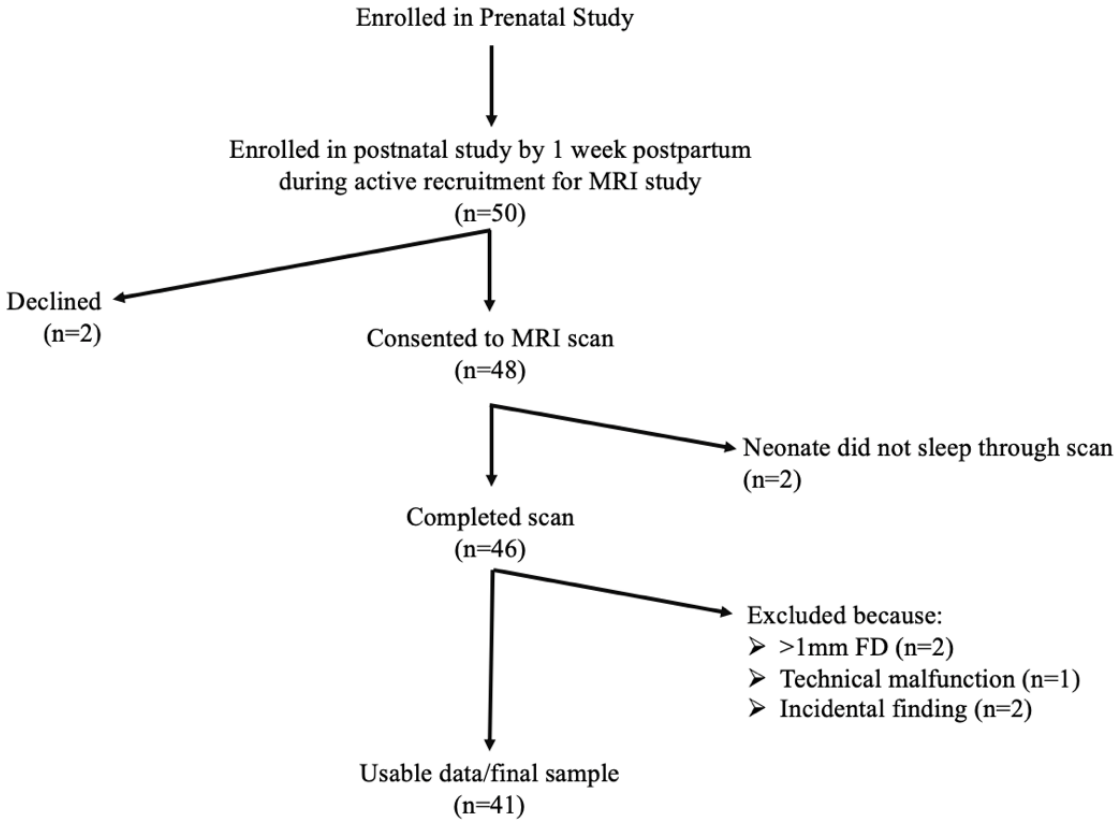


Table 1. Demographics of sample and differences between included and excluded dyads.

Variable	Included in final sample (n=41)	Excluded[+] (n=7)
Demographics		
Gestational age at birth, M (SD)	38.7 (1.4) weeks	38.5 (2.1)
Preterm, N (%)	3 (7.3) yes	1 (14.3)
Infant gestational age at scan, M (SD)	44.5 (2.8) weeks	44.2 (0.9)
Infant age at scan, M (SD)	41.2 (17.1) days	40.9 (15.8)
Infant sex, N (%)	23 (56.1) female	5 (71.4)
Cohabitating with partner, N (%)	16 (39.0) cohabitating	2 (28.6)
Mom ethnicity, N (%)	41 (100) African American	7 (100)
Mom education, N (%)	13 (31.7) some college or more	2 (28.6)
Insurance type, N (%)	8 (19.5) low-income Medicaid	0 (0)
Maternal Childhood Adversity		
CTQ emotional neglect, M (SD)	9.9 (5.5)	9.4 (5.2)
CTQ physical neglect, M (SD)	8.2 (3.6)	6.4 (2.7)
CTQ any moderate to severe abuse or neglect, N (%)	20 (48.8) yes	3 (42.9)
CTQ any sexual, physical, or emotional abuse, N (%)	15 (36.6) yes	4 (57.1)
Maternal Prenatal Distress		
1st Trimester EDS, M (SD)	7.1 (5.8)	5.6 (5.4)
1st Trimester PSS, M (SD)	23.0 (7.8)	19.4 (6.2)
1st Trimester STAI, M (SD)	33.4 (11.1)	30.3 (10.8)
3rd Trimester EDS, M (SD)	7.6 (5.6)	6.2 (8.7)
3rd Trimester PSS, M (SD)	22.9 (7.0)	21.6 (10.7)
3rd Trimester STAI, M (SD)	34.3 (10.7)	33.2 (11.3)

Note. There were no significant differences between mother-infant dyads who were and were not included in the final analyses. Dyads were excluded from the final sample because they did not sleep through the MRI scan (n=2), had too much motion during the scan (>1mm, n=2), data was lost due to technical malfunction (n=1), or there was an incidental finding that indicated non-normative neural development (n=2). CTQ=Childhood Trauma Questionnaire. EDS=Edinburgh Depression Scale. PSS=Perceived Stress Scale. STAI=State-Trait Anxiety Inventory.

Measures.

Maternal Childhood Adversity. Mothers' experiences of childhood adversity were assessed via retrospective report during the first trimester of pregnancy using the Childhood Trauma Questionnaire-Short Form (CTQ; Bernstein et al., 2003), a 28-item self-report questionnaire assessing objective and subjective evaluations of childhood abuse and neglect. The CTQ is comprised of five subscales: Sexual Abuse, Physical Abuse, Emotional Abuse, Physical Neglect, and Emotional Neglect. High scores are indicative of more severe neglect and abuse.

Forty-five percent (n=21) of women in the current sample reported experiencing at least one form of moderate to severe abuse or neglect during childhood, which is consistent with national prevalence rates of childhood trauma exposure among AA women (Koenen et al., 2010). Although experiences of neglect were common in this sample, few women reported childhood physical, emotional, or sexual abuse, resulting in severely restricted range for these variables. As such, these variables were dichotomized and combined into a single variable that reflected whether a mother was the victim of any sexual, physical, or emotional abuse as a child (Bernstein & Fink, 1998). Physical neglect and emotional neglect showed good range in our sample (physical neglect range: 5-17; emotional neglect: 5-24) and were therefore used in their continuous form to examine potential dosage effects.

Maternal Prenatal Stress. Maternal prenatal distress was measured via multiple self-report measures that were completed during the first trimester of pregnancy and again during the third trimester. The Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983; Cohen, 1988) assesses the degree of stress an individual perceives in their current life, and has demonstrated construct validity (Roberti et al., 2006). Mothers also completed the Spielberger State Trait Anxiety Inventory (STAI; Gaudry, Vagg, & Spielberger, 1975; Spielberger, Gorsuch, & Lushene, 1970), a 20-item measure that assesses state and trait-like anxiety and stress. Finally, mothers completed the Edinburgh Depression Scale (EDS; Cox, Holdenand, & Sagovsky, 1987) to assess current depressive symptoms. A composite prenatal distress variable was created from these three measures of prenatal adversity by standardizing and averaging the total score of the PSS, STAI, and EDS. The creation of this composite score was based

on a principle components analysis (PCA) completed with the full prenatal study cohort (n>500; Corwin et al., 2017) and visual inspection of correlations between the PSS, EDS, and STAI (See Table 2).

Table 2. Intercorrelations between primary measures of adversity.

	Childhood Maternal Adversity		*1st Trimester Maternal Distress*				*3rd Trimester Maternal Distress*		
	Emo. Neg.	**Phys. Neg.**	**PSS**	**STAI**	**EDS**	**Composite Distress**	**PSS**	**STAI**	**EDS**
Maternal childhood adversity									
Phys. Neg.	**r=0.69, p<0.001**	--	--	--	--	--	--	--	--
1st trimester maternal prenatal distress									
PSS	**r=0.50, p<0.01**	**r=0.39, p=0.01**	--	--	--	--	--	--	--
STAI	**r=0.74, p<0.001**	**r=0.58, p<0.001**	**r=0.55, p<0.001**	--	--	--	--	--	--
EDS	**r=0.52, p<0.01**	**r=0.42, p<0.01**	**r=0.64, p<0.001**	**r=0.59, p<0.001**	--	--	--	--	--
Comp Stress	**r=0.69, p<0.001**	**r=0.54, p<0.001**	**r=0.86, p<0.001**	**r=0.83, p<0.001**	**r=0.89, p<0.001**	--	--	--	--
3rd trimester maternal prenatal distress									
PSS	r=0.29, p=0.08	**r=0.35, p=0.03**	**r=0.63, p<0.001**	**r=0.55, p<0.001**	**r=0.48, p<0.01**	**r=0.64, p<0.001**	--	--	--
STAI	**r=0.53, p<0.01**	**r=0.51, p<0.01**	**r=0.51, p<0.01**	**r=0.74, p<0.001**	**r=0.60, p<0.001**	**r=0.70, p<0.001**	**r=0.66, p<0.001**	--	--
EDS	r=0.24, p=0.14	**r=0.44, p<0.01**	**r=0.45, p<0.01**	**r=0.55, p<0.001**	**r=0.69, p<0.001**	**r=0.64, p<0.001**	**r=0.58, p<0.001**	**r=0.66, p<0.001**	--
Comp Stress	**r=0.41, p=0.01**	**r=0.50, p<0.01**	**r=0.61, p<0.001**	**r=0.71, p<0.001**	**r=0.68, p<0.001**	**r=0.76, p<0.001**	**r=0.85, p<0.001**	**r=0.89, p<0.001**	**r=0.86, p<0.001**

Note. All measures of maternal prenatal distress (i.e., the PSS, STAI, and EDS) were positively correlated with each other in our final sample (n=41), supporting the creation of two composite measures of maternal prenatal distress: prenatal distress during the first trimester and prenatal distress during the third trimester. CTQ=Childhood Trauma Questionnaire. PSS=Perceived Stress Scale. STAI=State Trait Anxiety Inventory. EDS=Edinburgh Depression Scale. Comp. Distress=Composite prenatal distress (i.e., the average of PSS, STAI, and EDS standardized scores).

Infant MRI. All scanning procedures were completed by two trained research assistants and an MRI technician. After the mother completed an MRI safety screening form for her infant, the infant was weighed, swaddled, and encouraged to sleep by appropriate means (e.g., rocking, feeding). The infant was then fitted with earplugs (EAR Taper Fit™2) and disposable earmuffs (Natus Pediatrics MiniMuffs®) to reduce exposure to scanner noise and was placed in a MedVac infant immobilizer to reduce movement during scanning procedures. If the infant awoke during the scan, the scan was suspended, and the infant was physically comforted. When the infant calmed, one additional scan was attempted if the mother consented. While the infant was in natural sleep, the following scans were collected using a standard 32-channel head matrix coil: at least one echo planar imaging (EPI) resting state scan (TR=1000ms, TE=30, acquisition matrix=72 x 72 x 39, and voxel size=2.5 x 2.5 x 2.5 mm^3, 300 volumes), a T1 structural scan, and/or a T2w structural scan.

Preprocessing and data analysis. FSL (5.0.11) was used to analyze functional data. Preprocessing included motion correction, detrending, slice time correction, intensity normalization, and spatial smoothing using an 8mm FWHM Gaussian kernel. We also repeated all analyses after smoothing with a 5mm FWHM kernel and the results were unchanged. The first 20 volumes were discarded to account for scanner start, and images were bandpass filtered (0.01-0.08 Hz) to retain low-frequency signal. Signal from six motion parameters, signal from a 3mm sphere surrounding a voxel that was manually placed within the ventricle, signal from a 3mm white matter sphere, and the mean global signal were included as nuisance regressors.

ROI selection. ROIs were defined using a publicly available neonatal anatomical atlas (Shi et al., 2010), and included the amygdala, medial orbitofrontal cortex (i.e., vmPFC), and dACC. Parcels were registered from standard space to each participant's functional space using

the FSL linear registration tool. Visual inspection of each infant brain was used to validate parcel registration.

Resting-state correlation. Resting-state functional correlations were operationally defined as the correlation of the time-varying BOLD signal between two ROIs. After preprocessing, the continuous time series for each voxel within an ROI was extracted and averaged together to create an average time series for that ROI. The average time series for one ROI was then correlated with the average time series from another ROI. The resulting correlation coefficient (r) was transformed to Gaussian-distributed z-scores using Fishers transformation, and these z-scores were used as our measure of functional connectivity (FC) in further analyses (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Zhu, Zhang, Luo, Dilks, & Liu, 2011). We averaged ipsilateral connections from the right and left hemispheres (e.g., right amygdala to right dACC was averaged with left amygdala to left dACC) to create our measures of frontoamygdala connectivity. However, we examined left and right hemispheric connections separately in follow up analyses to determine whether the associations with maternal adversity were lateralized.

Data analysis plan. Descriptives and measures of variability were examined for all variables to assess for skew and kurtosis. Physical neglect and emotional neglect subscales from the CTQ were log transformed to correct for positive skew, which was effective at improving distribution normality. Hierarchical linear regressions were used to test study hypotheses, with relevant covariates (i.e., variables correlated with resting-state FC) entered into the first step, and the primary predictor variable entered in the second step. Cohen's f^2 was calculated as an additional measure of effect size (Selya, Rose, Dierker, Hedeker, & Mermelstein, 2012), with cutoffs for small (f^2=0.02), medium (f^2=0.15), and large (f^2=0.35) based on Cohen's (1988) guidelines. Linear regression assumptions were assessed in several ways. Unstandardized

residuals were visually examined using histograms to determine normality and residuals were plotted against predicted values to ensure homoscedasticity. Finally, Cook's D was used to identify potential outliers since it considers both leverage and discrepancy. Univariate ANCOVAs were used for analyses examining childhood abuse history as a predictor of neonatal connectivity.

Results

Preliminary analyses. Given that motion is a known confound of rsfMRI, we limited the effects of motion in several ways. In addition to correcting for motion during preprocessing, we excluded infants who had more than 1mm of framewise displacement from the analyses (n=2). Finally, we confirmed that frame to frame motion displacement was not associated with amygdala-dACC FC ($r(41)$=0.18, p=0.26) or amygdala-vmPFC FC ($r(41)$=-0.12, p=0.45) in our final sample. Neonatal framewise displacement was also unrelated to our measures of maternal adversity (p's>0.12).

Maternal childhood adversity. Next, we examined whether maternal experiences of neglect and abuse from her own childhood predicted frontoamygdala circuitry in neonates. Neither emotional (β=0.18, ΔR^2=0.03, f^2=0.03, p=0.27) nor physical neglect (β=0.03, ΔR^2<0.01, f^2<0.01, p=0.87) predicted amygdala-dACC connectivity in neonates. Neonatal amygdala-dACC FC also was not predicted by maternal exposure to abuse during childhood ($F(39,1)$=0.68, p=0.41).

By contrast, being emotionally neglected during a mother's own childhood predicted stronger positive amygdala-vmPFC FC in neonates (β=0.30, ΔR^2=0.09, f^2=0.10, p=0.04), even after controlling for relevant covariates (i.e., maternal education). That is, the more emotional neglect mothers experienced during their own childhood, the stronger the functional coupling

was between the amygdala and vmPFC in her neonate (see Figure 2). Moreover, the effect on amygdala-vmPFC FC was specific to emotional neglect from the mother's childhood. Maternal experiences of physical neglect did not predict amygdala-vmPFC FC in neonates (β=0.09, ΔR^2<0.01, f^2<0.01, p=0.53), nor did experiencing abuse during childhood (F(38,1)=0.39, p=0.54).

In follow-up analyses, we examined whether the effect of maternal exposure to emotional neglect during childhood was lateralized to one hemisphere of the neonatal brain (see Tables 3 and 4) given that previous research has found stronger associations between maternal stress and left hemispheric alterations in offspring (Acosta et al., 2019; Posner et al., 2016). The association between maternal childhood emotional neglect and neonatal amygdala-vmPFC FC remained when considering only the ipsilateral connection in the left hemisphere (β=0.30, ΔR^2=0.09, f^2=0.10, p<0.05) and a similar pattern of results emerged for right neonatal amygdala-vmPFC connectivity, but this association was only marginally significant (β=0.25, ΔR^2=0.06, f^2=0.06, p=0.09). These results suggest strong specificity for an intergenerational effect of childhood emotional neglect on frontoamygdala circuitry into the next generation.

Maternal prenatal adversity. The relationship between maternal childhood emotional neglect and neonatal frontoamygdala connectivity was not explained by maternal prenatal distress. Although childhood experiences of emotional neglect strongly predicted heightened maternal distress during the first (β=0.69, ΔR^2=0.47, f^2=0.89, p<0.001) and third (β=0.41, ΔR^2=0.17, f^2=0.20, p=0.01) trimesters of pregnancy, maternal prenatal distress did not significantly predict amygdala-dACC connectivity (*1st trimester distress:* β=-0.10, ΔR^2=0.01, f^2=0.01, p=0.56; *3rd trimester distress:* β=-0.10, ΔR^2<0.01, f^2<0.01, p=0.58) or amygdala-vmPFC

connectivity in neonates (*1st trimester distress:* β=0.10, ΔR^2=0.01, f^2=0.01, p=0.49; *3rd trimester distress:* β=0.02, ΔR^2<0.001, f^2<0.01, p=0.91).

After controlling for distress during the first trimester of pregnancy, maternal emotional neglect from childhood continued to show a marginally significant association with neonatal amygdala-vmPFC FC (β=0.35, ΔR^2=0.06, f^2=0.06, p=0.08), and remained a statistically significant predictor of left hemispheric amygdala-vmPFC FC in neonates (see Table 4). Intriguingly, controlling for first trimester maternal distress strengthened the effect of maternal childhood emotional neglect on neonatal amygdala-dACC FC, making it marginally significant and more than doubling the amount of unique variance accounted for by maternal childhood emotional neglect (β=0.38, ΔR^2=0.08, f^2=0.09, p=0.09). In examining left and right ipsilateral connections separately, this effect was primarily driven by the left hemisphere (β=0.49, ΔR^2=0.11, f^2=0.12, p=0.03; see Table 3). Controlling for maternal distress during the third trimester of pregnancy yielded similar results that also appeared to be primarily driven by connectivity alterations within the left hemisphere (see Tables 3 and 4). Including maternal distress during pregnancy in our model also did not change associations between maternal childhood physical neglect and neonatal frontoamygdala FC (*amygdala-dACC FC*: β=0.12, ΔR^2=0.01, f^2=0.01, p=0.55; *amygdala-vmPFC FC:* β=0.07, ΔR^2<0.01, f^2<0.01, p=0.70), or between maternal childhood abuse and neonatal frontoamygdala FC (*amygdala-dACC FC:* F(38,1)=0.77, p=0.39; *amygdala-vmPFC FC:* F(37,1)=0.33, p=0.57).

Medial prefrontal connectivity. Finally, we examined whether experiences of emotional neglect from the mother's childhood predicted alterations in neonatal FC between our two frontal regions of interest. As shown in Figure 2, mothers' childhood emotional neglect did not predict dACC-vmPFC FC before (β=-0.04, ΔR^2<0.01, f^2<0.01, p=0.81) or after controlling for first

trimester prenatal distress (β=-0.11, ΔR^2<0.01, f^2<0.01, p=0.64). This finding suggests the intergenerational impact of early life emotional neglect is specific to communication between the amygdala and mPFC, at least at this early stage of development.

Table 3. Predictors of ipsilateral connectivity between the amygdala and dACC.

	β	t	b 95% CI	p	R^2	ΔF	ΔR^2
Outcome: Left neonatal amygdala-dACC FC							
Step 1					<0.01	0.12	<0.01
1st Trimester Prenatal Distress	-0.05	-0.35	-0.12, 0.08	0.79			
Step 1					<0.01	0.12	<0.01
3rd Trimester Prenatal Distress	-0.06	-0.34	-0.11, 0.08	0.72			
Step 1					<0.01	0.12	<0.01
1st Trimester Prenatal Distress	-0.05	-0.35	-0.11, 0.07	0.73			
Step 2					**0.11**	**4.70**	**0.11**
Childhood Emotional Neglect	**0.49**	**2.29**	**0.01, 0.17**	**0.03**			
Step 1					<0.01	0.17	<0.01
1st Trimester Prenatal Distress	-0.07	-0.41	-0.10, 0.07	0.69			
Step 2					0.02	0.55	0.01
Childhood Physical Neglect	0.14	0.74	-0.30, 0.65	0.46			
Outcome: Right neonatal amygdala-dACC FC							
Step 1					0.02	0.58	0.02
1st Trimester Prenatal Distress	-0.12	-0.76	-0.12, 0.05	0.45			
Step 1					0.01	0.49	0.01
3rd Trimester Prenatal Distress	-0.11	-0.70	-0.12, 0.06	0.49			
Step 1					0.02	0.58	0.02
1st Trimester Prenatal Distress	-0.12	-0.76	-0.12, 0.05	0.45			
Step 2					0.05	1.27	0.03
Childhood Emotional Neglect	0.24	1.13	-0.04, 0.14	0.27			
Step 1					0.02	0.69	0.02
1st Trimester Prenatal Distress	-0.12	-0.76	-0.12, 0.05	0.45			
Step 2					0.02	0.17	<0.01
Childhood Physical Neglect	0.08	0.41	-0.39, 0.60	0.68			

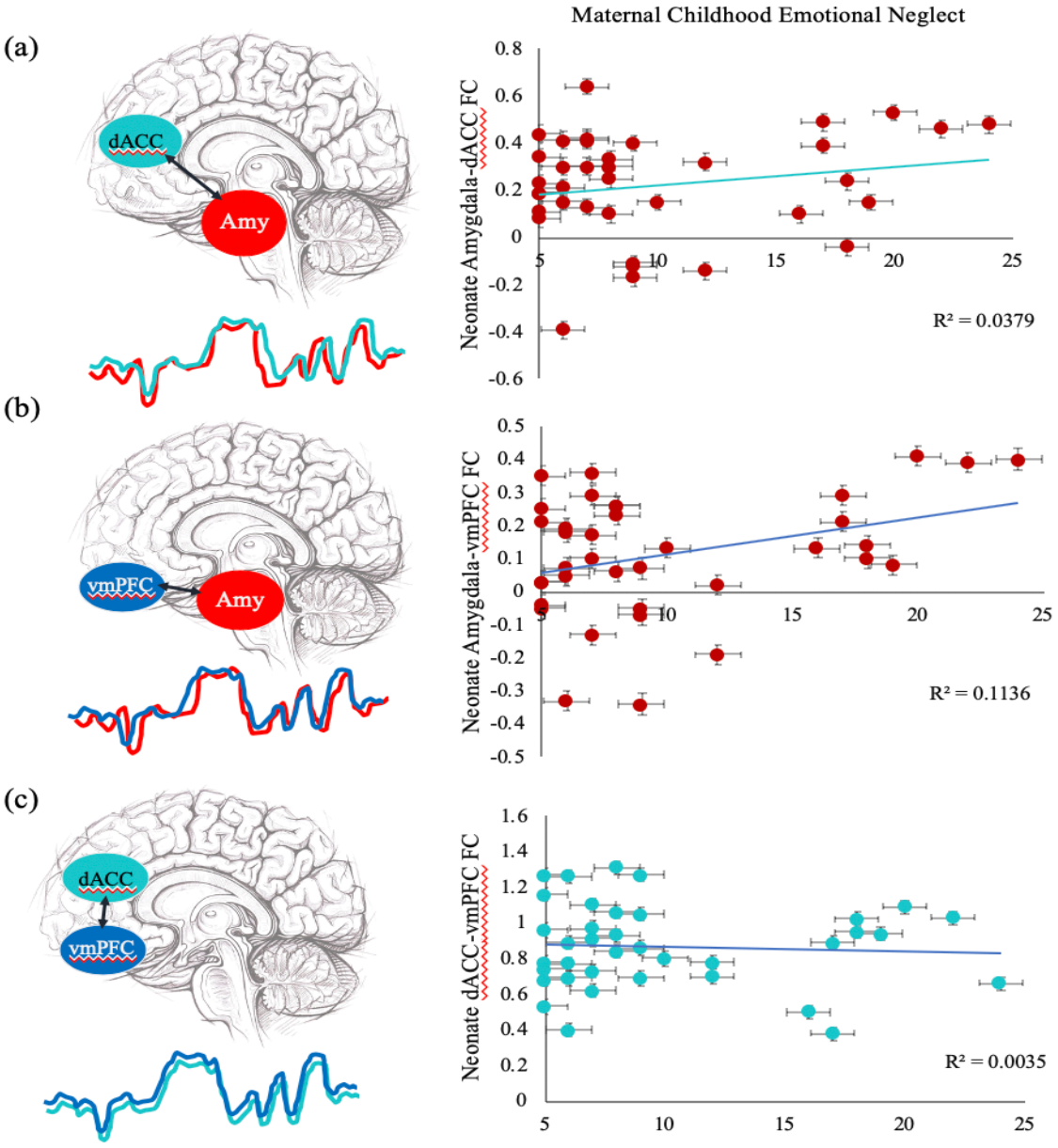
Note. We examined different types of maternal adversity as predictors of neonatal amygdala-dACC connectivity separately for ipsilateral connections within the left and right hemispheres. Mothers' experiences of emotional neglect from her childhood predicted stronger functional coupling of the amygdala and dACC in neonates on average one month after birth, particularly for the left hemispheric ipsilateral connection. This effect persisted even after controlling for maternal prenatal adversity. Results are similar when controlling for prenatal distress during the 3rd trimester instead of during the 1st trimester.

Table 4. Predictors of ipsilateral connectivity between the amygdala and vmPFC by hemisphere.

	β	**t**	**b 95% CI**	**p**	**R^2**	**ΔF**	**ΔR^2**
Outcome: Left neonatal amygdala-vmPFC FC							
Step 1					0.13	5.71	0.13
Maternal education	0.36	2.39	0.02, 0.26	0.02			
Step 2					0.13	0.21	<0.01
1st trimester distress	0.07	0.46	-0.05, 0.08	0.65			
Step 1					0.11	4.58	0.11
Maternal education	0.33	2.14	0.01, 0.26	0.04			
Step 2					0.11	0.05	<0.01
3rd trimester distress	0.04	0.22	-0.06, 0.08	0.83			
Step 1					0.15	3.28	0.15
Maternal education	0.38	2.46	-0.69, 0.003	0.02			
1st trimester distress	0.05	0.35	-0.05, 0.07	0.73			
Step 2					**0.24**	**4.20**	**0.09**
Childhood emo. neglect	**0.41**	**2.05**	**0.004, 0.70**	**0.048**			
Step 1					0.15	3.28	0.15
Maternal education	0.38	2.46	0.03, 0.27	0.02			
1st trimester distress	0.05	0.35	-0.05, 0.07	0.73			
Step 2					0.16	0.58	0.01
Childhood phys. neglect	0.14	0.76	-0.23, 0.51	0.45			
Outcome: Right neonatal amygdala-vmPFC FC							
Step 1					0.19	9.35	0.19
Maternal education	0.44	3.06	0.07, 0.33	<0.01			
Step 2					0.21	0.59	0.01
1st trimester distress	0.11	0.77	-0.04, 0.10	0.45			
Step 1					0.17	7.79	0.17
Maternal education	0.42	2.79	0.05, 0.32	<0.01			
Step 2					0.17	<0.01	<0.001
3rd trimester distress	<0.001	<0.001	-0.08, 0.08	1.00			
Step 1					0.23	5.62	0.23
Maternal education	0.46	3.16	0.07, 0.33	<0.01			
1st trimester distress	0.10	0.65	-0.05, 0.09	0.52			
Step 2					0.29	3.11	0.06
Childhood emo. neglect	0.34	1.77	-0.002, 0.03	0.09			
Step 1					0.23	5.62	0.23
Maternal education	0.46	3.16	0.07, 0.33	<0.01			
1st trimester distress	0.10	0.65	-0.05, 0.09	0.52			
Step 2					0.23	<0.01	<0.001
Childhood phys. neglect	-0.007	-0.04	-0.41, 0.40	0.97			

Note. We examined different types of maternal adversity as predictors of neonatal amygdala-vmPFC connectivity separately for ipsilateral connections within the left and right hemispheres. Mothers' experiences of emotional neglect from her childhood predicted stronger functional coupling of the amygdala and vmPFC in neonates on average one month after birth, particularly for the left hemispheric ipsilateral connection. This effect persisted even after controlling for maternal prenatal adversity. Results are similar when controlling for prenatal distress during the 3rd trimester instead of during the 1st trimester.

Figure 2. The functional correlation between the amygdala and dACC in each neonate was calculated by averaging the BOLD time series of each voxel within the ROI mask and correlating the average time series of the amygdala with the average time series of the dACC. The same procedure was used to calculate the functional correlation (FC) between the amygdala and vmPFC and between the dACC and vmPFC. Next, maternal experiences of adversity were examined as predictors of these FCs in 1-month-old sleeping neonates. (a) There was a marginal effect of maternal childhood neglect predicting amygdala-dACC FC in neonates. (b) However, a moderately sized effect emerged for emotional neglect from the mother's own childhood predicting stronger amygdala-vmPFC FC. (c) Maternal childhood neglect did not predict neonatal vmPFC-dACC FC.



Discussion

This study is the first to examine associations between maternal experiences of early life adversity and neonatal neural connectivity. We found that maternal childhood experiences of emotional neglect robustly predict *stronger* functional coupling between the amygdala and vmPFC and between the amygdala and dACC in the next generation. These effects were primarily driven by alterations to ipsilateral frontoamygdala connections within the left hemisphere. Importantly, changes in neonatal frontoamygdala connectivity were specific to emotional neglect and persisted even when controlling for relevant statistical covariates and prenatal distress. These novel findings illustrate that certain experiences from a mother's own childhood are associated with differences in the development of frontoamygdala circuitry in the next generation as early as one month after birth.

Notably, mothers being emotionally neglected during their own childhood predicted *strengthened* functional coupling of the amygdala with medial prefrontal regions in offspring. This enhanced positive coupling is especially interesting given that connectivity between these regions increases in the context of fear learning (Tzschoppe et al., 2014) and following an acute stressor (van Marle, Hermans, Qin, & Fernández, 2010). The present results are also consistent with the stress acceleration hypothesis (Callaghan & Tottenham, 2016), which posits that exposure to emotional neglect (e.g., parental deprivation) and other forms of early life stress may lead to the early maturation of frontoamygdala circuitry. This accelerated development may predispose children to more readily detect threat or to self-regulate in an environment that lacks the buffering influence of an involved caregiver. However, this early acceleration may also come at the cost of decreasing neural plasticity (Tottenham, 2019) and increasing risk for anxiety disorders long-term. Indeed, descriptive research shows stronger resting-state FC between the

amygdala and mPFC among individuals with anxiety disorders (Kim, Gee, et al., 2011), which is consistent with the observed neural phenotype we found in neonates of emotionally neglected mothers. Our findings contribute to extant research by showing that childhood experiences of emotional neglect may also strengthen frontoamygdala FC into the next generation. However, more work is needed to determine whether the present results represent accelerated development, transient increases in frontoamygdala connectivity, or persistently high functional correlations between frontoamygdala regions.

It is important to note that the behavioral consequences of strengthened connectivity between the amygdala and mPFC *during the neonatal period* remain unclear. Indeed, there is evidence that certain regions do not develop functional selectivity before six months of age, but instead are refined after months, or even years, of postnatal experience (Deen et al., 2017). Although the functions of many regions during the neonatal period remain unknown, examining resting-state FC patterns still offers important insight into the developing brain given that connectivity between regions may precede the development of functional selectivity (Kamps, Hendrix, Brennan, & Dilks, 2020). Moreover, neural connectivity patterns early in life can be used to predict what a specific region will become selective for in the future (Li, Osher, Hansen, & Saygin, 2019) as well as future emotional functioning in children (Thomas et al., 2019). In sum, the inputs of a given region (i.e., what it is connected to) may drive its specialization later in development, making infant resting-state connectivity patterns a promising tool for understanding the neural underpinnings of neuropsychiatric illness and risk transmission.

The association between maternal childhood emotional neglect and infant frontoamygdala connectivity was not explained by maternal prenatal distress in the present study. This result was surprising given that at least one other study found that maternal prenatal

depression (which was included in our composite prenatal distress measure) modulates amygdala-dACC and amygdala-vmPFC connectivity in neonates (Posner et al., 2016). Although we used similar analytic techniques, sampling differences may explain our inability to replicate this effect. Our sample is comprised entirely of AA mother-neonate dyads which is rare among neuroscientific research (e.g., in Posner et al. (2016), AA dyads made up less than 13% of the study sample). It is possible that early life adversity impacts neonatal frontoamygdala connectivity more strongly than prenatal adversity specifically for AA mother-neonate dyads. Indeed, recent work suggests that AA individuals are more impacted by early life adversity compared to their European American counterparts and that these differences persist into adulthood (Slopen et al., 2010). Such differences speak to the importance of increasing sample diversity in developmental neuroscience, and are consistent with findings that suggest sample ethnicity and socioeconomic status influence study findings related to brain development (Falk et al., 2013). The present study makes an important contribution to the field by examining brain development in an underrepresented sample who may be disproportionately exposed to and affected by adversity.

There may also be other mediating processes that were not measured in the present study. Evidence suggests that early adversity may induce lasting epigenetic changes – such as alterations to DNA methylation, which in turn controls gene expression (Jawaid, Roszkowski, & Mansuy, 2018) – that can influence the uterine environment during pregnancy and shape offspring neurodevelopment. For example, increased methylation (and decreased expression) of the 11β-HSD-2 gene has been demonstrated in women exposed to early adversity (Bierer et al., 2014). 11β-HSD-2 regulates fetal exposure to glucocorticoids by converting cortisol to its benign form (i.e., cortisone) as it crosses the placental barrier. Therefore, offspring of mothers with

reduced 11β-HSD-2 expression are likely exposed to elevated levels of cortisol *in utero,* which has been associated with an increased risk for depression and anxiety across the lifespan (Harris & Seckl, 2011). Elevated glucocorticoid levels have also been shown to mediate the association between early maternal separation (an extreme form of childhood emotional neglect) and increased frontoamygdala connectivity in children (Gee et al., 2013).

Notably, reduced 11β-HSD-2 expression is most strongly associated with women's exposure to *early* versus later life adversity (Bierer et al., 2014). This aligns with the finding from the present study that maternal experiences of emotional neglect during her childhood were more closely associated with offspring frontoamygdala connectivity compared to maternal distress during pregnancy. Together, it is possible that emotional neglect during childhood enacts epigenetic alterations that lead to elevated fetal glucocorticoid exposure, which in turn strengthens frontoamygdala circuitry in neonates.

Although we identified effects on child neural connectivity strikingly early in development, these neonates were exposed to one month of parenting before completing the fMRI scan. This first month of parenting behavior, although limited, could mediate the relationship between maternal childhood emotional neglect and offspring neural development as mothers who were emotionally neglected during their own childhood may engage in fewer behaviors that buffer their neonate from the effects of stress (Bert, Guner, & Lanzi, 2009). For instance, these mothers may be slower to pick up their newborn infant when he/she cries, which offers the infant more opportunities to self-soothe. These repeated opportunities to self-soothe may contribute to the strengthened frontoamygdala connectivity observed in this study. Mothers who were emotionally neglected as children may also continue to lack emotional support during pregnancy and early in the postnatal period. This lack of emotional support may manifest as the

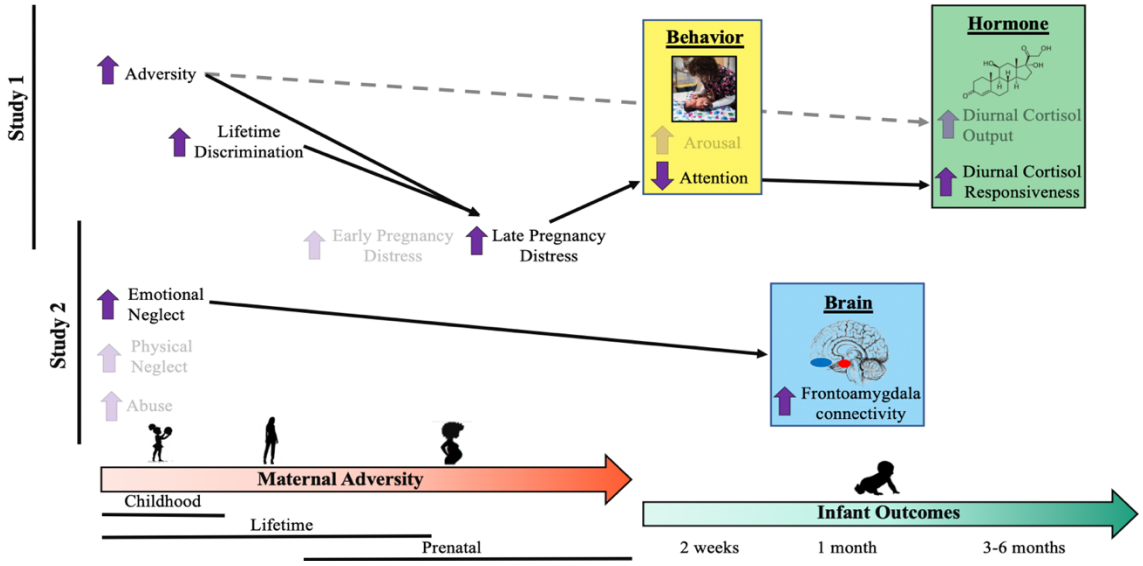
infant's father being less involved and less available to offer sensitive parenting in the manner described above. Indeed, in our sample, only 37% of women co-habitated with a partner.

The findings from this novel study suggest that childhood experiences of emotional neglect may have potent intergenerational effects on infant neural connectivity and especially on left hemispheric frontoamygdala circuitry. This finding advances our knowledge of factors that shape the development of emotion-related neural circuits and highlights that certain maternal experiences that occur years before conception may shape child development in impactful ways. It will therefore be important to include measures of maternal early life adversity in future research examining the effects of prenatal stress on child development in order to delineate cumulative, interactive, or competing effects. In turn, this will lay the groundwork for creating a comprehensive model that explains the intergenerational transmission of adversity and neuropsychiatric risk.

General Discussion

The overarching goal of this dissertation was to explore the intergenerational influence of maternal stress during pregnancy on infant stress functioning across multiple levels of analysis. The hypothesis that prenatal distress would exert potent programming effects on infant behavior, HPA axis activity, and neural connectivity was partially supported. Prenatal distress predicted alterations in neonatal behavior but did not predict infant diurnal cortisol or frontoamygdala circuitry. Instead, we found adversity *from a mother's own childhood* to predict stronger frontoamygdala circuitry in infants as well as trend-level increases in infant diurnal cortisol output, over and above a mother's experience of prenatal distress (see Figure 1 for graphical depiction of dissertation findings across both studies). These novel findings raise the intriguing possibility that different types and timing of adversity become biologically embedded through a variety of mechanisms, even into the next generation. Taken together, these two papers suggest the need to broaden our conceptualization of intergenerational adversity transmission to include maternal stress prior to pregnancy, and even as far back in time as her own childhood. Such work is necessary in order to illuminate the developmental origins of psychological risk.

Figure 1. Summary of dissertation findings.



Does prenatal stress confer psychological risk or enhanced plasticity?

In Study 1, prenatal maternal distress late in gestation was associated with decreased attention shortly after birth in the context of a stressor paradigm. One interpretation of these findings presumes that newborn attention is an early marker of later executive functioning abilities. This interpretation is consistent with research that links prenatal stress to impaired executive functioning in childhood (Neuenschwander et al., 2018), which in turn may hold implications for a child's psychological risk. Although attentional control by 6 months of age is considered to be a foundational skill underlying executive functioning ability in childhood, it remains unclear whether attention orienting during the neonatal period is a stable marker of future executive functioning abilities (Hendry, Jones, & Charman, 2016). Our finding of lower newborn attention in the context of stress may not necessarily predict long-term executive functioning deficits.

The association between attention orienting and cortisol also shows an interesting connection across levels of analysis, namely behavior to biomarker, and may offer additional insight into how to interpret the finding linking prenatal stress to decreased orienting in newborns. Greater HPA axis daily responsiveness reflects heightened sensitivity of this neurobiological system and may be a biological marker of enhanced sensitivity to environmental input more broadly (Boyce & Ellis, 2005; Del Giudice et al., 2011; Hartman & Belsky, 2018). In Study 1, lower newborn attention predicted greater HPA axis responsivity, which raises the possibility that inter-individual differences in early attention orienting, at least in the context of stress, may be markers of sensitivity to environmental input rather than early markers of executive functioning per se (Aron, Aron, & Jagiellowicz, 2012). Infants who are more sensitive to environmental input may struggle to filter out unimportant information, leading them to

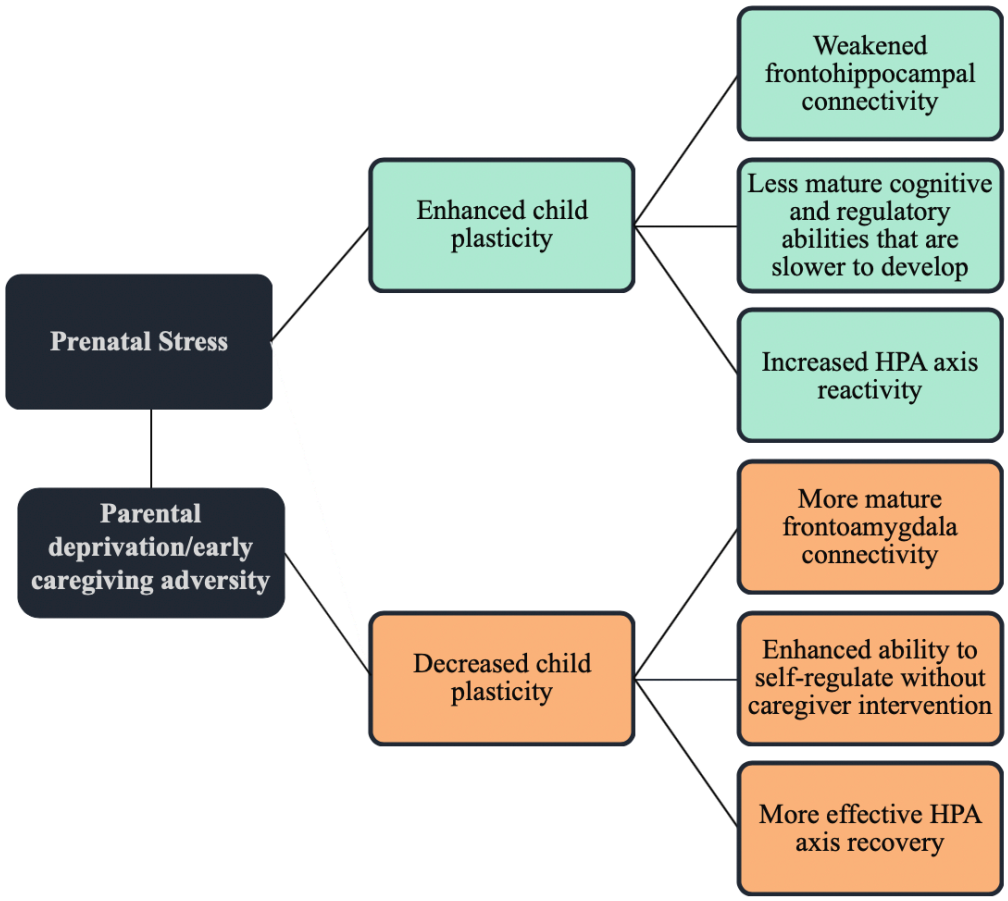
exhibit lower performance on orienting tasks, particularly when they are required to complete them in a stressful context.

There is also some evidence that early attention orienting and HPA axis responsivity are regulated by overlapping neural mechanisms, such as the PFC. Lesion studies reveal that damage to the dorsolateral prefrontal cortex interrupts an individual's ability to orient their attention to objects in the contralateral visual field (Barcelo et al., 2000; Szczepanski et al., 2014) and damage to the vmPFC seems to yield specific effects on visual attention to emotionally valenced faces (Richard et al., 2014). The vmPFC is additionally involved in modulating emotional responses (Rule, Shimamura, & Knight, 2002), diurnal HPA axis activity (Urry et al., 2006) – again, a purported marker of environmental sensitivity (Del Giudice, Ellis, & Shirtcliff, 2011; Ellis & Del Giudice, 2019; Hartman & Belsky, 2018) – and can be impacted by prenatal stress exposure (Mareckova et al., 2019), making it a potential neural mechanism that could underlie attentional control and environmental sensitivity.

Pluess and Belsky (2011) argue that exposure to prenatal stress does not inherently lead to negative child outcomes, but instead confers enhanced sensitivity to the postnatal environment. That is, maternal stress during pregnancy may indicate a changing or unpredictable extrauterine environment, leading the fetus to become more sensitive to postnatal influences and more readily able to adapt to an unpredictable context. Our results do not fully support this argument given that maternal prenatal distress continued to predict lower newborn attentional abilities even after controlling for the same maternal stress measure postnatally. Instead, the present results suggest the need to consider stress that occurs prior to pregnancy and during sensitive times in the mother's own life (i.e., during childhood) rather than exclusively examining stress that occurs during pregnancy and forward (i.e., during the child's postnatal

life). Thus, as we try to elucidate the overall model of how maternal stress shapes child development, it is important to broaden our conceptualization of the types and timing of maternal adversity that can yield intergenerational effects. A potential conceptual model based on findings from Study 1 and Study 2 is depicted in Figure 2.

Figure 2. Conceptual model describing the potential competing effects of maternal prenatal and early life stress.



Competing effects: Infants show premature neural development in the context of maternal early life neglect

In Study 2, we found robust evidence that maternal experiences of emotional neglect from her own childhood predict stronger amygdala-vmPFC and amygdala-dACC connectivity in neonates. Although follow up neuroimaging visits are required to confirm this interpretation, one

possibility is that these neural phenotypes represent accelerated development (Callaghan & Tottenham, 2016). Certain neural systems, such as frontoamygdala circuitry, are typically slow to develop across childhood, thereby prolonging plasticity and offering ample opportunity for caregivers to shape their development (Tottenham, 2019). However, in the absence of caregiving figures – for instance in the context of emotional neglect or institutionalization – early maturation of frontoamygdala circuitry can occur, with younger children evidencing more mature patterns of frontoamygdala connectivity that are typically not observed until adolescence (Gee et al., 2013). Such findings gave rise to the stress acceleration hypothesis, which posits that early parental deprivation leads to the premature maturation of neural systems involved in self-regulation and threat detection (i.e., frontoamygdala circuitry). This premature development sacrifices the benefits of prolonged plasticity in favor of greater independence, which may enhance survival in the context of absent or inconsistent caregiving (Callaghan & Tottenham, 2016). The findings from Study 2 are consistent with and extend this theory by showing that early caregiving adversity may even accelerate frontoamygdala development into the next generation. Indeed, the effect of early caregiving adversity may be potent enough to overshadow the effects of prenatal stress on this neural circuitry. The pattern of findings across Study 1 and Study 2 raises an interesting question about the situations in which maternal adversity may decrease, versus increase, plasticity of developing biobehavioral networks and processes.

If early caregiving adversity accelerates development, but prenatal stress slows development (i.e., enhances plasticity), how do these competing processes interact with one another? One answer to this question is that the competing effects of prenatal stress may occur via differential impacts on other neural circuits not examined in Study 2. Although speculative, it is possible that prenatal stress slows development (and thereby enhances plasticity) of neural

circuits that are specifically involved in attentional and cognitive development while maternal early life neglect accelerates circuitry underlying emotion regulation. In preliminary support of this possibility, a recent study found that maternal distress during the 3rd trimester was associated with weaker frontohippocampal functional connectivity in neonates, which in turn was linked to worse memory at 4 months of age (Scheinhost et al., 2020). Such findings suggest that prenatal stress has either damaged this circuitry, thus leading to weaker connectivity, or has slowed its development, thereby prolonging its plasticity. Additional longitudinal research is needed to determine whether this prenatal distress-induced neural phenotype 1) can be replicated in diverse samples, 2) represents slowed vs. halted development, and 3) is impacted by stress from other times in the mother's life, such as her childhood. It will also be important to examine whether prenatal stress interacts with lifetime discrimination and/or childhood adversity to shape neonatal neural connectivity more broadly. We were underpowered to examine such interactions, but this remains an important and intriguing question for future research.

We are only beginning to understand the intergenerational impacts of early life stress. Results from Study 2 and trend-level findings from Study 1 (i.e., that maternal childhood adversity was marginally related to infant HPA axis activity) highlight the long-term influence of early stress exposure on an individual's own stress responses and on stress functioning observed in the next generation. Understanding the specific impact of prenatal stress on infant development becomes increasingly complicated given 1) the demonstrated association of maternal early life stress with continued maternal stress into the perinatal period and 2) the strong impact of maternal early life stress into the next generation. Growing evidence suggests that maternal early life adversity exerts lasting biological changes into adulthood, and that some of these changes may have significant impacts on the intrauterine environment. For instance,

experiencing adversity prior to conception, especially during childhood, has been linked to decreased expression of 11β-HSD-2 (Bierers et al., 2014), an enzyme that converts cortisol to inactive cortisone. The expression of 11β-HSD-2 in the placenta protects the developing fetus from excessive exposure to maternal glucocorticoids, but prenatal stress, similar to childhood adversity, decreases the expression of placental 11β-HSD-2 (Glover, 2015; Pena, Monk, & Champagne, 2012). Given the overlap in these adversity-related biological alterations, it remains unclear *how* early life stress (particularly caregiving adversity) would yield potential accelerating effects on brain development while prenatal distress may slow other aspects of postnatal development. Disentangling the biological changes in the intrauterine environment that underlie these differences in biobehavioral outcomes in infancy and beyond is an important next step in future research.

Future Directions

Both Study 1 and Study 2 controlled for postnatal stress exposure statistically and by studying stress functioning when postnatal exposure is inherently limited (i.e., at a very young age, as early as 2 weeks postpartum on average). Although these are strengths of the present studies, these remain imperfect controls for postnatal exposure. Yet, there is hope we will be better able to control for postnatal exposures in future studies. Recent technological advances in fertility will enable researchers to conduct carefully controlled natural experiments on prenatal stress exposure in human participants. Using a combination of IVF and adoption (Rice et al., 2010), psychologists may be able to replicate the cross-fostering studies in animal models that completely control for postnatal exposures and have thus played a crucial role in enhancing our understanding of the unique impact of prenatal stress on child development. Advances in fetal MRI (van den Huevel & Thomason, 2016) will additionally enable researchers to examine brain

development earlier than ever before to determine whether the intergenerational signatures of maternal adversity are present even before birth. These exciting scientific advances lay the groundwork for breakthrough discoveries in the field of developmental neuroscience and in the study of intergenerationally transmitted adversity-induced biobehavioral alterations.

Many models of early life stress exposure inherently infer or imply that responses to stress are necessarily detrimental to development (e.g., diathesis stress, allostatic load). However, it remains possible, and even likely, that adapting to a stressful environment confers protective benefits such as enhanced likelihood of survival or earlier reproduction in the context of future stress (Ellis & DelGuidice, 2019). These adaptations may come at a cost, such as increased risk for psychopathology like depression and anxiety, with decades of research exposing many negative consequences of early stress exposure. Yet an exclusive focus on risk may be limiting. For instance, in adults who experienced childhood maltreatment, resilience (i.e., the lack of psychopathology) is linked to effective downregulation of amygdala activity by the mPFC and strengthened frontoamygdala connections (Moreno-López et al., 2019). We observed a similar neural phenotype (stronger functional connectivity between the amygdala and mPFC) in infants whose mothers were exposed to emotional neglect in childhood. It is possible this enhanced frontoamygdala connectivity in infancy is indicative of premature self-regulatory development (and potentially decreased neural plasticity) or increased risk for anxiety long-term, but it is also possible that this neural phenotype represents a compensatory process that may ultimately confer resilience for these infants. It will be necessary to follow these infants over time to determine what this neural phenotype indicates about their long-term outcomes.

Without considering the potential protective aspects of stress-induced adaptations, it will be difficult to fully understand how stress induces lasting changes in our behavior and biology,

and why those changes would be transmitted across generations. If we do not understand the protective benefits of stress-related adaptation in addition to its risks, we could unknowingly design interventions that change helpful aspects of stress-induced adaptation and create just as many, if not more, problems than we solve. Additionally, it remains an open question of how and why some individuals do not develop psychiatric illnesses in the context of early and intergenerational stress exposure. As clinical scientists, it is equally important that we study health in addition to studying disease. In particular, learning how to identify these resilient individuals early in life and illuminating which aspects of their neurobiological development confer resilience in the context of adversity could significantly improve our individual, group, and societal interventions.

The importance of sample diversity

Several findings from previous studies were not replicated in our sample of mixed SES AA mother-infant dyads. For instance, we did not find an association between prenatal distress and infant arousal or between prenatal distress and infant HPA axis activity, both of which have been identified in middle to high SES, predominantly Caucasian samples (Davis, Glynn, Waffarn, & Sandman, 2011; Tollenaar et al., 2011). These discrepant findings underscore the importance of sample diversity as well as the importance of replicating findings across and within different racial, ethnic, and socioeconomic groups (Nielson et al., 2017). Such replication is integral to avoiding the pitfall of misconstruing culturally and racially specific findings as universal phenomena.

Some processes that were previously believed to be universal across people have been guided by ancestral history in surprising ways. For instance, weighting a sample to better represent U.S. Census data changes associations between age and brain volumes, with a

representative sample showing earlier brain maturation compared to the original convenience sample (LeWinn et al., 2017). Among other differences, the original convenience sample was oversampled for Caucasians and was of higher SES compared to the actual U.S. population. Novel evidence also suggests that placental responses to prenatal stress may differ between Caucasian and non-Caucasian samples (Capron, Ramchandani, & Glover, 2018). Although prenatal distress has repeatedly been linked to decreased 11β-HSD-2 placental expression (O'Donnell et al., 2012; Monk et al., 2016; Seth et al., 2015) and decreased expression of the glucocorticoid receptor gene NR3C1(Conradt, Lester, Appleton, Armstrong, & Marsit, 2013; Isgut et al., 2017), these associations are not present among UK minority women (Capron, Ramchandani, & Glover, 2018). Although the study from Capron, Ramchandani, and Glover (2018) did not focus on AA women in particular, it still raises the interesting possibility of race-related differences in placental functioning and offers potential insight into why some of the expected associations between prenatal stress and infant outcomes were not observed in our sample of AA mother-infant dyads. It is also possible that some associations observed in predominantly Caucasian samples do not generalize because certain stressors are uniquely experienced by AA women in the United States (Lu & Halfon, 2003).

Although the present sample of AA mother-infant dyads is fairly diverse in terms of SES, it remains likely that we are still missing families who live in extreme poverty and/or have the highest levels of stress given our sampling strategy. Because we recruited from prenatal clinics in Atlanta, all women in our study were receiving prenatal care during their first trimester of pregnancy. Many women who live in extreme poverty or other intensely stressful conditions may not realize they are pregnant as early as the first trimester, preventing them from seeking medical

care. Even if these women do realize they could be pregnant, they may not be able to access prenatal care, again preventing them from enrolling in the present studies.

Such sampling bias is not unique to this dissertation. Enrolling and retaining disproportionately affected families in research is pragmatically difficult for a number of reasons (e.g., transportation issues, inconsistent phone access, housing instability, etc.). Despite these challenges, it is necessary to include these difficult-to-reach individuals in our research if we are to truly understand the human condition across typical and extreme conditions. While we work to overcome the challenges of contacting, enrolling, and retaining these families in studies, it is important to remember the individuals who are excluded from participation in scientific research and to consider the impact their *absence* exerts on study findings.

Conclusion

The two studies in this dissertation both challenge and extend current theory and research practices in the field of prenatal stress research. In addition to highlighting the importance of replicating extant findings in AA mother-infant dyads, these papers showcase the benefits of expanding our narrow conceptualization of the intergenerational impacts of maternal stress to include adversity from as early as a mother's childhood. These papers are also unique in that they combine infant neuroimaging, salivary assays, and behavior, thus enhancing our understanding of how adversity becomes biologically embedded into the next generation and how it manifests in a variety of measurable outcomes. Exploring this biological embedding across multiple levels of analysis aids in identifying converging and diverging findings and is integral to understanding, and potentially disrupting, the intergenerational cycle of adversity-associated psychological risk.

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