The Impact of Prenatal Stress on the Development of Limbic System Structures

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Abstract

Stress in early life is well documented as detrimental for the brain’s developmental trajectory, while prenatal stress is minimally explored. In the prenatal period, the placenta prevents much of the mother’s cortisol from reaching the fetus, but the fetus is still exposed to some maternal cortisol, and exposure increases with increasing stress. One neural structure particularly susceptible to stress is the hippocampus. The goal of this review is to address the role prenatal stress may play in damaging the hippocampus, a structure integral to learning and memory functions. Correlations between prenatal stress and a reduction in volume and function of the hippocampus are evidenced in rodent and non-human primate studies, but less conclusive in humans. In addition to macroscopic changes, microscopic hippocampal changes in glucocorticoid and mineralocorticoid receptor numbers are addressed to show how prenatal stress can reduce feedback inhibition of the hypothalamic-pituitary-adrenal axis, thus potentially increasing infants’ stress reactivity in the postnatal period. Awareness of the role of stress in pregnancy could change the way prenatal visits are structured, and high-risk women could be connected with necessary resources to reduce exposure to ongoing stressors in the perinatal period.

Introduction

Much research in the realm of human development in recent years suggests that lifelong pathologies begin with early life adversity, frequently referred to as toxic stress (Institute of Medicine and National Research Council, 2012). Much of this research focuses on the origins of chronic disease, health risk behavior, and mental health problems (Felitti et al., 1998). However, these childhood experiences also have implications for the learning and memory processes necessary for school achievement in early childhood (National Scientific Council on the
Developing Child, 2010). Less research has explored the impact of prenatal stress on a child’s neurodevelopment and brain structures relevant to learning and memory.

Childhood toxic stress often refers to substantiated neglect and abuse (Shonkoff et al., 2012), but stress transmitted to a fetus during a pregnancy could be induced by living in a dangerous neighborhood, intimate partner violence, poverty, discrimination, or pregnancy-related medical stress, as defined by Buss et al. (2011). Some of these stressors may or may not resolve in the child’s postnatal environment. Because these experiences are transmitted via maternal hormonal signals to a fetus, the neural rewiring and anatomical changes in the brain seen with early life stress could begin prior to birth (Harris and Seckl, 2011).

The focus of this review will be on the impact of prenatal stress on the limbic system. Particularly, this focus will be on the hippocampus due to its role in learning and memory. While early childhood stressful experiences may lead to troubles in school (Shonkoff, 2012), further research needs to be conducted on the role of prenatal stress in changing the child’s future learning and memory capabilities. Due to the confounding effects of postnatal stress in human studies, obtaining such research is difficult. However, the macroscopic and microscopic impacts of prenatal stress on the hippocampus, a neural structure involved in both learning and memory as well as in the feedback of the body’s natural stress response, provide some preliminary evidence for the detrimental effects of prenatal stress on learning, memory, and the perpetuation of high levels of stress for a lifetime.

**How excess maternal glucocorticoids reach the fetus**

In response to stressful stimuli, the body initiates the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus releases corticotropin releasing hormone (CRH), which stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH), which then
stimulates glucocorticoid production in the adrenal cortex. The mediator of the human stress response is the hormone cortisol, which is a glucocorticoid. The HPA axis typically operates by a negative feedback mechanism, meaning that sufficient cortisol will shut off the stress response in the hypothalamus when a threat is no longer perceived, but higher brain input can override this system (Herman et al., 2005). Significant, prolonged stress means that more cortisol continuously circulates in the bloodstream. For a pregnant woman experiencing stress, there are protective mechanisms in the placenta to make sure she does not pass along excess cortisol to the fetus. These protective mechanisms allow only about 10-20% of circulating maternal cortisol to reach the fetus (Harris and Seckl, 2011). Thus, the placenta moderates fetal exposure to maternal stress through glucocorticoids (GCs).

A number of review articles, notably Harris and Seckl (2011), and Seckl and Meaney (2004), discuss the patterns of maternal blood cortisol and the enzymes that mediate how cortisol reaches the fetus during pregnancy. The enzyme responsible for controlling GC levels in the bloodstream of the fetus, and expressed by the placenta, is 11ß-Hydroxysteroid Dehydrogenase Type 2 (11ß-HSD2). This enzyme inactivates cortisol to cortisone and reduces fetal cortisol blood concentrations to approximately 13 times lower than maternal levels (Duthie and Reynolds, 2013). In addition, 11ß-HSD2 generally increases throughout pregnancy except in the third trimester when these levels diminish to allow a higher concentration of cortisol to enter the fetal bloodstream to facilitate lung maturation (Murphy et al., 2006). The maternal blood cortisol concentration also increases throughout pregnancy with the assistance of a feed-forward mechanism facilitated by the placenta in which CRH released by the placenta in the second and third trimesters gradually begins to add CRH to the woman’s own HPA axis (Duthie & Reynolds, 2013, Waffarn & Davis, 2012).
Greater-than-typical prenatal stress can impact the concentration of glucocorticoids reaching the fetus. Despite the very low (10-20%) percentage of maternal glucocorticoids reaching the fetus, a mother experiencing chronically high levels of stress will transmit a higher glucocorticoid concentration to the fetus. In a seminal work on 11ß-HSD2 and stress, Mairesse et al. (2007) demonstrated that 11ß-HSD2 mRNA levels decreased with increasing restraint stress in rat models. Further clarification in rat models showed that chronic stress, as opposed to acute stress, was more potent at down-regulating 11ß-HSD2 activity (Welberg et al., 2005). Human models seem to concur with these findings, indicating that higher levels of self-reported anxiety during pregnancy correlate with lower 11ß-HSD2 mRNA levels assayed from placental tissue, which further increases fetal glucocorticoid exposure (O’Donnell et al., 2011).

**Role of the hippocampus in learning and memory**

The hippocampus is a temporal lobe brain structure within the limbic system accessed by the entorhinal cortex (Lövblad et al., 2014). Current consensus in the field of learning and memory states that the hippocampus is centrally involved in developing certain types of memory in the mammalian brain utilizes. The hippocampus consists of the CA (Cornu Ammonis) areas, the dentate gyrus, and the hippocampal formation, which includes the subiculum, and the hippocampal complex (Nadel et al., 2003).

Examining the role of the hippocampus in learning and memory processes requires an understanding of the various types of memory and their unique processing in the brain. The traditional understanding of memory states that humans have declarative and nondeclarative memory (Squire, 2004). Declarative memory implies recall of a storyline of memories across one’s life, whereas nondeclarative memory is a seemingly innate reactivation of processes that once required active learning (Squire, 2004). An example of declarative memory is recalling the
events of the past three weekends with a distinct context for each. Nondeclarative memory is
more ingrained, such as the seemingly reflexive way a driver knows exactly where to go without
conscious thought on a route frequently traveled. These two types of memory are encoded
differently in the brain. The hippocampus is essential for declarative memory, which is further
divided into episodic and semantic memory. Episodic memory is memory for life experiences
and occurs within a context for the time and space in which the memory occurred (Nadel et al.,
2003), whereas semantic memory encompasses the facts learned during life experiences (Nadel
et al., 2003). Seminal case studies on medial temporal lobe resection or medial temporal lobe
damage reveal that the hippocampus is highly involved with short-term memory storage before
long-term consolidation, but that may not be its only role (Nadel et al., 2003, Sutherland et al,
2010).

Various theories exist to explain the hippocampus’ role in learning and memory storage.
Nadel and Moscovitch (1998) proposed that the hippocampus is involved with the retrieval
process for long-term memory, acting as a connecting point for information about a particular
episode scattered throughout the cortex. While case studies demonstrate that learning new
semantic information is possible in people with hippocampal damage, the hippocampus still
could play an integral role in setting the framework for storage and retrieval of semantic
information due to the network that connects to the hippocampus (Nadel and Moscovitch, 1998).
Under this hypothesis, the hippocampus is always necessary for reactivating episodic
information, but only necessary for accessing learned semantic information until it is encoded in
the cortex (Nadel and Moscovitch, 1997). Researchers use temporally graded retrograde
amnesia in human and non-human examples of hippocampal damage as evidence for this
concurs with these findings, suggesting that the hippocampus facilitates complete memory consolidation after the time of learning, creating a lag time between the learning episode and memory consolidation.

Beyond the scientific consensus that the hippocampus is responsible for encoding an episode for a period of time after the experience, much of the hippocampus’ role in memory and learning is purely speculative based on observations following temporal lobe resection or damage. The hippocampus is even hypothesized to provide support for stimulus-response learning, as evidenced by limbic system transection in rats (Brasted et al., 2003). While the theories on the role of the hippocampus in learning and memory were formed largely from observed retrograde amnesia, there are limitations to what can be uncovered. Human study is limited to case studies, and Sutherland et al. (2010) admits that there is no scientific consensus on the similarities and differences between rodent and human memory.

Viewing the hippocampus as an integrated structure is important, but so is understanding the roles of the unique subregions. Research on prenatal stress and the hippocampus shows that one particular region of the hippocampus, the dentate gyrus, is particularly susceptible to changes following prenatal stress (Coe et al., 2003, Lemaire et al, 2000). Understanding its role in learning and memory may elucidate a possible mechanism for some of the neural deficits seen in prenatally stressed human or non-human subjects.

The hippocampus, specifically the dentate gyrus, is one of very few brain structures capable of lifetime neurogenesis (Drew et al., 2013). This unique property suggests its vital role in neuroplasticity (Drew et al., 2013). The dentate gyrus is generally accepted to be involved with creating a spatial context for information encoded at different time intervals (Rangel et al., 2014). A number of researchers have explored how the dentate gyrus is able to create contexts
for memories. Notably, Rangel, et al. (2014) studied how reduced neurogenesis would facilitate encoding of context with a long period of separation and moderate periods of separation with reduced neurogenesis. The resulting suggestion was that a unique set of cells could contextualize an experience in a single setting, and that new cell groupings are continually created (Rangel et al., 2014). Shors et al. (2002) assessed reduced hippocampal neurogenesis and neural deficit as well by establishing that rats with halted neurogenesis struggled with some hippocampal-dependent learning such as associating a conditioned and unconditioned stimulus together even when they are separated in time. As one of the few structures capable of adult neurogenesis in the brain, this capability is necessary for unique adult adaptive functions.

**Macroscopic hippocampal changes following prenatal stress**

A growing body of evidence in rodent, non-human primate, and human studies suggests that adverse, stress-inducing experiences during pregnancy can lead to structural changes in the developing fetal brain. The hippocampus is a target structure of such damage, and is of particular interest because it, along with the amygdala, develops early in pregnancy compared to other brain structures (Buss et al., 2012). To date, the most salient findings regarding gestational glucocorticoid exposure and hippocampal damage have been in rodents and non-human primates. Some investigators study the correlation between maternal cortisol levels and hippocampal volume. They presume that maternal cortisol is an indicator of stress level as well as an indicator fetal glucocorticoid exposure. While stress-induced limbic system damage mediates behavioral and HPA axis changes as well, the scope of this review will focus on the cognitive effects associated with hippocampal changes.
Animal Studies

Animal studies, in both rodents and primates, show mostly uniform results regarding the impact of maternal stress on the hippocampus. In these studies, the hippocampus of prenatally stressed rats and rhesus monkeys displayed a smaller hippocampus as compared to the control group (Coe et al., 2003, Lemaire et al., 2000). In a seminal work on prenatal stress and hippocampal size, Lemaire et al. (2000) demonstrated that prenatal stress causes a permanent reduction in neurogenesis in the dentate gyrus of the hippocampus. In addition, prenatally stressed rats performed poorly on a spatial learning task, a process dependent on dentate gyrus cell proliferation (Lemaire et al., 2000). Fujioka et al. (2006) concurs with these findings by reporting that long-lasting prenatal stress inhibits neurogenesis in the dentate gyrus of neonatal rats, while short-lasting stress enhances neurogenesis.

Non-human primate studies extend the body of work on prenatal stress and hippocampal neurogenesis. Coe et al. (2003) found similar inhibition of neurogenesis in the dentate gyrus in addition to a general volume reduction of the hippocampus in rhesus monkeys whose mothers were exposed to a variety of distressing environments during pregnancy. Prenatal stress experienced in early and late gestation resulted in a reduction in hippocampal volume and neurogenesis (Coe et al., 2003). Pryce et al. (2011) concurs with this finding in rhesus monkeys. Collectively, these studies establish a link between prenatal stress and hippocampal damage that adversely affect the subjects’ ability to learn.

Human Studies

Human studies assessing maternal stress and anxiety during pregnancy produce less-conclusive results on the impact of stress on the hippocampus during the gestational period. Some experimental designs choose salivary cortisol as a measure of stress, whereas others rely
on self-reported anxiety. Both measures of the human stress response will be considered in this review. Additionally, due to the various study designs on the effects of prenatal stress and limbic system structures, studies involving specifically the hippocampus, the limbic system as a whole, and the effects of prenatal stress on learning and memory outcomes will be considered. Since the hippocampus is integral to learning and memory, studies showing impairment in learning and memory following prenatal stress should be considered, even though the hippocampus may or may not be the mediator of these problems.

One approach to studying the human stress response in the prenatal period is to retrospectively assess mothers’ stress and anxiety levels during gestation, and subsequently study the hippocampus after birth through brain imaging or hippocampal-dependent learning mechanisms. Qiu et al. (2013) demonstrated the effect of self-reported maternal anxiety, via the State-Trait Anxiety Inventory, on hippocampal growth at birth and 6 months of age. Higher reported maternal anxiety was not linked to smaller hippocampi at birth (Qiu et al., 2013). However, at 6 months of age, prenatal maternal anxiety correlated with smaller left hippocampi and postnatal maternal anxiety correlated with greater right hippocampal growth (Qiu et al., 2013). A possible explanation for the right hippocampus’ postnatal growth in response to maternal postnatal anxiety is the right hippocampus’ role in anxiety development (Qiu et al., 2013). Growth in both hemispheres may be constrained by prenatal stress, but the child’s reaction to stress in his/her environment may initially enhance the development of the right hippocampus (Qiu et al., 2013). In addition, retrospectively assessing prenatal maternal anxiety through adverse life events that occurred during pregnancy shows altered hippocampal-dependent spatial learning strategies in young adults (Schwabe et al., 2012). Prenatal events such as death of a loved one, loss of one’s home, divorce or separation, or illness, independent of
postnatal adversity, correlate with more simplistic spatial navigation strategies as opposed to abstract cognitive planning (Schwabe et al., 2012). Other studies examining prenatal anxiety have suggested a possible link between pregnancy-specific anxiety and childhood cognitive deficit (Buss et al., 2011, Davis & Sandman, 2010).

A second emerging approach to studying prenatal stress and neurological outcomes involves first measuring maternal cortisol over the course of the entire pregnancy, followed by neural imaging studies or general infant neurodevelopmental studies. Salivary cortisol studies are an emerging approach because they are more objective than relying on self-reporting. High maternal cortisol at gestational week 15 produces no difference in hippocampal volume in children at seven years of age, with only slightly smaller hippocampi found in boys (Buss et al., 2012). A much larger body of evidence links high prenatal cortisol levels to infant and child cognitive deficits that may or may not be linked to the evidence of hippocampal damage seen in animal studies. For example, the timing of various indicators of prenatal stress has been shown to affect the mental development of infants at one year of age (Davis & Sandman, 2010). Increased salivary cortisol at 13 weeks and decreased salivary cortisol at 38 weeks correlates with a significant decrease in infant Mental Development Index scores measured at 3, 6, and 12 months of age, indicating slower psychomotor and mental development (Davis & Sandman, 2010). Self-reported maternal anxiety alone, including pregnancy-related anxiety, is not associated with significant changes in infants’ mental development (Davis & Sandman, 2010). Additional studies with salivary cortisol are necessary to replicate both the present MRI and infant development studies.

Current human studies are fraught with issues that prevent the type of research that will elucidate some of the questions regarding the impact of stress, anxiety, and glucocorticoids
during pregnancy on hippocampal function. Techniques of study are the predominant inhibiting factor because studies of specific brain structures in humans are typically performed using magnetic resonance imaging. MRI indicates changes in hippocampal volume, but cannot replicate findings such as an inhibition in neurogenesis in the dentate gyrus. Additionally, studies that rely on self-reporting of stress levels may produce variable or unreliable results based on the mother’s resiliency. Several other review articles also address the problems associated with studying antenatal maternal stress and any neurodevelopmental outcome. For example, Van den Bergh et al. (2005) emphasizes the importance of giving special consideration to studies that do not control for postnatal maternal stress when assessing infant outcomes. Other factors that may contribute to the high variability in human studies include gestational timing and frequency of stress assessment (Van den Bergh et al., 2005), definition of stress, types of stress, and difficulty forming samples of mothers representative of the population (Graignic-Phillipe et al., 2014). As current research begins to clarify the of the early-life influences on adult health, researchers may develop more standardized ways of assessing maternal stress and infant neurological development, as well as advance the study of specific neural structures such as the hippocampus.

**Examing hippocampal changes following postnatal stress: A comparison**

While an understanding of the impact of prenatal stress on the human hippocampus is limited to the few studies performed, the techniques available for human study, and varied methodological approaches, there is a larger body of evidence detailing the changes observed in the hippocampus due to toxic stress during the lifespan. Similar to the studies of prenatal stress, a variety of approaches exist to measure and analyze the role that early life trauma has on the hippocampus. This review is limited to studies in children and adolescents. However, as with
prenatal studies, a limited number of studies on postnatal stress and the hippocampus in children exist, while adult studies conclusively find evidence that early-life stress produces smaller hippocampi (Smith, 2005). While the results of these studies are not directly comparable to prenatal stress research, they may provide a comparable mechanism by which glucocorticoids have a toxic impact on the developing hippocampus.

A number of studies use MRI as a tool to analyze hippocampal volume in children and adolescents with a history of early life stress. However, these studies produce a variety of results. Carrion et al. (2007) analyzed the longitudinal associations between cortisol, post-traumatic stress disorder (PTSD) diagnosis, hippocampal volume, and a known history of child traumatic stress in 15 prepubescent children with a history of multiple traumas. More severe PTSD symptoms correlated positively with higher basal cortisol levels, and negatively with volume of the right hippocampus from time 1 to reassessment 12-18 months later (Carrion et al., 2007). Meanwhile, other MRI studies using control groups have demonstrated opposite results. In a longitudinal study of 9 prepubescent maltreated subjects and 9 healthy subjects, MRI showed no difference in temporal lobe, amygdala, and hippocampal volumes among the two groups at baseline, or after follow-up after a minimum of two years (DeBellis et al., 2001). The small sample sizes of these two studies makes generalizability of these results difficult. Additionally, a larger study of maltreated children with control subjects demonstrated that the hippocampal volumes of children with PTSD were actually slightly larger than the controls (Tupler & DeBellis, 2006). Mehta et al. (2009) found that Romanian adolescent adoptees that were exposed to early-life neglect had reduced total gray and white brain matter, but the hippocampus size was not comparatively smaller. One possible explanation for the lack of congruency between adult imaging studies with PTSD due to early life stress subjects and child
studies is that hippocampal changes may be age-dependent, and atrophy of the hippocampus may occur in the years following puberty (DeBellis et al., 2001). Additional work is necessary with more consistent age ranges and measurement techniques to establish more consistent trends.

A novel approach to assessing the damage of early life stress on the hippocampus is to study its function, not its overall volume. In an assessment of 10-17 year-old subjects split into a post-traumatic stress symptoms (PTSS) group and control group, Carrion et al. (2010) demonstrated the control group of healthy individuals had significantly higher right hippocampus activity during retrieval of words previously exposed to during a verbal memory task. Additionally, more severe the PTSS symptoms correlated negatively with hippocampal activation at retrieval (Carrion et al., 2010). This approach needs more investigation, as it may demonstrate that the damage of chronic, traumatic stress on the hippocampus is not always obviously visible in terms of size difference.

As with studies on the effect of prenatal stress on the hippocampus, there are significant barriers to forming an association between early life stress and observable changes to the hippocampus. One of the most significant barriers is producing enough subjects to do MRI research, a problem also encountered with MRI research on infants. Early life trauma research also categorizes subjects very differently. For example, some studies examine subjects with PTSD diagnosis (Carrion et al., 2007, Tulper & Debellis, 2006), while others examine subjects with PTSS (Carrion et al., 2010), or even just with a history of trauma. Despite incongruences in the literature, early life trauma research has a greater understanding of the effects of postnatal stress as compared to prenatal work.
**Microscopic stress-induced hippocampal damage**

The traditional negative feedback mechanism of the HPA axis occurs at the level of the paraventricular nucleus of the hypothalamus, but limbic system structures, including the hippocampus, can modify the negative feedback of the HPA axis and increase glucocorticoid production (Herman et al., 2005). Excess glucocorticoids may mediate damage to the hippocampus by altering the expression of various receptors for glucocorticoids. Excess glucocorticoids greatly impact the expression of glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). How these mechanisms may mediate some of the other hippocampal changes such as volume reduction and inhibition of neurogenesis remains elusive but altered expression of glucocorticoid receptors causes potentially permanent neuroendocrine deficit in the hippocampus.

If excess glucocorticoids are a possible mediator of prenatal stress effects on the hippocampus, then understanding of the role of the receptors in hippocampal tissue is necessary. Mineralocorticoid receptors respond to hormones such as aldosterone and deoxycorticosterone, along with cortisol. Glucocorticoid receptors are activated by cortisol and corticosterone in humans (Lupien et al., 2009). Exposure of these receptors to abnormal levels of glucocorticoids can regulate how they are expressed. Ultimately, a reduction in the expression of hippocampal MRs and GRs suggests a mechanism for increased HPA axis activity, since the hippocampus participates in the negative feedback of the HPA axis (Noorlander et al., 2006). Due to the invasive techniques required to examine hippocampal GR and MR expression, examination of the role of prenatal stress on the MR and GR receptors of the hippocampus is mainly limited to animal studies. Additionally, both prenatal and postnatal exposure to glucocorticoids will be
considered in this review to understand the overall mechanism of increased glucocorticoid exposure on GR and MR expression.

Human MRs and GRs differ in their affinity for glucocorticoids, and the types of stress they mediate. The MR has a greater affinity for external sources of glucocorticoids such as synthetic glucocorticoids, whereas the GR has a lower affinity for glucocorticoids except in situations of intense stress when many corticosteroids are present (Reul & de Kloet, 1985). The differential roles of MRs and GRs in feedback regulation of the HPA axis are outlined in the review article by Ulrich-Lai & Herman (2009).

**Animal Studies**

Rodent models demonstrate how early life attachment promotes proper expression of MRs and GRs through epigenetics. Rat mothers that practice licking and grooming and arched-back nursing have pups that exhibit an altered methylation pattern of the GR promoter, altered binding of the transcription factor NGFI-A for the hippocampal GR gene which ultimately up-regulates GR expression (Weaver et al., 2004). Results were most salient in the pups’ first week of life. Despite these significant findings, the differences in rodent and primate neuroendocrine development must be considered. Rodents complete most of their neuroendocrine development post-natally, while primates complete much of their neuroendocrine development in utero (Ulrich-Lai & Herman, 2009), indicating that the timing of this study more closely parallels human in utero GR development.

In rodent models, prenatal stress produces similar epigenetic patterns: stress causes a down-regulation of GR expression unlike the up-regulation seen in stress-free development. Levitt et al. (1996) first established this phenomenon in rats exposed to prenatal dexamethasone, a synthetic glucocorticoid. GR mRNA was significantly reduced in rats whose mothers were
treated with dexamethasone in the last week of pregnancy, which translates to approximately the third trimester in humans (Levitt et al., 1996). Expression of GR mRNA was 20% lower in the dentate gyrus and 15% lower in the CA1 region, while MR mRNA expression was significantly reduced in the CA1 and CA2 regions (Levitt et al., 1996). Noorlander et al. (2006) reported similar findings in mice by establishing that dexamethasone treatment in the last week of pregnancy decreased the MR mRNA expression in the hippocampus in the day after treatment, but GR levels could not be assessed because they were not expressed at the time of treatment.

Studies on prenatal GC exposure and MR and GR receptors in the hippocampus are limited in primates, but mainly focus on establishing normal GC receptor development to set the stage for later work. Pryce et al. (2005) established GC receptor development in the common marmoset, but higher order primates were not studied. Hippocampal MR mRNA is expressed greater at infancy as compared to the neonatal period, juvenile period, or adult period, and GR mRNA follows a similar pattern (Pryce et al., 2005). This emphasizes the neurodevelopmental differences between various animal models when interpreting studies of receptor development because rodents are fairly underdeveloped in infancy. Studies in the common marmoset do follow suit with the postnatal pattern of down-regulated MRs and GRs following early life deprivation (Pryce et al., 2011).

**Human Studies**

Since studies of the hippocampal GC receptors are performed postmortem, human studies are limited. However, as with rodents and non-human primates, some studies are beginning to establish the activity of the GR and MR receptor proteins under stressed and normal development in the prenatal and neonatal period. When the hippocampi of infants 24-34 weeks who died of a non-congenital cause were assessed, Noorlander et al. (2006) found that both MRs
and GRs were expressed, although GRs were expressed at a lower level, indicating that these receptors are expressed as early as 24 weeks. Additionally, some of these infants were exposed to dexamethasone if their mothers were at risk of preterm labor, and no difference in hippocampal GC receptor expression was observed for dexamethasone or non-dexamethasone treated infants (Noorlander et al., 2006). Results of this study could be confounded by the fact that dexamethasone was clinically administered in therapeutic amounts to promote fetal lung maturation, and other prenatal stress factors were not assessed. While studies of GC receptors in infants are limited, there are other measures GC receptor programming in infants who experience prenatal stress. PCR amplification of the NRC31 gene, the promoter for the GR gene, from the mononuclear cord blood cells of pregnant mothers with varying basal cortisol levels demonstrates that maternal emotional state is associated with methylation of a particular exon for this promoter (Hompes et al., 2013). This receptor is expressed throughout the body, so assessing NR3C1 in cord blood stem cells could be indicative of other methylation patterns developing throughout the body, such as in the hippocampus. Hypermethylation of this region in cord blood cells was associated most significantly with pregnancy-related anxiety (Hompes et al., 2013).

Postnatal examination of the effects of chronic early-life stress may provide a mechanism by which prenatal stress could regulate GR and MR expression, since these receptors are expressed by mid-gestation (Noorlander et al., 2006). GR mRNA expression is significantly reduced in the hippocampi of suicide victims with a history of childhood abuse compared to non-abused suicide victims or controls upon postmortem examination (McGowan et al., 2009). In this study, methylation of the promoter NRC31 for GRs led to decreased expression of GR receptor mRNA (McGowan et al., 2009). Additionally, methylation of NRC31 was also
associated with down-regulation of NGF1-A, a transcription factor for NRC31 (McGowan et al., 2009). While assessing measures of early life stress in adulthood may present many confounding variables, such as the accumulation of a lifetime of stress, they develop a mechanism for excess glucocorticoid exposure mediating reduced GC receptor expression, which could be applied to future prenatal work.

**Implications for obstetrics, perinatology, and clinical practice**

Despite the detrimental effects of prenatal stress on the limbic system, specifically the hippocampus, there is evidence that prenatal intervention and postnatal care could moderate the altered neurodevelopment of fetuses exposed to prenatal stress. Awareness of damage that can occur in the perinatal period could translate to clinical changes in how prenatal visits are structured and postnatal support is provided.

Evidence suggests that postnatal maternal care improves the effects of prenatal stress on the hippocampus. In rodent models, Lemaire et al. (2006) demonstrated that postnatal handling seemed to reverse the effects of prenatal stress on a reduction of neurogenesis in the hippocampus, and these findings were consistent when rats were tested at a more mature age. In humans, studying birth weight, self-reported parental bonding, and hippocampal volume via MRI reveals also reveals potential reversal of prenatal damage in response to maternal care (Buss et al., 2007). While not a direct measure of prenatal stress, birth weight can be used as an indicator of intrauterine distress (Buss et al., 2007). Low birth weight combined with low maternal care are associated with reduced hippocampal volume in young women compared to women who had an average birth weight and report high maternal care as a child (Buss et al., 2007). The results were not as significant in young men (Buss et al., 2007). While not a direct indicator of hippocampal size or function, high amniotic fluid cortisol levels and low infant-mother
attachment correlate with reduced infant cognitive functioning at 17 months of age, whereas this same pattern is not observed for infants with high prenatal cortisol exposure and secure attachment (Bergman et al., 2010). These findings give credence to the idea that proper intervention with postnatal care could reverse the effects of prenatal stress on the trajectory of neurodevelopment.

Scientific evidence for the role of prenatal stress on a child’s future capacity for learning and memory, in addition to other detriments produced by prenatal stress, may present the need for translational research in interventions during prenatal visits to identify high risk women. While limited research exists for the success of screening for prenatal toxic stress during prenatal visits, there is clinical evidence for the efficacy of screening for other adverse prenatal experiences such as drug and alcohol exposure. Dr. Ira Chasnoff, a pediatrician focused on prenatal substance abuse prevention, established the success of a particular screening questionnaire that identified women at risk for both high and low levels of alcohol and drug abuse during pregnancy in a non-judgmental, indirect manner (Chasnoff et al., 2005). Additionally, simply using a few very targeted questions about past substance abuse during prenatal primary care visits was sufficient to identify high risk women in a Medicaid-using population visiting prenatal health clinics (Chasnoff et al., 2001). While these studies identified ways to target high-risk women, Goler et al. (2008) demonstrated the effectiveness of referring women to an established clinic for pregnant women abusing substances in improving perinatal outcomes by providing education and counseling. While these treatment programs may demonstrate some efficacy, the intense focus on prenatal substance abuse as a problem may be missing the underlying stress contributing to substance abuse. Prenatal primary care visits could
include targeted, non-judgmental screenings for toxic stress because substance abuse may a
coping mechanism for toxic stress.

Some practitioners do screen for a source of prenatal stress: intimate partner violence. However, the urgency to screen is not recognized by all prenatal care providers. In a comprehensive survey of obstetricians-gynecologists, approximately 39% of providers screened for domestic violence at the first prenatal visit, but the majority did screen when they suspected abuse (Horan et al., 1998). Further study reveals that the vast majority of women, when asked postpartum about their experiences with domestic violence screening in various healthcare settings while pregnant, are not offended by the inquiry (Renker & Tonkin, 2006). Women also may be more forthcoming if they are informed of reporting laws in their state (Renker & Tonkin, 2006). These approaches demonstrate that healthcare professionals can provide a safe space for informed, confidential, and safe disclosure about stressful prenatal experiences.

The proven effectiveness of existing screening techniques for other factors that lead to an adverse intrauterine environment, such as prenatal substance abuse, demonstrate that additional tools could be developed to measure stress and anxiety levels at prenatal visits, with or without salivary cortisol testing upon consent. Investigation into the mediators of maternal toxic stress could protect the fetus from an adverse postnatal environment that could compound the damage toxic stress causes in the developing brain. Additionally, providers could connect women who qualify with programs such as the Nurse Family Partnership that are proven to improve perinatal outcomes (Dawley et al., 2007), or other therapies that build resilience in the mother and infant’s lives such as bonding and emotional regulation in the postnatal environment.
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