The Impact of Prenatal Stress on the Developing Hippocampus

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Undergraduate Honors Thesis
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Can a mother’s health, social, and economic status affect her child’s capacity to learn, and can these effects appear prenatally?
Research Questions

• Can a mother experiencing toxic stress during her pregnancy transmit her experiences to her child through stress hormones?
• Will the child have changes to his/her hippocampus, a neural structure susceptible to stress?
• Will the child experience learning and memory deficits as a result of prenatal stress?
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• Early life stress and lifelong adversity
• What is prenatal stress?
• How maternal glucocorticoids reach the fetus
• The role of the hippocampus in learning and memory
• Studies on prenatal stress and the hippocampus
• Postnatal stress comparison
• Prenatal/postnatal stress and hippocampal glucocorticoid receptors
• Implications and suggestions for clinical practice
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Glucocorticoids

Adrenal co

FIG. Na

Hippoc

GR s

MR s and

GR s

Hypothalamus

Amygdala

Hippocampus

Frontal cortex

MRs and

GRs

CRH

AVP

ACTH

Glucocorticoids

Adrenal cortex

Anterior pituitary

Hypothalamus

Lupien et al., 2009

Nature Reviews | Neuroscience

FOCUS ON STRESS
3 Types of stressors¹:

1. Positive stress
2. Tolerable stress
3. **Toxic stress**—unrelenting adverse experiences or stressors of great magnitude
Early Life Stress

- Rate of chronic diseases, health risk behaviors, depression, and suicide increase with increasing adverse childhood experiences (ACEs) such as abuse and caregiver dysfunction²
Early Life Stress

- Rate of chronic diseases, health risk behaviors, depression, and suicide increase with increasing adverse childhood experiences (ACEs) such as abuse and caregiver dysfunction\(^2\)
- Early life stress is associated with a hypersensitive stress response, behavioral problems, and memory problems in children\(^3\)
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Prenatal Stress

- Intimate partner violence
- Dangerous neighborhood
- Poverty
- Chronically high anxiety
- Major adverse life events (e.g. death of a loved one or natural disaster)
- Pregnancy-related medical stress
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The figure illustrates the maternal-fetal hypothalamic-pituitary-adrenal (HPA) axis during pregnancy. It shows the interaction between the mother, placenta, and fetus, with the involvement of cortisol and synthetic glucocorticoids. The diagram includes factors such as CRH (Corticotropin-Releasing Hormone), ACTH (Adrenocorticotropic Hormone), and 11βHSD2 (11ß-Hydroxysteroid Dehydrogenase Type 2) in regulating cortisol levels. The figure is from Waffarn and Davis, 2012.
How Glucocorticoids Reach the Fetus

• Only 10-20% of maternal cortisol reaches the fetus\(^7\)
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• 11\beta-HSD2 reduces fetal blood cortisol concentrations to 13 times lower than maternal levels\textsuperscript{8}
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• 11β-HSD2 increases throughout pregnancy and then is reduced in the 3\(^{rd}\) trimester\(^9\)
• The placenta contributes CRH in the 2\(^{nd}\) and 3\(^{rd}\) trimesters\(^6,8\)
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Types of Memory

- **Nondeclarative**- innate, reflexive reaction to something that once had to be learned\(^{11}\)

- **Declarative**- storyline of memories\(^{11}\)
  - Episodic-memory for life experiences with a unique temporal/spatial context for each event\(^{12}\)
  - Semantic-factual information learned during life experiences\(^{12}\)
The Hippocampus and Memory

• Involved in short-term memory storage before long-term consolidation$^{12,13}$
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• Information about an episode may be encoded in cortex, but connected to the hippocampus when retrieved\textsuperscript{14}
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- Associative or stimulus-response learning\(^{14,15}\)
The Hippocampus and Memory

• Involved in short-term memory storage before long-term consolidation\textsuperscript{12,13}

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• Associative or stimulus-response learning\textsuperscript{14,15}

• Many learning and memory functions are purely speculative
Neurogenesis

- The hippocampus is one of very few brain structures capable of adult neurogenesis.
- Neurogenesis occurs in the dentate gyrus.
- Continuous neurogenesis may create a temporal/spatial context for memories.\textsuperscript{16,17}
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Evidence in Animals

• Rodents
  – Prenatal stress causes a permanent reduction in neurogenesis in the dentate gyrus of rats\textsuperscript{18,19}
  – Prenatally stressed rats performed poorly on a learning task requiring spatial memory\textsuperscript{18}
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• Non-Human Primates
  – Reduction in hippocampal volume and neurogenesis in the dentate gyrus seen in prenatally stressed rhesus monkeys\(^{20,21}\)
  – Early or late gestational stress produces no difference\(^{20}\)
Dentate Gyrus Neurogenesis in rhesus monkeys

Hippocampal Volume in rhesus monkeys

Coe et al., 2013
Approaches to Human Studies

• Retrospectively determine stress and anxiety level, followed by MRI and/or study of subjects’ cognitive ability
• Study prenatal stress reports and hippocampal-dependent learning mechanisms
• Take salivary cortisol samples during pregnancy and subsequently study infant brains with MRI
Self-Reported Anxiety Studies

- Prenatal stress constrains left hippocampal growth from birth to 6 months of age\textsuperscript{22}
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- Prenatal stress constrains left hippocampal growth from birth to 6 months of age\textsuperscript{22}
- Self-reported adverse life events during gestation correlate with poor performance on spatial tasks in children in young adulthood\textsuperscript{23}
Maternal Cortisol Studies

• Increased salivary cortisol at 13 weeks and decreased salivary cortisol at 38 weeks correlate with significantly decreased Mental Development Index scores throughout infancy\textsuperscript{24}

• High maternal cortisol at 15 weeks does not correlate with reduced hippocampal volume in childhood\textsuperscript{25}
Flaws in Human Studies

- There are multiple techniques for assessing maternal stress level
- Relying on self-reported stress or anxiety is not objective
- Some studies only assess cortisol at one point in pregnancy
- Studies need to take careful consideration to control for postnatal stress
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Hippocampi of adults with a history of early life stress and PTSD are bilaterally smaller than controls\textsuperscript{26}
Postnatal Stress and the Hippocampus

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• Early life stress may significantly alter the hippocampus after brain remodeling in puberty\textsuperscript{28}
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This diagram illustrates the neural circuit involved in stress response. The circuit includes the hippocampus, hypothalamus, and amygdala, which are interconnected through pathways involving corticotropin-releasing hormone (CRH), corticotropin (ACTH), and glucocorticoids (Glucocorticoids). The anterior pituitary gland releases ACTH, which stimulates the adrenal cortex to produce glucocorticoids. This system is crucial in regulating the body's response to stress.

Lupien et al., 2009
Mineralocorticoid and Glucocorticoid Receptors

- Both mineralocorticoid (MR) and glucocorticoid receptors (GR) respond to glucocorticoids (cortisol and cortisone).
- MRs have a greater affinity for glucocorticoids\(^{30}\).
- Exposure to abnormally high levels of glucocorticoids alters how they are expressed in the hippocampus.
b) DNA Methylation

Gene transcription

Monk et al., 2012
MR and GR Expression in Animals

• Proper postnatal handling of rat pups results in an altered histone acetylation and DNA methylation pattern of the GR promoter region in the hippocampus, leading to increased expression\(^3\)\(^2\)

• Prenatal synthetic glucocorticoid exposure in rats results in down-regulation of GR receptor mRNA in the hippocampus\(^3\)\(^3\)
Fetuses express MRs and GRs in the hippocampus as early as 24 weeks \(^{34}\).

Hypermethylation of the promoter region for the GR gene occurs in the cord blood of mothers with high anxiety \(^{35}\).

Early life stress significantly reduces GR expression in the hippocampus \(^{36}\).
Fewer receptors = reduced HPA axis negative feedback

McGowan et al., 2009
Reduced numbers of hippocampal glucocorticoid receptors could result in elevated glucocorticoid exposure for the lifespan.
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Postnatal Intervention

- Postnatal care and attention by rat mothers reverses the inhibited neurogenesis in rats following prenatal stress\textsuperscript{37}
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• Postnatal care and attention by rat mothers reverses the inhibited neurogenesis in rats following prenatal stress\(^3\)\(^7\)

• Low birth weight combined low infant-mother attachment correlates with a smaller hippocampal volume in humans\(^3\)\(^8\)
Postnatal Intervention

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• Low birth weight combined low infant-mother attachment correlates with a smaller hippocampal volume in humans\textsuperscript{38}

• Low birth weight combined with high infant-mother attachment may correlate with normal hippocampal size\textsuperscript{38}
Can Providers Intervene?

- Effective screening tools for assessing the likelihood of prenatal substance abuse already exist\textsuperscript{39,40}
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• Treatment clinics for prenatal substance abuse are shown to be effective in improving perinatal outcomes\textsuperscript{41}
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• Treatment clinics for prenatal substance abuse are shown to be effective in improving perinatal outcomes\textsuperscript{41}

• Are providers missing the underlying stress contributing to prenatal substance abuse?
• Prenatal care providers need to be informed about trauma and ACE
Suggestions

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- Prenatal care providers should develop assessment tools for toxic stress and major life events during pregnancy
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• Recommend therapies to assist with mother/infant postnatal emotional regulation
Conclusions

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• Human studies may indicate preliminary evidence for prenatal stress and hippocampal changes
• Prenatal screening should be implemented
• **Thesis Mentor**
  – Dr. Nicholas Andreadis

• **Committee**
  – Mr. David Paul
  – Dr. Christopher Pearl
  – Dr. Mark Sloane
References


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