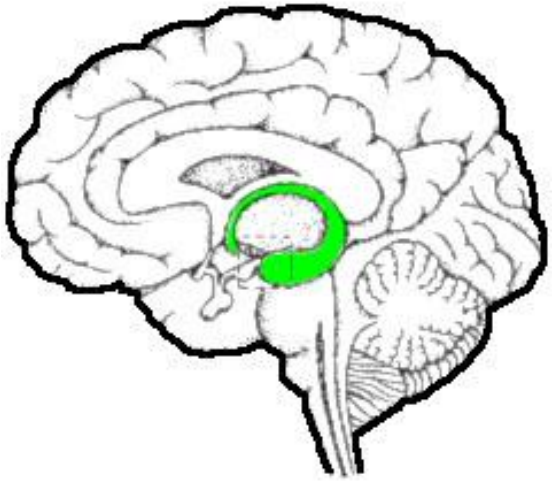
The Impact of Prenatal Stress on the Developing Hippocampus



Alyssa Murray

Undergraduate Honors Thesis

December 5th, 2014

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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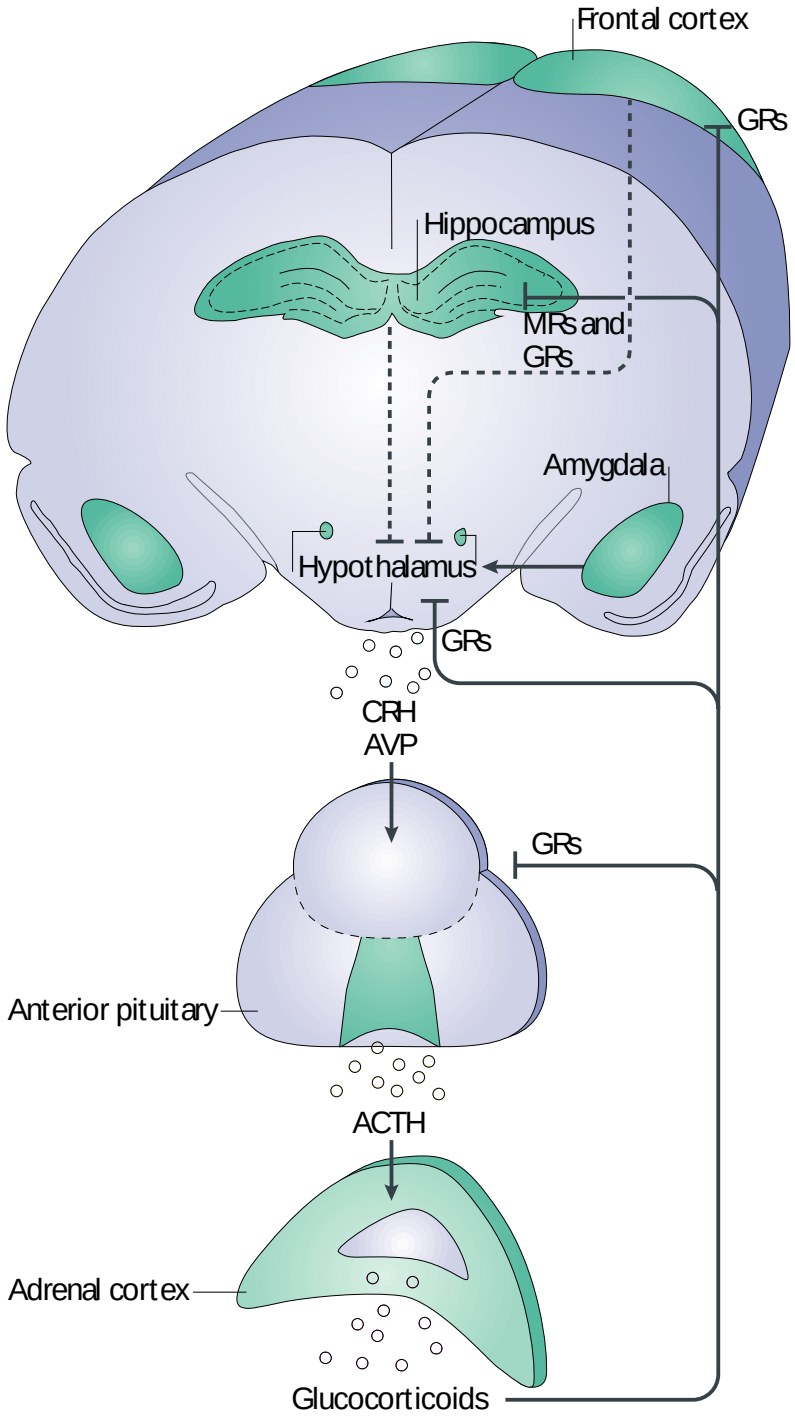

Lupien et al., 2009

Early Life Stress

3 Types of stressors[1]:

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 dysfunction[2]

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- 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 [5]

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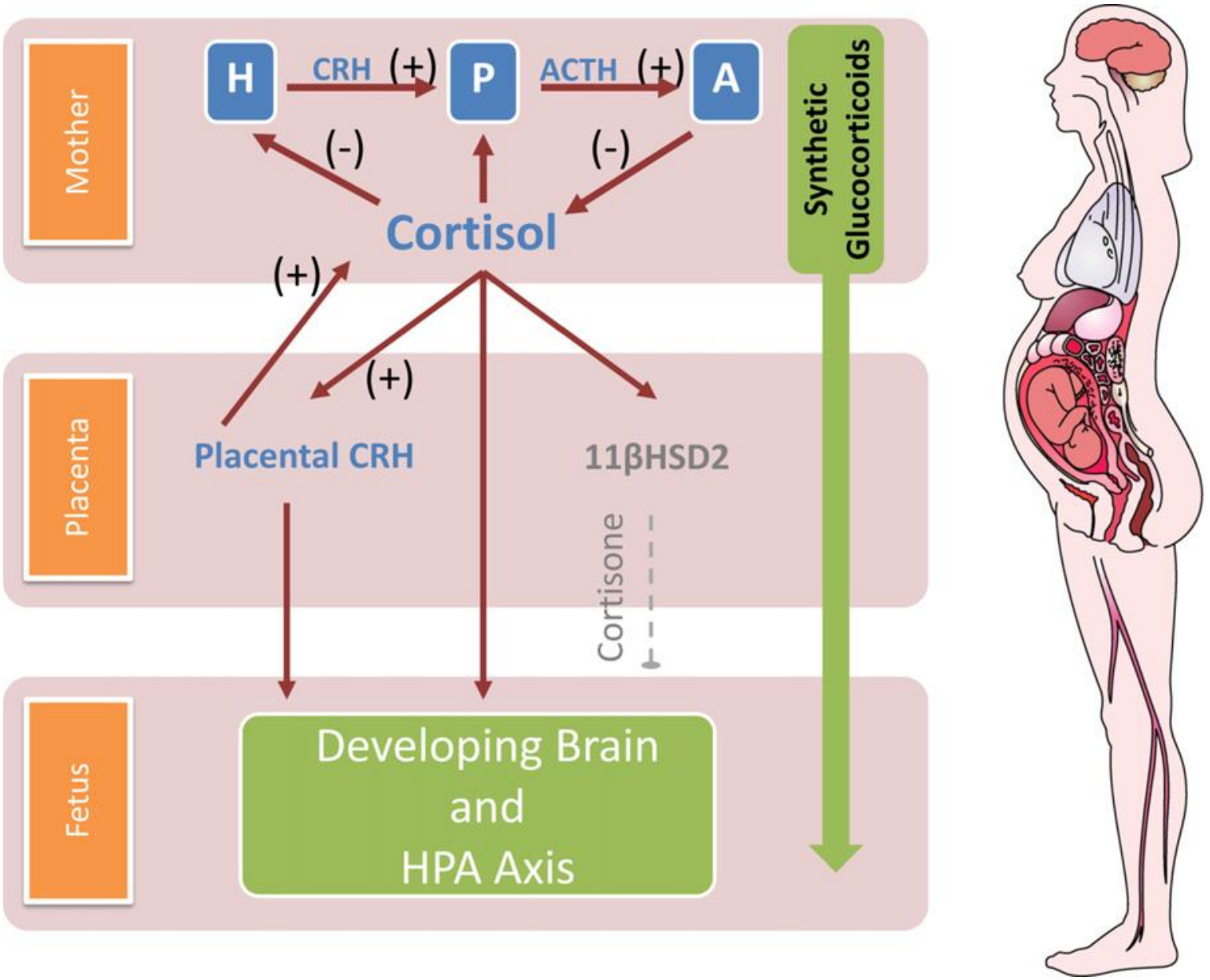

Waffarn and Davis, 2012

How Glucocorticoids Reach the Fetus

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- The placenta contributes CRH in the 2nd and 3rd trimesters[6,8]

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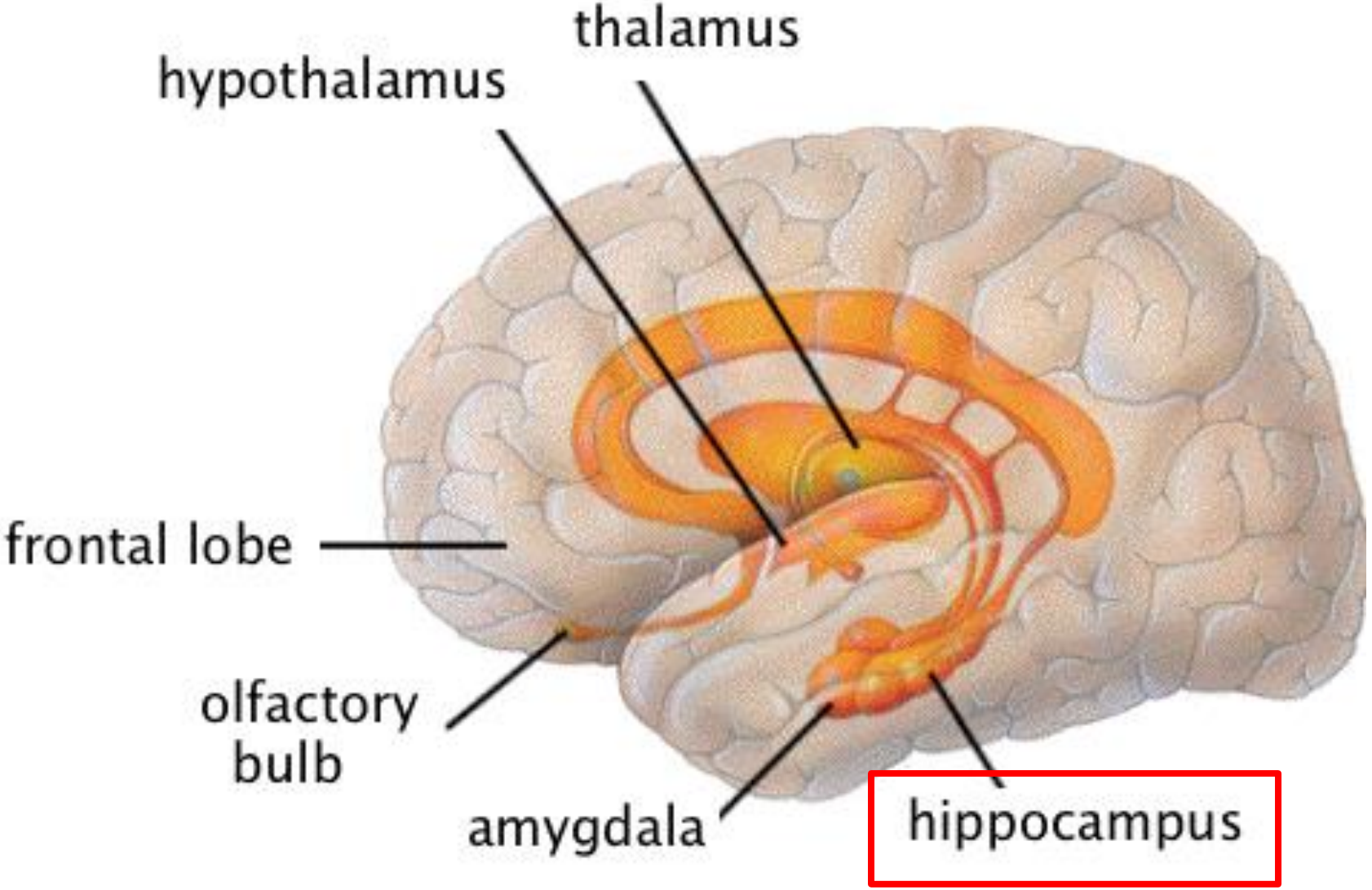

http://webspace.ship.edu/cgboer/limbicsystem.html

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[14]
- Associative or stimulus-response learning[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[16,17]

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Evidence in Animals

- Rodents
  - Prenatal stress causes a permanent reduction in neurogenesis in the dentate gyrus of rats[18,19]
  - Prenatally stressed rats performed poorly on a learning task requiring spatial memory[18]

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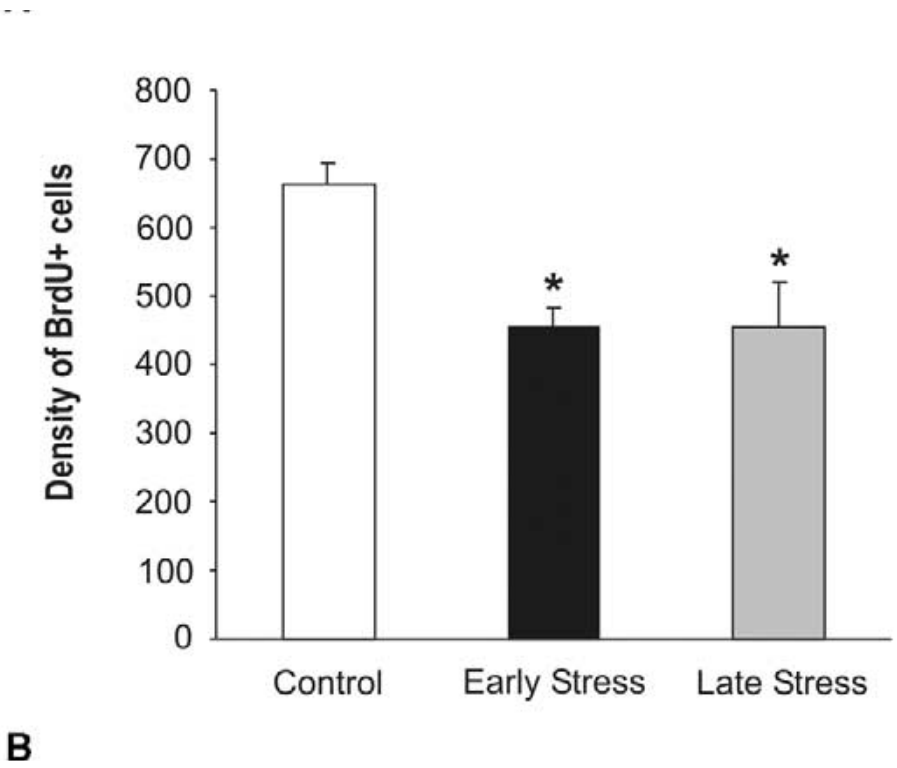
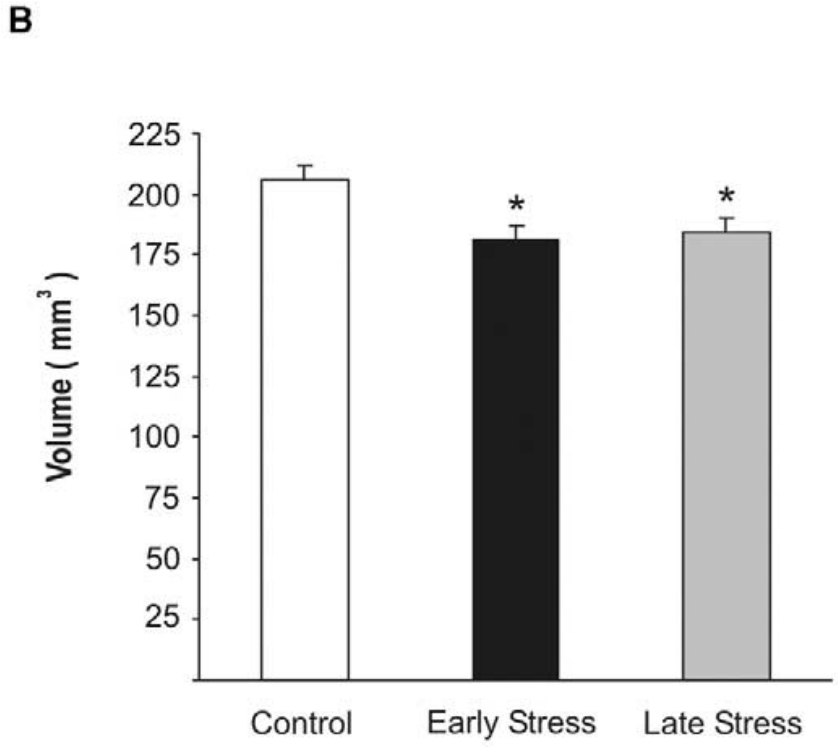
- Non-Human Primates
  - Reduction in hippocampal volume and neurogenesis in the dentate gyrus seen in prenatally stressed rhesus monkeys[20,21]
  - Early or late gestational stress produces no difference[20]



Dentate Gyrus Neurogenesis in rhesus monkeys



Hippocampal Volume in rhesus monkeys

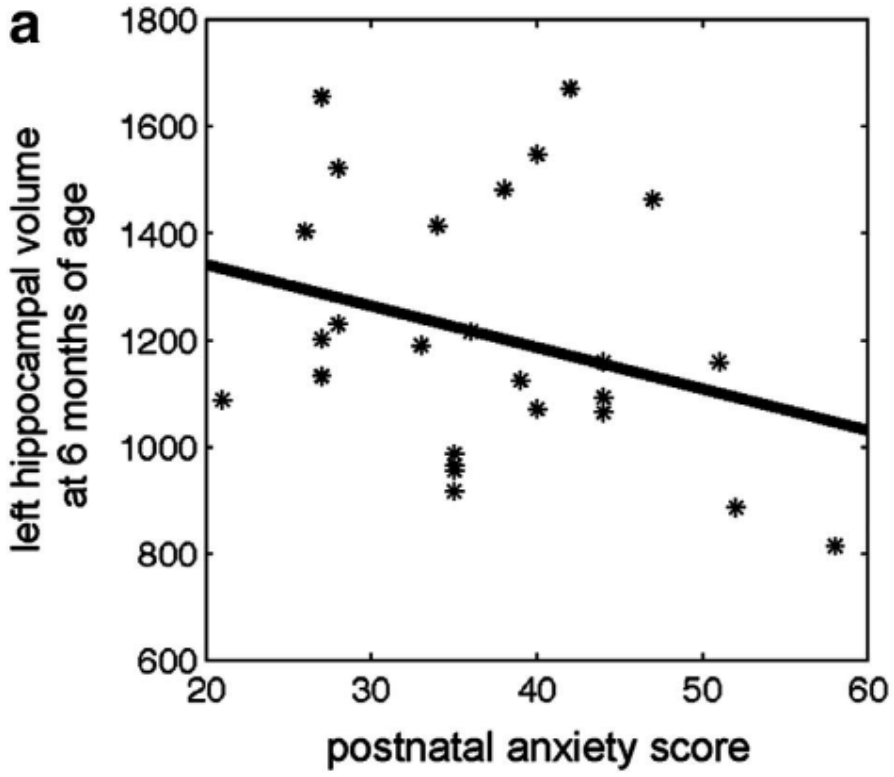
Coe et al., 2013

Approaches to Human Studies

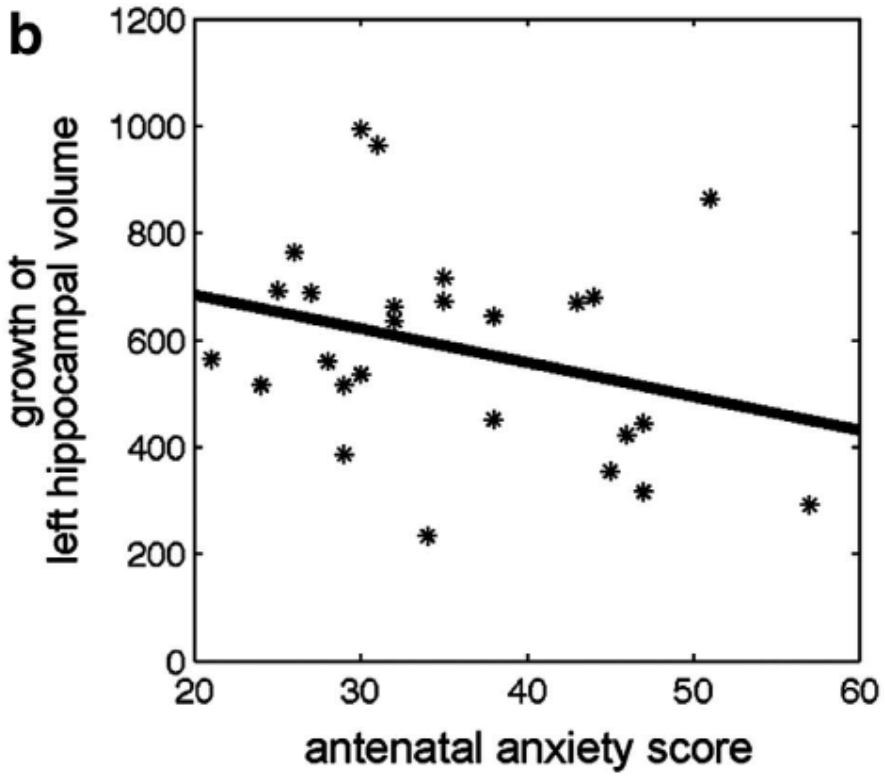
- Retrospectively determine stress and anxiety level, followed by MRI and/or study of subjects' cognitive ability
- Study prenatal stress reports and hippocampal-dependent learning mechanisms
- Take salivary cortisol samples during pregnancy and subsequently study infant brains with MRI

Self-Reported Anxiety Studies

- Prenatal stress constrains left hippocampal growth from birth to 6 months of age[22]



Left Hippocampal Volume



Left Hippocampal Growth

Qiu et al., 2013

Self-Reported Anxiety Studies

- Prenatal stress constrains left hippocampal growth from birth to 6 months of age[22]
- Self-reported adverse life events during gestation correlate with poor performance on spatial tasks in children in young adulthood[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[24]
- High maternal cortisol at 15 weeks does not correlate with reduced hippocampal volume in childhood[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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- Early life stress may significantly alter the hippocampus after brain remodeling in puberty[28]

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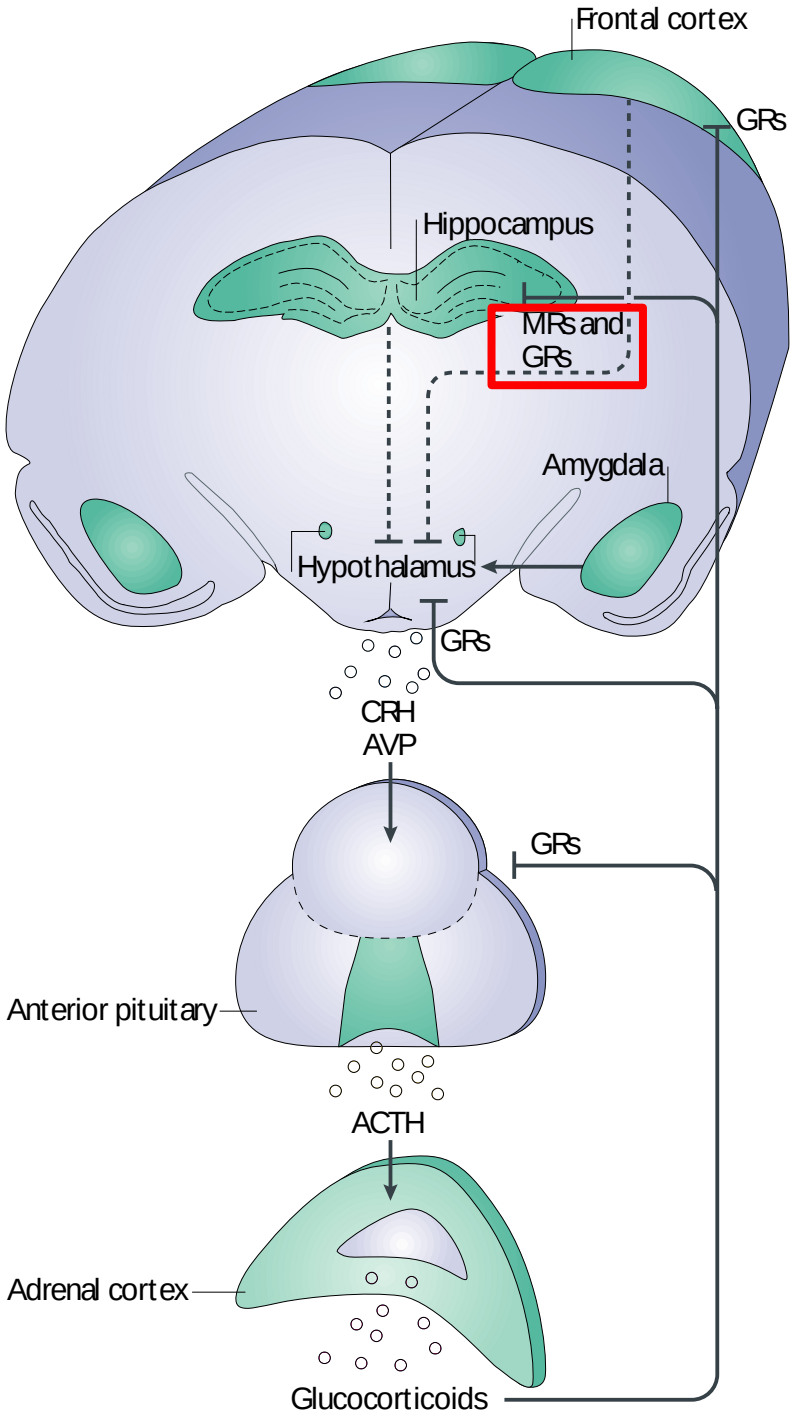
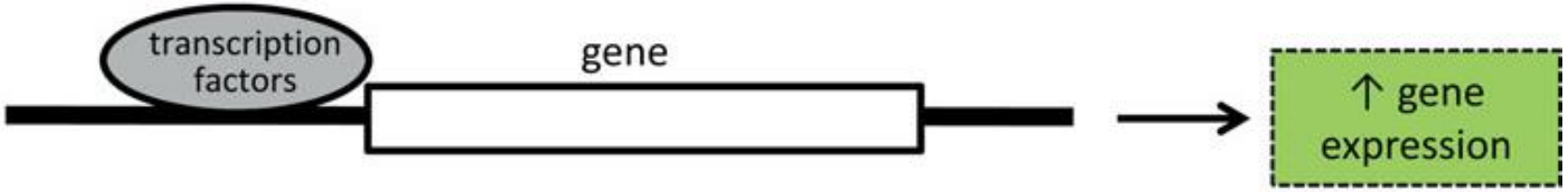


Lupien et al., 2009

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

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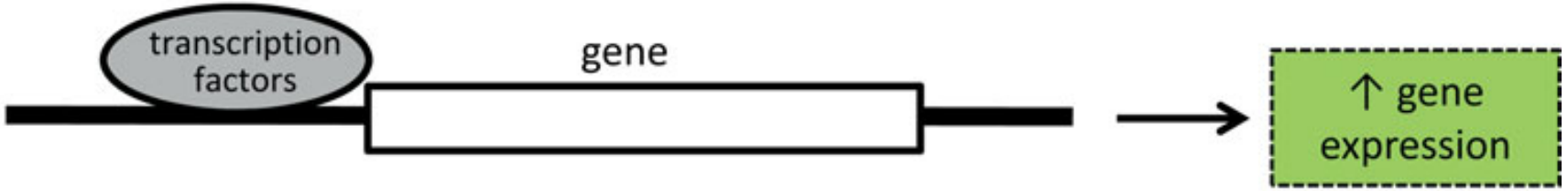
Gene transcription



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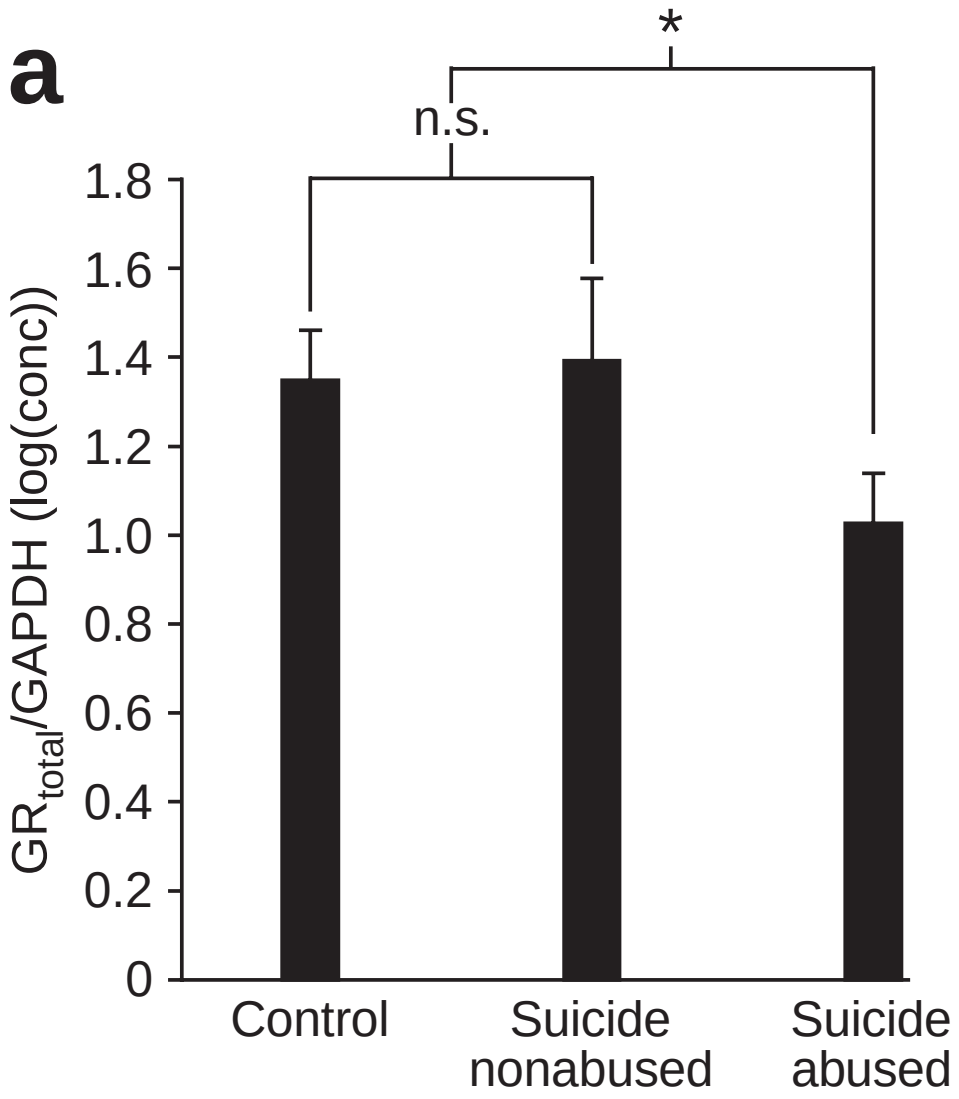
Monk et al., 2012

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[32]
- Prenatal synthetic glucocorticoid exposure in rats results in down-regulation of GR receptor mRNA in the hippocampus[33]

MR and GR Expression in Humans

- 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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- Low birth weight combined with high infant-mother attachment may correlate with normal hippocampal size[38]

Can Providers Intervene?

- Effective screening tools for assessing the likelihood of prenatal substance abuse already exist[39,40]

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- Are providers missing the underlying **stress** contributing to prenatal substance abuse?

Suggestions

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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

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  - Dr. Nicholas Andreadis
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