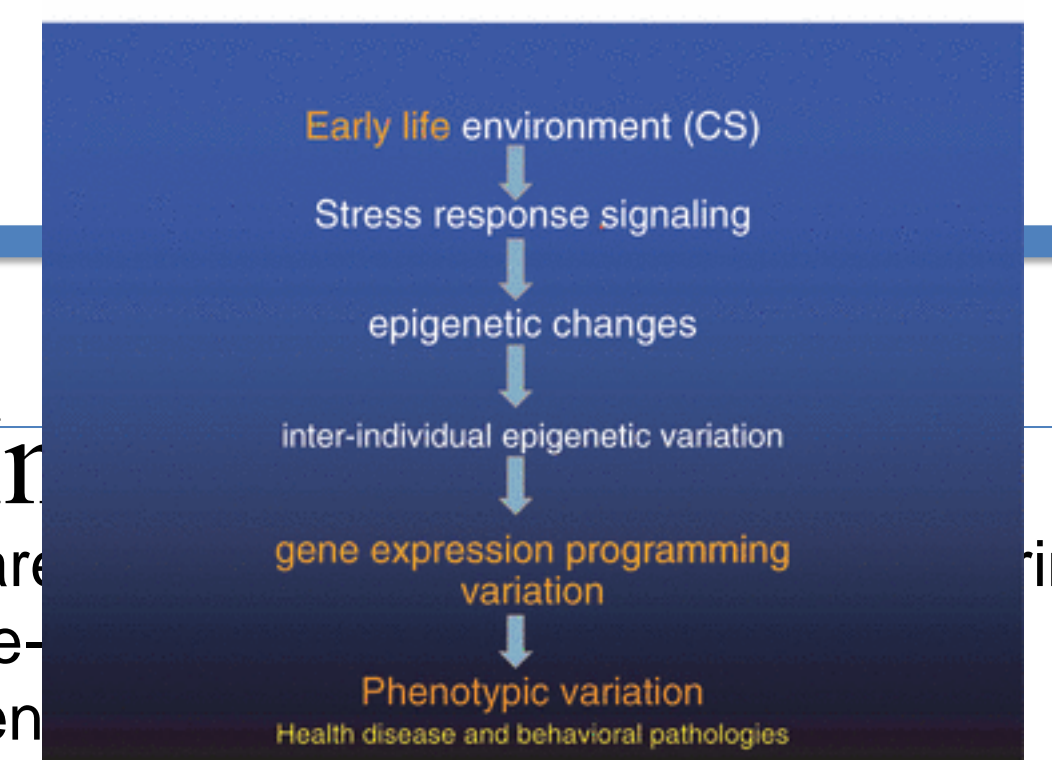
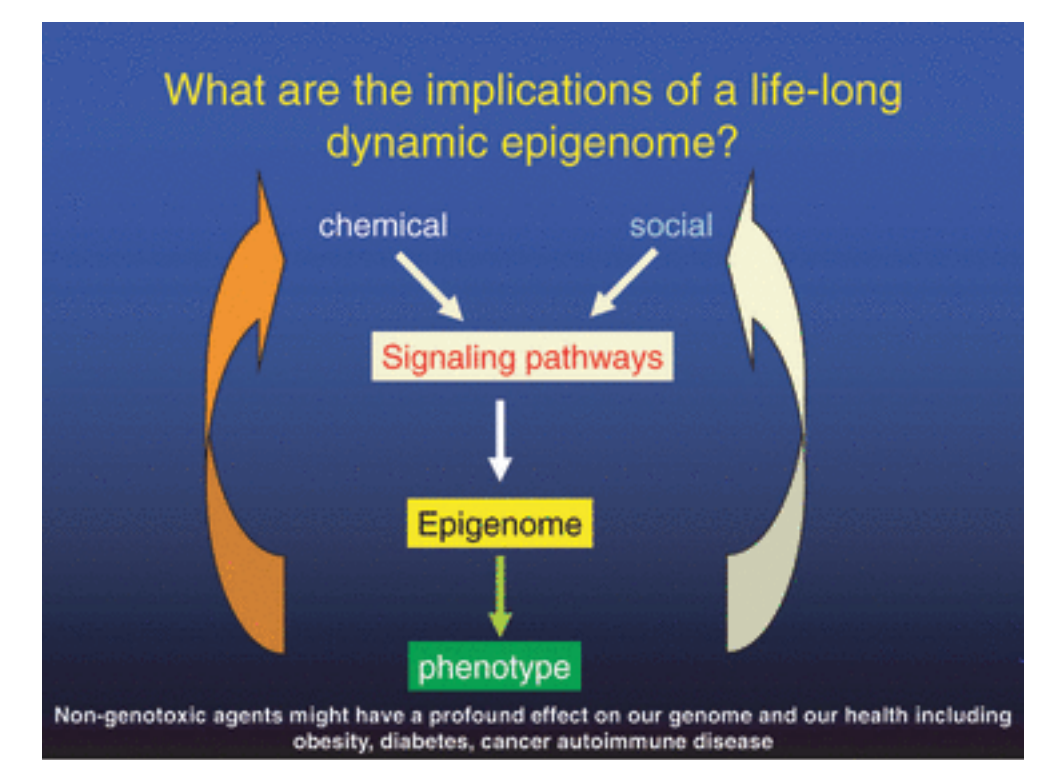




# Role of Parental Care in HPA Axis Regulation: Biological Mechanism and Policy Implications

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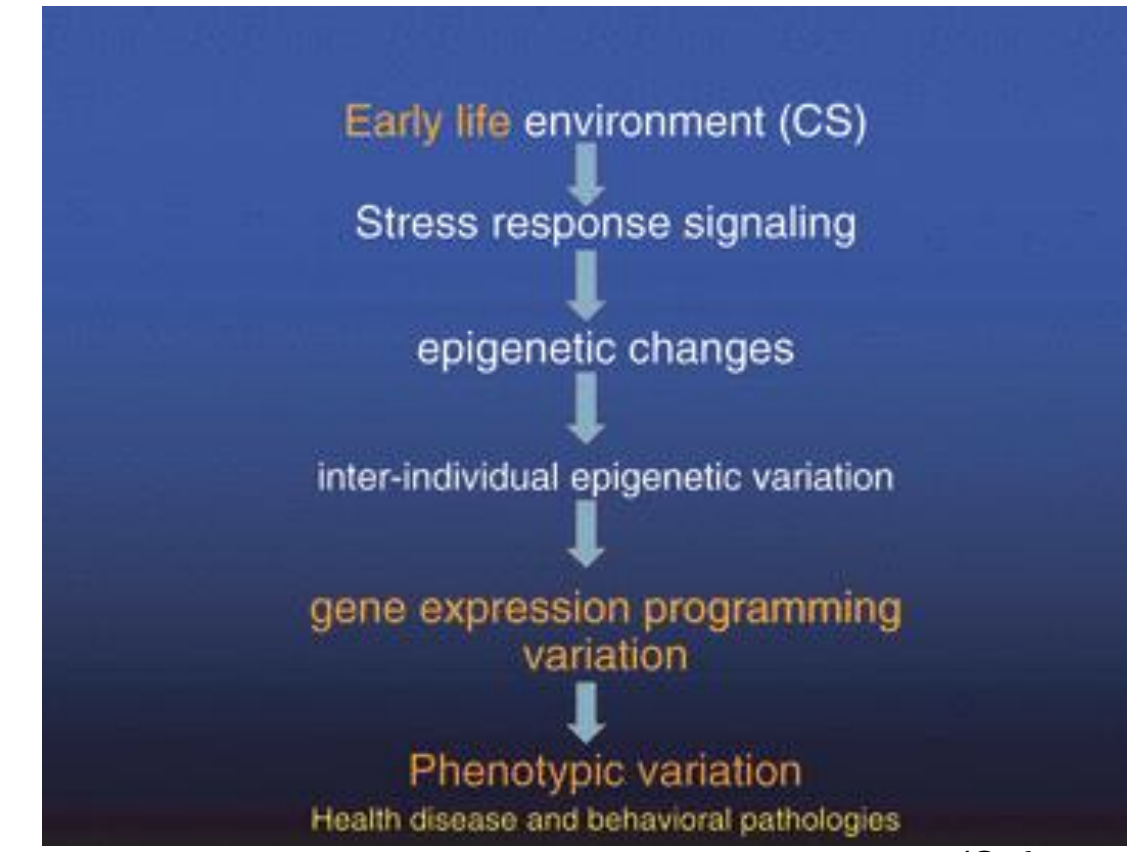
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## Introduction

A stable, responsive environment of relationships in early childhood is necessary for healthy development of neurobiological systems, including neuroendocrine maturation. Beginning in infancy, children reach out to adults through babbling, gestures, and facial expressions. When adults respond appropriately with warmth and individualized attention, it serves to promote development of new neural connections that create more efficient pathways between the different regions of the brain. Disruption of this "serve and return" interaction has been implicated in the development of impaired brain architecture and, subsequently, an increased vulnerability to a wide variety of physical and mental health impairments later in life. Recent research with both animal and human models indicates the principle pathway of our stress response, the limbic hypothalamic-pituitary-adrenocortical axis (HPA axis), is socially regulated early in development and differences in parental care are implicated in the development of individual variation in HPA responsiveness.

## Epigenetic Modification of GR Gene

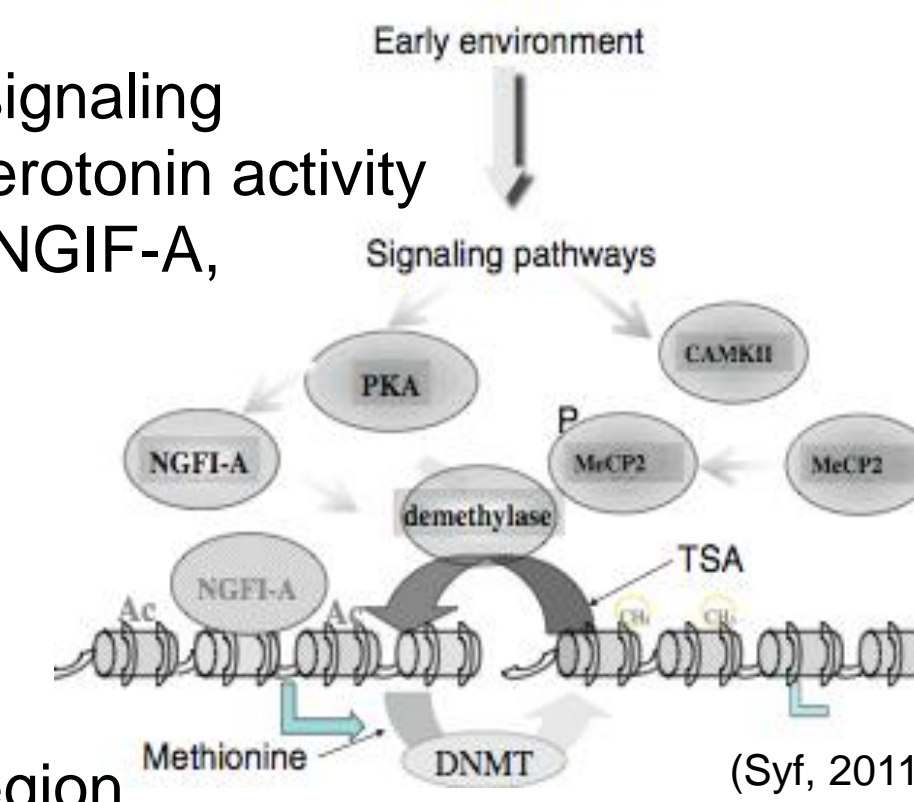


(Syf, 2009)

- Early- life experiences can alter patterns of gene expression through chemical modification of the structural genome

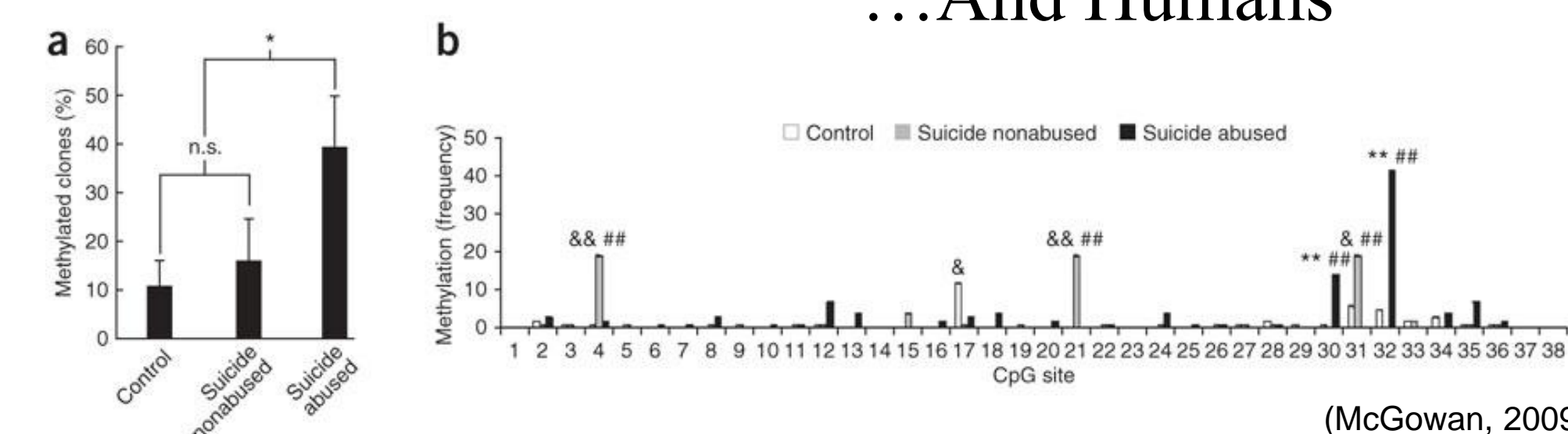
## In Rodents...

- LG-ABN behavior in rats triggers a signaling cascade beginning with increased serotonin activity
- Results in increased expression of NGIF-A, a transcription factor that binds to promoter region exon 1<sub>F</sub> of GR gene
- Histone acetylation activates chromatin and facilitates demethylation of an important cytosine residue within the 5' CpG dinucleotide of the NGIF-A binding region
- Results in increased NGIF-A binding and GR expression



(Syf, 2011)

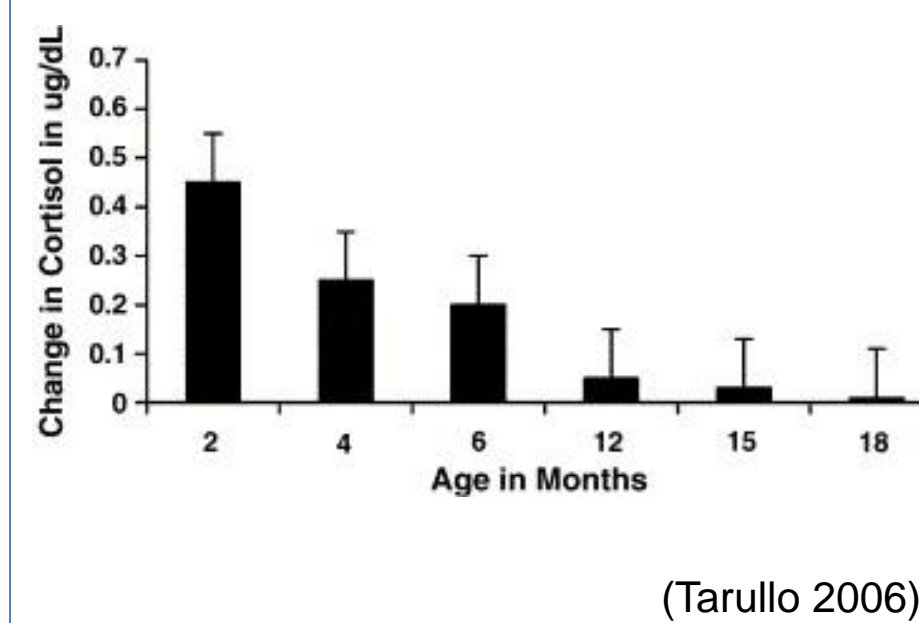
## ...And Humans



(McGowan, 2009)

- DNA methylation regulates the NR3C1 (GR) gene by interfering with transcription factor NGIF-A binding at the exon 1<sub>F</sub> site
- Methylated NR3C1 was shown to inhibit NGIF-A binding
- Suicide victims with a history of childhood abuse exhibit decreased levels of GR mRNA and decreased NR3C1 splice variant exon 1<sub>F</sub> expression compared to suicide victims without a history of childhood abuse and control

## Social Regulation of the HPA Axis



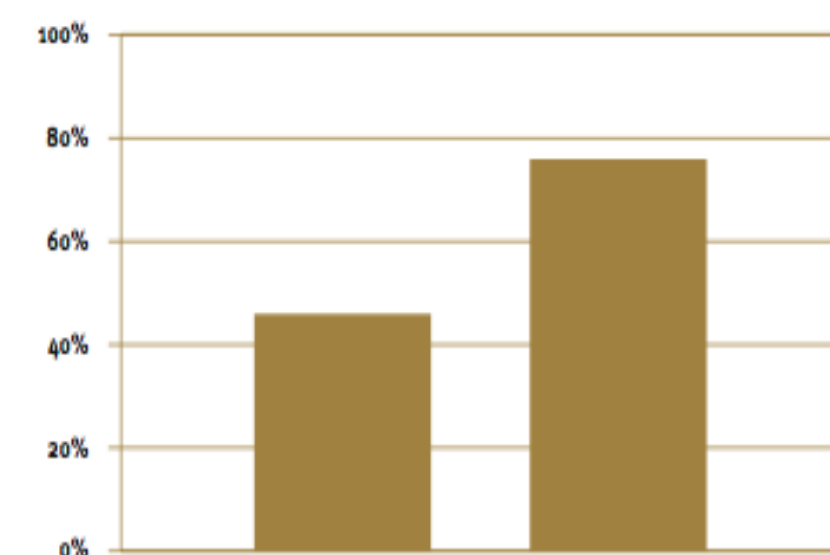
(Tarullo 2006)

- Healthy newborns initially have a highly reactive adrenocortical response but gradually enter a stress hypo-responsive period
- Responsive caregivers mediate this transition by helping children cope with stress

- Prolonged disruption of serve and return interaction can lead to lasting changes in HPA responsiveness

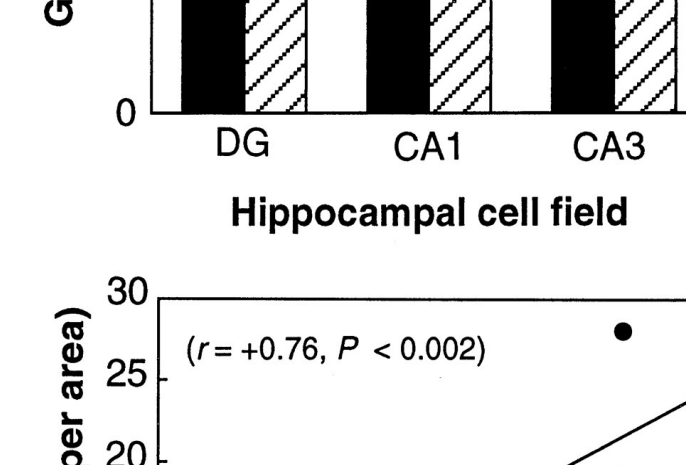
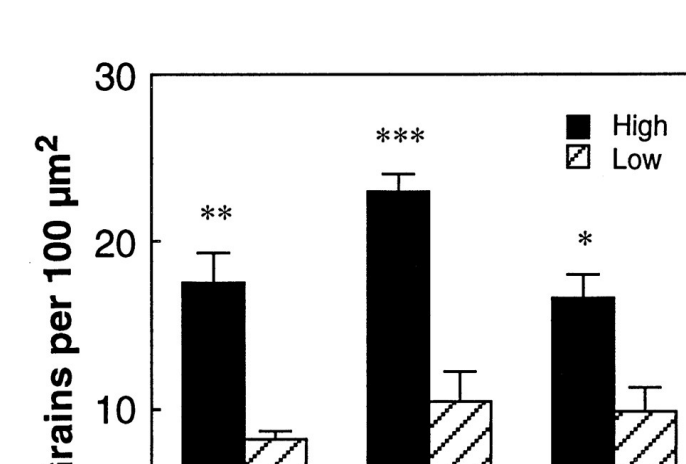
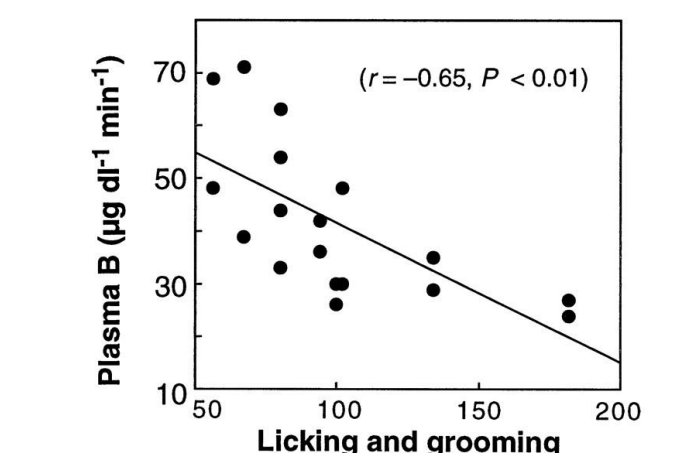
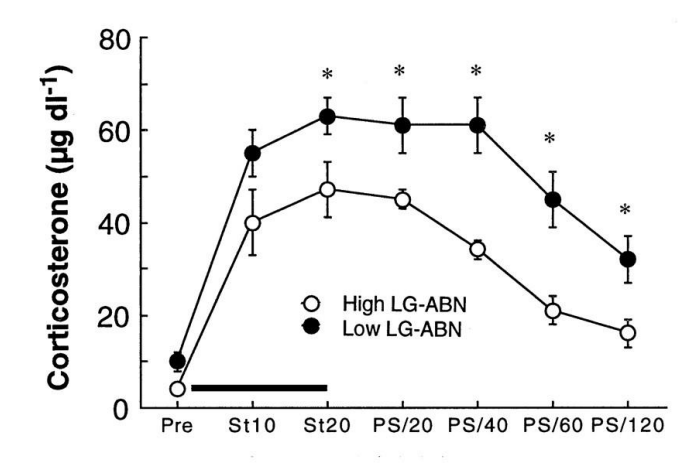
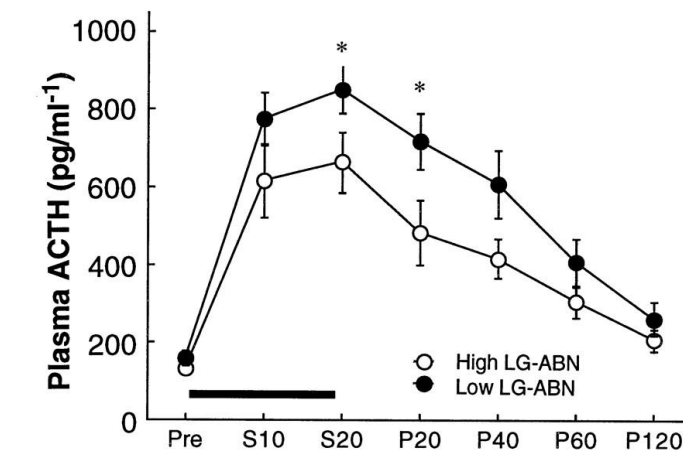
- Maternal depression during infancy leads to higher cortisol levels during adolescence

### Exposure to Maternal Depression in Infancy Causes Stress Hormone Levels to Become More Extreme in Adolescence



(Working Paper No. 8 2009)

## Maternal Care Regulates Gene Expression in Rodent Model



- Individual differences in frequency of licking/grooming and arched back nursing (LG-ABN) behavior are associated with long lasting differences in HPA response to stress
- ACTH and adrenal corticosterone response was significantly positively correlated to frequency of maternal LG-ABN behavior.
- High LG-ABN offspring exhibited higher glucocorticoid receptor mRNA expression than low LG-ABN offspring. This results in greater sensitivity to negative feedback inhibition. High LG-ABN offspring were able to suppress ACTH production to a greater extent than low LG-ABN offspring when treated with corticosterone before administering of stress.
- Low LG-ABN show more fearful behavior; they spend less time exploring new environments and greater latency to try novel foods
- Low LG-ABN offspring raised by high LG-ABN show significantly less fearful behavior than low LG-ABN offspring raised by their biological mother, further evidence of the role of maternal stimuli in regulation of this behavior

(Liu, 1997)

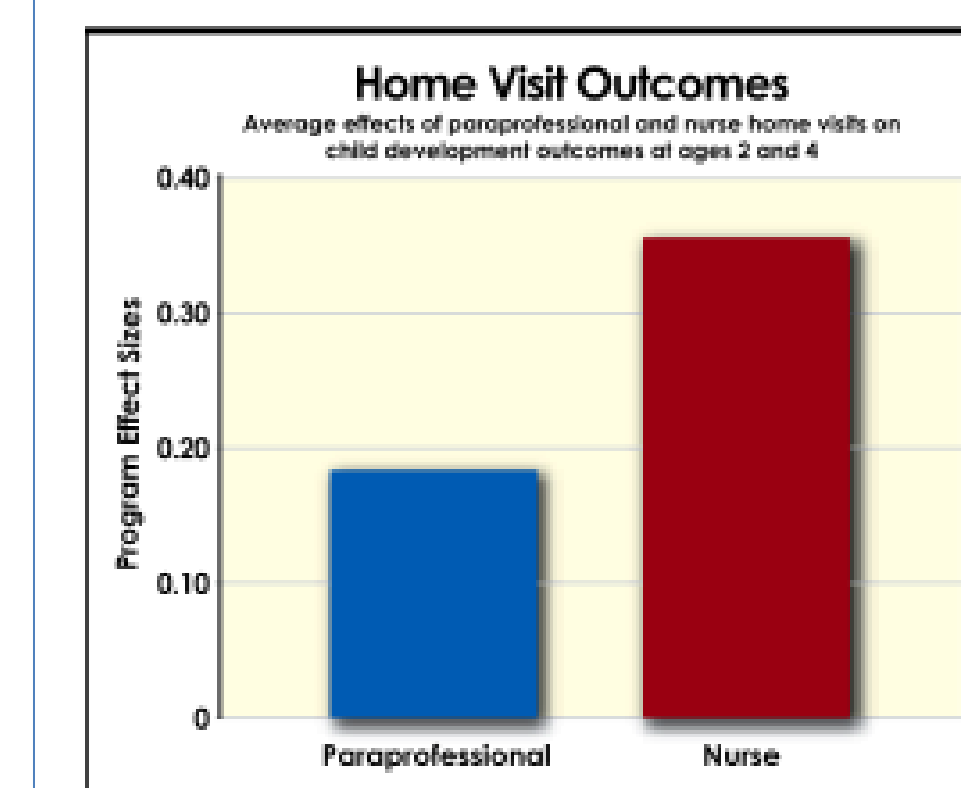
## Clinical Implications

The prominent role of quality of parental care on child health later in life necessitates a re-examination of current practices. Stress-related impairments in childhood experiences serve as a drain on our society's resources. Poor health reduces the productivity of the workforce, puts increased demand on social services and disability programs, and raises medical care costs. Therefore programs and policies that serve to prevent the early health origins of these diseases are a cost-effective investment toward improving, not only the physical health of our nation, but social and economic health as well.

### Workplace Policies

- In US, only half of workers qualify for guaranteed 3 months of unpaid parental leave through Family and Medical Leave Act
- Lack of universal subsidized parental leave means that only those who are wealthy enough to forgo three months of pay are able to take sufficient leave.

### Parenting Education and Home Visitation

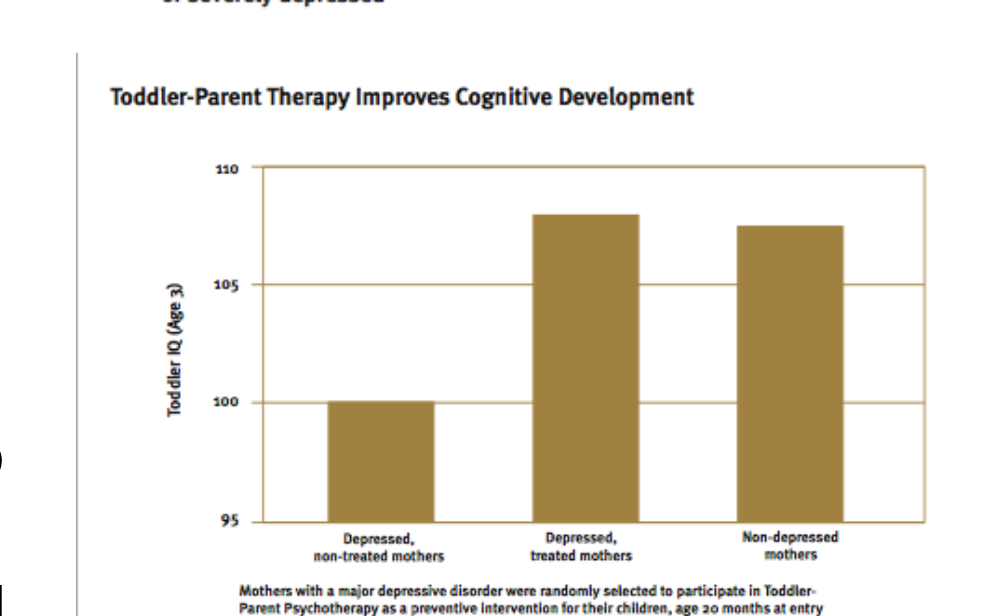
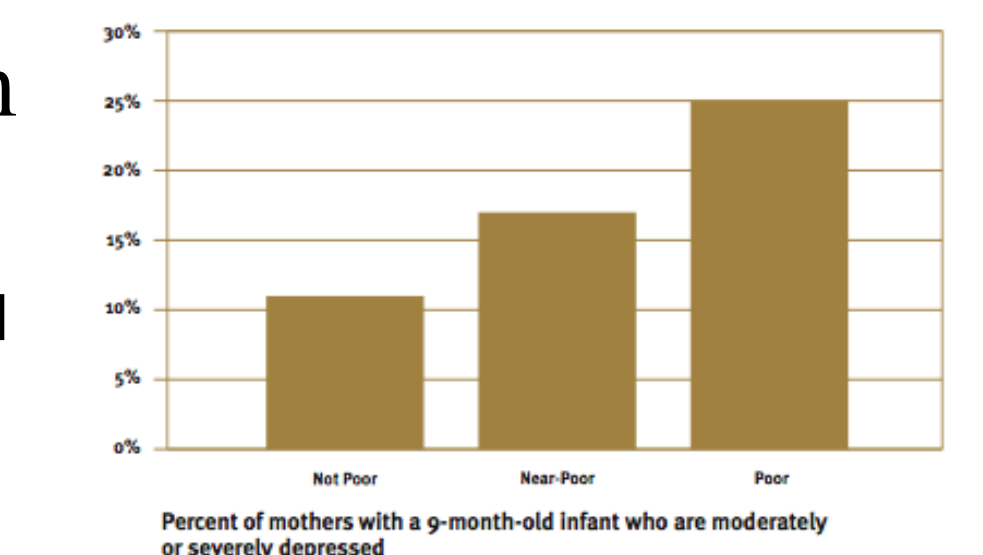


(Center for the Developing Child, 2007)

- Intensive home visitation programs such as Nurse Family Partnership have been shown to decrease subsequent pregnancies and increase maternal employment as well as increase cognitive development and decrease arrests in offspring adolescence
- Increased success with amount of education and training of care professionals

### Treatment of Mental Health Issues in Mother

- 10-20% of all mothers in the United States will experience moderate to severe depressive symptoms and that number jumps to 25% in low-income households
- Yet mothers are less likely to get help for depressive symptoms than other women
- Therapy for mother and child, if recognized early enough, can undo the deleterious alteration of neural circuits. These programs are varied and include massage therapy for mother and child and mother-child interaction instruction



(Working Paper No. 8, 2009)

## Conclusions

Social regulation of the HPA axis by parental care can have long-term effects on offspring health. In the absence of responsive, supportive interaction with caregivers, epigenetic modification of the GR gene results in decreased negative feedback inhibition and a hyper-reactive stress response. As we begin to understand this mechanism of this epigenetic programming, we can begin directing scientific research toward combating the specific targets of the signaling cascade. Still, preventative programs that serve to decrease childhood interaction with negative environmental stimuli is the most cost-effective way of improving the health of our nation