

Early Environmental Regulation of Gene Expression: How Early Experience Exerts a Sustained Influence on Neuronal Function

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Summary

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This effect is apparent even at the level of the DNA of the individual; the activity of genes implicated in brain development and function are directly regulated by the social environment.

This effect is potentially stable over time; the imprint of childhood adversity on the genome is apparent at later ages, providing a biological basis for an enduring effect on health and capacity.

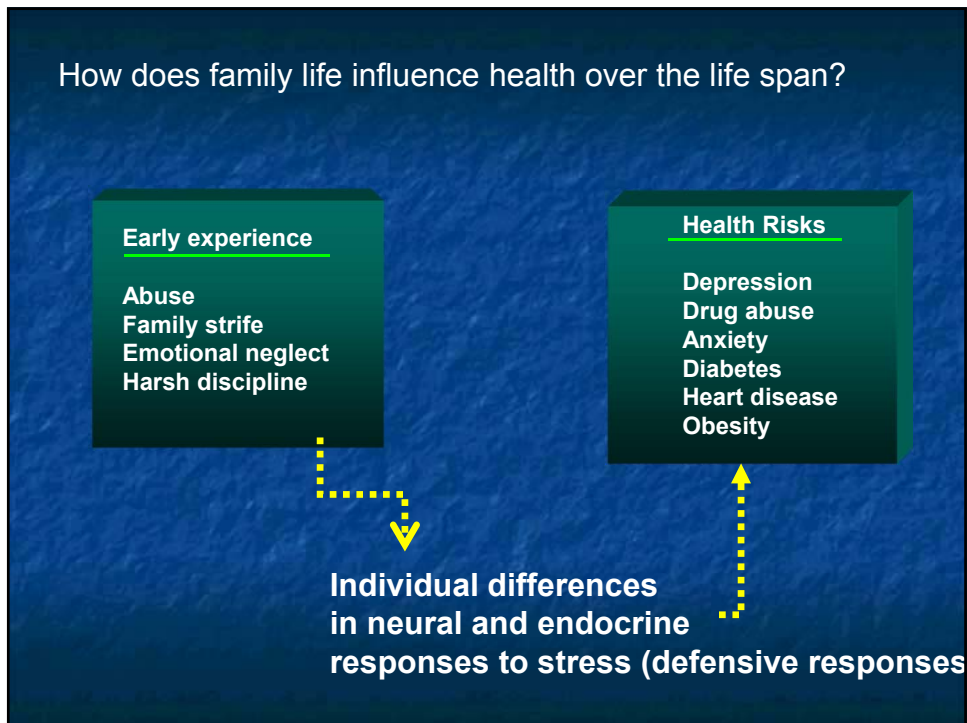
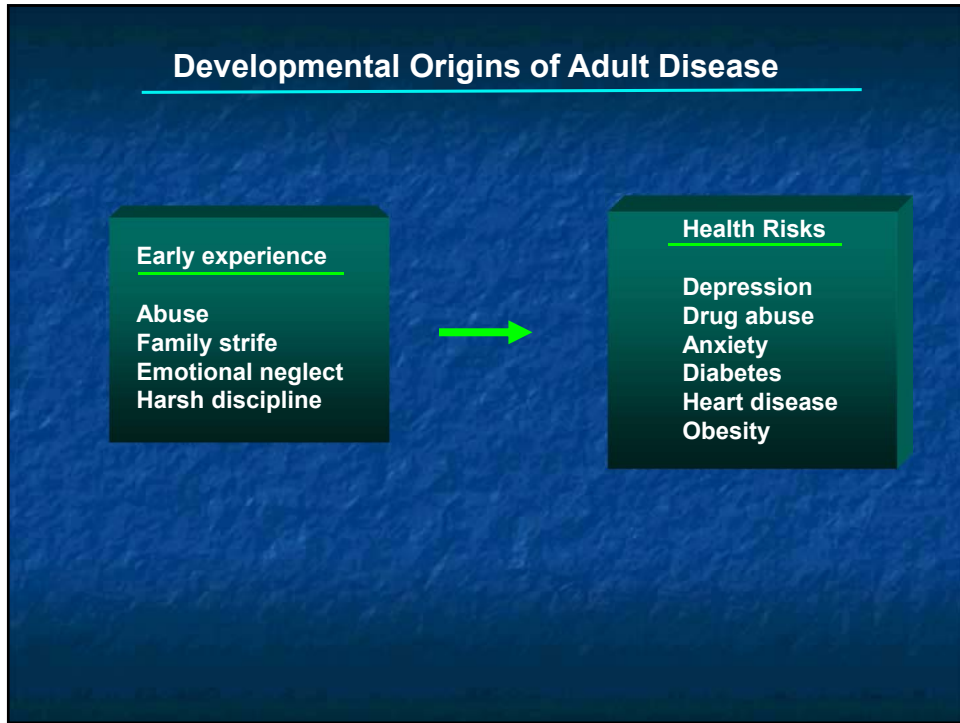
The development of an individual is an active process of adaptation that occurs within a social and economic context:

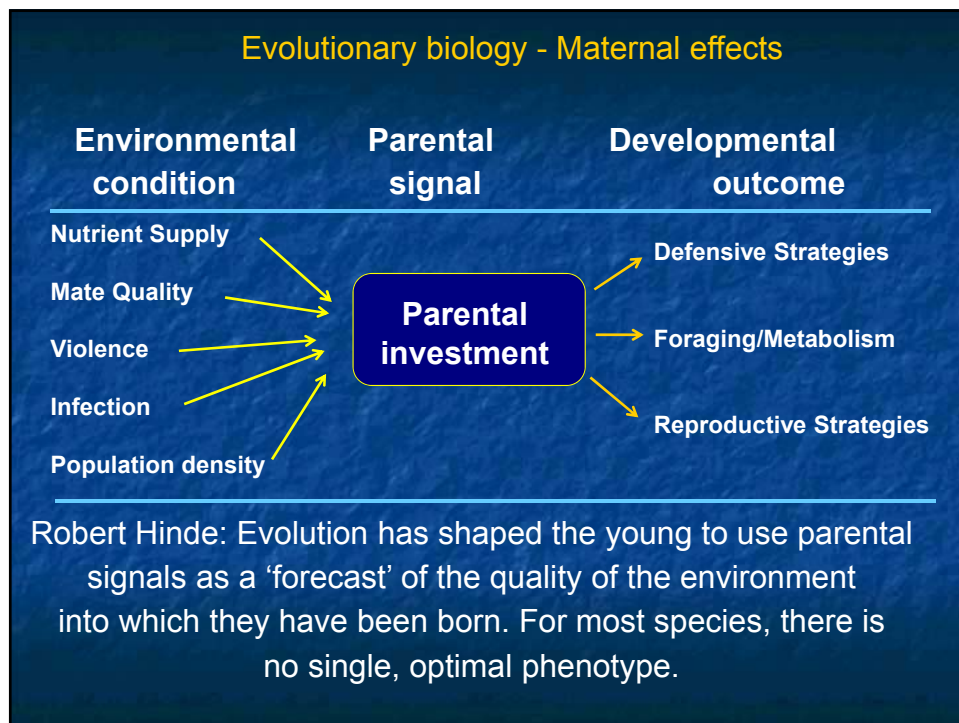
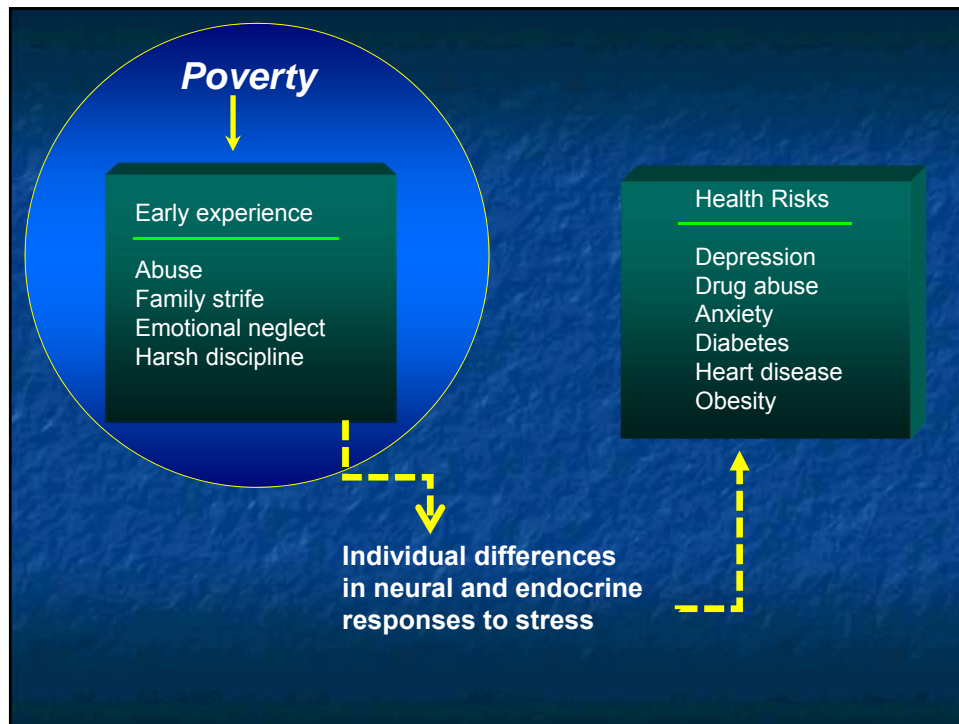
- To resource (food, shelter, safety) availability.
- To social interactions (e.g., parental signals).

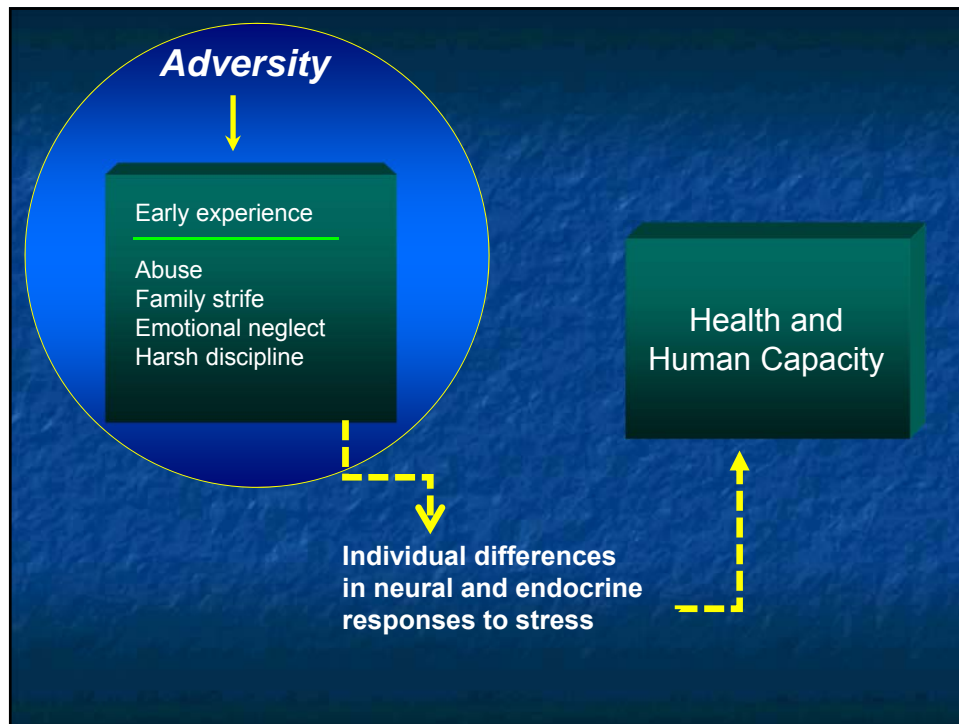
The development of an individual is an active process of adaptation that occurs within a social and economic context:

- To resource (food, shelter, safety) availability.
- To social interactions.

This influence is apparent in the epigenetic mechanisms that regulate genomic structure and function







Environmental regulation of phenotypic variation

What is the biological basis for 'programming' effects whereby environmental signals acting over perinatal development associate with stable changes in transcription and complex phenotypes (physiology, behaviour)?

Summary

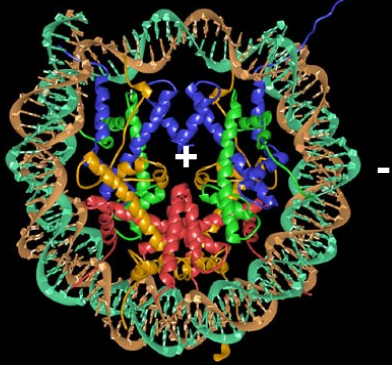
- Parental care affects the activity of genes in the brain that regulate stress responses, neural development and reproduction.
- This parental effect involves a form a “plasticity” at the level of the DNA.

Epigenetics: Any functional change in the genome that does not involve an alteration of DNA sequence.



If they ask you anything you don't know,
just say its due to epigenetics.

nucleosome core particle



- H2A
- H2B
- H3
- H4

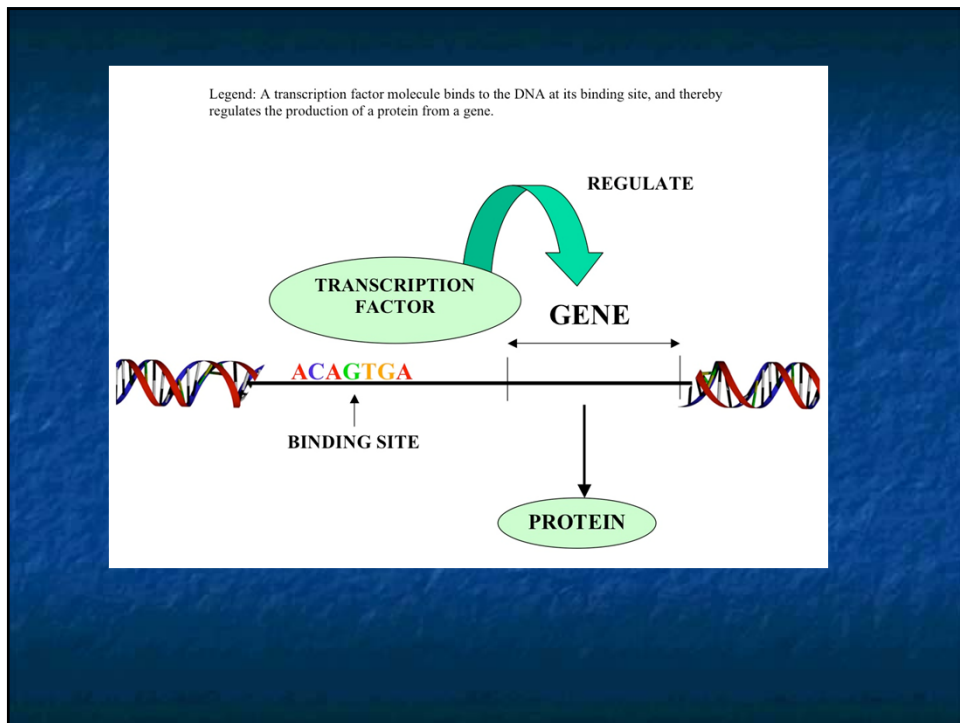
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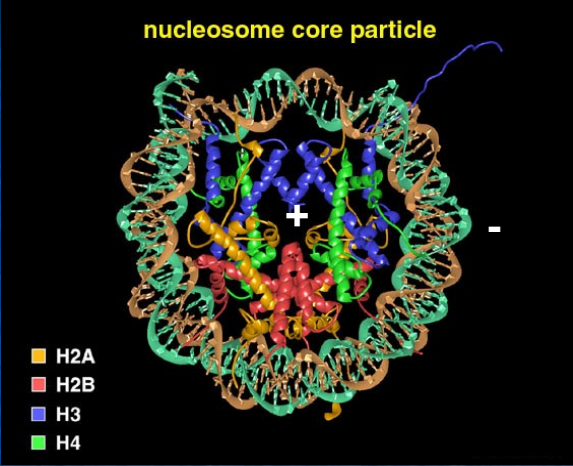
Prevents TF binding to DNA

TF binding involves alteration of chromatin structure

Nucleosome core particle: ribbon traces for the 146-bp DNA phosphodiester backbones (brown and turquoise) and eight histone protein chains (Luger et al. Nature 1997).



nucleosome core particle



+ -

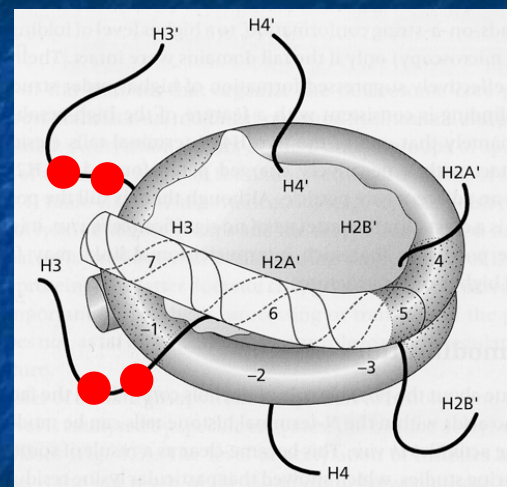
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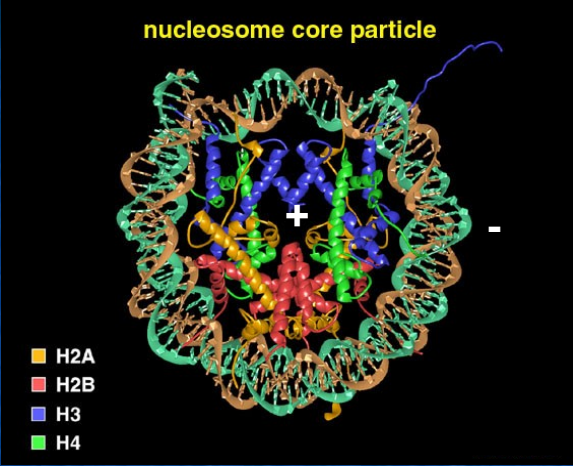
Nucleosome core particle: ribbon traces for the 146-bp DNA phosphodiester backbones (brown and turquoise) and eight histone protein chains (Luger et al. *Nature* 1997).

● Acetyl group



B. Turner. *Chromatin structure and gene regulation*. 2001

nucleosome core particle



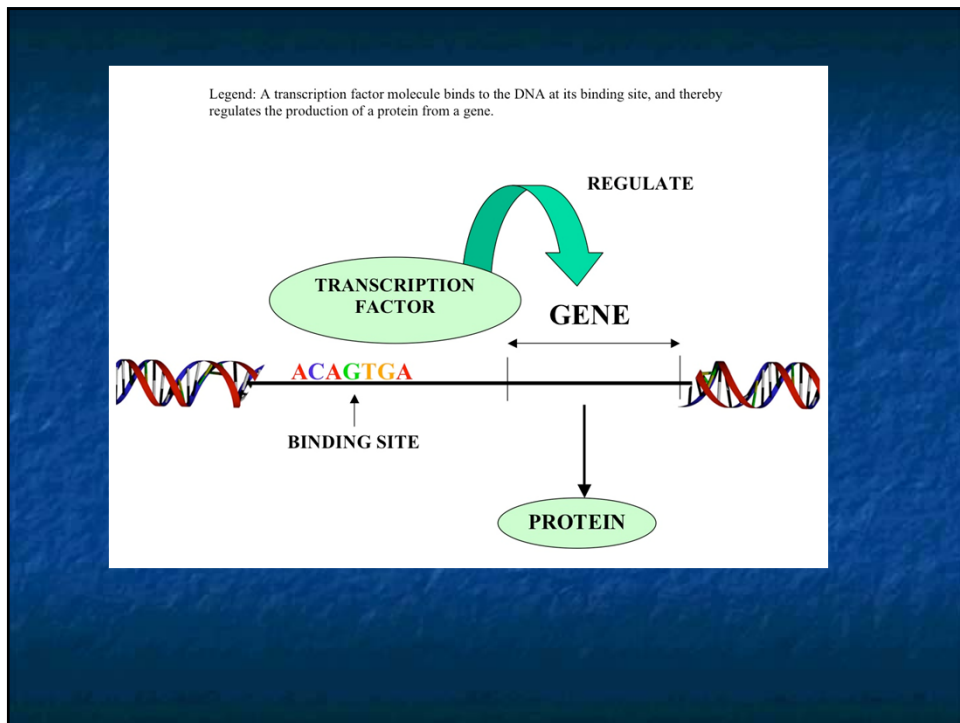
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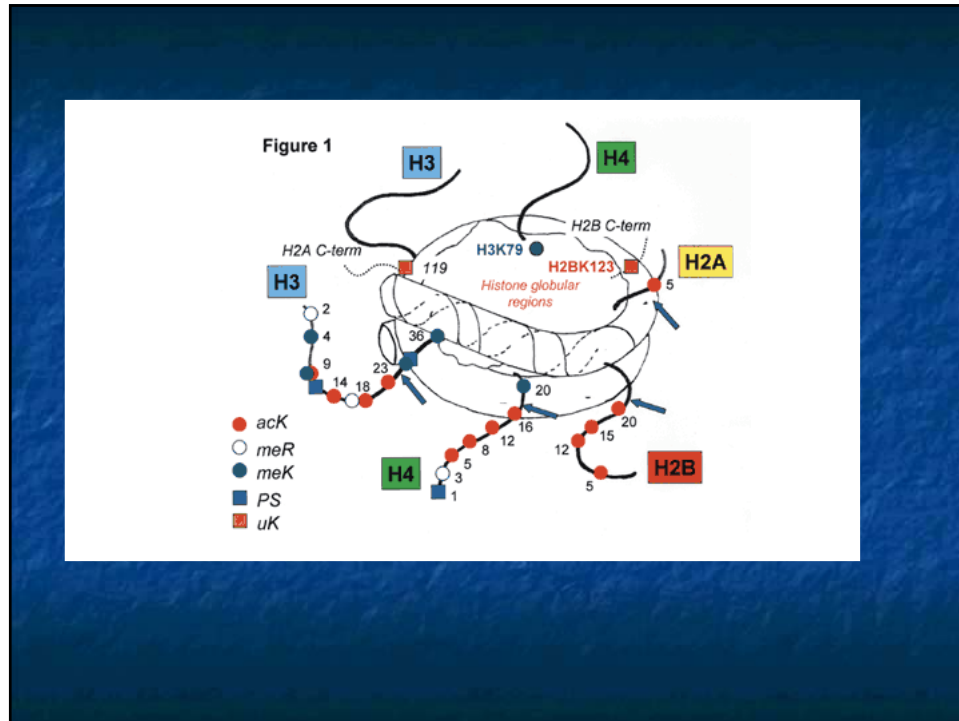
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Genetic code is defined by the sequence of four nucleotides that produce proteins.

CTACG TACTCG GAATCTCG

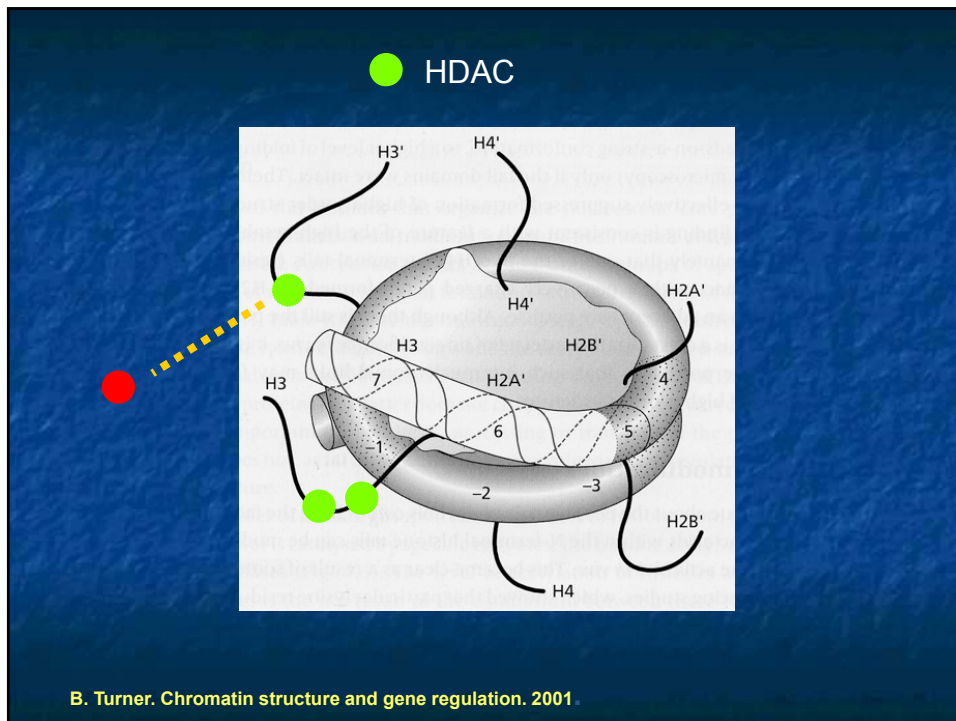
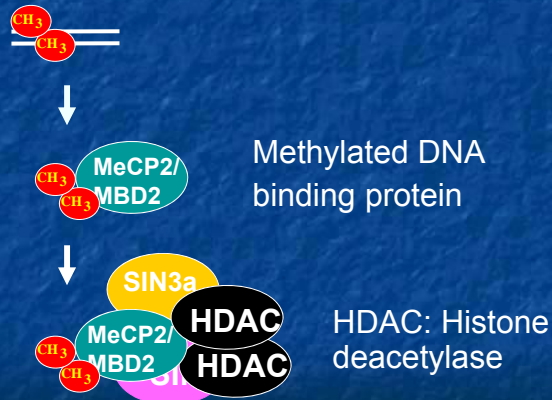


RNAs, proteins

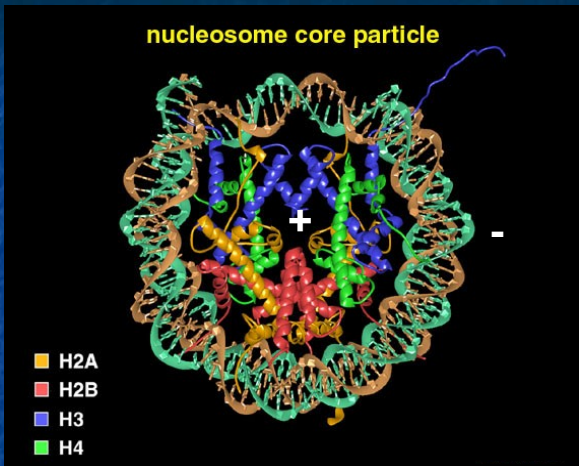
Epigenetic effects refer to modifications of the DNA that alter the activity of the gene, but not its function.

CTACG TACTCG GAATCTCG

DNA Methylation can inhibit gene expression by blocking transcription factor binding



nucleosome core particle



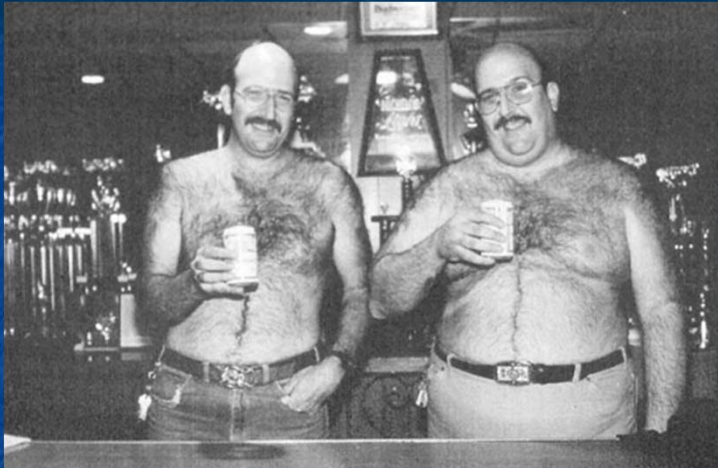
■ H2A
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Prevents TF binding to DNA

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Nucleosome core particle: ribbon traces for the 146-bp DNA phosphodiester backbones (brown and turquoise) and eight histone protein chains (Luger et al. Nature 1997).

Multiple phenotypes from a common genotype



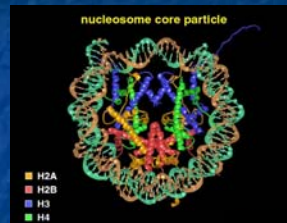
Every cell in your body has the same nuclear genes, but...?

Maternal licking/grooming



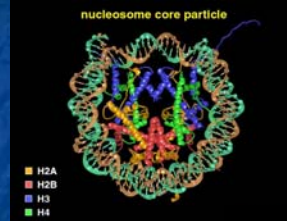
Environmental epigenetics hypothesis: Environmental events activate intracellular signals that remodel the epigenome, leading to sustained alterations in the structure and function of the genome, and thus stable effects on gene transcription.

Parental signals as a source of phenotypic plasticity?



Parental care → Epigenetic marks → Gene expression → Phenotype

Parental signals as a source of phenotypic plasticity?

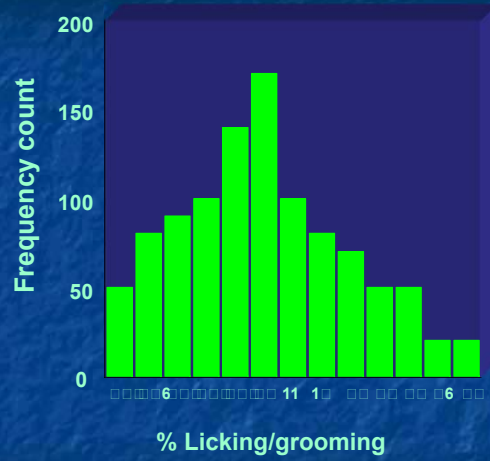


Maternal licking/grooming



Source of tactile stimulation/nurturance: Enhances activity of endocrine systems (e.g., GH/IGF) that promote somatic growth, suppresses those (glucocorticoids) that inhibit growth

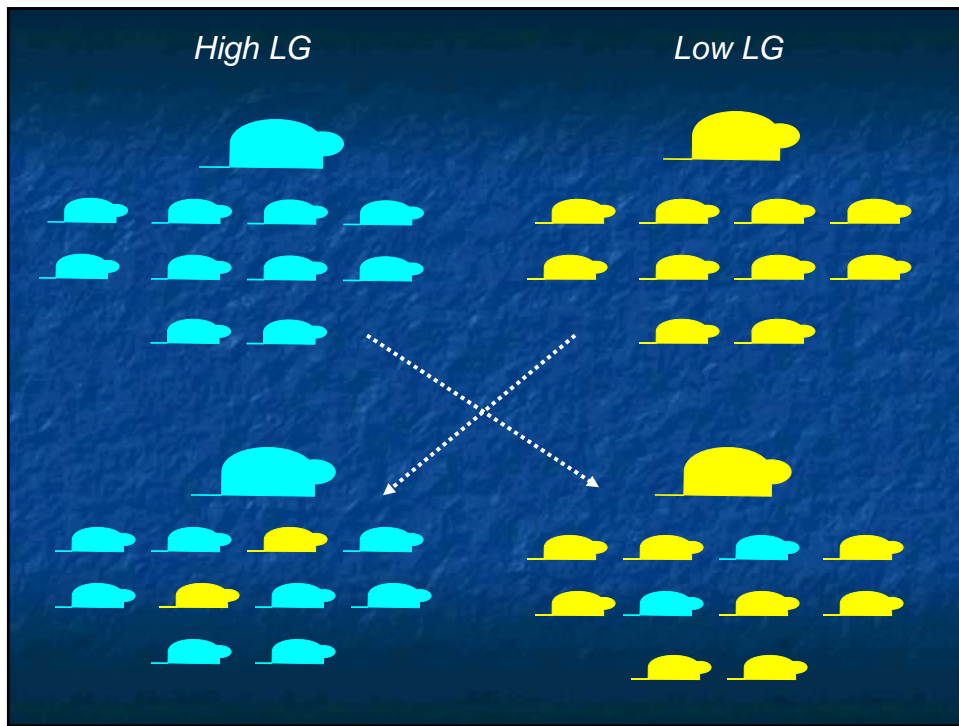
Variations in maternal care



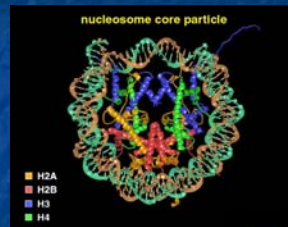
Broad range of parental effects



- Stress responses
- Neural development
- Learning & memory
- Metabolism
- Reproduction (females)



Parental signals as a source of phenotypic plasticity?



Broad range of parental effects



Stress responses

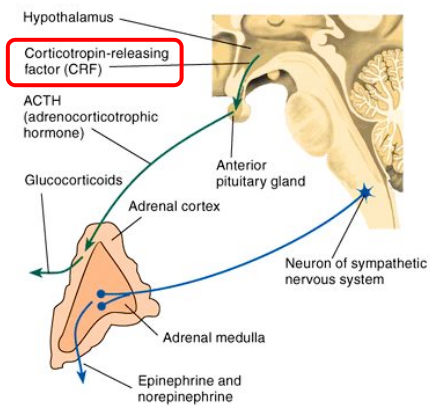
Neural development

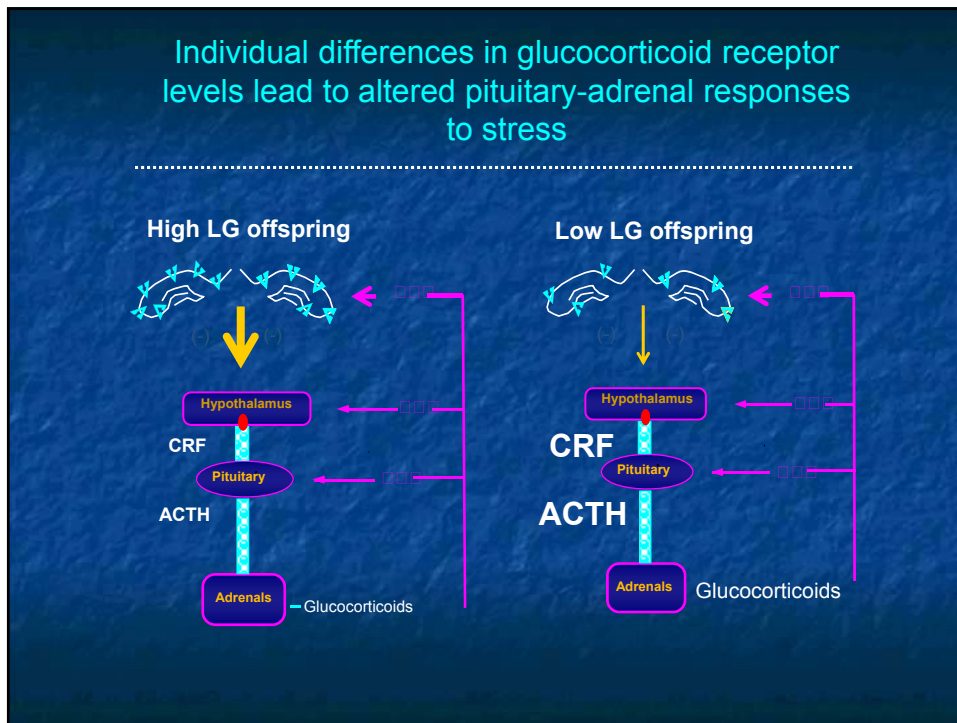
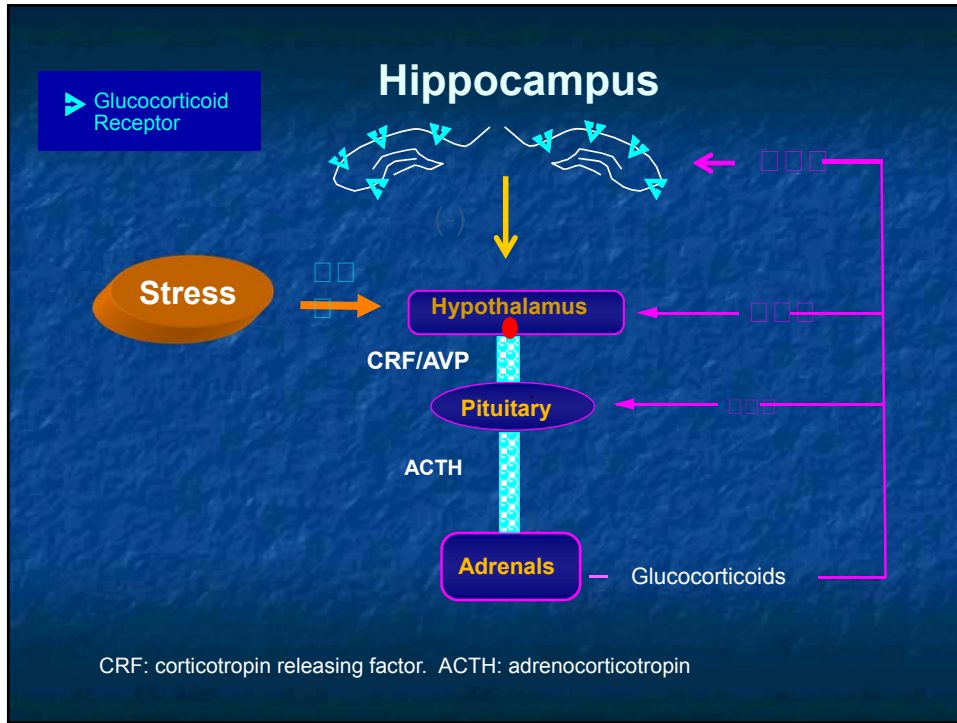
Learning & memory

Metabolism

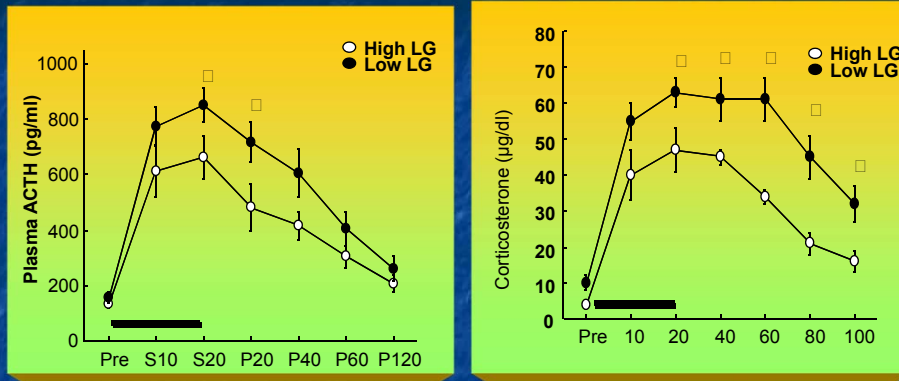
Reproduction (females)

► Control of the Secretion of Glucocorticoids by the Adrenal Cortex and of Catecholamines by the Adrenal Medulla



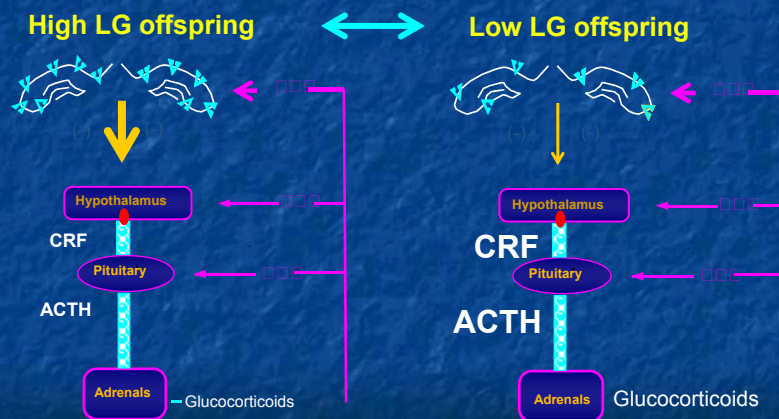


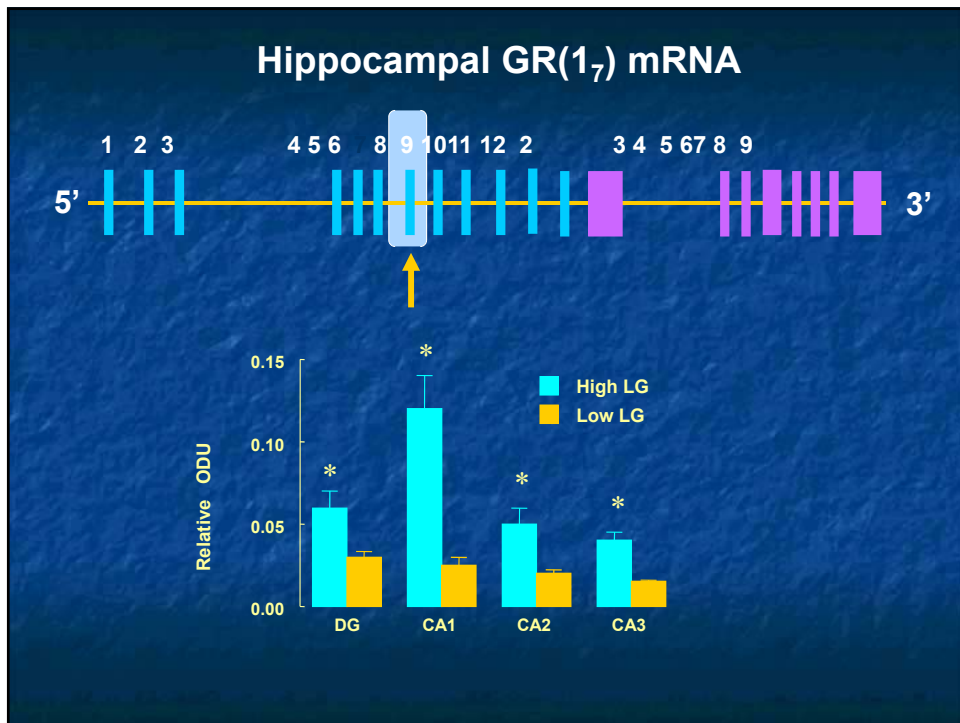
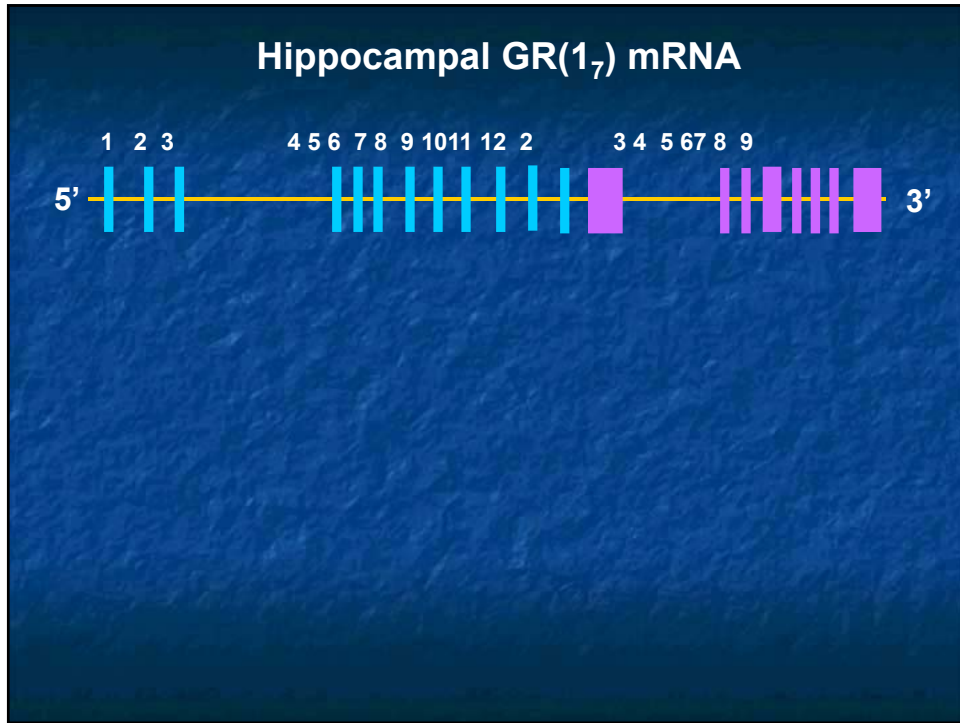
High LG offspring show more modest HPA stress responses

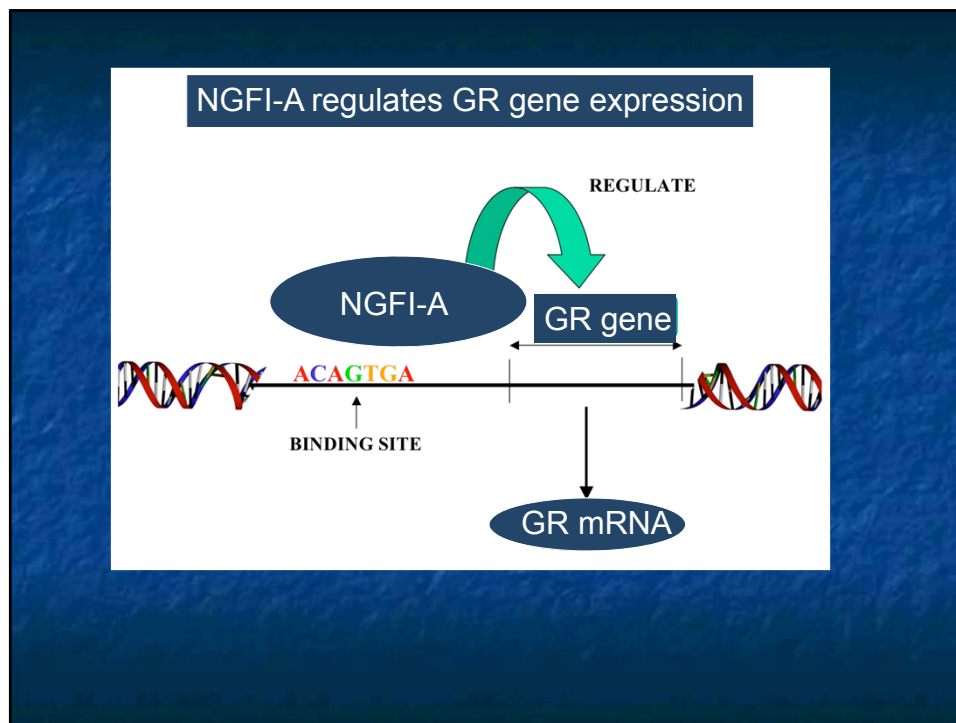
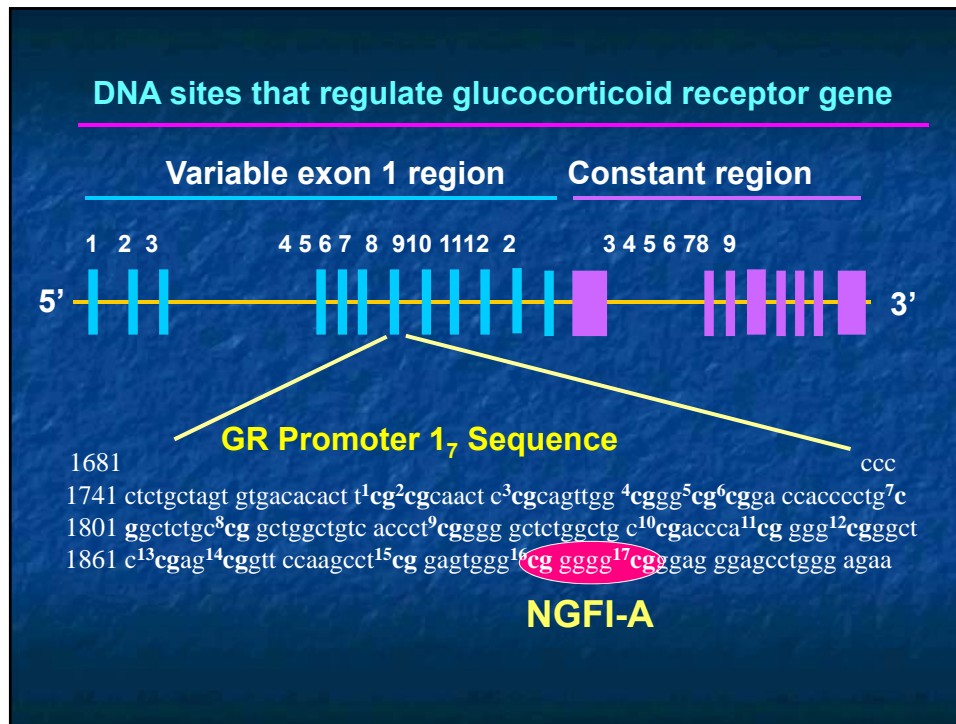


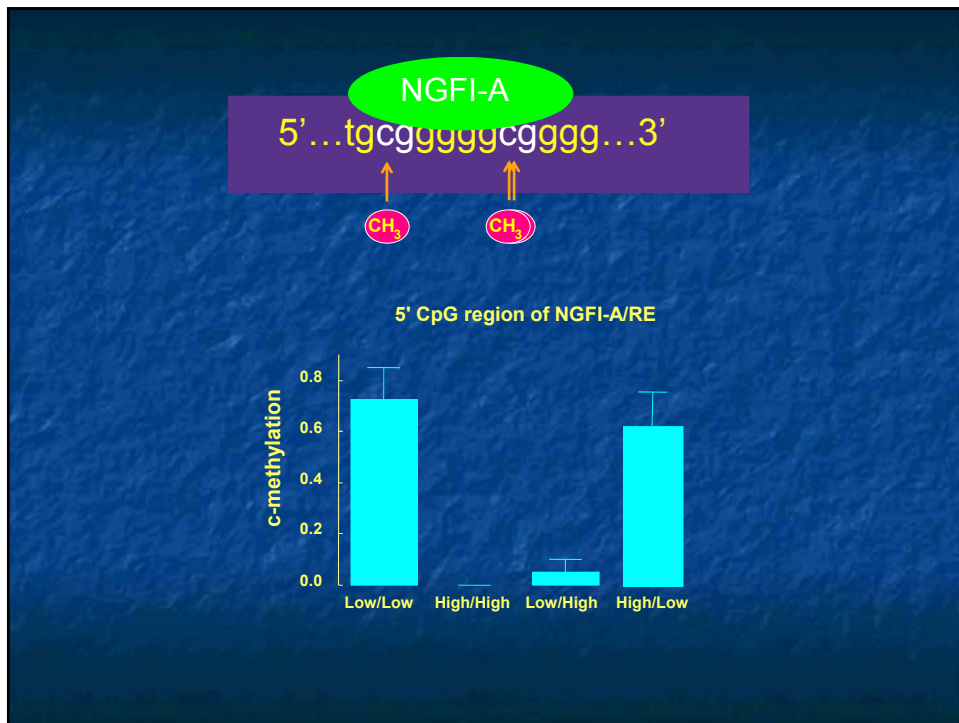
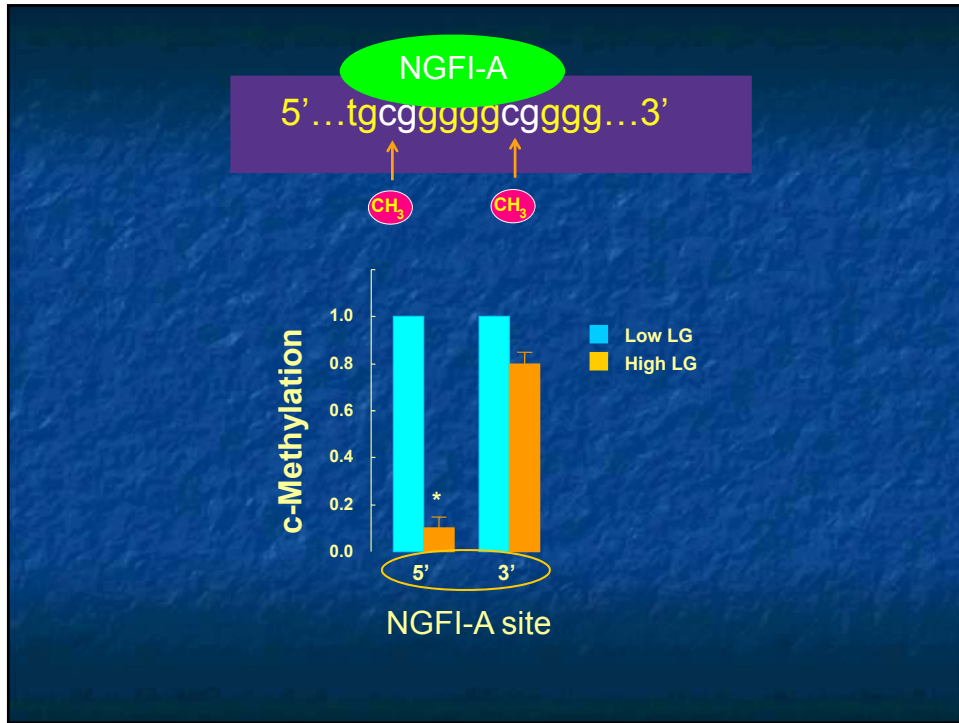
Disruption of hippocampal GR signaling eliminates this maternal effect

Cross-fostering reveals evidence for direct, postnatal effects of maternal care

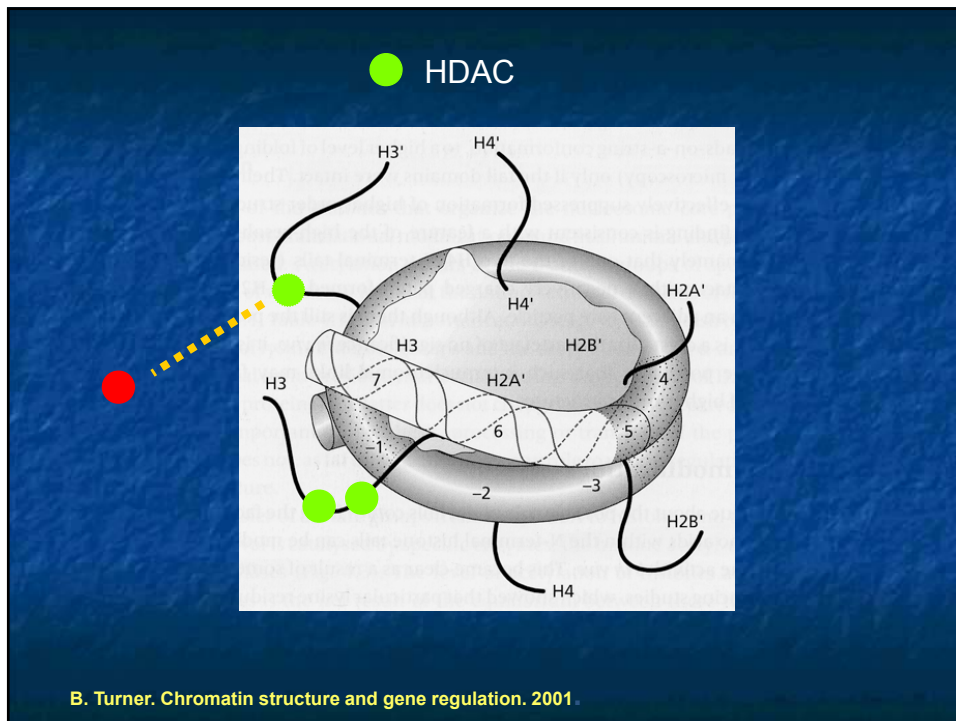
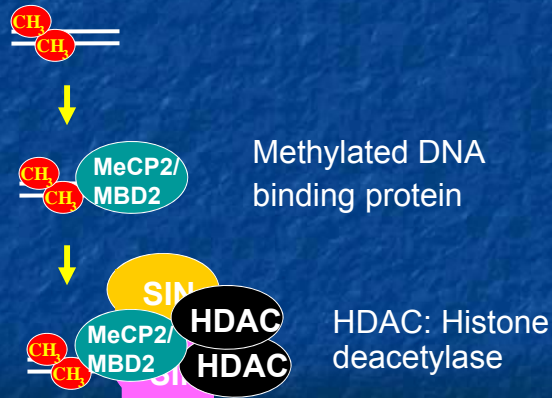


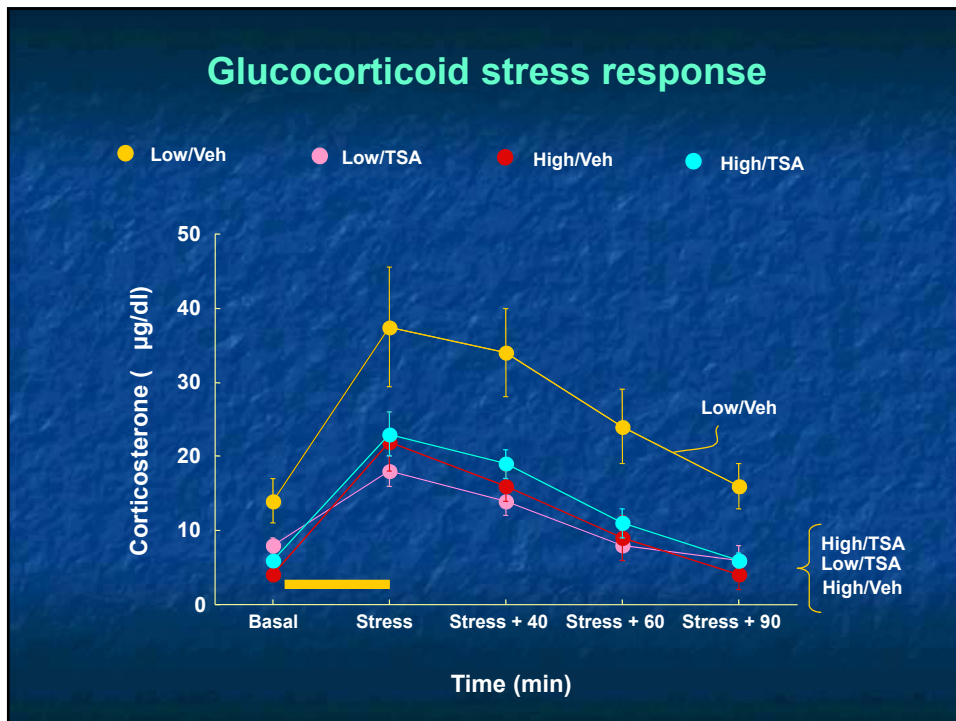
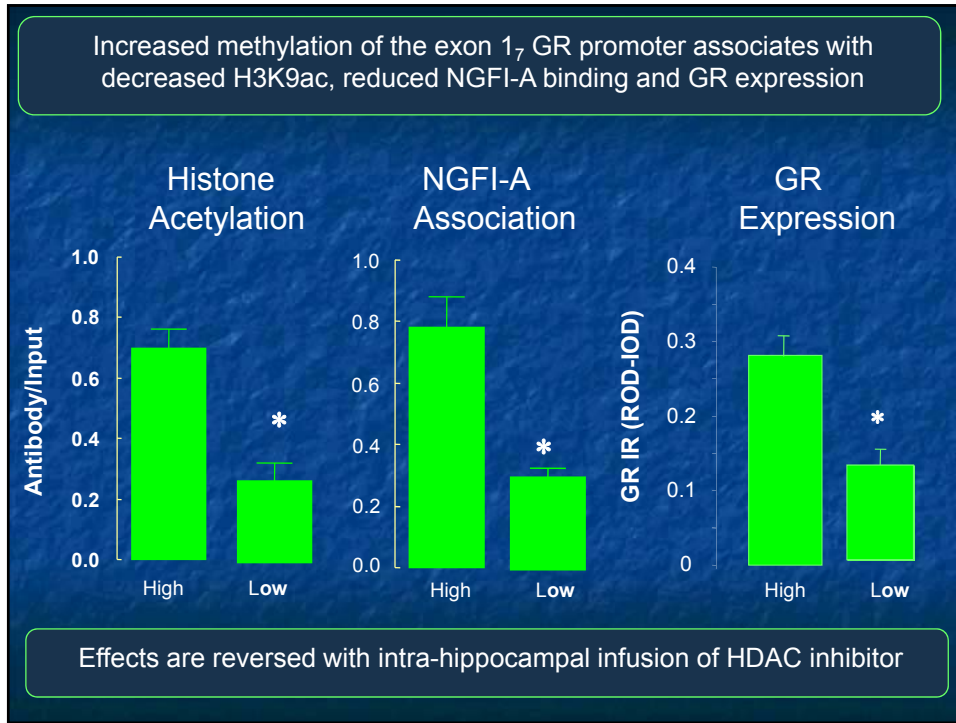






DNA Methylation can inhibit gene expression by blocking transcription factors binding





Offspring of Low LG mothers

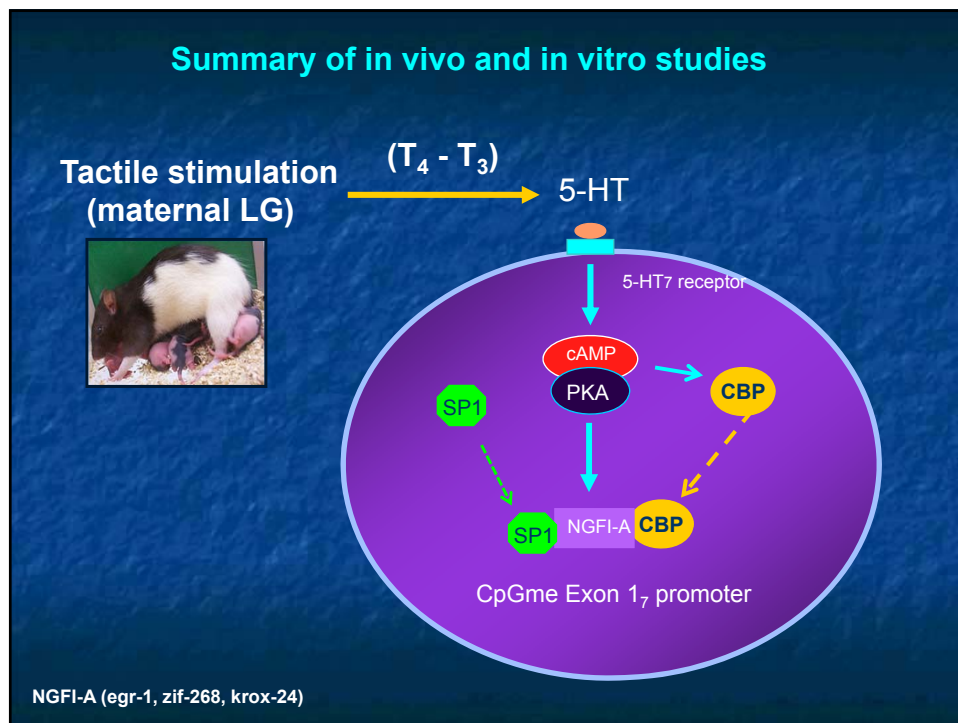
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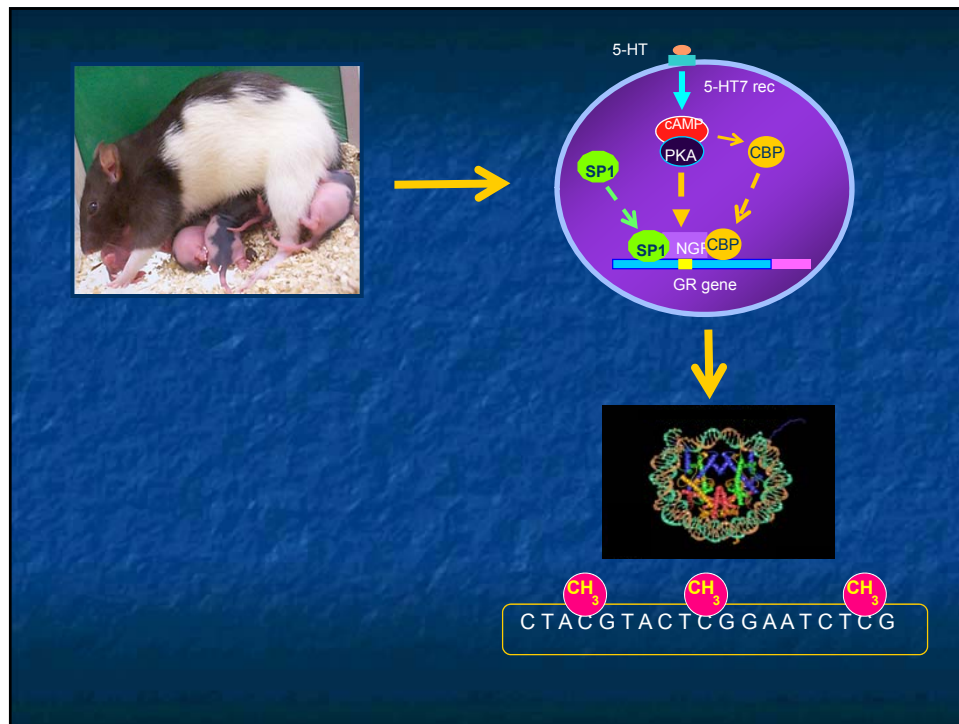
**Lower levels of GR in hippocampus -
Increased stress response**

Offspring of High LG mothers

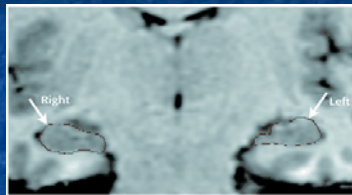
GGAGCCTGGGAGAACCAAGCCTCGGAGTGGGC^{CH₃}GGGGGCGGGAG

**High levels of GR in hippocampus -
Modest stress response**

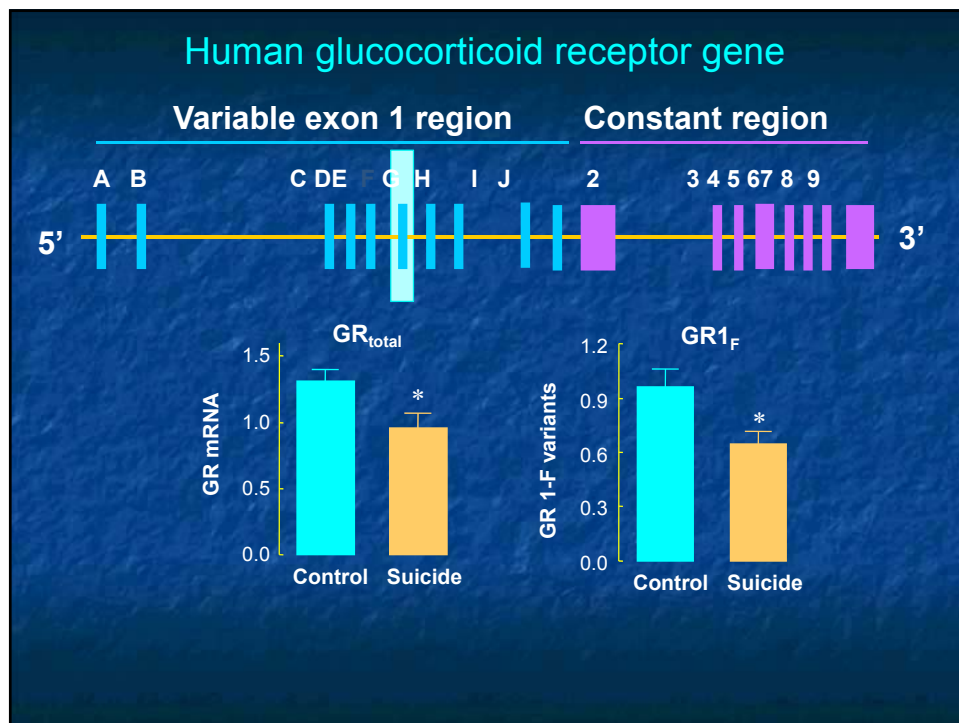
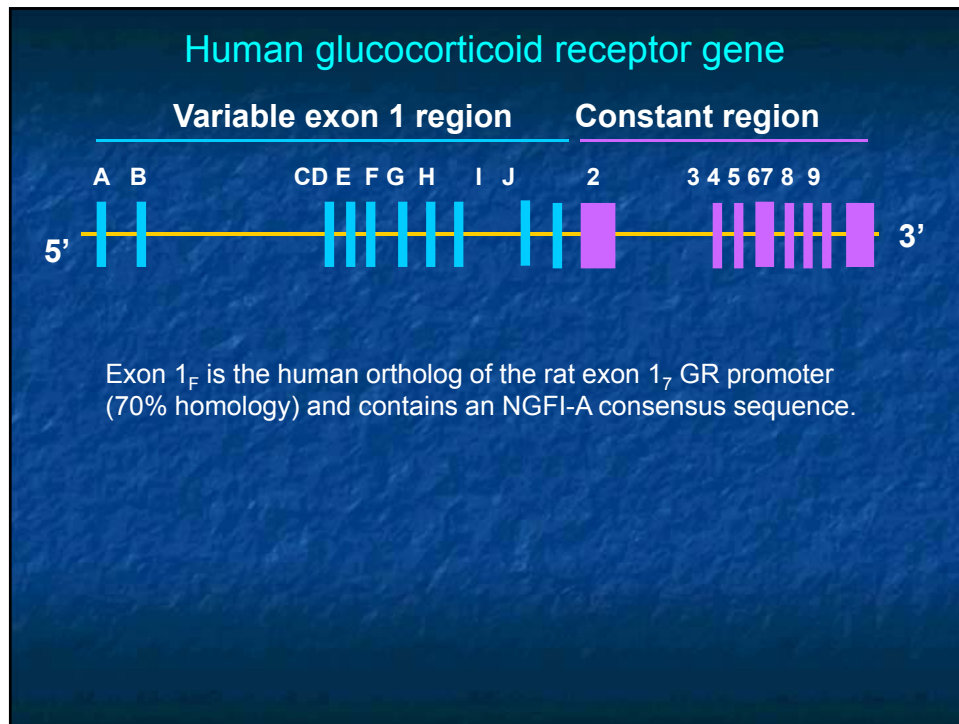


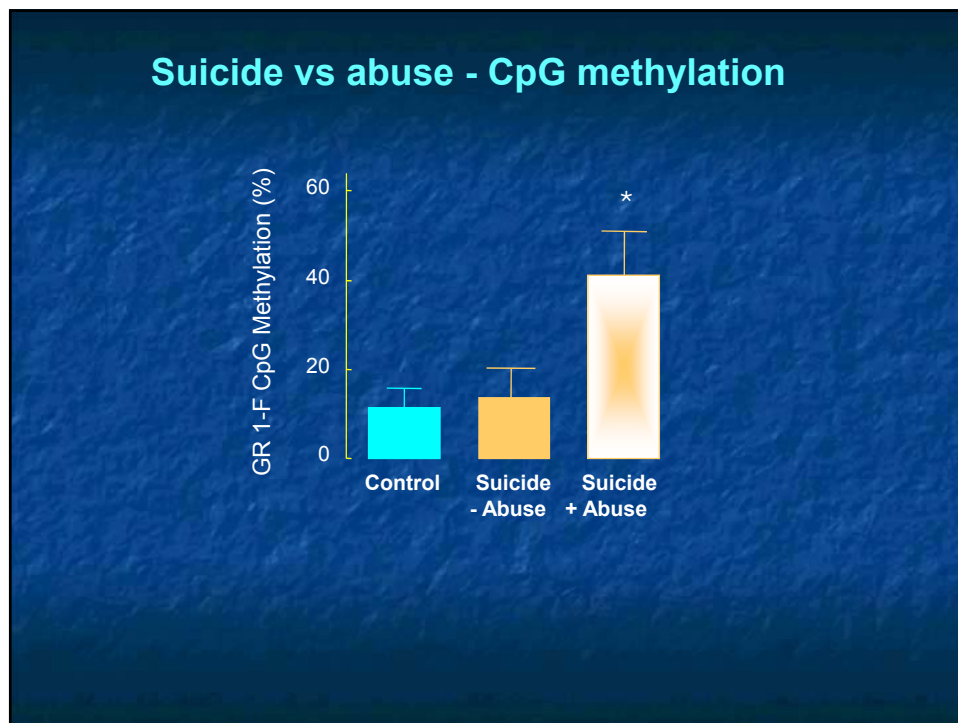
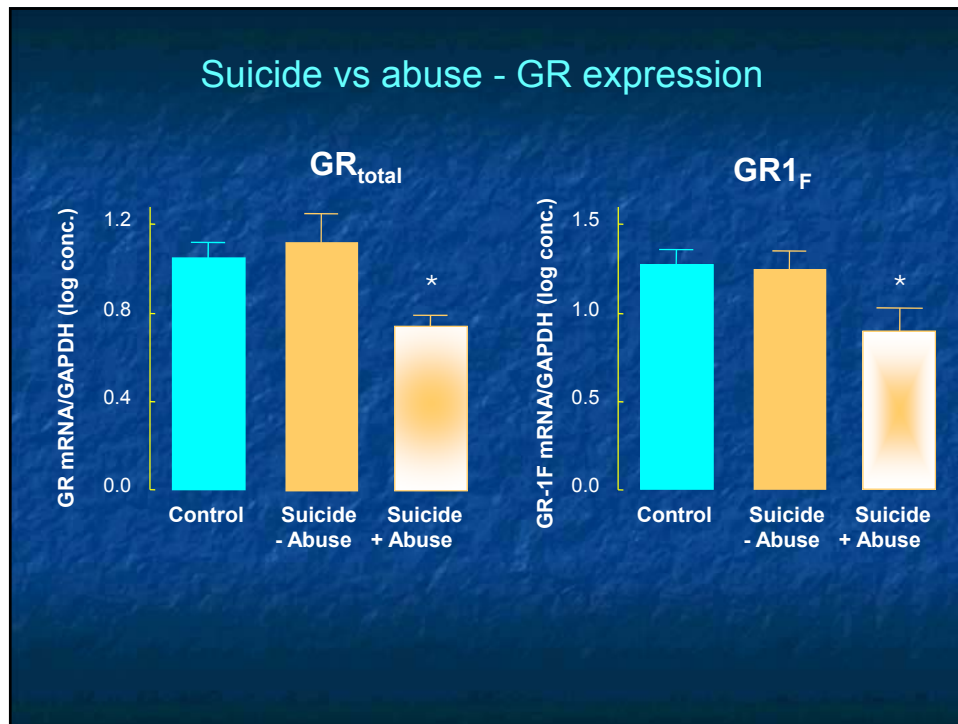


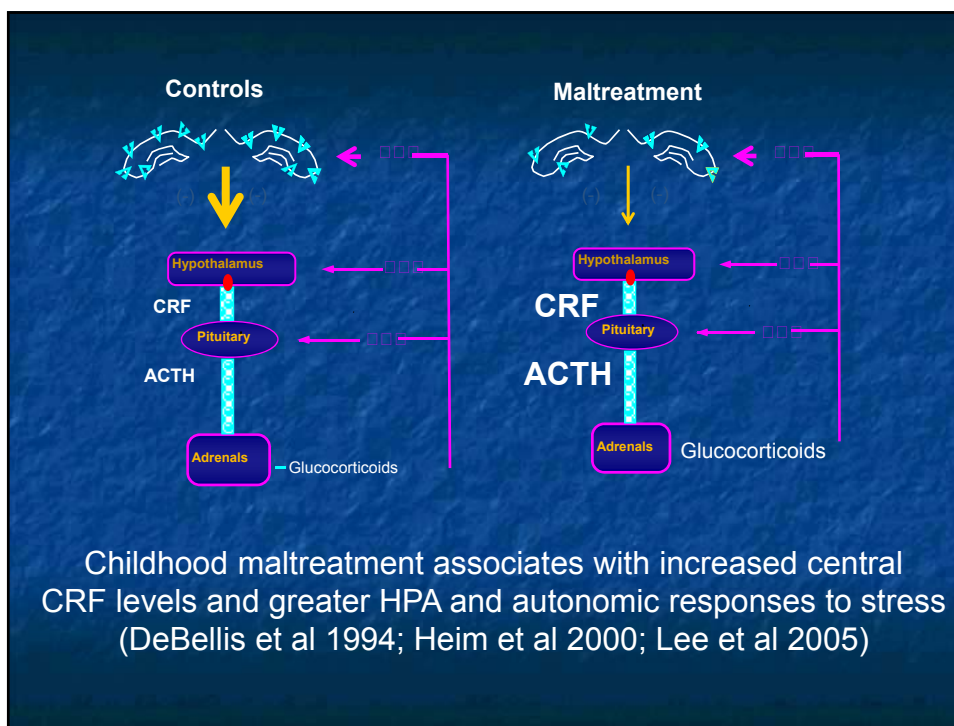
Do comparable processes occur in humans?



- Post-mortem studies of hippocampus.
- Samples from suicide victims/controls.
- QSBB (Gustavo Turecki) – forensic phenotyping.
- Human exon 1F promoter (Turner & Muller, 2005)







Childhood adversity and NR3C1 promoter methylation in DNA from peripheral samples

OPEN ACCESS Freely available online



Childhood Adversity and Epigenetic Modulation of the Leukocyte Glucocorticoid Receptor: Preliminary Findings in Healthy Adults

Audrey R. Tyrka^{1,2*}, Lawrence H. Price^{1,2}, Carmen Marsit³, Oakland C. Walters¹, Linda L. Carpenter^{1,2}

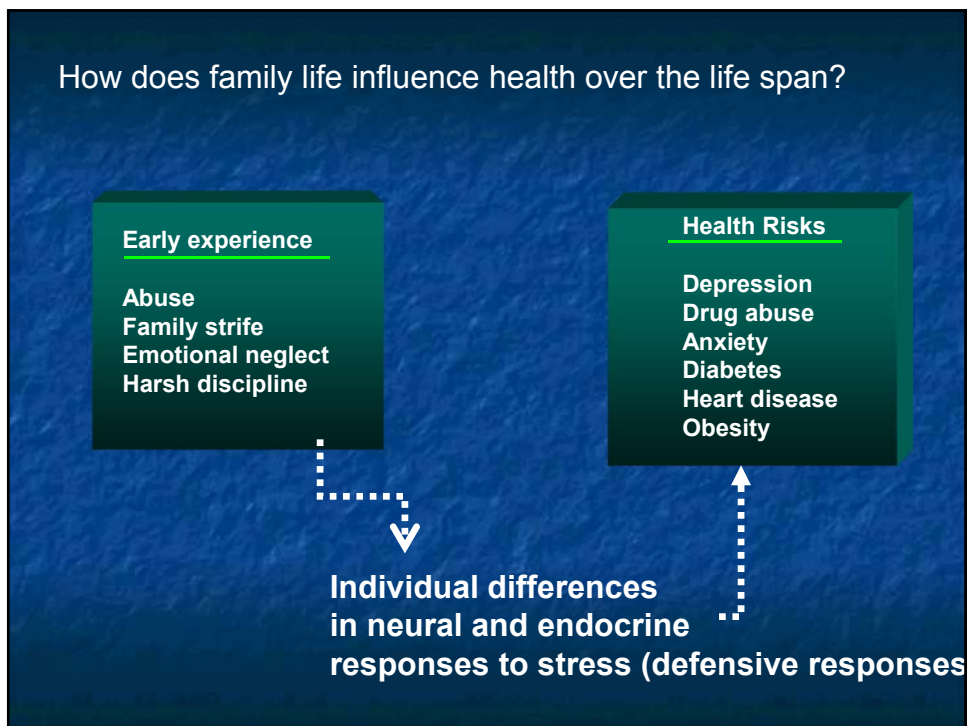
¹ Laboratory for Clinical Neuroscience, Mood Disorders Research Program, Butler Hospital, Providence, Rhode Island, United States of America, ² Department of Psychiatry and Human Behavior, Brown Medical School, Providence, Rhode Island, United States of America, ³ Department of Pharmacology and Toxicology, Department of Community and Family Medicine, Dartmouth Medical School, Hanover, New Hampshire, United States of America

Citation: *Transl Psychiatry* (2011) 1, e21, doi:10.1038/tp.2011.21
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 www.nature.com/tp



Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor

KM Radtke^{1,2,4}, M Ruf^{1,4}, HM Gunter^{2,3,4}, K Dohrmann¹, M Schauer¹, A Meyer² and T Elbert¹



Childhood adversity and NR3C1 promoter methylation in DNA from peripheral samples

OPEN ACCESS Freely available online

PLOS one

Childhood Adversity and Epigenetic Modulation of the Leukocyte Glucocorticoid Receptor: Preliminary Findings in Healthy Adults

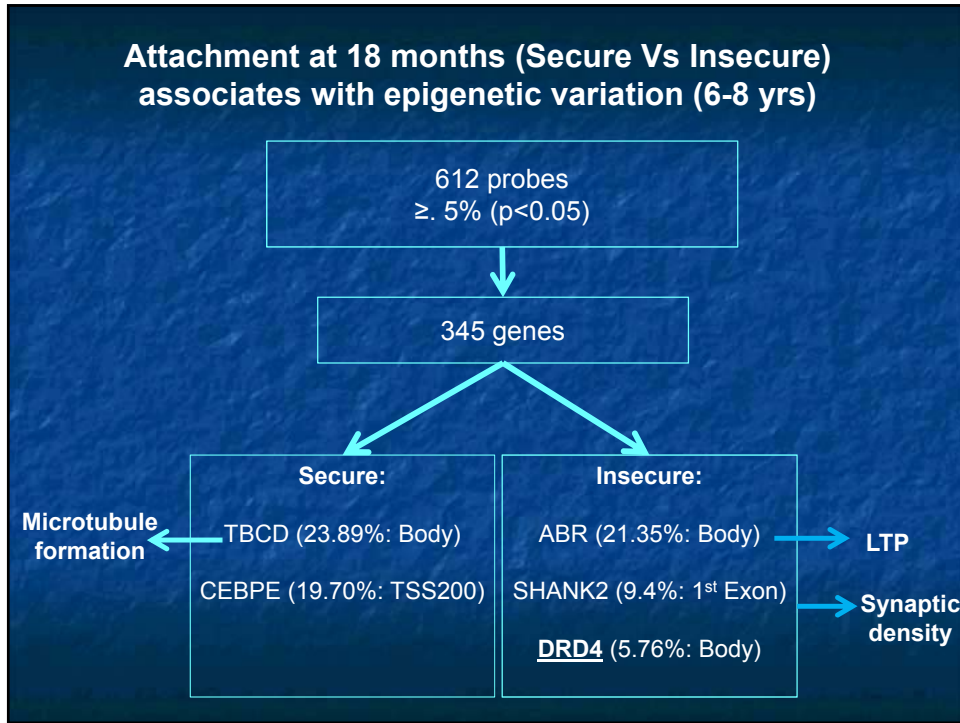
Audrey R. Tyrka^{1,2*}, Lawrence H. Price^{1,2}, Carmen Marsit³, Oakland C. Walters¹, Linda L. Carpenter^{1,2}

1 Laboratory for Clinical Neuroscience, Mood Disorders Research Program, Butler Hospital, Providence, Rhode Island, United States of America, 2 Department of Psychiatry and Human Behavior, Brown Medical School, Providence, Rhode Island, United States of America, 3 Department of Pharmacology and Toxicology, Department of Community and Family Medicine, Dartmouth Medical School, Hanover, New Hampshire, United States of America

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Reference 1: ADHDgene Database (I)

ADHDgene
A Genetic Database for Attention Deficit Hyperactivity Disorder

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Nucleic Acids Res. 2012;Jan;40(Database issue):D1003-9. Epub 2011 Nov 10.

ADHDgene: a genetic database for attention deficit hyperactivity disorder.

Zhang L, Chang S, Li Z, Zhang K, Du Y, Qi J, Wang J.
Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China.

Abstract

With a worldwide prevalence of ~5%, attention deficit hyperactivity disorder (ADHD) has become one of the most common psychiatric disorders. The polygenic nature of ADHD indicates that multiple genes jointly contribute to the development of this complex disease. Studies aiming to explore genetic susceptibility of ADHD have been increasing in recent years. There is a growing need to integrate the genetic data from various genetic studies to provide a comprehensive data set and uniform access for convenience of in-depth data mining. So far, there has been no such effort for ADHD. To address the genetic complexity of ADHD, we developed the ADHDgene database by integrating ADHD-related genetic factors by profound literature reading. Based on the data from the literature, extended functional analysis, including linkage disequilibrium analysis, pathway-based analysis and gene mapping were performed to provide new insights into genetic causes of ADHD. Moreover, powerful search tools and a graphical browser were developed to facilitate the navigation of the data and data connections. As the first genetic database for ADHD, ADHDgene aims to provide researchers with a central genetic resource and analysis platform for ADHD and is freely available at <http://adhd.psych.ac.cn/>.

Data Summary

- Published Variant
 - SNP: 941
 - CNV: 296
 - Others: 164
- **Published Gene: 213**
- Published Region: 127
- Pathway by PBA: 8
- Study: 303

Reference 1: ADHDgene Database (II)

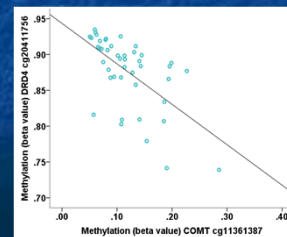
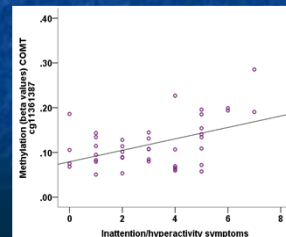
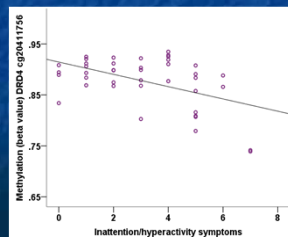
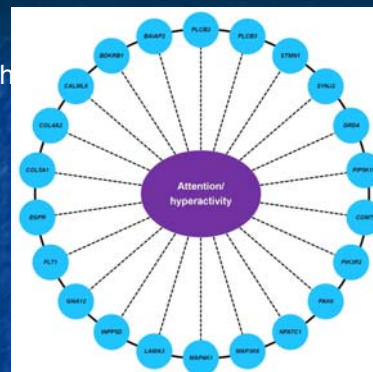
- 213 Genes in the ADHDgene database (24 Genes are **hot genes**)
- 36 Probes (25 Genes) of ADHD database genes are found in the 2907 DMPs list.

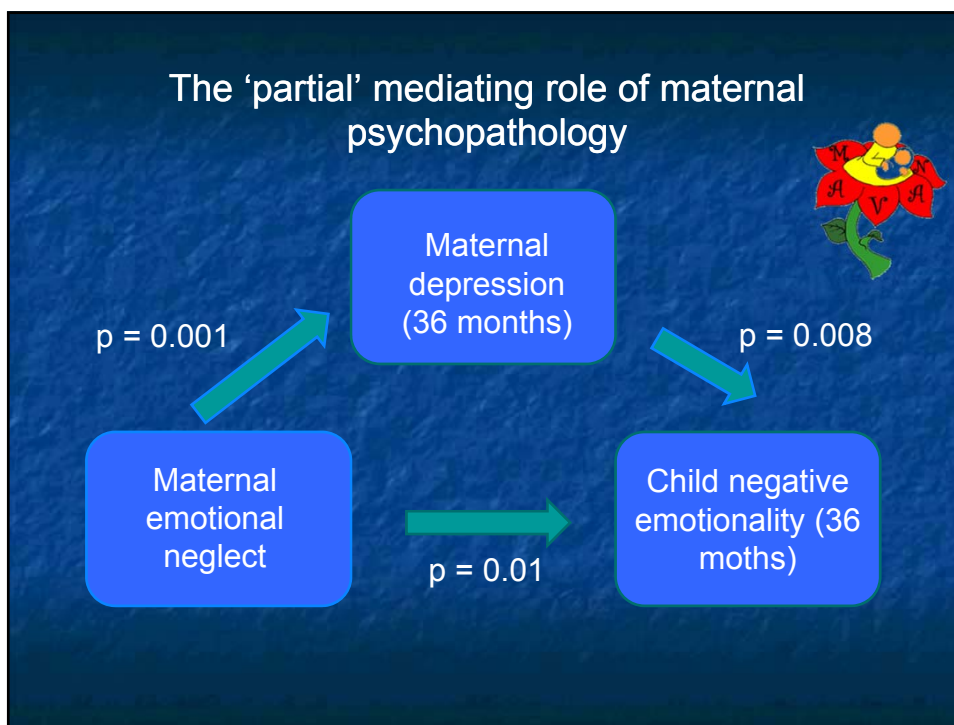
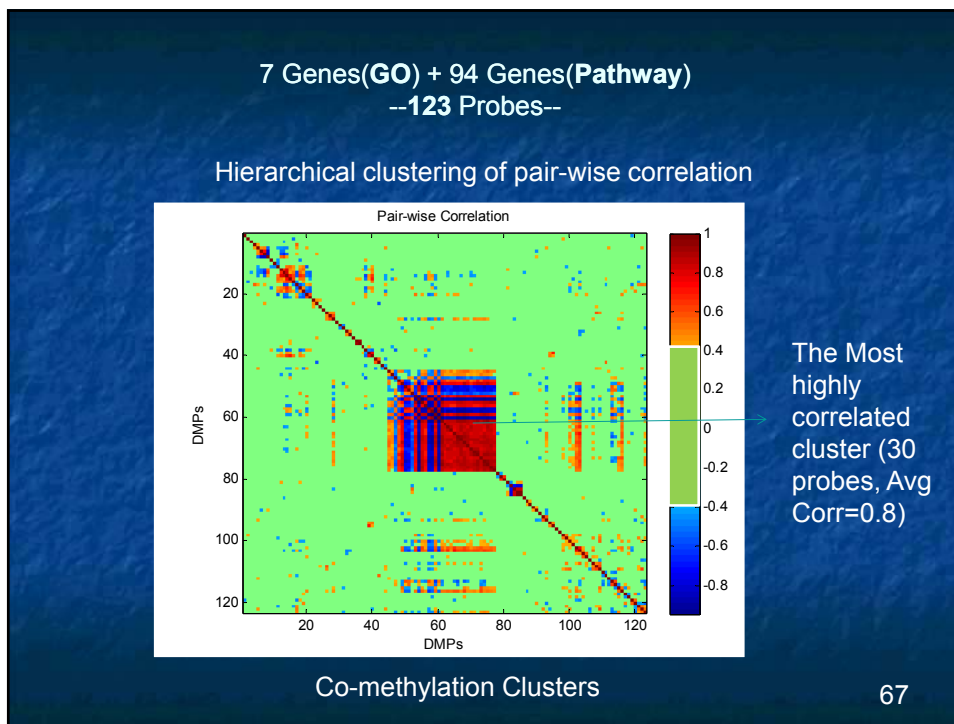
ADRA1A	FGF10
ANK3	GNAO1
ARRB2	HK1
ATXN1	HLA-DRB1
BAIAP2	ITGA11
BAIAP2	MEIS2
BAIAP2	MEIS2
BAIAP2	NCKAP5
BAIAP2	PTPRG
BDNF	PTPRG
CACNA1C	SH3BP5
CDH13	SH3BP5
CHRNA4	SLC6A3
CHRNA4	UNC5B
COMT	UNC5B
DBH	ZNF423
DRD4	ZNF423
EMP2	ZNF423

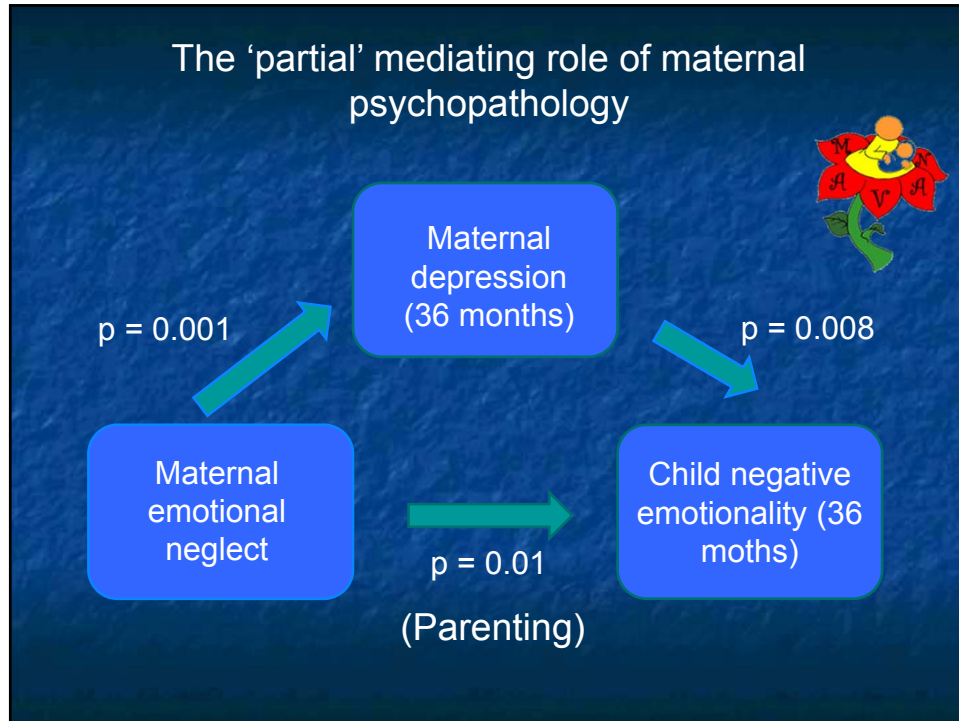
Child attention problems and co-methylation

Child attention problems (SDQ) associated with differential methylation of 1747 probes (957 genes).

30 probes (22 genes) associated with child attention problems ($-0.3 < r > 0.3$) show co-methylation ($-0.6 < r > 0.6$).







Do effective treatment programs that target mothers affect DNA methylation profiles in the children?



- 90 Unique Samples
- Infinium 450K Array
- Blood Samples
- 27 years old
- Variables:
 - methy_grp (0= control/no treatment ;1=intervention)
 - ETXGROUP: 1 and 2 = different forms of no treatment versus 3 and 4 which represent prenatal intervention and combined pre and postnatal intervention, respectively
 - CHILDGENDER 1=male 2=female
 - Child Abuse at age 4 and age 15

Child abuse is physical, sexual or emotional mistreatment or neglect

Principal Component Analysis

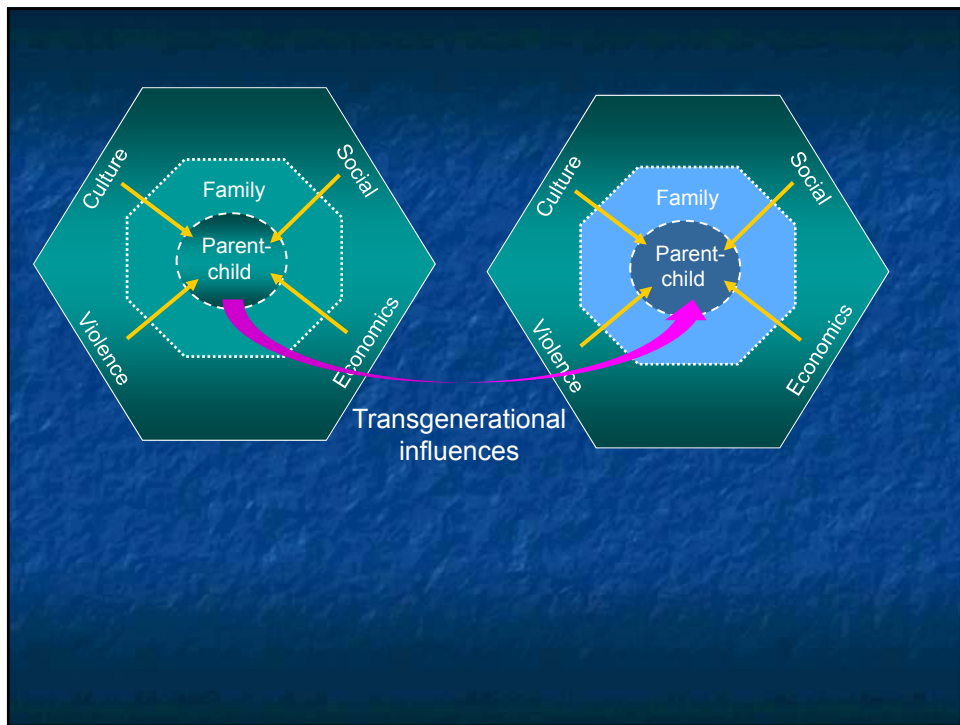
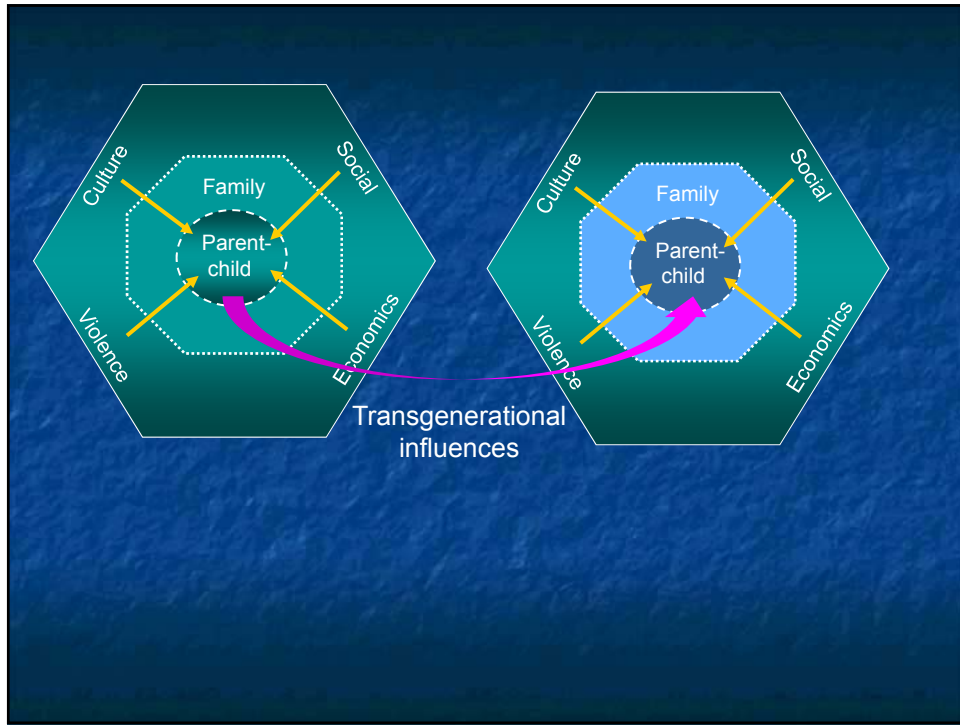
Component	Fstat	p
Gender (3.0%)	7.32	$.003 \times 10^{-8}$
Abuse/4 yrs (3%)	5.80	$.002 \times 10^{-2}$
Abuse/15yrs	1.67	ns

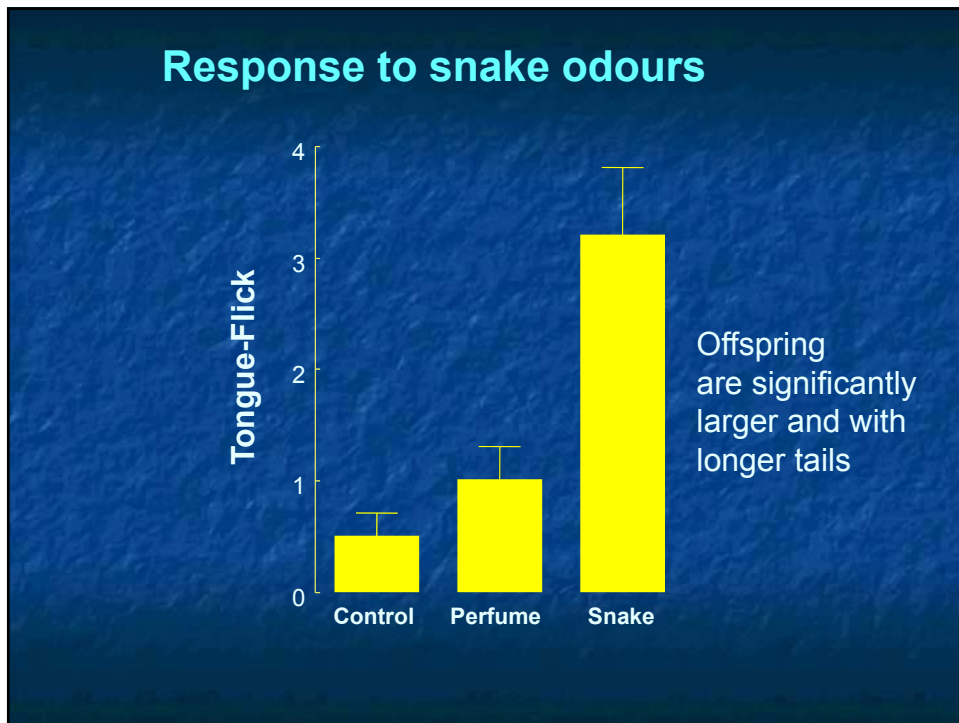
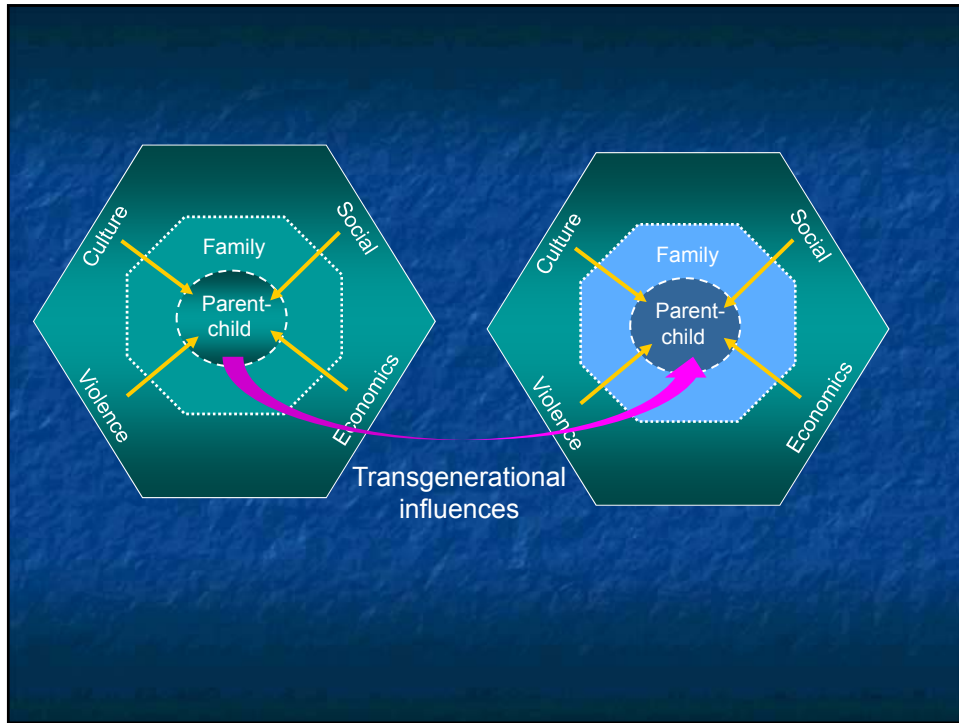
Principal Component Analysis

Component	Fstat	p
Gender (3%)	7.32	$.003 \times 10^{-8}$
Abuse/4 yrs (3%)	5.80	$.002 \times 10^{-2}$
Abuse/15yrs	1.67	ns
Treatment (8%)	3.07	$.002 \times 10^{-4}$

Conclusions

- The function of the genome is regulated by epigenetic signals that are subject to environmental regulation.
- These epigenetic signals reflect the quality of the deary environment, and guide the development and function of the brain.
- These effects are potentially stable, but are subject to modification, potentially over the lifespan.





Defense to snake predation in skink lizards

Most frequent prey

- smaller
- shorter tails
- less reactive to snake cues



If mother has been exposed to the scent of a predatory snake then offspring are larger, with longer tails and

Evolutionary biology - Maternal effects

