

Maternal care and Gene - Environment Interactions Defining Development

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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.
- To independence from the parent.

Developmental Origins of Adult Disease



Mechanism?

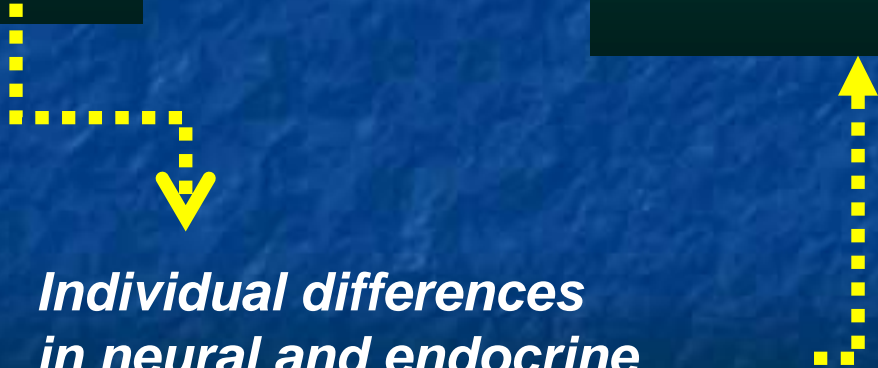
Stress Diathesis Models

Early experience

Abuse
Family strife
Emotional neglect
Harsh discipline

Health Risks

Depression
Drug abuse
Anxiety
Diabetes
Heart disease
Obesity



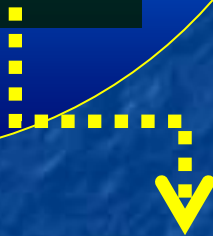
*Individual differences
in neural and endocrine
responses to stress (defensive responses)*

Poverty



Early experience

Abuse
Family strife
Emotional neglect
Harsh discipline

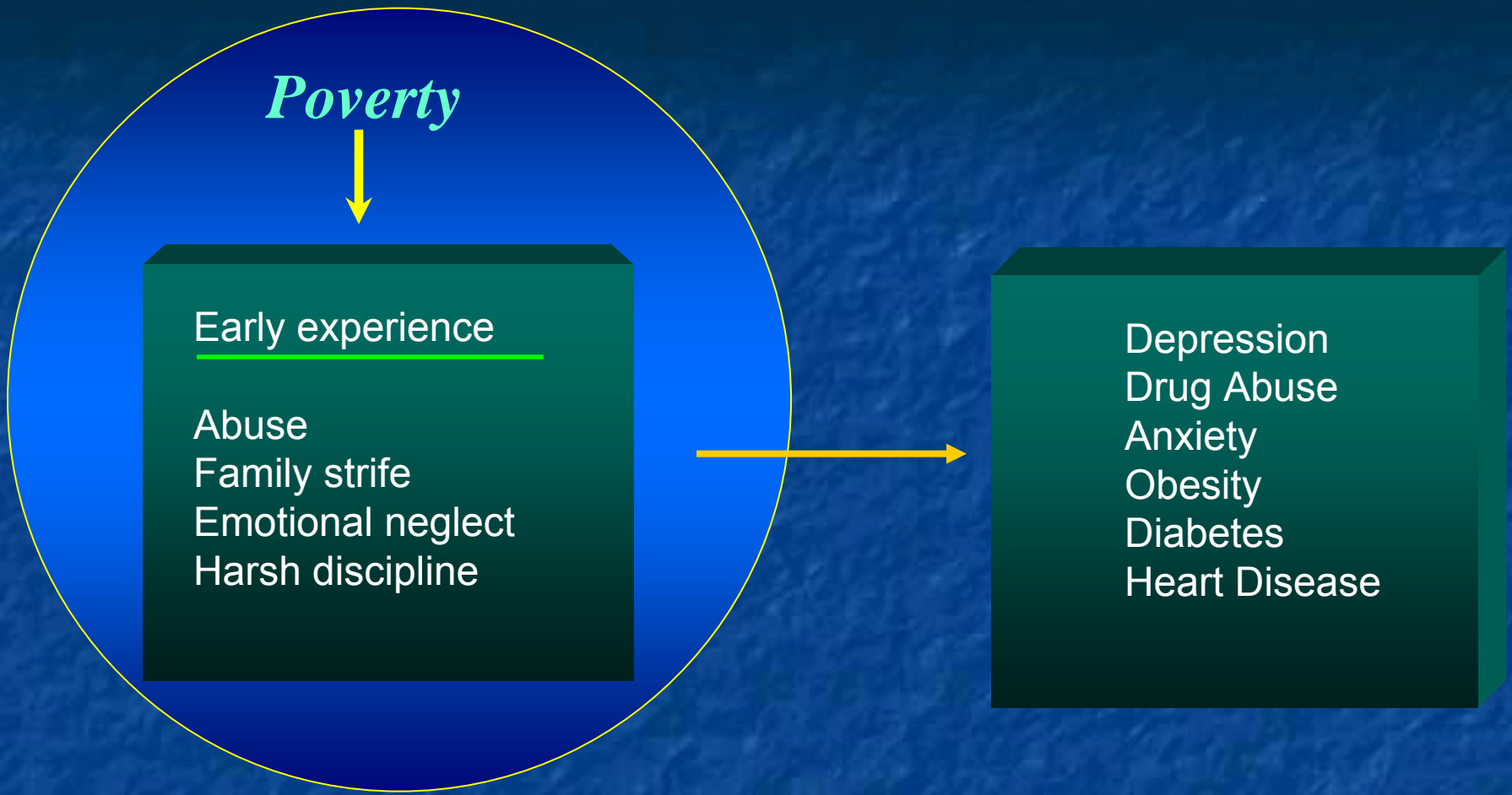


*Individual differences
in neural and endocrine
responses to stress*

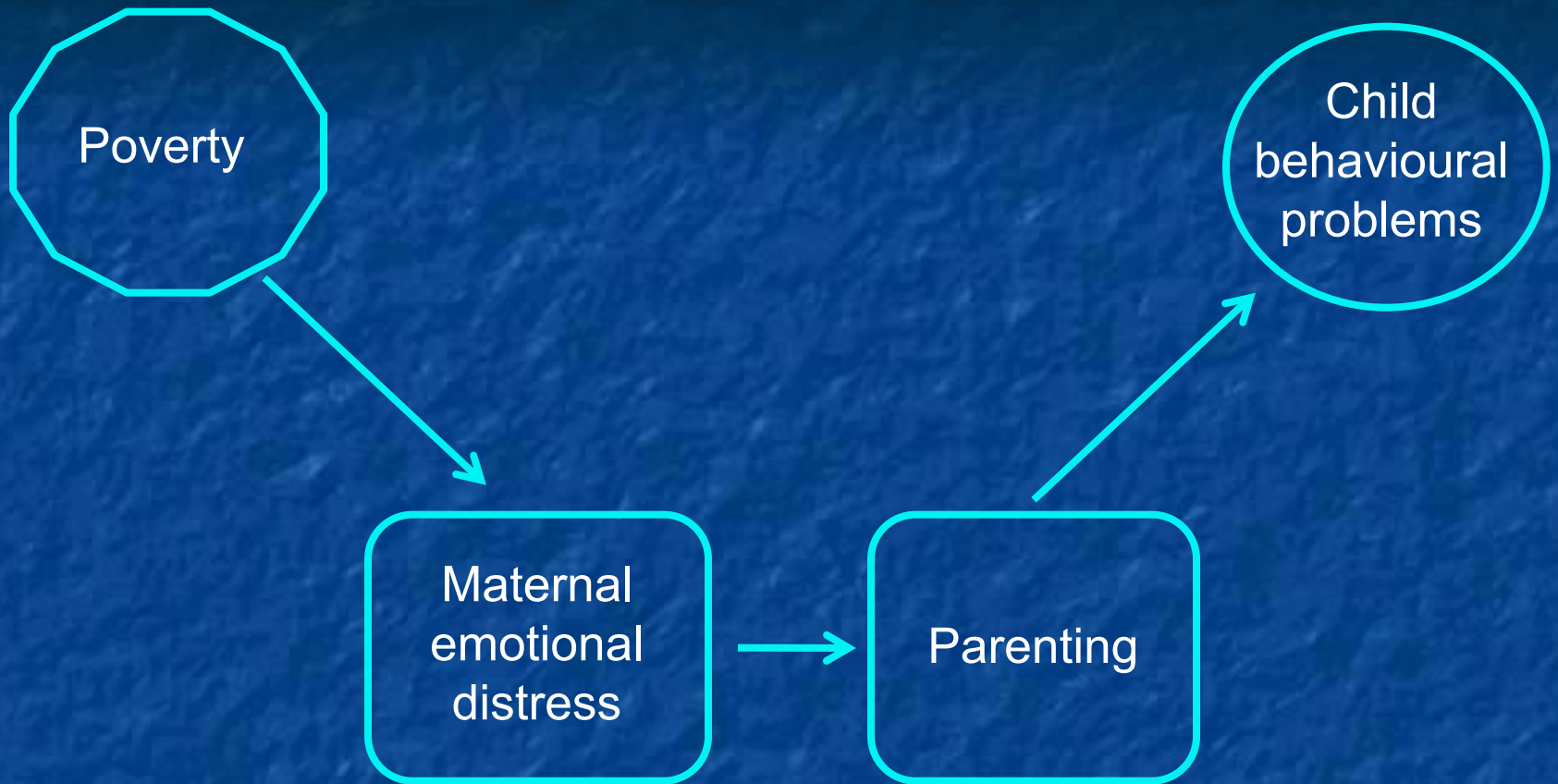


Health Risks

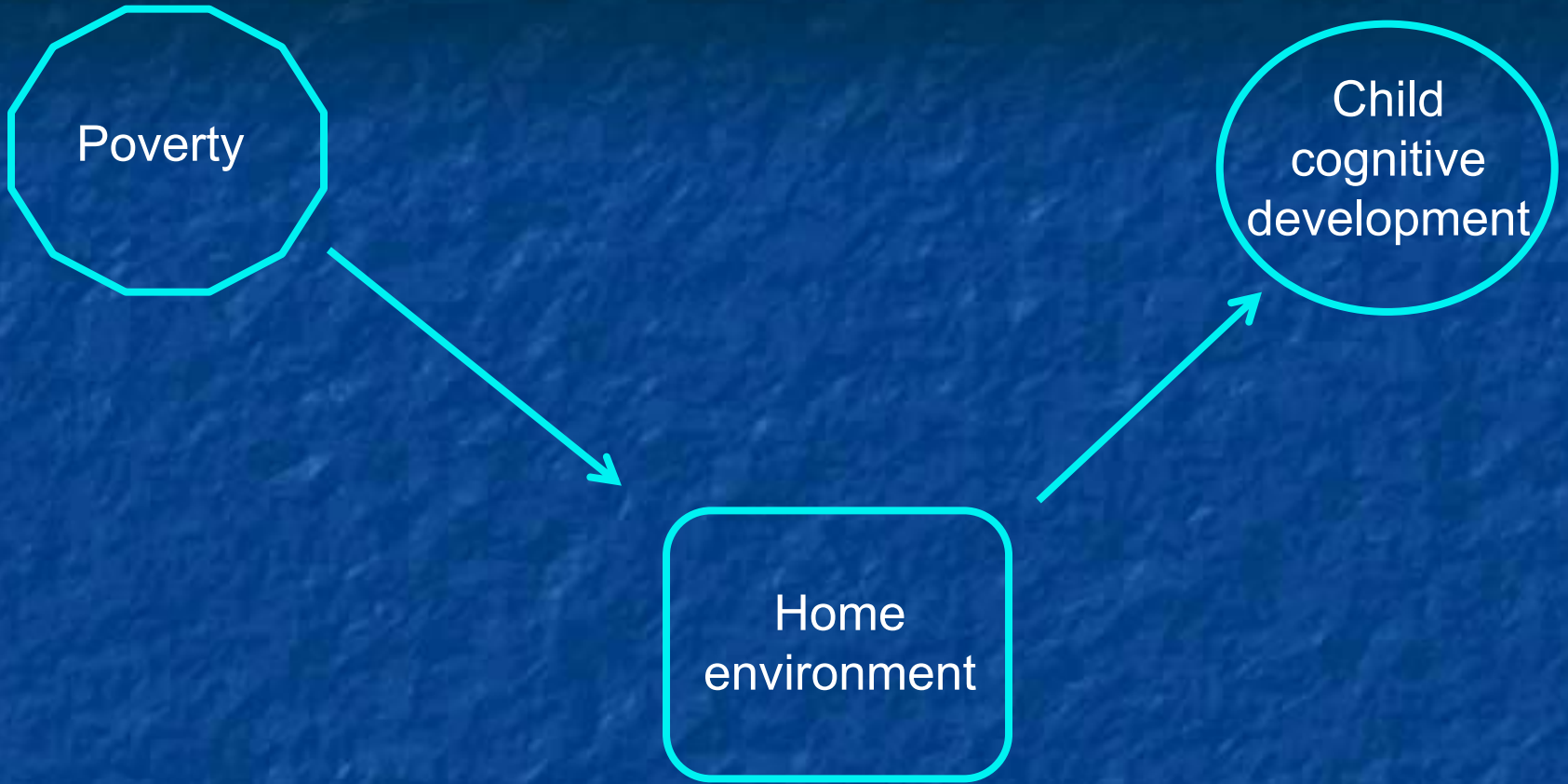
Depression
Drug abuse
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Heart disease
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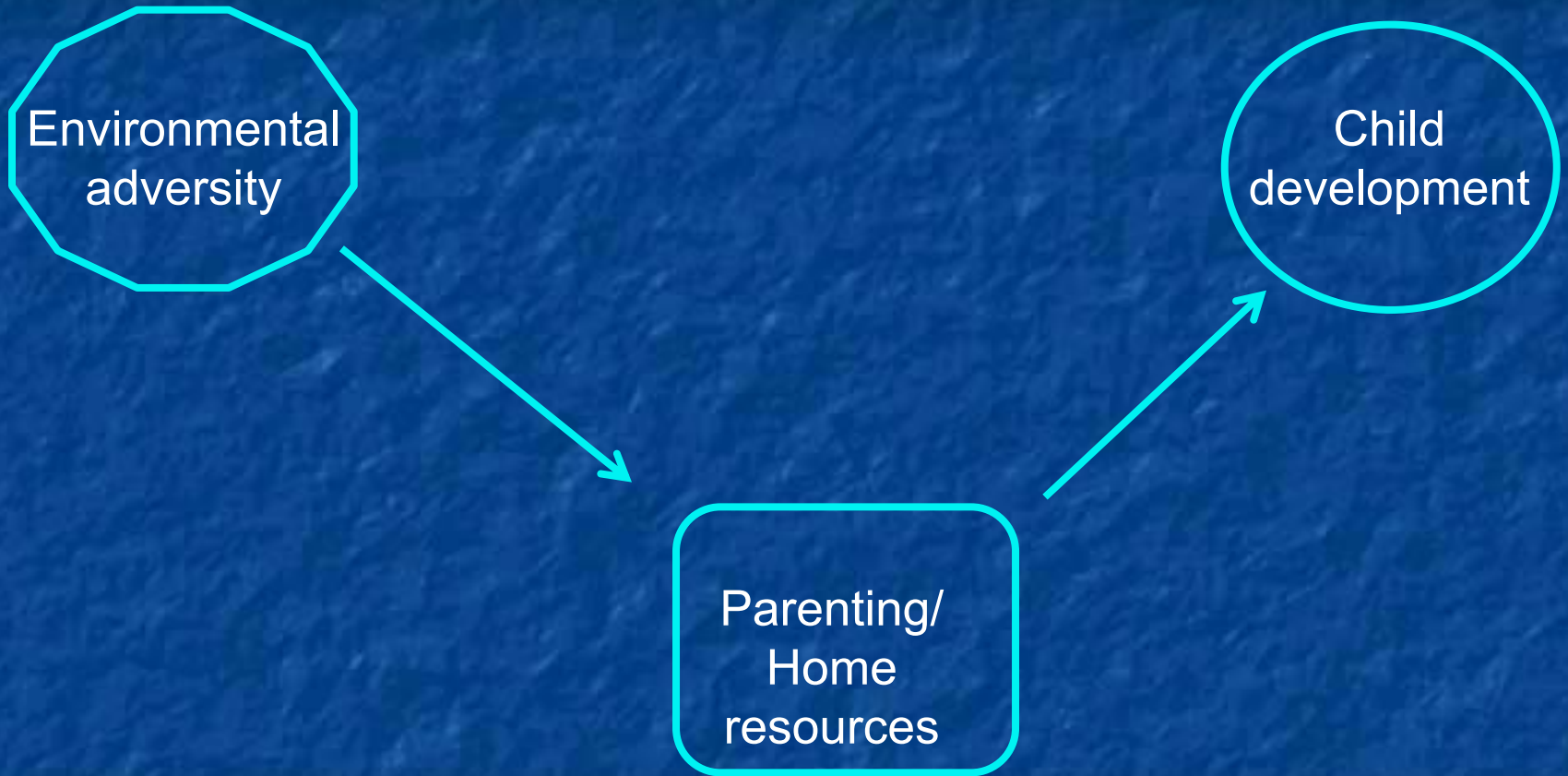


Effects of poverty on emotional and cognitive development are mediated by parental factors (Conger, McLloyd, Eisenberg).

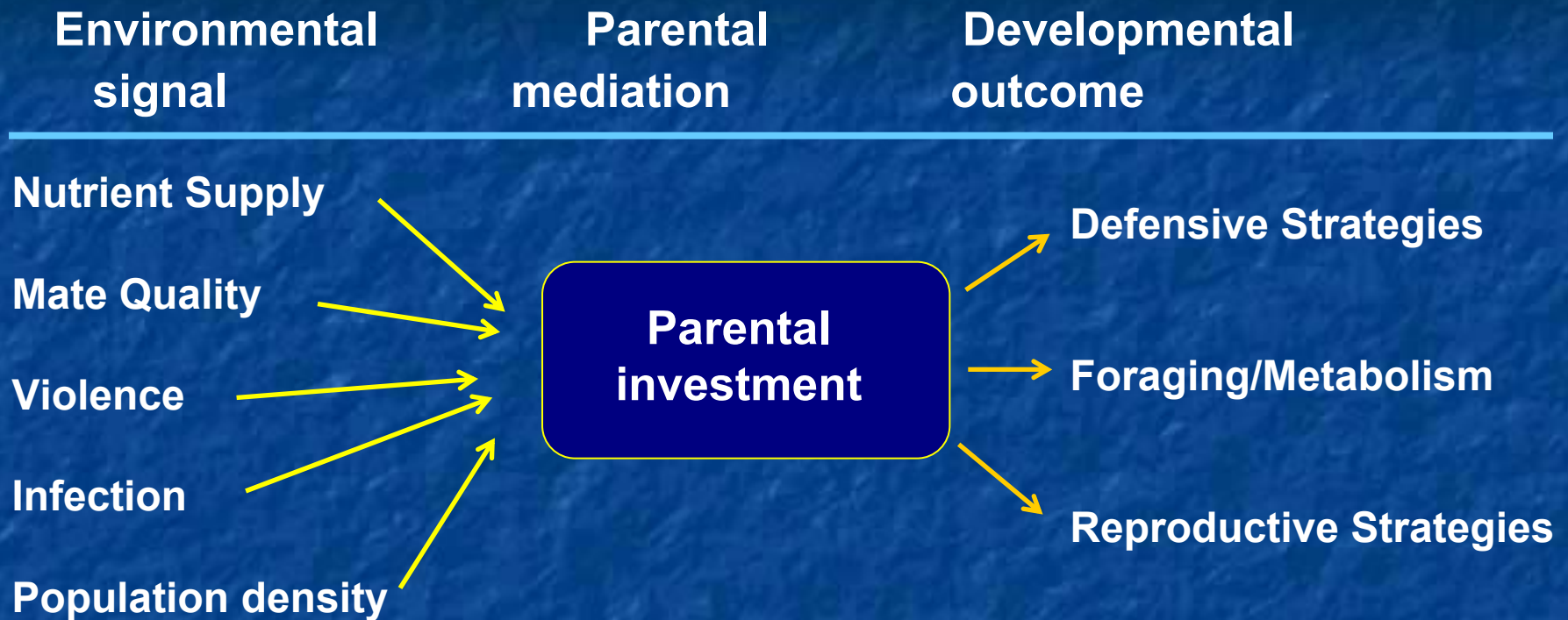


Linver, Brooks-Gunn & Kohen Dev Psychol 2002; same model predicts child cortisol levels (Lupien, McEwen, Meaney Biol Psychiatry 2000)



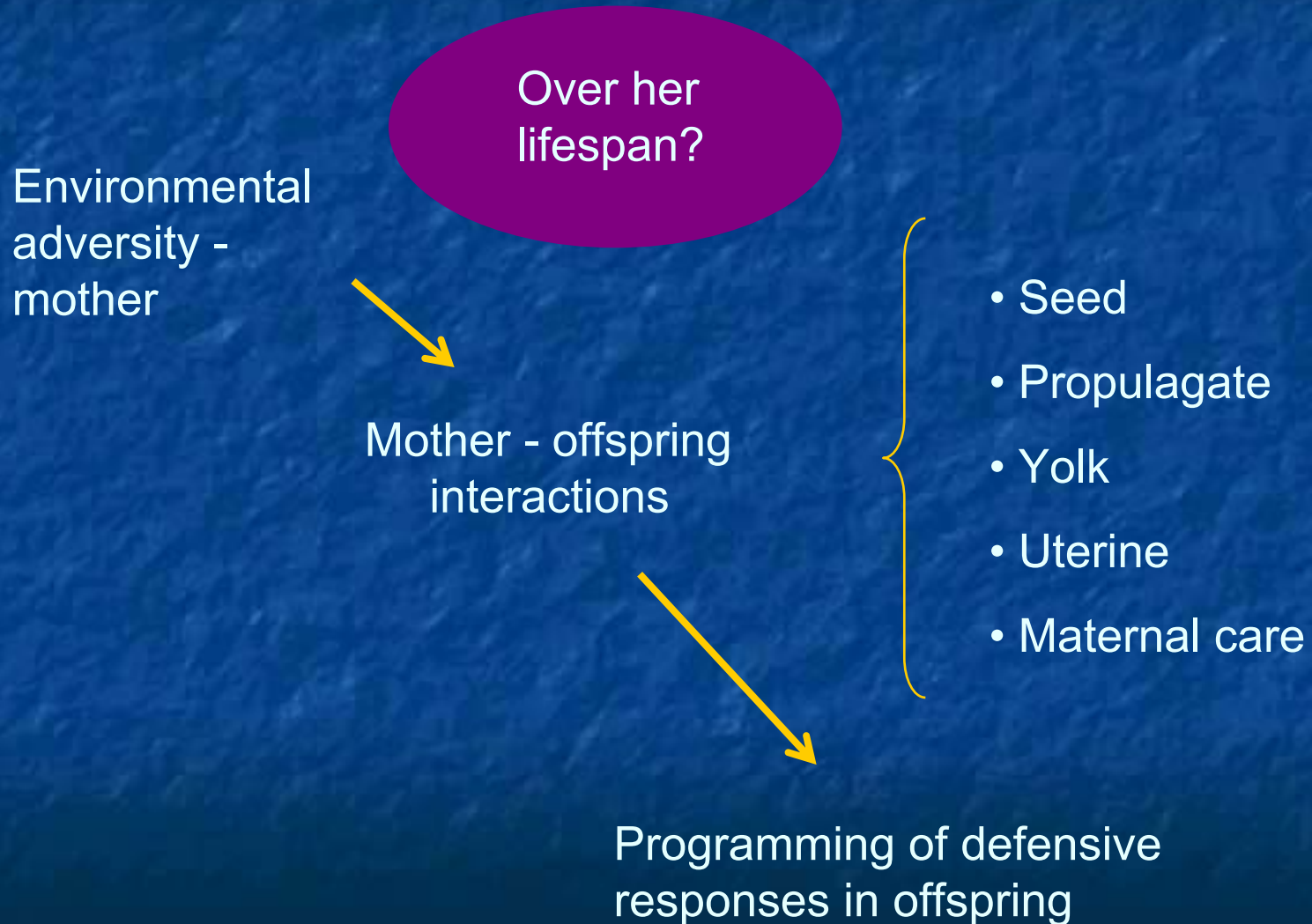


Evolutionary biology - Maternal effects



Robert Hinde: Evolution has shaped the young to use parental signals as a 'forecast' of the quality of the environment into which they have been born. For most species, there is no single, optimal phenotype.

Evolutionary Biology: Maternal Effects



Defense to snake predation in skink lizards

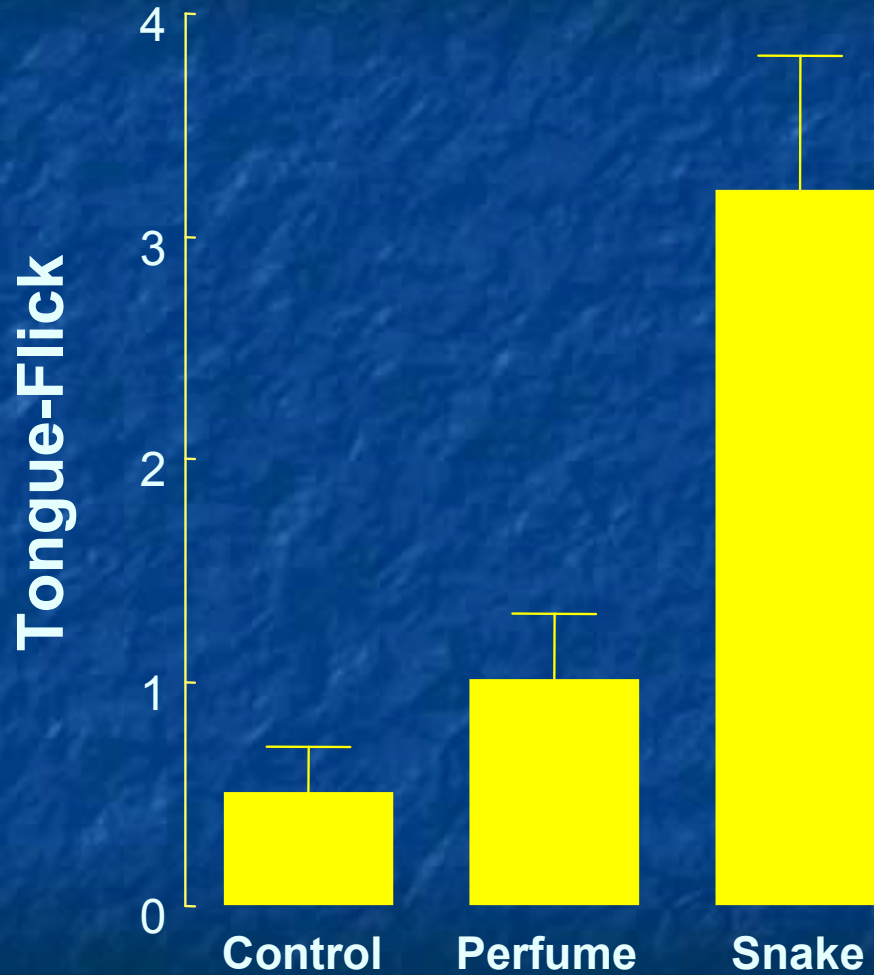
Most frequent prey

- 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

Response to snake odours



Offspring
are significantly
larger and with
longer tails

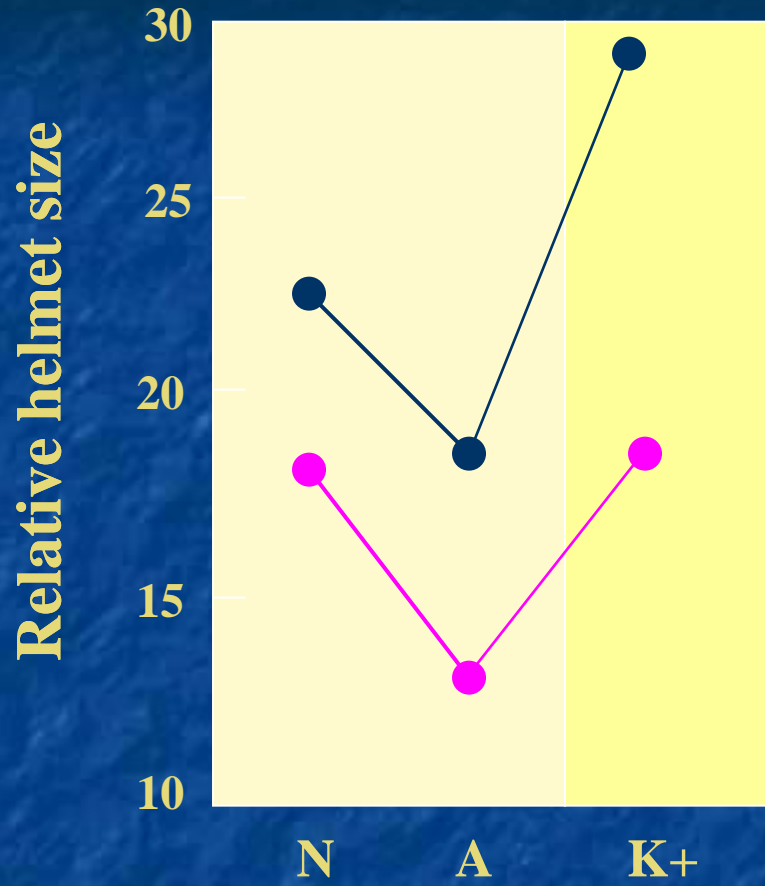
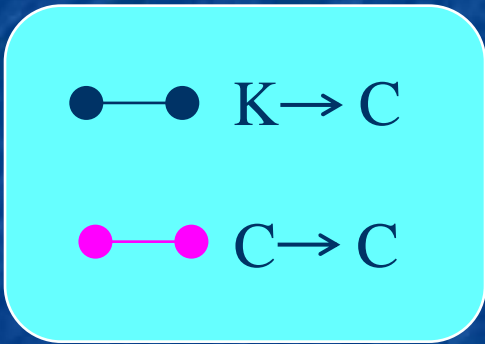
Inducible defenses

Predator
exposed

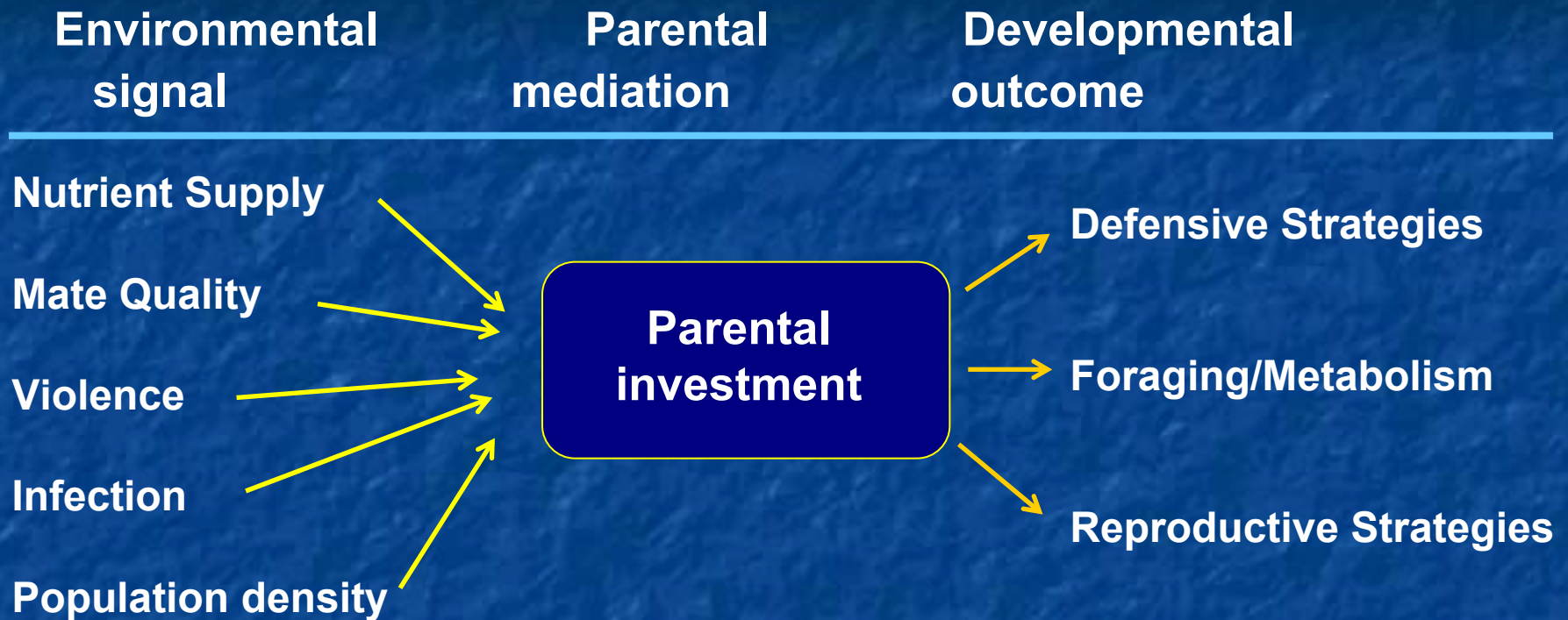


Control

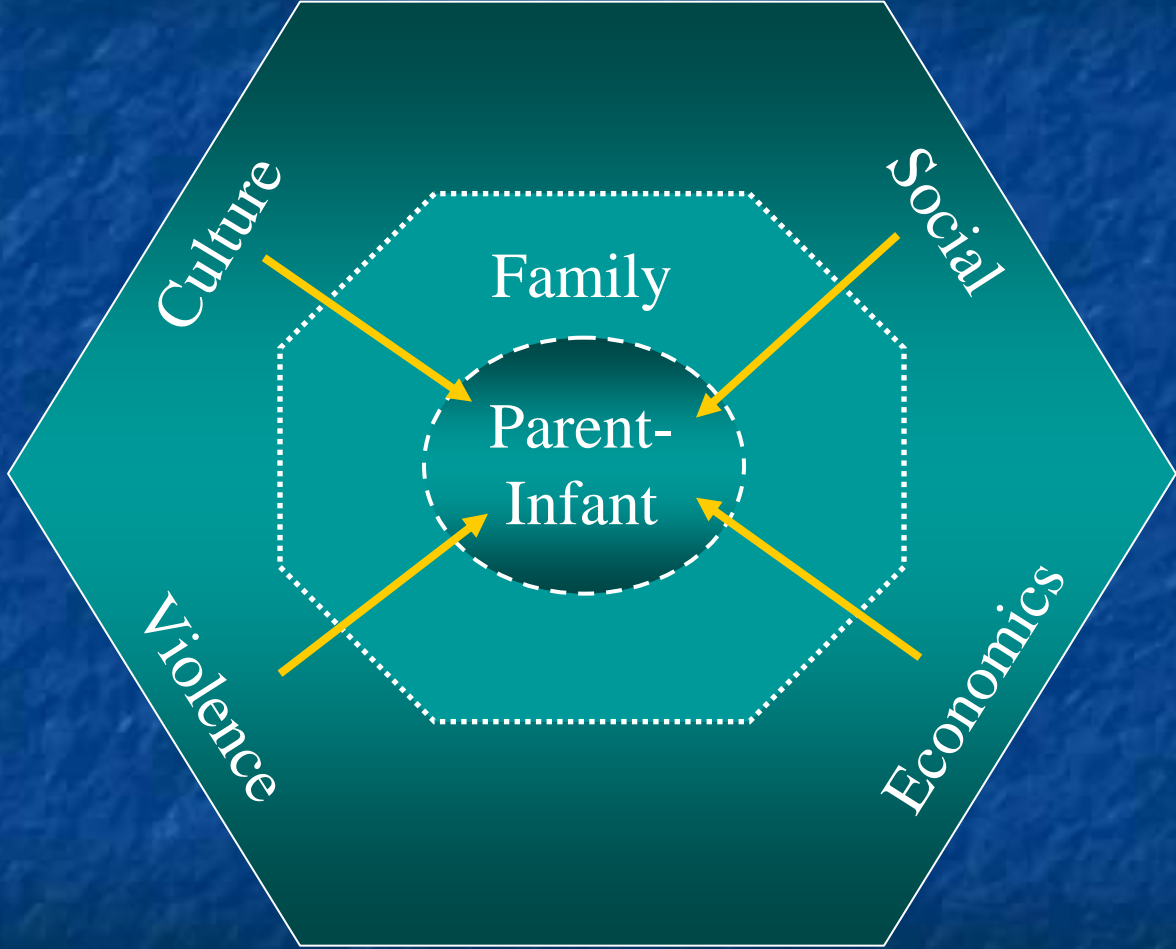
Scanning electron micrograph showing typical and predator-induced morphs of *Daphnia cucullata* of the same clone.



Evolutionary biology - Maternal effects



Robert Hinde: Evolution has shaped the young to use parental signals as a 'forecast' of the quality of the environment into which they have been born. For most species, there is no single, optimal phenotype.



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.

Multiple phenotypes from a common genotype



Creating diversity in phenotype from a common genome

Genetic code is defined by the sequence of four nucleotides that produce proteins and other molecules that serve cell function.

CTACGTA CT CGGAATCTCG



Protein

Epigenetic effects refer to modifications of the chemistry of the DNA, but not to a change of sequence. Epigenetics alters the activity of the gene, but not its function.

CTACGTA CT CGGAATCTCG

CH₃

CH₃

CH₃

Epigenetics

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CH₃ CH₃ CH₃
CTACGTA CT CGGAATCTCG

Warning!!!

Incomprehensible scientific jargon
will follow...

- Epigenetic effects refers to modifications of the chemistry of the DNA, but not to a change of sequence.
- Epigenetics alters the activity of the gene, but not its function.



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- DNA methylation: The addition of a methyl group onto a cytosine.

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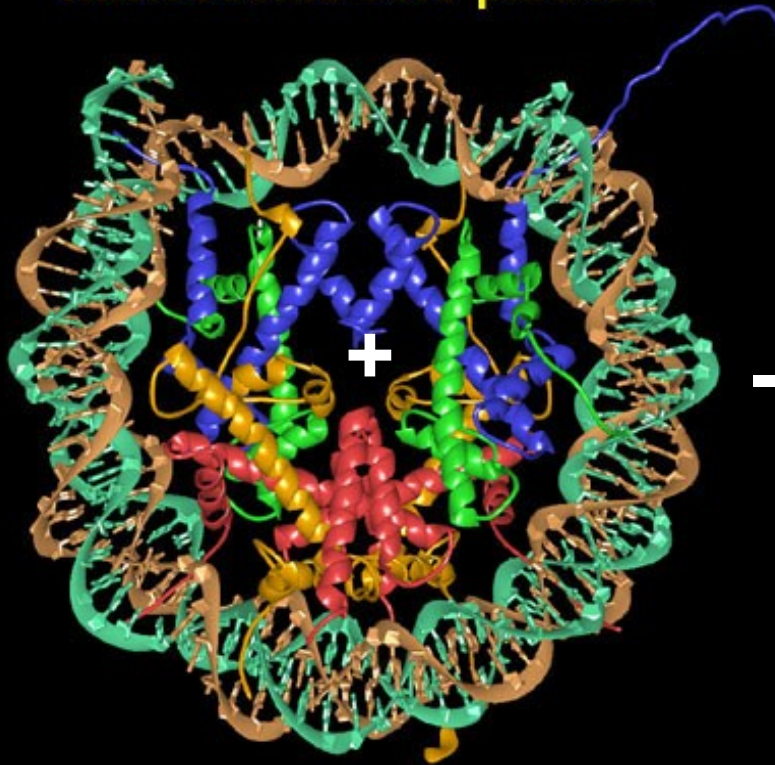
- DNA methylation: The addition of a methyl group onto a cytosine.
- DNA methylation is chemically very stable (potentially lasting for the life of the organism).

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- DNA methylation: The addition of a methyl group onto a cytosine.
- DNA methylation is chemically very stable (potentially lasting for the life of the organism).
- DNA methylation silences gene expression.

nucleosome core particle



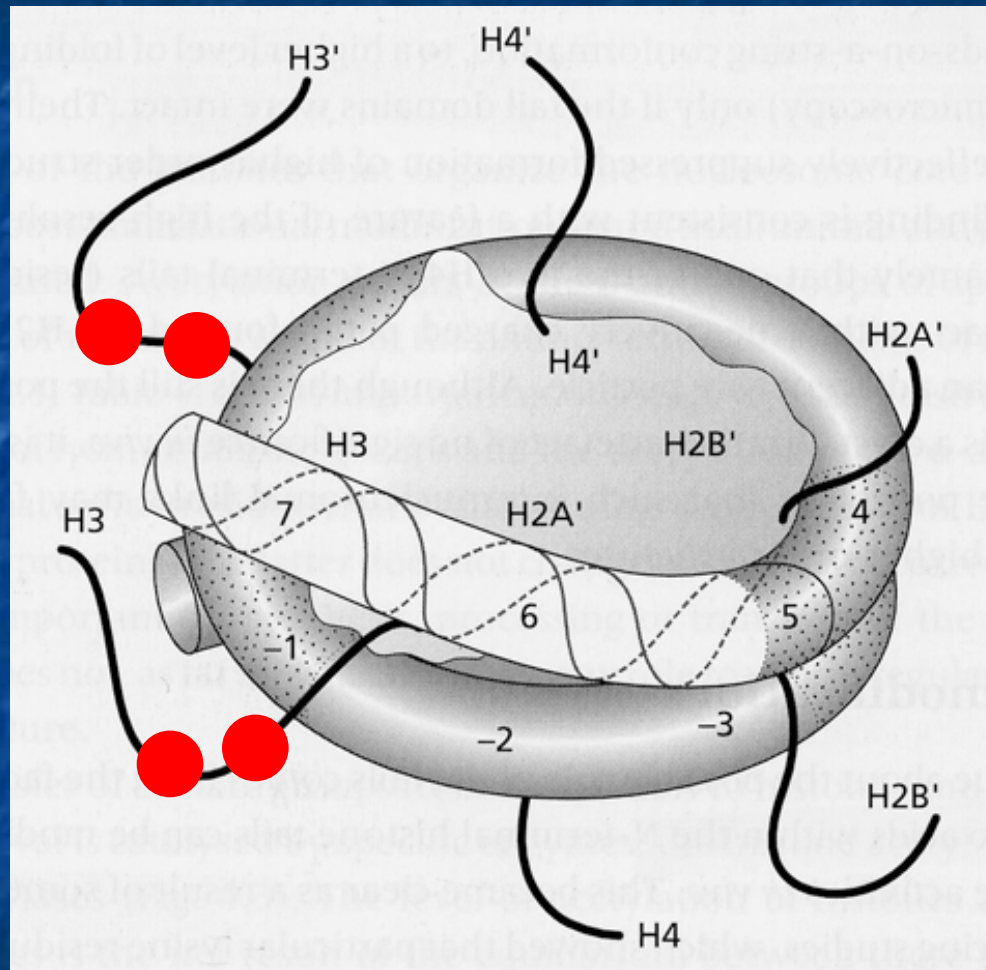
- H2A
- H2B
- H3
- H4

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).

● Acetyl group



Genetic code is defined by the sequence of four nucleotides that produce proteins and other molecules that serve cell function.

CTACGTA CT CGGAATCTCG



RNAs, proteins

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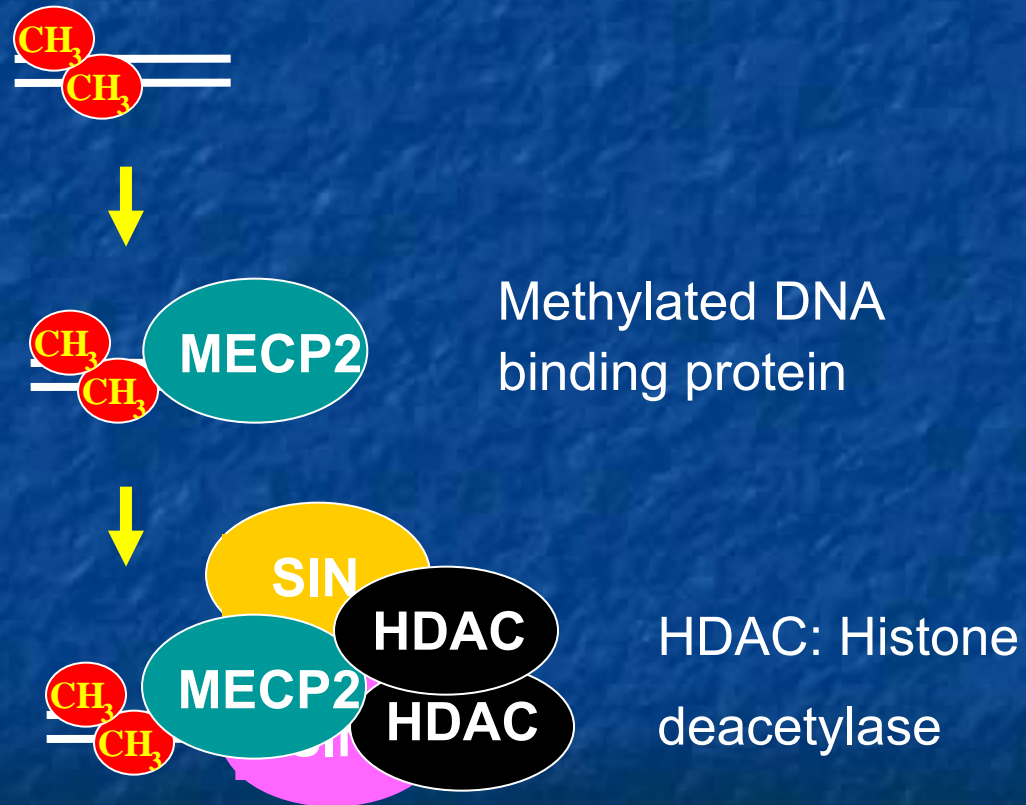
CTACGTA CT CGGAATCTCG

CH₃

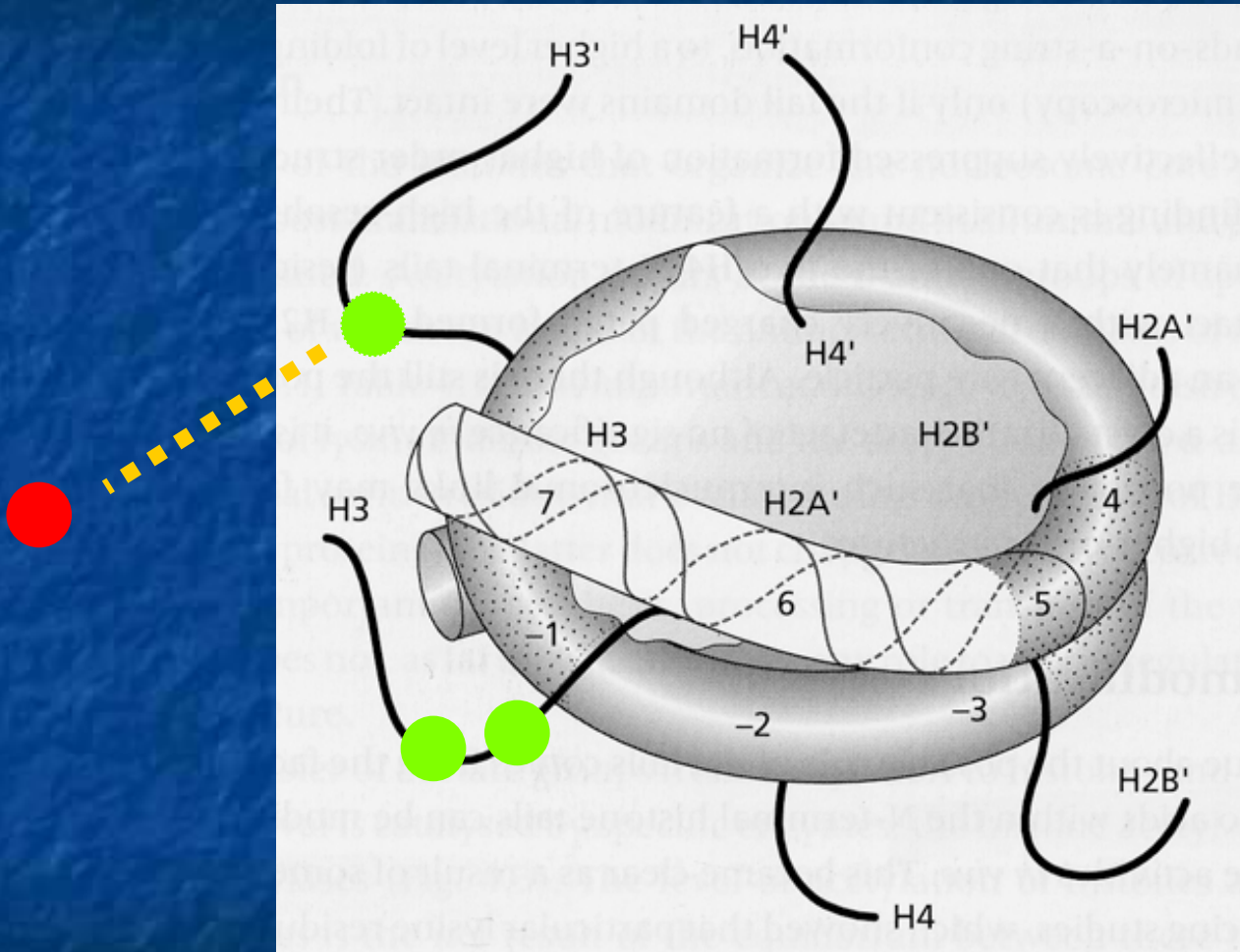
CH₃

CH₃

DNA Methylation can inhibit gene expression by blocking transcription factors binding



● HDAC





Parental care → Epigenetic mark → Gene expression → Phenotype

Naturally-occurring
variations in maternal care



Expression of specific genes
in brain regions



HPA function



Stable individual differences
in stress reactivity

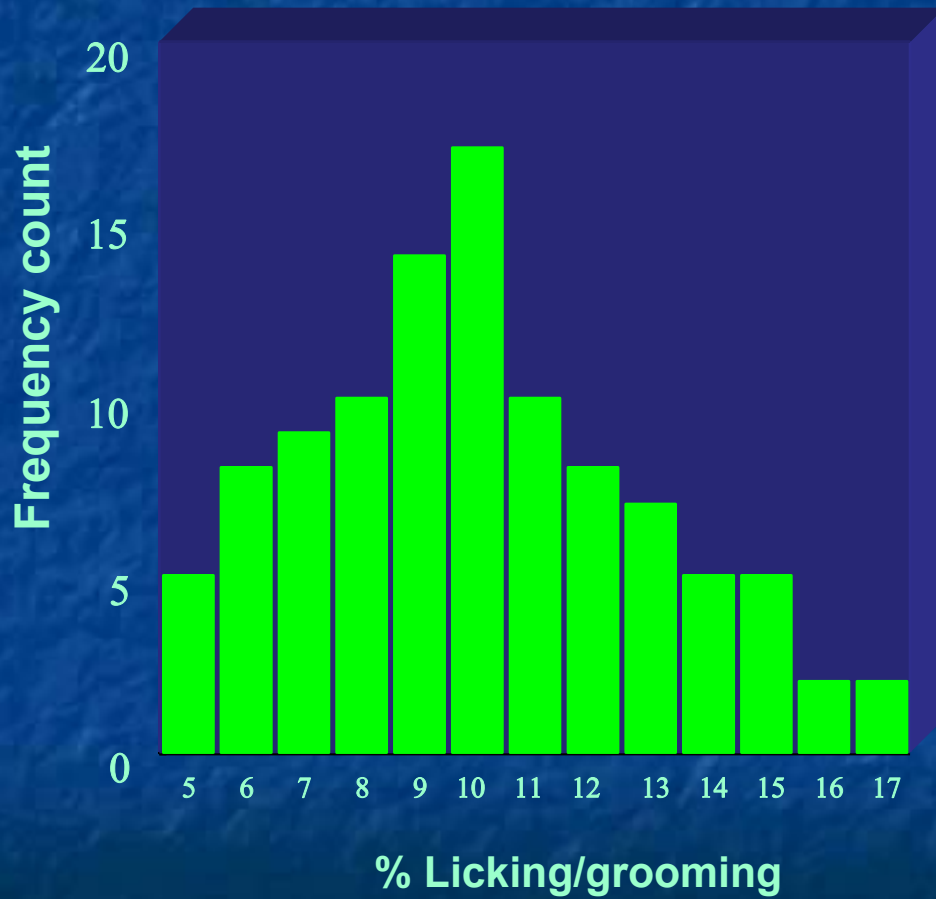


Maternal licking/grooming

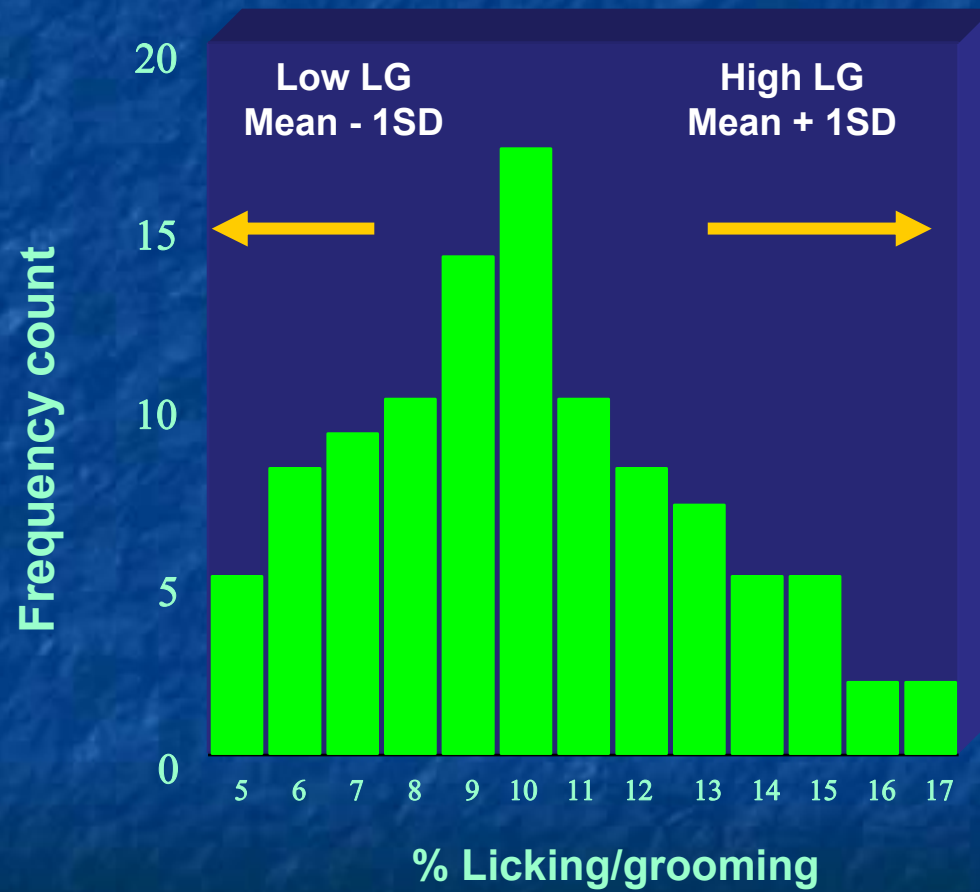


Source of tactile stimulation/nurturance: Enhances activity of endocrine systems (e.g., GH/IGF) that promote somatic growth, suppresses those (glucocorticoids) that inhibit growth

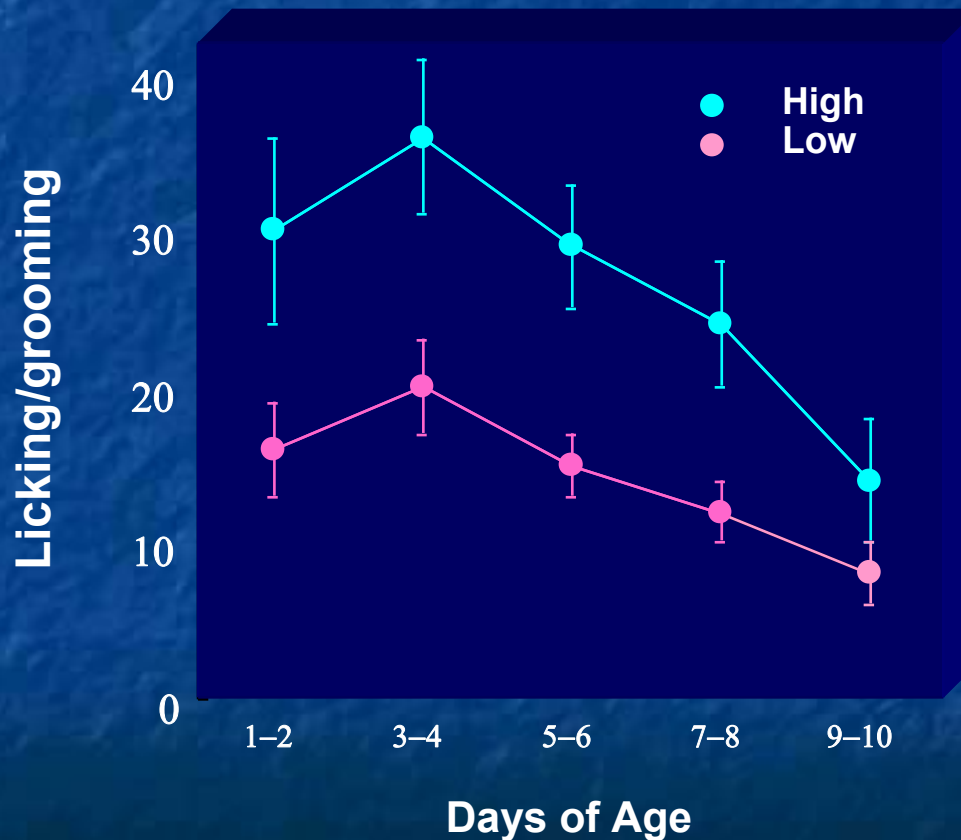
Variations in maternal care



Variations in maternal care



Variations in maternal care X Days



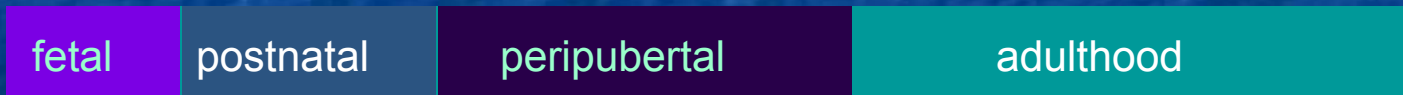
*** No differences
in time with pups**

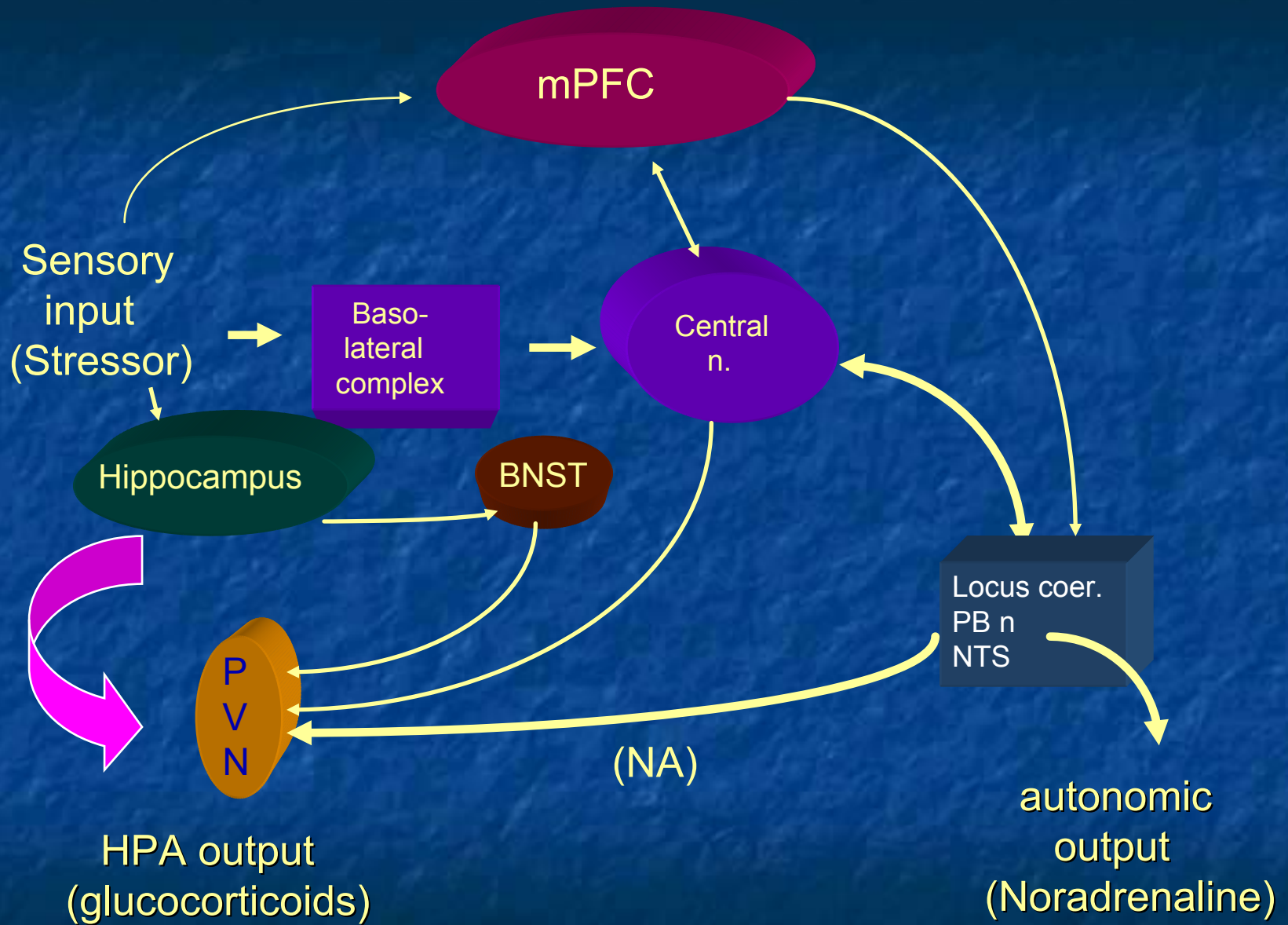
Are these naturally-occurring variations
in maternal behaviour associated with
the development of individual differences
in endocrine and behavioural responses
to stress?

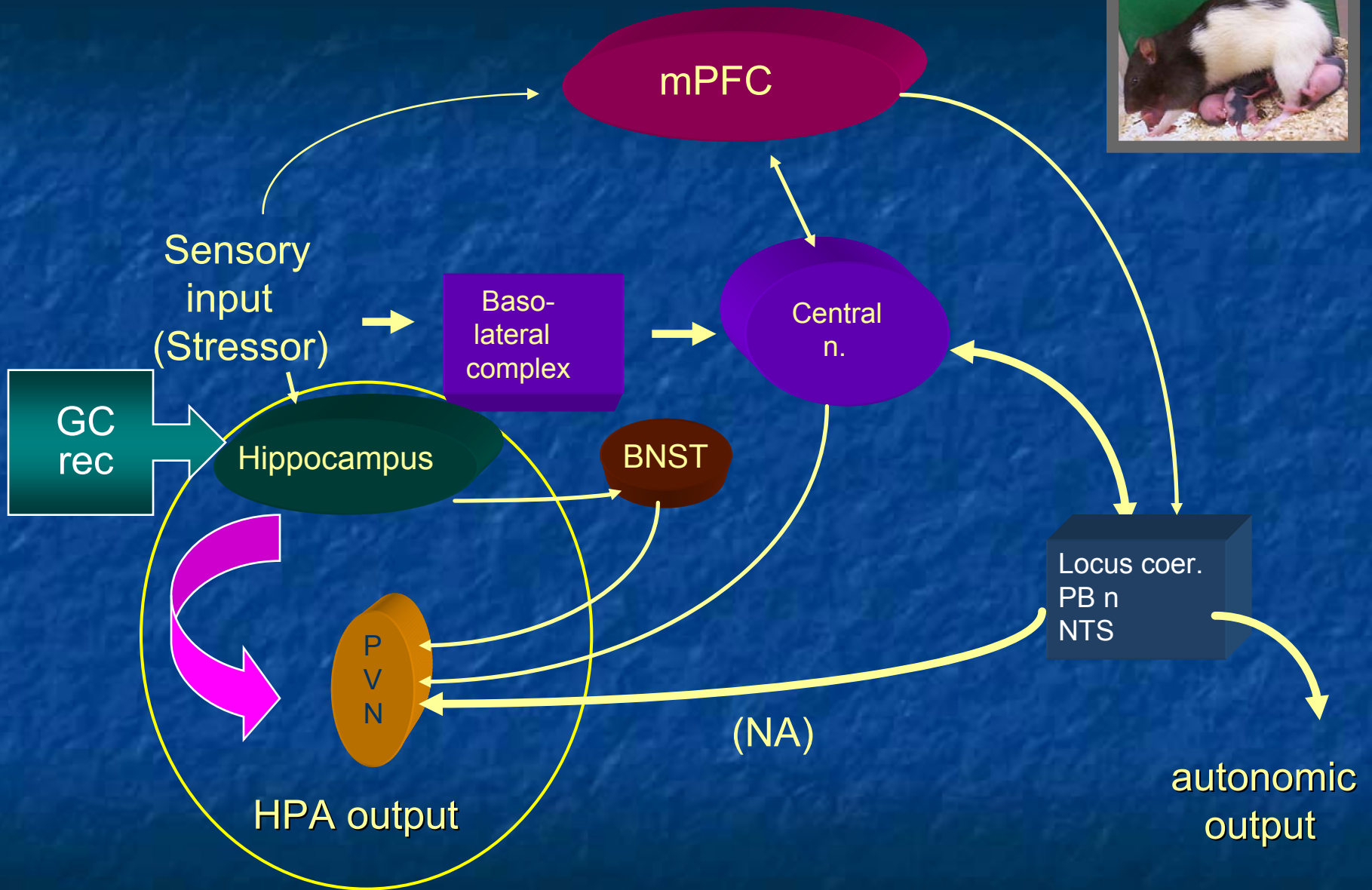
* Effects hold for both males and females

Maternal care

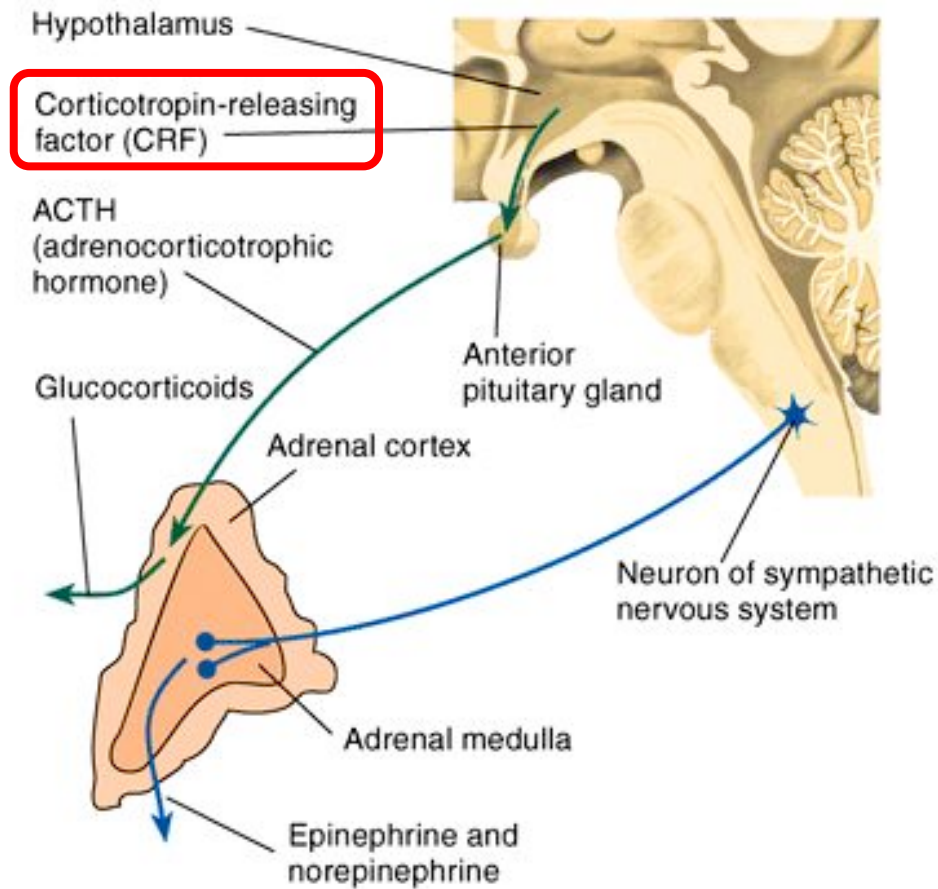
Outcomes





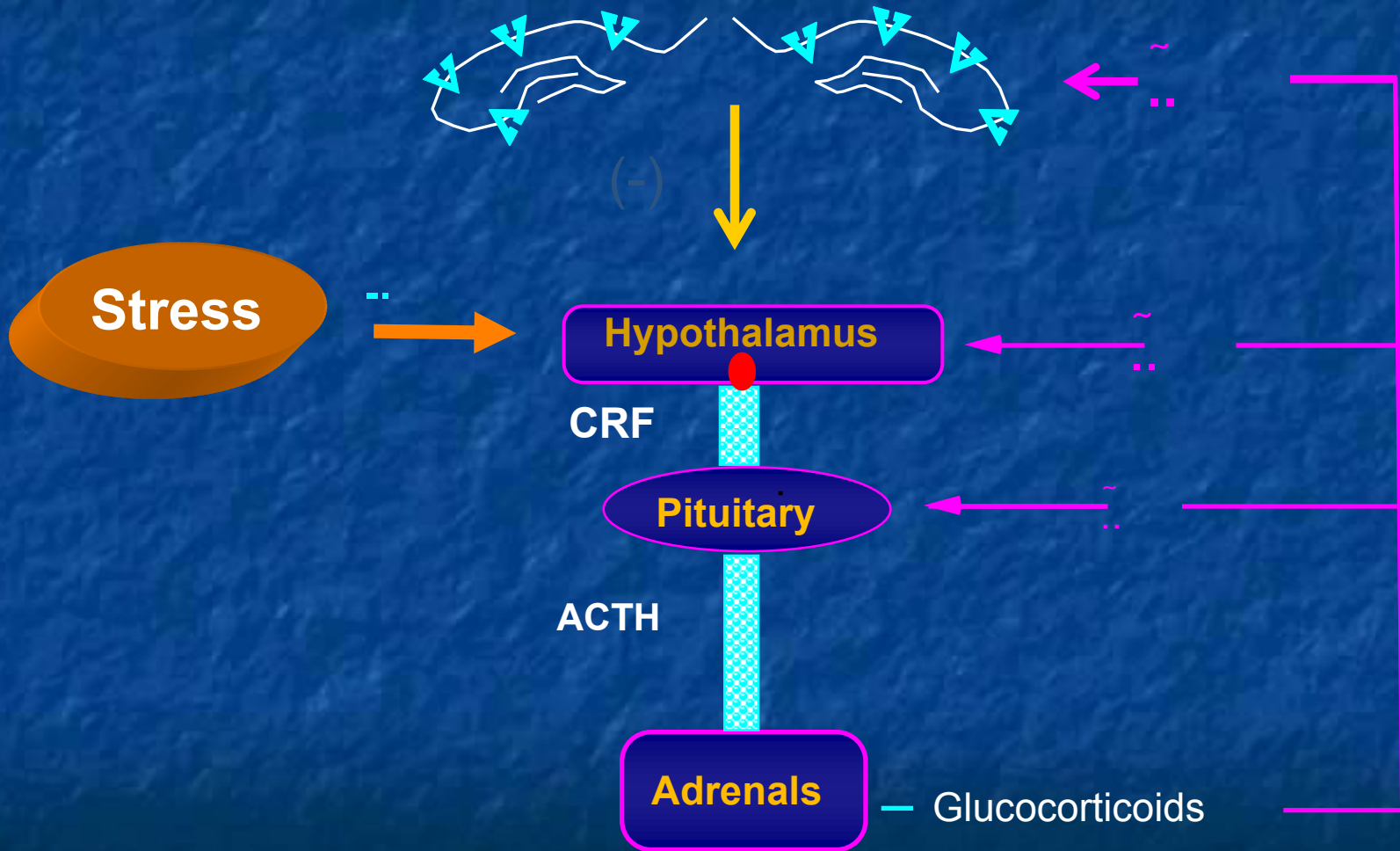


► **Control of the Secretion of Glucocorticoids by the Adrenal Cortex and of Catecholamines by the Adrenal Medulla**



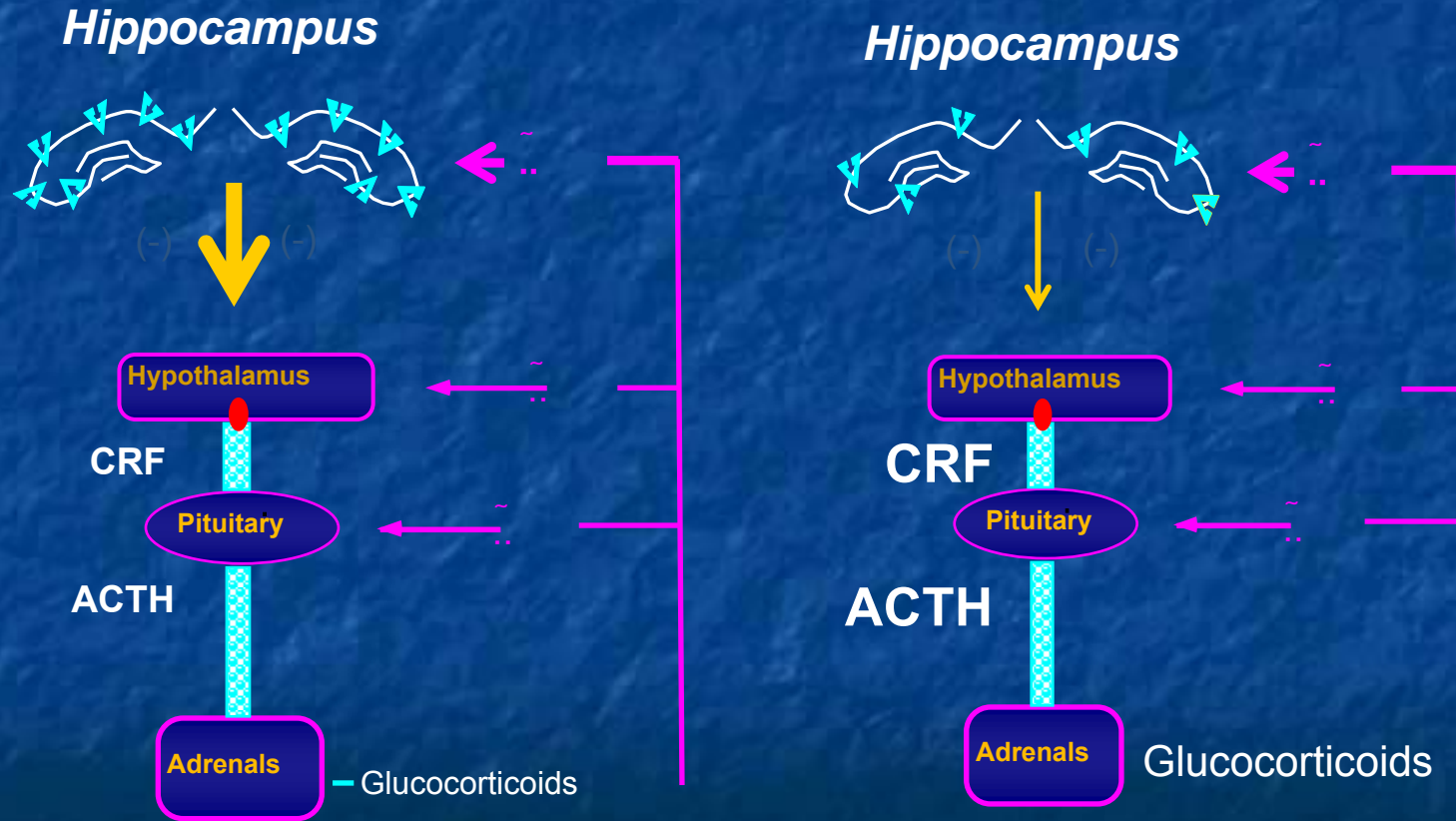
▶ Glucocorticoid Receptor

Hippocampus



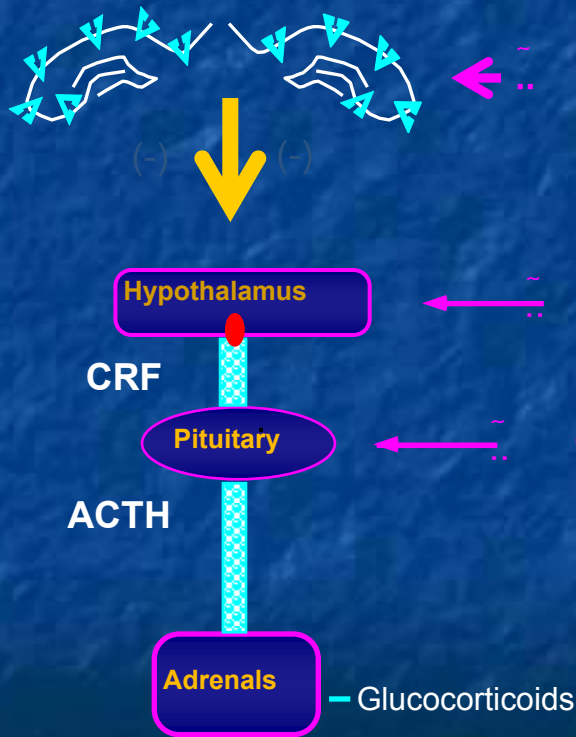
CRF: corticotropin releasing factor. ACTH: adrenocorticotropin

Individual differences in glucocorticoid receptor levels lead to altered pituitary-adrenal responses to stress

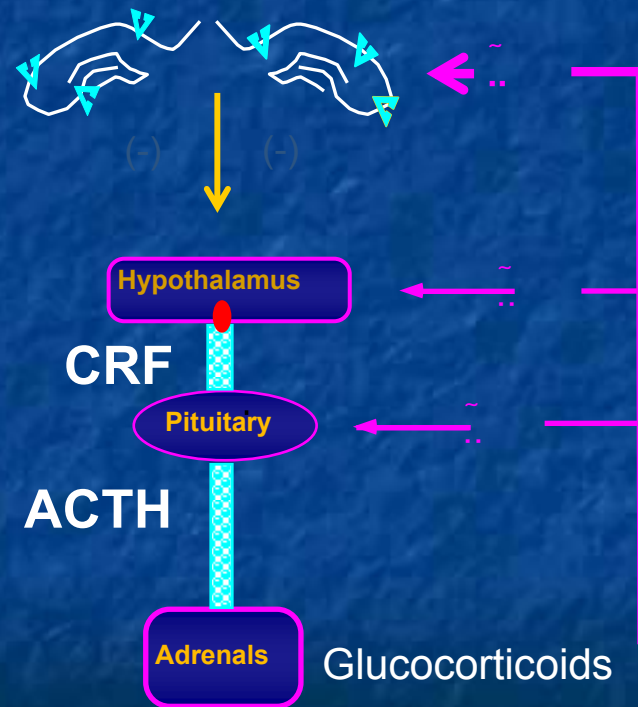


Individual differences in glucocorticoid receptor levels lead to altered pituitary-adrenal responses to stress

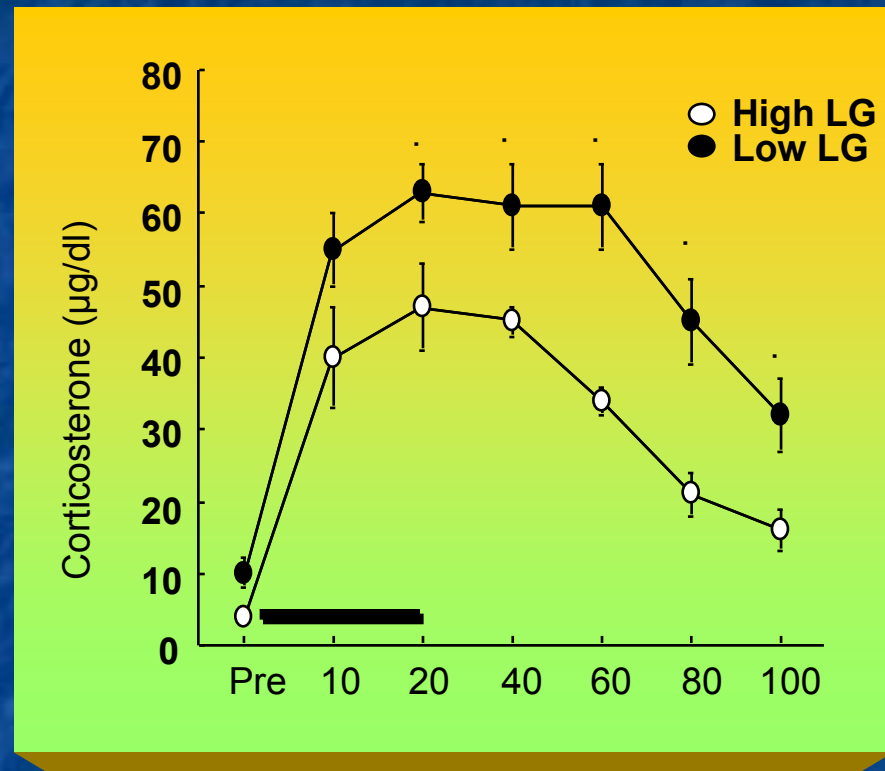
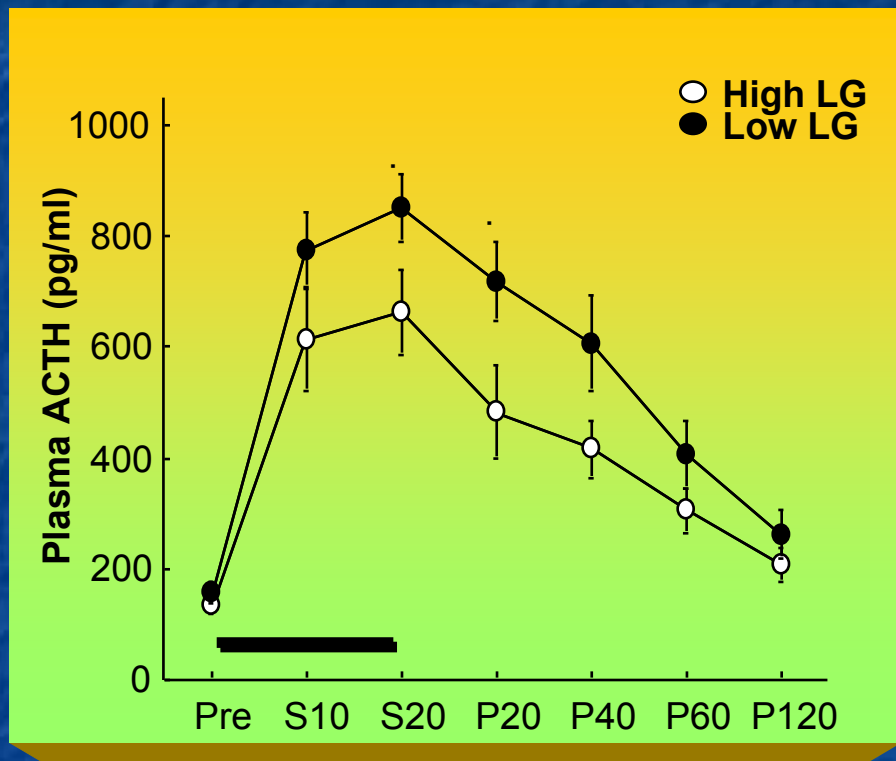
High LG offspring



Low LG offspring

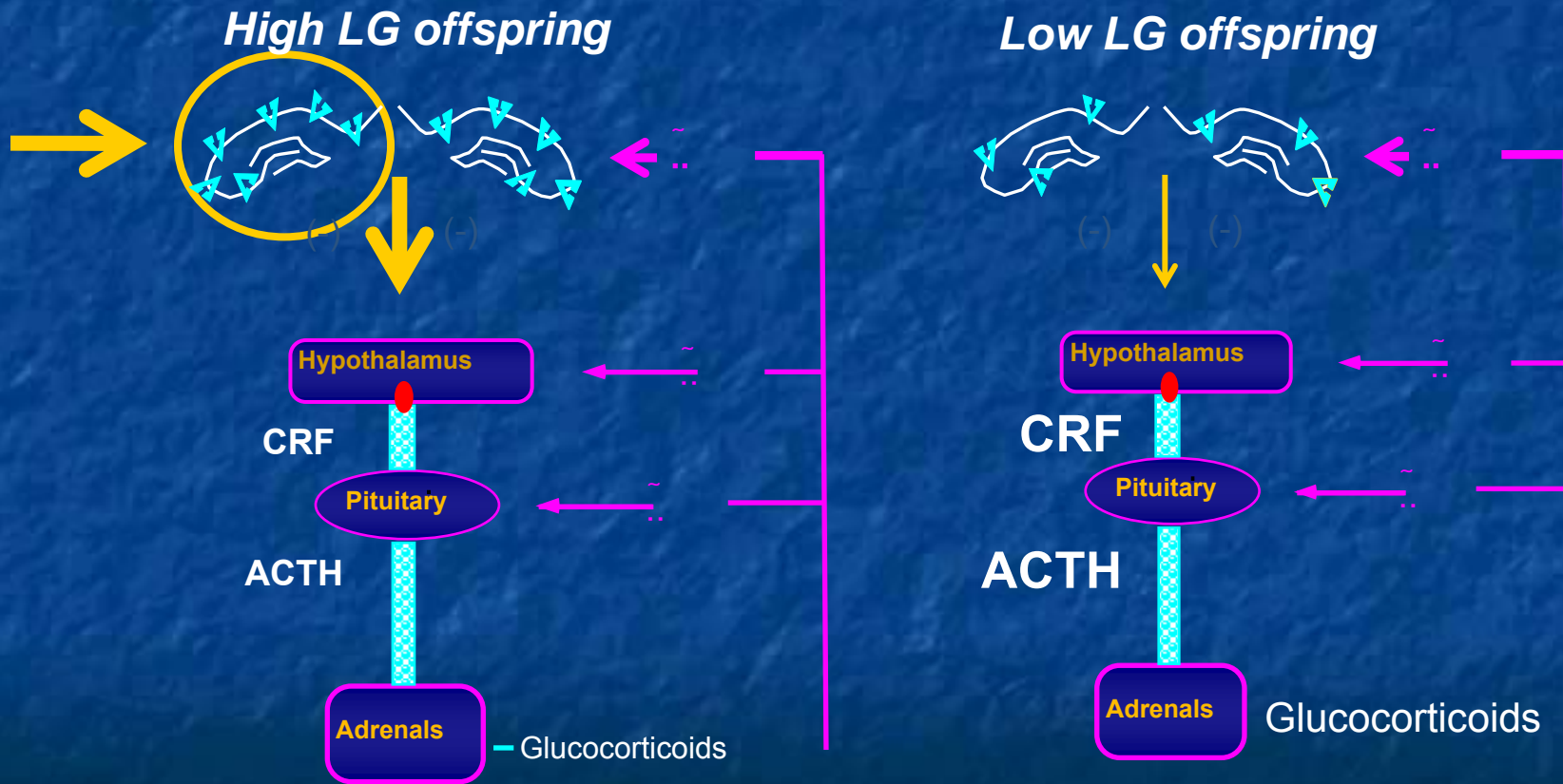


Adult offspring of High LG mothers show more modest HPA responses to stress



Intra-hippocampal infusion of a GR antagonist completely eliminates the maternal effect on HPA responses to stress

Individual differences in glucocorticoid receptor levels lead to altered pituitary-adrenal responses to stress

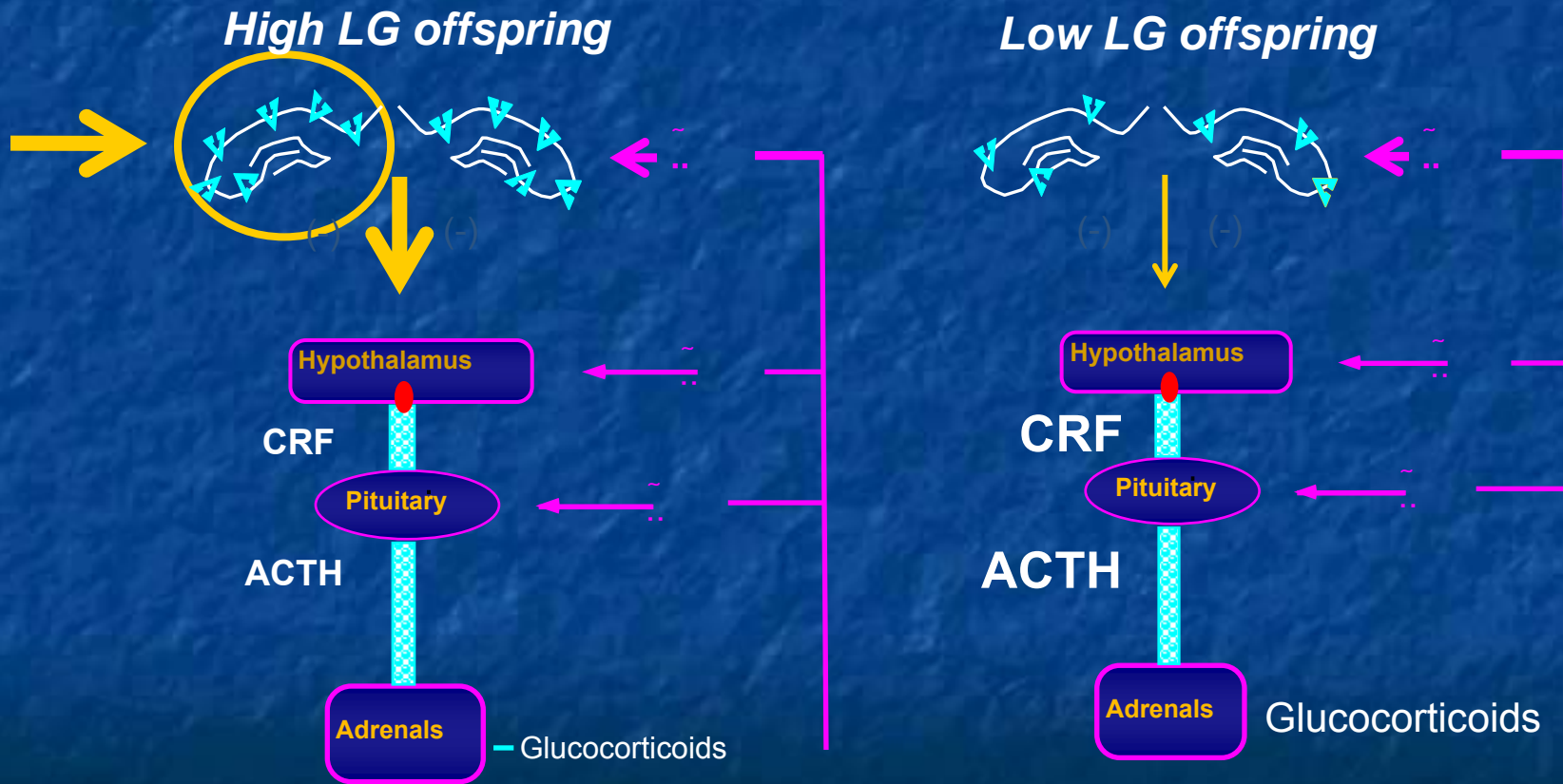


Adaptive advantages of *increased* stress reactivity (Central CRF systems, HPA axis, Catechols)

- Increased resistance to sepsis (infection).
- Increased resistance to famine.
- Decreased mortality due to aggressive conflict.

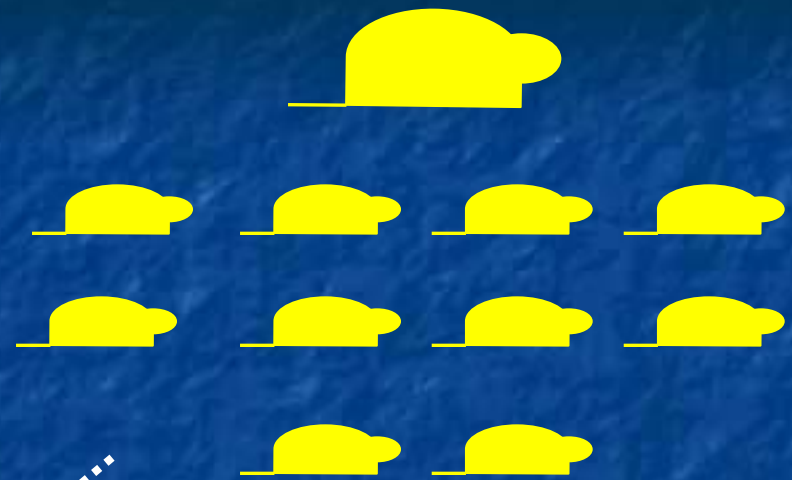
Poverty: Pathogens, nutritional deprivation and violence

Individual differences in glucocorticoid receptor levels lead to altered pituitary-adrenal responses to stress

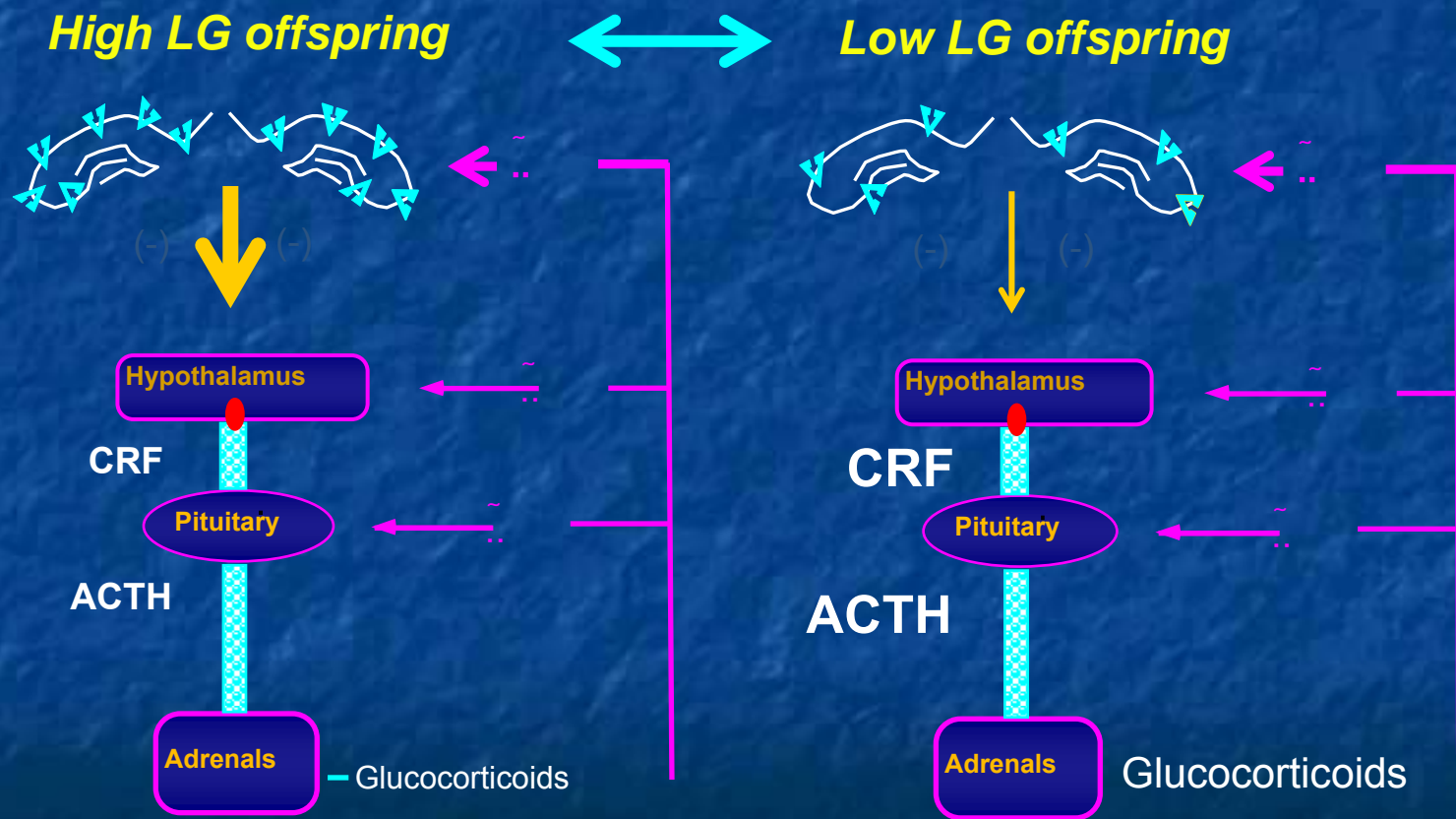


High LG

Low LG

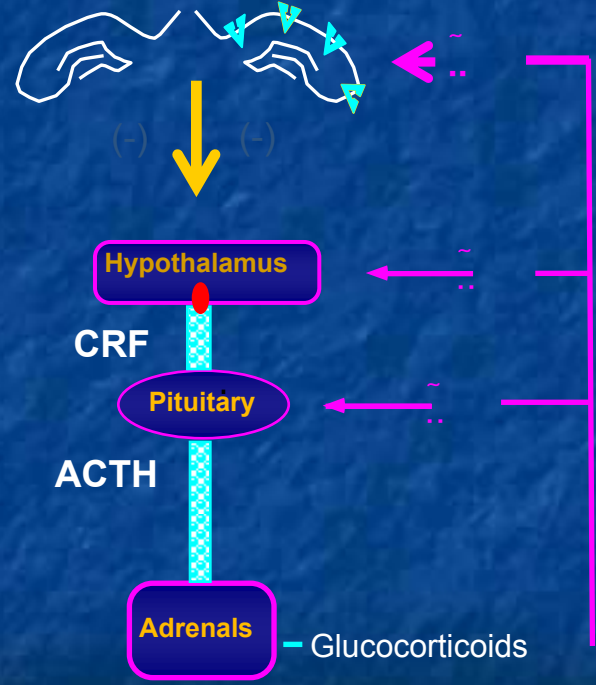


Cross-fostering reveals evidence for direct, postnatal effects of maternal care





Hippocampus



How might maternal licking/grooming regulate hippocampal glucocorticoid receptor gene activity and HPA function?

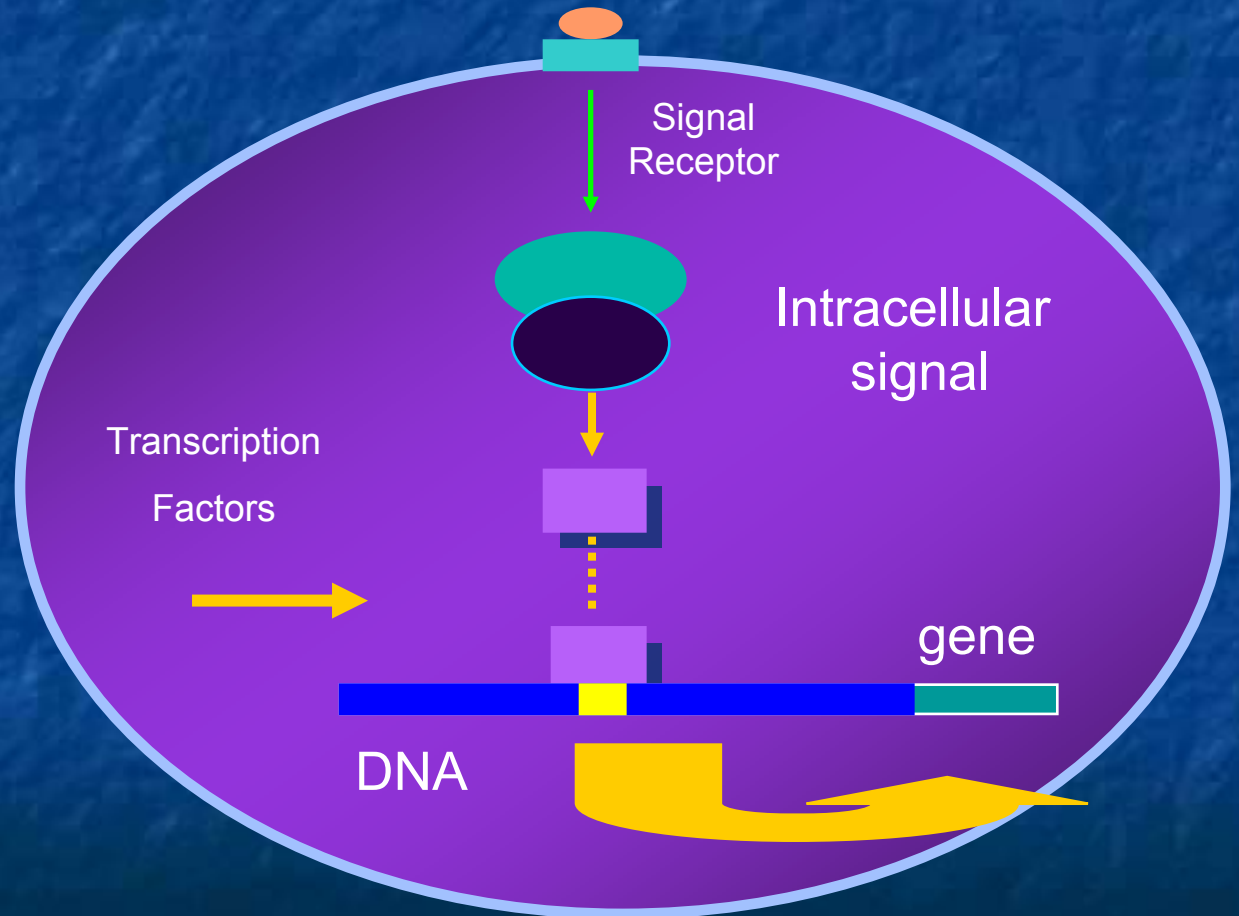
And how do these effects persist over the lifespan of the offspring?

Relevant gene - environment interaction

Maternal
Care

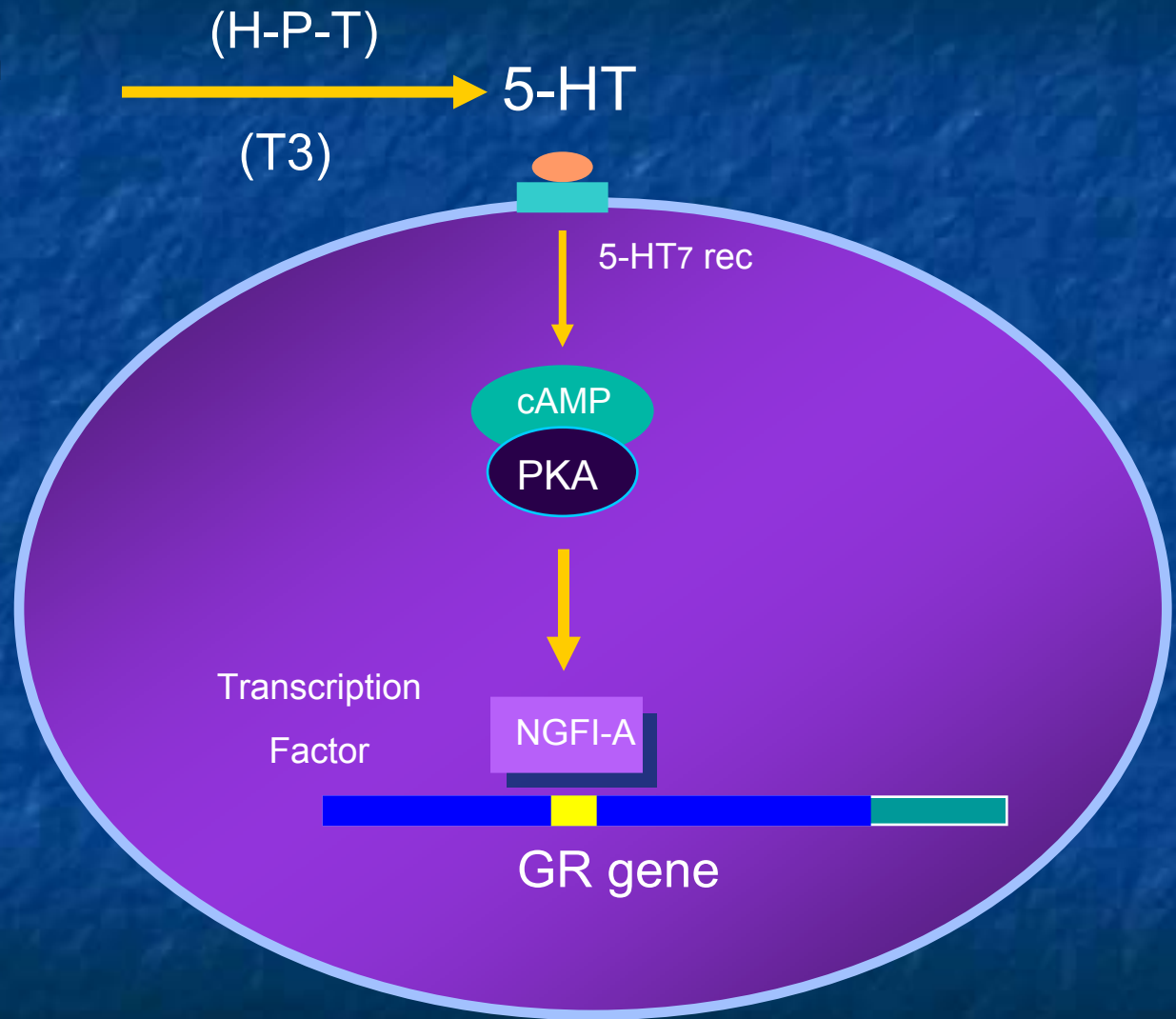


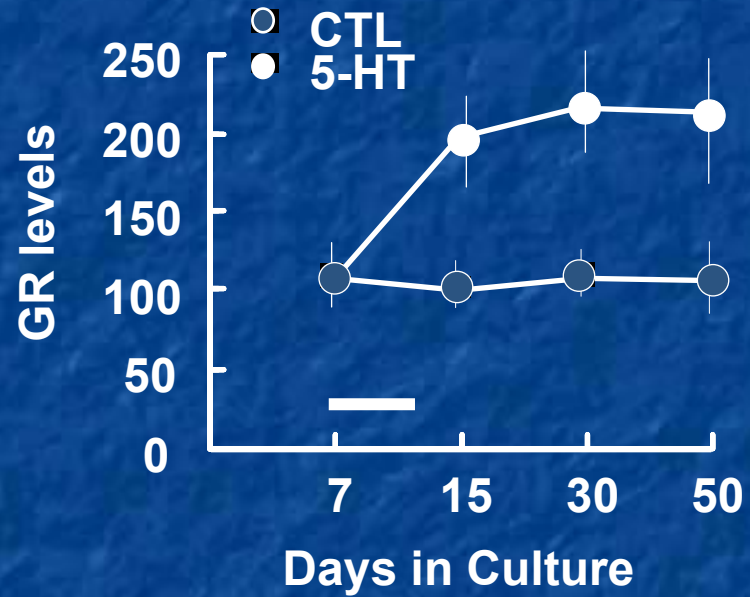
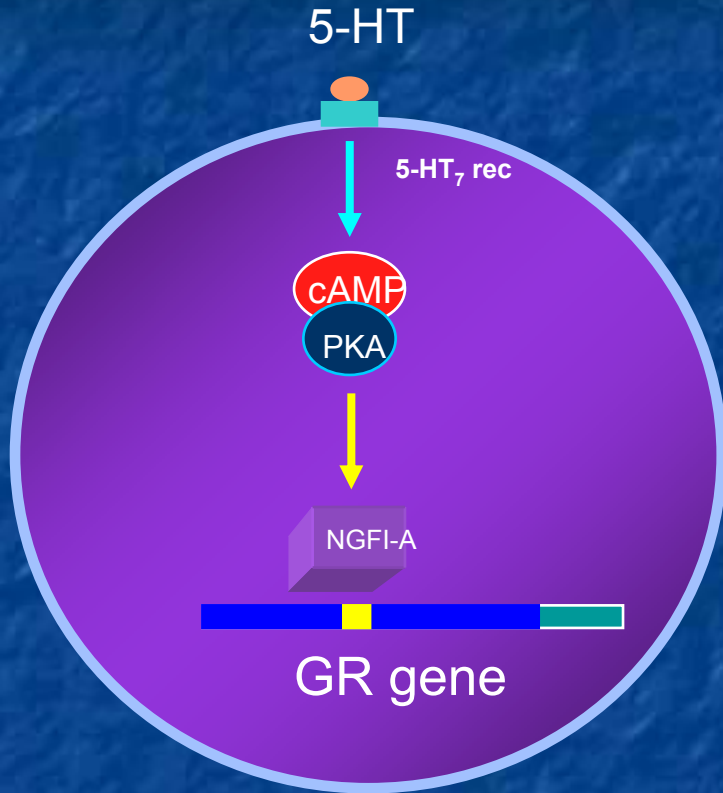
Extracellular signal



Summary of *in vivo* and *in vitro* studies

Tactile stimulation
(maternal LG)



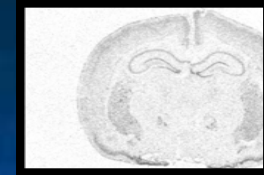


— Represents period of 5-HT exposure

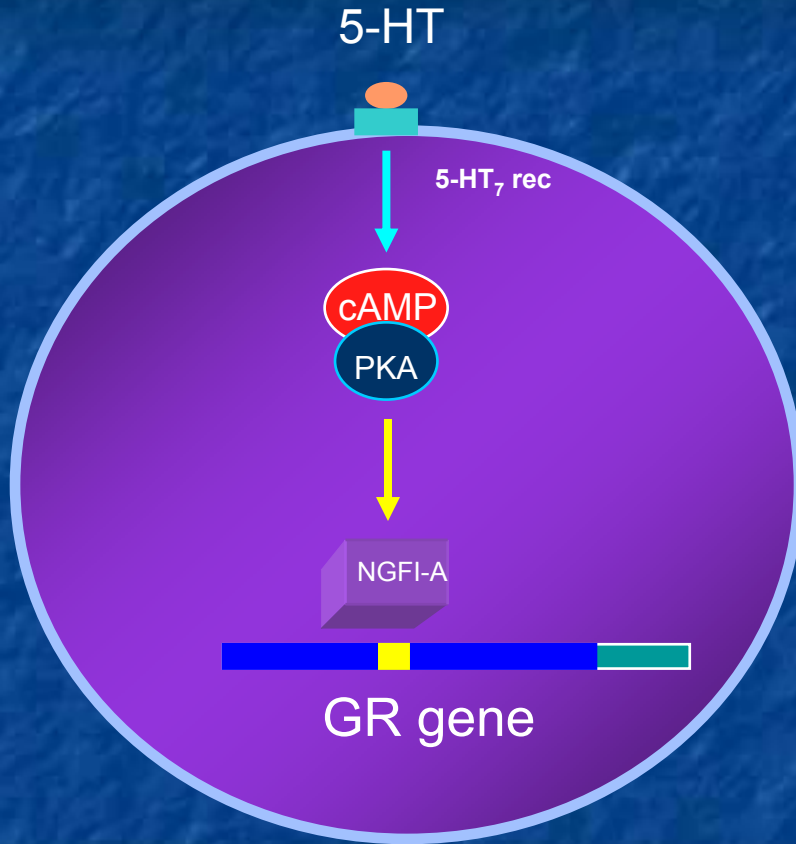
Day 6 pups



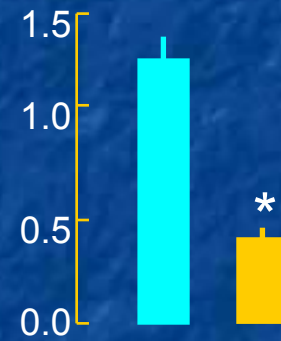
Low LG



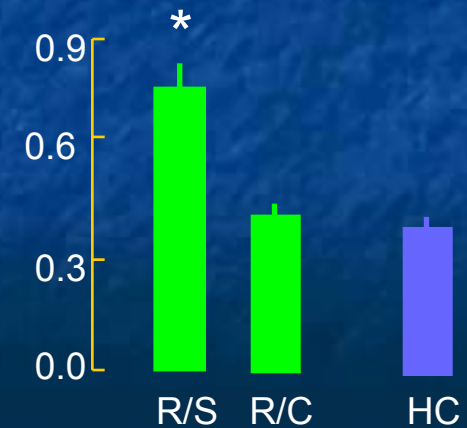
High LG



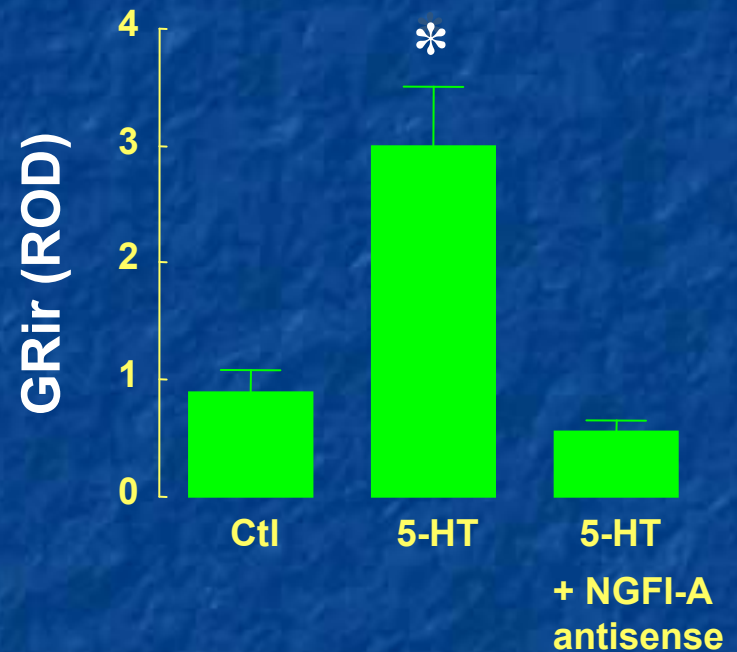
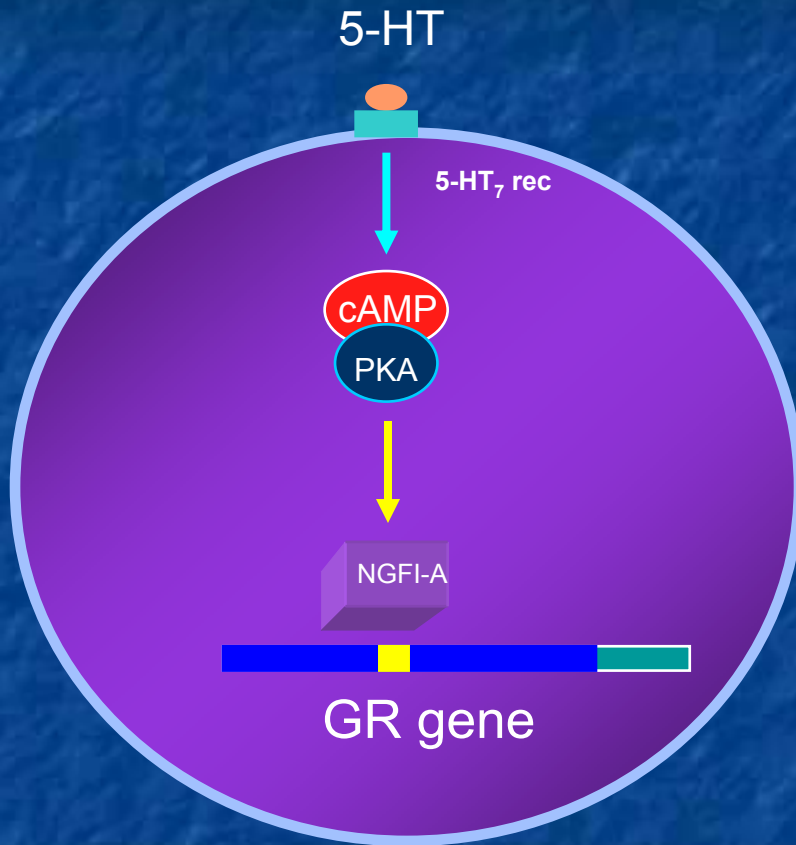
NGFI-A mRNA levels

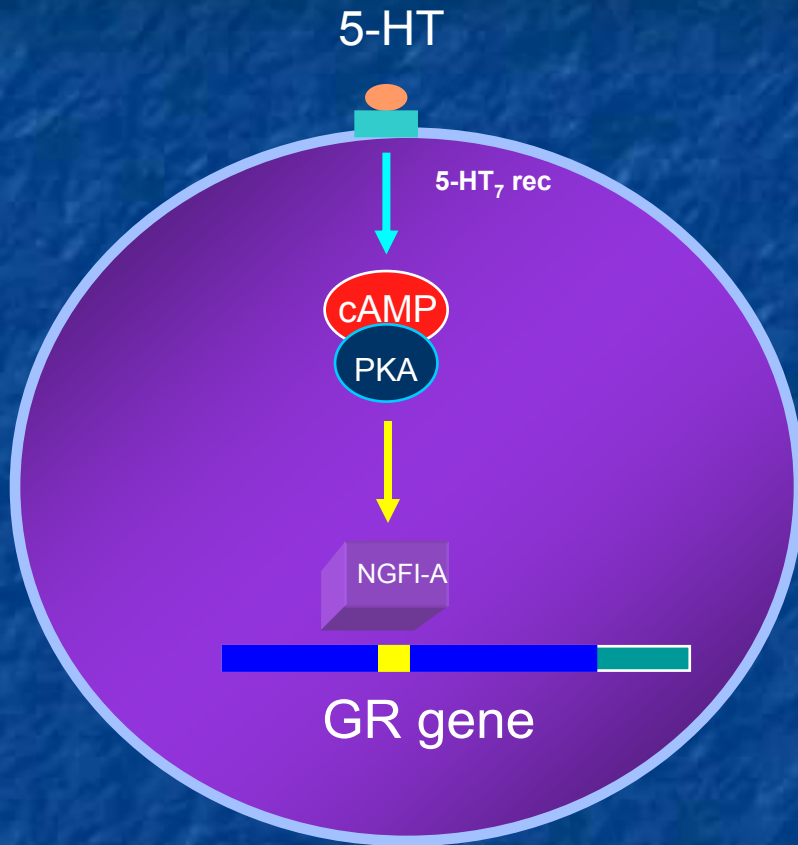


NGFI-A mRNA (stroking)



In vitro (primary hippocampal neuronal cultures) studies

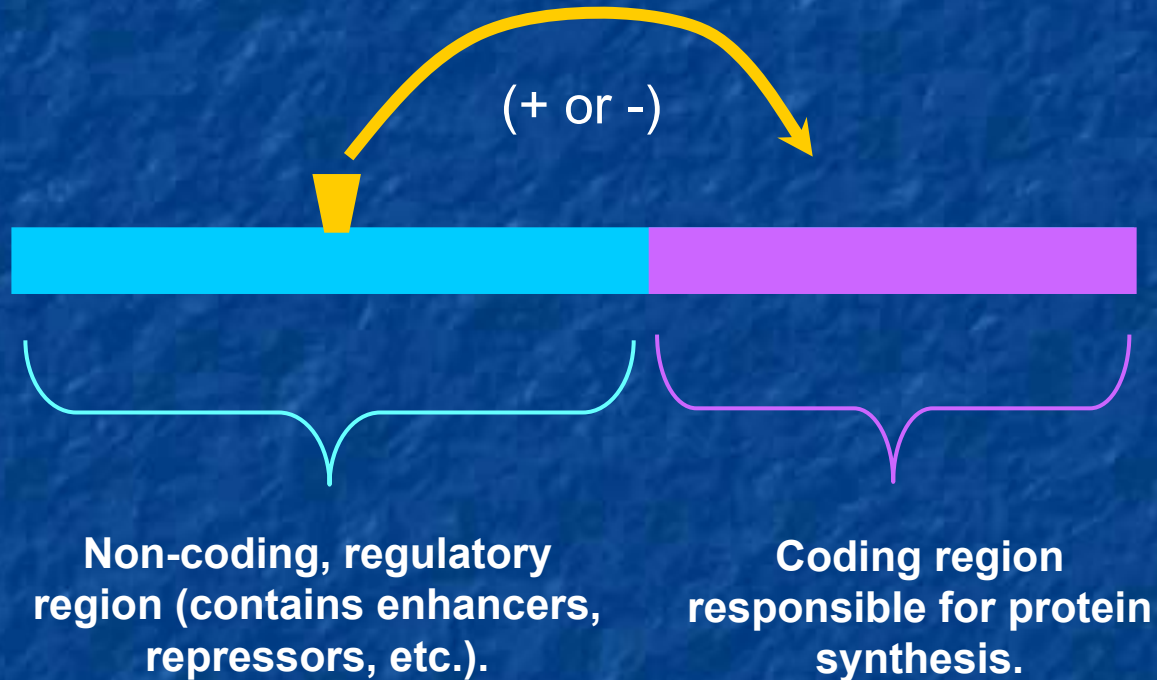




What are the relevant genomic targets?

Clone the 5' untranslated region of the rat hippocampal glucocorticoid receptor gene

Gene organization



Glucocorticoid receptor gene

Variable exon 1 region

Constant region

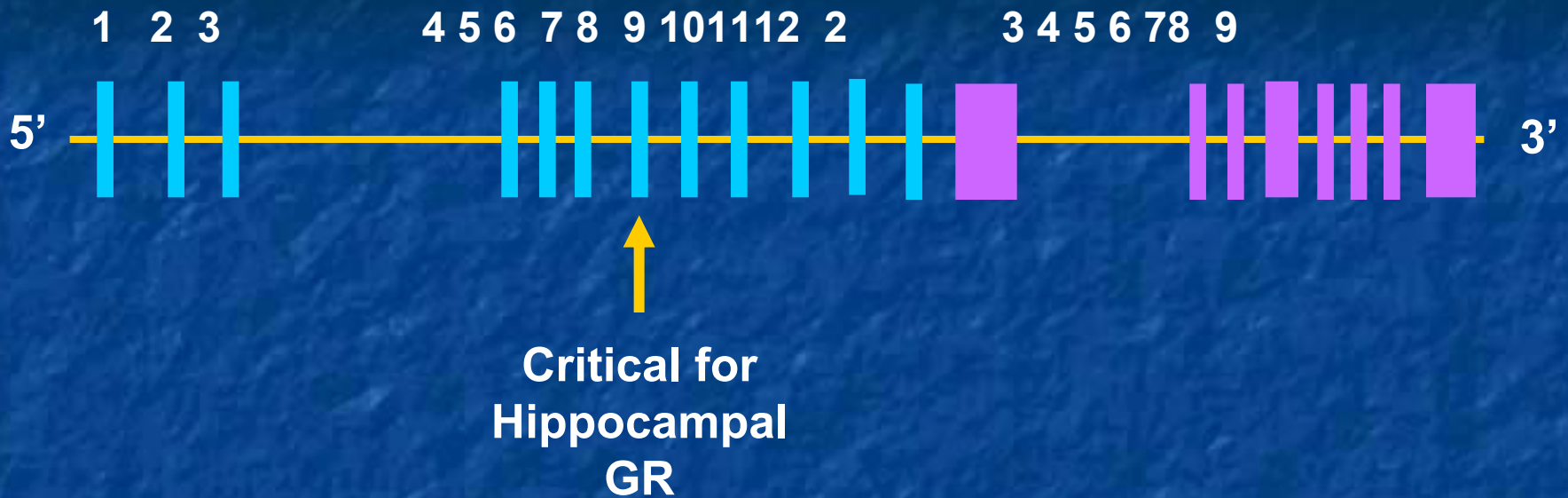


(~110 kb)

Clone the 5' untranslated region of the rat hippocampal glucocorticoid receptor gene

Variable exon 1 region

Constant region



Transfection studies with promoter-reporter constructs reveal exon 1₇ sequence has considerable transactivational capacity.

DNA sites that regulate glucocorticoid receptor gene



GR Promoter 1₇ Sequence

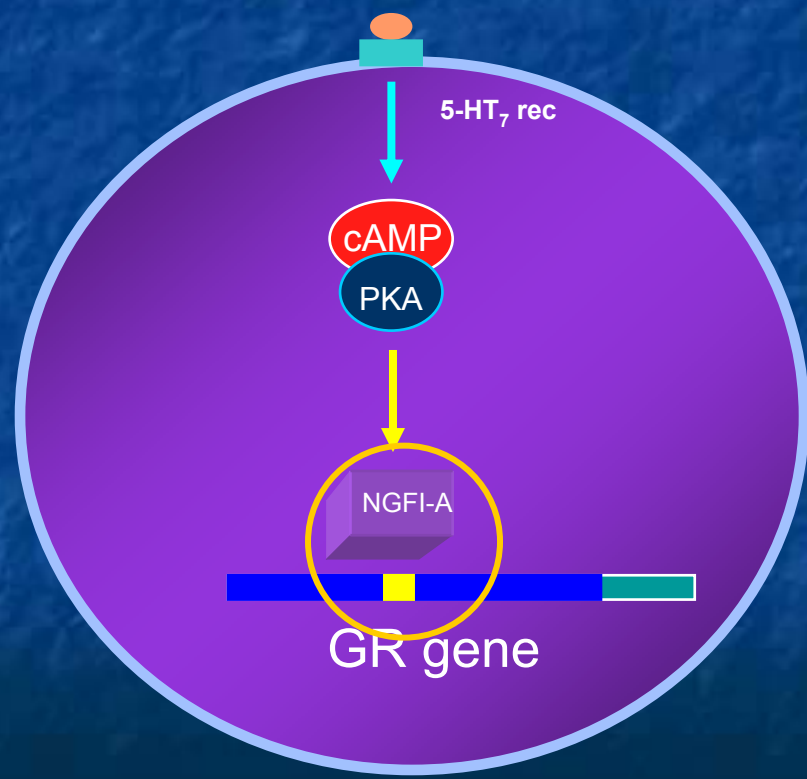
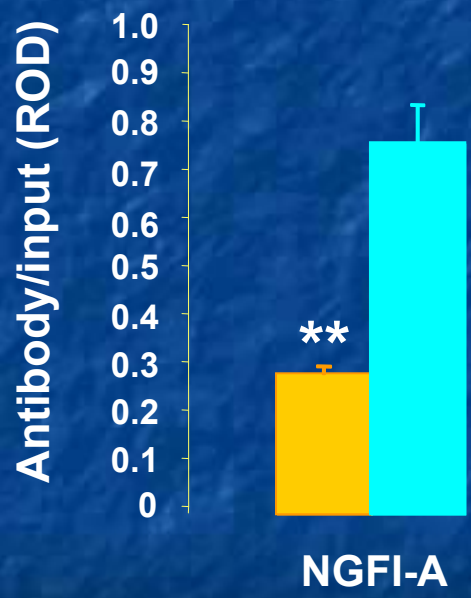
1681
 1741 ctctgctagt gtagacacact t¹cg²cgcaact c³cgcagttgg ⁴cggg⁵cg⁶cgga ccaccctg⁷c
 1801 ggctctgc⁸cg gctggctgtc accct⁹cgggg gctctggctg c¹⁰cgacca¹¹cg ggg¹²cgggct
 1861 c¹³cgag¹⁴cggtt ccaagcct¹⁵cg gagtggg¹⁶cg gggg¹⁷cgggag ggagcctggg agaa
 ccc

NGFI-A

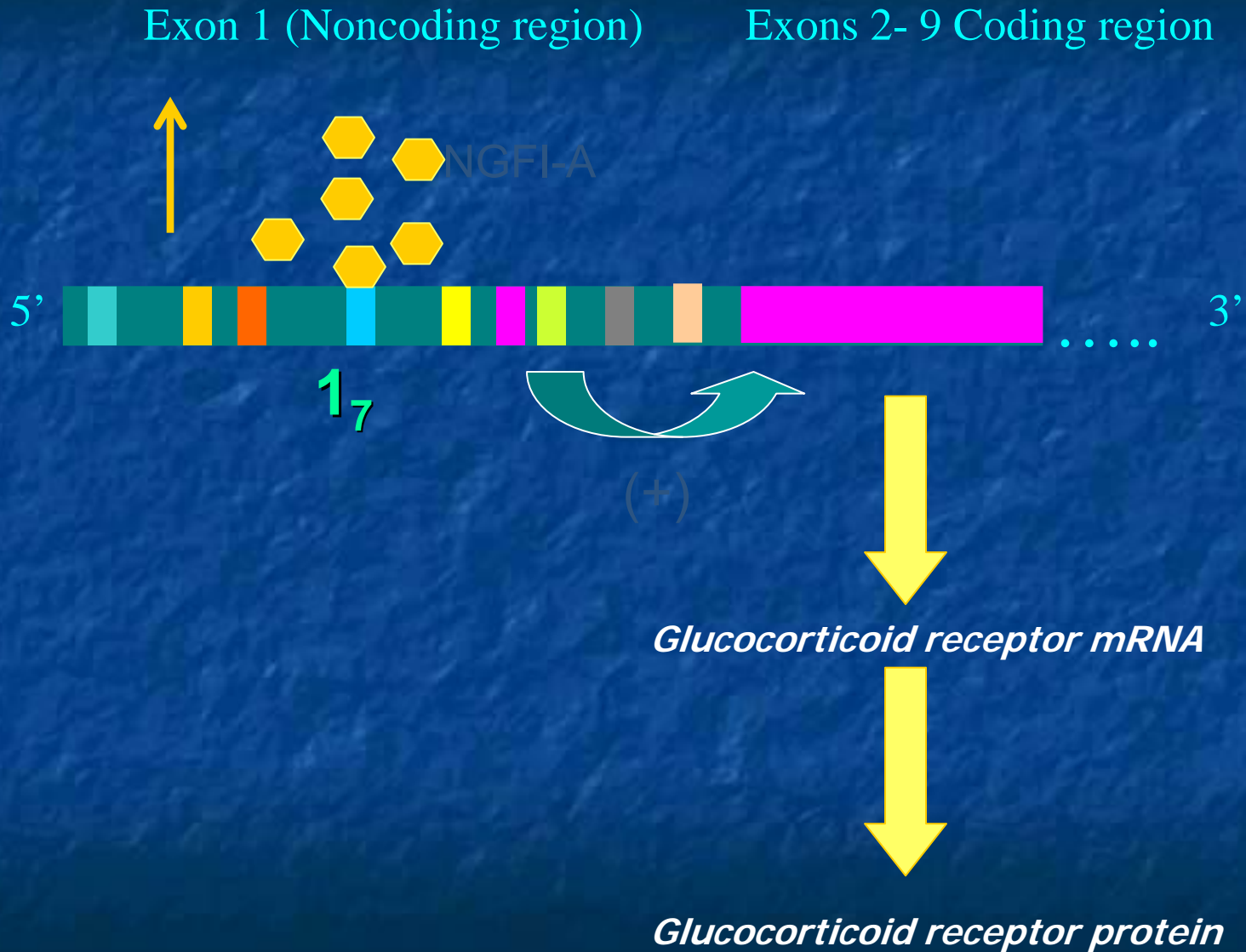
NGFI-A binding to the GR(1₇) promoter in neonates



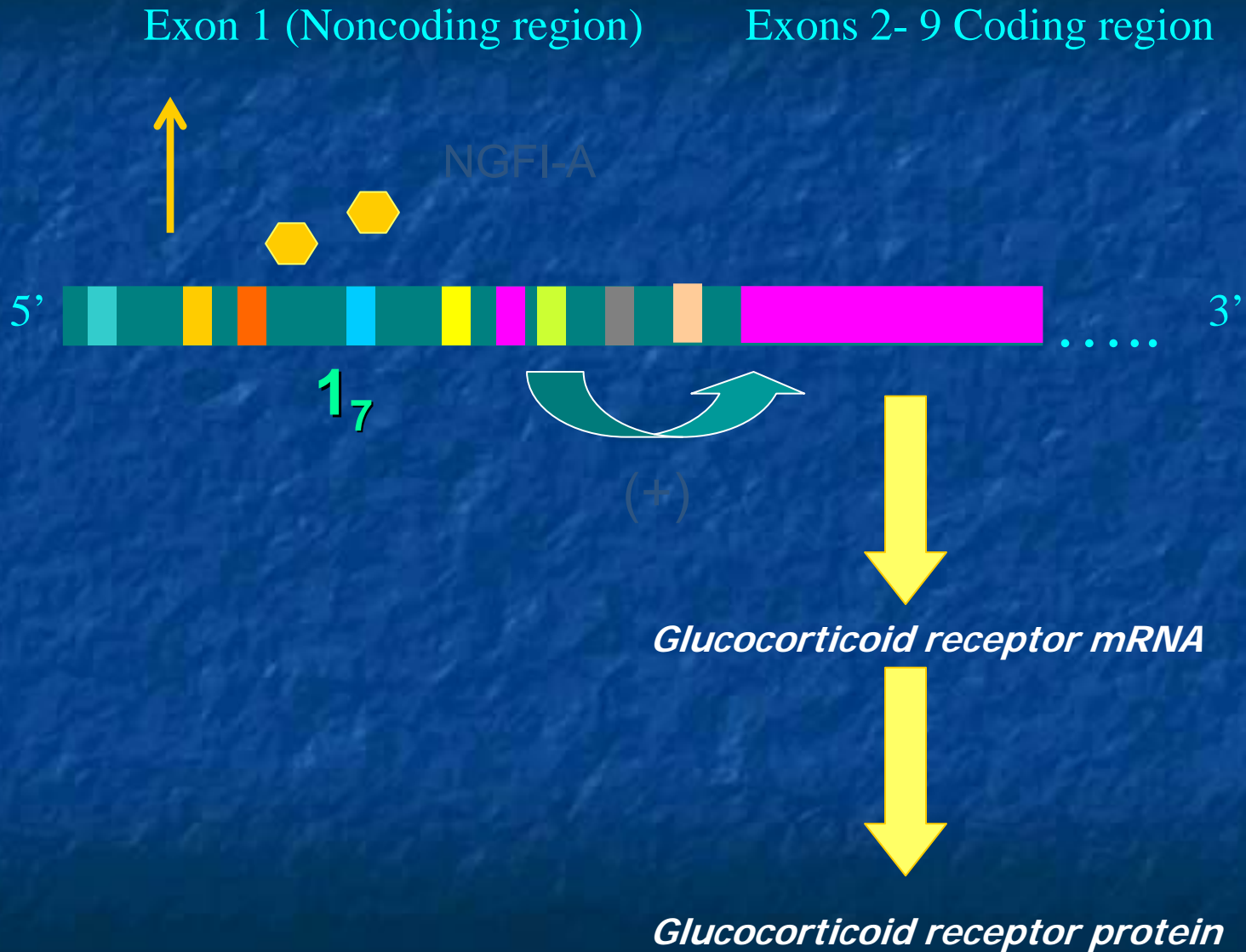
5-HT



Offspring of High LG mothers

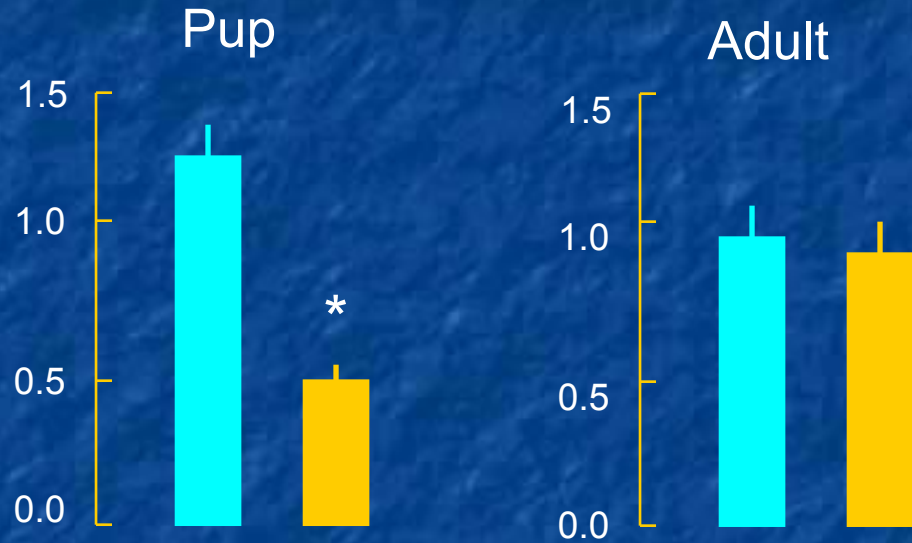


Offspring of High LG mothers



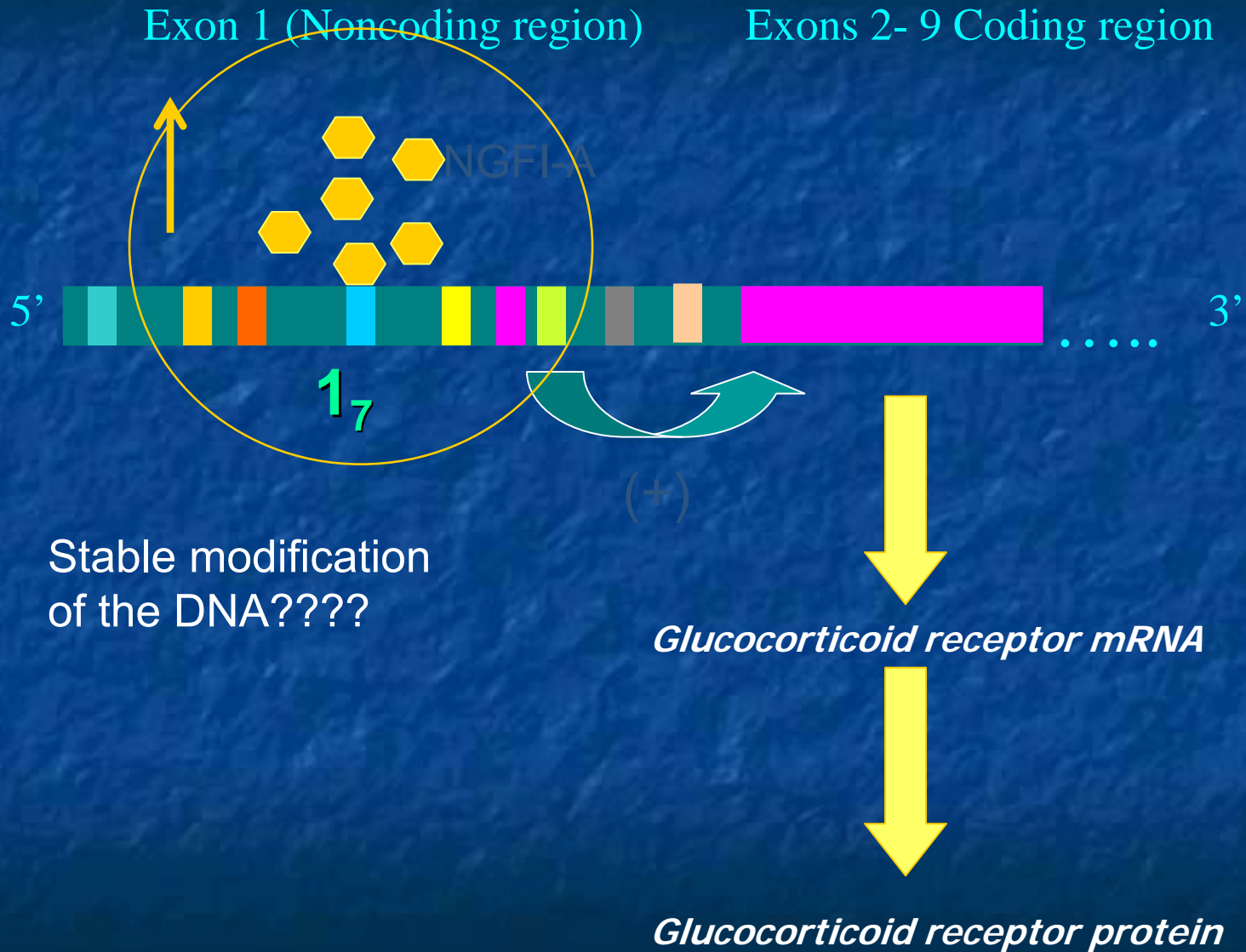
But.....

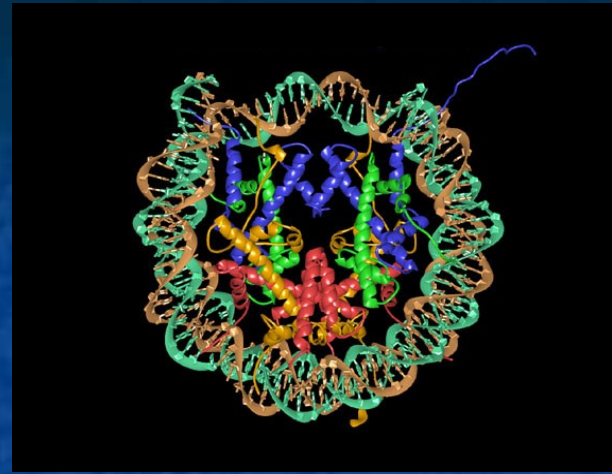
NGFI-A levels



So, while increased levels of NGFI-A can explain the increased activity of the glucocorticoid receptor gene in the pup, it does not explain why the difference is still observed in adult animals?

Offspring of High LG mothers



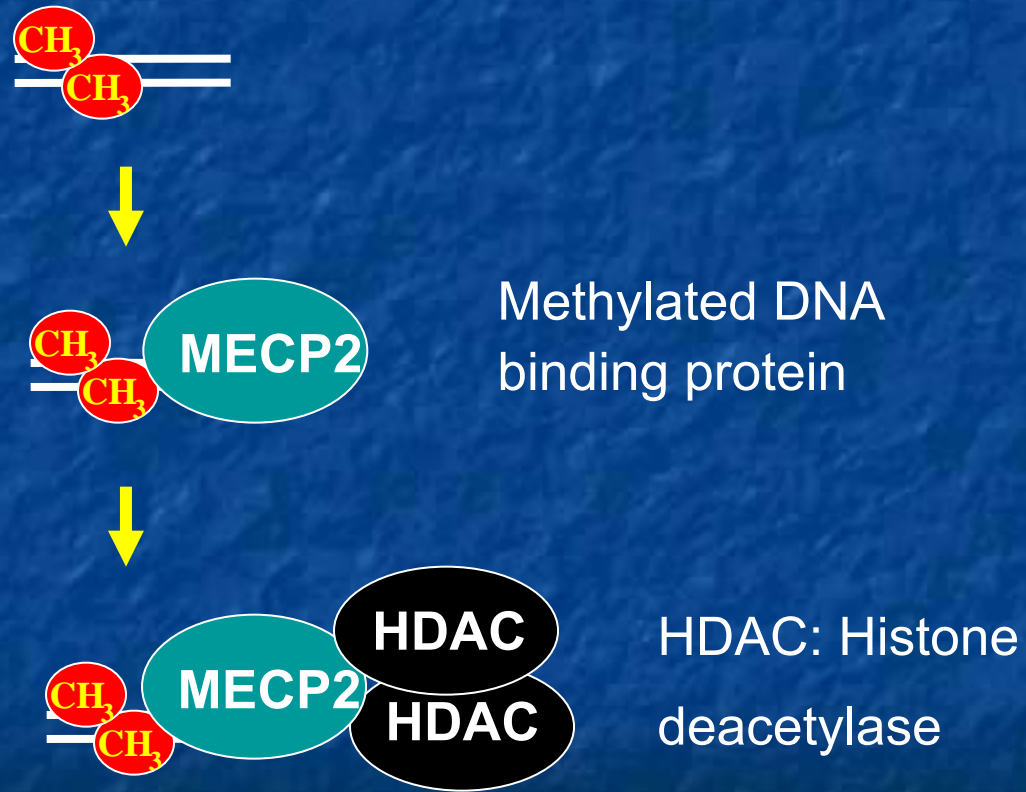


**GR expression & HPA
function**

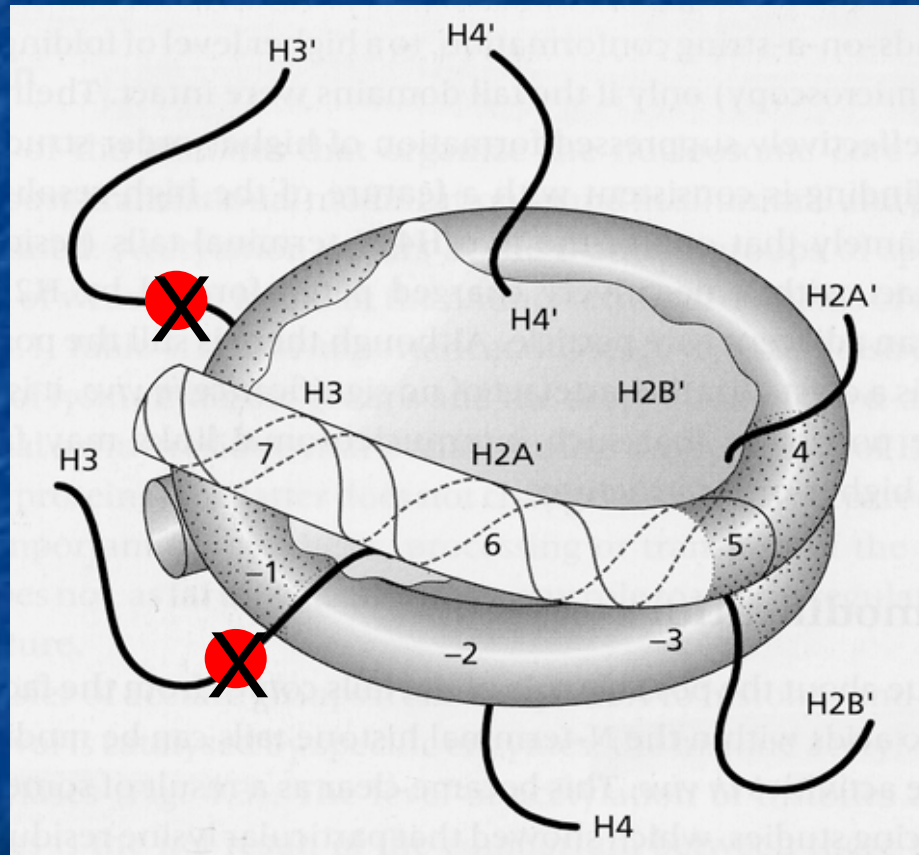


- DNA methylation occurs at cytosines.
- DNA methylation is chemically very stable.

DNA Methylation can inhibit gene expression by blocking transcription factors binding



DNA methylation silences gene expression



DNA sites that regulate glucocorticoid receptor gene



GR Promoter 1₇ Sequence

1681
 1741 ctctgctagt gtagacacact t¹cg²cgcaact c³cgcagttgg ⁴cggg⁵cg⁶cgga ccaccctg⁷c
 1801 ggctctgc⁸cg gctggctgtc accct⁹cgggg gctctggctg c¹⁰cgacca¹¹cg ggg¹²cgggct
 1861 c¹³cgag¹⁴cggtt ccaagcct¹⁵cg gagtggg¹⁶cg gggg¹⁷cgggag ggagcctggg agaa
 ccc

NGFI-A

High LG

Low LG



NGFI-A binding to

5'...TGCGGGGGCGGGG 3'

(no methylation)



(High LG)

5'...TGCGGGGGCGGGG3'

(methylated only at 3'; High LG)

CH₃



5'...TGCGGGGGCGGGG3'

(methylated only at 5')

CH₃



(Low LG)

5'...TGCGGGGGCGGGG 3'

(methylated at both 5' and 3'; Low LG)

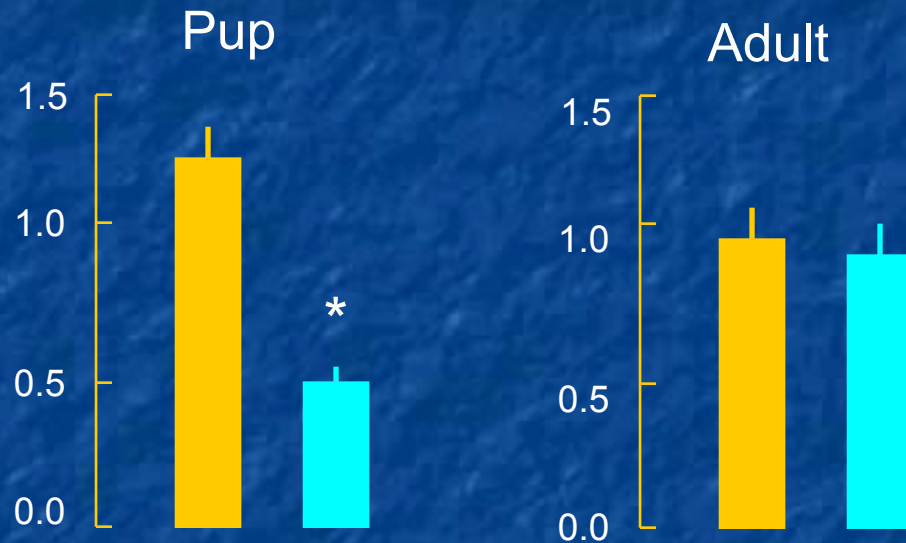
CH₃

CH₃

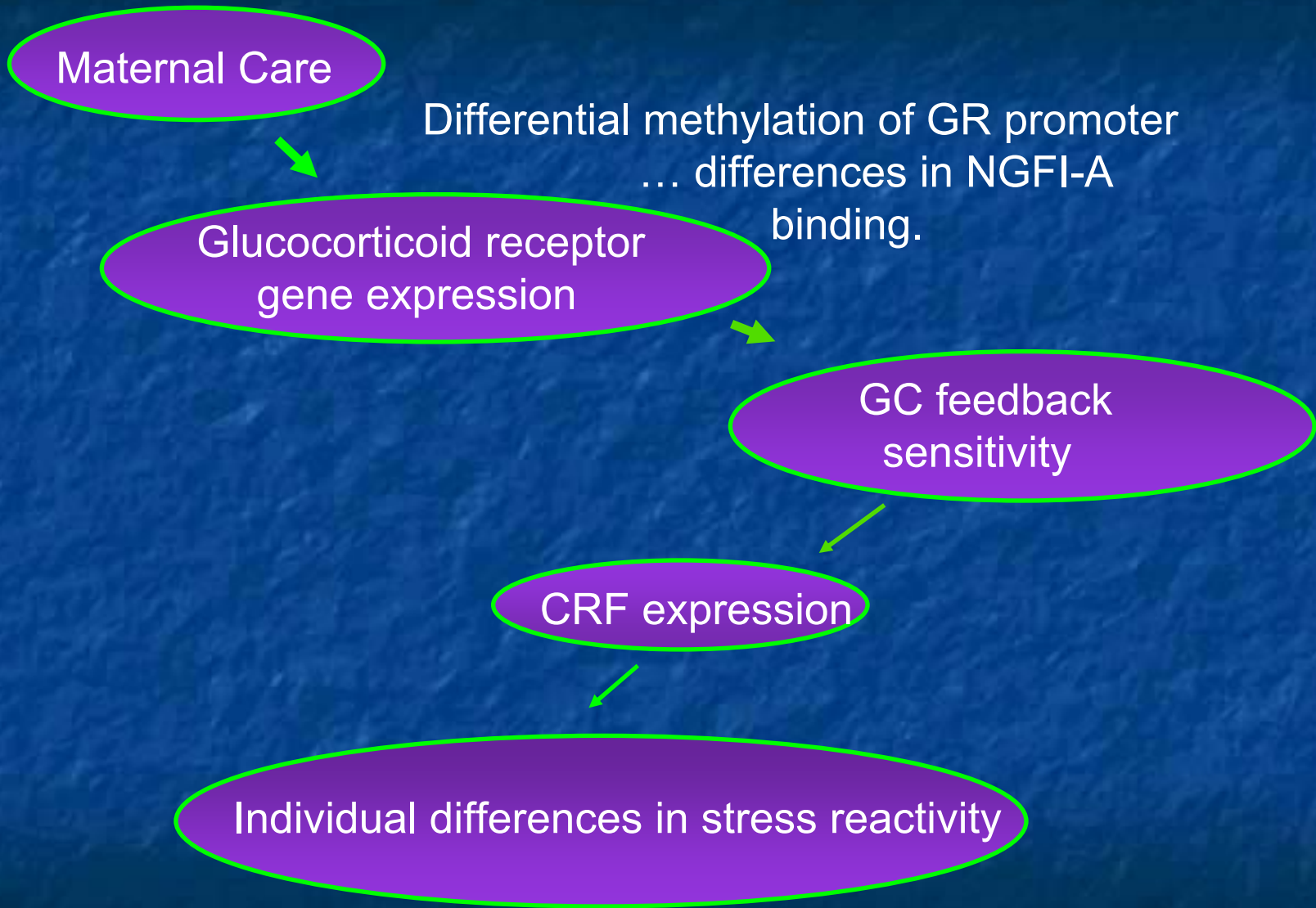


But....

NGFI-A levels

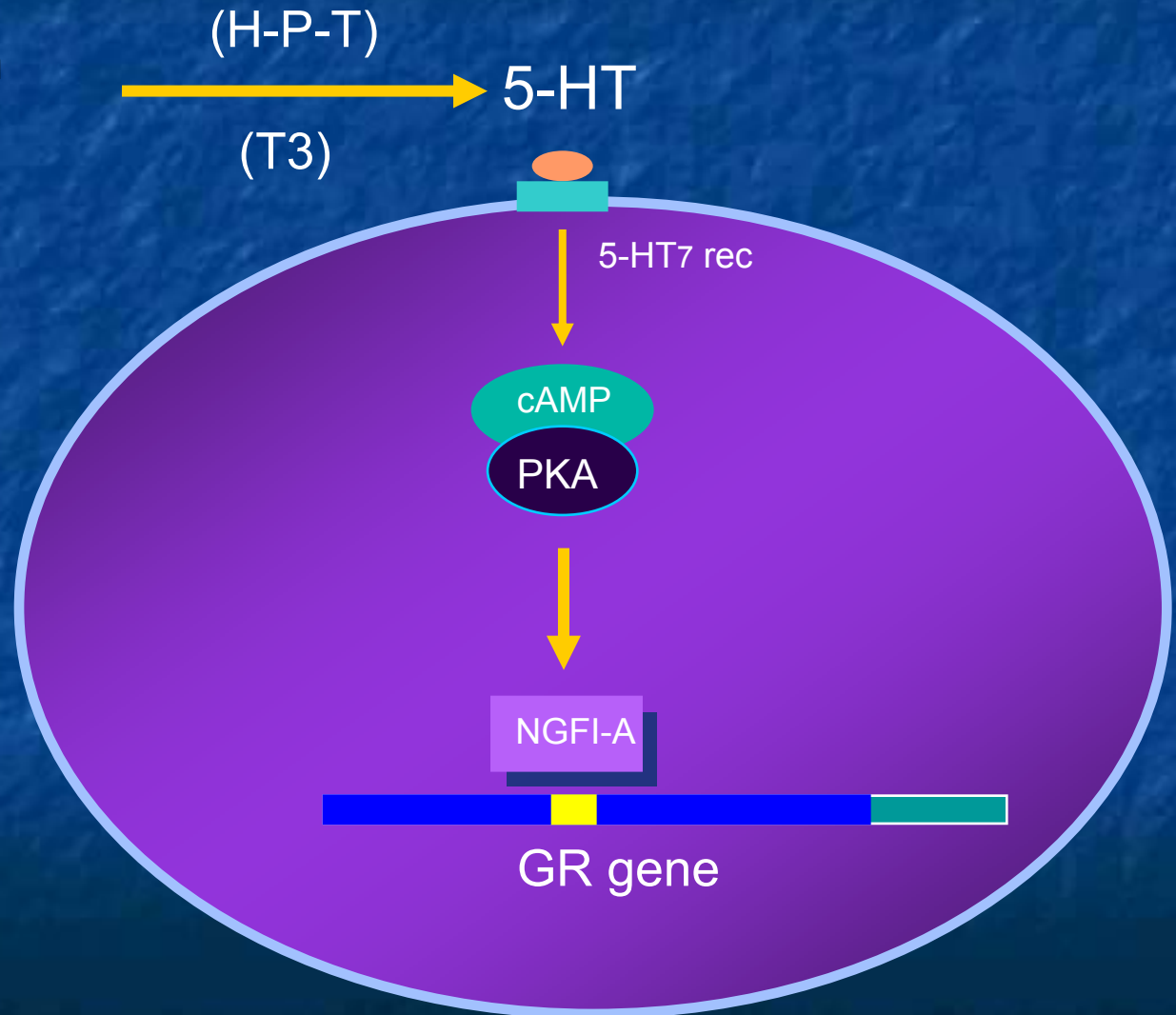


So while levels of NGFI-A are similar in animals reared by High or Low licking/grooming mothers, the NGFI-A site in the adult offspring of Low LG mothers is methylated and therefore cannot interact with NGFI-A.



Do these 'maternal' signals alter the methylation of the exon 17 GR promoter?

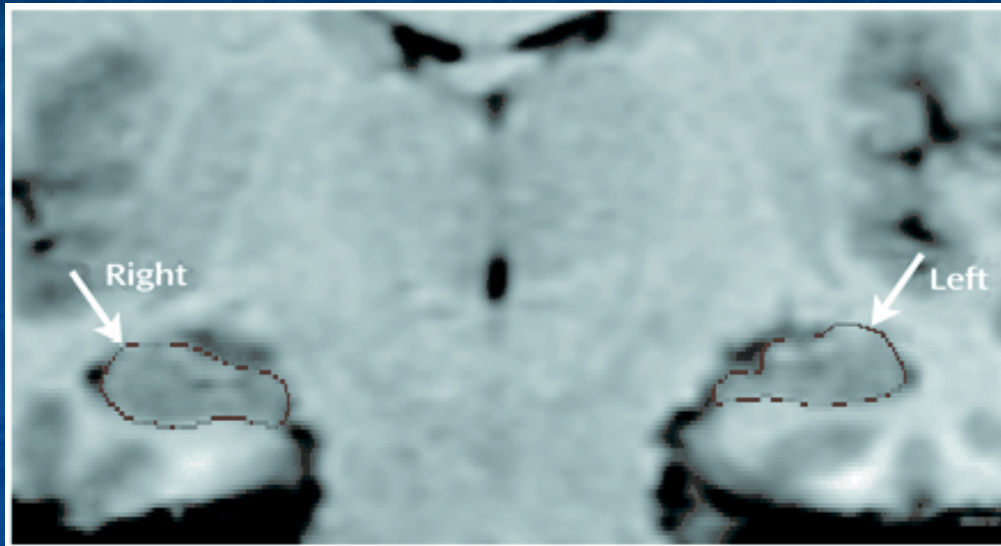
Tactile stimulation
(maternal LG)



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, J Molec Endo, 2005)

Hippocampal samples from humans

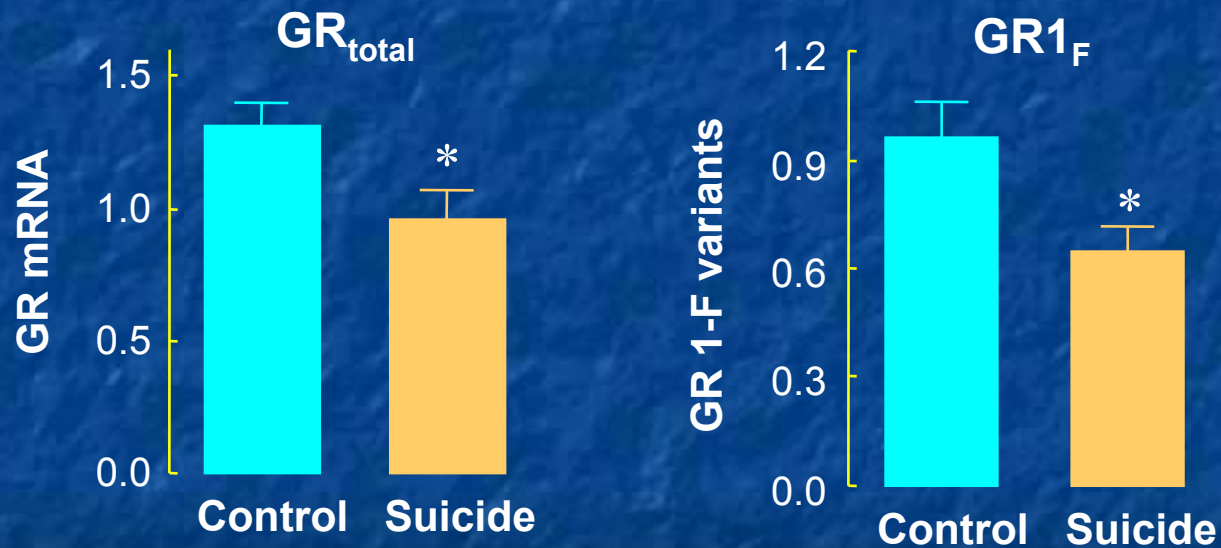


- Human brain bank (suicide victims vs controls).
- All suicide victims (and none of the controls) experienced verified abuse in childhood.

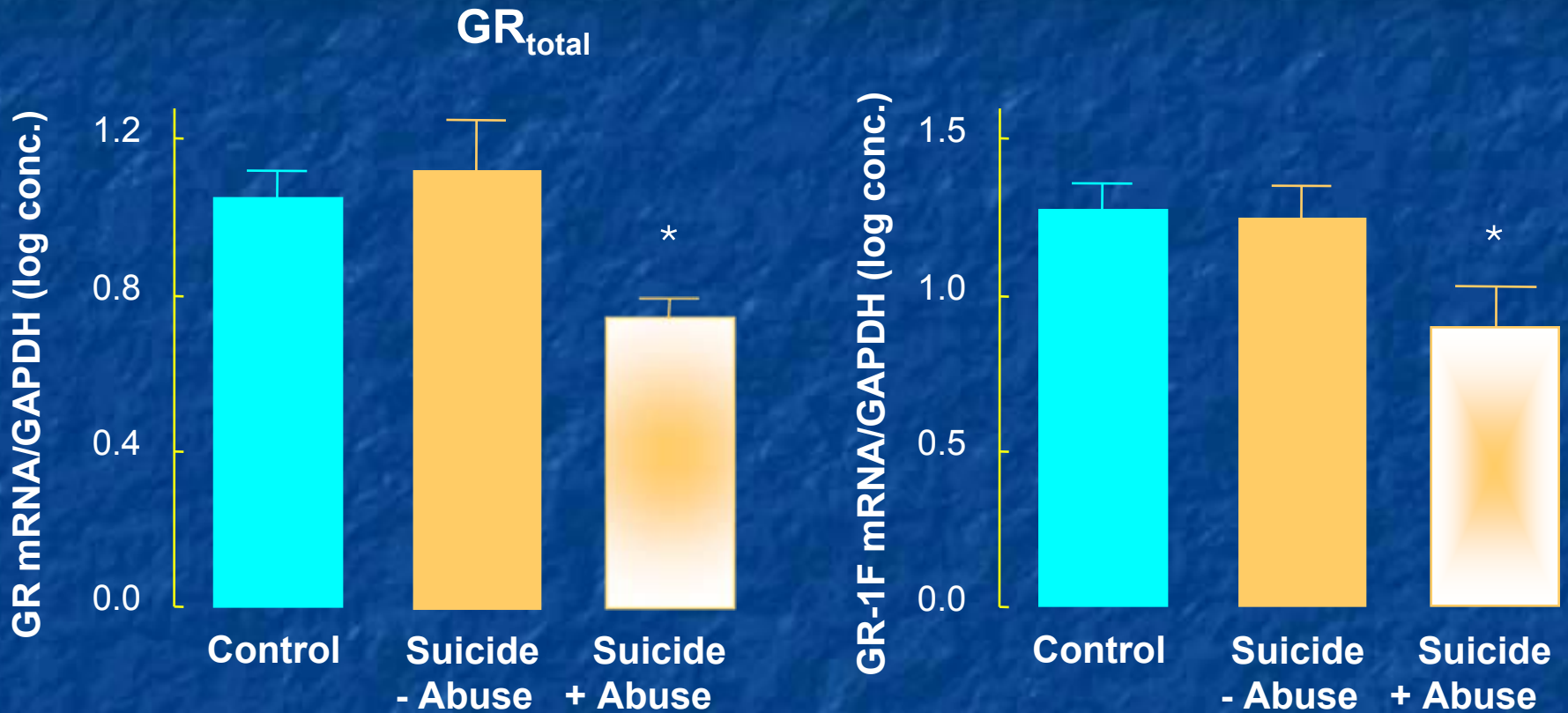
Human glucocorticoid receptor gene



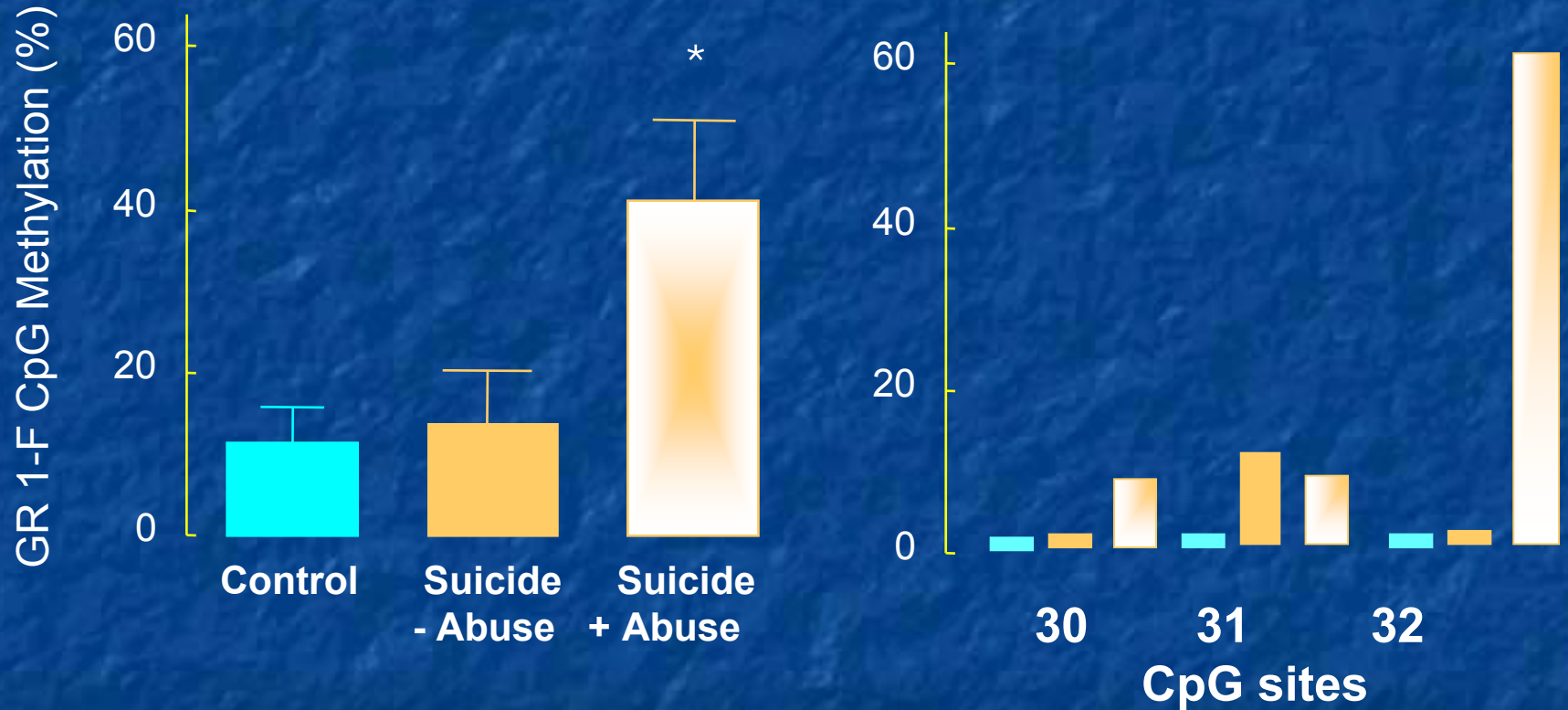
Human glucocorticoid receptor gene



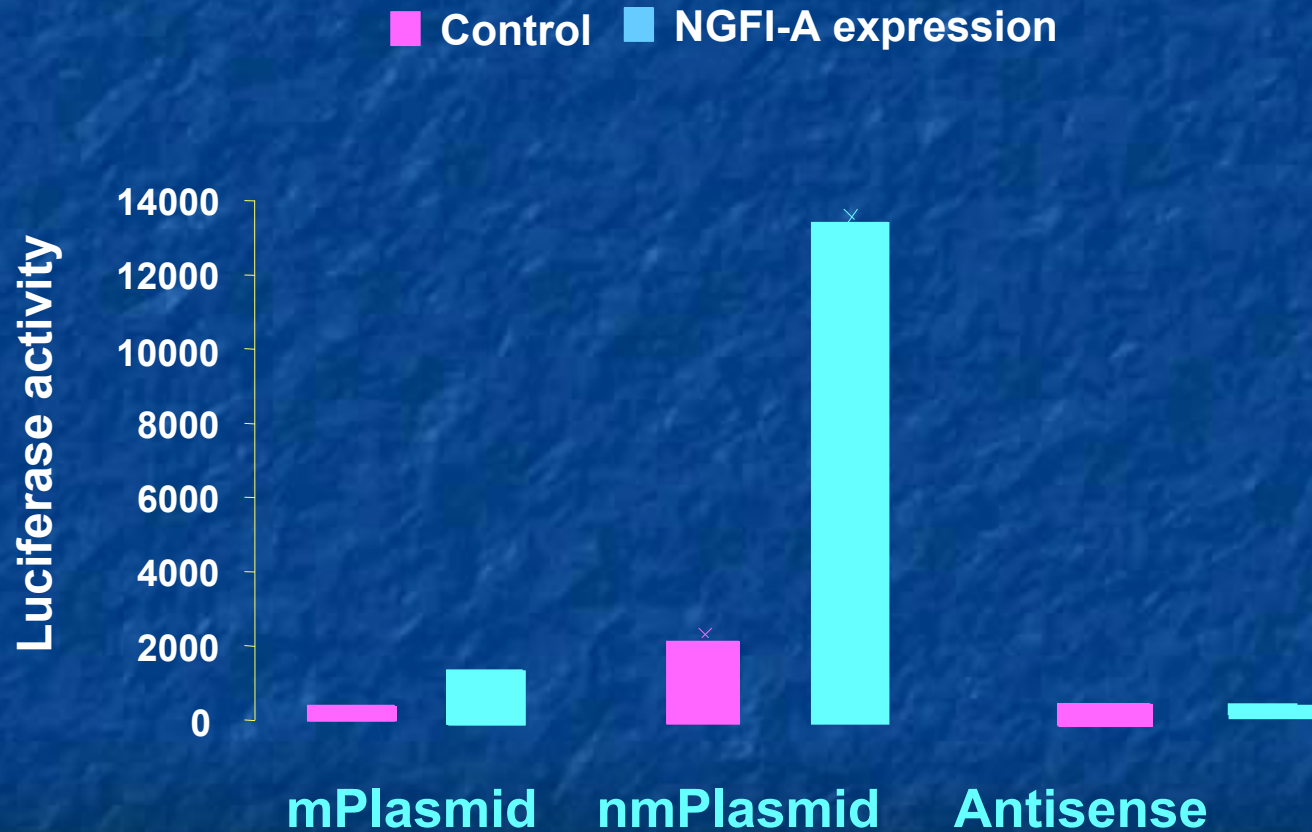
Suicide vs abuse - GR expression



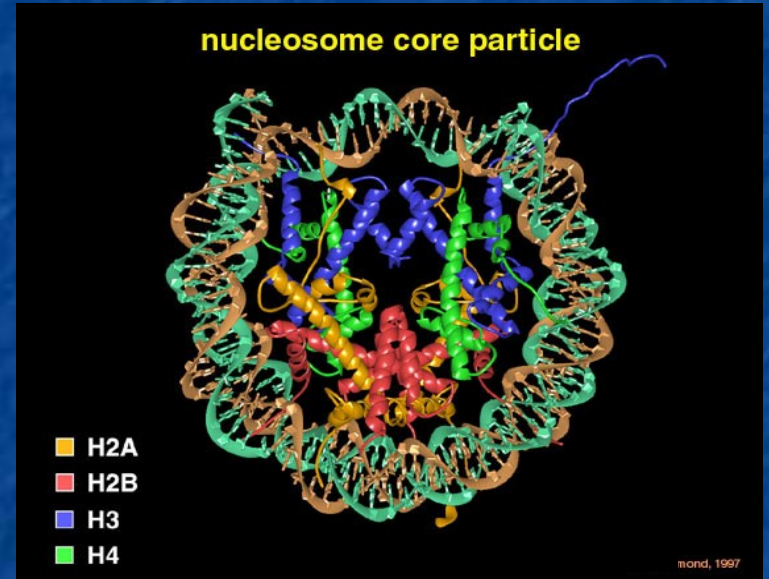
Suicide vs abuse - CpG methylation



Co-transfection studies (NGFI-A vector w/ human GR exon 1F-luciferase construct)

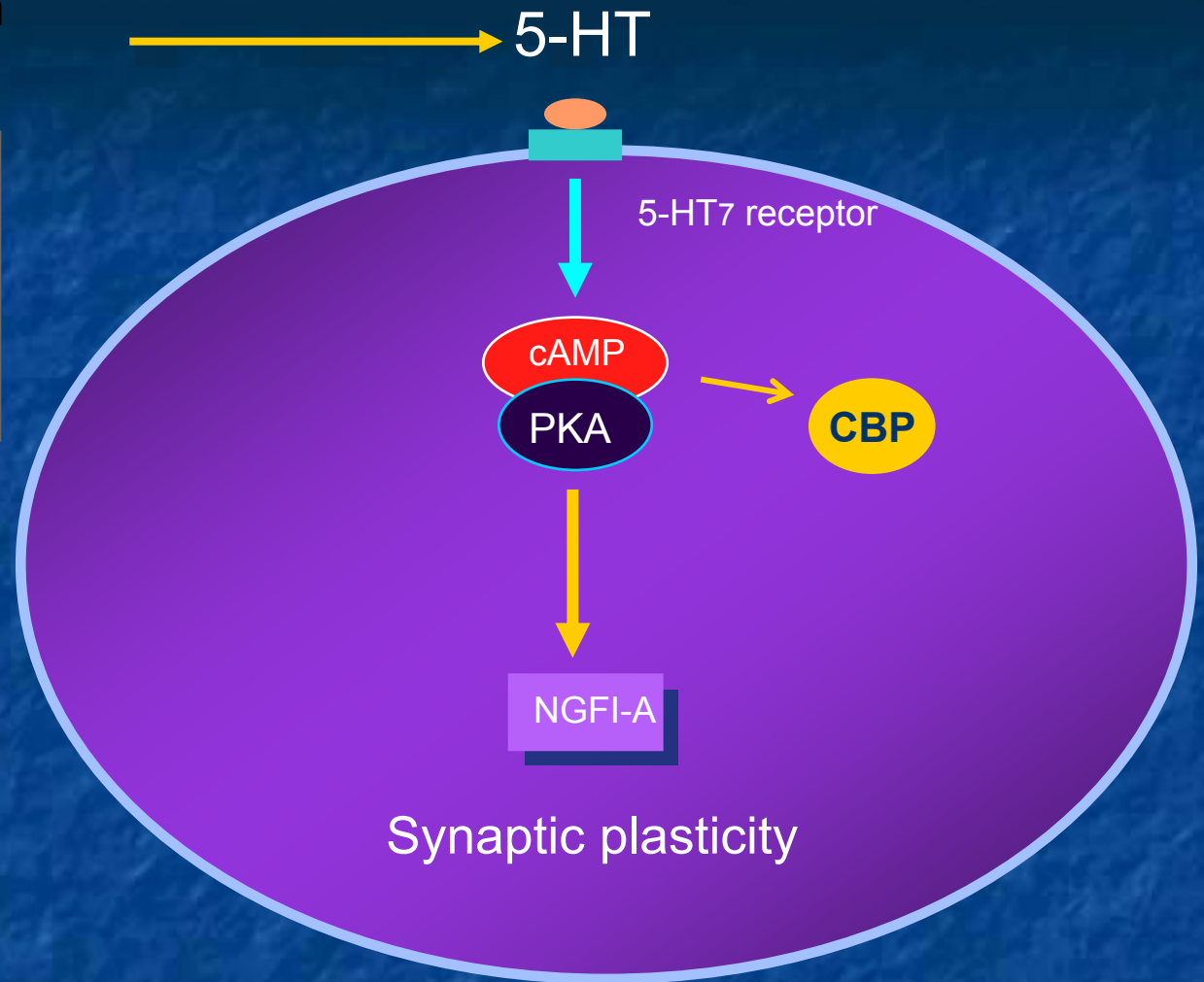


DNA methylation serves to imprint social factors, such as maternal behavior, upon the offspring's genome.



DNA methylation serves as an interface between the dynamic environment and the fixed genome

Tactile stimulation
(maternal LG)



Maternal Care



Expression of genes NMDA
rec sub-units (Hipp)



BDNF/bFGF



Synaptogenesis



Learning & Memory