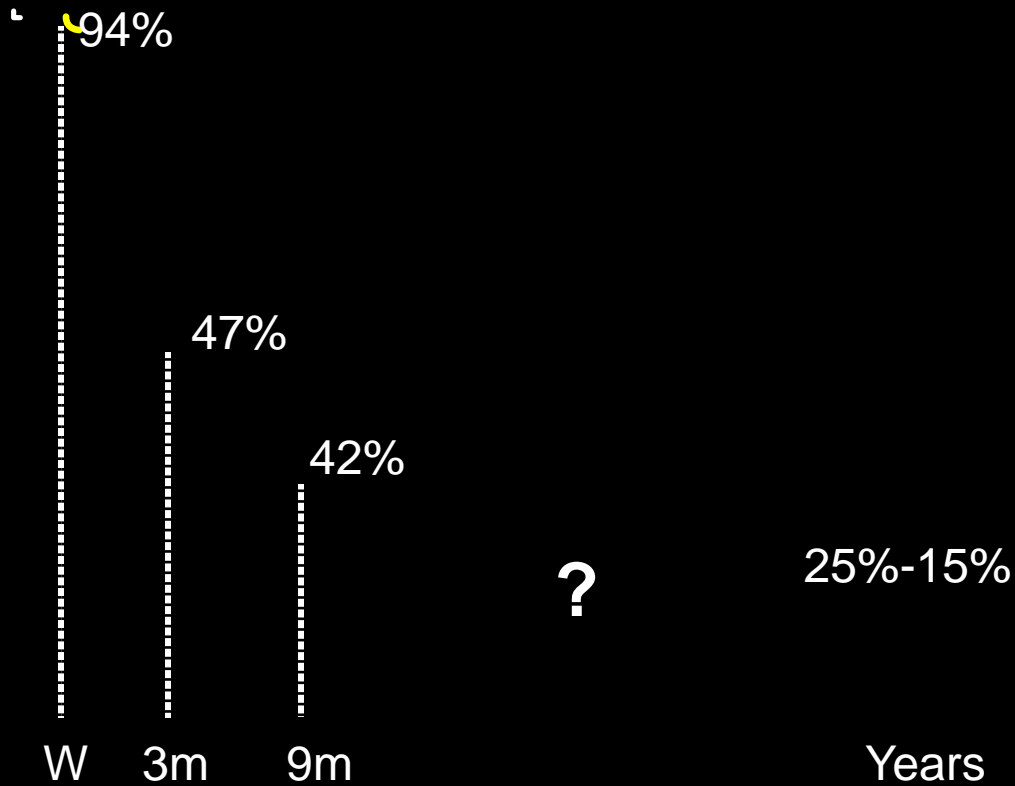


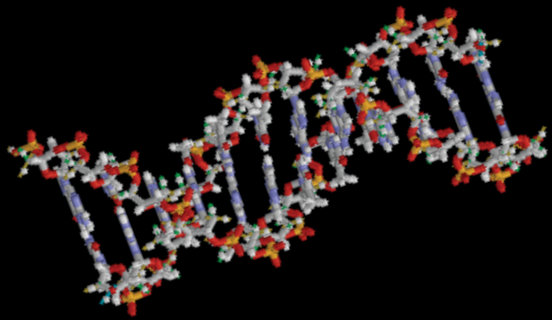
Prevalence of PTSD following Single Trauma



III. Beyond Narratives: Biological Concepts and Constructs

Plasticity

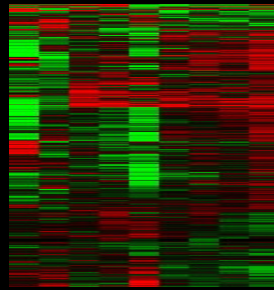
DNA



Epigenetic Programming



Gene Expression



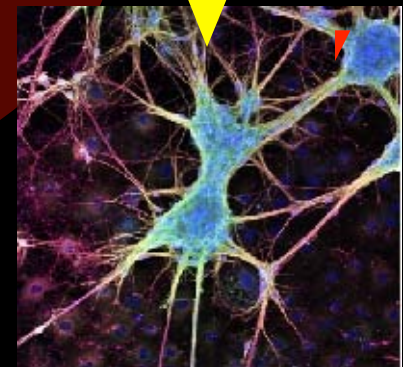
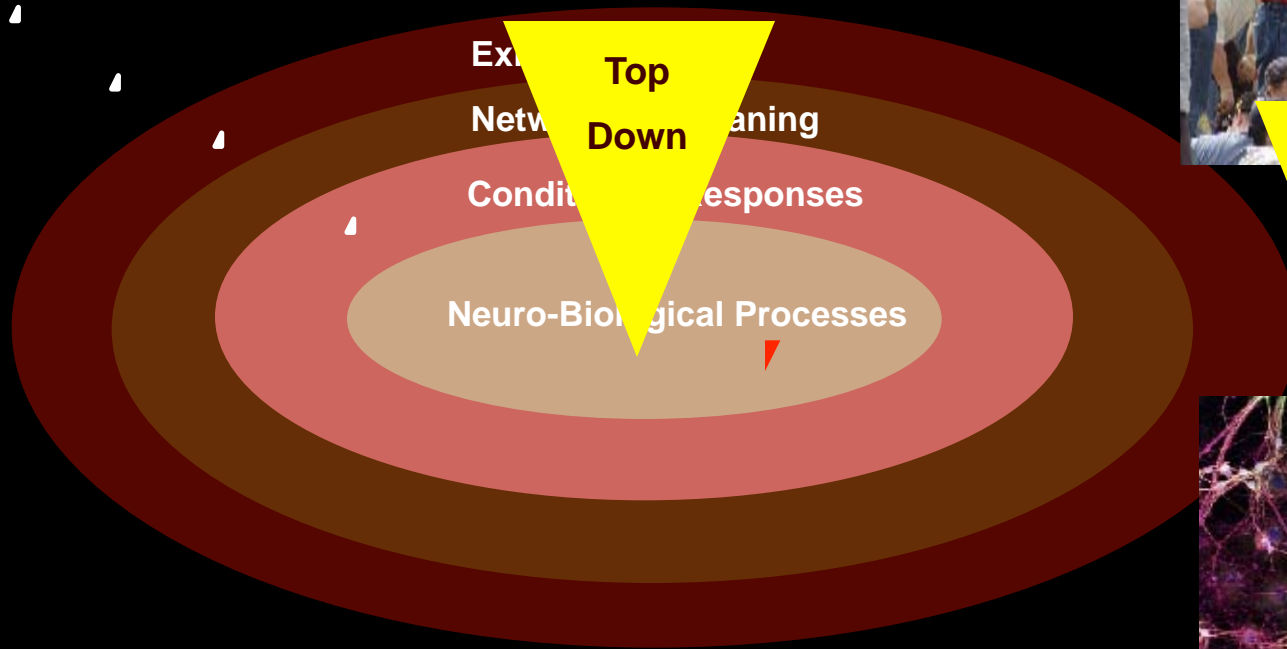
Real life = Performance



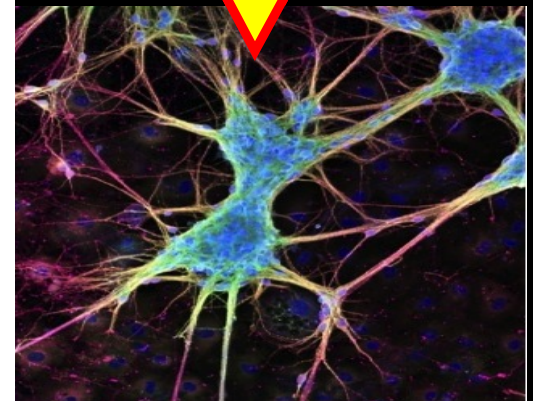
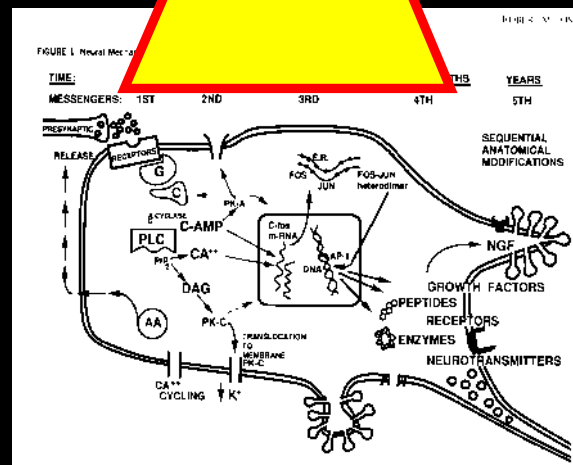
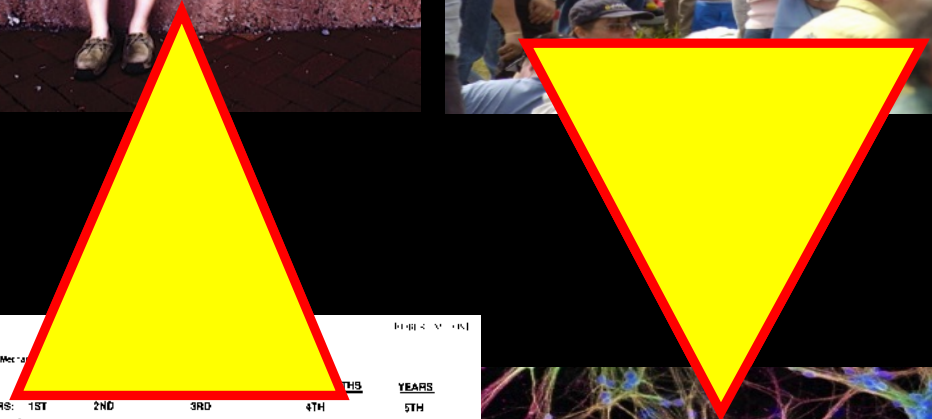
“Topographic” View

The Top-down View

Relative dominance of 'higher' processes



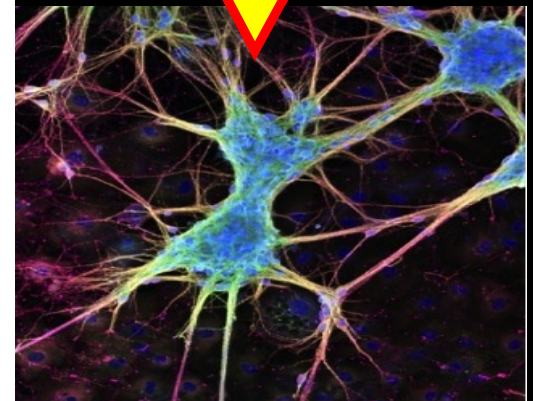
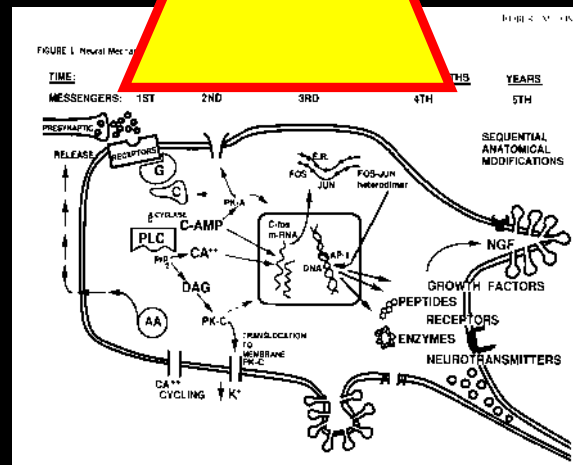
Smooth integration of top-down and bottom-up activities



Self-correcting cycle

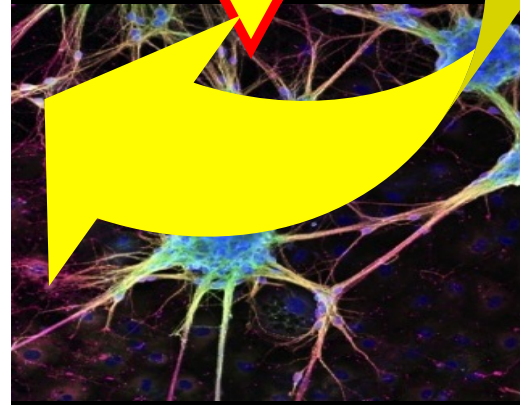
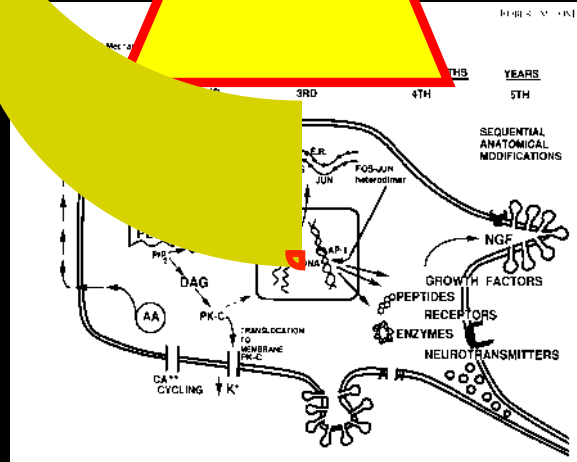


Reverberating self-amplifying cycle





PTSD – a disorder of self-reinforcing top-down and bottom-up processes



Complementary Processes

Complementary Processes

Threat Assessment

(e.g., Amygdala)

Emotion Regulation

(e.g., dmFPC, rACC, dACC)

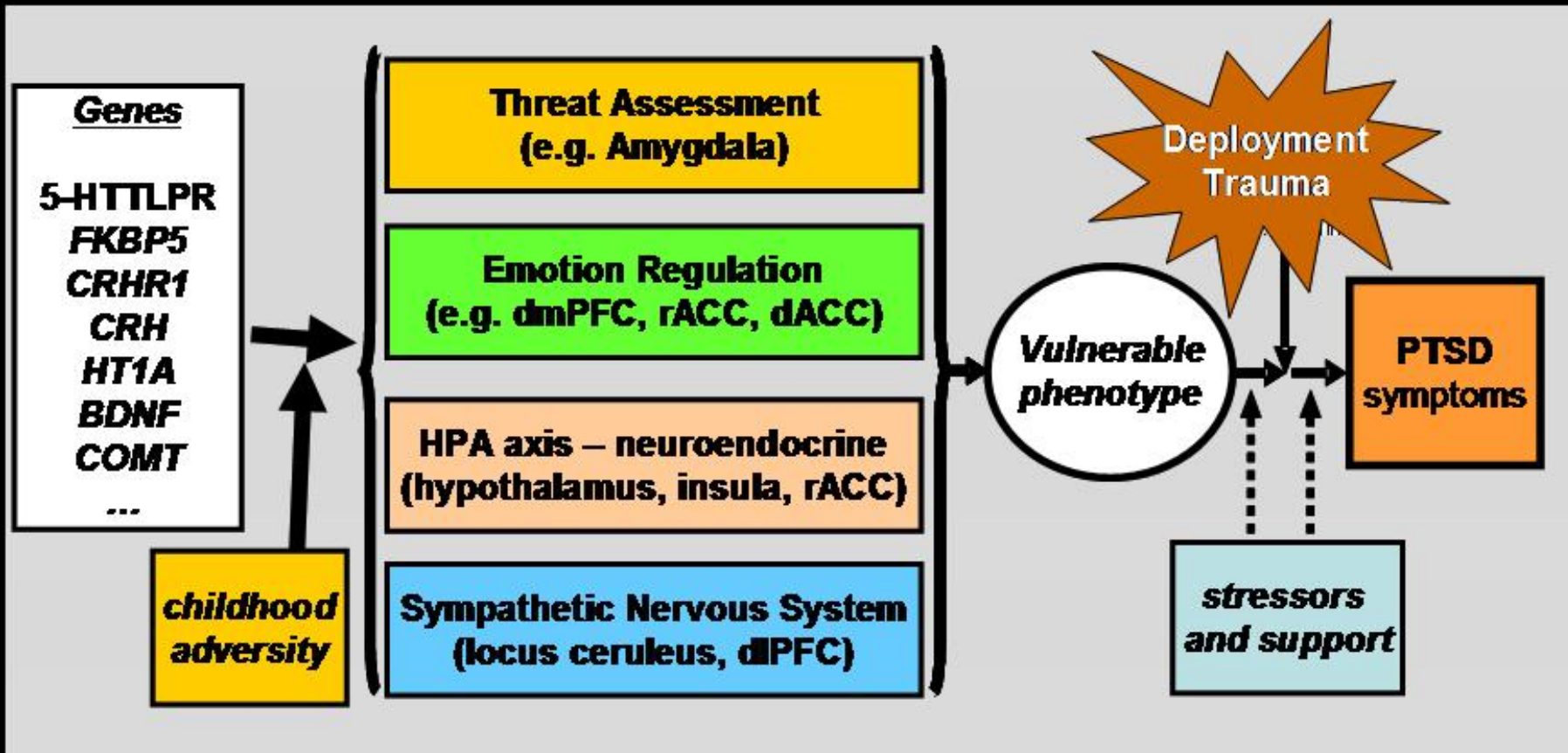
Response Modulators

HPA Axis (Hypothalamus, Insula, rACC)

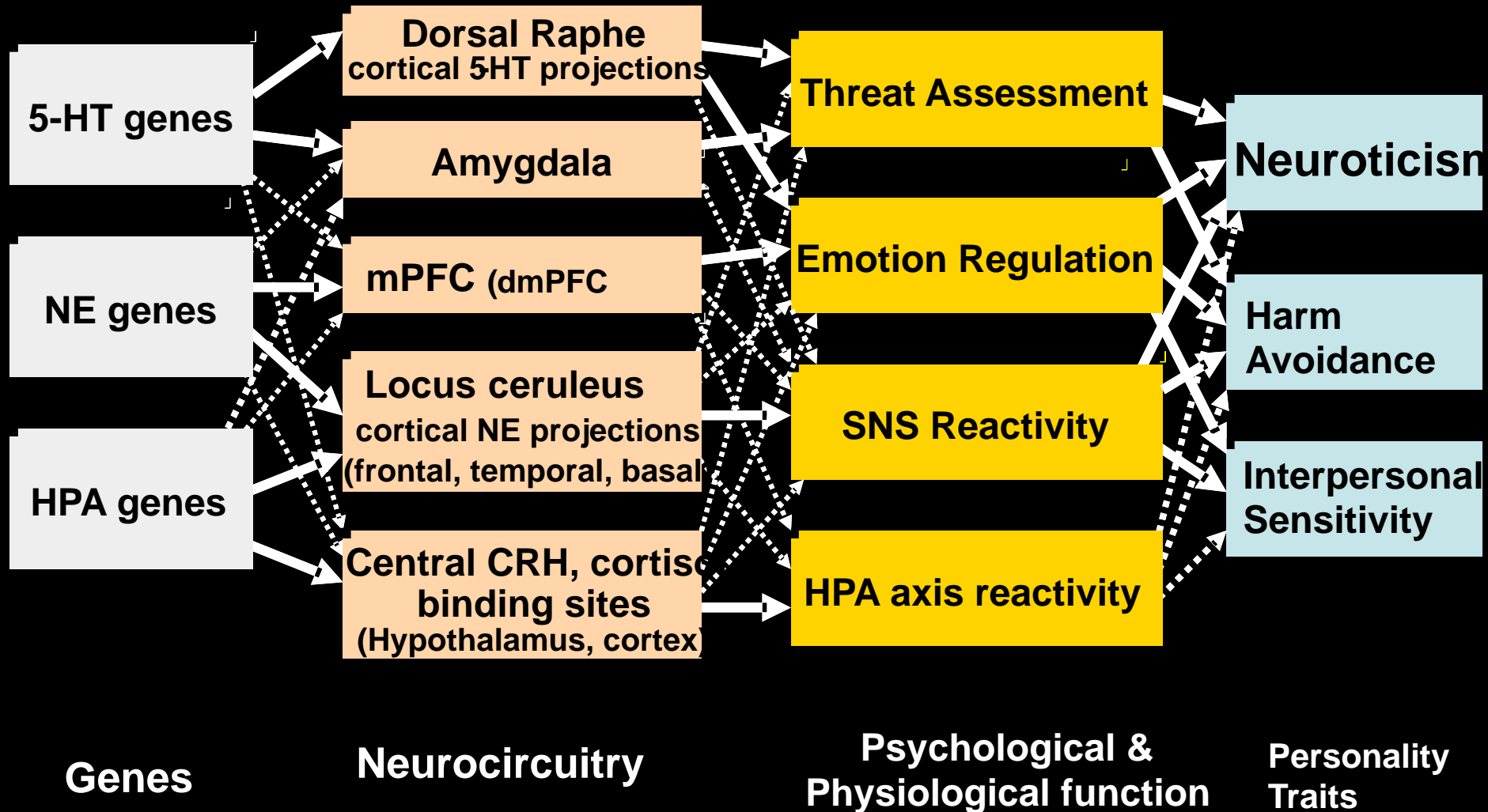
Sympathetic Nervous System (LC, dIPFC)

Other Neuromodulators (DHEA, SPY)

Extended View

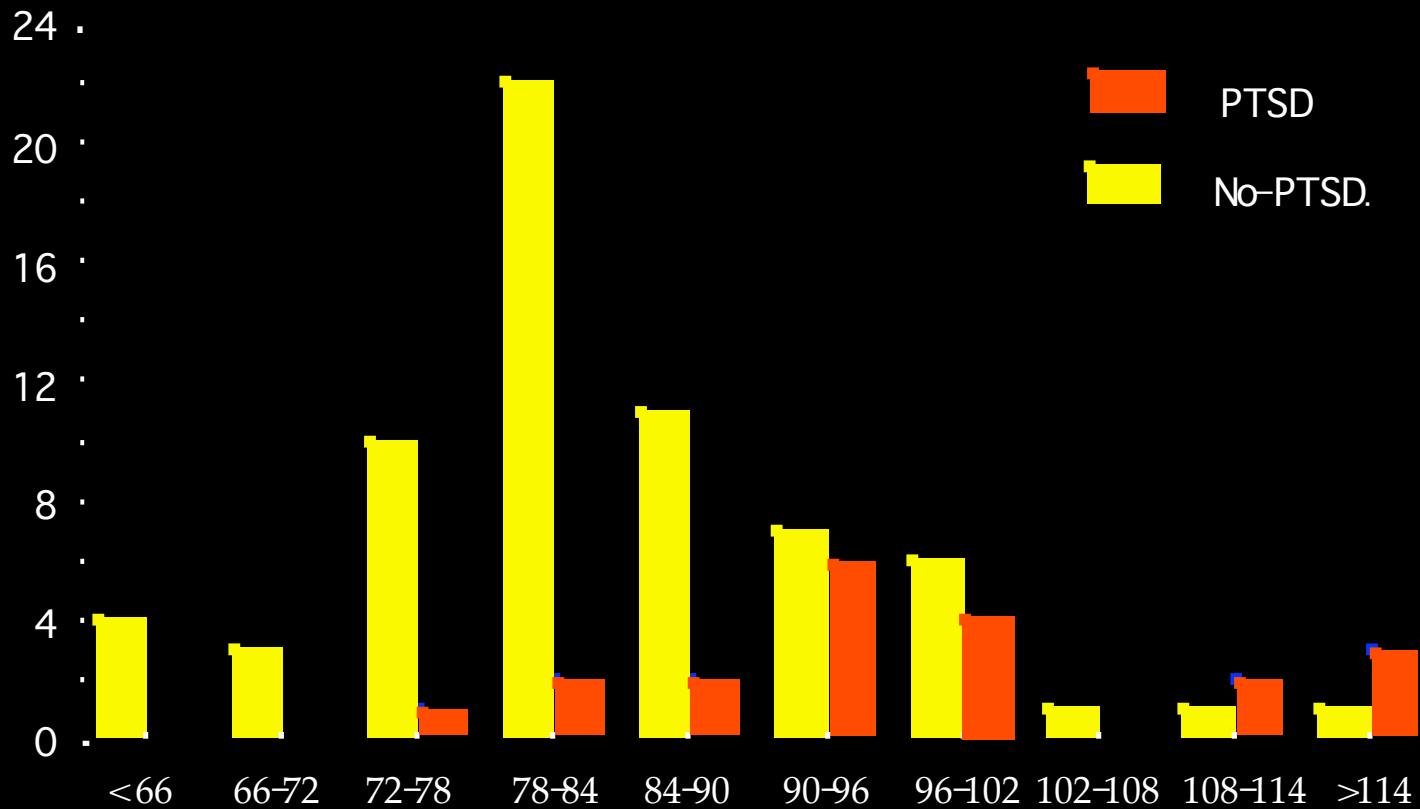


How genes may affect behavioral traits

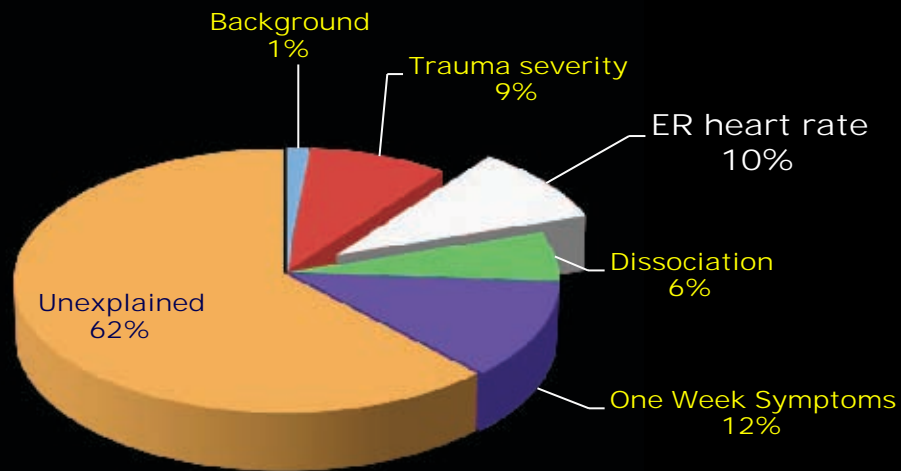


Overall Limited Power

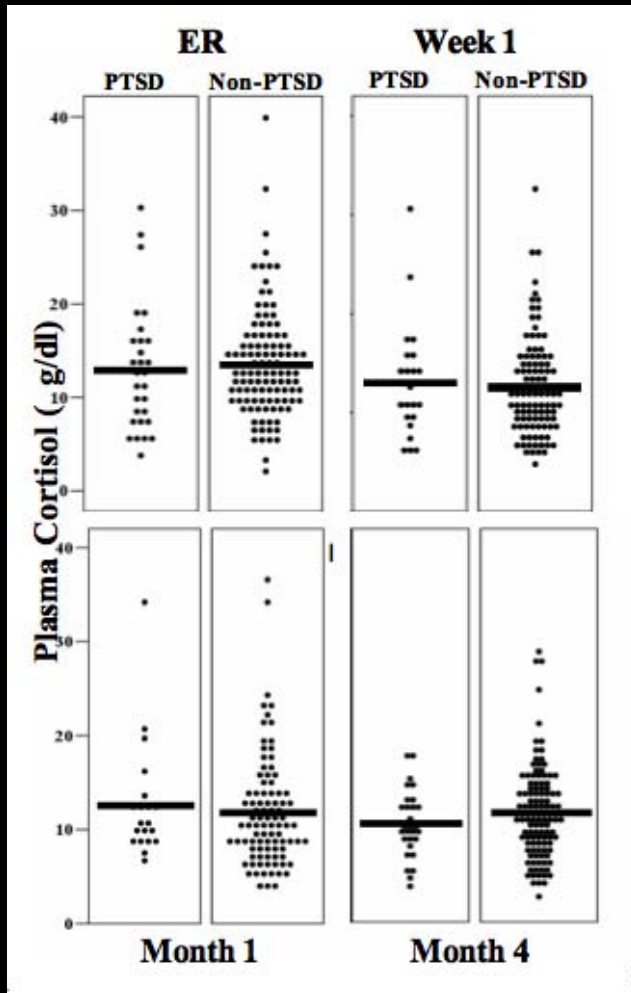
Elevated Physiological Response to the Trauma?



Explanatory Power of Biological Predictors



Prospective Study of HPA Axis in PTSD



Plasma Cortisol Levels in Trauma Survivors With (n=29) and Without (n=110) PTSD.

Also no mean difference for

ACTH

Saliva Cortisol

Urine cortisol

GR receptor density

Shalev et al., in press

IV. Defining Childhood Trauma?

Pertinent Childhood Trauma

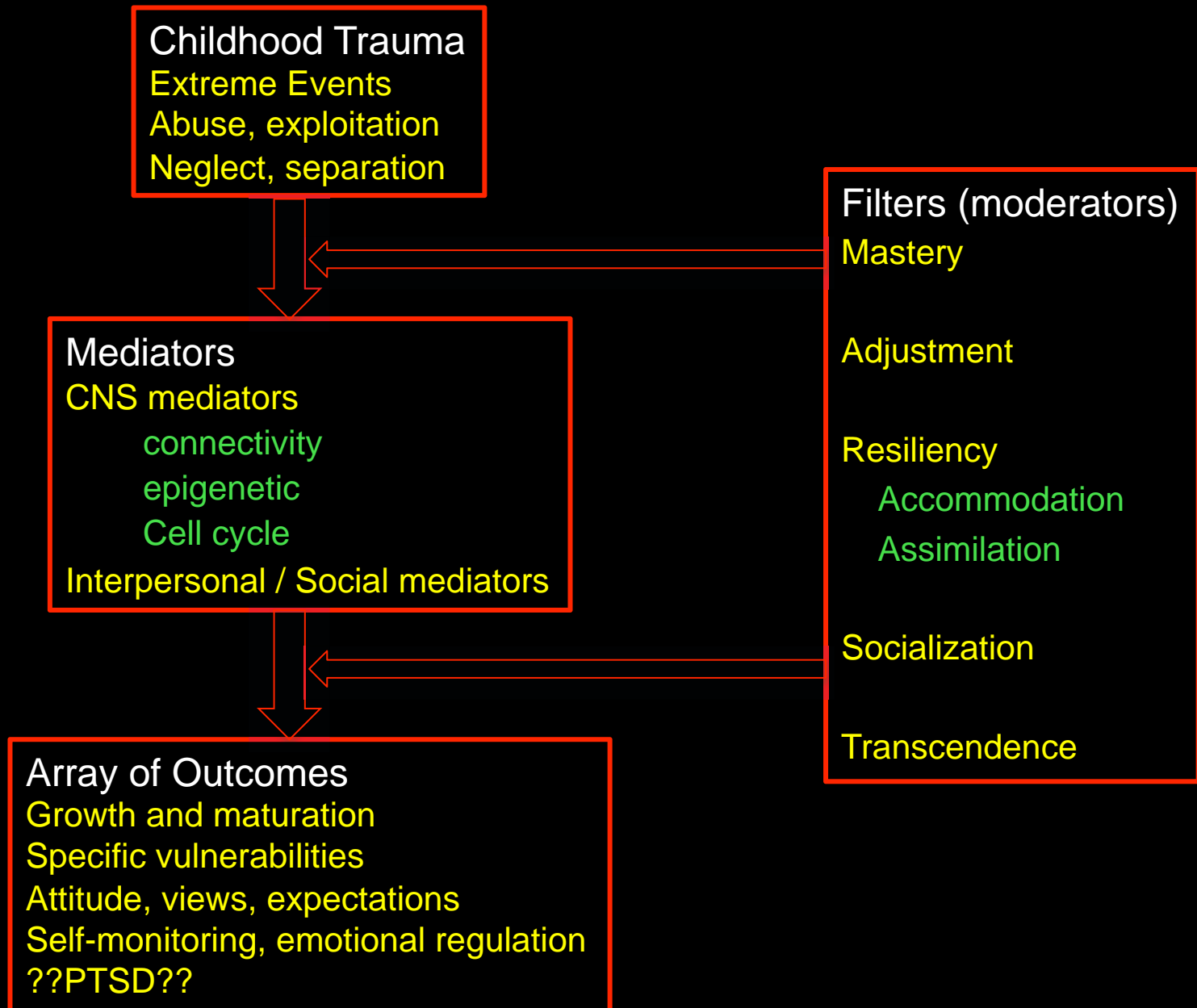
- Salient, single traumata
 - Fear related trauma
 - Atrocities, sexual content,
- Continuous adversity (“abuse”)
 - Physical
 - Psychological
- Neglect, parenting failure, societal failure.
 - Of the criminal type
 - Of the common type
- Separation, isolation,

Filters to the Effect of Childhood Trauma

- Mastery
- Adjustment
- Resilience
- “Surrogates” and replacements
 - Grouping
 - role models
 - experience of success

Relevant Child-Adult Effect

- **Direct evocation of past trauma**
- **Lack of CNS resources**
 - **To cope with the direct effect of trauma**
 - **Stress response modulators (Stress- and protective neuromodulators)**
 - **Threat assessment**
 - **To recover from initial responses**
 - **(extinction modulators: Allopregnanolol, DHEA)**
- **Lack of interpersonal / social resources**
- **General attitudes, beliefs and expectations**



V. Tools and Directions in Biological Research

- **Whole genome association studies**
- **Gene expression studies**
- **Gene-Environment studies**
- **Epigenetic studies**
- **Bio environment studies**

Whole Genome Association Studies

Idea:

Very large number of DNA 'errors' transcribed from one generation to another.

Tracking these variations in sick and healthy individuals may signal portion of DNA – and specific genes that are associated with the disorder.

Advantages:

- scanning the whole genome
- finding small effect genes

Disadvantages:

- Very large number of individuals needed
- Single genes do not tell the whole story

Gene Expression Studies

Idea:

Large number of genes are expressed with every activity
Disorder may be characterized by their differential gene expression

Advantages:

Documenting / discovering specific biological events
Understanding critical stages of disorders
Finding small effects

Disadvantages:

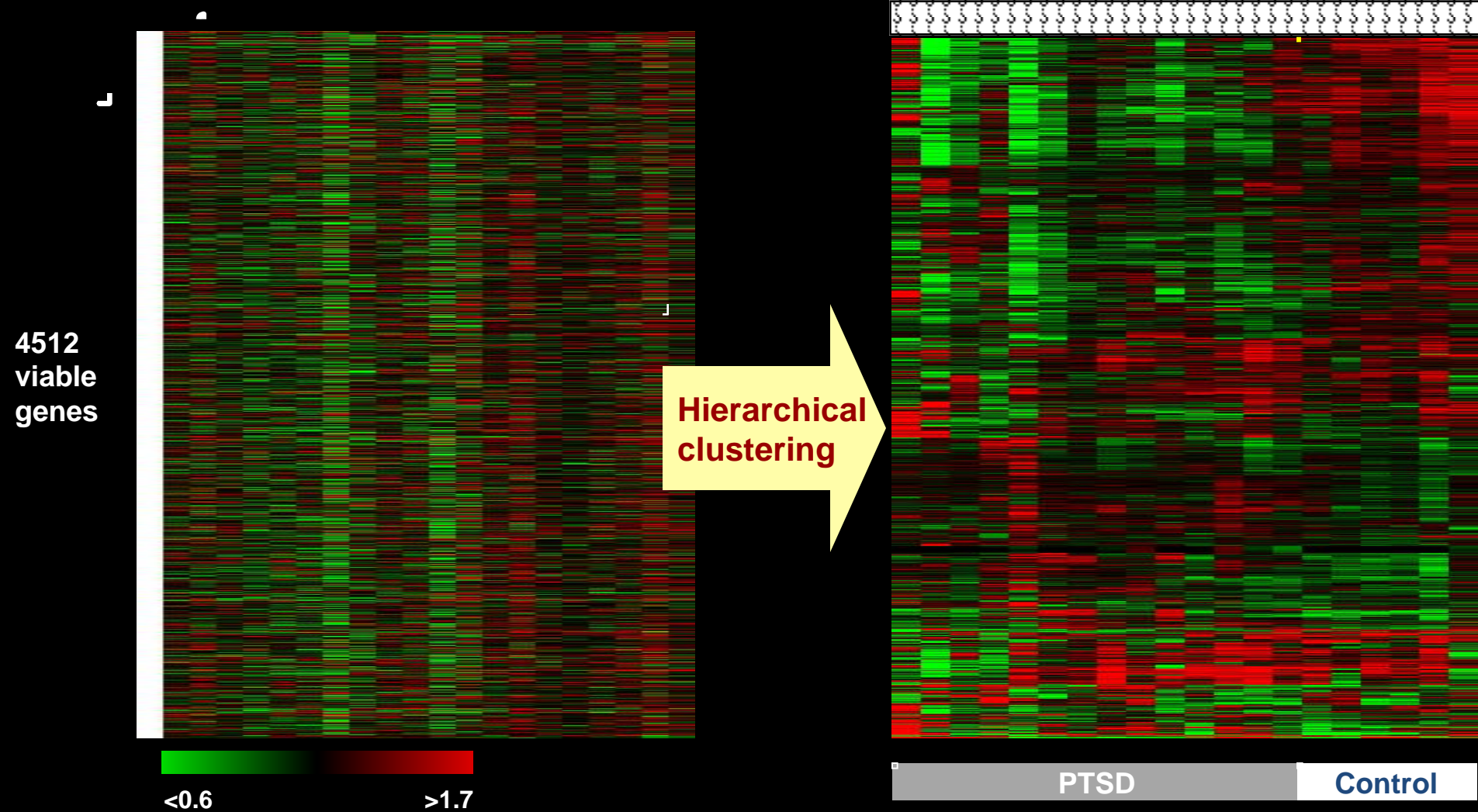
Peripheral tissue for mental disorders
Wide arrays of differentiating genes

A Gene Expression Study of PTSD



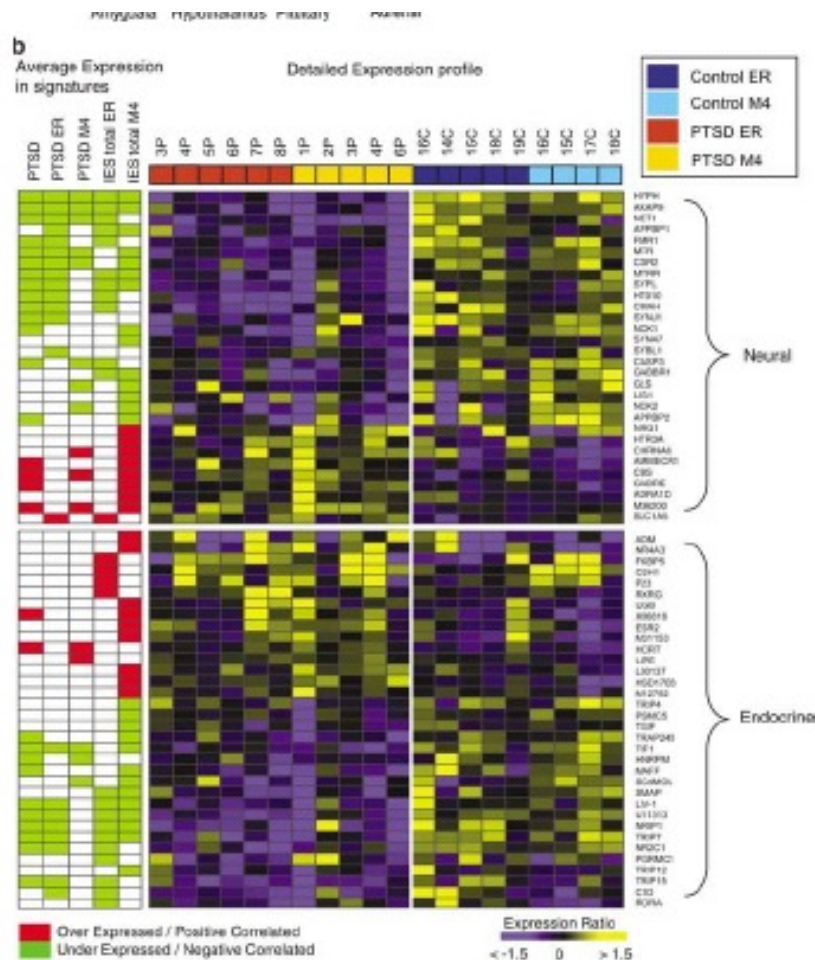
Unsupervised Clustering – All Samples

20 samples from ER and M4



Peripheral blood mononuclear cell gene expression profiles identify emergent post-traumatic stress disorder among trauma survivors

RH Segman¹, N Shefi^{2,*}, T Goltser-Dubner^{1,*}, N Friedman², N Kaminski^{3,4} and AY Shalev¹



Analysis of genes from neural and endocrine tissues that are differentially expressed between

Gene Environment Studies

Idea:

Certain genetic traits are expressed under specific (stressful) environmental conditions

Advantages:

Improve over studies of specific genes

Document the imprint of critical (childhood) periods

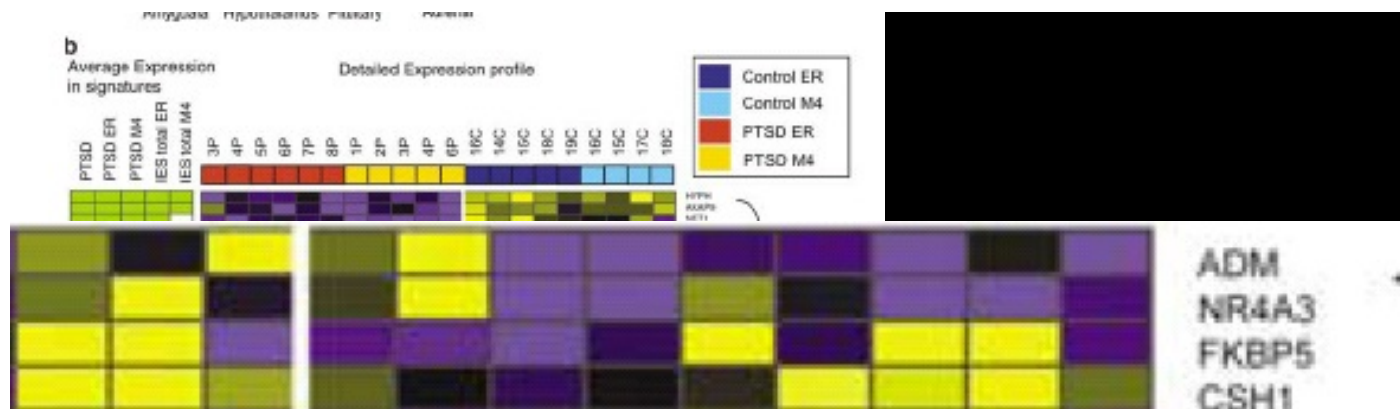
Disadvantages:

single candidate genes

Amount of variance explained

Peripheral blood mononuclear cell gene expression profiles identify emergent post-traumatic stress disorder among trauma survivors

RH Segman¹, N Shefi^{2,*}, T Goltser-Dubner^{1,*}, N Friedman², N Kaminski^{3,4} and AY Shalev¹



JAMA. 2008 Mar 19;299(11):1291-305. [Links](#)

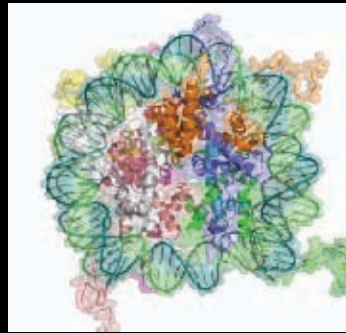
Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults.

[Binder EB](#), [Bradley RG](#), [Liu W](#), [Epstein MP](#), [Deveau TC](#), [Mercer KB](#), [Tang Y](#), [Gillespie CF](#), [Heim CM](#), [Nemeroff CB](#), [Schwartz AC](#), [Cubells JF](#), [Ressler KJ](#).



Analysis of genes from neural and endocrine tissues that are differentially expressed between

Epigenetic Programming



Epigenetic Programming

Idea:

All genetic traits are subject to regulation at the DNA level

DNA programming determines long-term, and often irreversible dispositions. It is the basis for life-long adaptation

DNA programming is guided by specific stimuli – including stress

Advantages:

A “royal way” to studying emerging long-term traits

Significant newborn / infant research shows significant, life-long effects of stress, during critical periods

Challenges:

Effect of trauma out of ‘critical periods’

Tissue specificity

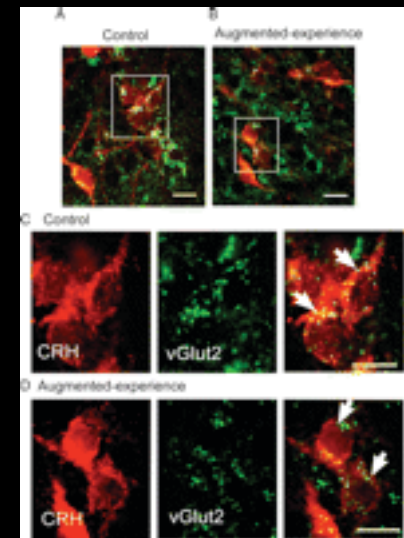
Amount of variance – need combinatorial statistics

Epigenetic Studies: Gene Expression Imprinting?

Environmental programming of stress responses through DNA methylation: **life at the interface between a dynamic environment and a fixed genome.**

Dialogues Clin Neurosci. 2005;7(2):103-23.

Meaney MJ, Szyf M.



Early-Life Experience Reduces
Reprograms the Expression of
Corticotropin-Releasing Hormone

Epigenetic Studies: Protective Factors?

nature neuroscience

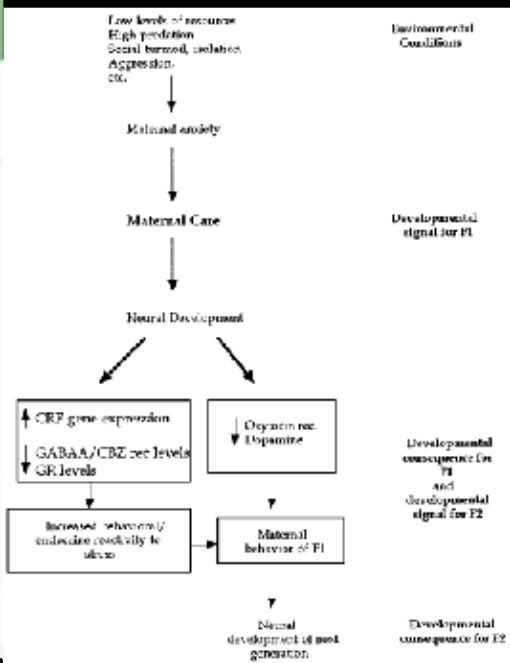
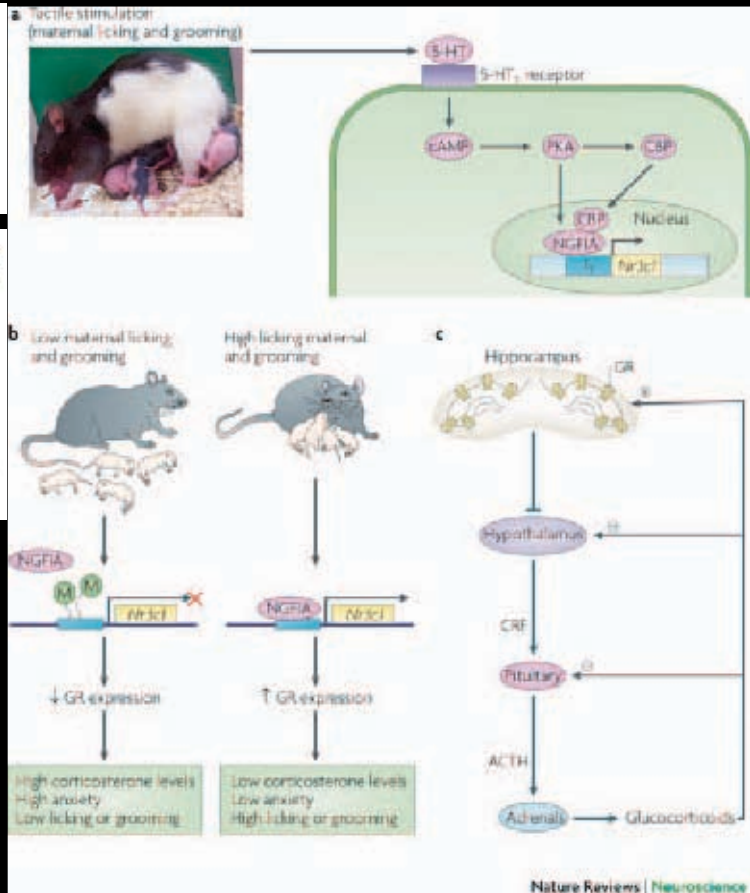
Epigenetic programming by maternal behavior

Jon C.G. Weaver^{1,2}, Nadia Cervoni³, Frances A. Champagne^{1,2}, Ana C.D. Alaisio³, Shakti Sharma¹, Jonathan R. Seckl⁴, Sergey Dymov⁵, Moshe Szyf^{1,4} & Michael J. Meaney^{1,2}

Nat. Rev. Neurosci. 2001, 4(11):81–89
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MATERNAL CARE, GENE EXPRESSION, AND THE TRANSMISSION OF INDIVIDUAL DIFFERENCES IN STRESS REACTIVITY ACROSS GENERATIONS

Michael J. Meaney



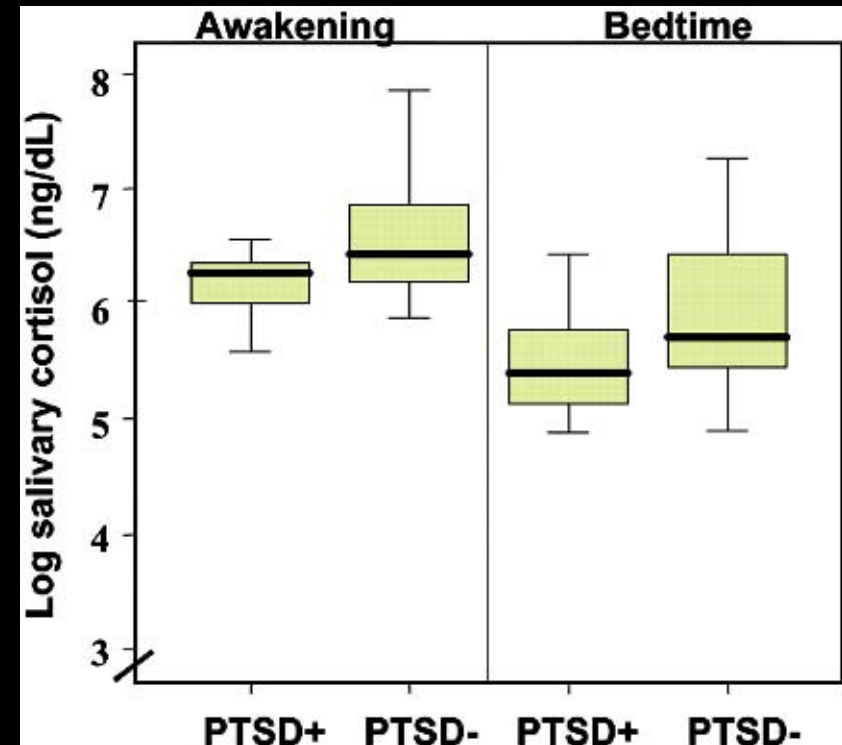
Epigenetic Studies: Trans-generational Transmission of PTSD

THE JOURNAL OF
CLINICAL
ENDOCRINOLOGY
& METABOLISM

Transgenerational Effects of Posttraumatic Stress Disorder in Babies of Mothers Exposed to the World Trade Center Attacks during Pregnancy

Rachel Yehuda, Stephanie Mulherin Engel, Sarah R. Brand, Jonathan Seckl, Sue M. Marcus and Gertrud S. Berkowitz

expand
article



Infant cortisol levels at awakening and bedtime, divided on the basis of presence or absence of maternal PTSD.

Bio-Environment Studies

Idea:

Evaluate the whole effect of biological environment on adult behavior and psychopathology

Advantages:

Allows post-hoc, archeological exploration

Can treat bio predictors of specific behavior

Disadvantages:

Choice of prior and predicted variables

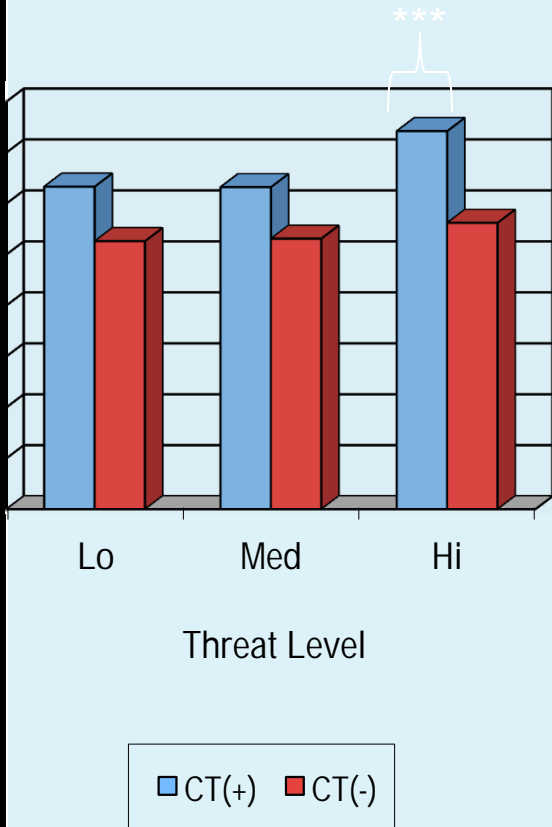
Amount of variance explained

?e ??Pd?E r??c yf?c EE??s? | ? E- ?
 ?c tidyE fE ny?? ? ??dx E- d?d?PE ?? ? ? k
 ?EP?- T? ?? ??P? Pfy n??Ei - ?d

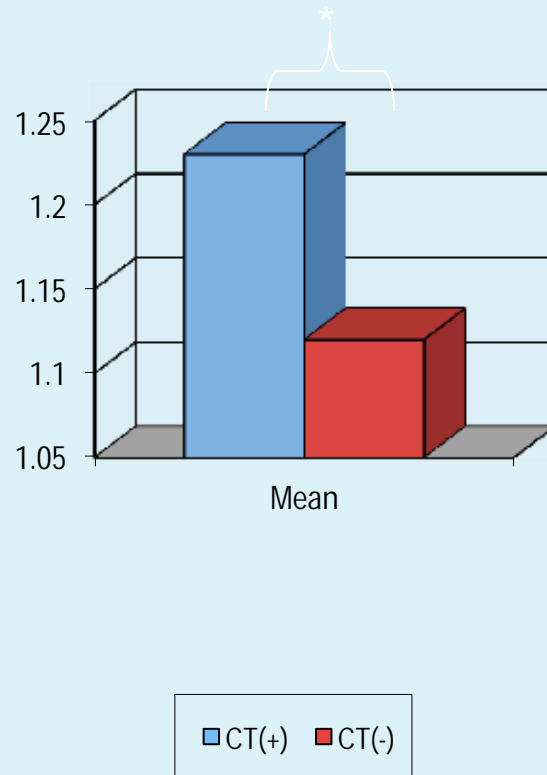
? - ?| ?y??E f?|??cEI ? ?? ?tif? V??csydT? ?? D?G|??i n? - ?? ?? ?dP??
 ?f? ??? ?- - k? ? ?W? ?c? f?d?? ? ? | ? V?
 ?

U?c?? - yR?sdypTi?E r?? y?c yn? ?
 V?c?? - yR?sdypTi?E r?? yEs- y? ?? ? ?s? ?yd?E?
 G? - yR?sdypTi?? E dx y? ? ? ?i snk?xx?- ?Esr?
 ?

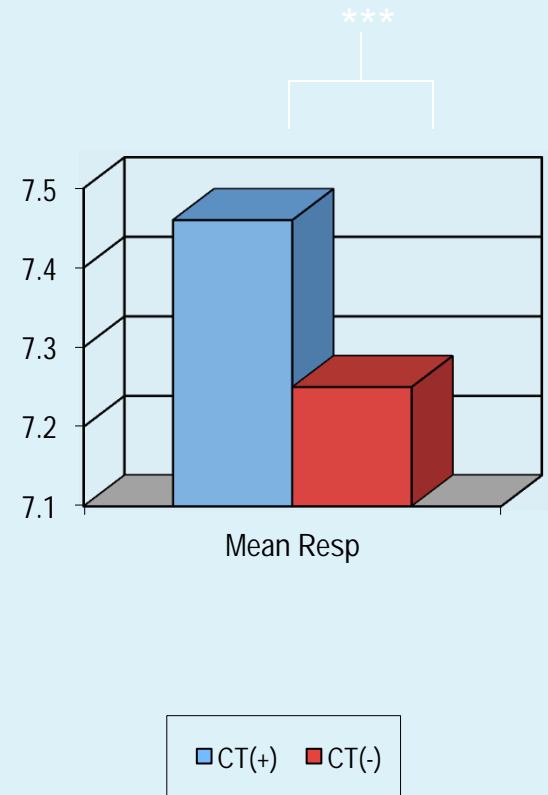
Eyeblink EMG



Skin Conductance1



Heart Rate



*p < .05, ***p < .001

¹Results are adjusted for baseline skin conductance differences.

VI. Summary and Conclusions

Back to Narratives and Holistic Constructs:

“Étayage”

“Complexité”

' P h

- dtic fidg

— sfiTE- VdP P- Psdxi fdyE- dVi ffdP
fidxi fdyE- dff PE-E- dsRT E- dxi s?l y?s?d?
dfi - Pff EsdE- TE- dRyP d?pi y?i s?
rEi s- ydd- P - dEi s?sn? ypi ?l - E? P - ?
ysTE- I P R - - P x d di y?
y Fx- - P d?

- F Eny?

— 'd- d?l f?d?y P?s? TE- d' d dP? ?
f' i f?x?sl ?D? P?'- r? P' x s- ?s?
Esn? yd?s?dE- ?i y?d - ??x Ei REys?FdEi ?s?
d?i fi - x sE?fi ??pi 'yf? ?R y P x d ?FdEi ?s? ?
Fx P h?



Array of Risk Factors, Outcomes Modulators and Moderators

Risk factors

Biological endowment

Neglect, abuse, lower SES, inadequate parenting, lower education...

Outcomes

Symptoms, well being, stable work, stable family, better life trajectory ...

Modulators

Recovery environment, social support, social discourse and s

Moderators

Continuous threat, escape, control, social role...

Complex Causation

Multi causality

(several contributing factors needed)

Equifinality

(many ways to an outcome)

Multifinality

(similar factors can lead to diverse outcomes).

Practical implications (how to interpret knowledge)

Context – driven effect

Unpredictability of single ‘markers’

Future research directions (how to create new knowledge)?

Continue to uncover pieces of the puzzle

Develop adequate computational models