The University of Texas at Austin
Dell Medical School

Paradise Lost: The Neurobiology of Child Abuse and Neglect

NASEM Consensus Study on Chronic Conditions in Women
August 9, 2023

Presented by:

Charles B. Nemeroff, M.D., Ph.D.

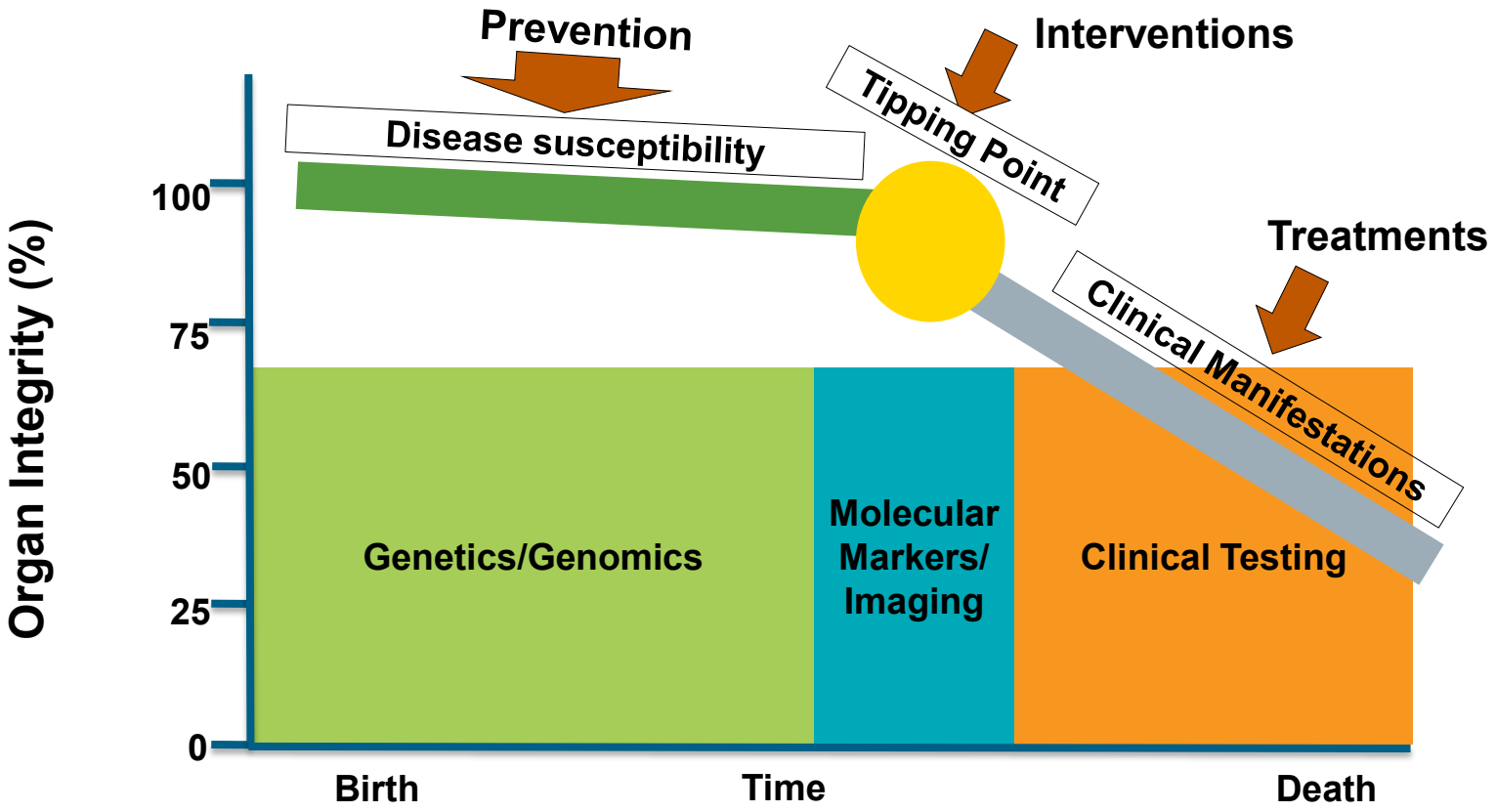
Matthew P. Nemeroff Professor and Chair
Department of Psychiatry and Behavioral Sciences
Mulva Clinic for the Neurosciences
Director, Institute of Early Life Adversity Research
Co-Director, Center for Psychedelic Research and Therapy
Dell Medical School | The University of Texas at Austin

CHARLES B. NEMEROFF, M.D., PH.D.

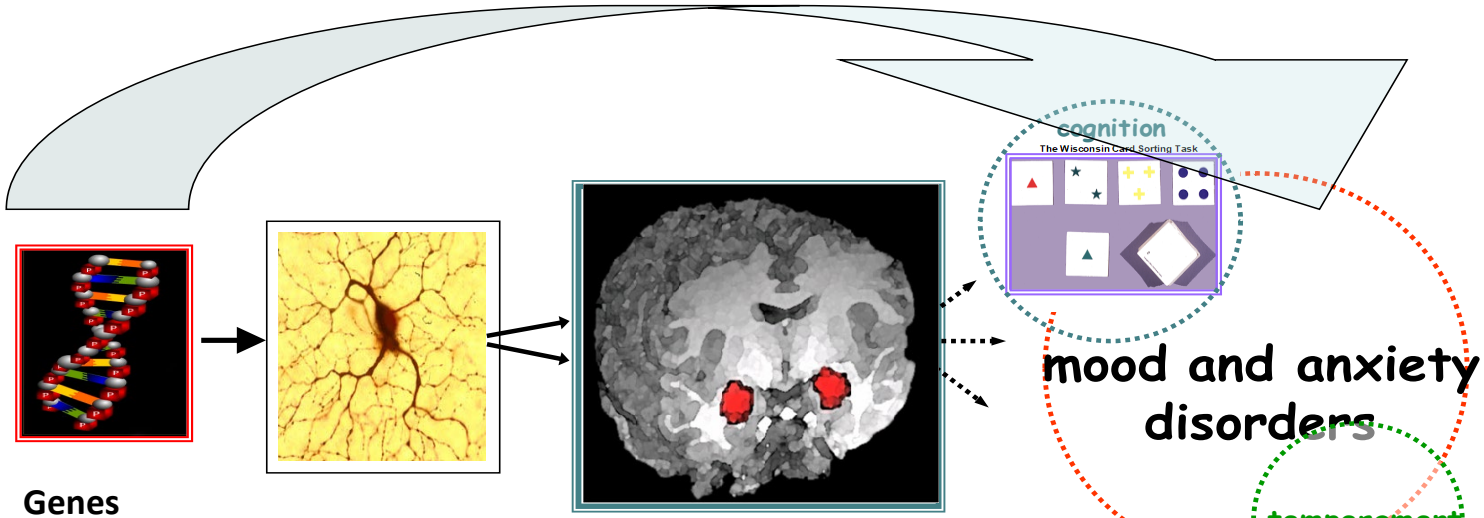
DISCLOSURES

Research/Grants:
National Institutes of Health (NIH), Texas Childhood Trauma Research Network
Consulting:
ANeuroTech (division of Anima BV), Signant Health., Intra-Cellular Therapies, Inc., Sage, Silo Pharma, Engrail Therapeutics, GoodCap Pharmaceuticals, Inc., Senseye, Clexio, EmbarkNeuro, Relmada Therapeutics, BioXCel Therapeutics, Janssen Research & Development, LLC, EcoR1 Capital, LLC, Galen Mental Health, LLC, LUCY Scientific Discovery, Precisement Health
Stockholder:
Seattle Genetics, Corcept Therapeutics Pharmaceuticals Company, EMA Wellness, PreciseMent Health, Relmada Therapeutics, Xhale, BI Gen Holdings, Inc.
Scientific Advisory Boards:
ANeuroTech (division of Anima BV), Brain and Behavior Research Foundation (BBRF), Skyland Trail, Signant Health, Laureate Institute for Brain Research (LIBR), Inc., Heading Health, Pasithea Therapeutic Corp., Sage Therapeutics, Inc., Senseye, Inc., Galen Mental Health, LLC
Board of Directors:
Gratitude America, ADAA, Lucy Scientific Discovery, Inc.
Patents:
Method and devices for transdermal delivery of lithium (US 6,375,990B1)
Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2)
Speakers Bureau:
None

21st Century Medicine



Depression and Anxiety are Ultimately about How the Brain Responds to the Environment



Genes
sequence variants and variable gene processing

Cells
molecular pathways

Systems
activity in emotion processing circuitry

Behavior
clinical phenotype

TABLE 1.

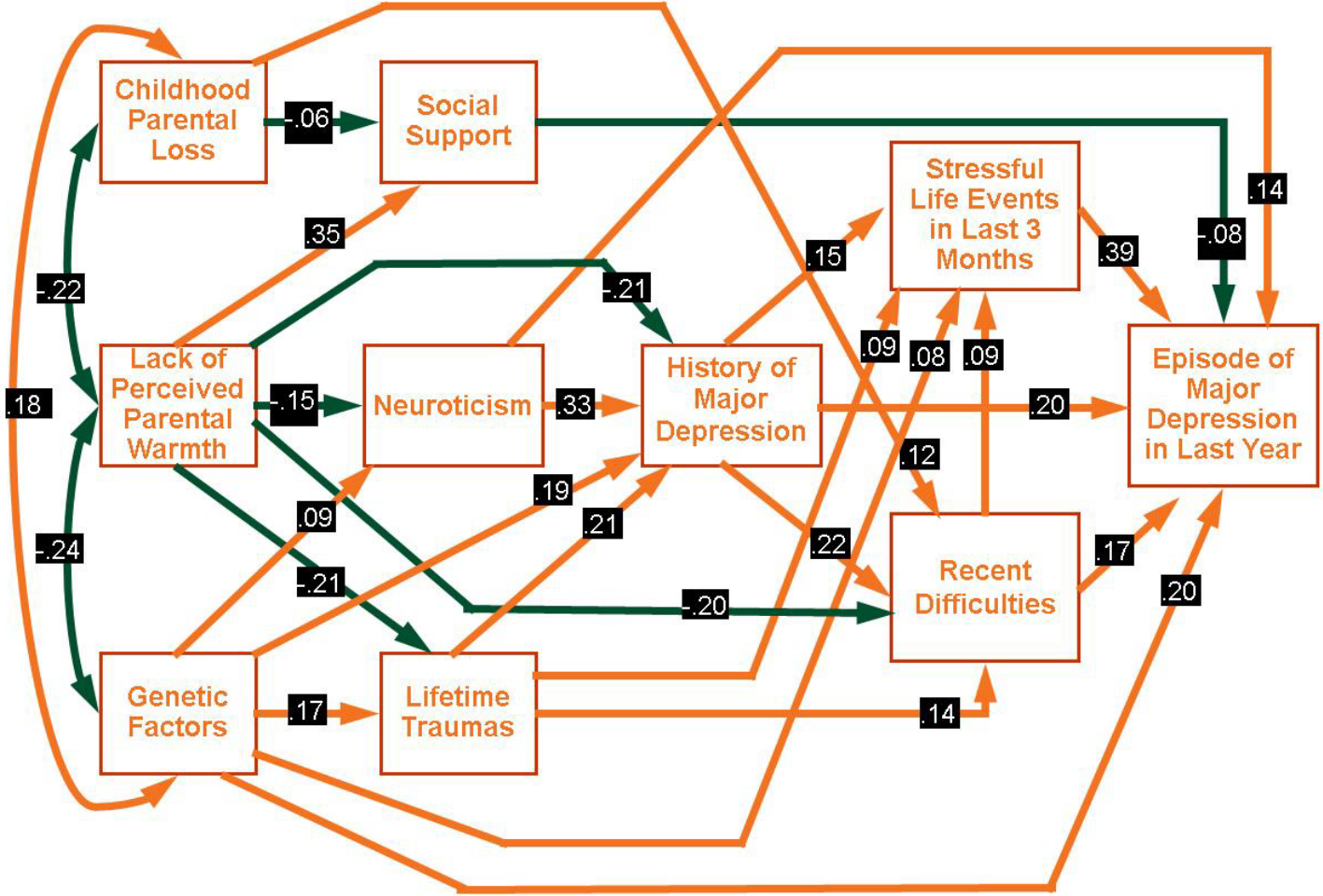
Prevalence of Adverse Childhood Experiences in Three Studies

	ACE Study	CDC Behavioral Risk Factor Surveillance System, 5-State ACE Study[4]	CDC Behavioral Risk Factor Surveillance System, 10-State* ACE Study[3]
Year(s)	1995-1997	2009	2010
Sample size	17,337	26,229	53,998
Study site(s)	San Diego, CA	AR, LA, NM, TN, WA	DC, HI, ME, NE, NV, OH, PA, UT, VT, WA, WI
Physical abuse	28.3%	14.8%	16.0%
Sexual abuse	20.7%	12.2%	10.9%
Emotional abuse	10.6%	25.9%	35.1%
Parents separated/divorced	23.3%	26.6%	28.1%
HM with an alcohol or drug problem	26.9%	29.1%	21.7% (alcohol) 9.4% (drug)
HM with a mental illness	19.4%	19.4%	16.4%
HM incarceration	4.7%	7.2%	5.9%
HM intimate partner violence	12.7% (mother only)	16.3%	15.0%
Physical neglect†	9.9%	–	–
Emotional neglect†	14.8%	–	–

**10 States and the District of Columbia.*

†Questions included only in ACE Study Wave 2 (n = 8,667).

ACE Study = Adverse Childhood Experiences Study; CDC = U.S. Centers for Disease Control and Prevention; HM = household member.


Childhood Parental Loss
Social Support
Lack of Perceived Parental Warmth
Neuroticism
History of Major Depression
Stressful Life Events in Last 3 Months
Episode of Major Depression in Last Year
Recent Difficulties
Genetic Factors
Lifetime Traumas
-.06
.35
-.22
-.21
.15
.39
.14
-.08
.18
-.15
.33
.09
.08
.09
.20
.12
.19
.09
.21
-.24
.22
.17
-.21
-.20
.20
.17
.14

Trajectories to Health and Disease

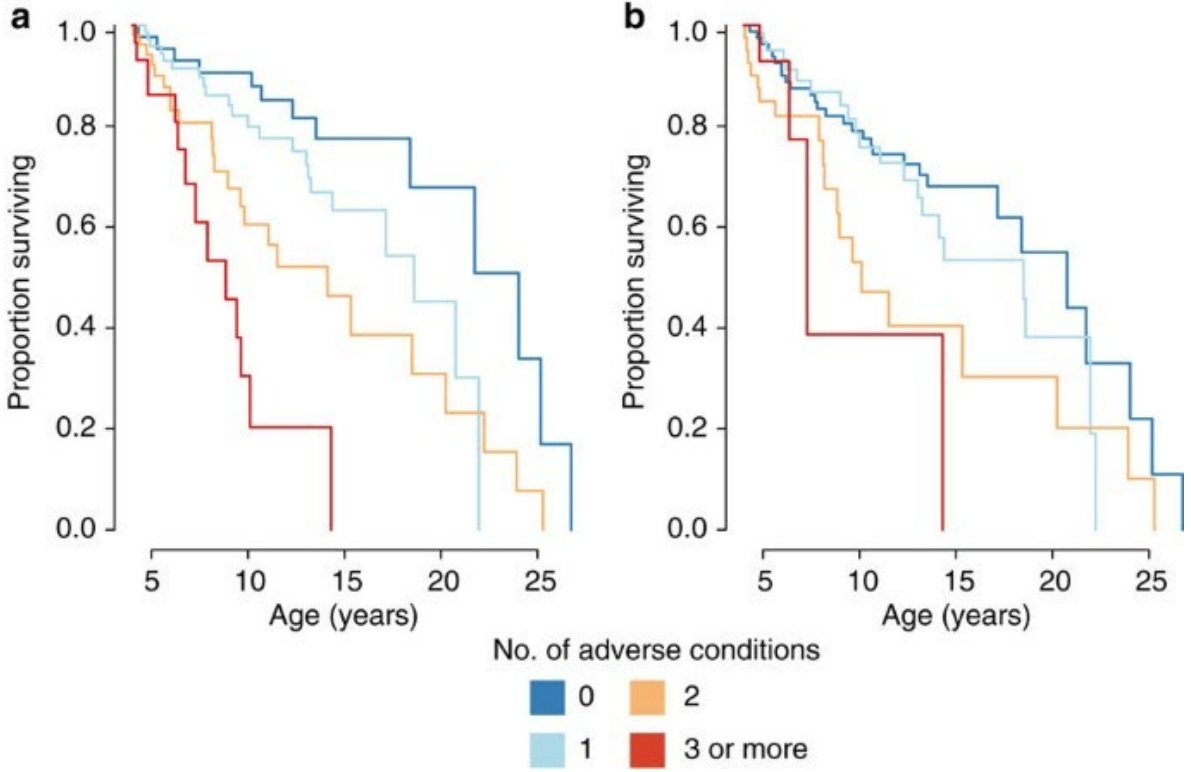
Exposure to early adversity changes likelihood of well-being

- **Epigenetic mechanisms**
- **Genetic moderation**

Lupien et al., 2009, Heim et al., 2010, Danese & McEwen 2012, Wadhwa 2005

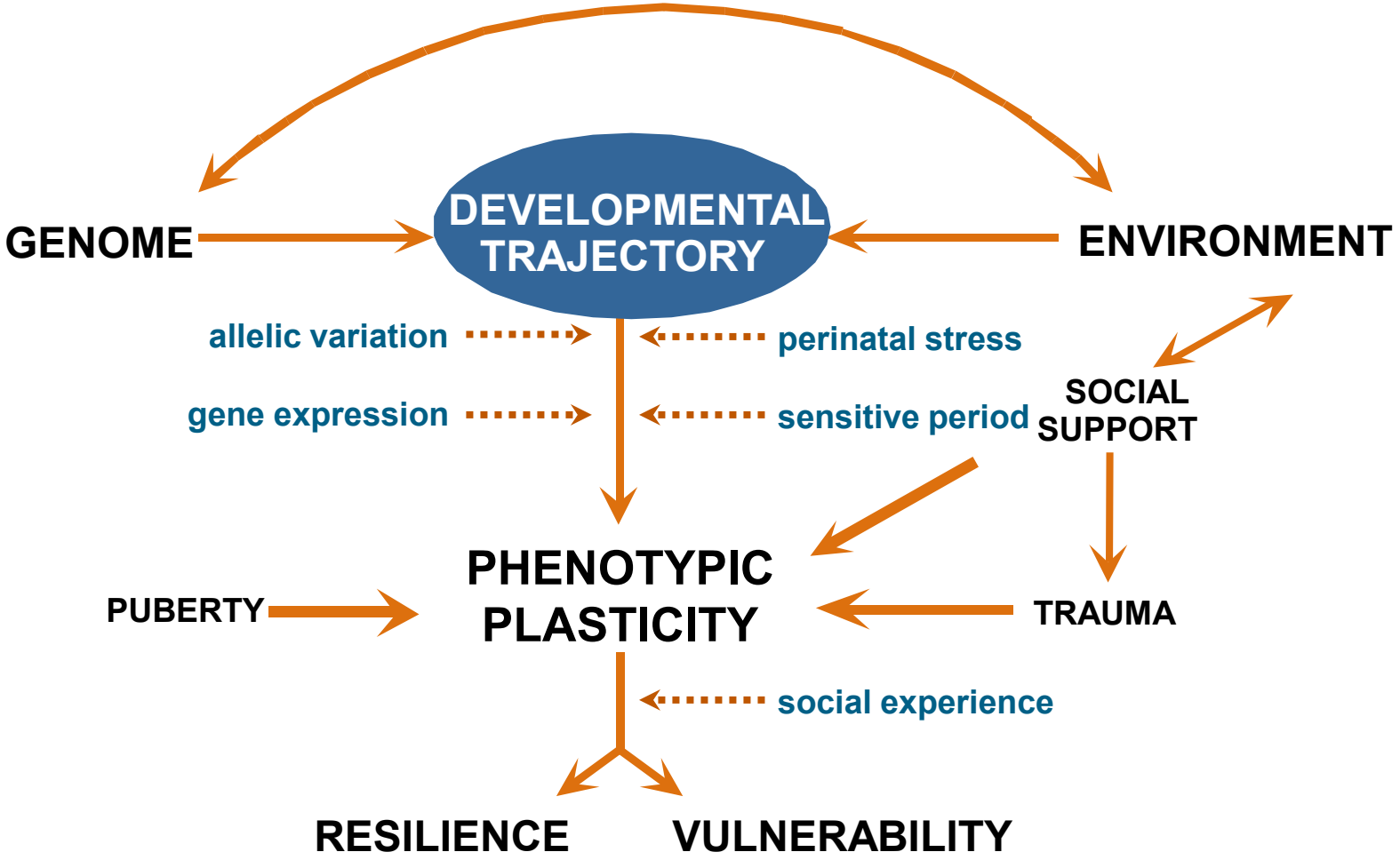
Figure 2. The Adverse Childhood Experiences Study Pyramid. (From US Centers for Disease Control and Prevention[9]).

Figure 3. Effect of cumulative early adversity on lifespan in female baboons.



(a) Survival curves using the full six factor cumulative adversity index (Wald test P = 7.75 x 10^{-7} , N = 196); (b) Survival curves using a reduced four factor adversity index, without the effects of early maternal loss and competing younger sibling (Walk test P = 0.004, N = 196). Colors indicate the number of adverse conditions in early life.

From Tung J, Archie EA, Altmann J, Alberts SC. Cumulative early life adversity predicts longevity in wild baboons. Nature Communications. 2016;7:11181. Creative Commons CC BY license.


GENOME
DEVELOPMENTAL TRAJECTORY
ENVIRONMENT
allelic variation
perinatal stress
gene expression
sensitive period
SOCIAL SUPPORT
PUBERTY
PHENOTYPIC PLASTICITY
TRAUMA
social experience
RESILIENCE
VULNERABILITY

Clinical Characteristics of Women With a History of Childhood Abuse: Unhealed Wounds

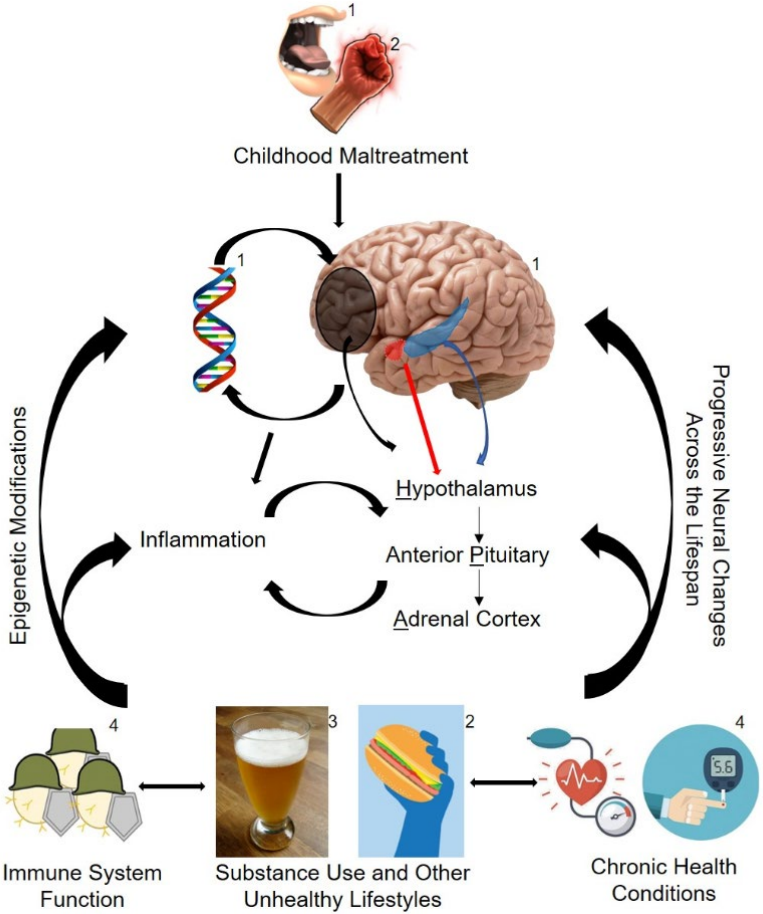
Jeanne McCauley, MD, MPH; David E. Kern, MD, MPH; Ken Kolodner, ScD; Laurie Dill, MD; Arthur F. Schroeder, MD; Hallie K. DeChant, MD; Janice Ryden, MD; Leonard R. Derogatis, PhD; Eric B. Bass, MD, MPH

JAMA (1997) 277:1362-1368.

Results: Of the 1931 respondents, 424 (22.0%) reported childhood or adolescent physical or sexual abuse. Compared with women who reported never having experienced abuse (n=1257), women who reported abuse as children but not adults (n=204) had more physical symptoms (mean +/-SE, 6.2 +/-0.2 vs 4.0 +/-0.9; P<.001) and had higher scores for depression, anxiety, somatization, and interpersonal sensitivity (low self-esteem) (P<.001); were more likely to be abusing drugs (prevalence ratio [PR], 4.7; 95% confidence interval [CI], 2.9-7.6) or to have a history of alcohol abuse (PR, 2.2; 95% CI, 1.5-3.2); were more likely to have attempted suicide (PR, 3.7; 95% CI, 2.6-5.1); and were more likely to have had a psychiatric admission (PR, 3.2; 95% CI, 2.2-4.7). Women abused only as children did not differ from women who reported current, but not childhood, abuse in number of physical symptoms, emotional distress, substance abuse, or suicide attempts. Patients who reported both childhood and adult abuse had higher levels of psychological problems and physical symptoms than those who reported childhood or adult abuse alone.

Conclusions: Childhood physical or sexual abuse is associated with adult health problems including physical symptoms, psychological problems, and substance abuse; for many variables, this association is as strong as for patients experiencing current abuse.

JAMA.1997;277:1362-1368

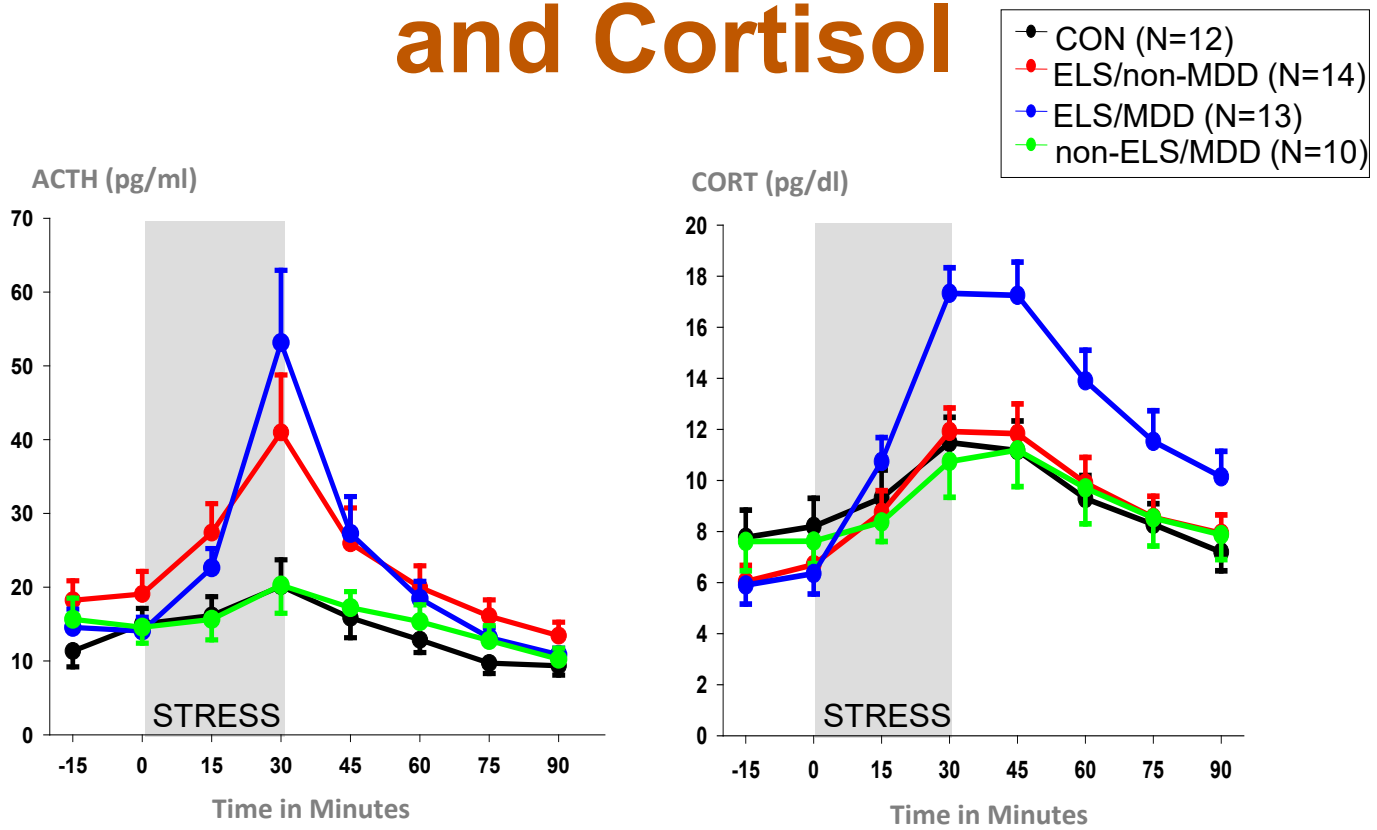

1
2
Childhood Maltreatment
1
1
Hypothalamus
Anterior Pituitary
Adrenal Cortex
Inflammation
Epigenetic Modifications
Progressive Neural Changes
Across the Lifespan
4
3
2
4
Immune System
Function
Substance Use and Other
Unhealthy Lifestyles
Chronic Health
Conditions

Pituitary-Adrenal and Autonomic Responses to Stress in Women After Sexual and Physical Abuse in Childhood

Christine Heim, PhD
D. Jeffrey Newport, MD
Stacey Heit, MD
Yolanda P. Graham, MD
Molly Wilcox, BA
Robert Bonsall, PhD
Andrew H. Miller, MD
Charles B. Nemeroff, MD, PhD

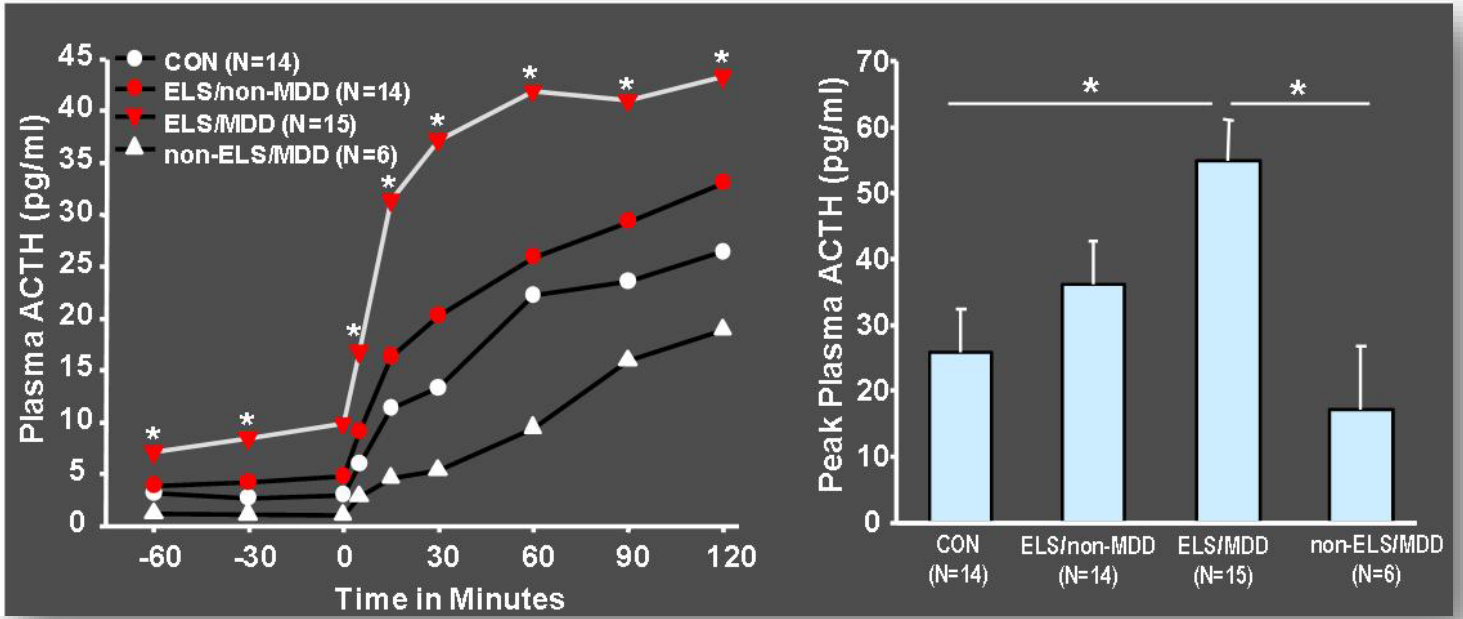
JAMA. 2000;284:592-597

Trier Social Stress Test: Plasma ACTH and Cortisol



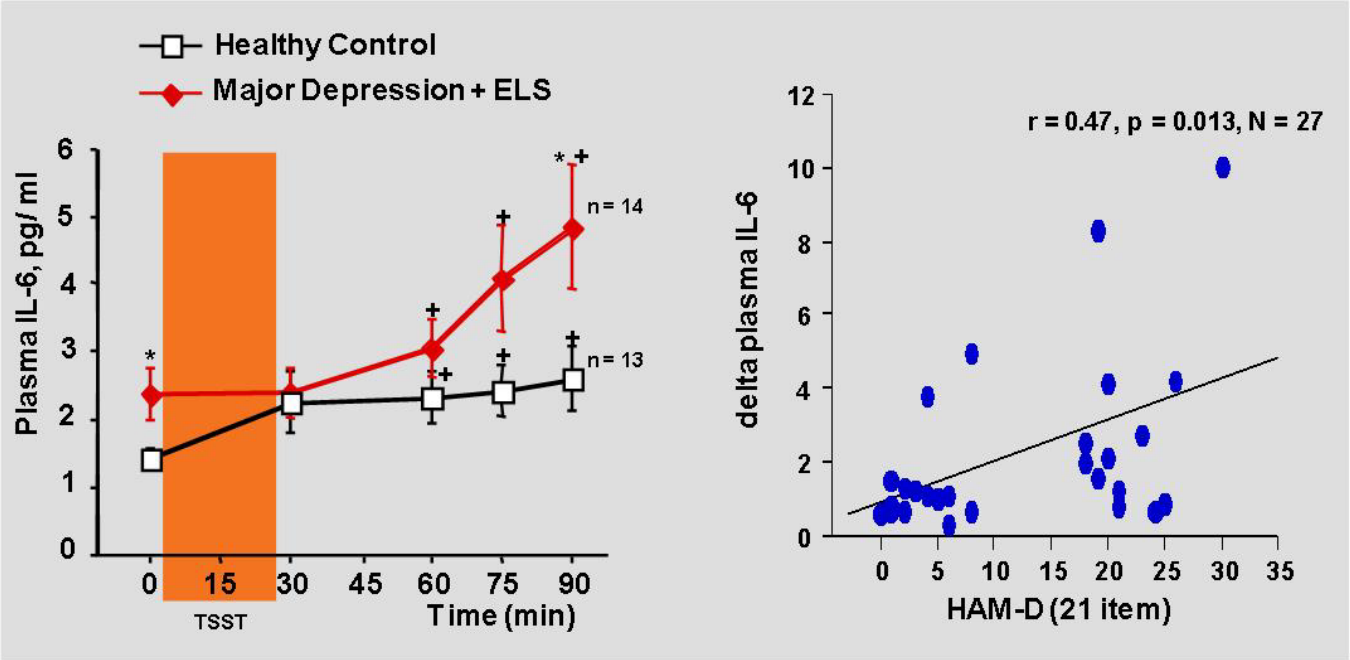
Abused Men with Current Depression, but Not Depressed Men without Childhood Abuse, Demonstrate Increased HPA Axis Responses

ACTH



Heim et al (2008) *Biol Psychiatry* 63:398-405

Patients with Major Depression and Early Life Stress Exhibit Greater Baseline and TSST-Induced Plasma IL-6 Levels Compared to Healthy Controls; IL-6 Responses are Correlated with Depression Severity

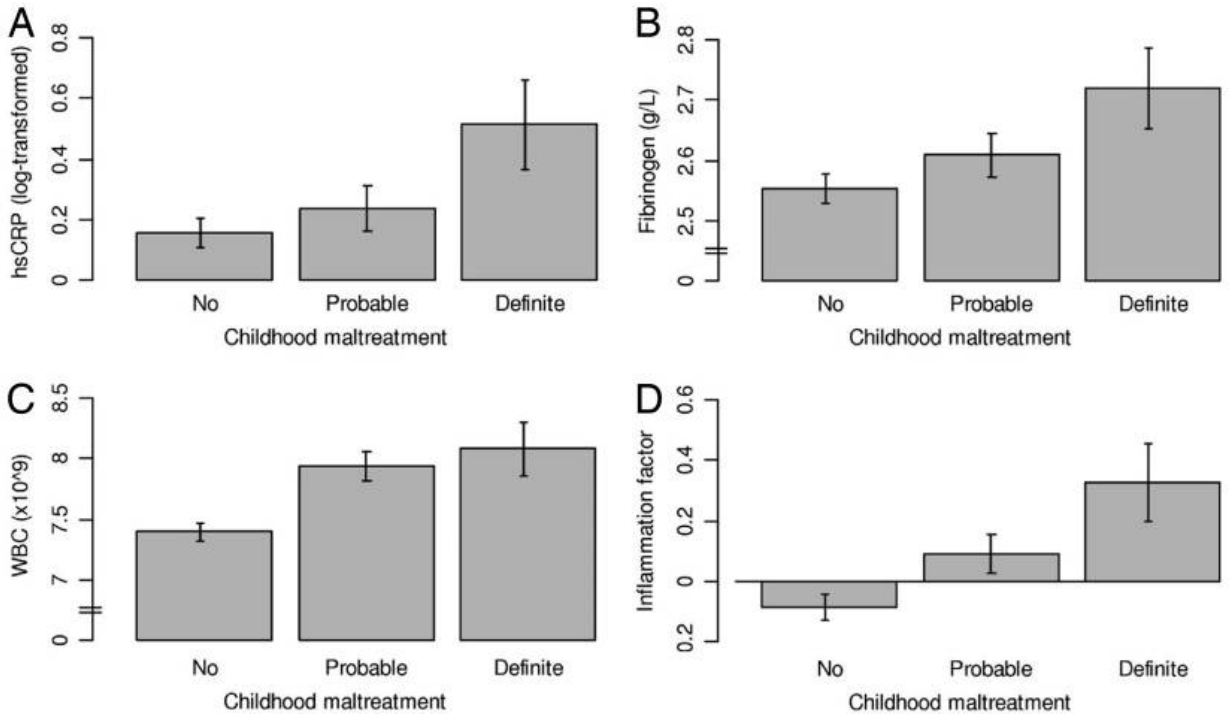


* vs. controls at same timepoint, $p < 0.04$;

+ vs. 0 min, same group, $p \leq 0.017$

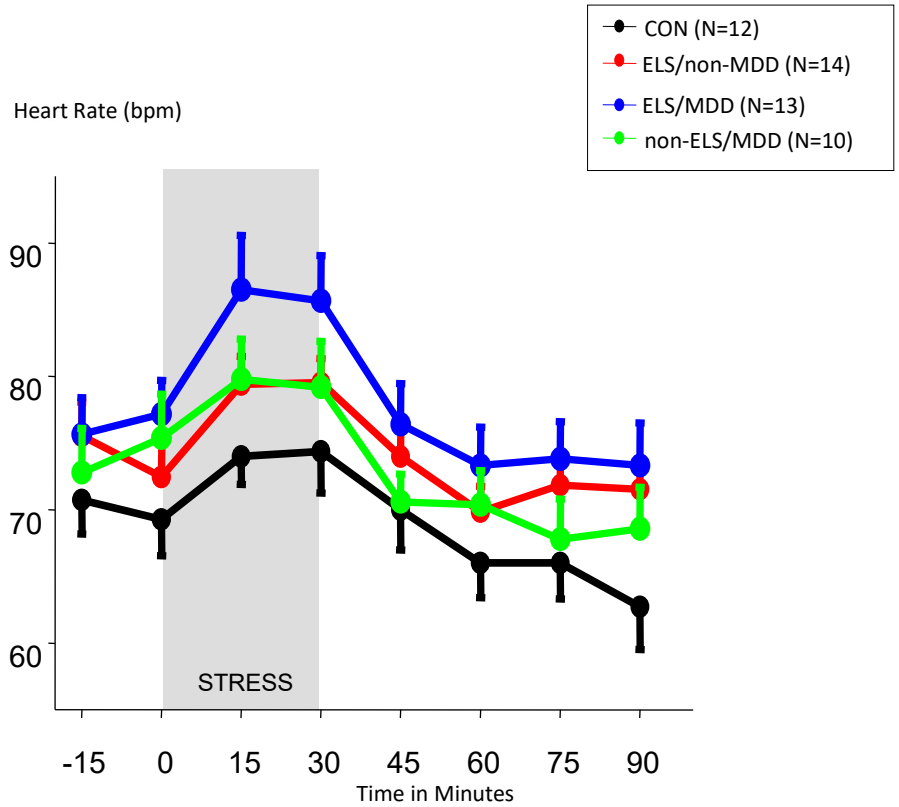
Pace et al (2006) *Am J Psychiatry* 163:1630-1633

The Association of Childhood Maltreatment with Biomarkers of Inflammation



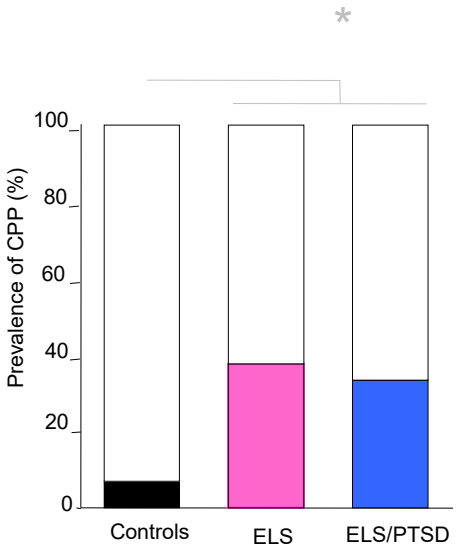
Danese et al., (2007) *PNAS* 104(4):1319-1324

Trier Social Stress Test: Heart Rate

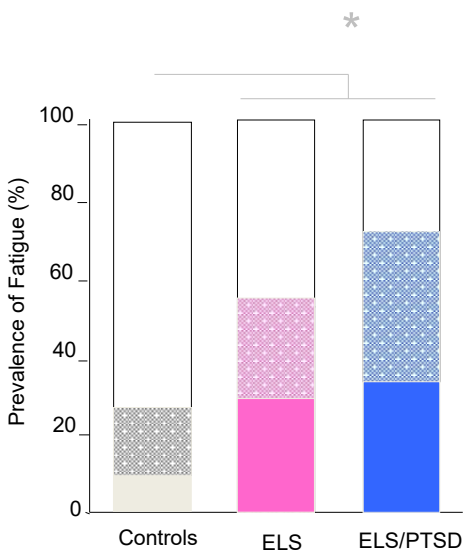


Chronic Pelvic Pain, Fatigue and Physical Symptoms

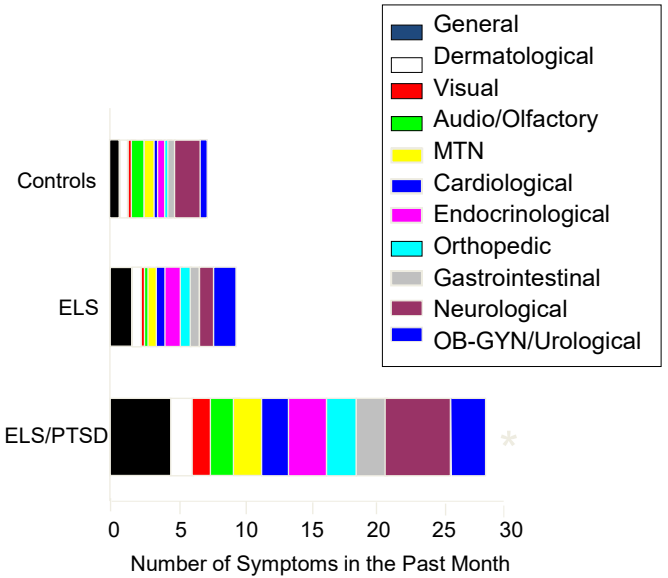
Acyclic Chronic Pelvic Pain



Loss of Energy/Fatigue



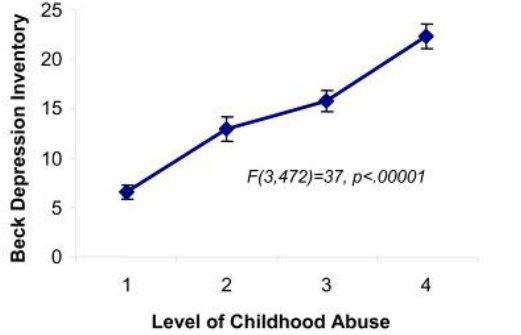
General Health Checklist



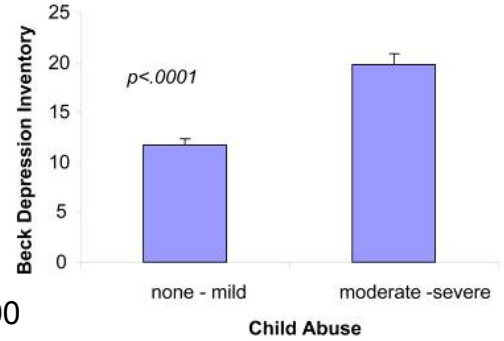
Dotted bar: Loss of energy
Filled bar: Tired all the time

Early Life Stress Significantly Enhances Risk for Depression in Adults

Beck Depression Inventory (BDI) scores are predicted by continuous scores on the childhood trauma questionnaire.

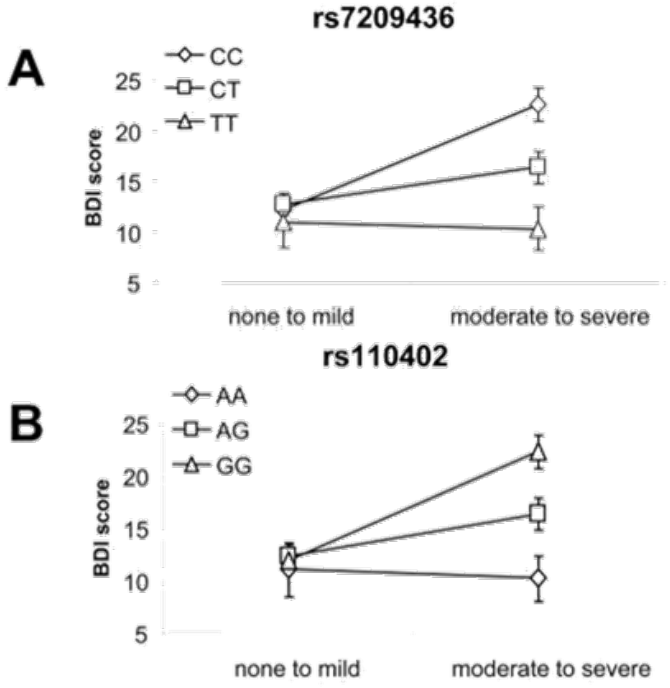


Depression is predicted by presence/absence of childhood trauma.

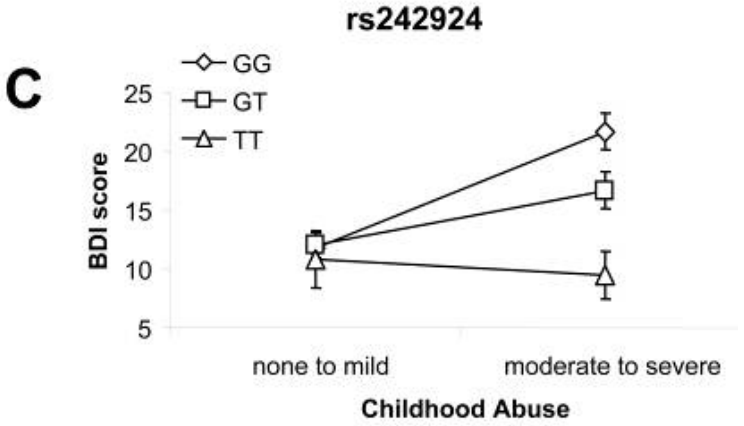


Bradley, Binder et al (2008) *Arch Gen Psychiatry* 65:190-200

Effect of Genotypes and Childhood Abuse on Adult Depression



Panels A and B. In individuals having experienced high levels of early life stress, the rare allele of two SNPs had a protective effect on the severity of adult depressive symptoms



Similar interactive gene dosage patterns were seen across the other SNPs that were significant prior to correction.

Bradley, Binder et al (2008) *Arch Gen Psychiatry* 65:190-200

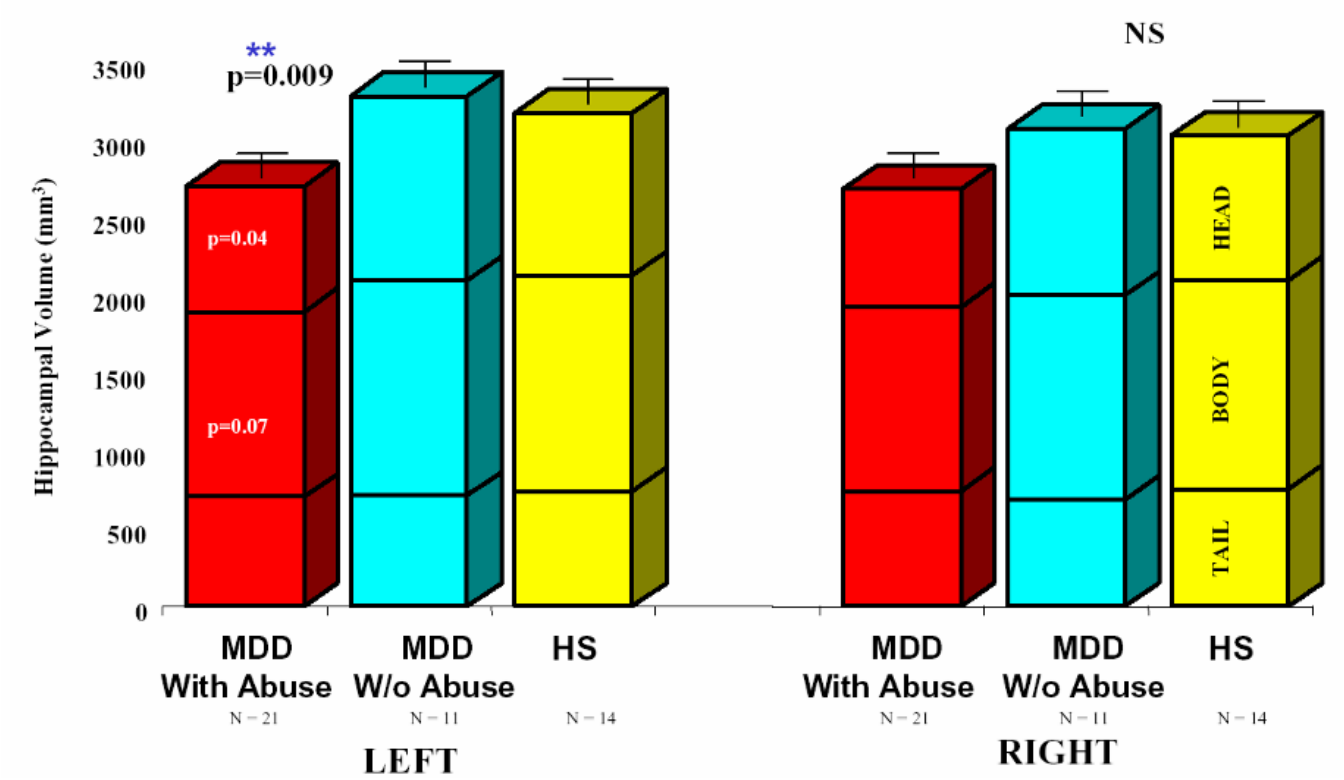
Allele-specific *FKBP5* DNA demethylation mediates gene–childhood trauma interactions

Torsten Klengel[1], Divya Mehta[1], Christoph Anacker[2], Monika Rex-Haffner[1], Jens C Pruessner[3], Carmine M Pariante[2], Thaddeus W W Pace[4], Kristina B Mercer[5], Helen S Mayberg[4], Bekh Bradley[4,6], Charles B Nemeroff[7], Florian Holsboer[1], Christine M Heim[4,8], Kerry J Ressler[4,5,9], Theo Rein[1] & Elisabeth B Binder[1,4]

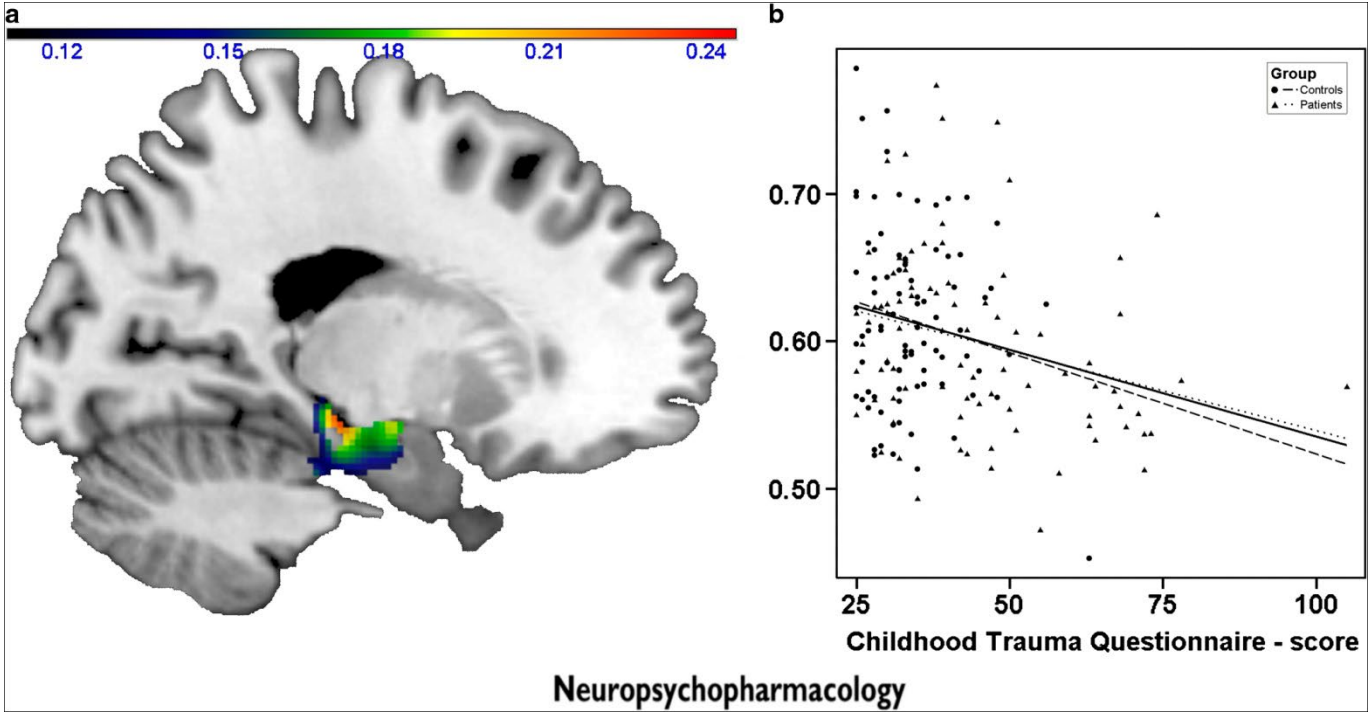
A polymorphism in the FK506 binding protein 5 (FKBP5) gene, an important regulator of the stress hormone system, increase the risk of developing stress-related psychiatric disorders in adulthood by allele-specific, childhood trauma-dependent DNA demethylation in functional glucocorticoid response elements (GREs) of FKBP5. This demethylation is linked to increased stress-dependent gene transcription followed by a long-term dysregulation of the stress hormone system and a global impact on the function of immune cells and brain areas associated with stress regulation.

Klengel et al., (2013) *Nature Neuroscience* 16:33-41

Smaller Left Hippocampal Volume in Abused Women with MDD*



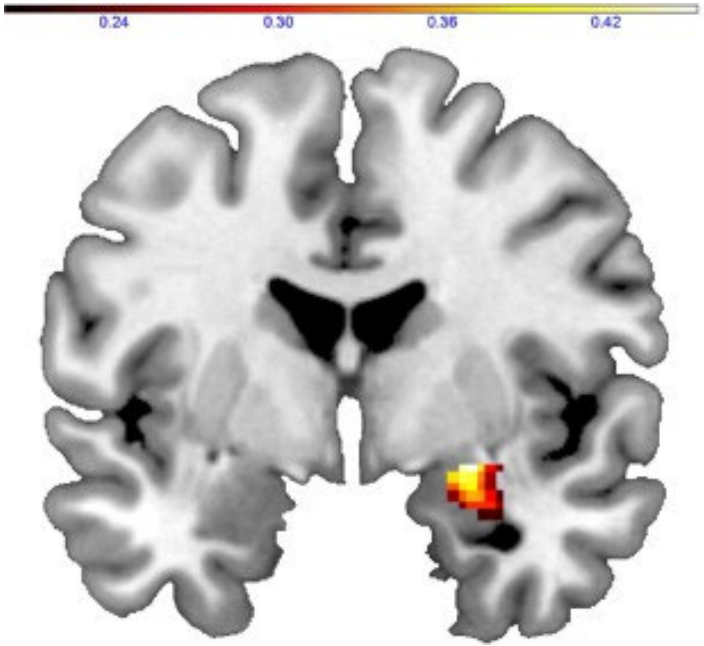
Effect of Childhood Maltreatment on Hippocampal Gray Matter Volume in the Entire Study Sample

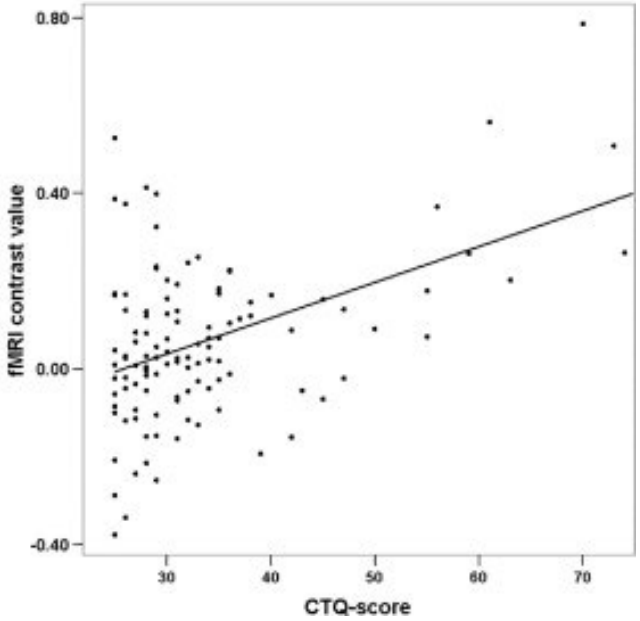


(a) Coronal view (x = 0.75, 14) depicting gray matter volume negatively associated with Childhood Trauma Questionnaire (CTQ) scores; color bar, negative correlation coefficient r. (b) Scatter plot depicting gray matter volume at x = 0.75, 14; y = 0.75, 10; z = 0.75, 24 correlated with CTQ scores within the entire sample. Dotted lines: regression slope in the entire sample.

Neuropsychopharmacology (2014) **39**, 2723-2731;
doi:10.1038/npp.2014.145

Childhood maltreatment (Childhood Trauma Questionnaire [CTQ] scores) is positively associated with right amygdala responsiveness to negative facial expressions

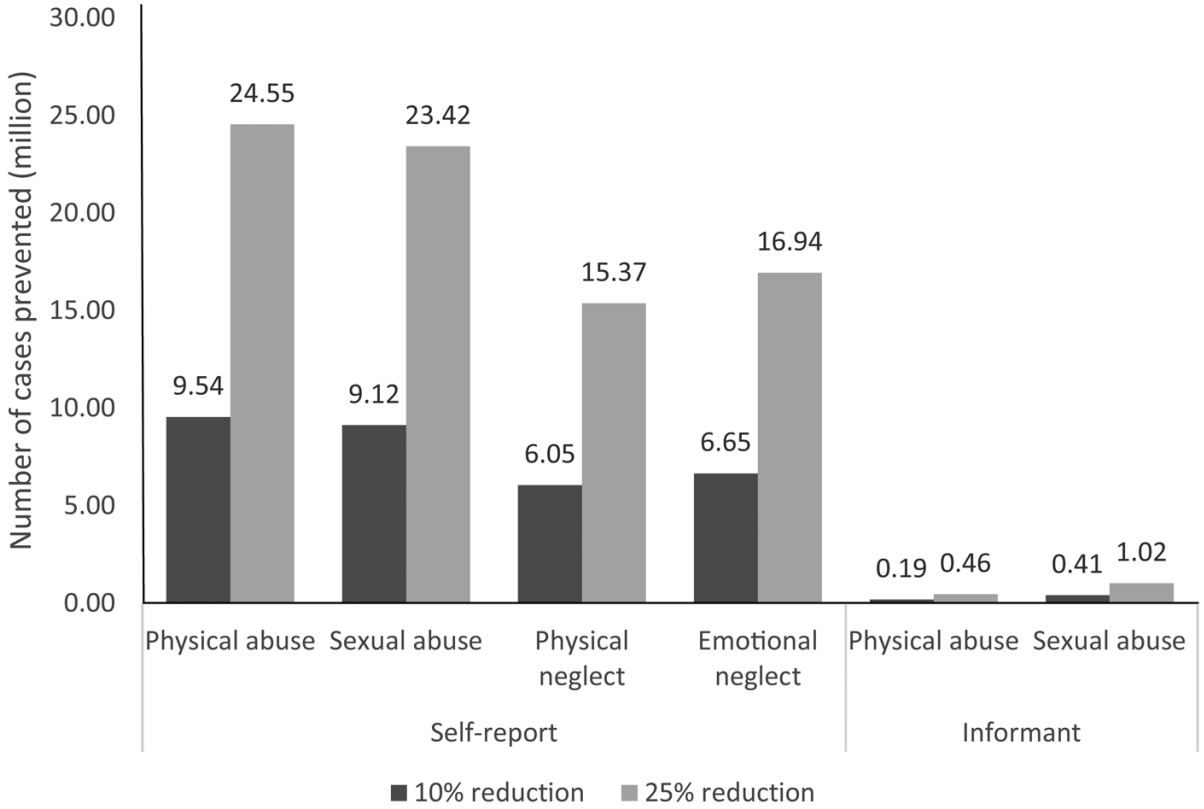




Left: Coronal view (y = -2) depicting amygdala responsiveness modulated by CTQ scores. For display reasons, the statistical threshold was set to $p < 01$, uncorrected. Color bar, correlation coefficient *r*. Right: Scatter plot depicting the positive correlation ($r = .456$, $p < .0001$) of the mean cluster activation values (left panel) and CTQ scores. fMRI function magnetic resonance imaging.

Biological Psychiatry (2012) **71-4**, 286-293;
doi:10.1016/j.biopsych.2011.10.021

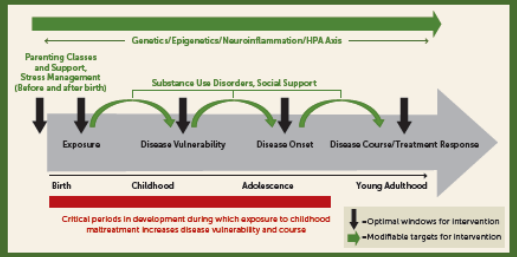
Potential depression and anxiety cases that could be prevented through child maltreatment reduction worldwide



From Li M, ,D'Arcy C, Meng X. Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions. Psychological Medicine. 2016;46(4):717-730. Reprinted with permission from Cambridge University Press.

AUGUST 2023 | VOLUME 180 | NUMBER 8

The American Journal of Psychiatry



The Devastating Clinical Consequences of Child Abuse and Neglect: Increased Disease Vulnerability and Poor Treatment Response in Mood Disorders

Overview of Alcohol Use Disorder

A Comprehensive Multilevel Analysis of the Bucharest Early Intervention Project: Causal Effects on Recovery From Early Severe Deprivation

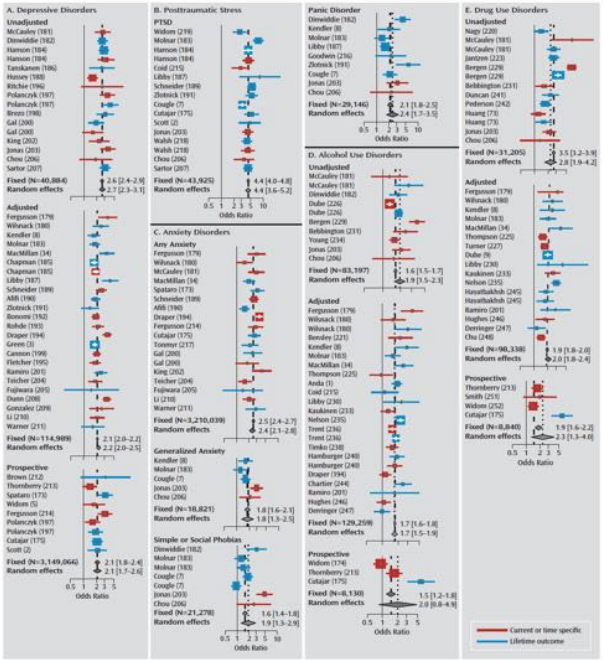
Genetic Underpinnings of the Transition From Alcohol Consumption to Alcohol Use Disorder

AMERICAN PSYCHIATRIC ASSOCIATION
ajp.psychiatryonline.org

Poor Health Outcomes

Trauma in Childhood Increases Risk for a Number of Psychiatric Disorders

Depression	**2.7 x**
PTSD	**4.4 x**
Anxiety	**2.5 x**
Alcohol abuse	**1.9 x**
Substance abuse	**3.5 x**



Teicher and Samson 2013

Poor Health Outcomes

Childhood Maltreatment Predicts Unfavorable Course of Illness and Treatment Outcome in Depression: A Meta-Analysis

Valentina Nanni, M.D.

Rudolf Uher, M.U.Dr., Ph.D.

Andrea Danese, M.D., Ph.D.

Objectives: Evidence suggests that childhood maltreatment may negatively affect not only the lifetime risk of depression but also clinically relevant measures of depression, such as course of illness and treatment outcome. The authors conducted the first meta-analysis to examine the relationship between childhood maltreatment and these clinically relevant measures of depression.

Results: A meta-analysis of 16 epidemiological studies (23,544 participants) suggested that childhood maltreatment was associated with an elevated risk of developing recurrent and persistent depressive episodes (odds ratio=2.27, 95% confidence interval [CI]=1.80–2.87). A meta-analysis of 10 clinical trials (3,098 participants) revealed that childhood maltreatment was associated with lack of response or remission during treatment for depression (odds ratio=1.43, 95% CI=1.11–1.83). Meta-regression analyses suggested that the results were not significantly affected by publication bias, choice of outcome measure, inclusion of prevalence or incidence samples, study quality, age of the sample, or lifetime prevalence of depression.

Conclusions: Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression.

Am J P sychiatry 2012; 169:141 –151

What are the big unanswered questions?

Can the biological consequences of child abuse and neglect be reversed with treatment?

What is the optimal treatment for adults with child abuse & neglect histories?
For depression?
PTSD?
Heart disease?
Obesity?

What is known about early life trauma from in utero insult?
Depression during pregnancy and postpartum?
Other forms of in utero insult?

What is the evidence for best treatment of adults with a child abuse history?