Paradise Lost: The Neurobiology of Child Abuse and Neglect

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DISCLOSURES

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2017

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Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2)

Speakers Bureau:
None

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D. Jeffrey Newport, M.D.

Eleonore Beurel, Ph.D.

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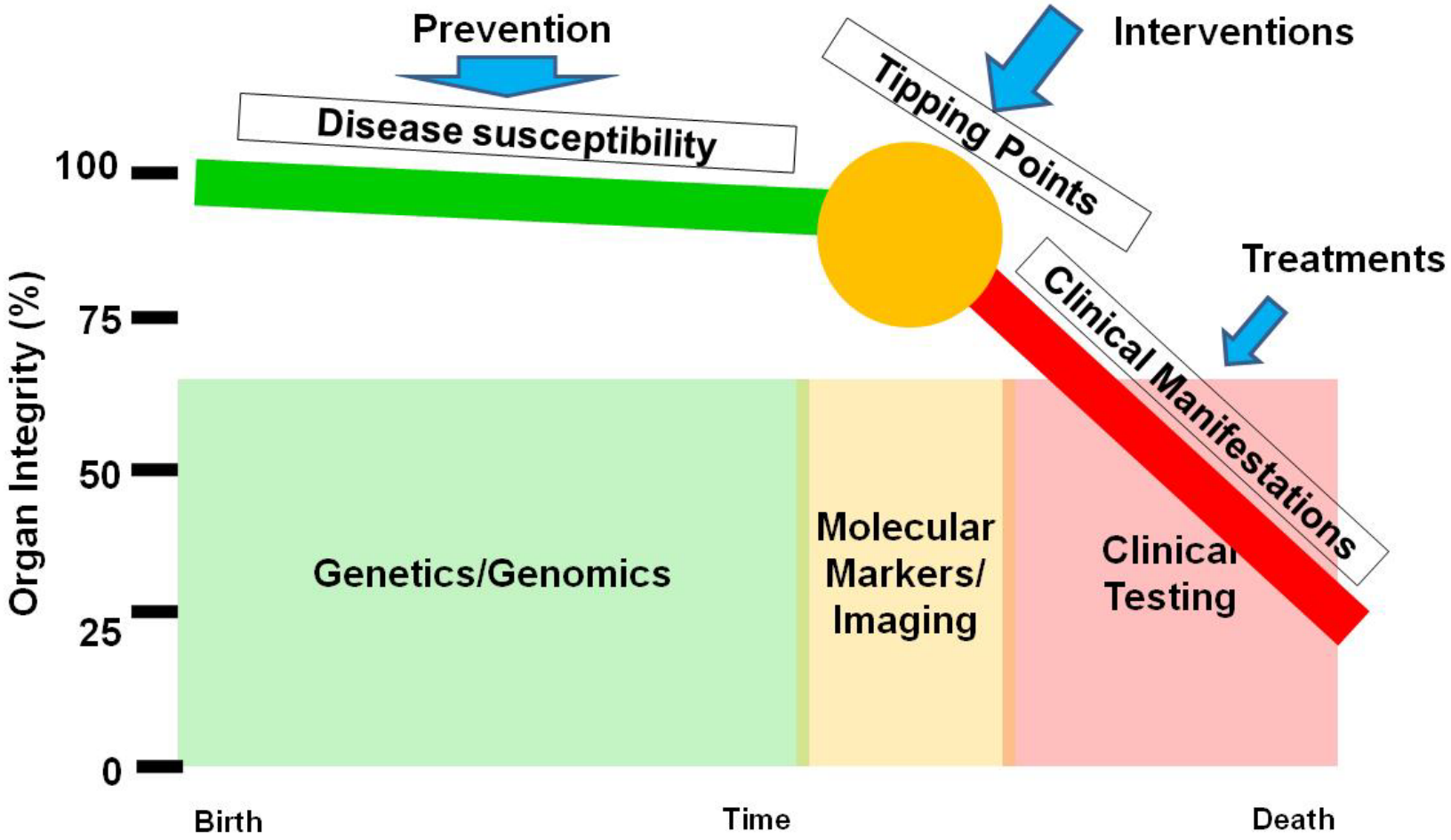
Elizabeth Binder, M.D., Ph.D.

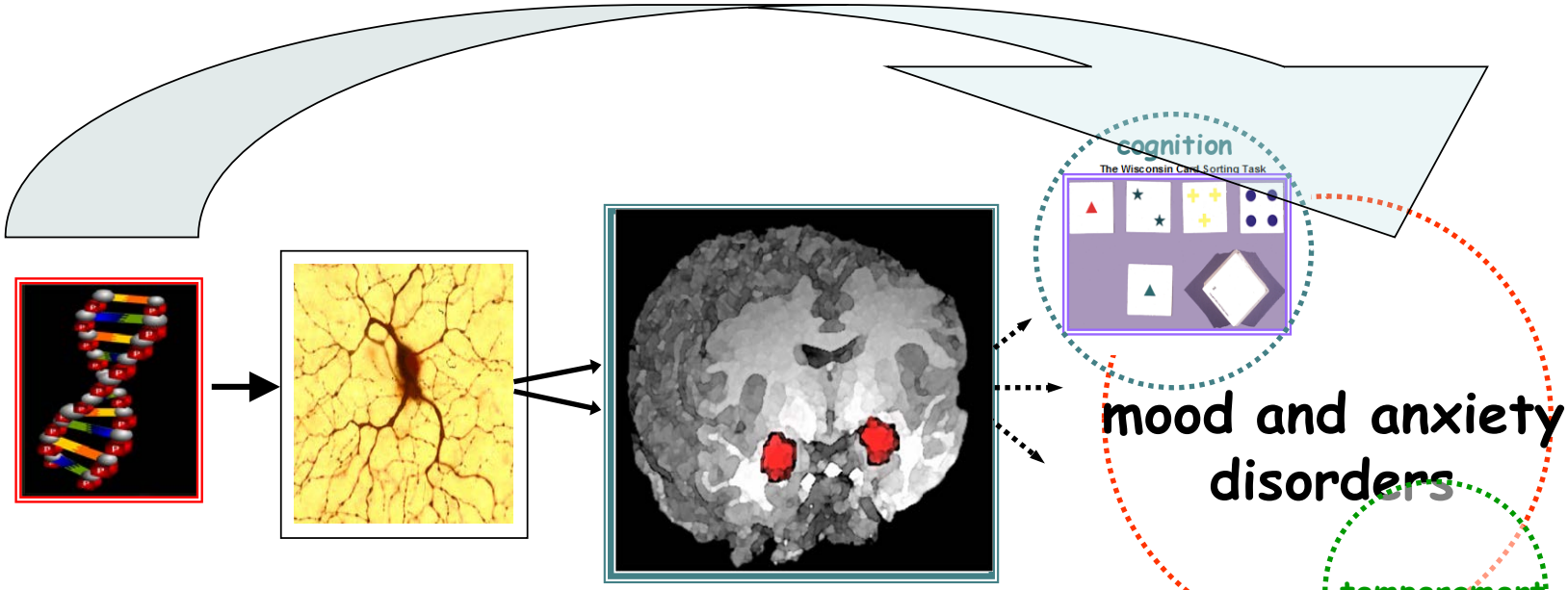
Depressive Disorders: The Essentials

- Stress is an important risk factor for depression
- Early life stress is an important risk factor
- Genes account for a substantial variation in risk
- Brain systems related to the regulation of emotion are functionally impaired during an episode

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

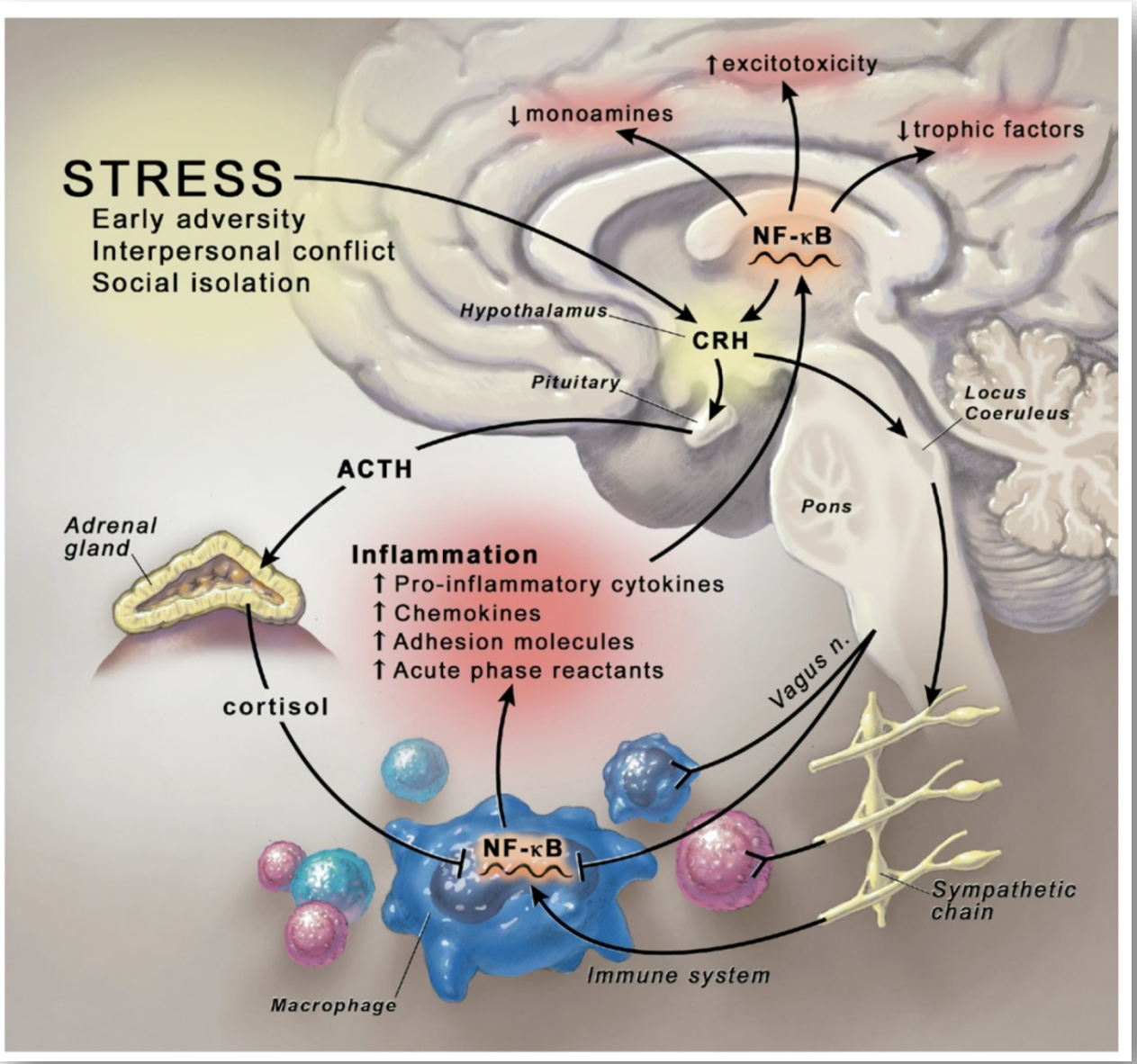
Behavior:

Clinical phenotype

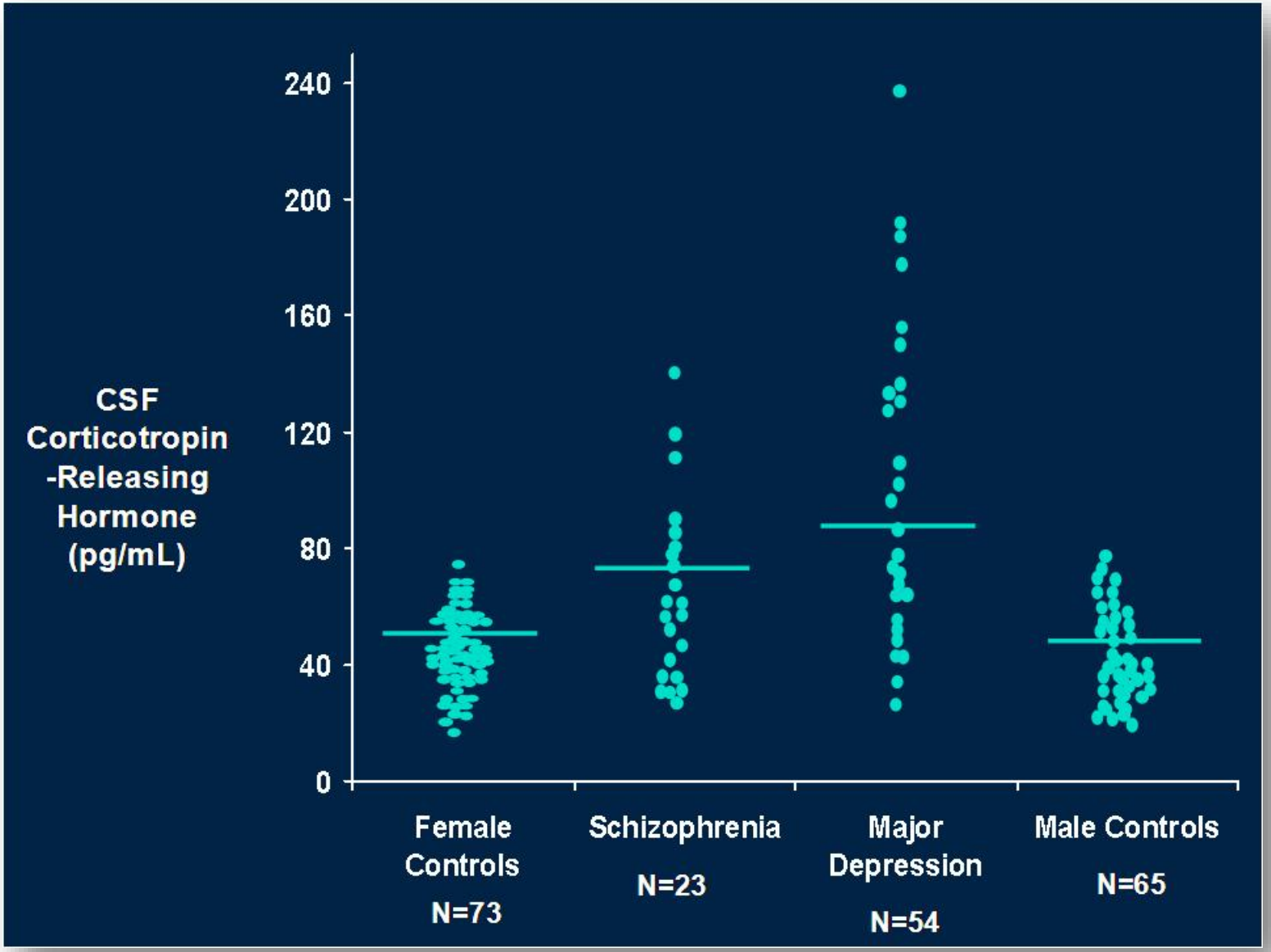
Risk Factors for Depressive Disorders

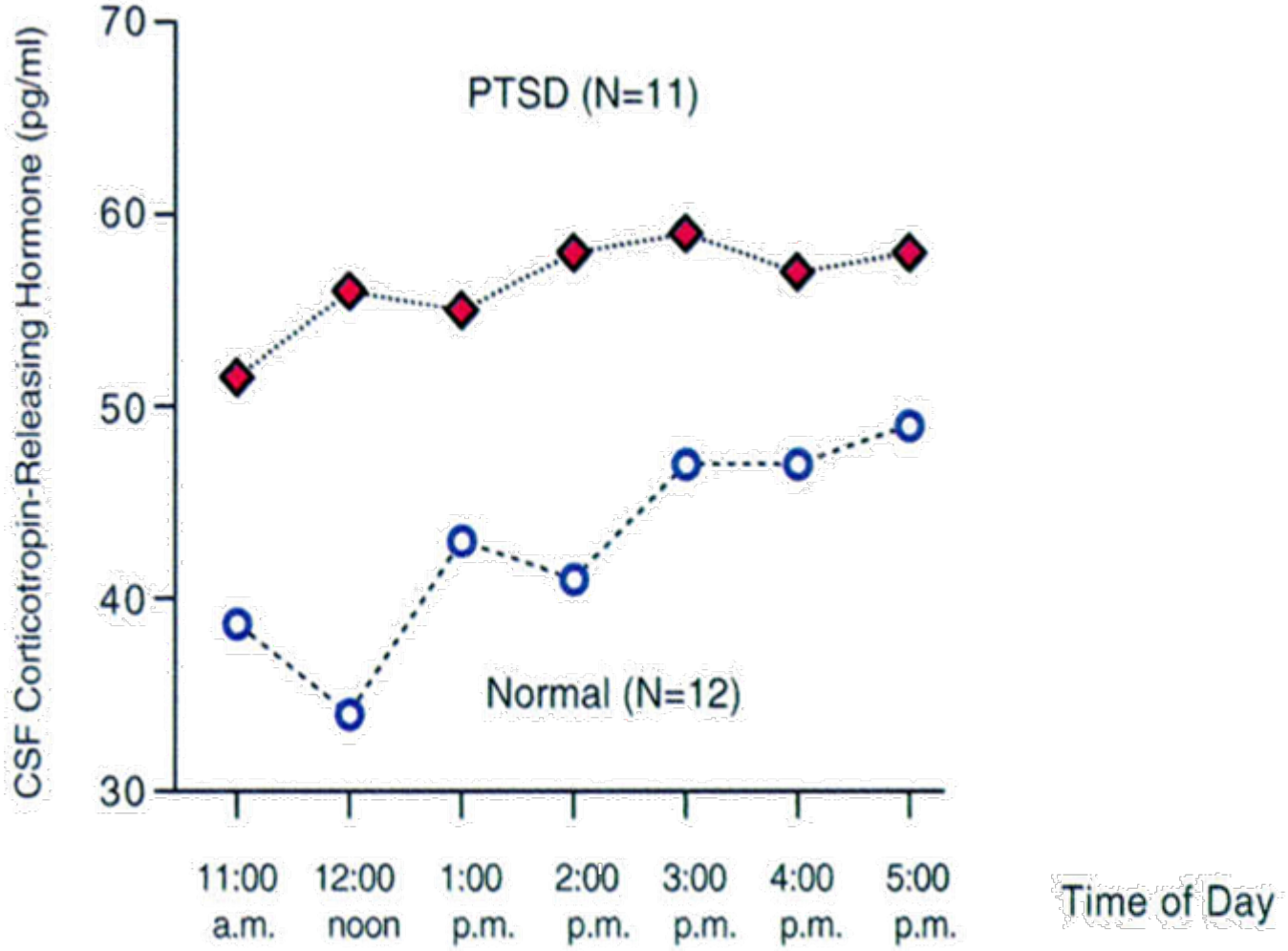
- **Family History of depressive disorders**
- **Prior personal history of a depressive disorder**
- **Female gender**
- **Life stressor (eg, bereavement, chronic financial problems)**
- **Certain personality traits**
- **Loss of parents at an early age**
- **Childhood abuse**
- **Alcohol or drug abuse**
- **Anxiety disorders**
- **Neurologic disorders (eg, Parkinson's, Alzheimer's, stroke)**
- **Primary sleep disorders**

Hirschfeld RMA, Goodwin FK. In: *The American Psychiatric Press Textbook of Psychiatry*. 1987: 403-441
Depression Guideline Panel. *Depression in Primary Care: Volume 1*. Detection and Diagnosis. 1993: 1-65



Miller et al (2009) Biol Psychiatry 65:732-741.

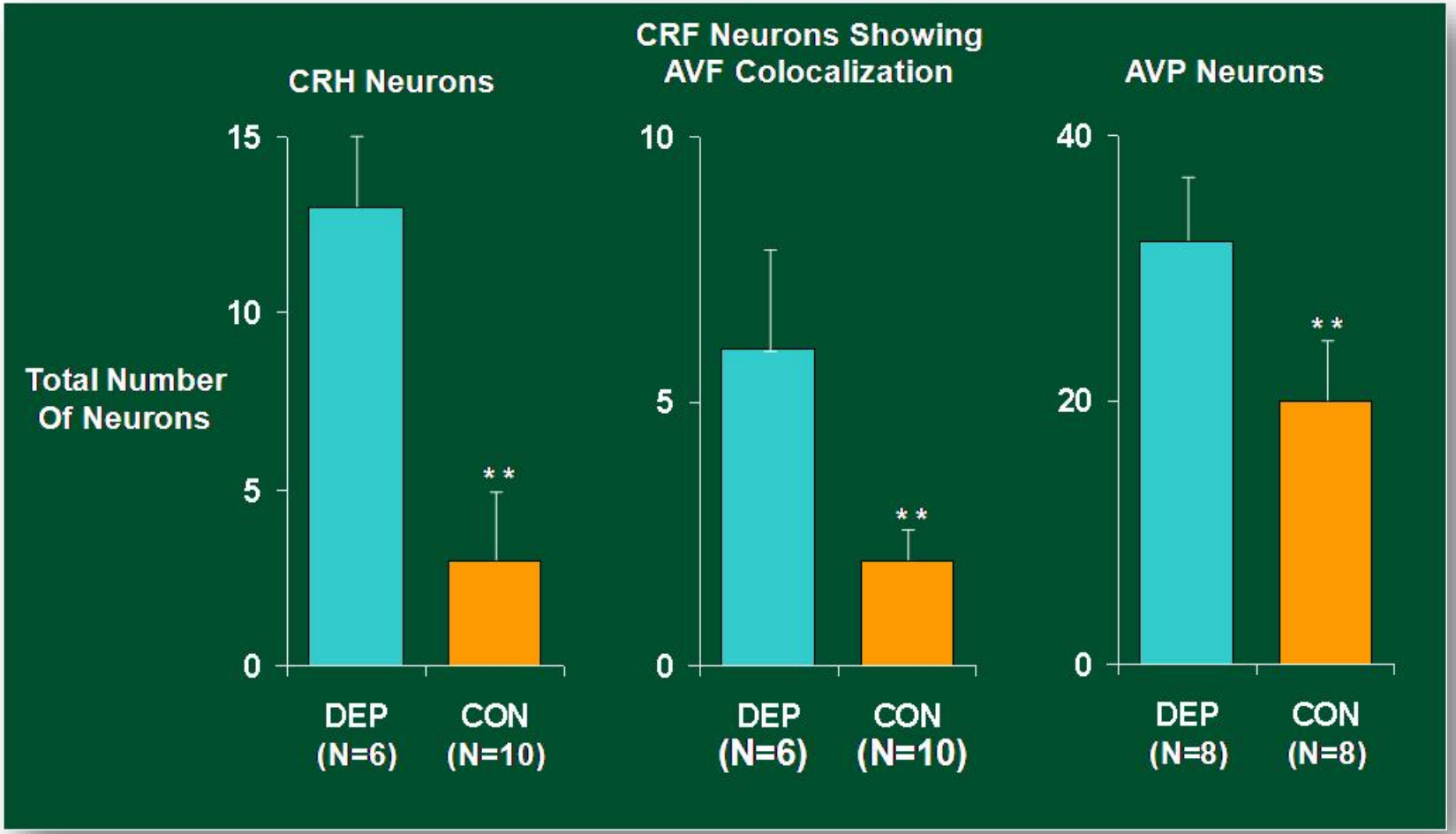

CSF Corticotropin -Releasing Hormone (pg/mL)
240
200
160
120
80
40
0
Female Controls N=73
Schizophrenia N=23
Major Depression N=54
Male Controls N=65



[a] Beginning after 15 hours of fasting and 3 hours after subarachnoid catheter placement, CSF was continuously withdrawn and aliquoted at 1-hour intervals from 11:00 a.m. to 5:00 p.m. Each point represents the mean.

Am J Psychiatry 1999; 156:585-588.

CRH And AVP Neurons In The Hypothalamic Paraventricular Nucleus Of Depressed Patients



Purba et al. 1995; Readsheer et al.1994.
** *P*=.01; mean ± SEM


SPECIAL EDITION
YOUR CHILD
Newsweek
Spring/Summer 1997 : $3.50
From Birth to Three
What You Need To Know
How Speech Begins
A Baby's Brain
Genes & Emotions
What's Normal, What's Not

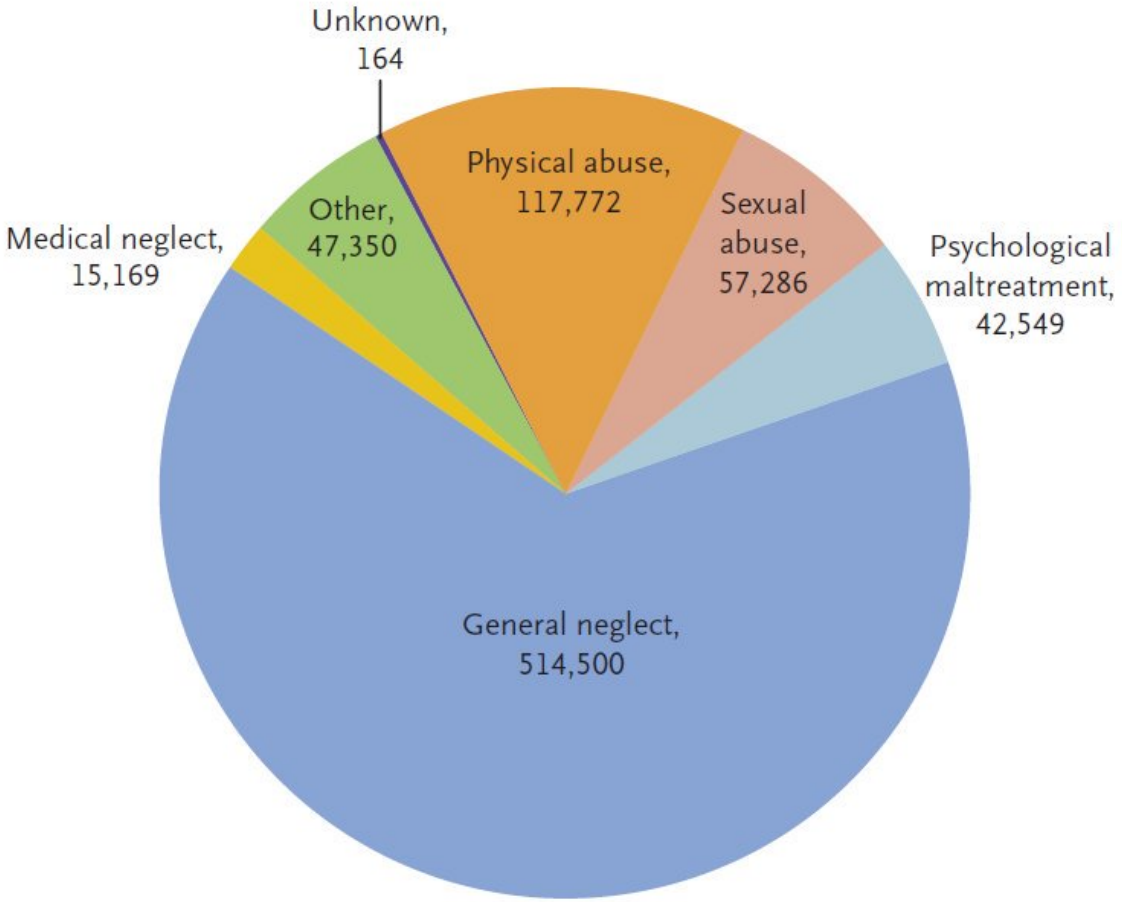


Figure 1. Number of Cases of Child Abuse in the United States in 2015, According to the Type of Abuse.

Adapted from the U.S. Department of Health and Human Services.[2]

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 Abuse, Household Dysfunction, and the Risk of Attempted Suicide Throughout the Life Span: Findings From the Adverse Childhood Experiences Study

Shanta R. Dube, MPH; Robert F. Anda, MD, MS;
Vincent J. Felitti, MD; Daniel P. Chapman, PhD;
David F. Williamson, PhD; Wayne H. Giles, MD, MS

JAMA (2001) 286: 3089-3096

Context: Suicide is a leading cause of death in the United States, but identifying persons at risk is difficult. Thus, the US surgeon general has made suicide prevention a national priority. An expanding body of research suggests that childhood trauma and adverse experiences can lead to a variety of negative health outcomes, including attempted suicide among adolescents and adults.

Objective: To examine the relationship between the risk of suicide attempts and adverse childhood experiences and the number of such experiences (adverse childhood experiences [ACE] score).

Design, Setting, and Participants: A retrospective cohort study of 17337 adult health maintenance organization members (54% female; mean [SD] age, 57 [15.3] years) who attended a primary care clinic in San Diego, Calif, within a 3-year period (1995-1997) and completed a survey about childhood abuse and household dysfunction, suicide attempts (including age at first attempt), and multiple other health-related issues.

JAMA. 2001; 286: 3089-3096

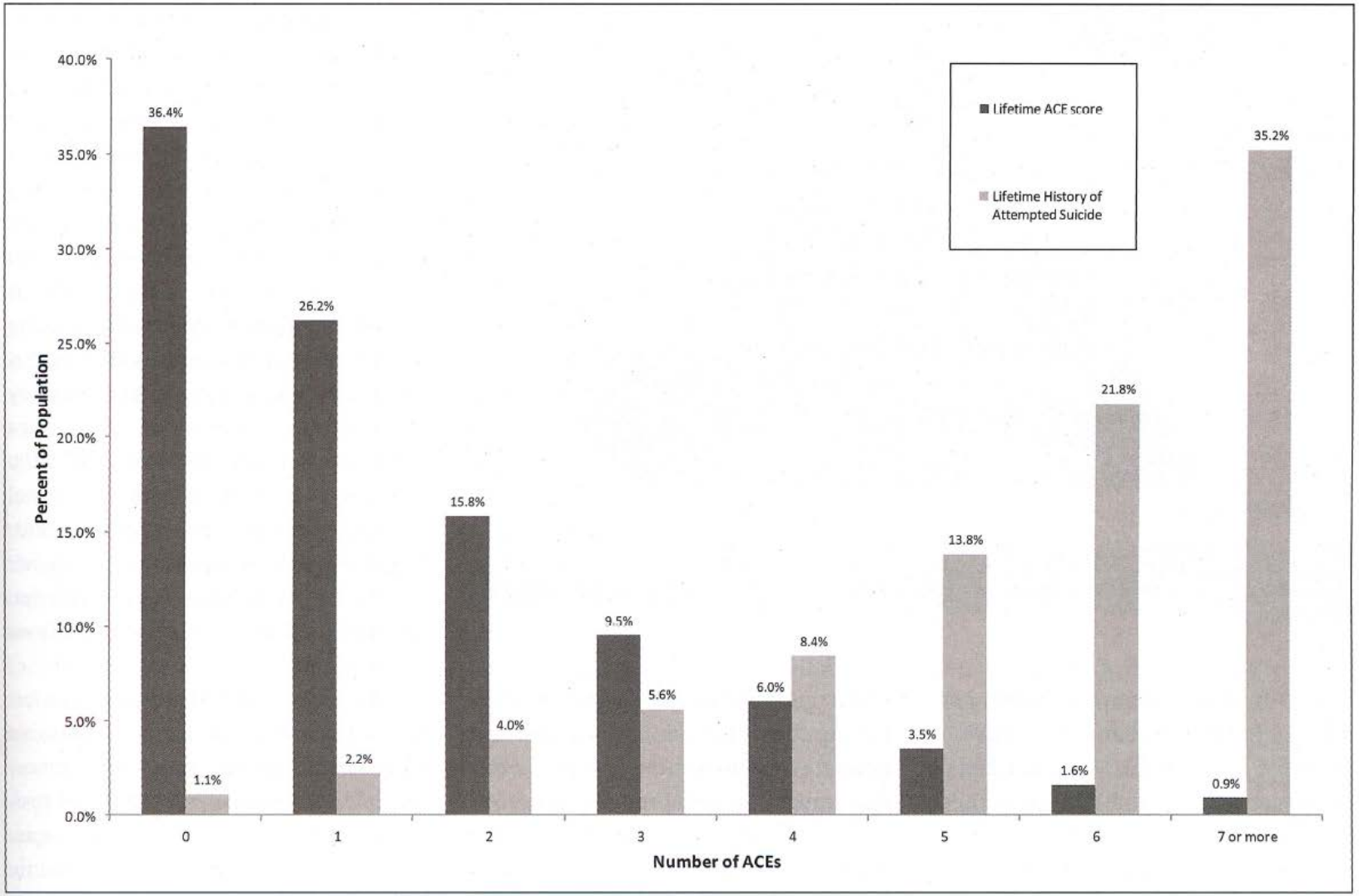


Figure 1. Prevalence of multiple childhood adverse experiences (ACEs) and association between number of ACEs and lifetime history of attempted suicide ($n = 17,337$). (Adapted from Dube et al[11])

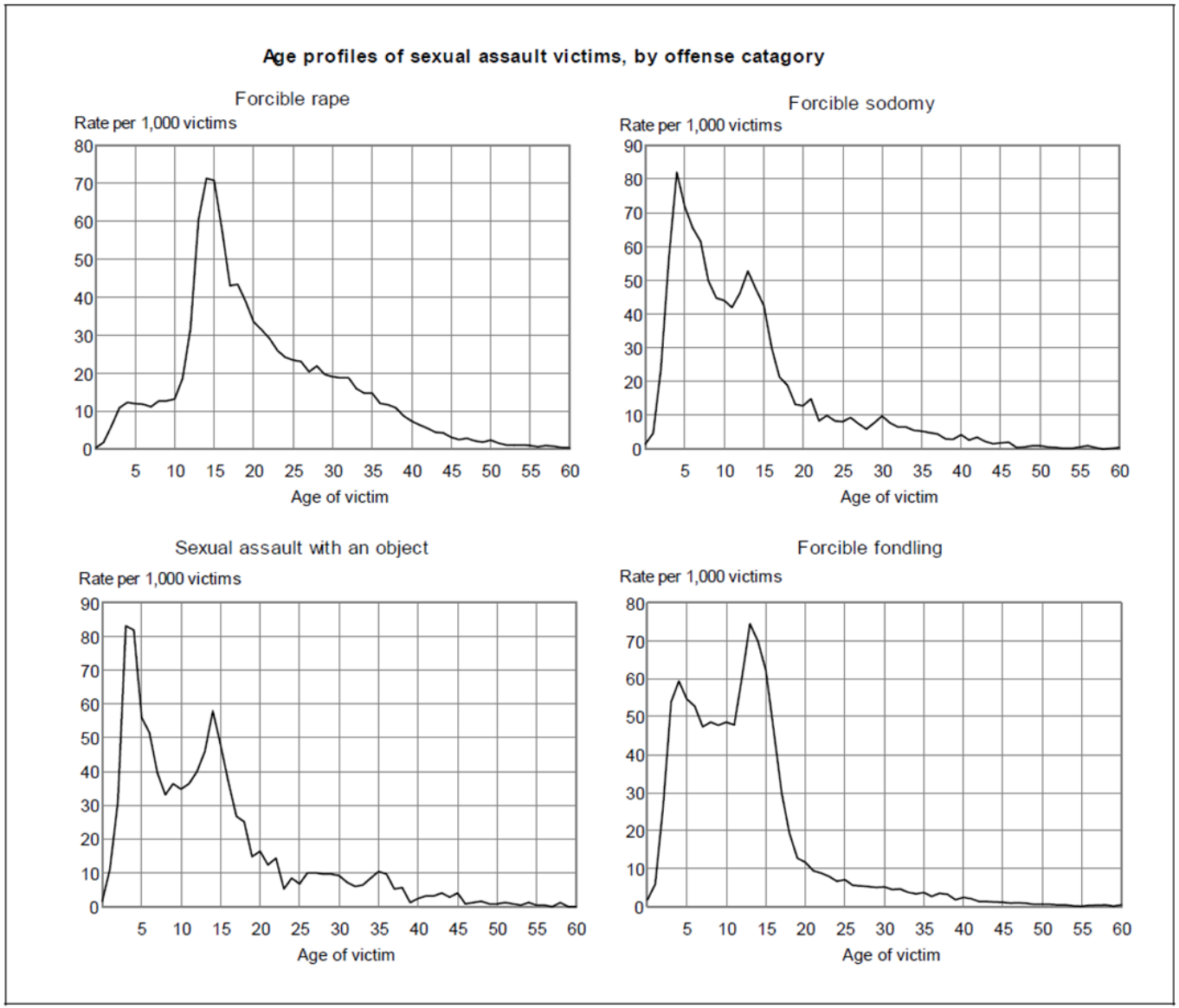

Age profiles of sexual assault victims, by offense catagory
Forcible rape
Rate per 1,000 victims
Age of victim
Forcible sodomy
Rate per 1,000 victims
Age of victim
Sexual assault with an object
Rate per 1,000 victims
Age of victim
Forcible fondling
Rate per 1,000 victims
Age of victim

Figure 1

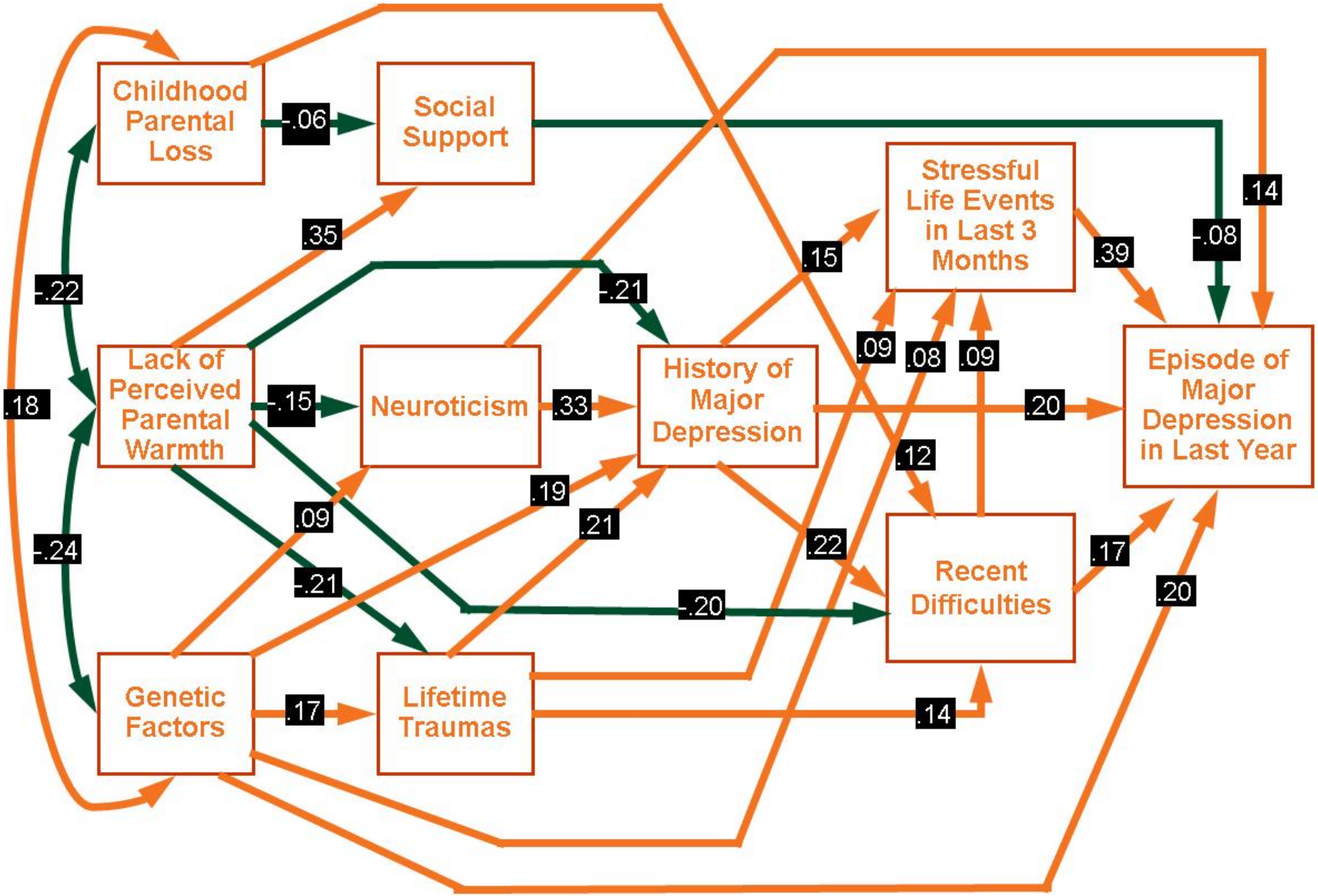
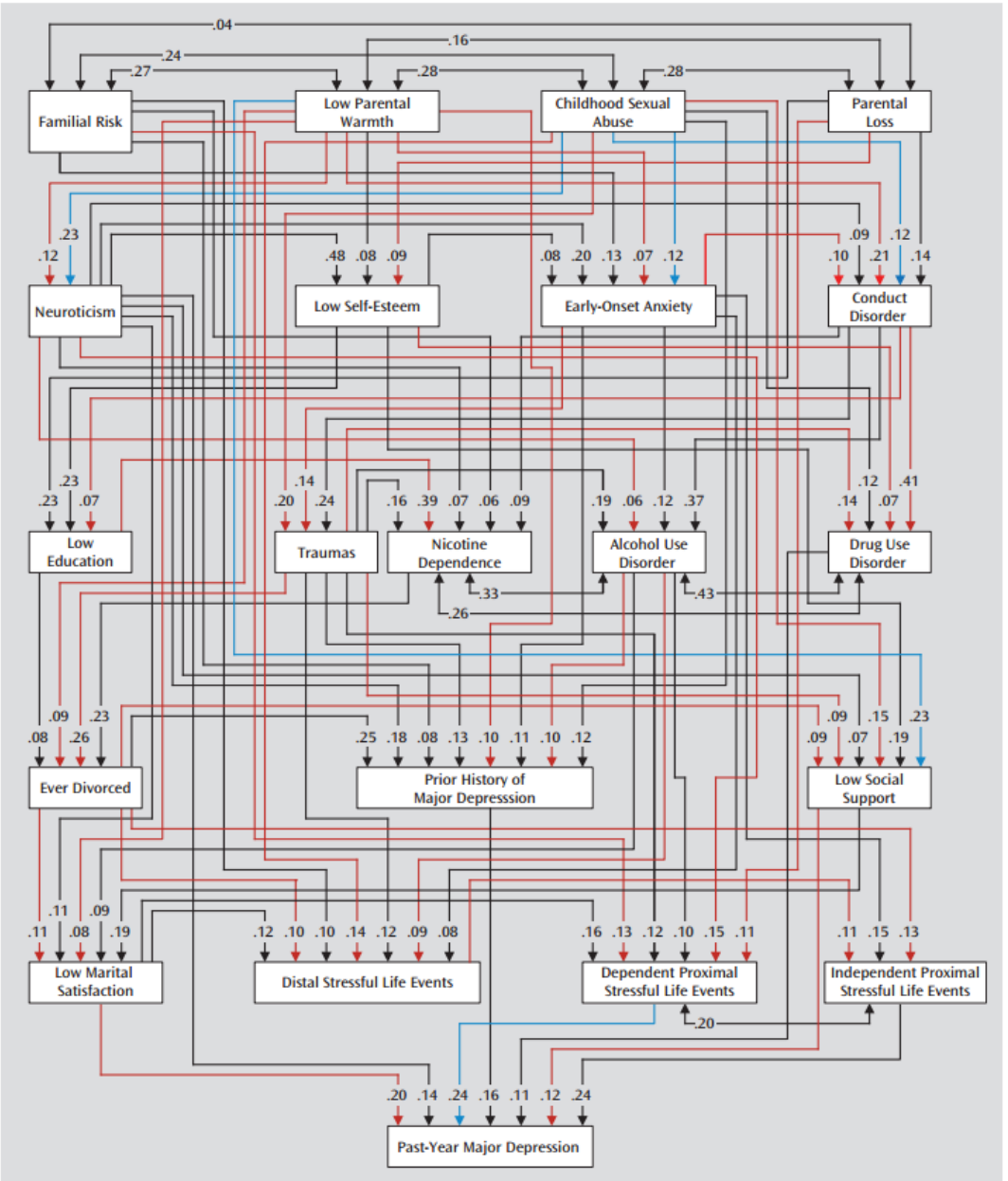

Childhood Parental Loss
Social Support
Lack of Perceived Parental Warmth
Neuroticism
History of Major Depression
Stressful Life Events in Last 3 Months
Episode of Major Depression in Last Year
Recent Difficulties
Genetic Factors
Lifetime Traumas
-.06
.35
-.22
-.21
.15
.14
-.08
.39
.09
.08
.09
.18
-.15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

FIGURE 1. Path Estimates for Best-Fit Model for Causal Pathways to Major Depression in Females[a]



[a] Parameters estimated to be equal across sexes, greater in females than males, and greater in males than females are depicted in black, red, and blue, respectively. If a path is not present between two variables, that is because it was estimated to have a zero value. Appendix II in the online data supplement contains the best-fit model estimates for all these paths, along with their statistical significance and the equality or nonequality of that path across sexes. The test of equality across sexes was based on raw path coefficients. However, for ease of interpretation and a consistent measure of effect size, we report standardized path coefficients. Thus, paths that are depicted as equal (using raw coefficients) can differ slightly using standardized paths.

Kendler and Gardner, *Am J Psychiatry* 171:4

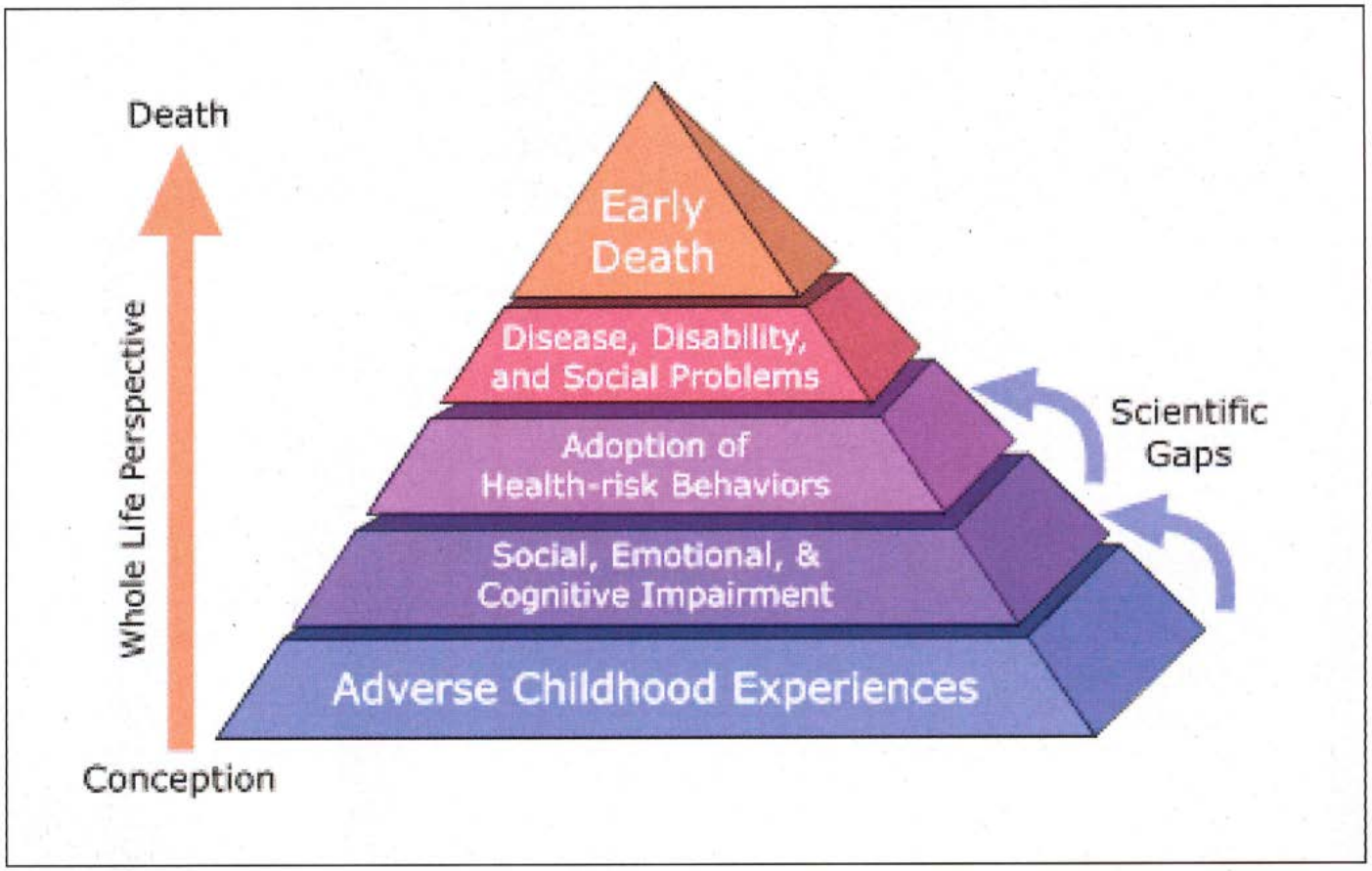
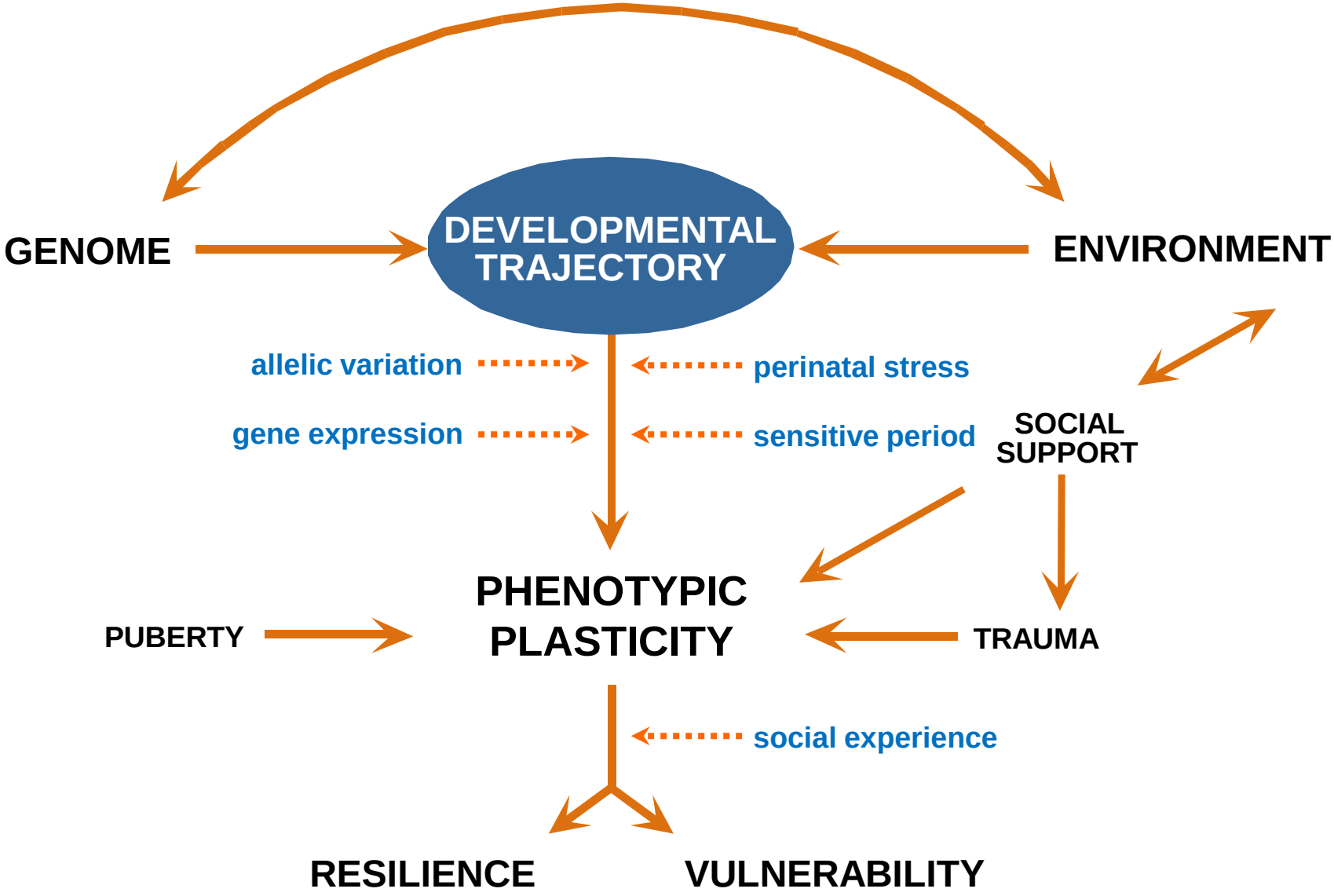
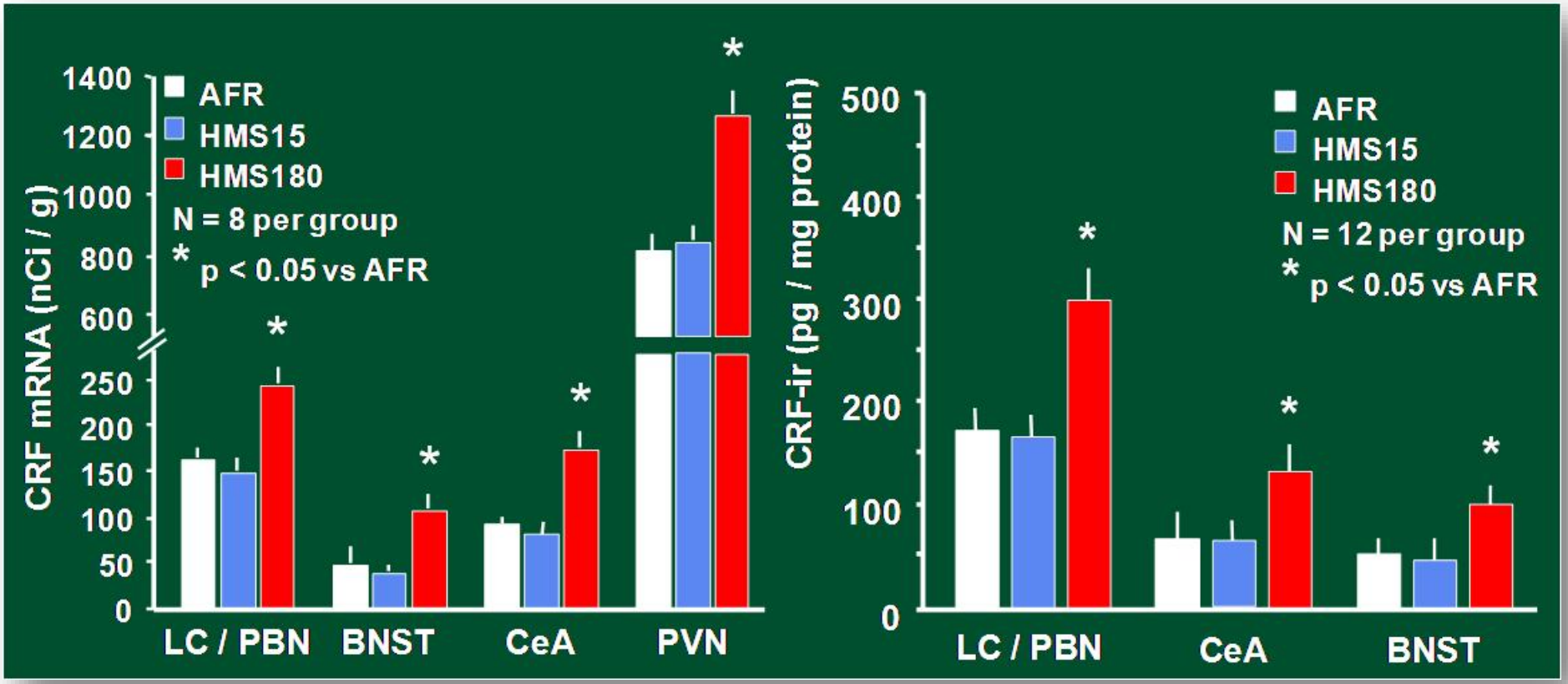


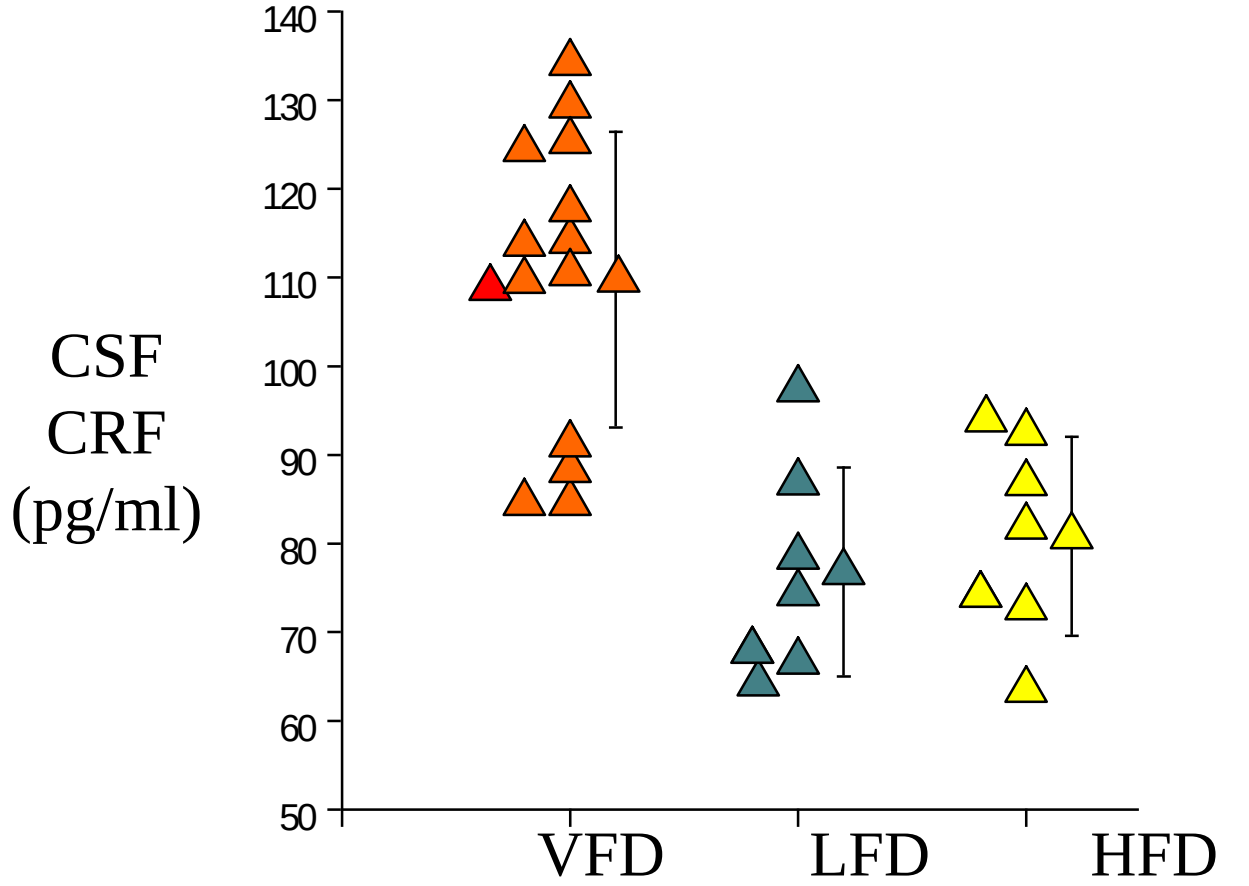
Figure 2. The Adverse Childhood Experiences Study Pyramid. (From US Centers for Disease Control and Prevention[9]).


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

Rearing-Associated Differences in Basal Adult CRF mRNA & Content

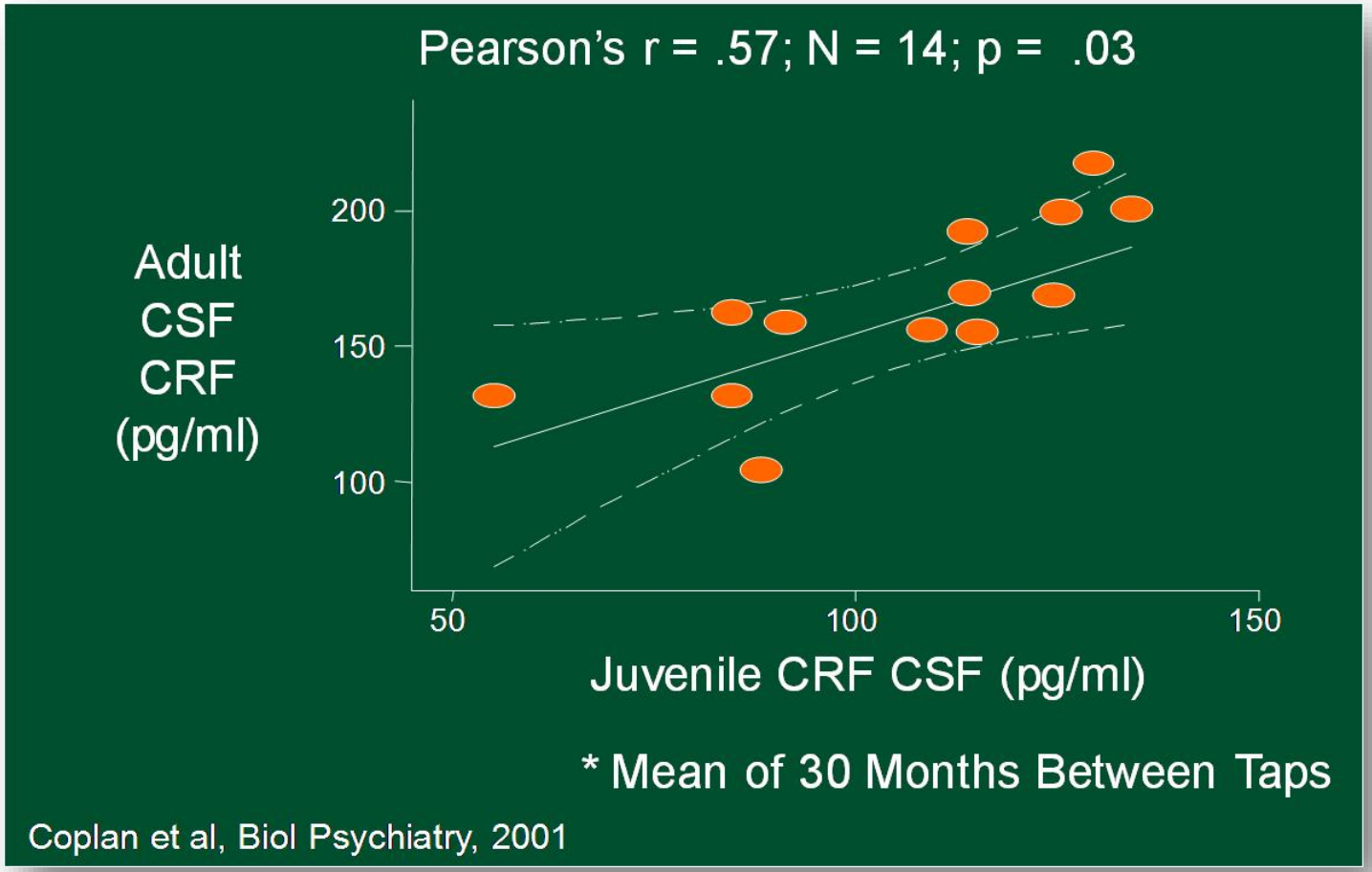


CSF CRF Concentrations in Differentially-Reared Juvenile Primates:



Coplan et al; *PNAS*, 1996

Stability of CSF CRF in VFD-Reared Primates: Juveniles to Adults



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

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

Deptartment of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia 30322

JAMA. 2000;284:592-597

Study Design

18-45 years with regular menses, no history of mania or psychosis, no active substance abuse or eating disorders, no medication

Subjects

- **12 women with no history of early life stress or psychiatric disorder (CON)**
- **14 women with a history of childhood abuse without major depression (ELS/non-MDD)**
- **13 women with a history of childhood abuse and major depression (ELS/MDD)**
- **10 women with no history of early life stress with major depression (non-ELS/MDD)**

Methods

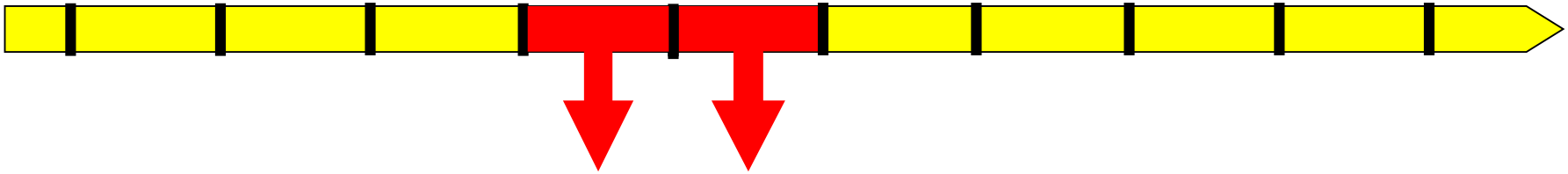
- **Structured Clinical Interview for DSM IV**
- **Structured interviews for the assessment of childhood abuse**
- **Psychometric assessment of depression, PTSD, and stress experiences**
- **Trier Social Stress Test**

Study Population

	CON (N=12)	ELS/non-MDD (N=14)	ELS/MDD (N=13)	non-ELS/MDD (N=10)	Statistics
Age	29.3 (2.2)	30.2 (1.5)	32.4 (2.1)	34.6(2.7)	NS
Race					
Afr.-Amer.	4	8	1	2	NS
Caucasian	8	6	12	8	
Education	26.08	24.96	21.50	28.30	NS
Abuse					
ETI Sexual	-	131.7 (70.6)	70.8 (32.2)	-	NS
ETI Physical	-	199.4 (75.1)	173.8 (39.0)	-	NS
HRSD	2.1 (.5)	6.8 (1.5)	19.0 (2.5)	21.1 (.8)	F=49.6, p<.001
PTSD					
N, %	-	5 (35.7)	11 (84.6)	-	χ^2=6.7, p<.01
CAPS	-	25.1 (5.1)	47.2 (3.9)	-	t=-3.38, p<.01

Trier Social Stress Test

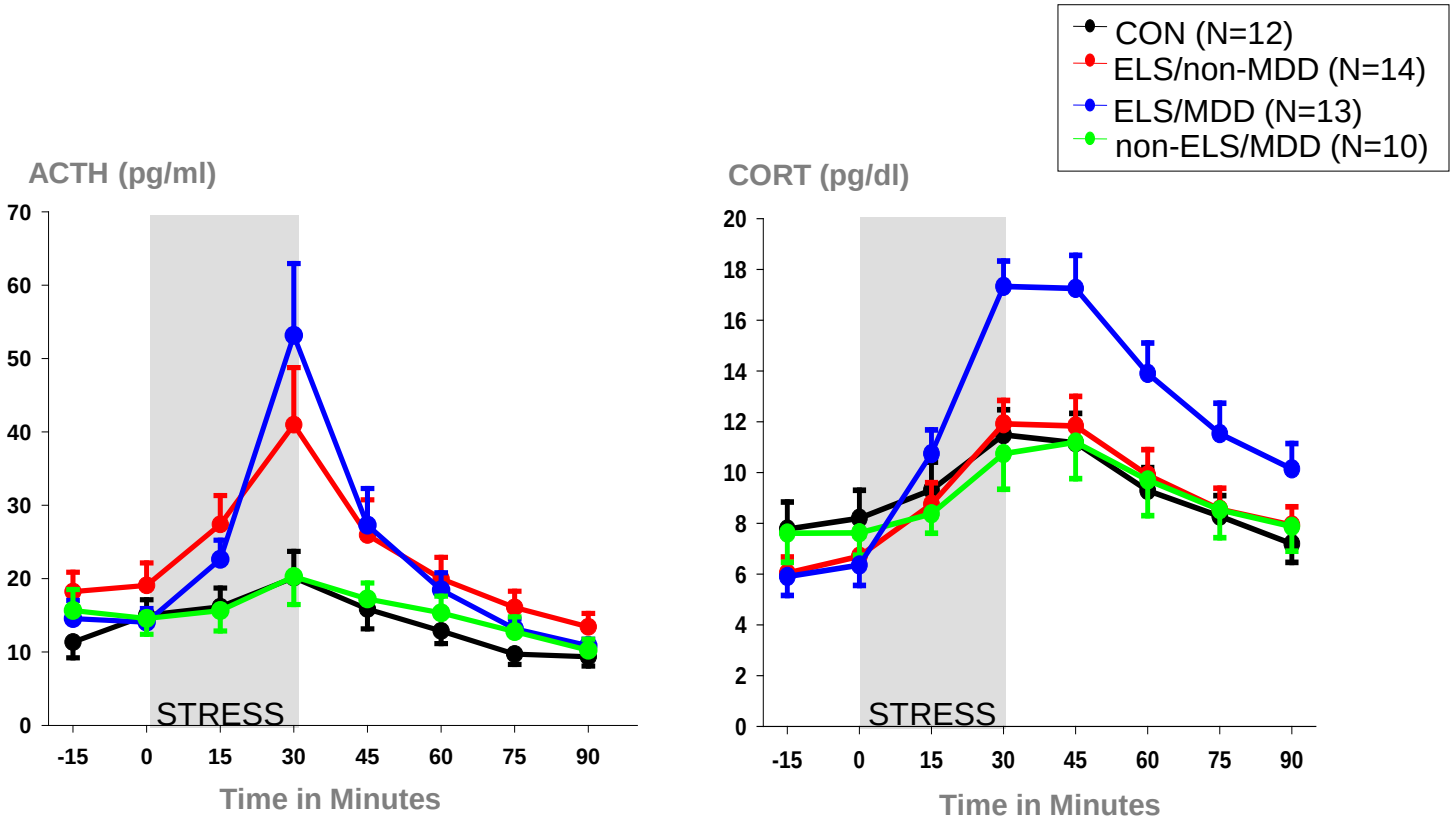
12:00	1:25	1:40	1:55	2:10	2:25	2:40	2:55	3:10	3:25
Minutes		-15	0	+10	+30	+45	+60	+75	+90
IV	Moved to test area	Blood HR	Blood HR	Blood HR	Blood HR	Blood HR	Blood HR	Blood HR	Blood HR



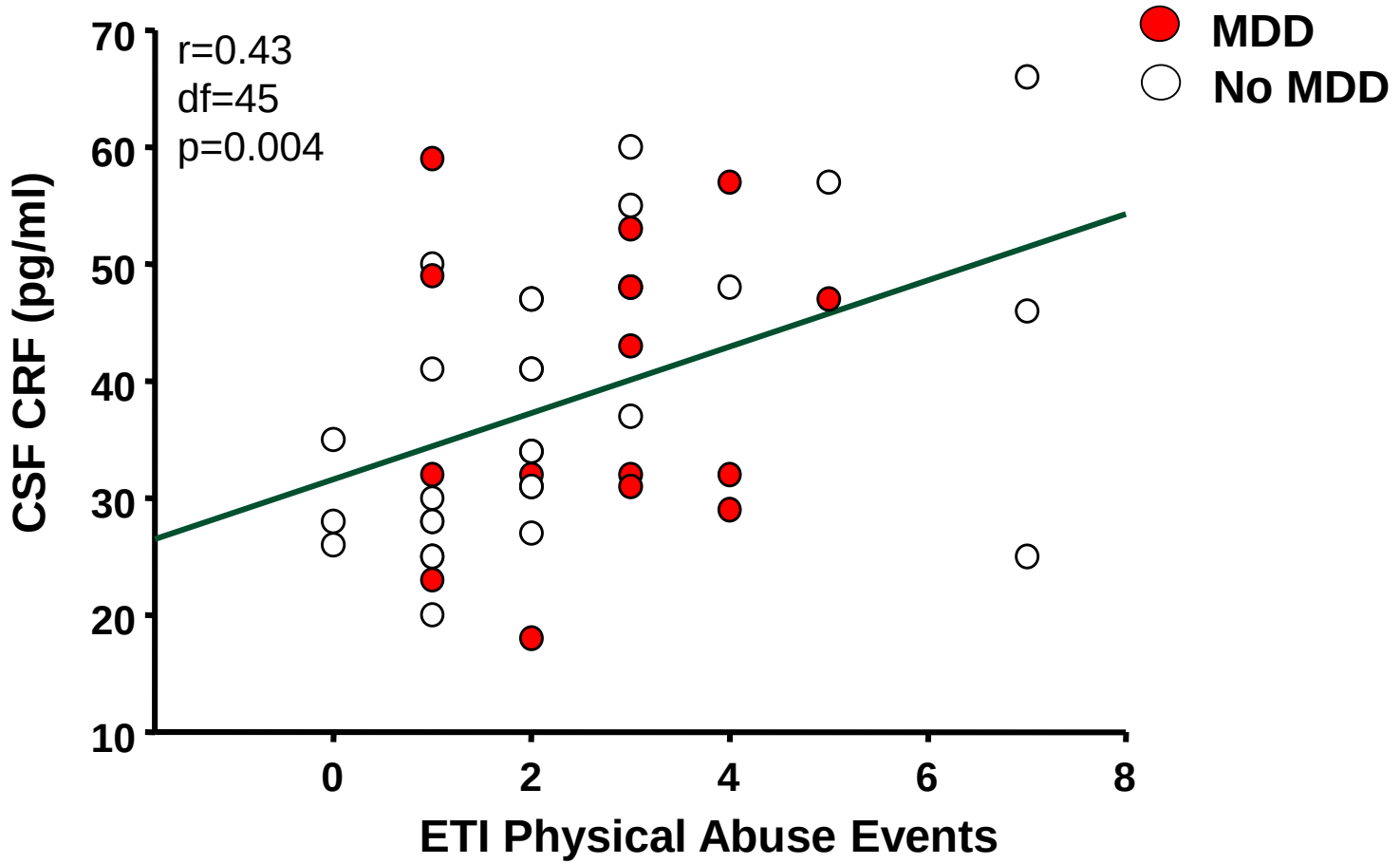
ANTICIPATION
PREPARATION

FREE SPEECH
ARITHMETICS

Trier Social Stress Test: Plasma ACTH and Cortisol



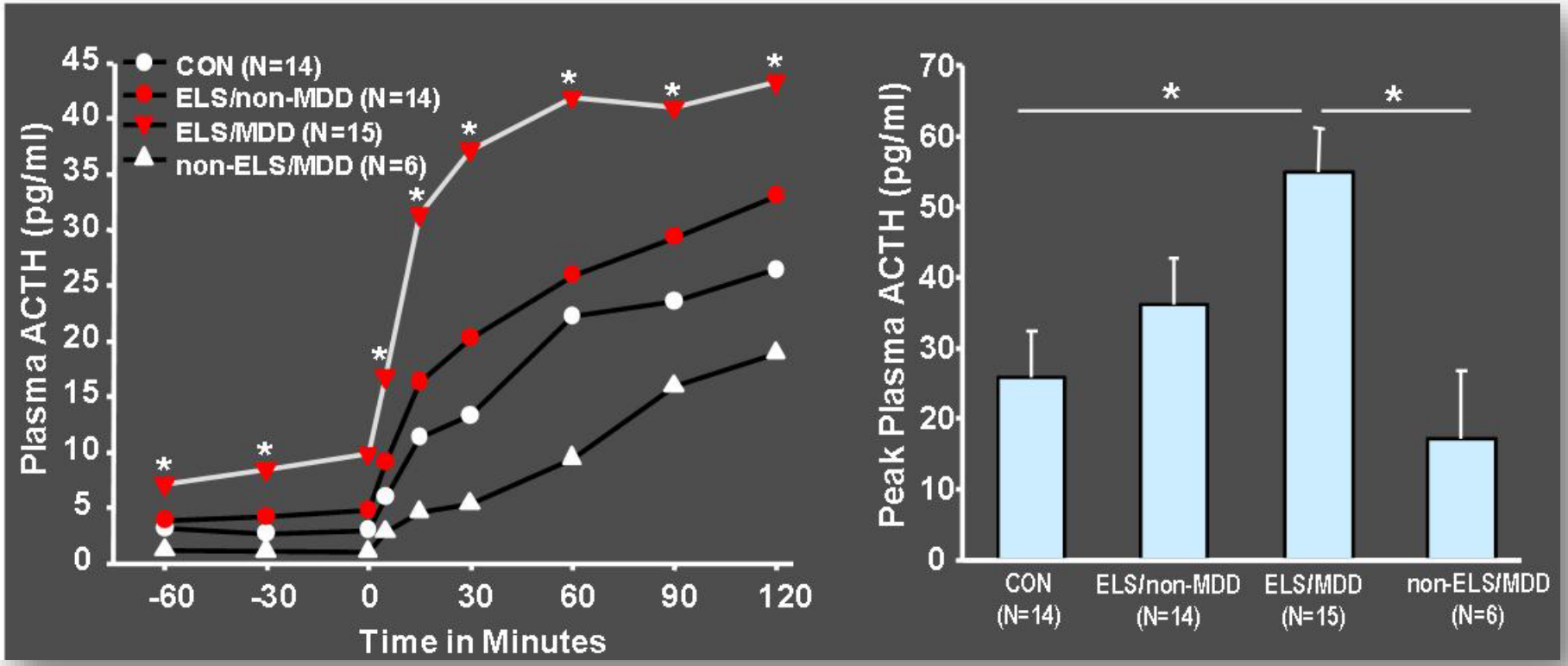
CSF CRF concentrations are correlated with the severity of the abuse events



Heim, Newport, Mletzko, Bonsall, Miller, Nemeroff (in preparation)

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.

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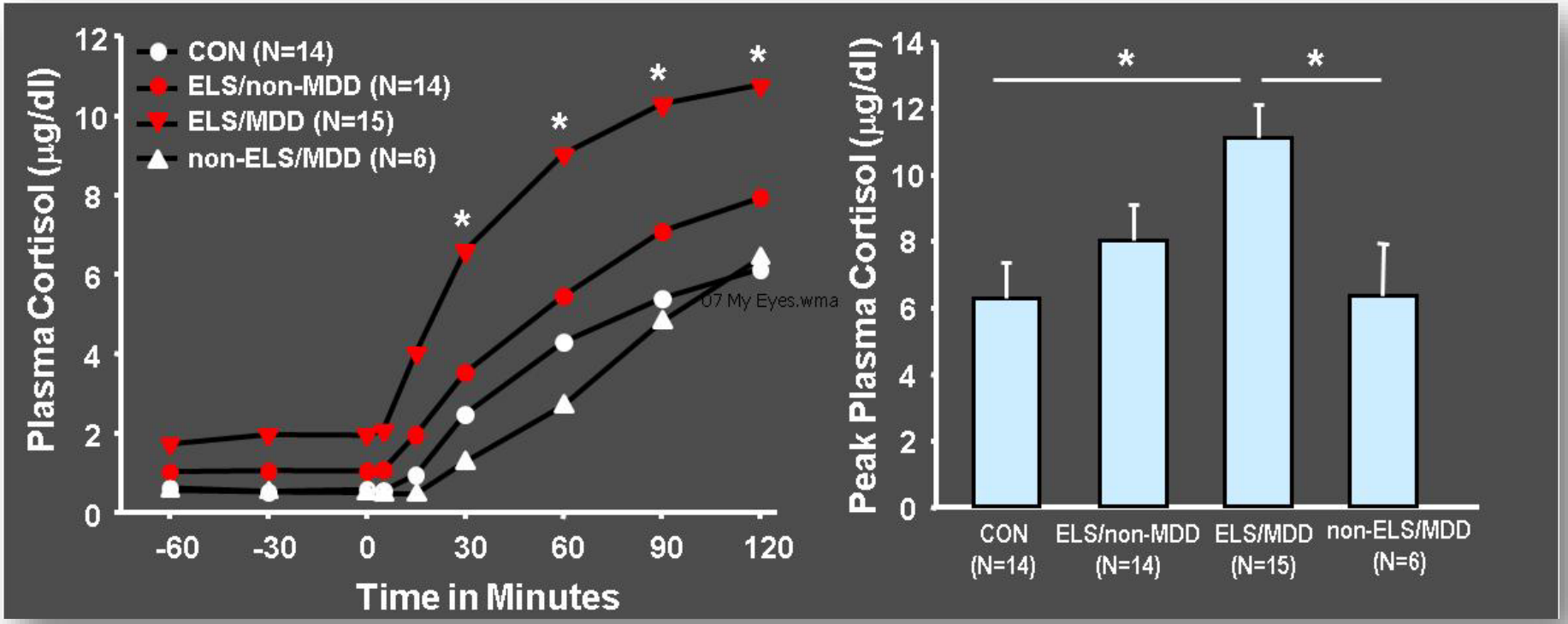
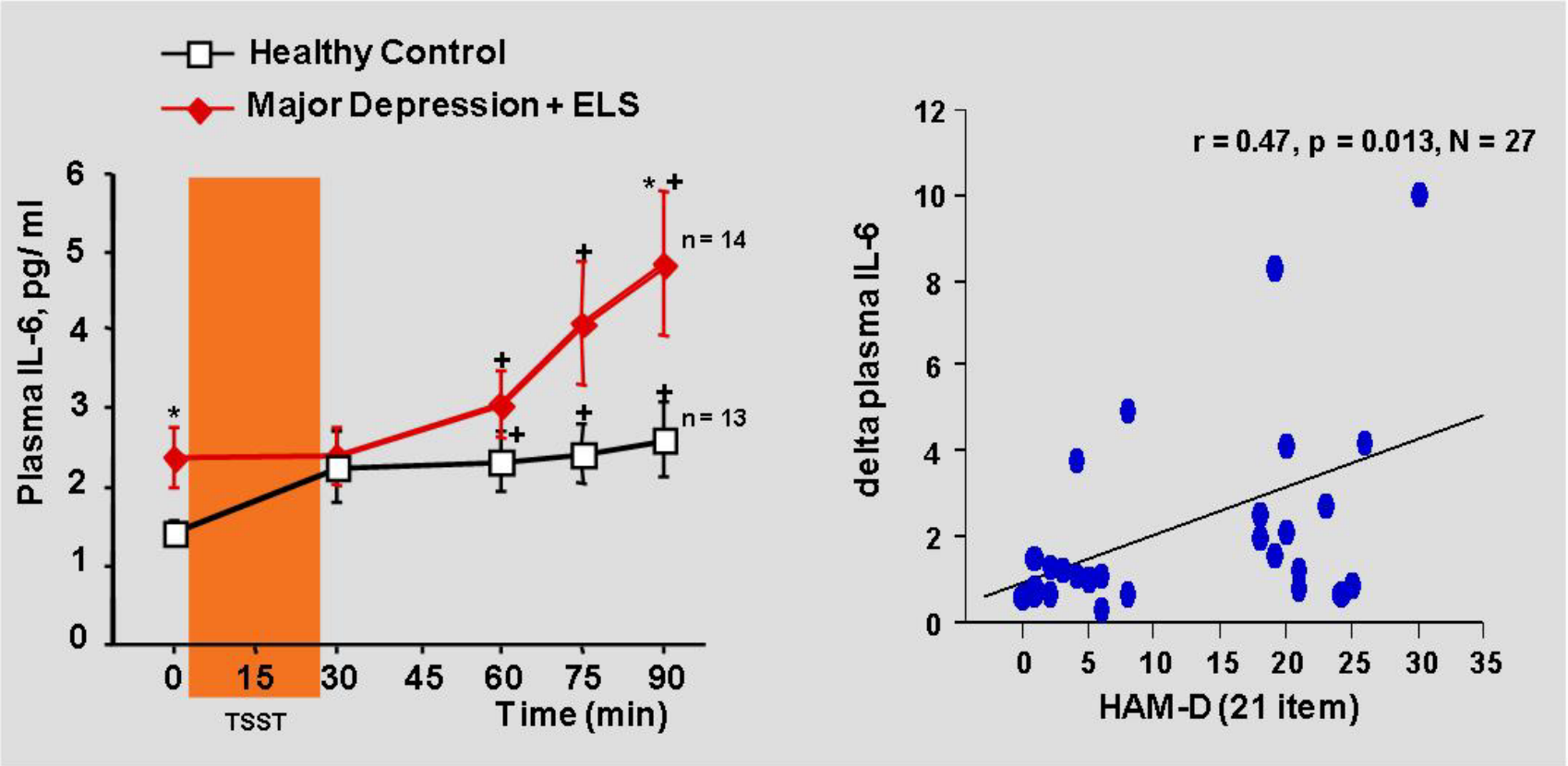
Abused men with current depression, but not depressed men without childhood abuse, demonstrate increased HPA axis responses

Cortisol



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.

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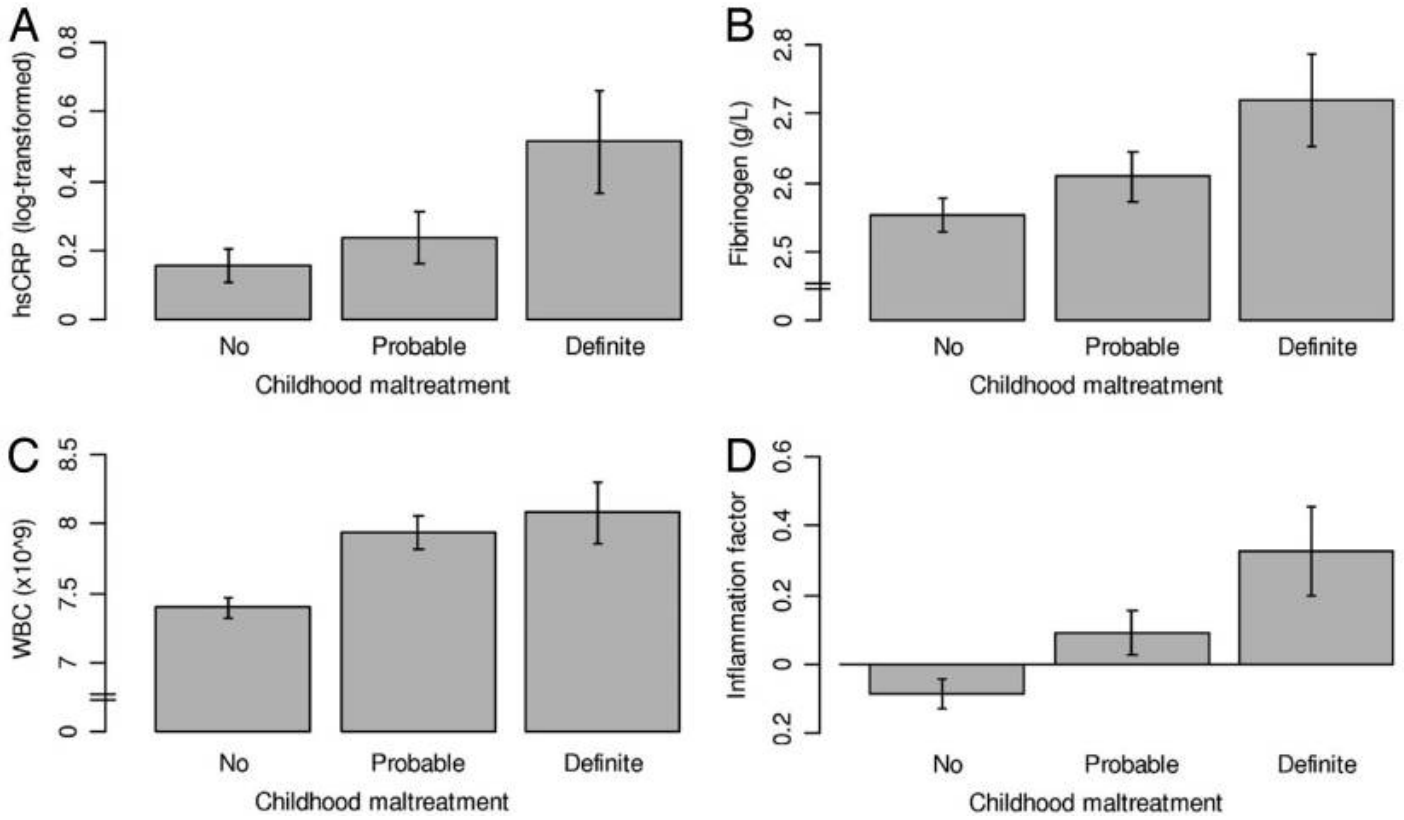
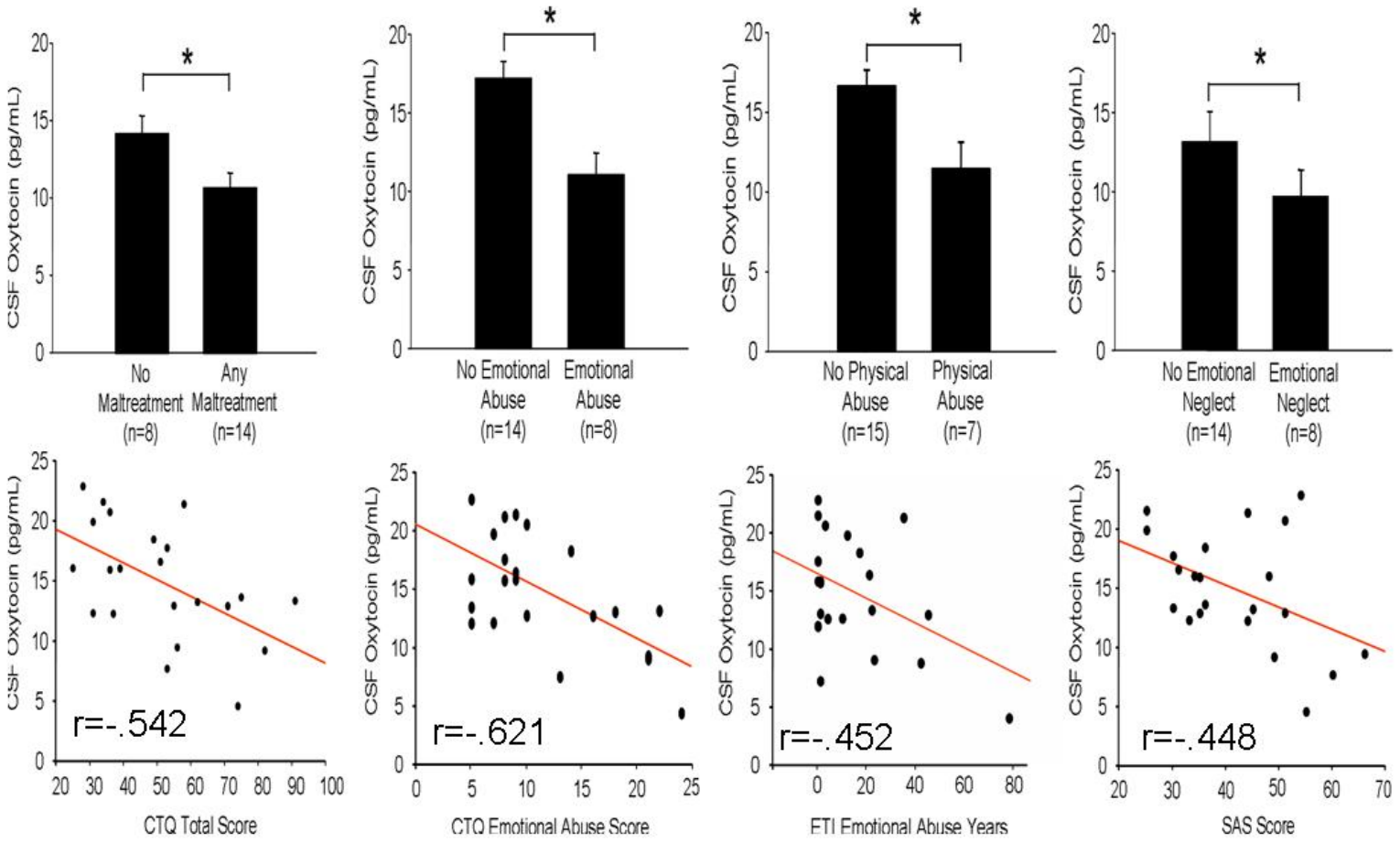
The Association of Childhood Maltreatment with Biomarkers of Inflammation



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

CSF OT Concentrations



Heim et al (2008) Mol Psychiatry, epub ahead of print

Variation in the oxytocin receptor gene is associated with increased risk for anxiety, stress and depression in individuals with a history of exposure to early life stress

Amanda J. Myers [a, *], Leanne Williams [b, c], Justine M. Gatt [b, d, e], Erica Z. McAuley-Clark [e], Carol Dobson-Stone [e, f], Peter R. Schofield [e, f], Charles B. Nemeroff [a]

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[b] The Brain Dynamics Centre, Sydney Medical School, University of Sydney, and Westmead Millennium Institute, Westmead Hospital, Westmead, NSW 2145, Australia
[c] Department of Psychiatry and Behavioral Neuroscience, Stanford University, CA, USA
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[f] School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia

Journal of Psychiatric Research 59 (2014) 93-100

A B S T R A C T

Background: Oxytocin is a neuropeptide that is involved in the regulation of mood, anxiety and social biology. Genetic variation in the oxytocin receptor gene (*OXTR*) has been implicated in anxiety, depression and related stress phenotypes. It is not yet known whether *OXTR* interacts with other risk factors such as early life trauma to heighten the severity of experienced anxiety and depression.

Methods: In this study, we examined genotypes in 653 individuals and tested whether SNP variation in *OXTR* correlates with severity of features of self-reported experience on the Depression Anxiety and Stress Scale (DASS), and whether this correlation is enhanced when early life trauma is taken into account. We also assessed the effects of *OXTR* SNPs on RNA expression levels in two separate brain tissue cohorts totaling 365 samples.

Results: A significant effect of *OXTR* genotype on DASS anxiety, stress and depression scores was found and ELS events, in combination with several different *OXTR* SNPs, were significantly associated with differences in DASS scores with one SNP (rs139832701) showing significant association or a trend towards association for all three measures. Several *OXTR* SNPs were correlated with alterations in *OXTR* RNA expression and rs3831817 replicated across both sets of tissues.

Conclusions: These results support the hypothesis that the oxytocin system plays a role in the pathophysiology of mood and anxiety disorders.

Journal of Psychiatric Research 59 (2014) 93-100

Sample Characteristics

	ELS Group	Control Group
	N	N
Male	15	13
Female	45	20
Total	60	33
Emotional Abuse	43	
Physical Abuse	38	
Sexual Abuse	34	
Emotional Neglect	34	
Physical Neglect	29	
	Mean(SD)	Mean(SD)
Age	30.20(7.38)	29.15(7.88)
HAMD	13(11)	6.4(8.8)
WRAT-3	50.72 (3.87)	51.42(3.8)

- First day of hospital admission, subjects completed the Cambridge Neuropsychological Testing Automated Battery (CANTAB)

- We utilized the following CANTAB modules
  - Psychomotor Coordination and Motor Speed
  - Reasoning and Planning Abilities
  - Memory (Spatial Working Memory, Pattern Recognition Memory, Spatial Recognition Memory)
  - Attention (Attention Shift and Sustained Attention)

Results

First Nonlinear Canonical Correlation

- Visual memory, executive functioning and spatial working memory deficits were associated with both abuse and neglect
- Emotional processing/ emotional inhibition deficits were associated with neglect, but not abuse

Results

Second Nonlinear Canonical Correlation

- Sexual abuse is associated with deficits in visual working memory
- Emotional processing and processing speed deficits are associated with neglect
- Executive functioning deficits are associated with sexual abuse

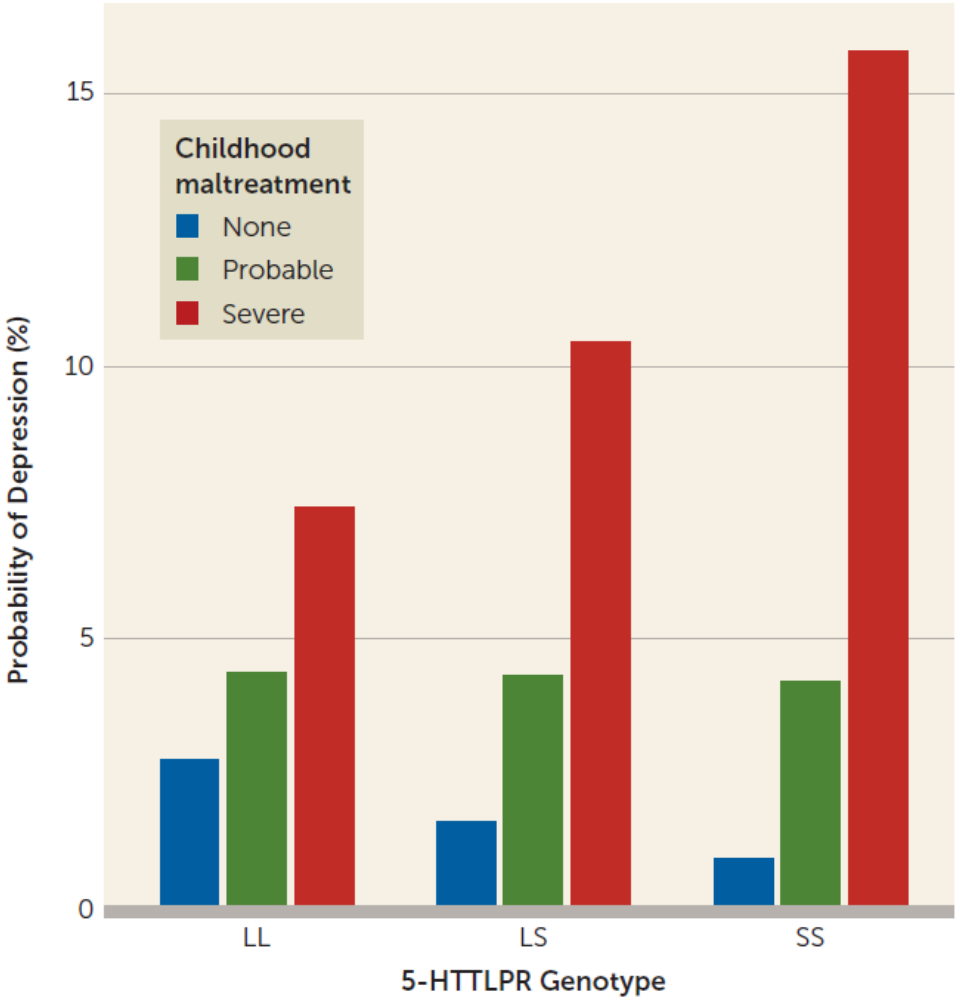
Gene-Environment Interaction in Youth Depression: Replication of the 5-HTTLPR Moderation in a Diverse Setting

Thiago Botter-Maio Rocha, M.D., Mara H. Hutz, Ph.D., Angélica Salatino-Oliveira, B.S., Júlia P. Genro, Ph.D., Guilherme V. Polanczyk, M.D., Ph.D., João Ricardo Sato, Ph.D., Fernando C. Wehrmeister, Ph.D., Fernando C. Barros, M.D., Ph.D., Ana M.B. Menezes, M.D., Ph.D., Luis Augusto Rohde, M.D., Ph.D., Luciana Anselmi, Ph.D., Christian Kieling, M.D., Ph.D.

Am J Psychiatry 2015; 172:978–985; doi: 10.1176/appi.ajp.2015.14070896

Conclusions: After following a research strategy as comparable as possible to that of the original study, the results corroborated the existence of a measured G×E, now in a large sample from a different sociocultural context. These findings provide further evidence that a genetic variant in the 5-HTTLPR moderates the link between childhood maltreatment and youth depression.

FIGURE 1. Probability of a Diagnosis of a Depressive Episode at Age 18/19 for Each Childhood Maltreatment Exposure Group, by 5-HTTLPR Genotype, Adjusted for Gender[a]



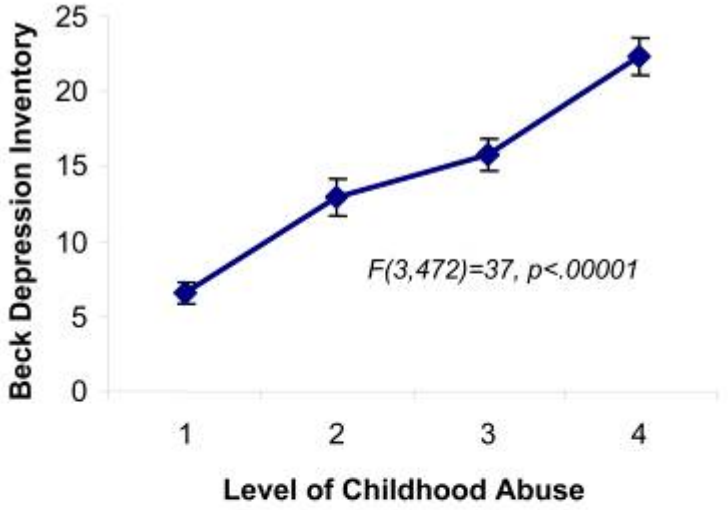
Sample Demographics

	N	Percentage
Gender		
Male	194	39%
Female	303	61%
Self-Identified Race/Ethnicity		
African American or Black	484	97%
Caucasian or White	4	.8%
Hispanic or Latino	2	.4%
Asian	1	.2%
Mixed	5	1%
Other	3	.6%
Education		
< 12th Grade	153	31%
High School Graduate or GED	217	44%
Some College or Technical School	78	15%
Technical School Graduate	21	4%
College Graduate	21	4%
Some Graduate School	9	2%
Employment Status		
Currently Unemployed	338	68%
Currently Employed	162	32%
Disability Status		
Not Currently Receiving Disability	394	79%
Currently Receiving Disability	103	21%
Household Monthly Income		
$0 – $249	158	32%
$250 – $499	51	10%
$500 - $999	136	28%
$1000 - $1999	106	21%
$2000 or more	158	9%

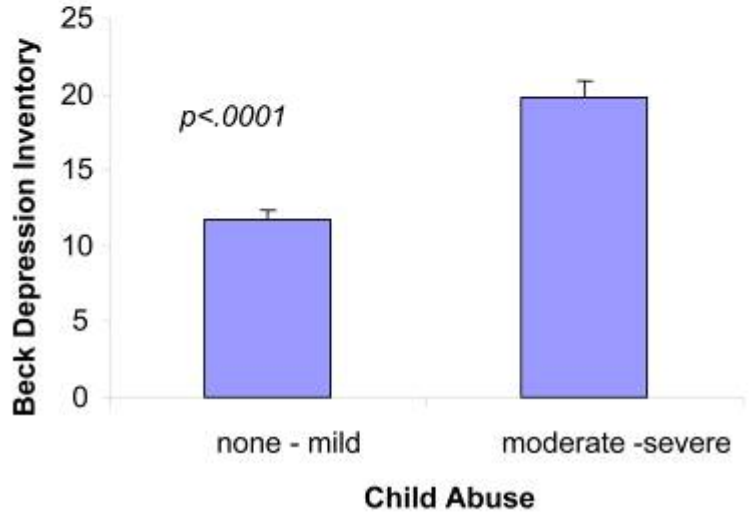
Bradley, Binder et al (2008) Arch Gen Psychiatry 65:190-200.

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.

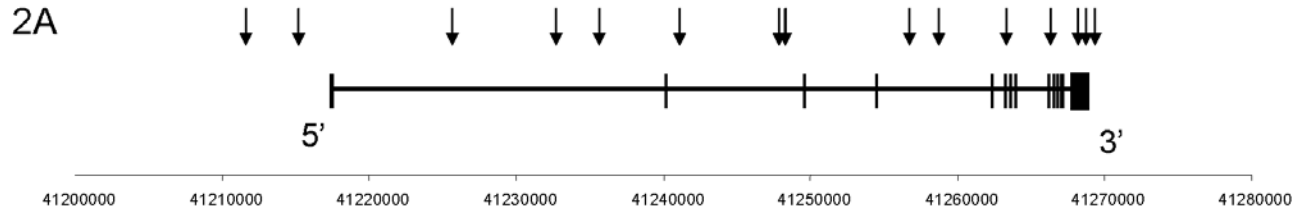


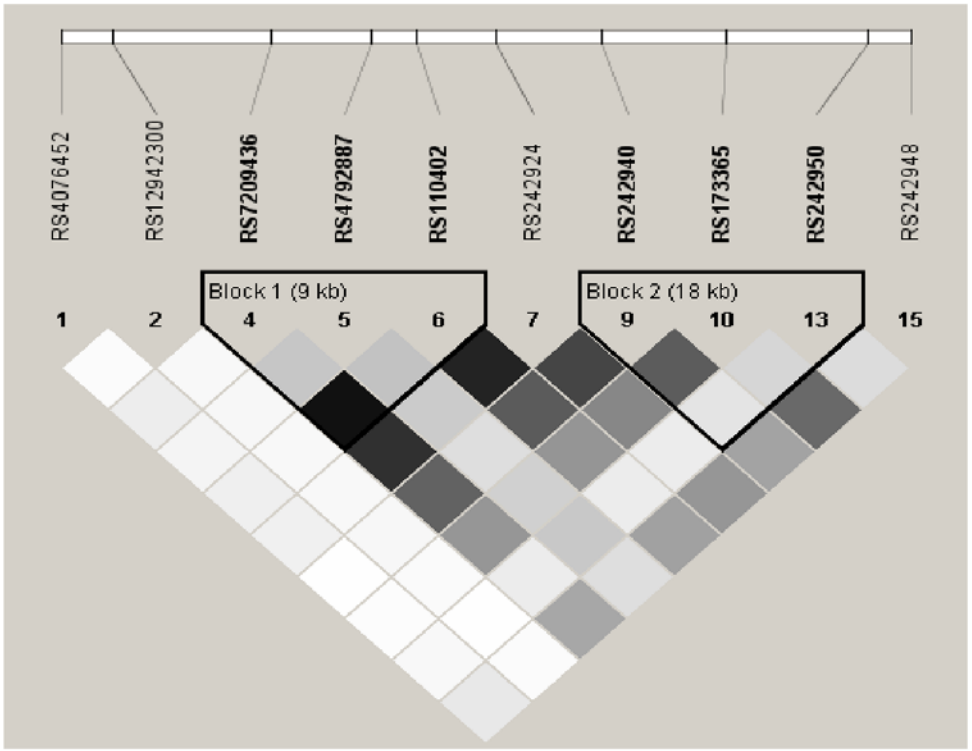
Depression is predicted by presence/absence of childhood trauma.



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

CRHR1 Linkage Disequilibrium Map and Interaction with Early Life Stress and Depression

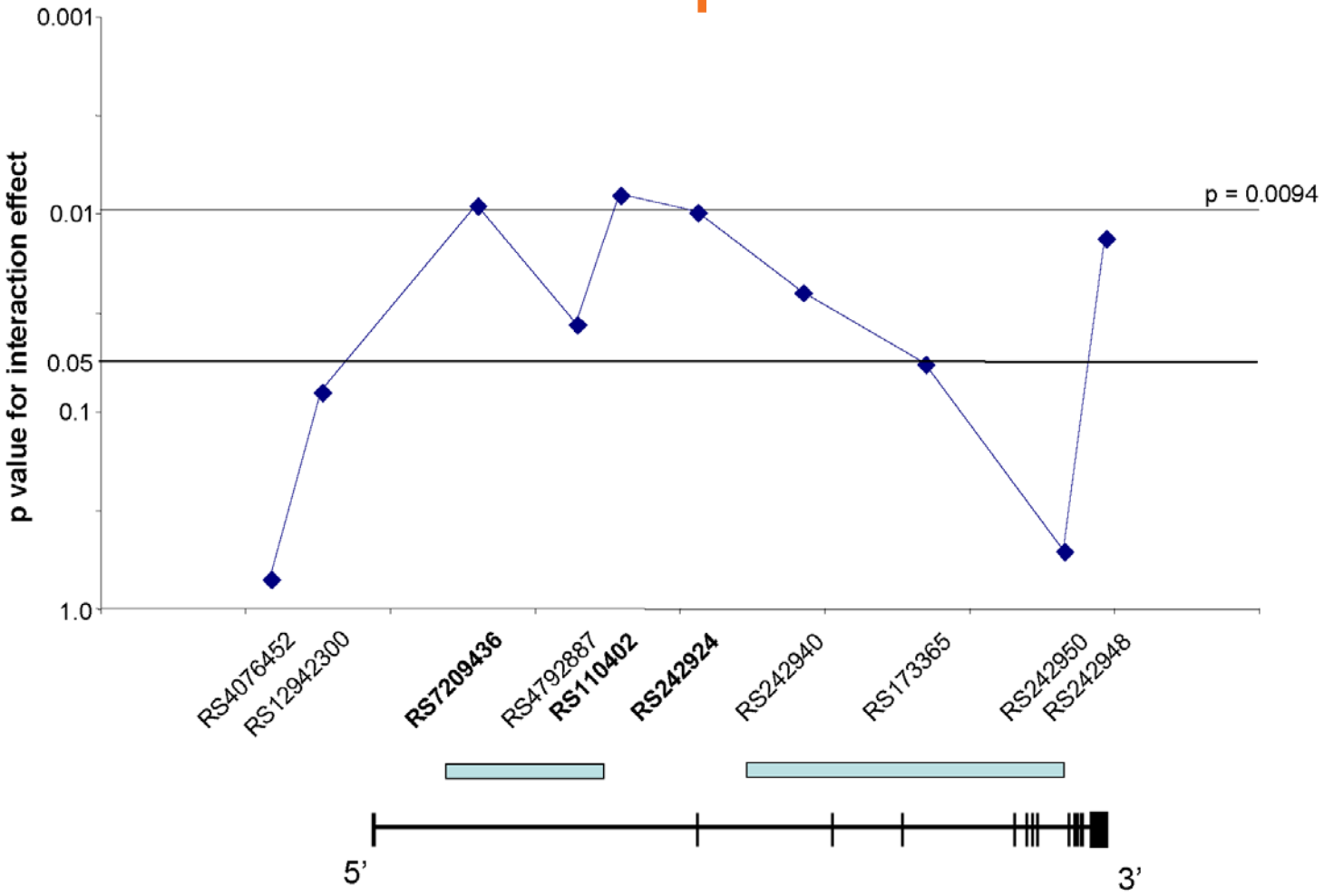




Bradley, Binder et al (2008) Arch Gen Psychiatry 65:190-200.

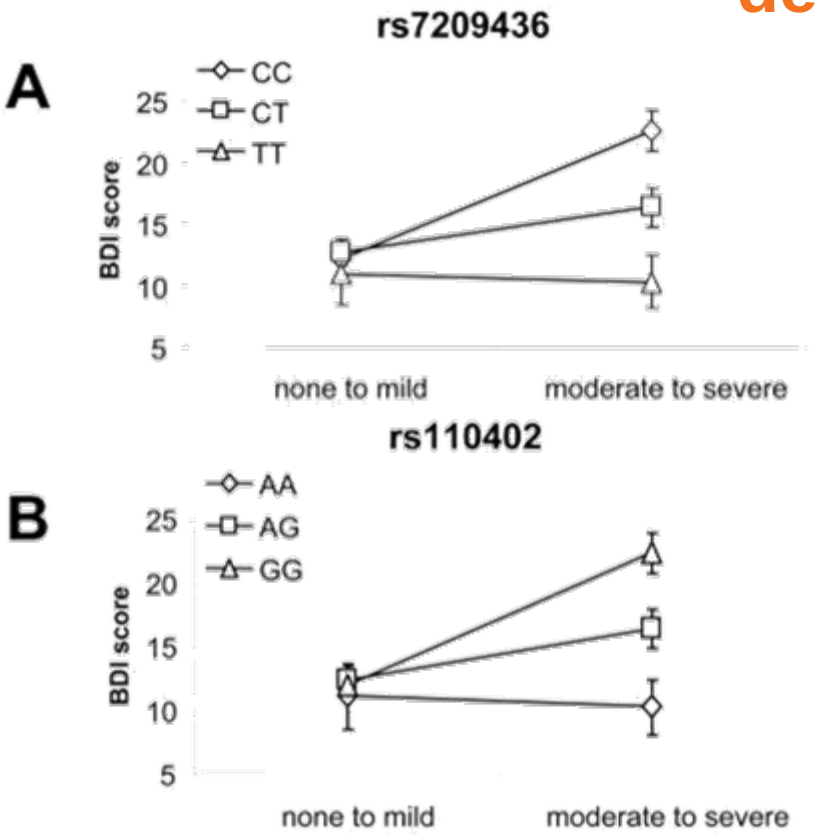
UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM
UNIVERSITY OF MIAMI
MILLER SCHOOL
of MEDICINE

Interaction effect of *CRHR1* SNPs with early life stress on adult depression.

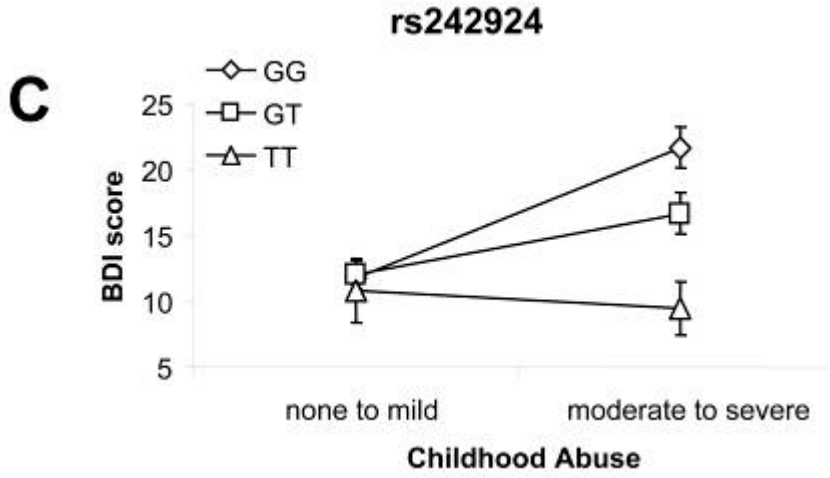


Bradley, Binder et al (2008) Arch Gen Psychiatry 65:190-200.

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.

Effect of estimated *CRHR1* haplotypes and childhood abuse on adult depressive symptoms.

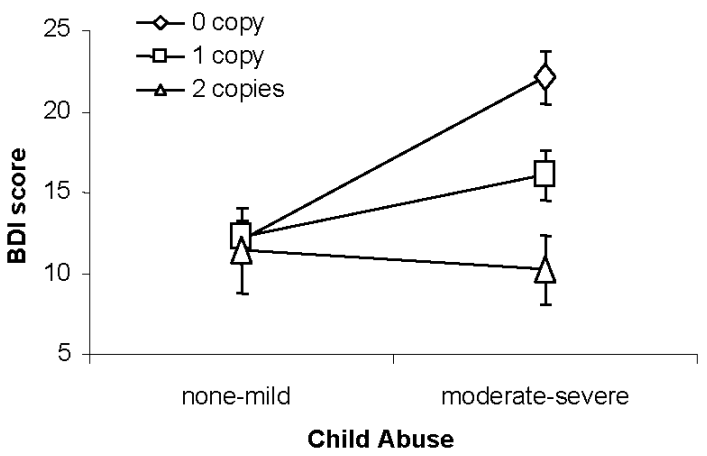
A

Block 1 haplotypes

rs7209436	rs4792887	rs110402	Frequency %
C	T	G	34.1
C	C	G	34.0
T	C	A	30.4

frequencies of the estimated individual haplotypes within the first LD block

B

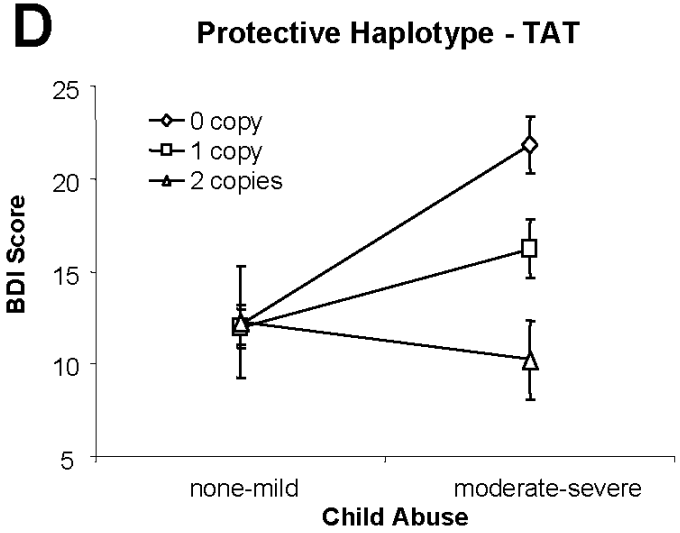


C

3 most significant SNPs haplotypes

rs7209436	rs110402	rs242924	Frequency %
C	G	G	66.5
T	A	T	28.8

D

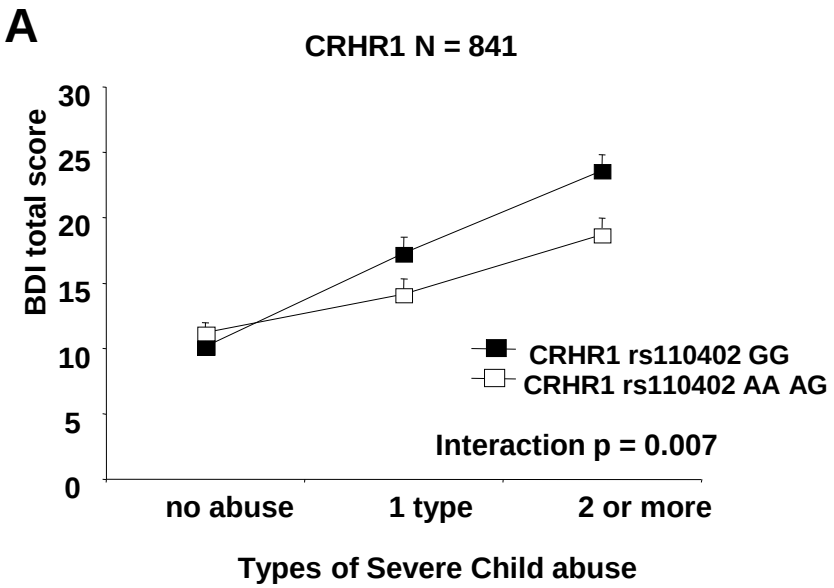


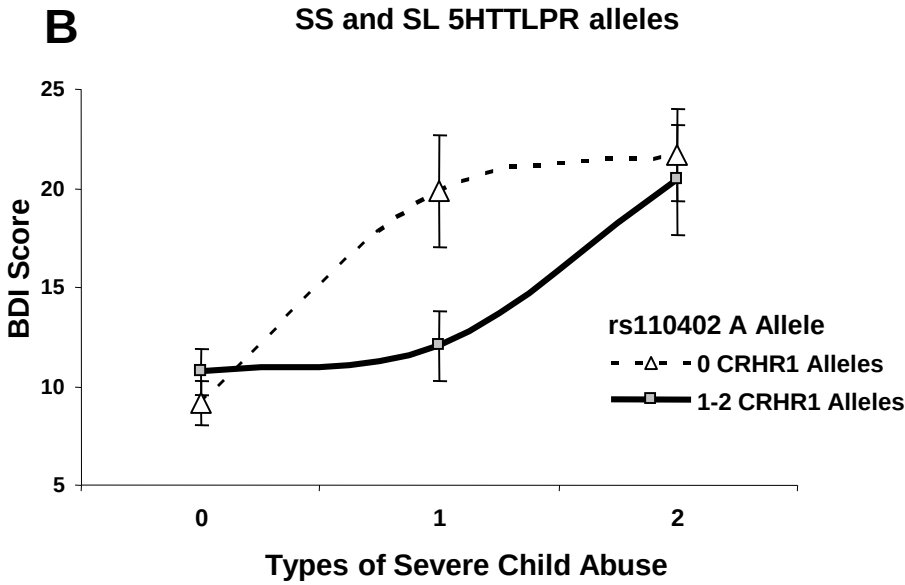
Bradley, Binder et al (2008) Arch Gen Psychiatry 65:190-200.

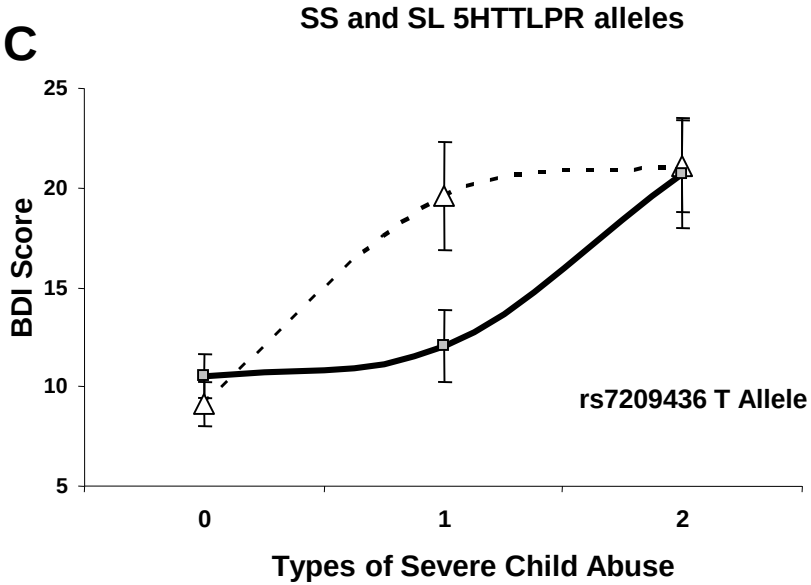
Summary: Gene by environment effects of the CRHR1 gene

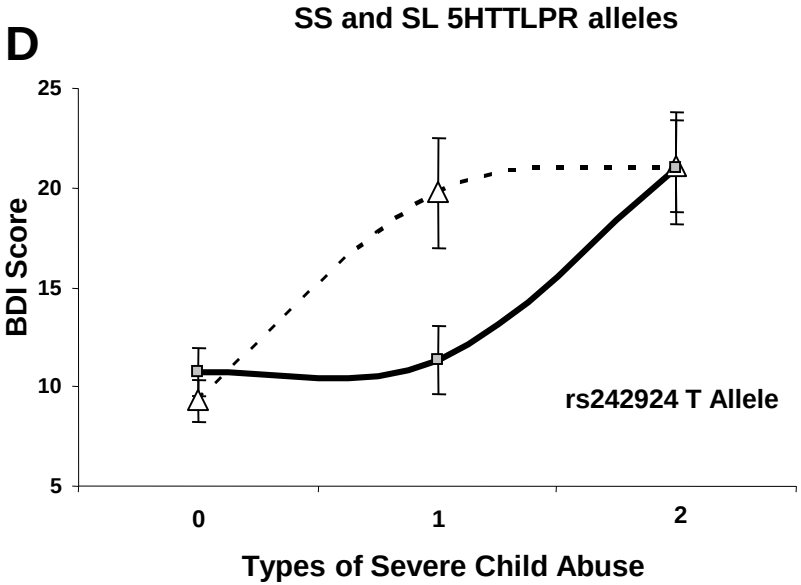
- Early results suggest that polymorphisms at the CRH R1 receptor may be involved in interaction of childhood trauma and developmental risk for depressive symptoms
- This may occur through developmental sensitization of the HPA axis, in part through the effects of early trauma and abuse, and their lasting effects on the CRH system.
- Initially, no effect was found with CRHR1 genotype, child abuse, and PTSD.
- Follow up data suggest that an 'anxious' subtype of depression may carry the primary effect

Larger Cohort (N=800-900):
3-way 5HTTLPR x CRHR1 SNP x Child Abuse Interaction



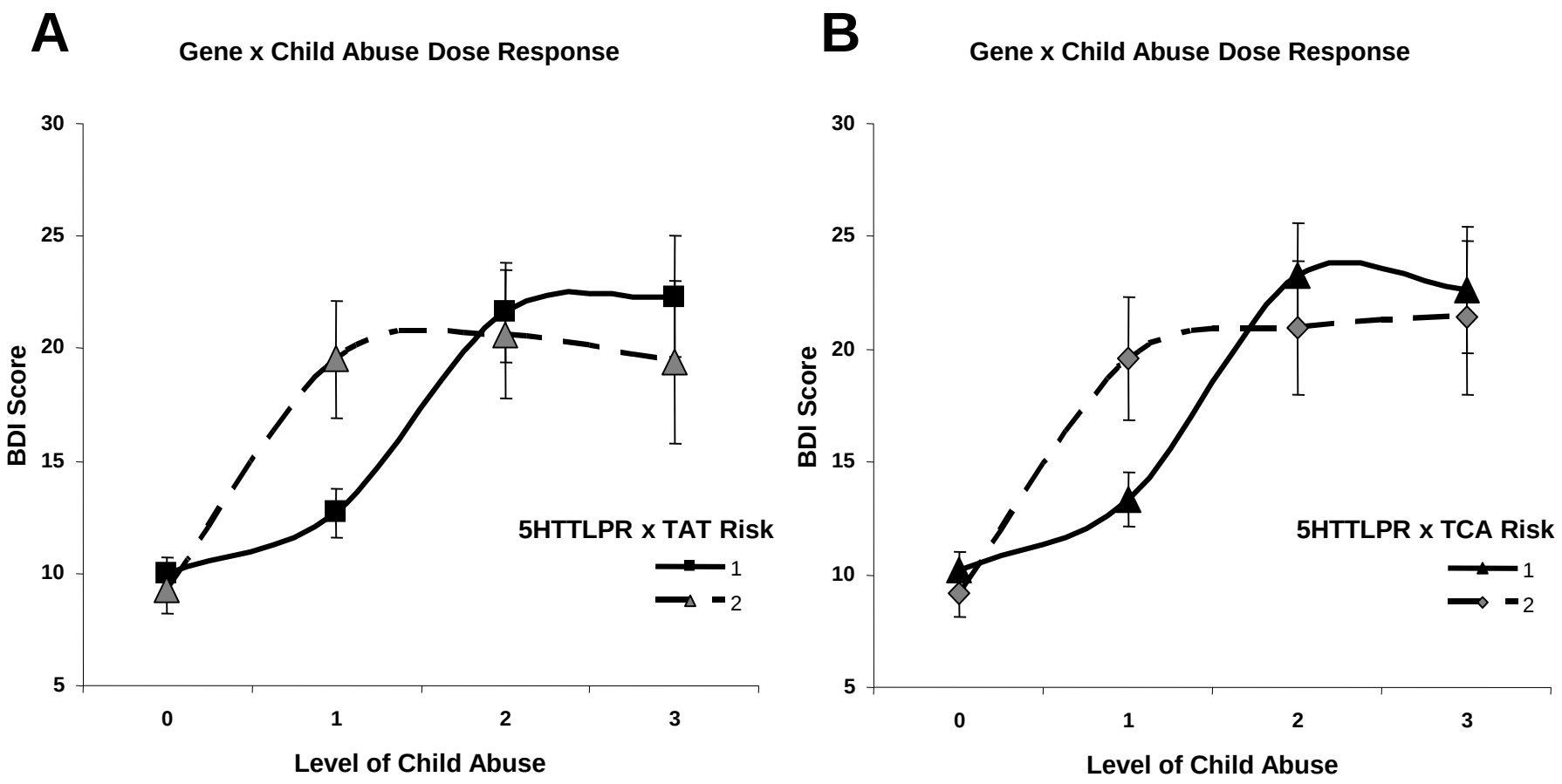






Ressler et al., Am J Hum Gen B

Figure 5: Combined Genetic Risk predicts Dose-Response Effect of Child Abuse on Depression

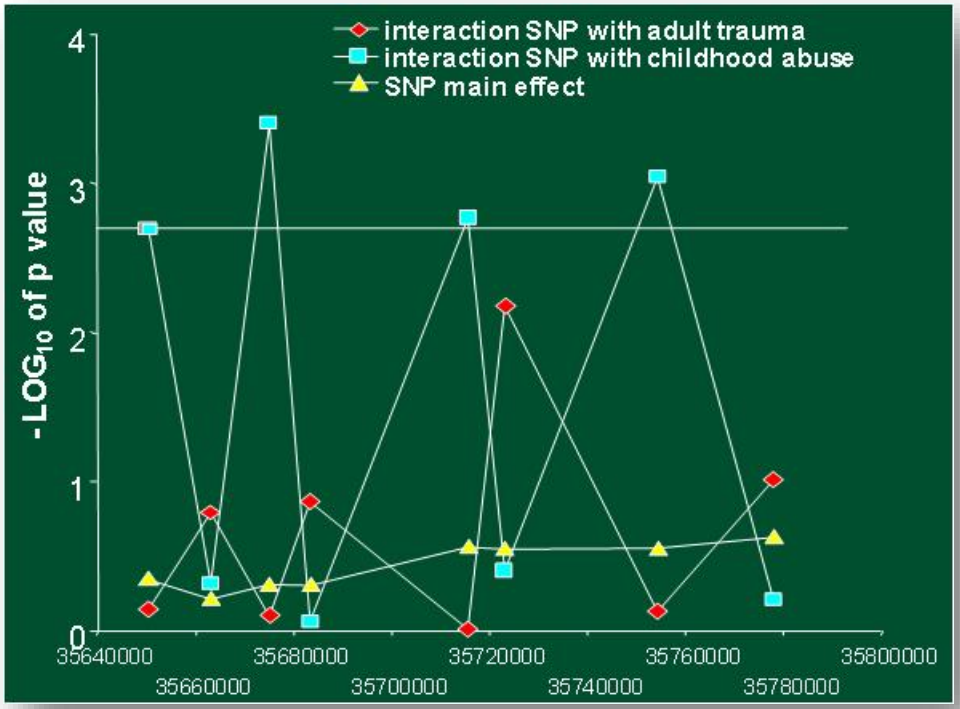


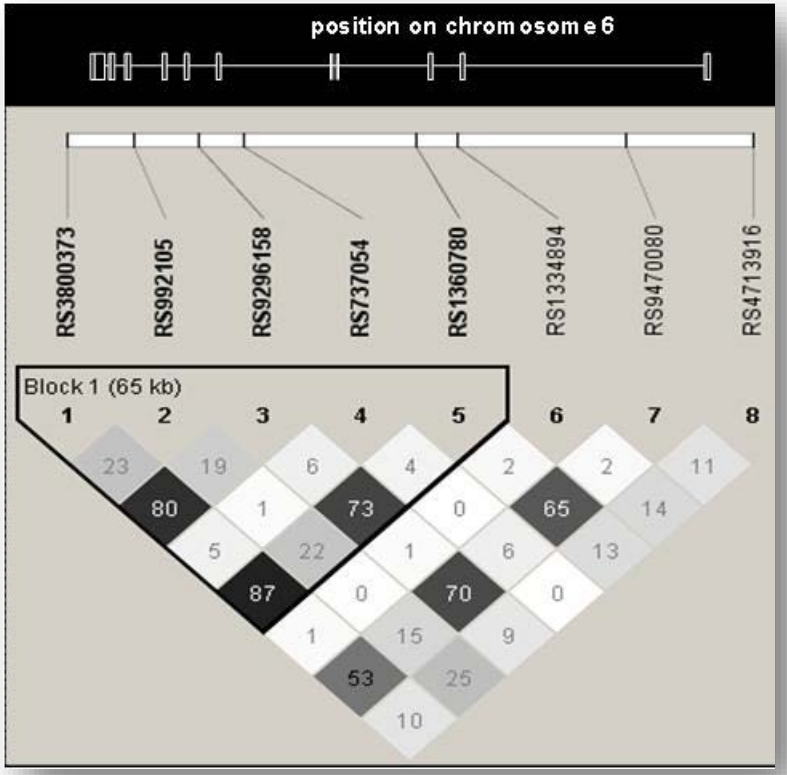
Ressler et al., Am J Hum Gen B

Another HPA Axis Gene: FKBP5 and PTSD

- PTSD associated with GR super-sensitivity (Yehuda et al., 2004)
- FKBP5 chaperone protein is critically involved in the feedback regulation of GR sensitivity
- Evidence of FKBP5 in dissociation with trauma and in post-trauma prediction of later PTSD

FKBP5 SNPs and main genetic effect on PTSD symptoms and interaction effects with adult trauma levels and child abuse

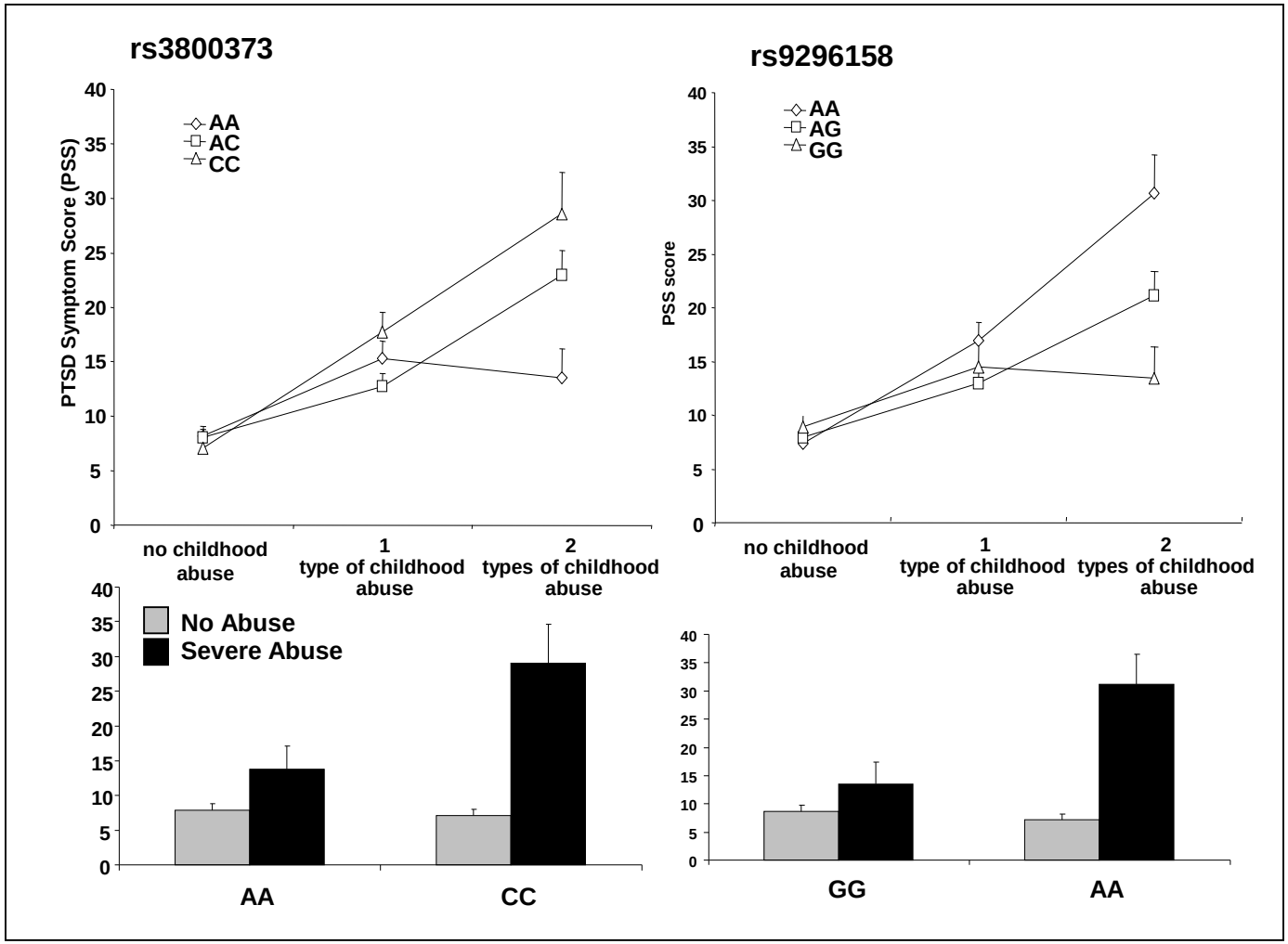




Binder et al (2008) JAMA 299:1291-1305.

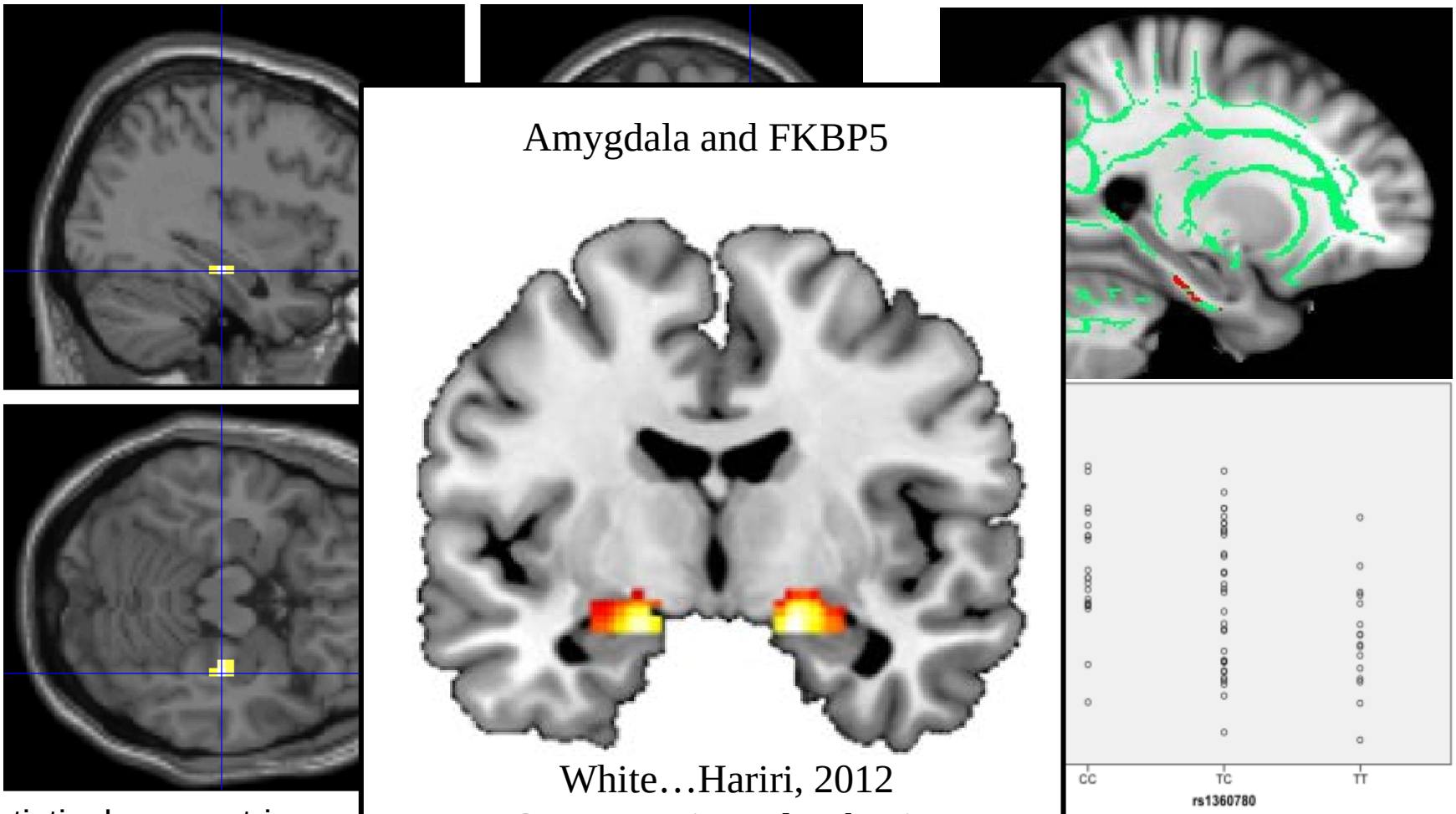
PTSD Severity, *FKBP5* SNP Genotypes and child abuse

For all 4 SNPs (rs1360780 and rs9470080 not shown)
an additive interaction effect with child abuse on PSS score is observed



Binder et al (2008) JAMA 299:1291-1305.

Hippocampal activation and structural differences in FKBP5 risk allele carriers



Amygdala and FKBP5

White…Hariri, 2012
Genes, Brain and Behavior

Statistical parametric map
processing of threat incon
faces in

enotype and Structural Integrity
of Posterior Cingulum
Fani et al., *2013, Neuropsychopharm.*

Fani et al., 2013, *JAMA Psychiatry*

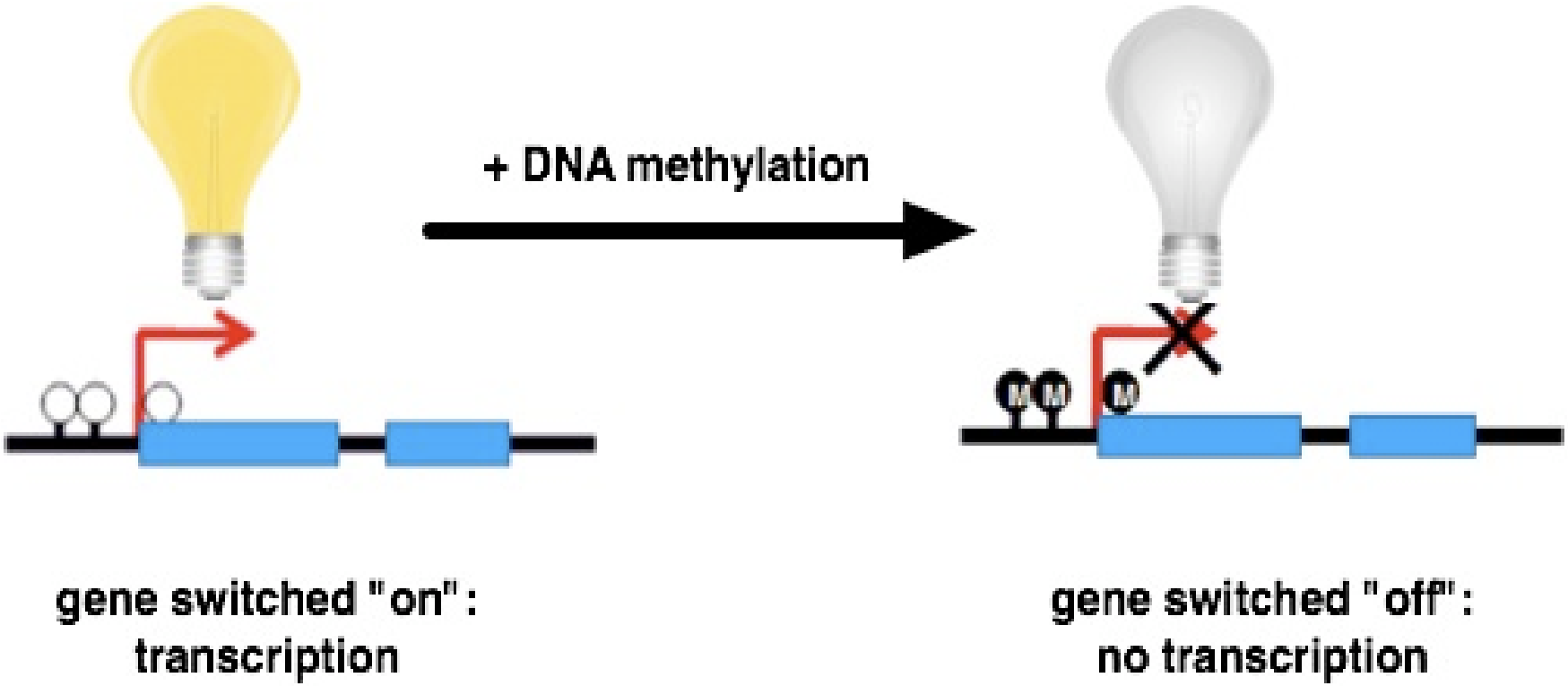


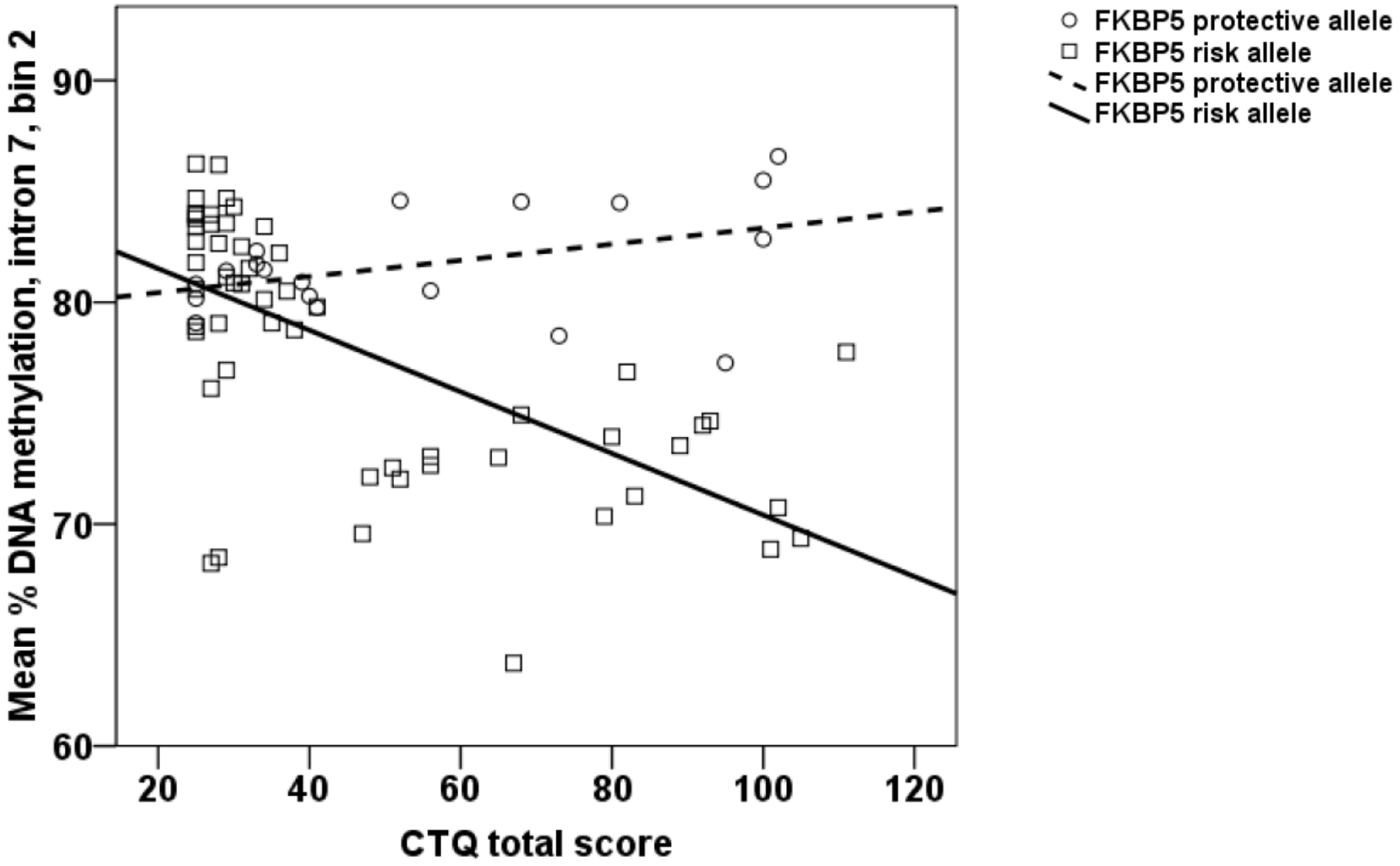
figure 1: Transcriptional silencing of gene promoters via DNA methylation

Klengel et al., 2013, *Nature Neurosci*

Allele-specific DNA demethylation in FKBP5: a molecular mediator of gene x childhood trauma interactions

Torsten Klengel, Divya Mehta, Christoph Anacker, Jens C. Pruessner, Carmine M. Pariante, Thaddeus W.W. Pace, Kristina B. Mercer, Helen S. Mayberg, Bekh Bradley, Charles B. Nemeroff, Florian Holsboer, Christine M. Heim, Kerry J. Ressler, Theo Rein, and Elisabeth B. Binder

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.


FKBP5 protective allele
FKBP5 risk allele
FKBP5 protective allele
FKBP5 risk allele
Mean % DNA methylation, intron 7, bin 2
90
80
70
60
20
40
60
80
100
120
CTQ total score

[VIDEO PLACE HOLDER]

Video also located @
https://www.youtube.com/watch?v=3ZChSSw95Tg

ARTICLE

doi:10.1038/nature09856

Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor

Kerry J. Ressler[1,2,4], Kristina B. Mercer[1], Bekh Bradley[2,3], Tanja Jovanovic[2], Amy Mahan[4], Kimberly Kerley[1], Seth D. Norrholm[2,3], Varun Kilaru[2], Alicia K. Smith[2], Amanda J. Myers[5], Manuel Ramirez[5], Anzhelika Engel[5], Sayamwong E. Hammack[6], Donna Toufexis[4,6], Karen M. Braas[7], Elisabeth B. Binder[2,8] & Victor May[7]

Pituitary adenylate cyclase-activating polypeptide (PACAP) is known to broadly regulate the cellular stress response. In contrast, it is unclear if the PACAP–PAC1 receptor pathway has a role in human psychological stress responses, such as post-traumatic stress disorder (PTSD). Here we find, in heavily traumatized subjects, a sex-specific association of PACAP blood levels with fear physiology, PTSD diagnosis and symptoms in females. We examined 44 single nucleotide polymorphisms (SNPs) spanning the PACAP (encoded by *ADCYAP1*) and PAC1 (encoded by *ADCYAP1R1*) genes, demonstrating a sex-specific association with PTSD. A single SNP in a putative oestrogen response element within *ADCYAP1R1*, rs2267735, predicts PTSD diagnosis and symptoms in females only. This SNP also associates with fear discrimination and with *ADCYAP1R1* messenger RNA expression in human brain. Methylation of *ADCYAP1R1* in peripheral blood is also associated with PTSD. Complementing these human data, *ADCYAP1R1* mRNA is induced with fear conditioning or oestrogen replacement in rodent models. These data suggest that perturbations in the PACAP–PAC1 pathway are involved in abnormal stress responses underlying PTSD. These sex-specific effects may occur via oestrogen regulation of *ADCYAP1R1*. PACAP levels and *ADCYAP1R1* SNPs may serve as useful biomarkers to further our mechanistic understanding of PTSD.

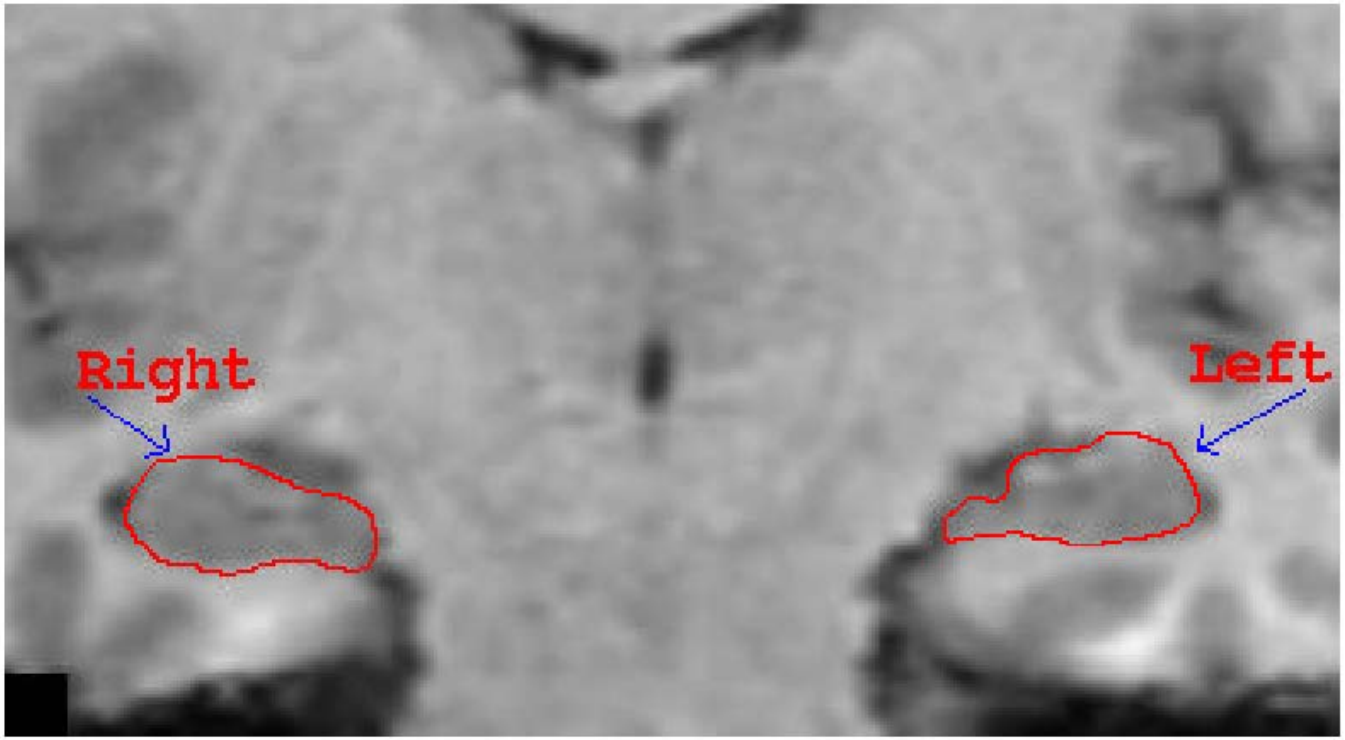
Amygdala-Dependent Fear Is Regulated by *Oprl1* in Mice and Humans with PTSD

Raül Andero,[1,2] Shaun P. Brothers,[3] Tanja Jovanovic,[2] Yen T. Chen,[4]* Hasib Salah-Uddin,[3] Michael Cameron,[5] Thomas D. Bannister,[4] Lynn Almli,[2] Jennifer S. Stevens,[2] Bekh Bradley,[2] Elisabeth B. Binder,[2,6] Claes Wahlestedt,[3] Kerry J. Ressler[1,2,7]†

The amygdala-dependent molecular mechanisms driving the onset and persistence of posttraumatic stress disorder (PTSD) are poorly understood. Recent observational studies have suggested that opioid analgesia in the aftermath of trauma may decrease the development of PTSD. Using a mouse model of dysregulated fear, we found altered expression within the amygdala of the Oprl1 gene (opioid receptor–like 1), which encodes the amygdala nociceptin (NOP)/orphanin FQ receptor (NOP-R). Systemic and central amygdala infusion of SR-8993, a new highly selective NOP-R agonist, impaired fear memory consolidation. In humans, a single-nucleotide polymorphism (SNP) within OPRL1 is associated with a self-reported history of childhood trauma and PTSD symptoms (n = 1847) after a traumatic event. This SNP is also associated with physiological startle measures of fear discrimination and magnetic resonance imaging analysis of amygdala-insula functional connectivity. Together, these data suggest that Oprl1 is associated with amygdala function, fear processing, and PTSD symptoms. Further, our data suggest that activation of the Oprl1/NOP receptor may interfere with fear memory consolidation, with implications for prevention of PTSD after a traumatic event.

Science Translational Medicine 5 June 2013 Vol 5 Issue 188 188ra73

Fig 1. WHOLE HIPPOCAMPAL MEASUREMENT

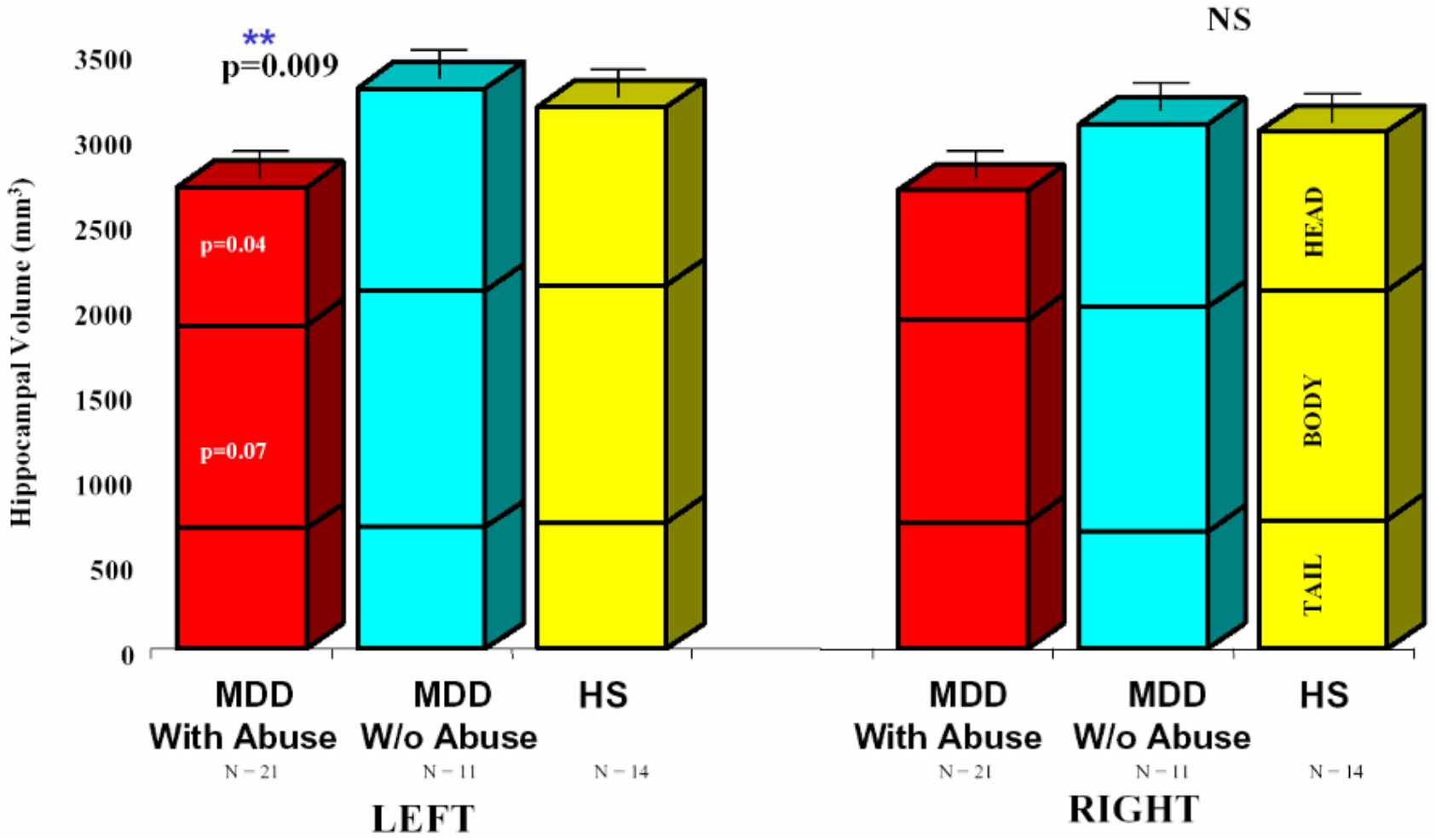


Boundaries
- Anterior: amy/hipp junc.
- Posterior boundary
- Head, body, tail

Includes:
- Dentate Gyrus
- Subiculum
- Fimbria
- Grey matter

Excludes:
- Parahipp Gyrus
- Fornix
- Amygdala

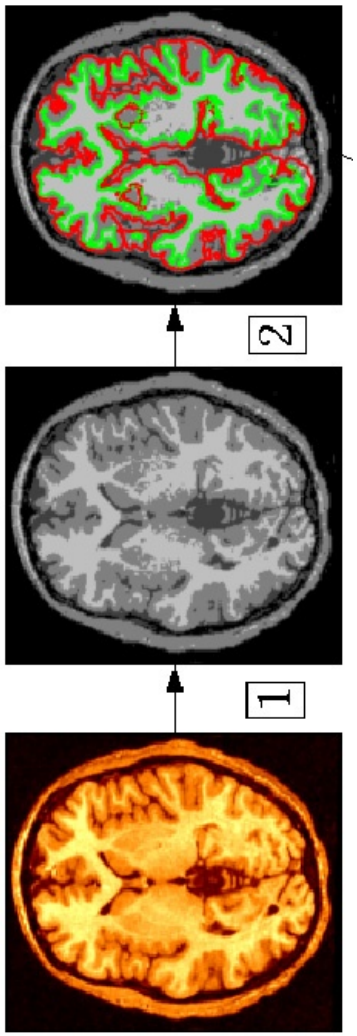
Smaller Left Hippocampal Volume in Abused Women with MDD*



Subjects

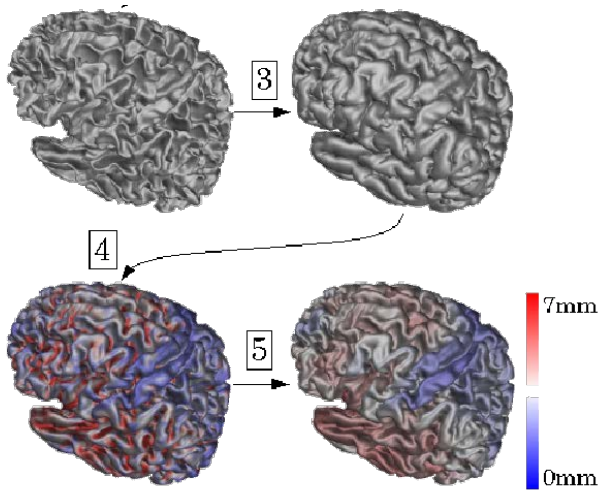
- CONTE Center study subjects (NIH MH-58922)
- N=56, 18-45 years of age, all female
- Recruited with and without histories of childhood trauma and/or current major depression
- For this analysis, Childhood Trauma Questionnaire (CTQ; Bernstein et al. 2003) total scores were regressed against cortical thickness

Cortical Thickness Analysis



- Segmentation into gray / white / CSF using neural net classifier
- Surface deformation algorithm to fit individual's white matter surface and then expand outward to gray matter surface
- The individual distance between gray and white matter surface defines cortical thickness at each point (vertex) on the cortical mantle
- The number of surface points was set to 41,000 vertices in the current study
- The cortical thickness maps containing these vertices were then blurred using a 30 mm blurring kernel and resampled back into native space for statistical analyses

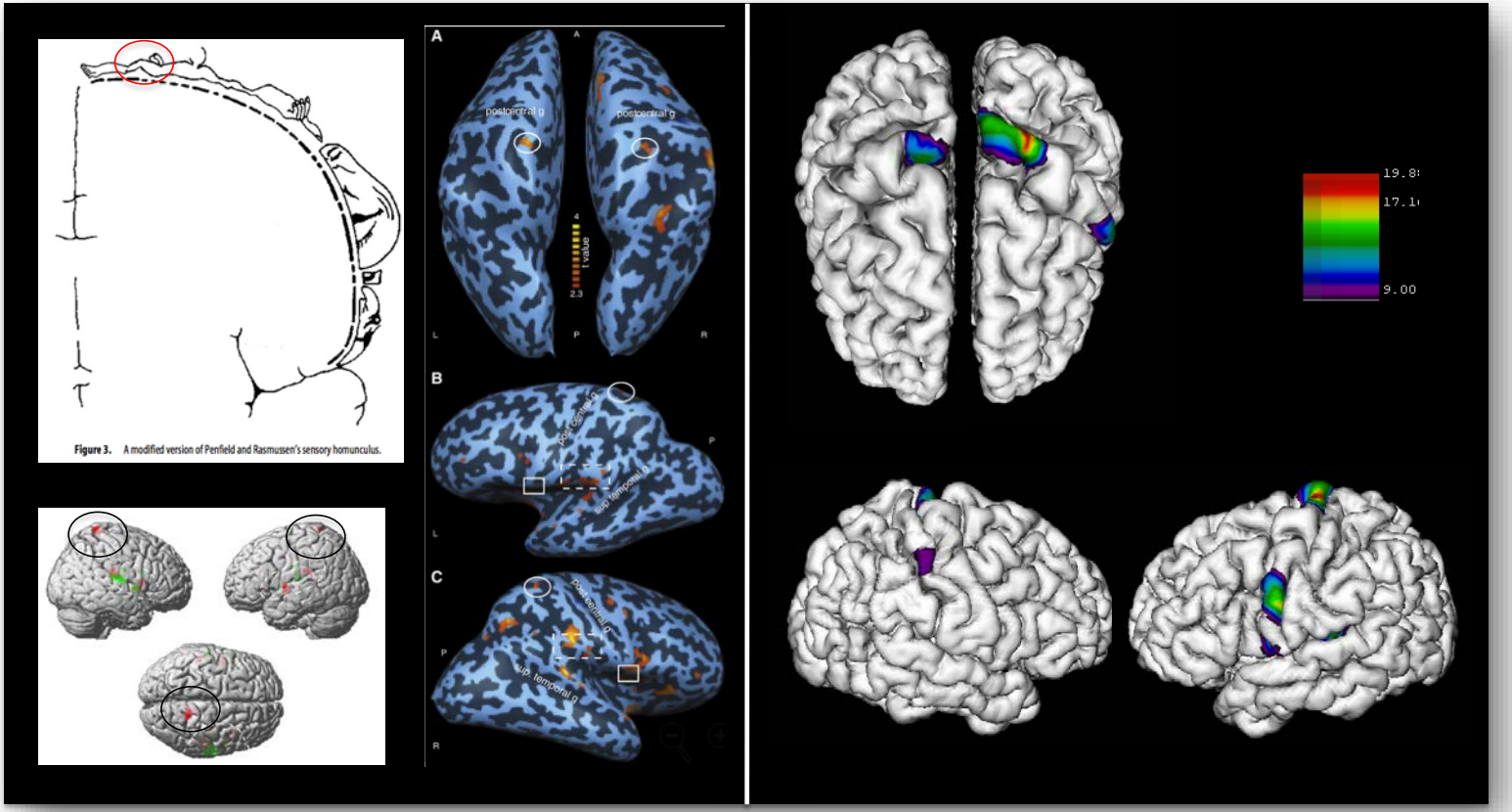
➔ Regression analysis was used to examine the association between CTQ total score and cortical thickness, controlling for age.



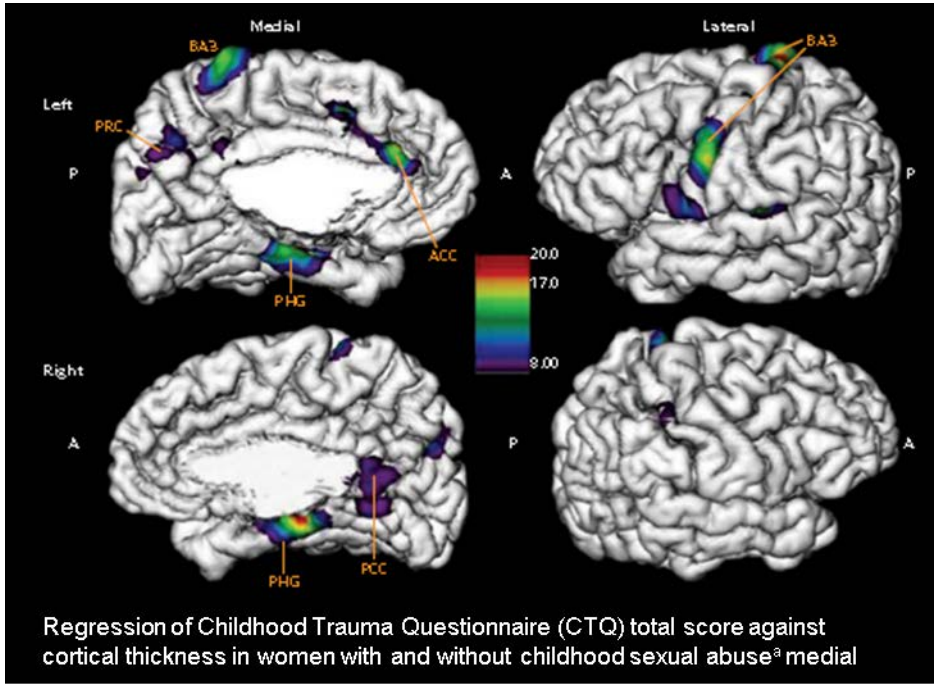
Childhood Trauma Associated with DecreasedThickness of Somatosensory Cortex Genital Field

Somatosensory Homunculus and fMRI studies showing somatosensory representation of the human genital area (circles and rectangles)
(Michels et al., 2010; Kell et al., 2005)

Main effect of childhood trauma score (including physical, sexual and emotional abuse) on cortical thickness in 54 adult women
(Heim et al, in prep.)

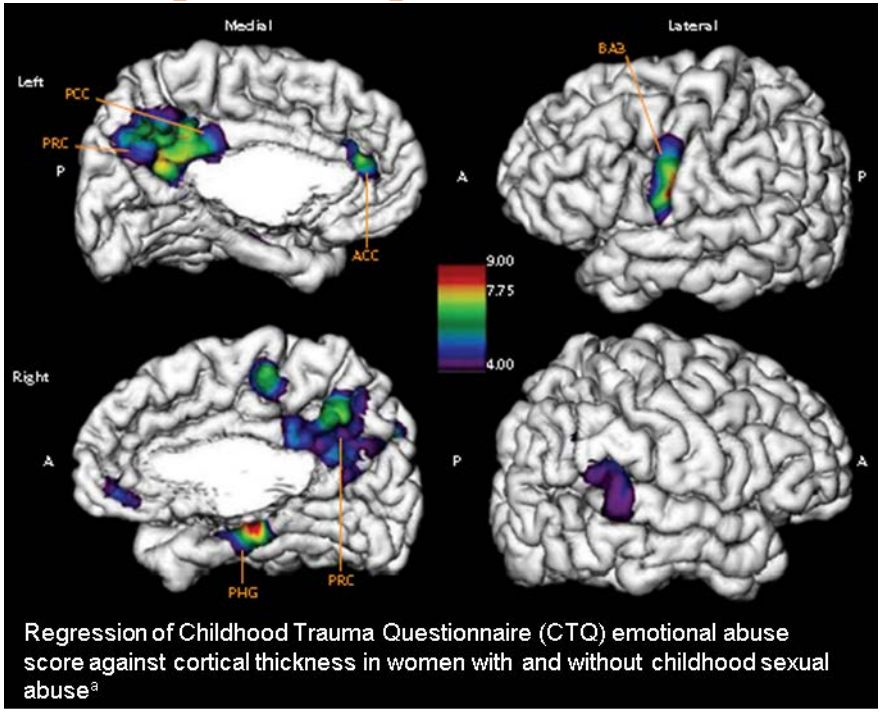


Regression of Childhood Trauma Questionnaire (CTQ)



Regression of Childhood Trauma Questionnaire (CTQ) total score against cortical thickness in women with and without childhood sexual abuse[a] medial

[a] Cortical thickness analysis results after regressing CTQ total score against thickness across the entire cortex. Control variables included age and depression scores. Main effects are seen in the somatosensory cortex in the female genital and mouth area on the left, the parahippocampal gyrus (PHG) bilaterally, the left anterior cingulate cortex (ACC), and the precuneus (PRC) bilaterally. For the precise location of the genital sensory field as identified using functional MRI of neural response to stimulation, see references 22 and 23. BA3=Brodmann's area 3; PCC=posterior cingulate cortex; A=anterior; P=posterior. The color scale refers to the F values of the linear regression (significance threshold: F.4.33).



Regression of Childhood Trauma Questionnaire (CTQ) emotional abuse score against cortical thickness in women with and without childhood sexual abuse[a]

[a] Cortical thickness analysis results after regressing CTQ emotional abuse score against thickness across the entire cortex. Control variables included age, depression, and all other CTQ subscales. Main effects are seen in the left and right precuneus (PRC), left anterior cingulate cortex (ACC), right parahippocampal gyrus (PHG), and left somatosensory cortex in the area of the face. BA3=Brodmann's area 3; PCC=posterior cingulate cortex; A=anterior; P=posterior. The color scale refers to the F values of the linear regression (significance threshold: F.4.33).

An [^{15}O]H_2PET Study of Emotional Memory in Childhood Abuse-Related PTSD and Major Depression

STUDY DESIGN

Women with Early Life Stress (ELS) histories with (+) or without (-) MD and PTSD, or women without ELS, MD or PTSD

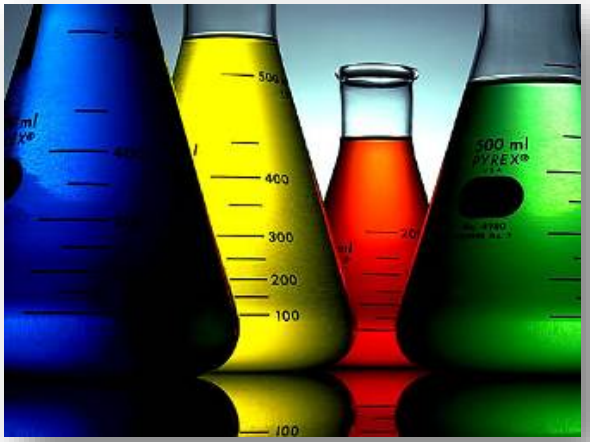
[^{15}O]H_2PET scans acquired while viewing blocks of aversive, pleasant, interesting and neutral stimuli (IAPS)

Delayed recognition memory assessed 1 week later

Examples from the IAPS

Positive

Negative



Interesting

Neutral

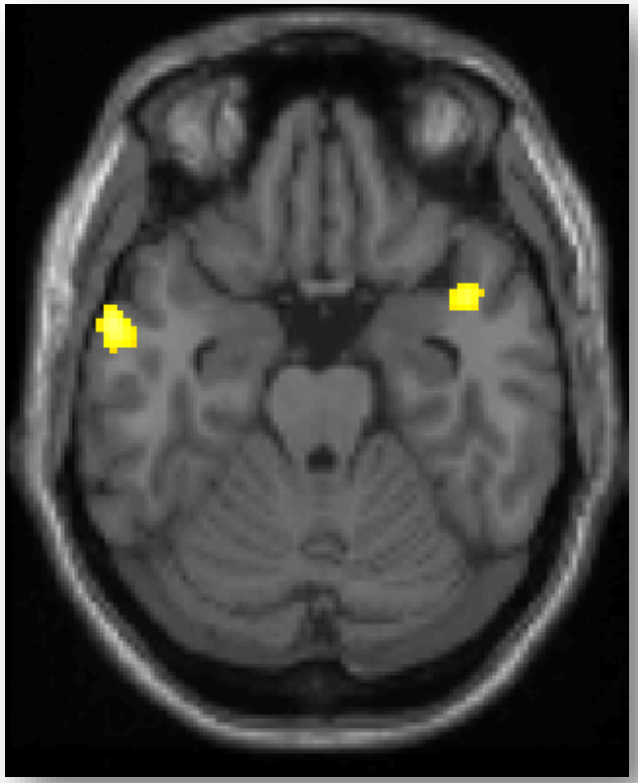
d’ for recognition 1 week post scan

		positive	negative	interesting	neutral
Control Subjects	Mean	1.82	1.92	1.84	1.20
	Std. Err.	0.12	0.21	0.19	0.09
ELS Subjects	Mean	1.57	2.11	1.63	1.06
	Std. Err.	0.19	0.18	0.14	0.22

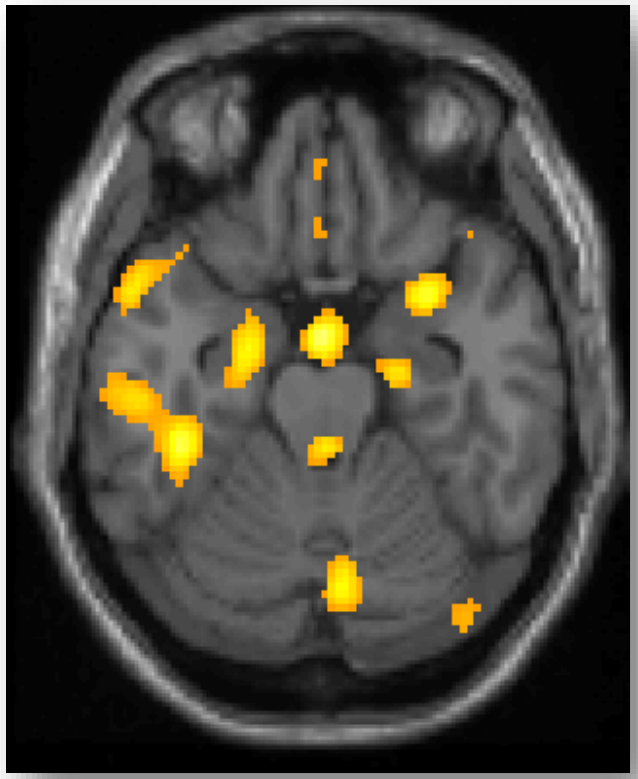
d’ for recognition 1 week post scan

		positive	negative	interesting	neutral
ELS Subjects +MD	Mean	1.33	2.14	1.63	1.07
	Std. Err.	0.26	0.30	0.22	0.36
ELS Subjects -MD	Mean	1.77	2.07	1.63	1.06
	Std. Err.	0.26	0.22	0.22	0.32

Negative >neutral



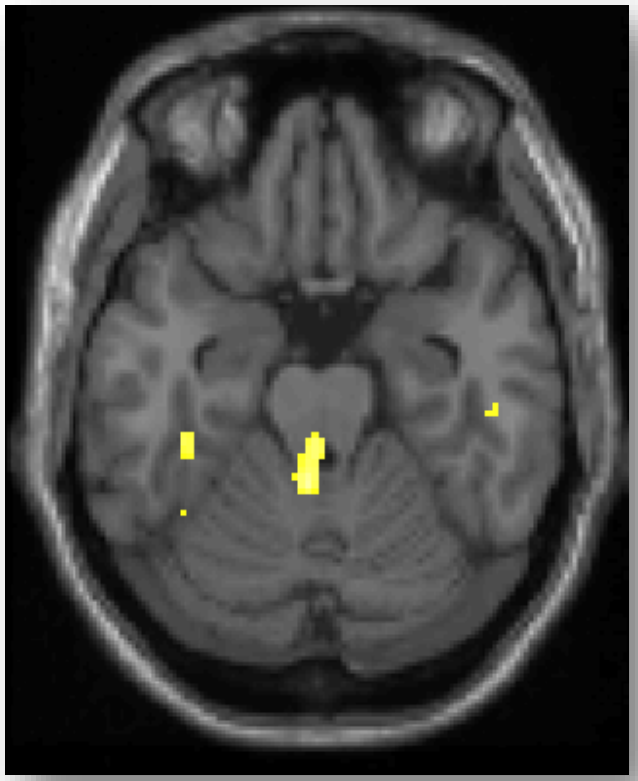
Control subjects



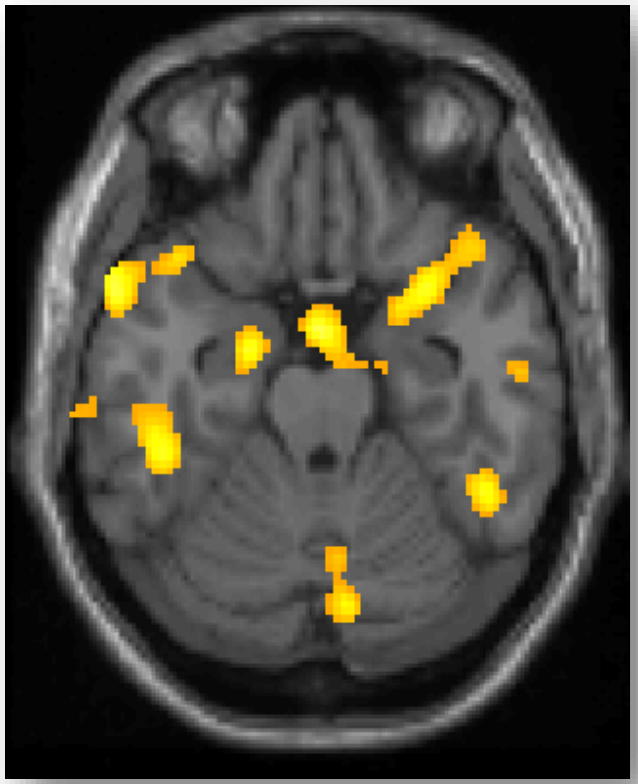
ELS subjects

p<0.005

ELS subjects



ELS
(-MD/PTSD)



ELS
(+MD/PTSD)

Negative >neutral

p<0.005

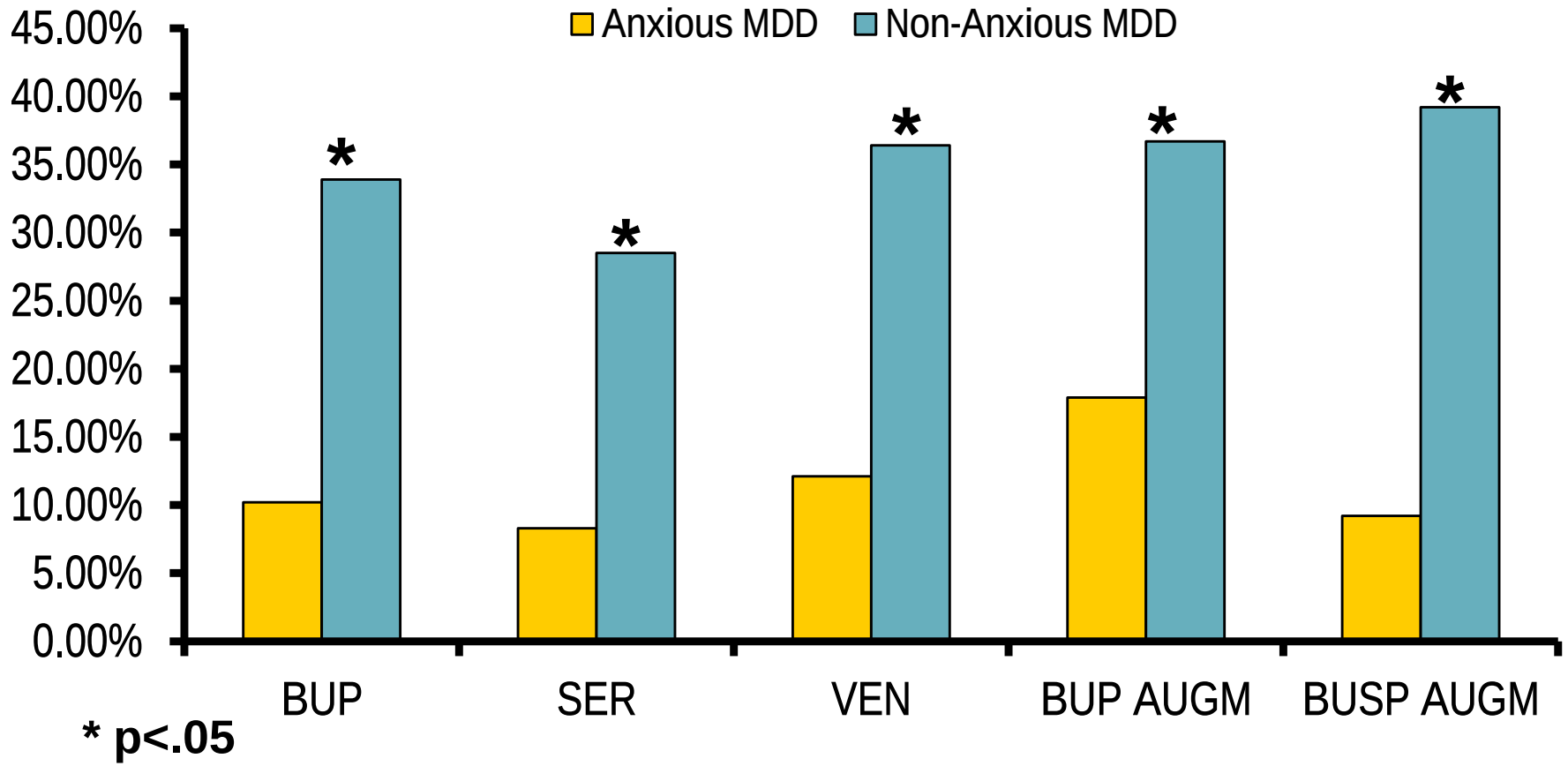
TABLE 2.

Associations Between Adverse Early Life Experiences and Mental Health Outcomes, Odds Ratios, and 95% Confidence Intervals: Results from a Meta-Analysis of 124 Studies

	Depressive Disorders	Drug Use	Suicide Attempts	Sexually Transmitted Infections and Risky Sexual Behavior
Physical Abuse	1.54 (1.16-2.04)	1.92 (1.67-2.20)	3.40 (2.17-5.32)	1.78 (1.50-2.10)
Emotional Abuse	3.06 (2.43-3.85)	1.41 (1.11-1.79)	3.37 (2.44-4.67)	1.75 (1.49-2.04)
Neglect	2.11 (1.61-2.77)	1.36 (1.21-1.54)	1.95 (1.13-3.37)	1.57 (1.39-1.78)

Adapted from Norman et al[16]

Remission Rates in Level 2 of STAR*D: Anxious vs. Non-Anxious MDD



* p<.05

Fava M et al (2008) Am J Psychiatry 165:342-351.

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.

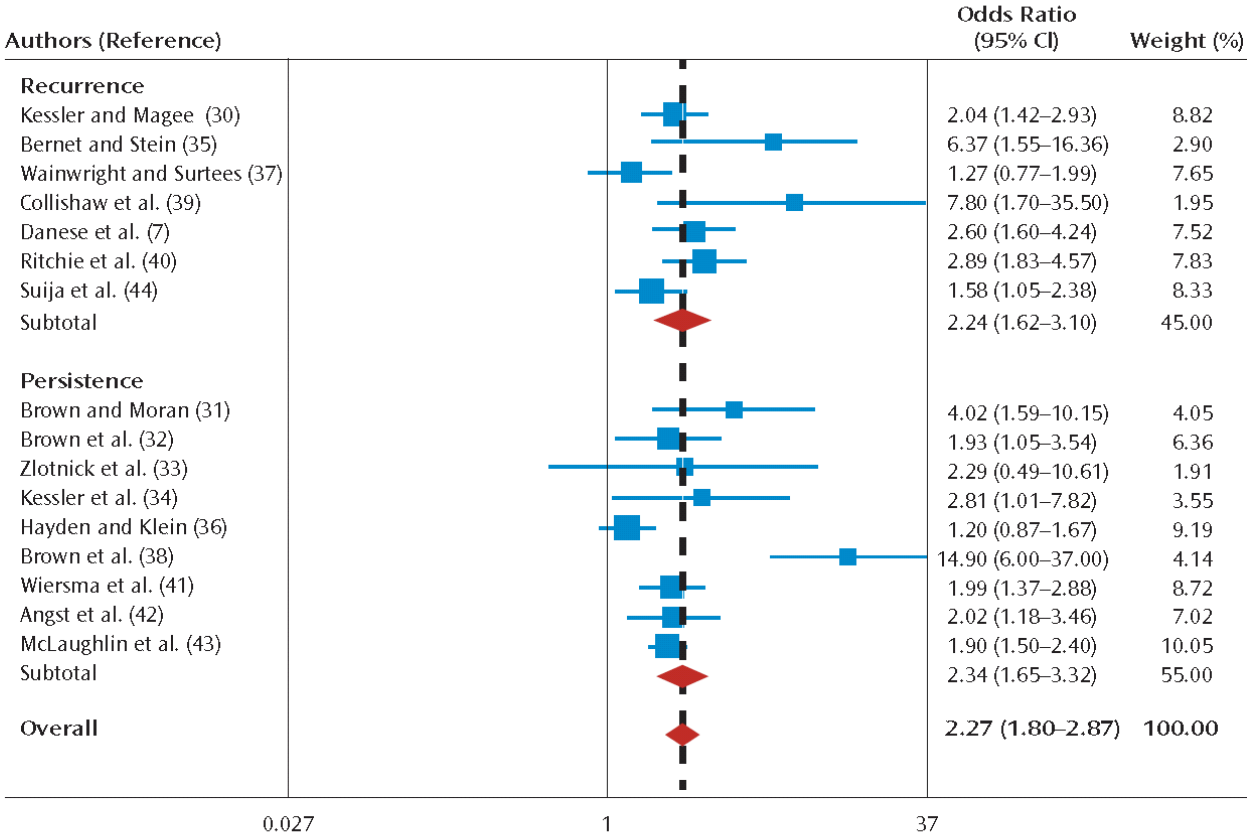
Objectives: Evidence suggests that childhood maltreatment may negatively affect not only the lifetime risk of depression but also clinically relevant measures of depression, such as course of illness and treatment outcome. The authors conducted the first meta-analysis to examine the relationship between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

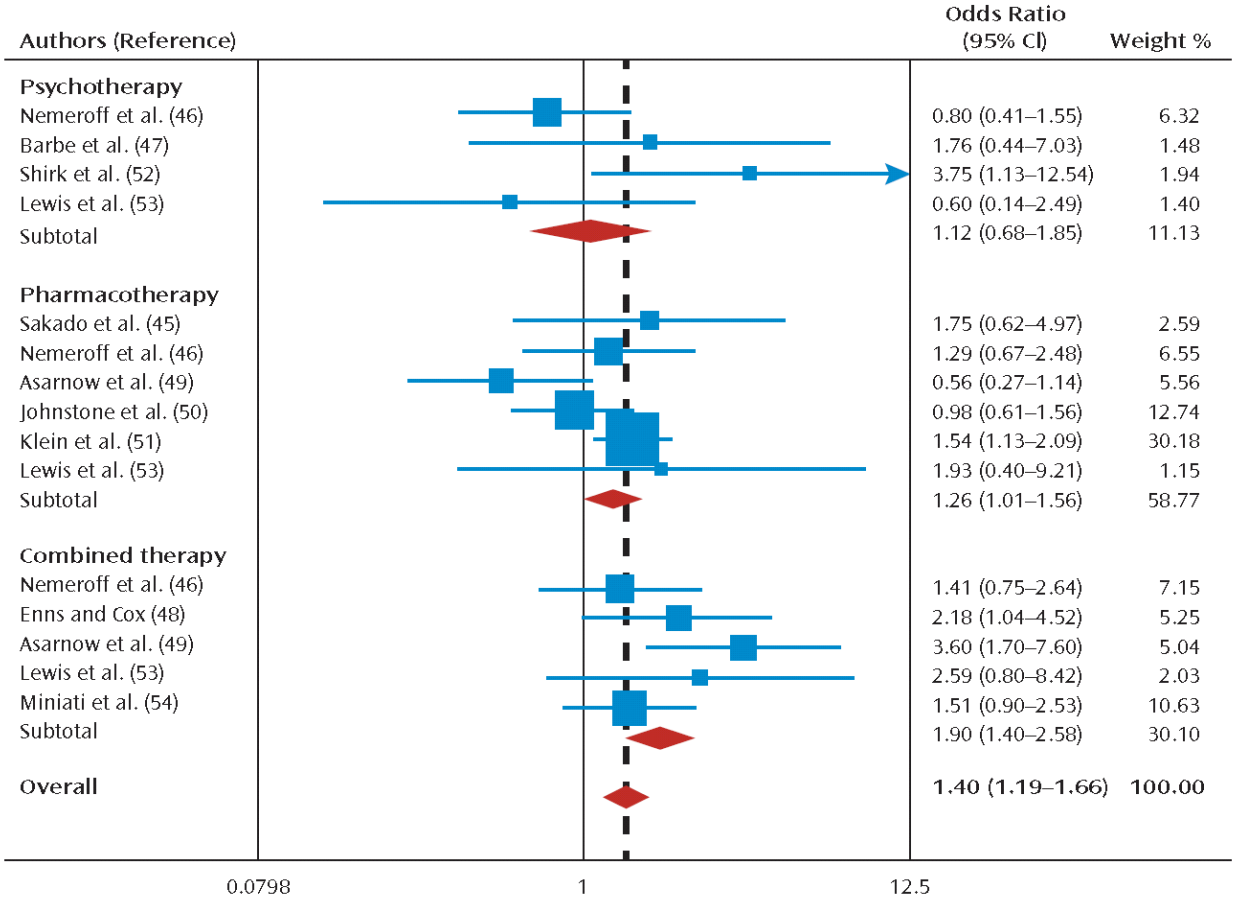
FIGURE 2. Meta-Analysis of Epidemiological Studies Investigating the Association Between Childhood Maltreatment and Depression Course (Random Effects)[a]



[a] The red diamonds show the combined effect sizes for studies concerned with depression recurrence and depression persistence as well as the overall effect size of the meta-analysis (top to bottom).

Am J P sychiatry 2012; 169:141 –151

FIGURE 3. Meta-Analysis of Clinical Trials Investigating the Association Between Childhood Maltreatment and Treatment Outcome of Depression (Fixed Effects)[a]



[a] Based on the evidence of homogeneous distributions of effect sizes within treatment groups, we present here the results of fixed-effects model meta-analyses for different treatment groups. The overall effect size across treatment groups was estimated with a random-effects model meta-analysis with the following study weights: Nemeroff (psychotherapy): 7.88; Barbe: 2.78; Shirk: 3.49; Lewis (psychotherapy): 2.65; Sakado: 4.36; Nemeroff (pharmacotherapy): 8.03; Asarnow (pharmacotherapy): 7.32; Johnstone: 10.96; Klein: 14.09; Lewis (pharmacotherapy): 2.25; Nemeroff (combined therapy): 8.42; Enns: 7.07; Asarnow (combined therapy): 6.90; Lewis (combined therapy): 3.61; Miniati: 10.18. The red diamonds show the combined effect sizes for studies concerned with psychotherapy, pharmacotherapy, and combined therapy, as well as the overall effect size of the meta-analysis (top to bottom).

Am J P sychiatry 2012; 169:141 –151

Early Childhood Trauma and Antidepressant Response in Adults with Major Depression: Data from the Randomized International Study to Predict Optimized Treatment of Depression

Charles Debattista, MD Leanne M Williams PhD, Anne-Marie Duchemin, MD,

Ana F Schatzberg, MD and Charles B Nemeroff, MD, PhD.

Translational Psychiatry

To evaluate the role of early life trauma in predicting acute response outcomes to antidepressants in a large sample of well-characterized patients with major depressive disorder (MDD). Randomized clinical trial at 8 academic and nine private clinical settings in five countries. Patients (n=1008) who met DSM-IV criteria for MDD and 336 matched healthy controls in the International Study to Predict Optimized Treatment for Depression. Randomization to 8 week's treatment with escitalopram, sertraline or venlafaxine with dose adjusted by participant's treating clinician per routine clinical practice. Exposure to 18 types of traumatic events before age of 18 was assessed using the Early Life Stress Questionnaire. Depressed participants were significantly more likely to report early life stress than controls; 62.5% of MDD participants reported more than two traumatic events compared to 28.4% of controls. Abuse and notably abuse occurring at ≤7 years of age predicted poorer outcomes after 8 weeks of antidepressants, across the three treatment arms.

Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis

Jessica Agnew-Blais, Andrea Danese
www.thelancet.com/psychiatry **Vol 3 April 2016**

Summary

Background Bipolar disorder affects up to one in 25 individuals and identification of early risk indicators of negative outcomes could facilitate early detection of patients with greatest clinical needs and risk. We aimed to investigate the association between childhood maltreatment and key negative outcomes in patients with bipolar disorder.

Findings We initially identified 527 records and after unsuitable studies were removed, our search yielded 148 publications of which 30 were used in the meta-analysis. Patients with bipolar disorder and history of childhood maltreatment had greater mania severity (six studies, 780 participants; odds ratio [OR] 2·02, 95% CI 1·21–3·39, p=0·008), greater depression severity (eight studies, 1007 participants; 1·57, 1·25–1·99, p=0·0001), greater psychosis severity (seven studies, 1494 participants; 1·49, 1·10–2·04, p=0·011), higher risk of comorbidity with post-traumatic stress disorder (eight studies, 2494 participants; 3·60, 2·45–5·30, p<0·0001), anxiety disorders (seven studies, 5091 participants; 1·90, 1·39–2·61, p<0·0001), substance misuse disorders (11 studies, 5469 participants; 1·84, 1·41–2·39, p<0·0001), alcohol misuse disorder (eight studies, 5040 participants; 1·44, 1·13–1·83, p=0·003), earlier age of bipolar disorder onset (14 studies, 5733 participants; 1·85, 1·43–2·40, p<0·0001), higher risk of rapid cycling (eight studies, 3010 participants; 1·89, 1·45–2·48, p<0·0001), greater number of manic episodes (seven studies, 3909 participants; 1·26, 1·09–1·47, p=0·003), greater number of depressive episodes (eight studies, 4025 participants; 1·38, 1·07–1·79, p=0·013), and higher risk of suicide attempt (13 studies, 3422 participants; 2·25, 1·88–2·70, p<0·0001) compared with those with bipolar disorder without childhood maltreatment. Overall, these associations were not explained by publication bias, undue effects of individual studies, or variation in study quality.

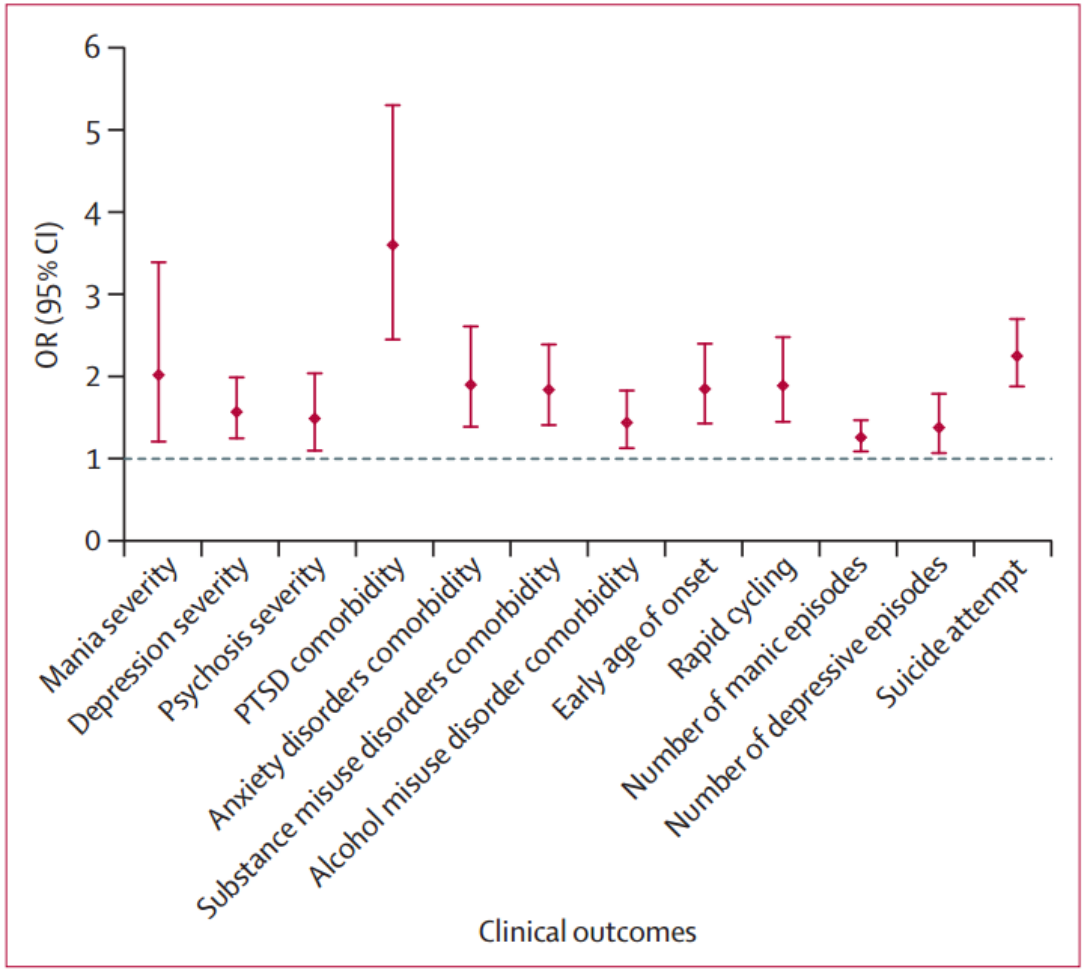


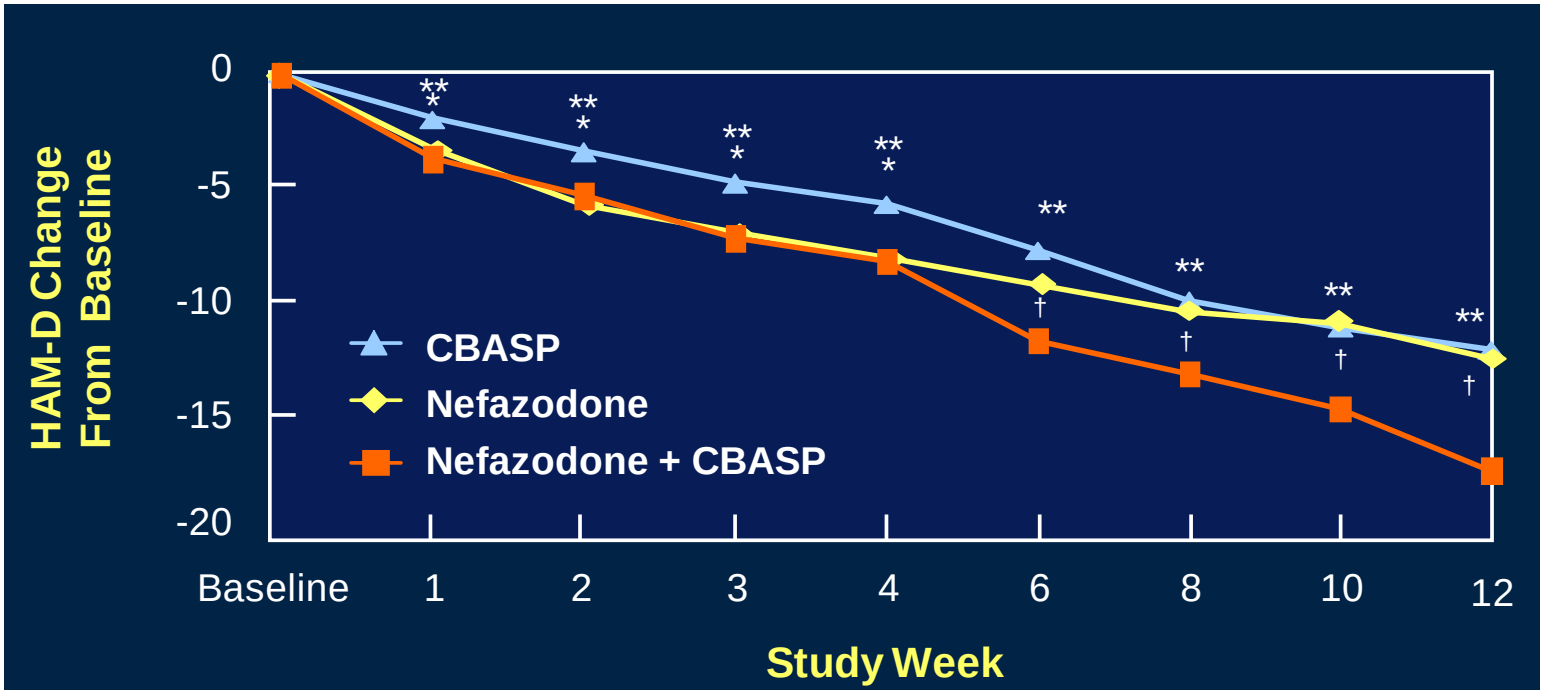
Figure 2: **Combined effect sizes and 95% CIs from 12 independent meta-analyses testing the association of childhood maltreatment with course of illness and clinical features in bipolar disorder**

Error bars show 95% CIs. OR=odds ratio. PTSD=post-traumatic stress disorder.

Nefazodone Chronic Depression Study

Acute-Phase

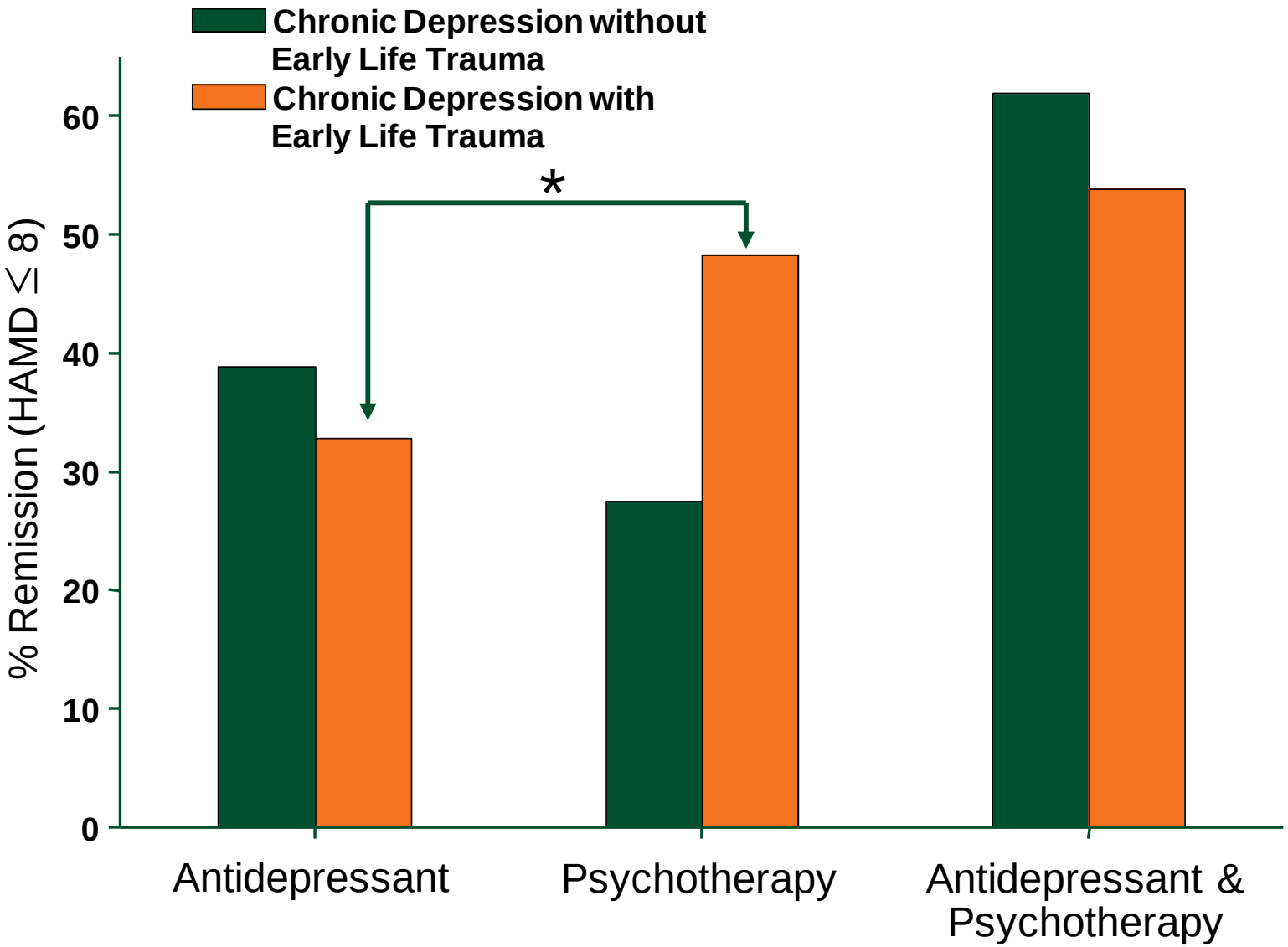
Change From Baseline in Mean HAM-D Scores



Observed cases, LS means.
*$P < 0.05$ Nefazodone compared with CBASP.
**$P < 0.01$ Nefazodone + CBASP compared with CBASP.
†$P < 0.01$ Nefazodone + CBASP compared with Nefazodone.
No statistical difference between Nefazodone compared with Nefazodone + CBASP through Week 4.
Keller MB et al. *N Engl J Med*. 2000;342:1462-1470.

Description of Childhood Adverse Experiences of Subjects Stratified

Childhood Trauma Characteristic	Nefazodone (N=226)	Psychotherapy (N=228)	Nefazodone & Psychotherapy (N=227)	Statistics
Parental loss ≤ age of 15 yrs (%)	34.3	36.1	32.14	χ^2=0.77, df=2, NS
Physical Abuse (%)	40.9	41.7	47.8	χ^2=2.56, df=2, NS
Sexual Abuse (%)	15.0	15.3	18.8	χ^2=1.42, df=2, NS
Neglect (%)	11.8	7.9	10.3	χ^2=1.91, df=2, NS
Age at earliest loss (Yr)	6.9 ± 5.0	6.9 ± 4.7	6.9 ± 4.4	F=0.00, df=2,220, NS
Age at earliest physical abuse (Yr)	6.3 ± 3.1	6.1 ± 3.4	6.4 ± 3.4	F=0.13, df=2,201, NS
Age at earliest sexual abuse (Yr)	9.3 ± 3.2	8.4 ± 3.0	8.5 ± 3.6	F=0.91, df=2,133, NS
Age at earliest neglect (Yr)	6.7 ± 4.0	7.3 ± 4.2	6.6 ± 4.1	F=0.11, df=2,52, NS
Age at earliest trauma (Yr)	6.1 ± 4.0	6.4 ± 4.1	6.0 ± 3.9	F=0.24, df=2,379, NS
Duration of physical abuse (Yr)	7.5 ± 4.1	7.3 ±5.6	7.9 ± 5.3	F=0.33, df=2,198, NS
Duration of sexual abuse (Yr)	1.2 ± 1.8	2.0 ± 2.9	2.7 ± 3.8	F=2.43, df=2,127, NS
Duration of neglect (Yr)	8.2 ± 5.2	6.2 ± 6.5	7.2 ± 5.5	F=0.61, df=2,52, NS
Duration of overall trauma (Yr)	7.2 ± 4.7	6.9 ± 5.7	7.4 ± 5.8	F=0.19, df=2,279, NS
Childhood trauma severity (%)				χ^2=5.39, df=8, NS
No trauma	38.4	36.1	32.1	
One trauma type	34.7	36.1	38.8	
Two trauma types	16.0	19.9	18.3	
Three trauma types	8.2	6.5	9.4	
Four trauma types	2.7	1.4	1.3	


Chronic Depression without Early Life Trauma
Chronic Depression with Early Life Trauma
*
% Remission (HAMD ≤ 8)
60
50
40
30
20
10
0
Antidepressant
Psychotherapy
Antidepressant & Psychotherapy

Developmental Psychopathology: Diathesis-Stress Model