Early-Life Trauma and Depression

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Disclosures

- Neither I nor any member of my immediate family has a financial relationship or interest (currently or within the past 12 months) with any proprietary entity producing health care goods or services consumed by, or used on, patients related to the content of this CME activity
- I do not intend to discuss an unapproved/ investigative use of a commercial product/device

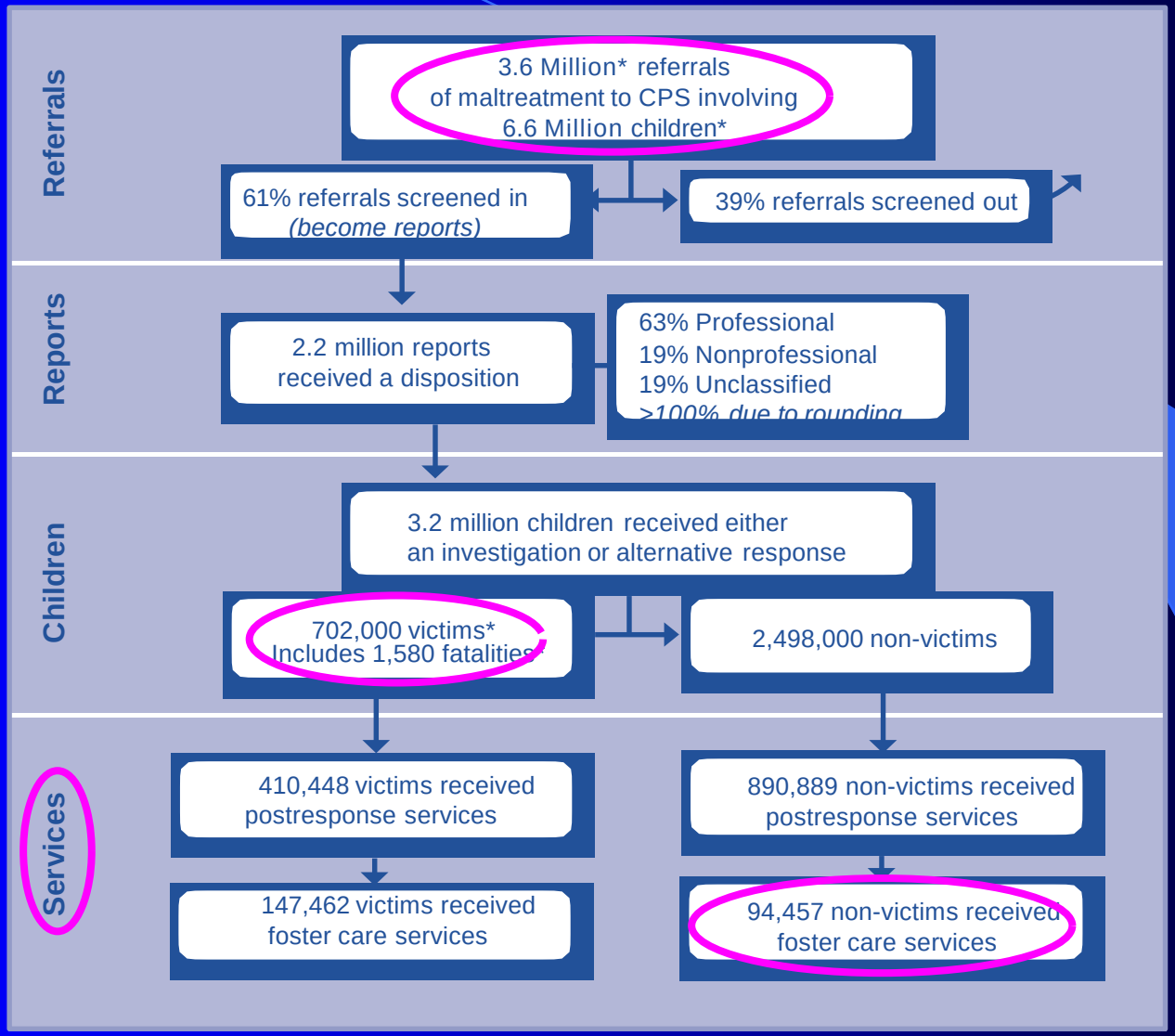
Overview

- Background information: early-life trauma and depression
- Findings on depression phenotypes: early-life trauma vs. other causes
- Clinical and research implications

Childhood Trauma

- Parental separation
- Parental death
- Physical/mental illness of caretaker
- Exposure to domestic violence
- Natural disasters and political instability
- Childhood maltreatment
  - abuse (emotional, physical, sexual)
  - neglect (emotional, physical)

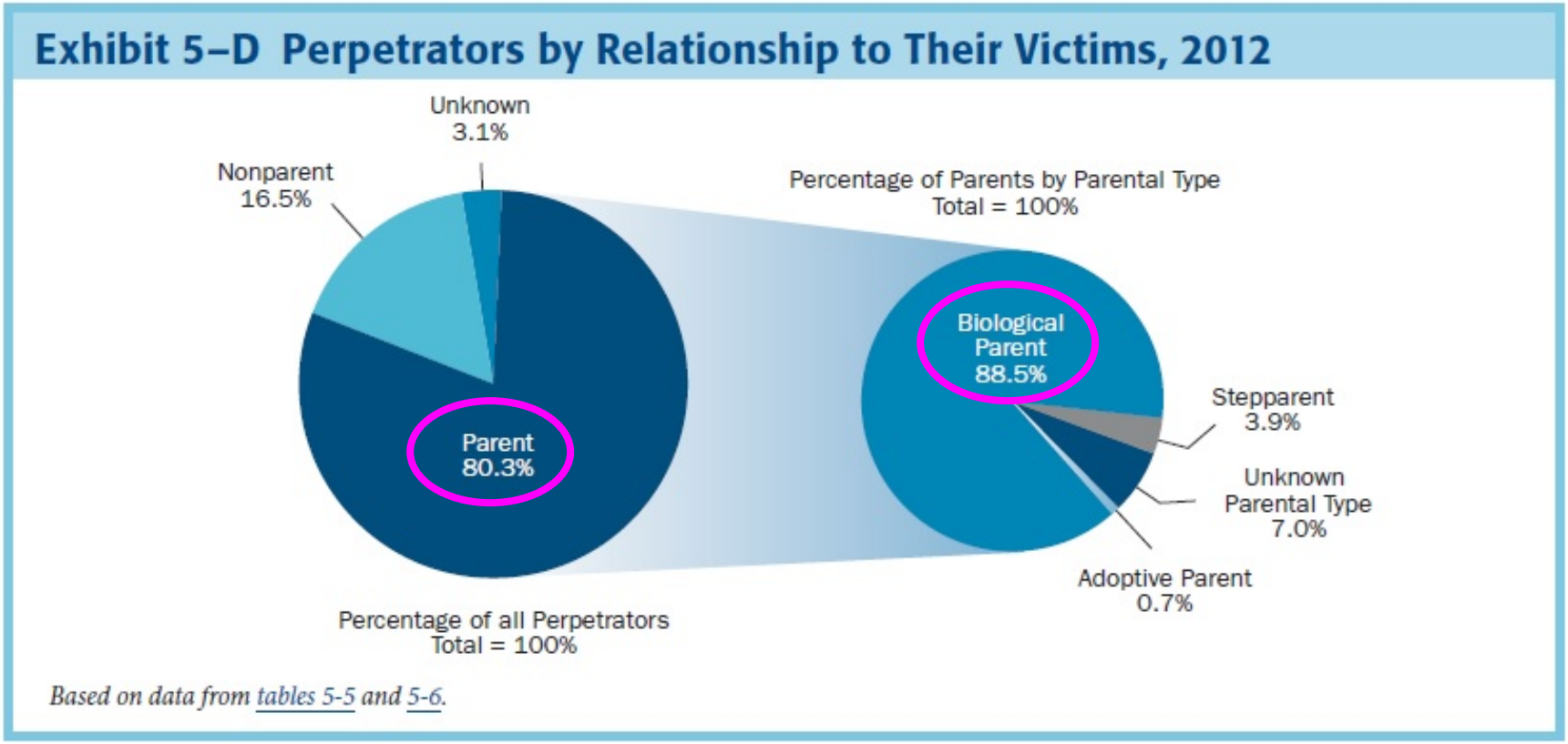
Maltreatment Statistics



DHHS, ACF 2016

http://www.acf.hhs.gov/programs/cb/research-data-technology/statistics-research/child-maltreatment

Maltreatment - Perpetrators



DHHS; ACF 2012

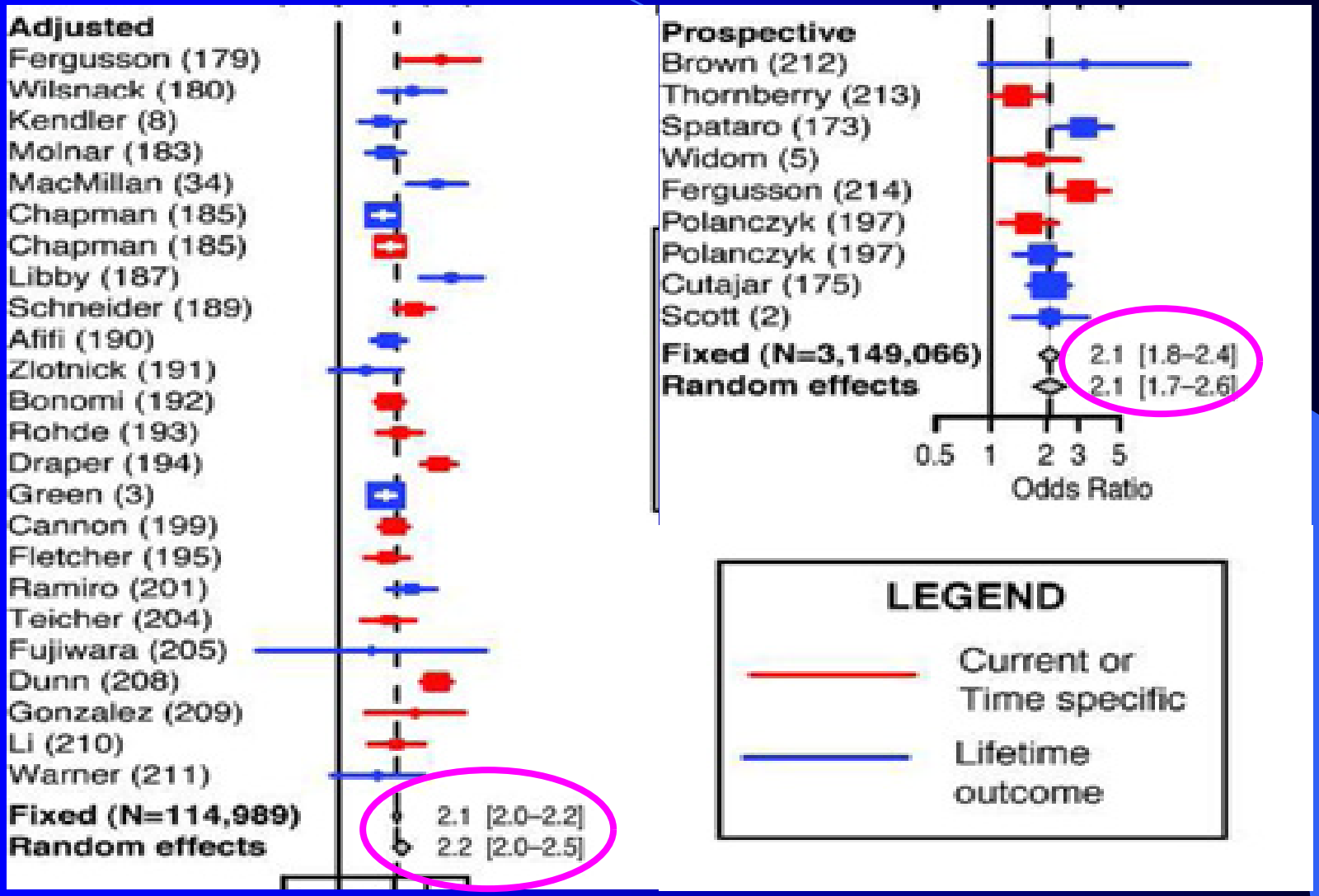
Early-Life Trauma: Sequelae

- Physical
  - impaired development, medical illnesses
- Behavioral
  - delinquency, aggression, suicidality
- Psychological
  - impaired social competence, emotional regulation and cognition, psychopathology
- Biological
  - alterations in autonomic reactivity, stress response and brain structure and function

Impact of Early-Life Trauma

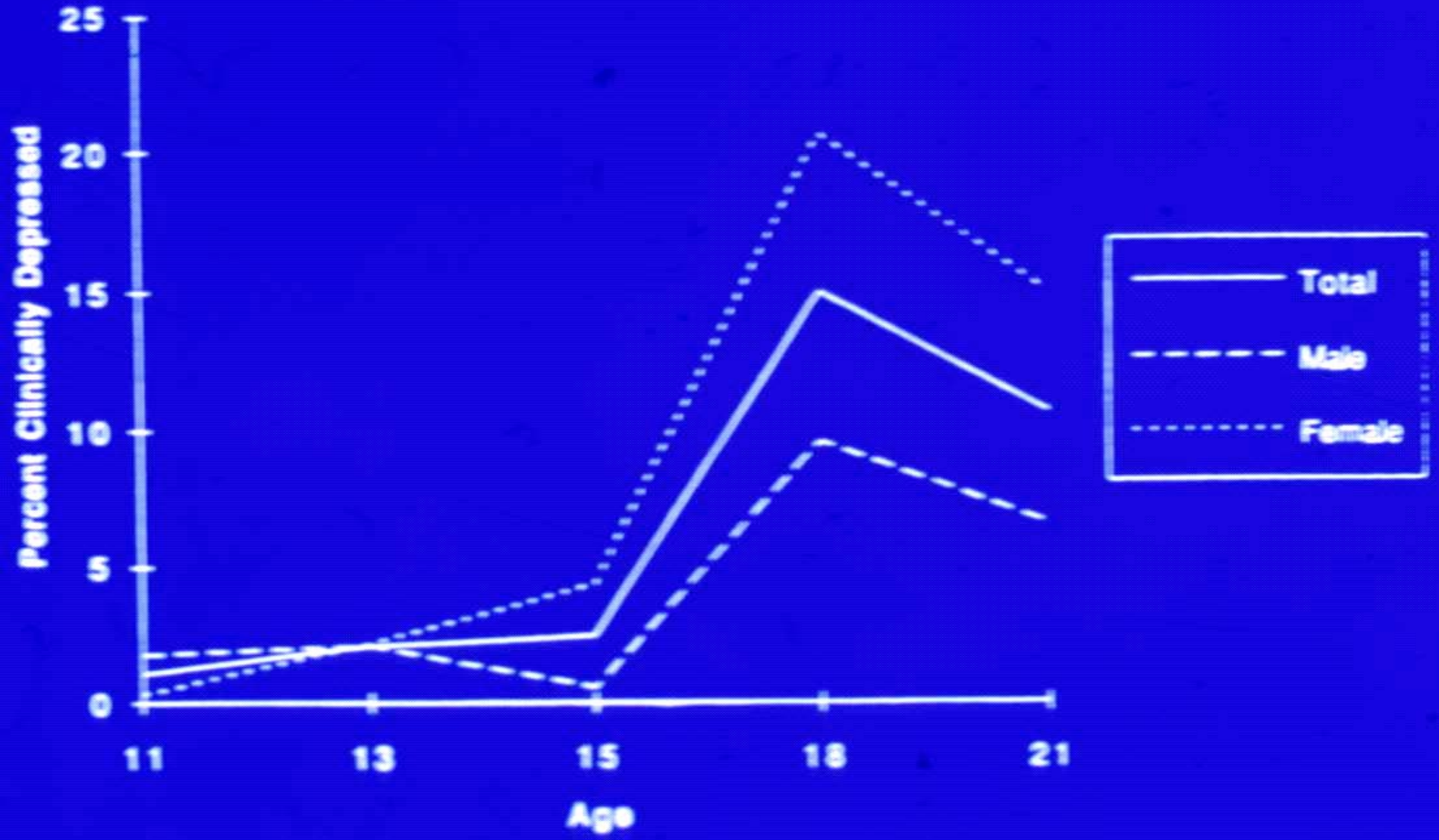
- Effects of early-life trauma can be long-lasting and occur in multiple systems
  - progressive physical, cognitive and emotional development
  - dramatic changes in brain development
  - stress during neuronal plasticity can result in persistent sensitization of the neurobiological systems to mild stress

Maltreatment: Depression Risk



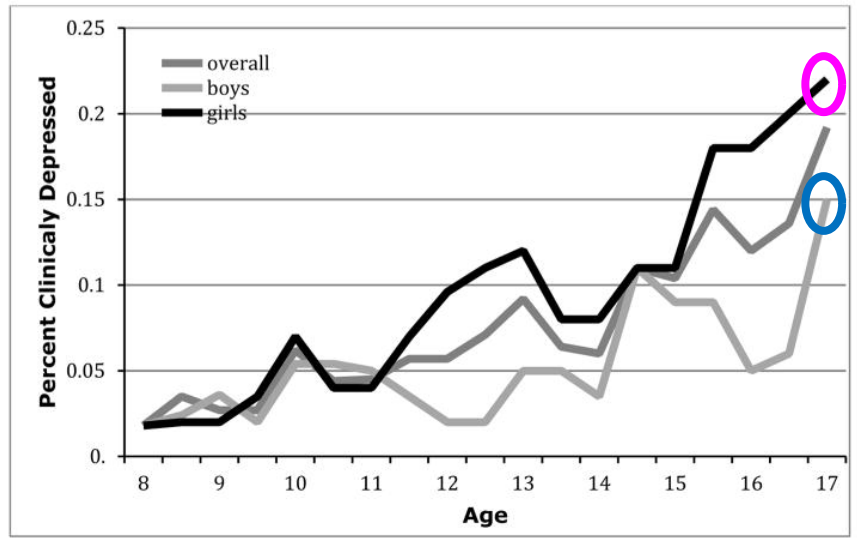
Teicher & Sampson, Am J Psychiatry 2013;170:1114–1133

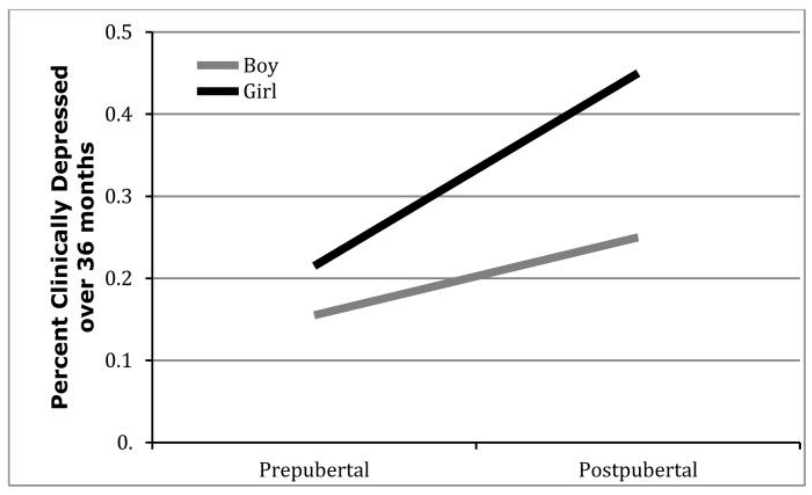
One-year Incidence of Major Depression



Hankin et al., Journal of Abnorm Psychology
107:128-140, 1998

Depression: Age, Sex and Puberty





Hankin et al., J Abnorm Psychol 2015; 124: 803-816

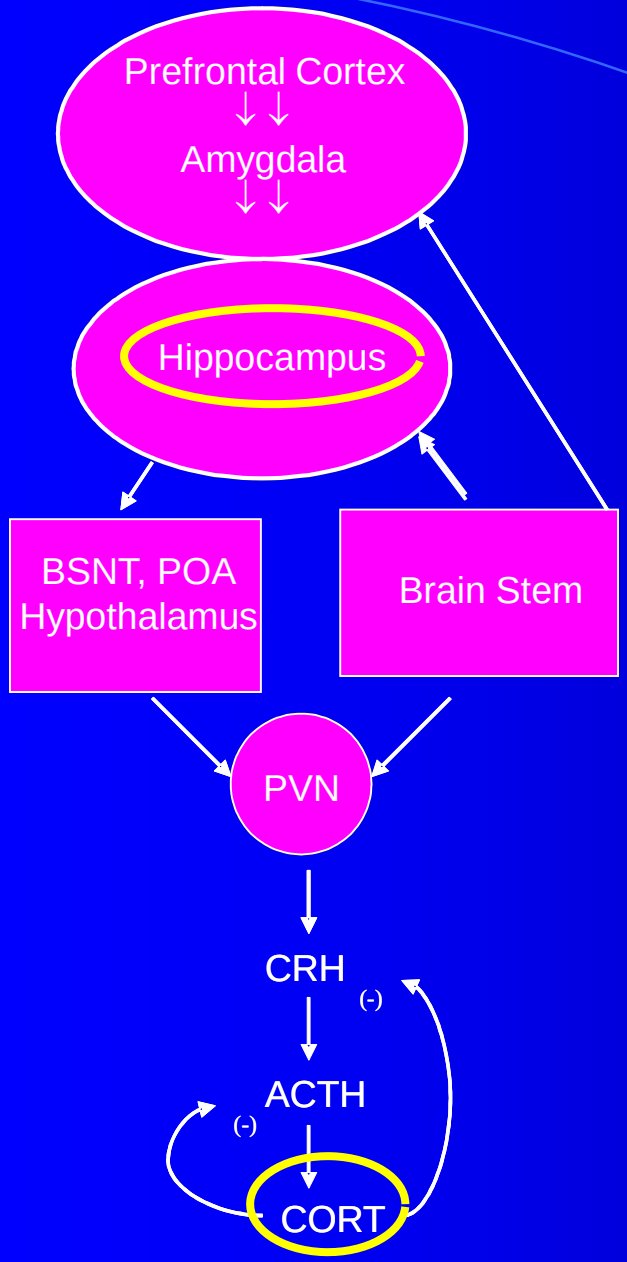
Pediatric Depression: Sequalae

- Suicidal behavior
- Risk for recurrent episodes
- Risk for other psychopathology
- Persistence into adult life
- Psychosocial difficulties
  - interpersonal problems
  - early pregnancy
  - school dropout
  - unemployment

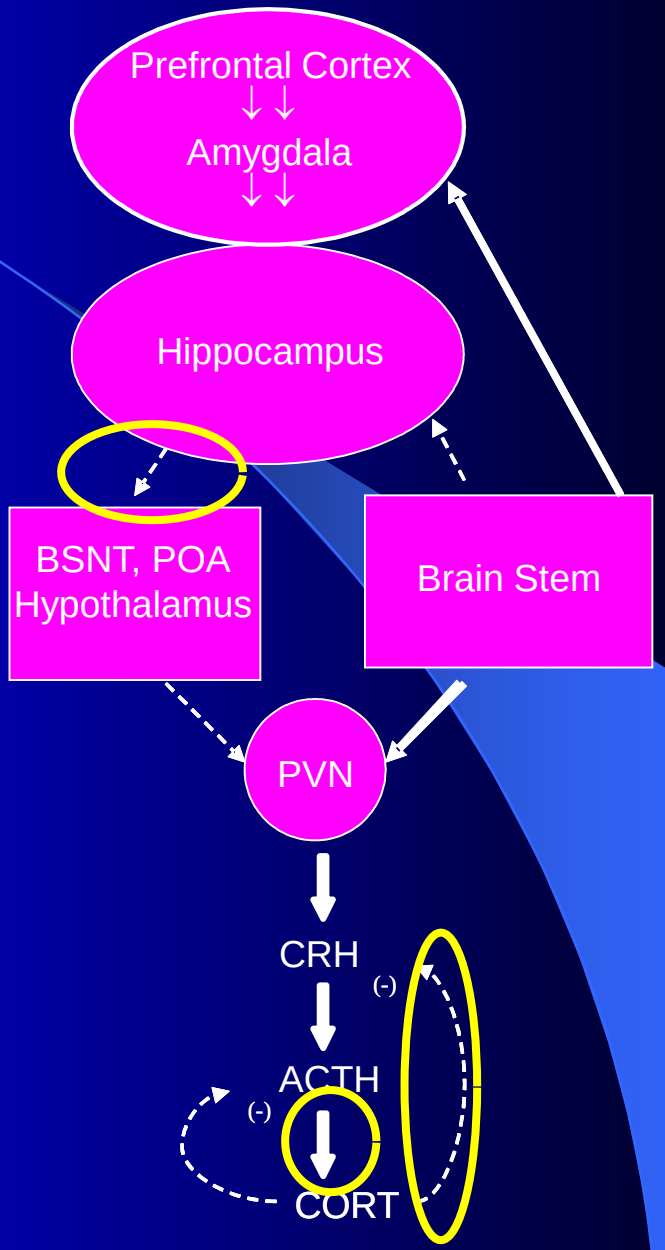
Is depression associated with maltreatment different from depression without maltreatment?

Phenotypes: Clinical Differences

- Depression + maltreated phenotype
  - earlier onset of depression
  - more severe symptoms
  - higher rates of comorbidity
  - more chronic and recurrent episodes
  - greater risk for suicidality
  - poorer response to treatment



Normal LHPA Response



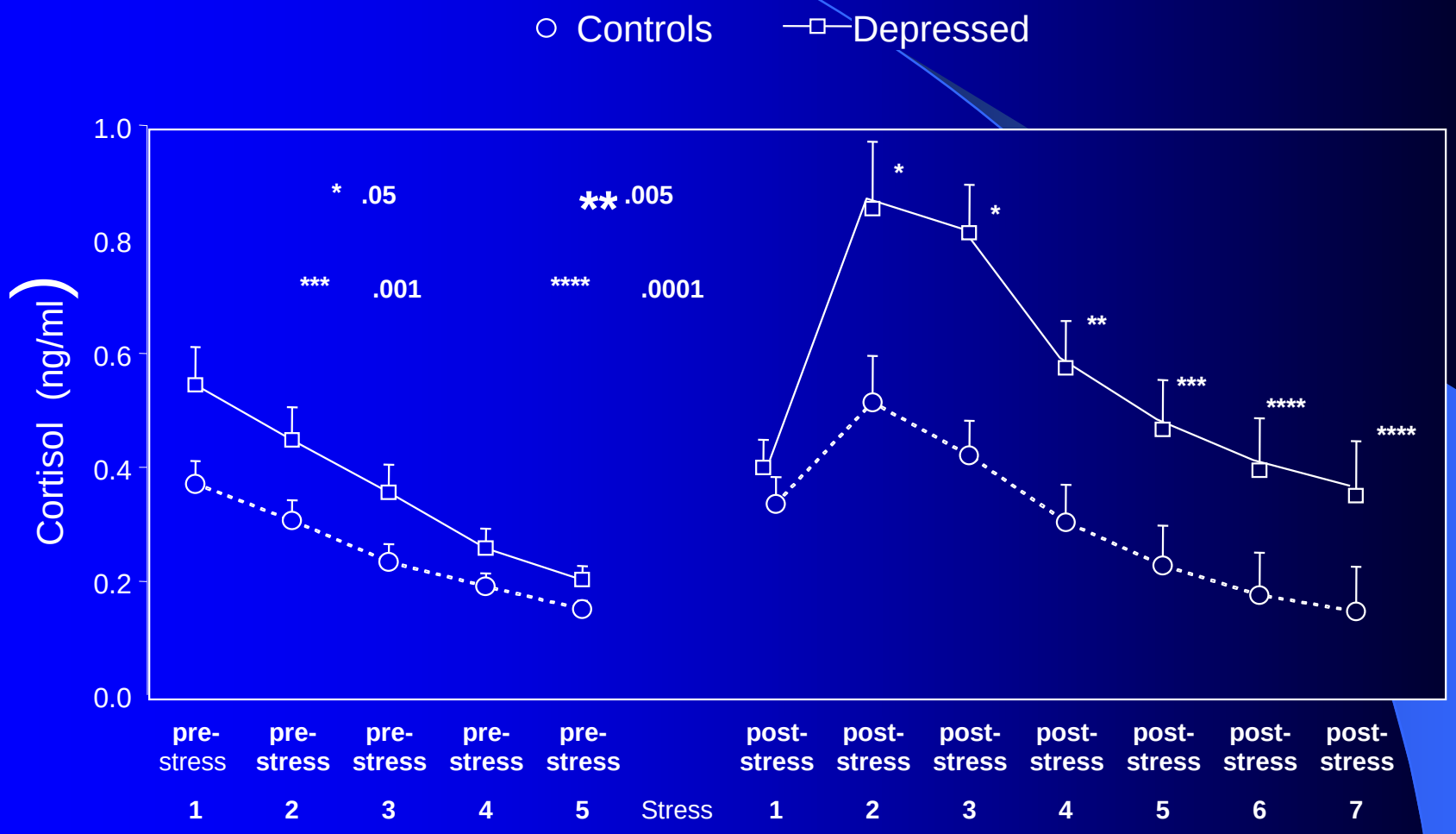
Response in Early Adversity

Hypothalamic-Pituitary-Adrenal (HPA) Axis Assessment



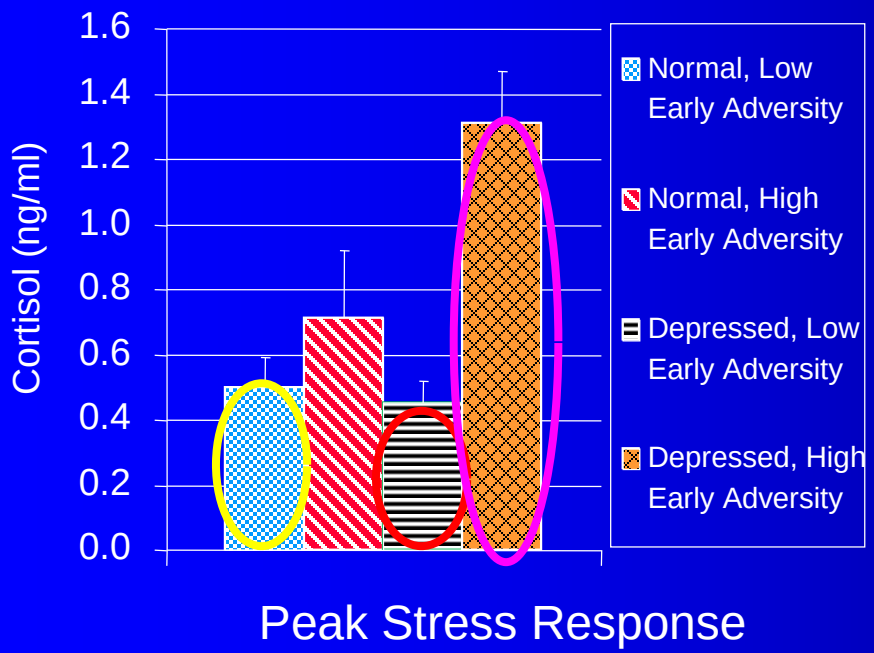



HPA Response to Stress in Depression

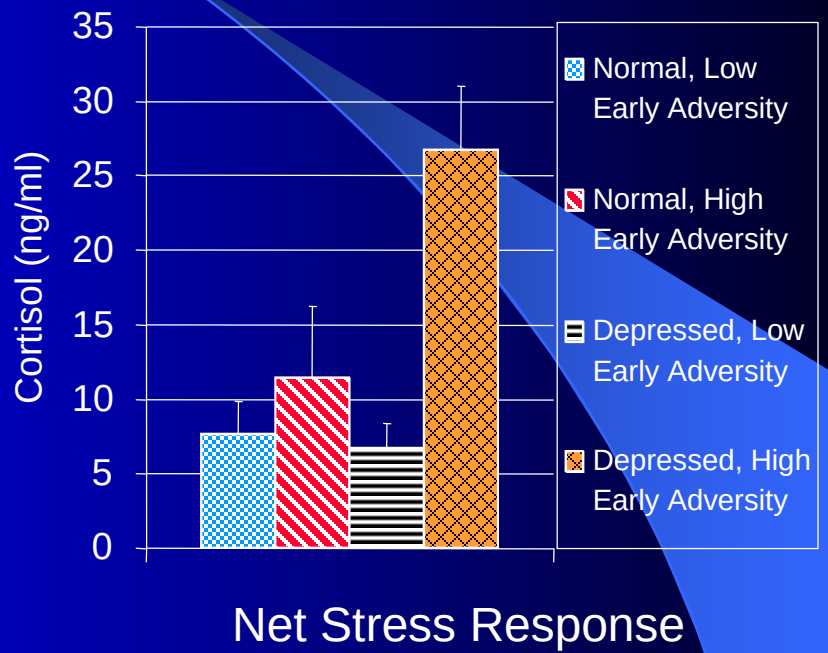


Rao et al., Biological Psychiatry 2008;64:521-526

ELA Effects on HPA in Depression



Peak Stress Response

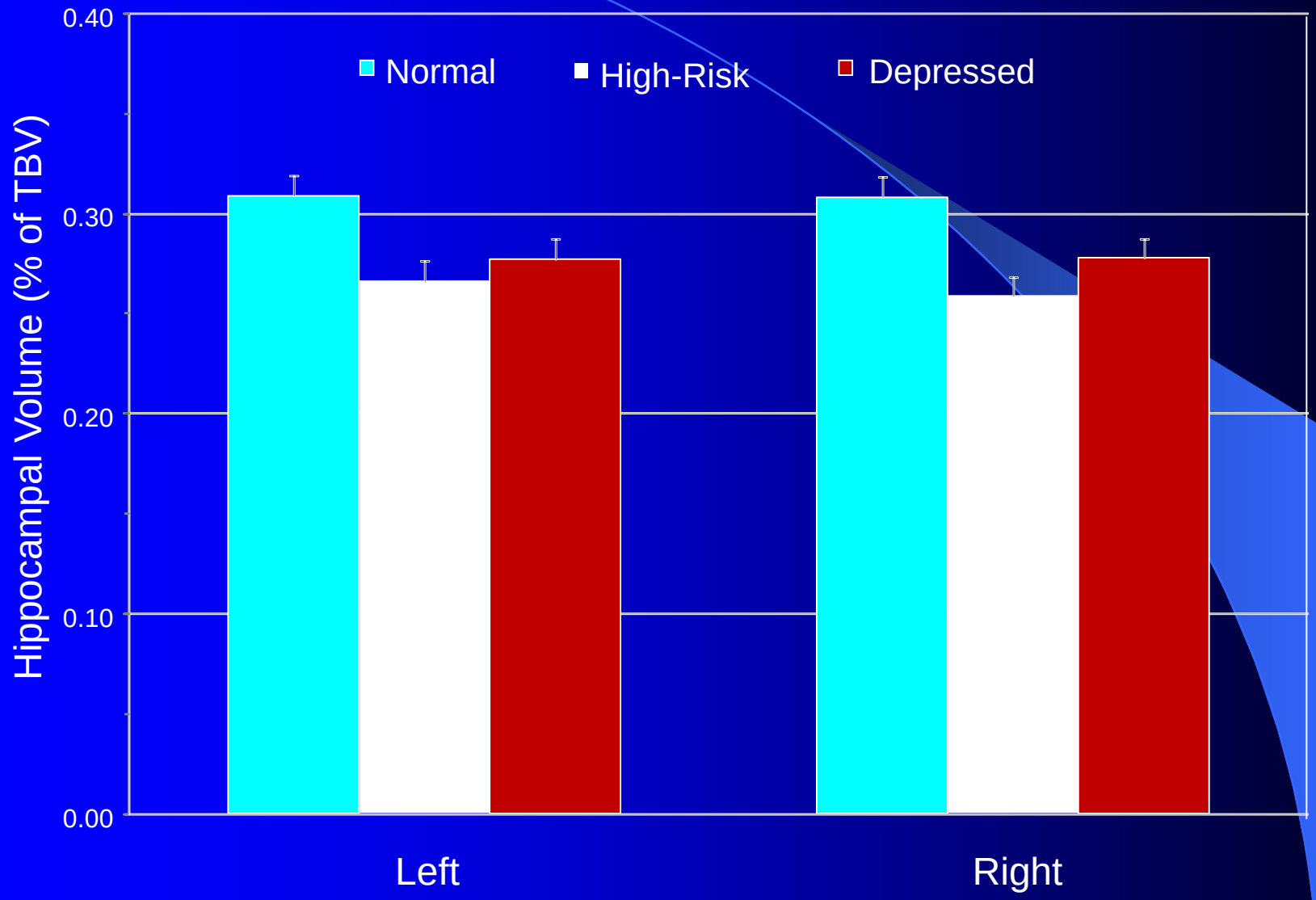


Net Stress Response

Rao et al., Biological Psychiatry 2008;64:521-526

ELA = early-life adversity

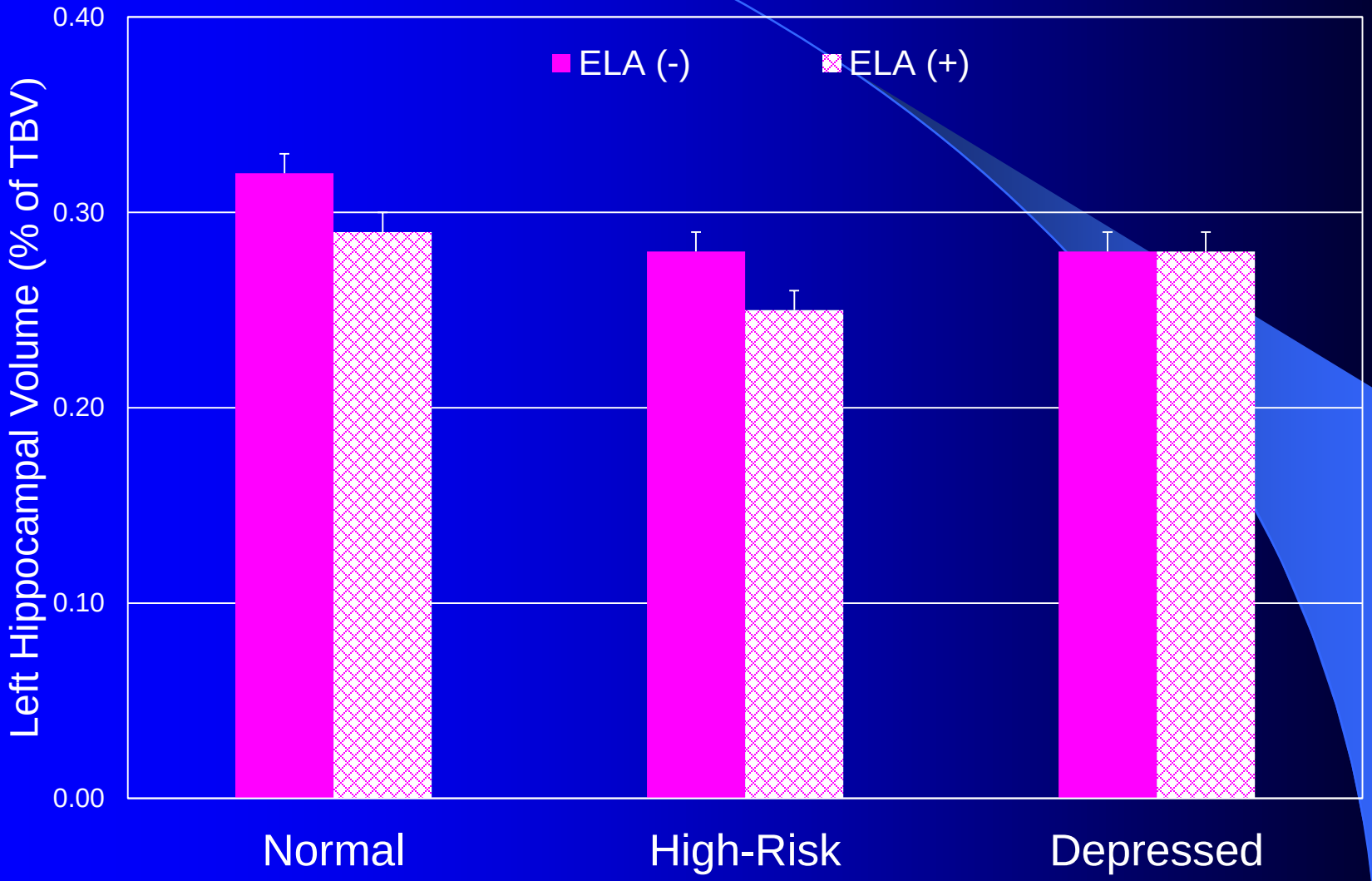
Depression Risk and HIPP Size



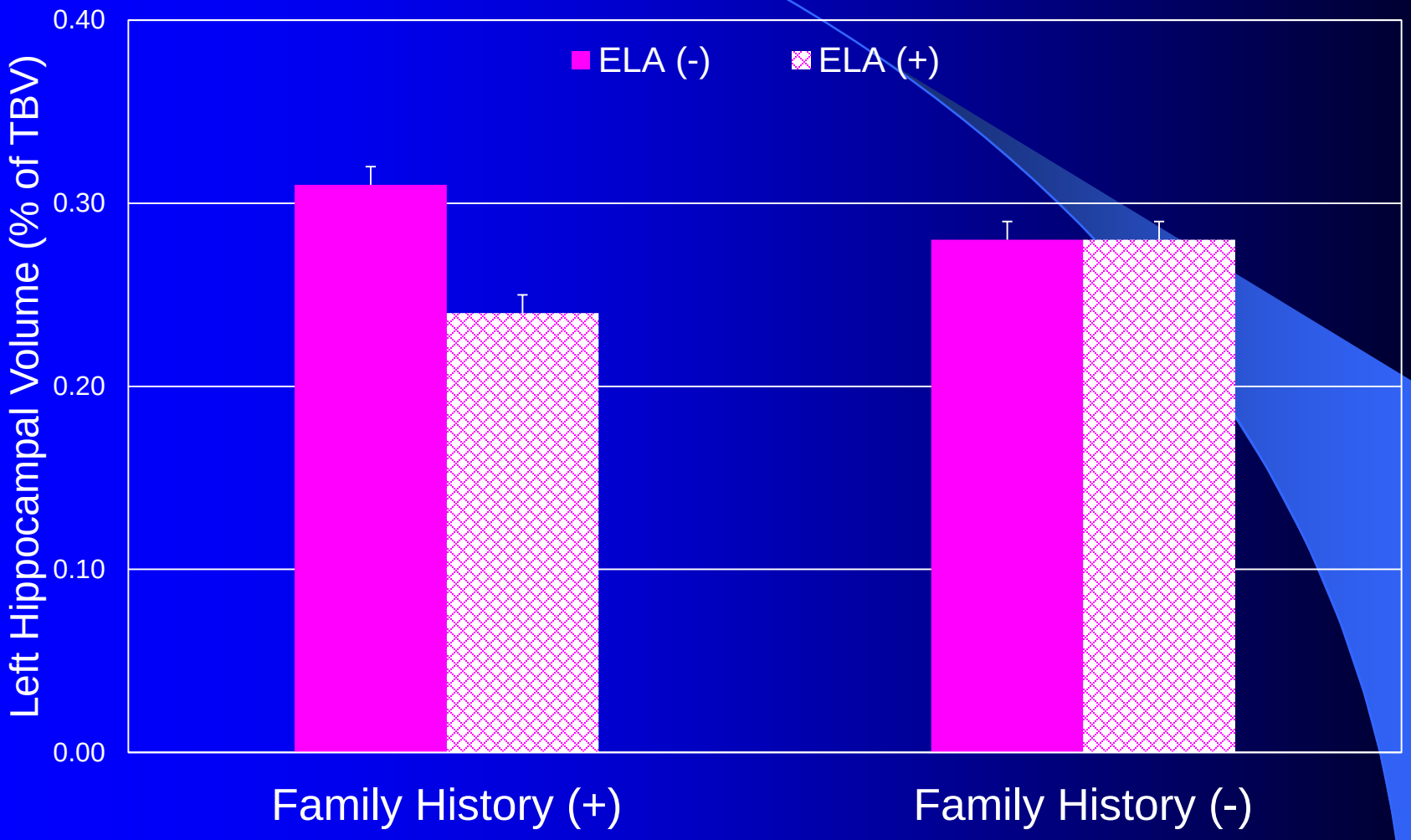
HIPP = hippocampus

Rao et al., Biological Psychiatry 2010;67:357-364

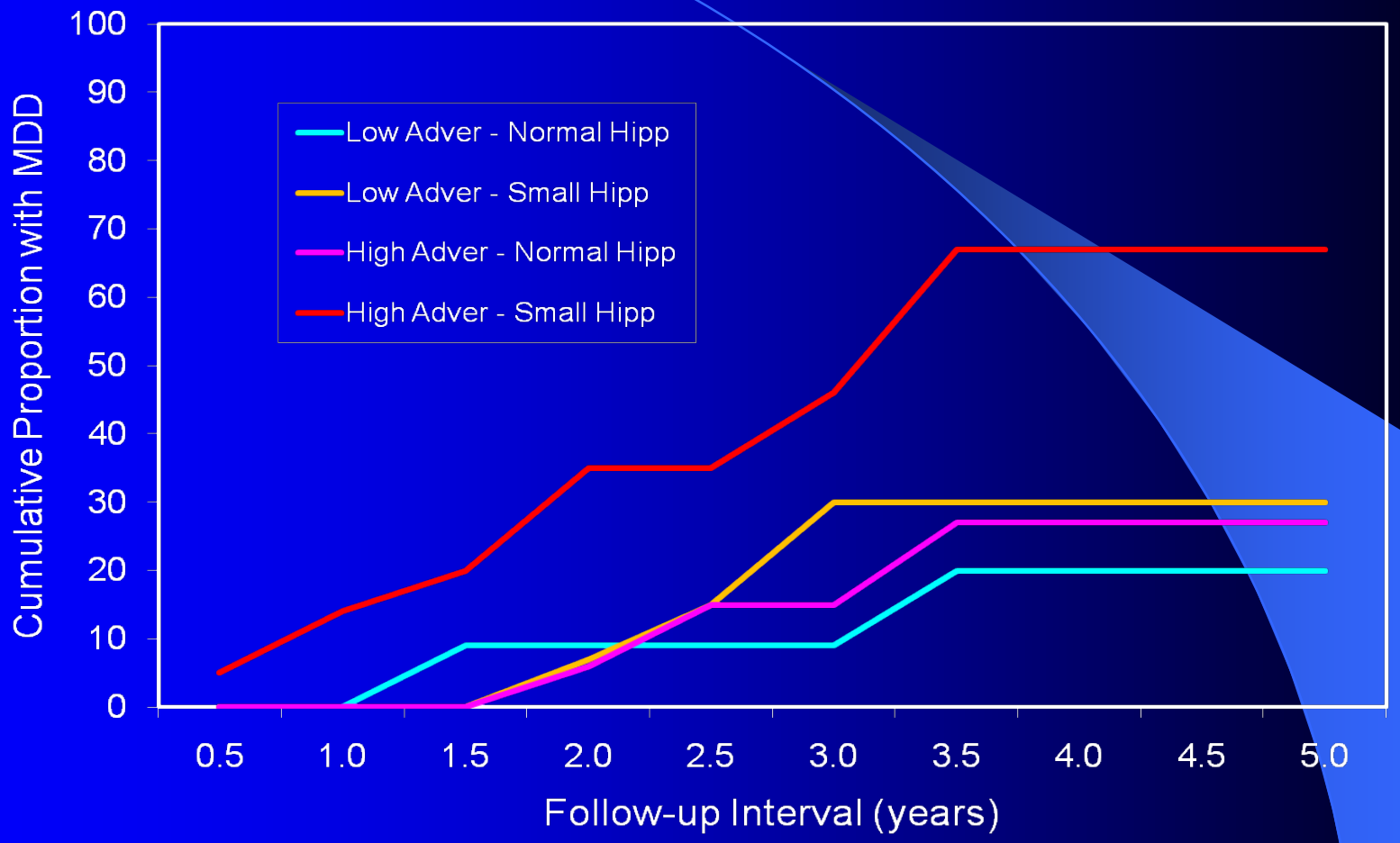
Effect of ELA on HIPP Size



Effects of FH and ELA on HIPP

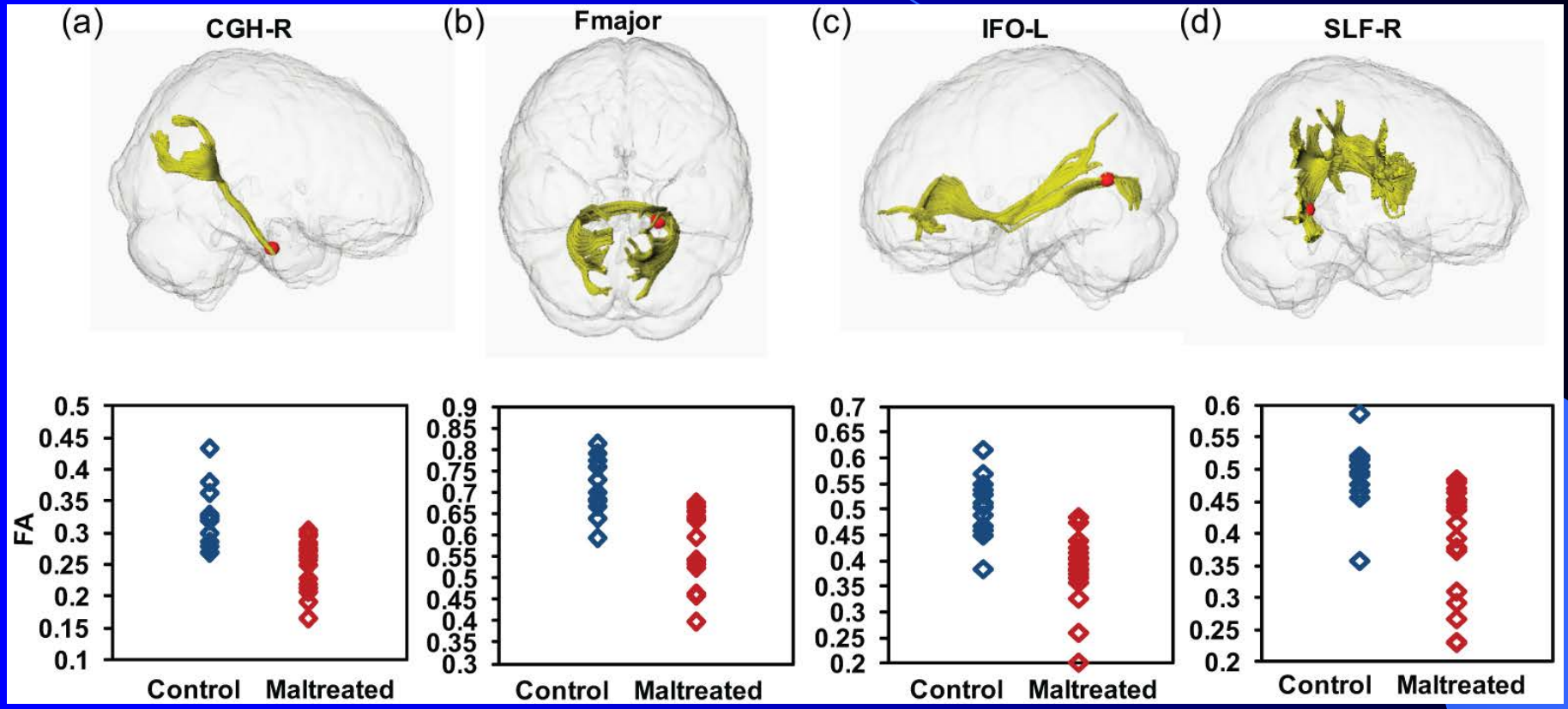


Adversity-HIPP: Depression Risk



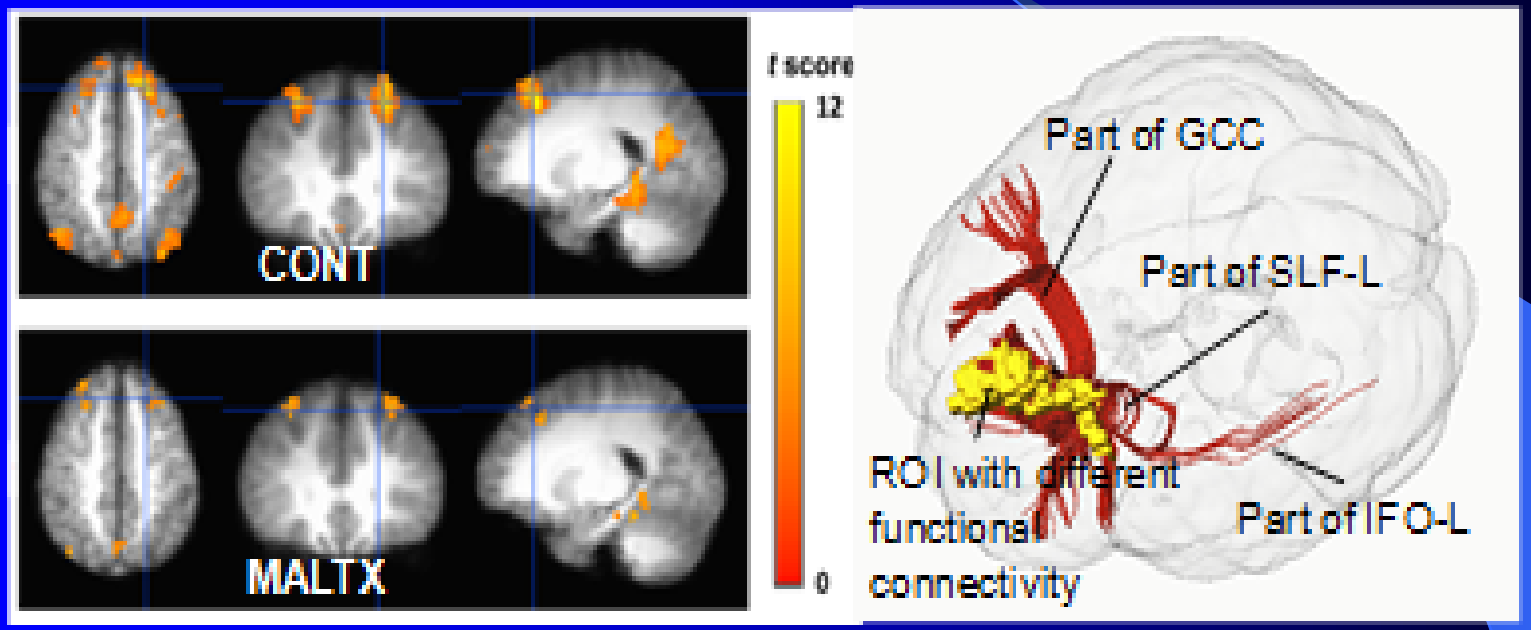
Rao et al., Biological Psychiatry 2010;67:357-364

Maltreatment & White Matter Tracts



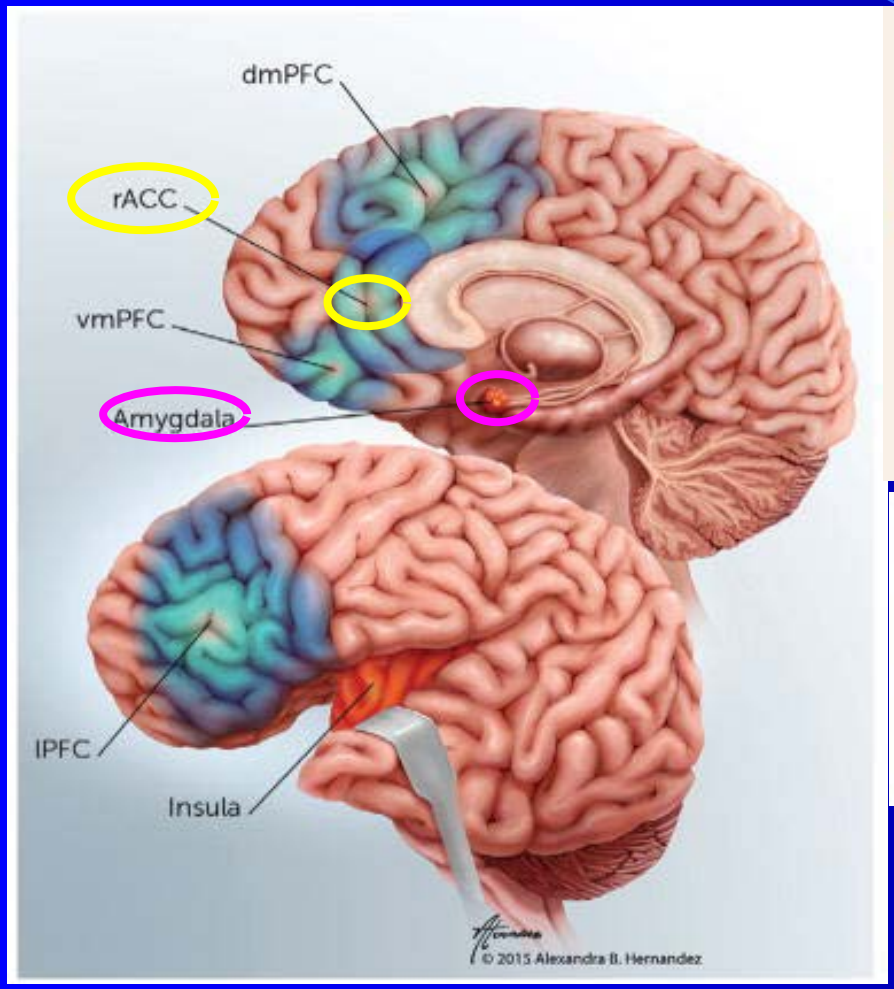
Huang et al., Neuropsychopharmacology 2012;37:2693-2701

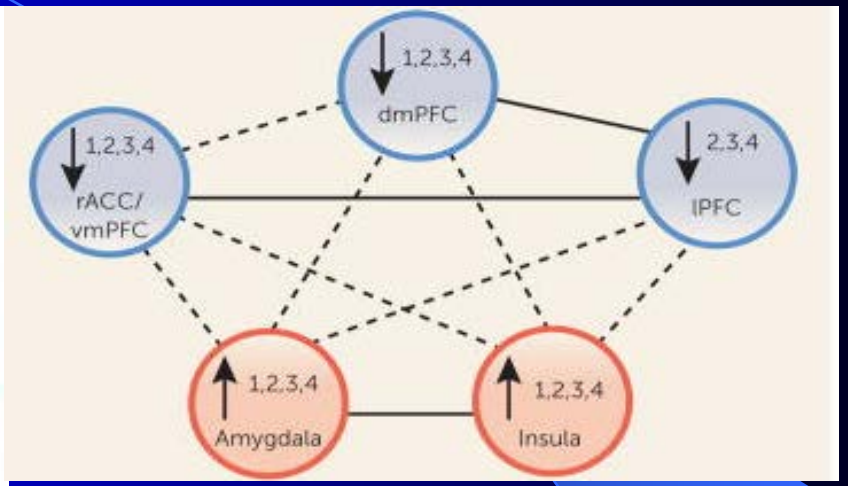
Intrinsic Functional Connectivity



Rao et al., unpublished data

Emotion Regulation Neural Circuit





Resting state functional connectivity and/or structural connectivity, relative to healthy subjects

- - - - - Decreased connectivity

——— Mixed results or no difference

Activation during fMRI while performing emotion regulation tasks, relative to healthy subjects

↓ Less activation

↑ More activation

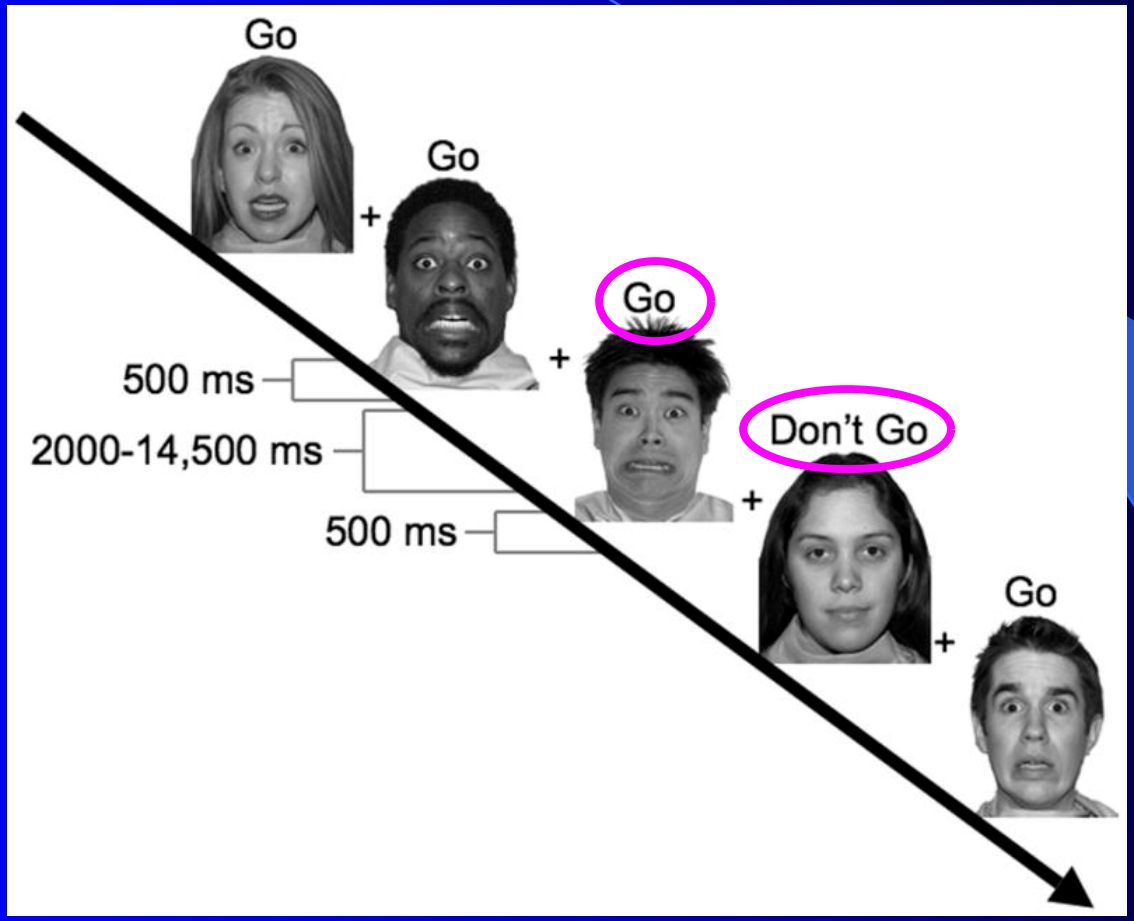
↔ Mixed results or no difference

Dimension of emotion regulation

1 Affect intensity/reactivity
2 Affective modulation
3 Cognitive modulation
4 Behavioral control

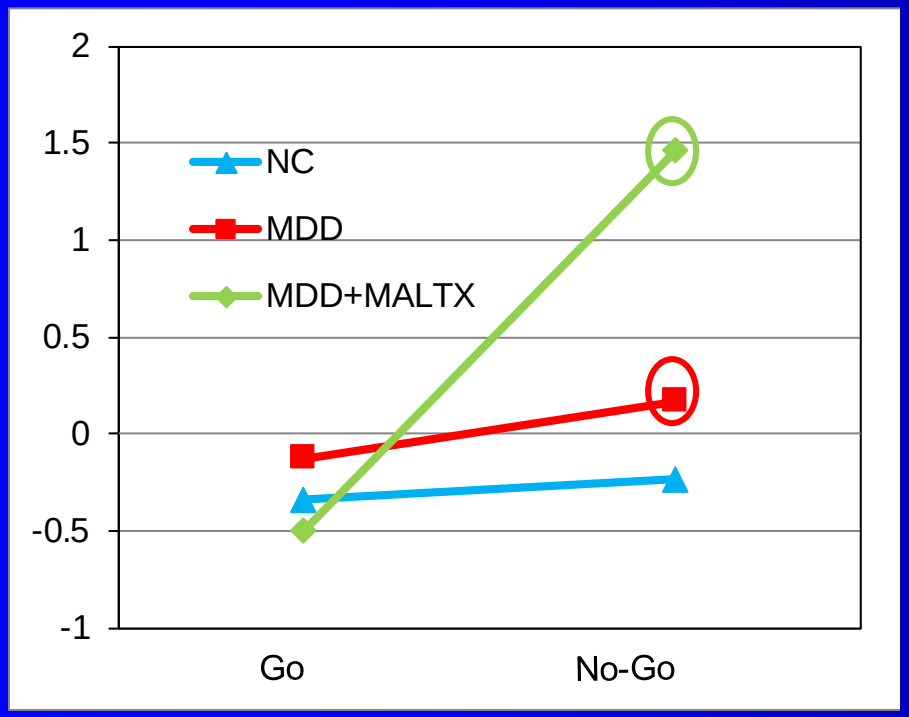
Wilcox et al., Am J Psychiatry 2016;173:344-361

Fronto-Limbic Circuit: Go/No-Go Task

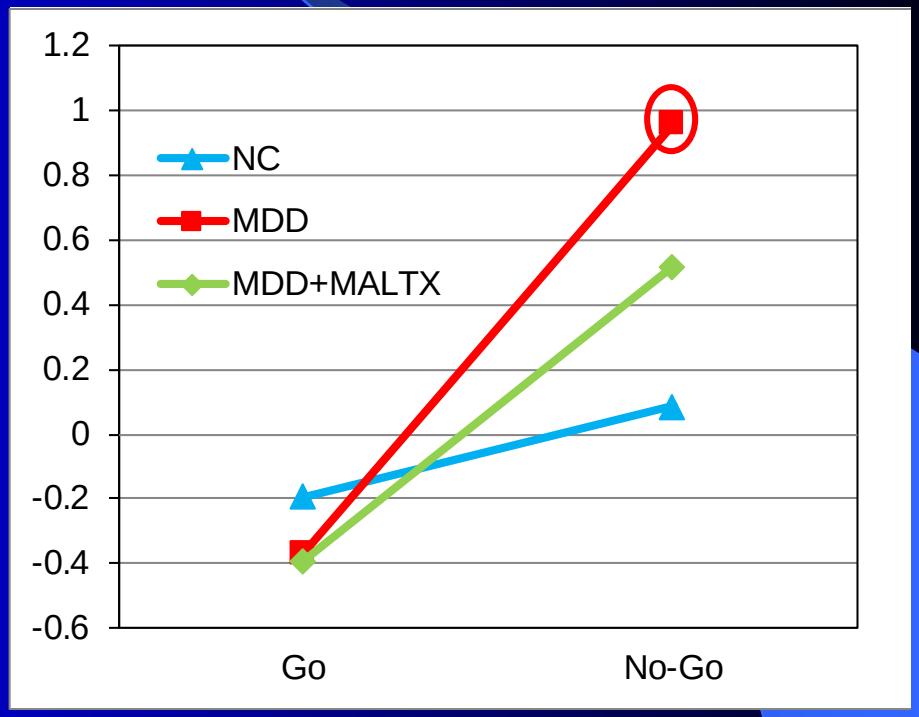


Hare et al., Biol Psychiatry 2008;63:927-9345

Maltreatment Effects on Fronto-limbic Circuit

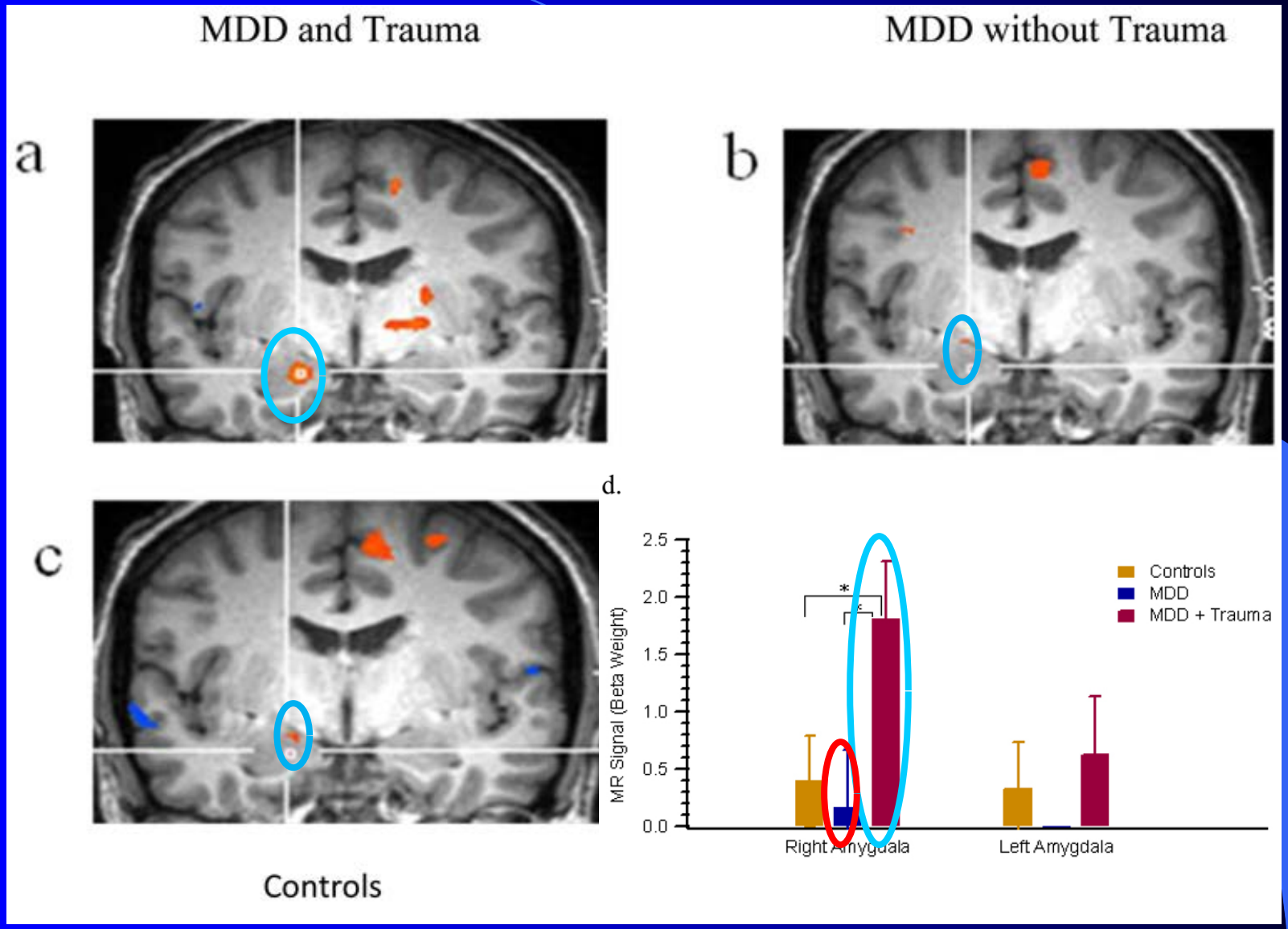


Amygdala Response



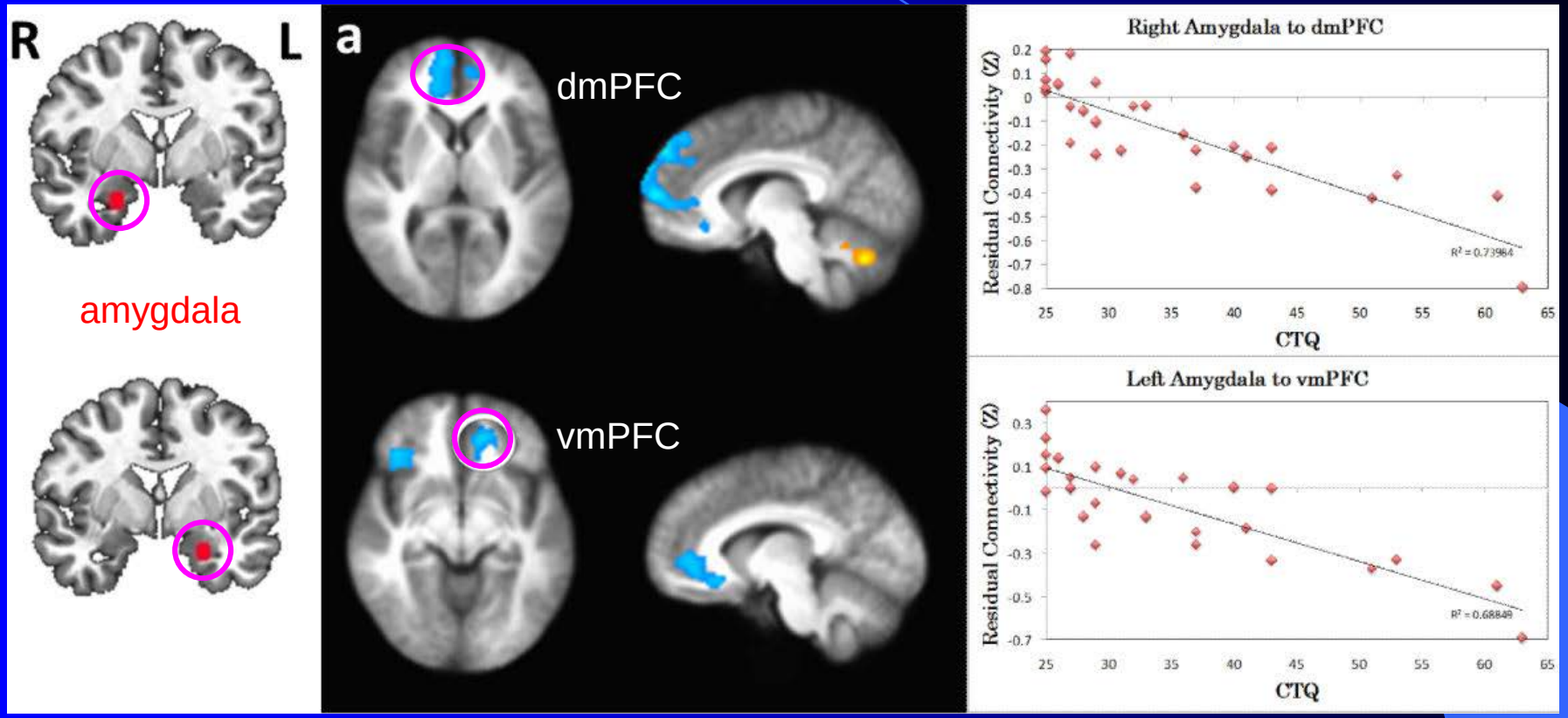
ACC/PFC Response

Trauma Effects on Amygdala Response



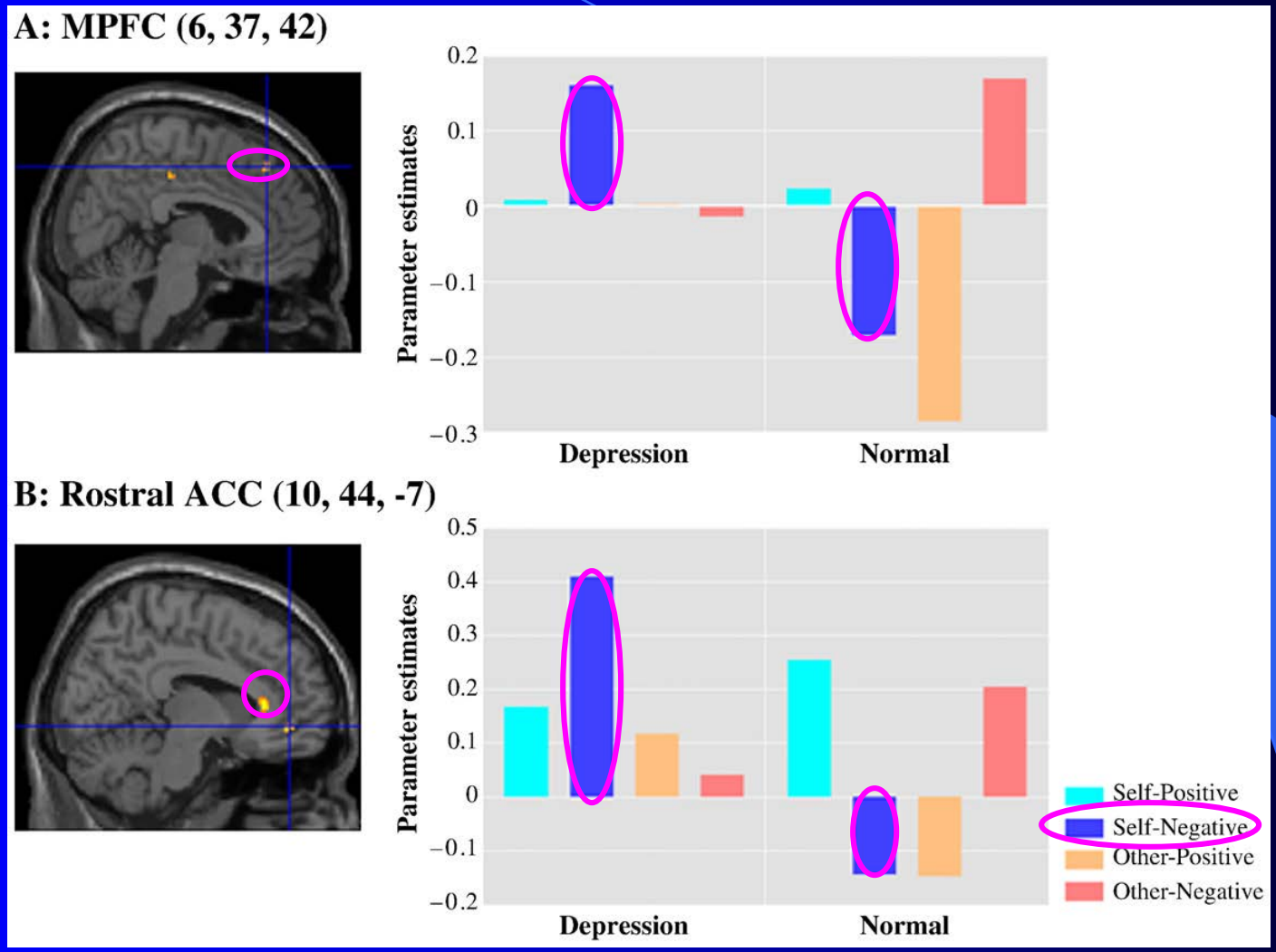
Grant et al., J Psychiatr Res 2011;45:886-895

Maltreatment: AMG-PFC Connectivity



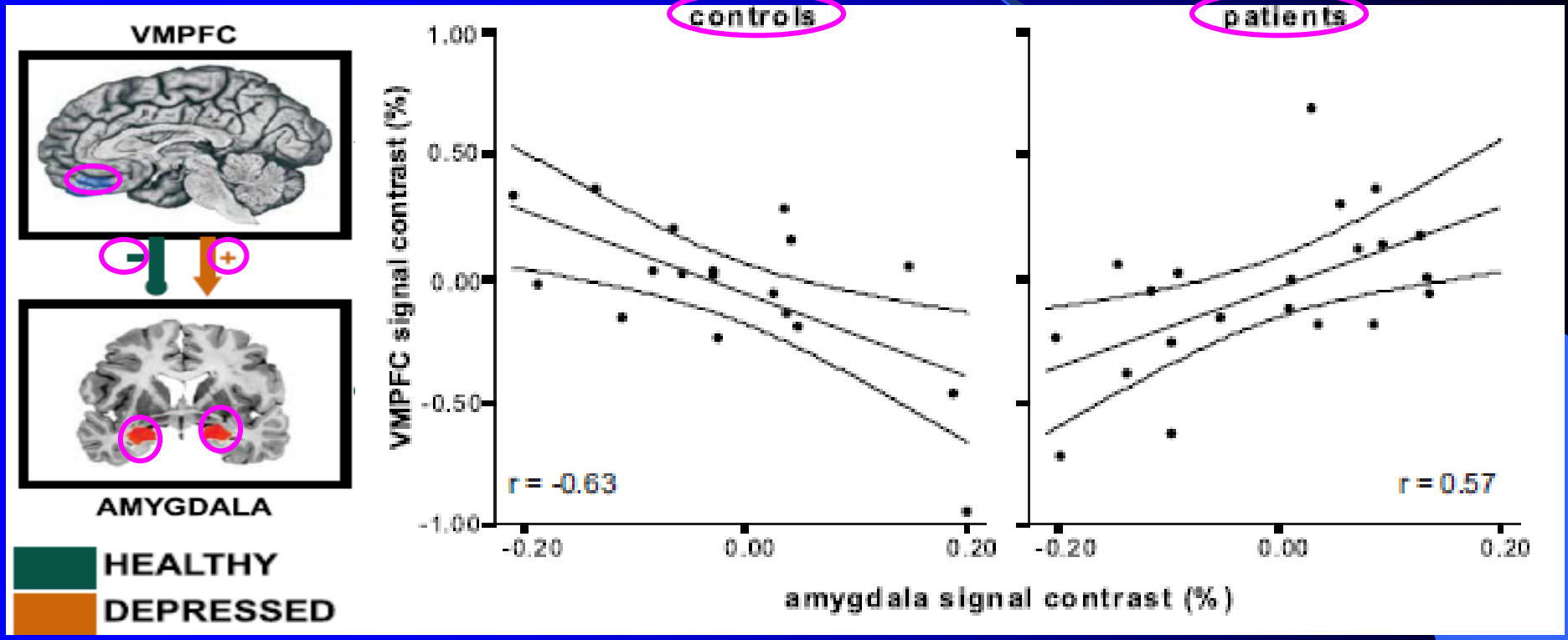
Birn et al., Depress Anxiety 2014;31:880-892

Depression: Self-Referential Thinking



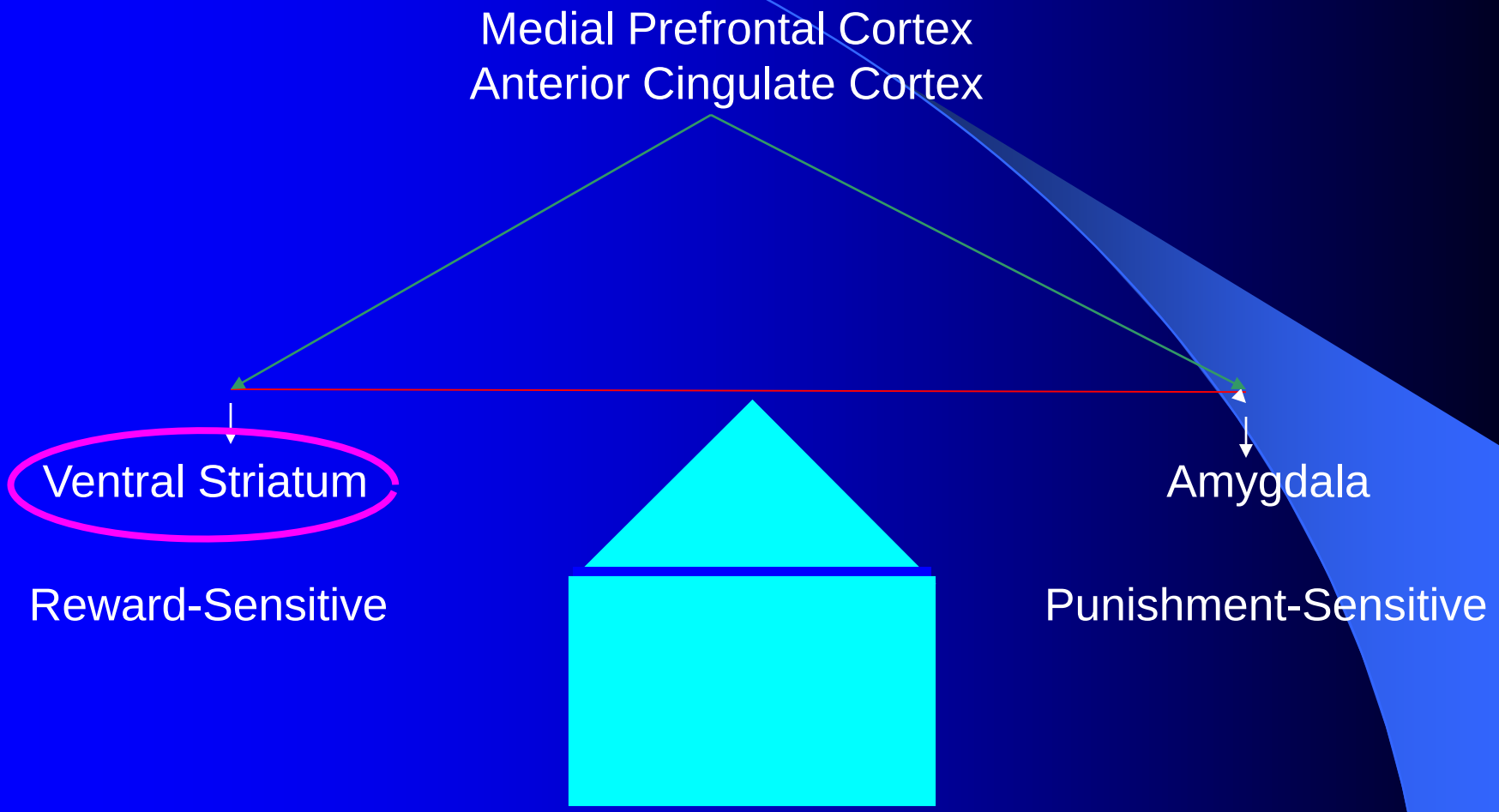
Yoshimura et al., J Affect Disord 2010;122:76-85

Depression: AMG-PFC Connectivity



Johnstone et al., J Neurosci 2007;27:8877-8884

Reward Neurocircuitry



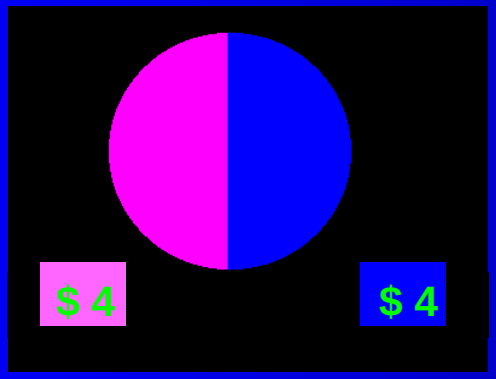
Ernst et al., Psychol Med 2006;36:299-312

Wheel of Fortune: Monetary Conditions

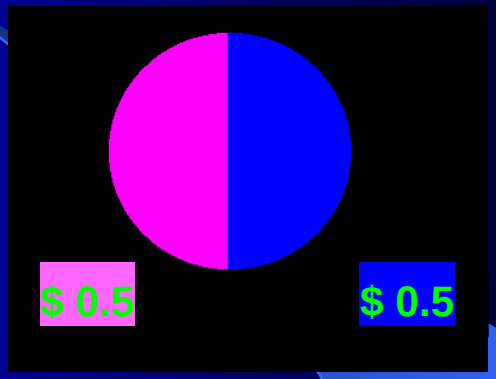
Equal Risk

Equal Reward

50/50

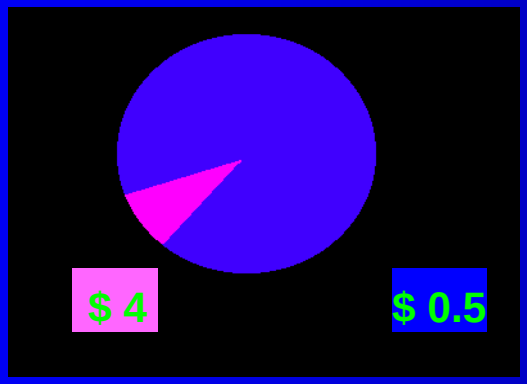


50/50



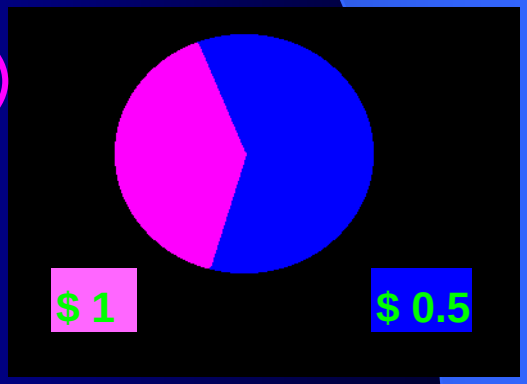
High Risk
High Reward

10/90

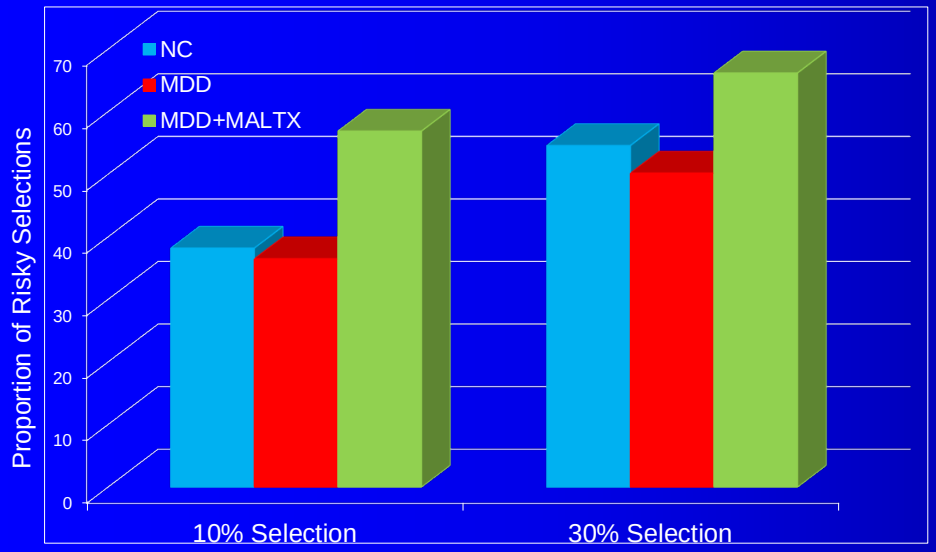


Moderate Risk
Moderate Reward

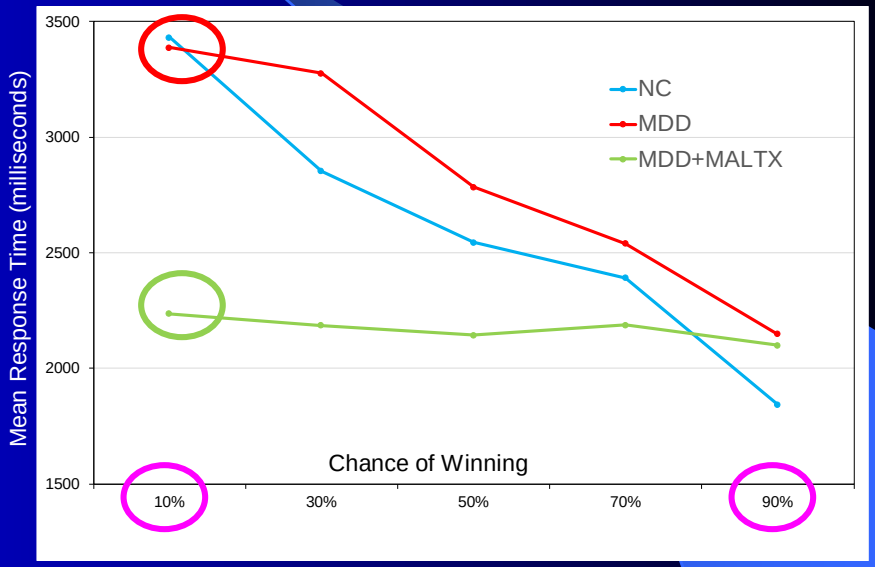
30/70



Maltreatment Effects on Risk-taking Behavior

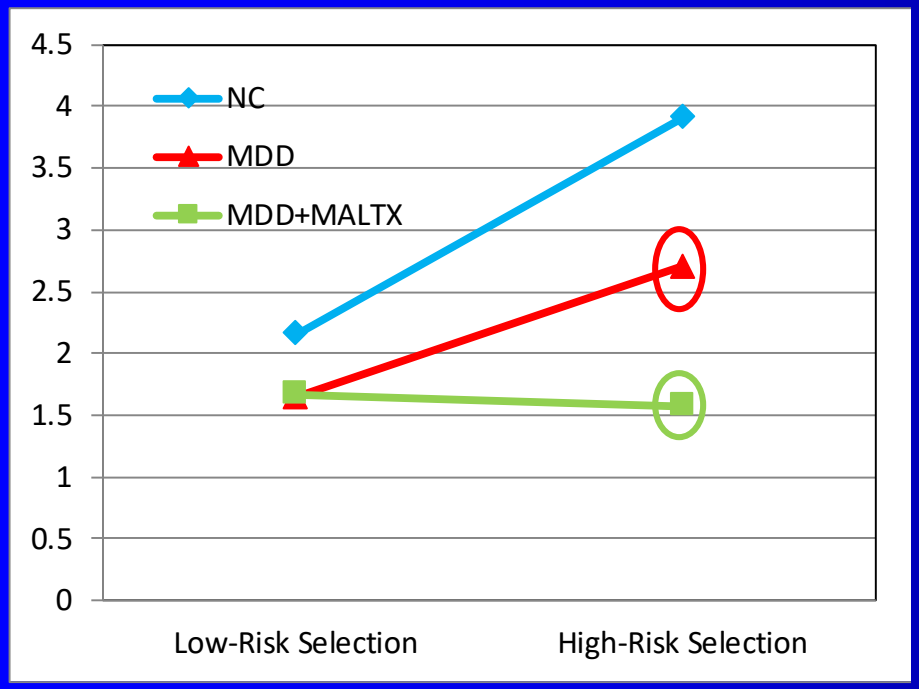


Risky Choice

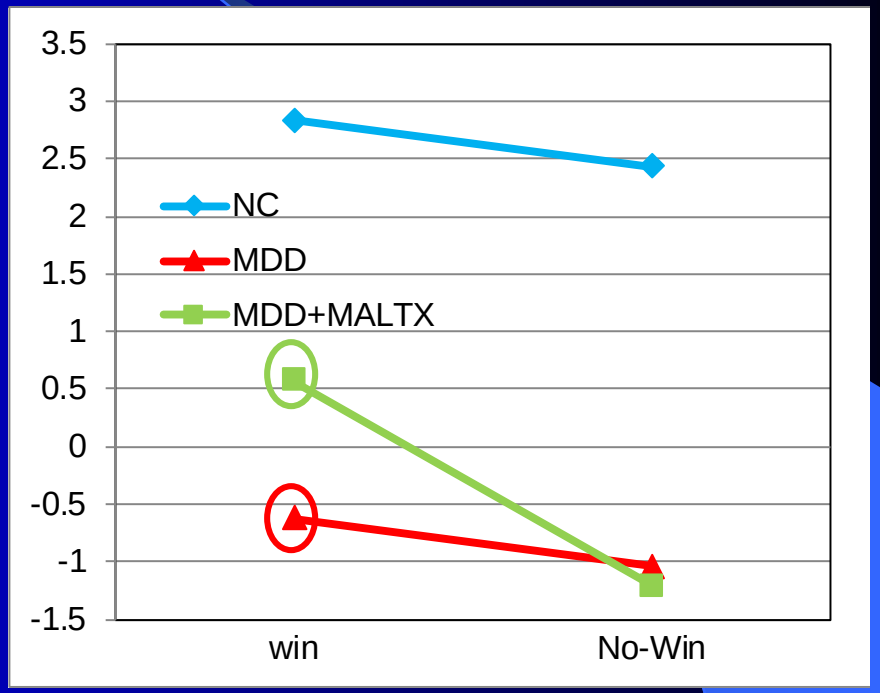


Reaction Times

Maltreatment Effects on Reward-processing Circuitry

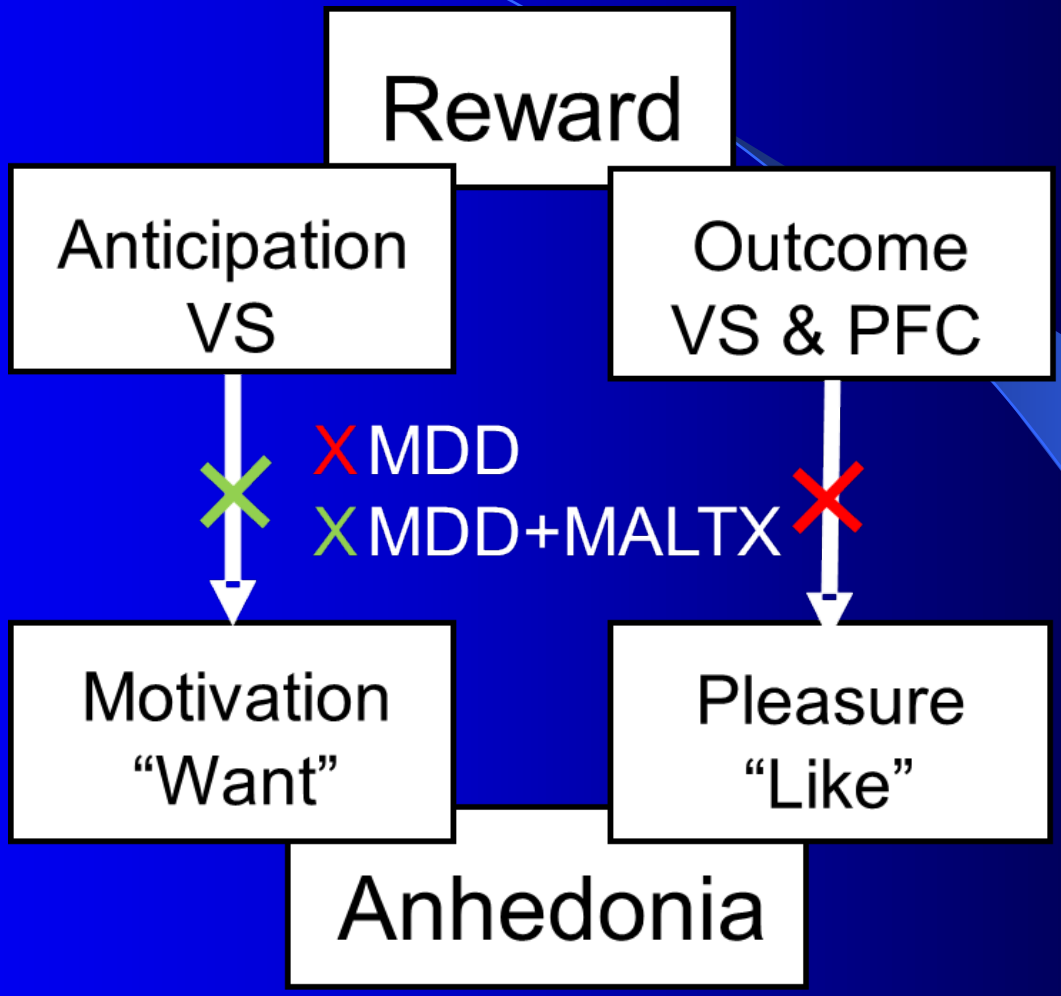


Ventral Striatal Response Selection Phase



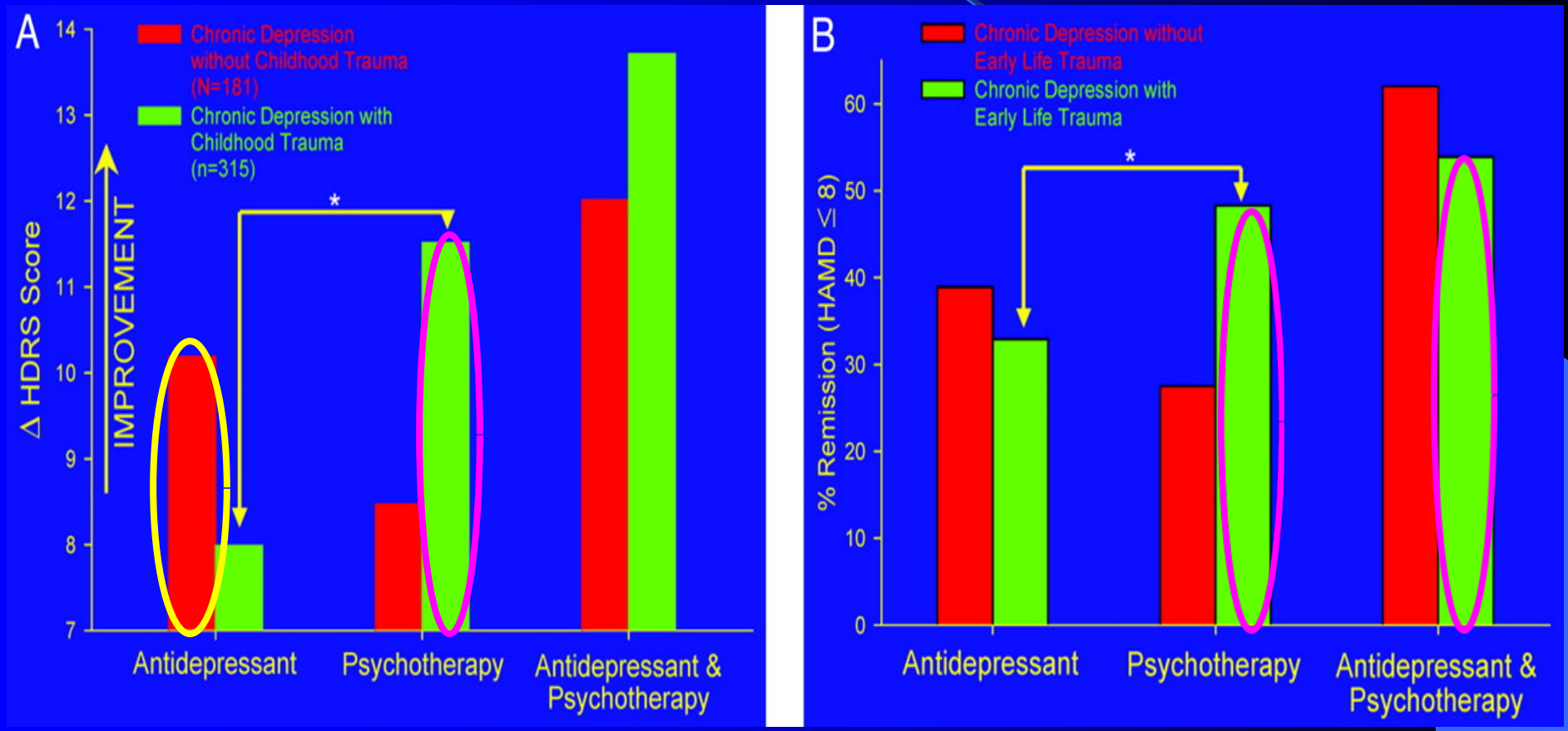
Ventral Striatal Response Feedback Phase

Anhedonia: Reward Circuitry



Adapted from Simon et al., Schizophr Res 2010;118:154-156

Maltreatment Effects on Response to Treatment of Depression



Nemeroff et al 2003; PNAS 100:14293-14296

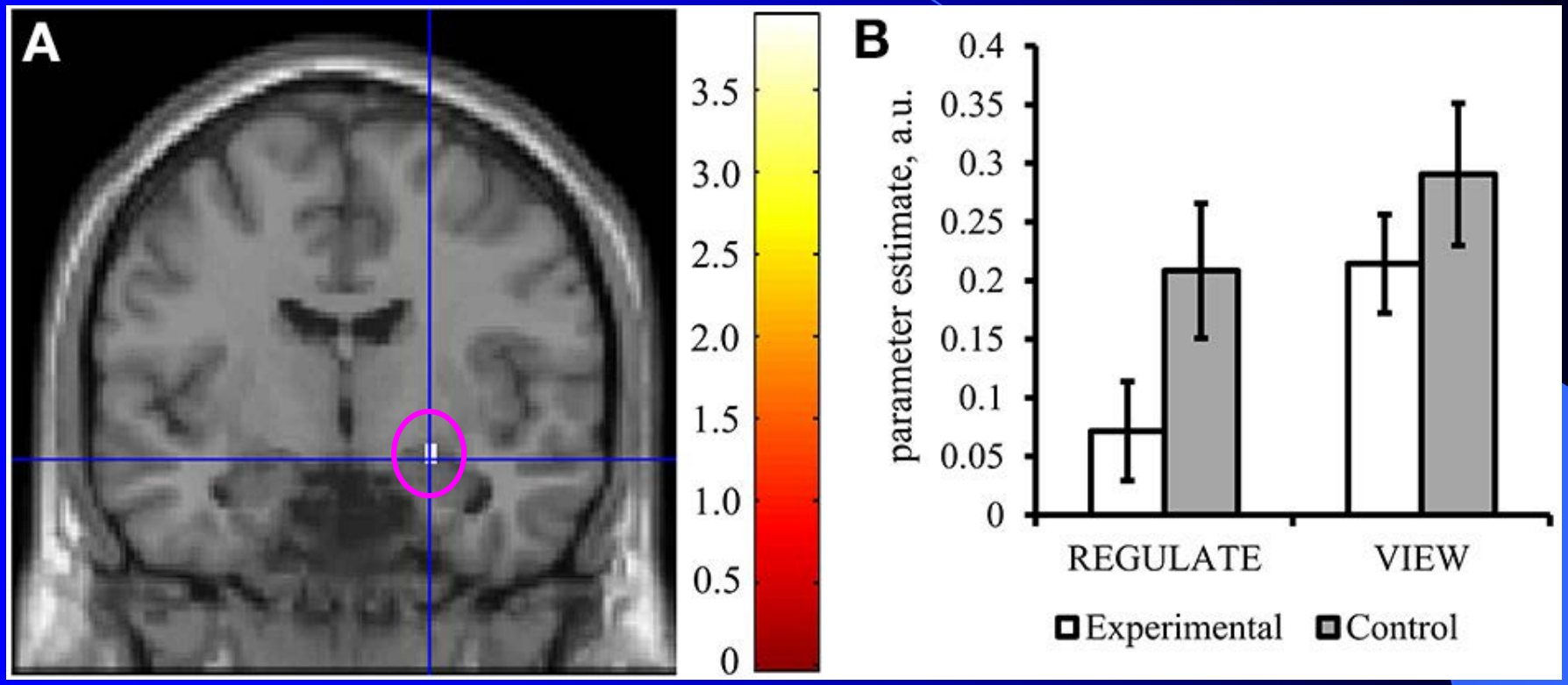
Interim Summary

- Depression due to early-life trauma may be a different phenotype
  - different clinical profile
  - different neurobiology
  - different treatment response

Next Steps

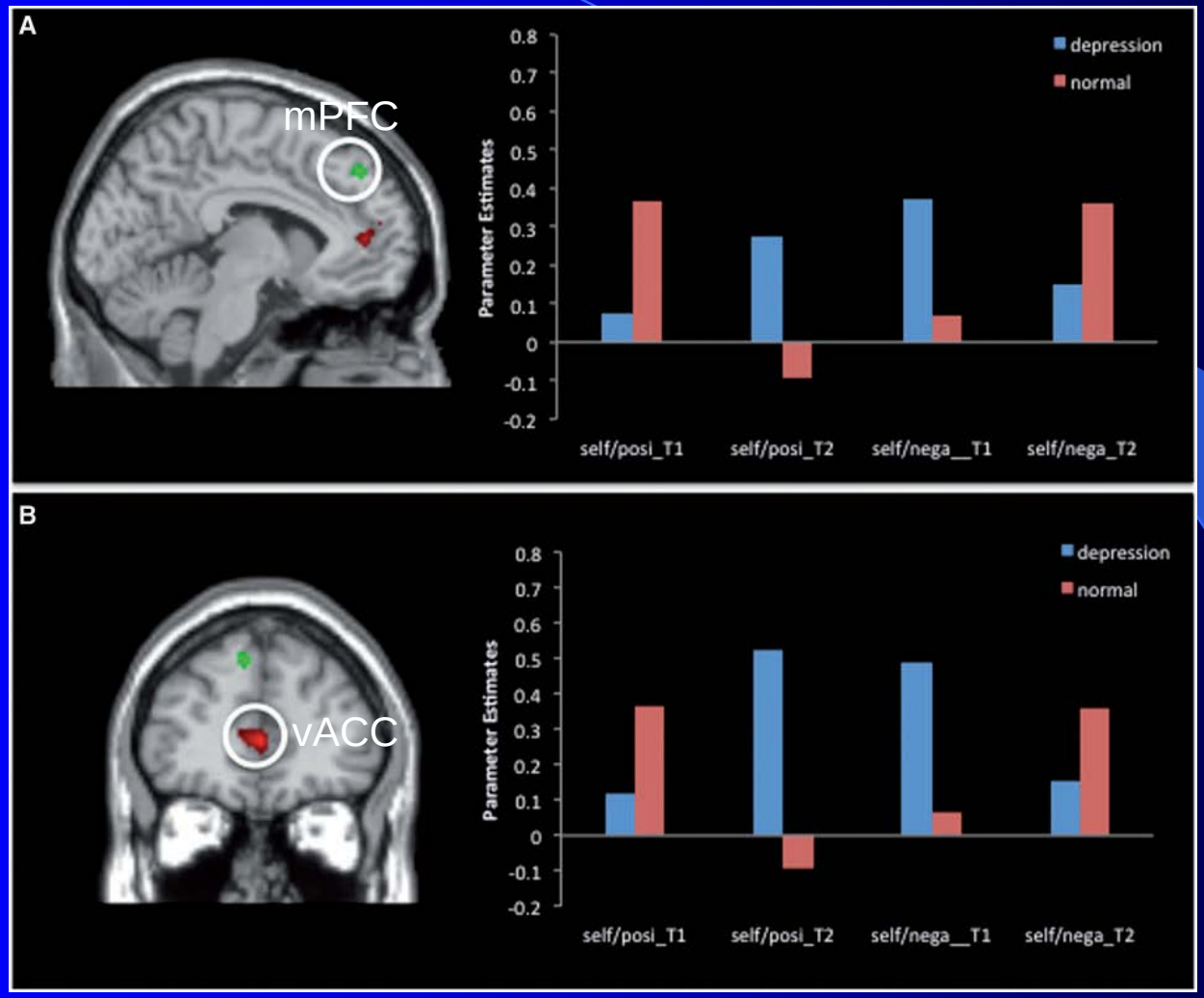
- Develop and test treatments based on differential neurobiological profiles
- Test whether the treatments affect observed neurobiological deficits

Neurofeedback: AMG Downregulation



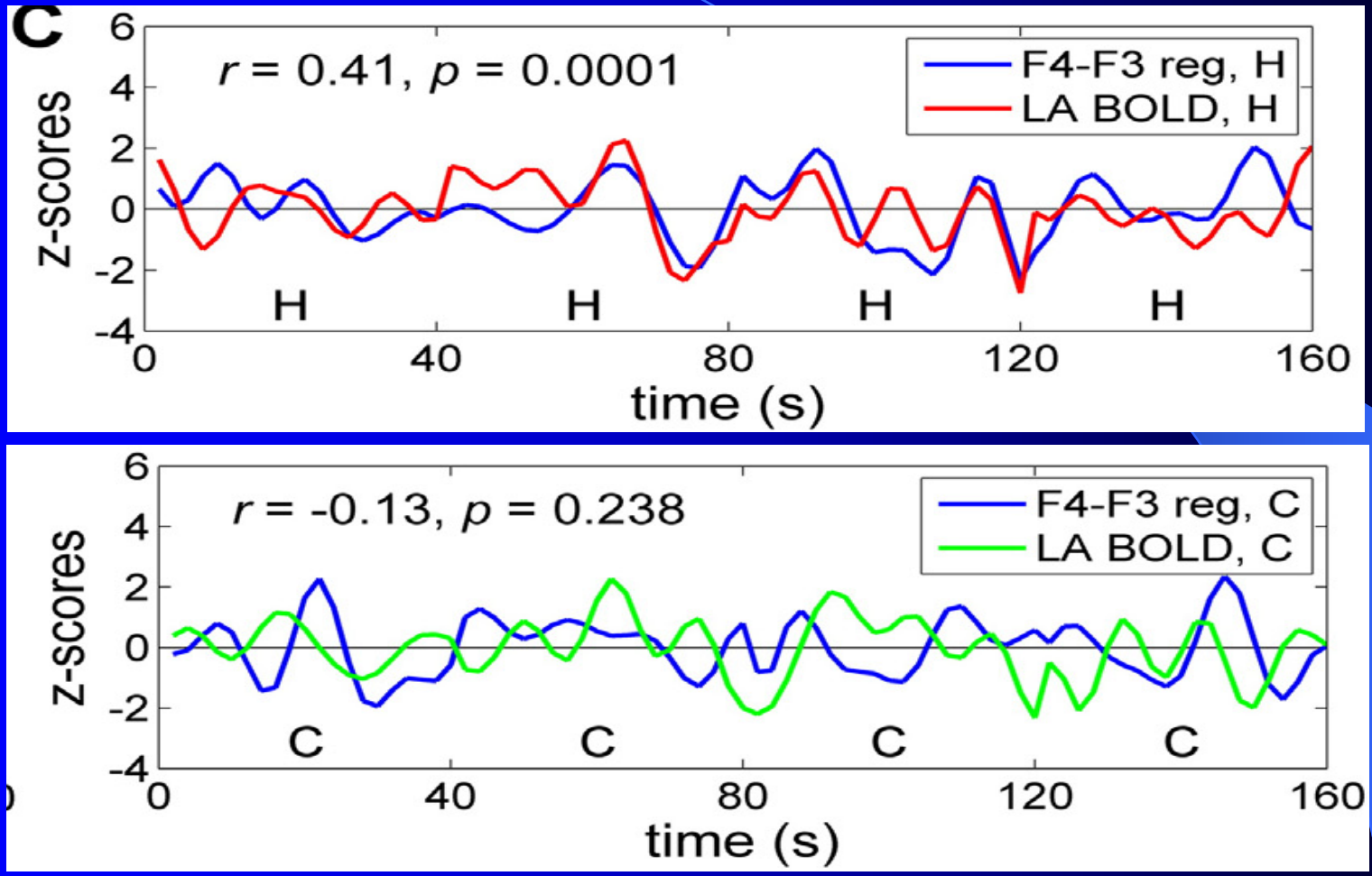
Paret et al., Front Behav Neurosci 2014;8:299

Tx Effects on Self-Referential Thinking



Yoshimura et al., Soc Cogn Affect Neurosci 2014;9:487-493

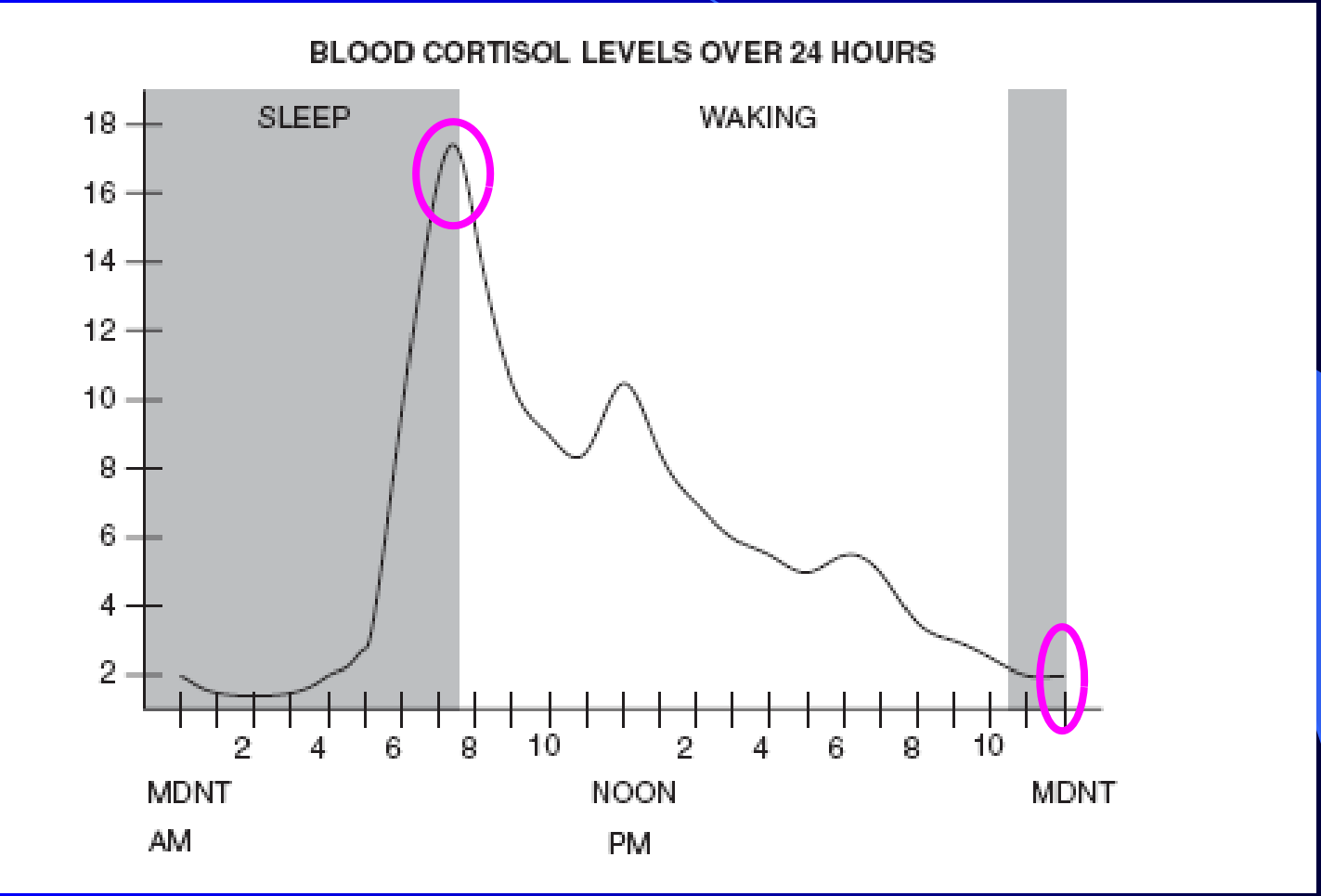
Neurofeedback: Positive Memories



Zotev et al., Neuroimage Clin 2016;11:224-238

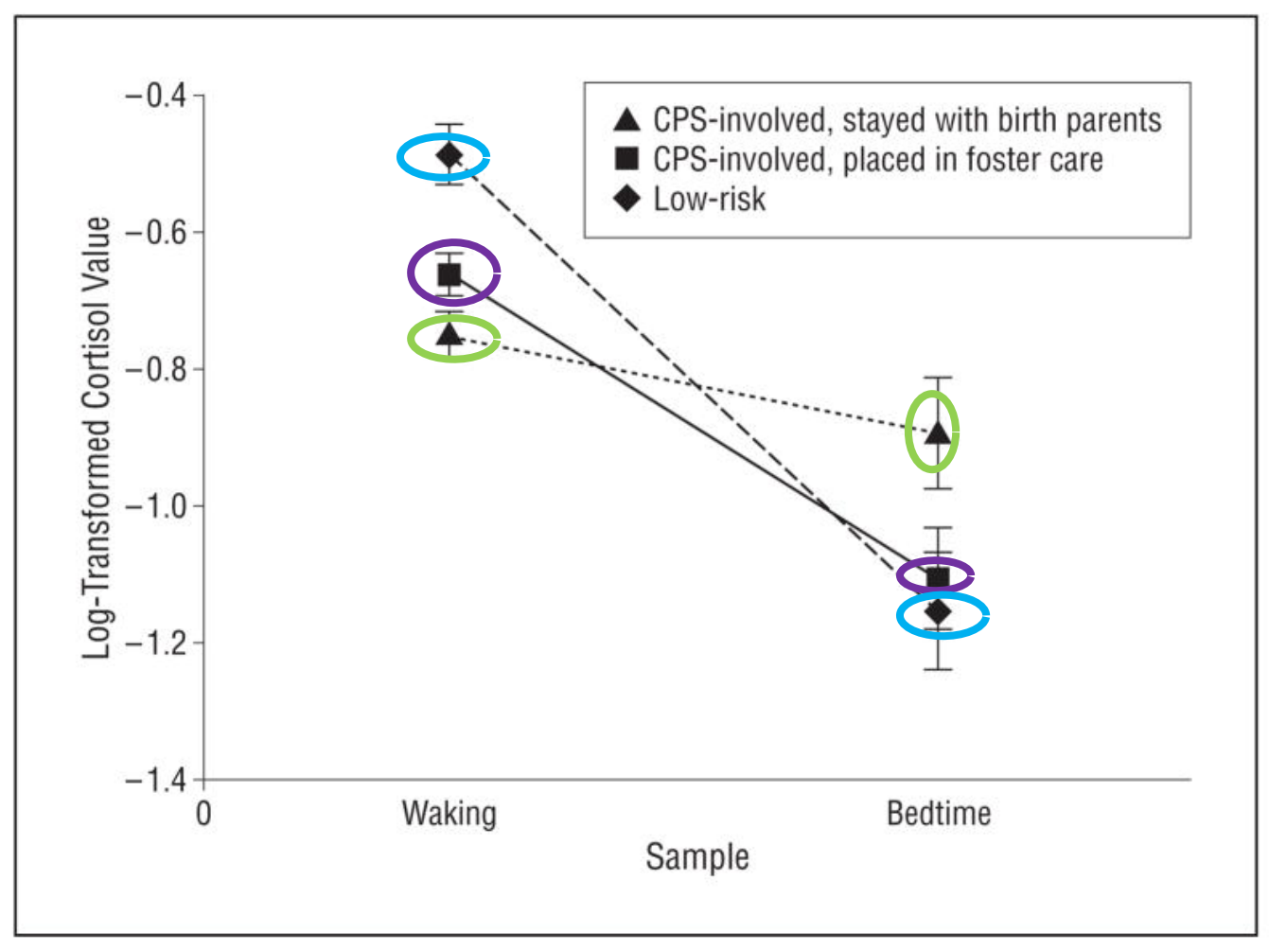
Can social policy affect changes in neurobiology?

Cortisol: 24-Hour (Diurnal) Pattern



Lovallo, Int J Psychophysiol 2006;59:195-202

Social Support Effects on HPA Axis



Bernard et al., Arch Pediatr Adolesc Med 2010;164:438-443

Summary

- Early-life trauma increases the risk for depression and other problems
- Trauma interacts with genetic factors to induce neurobiological changes and increase risk for psychopathology
- Neurobiological deficits can be altered by social policy and other interventions

BRoAD Lab Team & Funding Sources

Research Staff
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- Frank Zaldivar, PhD

Collaborating Institutions
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- CHOC Children's Hospital
- Christ Our Redeemer Church
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- Sigma Beta Xi, Inc.

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