YOU RUINED ME: MENTAL HEALTH IN THE FACE OF EARLY LIFE ADVERSITY
Learning Objectives

• Describe the impact of childhood abuse and neglect on brain structure and function

• Explore the influence of childhood abuse and neglect on the epigenome
Early Life Adversity (ELA)

- Childhood adversity can increase morbidity and mortality in adulthood
- ELA may include:

  - Physical abuse
  - Sexual abuse
  - Household substance abuse
  - Parental separation or divorce
  - Emotional abuse
  - Household mental illness
  - Incarcerated household member
  - Household domestic abuse

U.S. Prevalence of Adverse Childhood Experiences (ACE)

- Prevalence of having ≥1 adverse childhood experience: 61.55%
- Prevalence of having ≥3 adverse childhood experiences: 24.64%
- The most prevalent ACE is emotional abuse: 34.42%

Higher ACE exposure among individuals who...

- Are Black, Hispanic, or multiracial versus White
- Have less than a high school education versus completed high school or more education
- Are unemployed or unable to work versus employed
- Have an annual income less than $15,000 versus income greater than $15,000
- Are lesbian, gay, or bisexual (LGB) versus straight
- Are transgender versus LGB cisgender

Impact of Child Abuse and Neglect on Mental Health

• Child abuse and neglect is associated with increased risk for major psychiatric disorders and suicide
  • The course of psychiatric disorders in individuals exposed to childhood maltreatment is more severe
  • Characterized by altered brain structure, brain function, and epigenetics

Childhood Maltreatment Increases Risk of Suicidal Behavior

- Emotional abuse increases odds of suicidal behavior by 133%
- Physical abuse increases odds of suicidal behavior by 54%
- Physical neglect increases odds of suicidal behavior by 40%
- Sexual abuse increases odds of suicidal behavior by 36%
- Emotional neglect increases odds of suicidal behavior by 27%

History of Childhood Trauma Is Associated With Reduced Gray Matter Volume in Hippocampus and Amygdala

- Individuals with a history of childhood maltreatment, particularly adults with psychiatric diagnoses, display smaller bilateral hippocampus and amygdala than controls.

- There is some evidence of reduced gray matter volume in right dorsolateral prefrontal cortex, right orbitofrontal-temporal-limbic regions, and left inferior frontal gyrus.

Early Life Adversity Is Associated With Altered Brain Function in Childhood/Adolescence

Meta-analysis of 21 functional magnetic resonance imaging (fMRI) studies including children/adolescents (<18 years old; n=1,341), showed that early life adversity was associated with greater activation of amygdala (AMY), globus pallidus (GP)/parahippocampal gyrus, superior temporal gyrus, middle temporal gyrus (MTG), cerebellum, and thalamus.

DNA Methylation: An Epigenetic Mechanism

Early life abuse/neglect

DNA methyltransferase altered
- Adds methyl groups to promoter regions of genes turning them “off”

Gene expression off when it’s supposed to be on
Epigenetic Alterations Associated With Childhood Trauma and Adult Mental Health

- Methylation of the following genes is most consistently associated with childhood trauma in healthy and psychiatric populations:
  - Glucocorticoid receptor gene/nuclear receptor subfamily 3, group C (NR3C1)
  - Serotonin transporter gene/solute carrier family 6 (SLC6A4)
  - Brain-derived neurotrophin factor (BDNF)
  - Oxytocin receptor (OXTR)

Early life abuse/neglect

Altered DNA methylation

Increased risk for psychiatric illness

Impaired neurotransmission

Impaired neurodevelopment and plasticity

BDNF, SLC6A4, OXTR, NR3C1

DNA methyltransferase

Impaired stress response

Increased risk for psychiatric illness
NR3C1 codes for the glucocorticoid receptor (GR), which is a critical component of the stress response system and is heavily expressed in hippocampus.

NR3C1 methylation reduces GRs and may play a role in stress-related psychopathology.

Aberrant NR3C1 methylation may lead to hippocampal volume loss, which is characteristic of stress-related psychopathology.
Childhood Abuse Is Associated With Methylation of Hippocampal Glucocorticoid Receptor (NR3C1)

In abused suicide victims, there was increased methylation of hippocampal glucocorticoid receptor (NR3C1) promoter

Analysis of post-mortem hippocampal tissue obtained from suicide victims with (n=12) or without (n=12) history of childhood abuse (matched for psychiatric diagnoses) and controls (n=12)

Interaction of Early Life Adversity and MAOA Genotype Is Associated With NR3C1 Methylation

- The monoamine oxidase A (MAOA) gene codes for a mitochondrial enzyme that metabolizes monoamines, and contains a functional length polymorphism.

- The MAOA-L allele is transcribed less efficiently than the MAOA-H allele and is associated with psychopathology and childhood adversity.

Data from analysis comparing NR3C1 methylation of women (depression and healthy controls) with MAOA-L and MAOA-H genotype based on a history of early parental death (EPD)

SLC6A4

• Methylation of SLC6A4, the serotonin transporter (5-HTT) gene, is associated with childhood trauma and depression

• Serotonin is known to regulate the hypothalamic-pituitary-adrenal axis stress response by way of the hippocampus, amygdala, and prefrontal cortex

• Increased methylation of SLC6A4 following childhood trauma may lead to decreased gene expression that leads to the development of stress-related hippocampal alterations

Childhood Trauma and Hippocampal Volume Are Associated With SLC6A4 Methylation

Findings from a study of 33 adults with major depressive disorder (MDD) and 36 matched healthy controls. Physical abuse was most strongly associated with SLC6A4 methylation across the whole sample ($r=0.33$, $p=0.006$).

5-HTTLPR Genotype Moderates Association of Early Life Stress and SLC6A4 Methylation

Greater impact of stressful life events on SLC6A4 methylation among adolescents who were L-allele homozygotes

SLC6A4 methylation was more strongly associated with ASPD symptoms for those with a greater number of s alleles.

Findings from study of women with and without a history of child sex abuse (n=155)

BDNF

• BDNF is a neurotrophin that plays an important role in regulating neuronal development, plasticity, and survival

• BDNF is highly expressed throughout the brain, with strongest expression in the hippocampus

• BDNF methylation in rodent hippocampal tissue due to early life stress has been associated with long-term deleterious effects on plasticity

• In humans, BDNF methylation due to ELA may lead to structural alterations of other stress-responsive brain regions like the orbitofrontal cortex

BDNF Val66Met Genotype Is Associated With Limbic Volumes and Childhood Trauma

Studies examining the interaction of childhood trauma, BDNF genotype, and BDNF methylation to predict limbic volumes are needed.

BDNF Val66Met Genotype Is Associated With Childhood Trauma and Psychiatric Symptoms

Studies examining the interaction of childhood trauma, BDNF genotype, and BDNF methylation to predict psychiatric symptoms are needed

Oxytocin

• Oxytocin is a neuropeptide that influences the salience of social cues and interactions, regardless of valence

• The OXTR gene is a key player in oxytocin signaling

• Childhood trauma may lead to increased methylation of OXTR that impacts brain structure and psychiatric symptoms

OXTR Methylation Is Associated With Childhood Maltreatment and Orbitofrontal Cortex Volume

Findings from cross-sectional study of children and adolescents (ages 6–20) with a history of childhood maltreatment (CM=24; red) or no history of maltreatment (Non-CM=31; blue).

OXTR Methylation Mediates the Association Between ELA and Childhood Anxiousness

- Anxiousness rated yearly by teachers
- Retrospective assessment of childhood abuse
- Assessed OXTR methylation

$\text{a} = 8.04 (3.39)^*$
$\text{b} = 0.04 (0.01)^*$
$\text{c} = 0.72 (0.23)^*$
$\text{c'} = 0.37 (0.12)$

$\text{N=46}$

SNPs identified from a sample of 393 African American adults (mean age 41 ± 12.8 years) with varying degrees of physical, emotional, or sexual abuse (‘none to mild,’ ‘moderate,’ or ‘severe’).

**rs237897**
Previously associated with emotion recognition and autism spectrum disorder

**rs7629329**
Previously associated with OXTR methylation in brain tissue

**rs2301261**
Previously associated with ventral striatum activity during emotional face processing

Studies examining the interaction of childhood trauma, OXTR genotype, and OXTR methylation to predict psychiatric symptoms are needed

What About FK506 Binding Protein 5 (FKBP5)?

- FKBP5 regulates glucocorticoid receptor (GR) sensitivity and the stress hormone system
- Early life adversity (ELA) is associated with FKBP5 methylation
- Since FKBP5 is responsive to cortisol, epigenetic modification of FKBP5 via ELA alters the stress hormone axis and increases the risk for stress-related disorders

Binder EB. Psychoneuroendocrinology 2009;34(Suppl 1):S186-95;
FKBP5 Methylation May Partially Mediate the Association Between Early Life Stress and Prefrontal Activity

Findings from longitudinal study where early life stress was assessed in childhood (9–13 years old) and FKBP5 methylation and brain activity during inhibitory control were measured in early adulthood (19–24 years old).

Genotype May Moderate the Association Between FKBP5 Methylation and Early Life Adversity

Among carriers of the FKBP5 rs1360780 risk allele, childhood adversity is negatively associated with FKBP5 methylation in adulthood.

CTQ=Childhood Trauma Questionnaire

Tozzi L et al. Neuropsychopharmacology 2018;43(5):1138-45;
Early life abuse/neglect

Altered DNA methylation

BDNF
SLC6A4
OXTR
NR3C1
FKBP5

Impaired neurodevelopment and plasticity
Impaired neurotransmission
Impaired stress response

Increased risk for psychiatric illness
Treatment Implications: NR3C1 and FKBP5

• Higher NR3C1 methylation has been associated with better treatment outcomes with a CRF₁ receptor antagonist in patients with posttraumatic stress disorder who have a history of child abuse versus those without a history of child abuse.

• Reduction in anxiety symptoms following cognitive behavioral therapy was associated with reduction in FKBP5 methylation in patients with anxiety disorders who had FKBP5 risk alleles.

• The interaction effect of ELA x genotype x methylation on treatment outcomes requires further investigation.

Roberts S et al. Depress Anxiety 2015;32(12):861-70;
Treatment Implications: SLC6A4

- Treatment response in depressed patients with a history of ELA is typically worse than their non-ELA counterparts.

- Higher SLC6A4 methylation has been associated with better antidepressant treatment response in Caucasian and Japanese patients with major depressive disorder (MDD), regardless of 5-HTTLPR genotype.

- 5-HTTLPR l/l and l/s genotypes may be associated with better therapeutic response to selective serotonin reuptake inhibitor treatment in Caucasian patients with MDD.

- The interaction effect of ELA x genotype x methylation on treatment outcomes requires further investigation.

• BDNF Met carriers have better antidepressant response than Val/Val carriers

• Lower BDNF methylation has been associated with impaired antidepressant response in patients with depression
  • Patients with lower life stress scores and higher BDNF methylation showed superior antidepressant treatment than those with higher life stress scores and lower BDNF methylation

• The interaction effect of ELA x genotype x methylation on treatment outcomes requires further investigation

Yan T et al. Asia Pac Psychiatry 2014;6(3):241-51;
Summary

• Childhood abuse and neglect are alarmingly common and are associated with poor mental health outcomes

• ELA is associated with neural alterations in brain regions associated with social and emotional processing

• ELA is associated with epigenetic alterations of genes implicated in impaired neurodevelopment and plasticity, neurotransmission, and stress response

• The association between ELA and poor mental health outcomes may be mediated by epigenetic and neural alterations and moderated by genotype, but more research is needed to confirm
Posttest Question 1

Approximately, what is the prevalence of having one or more adverse childhood experiences in the United States?

A. 15%
B. 25%
C. 62%
D. 72%
Posttest Question 2

For which of the following neural structure(s) is there evidence of gray matter reduction following childhood trauma?

A. Fusiform gyrus
B. Amygdala and hippocampus
C. Nucleus accumbens and dorsal striatum
D. Cerebellum
The term epigenetics refers to:

A. An inherited sequence of DNA that contains a mutation
B. A process determining whether a given gene is expressed or silenced