Childhood Abuse, Brain Development and Psychopathology

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In cooperation with the
Department of Psychiatry
Department of Child Psychiatry
Academic Medical Centre of
The University of Amsterdam

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Information

I post the slides for my talks at -

https://drteicher.wordpress.com/

I can be reached at -

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The content of this talk is covered in detail in the following review articles.


Introduction

- Impulse control disorders
- Drug and Alcohol Abuse
- Antisocial Personality DO
- Generalized Anxiety & Phobias
- Major Depression
- Bipolar DO (early onset)
- Post-traumatic Stress
- Borderline Personality DO
- Dissociative Identity DO
- Psychotic Disorders

Childhood Abuse
Adverse Childhood Experience Study
Dr. Vincent Fellitti and Dr. Robert Anda

Epidemiological survey of the medical, psychiatric and developmental history of 17,337 individuals enrolled in the Kaiser-Permanente Health Plan in California.

Prospective pharmacy records were available on 15,033 (86.7% of the analytic sample).
Adverse Childhood Experience Study

Dr. Vincent Fellitti and Dr. Robert Anda

1. Emotional Abuse
2. Physical Abuse
3. Sexual Abuse
4. Living with Substance Abuser
5. Living with Mentally Ill family member
6. Witness Mother treated violently
7. Incarcerated household member
8. Parental separation or divorce
9. Emotional Neglect
10. Physical Neglect
ACE Score vs. Depression

ACE Score vs. Intravenous Drug Use

ACE Score vs. Attempted Suicide
Population attributable risk associated with early adversity:

- 50% for drug abuse
- 54% for current depression
- 65% for alcoholism
- 67% for suicide attempts
- 78% for iv drug use

Pharmacological Consequences of Childhood Maltreatment

**Increased Risk of Prescriptions with > 5 ACEs**

- Anxiolytics 2.1 fold
- Antidepressants 2.9 fold
- Antipsychotics 10.3 fold
- Mood-Stabilizers 17.3 fold
Medical Consequences of Childhood Maltreatment

Individual with > 6 of 10 ACEs

Nearly 20 year reduction in life span

Questions

What brain structures are affected by exposure to childhood maltreatment?

Does the type of maltreatment matter or are they all stressors?

What is the relationship between childhood abuse, brain changes and psychiatric illness?
First Neuroimaging Findings
Childhood Abuse and the Regional Anatomy of the Corpus Callosum

Myelinated regions, such as the corpus callosum (CC) are potentially vulnerable to the impacts of early exposure to excessive levels of stress hormones, which suppress glial cell division critical for myelination.
Comparison between abused/neglected boys, non-abused psychiatric control boys (contrast group), and healthy boys.

<table>
<thead>
<tr>
<th>Region</th>
<th>Abused/neglected</th>
<th>Contrast</th>
<th>Healthy</th>
<th>Group diff.</th>
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<tr>
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<td>0.889</td>
<td>1.100</td>
<td>1.152</td>
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<tr>
<td>7 (spleenium)</td>
<td>0.403</td>
<td>0.466</td>
<td>0.496</td>
<td>0.5450</td>
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(n) 13 13 61

Overall differences between groups, MANCOVA, p < 0.0001
Association of Early Experience and Age on Regional Anatomy of Corpus Callosum in Boys, Based on Step-wise Regression.

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†p < 0.10, ζp < .05, ξp < .01, ¥p < .001
*Values are expressed as % change in volume associated with positive history
**Values are expressed as % change in volume per year of age.
Childhood abuse affects corpus callosum

The morphology of the corpus callosum is significantly affected by early neglect (as well as physical abuse and sexual abuse).

Teicher et al. (2004) Biological Psychiatry 56, 80-85
Association of Early Experience and Age on Regional Anatomy of the Corpus Callosum in Girls, Based on Step-wise Regression.

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Corpus Callosum

Reduced area or integrity of the corpus callosum is the most consistent neurobiological finding in children and adults with histories of exposure to childhood abuse.

Significant reduction in 20/24 studies involving both children and adults - total N ~ 2053
Sensitive Periods
Time is of the essence
Sensitive Exposure Periods

Volume Mid Anterior Portion of Corpus Callosum - Females

Volume Central Portion of Corpus Callosum - Females

n=185
Sensitive Exposure Periods

Volume Mid Posterior Portion of Corpus Callosum - Males

Volume Posterior Portion of Corpus Callosum - Males

Recalled Ages of Exposure (years)

n=115
Fred Schiffer, M.D.
Corpus Callosum and Hemispheric Laterality

- Hemispheric brain activity was measured in adult subjects under two conditions: first, during recall of a neutral memory, and then during recall of an unpleasant affectively-laden early experience.
Deficient Hemispheric Integration

Our discoveries that abused patients have diminished right-left hemisphere integration and a smaller corpus callosum suggest an intriguing model for the emergence of borderline splitting.

With less integrated hemispheres, they may shift between logical and rational state to highly emotional state.
Deficient Hemispheric Integration

Lack of integration between the hemispheres may also be a factor in the genesis of dissociation and multiple distinct identities.
Stress
The logical alternative is that exposure to early stress generates molecular and neurobiological effects that alter neural development in an adaptive way that prepares the brain to survive and reproduce in a malevolent world.

Teicher MH: Scars that won't heal: the neurobiology of child abuse. Scientific American 2002; 286(3):68-75
Adaptive in our evolutionary past

Exposure to 6 or more ACEs - Accelerated Aging
20 year reduction in life span

Past epoch when life expectancy was very short. Many individuals died in childhood before passing on their genes

Accelerated aging - earlier onset of puberty

May initially foster survival - bigger, stronger
Reproduce at earlier age - greater chance of passing along genes
Threat Detection, Response and Recovery
Childhood Abuse and the Amygdala

Fear Circuit Regions & Pathways

1. Amygdala
2. Hippocampus
3. Sensory Cortex
4. Prefrontal Cortex
5. Pathways - AF, CB, Fornix, ILF
Amygdala

Exposure to stress leads to:

Persistent neuronal hypertrophy and symptoms of anxiety
Does not reverse with time
Does not abate with prefrontal cortical development
Childhood Abuse and the Amygdala

Result of studies assessing maltreatment and amygdala volume are inconsistent 41 studies, N ~ 5074.

<table>
<thead>
<tr>
<th>Description</th>
<th>Number of Studies</th>
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<tr>
<td>Significant decrease</td>
<td>14 studies</td>
</tr>
<tr>
<td>Non-significant decrease</td>
<td>11 studies</td>
</tr>
<tr>
<td>No difference</td>
<td>6 studies</td>
</tr>
<tr>
<td>Non-significant increase</td>
<td>4 studies</td>
</tr>
<tr>
<td>Significant increase</td>
<td>6 studies</td>
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Childhood Abuse and the Amygdala

**Decreased Volume**

Adults with Borderline Personality Disorder or Dissociative Identity Disorder *(often exposed to very severe abuse)*

**Increased Volume**

Institutionally-reared children with low degree of attention or children of chronically-depressed mothers *(often deprived of sufficient attention and affection - emotional neglect)*
Childhood Abuse and the Amygdala

Decreased Volume

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Childhood Abuse and the Amygdala

**Decreased Volume**

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**Increased Volume**

*Institutionally-reared* children with low degree of attention or *children* of chronically-depressed mothers
  *(often deprived of sufficient attention and affection - emotional neglect)*
Karlen Lyons-Ruth, Ph.D.
Assessed amygdala volume in 18 adults who as infants had mothers who were approach avoidant leading to disrupted attachment.

These subjects were compared to 33 young adults who were not exposed to significant maltreatment and who had no history of psychopathology.
3.8% increase bilaterally p < 0.04
Childhood Maltreatment (Severity of Exposure) vs. Adjusted Amgydala Volume

Right Amygdala

Adjusted Amygdala Volume

Childhood Maltreatment (Severity of Exposure)

MACE Score

Left Amygdala

Amygdala - Sensitive Period

Amygdala - Sensitive Period

In contrast, volume of the left but not right amygdala was sensitive to quality of care in infancy - particularly at 18 months.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Left</th>
<th>Right</th>
</tr>
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<tbody>
<tr>
<td>Infant disorganized attachment behavior</td>
<td>0.55*</td>
<td>0.26</td>
</tr>
<tr>
<td>Maternal disrupted communication</td>
<td>0.66*</td>
<td>-0.03</td>
</tr>
<tr>
<td>Overall attachment risk</td>
<td>0.68**</td>
<td>0.15</td>
</tr>
</tbody>
</table>
Two Critical Developmental Threats

1. Rejection/Neglect - Left Amygdala - Infancy

2. Abuse - Right Amygdala - Preadolescence
Two Critical Developmental Threats

1. Rejection/Neglect - Left Amygdala - Infancy - **Approach**

2. Abuse - Right Amygdala - Preadolescence - **Withdrawal**
Amygdala Volume - Complex Interaction Between Early and Later Periods of Exposure
Does exposure to stress from birth thru 11 years of age sensitize the amygdala to diminish in size with exposure to maltreatment between 12-15 years of age (controlling for exposure from 16-18 years)?
Interactive Effects of Early and Later Maltreatment on Amygdala Volume

$n = 300$
Interactive Effects of Early and Later Maltreatment on Amygdala Volume

n = 300
Interactive Effects of Early and Later Maltreatment on Amygdala Volume

n = 300
Interactive Effects of Early and Later Stress on Amygdala Volume

- Early Stress
- No Early Stress
- Later Stress
- No Later Stress
- No Later Stress
- Later Stress
Increased Versus Decreased Amygdala Volume

Does it imply opposite effects on function?

Preclinical studies have shown that environmental experiences (for example, being in an enriched environment) that lead to behavioural changes (e.g., improved reaching ability) may be associated with either an increase or decrease in synaptic spine density within sensory and motor cortices, depending on the age at which the experience occurred.

Similarly, increases or decreases in amygdala volume may be strongly dependent on the ages of exposure to maltreatment but result in comparable consequences.
Fear Circuit Regions & Pathways

1. Amygdala
2. Hippocampus
3. Sensory Cortex
4. Prefrontal Cortex
5. Pathways - AF, CB, Fornix, ILF
The primary effects of stress or glucocorticoids on the hippocampus are to:

- Suppress neurogenesis in the dentate gyrus
- Provoke the remodeling of dendrites in the Cornu Ammonis, particularly CA3
- Effects may be reversible with time
Stress & Hippocampus

- Suppresses neurogenesis in the dentate gyrus (DG)
- Provokes remodeling of dendrites in Cornu Ammonis, particularly CA3
**Childhood Abuse and the Hippocampus**

Result of studies assessing maltreatment and hippocampal volume are pretty consistent in adults 47 studies, $N \sim 5074$.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
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<tr>
<td>Significant decrease</td>
<td>32</td>
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<tr>
<td>Non-significant decrease</td>
<td>6</td>
</tr>
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Carl M. Anderson Ph.D.
Teicher MH, Anderson CM, Polcari A. Childhood maltreatment is associated with reduced volume in hippocampal subfields CA3, dentate gyrus and subiculum. PNAS. 2012, 109:E563-572
Adaptive Significance

Rodent studies strongly support the hypothesis that early-life stress produces potentially adaptive brain modifications.

Adult rats that experienced low levels of licking and grooming in infancy had shorter dendritic branch length, lower spine density and impaired long-term potentiation (LTP) in their hippocampus under basal conditions\(^{164}\).

However, when corticosterone levels were elevated, LTP in these animals exceeded controls and their memory was enhanced relative to controls when tested in a stressful contextual fear-conditioning paradigm.

## Corpus Callosum

### Males

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Fear Circuit Regions & Pathways

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5. Pathways - AF, CB, Fornix, ILF
Jeewook Choi  
M.D., Ph.D.  

Akemi Tomoda  
M.D., Ph.D.
Does the nature of the maltreatment matter?
Verbal Abuse

*!#$^&@
Witnessing Domestic Violence
Childhood Sexual Abuse
Effects of Verbal Abuse on Brain Structure

Fiber tracts (white matter) using diffusion tensor imaging and tract-based spatial statistics (TBSS).

Gray matter analyzed using voxel based morphometry (VBM).
Childhood Abuse Targets Sensory Systems

- Parental verbal abuse: ↑ GMV in auditory cortex
- Witnessing domestic violence: ↓ GMV in V1, ↓ Integrity of left ILF
- Childhood sexual abuse: ↓ GMV in V2, Thinning of somatosensory cortex

Nature Reviews | Neuroscience
Fear Circuit Regions & Pathways

1. Amygdala
2. Hippocampus
3. Sensory Cortex

4. Prefrontal Cortex

5. Pathways - AF, CB, Fornix, ILF
Prefrontal Cortex
Prefrontal Cortex

The frontal lobes are important for

- Attention
- Executive Function
- Working Memory
- Motivation
- Behavioral Inhibition.
Prefrontal Cortex

They are important in

Planning and anticipating outcomes.

Self-monitoring and self-awareness - necessary for appropriateness of behavior.
Thoughts can activate the amygdala.

Thoughts are less effective in turning the amygdala off.

Fear and Anxiety

Joseph LeDoux
Childhood Abuse and Neocortex

Decrease measures of anterior cingulate 17/19 studies

Decreased orbitofrontal or ventromedial PFC 14 studies

Decreased measures of dorsolateral PFC 7/8 studies
Corporal Punishment

Right Ventromedial Prefrontal Cortex (BA10)
Left medial frontal gyrus (DLPFC) (BA9)
Right anterior cingulate gyrus (BA24)

This early sensitive period for the anterior cingulate cortex is supported by results of the Avon Longitudinal Study of Parents and Children, which is a large scale prospective longitudinal study of a birth cohort, in which exposure to childhood adversity was assessed at 8, 21, 33, 47, 61, and 73 mo of age, with neuroimaging obtained in 494 participants at 18-21 years of age.

They found that severity of early adversity from 0-6 years was specifically associated with reduction in gray matter volume in ACC.

Threat Detection and Response System

Sensitive Periods for the Different Components

- L Amygdala
- Hippocampus
- Thalamus
- Vis Ctx
- Ventromed PFC
- R Amygdala
- Ventromed PFC
- Inferior Long. Fasciculus
- Thalamus
- dACC
- Hippocampus
- dACC
- L Amygdala

Age of Exposure (years)
Conclusions

Childhood maltreatment is associated with structural alterations in primary regions and pathways that constitute the threat detection and response or ‘fear’ circuit.
Conclusions

However, components of this circuit have different sensitive periods. Maltreatment appears to universally affect the development of the threat response system, but it does so in different ways depending on type and timing of maltreatment.
Reward Anticipation
Circuits & Networks
Kyoko Ohashi, Ph.D.
Types of Networks

1. Functional connectivity networks discernible in resting state fMRI.

2. Structural connectivity networks based on diffusion tensor imaging and tractography.

3. Structural connectivity networks delineated by between subject intraregional correlations in measures of cortical thickness, gray matter volume or shape.

Structural Connectivity Networks (Cortical Thickness)
Large-scale cortical morphometric networks

1. Positive thickness correlations were often associated with convergent diffusion connections across the cerebral cortex.

2. This technique has been used to assess network abnormalities in Alzheimer’s disease, schizophrenia, epilepsy, multiple sclerosis, and aging.

Structural Connectivity Networks

• N=265 unmedicated, right handed subjects

• Varying degrees of self-reported exposure to childhood maltreatment

• Selected without regard to psychopathology, except substance abuse

• Divided into maltreated (n=142) and non-maltreated (n=123) based on semi-structured TAQ interviews

• Siemens 3T Trio Scanner, MPRAGE sequence

• Cortical thickness in 112 regions measured using FreeSurfer v5.1
Structural Connectivity Networks (Cortical Thickness)

The greatest centrality differences between networks was observed in the left anterior cingulate gyrus and sulcus.
Left Anterior Cingulate

Unexposed

Maltreated
Right Precuneus

Unexposed

Maltreated
Right Anterior Insula

Unexposed

Maltreated
Structural Connectivity Networks

- The anterior cingulate plays an important role in the regulation of emotions\(^1\).
- The anterior insular cortex is involved in interoception, subjective feelings and possibly self-awareness\(^3\).
- The precuneus is a major component of the default mode network and is involved in self-referential, self-centered mental imagery\(^2\).

Precuneus

- Autobiographical memory
- Self versus non-self representation
- Self-referential judgements
- First- versus third-person perspective
- Perceived agency
- Mind reading/social cognition.
Hence, maltreated individuals may be at increased risk for psychopathology due to reduced centrality of the anterior cingulate (decreased ability to regulate emotions), coupled with increased centrality in the precuneus and anterior insula (increased emotional and internal perceptions, self-awareness and self-referential thinking).
Delayed Effects
Delayed Effects – Silent Period
Delayed Effects – Silent Period
Delayed Effects – Silent Period

Childhood exposure sensitizes the individual to later emergence of depression during adolescence.

On average, 9 year gap between exposure to childhood sexual abuse and emergence of depression and emergence of PTSD.

Possibility to preempt.
## Childhood Abuse and the Hippocampus

Results of studies assessing maltreatment and hippocampal volume are pretty consistent in adults. 47 studies, $N \sim 5074$.

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<td>Significant decrease</td>
<td>32 studies</td>
</tr>
<tr>
<td>Non-significant decrease</td>
<td>6 studies</td>
</tr>
<tr>
<td>No difference</td>
<td>9 studies</td>
</tr>
<tr>
<td>Non-significant increase</td>
<td>0 studies</td>
</tr>
<tr>
<td>Significant increase</td>
<td>0 studies</td>
</tr>
</tbody>
</table>
Childhood Abuse and the Hippocampus

Result of studies assessing maltreatment and hippocampal volume are inconsistent in children 23 studies, $N \sim 1951$.

- Significant decrease: 10 studies
- Non-significant difference: 13 studies
Delayed Manifestations

- Sexualized Behaviors
  - Prevent
  - Preempt

- Onset of Depression
  - Treat

- Recurrent Depressions

Sensitive periods

Time
Ecophenotypes

Jacqueline Samson, Ph.D.
For some highly prevalent disorders (i.e., major depression, anxiety disorders, PTSD and substance abuse) there is a substantial subset of individuals with maltreatment histories/early life stress and a substantial subset without.

Ecophenotypes
Ecophenotypes

Hypothesis

ELS+ and ELS– individuals with the same primary DSM-5 diagnosis are clinically, neurobiologically and genetically distinct.

Ecophenotypes

Earlier Onset
More Severe Course
More Comorbidities
Greater Symptom Severity
Poorer Response to Treatment
Depression with Early Trauma/Loss

Nemeroff et al., Proceedings of the National Academy of Science, 2003, 100(24): 14293–14296
Effects of abuse at 4-7 years on prediction for HDRS$_{17}$, 17-item Hamilton Rating Scale for Depression

Ecophenotypes

Autoimmune
Metabolic
Cardiovascular
(Mirgaine)
Inflammation
Ecophenotypes

Hippocampal & Amygdala Differences
Ecophenotypes

Major Depression
Hippocampal Volume
Amygdala Response Sad Faces
Network Architecture

Bipolar Disorder
Corpus Callosum and white matter abnormalities
Inferior frontal gyrus

Schizophrenia
Dorsolateral PFC and thalamus
Inferior frontal gyrus
Insula and thalamus
Poletti et al (2016) studied 206 depressed patients with bipolar disorder (BPD), 96 patients with schizophrenia (SCZ) and 136 healthy controls (HC). Subjects were categorized into those with low or high levels of Adverse Childhood Experiences (ACES). VBM was used to detect group differences in gray matter volume.
An effect of diagnosis was observed in orbitofrontal cortex encompassing BA 47 and insula, and in the thalamus. HC had the highest volume and SCZ patients the lowest with BD patients showing an intermediate volume.

This pattern was present only in subjects with high ACE scores.

No differences were observed in GMV between SCZ, BPD and HC in low ACE subjects.

Ecophenotypes

Corollary

Studies that compare DSM clinical groups (e.g., MDD) to controls, and which do not collect data on ELS, will provide inconsistent results based on differing prevalence rates of ELS in their clinical and control samples versus other researcher’s samples.
Researchers studying different disorders who do not collect data on ELS may identify the same constellation of neurobiological findings in these different disorders. These findings may be due to higher rates of ELS in the disorder versus control group and be unrelated to the specific disorders being studied.
Ecophenotypes

- Drug/Alcohol Abuse
- Antisocial Personality DO
- Major Depression
- Bipolar DO (early onset)
- Post-traumatic Stress
- Borderline Personality DO
- Dissociative Identity DO
- Psychotic Disorders

- Reduced Hippocampal Volume
Ecophenotypes

Childhood Maltreatment ELS

- Drug/Alcohol Abuse
- Antisocial Personality DO
- Major Depression
- Bipolar DO (early onset)
- Post-traumatic Stress
- Borderline Personality DO
- Dissociative Identity DO
- Psychotic Disorders

Reduced Hippocampal Volume
Implications for Treatment
Abnormal EEGs
72% children severe physical and sexual abuse (Ito et al., 1994)
72% incest survivors (Davies, 1979)
36% seizure disorders
Harlow’s monkeys (Heath, 1972)

Hypersensitive
Hyper-responsive
Limbic Irritability
Anticonvulsants
Cerebellar vermis

a.k.a.

arborvitae

“the tree of life”

anterior lobe (lobules I-V)

posterior superior lobe (lobules VI-VII)

posterior inferior lobe (lobules VIII-X)
Infants maintained in partial isolation manifest violence and aggression as adults.

From Harlow, “The nature of love.” American Psychologist 13;673-85, 1958
• William Mason (1968), working with Harlow, found that a lack of somatosensory stimulation (especially vestibular proprioception) was the ingredient responsible for disturbed behavior in sensory-isolated monkeys.

• James Prescott (1971) proposed that early vestibular stimulation was important in the development of appropriate emotional behavior.
Mindfulness-Based Stress Reduction

Diane Yan, Ph.D. and Sarah Lazar, Ph.D.

Mindfulness-based training versus waiting list control

Pre and post measures:
symptoms
hippocampal volume
hippocampal cognitive task
functional connectivity
Mindfulness-Based Stress Reduction

Preliminary Data - 11 subjects completed mindfulness-based training, 13 waiting list controls.
Mindfulness-Based Stress Reduction

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Mindfulness-Based Stress Reduction

Preliminary Data - 11 subjects completed mindfulness-based training, 13 waiting list controls.
Mindfulness-Based Stress Reduction

Preliminary Data - 11 subjects completed mindfulness-based training, 13 waiting list controls.

Reduced pre-post training functional connectivity between hippocampus and amygdala in mindfulness versus waiting list controls (p < 0.001).
Right-Left Evoked Response Asymmetry

How Does Maltreatment Get Under the Skin?

• Epigenetics
• Neuroinflammation
• Sleep Deprivation
DNA methylation
Methyl markers added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the ‘tails’ of proteins called histones. These alter the activity of the DNA wrapped around them.
Mechanisms Linking Childhood Maltreatment To Mood Dysregulation in Adolescence

Preliminary Data
   N = 38 (18-19 years)
      N = 16 Unexposed
      N = 22 Maltreated (without PTSD)

Ecological Momentary Assessment
Actigraphy (sleep)
3T MRI
Epigenetics (FKBP5, NR3C1)
Neuroinflammation (C reactive Protein, IL6)
FKBP5

Increased methylation in Intron 7 bin 1 CG1 with maltreatment.

Significant inverse correlation (-0.4 - -0.6) with GMV in CA3, CA4 and DG of hippocampus.

Significant inverse correlation (-0.5 - -0.7) with GMV in components of insula.
Neuroinflammation

Briefly, pro-inflammatory cytokines reduce the availability of serotonin, dopamine, norepinephrine and brain-derived neurotrophic factor (BDNF)\textsuperscript{165} through multiple mechanisms\textsuperscript{165}.

Activated microglia convert kynurenine into quinolinic acid, which binds to the N-methyl-d-aspartate (NMDA) receptor.

Cytokine effects on the dopamine system can inhibit several aspects of reward motivation leading to anhedonia and psychomotor retardation by targeting striatum, ventromedial PFC and anterior cingulate cortex.

Cytokines also activating threat detection circuits regulating anxiety, arousal, alarm and fear including amygdala, hippocampus and insula.
IL6, CRP & Hippocampus

<table>
<thead>
<tr>
<th>Region</th>
<th>IL6</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>prob</td>
</tr>
<tr>
<td>Left Dentate Gyrus</td>
<td>-0.23</td>
<td>p&gt;0.2</td>
</tr>
<tr>
<td>Left CA3</td>
<td>-0.12</td>
<td>p&gt;0.5</td>
</tr>
<tr>
<td>Right Dentate Gyrus</td>
<td>-0.42</td>
<td>p&lt;0.03</td>
</tr>
<tr>
<td>Right CA3</td>
<td>-0.43</td>
<td>p&lt;0.02</td>
</tr>
</tbody>
</table>
Maltreatment & Insula
### IL6, CRP & Insula

![Diagram of brain regions](image)

<table>
<thead>
<tr>
<th>Region</th>
<th>r</th>
<th>prob</th>
<th>r</th>
<th>prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Short Insula Gyrus</td>
<td>-0.53</td>
<td>p&lt;0.003</td>
<td>-0.62</td>
<td>p&lt;0.0006</td>
</tr>
<tr>
<td>L Circular Insula Ant. Sulcus</td>
<td>-0.22</td>
<td>p&gt;0.2</td>
<td>-0.54</td>
<td>p&lt;0.004</td>
</tr>
<tr>
<td>L Cincular Insula Inf. Sulcus</td>
<td>-0.57</td>
<td>p&lt;0.002</td>
<td>-0.46</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>R Short Insula Gyrus</td>
<td>-0.28</td>
<td>p&gt;0.1</td>
<td>-0.59</td>
<td>p&lt;0.002</td>
</tr>
<tr>
<td>R Cinrcular Insula Ant. Sulcus</td>
<td>-0.24</td>
<td>p&gt;0.2</td>
<td>-0.66</td>
<td>p&lt;0.0002</td>
</tr>
<tr>
<td>R Cincular Insula Inf. Sulcus</td>
<td>-0.52</td>
<td>p&lt;0.004</td>
<td>-0.54</td>
<td>p&lt;0.004</td>
</tr>
</tbody>
</table>
Stimuli that activate the right anterior insular cortex are generally arousing to the body (for example, pain).

The left anterior insular cortex is activated mainly by positive and affiliative emotional feelings (e.g., mothers viewing photos of their child, maternal and romantic love, seeing or making a smile, attended to happy voices, hearing pleasant music, experiencing joy).
## IL6, CRP & Symptoms

<table>
<thead>
<tr>
<th>Region</th>
<th>r</th>
<th>prob</th>
<th>r</th>
<th>prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>0.40</td>
<td>p&lt;0.03</td>
<td>0.32</td>
<td>p&lt;0.1</td>
</tr>
<tr>
<td>Depression</td>
<td>0.26</td>
<td>p&gt;0.1</td>
<td>0.31</td>
<td>p&gt;0.1</td>
</tr>
<tr>
<td>Somatization</td>
<td>0.42</td>
<td>p&lt;0.02</td>
<td>0.35</td>
<td>p&lt;0.07</td>
</tr>
<tr>
<td>Anger-Hostility</td>
<td>0.58</td>
<td>p&lt;0.0007</td>
<td>0.49</td>
<td>p&lt;0.009</td>
</tr>
<tr>
<td>EMP Pos Affect mean</td>
<td>0.02</td>
<td>p&gt;0.9</td>
<td>-0.05</td>
<td>p&gt;0.7</td>
</tr>
<tr>
<td>EMA Neg Affect mean</td>
<td>0.08</td>
<td>p&gt;0.6</td>
<td>0.41</td>
<td>p&lt;0.04</td>
</tr>
<tr>
<td>EMA Somatic mean</td>
<td>0.47</td>
<td>p&lt;0.02</td>
<td>0.52</td>
<td>p&lt;0.008</td>
</tr>
<tr>
<td>EMP Pos Affect var</td>
<td>0.17</td>
<td>p&gt;0.3</td>
<td>0.42</td>
<td>p&lt;0.04</td>
</tr>
<tr>
<td>EMA Neg Affect var</td>
<td>0.10</td>
<td>p&gt;0.6</td>
<td>0.36</td>
<td>p&lt;0.07</td>
</tr>
<tr>
<td>EMA Somatic Var</td>
<td>0.34</td>
<td>p&lt;0.08</td>
<td>0.51</td>
<td>p&lt;0.009</td>
</tr>
</tbody>
</table>
History of Maltreatment

Actigraph Assessed Sleep
## Subcortical Regions

<table>
<thead>
<tr>
<th>Measure</th>
<th>Effect of Maltreatment</th>
<th>Significantly Mediated by Sleep Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Putamen</td>
<td>-0.538**</td>
<td></td>
</tr>
<tr>
<td><strong>Right Hippocampus</strong></td>
<td>-0.525**</td>
<td>-0.243</td>
</tr>
<tr>
<td>Left CA4</td>
<td>-0.517**</td>
<td></td>
</tr>
<tr>
<td>Left Putamen</td>
<td>-0.502**</td>
<td></td>
</tr>
<tr>
<td>Right Dentate Gyrus</td>
<td>-0.500**</td>
<td></td>
</tr>
<tr>
<td>Left Pallidum</td>
<td>-0.497**</td>
<td></td>
</tr>
<tr>
<td>Right CA4</td>
<td>-0.497**</td>
<td></td>
</tr>
<tr>
<td>Left Dentate Gyrus</td>
<td>-0.488**</td>
<td></td>
</tr>
<tr>
<td>Left CA1</td>
<td>-0.480**</td>
<td></td>
</tr>
<tr>
<td><strong>Right Hippocampal molecular layer</strong></td>
<td>-0.479**</td>
<td>-0.203</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>-0.471**</td>
<td></td>
</tr>
<tr>
<td><strong>Right presubiculum</strong></td>
<td>-0.461**</td>
<td>-0.25</td>
</tr>
<tr>
<td><strong>Left Hippocampal molecular layer</strong></td>
<td>-0.455**</td>
<td>-0.222</td>
</tr>
<tr>
<td>Left Hippocampus</td>
<td>-0.428*</td>
<td></td>
</tr>
</tbody>
</table>
Take Home Messages

1. Childhood maltreatment is associated with marked effects on brain morphology, function and network architecture.
Take Home Messages

2. The impact of maltreatment on trajectories of brain development provides a strong signal that appears in many instances to be much larger than signals associated with psychopathology per se.
3. Childhood maltreatment is associated with structural and functional alterations in key components of threat detection and response circuit.

4. These different components have their own unique sensitive periods so that maltreatment at different ages will target this circuit - but in different ways.
5. Childhood maltreatment is associated with structural and functional alterations in key components of reward system.

6. Diminished anticipatory reward response and increased threat detection may have marked influence on approach-avoidance, and increase risk for depression and substance abuse.
Take Home Messages

7. Maltreatment-related alterations in threat detection and response are likely adaptive alterations designed to reduce distress and to help individuals reproduce and survive in what appears to be a malevolent world.
8. There are silent periods between time of exposure and emergence of discernible brain differences and psychiatric symptoms.

9. Because of these silent periods one can not conclude that an abused on neglected child was unaffected even if they are currently asymptomatic.
10. Childhood maltreatment / early life stress is a huge confound in studies on biology or treatment of psychiatric disorders when not taken into account.

11. Maltreated and non-maltreated individuals with the same primary DSM-5, ICD-10 disorder appear to differ clinically, neurobiologically and genetically.
Take Home Messages

12. Epigenetic changes, sleep problems and inflammation are factors may mediate or amplify the effects of maltreatment.

13. Epigenetic changes, sleep problems and inflammation may be key factors that if addressed may help to reduce the adverse consequence of childhood maltreatment.
Maltreatment and Trauma Studies Support

NIMH
RO1 MHT3636 (1997-2001)
RO1 MH66222 (2003-2008)
RO1 MH91391 (2010-2015)

Harvard Catalyst
(2010-2011)
(2015-2016)

NIDA
RO1 DA16934 (2003-2007)

NARSAD
(2005-2007)

NICHD
RO1 HD079484 (2015-2020)

PRIVATE DONORS
Simches Family
Susan Miller
The End

Thank you!