Child Maltreatment, Brain Imaging and Mental Illness

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Maltreatment and Trauma Studies Support

**NIMH**
- RO1 MHT3636 (1997-2001)
- RO1 MH66222 (2003-2008)
- RO1 MH91391 (2010-2015)
- RO3 MH113077 (2017-2019)

**NIDA**
- RO1 DA16934 (2003-2007)

**NICHD**
- RO1 HD079484 (2015-2020)

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

**NARSAD**
- (2005-2007)
- (2017-2018 - Kim)

**PRIVATE DONORS**
- Simches Family
- Susan Miller

Information

I post the slides for my talks at -

https://drteicher.wordpress.com/

I can be reached at -

martin_teicher@hms.harvard.edu
Introduction

Childhood Abuse

- 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

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

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
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


Medical Consequences of Childhood Maltreatment

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

Introduction

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- Dissociative Identity DO
- Psychotic Disorders

Questions

What brain structures are affected by exposure to childhood maltreatment?

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

Does age at the time of abuse matter?

What is the relationship between childhood abuse, brain changes and psychiatric illness?
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>
</tr>
</thead>
<tbody>
<tr>
<td>1 (rostrum)</td>
<td>0.306</td>
<td>0.109</td>
<td>0.128</td>
<td>0.1000</td>
</tr>
<tr>
<td>2 (genu)</td>
<td>0.761</td>
<td>0.900</td>
<td>0.864</td>
<td>0.1300</td>
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<tr>
<td>3 (rostral body)</td>
<td>0.463</td>
<td>0.615</td>
<td>0.566</td>
<td>0.0020</td>
</tr>
<tr>
<td>4 (ant. midbody)</td>
<td>0.361</td>
<td>0.486</td>
<td>0.523</td>
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</tr>
<tr>
<td>5 (post. midbody)</td>
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<td>0.416</td>
<td>0.429</td>
<td>0.0055</td>
</tr>
<tr>
<td>6 (isthmus)</td>
<td>0.889</td>
<td>1.100</td>
<td>1.152</td>
<td>0.0043</td>
</tr>
<tr>
<td>7 (splenium)</td>
<td>0.403</td>
<td>0.466</td>
<td>0.496</td>
<td>0.5450</td>
</tr>
</tbody>
</table>

(n) 13 13 61

Overall differences between groups, MANOVA, p < 0.0001

Association of Early Experience and Age on Regional Anatomy of Corpus Callosum in Boys, Based on Step-wise Regression.

<table>
<thead>
<tr>
<th>Region</th>
<th>Physical Abuse</th>
<th>Sexual Abuse*</th>
<th>Neglect*</th>
<th>Age**</th>
<th>PTSD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (rostrum)</td>
<td>--</td>
<td>--</td>
<td>-41.7%†</td>
<td>7.4%‡</td>
<td>--</td>
</tr>
<tr>
<td>2 (genu)</td>
<td>--</td>
<td>--</td>
<td>-29.2%*</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3 (rostral body)</td>
<td>--</td>
<td>--</td>
<td>-33.2%*</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4 (ant. midbody)</td>
<td>-9.6%†</td>
<td>--</td>
<td>-30.7%*</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5 (post. midbody)</td>
<td>--</td>
<td>--</td>
<td>-40.2%*</td>
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<td>--</td>
</tr>
<tr>
<td>6 (isthmus)</td>
<td>--</td>
<td>--</td>
<td>-45.7%*</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>7 (splenium)</td>
<td>-18.3%†</td>
<td>--</td>
<td>-24.2%*</td>
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<td>--</td>
</tr>
</tbody>
</table>

†p < 0.10, \*p < 0.05, \#p < .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.

<table>
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<tr>
<th>Region</th>
<th>Physical Abuse</th>
<th>Sexual Abuse*</th>
<th>Neglect*</th>
<th>Age**</th>
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<td>--</td>
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<tr>
<td>3 (rostral body)</td>
<td>--</td>
<td>--</td>
<td>-20.8%*</td>
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<td>--</td>
</tr>
<tr>
<td>4 (ant. midbody)</td>
<td>--</td>
<td>--</td>
<td>-29.7%*</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5 (post. midbody)</td>
<td>--</td>
<td>--</td>
<td>-17.7%*</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>6 (isthmus)</td>
<td>--</td>
<td>--</td>
<td>-23.7%*</td>
<td>+37.8%</td>
<td>--</td>
</tr>
<tr>
<td>7 (splenium)</td>
<td>--</td>
<td>--</td>
<td>-43.9%†</td>
<td>+5.2%</td>
<td>--</td>
</tr>
</tbody>
</table>

†p < 0.10, \*p < 0.05, \#p < .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.

Infant male monkeys raised individually in a nursery from 2 to 12 months were compared to age-matched infants raised in a semi-naturalistic social environment. Although overall brain volumes did not differ, the corpus callosum was significantly decreased in the nursery group.

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

Using Diffusion Tensor Imaging we found that the integrity of the middle portion of the corpus callosum correlated inversely with degree of exposure (ACE score) to childhood abuse in young adults (n = 191).
Sensitive Periods

The brain is molded by experiences that occur throughout the lifespan. However, there are particular stages of development when experience exerts either a maximal (sensitive period) or essential (critical period) effect.

* Hubel and Wiesel - Nobel Prize Medicine 1981
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.

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

- The amygdala is a key limbic structure that is critically involved in encoding of implicit emotional memories and in detecting and responding to salient stimuli such as facial expressions and potential threats.

- Structural or functional abnormalities in the amygdala have been observed in a wide array of psychiatric disorders including: post-traumatic stress disorder, social phobias and specific phobias; unipolar and bipolar depression; drug addiction; autism; borderline personality disorder and schizophrenia.

**Exposure to stress leads to:**

Persistent neuronal hypertrophy and symptoms of anxiety

- Do not reverse with time
- Do 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.

- Significant decrease: 14 studies
- Non-significant decrease: 11 studies
- No difference: 6 studies
- Non-significant increase: 4 studies
- Significant increase: 6 studies
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)*

---

**Type of exposure**

**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)*

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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.

Sensitive Periods

Windows of Vulnerability

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>
</thead>
<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

Childhood Abuse and the Amygdala

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>

Interactive Effects of Early and Later Stress on Amygdala Volume
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.

Amygdala Volume – Is Bigger Better?

Does small/large imply opposite effects on function?

Fear Circuit Regions & Pathways

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

Hippocampus

- The hippocampus is a key limbic structure that is critically involved in the formation and retrieval of explicit memories, including autobiographical memories.

- The hippocampus also contains place cells, which along with grid cells in the interconnecting entorhinal cortex, provide an internal positioning system for the spatiotemporal representation of places, routes, and associated experiences.
Hippocampus

- Hippocampal abnormalities have been reported in several different psychiatric disorders including: post-traumatic stress disorder, major depression, schizophrenia, bipolar disorder, drug addiction and borderline personality disorder.

Stress & Hippocampus

- Suppresses neurogenesis in the dentate gyrus (DG)
- Provokes remodeling of dendrites in Cornu Ammonis, particularly CA3

The primary effects of stress or glucocorticoids on the hippocampus are to:

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

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

Role of Psychopathology
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.
- 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.


Fear Circuit Regions & Pathways

1. Amygdala
2. Hippocampus
3. Sensory Cortex
4. Prefrontal Cortex
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?

Witnessing Domestic Violence

Childhood Sexual Abuse
Effects of Verbal Abuse on Brain Structure

Fiber tracts (white matter) using diffusion tensor imaging.

Gray matter analyzed using voxel based morphometry.

Fear Circuit Regions & Pathways

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

Avon Longitudinal Study of Parents and Children

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

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
Reward Anticipation

Ventral Striatum - nucleus accumbens and ventral putamen

Monetary > verbal reward during reward anticipation

Decreased Reward Anticipation


Increased Reward Response

Don’t anticipate reward...

Expect to be maltreated.

If you experience reward...

Keep at it.

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)**

- 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
- Cortical thickness in 112 regions measured using FreeSurfer v5.1

The centrality parameters of a handful of cortical regions differed substantially between the network for maltreated subjects versus the network for non-maltreated individuals.
The greatest centrality differences between networks was observed in the left anterior cingulate gyrus and sulcus.
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\(^2\).


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).

Brain Fiber Tract Network

- **Edges -> Fiberstreams**
  - Diffusion tensor imaging (DTI)
  - Tractography

- **Nodes -> Regions**
  - AAL (Automated Anatomical Labeling) template
  - 90 regions from cerebrum using the anatomically labeled template by Tzourio-Mazoyer et al. (Neuroimage, 2002)
Brain Fiber Tract Networks

Brain network architecture needs to balance the opposing demands of integration and segregation in order to combine the presence of functionally specialized and segregated modules with a robust number of connecting links. This tradeoff is reflected in the small-worldness properties of the network, which reflect the ratio of the local clustering coefficient to overall pathlength.

Global Network Measures

- N=262 (102M/160F; 18-25 years)

The greater small-worldness in maltreated individuals is a consequence of preserved local modular architecture but lower connectivity between modules. This, in turn, makes the maltreated network more vulnerable to abnormalities occurring within a node or module.

The waxing and waning of symptoms within different disorders may then reflect efforts of a less integrated network to compensate, shifting between periods of pathology and health as quasi-stable states.
Ecophenotypes

Jacqueline Samson, Ph.D.

Ecophenotypes

**Hypothesis**

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

Depression with Early Trauma/Loss

Effects of abuse at 4-7 years on prediction for HDRS17, 17-item Hamilton Rating Scale for Depression


Ecophenotypes

Autoimmune
Metabolic
Cardiovascular
(Migraine)
Inflammation

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.


Ecophenotypes - Schizophrenia and Bipolar Disorder

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 - Schizophrenia and Bipolar Disorder

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.

Ecophenotypes

**Corollary**

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.
Resilience

Susceptibility

Susceptibility & Resilience

Resilience

Are individuals with histories of maltreatment but without psychopathology unaffected?
Abnormalities reported in maltreated individuals without psychopathology

- Anterior cingulate volume
- Subgenual cingulate volume
- Dorsolateral prefrontal vol
- Medial prefrontal cortex volume
- Rostral prefrontal cortex
- Orbitofrontal cortex volume
- Sensory Association cortex
- Insula volume
- Hippocampal volume
- Caudate volume
- Ventral striatal volume
- Cerebellar volume
- Corpus callosum – Vol / FA
- Corona radiate – FA
- Fornix – FA
- Inf frontal occipital fasciculus – FA
- Sup longitudinal fasciculus – FA
- Cingulum bundle – FA
- Amygdala response to threat
- Reward-related VS activity
- Default Network deactivation

Symptomatic vs Asymptomatic Maltreated Individuals

Brain Fiber Tract Networks

Brain network architecture needs to balance the opposing demands of integration and segregation in order to combine the presence of functionally specialized and segregated modules with a robust number of connecting links. This tradeoff is reflected in the small-worldness properties of the network, which reflect the ratio of the local clustering coefficient to overall pathlength.
The greater small-worldness in maltreated individuals is a consequence of preserved local modular architecture but lower connectivity between modules. This, in turn, makes the maltreated network more vulnerable to abnormalities occurring within a node, community or module (second hit).

True resilience occurs in maltreated individuals who have sustained a second hit but are effectively compensated. Their resilience may result from partially isolating and limiting the impact of potentially problematic nodes.

Current Question

• Does successful treatment reverse abnormalities in maltreated individuals with psychopathology – or does it alter the neurobiology of susceptible maltreated individuals to more closely match those of resilient maltreated subjects?
How Does Maltreatment Get Under the Skin?

- Epigenetics
- Neuroinflammation
- Sleep Deprivation
- Accelerated Aging

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) through multiple mechanisms.

- 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 r</th>
<th>IL6 prob</th>
<th>CRP r</th>
<th>CRP prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Dentate Gyrus</td>
<td>-0.23</td>
<td>p&gt;0.2</td>
<td>-0.28</td>
<td>p&gt;0.1</td>
</tr>
<tr>
<td>Left CA3</td>
<td>-0.12</td>
<td>p&gt;0.5</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>
<td>-0.33</td>
<td>p&lt;0.1</td>
</tr>
<tr>
<td>Right CA3</td>
<td>-0.43</td>
<td>p&lt;0.02</td>
<td>-0.40</td>
<td>p&lt;0.04</td>
</tr>
</tbody>
</table>

Maltreatment & Insula
**IL6, CRP & Insula**

- Central sulcus
- Circular sulcus
- Short gyri
- Long gyrus

<table>
<thead>
<tr>
<th>Region</th>
<th>IL6</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Short Insula Gyrus</td>
<td>-0.53</td>
<td>p&lt;0.003</td>
</tr>
<tr>
<td>L Circular Insula Ant. Sulcus</td>
<td>-0.22</td>
<td>p&gt;0.1</td>
</tr>
<tr>
<td>L Circular Insula Inf. Sulcus</td>
<td>-0.57</td>
<td>p&lt;0.004</td>
</tr>
<tr>
<td>R Short Insula Gyrus</td>
<td>-0.28</td>
<td>p&gt;0.1</td>
</tr>
<tr>
<td>R Circular Insula Ant. Sulcus</td>
<td>-0.24</td>
<td>p&gt;0.1</td>
</tr>
<tr>
<td>R Circular Insula Inf. Sulcus</td>
<td>-0.52</td>
<td>p&lt;0.004</td>
</tr>
</tbody>
</table>

**IL6, CRP & Symptoms**

<table>
<thead>
<tr>
<th>Region</th>
<th>IL6</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>0.40</td>
<td>p&lt;0.03</td>
</tr>
<tr>
<td>Depression</td>
<td>0.25</td>
<td>p&gt;0.1</td>
</tr>
<tr>
<td>Somatization</td>
<td>0.42</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>Anger-Hostility</td>
<td>0.58</td>
<td>p&lt;0.007</td>
</tr>
<tr>
<td>EMP Pos Affect mean</td>
<td>0.02</td>
<td>p&gt;0.1</td>
</tr>
<tr>
<td>EMA Neg Affect mean</td>
<td>0.08</td>
<td>p&gt;0.1</td>
</tr>
<tr>
<td>EMA Somatic mean</td>
<td>0.47</td>
<td>p&lt;0.004</td>
</tr>
<tr>
<td>EMP Pos Affect var</td>
<td>0.17</td>
<td>p&gt;0.1</td>
</tr>
<tr>
<td>EMA Neg Affect var</td>
<td>0.10</td>
<td>p&gt;0.1</td>
</tr>
<tr>
<td>EMA Somatic Var</td>
<td>0.34</td>
<td>p&lt;0.08</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>Right Hippocampus</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>Right Hippocampal molecular layer</td>
<td>-0.479**</td>
<td>-0.203</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>-0.471**</td>
<td></td>
</tr>
<tr>
<td>Right presubiculum</td>
<td>-0.461**</td>
<td>-0.250</td>
</tr>
<tr>
<td>Left Hippocampal molecular layer</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.

2. The nature or magnitude of the effect depends to a substantial degree on type and timing of maltreatment during developmental sensitive periods.

3. Sensitive periods detected to date were often surprisingly brief and associated with vulnerability to one or two specific types of maltreatment.

4. Sensitive periods are present throughout childhood but different brain regions are affected at different times. Hence, the affects of exposure to abuse and neglect are complex and can vary markedly from individual to individual.

5. 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.

6. Childhood maltreatment is associated with structural and functional alterations in key components of threat detection and response circuit.

7. These different components have their own unique sensitive periods so that maltreatment at different ages will target this circuit - but in different ways.
8. Maltreatment is associated with marked effects on sensory processing systems.

9. Parental verbal abuse was associated with alterations in gray matter volume in auditory cortex and reduced integrity of the arcuate fasciculus.

10. Visually witnessing domestic violence was associated with alterations in GMV in visual cortex and reduced integrity of the inferior longitudinal fasciulus.

11. Childhood sexual abuse in females was associated with thinning of somatosensory cortex representing clitoris and surrounding genital area.

12. Childhood maltreatment / early life stress is a huge confound in studies on biology or treatment of psychiatric disorders when not taken into account.

13. Maltreated and non-maltreated individuals with the same primary DSM-5 disorder appear to differ clinically, neurobiologically and genetically.

14. Maltreated individuals appear to respond much more poorly to first-line treatments than non-maltreated individuals with the same primary DSM diagnosis.
15. Recognizing this ecophenotypic variation may be crucial in advancing our mission to understand the biological basis of mental illness and to discover and develop effective means of preventing, preempting or treating these disorders.
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

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).