Childhood Abuse, Brain Development and Psychopathology

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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

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

Dr. Vincent Felitti 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

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

Medical Consequences of Childhood Maltreatment

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

Mechanisms by Which Adverse Childhood Experiences Influence Health and Well-being Throughout the Lifespan
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>
</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>
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<tr>
<td>3 (rostral body)</td>
<td>0.463</td>
<td>0.615</td>
<td>0.606</td>
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<tr>
<td>4 (ant. midbody)</td>
<td>0.361</td>
<td>0.486</td>
<td>0.523</td>
<td>0.0001</td>
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<tr>
<td>5 (post. midbody)</td>
<td>0.331</td>
<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>
<tr>
<td>(n)</td>
<td>13</td>
<td>13</td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

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
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
Time is of the essence
Sensitive Exposure Periods

Volume Mid Anterior Portion of Corpus Callosum - Females

Volume Central Portion of Corpus Callosum - Females

Recalled Ages of Exposure (years)

Importance (±95% Conf. Interval)

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)

Importance (±95% Conf. Interval)
A parent or other important parental figure was very difficult to please.

A parent or other important parental figure did not have the time or interest to talk to you.

You felt that you had to shoulder adult responsibilities.

One or more individuals kept important secrets or facts from you.
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
Partners in Fear

hippocampus

context

Emotional Stimulus ➔ amygdala ➔ Emotional Responses

regulation

medial prefrontal cortex

Joseph LeDoux
Thoughts can activate the amygdala

Thoughts are less effective in turning the amygdala off

Fear and Anxiety

Joseph LeDoux
(From: LeDoux 1994)
Influence of Childhood Maltreatment on Threat Response System

- Unchanged (or not studied)
- Increased
- Decreased

Threatening Stimuli
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
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>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>
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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  *(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
Adjusted Amygdala Volume

Childhood Maltreatment (Severity of Exposure)

MACE Score

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
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
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
Hippocampus

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 ~ 5074.

- Significant decrease: 32 studies
- Non-significant decrease: 6 studies
- No difference: 9 studies
- Non-significant increase: 0 studies
- Significant increase: 0 studies
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
Recalled Ages of Exposure (years)

Importance (± SD)

Bilateral Hippocampus - Male

Abuse

Neglect

Males

Females

Hippocampus N=336
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\textsuperscript{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

<table>
<thead>
<tr>
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<tr>
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Fear Circuit Regions & Pathways

1. Amygdala
2. Hippocampus
3. Sensory Cortex
4. Prefrontal Cortex
5. Pathways - AF, CB, Fornix, ILF
Does the nature of the maltreatment matter?
Hypothesis

Sexual Abuse
Physical Abuse
Witness Domestic Violence
Verbal Abuse

Common consequences relating to the effects of stress, fear, anxiety, humiliation, etc. on the developing brain
Hypothesis

Sexual Abuse
Physical Abuse
Witness Domestic Violence
Verbal Abuse
Hypothesis

Sexual Abuse

Physical Abuse

Witness Domestic Violence

Verbal Abuse

Unique effects relating to sensory systems activated, and ways in which specific events are processed.
Verbal Abuse

*!#$^&@
Sticks and stones may break my bones, but words will never hurt me.

WRONG!!!
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
- ↓ Integrity of left AF

**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)

Left Anterior Cingulate Area - Males

- Physical Neglect

Left Anterior Cingulate Area - Females

- Physical Abuse
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.

Social-emotional processing network

PFC
vmPFC
ACC
VS
AMY
Threat Detection and Response System

Sensitive Periods for the Different Components

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.
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
Brain Reward Circuit

Prefrontal cortex → PFC → Cingulate gyrus → Striatum → NAc → Ventral tegmental area

OFC → NAc

Nucleus accumbens

Substantia nigra

Hip

**B Non-addicted brain**

Control & Self-regulation (PFC, CG) → Salience (NAC) → Drive (OFC) → Memory (Am, Hip) → NOT Go

**C Addicted brain**

Control & Self-regulation (PFC, CG) → Salience (NAC) → Drive (OFC) → Memory (Am, Hip) → Go
Avoid  Approach

Negative Valence
Fear

Positive Valence
Reward
Ventral Striatum - nucleus accumbens and ventral putamen
Reward Anticipation - Anhedonia

Reactive Attachment Disorder

Reactive attachment disorder is a rare but serious condition in which an infant or young child doesn't establish healthy attachments with parents or caregivers. Reactive attachment disorder may develop if the child's basic needs for comfort, affection and nurturing aren't met and loving, caring, stable attachments with others are not established.
Reward Response
Reactive Attachment Disorder
Sensitive Exposure Period – RAD

Right Striatum

Left Striatum
Evolutionary Consideration

Teicher MH: Scars that won't heal: the neurobiology of child abuse. Scientific American 2002; 286(3):68-75
Don’t anticipate reward...
Expect to be maltreated.
Avoid  Approach

Negative Valence
Fear

Positive Valence
Reward
If you experience reward...

Keep at it.
Corporal Punishment
Harsh Corporal Punishment

Increased T2-RT (decreased blood flow) in right putamen
Increased T2-RT (decreased blood flow) in right caudate
Corporal Punishment

**Results:** ROI analyses also indicated increased T2-RT in dorsolateral prefrontal cortex, nucleus accumbens, substantia nigra and thalamus, but not globus pallidus or cerebellum.
Table 4: Correlations for the relationship between regional T2-RT in dopamine-rich regions and extent of drug and alcohol use.

<table>
<thead>
<tr>
<th>Region</th>
<th>Drug Use</th>
<th>Alcohol Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-value</td>
</tr>
<tr>
<td>Anterior Cingulate Cortex</td>
<td>0.406</td>
<td>0.009</td>
</tr>
<tr>
<td>Caudate</td>
<td>0.133</td>
<td>0.412</td>
</tr>
<tr>
<td>Dorsolateral Prefrontal Cortex</td>
<td>0.416</td>
<td>0.008</td>
</tr>
<tr>
<td>Nucleus Accumbens</td>
<td>-0.225</td>
<td>0.163</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.105</td>
<td>0.521</td>
</tr>
<tr>
<td>Substantia Nigra</td>
<td>0.140</td>
<td>0.390</td>
</tr>
</tbody>
</table>

Values in bold are significant with an overall False Discovery Rate < 0.05
Circuits & Networks
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 techniques 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
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

Subjects with History of Depression

Cases abused (per year)

Cumulative Cases Depressed (%)

Age (years)
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

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

<table>
<thead>
<tr>
<th>Type of Change</th>
<th>Number of Studies</th>
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<tbody>
<tr>
<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>
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</table>
Childhood Abuse and the Hippocampus

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

<table>
<thead>
<tr>
<th>Significant decrease</th>
<th>10 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-significant difference</td>
<td>13 studies</td>
</tr>
</tbody>
</table>
Delayed Manifestations

Sexualized Behaviors

Onset of Depression

Recurrent Depressions

PREVENT

PREEMPT

PREEMPT

TREAT

time

sensitive periods

stress

PREEMPT
Ecophenotypes

Jacqueline Samson, Ph.D.
Ecophenotypes

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

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

- PTSD
- ELS–
- SUD
- ELS–
- MDD
- ELS–

Autoimmune
Metabolic
Cardiovascular
(Mirgaine)
Inflammation
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.

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)
Amygdala

Eye Movements

Vestibular and Proprioceptive Stimulation
Cerebellar vermis

a.k.a.

arborvitae

“the tree of life”
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.

Harlow’s Surrogate Mother Studies

Figure 115. Diagram of the projection of vermal cortex and the fastigial nucleus on the lateral vestibular nucleus. Based on Jansen and Brodal (1940, 1942), Walberg et al. (1962) and Brodal et al. (1962).
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

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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).
Summary

Decreased hemispheric Integration
Integration
Richard P. Kluft, M.D.
Catherine G. Fine, Ph.D.
How Does Maltreatment Get Under the Skin?

- Epigenetics
- Neuroinflammation
- Sleep Deprivation
Epigenetics

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 P1-S1-Pos1 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

Interactive Poster: biolegend.com/neuroinflammation
We would like to thank Prof. Dr. Michael Schlossmacher of the University of Ottawa, Canada for his contributions to this poster.
Neuroinflammation

Aberrant Synaptic Pruning

Complement Shedding and Activation

Neuron

Reactive Microglia

CR

C1q

Neuron

C3

Protein X

C3b

Astrocyte

Interactive Poster: biolegend.com/neuroinflammation

We would like to thank Prof. Dr. Michael Schlossmacher of the University of Ottawa, Canada for his contributions to this poster.
Neuroinflammation

Suppressing the neurogenesis of neural stem cells leads to cytotoxic cytokines.

Interactive Poster: biolegend.com/neuroinflammation

We would like to thank Prof. Dr. Michael Schlossmacher of the University of Ottawa, Canada for his contributions to this poster.
Neuroinflammation
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.
# IL-6 Amygdala & Striatum

![Brain diagram showing the amygdala and striatum](image)

<table>
<thead>
<tr>
<th>Gray Matter Volume</th>
<th>Corr IL-6</th>
<th>p value</th>
<th>Gray Matter Volume</th>
<th>Corr IL-6</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Amygdala</td>
<td>-0.487</td>
<td>p&lt;0.005</td>
<td>Right Amygdala</td>
<td>-0.345</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Left Caudate</td>
<td>-0.170</td>
<td>p&gt;0.3</td>
<td>Right Caudate</td>
<td>-0.104</td>
<td>p&gt;0.5</td>
</tr>
<tr>
<td>Left Putamen</td>
<td>-0.497</td>
<td>p&lt;0.004</td>
<td>Right Putamen</td>
<td>-0.502</td>
<td>p&lt;0.003</td>
</tr>
<tr>
<td>Left Pallidum</td>
<td>-0.526</td>
<td>p&lt;0.002</td>
<td>Right Pallidum</td>
<td>-0.425</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>Left Accumbens</td>
<td>-0.125</td>
<td>p&gt;0.4</td>
<td>Right Accumbens</td>
<td>0.083</td>
<td>p&gt;0.6</td>
</tr>
<tr>
<td>Left Thalamus</td>
<td>-0.196</td>
<td>p&gt;0.2</td>
<td>Right Thalamus</td>
<td>-0.329</td>
<td>p&lt;0.07</td>
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</table>
**IL-6 & Hippocampus**

<table>
<thead>
<tr>
<th>Gray Matter Volume</th>
<th>Corr IL-6</th>
<th>p value</th>
<th>Gray Matter Volume</th>
<th>Corr IL-6</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Whole hippocampus</td>
<td>-0.456</td>
<td>p&lt;0.008</td>
<td>Right Whole hippocampus</td>
<td>-0.520</td>
<td>p&lt;0.002</td>
</tr>
<tr>
<td>Left CA1</td>
<td>-0.520</td>
<td>p&lt;0.002</td>
<td>Right CA1</td>
<td>-0.469</td>
<td>p&lt;0.006</td>
</tr>
<tr>
<td>Left CA3</td>
<td>-0.431</td>
<td>p&lt;0.02</td>
<td>Right CA3</td>
<td>-0.424</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>Left CA4</td>
<td>-0.525</td>
<td>p&lt;0.002</td>
<td>Right CA4</td>
<td>-0.504</td>
<td>p&lt;0.003</td>
</tr>
<tr>
<td>Left Dentate Gyrus</td>
<td>-0.502</td>
<td>p&lt;0.003</td>
<td>Right Dentate Gyrus</td>
<td>-0.511</td>
<td>p&lt;0.003</td>
</tr>
<tr>
<td>Left hipp molecular layer</td>
<td>-0.495</td>
<td>p&lt;0.004</td>
<td>Right hipp molecular layer</td>
<td>-0.522</td>
<td>p&lt;0.002</td>
</tr>
</tbody>
</table>
Maltreatment & Insula
IL-6 & Insula

<table>
<thead>
<tr>
<th>Gray Matter Volume</th>
<th>Cor IL6</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left short insular gyri</td>
<td>-0.569</td>
<td>p&lt;0.0006</td>
</tr>
<tr>
<td>Left inferior circular insular sulcus</td>
<td>-0.491</td>
<td>p&lt;0.004</td>
</tr>
<tr>
<td>Right anterior circular insular sulcus</td>
<td>-0.456</td>
<td>p&lt;0.008</td>
</tr>
<tr>
<td>Right inferior circular insular sulcus</td>
<td>-0.455</td>
<td>p&lt;0.008</td>
</tr>
<tr>
<td>Right superior circular insular sulcus</td>
<td>-0.375</td>
<td>p&lt;0.04</td>
</tr>
</tbody>
</table>

Central sulcus
Circular sulcus
Short gyri
Long gyrus
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).
History of Maltreatment

Actigraph Assessed Sleep
# Maltreatment and Sleep

<table>
<thead>
<tr>
<th></th>
<th>Maltreatment (# types)</th>
<th>Days of the Week</th>
<th>Maltreatment x Days of Week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F₁,₃₀</td>
<td>p</td>
<td>F₆,₄₀₁</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>9.84</td>
<td>0.004</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>Wake After Sleep Onset</td>
<td>7.85</td>
<td>0.009</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>Total Sleep Time</td>
<td>1.51</td>
<td>0.23</td>
<td>3.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.44</td>
</tr>
<tr>
<td>Number of Awakenings</td>
<td>4.69</td>
<td>0.04</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Duration of Awakenings</td>
<td>4.41</td>
<td>0.05</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
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</table>
## 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></td>
<td>c</td>
<td>ab</td>
</tr>
<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>
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</tr>
<tr>
<td>Left Pallidum</td>
<td>-0.497**</td>
<td></td>
</tr>
<tr>
<td>Right CA4</td>
<td>-0.497**</td>
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<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>
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<tr>
<td><strong>Left Hippocampal molecular layer</strong></td>
<td>-0.455**</td>
<td>-0.222</td>
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<tr>
<td>Left Hippocampus</td>
<td>-0.428*</td>
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</tbody>
</table>

Note: The values are correlation coefficients. ** indicates significance at p < 0.01. * indicates significance at p < 0.05.
Take Home Messages

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

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.
Take Home Messages

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

<table>
<thead>
<tr>
<th>Agency</th>
<th>Project Numbers</th>
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<td>RO1 MH66222 (2003-2008)</td>
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<td></td>
<td>RO1 MH91391 (2010-2015)</td>
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<td>NIDA</td>
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<td>NICHD</td>
<td>RO1 HD079484 (2015-2020)</td>
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<td>NARSAD</td>
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<td>(2005-2007)</td>
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<td>PRIVATE DONORS</td>
<td>Simches Family</td>
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<td></td>
<td>Susan Miller</td>
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</tbody>
</table>
Developmental Biopsychiatry Research Program

Liz Bolger
Ann Polcari
Cindy McGreener
Hannah McCormack
The End

Thank you!