Enduring Neurobiological Consequences of Abuse and Neglect

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

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
Hypothesis

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?

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
Psychopathology may emerge due to the mismatch between the world the brain was modified to survive in and the world it finds itself in during subsequent developmental stages.

Teicher MH: Scars that won’t heal: the neurobiology of child abuse. Scientific American 2002; 286(3):68-75

Does the nature of the maltreatment matter?
Threat Detection, Response and Recovery

Childhood Abuse and the Amygdala


The brain’s fear circuit

vmPFC=ventromedial prefrontal cortex; ACC=anterior cingulate cortex
dm/dlPFC=dorsomedial/dorsolateral prefrontal cortex

Fear Circuit Regions & Pathways

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

Time is of the essence
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups (n)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bremner et al 1997</td>
<td>PTSD (17), NL (17)</td>
<td>NS</td>
</tr>
<tr>
<td>De Bellis et al 1999</td>
<td>PTSD (44), NL (61)</td>
<td>NS</td>
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<tr>
<td>Dreissen et al 2000</td>
<td>Borderline (21), NL (21)</td>
<td>Decreased Volume</td>
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<tr>
<td>De Bellis et al 2002</td>
<td>PTSD (28), NL (66)</td>
<td>NS</td>
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<tr>
<td>Schmahl et al, 2003</td>
<td>Borderline (10), NL (23)</td>
<td>Decreased Volume</td>
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<tr>
<td>Brambilla et al, 2004</td>
<td>Borderline (10), NL (20)</td>
<td>NS</td>
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<tr>
<td>Cohen et al, 2006</td>
<td>ACE 0 (84) ACE&gt;2 (122)</td>
<td>NS</td>
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### Childhood Abuse and the Amygdala

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<tr>
<td>Vermetten et al, 2006</td>
<td>DID (15), NL (23)</td>
<td>Decreased Volume</td>
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<tr>
<td>Andersen et al, 2008</td>
<td>CSA (26), NL (17)</td>
<td>NS</td>
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<tr>
<td>Weniger et al 2009</td>
<td>Borderline (24), NL (25)</td>
<td>Decreased Volume</td>
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<tr>
<td>Mehta et al 2009</td>
<td>Romanian Orphans (14), NL (11)</td>
<td>Increased Volume</td>
</tr>
<tr>
<td>Tottenham et al 2010</td>
<td>Early Adopted (17), Late Adopted (17), NL (28)</td>
<td>Increased Volume</td>
</tr>
<tr>
<td>Lupien et al 2011</td>
<td>Children of chronically depressed mothers (17), NL (21)</td>
<td>Increased Volume</td>
</tr>
<tr>
<td>Malykhin et al 2012</td>
<td>MDD w/o abuse (20), MDD + abuse (19), NL (34)</td>
<td>Increased volume w or w/o abuse</td>
</tr>
</tbody>
</table>
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

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.

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>
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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

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 *Corru Ammonis*, particularly CA3
- Effects may be reversible with time
### Childhood Abuse and the Adult Hippocampus

<table>
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<tr>
<td>Bremner et al 1997</td>
<td>PTSD (17), NL (17)</td>
<td>-12% L</td>
</tr>
<tr>
<td>Stein et al 1997</td>
<td>PTSD/DID (21) NL (21)</td>
<td>-5% L</td>
</tr>
<tr>
<td>Dreissen et al 2000</td>
<td>Borderline (21), NL(21)</td>
<td>-16% L,R</td>
</tr>
<tr>
<td>Vythilingam et al, 2002</td>
<td>Depressed (21), NL (14)</td>
<td>-15% L</td>
</tr>
<tr>
<td>Schmahl et al, 2003</td>
<td>Borderline (10), NL (23)</td>
<td>-11% L, -16% R</td>
</tr>
<tr>
<td>Brambilla et al, 2004</td>
<td>Borderline (10), NL (20)</td>
<td>-6.8% L,R</td>
</tr>
<tr>
<td>Pederson et al, 2004</td>
<td>Abuse with PTSD (17),without PTSD (17), NL (17)</td>
<td>-4.5% L (NS)</td>
</tr>
</tbody>
</table>

### Childhood Abuse and the Developing Hippocampus

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<tr>
<td>De Bellis et al 1999</td>
<td>PTSD (44), NL (61)</td>
<td>NS</td>
</tr>
<tr>
<td>Carrion et al 2001</td>
<td>PTSD Sx (24), Hx NL (24)</td>
<td>NS</td>
</tr>
<tr>
<td>De Bellis et al 2002</td>
<td>PTSD (28), NL (66)</td>
<td>NS</td>
</tr>
<tr>
<td>Tuppler &amp; De Bellis 2006</td>
<td>MAL-PTSD (61) NL (122) reanalysis</td>
<td>NS gray, Increased white</td>
</tr>
<tr>
<td>Carrion et al 2007</td>
<td>PTSD Sx (15)</td>
<td>Inverse correlation r = -0.48 volume and cort 12-18 months</td>
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<tr>
<td>Rao et al 2010</td>
<td>Depr (30), High risk depr (22), NL (33) adol 12-20</td>
<td>Early adversity - decre.vol. in high risk &amp; NL</td>
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<tr>
<td>Carrion et al 2010</td>
<td>PTSD Sx (16), NL (11)</td>
<td>Abnormal (decr) R BOLD response verbal memory task</td>
</tr>
<tr>
<td>Edmiston et al 2011</td>
<td>CTQ scores (42) adol</td>
<td>NS: PA, SA, EA &amp; PN Signif EN</td>
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<tr>
<td>Lupien et al 2011</td>
<td>Children chronic depr mothers (17) controls (21)</td>
<td>NS</td>
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Translational Support


Stress & Hippocampus

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

Carl M. Anderson Ph.D.

Hippocampal Subfields

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
Types of Maltreatment with Significant Importance During Specific Years

Males
- Physical Neglect
- Emotional Neglect

Females
- Non-verbal Emotional Abuse
- Physical Abuse
- Witnessing Interparental Violence
- Witnessing Violence to Siblings
- Sexual Abuse
Hippocampus

Gender and hemisphere differences in effect size.

Percent variance accounted for by exposure at peak type and time.

Females
Left 4.3%,
Right 2.4%

Males
Left 16.8%,
Right 11.4%

Fear Circuit Regions & Pathways

1. Amygdala
2. Hippocampus
3. Sensory Cortex
4. Prefrontal Cortex
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Childhood Abuse and Neocortex

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<tr>
<td>De Bellis et al 1999</td>
<td>Child PTSD (44) NL (61)</td>
<td>Incr. Prefrontal CSF</td>
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<tr>
<td>De Bellis et al 2000</td>
<td>Child PTSD (11) NL (11)</td>
<td>Decr NAA/Cr ACC</td>
</tr>
<tr>
<td>Carrion et al 2001</td>
<td>Abused (24) NL (24) Child</td>
<td>Decr Frontal Asymmetry</td>
</tr>
<tr>
<td>De Bellis et al 2002</td>
<td>Child PTSD (28) NL (66)</td>
<td>Incr. Prefrontal CSF</td>
</tr>
<tr>
<td>De Bellis et al 2003</td>
<td>Child PTSD (61) NL (122)</td>
<td>Incr. Prefrontal CSF</td>
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<tr>
<td>Brambilla et al, 2004</td>
<td>BPD (10), NL (20)</td>
<td>No difference</td>
</tr>
<tr>
<td>Richert et al, 2006</td>
<td>Abused (23) NL (24) Child</td>
<td>Incr Mid Inf-Ventr PFC</td>
</tr>
<tr>
<td>Cohen et al, 2006</td>
<td>ACE 0 (84) ACE&gt;2 (122)</td>
<td>Decr Anterior Cingulate vol</td>
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<tr>
<td>Andersen et al, 2008</td>
<td>CSA (26), NL (17)</td>
<td>Decr Frontal GMV</td>
</tr>
<tr>
<td>Tomoda et al 2009b</td>
<td>HCP (23) NL (22)</td>
<td>Decr DLPCF, ACC, MPFC</td>
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### Ventromedial Prefrontal Cortex

**Females**

- **WIPV**
- **Peer Em**

**Males**

- **Parental Verbal**
- **Peer Em**

### Left Dorsal Anterior Cingulate Volume

**Females**

- **Peer physical abuse**
- **NVEA**

**Males**

- **Physical abuse**
- **Peer physical abuse**
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 Response - Romanian Adoptees**


**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.

**Sensitive Exposure Period - RAD**

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.
Don’t anticipate reward...
Expect to be maltreated.

But if you experience reward...
Keep at it.
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.

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 (Cortical Thickness)

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

Left Anterior Cingulate

Right Precuneus

Unexposed  Maltreated  Unexposed  Maltreated
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).
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.

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

**Hypothesis**

Earlier Onset
More Severe Course
More Comorbidities
Greater Symptom Severity
Poorer Response to Treatment

Ecophenotypes

Autoimmune
Metabolic
Cardiovascular
(Migaine)
Inflammation

Hippocampal
& Amygdala
Differences

Ecophenotypes

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

Corollary

Corollary
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

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.

Reduced pre-post training functional connectivity between hippocampus and amygdala in mindfulness versus waiting list controls (p < 0.001).
Take Home Messages

1. Childhood maltreatment is associated with marked effects on brain morphology, function and circuitry.

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. While type and timing is often the most important predictive factor, there are some consequences of maltreatment that depend more on severity and multiplicity of exposure.

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

6. These different components have their own unique sensitive periods so that maltreatment at different ages will target this circuit - but in different ways.

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. 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.

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

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

11. It is crucial to recognize that early traumatic stress is not just as a risk factor for psychopathology. Rather, it is a critical element that subdivides psychiatric disorders in a way that has far reaching implications for research, treatment and prevention.
The End

Thank you!