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 Felliti and Dr. Robert Anda

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

Prospective pharmacy records were available on 15,033 (86.7% of the analytic sample).
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?

Does age at the time of abuse matter?

What is the relationship between childhood abuse, brain changes and psychiatric illness?
First Neuroimaging Findings

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.

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>
</tr>
<tr>
<td>3 (rostral body)</td>
<td>0.463</td>
<td>0.615</td>
<td>0.606</td>
<td>0.0020</td>
</tr>
<tr>
<td>4 (ant. midbody)</td>
<td>0.361</td>
<td>0.486</td>
<td>0.523</td>
<td>0.0001</td>
</tr>
<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>0.3450</td>
</tr>
</tbody>
</table>

(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.

<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>--</td>
<td>41.7%†</td>
<td>7.4%†</td>
</tr>
<tr>
<td>2 (genu)</td>
<td>--</td>
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</tr>
<tr>
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</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.

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*Values are expressed as % change in volume associated with positive history
**Values are expressed as % change in volume per year of age.
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).

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.
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.

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
Cortisol
Norepinephrine
Autonomic Nervous System
ACTH
Threatening Stimuli

Top Down Regulation

Childhood Abuse and the Amygdala

Sensitive Exposure Periods

Time is of the essence

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

Inconsistent Effects of Maltreatment on Amygdala Volume

<table>
<thead>
<tr>
<th>Difference</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reported difference</td>
<td>5</td>
</tr>
<tr>
<td>NS decrease</td>
<td>11</td>
</tr>
<tr>
<td>Signif decrease</td>
<td>13</td>
</tr>
<tr>
<td>NS increase</td>
<td>4</td>
</tr>
<tr>
<td>Signif increase</td>
<td>5</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**
- 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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**30 Year Longitudinal Study of Attachment - Karlen Lyons-Ruth**

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.
Two Critical Developmental Threats

1. Rejection/Neglect - Left Amygdala - Infancy

2. Abuse - Right Amygdala - Preadolescence

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>

Amygdala Volume - Complex Interaction Between Early and Later Periods of Exposure


<table>
<thead>
<tr>
<th>Child 6-12 yrs</th>
<th>NS 9% incr amyg vol in high vs low</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 - High ELS</td>
<td>48 - Low ELS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adol 13-18 yrs</th>
<th>Signif 7.5% decr amyg vol high vs low</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 - High ELS</td>
<td>70 - Low ELS</td>
</tr>
</tbody>
</table>

n=136 child/adolescent


Does exposure to stress from birth thru 11 years of age sensitizes 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

n = 300
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 behavioral 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.

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

Fear Circuit Regions & Pathways

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

Childhood Abuse and the Adult Hippocampus

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups (n)</th>
<th>Reduction / Side</th>
</tr>
</thead>
<tbody>
<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 Adult Hippocampus

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups (n)</th>
<th>Reduction / Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vermetten et al, 2006</td>
<td>DID (15), NL (23)</td>
<td>-19.2% L,R</td>
</tr>
<tr>
<td>Cohen et al, 2006</td>
<td>ACE 0 (84) ACE&gt;2 (122)</td>
<td>L p=0.07, R p=0.06</td>
</tr>
<tr>
<td>Andersen et al, 2008</td>
<td>CSA (26), NL (17)</td>
<td>-6.8% bilateral</td>
</tr>
<tr>
<td>Bonne et al, 2008</td>
<td>Prepub Abused (11), NL (22)</td>
<td>~9% bilateral</td>
</tr>
<tr>
<td>Weniger et al, 2009</td>
<td>Borderline (24), NL (25)</td>
<td>-12% bilateral</td>
</tr>
<tr>
<td>Gatt et al, 2009</td>
<td>Healthy (89) - ratings of ELS</td>
<td>Reduction in GMV in ELS with MET poly BDNF</td>
</tr>
<tr>
<td>Frodl et al, 2010</td>
<td>MDD (43), NL (42)</td>
<td>EN: L.9, L,R-σ²</td>
</tr>
</tbody>
</table>

## Childhood Abuse and the Developing Hippocampus

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups (n)</th>
<th>Reduction / Side</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>Rao et al, 2010</td>
<td>Depr (20), High risk depr (22), NL (35)</td>
<td>Early adversity - decs vol. in high risk &amp; NL</td>
</tr>
<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>
</tr>
<tr>
<td>Lupien et al, 2011</td>
<td>Children chronic depr mothers (17) controls (21)</td>
<td>NS</td>
</tr>
</tbody>
</table>

## Translational Support

### Hippocampus:CA3

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups (n)</th>
<th>Reduction / Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everaerd et al, 2012</td>
<td>NL (357) Ratings of Child Adv</td>
<td>Reduced hipp in males with CA and SHTTLPR poly</td>
</tr>
<tr>
<td>Teicher et al, 2012</td>
<td>ACE score = 0 (89) ACE ≥ 1(104)</td>
<td>~6% L CA3 DG</td>
</tr>
<tr>
<td>Dannlowski et al, 2012</td>
<td>CTQ scores (148) no Psych Hx</td>
<td>R p&lt;0.05</td>
</tr>
<tr>
<td>Carballedo et al, 2012</td>
<td>Family Hx MDD (20), NL (20)</td>
<td>Reduced R/L hipp heads in FHx+ and EA</td>
</tr>
</tbody>
</table>

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

Subjects

300 unmedicated right-handed subjects (115M/185F, 23.2±1.7 year, range 18-25) selected from the community and enriched to have an increased percentage of subjects exposed to moderate to high levels of maltreatment.

Type and Timing of Exposure

Maltreatment and Abuse Chronology of Exposure (MACE) scale. Retrospectively assessed severity of exposure to 10 types of maltreatment across each year of childhood. Developed using item response theory, good-excellent test-retest reliability for entire scale, for each type of abuse and for each age

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

Sensitive Period Study

**Analytical Method:** We used random forest regression with conditional trees (a type of artificial intelligence - machine learning approach) to simultaneously assess importance of exposure at each age to each type of maltreatment.

Few Variables
Conventional Statistics

Many Variables “Big Data”
Data Mining
Predictive Analytics
**Hippocampus**

*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

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**Corpus Callosum**

**Males**

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<td>--</td>
<td>--</td>
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<td>2 (genu)</td>
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<td>--</td>
<td>-29.2%ζ</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3 (rostral body)</td>
<td>--</td>
<td>--</td>
<td>-33.2%ζ</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4 (ant. midbody)</td>
<td>--</td>
<td>--</td>
<td>-30.7%ζ</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5 (post. midbody)</td>
<td>--</td>
<td>--</td>
<td>-40.2%ζ</td>
<td>1.5%†</td>
<td>--</td>
</tr>
<tr>
<td>6 (isthmus)</td>
<td>--</td>
<td>--</td>
<td>-45.7%ζ</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>7 (splenium)</td>
<td>--</td>
<td>-18.3%†</td>
<td>-24.2%ζ</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

**Females**

<table>
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<th>PTSD</th>
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<tbody>
<tr>
<td>1 (rostrum)</td>
<td>--</td>
<td>--</td>
<td>-20.6%ζ</td>
<td>--</td>
<td>--</td>
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<td>--</td>
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<td>3 (rostral body)</td>
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<td>--</td>
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<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4 (ant. midbody)</td>
<td>--</td>
<td>--</td>
<td>+37.6%ζ</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5 (post. midbody)</td>
<td>--</td>
<td>--</td>
<td>-23.7%ζ</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>6 (isthmus)</td>
<td>--</td>
<td>--</td>
<td>-43.9%†</td>
<td>+5.2%ζ</td>
<td>--</td>
</tr>
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**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
5. **Pathways** - AF, CB, Fornix, ILF

---

Does the nature of the maltreatment matter?
Verbal Abuse

Witnessing Domestic Violence

Childhood Sexual Abuse

Childhood Abuse Targets Sensory Systems
Fear Circuit Regions & Pathways

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2. Hippocampus
3. Sensory Cortex
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### Childhood Abuse and Neocortex

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<td>Child PTSD (44) NL (61)</td>
<td>Incr. Prefrontal CSF</td>
</tr>
<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>
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<tr>
<td>De Bellis et al 2002</td>
<td>Child PTSD (28) NL (66)</td>
<td>Incr. Prefrontal CSF</td>
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<tr>
<td>De Bellis et al 2003</td>
<td>Child PTSD (61) NL (122)</td>
<td>Incr. Prefrontal CSF</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Groups (n)</th>
<th>Region</th>
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<tbody>
<tr>
<td>Brambilla et al, 2004</td>
<td>BPD (10), NL (20)</td>
<td>No difference</td>
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<tr>
<td>Richert et al, 2006</td>
<td>Abused (23) NL (24) Child</td>
<td>Incr Mid Inf-Ventr PFC</td>
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<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 DLPC, ACC, MPFC</td>
</tr>
</tbody>
</table>

---

### Physical Neglect

- **Sheu et al 2010**
  - HCP (19), NL (23)
  - Incr T2RT DLPFC

- **Hanson et al 2010**
  - CPA (31) NL (41) child
  - Decr OFC, PFC, TMP

- **Frodil et al 2010**
  - MDD (43), NL (42)
  - PN, Decr PFC

- **van Harmelen et al 2010**
  - CEM (84, 71 with Anx/Dep), No CEM (97, 57 with Anx/Dep)
  - Decr I DMPFC

- **Edmiston et al 2011**
  - CTQ scores (42) adol
  - Decr DLPFC, RPFC, OFC, T-Assoc

- **Gerritsen et al 2012**
  - NL (568) Ratings of Child Adv
  - Interaction CA/BDNF on ACC

- **Carballedo et al 2012**
  - Family Hx MDD (20), NL (20)
  - Reduced DLPFC, MPFC, ACC in FHx+ with EA

---

### Left Anterior Cingulate Area - Males

**Physical Neglect**

![Graph showing Physical Neglect](image)

**Recalled Ages of Exposure (years)**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

**Recalled Ages of Exposure (years)**

---

### Left Anterior Cingulate Area - Females

**Physical Abuse**

![Graph showing Physical Abuse](image)

**Recalled Ages of Exposure (years)**

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

**Recalled Ages of Exposure (years)**

---
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.


Kyoko Ohashi, Ph.D.
Amygdala Functional Connectivity

Emotional Regulation

<table>
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<td>rostral ACC</td>
</tr>
<tr>
<td></td>
<td>ventromedial prefrontal cortex</td>
</tr>
<tr>
<td>Negative prediction of spontaneous activity</td>
<td>dorsal ACC</td>
</tr>
<tr>
<td></td>
<td>middle frontal gyrus</td>
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n = 208
Amygdala Functional Connectivity

*Emotional Regulation*

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<tr>
<td>Negative prediction of spontaneous activity</td>
<td>dorsal ACC, middle frontal gyrus</td>
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</table>

**MALES > FEMALES**

- **R Amygdala - R middle orbital**
- **L Amygdala - L middle frontal**
- **L Amygdala - R middle frontal**

**MALES**

- **R Amygdala - R middle orbital**
- **L Amygdala - L middle frontal**
- **L Amygdala - R middle frontal**

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Amygdala Functional Connectivity

**Emotional Regulation**

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**MALES**

- **R Amygdala - L middle frontal**
  - Recalled Ages of Exposure (years)

- **R Amygdala - R middle frontal**
  - Recalled Ages of Exposure (years)

**FEMALES**

- MALES < FEMALES

- **L Amygdala - R ACC**
  - Recalled Ages of Exposure (years)

- **L Amygdala - L ACC**
  - Recalled Ages of Exposure (years)

- **L Amygdala - R ACC**
  - Recalled Ages 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


Ventral Striatum - nucleus accumbens and ventral putamen
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

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

- 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.
The anterior cingulate plays an important role in the regulation of emotions\textsuperscript{1}.

The anterior insular cortex is involved in interoception, subjective feelings and possibly self-awareness\textsuperscript{3}.

The precuneus is a major component of the default mode network and is involved in self-referential, self-centered mental imagery\textsuperscript{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).

Alaptagin Khan, M.D.
Multiplicity of Exposure

*a measure of the cumulative exposure to traumatic stress during childhood*

Alternative Explanation

Multiplicity is a statistical illusion. What really matters is type and timing of maltreatment. Being exposed to more types of maltreatment increases the odds that an individual experienced a critical type of maltreatment at a critical age.

Sensitive Exposure Period

**Definition:**

A sensitive exposure period can be said to exist if exposure to maltreatment during a specific developmental stage is a more important predictor of outcome than overall measures of exposure as indexed by severity of exposure, duration of exposure and number of different types of adversity experienced during childhood.

### History of Major Depression

#### Females

- n = 337
- Odds ratio 36.0 (95% CI 13.8–93.8)

#### Males

- n = 223
- Odds ratio 28.4 (95% CI 9.4–85.9)
Non-Verbal Emotional Abuse

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.
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.

Hypothesis

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

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

Autoimmune
Metabolic
Cardiovascular
(Mirgaine)
Inflammation

Hippocampal & Amygdala Differences

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 - Schizophrenia and Bipolar Disorder

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

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.

Ecophenotypes

Corollary

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

Brain Changes and Psychopathology

Childhood Maltreatment ELS → Neurobiology → Psycho-pathology

Childhood Maltreatment ELS → Psycho-pathology → Neurobiology

Neurobiology → Psycho-pathology → Childhood Maltreatment ELS

Douglas Bremner Model

Childhood Maltreatment ELS

Susceptible PTSD/MDD → Hippocampus

Resilient → Hippocampus

Hippocampal Subfields

CTQ Score

- Left CA2-CA3
- Left CA4-DG
- Left Subiculum
- Left Preubiculum

- History Major Depression
- History Post-traumatic Stress
- History

b = 0.20
b = 0.36
b = 0.06
b = 0.10
b = 0.09
b = 0.12
b = 0.07
b = 0.13
b = 0.21
b = 0.02
Hippocampal Subfields


Hippocampal Volume and Maltreatment

Current Observation

Psychiatrically and neurobiologically susceptible

Psychiatrically resilient but neurobiologically susceptible
Resilient subjects – exposed to significant childhood maltreatment but have not developed depression, PTSD or other psychiatric disorders.

Recovered subjects – exposed to significant childhood maltreatment, developed MDD and/or PTSD but are currently asymptomatic.

Resilient and recovered subjects may well have reduced hippocampal volume and hyperreactive amygdala, yet they appear to be mentally healthy.

Hypothesis: Some other compensatory changes have occurred that enable them to be this healthy. However, this compensation is a ‘fix’ not a cure, and if you probe deep enough you’ll find that they differ in meaningful ways from healthy controls.

Compensated versus Unaffected

Affective Stability & Mood Regulation

Ecological Momentary Assessment

Healthy controls: n = 22
Maltreated subjects: n = 38

Positive Affect
Enthusiastic
Inspired
Excited
Determined
Alert

Negative Affect
Afraid
Distressed
Scared
Upset
Nervous

Face Flushed
Wobbly knees
Heart/Racing
Hard to Breathe
Feeling Hot
Dizzy/Lightheaded

22 Unexposed Controls (x ACE = 0)
38 with History of Maltreatment (x ACE = 2.5)
18-25 years of age, unmedicated
Regulation of Positive Affect

- No difference between groups in overall levels of positive affect ($F_{1,56} = 0.02, p > 0.8$).

- Positive affect rating were 26% more variable in maltreated subjects than unexposed controls (Likelihood Ratio (LR) test = 36.28, $p < 10^{-8}$).

- No difference between groups in persistence ($H$ exponent) of positive affect ($F_{1,56} = 0.09, p > 0.7$).

Resilient and recovered subjects did not differ from controls in current levels of depression or anxiety and did not differ from controls in mean levels of positive or negative affect. However, positive affect ratings were more variable and negative affect ratings were more persistent.

Regulation of Negative Affect

- No difference between groups in overall levels of negative affect ($F_{1,56} = 2.29, p > 0.13$).

- Negative affect rating were 8% more variable in maltreated subjects than unexposed controls (LR test = 4.58, $p < 0.07$).

- Persistence ($H$ exponent) of negative affect was 45% greater in maltreated subjects than unexposed controls ($F_{1,56} = 9.54, p < 0.004$).

Possible Compensatory Differences

1. Increased fibre density of anterior corpus callosum
2. Increased connectivity of the ventrolateral prefrontal cortex
3. Increased connectivity of dorsal ACC to lingual and fusiform gyri
4. Increased thickness of extrastriate visual cortex
5. Increased left amygdala volume
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. Childhood maltreatment is associated with structural and functional alterations in key components of reward system.

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

11. The impact of maltreatment on trajectories of brain development are not mediated by psychopathology and are discernible in maltreated individuals with no history of psychopathology (yet).

12. It may turn out that comparably maltreated groups with and without specific DSM disorders will have the same basic constellation of brain alterations but the maltreated group without psychopathology may have some additional changes that provide protection.

10. 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.
13. Childhood maltreatment / early life stress is a huge confound in studies on biology or treatment of psychiatric disorders when not taken into account.

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

15. 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!