Windows of Vulnerability: Neurobiology of Childhood Abuse

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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
Impact of Adverse Childhood Experiences (ACEs) (e.g., physical, sexual and emotional abuse)

ACE Score vs. Depression

ACE Score vs. Intravenous Drug Use

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

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


Key Lessons About the Neurobiology of Abuse

Both gray matter and white matter (fiber tracts) appear to be affected.

Brain regions differ in susceptibility - key targets appear to be cortico-limbic.

Also sensory systems and pathways that convey the adverse sensory input appear to be affected.
Key Lessons About the Neurobiology of Abuse

Neurobiological effects depend on the timing of exposure (sensitive periods)

Neurobiological and clinical consequences may be delayed (silent periods)
Key Abuse-Sensitive Structures

- Corpus Callosum
- Prefrontal Cortex
- Temporal Lobe
- Amygdala
- Hippocampus
- Thalamus
- Hypothalamus
- Cerebellar Vermis
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.
SUBDIVISIONS OF THE CORPUS CALLOSUM

- rostral body
- anterior midbody
- posterior midbody
- isthmus
- genu
- rostrum
- splenium
## Childhood Abuse and the Corpus Callosum

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups (n)</th>
<th>Region / Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teicher et al 1997•</td>
<td>Child inpatients w/wo abuse (51)</td>
<td>Region 4, 3 M &gt; F</td>
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<tr>
<td>De Bellis et al 1999</td>
<td>Child PTSD (44) NL (61)</td>
<td>Region 4, 5-7 M &gt; F</td>
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<tr>
<td>De Bellis et al 2002</td>
<td>Child PTSD (28) NL (66)</td>
<td>Region 7, 4-6</td>
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<tr>
<td>De Bellis et al 2003</td>
<td>Child PTSD (61) NL (122)</td>
<td>Region 7, 1,6 M &gt; F</td>
</tr>
<tr>
<td>Teicher et al, 2004•</td>
<td>Child abuse (28) Contrast (23) NL (115)</td>
<td>Region 4, 5-7 M-negl F-CSA</td>
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<tr>
<td>Jackowski et al, 2008</td>
<td>Child PTSD (17), NL (15)</td>
<td>FA Mid &amp; Posterior</td>
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<tr>
<td>Andersen et al, 2008•</td>
<td>CSA (26), NL (17) - Adults</td>
<td>Region 3</td>
</tr>
<tr>
<td>Teicher et al, 2010•</td>
<td>Degree of peer verbal abuse (63) - Adults</td>
<td>FA Adult Region 7 M = F</td>
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</tbody>
</table>
Peer Verbal Abuse
Hippocampus plays a critical role in memory consolidation and retrieval.

Recent theories postulate that impaired hippocampal function (particularly suppressed neurogenesis) is involved in the pathophysiology of depression.
## Childhood Abuse and the Adult Hippocampus

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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>BPD (10), NL (23)</td>
<td>-11% L, -16% R</td>
</tr>
<tr>
<td>Brambilla et al, 2004</td>
<td>BPD (10), NL (20)</td>
<td>-6.8% L,R</td>
</tr>
<tr>
<td>Vermetten et al, 2006</td>
<td>DID (15), NL (23)</td>
<td>-19.2% L,R</td>
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<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>BPD (24), NL (25)</td>
<td>-12% bilateral</td>
</tr>
<tr>
<td>Frodl et al 2010</td>
<td>MDD (43), NL (42)</td>
<td>EN: L-♀, L,R-♂</td>
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<tr>
<td>Teicher et al 2012•</td>
<td>ACE score = 0 (89) ACE ≥ 1(104)</td>
<td>~6% L CA3 DG</td>
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<tr>
<td>Dannlowski et al 2012</td>
<td>CTQ scores (148) no Psych Hx</td>
<td>R p&lt;0.05</td>
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</table>
Hippocampus

Left-Sided Volume Reduction

*Maltreated subjects primarily with PTSD or Depression*

- Bremner et al., 1997
- Stein et al., 1997
- Vythilingam et al., 2002
- Frodl et al., 2010
- Teicher et al., 2012

Bilateral Volume Reductions

*Maltreated subjects with Borderline Personality Disorder or Dissociative Identity Disorder*

- Driessen et al., 2002
- Schmahl et al., 2003
- Brambilla et al., 2004
- Vermetten et al., 2006; Weniger et al., 2009
Stress & Hippocampus

• Suppresses neurogenesis in the dentate gyrus (DG)
• Provokes remodeling of dendrites in Cornu Ammonis, particularly CA3
Teicher, M. H., et al. (in press). "Childhood maltreatment is associated with reduced volume in hippocampal subfields CA3, dentate gyrus and subiculum." Proc Natl Acad Sci U S A
Subiculum

Helps Regulate HPA Axis Response
Suppresses HPA response to psychogenic (but not physical) stimuli

Helps Regulate Dopaminergic Responses
Direct pathway between ventral subiculum and nucleus accumbens (NA) pathway. Subiculum helps regulates tonic firing of DA cells in the ventral tegmentum and release of DA in the NA. May have a role in substance abuse and psychosis.

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.
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<td>Child PTSD (44) NL (61)</td>
<td>Incr. Prefrontal CSF</td>
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<td>Carrion et al 2001</td>
<td>Abused (24) NL (24) Child</td>
<td>Decr Frontal Asymmetry</td>
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<td>Incr. R,L Sup Temp Gyrus</td>
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## Childhood Abuse and Neocortex

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<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>
</tr>
<tr>
<td>Andersen et al, 2008•</td>
<td>CSA (26), NL (17)</td>
<td>Decr Frontal GMV</td>
</tr>
<tr>
<td>Tomoda et al 2009a•</td>
<td>CSA (23), NL (14)</td>
<td>Decr Occipital GMV</td>
</tr>
<tr>
<td>Tomoda et al 2009b•</td>
<td>HCP (23) NL (22)</td>
<td>Decr DLPFC, ACC, MPFC</td>
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<td>CEM (84) NL (97)</td>
<td>Decr L DMPFC</td>
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<tr>
<td>Sheu et al 2010·</td>
<td>HCP (19), NL (23)</td>
<td>Incr T2RT DLPFC</td>
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<tr>
<td>Hanson et al 2010</td>
<td>CPA (31) NL (41) child</td>
<td>Decr OFC, PFC, TMP</td>
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<td>PN: Decr Prefrontal ctx</td>
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<tr>
<td>Tomoda et al 2011·</td>
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<td>Incr STG GMV</td>
</tr>
<tr>
<td>Edmiston et al 2011</td>
<td>CTQ scores (42) adol</td>
<td>Decr DLPFC, RPFC, OFC, T-Assoc</td>
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Sensitive Periods
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
Sensitive Periods


Sensitive Periods and Psychopathology

If stress exposure targets different brain regions based on ages of exposure, then exposure at different ages may lead to different clinical outcomes.
Delayed Effects – Silent Periods
Delayed Effects – Silent Periods

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.
Delayed Effects – Silent Period

![Graphs illustrating the relationship between maltreatment and drug use, and binge drinking frequency.](image)

A. Maltreatment and Drug Use

B. Drug Use (days/month) vs. Age

C. Binge Drinking Frequency

- Maltreatment: None, Once, Twice, 3-5 times, 6-10 times, >10 times
## Childhood Abuse and the Developing Hippocampus

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<td>NS</td>
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<td>NS: PA, SA, EA &amp; PN Signif: EN</td>
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Translational Support

sensitive periods

early manifestations

intermediate manifestations

late manifestations

time is of the essence

Time is of the essence
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.
Childhood Sexual Abuse
Repeated Exposure to Childhood Sexual Abuse

Reduces gray matter volume 14.1% in left primary and secondary visual cortex.

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

Depression
Dissociation
Fornix

Anxiety Somatization

Increased gray matter volume left superior temporal gyrus - auditory cortex

Tomoda A et al., Exposure to parental verbal abuse is associated with increased gray matter volume in superior temporal gyrus. Neuroimage 54 Suppl 1: S280-286
Witnessing Domestic Violence
WDV subjects had a 20.5% GMV reduction in right Lingual Gyrus, (BA17), 6.8% reduction in right BA18, and 16.4% reduction in left BA17.
Inferior Longitudinal Fasciculus


Key component of visual-limbic pathway. Helps determine our emotional and memory responses to things that we see.
Neglect:

More consistent effect on volume of amygdala than hippocampus (but subjects still young). Amygdala volume increased.

Mehta et al 2009

Tottenham et al 2010

Lupien et al 2011
Neurobiology of Abuse vs Neglect

Abuse:

More consistent effect on volume of hippocampus (~14/14) than amygdala (5/14). When observed, amygdala volume decreased.

Driessen et al 2000; Schmahl et al 2003;
Vermetten et al 2006; Weniger et al 2009;
Edmiston et al 2011
Neurobiology of Abuse vs Neglect

**Similarities:**

Increased amygdala activation to emotional faces.

Neglect: left sided (Maheau et al 2010)

Abuse: right sided (Grant et al 2011; Dannlowski et al 2012)

Emotional abuse ± neglect – bilateral (van Harmelen et al 2012)
Summary

Sensory Stimuli
Possible Threat

Visual Cortex
Auditory Cortex

Thalamus

Sensory Cortex

Prefrontal Cortex

Hippocampus
Subiculum

Bed n. stria terminalis

Inferior Longitudinal Fasciculus

Cingulum Bundle

Arcuate Fasciculus

Pituitary

Hypo-thalamus

Locus ceruleus

Autonomic Nervous System

Norepinephrine

Cortisol
Summary

Decreased hemispheric Integration
The End

Thank you!