Childhood Abuse: A Neurobiological Perspective

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Support - Maltreatment and Trauma Studies

NIMH  ROI MH53636 (1997-2001)
ROI MH66222 (2003-2008)
ROI MH91391 (2010-2015)

NIDA  ROI DA16934 (2003-2007)
ROI DA17846 (2004-2009)

NARSAD (2005-2007)

Simches Family
Introduction

Physical, sexual, and psychological trauma in childhood may lead to medical and psychiatric difficulties that show up in childhood, adolescence, or adulthood.
Introduction

Childhood Abuse

- Death
- Failure to Thrive
- Burns
- Mechanical Brain Injury
- Fractures
- Chronic GI Distress
- Obesity
- Recurrent Headaches
- Seizure Disorders
- Sexually Transmitted Diseases

medical
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
- ADHD-like behaviors

psychiatric
What factor, or combination of factors, shape outcome?
Resilience  
Fixed

Vulnerability  
Malleable
Possibilities

- Genes
- Timing (developmental stage when abuse occurs)
- Type of abusive experience
- Protective factors
Possibilities

- Genes
- Timing (developmental stage when abuse occurs)
- Type of abusive experience
- Protective factors
Hypothesis

We have proposed that early childhood maltreatment acts as a severe stressor, that produces a cascade of physiological and neurohumoral responses which leads to enduring alterations in the patterns of brain development, and that alterations in brain function set the stage for the emergence of psychiatric disorders.
Introduction

Childhood adversity
- number
- type

Brain development

Genetics

Age

PTSD

Depression

Addiction

Medical Disorders

Dissociation

Cognition

Other psych disorders
How can stressful experience influence the developing brain?
How stressful early experience influences the developing brain.

Early stress programs our stress hormone systems to have a more exaggerated and prolonged response to subsequent stressors.
How stressful early experience influences the developing brain.

Step 2

Exposure of the developing brain to stress hormones exerts consequences by affecting gene expression, myelination, neural morphology, neurogenesis and synaptogenesis.
Early stress affects the two pivotal components of postnatal brain development.

- Myelination
- Synaptogenesis
# Human Brain Development

**Enlarged 4x**

<table>
<thead>
<tr>
<th>Embryonic</th>
<th>Postnatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week: 0 6 12 18 24 30 36</td>
<td>Month: 0 6 12 18 24 30 36 Year: 4 8 12 16 20 24</td>
</tr>
</tbody>
</table>

- **Cell Birth**
- **Migration**
- **Axonal/Dendritic Outgrowth**
- **Programmed Cell Death**
- **Synaptic Production**
- **Myelination**
- **Synaptic Elimination/Pruning**

- Majority of Neurons
- Fewer Neurons, primarily in cortex
Impact of early stress on the developing brain depends on timing, vulnerability of specific brain regions, and genetic factors.
First Neuroimaging Findings

- Corpus Callosum
- Prefrontal Cortex
- Thalamus
- Hypothalamus
- Temporal Lobe
- Amygdala
- Hippocampus
- 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
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>0.5450</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>-41.7%†</td>
<td>7.4%ζ</td>
<td>--</td>
</tr>
<tr>
<td>2 (genu)</td>
<td>--</td>
<td>--</td>
<td>-29.2%￥</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3 (rostral body)</td>
<td>--</td>
<td>--</td>
<td>-33.2%￥</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4 (ant. midbody)</td>
<td>-9.6%†</td>
<td>--</td>
<td>-30.7%￥</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5 (post. midbody)</td>
<td>--</td>
<td>--</td>
<td>-40.2%￥</td>
<td>1.5%†</td>
<td>--</td>
</tr>
<tr>
<td>6 (isthmus)</td>
<td>--</td>
<td>--</td>
<td>-45.7%￥</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>7 (splenium)</td>
<td>--</td>
<td>-18.3%†</td>
<td>-24.2%ξ</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

†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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<td>--</td>
</tr>
<tr>
<td>2 (genu)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3 (rostral boc)</td>
<td>--</td>
<td>-20.8%ζ</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4 (ant. midboc)</td>
<td>--</td>
<td>-29.7%¥</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5 (post. midboc)</td>
<td>--</td>
<td>-17.7%ζ</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>6 (isthmus)</td>
<td>--</td>
<td>-23.7%ζ</td>
<td>+37.6ξ</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>7 (spleenium)</td>
<td>--</td>
<td>--</td>
<td>-43.9%†</td>
<td>+5.2%ζ</td>
<td>--</td>
</tr>
</tbody>
</table>

†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.
44 maltreated children and adolescents with PTSD and 61 matched controls underwent comprehensive assessments and MRI.

Most significant finding was reduced midsagittal area of corpus callosum in PTSD subjects.

There was a greater corpus callosum area reduction in maltreated males than maltreated females with PTSD.

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

Degree of cognitive impairment correlated with alterations in corpus callosum size.
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.
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).
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.
Right-Left Evoked Response Asymmetry

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. Lack of integration between the hemispheres may also be a factor in the genesis of dissociation and multiple distinct identities.
Sensitive Periods
Sensitive Periods

The brain is molded by experiences, such as stress, 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 won the Nobel Prize in Medicine and Physiology (1981) for this discovery.
Sensitive Periods

Time
Sensitive Periods

Study I

Subjects: 18-22 year olds with history of 3 or more episodes of forced sexual contact, by individuals outside the immediate family, accompanied by fear or terror and threats of harm to self or others (n=30).
Sensitive Periods

Subjects: Recruited from the community and were selected based on childhood history with no prerequisite for any degree or type of psychiatric difficulty.

564 screened / 30 abused, 30 controls
SUBDIVISIONS OF THE CORPUS CALLOSUM

- genu
- rostrum
- rostral body
- anterior midbody
- posterior midbody
- isthmus
- splenium

Each numbered section corresponds to a specific part of the corpus callosum.
Corpus Callosum - Rostral Body

Abused at index age vs abused at other ages

Effect Size (eta squared)

Index Age of Abuse (years)

CC area reduced 22.4% in subjects who experienced abuse at age 10 (n=5).
Hippocampus
Preclinical studies have demonstrated the marked vulnerability of the hippocampus to ravages of stress. This region has a protracted ontogeny, persistent postnatal neurogenesis, and a high density of stress hormone receptors. Exposure to stress can effect the development of synapses, the birth of new neurons, the dendritic branching of neurons and the survival of neurons in the hippocampus.
Hippocampal volume reduced 13.2% in subjects who experienced abuse at age 4 (n=7).
Hippocampus plays a critical role in memory consolidation and retrieval.

Hippocampus may also play a critical role in the development of depression. It appears that medications and interventions that treat depression restore or enhance hippocampal neurogenesis.
Frontal Lobes
Frontal Lobes

The frontal lobes are important for attention, executive function, working memory, motivation, and behavioral inhibition.

Executive functions are cognitive abilities necessary for complex goal-directed behavior and adaptation to a range of environmental changes and demands.
The frontal lobes are important in our ability to plan and anticipate outcomes (cognitive flexibility) and to direct attentional resources to meet the demands of non-routine events.

The frontal lobes are important in self-monitoring and self-awareness - necessary for appropriateness of behavior and behavioral flexibility.
Prefrontal Cortex

Abused at index age vs abused at other ages

PFC GMV reduced 5.8% in subjects who experienced abuse at age 14 (n=4).
Depression Associated with Trauma/Loss
Reduction in both prefrontal cortex and hippocampal volume have been reported in subjects with depression.

Depression is the most common adult psychiatric consequence of exposure to childhood sexual abuse.

Do young adults with exposure to CSA during hippocampal or prefrontal cortex sensitive periods have higher ratings of depression?
Dissociation and Sexual Abuse

Stage of Abuse and DES Score

% Increase Mean Square Error

Hippocampus

Corpus Callosum

Age Range (years)
Childhood abuse has been associated with vulnerability to a host of psychiatric disorders and behavioral problems. Based on the present findings, there may be different abuse-related syndromes associated with particular ages of abuse and specific regional brain changes.
Windows of Opportunity

Identifying sensitive periods may also provide insight into key ages at which stimulation or environmental enrichment may optimally benefit development of specific brain regions.
Delayed Effects of Early Abuse
Overall, these findings are most compatible with the hypothesis that childhood exposure to sexual abuse sensitizes the individual to later emergence of depression during adolescence, and that it shifts the peak period of risk from mid-adolescence to early adolescence.
Childhood abuse leading to PTSD, Dissociative Identity Disorder, Borderline Personality Disorder, or Major Depression has been associated with reduced hippocampal size in adulthood.

<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 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>Vermetten et al, 2006</td>
<td>DID (15), NL (23)</td>
<td>19.2% L,R</td>
</tr>
<tr>
<td>Andersen et al, 2008</td>
<td>Abused (26), NL (17)</td>
<td>6.8% L,R</td>
</tr>
</tbody>
</table>
Childhood abuse leading to PTSD has **not been associated with reduced hippocampal size in childhood**.

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups (n)</th>
<th>Result</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>
</tbody>
</table>
Does the nature of the maltreatment matter?
DES Score

Type of Childhood Maltreatment

- Emotional Only (N=52)
- Domestic violence (N=24)
- Verbal abuse (N=20)
- Both (N=8)
- Physical Only (N=35)
- Nonfamilial (N=7)
- Familial (N=18)
- Both (N=10)
- Sexual Only (N=53)
- Nonfamilial (N=40)
- Familial (N=13)
- Any Two Categories (N=111)
- All Three Categories (N=53)

Size of Effect (Cohen’s d’) on Score on Dissociative Experience Scale (±95% CI)
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.
Goal: Recruit ideal groups of subjects to test hypotheses regarding the relationship between early adverse experience and brain development.
Ideal: As free as possible from confounding factors that can affect brain development.

No head trauma, neurological disorders, perinatal problems, maternal substance abuse, or exposure to any other form of trauma (MVA, natural disasters, near drownings, animal attacks, etc.)
Study Design

ROI 1 (1999-2004)
Childhood Sexual Abuse

ROI 2-4 (2003-09)
Verbal Abuse
Witnessing Domestic Violence
Harsh Corporal Punishment
Trauma (PA/SA)
Study Design

Advertise Aggressively

ROI 1 (1999-2004)
“Psychiatric Research”
18-22 years
right handed
unmedicated

ROI 2-4 (2003-09)
“Memories of Childhood”
18-25 years
right handed
unmedicated
Study Design

Collect Extensive Information

ROI 1 (1999-2004)
Mailed booklets
350 items
n = 564

ROI 2-4 (2003-09)
Online enrollment
2342 items
n = 1663
Study Design

Prescreen, Invite & Interview

ROI 1 (1999-2004)
  - SCID Axis I
  - DIB
  - SCID-D
  - TAI

ROI 2-4 (2003-09)
  - SCID Axis I
  - SCID Axis II
  - TAI
Study Design

Neuroimaging

ROI 1 (1999-2004)
GE 1.5T Scanner
T1 volumetric morph
T2-relaxometry
Dynamic Susceptibility Contrast
(n=60)

ROI 2-4 (2003-09)
Siemens 3T Trio
T1 volumetric morph
T2-relaxometry
Diffusion Tensor Imaging
Functional Connectivity
Spectroscopy
MPH-challenge
(n=193)
Childhood Sexual Abuse
Voxel-Based Morphometry

VBM is a fully automated whole-brain morphometric technique that detects regional structural differences in gray matter volume between groups on a voxel-by-voxel basis.
Repeated Exposure to Childhood Sexual Abuse

FreeSurfer
Cortical Surface Analysis
Cortical Thickness

Fig. 1. Coronal (Left) and horizontal (Right) slices of the left hemisphere with gray/white (yellow) and pial (red) surfaces overlaid. The green crosses indicate a point at which using the coronal view only would result in a dramatic overestimation of the thickness of the cortex.
The orbitofrontal cortex (OFC) is a region of association cortex of the human brain involved in cognitive processes such as decision making. In particular, the human OFC is thought to regulate planning behavior associated with sensitivity to reward and punishment.

Bechara, A.; Damasio, A. R.; Damasio H. & Anderson, S.W. (1994) "Insensitivity to future consequences following damage to human prefrontal cortex". *Cognition* 50: 7-15
The interconnected medial prefrontal regions and the posteromedial parietal cortex have been proposed to represent a network through which personal identity and past personal experiences are interlinked with one another, with the net interactions permitting us to move between representation and awareness of self.

Precuneus

- Autobiographical memory
- Self versus non-self representation
- Self-referential judgements
- First- versus third-person perspective
- Perceived agency
- Mind reading/social cognition.
Verbal Abuse
*!#$^&@
Verbal Abuse

*!#$^&@
Diffusion Tensor Imaging

Diffusion perpendicular to long axis

Diffusion parallel to long axis
Diffusion Tensor Imaging

Isotropic Tensor

ANISOTROPY
Fornix

Anxiety Somatization

Verbal Abuse: Voxel-based morphometry

Increased gray matter volume
left superior temporal gyrus
Peer Verbal Abuse
Peer Verbal Abuse

FIGURE 3. Effect of Exposure to Parental Verbal Abuse and Peer Verbal Abuse on Symptom Ratings and Drug Use in 848 Young Adults

Dependent Measures

- Anxiety
- Depression
- Somatization
- Anger-Hostility
- Dissociation
- Limbic Irritability
- Drug Use

Regression Coefficients
Peer Verbal Abuse

FIGURE 4. Percentage of 1,662 Young Adults in a Community Sample Reporting Exposure to Significant Peer Verbal Abuse Between Ages 5 and 18

\[ \text{Percent Exposed} \]

\[ \text{Age (years)} \]

\[ ^a \text{Significant peer verbal abuse was defined as maximal peer Verbal Abuse Questionnaire scores } \geq 30). \text{ Note that exposure peaks at ages 12–13.} \]
Figure 5. Regions identified by TBSS in the corpus callosum (CC) and posterior corona radiata (PCR) in which there were correlations between degree of exposure to peer verbal abuse and mean diffusivity (MD), radial diffusivity (RD) and fractional anisotropy (FA) (n = 63).
Witnessing Domestic Violence
Witnessing Domestic Violence
1402 volunteers screened

(16F/4M, 22.4±2.48 yrs) who witness domestic violence but were exposed to no other forms of trauma

(19F/8M, 21.9±1.97 yrs) healthy controls
Witnessing Domestic Violence
Inferior Longitudinal Fasciculus
FA values in this region were significantly associated with ratings of depression, anxiety, somatization, and dissociation (r=-0.502, p<0.001; r=-0.421, p=0.003; r=-0.377, p=0.01; r=-0.365, p=0.012).
The inferior longitudinal fasciculus connects occipital and temporal cortex, and is the main component of the visual-limbic pathway that subserves emotional, learning and memory functions that are modality specific to vision.
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.
Corporal Punishment
Corporal Punishment

Right Medial Medial Prefrontal Cortex (BA10)
Left medial frontal gyrus (DLPFC) (BA9)
Right anterior cingulate gyrus (BA24)

Harsh Corporal Punishment

Cortical pain pathway

ACC

IPL

STG

Control

Corporal Punishment

L
Joseph LeDoux

- Hippocampus: Memory About the Emotion, Consciously Accessible, Conscious Thought
- Amygdala: Emotional Memory, Consciously In-accessible, Brain Activity & Bodily Response
Partners in Fear

- **Hippocampus**
- **Amygdala**
- **Medial Prefrontal Cortex**

Steps:
- Emotional Stimulus → Amygdala
- Emotional Responses
- Context → Amygdala
- Regulation → Amygdala
Thoughts can activate the amygdala

Thoughts are less effective in turning the amygdala off

Fear and Anxiety

Joseph LeDoux
(From: LeDoux 1994)
Fear Circuit

- Sensory Cortex
- Prefrontal Cortex
- Hippocampus
- Thalamus
- Amygdala
  - Arcuate Fasciculus
  - Cortical pain pathway
  - Inferior Longitudinal Fasciculus
- Visual Cortex
- Auditory Cortex
- Hypothalamus
- Pituitary
- Locus ceruleus
- Norepinephrine
- Autonomic Nervous System
- Cortisol
Pathway through which thoughts activate limbic system structures and produce the various behavioral and autonomic manifestations of emotion.
• Autobiographical memory
• Self versus non-self representation
• Self-referential judgements
• First- versus third-person perspective
• Perceived agency
• Mind reading/social cognition.
The mammalian brain has evolved to be sculpted by early experience, and adverse stressful early experience has been a routine part of our ancestry.

Is it plausible that the developing brain never evolved to cope with exposure to stress or maltreatment and is damaged in a non-adaptive manner?
The counterintuitive but logical alternative is that exposure to early stress produces a cascade of molecular and neurobiological effects that alters neural development in an adaptive way that prepares the adult brain to survive and reproduce in what it predicts will be a malevolent world.

Psychosocial acceleration, other adaptations?
In contrast, we hypothesize that adequate nurturing and absence of intense early stress permits our brains to develop in a manner that is less aggressive, more emotionally stable, social, empathic, and hemispherically-integrated. We believe that this enhances the ability of social animals to build more elaborate social structures and enables humans to better realize their creative potentials.

This may be more the exception than the rule.