Impact of Childhood Maltreatment on Brain Development and the Critical Importance of Distinguishing Between Maltreated and Non-Maltreated Diagnostic Subtypes

Maltreatment and Trauma Studies Support

**NIMH**
- RO1 MHT3636 (1997-2001)
- RO1 MH66222 (2003-2008)
- RO1 MH91391 (2010-2015)
- RO3 MH113077 (2017-2019)

**NIDA**
- RO1 DA16934 (2003-2007)

**NICHD**
- RO1 HD079484 (2015-2020)

**Harvard Catalyst**
- (2010-2011)
- (2015-2016)

**NARSAD**
- (2005-2007)

**PRIVATE DONORS**
- Simches Family
- Susan Miller

Information

I post the slides for my talks at -
https://drteicher.wordpress.com/

I can be reached at -
martin_teicher@hms.harvard.edu
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 Felitti 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).
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

The Year Was 1984 And It All Began With Three Patients


Challenging the Prevailing Model

Challenging the Prevailing Model
Study 1.

Childhood Abuse and Limbic Irritability

To explore the potential relationship between early abuse and limbic system dysfunction, we devised a self-report questionnaire, the Limbic System Checklist-33 (LSCL-33), which ascertains the frequency with which patients experienced symptom often encountered during seizures in patients with temporal lobe epilepsy (psychomotor or limbic seizures).

**Limbic System Checklist (LSCL-33)**

In the following questions, you will be asked how often you experience certain symptoms. To help you in selecting the best answer, the following guidelines are provided. If you have never experienced a certain symptom, or are not sure if you have experienced it, check NEVER. If you have experienced a symptom, but only a very few times in your entire life (e.g., 1 to 3 times), check RARELY. If you have experienced a symptom more than a few times, but not regularly, or with disturbing frequency, check SOME TIMES. If you have experienced the symptom with some regularity, consistency, or disturbing frequency check OFTEN.

### Paroxysmal Somatic Disturbances

#### Brief Hallucinatory Events

B. How often have you experienced - for no particular reason:

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Most of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Flashing lights - either white or colored</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>10. Seeing patterns or geometric shapes</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>11. Seeing fully formed shapes such as a person in a doorway, a demon, a God-like image</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>12. Hearing a ringing or a throbbing sound</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>13. Hearing a voice calling your name</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>14. Hearing a voice repeating a sentence or phrase</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>15. Feeling a metallic or foul taste in your mouth</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>16. Smelling an odor such as ammonia, burning rubber, decaying waste, or garbage</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>17. Smelling an overpowering or understandably sweet smell</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
</tbody>
</table>

#### Limbic System Checklist (LSCL-33)

C. How frequently have you had unexplained or uncontrolled episodes in which you experienced or engaged in:

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Most of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. Complex automatic behavior - such as purposeless humming in corners, passing window or picking at one's clothes</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>19. Turning your hand, looking over your shoulder, sensing your surroundings</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>21. Twitching or jerking of the arms or legs</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>23. Tremendous weakness in the arms or legs, possibly resulting in falling to one side</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
</tbody>
</table>

#### Automatisms

- An object or person suddenly became distorted or transformed
- An object or person suddenly looked smaller, farther away, or out of reach
- An object or person suddenly looked larger, closer or lowered over you
Dissociative Disturbances

Limbic System Checklist (LSCL-33)

The ability of the instrument to detect ictal symptoms suggestive of TLE was ascertained by comparing a group of normal adult control subjects (n=10) without psychiatric or neurological abnormalities (or childhood abuse histories) to patients with well documented TLE responsive to anticonvulsants (n=8). Normal controls invariably had total scores <10, while patients with documented TLE had scores >23 (range 23-60).

Childhood Abuse and Limbic Irritability

McLean -- Adult Outpatient Clinic

<table>
<thead>
<tr>
<th>HISTORY</th>
<th>No Abuse</th>
<th>Physical</th>
<th>Sexual</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>109</td>
<td>77</td>
<td>26</td>
<td>41</td>
</tr>
<tr>
<td>%</td>
<td>38%</td>
<td>49%</td>
<td>113%</td>
<td></td>
</tr>
</tbody>
</table>

p < 0.0001
Abuse History | N | % Female | Age | VIQ | PIQ
---|---|---|---|---|---
Non-abused group | 27 | 26% | 13.5 | 102 | 104
Any abuse | 77 | 60% | 12.8 | 100 | 104
Psychological | 22 | 41% | 12.9 | 100 | 109
Phys./Sexual (all) | 55 | 67% | 12.8 | 99 | 102
Phys./Sexual (severe) | 38 | 68% | 13.0 | 87 | 102

Early Abuse and EEG Abnormalities in Children

- Abused and non-abused patients differed most clearly in the prevalence of left-sided frontal or temporal abnormalities ($p = 0.036$). They did not differ in either the prevalence of right-sided abnormalities ($p > 0.8$), or bilateral abnormalities ($p > 0.5$).

- EEG abnormalities were associated with a greater likelihood of self-destructive behavior and suicidal thinking.
The previous study provided evidence that childhood abuse was predominantly associated with left-sided EEG and neuropsychological abnormalities.

We then sought to ascertain whether abuse affected the maturation (differentiation) of the left and right cortex.

EEG coherence is a parameter that indicates the degree of synchrony ("shared activity" or interconnectivity) between two EEG leads across a portion of the bandwidth (Thatcher et al 1987; 1992). Highly developed local cortical connections modify the EEG signal under the lead and decrease coherence between leads. In most instances, abnormally elevated levels of coherence are an indication of inadequate cortical development or maturation.

Further, coherence decreases as EEG leads are moved further apart. The rate of decay of coherence over distance is a direct index of the complexity and differentiation of local cortical connections (Thatcher et al 1986). Hence, combined assessment of EEG coherence and coherence decay provides an objective measure of cortical maturation and differentiation.

Fifteen child or adolescent inpatients (10.7±2.5 yr, 7M:8F) with a history of intense physical or sexual abuse, (confirmed by the Mass. Dept. of Social Services). Controls were 15 healthy volunteers. All subjects were between 6 to 15 years of age, right handed with no history of neurological disorders nor abnormal intelligence.

We first sought to ascertain whether there was any evidence for asymmetric cortical development (Teicher et al., 1997; Ito et al., 1998).
Abused children had greater average left hemisphere coherence than normal children (p=0.007), but a comparable degree of right hemisphere coherence (p>0.7).

- EEG coherence declined at a more gradual rate across electrode distance in the left hemisphere of subjects with a history of early abuse (p < 0.05).

- Normal controls had a 16.3% greater rate of coherence decay in their left vs right hemisphere, while abused subjects had a 6.8% lower rate of coherence decay in their left vs. right hemisphere (p < 0.04).
This suggests that the left hemisphere of abused subjects was more poorly developed (differentiated) than the left hemisphere of controls. Also, the left hemisphere of abused children was less developed than their own right hemisphere, which was opposite to the pattern found in healthy controls.

**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?*
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.
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

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 Exposure Periods

Volume Mid Anterior Portion of Corpus Callosum - Females

Volume Central Portion of Corpus Callosum - Females

Volume Mid Posterior Portion of Corpus Callosum - Males

Volume Posterior Portion of Corpus Callosum - Males

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.

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.

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
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
**Amygdala**

- The amygdala is a key limbic structure that is critically involved in encoding of implicit emotional memories and in detecting and responding to salient stimuli such as facial expressions and potential threats.

**Amygdala**

- Structural or functional abnormalities in the amygdala have been observed in a wide array of psychiatric disorders including: post-traumatic stress disorder, social phobias and specific phobias; unipolar and bipolar depression; drug addiction; autism; borderline personality disorder and schizophrenia.

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**Amygdala**

Exposure to stress leads to:

- Persistent neuronal hypertrophy and symptoms of anxiety
- Does not reverse with time
- Does not abate with prefrontal cortical development

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**Childhood Abuse and the Amygdala**

Result of studies assessing maltreatment and amygdala volume are inconsistent 41 studies, N ~ 5074.

- Significant decrease: 14 studies
- Non-significant decrease: 11 studies
- No difference: 6 studies
- Non-significant increase: 4 studies
- Significant increase: 6 studies
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)

Karlen Lyons-Ruth, Ph.D.
30 Year Longitudinal Study of Attachment - Karlen Lyons-Ruth

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.

Sensitive Periods

Windows of Vulnerability

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

Childhood Abuse and the Amygdala

Result of studies assessing maltreatment and amygdala volume are inconsistent: 41 studies, N ~ 5074.

- Significant decrease: 14 studies
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- Significant increase: 6 studies

Interactive Effects of Early and Later Stress on Amygdala Volume
Fear Circuit Regions & Pathways

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

**Hippocampus**

The hippocampus is a key limbic structure that is critically involved in the formation and retrieval of explicit memories, including autobiographical memories.

The hippocampus also contains place cells, which along with grid cells in the interconnecting entorhinal cortex, provide an internal positioning system for the spatiotemporal representation of places, routes, and associated experiences.

Hippocampal abnormalities have been reported in several different psychiatric disorders including: post-traumatic stress disorder, major depression, schizophrenia, bipolar disorder and borderline personality disorder.
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

Carl M. Anderson Ph.D.

Stress & Hippocampus

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

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
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.

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.


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

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

Verbal Abuse
*!#$^&@

Childhood Sexual Abuse

Sticks and stones may break my bones, but words will never hurt me.

WRONG!!!
Effects of Verbal Abuse on Brain Structure

Fiber tracts (white matter) using diffusion tensor imaging.

Gray matter analyzed using voxel based morphometry.

Childhood Abuse Targets Sensory Systems

Visual Evoked Potential

Auditory Oddball
Fear Circuit Regions & Pathways

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

Fear regulatory circuits

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

Avon Longitudinal Study of Parents and Children

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

**Threat Detection and Response System**

*Sensitive Periods for the Different Components*

- dACC
- Ventromed PFC
- Thalamus
- Vis Ctx
- Hippocampus
- R Amygdala
- Ventromed PFC
- Inferior Long. Fasciculus
- Thalamus
- dACC
- Hippocampus
- L. Amygdala

**Age of Exposure (years)**

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

---

**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.
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

- 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 centrality parameters of a handful of cortical regions differed substantially between the network for maltreated subjects versus the network for non-maltreated individuals.

The greatest centrality differences between networks was observed in the left anterior cingulate gyrus and sulcus.
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\(^2\).

Brain Fiber Tract Network

- Nodes -> Regions
  - AAL (Automated Anatomical Labeling) template
    - 90 regions from cerebrum using the anatomically labeled template by Tzourio-Mazoyer et al. (Neuroimage, 2002)

- Edges -> Fiberstreams
  - Diffusion tensor imaging (DTI)
  - Tractography

Edges

Number of fiberstreams connecting 2 regions

Left Fusiform & Left superior temporal gyrus
Global Network Measures

- N=262 (102M/160F; 18-25 years)

Brain network architecture needs to balance the opposing demands of integration and segregation in order to combine the presence of functionally specialized and segregated modules with a robust number of connecting links. This tradeoff is reflected in the small-worldness properties of the network, which reflect the ratio of the local clustering coefficient to overall pathlength.

Brain Fiber Tract Networks

The greater small-worldness in maltreated individuals is a consequence of preserved local modular architecture but lower connectivity between modules. This, in turn, makes the maltreated network more vulnerable to abnormalities occurring within a node or module.

Ecophenotypes

Jacqueline Samson, Ph.D.
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.


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 HDRS17, 17-item Hamilton Rating Scale for Depression


**Ecophenotypes**

Autoimmune
Metabolic
Cardiovascular (Mirgaine)
Inflammation

**Ecophenotypes**

Hippocampal & Amygdala Differences

**Inflammation and Non-Response to Antidepressants**

<table>
<thead>
<tr>
<th>Number of Molecules (IL-1β or MIF)/μg Total RNA</th>
<th>IL-1β ≤ 50 × 10⁶</th>
<th>50 × 10⁶ &lt; IL-1β ≤ 85 × 10⁶</th>
<th>IL-1β &gt; 85 × 10⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIF ≤ 60 × 10⁶</td>
<td>Responder probability &gt; 0.99 Nonresponder probability &lt; 0.001</td>
<td>Responder probability &gt; 0.82 Nonresponder probability &lt; 0.13</td>
<td>Responder probability &gt; 0.39 Nonresponder probability &lt; 0.61</td>
</tr>
<tr>
<td>60 × 10⁶ &lt; MIF ≤ 95 × 10⁶</td>
<td>Responder probability &gt; 0.24 Nonresponder probability &lt; 0.72</td>
<td>Responder probability 0.001-0.99 Nonresponder probability &gt; 0.18</td>
<td>Responder probability &gt; 0.82 Nonresponder probability &gt; 0.18</td>
</tr>
<tr>
<td>MIF &gt; 95 × 10⁶</td>
<td>Responder probability &gt; 0.97 Nonresponder probability &gt; 0.99</td>
<td>Responder probability &gt; 0.26 Nonresponder probability &gt; 0.27</td>
<td>Responder probability &gt; 0.81 Nonresponder probability &gt; 0.39</td>
</tr>
</tbody>
</table>

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.

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.
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)

Fig 2. Change in PTSD symptom severity (Total CAPS score) as a function of treatment condition.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0166752
Summary

Decreased hemispheric Integration

Richard P. Kluft, M.D.
Catherine G. Fine, Ph.D.

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>Wake After Sleep Onset</td>
<td>7.85</td>
<td>0.009</td>
<td>0.75</td>
</tr>
<tr>
<td>Total Sleep Time</td>
<td>1.51</td>
<td>0.23</td>
<td><strong>3.52</strong></td>
</tr>
<tr>
<td>Number of Awakenings</td>
<td>4.69</td>
<td>0.04</td>
<td>0.73</td>
</tr>
<tr>
<td>Duration of Awakenings</td>
<td>4.41</td>
<td>0.05</td>
<td>0.38</td>
</tr>
</tbody>
</table>

## Subcortical Regions

<table>
<thead>
<tr>
<th>Measure</th>
<th>Effect of Maltreatment</th>
<th>Sig. Mediated by Sleep Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Putamen</td>
<td>-0.538**</td>
<td></td>
</tr>
<tr>
<td>Right Hippocampus</td>
<td>-0.525**</td>
<td>-0.243 46%</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>
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<tr>
<td>Left CA1</td>
<td>-0.480**</td>
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<tr>
<td>Right Hippocampal molecular layer</td>
<td>-0.479**</td>
<td>-0.203 42%</td>
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<tr>
<td>Left Amygdala</td>
<td>-0.471**</td>
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</tr>
<tr>
<td>Right presubiculum</td>
<td>-0.461**</td>
<td>-0.250 54%</td>
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<tr>
<td>Left Hippocampal molecular layer</td>
<td>-0.455**</td>
<td>-0.222 49%</td>
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<tr>
<td>Left Hippocampus</td>
<td>-0.428*</td>
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</table>

### 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

Preliminary Data - 11 subjects completed mindfulness-based training, 13 waiting list controls.
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 ($p < 0.001$).

Effects of abuse at 4-7 years on prediction for HDRS$_{17}$, 17-item Hamilton Rating Scale for Depression


Anti-inflammatories???
1. Childhood maltreatment is associated with marked effects on brain morphology, function and network architecture.

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. Sensitive periods are present throughout childhood but different brain regions are affected at different times. Hence, the effects of exposure to abuse and neglect are complex and can vary markedly from individual to individual.

5. 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.

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

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

8. Maltreatment is associated with marked effects on sensory processing systems.

9. Parental verbal abuse was associated with alterations in gray matter volume in auditory cortex and reduced integrity of the arcuate fasciculus.

Take Home Messages

10. Visually witnessing domestic violence was associated with alterations in GMV in visual cortex and reduced integrity of the inferior longitudinal fasciulus.

11. Childhood sexual abuse in females was associated with thinning of somatosensory cortex representing clitoris and surrounding genital area.

Take Home Messages

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

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

Take Home Messages

14. Maltreated individuals appear to respond much more poorly to first-line treatments than non-maltreated individuals with the same primary DSM diagnosis.
15. Recognizing this ecophenotypic variation may be crucial in advancing our mission to understand the biological basis of mental illness and to discover and develop effective means of preventing, preempting or treating these disorders.

Society reaps what it sows in nurturing its children. Whether abuse of a child is physical, psychological, or sexual, it sets off a ripple of hormonal changes that wire the child’s brain to cope with a malevolent world. It predisposes the child to have a biological basis for fear, though he may act and pretend otherwise.

Efforts to reduce exposure to childhood abuse and neglect have far reaching impact on brain development and medical and psychiatric health.