Brain structural and functional sequelae of early life adversity

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Maltreatment and Trauma Studies Support

NIMH
RO1 MHT3636 (1997-2001)
RO1 MH66222 (2003-2008)
RO1 MH91391 (2010-2015)

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
Information

The content of this talk is covered in detail in the following review articles.


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?
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.

<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>1.132</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>

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%‡</td>
<td>--</td>
</tr>
<tr>
<td>2 (genu)</td>
<td>--</td>
<td>--</td>
<td>-29.2%§</td>
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</tr>
<tr>
<td>3 (rostral body)</td>
<td>--</td>
<td>--</td>
<td>-33.2%¶</td>
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<td>--</td>
</tr>
<tr>
<td>4 (ant. midbody)</td>
<td>-9.6%‡</td>
<td>--</td>
<td>-30.7%/#</td>
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<td>--</td>
</tr>
<tr>
<td>5 (post. midbody)</td>
<td>--</td>
<td>--</td>
<td>-40.2%∥</td>
<td>1.5%†</td>
<td>--</td>
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<tr>
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<td>--</td>
<td>-18.3%†</td>
<td>-24.2%∂</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

†p < 0.10, ‡p < .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


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.

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 Exposure Periods**

- 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.

**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.
Females

Hofer & Frahm's Scheme

Cortical areas related to the parietofrontal mirror system responding to different types of motor acts

Sensitive Exposure Periods

n=115

<table>
<thead>
<tr>
<th>Segment</th>
<th>Cortical Representations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Prefrontal Cortex</td>
</tr>
<tr>
<td>II</td>
<td>Premotor &amp; Supplementary Motor</td>
</tr>
<tr>
<td>III</td>
<td>Primary Motor Cortex</td>
</tr>
<tr>
<td>IV</td>
<td>Primary Sensory Fibers</td>
</tr>
<tr>
<td>V</td>
<td>Temporal Gyrus, Parietal, Occipital</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Volume Mid Posterior Portion of Corpus Callosum - Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recalled Ages of Exposure (years)</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>1</td>
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<td>2</td>
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<tr>
<td>18</td>
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Hofer & Frahm’s Scheme

Males

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Cortical areas related to the parietofrontal mirror system responding to different types of motor acts
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.
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.

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

**Emotional Stimulus** → **Amygdala** → **Emotional Responses**

**Hippocampus**

**Medial Prefrontal Cortex**

**Cortisol**

**Norepinephrine**

**Autonomic Nervous System**

**ACTH**

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**Influence of Childhood Maltreatment on Threat Response System**

- Unchanged (or not studied)
- Increased
- Decreased

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**Threatening Stimuli**

- Sensory Cortex
- Prefrontal Cortex
- Amygdala
- Hippocampus
- Thalamus
- Cortex

(From: LeDoux, 1994)

Childhood Abuse and the Amygdala

Introduction:

Exposure to stress leads to:

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

Fear Circuit Regions & Pathways

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

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.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Adjusted Amygdala Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1200</td>
</tr>
<tr>
<td>ELS</td>
<td>1400</td>
</tr>
</tbody>
</table>

3.8% increase bilaterally p < 0.04

<table>
<thead>
<tr>
<th>Groups</th>
<th>Adjusted Amygdala Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2000</td>
</tr>
<tr>
<td>ELS</td>
<td>1800</td>
</tr>
</tbody>
</table>

Sensitivity Periods

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.

Two Critical Developmental Threats

1. Rejection/Neglect - Left Amygdala - Infancy
2. Abuse - Right Amygdala - Preadolescence

<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 - Approach

2. Abuse - Right Amygdala - Preadolescence - Withdrawal

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

Does exposure to stress from birth thru 11 years of age sensitize 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
Preclinical studies have shown that environmental experiences (for example, being in an enriched environment) that lead to behavioural 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

**Increased Versus Decreased Amygdala Volume**

Does it imply opposite effects on function?

**Hippocampus**

• Suppress neurogenesis in the dentate gyrus
• Provoke the remodeling of dendrites in the *Cornu Ammonis*, particularly CA3
• Effects may be reversible with time

**Childhood Abuse and the Hippocampus**

Result of studies assessing maltreatment and hippocampal volume are pretty consistent in adults 47 studies, N ~ 5074.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
</tr>
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<tbody>
<tr>
<td>Significant decrease</td>
<td>32</td>
</tr>
<tr>
<td>Non-significant decrease</td>
<td>6</td>
</tr>
<tr>
<td>No difference</td>
<td>9</td>
</tr>
<tr>
<td>Non-significant increase</td>
<td>0</td>
</tr>
<tr>
<td>Significant increase</td>
<td>0</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.

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

Hippocampal Subfields

Types of Maltreatment with Significant Importance During Specific Years

**Males**
- Physical Neglect
- Emotional Neglect

**Females**
- Non-verbal Emotional Abuse
- Physical Abuse
- Witnessing Interparental Violence
- Witnessing Violence to Siblings
- Sexual Abuse
### Hippocampus - Sensitive Period

![Graph showing recall ages of exposure years](image)

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

<table>
<thead>
<tr>
<th>Gender</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>4.3%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Males</td>
<td>16.8%</td>
<td>11.4%</td>
</tr>
</tbody>
</table>

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### Corpus Callosum

#### Males

<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%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>-9.6%†</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 (spleenium)</td>
<td>--</td>
<td>-18.3%†</td>
<td>-24.2%ζ</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

#### Females

<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>-20.6%ζ</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2 (genu)</td>
<td>--</td>
<td>--</td>
<td>-29.7%ζ</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3 (rostral body)</td>
<td>--</td>
<td>--</td>
<td>-17.7%ζ</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4 (ant. midbody)</td>
<td>--</td>
<td>--</td>
<td>+37.6%ζ</td>
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<tr>
<td>5 (post. midbody)</td>
<td>--</td>
<td>--</td>
<td>-43.9%†</td>
<td>+5.2%ζ</td>
<td>--</td>
</tr>
<tr>
<td>6 (isthmus)</td>
<td>--</td>
<td>--</td>
<td>-23.7%ζ</td>
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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?

Jeewook Choi  
M.D., Ph.D.

Akemi Tomoda  
M.D., Ph.D.
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.
Witnessing Domestic Violence

Childhood Sexual Abuse

Effects of Specific Types of Abuse on Brain Structure

Fiber tracts (white matter) using diffusion tensor imaging.

Gray matter analyzed using voxel based morphometry.
Fear Circuit Regions & Pathways

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

Joseph LeDoux

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

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**

<table>
<thead>
<tr>
<th>Age of Exposure (years)</th>
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<tbody>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

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

---

**Corporal Punishment**

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


Results: ROI analyses also indicated increased T2-RT in dorsolateral prefrontal cortex, nucleus accumbens, substantia nigra and thalamus, but not globus pallidus or cerebellum.
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.


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

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Precuneus

- Autobiographical memory
- Self versus non-self representation
- Self-referential judgements
- First- versus third-person perspective
- Perceived agency
- Mind reading/social cognition.

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).

Anterior Insula Cortex

Stimuli that activate the right anterior insular cortex are generally arousing to the body (for example, pain).

The left anterior insular cortex is activated mainly by positive and affiliative emotional feelings (e.g., mothers viewing photos of their child, maternal and romantic love, seeing or making a smile, attended to happy voices, hearing pleasant music, experiencing joy).
Mindfulness-Based Stress Reduction

Diane Yan, Ph.D. and Sarah Lazar, Ph.D.

Mindfulness-based training versus waiting list control

Pre and post measures:
symptoms
hippocampal volume
hippocampal cognitive task
functional connectivity

Mindfulness-Based Stress Reduction

Preliminary Data - 11 subjects completed mindfulness-based training, 13 waiting list controls.
Mindfulness-Based Stress Reduction

Preliminary Data - 11 subjects completed mindfulness-based training, 13 waiting list controls.

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

Take Home Messages

1. Childhood maltreatment is associated with marked effects on brain morphology, function and 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 affects of exposure to abuse and neglect are complex and can vary markedly from individual to individual.

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

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

5. 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.

6. The impact of maltreatment on trajectories of brain development provides a strong signal that appears in many instances to be much larger than signals associated with psychopathology per se.

9. Childhood maltreatment is associated with structural and functional alterations in key components of reward system.

10. Diminished anticipatory reward response and increased threat detection may have marked influence on approach-avoidance, and increase risk for depression and substance abuse.
11. There are silent periods between time of exposure and emergence of discernible brain differences and psychiatric symptoms.

12. Because of these silent periods one cannot conclude that an abused or neglected child was unaffected even if they are currently asymptomatic.

The End

Thank you!