Childhood Abuse, Brain Development and Psychopathology

Martin H. Teicher, M.D., Ph.D.
Department of Psychiatry, Harvard Medical School
Developmental Biopsychiatry Research Program
McLean Hospital, Belmont MA 02478

Jaap Chrisstoffels Visiting Professorship

In cooperation with the
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Department of Child Psychiatry
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The University of Amsterdam

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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.


Introduction

- 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

Hypothesis

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
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

Exposure to stress leads to:

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

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

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

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

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**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.

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3.8% increase bilaterally p < 0.04
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 - Approach

2. Abuse - Right Amygdala - Preadolescence

Amygdala Volume - Complex Interaction Between Early and Later Periods of Exposure
Interactive Effects of Early and Later Stress on Amygdala Volume

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.

Fear Circuit Regions & Pathways

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

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

Amygdala Volume – Is Bigger Better?

Does small/large imply opposite effects on function?

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Similarly, increases or decreases in amygdala volume may be strongly dependent on the ages of exposure to maltreatment but result in comparable consequences.
Stress & Hippocampus

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

Carl M. Anderson Ph.D.

Childhood Abuse and the Hippocampus

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

- Significant decrease: 32 studies
- Non-significant decrease: 6 studies
- No difference: 9 studies
- Non-significant increase: 0 studies
- Significant increase: 0 studies

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\textsuperscript{164}.

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?

Witnessing Domestic Violence

Verbal Abuse

*!#%^&@
Childhood Sexual Abuse

Effects of Verbal Abuse on Brain Structure

Fiber tracts (white matter) using diffusion tensor imaging and tract-based spatial statistics (TBSS).

Gray matter analyzed using voxel based morphometry (VBM).

Fear Circuit Regions & Pathways

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

They are important in
Planning and anticipating outcomes.
Self-monitoring and self-awareness - necessary for appropriateness of behavior.

Prefrontal Cortex

The frontal lobes are important for
- Attention
- Executive Function
- Working Memory
- Motivation
- Behavioral Inhibition.

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

Corporal Punishment

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

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

Kyoko Ohashi, Ph.D.
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.

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.

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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).

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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


Ecophenotypes

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

Ecophenotypes

ELS+ and ELS– individuals with the same primary DSM-5 diagnosis are clinically, neurobiologically and genetically distinct.
Depression with Early Trauma/Loss

Effects of abuse at 4-7 years on prediction for HDRS17, 17-item Hamilton Rating Scale for Depression

Nemeroff et al., Proceedings of the National Academy of Science, 2003, 100(24): 14293–14296


Ecophenotypes

Autoimmune
Metabolic
Cardiovascular
(Migtaine)
Inflammation

Hippocampal
& Amygdala
Differences
Ecophenotypes

Major Depression
Hippocampal Volume
Amygdala Response Sad Faces
Network Architecture

Bipolar Disorder
Corpus Callosum and white matter abnormalities
Inferior frontal gyrus

Schizophrenia
Dorsolateral PFC and thalamus
Inferior frontal gyrus
Insula and thalamus

Ecophenotypes - Schizophrenia and Bipolar Disorder

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.

No differences were observed in GMV between SCZ, BPD and HC in low ACE subjects.

Ecophenotypes - Schizophrenia and Bipolar Disorder

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

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.

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.

How Does Maltreatment Get Under the Skin?

- Epigenetics
- Neuroinflammation
- Sleep Deprivation
Epigenetics

DNA methylation
Methyl markers added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the ‘tails’ of proteins called histones. These alter the activity of the DNA wrapped around them.

Mechanisms Linking Childhood Maltreatment To Mood Dysregulation in Adolescence

Preliminary Data
N = 38 (18-19 years)
N = 16 Unexposed
N = 22 Maltreated (without PTSD)

Ecological Momentary Assessment
Actigraphy (sleep)
3T MRI
Epigenetics (FKBP5, NR3C1)
Neuroinflammation (C reactive Protein, IL6)

FKBP5

Increased methylation in Introns 7 bin 1 CG1 with maltreatment.

Significant inverse correlation (-0.4 - -0.6) with GMV in CA3, CA4 and DG of hippocampus.

Significant inverse correlation (-0.5 - -0.7) with GMV in components of insula.
Neuroinflammation

Briefly, pro-inflammatory cytokines reduce the availability of serotonin, dopamine, norepinephrine and brain-derived neurotrophic factor (BDNF) through multiple mechanisms.

Activated microglia convert kynurenine into quinolinic acid, which binds to the N-methyl-d-aspartate (NMDA) receptor.

Cytokine effects on the dopamine system can inhibit several aspects of reward motivation leading to anhedonia and psychomotor retardation by targeting striatum, ventromedial PFC and anterior cingulate cortex.

Cytokines also activating threat detection circuits regulating anxiety, arousal, alarm and fear including amygdala, hippocampus and insula.
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).
Subcortical Regions

<table>
<thead>
<tr>
<th>Measure</th>
<th>Effect of Maltreatment</th>
<th>Significantly Mediated by Sleep Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Putamen</td>
<td>-0.538***</td>
<td>ab % Total</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>
<td></td>
</tr>
<tr>
<td>Left Pallidum</td>
<td>-0.497***</td>
<td></td>
</tr>
<tr>
<td>Right CA4</td>
<td>-0.497***</td>
<td></td>
</tr>
<tr>
<td>Left Dentate Gyrus</td>
<td>-0.488***</td>
<td></td>
</tr>
<tr>
<td>Left CA1</td>
<td>-0.480***</td>
<td></td>
</tr>
<tr>
<td>Right Hippocampal molecular layer</td>
<td>-0.479***</td>
<td>-0.203 42%</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>-0.471***</td>
<td></td>
</tr>
<tr>
<td>Right presubiculum</td>
<td>-0.461***</td>
<td>-0.25 54%</td>
</tr>
<tr>
<td>Left Hippocampal molecular layer</td>
<td>-0.455***</td>
<td>-0.222 49%</td>
</tr>
<tr>
<td>Left Hippocampus</td>
<td>-0.428*</td>
<td></td>
</tr>
</tbody>
</table>

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)
Cerebellar
vermis
a.k.a.
arborvitae
“the tree of
life”

Harlow’s Surrogate Mother Studies

- William Mason (1968), working with Harlow, found that a lack of somatosensory stimulation (especially vestibular proprioception) was the ingredient responsible for disturbed behavior in sensory-isolated monkeys.

- James Prescott (1971) proposed that early vestibular stimulation was important in the development of appropriate emotional behavior.

From Harlow, “The nature of love.” American Psychologist 13;673-85, 1958
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 training versus waiting list control

Pre and post measures:
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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 HDRS17, 17-item Hamilton Rating Scale for Depression

Anti-inflammatories???

Take Home Messages

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

2. 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.

Take Home Messages

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

4. These different components have their own unique sensitive periods so that maltreatment at different ages will target this circuit - but in different ways.
5. Childhood maltreatment is associated with structural and functional alterations in key components of reward system.

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

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

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

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.

10. Epigenetic changes, sleep problems and inflammation are factors may mediate or amplify the effects of maltreatment.

11. Epigenetic changes, sleep problems and inflammation may be key factors that if addressed may help to reduce the adverse consequence of childhood maltreatment.
Maltreatment and Trauma Studies Support

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

NIDA
RO1 DA16934 (2003-2007)  

NICHHD
RO1 HD079484 (2015-2020)

NARSAD
(2005-2007)

PRIVATE DONORS
Simches Family  
Susan Miller

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

Developmental Biopsychiatry Research Program

The End
Thank you!