The Neurobiological Impact of Childhood Maltreatment and Substance Abuse

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“L’ENJEU DES COMORBIDITÉS DANS LES ADDICTIONS”
“COMORBIDITIES IN ADDICTIONS: WHAT’S AT STAKE?”

* En attente du renouvellement des accords
Maltreatment and Trauma Studies Support

<table>
<thead>
<tr>
<th>Organization</th>
<th>Grants and Years</th>
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<tbody>
<tr>
<td>NIMH</td>
<td>RO1 MHT3636 (1997-2001)</td>
</tr>
<tr>
<td></td>
<td>RO1 MH66222 (2003-2008)</td>
</tr>
<tr>
<td></td>
<td>RO1 MH91391 (2010-2015)</td>
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<tr>
<td>NIDA</td>
<td>RO1 DA16934 (2003-2007)</td>
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<tr>
<td>NICHD</td>
<td>RO1 HD079484 (2015-2020)</td>
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<tr>
<td>Harvard Catalyst</td>
<td>(2010-2011)</td>
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<tr>
<td></td>
<td>(2015-2016)</td>
</tr>
<tr>
<td>NARSAD</td>
<td>(2005-2007)</td>
</tr>
<tr>
<td>PRIVATE DONORS</td>
<td>Simches Family</td>
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<td></td>
<td>Susan Miller</td>
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</tbody>
</table>

No conflicts of interest to report
Information

I post the slides for my talks at -

https://drteicher.wordpress.com/

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Information

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


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 Fellitti 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

Stress
Hypothesis

Childhood adversity
  - number
  - type

Genetics

Brain development

Age

PTSD

Depression

Medical Disorders

Addiction

Dissociation

Other psych disorders

Cognition
Questions

What brain structures are affected by exposure to childhood maltreatment?

Does the type of maltreatment matter or are they all stressors?

How does maltreatment increase risk for substance use and abuse?
Does the nature of the maltreatment matter?
Hypothesis

Sexual Abuse
Physical Abuse
Witness Domestic Violence
Verbal Abuse

Common consequences relating to the effects of stress, fear, anxiety, humiliation, etc. on the developing brain
Hypothesis

- Sexual Abuse
- Physical Abuse
- Witness Domestic Violence
- Verbal Abuse
Hypothesis

Sexual Abuse

Physical Abuse

Witness Domestic Violence

Verbal Abuse

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

*!#$^&@
Witnessing Domestic Violence
Childhood Sexual Abuse
Effects of Specific Types of 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).
Childhood Abuse Targets Sensory Systems

- Parental verbal abuse:
  - ↑ GMV in auditory cortex
  - ↓ Integrity of left AF

- Witnessing domestic violence:
  - ↓ GMV in V1
  - ↓ Integrity of left ILF

- Childhood sexual abuse:
  - ↓ GMV in V2
  - Thinning of somatosensory cortex

Nature Reviews | Neuroscience
Neurobiology of Addiction

Maltreatment & Addiction

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.
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
Stress & Hippocampus

- Suppresses neurogenesis in the dentate gyrus (DG)
- Provokes remodeling of dendrites in Cornu Ammonis, particularly CA3
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>Result</th>
<th>Number of Studies</th>
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<tr>
<td>Significant decrease</td>
<td>32 studies</td>
</tr>
<tr>
<td>Non-significant decrease</td>
<td>6 studies</td>
</tr>
<tr>
<td>No difference</td>
<td>9 studies</td>
</tr>
<tr>
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<td>0 studies</td>
</tr>
<tr>
<td>Significant increase</td>
<td>0 studies</td>
</tr>
</tbody>
</table>
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
Sensitive Periods
Time is of the essence
Recalled Ages of Exposure (years)

Importance (± SD)

Bilateral Hippocampus - Male

Abuse

Neglect

Males

Females

Hippocampus N=336
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.

Contextual Memory
Prefrontal Cortex
Prefrontal Cortex

The frontal lobes are important for

- Attention
- Executive Function
- Working Memory
- Motivation
- Behavioral Inhibition.
Prefrontal Cortex

They are important in

Planning and anticipating outcomes.

Self-monitoring and self-awareness - necessary for appropriateness of behavior.
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)

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.

Circuits & Networks
Structural connectivity

Functional connectivity

Resting state

fMRI

DTI and fiber tracking

Superior Putamen

Central Thalamus

TrackVis

Autopsy

Caudate Nucleus

Haas, Hodneland, Ystad, Westlye, Eichele, Lundervold, UiB

Zosovic & Apuzzo, 1998
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
(Cortical Thickness)
Large-scale cortical morphometric networks

1. Positive thickness correlations were often associated with convergent diffusion connections across the cerebral cortex

2. This techniques has been used to assess network abnormalities in Alzheimer’s disease, schizophrenia, epilepsy, multiple sclerosis and aging.

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
Structural Connectivity Networks

- Cortical thickness adjusted for race, ethnicity, parental education, parental finances, gender, cortical GMV

- Partial correlations used to assess the degree of interdependence between regional thickness measures across all subjects within a group

- 112 x 112 partial correlation matrix thresholded to provide the lowest equivalent cost networks per group that were fully connected (14% of possible edges)

- Permutation tests were used to ascertain whether maltreatment was associated with alterations in the primary nodal properties (e.g., degree, betweenness, closeness centrality) of specific cortical regions.
Left Anterior Cingulate

Unexposed

Maltreated
Right Precuneus

Unexposed  Maltreated
Right Anterior Insula

Unexposed

Maltreated
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\(^2\).

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).
Left Anterior Cingulate
Reduced control

Unexposed

Maltreated
Right Anterior Insula

Increased craving

Unexposed  Maltreated
Cerebellar vermis
Reward Anticipation
Reward Anticipation

Ventral Striatum - nucleus accumbens and ventral putamen
Reactive Attachment Disorder

Reactive attachment disorder is a rare but serious condition in which an infant or young child doesn't establish healthy attachments with parents or caregivers. Reactive attachment disorder may develop if the child's basic needs for comfort, affection and nurturing aren't met and loving, caring, stable attachments with others are not established.
Reward Response
Reactive Attachment Disorder
Sensitive Exposure Period – RAD

**Right Striatum**

Importance (increase MSE)

Ages of Exposure (years)

**Left Striatum**

Importance (increase MSE)

Ages of Exposure (years)
Don’t anticipate reward...

Expect to be maltreated.
If you experience reward...
Keep at it.
Harsh Corporal Punishment

Increased T2-RT (decreased blood flow) in right putamen
Increased T2-RT (decreased blood flow) in right caudate
**Results:** ROI analyses also indicated increased T2-RT in dorsolateral prefrontal cortex, nucleus accumbens, substantia nigra and thalamus, but not globus pallidus or cerebellum.
### Table 4: Correlations for the relationship between regional T2-RT in dopamine-rich regions and extent of drug and alcohol use.

<table>
<thead>
<tr>
<th>Region</th>
<th>Drug Use</th>
<th></th>
<th>Alcohol Use</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-value</td>
<td>r</td>
<td>p-value</td>
</tr>
<tr>
<td>Anterior Cingulate Cortex</td>
<td>0.406</td>
<td>0.009</td>
<td>0.392</td>
<td>0.012</td>
</tr>
<tr>
<td>Caudate</td>
<td>0.133</td>
<td>0.412</td>
<td>0.089</td>
<td>0.584</td>
</tr>
<tr>
<td>Dorsolateral Prefrontal Cortex</td>
<td>0.416</td>
<td>0.008</td>
<td>0.444</td>
<td>0.004</td>
</tr>
<tr>
<td>Nucleus Accumbens</td>
<td>-0.225</td>
<td>0.163</td>
<td>-0.204</td>
<td>0.206</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.105</td>
<td>0.521</td>
<td>0.067</td>
<td>0.682</td>
</tr>
<tr>
<td>Substantia Nigra</td>
<td>0.140</td>
<td>0.390</td>
<td>0.038</td>
<td>0.814</td>
</tr>
</tbody>
</table>

Values in bold are significant with an overall False Discovery Rate < 0.05
Maltreatment & Addiction

Hyperreactivity
Increased or
Decreased volume

Withdrawal/Negative Affect
Basolateral Amygdala (BLA)
Central Amygdala (CeA)

Amygdala
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.

• 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.
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

Childhood Abuse and the Amygdala

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

<table>
<thead>
<tr>
<th>Change Description</th>
<th>Number of Studies</th>
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<tr>
<td>Significant decrease</td>
<td>12 studies</td>
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<tr>
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<td>11 studies</td>
</tr>
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<td>6 studies</td>
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<tr>
<td>Non-significant increase</td>
<td>3 studies</td>
</tr>
<tr>
<td>Significant increase</td>
<td>9 studies</td>
</tr>
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</table>
Childhood Abuse and the Amygdala

Decreased Volume

Adults with Borderline Personality Disorder or Dissociative Identity Disorder
\textit{(often exposed to very severe abuse)}

Increased Volume

Institutionally-reared children with low degree of attention or children of chronically-depressed mothers
\textit{(often deprived of sufficient attention and affection - emotional neglect)}
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

**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)*
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.
3.8% increase bilaterally $p < 0.04$
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>
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</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
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 Stress on Amygdala Volume
Increased Versus Decreased Amygdala Volume

Does it imply opposite effects on function?

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.
Neurobiology of Addiction

The Cycle of Addiction

Binge/Intoxication
- Dorsal Striatum
- Ventral Tegmental Area
- Cerebellum

Preoccupation/Anticipation
- Prefrontal Cortex (PFC)
- Hippocampus

Withdrawal/Negative Affect
- Basolateral Amygdala (BLA)
- Central Amygdala (CeA)

Delayed Effects
Childhood Abuse and the Hippocampus

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

<table>
<thead>
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<th>Outcome</th>
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<tr>
<td>Significant decrease</td>
<td>32 studies</td>
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<td>6 studies</td>
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</tr>
<tr>
<td>Significant increase</td>
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</table>
Childhood Abuse and the Hippocampus

Result of studies assessing maltreatment and hippocampal volume are inconsistent in children 23 studies, N ~ 1951.

- Significant decrease: 10 studies
- Non-significant difference: 13 studies
Delayed Effects – Silent Period

[Maltreatment and Drug Use graph]

[Drug Use (%) against Age (years) for different levels of maltreatment]

[Binge Drinking graph]

[Drug Use (days/month) against Age (years) for different ACE scores]
The End

Thank you!
Hippocampus & Subiculum

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

*Helps Regulate Dopaminergic Responses*
Ventral subiculum to nucleus accumbens pathway - which then proceeds to ventral pallidum and ventral tegmental area. Regulates tonic firing in the VTA and release of DA in the NA.
Thoughts can activate the amygdala

Thoughts are less effective in turning the amygdala off

Fear and Anxiety

Joseph LeDoux
Fear regulatory circuits

Threat Detection, Response and Recovery
Diagram showing the connections between thalamus, cortex, hippocampus, stimulus, and amygdala. (From: LeDoux 1994)
Influence of Childhood Maltreatment on Threat Response System

Unchanged (or not studied)
- Increased
- Decreased

Threatening Stimuli