Drug addicted mothers show reduced brain reward response to their infants: Can oxytocin reverse the trend?

Dr. Lane Strathearn, MBBS FRACP PhD
Stead Family Professor, Department of Pediatrics, University of Iowa
Director, Division of Developmental and Behavioral Pediatrics, and the Center for Disabilities and Development, University of Iowa Children’s Hospital
Maternal care and addiction

- In 2011, 22.5 million (age 12+), 8.7% of the population, used illicit drug in the past month.

- Drug use is the highest among people in late teens and twenties.

- Almost 90% of drug-abusing women are of reproductive age.

- Maternal addiction is associated with a range of parenting difficulties, including child abuse and neglect.

US Department of Health and Human Services, 2012
Neglect/emotional abuse predicts teenage alcohol use

Table 2 Odds ratios (OR) for any alcohol use (i.e. ever drunk a full glass of alcohol) and heavy alcohol use (five or more drinks in a session or three or more at least monthly) at 14-year follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR (95% CI) (n = 5153)</th>
<th>Adjusted OR* (95% CI) (n = 5153)</th>
<th>Adjusted OR** (95% CI) (n = 5153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No reported maltreatment</td>
<td>1.62 (1.27, 2.06) *&lt;0.001</td>
<td>1.42 (1.10, 1.83) 0.007</td>
<td>1.13 (0.85, 1.50) 0.413</td>
</tr>
<tr>
<td>Any reported maltreatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical abuse only</td>
<td>1.09 (0.45, 2.63) 0.845</td>
<td>1.11 (0.45, 2.71) 0.822</td>
<td>0.79 (0.30, 2.12) 0.641</td>
</tr>
<tr>
<td>Sexual abuse only</td>
<td>0.61 (0.24, 1.53) 0.291</td>
<td>0.52 (0.20, 1.33) 0.171</td>
<td>0.44 (0.16, 1.21) 0.112</td>
</tr>
<tr>
<td>Neglect/emotional abuse</td>
<td>2.91 (1.89, 4.46) *&lt;0.001</td>
<td>2.38 (1.52, 3.74) *&lt;0.001</td>
<td>1.78 (1.06, 2.97) 0.028</td>
</tr>
<tr>
<td>Sexual + 1 or more other</td>
<td>1.60 (0.95, 2.68) 0.077</td>
<td>1.40 (0.82, 2.40) 0.216</td>
<td>1.24 (0.68, 2.25) 0.486</td>
</tr>
<tr>
<td>Physical + neglect/emotional</td>
<td>1.48 (1.01, 2.19) 0.045</td>
<td>1.33 (0.89, 1.99) 0.169</td>
<td>1.05 (0.67, 1.65) 0.819</td>
</tr>
<tr>
<td>Heavy alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No reported maltreatment</td>
<td>2.55 (1.80, 3.61) *&lt;0.001</td>
<td>1.95 (1.34, 2.84) *&lt;0.001</td>
<td>1.36 (0.89, 2.09) 0.890</td>
</tr>
<tr>
<td>Any reported maltreatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical abuse only</td>
<td>0.65 (0.09, 4.76) 0.669</td>
<td>0.61 (0.08, 4.58) 0.634</td>
<td>0.34 (0.04, 2.80) 0.318</td>
</tr>
<tr>
<td>Sexual abuse only</td>
<td>0.86 (0.21, 3.58) 0.838</td>
<td>0.67 (0.16, 2.85) 0.590</td>
<td>0.56 (0.12, 2.69) 0.472</td>
</tr>
<tr>
<td>Neglect/emotional abuse</td>
<td>5.63 (3.27, 9.69) *&lt;0.001</td>
<td>3.82 (2.13, 6.84) *&lt;0.001</td>
<td>2.63 (1.31, 5.26) 0.006</td>
</tr>
<tr>
<td>Sexual + 1 or more other</td>
<td>1.79 (0.77, 4.18) 0.178</td>
<td>1.34 (0.56, 3.24) 0.510</td>
<td>1.00 (0.37, 2.70) 0.999</td>
</tr>
<tr>
<td>Physical + neglect/emo</td>
<td>2.48 (1.45, 4.26) 0.001</td>
<td>1.98 (1.11, 3.50) 0.019</td>
<td>1.37 (0.71, 2.63) 0.349</td>
</tr>
</tbody>
</table>

*Adjusted for: family income, maternal alcohol use and maternal smoking (14-year follow-up); maternal education and marital status (prenatal); and race, age and gender. **Additional adjustment for youth smoking (14-year follow-up). CI = confidence interval.
Neglect/emotional abuse predicts teenage alcohol use

<table>
<thead>
<tr>
<th>Alcoholic use</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR\textsuperscript{a} (95% CI)</th>
<th>Adjusted OR\textsuperscript{b} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No reported maltreatment</td>
<td>1.62 (1.27, 2.06)</td>
<td>&lt;0.001</td>
<td>1.42 (1.10, 1.83)</td>
</tr>
<tr>
<td>Any reported maltreatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical abuse only</td>
<td>1.09 (0.45, 2.63)</td>
<td>0.845</td>
<td>1.11 (0.45, 2.71)</td>
</tr>
<tr>
<td>Sexual abuse only</td>
<td>0.61 (0.24, 1.53)</td>
<td>0.291</td>
<td>0.52 (0.20, 1.33)</td>
</tr>
<tr>
<td>Neglect/emotional abuse</td>
<td>2.91 (1.89, 4.46)</td>
<td>&lt;0.001</td>
<td>2.38 (1.52, 3.74)</td>
</tr>
<tr>
<td>Sexual + 1 or more other</td>
<td>1.60 (0.95, 2.68)</td>
<td>0.077</td>
<td>1.40 (0.82, 2.40)</td>
</tr>
<tr>
<td>Physical + neglect/emotional</td>
<td>1.48 (1.01, 2.19)</td>
<td>0.045</td>
<td>1.33 (0.89, 1.99)</td>
</tr>
<tr>
<td>Heavy alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No reported maltreatment</td>
<td>2.55 (1.80, 3.61)</td>
<td>&lt;0.001</td>
<td>1.95 (1.34, 2.84)</td>
</tr>
<tr>
<td>Any reported maltreatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical abuse only</td>
<td>0.65 (0.09, 4.76)</td>
<td>0.669</td>
<td>0.61 (0.08, 4.58)</td>
</tr>
<tr>
<td>Sexual + 1 or more other</td>
<td>1.79 (0.37, 4.18)</td>
<td>0.178</td>
<td>1.34 (0.56, 5.24)</td>
</tr>
<tr>
<td>Physical + neglect/emotional</td>
<td>2.48 (1.45, 4.26)</td>
<td>0.001</td>
<td>1.98 (1.11, 3.50)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Adjusted for: family income, maternal alcohol use and maternal smoking (14-year follow-up); maternal education and marital status (prenatal); and race, age and gender.\textsuperscript{b} Additional adjustment for youth smoking (14-year follow-up). CI = confidence interval.

Mills, 2013
Neglect/emotional abuse predicts teenage smoking

Table 3 Odds ratios (OR) for any smoking in last week, and heavy smoking (≥10 in week) at 14-year follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR (95% CI) (n = 5154)</th>
<th>Adjusted OR(^a) (95% CI) (n = 5154)</th>
<th>Adjusted OR(^b) (95% CI) (n = 5154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No reported maltreatment</td>
<td>1.00 (P-value)</td>
<td>1.00 (P-value)</td>
<td>1.00 (P-value)</td>
</tr>
<tr>
<td>Any reported maltreatment</td>
<td>2.63 (2.07, 3.35) (&lt;0.001)</td>
<td>1.86 (1.43, 2.41) (&lt;0.001)</td>
<td>1.76 (1.32, 2.34) (&lt;0.001)</td>
</tr>
<tr>
<td>Physical abuse only</td>
<td>2.41 (1.09, 5.32) (0.029)</td>
<td>2.09 (0.92, 4.70) (0.077)</td>
<td>2.28 (0.95, 5.51) (0.066)</td>
</tr>
<tr>
<td>Sexual abuse only</td>
<td>1.61 (0.75, 3.44) (0.222)</td>
<td>1.10 (0.50, 2.43) (0.726)</td>
<td>1.40 (0.58, 3.36) (0.455)</td>
</tr>
<tr>
<td>Neglect/emotional abuse</td>
<td>3.89 (2.50, 6.06) (&lt;0.001)</td>
<td>2.62 (1.64, 4.19) (&lt;0.001)</td>
<td>2.03 (1.20, 3.42) (0.008)</td>
</tr>
<tr>
<td>Sexual + 1 or more other</td>
<td>2.30 (1.36, 3.91) (0.002)</td>
<td>1.47 (0.84, 2.57) (0.173)</td>
<td>1.29 (0.69, 2.42) (0.360)</td>
</tr>
<tr>
<td>Physical + neglect/emotional</td>
<td>2.54 (1.74, 3.71) (&lt;0.001)</td>
<td>1.87 (1.25, 2.79) (0.002)</td>
<td>1.85 (1.19, 2.88) (0.001)</td>
</tr>
<tr>
<td>Heavy smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No reported maltreatment</td>
<td>1.00 (P-value)</td>
<td>1.00 (P-value)</td>
<td>1.00 (P-value)</td>
</tr>
<tr>
<td>Any reported maltreatment</td>
<td>3.76 (2.75, 5.15) (&lt;0.001)</td>
<td>2.43 (1.73, 3.41) (&lt;0.001)</td>
<td>2.36 (1.61, 3.47) (&lt;0.001)</td>
</tr>
<tr>
<td>Physical abuse only</td>
<td>3.00 (1.04, 8.65) (0.041)</td>
<td>2.54 (0.86, 7.52) (0.092)</td>
<td>3.10 (0.94, 10.27) (0.064)</td>
</tr>
<tr>
<td>Sexual abuse only</td>
<td>2.00 (0.71, 5.64) (0.189)</td>
<td>1.28 (0.44, 3.79) (0.646)</td>
<td>1.81 (0.52, 6.27) (0.351)</td>
</tr>
<tr>
<td>Neglect/emotional abuse</td>
<td>4.85 (2.72, 8.66) (&lt;0.001)</td>
<td>2.88 (1.55, 5.33) (&lt;0.001)</td>
<td>2.16 (1.09, 4.31) (0.028)</td>
</tr>
<tr>
<td>Sexual + 1 or more other</td>
<td>3.50 (1.82, 6.74) (&lt;0.001)</td>
<td>2.07 (1.03, 4.15) (0.042)</td>
<td>1.75 (0.78, 3.92) (0.175)</td>
</tr>
<tr>
<td>Physical + neglect/emotional</td>
<td>4.10 (2.59, 6.50) (&lt;0.001)</td>
<td>2.77 (1.69, 4.54) (&lt;0.001)</td>
<td>2.97 (1.68, 5.23) (&lt;0.001)</td>
</tr>
</tbody>
</table>

*Adjusted for: family income, maternal alcohol use and maternal smoking (14-year follow-up); maternal education and marital status (prenatal); and race, age and gender. \(^a\)Additional adjustment for any youth alcohol use (14-year follow-up). CI = confidence interval.

Mills, 2013
Neglect/emotional abuse predicts teenage smoking

<table>
<thead>
<tr>
<th>Any smoking</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR$^a$ (95% CI)</th>
<th>Adjusted OR$^b$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reported maltreatment</td>
<td>1.00 P-value</td>
<td>1.00 P-value</td>
<td>1.00 P-value</td>
</tr>
<tr>
<td>Any reported maltreatment</td>
<td>2.63 (2.07, 3.35)</td>
<td>1.86 (1.43, 2.41)</td>
<td>1.76 (1.32, 2.34)</td>
</tr>
<tr>
<td>Physical abuse only</td>
<td>2.41 (1.09, 5.32)</td>
<td>2.09 (0.92, 4.70)</td>
<td>2.28 (0.95, 5.51)</td>
</tr>
<tr>
<td>Sexual abuse only</td>
<td>1.61 (0.75, 3.44)</td>
<td>1.10 (0.50, 2.43)</td>
<td>1.40 (0.58, 3.36)</td>
</tr>
<tr>
<td>Neglect/emotional abuse</td>
<td>3.89 (2.50, 6.06)</td>
<td>2.62 (1.64, 4.19)</td>
<td>2.03 (1.20, 3.42)</td>
</tr>
<tr>
<td>Sexual + 1 or more other</td>
<td>2.30 (1.36, 3.91)</td>
<td>1.47 (0.84, 2.57)</td>
<td>1.29 (0.69, 2.42)</td>
</tr>
<tr>
<td>Physical + neglect/emotional</td>
<td>2.54 (1.74, 3.71)</td>
<td>1.87 (1.25, 2.79)</td>
<td>1.85 (1.19, 2.88)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heavy smoking</th>
<th>P-value</th>
<th>Adjusted OR$^a$ (95% CI)</th>
<th>Adjusted OR$^b$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any reported maltreatment</td>
<td>&lt;0.001 P-value</td>
<td>2.36 (1.61, 3.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical abuse only</td>
<td>2.43 (1.73, 3.41)</td>
<td>&lt;0.001</td>
<td>3.10 (1.94, 5.02)</td>
</tr>
<tr>
<td>Sexual abuse only</td>
<td>2.54 (1.86, 3.72)</td>
<td>&lt;0.001</td>
<td>3.10 (1.86, 5.23)</td>
</tr>
<tr>
<td>Neglect/emotional abuse</td>
<td>1.56 (1.56, 1.56)</td>
<td>1.28 (0.44, 3.79)</td>
<td>1.29 (0.69, 2.42)</td>
</tr>
<tr>
<td>Sexual + 1 or more other</td>
<td>2.88 (1.55, 5.33)</td>
<td>&lt;0.001</td>
<td>2.97 (1.68, 5.23)</td>
</tr>
<tr>
<td>Physical + neglect/emotional</td>
<td>4.10 (2.59, 6.50)</td>
<td>2.77 (1.69, 4.54)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for: family income, maternal alcohol use and maternal smoking (14-year follow-up); maternal education and marital status (prenatal); and race, age and gender. $^a$Additional adjustment for any youth alcohol use (14-year follow-up). CI = confidence interval.

Mills, 2013
Adverse Childhood Experience (ACE) Study

• Over 17,000 adults retrospectively report adverse childhood experiences, such as:
  - abuse
  - neglect
  - witnessing domestic violence, and
  - serious household dysfunction

• An ACE score, based on the number of adverse conditions experienced in childhood, was linked to current and past medical and psychiatric conditions
Adverse Childhood Experience (ACE) Study

- ACE score was progressively associated with an increased risk of:
  - coronary artery disease
  - chronic pulmonary disease
  - cancer
  - severe obesity
  - **alcoholism**
  - depression and anxiety
  - **drug addiction**
  - sexual promiscuity
  - perpetrating intimate partner violence
ACE Score predicts substance use risk

ACE Score
1
2
3
>=4

Alcoholic
Illicit drug use
Injected drugs

Adjusted Odds Ratio

Felitti, 1998
ADVERSE CHILDHOOD EXPERIENCE

CHILDHOOD NEGLECT

Increased susceptibility to addiction

Impaired maternal brain response and caregiving behavior

ABUSE AND TRAUMA
Possible Mechanisms

1. Cumulative exposures to stressful experiences

2. Latent effects of adversity during sensitive periods of development

What are the molecular and neuroendocrine mechanisms underlying these differences in health and behavioral outcomes?

Shonkoff et al, JAMA (2009)
Maternal Behavior in the Rat

- Pup vocalization
- Licking and grooming
- Arched-back nursing

Champagne, 2003
Frequency Distribution of Time Spent Licking/ Grooming by Lactating Mothers

Champagne, 2003
EPIGENETIC MECHANISMS
are affected by these factors and processes:
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Histones are proteins around which DNA can wind for compaction and gene regulation.

Histone modification
The binding of epigenetic factors to histone “tails” alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.
Epigenetic regulation of infant development – Two Examples

1. Stress Reactivity

2. Maternal Caregiving / Social Behavior
Epigenetic regulation of infant development – Stress Reactivity

• Offspring of High Licking/Grooming Rat Dams
  - DNA methylation of glucocorticoid (stress hormone) receptor (GR) promoter
  - GR gene expression in the hippocampus
  - regulation of stress response (glucocorticoid release)
  - stress/anxiety related behaviors

Epigenetic regulation of infant development – Caregiving behavior

- Offspring of High Licking/Grooming Rat Dams
  - ↓ DNA methylation of estrogen receptor-α (ERα) promoter
  - ↑ ERα gene expression in the brain (MPOA)
  - ↑ oxytocin receptor binding in the MPOA
  - ↑ maternal caregiving/social behaviors (licking/grooming, arched back nursing)

Champagne et al., Endocrinology (2006)
ADVERSE CHILDHOOD EXPERIENCE

CHILDHOOD NEGLECT

Increased susceptibility to addiction

ABUSE AND TRAUMA

RDoC categories

Positive Valence Systems
- Approach motivation & reward valuation
  - Dopamine (DA) System

Social Processes
- Affiliation, attachment & social communication
  - Oxytocin (OT) System

Negative Valence Systems
- Loss or threat (stress)
  - Glucocorticoid (GC) System

Genes/Molecules/Cells

Circuits/Physiology

Behavior/Self-reports

University of Iowa Children’s Hospital
Texas Children’s Hospital
Baylor College of Medicine
ADVERSE CHILDHOOD EXPERIENCE

CHILDHOOD NEGLECT
- Altered DA rec expression and DA production
  - Altered brain reward sensitivity (e.g. striatum)
  - Sensation- or novelty-seeking; risk-taking behavior

ABUSE AND TRAUMA
- Altered OT rec expression and OT production
  - Altered brain sensitivity to social cues (e.g. PFC)
  - Social impairment, isolation and insecure attachment
- Altered GC rec expression and CRF production
  - Altered amygdala activation and HPA stress response
  - Anxiety, depression and trauma symptoms

Increased susceptibility to addiction
Impaired maternal brain response and caregiving behavior
SENSORY INPUT (e.g. child face/cry cues) → ? → MOTOR OUTPUT (e.g. caregiving behavior)
SENSORY INPUT
(e.g. child face/cry cues)

MOTOR OUTPUT
(e.g. caregiving behavior)

(NAC: Nucleus Accumbens)
MOTOR OUTPUT
(e.g. caregiving
behavior)

FOREBRAIN
“Frontal Cortex”

SENSORY INPUT
(e.g. child
face/cry cues)

LIMBIC BRAIN
“Striatum”

MIDBRAIN
“Meso/Nigro…”
**Nigrostriatal Dopamine Pathway:** “Habit Formation”

**Mesocorticolimbic Dopamine Pathway:** “Reward”

**SENSORY INPUT**
(e.g. child face/cry cues)

**HYPO-THALAMUS**

**VENTRAL STRIATUM**

**AMYGDALA**

**VENTRAL TEGMENTAL AREA**

**DORSAL STRIATUM**

**SUBSTANTIA NIGRA**

**DORSOLATERAL PREFRONTAL CORTEX**

**VENTROMEDIAL PREFRONTAL CORTEX**

**MOTOR OUTPUT**
(e.g. caregiving behavior)
Visit 1: Pregnancy

- 3rd trimester: Mother-infant separation 1
  - AAI-DMM
  - Demographics
  - PDQ
  - BDI
  - PANAS (1)
  - Demographics
  - ATQ
  - Infant face images

- CARE-Index: Mirror-based interaction
- 7 mths: Blood draws
  - Oxytocin
  - Cortisol
  - Adrenaline
  - Noradrenaline
  - PANAS (2)
  - IBQ
  - PSI

- 10 mths: Mother-infant separation 2
  - WTAR
  - Breastfeeding duration
  - Hours separated per week

- 14 mths: Bayley Scales of Infant Development
  - Strange Situation Procedure

Visit 2: Videotaping

- 7 mths: Blood draws
- 20 min: Mirror-based interaction

Visit 3: Scanning

- 10 mths: Blood draws
- 20 min: Mirror-based interaction

Visit 4: Follow-Up

- 14 mths: Blood draws
- 20 min: Mirror-based interaction
Visit 2: Videotaping

Visit 1: Pregnancy
- 3rd trimester
- BIRTH

Visit 2: Videotaping
- 7 mths
- Mother-infant separation 1
- 20 min
- CARE-Index
- Mirror-based interaction
- 5 min
- Blood draws
- • Oxytocin
- • Cortisol
- • Adrenaline
- • Noradrenaline

Visit 3: Scanning
- 10 mths
- Mother-infant separation 2
- 20 min
- • PANAS (2)
- • IBQ
- • PSI

Visit 4: Follow-Up
- 14 mths
- WTAR
- • Breastfeeding duration
- • Hours separated per week
- • Bayley Scales of Infant Development
- • Strange Situation Procedure

Data Collected
- AAI
- Demographics
- PDQ
- BDI
- PANAS (1)
- Demographics
- ATQ
- Infant face images
- PANAS (2)
- IBQ
- PSI

Study Timeline
- 14 mths
- Mother-infant separation 2
- Visit 2: Videotaping
- 5 min
- Bayley Scales of Infant Development
- Strange Situation Procedure

ADULT ATTACHMENT
Visit 3: Scanning

Study Timeline
- Visit 1: Pregnancy
  - 3rd trimester
  - BIRTH
- Visit 2: Videotaping
  - 7 mths
  - Mother-infant separation 1
  - CARE-Index
  - Mirror-based interaction
  - Blood draws
    - Oxytocin
    - Cortisol
    - Adrenaline
    - Noradrenaline
- Visit 3: Scanning
  - 10 mths
  - Mother-infant separation 2
  - PANAS (2)
  - IBQ
  - PSI
  - WTAR
  - Breastfeeding duration
  - Hours separated per week
- Visit 4: Follow-Up
  - 14 mths
  - Bayley Scales of Infant Development
  - Strange Situation Procedure

Data Collected
- AAI-DMM
- Demographics
- PDQ
- BDI
- PANAS (1)
- Demographics
- ATQ
- Infant face images
- PANAS (2)
- IBQ
- PSI
- WTAR
- Breastfeeding duration
- Hours separated per week

ADULT ATTACHMENT → BRAIN / HORMONE /BEHAVIOR

University of Iowa Children’s Hospital
Texas Children’s Hospital
Baylor College of Medicine
Visit 4: Follow-Up

Study Timeline

Data Collected

Visit 1: Pregnancy
- $3^{rd}$ trimester
- BIRTH
- Mother-infant separation 1
  - 20 min
  - AAI-DMM
  - Demographics
  - PDQ
  - BDI

Visit 2: Videotaping
- 7 mths
- CARE-Index
- Mirror-based interaction
- Blood draws
  - Oxytocin
  - Cortisol
  - Adrenaline
  - Noradrenaline
- PANAS (1)
- Demographics
- ATQ
- Infant face images

Visit 3: Scanning
- 10 mths
- Mother-infant separation 2
- PANAS (2)
- IBQ
- PSI
- WTAR
- Breastfeeding duration
- Hours separated per week
- Bayley Scales of Infant Development
- Strange Situation Procedure

Visit 4: Follow-Up
- 14 mths
- WTAR
- Breastfeeding duration
- Hours separated per week
- Bayley Scales of Infant Development
- Strange Situation Procedure

ADULT ATTACHMENT ➔ BRAIN / HORMONE / BEHAVIOR ➔ INFANT ATTACHMENT

Group Comparisons

- Comparison of 15 Type B and 15 Type A mothers
- No significant group differences:
  - Maternal SES, race, education or IQ
  - Self-reported parenting stress
  - Pre- or post-natal depression
  - Psychopathology risk
  - Mother or infant temperament
  - Infant development at 14 months
  - Breastfeeding duration
## Secure vs. Insecure/Dismissing

<table>
<thead>
<tr>
<th>TYPE B</th>
<th>TYPE A</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Medial PFC</td>
<td>- Dorsolateral PFC</td>
</tr>
<tr>
<td>- Orbitofrontal cortex</td>
<td></td>
</tr>
<tr>
<td>- Ventral striatum</td>
<td></td>
</tr>
</tbody>
</table>

Pediatrics
Own Happy Faces: Secure vs. Insecure

Bilateral Ventral Striatum

Right Medial PFC

Secure

Insecure/Dismissing

% Signal Change

(se=1.0, t=3.0, p=0.006)

(se=0.4, t=3.1, p=0.005)
### Secure vs. Insecure/Dismissing

<table>
<thead>
<tr>
<th>TYPE B</th>
<th>TYPE A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial PFC</td>
<td>Dorsolateral PFC</td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td></td>
</tr>
<tr>
<td>Ventral striatum</td>
<td></td>
</tr>
<tr>
<td>Ventral striatum</td>
<td>Dorsolateral PFC</td>
</tr>
<tr>
<td></td>
<td>Anterior insula</td>
</tr>
</tbody>
</table>
Own Sad Faces: Type B vs. Type A

R Ventral Striatum

R Insula

Strathearn et al. Neuropsychopharmacology (2009)
**A**

![Graph showing changes in oxytocin with different interaction scenarios.](image)

- **OXYTOCIN REGION**
- **DOPAMINE REGION**

**B**

- **Hypothalamus**
  - Brain Activation (beta weights) vs. Change in Oxytocin (%)
  - Secure (△) vs. Insecure (○)
  - R^2 Linear = 0.297

- **Ventral striatum**
  - Brain Activation (beta weights) vs. Change in Oxytocin (%)
  - Secure (△) vs. Insecure (○)
  - R^2 Linear = 0.258

Strathearn et al., *Neuropsychopharmacology* (2009)
Unresolved trauma in mothers

• Includes occurrences of childhood abuse, neglect, or death of a parent

• Current discourse from Adult Attachment Interview indicates that the trauma has not been adequately processed, and continues to interfere with current functioning

• In our cohort of mothers with addiction (n=44), 98% had unresolved trauma, vs. 67% of control mothers (n=18) ($\chi^2=12.3$, $p<0.001$).
Amygdala activation to infant distress in mothers with unresolved trauma

Amygdala BOLD Signal Change (Estimated Marginal Means)

A. No trauma
B. Unresolved trauma

Infant Identity
- Own
- Unknown

Happy  Sad  Happy  Sad

Kim et al. Social Neuroscience (2014)
What happens in addiction?

**SENSORY INPUT**
(e.g. child face/cry cues)

**HYPO-THALAMUS**

**ENDOGENOUS OXYTOCIN**

**VENTRAL TEGMENTAL AREA**

**AMYGDALA**

**VENTRAL STRIATUM**

**DORSAL STRIATUM**

**SUBSTANTIA NIGRA**

**DORSOLATERAL PREFRONTAL CORTEX**

**DORSAL PREFRONTAL CORTEX**

**MOTOR OUTPUT**
(e.g. caregiving behavior)

**VENTROMEDIAL PREFRONTAL CORTEX**

**Mesocorticolimbic Dopamine Pathway:**
“Reward”

**Nigrostriatal Dopamine Pathway:**
“Habit Formation”
Addicted Mothers (n=39) vs Normative Mothers (n=36)

VENTRO-MEDIAL PFC

VENTRAL STRIATUM

Pediatrics
OWN-HAPPY vsUNKNOWN-HAPPY

Ventral Striatum

Normative Mothers (n=36)

Addicted Mothers (n=39)

Ventral Medial PFC

University of Iowa Children’s Hospital

Texas Children’s Hospital

Baylor College of Medicine
Own-Happy > Unknown-Happy

Normative Mothers (n=36)  
Addicted Mothers (n=39)

HYPOTHALAMUS
Decreased brain response to own-infant in addicted mothers
Where to from here?

• Randomized controlled trials of intranasal oxytocin
  - Mothers with addiction
  - Post-natal depression
  - Mothers with insecure attachment

• Comparing maternal brain and oxytocin responses in mothers with or without obesity
**Mesocorticolimbic Dopamine Pathway:** “Reward”

**Nigrostriatal Dopamine Pathway:** “Habit Formation”

**SENSORY INPUT** (e.g. child face/cry cues)

**VENTROMEDIAL PREFRONTAL CORTEX**

**ventral striatum**

**amygdala**

**DORSOLATERAL PREFRONTAL CORTEX**

**DORSAL STRIATUM**

**SUBSTANTIA NIGRA**

**SENSORY INPUT** (e.g. child face/cry cues)

**INTRANASAL OXYTOCIN**

**MOTOR OUTPUT** (e.g. caregiving behavior)
Oxytocin increases reward and amygdala response to infant faces

Own-Happy > Unknown-Happy

Normative Mothers (n=10)

Ventral/DO
RSAL
STRIATUM

Amygdala

Ventral Tegmental Area (VTA)

Oxytocin

Placebo
Oxytocin increases reward and amygdala response to infant faces in addicted mothers
In Summary

• Children who are exposed to early life adversity, including abuse and neglect, are at greater risk of developing addiction problems.

• Unresolved trauma is almost universally seen in mothers with substance addictions.

• Addiction and early life adversity may impair a mother’s ability to provide sensitive caregiving of her offspring, via reduced processing of natural reward cues in the brain.

• Oxytocin may help to ameliorate some of these effects.
Acknowledgements

- Attachment and Neurodevelopment Lab members
  - Sohye Kim, Research Associate
  - Udita Iyengar, Graduate Student
  - Sheila Martinez, Ana Sanchez, and Leah Sanchez, Research Assistants

- Peter Fonagy, University College London
- Collaborators at Yale Child Study Center: Linda Mayes, Helena Rutherford, Marc Potenza
- NIH Grant Support: NICHD K23 HD43097 and R01 HD065819; K12 HD41648 Baylor Child Health Research Center: Pediatrics Mentored Research Program; NIDA R01 DA026437
- USDA CRIS grant 6250-51000-054-00D

Follow us on Facebook: AttachmentNeurodevelopmentLab