Early Life Stress and Epigenetic Development

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Early Psychosocial Stress and Health

Abuse, Neglect, Poverty

≈ 80 Years

Wegman and Stetler, 2009
SES, Stress, and Epigenetics

• Recent epigenetic studies have examined either early stress or early SES, not both.

• Poverty may be a kind of psychosocial stressor.

• Studies that target stress pathway genes may help us understand the embedding of early experiences like poverty.
Rhesus Macaques (Macaca mulatta)
Outline

• How nurture shapes nature: The serotonin transporter

• Study 1: Epigenetics and early environment in an experimental non-human primate model

• Study 2: Translation to humans
Serotonin Transporter (5-HTT)

Across species, associated with early stress and behavioral disinhibition

- **Early Stress**
- **Low Early Stress/Control**

**Impulsivity**
(Frankle et al., 2005)

**Openness to Experience**
(Kalbitzer et al., 2009)

**Behavioral Inhibition**
(Oler et al., 2009)
Serotonin Transporter (5-HTT)

Canli and Lesch, 2007
Serotonin Transporter (5-HTT)

DNA

RNA

Protein
5-HTT Regulation
Serotonin Transporter Regulation

Regulatory Region  Gene  Expression
Serotonin Transporter Regulation

Transcription Factor Complex

Regulatory Region  Gene  Expression
Study One

Early Stress and Epigenetic Regulation of 5-HTT in Macaques
Macaque Early Stress

≈ 20 Years

Conti et al., 2012; Harlow and Zimmerman, 1956
NURSERY REARING (NR)

Harlow and Zimmerman, 1955
Early Stress, 5-HTT and Behavioral Disinhibition

Low Early Stress

↓

Inhibited

High Early Stress

↓

Disinhibited

Ichise et al., 2008; Kinnally et al., 2008; Kinnally et al., 2009; Oler et al., 2009; Fairbanks and Maguire, 1988;
Does epigenetic regulation of 5-HTT play a role in the effects of early stress in rhesus macaques?
Study One Methods

- Exposed 4 infants to NR, 2 to CONTROL rearing.

- Tested rearing effects on 5-HTT C-methylation in:
  - Brainstem (4 NR, 2 CONTROL) using t-tests

- All subjects underwent standardized behavioral assessment at CNPRC.
Brainstem 5-HTT Methylation is Higher in NR Macaques

Means presented +/- standard error of the mean

* p < .05 # p < .08

Kinnally et al., in preparation
Epigenetic Regulation of Brainstem Serotonin Transporter in Macaques

\[ F(1,6) = 121.523, \ p < .0001, \ R^2 = .968 \]
Brainstem 5-HTT Methylation Predicts Behavioral Disinhibition

\[ F (1, 6) = 4.848, \ p = .046, \ R^2 = .548 \]
Does epigenetic regulation of 5-HTT play a role in the effects of early stress in rhesus macaques?

Control-reared → Inhibited

Nursery-reared → Disinhibited
Study One Summary

• Epigenetics may be one of the mechanisms for early stress calibration in non-human primates.
Study Two

Human Translation
Human Early Stress
Brainstem 5-HTT is Lower In Childhood Abuse in Humans

Mixed Effects Model; \( F=5.27, \ p=0.032 \)

Miller et al., 2009
Does epigenetic regulation of 5-HTT play a role in the effects of early stress in humans?
Study Two Methods

• Multi-center clinical project (Columbia University; PIs: Mann, Parsey)

• Subjects (N = 32) underwent diagnostic interviews by clinical psychologists:
  • Major Depressive Disorder or Control Diagnosis
  • Abuse (physical or sexual) before 15 yr.
  • Barratt Impulsivity Scale (Barratt, 1965)

• Blood test for 5-HTT.

• Quantified blood 5-HTT C-methylation.
# Human Subjects

## DEMOGRAPHIC FACTORS BY CHILDHOOD ABUSE HISTORY

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<th>Childhood Abuse</th>
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<th>Total</th>
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<tr>
<td>Female</td>
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<td>12</td>
<td>6</td>
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<tr>
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<td>0</td>
<td>14</td>
<td>14</td>
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<tr>
<td><strong>Age</strong></td>
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<td>35</td>
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<td><strong>SES</strong></td>
<td>MID (50%)</td>
<td>MID (75%)</td>
<td>MID (69%)</td>
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<td><strong>RACE</strong></td>
<td>Caucasian (83%)</td>
<td>Caucasian (50%)</td>
<td>Caucasian (63%)</td>
</tr>
</tbody>
</table>
Blood 5-HTT is Lower In Childhood Abuse in Humans

ANOVA; F=2.927, p=0.042, \( R^2 = 0.156 \)

Kinnally et al., in preparation
Childhood Abuse Predicts 5-HTT Methylation in Humans

ANOVA: F=9.501, p=0.001

Means presented +/- standard error of the mean

Kinnally et al., in preparation
5-HTT Methylation Predicts Blood 5-HTT in Humans

Regression: $F = 5.641$, $p = .021$, $R^2 = .204$

Kinnally et al., in preparation
5-HTT Methylation Predicts Impulsivity in Humans

Regression: $F = 7.107$, $p = .015$, $R^2 = .262$
Does epigenetic regulation of 5-HTT play a role in the effects of early stress in humans?

No Childhood Abuse

Childhood Abuse

Inhibited

Disinhibited
Conclusions

• Early life experiences may change how genes work in macaques and humans.

• These changes may help calibrate how primates (including humans) respond to challenge across the lifespan.
Summary

• Epigenetic plasticity may be one mechanism for the biological embedding of early stress in humans.

• Platform to design prospective studies in at-risk children using blood biomarkers.
Nature and Nurture: Implications for Human Health
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