THE SCIENCE THAT HEALS: THE NEUROBIOLOGY OF STRESS, TRAUMA, AND RESILIENCE

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Professor and Dean
College of Health Sciences
Marquette University

Beyond MU
Quick Facts

- The human brain contains an estimated 86 billion neurons.
- Each neuron forms up to 10,000 connections with other neurons; these connections are called synapses.
- Synaptic communication involves more than 100 neurochemicals that act through more than 1000 different receptors.
Quick Facts

• Neurons work in close coordination with other cells types in the brain called astrocytes and form elaborate networks and systems that determine what we perceive and experience.

• Many of the key neuronal pathways and chemical neurotransmitters involved in mental illness are coming into sharper focus.
Homology Across Mammalian Species
CORTISOL
Prefrontal Cortex
Prefrontal Cortex

• Executive Function/Decision Making
• Planning Complex Behavior
• Impulse Inhibition
• Predicting Future Consequences of Actions
Prefrontal Cortex is Particularly Vulnerable to Glucocorticoids
Prefrontal Cortex is Among Last Brain Areas to Develop
• >20 college neuroscientists working in funded research laboratories
• Particular strengths in neuroscience underlying neuropsychiatric disease and in motor control
• Promentis Pharmaceuticals, Inc. now has an IND in Phase III FDA clinical trial following >$31 million in venture capital investment
Cognitive – Emotional -- Motivational Brain Circuitries
• Summer research program providing high impact experiences for undergraduate students

• 45-50 students across 23 faculty laboratories

• Large number of undergraduate students presenting at national scientific meetings and co-authors of publications
Billie and Michael Kubly

Eck Family Foundation

Dawne and Ray Manista

Kelly and Jim McShane

Michael Schmitz
THE NEUROBIOLOGY OF STRESS, TRAUMA, AND RESILIENCE

Paul Gasser, Ph.D
Department of Biomedical Sciences
Marquette University
How does stress affect the brain?

- The biology of stress
- Cortisol and the stress response
- Human stressors and cortisol
- Effects of cortisol on brain structure and function
What is stress?
Refocus attention
Mobilize and redirect resources
Redirect behavior
Prevent overshoot
Terminate the response
Promote recovery
Adapt/Prepare
HPA axis: part of the brain’s stress response system
Dysregulation of the HPA axis is linked to:

- Anxiety
- Depression
- Attention/Cognitive Impairment
- Digestive Problems
- Heart Disease
- Insomnia
HPA Axis Dysregulation in Depression

In depressed patients:

- Elevated diurnal cortisol and ACTH
- Decreased negative feedback
- Enhanced HPA axis drive

Poverty: A multidimensional stressor

- Food/nutrition
- Housing problems (crowding, etc)
- Warmth
- Environmental safety, stability
- Family turmoil, separation
- Violence

Table 2  Frequency of Multiple-Stressor Exposure as a Function of Poverty

<table>
<thead>
<tr>
<th>Number of Multiple Stressors</th>
<th>Poverty Frequency</th>
<th>Middle-Income Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5 (3)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>1</td>
<td>30 (18)</td>
<td>58 (49)</td>
</tr>
<tr>
<td>2</td>
<td>44 (25)</td>
<td>28 (24)</td>
</tr>
<tr>
<td>3</td>
<td>32 (19)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>4</td>
<td>31 (19)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>5</td>
<td>20 (12)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>6</td>
<td>6 (4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Evans & English, 2002
Poverty and the HPA Axis

• Low SES infants:
  • **higher cortisol throughout the day**

• Low, medium SES children:
  • **Higher awakening cortisol**

Effects on brain structure?

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Prefrontal cortex: Executive function & Emotional control

- Decision-making
- Impulse control
- Attention
- Emotional Regulation
- Stress coping
Cushing’s syndrome: Chronically elevated cortisol

Vergely et al (2002)

Cushing’s syndrome: Chronically elevated cortisol

<table>
<thead>
<tr>
<th></th>
<th>Cushing’s disease (n=25)</th>
<th>Matched controls (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inventory of Depression Symptomatology</td>
<td>46.8 ± 13.0</td>
<td>36.3 ± 5.8</td>
<td>0.005b</td>
</tr>
<tr>
<td>MADRS</td>
<td>6.3 ± 5.5</td>
<td>1.4 ± 1.8</td>
<td>0.000b</td>
</tr>
<tr>
<td>Beck Anxiety Inventory</td>
<td>28.4 ± 5.7</td>
<td>24.0 ± 3.1</td>
<td>0.003b</td>
</tr>
<tr>
<td>Fear Questionnaire</td>
<td>24.5 ± 17.4</td>
<td>14.2 ± 10.0</td>
<td>0.051b</td>
</tr>
<tr>
<td>Agoraphobia subscale</td>
<td>6.1 ± 7.9</td>
<td>3.4 ± 4.7</td>
<td>0.477b</td>
</tr>
<tr>
<td>Blood injury phobia subscale</td>
<td>6.2 ± 8.3</td>
<td>3.2 ± 4.1</td>
<td>0.118a</td>
</tr>
<tr>
<td>Social phobia subscale</td>
<td>12.2 ± 8.0</td>
<td>7.6 ± 4.9</td>
<td>0.034b</td>
</tr>
<tr>
<td>Irritability Scale</td>
<td>12.1 ± 8.7</td>
<td>8.0 ± 6.1</td>
<td>0.066a</td>
</tr>
<tr>
<td>Total score &gt;14</td>
<td>9 (36%)</td>
<td>6 (24%)</td>
<td></td>
</tr>
<tr>
<td>Apathy Scale</td>
<td>13.6 ± 6.6</td>
<td>7.8 ± 3.8</td>
<td>0.002b</td>
</tr>
<tr>
<td>Total score &gt;14</td>
<td>11 (44%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Cognitive Failures</td>
<td>38.0 ± 16.5</td>
<td>27.6 ± 9.7</td>
<td>0.023b</td>
</tr>
</tbody>
</table>

P values were tested with a independent-sample t-test and bMann–Whitney U test. Level of significance was set at P < 0.05 and significant values are in bold.

Poverty effects on Brain structure

• NIH MRI Study of Normal Brain Development
• 389 children
• Income range ($5000 - $150000)
• Neuroimaging
• Effects concentrated in children from the poorest households

Table 2. Socioeconomic Status and Brain Development

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frontal Gray Matter, ( \beta (SE) )</th>
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<tr>
<td>Model 1</td>
<td></td>
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<tr>
<td>Below 200% of the FPL</td>
<td>(-2.157^b (1.24))</td>
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<tr>
<td>Model 2</td>
<td></td>
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<tr>
<td>Below 150% of the FPL</td>
<td>(-3.532^b (1.546))</td>
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<tr>
<td>Model 3</td>
<td></td>
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<tr>
<td>Below 100% of the FPL</td>
<td>(-8.383^b (2.597))</td>
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Poverty effects on Executive function

- 1292 children
- Tasks to measure:
  - Working memory
  - Attention
  - Inhibitory control


**Figure 1.** Executive functioning (EF) at 48 months predicted by chronicity of income risk, where chronicity (i.e., a value of 0, 1, 2, or 3) is defined as the number of 12-month time periods in which family income falls at or below the U.S. poverty threshold.
Parental Attachment security buffers stress

- 177 toddlers with parents
- Well-child visits with innoculations
- 52% below 150% FPL
- 50% white
- Salivary cortisol collected at 3 time points
- Attachment security scored

Johnson et al (2018) Psychoneuroendocrinol. 95, 120-127
Poverty-alleviation and cortisol

- 1197 children (491 intervention)
- Cash-transfer program to alleviate extreme poverty
- 20-30% of household income transferred contingent on requirements
- Child salivary cortisol and response to stressor
- Cognitive tasks

Poverty: A multidimensional stressor

- Food/nutrition
- Housing problems (crowding, etc)
- Warmth
- Environmental safety, stability
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The Neurobiology of Stress, Trauma, and Resilience

Robert A Wheeler, Ph.D.
Department of Biomedical Sciences
Epigenetics is the process by which changes in an organism are caused by changes in gene expression rather than changes in the genetic code.
Epigenetics
Early Life Adversity Changes the Stress Response

[Diagram showing the stress response system with arrows indicating the regulation of glucocorticoids and GR receptors.]

- Hippocampus
- Amygdala
- Paraventricular nucleus
- CRF
- Pituitary
- Adrenal cortex
- Glucocorticoids

Regulation of brain and peripheral function (stress response)
Epigenetic Regulation of the Glucocorticoid Receptor

People who have experienced adversity in childhood often show abnormal stress responses.

Methylation of the analogous human gene has been observed in suicide completers who have a history of childhood sexual abuse.
Early Life Adversity Changes the Developing Brain

Bucharest Early Intervention Project

Photo by Michael Carroll

http://www.bucharestearyearlyinterventionproject.org/
Early Life Adversity Changes the Developing Brain

Institutionalized children show decreased white matter

http://www.bucharestearlyinterventionproject.org/

Center on the Developing Child
HARVARD UNIVERSITY
Adverse Childhood Experiences are associated with behavioral problems.

The Flanker Task

Press the left button
Press the right button
Do not press a button

Children placed into foster care showed greater accuracy and faster response times than children who remained in the institution.

McDermott et al., 2013
Animal Models Can Show Us How this Happens

Here at Marquette, researchers are using animal models to understand how stress changes brain activity and behavior.

Spring et al., J Neurosci, 2021
Interventions Confer Resilience

These studies illustrate the biological impact of adverse childhood experiences. They also provide hope that policy interventions can correct these physiological problems.
Chronic stress: a risk factor for trauma-related mental illness

- Living through dangerous events and traumas
- Getting hurt
- Seeing another person hurt, or seeing a dead body
- Childhood trauma
- Feeling horror, helplessness, or extreme fear
- Having little or no social support after the event
- Dealing with extra stress after the event, such as loss of a loved one, pain and injury, or loss of a job or home
- Having a history of mental illness or substance abuse

Fear circuitry

- Prefrontal Cortex
- Amygdala
- Hippocampus

Processing threat stimulus

Environmental threat

Sensory thalamus

Sensory cortex (fast)

Sensory cortex (slow)
Release of stress hormones

- Pituitary
- Adrenal gland
- Kidney
- Cortex
- Medulla
- Epinephrine and norepinephrine
- Glucocorticoids

- Increase in cardiovascular tone
- Increase in blood pressure
- Mobilization of stored energy to muscle
- Transient enhancement of immunity
- Inhibition of costly, long-term processes such as growth and reproduction
Fear circuitry

- Prefrontal Cortex
- Amygdala
- Hippocampus

Processing threat stimulus

Environmental threat

Sensory thalamus

Sensory cortex

(fast)

(slow)
Prefrontal cortical regulation of emotion
Brain mechanisms of courage

Nili et al., 2010 Neuron
Pathological fear and anxiety

- Prolonged emotional and stress reactions when triggered
- Impaired ability to suppress or extinguish fear
- Generalization of fear to non-threatening situations
- Avoidance of anxiety-provoking situations and people
HOW DOES CHRONIC STRESS AFFECT THESE BRAIN SYSTEMS?
Amygdala neurons increase in size after prolonged stress

From Vyas et al., 2002
Prefrontal & hippocampal neurons shrink after prolonged stress

From McEwan & Morrison, 2013
How does early life adversity affect threat-response circuits?
Childhood: a sensitive window of risk & resilience

Sensitive periods for sensory and cognitive skills in humans

KT Hensch, 2005
Sensitive Period:
PN≤9

Post-Sensitive Period:
>PN15

Odor-shock conditioning

Failure to learn threat

From Sullivan & Opendak, 2018
Early life adversity affects the parental buffer

Separation stress or a stressed caregiver produces adult-like activation of the fear system

From Sullivan & Opendak, 2018
Early life stress accelerates the maturation of fear systems

Amygdala-prefrontal connectivity matures earlier in children following early life stress (previously institutionalized)

Accelerated maturation at the expense of full functional capacity

Gee et al., 2013 PNAS
Resilience factors

- Social support (family, friends, a support group)
- Learning to feel good about one’s own actions in the face of danger
- Having a positive coping strategy
- Being able to act and respond effectively despite feeling fear
Complexity is an opportunity to identify resilience

McEwen & Akil, 2020 J Neuro
Complexity is an opportunity for resilience

Circulating sex hormones (e.g., Estrogen, Testosterone)

Galea et al., 1997

Zeidan et al., 2011
Sex hormones affect prefrontal response to shock

Matt Herbst, Matt LaViola