Dysregulated Fear Responses in Adults and Children from a Traumatized Inner City Population

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Severe Inner-city Trauma

<table>
<thead>
<tr>
<th>TRAUMATIC EVENTS INVENTORY</th>
<th>Percent of Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Disaster</td>
<td>20.69</td>
</tr>
<tr>
<td>Serious Accident or Injury</td>
<td>55.77</td>
</tr>
<tr>
<td>Sudden Life-Threatening Illness</td>
<td>38.00</td>
</tr>
<tr>
<td>Military Combat</td>
<td>9.26</td>
</tr>
<tr>
<td>Close Friend or Family Member Murdered</td>
<td>3.57</td>
</tr>
<tr>
<td>Close Friend or Family Member Committed Suicide</td>
<td>8.77</td>
</tr>
<tr>
<td>Attacked with Weapon</td>
<td>35.69</td>
</tr>
<tr>
<td>Attacked Without Weapon</td>
<td>24.55</td>
</tr>
<tr>
<td>Violence Between Parents or Caregivers</td>
<td>35.19</td>
</tr>
<tr>
<td>Beaten as a Child</td>
<td>35.71</td>
</tr>
<tr>
<td>Sexual Contact Before Age 13</td>
<td>21.43</td>
</tr>
<tr>
<td>Forced Sexual Contact Between 14 and 17</td>
<td>9.69</td>
</tr>
<tr>
<td>Forced Sexual Contact After Age 17</td>
<td>9.60</td>
</tr>
</tbody>
</table>

Grady Trauma Project: Risk and Resiliency

www.gradytraumaproject.com

PIs: Kerry Ressler, MD, PhD and Bekh Bradley, PhD

Exposure to multiple types of trauma is the rule rather than the exception

Trauma Exposures Often Include Childhood Abuse and Other Types of Family Violence
Case example 1 (8622)

T.D. is a 33 y/o AA female. From the age of six, she has sustained severe physical and emotional abuse by her father and repeated sexual abuse by her step brother. She was unwilling to talk about any of her traumas, but has significant symptoms of PTSD. She is also drinking about a 6 pack a day and is currently using cocaine. She has no close relationships with any of her family members. She has no friends, no hobbies, nor is she interested in leaving the house. Her current boyfriend has been taking care of her since her last suicide attempt a few weeks ago…this was her 3rd attempt. At that point the interview was discontinued and she was taken to be evaluated by a psychiatrist.

Case example 2 (8543)

T.I. is a 25 y/o AA female. Until the age of 7, she lived with her mother and father, who were addicted to crack cocaine. She witnessed a number of violent fights between her parents. At age 8 she moved in with her grandmother. But while still living with her parents, she was exposed to a lot of neighborhood violence. As a 7 y/o, she survived a shootout between neighbors and dropped to the floor in the living room, trying to protect herself and her siblings from shots that came through the windows. She met current PTSD for this trauma. She still avoids the apartment complex at which this shooting happened. Today she has a great relationship with her children’s father. She sees her mother weekly (sober for 4 years). She speaks with her father monthly (sober for 2 years), and she is still close with her grandmother. She has no history of substance abuse.

PTSD—The Disorder

- Onset determined by traumatic event, but low rates of illness relative to trauma exposure: gene X environment risk factors
- Heterogeneous: three major symptom clusters
  - Re-experiencing (intrusive) symptoms
  - Avoidance symptoms
  - Hyper-arousal symptoms
- High rates of comorbidity with depression, other anxiety disorders, substance abuse
Biomarkers

- http://www.youtube.com/watch?v=9V7zbWNznbs

Putative Biomarkers

- HPA axis
  - Low basal cortisol/CRH
  - Hyper-suppression by dexamethasone
- Low NPY
- Disrupted sleep patterns
- Elevated heart-rate
- Reduced hippocampus volume
- PACAP
- Exaggerated startle response

Pubmed search of PTSD and biomarker returned 136 articles

Biomarker:

ACOUSTIC STARTLE RESPONSE

Biomarkers: Neurobiological intermediate phenotypes

- Related to underlying neurobiology of the mental disorder
- Related to symptoms of the disorder
- Possible to model in preclinical studies—translational approach
Translational approach: HUMAN PSYCHOPHYSIOLOGICAL RESEARCH ON FEAR RESPONSES

Translational studies
- Fear-potentiated startle in healthy and clinical populations
- Exaggerated fear response in PTSD
- Impaired fear inhibition in PTSD
- Neural underpinnings of inhibition
- Development of inhibition

Simple Discrimination: A+/B-

Acquisition: 3 blocks of 4 trials
Cognitive discrimination between CS+ and CS-

Startle discrimination between CS+ and CS-

Startle discrimination between CS+ and CS-

Startle discrimination between CS+ and CS-
Correlation between startle to CS+ and CS- and PTSD symptoms

<table>
<thead>
<tr>
<th></th>
<th>TCI</th>
<th>CTQ</th>
<th>BDI</th>
<th>PSS Intriavse</th>
<th>PSS Avoidance</th>
<th>FSS Hyperarousal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAGER</td>
<td></td>
<td></td>
<td>57</td>
<td>.05</td>
<td>.27</td>
<td>.24</td>
</tr>
<tr>
<td>CS-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAFETY</td>
<td></td>
<td></td>
<td>26</td>
<td>.08</td>
<td>.13</td>
<td>.45</td>
</tr>
</tbody>
</table>

B) Outcome: Hyper-Arousal PTSD Symptoms

<table>
<thead>
<tr>
<th>Predictors:</th>
<th>Rs</th>
<th>Rs Change</th>
<th>F Change</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age, Sex, and Race</td>
<td>0.003</td>
<td>0.003</td>
<td>0.11</td>
<td>ns</td>
</tr>
<tr>
<td>2. Childhood and Adult Trauma</td>
<td>0.134</td>
<td>0.131</td>
<td>7.56</td>
<td><strong>0.001</strong>*</td>
</tr>
<tr>
<td>3. Startle to Safety Cue</td>
<td>0.191</td>
<td>0.057</td>
<td>7.00</td>
<td><strong>0.009</strong>*</td>
</tr>
<tr>
<td>4. SCR to Safety Cue</td>
<td>0.194</td>
<td>0.003</td>
<td>0.32</td>
<td>ns</td>
</tr>
</tbody>
</table>

Glover et al (2011) Depression & Anxiety

Fear inhibition is impaired in PTSD

- PTSD is associated with impaired fear inhibition using 3 fear-potentiated startle paradigms
- Impaired fear inhibition is a biomarker of PTSD in different trauma populations

Potential future approaches

- Identify at-risk individuals for early intervention
  - genes related to fear inhibition (GWAS)

- Track treatment efficacy

- Treatment target
  - Training intervention tasks
  - Stimulation (e.g. TMS)

- Developmental approach: emergence of biomarkers in traumatized pediatric populations

Longer-term effects:

NEUROBIOLOGY OF FEAR AND ANXIETY IN THE NEXT GENERATION
The psychiatric diagnostic system does not have a single diagnostic category that accounts for the symptoms associated with this complex trauma exposure and related developmental disruption. Some psychiatric diagnoses, however, are significantly more common among children who have been exposed to complex trauma.

- Attention Deficit Hyperactivity Disorder (ADHD)
- Oppositional Defiant Disorder (ODD)
- Mood Disorders
- Conduct Disorder
- Substance Use Disorders

Bad Dreams and Fears
- Externalizing or “acting out” behaviors including impulsivity, irritability/anger and inattentiveness.
- Re-enact traumas (e.g., aggression, sexualized behaviors, need to control others). Such behaviors may emerge in an automatic manner in response to reminders of their traumatic experiences.
Generalization of Danger

Nightmares

Re-enacting

Play or drawing of trauma
Kid Startle Team:
GTP Researchers:
Ami Smith, PhD
Dorthie Cross, MA
Will Holland
Jennifer Winkler
Sarah Spann
Jennifer Davis
Alicia Nelson
Bekh Bradley, PhD

Collaborators:
Erin Tone, PhD
Chaundrissa Smith, PhD
MaryAnn Jacobs, MD

Fear conditioning in children

Preliminary data: fear-potentiated startle in children

Fear-potentiated startle in children

CS- CS+

AGE<10

AGE=10-12

p<0.04

AGE=10-12
Startle in Children of Abused Mothers

Dark-Enhanced Startle
- Startle magnitude greater in dark than light
- Nonspecific anxiety marker
- Greater in “high-risk” adolescents (risk defined by parental anxiety or depression)

ACCLIMATION HABITUATION LIGHT DARK LIGHT DARK

2 min 2 min 2 min 2 min

Dark-enhanced startle is associated with anxiety in children
- \( r = 0.55, p < 0.03 \)

Children of abused mothers startle more in the dark
- Children of mothers with high levels of abuse have higher dark-enhanced startle than children of mothers with low levels of childhood physical abuse
- \( p < 0.05 \)

Increased dark-enhanced startle is not due to maternal mental illness or child’s own trauma

<table>
<thead>
<tr>
<th>Dark-Enhanced Startle</th>
<th>R²</th>
<th>R² Change</th>
<th>F Change</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Child’s Age and Sex</td>
<td>0.06</td>
<td>0.06</td>
<td>0.71</td>
<td>0.50</td>
</tr>
<tr>
<td>2. Child’s Trauma</td>
<td>0.09</td>
<td>0.03</td>
<td>0.75</td>
<td>0.40</td>
</tr>
<tr>
<td>3. Maternal PTSD</td>
<td>0.13</td>
<td>0.04</td>
<td>0.90</td>
<td>0.35</td>
</tr>
<tr>
<td>4. Maternal Depression</td>
<td>0.13</td>
<td>0.00</td>
<td>0.10</td>
<td>0.76</td>
</tr>
<tr>
<td>5. Maternal Childhood Physical Abuse</td>
<td>0.42</td>
<td>0.28</td>
<td>9.24</td>
<td>0.007</td>
</tr>
</tbody>
</table>

- T.D. has 4 children. Her 8 y/o stays with her mother, and the other children stay with her. She sounded annoyed by her own children ("my kids aggravate me") and is looking forward to having them stay with her mother for the summer. She described her relationship with her 15 y/o daughter as "she can’t stand me", her 16 y/o son as "iffy", her 9 y/o as "he loves me" and her 8 y/o as "he doesn’t know me". Having met her with her 9 y/o son, I was surprised by her lack of warmth toward him.

- T.I. now has a 5 y/o son and a 6 y/o daughter. She was inspired by her daughter’s strong interest in reading. She wants to be a role model for her children and is enrolled in a program to get her GED. Upon completing the GED program, T.I. hopes to do work in child advocacy.
Potential Mechanisms

- Mother’s behavior
  - Abusive behavior
  - Modeling /instructing fear

- Parenting style
  - Over-reactive
  - Laxness

- Genetics
  - Inheritance of risk genes

- Epigenetics
  - DNA methylation

- Stress during pregnancy
  - Cortisol levels during gestating

Parenting Scale Ratings

- Moms with PTSD more over-reactive parents, and more distressed by parenthood

- Moms with childhood trauma more distressed by parenthood, report higher scores of dysfunctional relationships and having a difficult child

Maternal Behavior
Genotype effects in PTSD

- PACAP receptor (PAC1R) gene ADCYAP1R1 SNP rs2267735 associated with impaired fear inhibition and higher dark-enhanced startle in women


Genotype effects in children

- PACAP receptor (PAC1R) gene ADCYAP1R1 SNP rs2267735 associated with higher dark-enhanced startle in children (after controlling for maternal and child trauma)


Conclusions

- Physiological markers such as the startle response provide potential biomarkers of PTSD risk in adults and children

- Trauma has long-term neurobiological consequences for the victim as well as the victim’s children: multigenerational effects

Future Directions

- Developmental trajectory of fear inhibition and dark-enhanced startle from pre- to post-puberty
  - Effects of estrogen in young and adolescent girls

- G X E effects and interaction with maternal behavior and puberty

- Neuroimaging in children
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