Identifying biomarkers of psychological vulnerability to stress

Johnna R. Swartz, Ph.D.
Postdoctoral Associate
Laboratory of NeuroGenetics, Duke University
Center for Developmental Science, University of North Carolina at Chapel Hill
Major Depression and Anxiety Disorders

• Response rates for currently available treatments are often less than 60% (Cipriani et al., 2009, Lancet; Gartlehner et al., 2011, Annals of Internal Medicine; de Maat et al., 2007, European Psychiatry)

• Brain biomarkers – observable before self-report of clinical symptoms

• Identifying brain biomarkers that predict risk:
  – Who develops depression or anxiety
  – How
Risk for Depression and Anxiety

- Family history of the disorder – Odds ratio (OR) = 3.3
  - (Weissman et al., 2006, *American Journal of Psychiatry*)
- Trauma or stressful life events – OR = 2.85
- Childhood maltreatment – OR = 2.27
  - (Nanni et al., 2012, *American Journal of Psychiatry*)
- Low socioeconomic status – OR = 1.81
  - (Lorant et al., 2003, *American Journal of Epidemiology*)
Risk for Depression and Anxiety

FIGURE 2. Cumulative Rates of Major Depressive Disorder Over 20 Years in Female and Male Offspring of Depressed Parents

Cumulative Proportion of Offspring With Major Depressive Disorder

Age at Onset (years)

Female (N=58)
Male (N=43)

\(^a\) Significant difference between groups according to test of equality of strata (Wilcoxon test) \((\chi^2=4.0, \text{df}=1, p=0.04)\).

(Weissman et al., 2006, American Journal of Psychiatry)
Can we predict who is at greatest risk?

1. Can we identify neural biomarkers that aid in predicting which individuals are at greatest risk?

2. How early in development can these neural biomarkers be detected?
Can we predict who is at greatest risk?

1. Can we identify neural biomarkers that aid in predicting which individuals are at greatest risk?

2. How early in development can these neural biomarkers be detected?
Amygdala reactivity to threat as a model biomarker of risk

- Vigilance and monitoring environment for threat
- Threat appraisal
Amygdala reactivity to threat as a model biomarker of risk

- **Stress reactivity**
  - (Herman & Cullinan, 1997, *Trends in Neurosciences*)

- **Attention bias to threat**
  - (Pessoa & Ungerleider, 2004, *Progress in Brain Research*)

- **Fear learning**

- **Memory for negative events**
  - (Hamilton & Gotlib, 2008, *Biological Psychiatry*)
Amygdala reactivity to threat as a model biomarker of risk

- Present in mood and anxiety disorder patients

- Differentiates treatment responders from non-responders

- Predisposing risk factor?
- Consequence of disorder?
Amygdala reactivity to threat as a model biomarker of risk

- Heightened threat-related amygdala reactivity predicts:
  - Greater increase in PTSD symptoms in combat paramedics
    • (Admon et al., 2009, *PNAS*)
  - Greater PTSD symptoms in adolescents after the 2013 Boston Marathon bombing
    • (McLaughlin et al., 2014, *Depression and Anxiety*)
  - Common stressful life events?
Research Question: Study 1

• Does heightened amygdala reactivity to threat prospectively predict future anxiety and depression symptoms in response to stressful life events?
Methods

- Participants were university students recruited as part of the Duke Neurogenetics Study (DNS)
  - Age: 18-22 at baseline
  - 57% female
  - No current anxiety or depression diagnosis at baseline (e-M.I.N.I.; Sheehan et al., 1998, *Journal of Clinical Psychiatry*)
Baseline

- fMRI: Amygdala reactivity to threat

- Questionnaires:
  - Anxiety and depression symptoms
    - Mood and Anxiety Symptom Questionnaire (Watson et al., 1995, *Journal of Abnormal Psychology*)
  - Stressful life events in the past year
    - Life Event Scale for Students (Clements & Turpin, 1996, *Personality and Individual Differences*)
  - Childhood trauma
    - Childhood Trauma Questionnaire (Bernstein et al., 2003, *Child Abuse and Neglect*)
  - Non-internalizing psychopathology
    - e-M.I.N.I.
Online follow-up

- Stressful life events experienced since last follow-up
- Current anxiety and depression symptoms
Study Design

- n=340 participants
- Mean time between scan and questionnaire=468 days
  --Min-Max=90-1402
Internalizing symptoms Time 2

Amygdala reactivity to fearful and angry faces (A.U.)

B=2.01, SE=.7, t(339)=3.08, p=.002

(Swartz et al., 2015, Neuron)
Long-term effects

- n=192 participants
- Mean time between scan and questionnaire=683 days
  --Min-Max=365-1402
Results: Long-term effects

$B=1.75, \ SE=.8, t(191)=2.33, p=.02$

(Swartz et al., 2015, Neuron)
Prospective measure of stress

- n=99 participants
- Mean time between scan and questionnaire=397 days
  --Min-Max=365-455
Results: Prospective measure of stress

B=5.56, SE=1.9, t(98)=2.96, p=.003

(Swartz et al., 2015, Neuron)
Summary

• Heightened amygdala reactivity to threat predicts greater increase in future depression and anxiety symptoms
• Controlling for baseline symptoms
• Effect holds 1 to 4 years post-scanning
Can we predict who is at greatest risk?

1. Can we identify neural biomarkers that aid in predicting which individuals are at greatest risk?
   
   Heightened threat-related amygdala reactivity

2. How early in development can these neural biomarkers be detected?
Can we predict who is at greatest risk?

1. Can we identify neural biomarkers that aid in predicting which individuals are at greatest risk?

2. How early in development can these neural biomarkers be detected?
Research Question: Study 2

• When can we begin to observe differences in threat-related amygdala reactivity?
  – High-risk sample
  – Adolescence
Defining risk

• Risk for depression:
  – Family history of depression
    • First- and second-degree relative with a history of depression (Williamson et al., 2004, *Journal of the American Academy of Child & Adolescent Psychiatry*)
Methods: Participants

• Teen Alcohol Outcomes Study
• Random sampling and phone screening for family history of depression (FH)
• 51% female in FH+ group; 49% female in FH-
• Exclusion criteria: No diagnosis of depression at baseline; anxiety disorder diagnosis permitted
Methods

• Wave 1
  – Age: 13.6 years (range=11 to 15)
  – 119 FH+ and 112 FH-

• Wave 2
  – Age: 15.7 years (range=13 to 18)
  – 100 FH+ and 96 FH-
Amygdala Reactivity to Emotional Faces

(Swartz et al., 2015, *American Journal of Psychiatry*)
Can we observe differences in the development of amygdala reactivity in adolescents with a family history of disorder?

Family history x age interaction: $F(1,220)=6.67, p=.01$. Remains significant excluding participants with internalizing disorders and controlling for depressive symptoms: $F(1,131)=5.29, p=.023$.

(Swartz et al., 2015, *American Journal of Psychiatry*)
Amygdala reactivity by family history

Wave 1 (M Age = 13 years)

Left Amygdala Reactivity to Fearful Faces

FH-

FH+

$t(229)=-.43, p=.67$

Wave 2 (M Age = 15 years)

$t(194)=-2.38, p=.02$
Do increases in amygdala reactivity predict future symptoms?

• Youth Self Report (YSR) Affective Problems Subscale (Achenbach et al., 2003, *Journal of Clinical Child & Adolescent Psychology*)

• Change in amygdala reactivity (Wave 1 to Wave 2) predicting change in future symptoms (Wave 2 to Wave 3)
  – Approximately 1 year later (M Age = 16 years)
Do increases in amygdala reactivity predict future symptoms?

FH+ group: $B=2.26$, $SE=.9$, $p=.011$

Swartz et al. In preparation
Summary

• Increased threat-related amygdala reactivity observed by mid-adolescence in high-risk individuals

• Increases in amygdala reactivity predict greater increases in depressive symptoms 1 year later
Can we predict who is at greatest risk?

1. Can we identify neural biomarkers that aid in predicting which individuals are at greatest risk?

2. How early in development can these neural biomarkers be detected?

Heightened amygdala reactivity to threat emerges by mid-adolescence
Future directions

• Improving our predictive power with neuroimaging biomarkers
Future directions

• Improving prediction: Additional biomarkers

Reward processing circuitry: Ventral Striatum
Future directions

• Improving prediction: Additional biomarkers
Future directions

• Improving prediction: Functional connectivity

Psychophysiological interaction (PPI) and Dynamic Causal Modeling (DCM)
Future directions

• Improving prediction: Network measures
Future directions

• Linking neural biomarkers to genetic markers (single nucleotide polymorphisms)
Future directions

- Linking neural biomarkers to genetic markers

**Sparse whole-genome sequencing identifies two loci for major depressive disorder**

CONVERGE consortium

Received 15 December 2014 | Accepted 11 June 2015 | Published online 15 July 2015

rs12415800 in SIRT1
Future directions

- Linking neural biomarkers to genetic markers

\[ F(2, 621) = 4.08, \ p = .017 \]

Bogdan, Swartz, et al. In preparation
Future directions

- Linking neural biomarkers to genetic markers

\[ F(2, 632) = 5.03, p = .007 \]

Bogdan, Swartz, et al. In preparation
Future directions

• Identify protective factors that can mitigate risk by influencing function of neural biomarkers (amygdala reactivity to threat, VS reactivity to reward)
  – Existing treatments (e.g., cognitive behavioral therapy)
  – Diet and nutrition
    • Epigenetic modifications
Take-home points

• Heightened amygdala reactivity to threat predicted the emergence of depression and anxiety symptoms in two independent cohorts

• This biomarker emerges over the course of adolescence

• Future directions: improve prediction, link to genetic biomarkers, identify protective factors
Acknowledgments

• Collaborators:
  – Ahmad Hariri
  – Douglas Williamson

• Funding:
  – National Institute on Alcohol Abuse and Alcoholism grant R01AA016274 and the Dielmann Family (DEW)
  – National Institute on Drug Abuse grant R01DA033369 and R01DA031579 (ARH)
  – Postdoctoral Fellowship provided by the National Institute of Child Health and Human Development through the Center for Developmental Science grant T32-HD07376 (JRS) and by NIH grant P30DA023026
## DNS Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline (n=753)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>19.6</td>
<td>1.2</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Childhood trauma</td>
<td>33.2</td>
<td>7.9</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Stressful life events Time 1</td>
<td>10.1</td>
<td>8.2</td>
<td>0</td>
<td>66</td>
</tr>
<tr>
<td>Internalizing symptoms Time 1</td>
<td>110.7</td>
<td>25.4</td>
<td>61</td>
<td>230</td>
</tr>
<tr>
<td><strong>Time 2 Scores: Model A (n=340)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.8</td>
<td>1.5</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Stressful life events Time 2</td>
<td>4.3</td>
<td>5.3</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>Internalizing symptoms Time 2</td>
<td>110.7</td>
<td>26.4</td>
<td>65</td>
<td>214</td>
</tr>
<tr>
<td>Days between imaging and assessment</td>
<td>467.6</td>
<td>326.7</td>
<td>90</td>
<td>1402</td>
</tr>
<tr>
<td><strong>Time 2 Scores: Model B (n=192)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>21.4</td>
<td>1.4</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>Stressful life events Time 2</td>
<td>5.4</td>
<td>6.2</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>Internalizing symptoms Time 2</td>
<td>111.6</td>
<td>27.2</td>
<td>65</td>
<td>211</td>
</tr>
<tr>
<td>Days between imaging and assessment</td>
<td>683.0</td>
<td>278.6</td>
<td>365</td>
<td>1402</td>
</tr>
<tr>
<td><strong>Time 2 Scores: Model C (n=99)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.5</td>
<td>1.1</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Stressful life events Time 2</td>
<td>3.3</td>
<td>4.2</td>
<td>0</td>
<td>27.7</td>
</tr>
<tr>
<td>Internalizing symptoms Time 2</td>
<td>109.9</td>
<td>29.2</td>
<td>65</td>
<td>230</td>
</tr>
<tr>
<td>Days between imaging and assessment</td>
<td>397.3</td>
<td>39.2</td>
<td>365</td>
<td>455</td>
</tr>
</tbody>
</table>
Analysis

• Regression analysis
  – Dependent variable: Internalizing symptoms at Time 2
  – Predictors: Amygdala Reactivity, Recent Stress at Time 2, Amygdala Reactivity x Stress
  – Covariates: Internalizing symptoms at Time 1, Age, Gender, Childhood Trauma, Non-internalizing psychopathology, Stressful life events at Time 1, Days between scanning and completing the questionnaire
Results: Model A

Swartz et al., revise and resubmit, Neuron
Results: Model B

The graph illustrates the relationship between Amygdala Reactivity to Fearful and Angry Faces and Internalizing Symptoms Post-Scanning. The data is categorized by stress levels: Low Stress, Moderate Stress, and High Stress. The scatter plot shows a trend where higher stress levels correlate with increased internalizing symptoms.
Model B: Change in Symptoms

Swartz et al., accepted pending minor revision, *Neuron*
Model C

- n=99 participants
- Assessments completed approximately 1 year post-scanning (range: 365-455 days)
Results: Model C

\[ B = 5.56, \text{SE} = 1.9, t(98) = 2.96, p = .003 \]

Swartz et al., revise and resubmit, *Neuron*
Is this moderated by stress?

Johnson-Neyman technique: FH- adolescents differ from FH+ adolescents at stress <2.73 (mean=2.49)

Swartz et al. (in press) *American Journal of Psychiatry*
Results: Model A

Johnson-Neyman approach: There is a significant effect of amygdala reactivity on internalizing symptoms at all values of stress above 6.428 (mean stress=4.28)

Swartz et al., revise and resubmit, Neuron
Participants scanned at Wave 1:
163 High and 168 Low
Total = 331

Participants scanned at Wave 2:
118 High and 126 Low
Total = 244

Participants meeting QC criteria at Wave 1:
120 High and 112 Low
Total = 232

Participants meeting QC criteria at Wave 2:
101 High and 96 Low
Total = 197

Participants meeting QC criteria at both Wave 1 and Wave 2:
85 High and 72 Low
Total = 157
Adolescence marks beginning of heightened risk for disorder

Weissman et al. (2006)
FIGURE 1. Overlap in Task-Related Activation at Wave 1 and Wave 2 in Adolescents With and Without a Family History of Depression and a History of Stressful Life Events.
Change over time

$F(1, 152) = 5.715, p = .018$
<table>
<thead>
<tr>
<th></th>
<th>High-Risk Group</th>
<th>Low-Risk Group</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Wave 1 (n=232)</td>
<td>13.61</td>
<td>1.0</td>
<td>13.55</td>
<td>.94</td>
<td>$t(230)$= .43</td>
<td>$p=.67$</td>
</tr>
<tr>
<td>Age Wave 2 (n=197)</td>
<td>15.69</td>
<td>1.0</td>
<td>15.63</td>
<td>1.1</td>
<td>$t(195)$= .39</td>
<td>$p=.70$</td>
</tr>
<tr>
<td>Emotional Neglect</td>
<td>8.42</td>
<td>3.4</td>
<td>7.49</td>
<td>2.6</td>
<td>$t(221)$= 2.29</td>
<td>$p=.02$</td>
</tr>
<tr>
<td>Depressive Symptoms 1</td>
<td>10.24</td>
<td>8.9</td>
<td>8.16</td>
<td>6.4</td>
<td>$t(230)$= 2.04</td>
<td>$p=.04$</td>
</tr>
<tr>
<td>Depressive Symptoms 2</td>
<td>7.27</td>
<td>9.0</td>
<td>5.79</td>
<td>7.6</td>
<td>$t(194)$= 1.24</td>
<td>$p=.22$</td>
</tr>
<tr>
<td>Stressful Life Event Severity 1</td>
<td>2.44</td>
<td>1.4</td>
<td>2.47</td>
<td>1.5</td>
<td>$t(221)$= -.15</td>
<td>$p=.88$</td>
</tr>
<tr>
<td>Stressful Life Event Severity 2</td>
<td>2.49</td>
<td>1.3</td>
<td>2.21</td>
<td>1.3</td>
<td>$t(187)$= 1.49</td>
<td>$p=.14$</td>
</tr>
<tr>
<td>Mean Accuracy 1</td>
<td>98.5%</td>
<td>3.0</td>
<td>98.6%</td>
<td>3.1</td>
<td>$t(222)$= -.21</td>
<td>$p=.83$</td>
</tr>
<tr>
<td>Mean Accuracy 2</td>
<td>98.4%</td>
<td>3.6</td>
<td>97.8%</td>
<td>4.4</td>
<td>$t(193)$= .98</td>
<td>$p=.33$</td>
</tr>
<tr>
<td>Mean RT 1</td>
<td>1290.3</td>
<td>239</td>
<td>1306.6</td>
<td>244</td>
<td>$t(222)$= -.50</td>
<td>$p=.62$</td>
</tr>
<tr>
<td>Mean RT 2</td>
<td>1236.3</td>
<td>292</td>
<td>1243.0</td>
<td>266</td>
<td>$t(193)$= -.17</td>
<td>$p=.87$</td>
</tr>
<tr>
<td>Mean Head Displacement 1</td>
<td>.044</td>
<td>.01</td>
<td>.046</td>
<td>.01</td>
<td>$t(230)$= -1.24</td>
<td>$p=.22$</td>
</tr>
<tr>
<td>Mean Head Displacement 2</td>
<td>.045</td>
<td>.01</td>
<td>.044</td>
<td>.01</td>
<td>$t(195)$= .84</td>
<td>$p=.40$</td>
</tr>
</tbody>
</table>
A. Baseline scan

Online assessments (every 3 months)

<table>
<thead>
<tr>
<th>Participant 1</th>
<th>Participant 2</th>
<th>Participant 3</th>
<th>Participant 4</th>
<th>Participant 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life stress Time 2 (mean of all assessments before 1 year post-scanning)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One-year post scanning

Internalizing symptoms Time 2

Amygdala reactivity

B. Internalizing symptoms Time 2

- Low life stress Time 2
- Mean life stress Time 2
- High life stress Time 2

Amygdala Reactivity to Fearful and Angry Faces (A.U.)

-0.4 -0.3 -0.2 -0.1 0 0.1 0.2 0.3 0.4

90 100 110 120 130
Research Question: Study 3

• Family history is a broad risk for disorder
• Can we identify specific mechanisms that explain the increase in threat-related amygdala reactivity in these individuals?
Low socioeconomic status

• Parental history of psychopathology is associated with lower SES
  – A finding also observed in our sample

• Low SES is associated with altered DNA methylation in gene promoter regions that affect how genes are expressed
  – Serotonin transporter gene (*SLC6A4*) promoter
Hypotheses

Low socioeconomic status → Increases in SLC6A4 methylation → Increases in amygdala reactivity → Increases in depressive symptoms
Lower SES predicts increases in SLC6A4 from baseline to 2-year follow-up

$B = -0.34, \ SE = 0.15, \ p = 0.02$

Swartz et al. (in preparation)
Increases in SLC6A4 methylation are associated with increases in amgydala reactivity

\[ B = .10, \ SE = .04, \ p = .016 \]

Swartz et al. (in prep)
Methods

• Same high-risk family sample
• SES = average of education and income levels for caregiver and spouse (standardized)
• DNA was extracted from whole blood and methylation levels at 20 CpG sites closest to the \textit{SLC6A4} promoter region were analyzed
• Participants reported depressive symptoms with the Youth Self Report
Hypotheses

Low socioeconomic status $\rightarrow$ Increases in SLC6A4 methylation
Lower SES predicts increases in SLC6A4 from baseline to 2-year follow-up

B = -0.34, SE = 0.15, p = 0.02

Swartz et al. (in prep)
Hypotheses

Low socioeconomic status \(\rightarrow\) Increases in SLC6A4 methylation \(\rightarrow\) Increases in amygdala reactivity
Increases in SLC6A4 methylation are associated with increases in amgydala reactivity.

B = .10, SE = .04, p = .016

Swartz et al. (in prep)
Hypotheses

- Low socioeconomic status
- Increases in SLC6A4 methylation
- Increases in amygdala reactivity
- Increases in depressive symptoms
Increases in amygdala reactivity predict increases in depressive symptoms 1 year later.

\[ B = 2.26, \text{SE} = .9, p = .011 \]

Swartz et al. (in prep)
Summary

• Adolescents with a family history of depression experience lower SES

• Lower SES predicts epigenetic modifications to the *SLC6A4* promoter over time

• Increases in *SLC6A4* methylation predict increases in amygdala reactivity

• Increases in amygdala reactivity predict future increases in depressive symptoms
12-month Prevalence of Major Depressive Episode among U.S. Adults (2012)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Overall</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-25</td>
<td>8.9</td>
<td>8.4</td>
<td>5.2</td>
</tr>
<tr>
<td>26-49</td>
<td>7.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>5.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>Hispanic</th>
<th>White</th>
<th>Black</th>
<th>Asian</th>
<th>AI/AN* 2 or More</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.0</td>
<td>7.1</td>
<td>6.3</td>
<td></td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>3.2</td>
<td></td>
<td></td>
<td></td>
<td>7.7</td>
</tr>
</tbody>
</table>

*AI/AN = American Indian/Alaska Native

Data courtesy of SAMHSA

<table>
<thead>
<tr>
<th>Sex</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>9.1</td>
<td>4.7</td>
<td>3.7</td>
<td>8.6</td>
<td>11.8</td>
<td>10.9</td>
</tr>
<tr>
<td>Female</td>
<td>13.7</td>
<td>7.1</td>
<td>7.9</td>
<td>11.8</td>
<td>11.8</td>
<td>10.5</td>
</tr>
<tr>
<td>Male</td>
<td>4.7</td>
<td>3.7</td>
<td>8.6</td>
<td>11.8</td>
<td>11.8</td>
<td>11.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Hispanic</th>
<th>White</th>
<th>Black</th>
<th>Asian</th>
<th>AI/AN* 2 or More</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>10.5</td>
<td>9.1</td>
<td>7.9</td>
<td>4.2</td>
<td>5.2</td>
</tr>
<tr>
<td>13</td>
<td>11.8</td>
<td>11.8</td>
<td>7.9</td>
<td>4.2</td>
<td>5.2</td>
</tr>
<tr>
<td>14</td>
<td>11.8</td>
<td>11.8</td>
<td>7.9</td>
<td>4.2</td>
<td>5.2</td>
</tr>
<tr>
<td>15</td>
<td>10.9</td>
<td>10.5</td>
<td>7.9</td>
<td>4.2</td>
<td>5.2</td>
</tr>
<tr>
<td>16</td>
<td>11.8</td>
<td>11.8</td>
<td>7.9</td>
<td>4.2</td>
<td>5.2</td>
</tr>
<tr>
<td>17</td>
<td>10.9</td>
<td>10.5</td>
<td>7.9</td>
<td>4.2</td>
<td>5.2</td>
</tr>
</tbody>
</table>

*AI/AN = American Indian/Alaska Native

Data courtesy of SAMHSA
## Model A: Results

Dependent variable: Internalizing symptoms at follow-up

<table>
<thead>
<tr>
<th>Predictor</th>
<th>B Coefficient</th>
<th>Standard Error</th>
<th>t(339)=</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala reactivity</td>
<td>3.67</td>
<td>3.7</td>
<td>1.00</td>
<td>.32</td>
</tr>
<tr>
<td>Stressful life events Time 2</td>
<td>.60</td>
<td>.3</td>
<td>2.32</td>
<td>.02</td>
</tr>
<tr>
<td>Interaction of amygdala reactivity x stressful life events Time 2</td>
<td>2.01</td>
<td>.7</td>
<td>3.08</td>
<td>.002</td>
</tr>
<tr>
<td>Gender</td>
<td>-3.02</td>
<td>2.3</td>
<td>-1.31</td>
<td>.19</td>
</tr>
<tr>
<td>Age</td>
<td>1.21</td>
<td>1.0</td>
<td>1.18</td>
<td>.24</td>
</tr>
<tr>
<td>Childhood Trauma</td>
<td>.29</td>
<td>.2</td>
<td>1.72</td>
<td>.09</td>
</tr>
<tr>
<td>Internalizing symptoms Time 1</td>
<td>.55</td>
<td>.1</td>
<td>8.21</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Psychopathology</td>
<td>2.75</td>
<td>3.5</td>
<td>.79</td>
<td>.43</td>
</tr>
<tr>
<td>Stressful life events Time 1</td>
<td>-.05</td>
<td>.2</td>
<td>-.31</td>
<td>.76</td>
</tr>
<tr>
<td>Days between MRI and completing questionnaire</td>
<td>-.0004</td>
<td>.004</td>
<td>-.12</td>
<td>.91</td>
</tr>
</tbody>
</table>

Swartz et al., accepted pending minor revision, *Neuron*