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Kathryn R. Cullen
Melinda Westlund
Ana Bortnova

The Neurobiology of Non-Suicidal Self Injury in Adolescents

Disclosures
• I have no financial relationships to disclose.

Overview
• Introduction
  – The problem in adolescents
  – Previous neurobiological work
• Conceptualizing brain-behavior relationships
• Our previous work with the methods
• 2 current studies in adolescents with NSSI
  – A cross-sectional imaging study
  – A pilot treatment study
• (Very) preliminary results

Non-suicidal Self Injury (NSSI)
The deliberate, direct destruction or alteration of body tissue, without conscious suicidal intent, but resulting in injury severe enough for tissue damage to occur.

NSSI in adolescents
• Worldwide, 18% of adolescents report a history of NSSI
• Average onset 12-14 years
• Up to 4 times more common in girls than boys
• On average, people with NSSI report 13 incidents in 12 months

NSSI and Adolescent Development
• As they face the challenges of this transition period, adolescents experiment with a range of coping mechanisms
• Some may be maladaptive such as NSSI, substance use, disordered eating behaviors, etc.

Brain Development in Adolescence

Adolescence: A window of opportunity
• Ongoing development means...
  – The neural structures may be more vulnerable to insult and following abnormal trajectory
  – System may be more amenable to change from intervention to restore healthy trajectories

Problems associated with NSSI
• Depression
• Anxiety
• Substance use
• Eating disorders
• Personality disorders
• Behavior disorders
• Autism spectrum disorders
NSSI time course: large-scale

NSSI time course: small scale

Functions of Self Harm

Neurobiological Underpinnings: Techniques in previous work

• Brain Imaging
• Physiological assessments
  – cortisol, heart rate variability, defensive startle reflex, electrodermal skin response
• Neurocognition

Imaging and NSSI

• PET study in adults with NSSI: reduced 5HT binding in the prefrontal cortex
• fMRI study in adolescents with NSSI: greater orbitofrontal, inferior and middle frontal cortex activity while viewing NSSI pictures

Physiology

• Adolescents with NSSI showed...
  – Diminished cortisol responses to a stressor
  – Greater subjective emotional responses but blunted defensive startle reflex modulation by emotion
  – Attenuated electrodermal response (EDR) during resting conditions but elevated EDR during frustration
  – Similar heart rate variability to controls
  – Greater sinus arrhythmia activity during negative mood induction in “parasuicidal” adolescents (combined NSSI and suicide attempters) compared to controls

Research Question #1

• What are the developmental neurobiological underpinnings of adolescent NSSI?
  – Focus on neural circuitry
• Approach: Research Domains Criteria Project (RDoC)
  – Identify psychological dimensions relevant to NSSI that can be mapped more directly to neural systems

Neurocognition

• Impulsivity is associated with nonclinical populations who engage in NSSI
• Adolescents with high-severity NSSI had impaired spatial working memory, whereas those with low-severity NSSI showed impaired inhibitory control
• Youth with borderline traits may tend to “hypermentalize”, or excessively and inaccurately attribute thoughts and feelings to others.

Brain-Behavior Relationships
**Research Question #2**

- Does treatment with N-acetyl cysteine (NAC) reduce NSSI in adolescents?
- Does NAC impact brain circuitry?

**N-acetyl cysteine (NAC)**

- Derivative of amino acid L-cysteine
- Complex mechanisms of action, impacting
  - Glutamate transmission
  - Oxidative balance
  - Inflammatory pathways
  - Neurotrophins
- Useful in other psychiatric disorders
  - Addiction, gambling, OCD, hair-pulling, skin-picking, schizophrenia, bipolar, autism

**University of Minnesota Academic Health Center Faculty Research Development Grant**

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**Berk et al. TIPS 2013**

**Our previous work in relevant populations**

- We examined brain connectivity in
  - Adolescents with MDD
  - Adult young women with borderline personality disorder

**DTI: Lower FA in adolescents with MDD**

While matter connection between Subgenual anterior cingulate cortex (sgACC) and amygdala

**Lower Functional Connectivity in Adolescents with MDD**

**Examining emotion pathways in borderline personality disorder (BPD)**

Individuals with BPD have high sensitivity to emotional stimuli, and strong reactions that are slow in returning to baseline (Linehan, 1995).

Early fMRI research has supported this clinical model examining amygdala response to threat showed that BPD subjects demonstrate:

1. ↑ amygdala response to stimuli (hyperactivity)
2. ↓ prefrontal cortical activity (dysregulation)

**Proposed Amygdala Pathways**

- Short Route (Bottom-Up): Direct connections between the thalamus and amygdala allow for a rapid response to potential threats in the environment
- Long Route (Top-Down): Connections between the prefrontal cortex and amygdala may allow for slower, cortically-driven interpretative aspects of emotion processing

**fMRI Task Design**

- 3 runs: Neutral/Neutral, Masked Fear/Unmasked Neutral
- Time: 24 sec
- Fixation: 5 min 20 s
- Trials: 20 ms probe, 180 ms mask, 1300 ms fixation

**Neutral Scan: Amygdala Connectivity**

Red: High amygdala seed correlation
Red: Low amygdala seed correlation

**Cullen et al., JAACAP 2010 Feb;49(2):173-183e**

Lower Functional Connectivity in Adolescents with MDD

Seed: Subgenual ACC (BA25) p = 0.003, corrected, effect size = 1.3

Cullen et al (2009)
Study Procedures
1. Comprehensive clinical assessment
2. MRI
3. Treatment with NAC
   - 800mg bid weeks 1-2
   - 1200mg bid weeks 3-4
   - 1800mg bid weeks 5-8
4. Repeat MRI

Participants to date
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean Age</th>
<th>Sex (M/F)</th>
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<tbody>
<tr>
<td>NSSI</td>
<td>11</td>
<td>16.6</td>
<td>10/1</td>
</tr>
<tr>
<td>Control</td>
<td>2</td>
<td>21</td>
<td>1/0</td>
</tr>
</tbody>
</table>

One participant participated in treatment study with NAC only
One participant participated in baseline scanning only
Consented and interviewed: n=15
Baseline scan: n=13
Post-treatment scan: n=7

Assessment Measures
- Kiddie-Schedule for Affective Disorders and Schizophrenia (KSADS-PL), Schedule for Clinical Disorders of DSM-IV (SCID)
- Deliberate Self Harm Inventory
- Inventory of Statements about Self-Injury
- Beck Depression Inventory-II
- Beck Depression Inventory-II
- Disturbance in Emotion Regulation Scale
- Symptom Checklist-90
- Barratt Impulsivity Scale
- Toronto Alexithymia Scale
- Personality Assessment Inventory
- Iowa Gambling Task

MRI protocol
- High-resolution T1 Anatomical
- Resting-state fMRI
- Diffusion tensor Imaging
- Task fMRI
  - Passive emotion face viewing
  - Matching task: emotion faces vs neutral shapes
- Spectroscopy

MRI advances
- Accelerated acquisition: multiband excitation of several slices at once
  - Allows for the feasibility of collecting much higher spatial and temporal resolution than previously possible
- fMRI dimensions: 2x2x2mm, 1.32s TR
- DTI: increase to 128 directions

Early Experience
- 8 subjects completed NAC treatment
- Everyone has tolerated the medication well
- No results yet on primary outcome measure
- Anecdotally, most subjects either decreased or stopped NSSI during the study (one exception)
  - "It helped with my mood swings."
  - "It decreased my urges to cut."

Preliminary Results
- Pre-post NAC: changes on Barat Impulsivity scale (BIS) and SCL-90 scores
  - BIS total: t=4.0, p=0.005
  - BIS attentional: t=2.4, p=0.049
  - SCL somatization: t=2.8, p=0.04
  - SCL hostility: t=2.2, p=0.06
  - SCL global: t=2.1, p=0.08
Spectroscopy

No significant changes in 3 subjects pre-post treatment.

Initial fMRI results: change with treatment

Before > after
Response to emotion faces
N=7
Cluster corrected p=0.05 z>2.0

Next Steps

• Neural circuitry of NSSI:
  – Need large sample to better understand biologically-based heterogeneity in adolescents with NSSI
  – Examine change over time: before onset, across episodes, across development
• Treatment with NAC:
  – Randomized controlled trial of NAC for adolescents with self-harm
  – Identify neural predictors of treatment response
  – Identify brain changes with successful treatment
• Move toward neurobiology-based personalized treatment approach

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Contact
Katie Cullen, M.D.
2450 Riverside Avenue
F256 West Building
Minneapolis, MN 55406
612-273-9711
rega0026@umn.edu