The Neurobiology of Non-Suicidal Self Injury in Adolescents

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Driven to Discover℠

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.

Winchel and Stanley *AJP* 1991

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

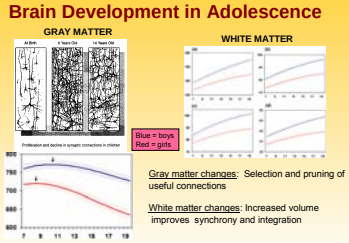
Muehlenkamp et al *Child Adolesc Psychiatry Ment Health* 2012
Lloyd-Richardson et al, *Psychol Med* 2007

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.

Spear *Neuroscience Biobehv Rev* 2000

Brain Development in Adolescence



Gray matter changes: Selection and pruning of useful connections

White matter changes: Increased volume improves synchrony and integration

Philip Seeman, *Am J Psychiatry* 1999; 156:2:168
R.K. Lenroot et al. *NeuroImage* 36 (2007) 1065–1073

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

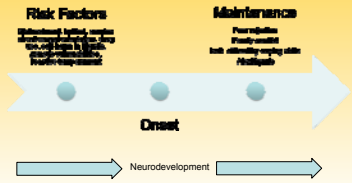
Problems associated with NSSI

- Depression
- Anxiety
- Substance use
- Eating disorders
- Personality disorders
- Behavior disorders
- Autism spectrum disorders

Some adolescents who engage in NSSI do not meet criteria for any mental illnesses

Favazza & Rosenthal *Behavioral Neurology* 1990; Klonsky *AJP* 2003; Stanford and Jones *J Child Psychol Psychiatry* 2009

NSSI time course: large-scale



NSSI time course: small scale

Van der Kolk et al, *AJP* 1991; McMahon *Soc Sci Med* 2010; Crowell et al *Psychol Bull* 2009; O'Connor *BJP* 2009

Functions of Self Harm

Nock's 4 Function Model

	Positive Reinforcement (PR)	Negative Reinforcement (NR)
Automatic (A) (Intrapersonal)	APR Reward, sense of control	ANR Relieve tension, end depersonalization/derealization
Social (S) (Interpersonal)	SPR Gain sympathy and attention, set boundaries	SNR Avoid social situation

Nock and Prinstein 2004, 2005; Klonsky *Psychiatry Research* 2009; Nock *Curr Dir Psychol Sci* 2009

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

Audenart et al *Eur J Nucl Med* 2001
Plener et al Psychiatry Research 2012

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

Kaess et al *Psychoneuroendocrinology* 2012; Glenn et al *Int J Psychophysiology* 2011; Crowell et al *J Abnormal Child Psychology* 2012; Nock et *al J Consult Clin Psychol* 2008; Crowell et al

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.

Stanford et al *J Child Psychol Psychiatry* 2009;
Fikke et al *Psycho Med* 2011; Sharp et al *JAACAP* 2011

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

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http://www.nimh.nih.gov/research-funding/rdoc/index.shtml

Brain-Behavior Relationships

Psychological construct	System	Brain areas
Emotional reactivity Poor *coping* Alexithymia	Emotion Regulation	amygdala, anterior cingulate, insula, prefrontal cortex
Positive reinforcement Habit	Reward	Midbrain, ventral striatum, dorsal striatum orbitofrontal cortex, medial prefrontal cortex
Rejection sensitivity Poor self esteem Peer connectedness Mentalization	Social Brain	Medial prefrontal, anterior cingulate, temporal-parietal junction, superior temporal sulcus, temporal pole
Rumination Self-referential processes	Default Mode	posterior cingulate, cuneus, medial temporal lobes, medial prefrontal cortex, inferior parietal
Impulsivity	Cognitive Control	Dorsolateral prefrontal cortex, thalamo-cortical
Decreased sensitivity to pain	Pain	Somatosensory cortex, insula, anterior cingulate, posterior parietal cortex, superior temporal sulcus

Research Question #2

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

University of Minnesota Academic Health Center Faculty Research Development Grant

N-acetyl cysteine (NAC)

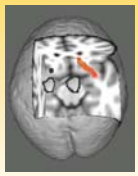
- Derivative of amino acid *L*-cysteine
- Complex mechanisms of action, impacting
  - Glutamate transmission
  - Oxidative balance
  - Inflammatory pathways
  - Neurotrophins
- Useful in other psychiatric disorders
  - Addiction, gambling, OCD, hair-pulling, skin-picking, schizophrenia, bipolar, autism

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

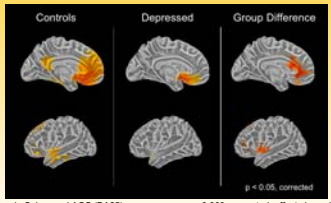
DTI: *Lower FA in adolescents with MDD*



White matter connection between Subgenual antierior cingulate cortex (sgACC) and amygdala

F=7.1, p=0.01, Effect size = 1.0
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)

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)

Herpertz et al., 2001, *Biological Psychiatry*
Donegan et al., 2003, *Biological Psychiatry*

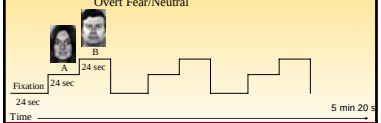
Proposed Amygdala Pathways

- 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

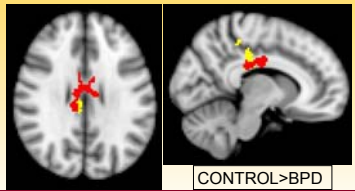
fMRI Task Design

3 runs
Neutral/Neutral
Masked Fear/Masked Neutral
Overt Fear/Neutral

Trials:
20ms probe
180ms mask
1300ms fixation



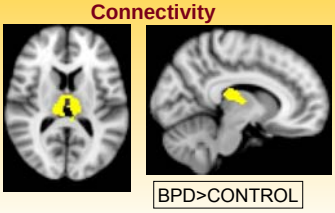
Neutral Scan: Amygdala Connectivity



CONTROL>BPD

Red=right amygdala seed
Yellow=left amygdala seed

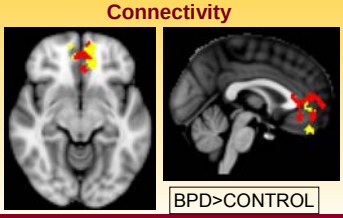
Masked Fear: Amygdala Connectivity



BPD>CONTROL

Yellow=right amygdala seed

Overt Fear Amygdala Connectivity



BPD>CONTROL

Red=right amygdala seed
Yellow=left amygdala seed

Study Procedures

1. Comprehensive clinical assessment
2. MRI
3. Treatment with NAC
   - 600mg bid weeks 1-2
   - 1200mg bid weeks 3-4
   - 1800mg bid weeks 5-8
4. Repeat MRI

Participants to date

Consented and interviewed: n=15
Baseline scan: n=13

Study	N	Mean Age	Sex (F/M)	
NSSI	11	16.6	10/1	
Controls	2	21	2/0	

Post-treatment scan: n=7

One participant participated in treatment study with NAC only
One participant participated in baseline scanning only

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
- Disturbance in Emotion Regulation Scale
- Symptom Checklist-90
- Baratt 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

Human Connectome Project

http://www.cmrr.umn.edu/multiband/
http://humanconnectome.org/about/project

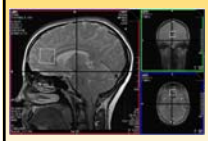
Early Experience

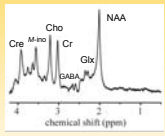
- 8 subjects completed NAC treatment
- Everyone has tolerated the medication well
- No results yet on primary outcome measure
- Anecdotally, most subjects either decreased or stopped NSSI during the study (one exception)
- "It helped with my mood swings."
- "It decreased my urges to cut."

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=2.6, p=0.04
  - SCL hostility: t=2.2, p=0.06
  - SCL global: t=2.0, p=0.08

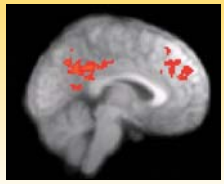
Spectroscopy





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

Emotion matching task: Hariri 2002

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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