NOT FEELING IT: ADOLESCENT DEPRESSION AND REWARD PROCESSING GONE AWRY

Erika E. Forbes, PhD

Professor of Psychiatry, Psychology, Pediatrics, and Clinical and Translational Science
Director, Affective Neuroscience and Developmental Psychopathology Lab

University of Pittsburgh
CURRENT FINANCIAL DISCLOSURES

- NIMH: Research funding
- Association for Psychological Science: Honorarium for editorial work
- Case Western Reserve University: Honorarium for grant review
- Durham VA (Sponsor), Otsuka (Funder): paid consultant for DSMB membership (no role as investigator, ongoing relationship, or product involvement)
DEPRESSION AND DISRUPTED REWARD FUNCTION

Forbes & Dahl, 2005, Development and Psychopathology
Forbes & Dahl, 2012
Gross & Muñoz, 1995
Phillips, Drevets, Rauch, & Lane, 2003
Clark & Watson, 1991
Fowles, 1994
Hasler et al., 2004
Davey, Yücel, & Allen, 2008
Treadway & Zald, 2011

• anhedonia
  • low motivation, fatigue, social withdrawal
  • mood, behavior, physiology

• depression
  • low motivation, fatigue, social withdrawal
  • mood, behavior, physiology
FRONTOSTRIATAL FUNCTION AND DEPRESSION

from Treadway & Zald, 2011, NBR
ADOLESCENCE AND REWARD

- Pleasant experiences
- Heightened neural and behavioral sensitivity during adolescence
- Problems of adolescence reflect altered reward processing

Davey, Yücel, & Allen (2008), NBBR
ADOLESCENCE AND MENTAL HEALTH

- Serious psychopathology emerges
  - Depression
  - Suicidality
  - Bipolar disorder
  - Schizophrenia

Paus et al., 2008

Whiteford et al., 2015, *Lancet*
HOW DO WE CAPTURE FUNCTION IN REWARD CIRCUITRY?
WHAT’S REWARDING?
REWARD FMRI: MONEY

guess, by button press, higher or lower than 5

4 sec

6 sec

number presented

Followed by up if correct, or down if incorrect, circle if neutral

500 ms

9 sec

1 Trial

Baranger et al., 2020 BioRXiv
REWARD FMRI: SOCIAL REWARD

Positive Block:
- Please take a short break. Faces will begin to show again in 8 seconds.
- Green bars indicate positive stimuli.

Neutral Block:
- Please take a short break. Faces will begin to show again in 8 seconds.
- Brown bars indicate neutral stimuli.
THE BFF FMRI TASK:
PERSONALLY RELEVANT SOCIAL REWARD

- Going to Kennywood
- Staying up late to watch TV show
- Graduating
- Being co-presidents of senior class
Friend Positive

Unfamiliar Peer Neutral

Friend Neutral

Unfamiliar Peer Positive

BFF fMRI Task
PATHOPHYSIOLOGY
ADOLESCENT DEPRESSION: LESS STRIATAL RESPONSE, MORE MPFC RESPONSE

Forbes et al., 2009, Am J Psychiatry
Predictor of Onset

IMAGEN study
$N = 1576$
Age: $14.5 \pm 0.4$ years
2 year follow-up

Stringaris et al. 2015. American Journal of Psychiatry
DEVELOPMENT
HIGH-RISK ADOLESCENTS

Mage = 15.7
73% female

Olino et al., 2014, Dev Cog Neurosci
PREDICTOR OF SYMPTOM INCREASE OVER 2 YEARS

72 adolescents typically developing 11-13 years

Morgan et al., 2013. Neurobiology of Disease
REWARD AND CBT +/- SSRI RESPONSE IN ADOLESCENT DEPRESSION

Age 10-16 (M = 12.9)
62% female
8-week course of CBT
CATS STUDY: REWARD AND TREATMENT RESPONSE

1. fMRI task & questionnaires
2. 16 weeks CBT or CCT
3. Interview, ratings, questionnaires

VS/sgACC Response

NAcc-VLPFC Functional Connectivity

Sequeira et al., in press, Am J Psychiatry (!!!)
RISK MECHANISMS
NEURAL RESPONSE TO REWARD EXPLAINS INSOMNIA → DEPRESSION

Pittsburgh Girls Study – Emotion Substudy
123 girls
Insomnia from age 9-13
Depression at 16 & 17

Casement et al., 2019, Sleep
ANHEDONIA
ANHEDONIA: CLINICAL ISSUES

• difficult-to-treat depression
• onset of clinical-level depression
• suicidality
• What is it? Is it one thing?
• How to address it?
  • Physical activity
  • Social activity
• treatments needed
  • BA
  • Positive Affect Treatment (Craske et al., 2019)
    • Improved PA, NA, depression, suicidal ideation
ANHEDONIA AND TREATMENT RESPONSE

Anhedonia Predicts Poorer Recovery Among Youth With Selective Serotonin Reuptake Inhibitor Treatment–Resistant Depression

McMakin et al., 2012

TORDIA Study
24 weeks, new med +/- CBT
Longer time to remission
TRANSCRANIAL MAGNETIC STIMULATION TO DMPFC

**A)** Electrical field modeling with the proposed coil position and orientation (top) and stimulation parameters generates surface normalized electrode strength (Norm E) with a field that reaches the dmPFC, including regions whose (B) response is associated with depression (top; Romens et al., 2015) and functional connectivity with the VS is associated with anhedonia (bottom; Healey et al., 2014).
NOW WHAT?
MAIN POINTS

- Adolescent depression is related to altered function in the brain’s reward circuitry
- Adolescence is a sensitive developmental point for depression and reward function
- Altered reward circuitry has prognostic clinical value
- Reward circuitry can be the mechanism through which risk factors influence development of depression
- Anhedonia deserves greater attention in investigations of depression and reward circuitry
IN-PROGRESS FINDINGS

- VS response fluctuates with severity over years (Jones)
- VS response helps explain disparities in development of depression in sexual minority youth (Eckstrand)
- Computationally defined functional connectivity patterns in reward circuitry reveal differences in depressive severity and can predict anhedonia (Beeney)
- Neural response to guessing task is stable (Baranger)
# REMAINING QUESTIONS

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>How does depression influence brain development and future functioning?</td>
</tr>
<tr>
<td>Can we target anhedonia?</td>
</tr>
<tr>
<td>How do depression and frontostriatal function co-fluctuate across development?</td>
</tr>
<tr>
<td>Can we re-set or interrupt altered system function with brain stimulation?</td>
</tr>
<tr>
<td>How are the dopamine system and neuroinflammation involved in reward-depression associations?</td>
</tr>
</tbody>
</table>
REWARD AND THE MENTAL HEALTH PANDEMIC

• Limited access to rewards
  • Social
  • Academic
  • Risky behavior
• Uncertainty
• Long-term social-affective consequences?
THANKS!

- Participants and families
- Pitt Depression: Ron Dahl, Neal Ryan, Jen Silk, Cecile Ladouceur
- At-large mentors: Danny Pine, David Kupfer
- PGS-E: Amanda Guyer, Kate Keenan, Alison Hipwell
- PMCP: Danny Shaw
- Mentees: Judith Morgan, Tom Olino, Melynda Casement, Sarah Romens, Neil Jones, Kristen Eckstrand, Luis Flores, Gaby Alarcón
- Staff (among many!): Marigrace Ambrosia, Melissa Nance, Morgan Lindenmuth, Rachel LePage, Marissa Cros, Samantha Martin, Samantha Sciarrillo, Sam Musselman

Affective Neuroscience and Developmental Psychopathology Lab
andp.pitt.edu
SUMMARY

- Adolescent depression is related to altered function in the brain’s reward circuitry
- Adolescence is a sensitive developmental point for depression and reward function
- Understanding development of depression is critical
  - How reward mechanisms operate
  - Whether and how we can change altered reward circuitry
  - How to address anhedonia
  - How to promote healthy development and functioning
NEURAL RESPONSE TO REWARD EXPLAINS HIGHER DEPRESSION IN GIRLS WITH LOW SOCIOECONOMIC STATUS

Romens et al., 2015, JCPP

123 girls PA from age 5-16

↑ dmPFC Response to Reward

Childhood Years on Public Assistance

Mean Anticipation-Related BOLD Activity in mPFC Cluster

Current Depressive Symptom Count (log-transformed)

Age 16 depression