Disentangling Neurobiological Risk for Versus Consequences of Adolescent Drinking

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April 5, 2016
Conflict of Interest Statement

- I had no relevant financial relationships with commercial interests over the last 12 months.

- I will present a balanced view of diagnostic or therapeutic options.

- This presentation does not contain trade names or promotes specific companies or products.

- This presentation does not contain advertising.
Learning Objectives

1. Understand driving theories of vulnerability in adolescence

2. Understand incidence of adolescent alcohol and drug use

3. Identify neurobiological markers of risk for adolescent alcohol use

4. Understand how emergent adolescent drinking impacts the developing brain
What is Adolescence?

- The transition from childhood to adulthood
  - Thought of as the “teen” years, but may extend longer
  - Marked by rapid biological, physical, social, and cognitive change - not all occurring simultaneously
- Time of increased vulnerability to psychopathology, including addictions
The Adolescent Brain is Developing

From Gogtay et al., Proc Natl Acad Sci U S A. 2004

From Peters et al., 2012
Develops with age/experience: **MATURES LATE IN ADOLESCENCE**

**Regulation, Judgment, Reasoning**

**Reward, Emotion**

**VULNERABILITY!**

Triggered with puberty/hormone changes: **ACTIVATED EARLY IN ADOLESCENCE**
Adolescent Vulnerability

- Adolescents tend to use emotion and reward areas of the brain rather than reasoning areas to process information and make decisions
  - Difference between “hot” and “cold” situations
  - Differences with and without peers

- Results in increased risk for developing mood and substance use disorders
Alcohol and Drug Use Among Youth

Monitoring the Future, 2013

- Alcohol (lifetime)
- Alcohol (past month)
- Cigarettes (lifetime)
- Cigarettes (daily use)
- Marijuana (lifetime)
- Marijuana (past month)
- "illicit Drugs" (lifetime)
- "illicit Drugs" (past month)
- Amphetamines
- Cocaine
- Inhalants
- Hallucinogens
- MDMA

8th grade
12th grade
Adolescent Alcohol Use is Prevalent

Monitoring the Future Survey, 2013

- Past Month Use
- Drunk in Past 30 days
- Drunk in Lifetime

8th Graders vs. 12th Graders

Monitoring the Future Survey, 2013
Alcohol is Toxic to the Developing Adolescent Brain

Cross-sectional studies of heavy drinking adolescents have shown:

- Reduced brain volume in prefrontal gray and white matter (De Bellis et al., 2005; Medina et al., 2008) and hippocampus (De Bellis et al., 2000; Nagel et al., 2005)

- Atypical cortical thickness (Squeglia et al., 2011)

- Reduced white matter integrity (McQueeny et al., 2009)

- Atypical brain functioning during executive and decision making tasks (Schweinsburg et al., 2011; Xiao et al., 2012)
Risk for Developing an Alcohol Use Disorder (AUD)

- Age of first drink
- Family history of alcohol use disorders (FHP)
- Sensation-seeking personalities
- Externalizing disorders
NEW AROUND THESE PARTS, STRANGER?

AND YET THE QUESTION REMAINED: "WHO CAME FIRST?"
Family History of Alcoholism
Brain Activity Using Functional Magnetic Resonance Imaging (fMRI)
Wheel of Fortune (WOF) Task: Decision Making and Reward Response

Adapted from Ernst et al., 2004 Neuropsychologia
FHP Youth Show Less Brain Response During Risk Taking and Greater Response During Safe Choices

From Cservenka & Nagel, 2012, ACER
Verbal Working Memory (VWM)
FHP Youth Show Less Prefrontal Brain Response During VWM, Comparable to Vigilance Response

From Cservenka, Herting, & Nagel, 2012, DAD
Emotional Go-NoGo Task

- ScaredGo-CalmNoGo
- HappyGo-CalmNoGo
- Go
- NoGo
- 500 msec
- 2-12 sec
Reduced Cognitive Control Region Brain Activity in FHP Youth During Positive and Negative Emotional Contexts

Cservenka, Fair, & Nagel, 2014
Structural Connectivity Using Diffusion Tensor Imaging (DTI)
Family History of Alcoholism

Herting et al., 2010

Yeh et al., 2009

Same frontal and fronto-striatal white matter regions implicated in cognitive control show abnormalities across at-risk and alcohol dependent populations!

Nagel et al., 2011

Adult Alcohol Dependence

Yeh et al., 2009
Functional Connectivity Using Resting State Functional Magnetic Resonance Imaging (rs-fcMRI)
What is rs-fcMRI?

- Rs-fcMRI measures correlated blood oxygen level dependent (BOLD) signal fluctuations between a seed region and other regions in the brain during rest.

- Regions whose activity is significantly correlated with the seed region are considered "functionally connected".

Adapted from Raichle 2011.


Adapted from Raichle 2011.
Temporal fluctuations in BOLD signal from two brain regions

Voxelwise functional connectivity map for a seed region in the right anterior insula/frontal operculum

Positive correlation between BOLD signal here and the BOLD signal of the seed region

Region negatively correlated with the seed region

Dosenbach, 2008
FHP Youth Show Atypical Fronto-Cerebellar Connectivity

Herting, Fair, & Nagel, 2011, NeuroImage
FHP Youth Show Atypical Amygdalar Connectivity With Prefrontal Cortex and Cerebellum

A. Left Amygdala

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<th>L SFG/BA6</th>
<th>L SFG/BA8</th>
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Positive Functional Connectivity

Negative Functional Connectivity

Correct Rejections on HappyGo-CalmNoGo Run

L Amygdala - L Superior Frontal Gyrus Connectivity

FHP: $r = 0.72, p = 0.0017$

FHN: $r = -0.13, p = 0.60$

Cservenka, Fair, & Nagel, 2014
FHP Youth Show Less Integration Between Right NAcc and Orbitofrontal Cortex - Circuitry Critical for Reward Valuation

Cservenka, Casimo, Fair, & Nagel, 2014, Psychiatry Res
Dissociating Risk From Consequences
Wheel of Fortune (WOF) Task: Decision Making and Reward Response

Adapted from Ernst et al., 2004 Neuropsychologia
Controls Show Greater Activation Than Binge Drinkers During Risk Taking in Control Circuitry Across Time

Risk Marker?

Consequences of Drinking - Dorsal Caudate Response During Risky Decision Making

Adolescent Binge Drinkers Show Less Cerebellar Response to Reward

Findings hold after controlling for pre-alcohol exposed brain response

Cservenka, Jones, & Nagel, *Dev Cogn Neurosci*, 2015
Conclusions

- FHP youth show less brain response in cognitive control regions during cognitively and emotionally demanding contexts, as well as atypical connectivity in related circuitry
  - Similar findings seen in other risk populations

- Adolescent binge drinkers show reductions in activity of cognitive control circuitry both prior to drinking, as well as additional functional abnormalities following drinking behavior

- While able to compensate in a laboratory setting, abnormalities may be exaggerated in contexts with greater socio-emotional influences or external demands

- Given the role of these brain regions in subserving executive and emotional functioning and decision making, abnormalities in this circuitry may heighten the risk for developing an AUD through reduced cognitive and emotional control
Significance and Next Steps

- Finding neurobiological commonalities and distinctions across risk factors will inform translational work necessary to probe mechanisms of addiction.

- Understanding neurobiology associated with known risk markers is necessary for the development of neurobiologically informed prevention and intervention strategies.

- Longitudinal studies are crucial to determine which risk markers are predictive of alcoholism, as well as which markers may suggest resilience.
Acknowledgments

■ Funding and Assistance
  – National Institute on Alcohol Abuse and Alcoholism (R01 AA017664, P60 AA010760, & U01 AA021691)
  – National Institute of Mental Health (R21 MH099618)
  – Oregon Clinical and Translational Research Institute (OCTRI)

■ Developmental Brain Imaging Laboratory
  – Kristen Mackiewicz-Seghete - Psychiatry Faculty Collaborator
  – Gaby Alarcón & Scott Jones - BEHN Graduate Students
  – Hannah Stein, Kristina Hernandez, Jesse Chiem, Alicia Johnson, & Darya Veach - Research Associates/Assistants

■ Collaborators
  – Damien Fair, PhD - OHSU
  – Chris Kroenke, PhD - OHSU
  – Bruce Boston, MD - OHSU
  – Suzanne Mitchell, PhD - OHSU
  – Joel Nigg, PhD - OHSU
  – NCANDA Consortium
  – ABCD Consortium