Adolescent Brain Development: Understanding the Impact of Substance Use

Adolescent Substance Abuse, Treatment Outcomes and Cognitive Functioning

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Underage Drinking Research: Early Work

• **Early Neuroscience** FOAs for NIAAA (1990-2002)
  - Recognized intersection of adolescent alcohol use and neurodevelopment
  - Division of Basic Research FOAs for both animal and human research

• **Epidemiology** - (1991-1992)
  - First National Longitudinal Alcohol Epidemiology Survey (NLAES)
  - Association between early drinking and later dependence.\(^1\)

• **Underage Drinking Research Initiative** (2003-2004)
  - Interdisciplinary Steering Committee to advise NIAAA
  - Broad range of experts: adolescent development; child health; brain imaging; genetics; neuroscience; prevention research; public policy; health communications

\(^1\) Grant & Dawson, JSA
Underage Drinking Initiative: Highlights

• **Clear: Underage Drinking is a Developmental Issue**
  • Alcohol abuse and alcoholism emerge from developmental processes
  • Reframing has influenced across federal agencies (e.g. NIAAA, SAMHSA, CDC, NHTSA, ED)
  • Adolescence in all its complexity is a primary locus for studying the gene environment interplay that NIAAA addresses

  • Developmental Framework
  • Science organized by age group (under 10, 10-15, 16-20) reports
  • Prevention and Treatment reviews

• **Surgeon General’s Call to Action to Prevent and Reduce Underage Drinking**
  • 2007 - National release with the SG’s office and State roll-outs
  • Governors’ Spouses Leadership in their respective states
Underage Alcohol Use and the Developing Brain: Key Questions

- **Short and long-term consequences of alcohol exposure** on brain, cognitive, and emotional/regulatory development during preadolescence and adolescence;
- **Effects of timing, dose and duration of alcohol** on brain and cognitive development;
- **Recovery of neural and behavioral function** to determine if the plasticity of the adolescent brain makes it more or less vulnerable to alcohol’s acute and chronic effects;
- **Risk and vulnerability factors** in alcohol’s effects on the brain; and
- **Identify early neural, cognitive, and affective markers** that may predict alcohol abuse and dependence during adolescence and/or adulthood.
Research on Underage Alcohol Use and the Developing Brain:

A Two-Phase Research Initiative in humans:

• Phase I: five R21 projects in humans (2007) to assess the practicability of moving forward with a large scale project

• Phase II: Multisite longitudinal study to evaluate alcohol’s effects on the developing adolescent brain (2012) before and as youth begin to have experience with alcohol.

Animal studies to clarify human research:

• Studies on alcohol, puberty, and adolescent brain development

• Neurobiology of Adolescent Drinking in Adulthood (NADIA) consortium is studying the effects of adolescent alcohol use on the adult brain.
Brain Architecture and Functioning Changes Throughout Childhood & Adolescence

Large volume of brain cells prior to adolescence

Begin to “Sculpt”

- Neural connections
- about age 11-12
- -activate or eliminate
- -posterior to anterior sequence
Brain Regulatory Systems Critical to Adolescent Success Begin to Develop Before Age 11

- Emotional Control
- Social Regulation
- Behavioral Control & Social Rules
- Regulation of Sleep & Activation Cycles
- Regulation of Stress Response

Zucker, 2006
Alcohol Treatment Teens Remember 10% Less Than Community Teens After 20 Minutes

Retention Rate

Verbal Information  Nonverbal Information

Alcohol Dependent  Nonabusing

Comparisons

• Gender
• Age
• Grade
• SES
• FH

Brown, et al. ACER. 2000
Neurocognitive Functioning Deteriorates with Continued Alcohol Use After Treatment

**Graph:**

- **Visuospatial T-score**
- **Timepoint:** Treatment, Four-Year Follow-Up

- **Good treatment outcome**
- **Post-tx withdrawal but No recent use**
- **Post-tx withdrawal and Recent use**

*Tapert & Brown (1999)*
Long Term Course of Treated Youth Varies Markedly:

- Abstention, Regular use, Age Dependent Problems and Chronic Problems

### Graph Description

- **Group 1:** Abstainers/Infrequent Users (n=44)
  - Abstain
- **Class 2:** Late Adolescent Resurgence (n=27)
  - Late Adolescent Resurgence
- **Class 3:** Emerging Adulthood Resurgence (n=22)
  - Young Adult Heavy Use
- **Class 4:** Heavy Drinkers (n=25)
  - Heavy Drinkers
- **Class 5:** Heavy Drinkers/Drug Dependent (n=26)
  - Heavy Drk/Drug Dep
- **Class 6:** Chronic/Severe (n=9)
  - Chronic Severe

**Composite Days Per Month Using**

**Time Since Treatment (years)**

Legend:
- White: Other Drugs
- Gray: Marijuana
- Black: Alcohol
Memory Performance over 10-Years: Concern for Heavy Drinkers & Drug Users

Hansen et al 2010
Memory Performance over 10-Years: Concern for Heavy Drinkers & Drug Users

![Graph showing long delay free recall over time for different groups of individuals with varying levels of alcohol and drug usage.](image-url)
Alcohol and Drug Trajectories from Adolescence to Mid-Twenties
Adolescent Binge Drinkers Display Learning and Memory Problems During Early Abstinence: Memory Errors

Winward et al. 2014
Adolescent Binge Drinkers Display Learning and Memory Problems During Early Abstinence: Visuospatial Ability

Winward et al. 2014
Adolescent Binge Drinkers Display Learning and Memory Problems During Early Abstinence: Visuospatial Accuracy
Brain Functioning: Multiple Methods to Understand Structure and Function

- Structural MRI
- DTI
- fMRI
White Matter Change in Late Adolescence

Significant fiber improvement, age 17.5 to 19
NC performance correlated with DTI changes

Bava, Thayer, Jacobus, Ward, Jernigan, & Tapert
Cerebellar Volume

Teens: higher peak drinks predicted smaller left cerebellar gray ($p=.02$) and white matter ($p=.02$) and right cerebellar gray matter ($p=.006$).

Lisdahl et al., 2013, Psychiatry Research
Increased Drinking → Worse White Matter

- Users showed poorer white matter integrity than Controls in 7 tracts ($p < .01$)
  
  **L PCR**  **Splenium**  **R PCR**  **R SLF**  **R STG**

**Right Superior Longitudinal Fasciculus Integrity,**
**Time 2**

More drinking during follow-up predicted worsened white matter
Neurocognitive Performance in relation to age of onset of MJ

Trails Number Sequencing

Digit Symbol Coding

$ r = .33 \text{ to } .44 $
Alcohol Cue Reactivity of Heavy Drinking Adolescents compared to Controls

**Alcohol Pictures**

**Non-Alcohol Pictures**

Matched: Color Light Content Valence

AUD Adolescent Response to Alcohol Cues is Pronounced Even with Abstinence

- Orange: AUD teens had greater increase in response to alcohol pictures relative to other beverages

Teen Substance Use & Brain

- Alcohol use
- Hangover, withdrawal, blackout
- Pre-existing neural features
- Gender
- Neurobiological processes:
  - Inflammation
  - Toll-like receptor activity
  - Myelin proteins
  - Oligodendrocyte death
- White matter compromise:
  - Myelination
  - Fiber organization
  - Extracellular fluid
- Gray matter compromise:
  - Especially frontal
- Cognition
  - Affect
- Adolescence neuromaturation (ages 12–25):
  - Myelination
  - Axonal density (especially frontoparietal)
  - Cortical thickness (especially frontal)

Adulthood:
- Use
- Problems
- Psychopathology

Tapert & Jacobus, 2013
National Consortium on Alcohol and Neurodevelopment in Adolescence: NCANDA

Sites  Advisors  Collaborations
>7,500 screened

830 baseline MRIs completed

50% Representative

50% High Risk

3 annual follow-ups: Interview, Neuropsych, MRI (~25% heavy drinkers)

Administration:
• Sandy Brown - Coordinator
• Susan Tapert

Data:
• Dolf Pfefferbaum
• Kilian Pohl
• Edie Sullivan

Sites:
• U Pittsburgh – Duncan Clark
• SRI – Ian Colrain & Fiona Baker
• Duke Univ – Mike DeBellis
• OHSU – Bonnie Nagel
• UCSD – Susan Tapert

>50,000 school and community recruitment
NCANDA CONCEPTUAL MODEL

Adolescent Alcohol Consumption
Dose/Duration/Timing

Developmental Context
Genetics
Age/Gender/Puberty
Risks

Structure

Function

Environment

Behavior
Neurocog Functioning
Alcohol Problems/AUD
Psychopathology
Maturation
Real Life Functioning

830+ 12-21yr olds followed annually for 3 years
NCANDA Sample (Ages 12-21): Build a sample representative of American youth

<table>
<thead>
<tr>
<th>Gender</th>
<th>Size</th>
<th>%</th>
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<tbody>
<tr>
<td>Female</td>
<td>411</td>
<td>49%</td>
</tr>
<tr>
<td>Male</td>
<td>423</td>
<td>51%</td>
</tr>
<tr>
<td>White</td>
<td>616</td>
<td>74%</td>
</tr>
<tr>
<td>AA/Black</td>
<td>100</td>
<td>12%</td>
</tr>
<tr>
<td>Asian</td>
<td>63</td>
<td>7.5%</td>
</tr>
<tr>
<td>Native American</td>
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<td>0.4%</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>5</td>
<td>0.6%</td>
</tr>
<tr>
<td>Multiple/Other</td>
<td>47</td>
<td>5.5%</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>99</td>
<td>12%</td>
</tr>
</tbody>
</table>
NCANDA Sample and Success

- Most Youth are Alcohol Naïve (70%)
- Most Youth are Binge Naïve (85%)
- Small Sample with Regular Drinking (6%)

**OVERALL FOLLOW-UP RATE: 90%**

1 Year Follow-ups = 90%
Mid-year interview (every 6 months) = 89%

**Special focus:**

- Inhibitory Response Dysregulation
- Sleep Disruption
- Neural Network Abnormalities
- Recoverability of Cognitive Deficits
NCANDA:

Data combined across sites with precision.

There are differences in the images across different scanners.
NCANDA: Maturation of white matter microstructure

Three dimensional rendering of the regions of greatest magnitude of white matter maturation in the adolescent brain derived from Diffusion Tensor Imaging (DTI).

Unpublished preliminary data.
NCANDA: White matter integrity by age suggest that boys and girls mature at a similar rate. Unpublished preliminary data.
Technology to Link Biological & Behavioral Systems

Increased sensitivity of biological and radiological measures

Increased visualization
Capacity to articulate
Multiple system/functioning

Treat, Mutchler, Schick, 2014