National Institute on Alcohol Abuse and Alcoholism

NIAAA

CONSORTIUM ON ALCOHOL AND NEURODEVELOPMENT IN ADOLESCENCE: THE FOUNDATIONAL RESEARCH

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Introduction

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Role of Early Exposure to Alcohol

(Animal Research)

- Alcohol consumption before and during adolescence produces long-lasting effects that increase alcohol consumption in adulthood.
- Adolescent alcohol exposure sometimes appears to "lock in" adolescent typical alcohol sensitivities
- Adolescent alcohol exposure alters forebrain cholinergic nuclei. Decreased adult ACH neurons are associated with loss of behavioral control and reversal learning deficits.
- Adolescent alcohol exposure induces persistent alterations in histone acetylation in amygdala associated with adult anxiety.
- Adolescent alcohol exposure results in increased adult cortical spine density, possibly due to disrupted cortical maturation of synapses.

Consequences of Adolescent Alcohol Use on the Developing Human Brain

- Binge-like drinking affects memory, alters sensitivity to motor impairment, and damages limbic and frontal-anterior cortical regions.
  - Increased brain activation while performing a spatial working memory task, i.e., the brain is working harder
  - Worsening visuo-spatial functioning over time for adolescents that continue to drink
- Some deficits appear to be gender specific
- Teenagers who begin drinking before age 15 have four times the risk of developing alcohol dependence later in life
- Prolonged ethanol exposure produces long-lasting structural & neurophysiological changes in cortex, hippocampus, cerebellum, corpus callosum.

A Low Level of Response to Alcohol Can Predict Future Alcoholism (Human Studies)

Individuals with a low level of response to alcohol

- experience less intense negative effects of alcohol
- require a higher blood alcohol concentration to feel intoxicated

Therefore, they may drink more heavily and more frequently, and are more likely to develop alcoholism

Previous Alcohol & Adolescence Studies

- The overall evidence suggest that the developing brain is more vulnerable to the effects of alcohol, e.g., predisposing it to later dependence and/or interfering with the normal developmental trajectory.
- But some limitations of the studies to date:
  - Largely cross-sectional assessing adolescents after they have initiated alcohol use
  - Some have focused on adolescents in treatment for AUDs
  - Some studies have included binge drinkers who do not meet criteria for an AUD
  - Longitudinal studies that enroll individuals prior to alcohol use are sparse and the number of subjects is relatively small

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National Consortium on Alcohol & Neurodevelopment in Adolescence (N-CANDA)

A multi-site longitudinal study using neuroimaging and neuropsychological measures to answer questions about the impact of child and adolescent alcohol use on the developing brain:

- what early brain and cognitive markers may predict alcohol use and/or dependence
- what are the short and long-term consequences of alcohol exposure on brain and cognitive development
- the effects of timing, dose, and duration of alcohol exposure on brain and cognitive development
- to what extent are these effects permanent or reversible
- what is the role of genetic and epigenetic factors

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Alcohol and the Adolescent Brain

- Study Design:
  - Longitudinal; plus “sequential longitudinal” imbedded
  - Assessment every 3 years: start age 12 thru 21
  - Broad range of neuropsychological testing
  - MRI, fMRI, dtMRI
  - Blood sample at every assessment point for genetic and epigenetic studies

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Today's symposium.....

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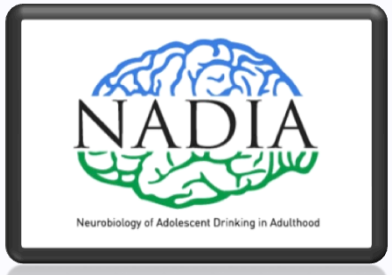
LONGITUDINAL CHANGES IN SLEEP EEG AND BRAIN STRUCTURE IN ADOLESCENCE Fiona Baker, Health Sciences Section, SRI International, Menlo Park, CA

USING FUNCTIONAL CONNECTIVITY TO IDENTIFY RISK FOR AND CONSEQUENCES OF ALCOHOL USE DURING ADOLESCENCE Bonnie Nagel, Oregon Health & Sciences University, Department of Psychiatry and Behavioral Neuroscience, Portland, OR

EARLY ABSTINENCE-RELATED IMPROVEMENTS FOLLOWING ADOLESCENT HEAVY EPISODIC DRINKING Susan Tapert, University of California San Diego and VA San Diego Healthcare System, San Diego, CA

NADIA (Neurobiology of Adolescent Drinking in Adulthood)



NADIA is a multi-investigator effort (*primarily an animal model study*) which will assess the effects of adolescent ethanol exposure on adult:

- **Brain structure** and neurochemistry
- **Impulsivity, reward** and responses to stress
- **Learning, memory and executive cognitive function**
- Sleep and arousal
- Social reward and anxiety
- **Epigenetic modifications and neuronal plasticity**
- **Drinking behavior** and withdrawal

Combining the efforts and expertise of the consortium investigators is expected to result in synergies which would not be achievable with single research projects.

NADIA- Major findings

- Adolescent thrill seeking, social reward and high emotionality mature in both sexes in parallel, consistent with brain developmental maturation through puberty.
- Voluntary drinking in adolescence increases voluntary drinking in adulthood.
- Alcohol exposure during adolescence disrupts maturation of alcohol tolerance causing persistent low response to alcohol in adulthood. For example, adolescent animals are less sensitive than adults to ethanol-induced motor impairment, but more sensitive to inhibitory effects on spatial learning.
- Adolescent alcohol exposure insults forebrain cholinergic nuclei. Decreased adult ACH neurons is associated with loss of behavioral control and reversal learning deficits.
- Adolescent alcohol exposure induces persistent alterations in histone acetylation in amygdala associated with adult anxiety.
- Adolescent alcohol exposure results in increased adult cortical spine density, possibly due to disrupted cortical maturation of synapses.

Early Results: Alcohol & the Adolescent Brain
Gender Differences in Binge Drinkers

- Neuropsychologic Findings
  - Female binge drinkers show worse visuospatial function whereas males show worse attention
- fMRI Findings
  - Only female binge drinkers show differences in parietal and frontal region activation during tasks of visual working memory, which is associated with worse neurocogitive functioning
- Structural MRI
  - Binge drinking females show thicker, less mature/developed cortices in frontal region which is associated with worse neurocognitive functioning; male binge drinkers are similar to male controls (normally gray matter decreases druing adolescences)

Adolescence with Alcohol Dependence

- Gray and white matter volume deficits in:
  - Hippocampus
  - Prefrontal cortex
  - Cerebellum
  - Corpus callosum

Alcohol & the Adolescent Brain

- Longitudinal Initiative
  - What structural and functional anomalies are the result of alcohol exposure and what predates, and may predict, heavy alcohol use
  - What timing, dose and duration of alcohol use can result in changes to the developing brain?
  - Do deficits resolve with abstinence?
  - Are there neuroimaging and/or neurocognitive markers that predict heavy alcohol use?
  - What does genetic and epigenetics contribute?