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BOWLES CENTER FOR ALCOHOL STUDIES

Mission

The mission of the UNC Center for Alcohol Studies is to conduct, coordinate, and promote basic and clinical research on the causes, prevention, and treatment of alcoholism and alcoholic disease.

ADOLESCENT DRINKING NEUROBIOLOGY OF NADIA IN ADULTHOOD

Supported by

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

The BRAIN Initiative

Foundation of Hope
Research & Treatment of Mental Illness

BRAIN & BEHAVIOR RESEARCH FOUNDATION
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NIH National Institute on Alcohol Abuse and Alcoholism

NIH National Institute on Drug Abuse
The Science of Drug Abuse & Addiction

NIH National Institute of Mental Health

abmrf
THE FOUNDATION FOR ALCOHOL RESEARCH

Adolescent alcohol abuse and Brain Development.

- **The adolescent brain has a unique response to alcohol.**
- **Adolescents binge drink often.**
- **Adolescent binge drinking causes lasting changes in brain physiology, structure and function.**
- **Age of drinking onset impacts adult drinking and risks of abuse and dependence.**
- **Protecting adolescents from early alcohol abuse could greatly reduce lifetime abuse and AUD.**

Fulton T. Crews, Ph.D.
John Andrews Distinguished Professor
Director of The Bowles Center For Alcohol Studies
University of North Carolina at Chapel Hill School of Medicine

ADOLESCENT DRINKING NEUROBIOLOGY OF NADIA IN ADULTHOOD

NIH National Institute on Alcohol Abuse and Alcoholism

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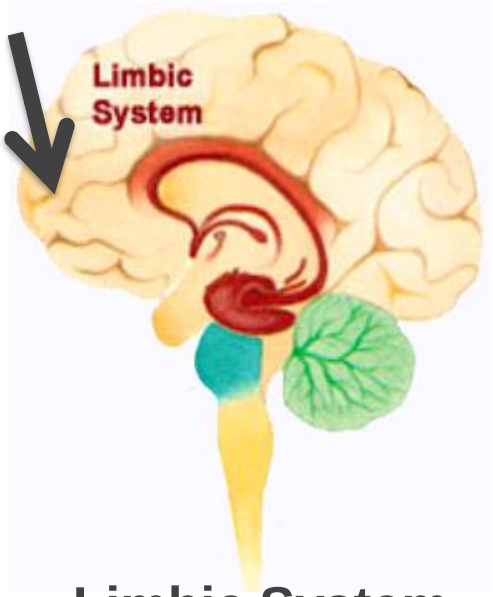
The Human Brain Continues to Develop Into the Early 30's

Adolescents have high social reward, during and after puberty, and a poorly developed frontal cortex which is needed for self-control, reflection on future consequences, planning, and developing socialization.

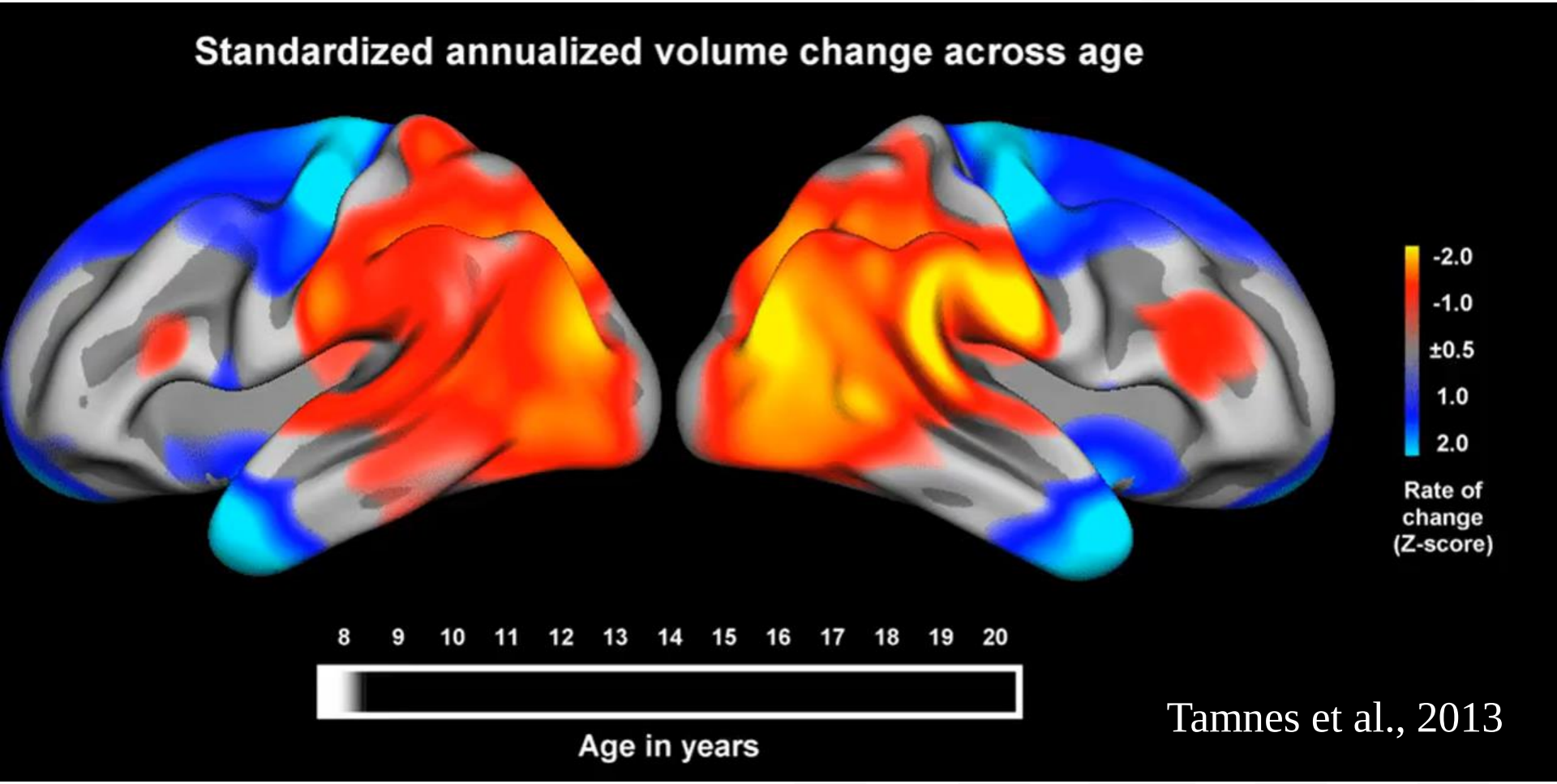


Limbic System: learning, emotions

The limbic system governing emotions matures earlier than the frontal cortex, responsible for planning, self-control, and decision-making.

Adolescent Alcohol Exposure Persistently Impacts Adult Neurobiology and Behavior.
Crews et al., Pharm Rev (2016)

Changes In Cortical Structure During Adolescence



Adolescent brain maturation involves growing white matter and alterations in cortical grey matter.
- One of the last areas of the brain to mature is the prefrontal cortex, a brain region involved in judgment, goals, and impulsivity control of emotional responses.

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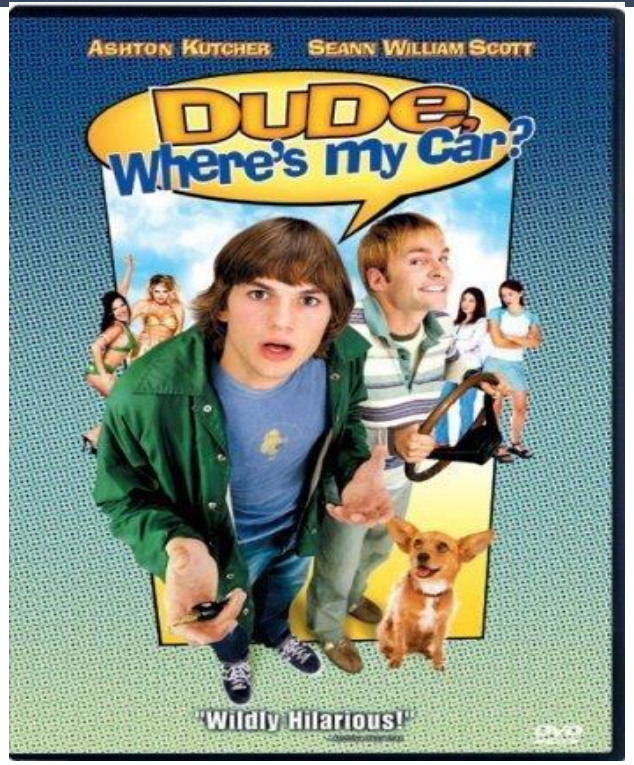
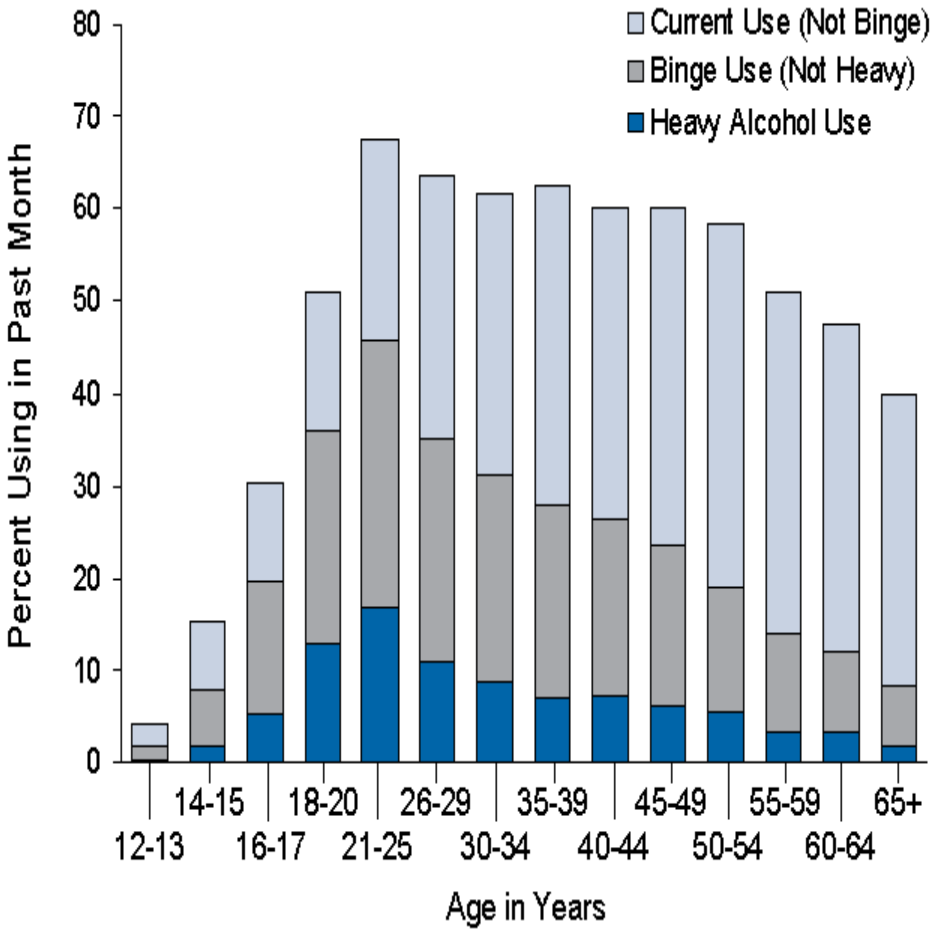
Adolescents Binge Drink More





ADOLESCENT DRINKING NEUROBIOLOGY OF NADIA IN ADULTHOOD

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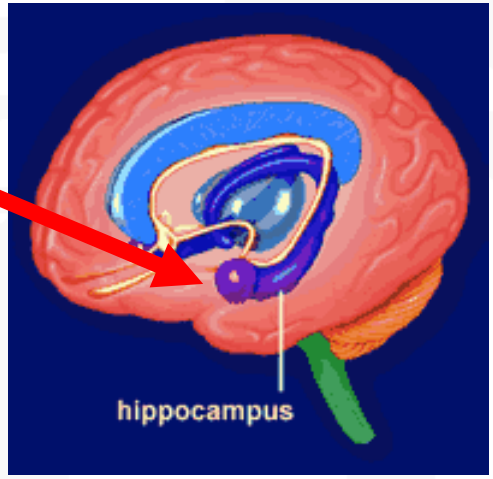
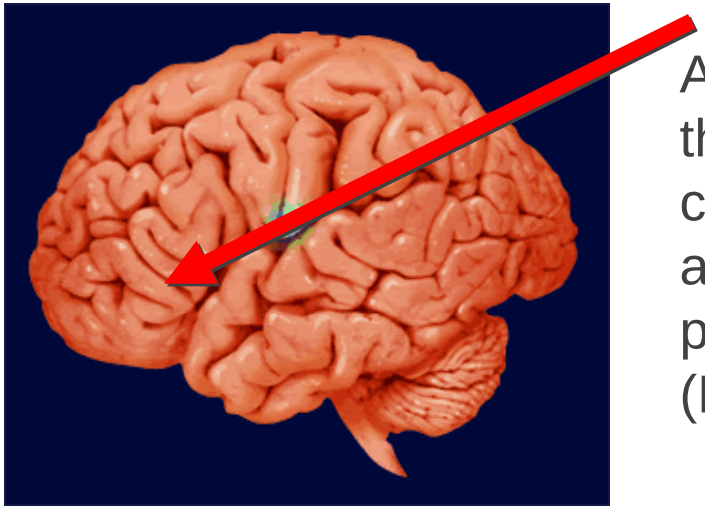
Adolescents Have a Unique Alcohol Response To Cognitive Disruption

Compared with adults, alcohol consumption during adolescence:

Greatly affects the hippocampal function, impairing learning and memory processes, which are important tacks for academic performance during adolescence



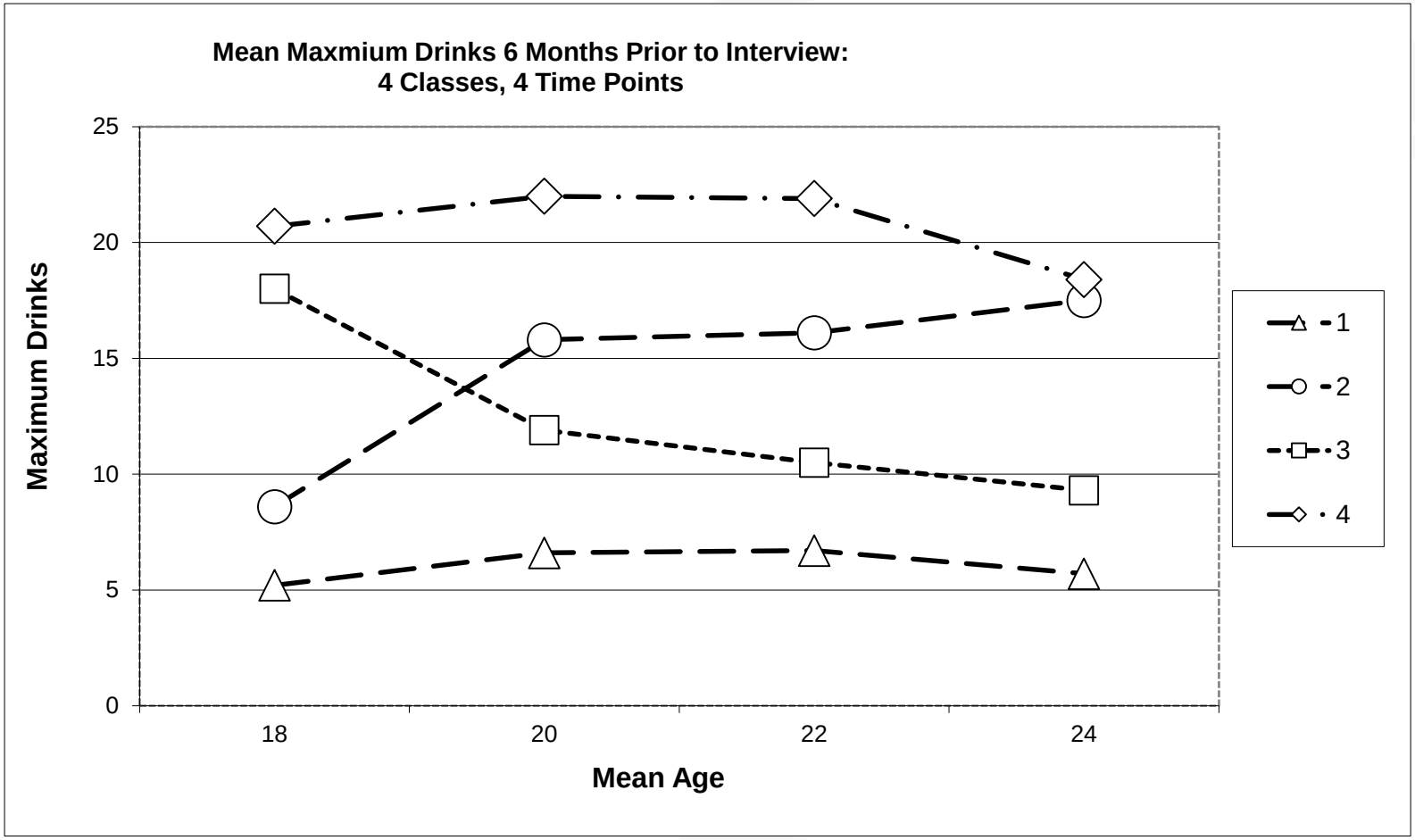


Alcohol induces attention deficits and affects the executive function tasks (prefrontal cortex). Studies of adolescent individuals with alcohol use disorder (AUD) have found prefrontal cortex reductions and abnormalities (De Bellis et al., 2005; Medina et al., 2008)

Adolescents are more sensitive to cognitive impairment and less sensitive than adults to the sedative effects of ethanol.

Adolescents Binge Drink Varied Amounts Of Alcohol

MAXIMUM DRINKS PER OCCASION OVER SIX YEARS FOR 833 ADOLESCENTS AND YOUNG ADULTS
Schuckit et al.,* Journal of Studies on Alcohol and Drugs, *2014.



Maximum drinks per occasion in the six months prior to each follow up between mean age 18 and 24 for 833 COGA adolescent and young adult men and women. Class 1 = 571 subjects; Class 2 = 123; Class 3 = 86; and Class 4 = 53 subjects.

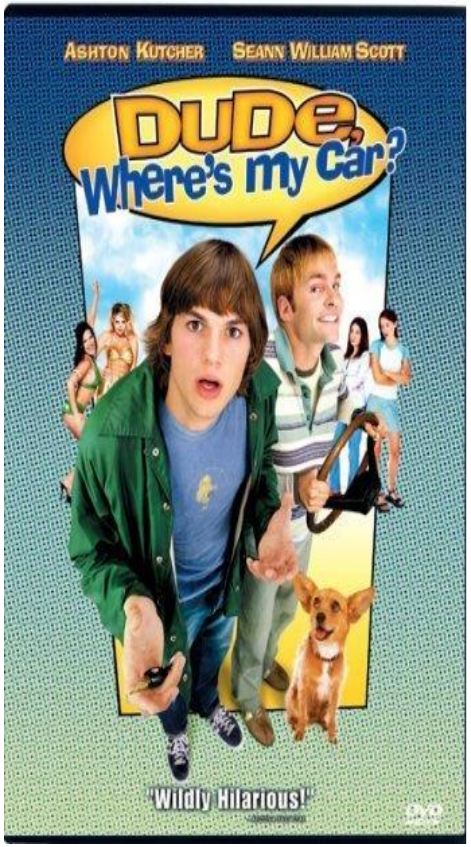
Adolescents Have A Low Sedative Response To Alcohol

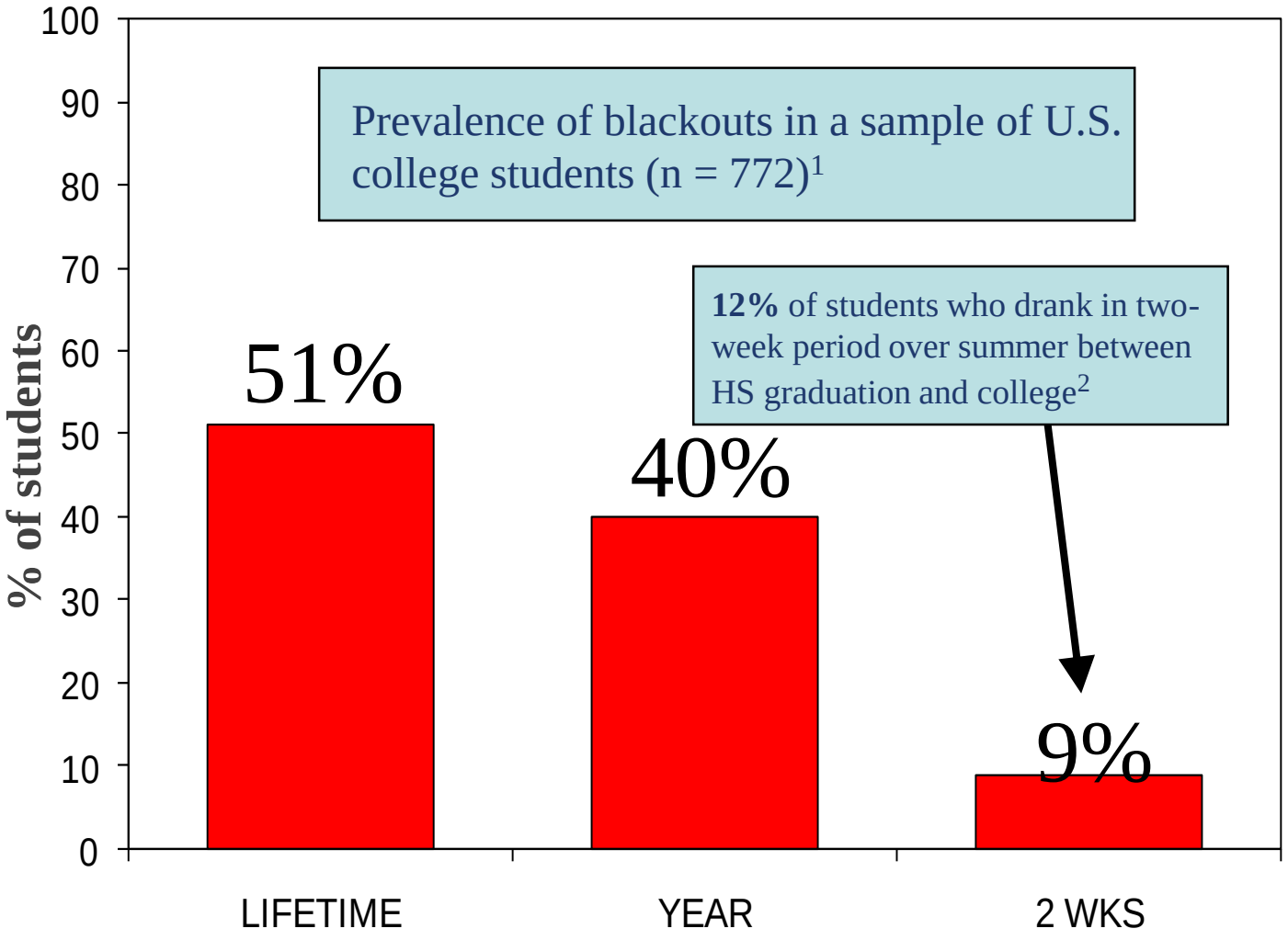
Adolescents have a different response to alcohol.

Adolescent

Adult

Adolescents Binge Drink to Blackouts.
Black outs reflect high blood alcohol levels



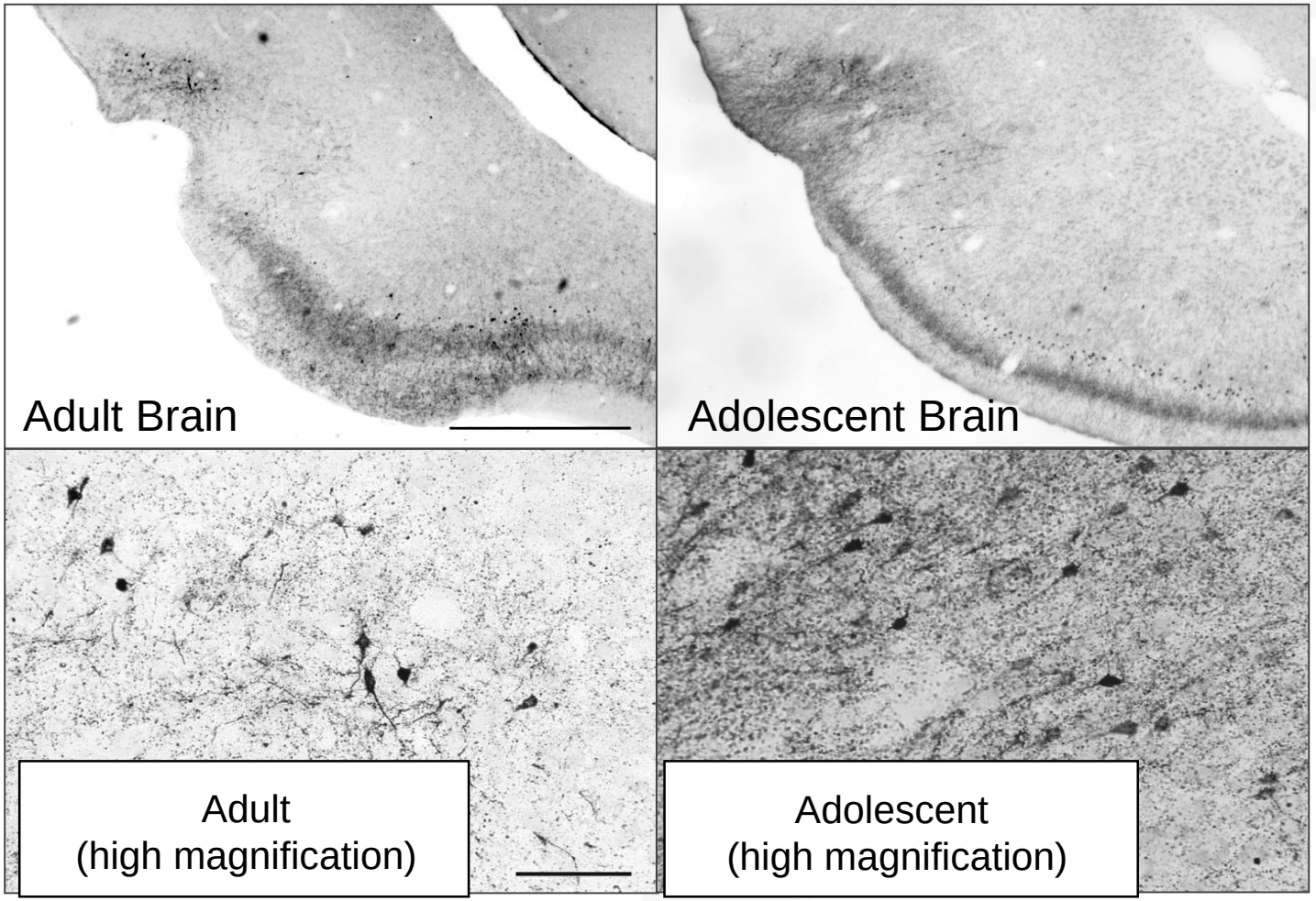


Average BAC = 0.3% (almost 4x legal limit)

Sources: [1]White et al, 2002, *American Journal of College Health*;
[2]White and Swartzwelder, 2009, *American Journal of Health Education*

Adolescent Brain is More Sensitive to Alcohol-Induced Brain Damage

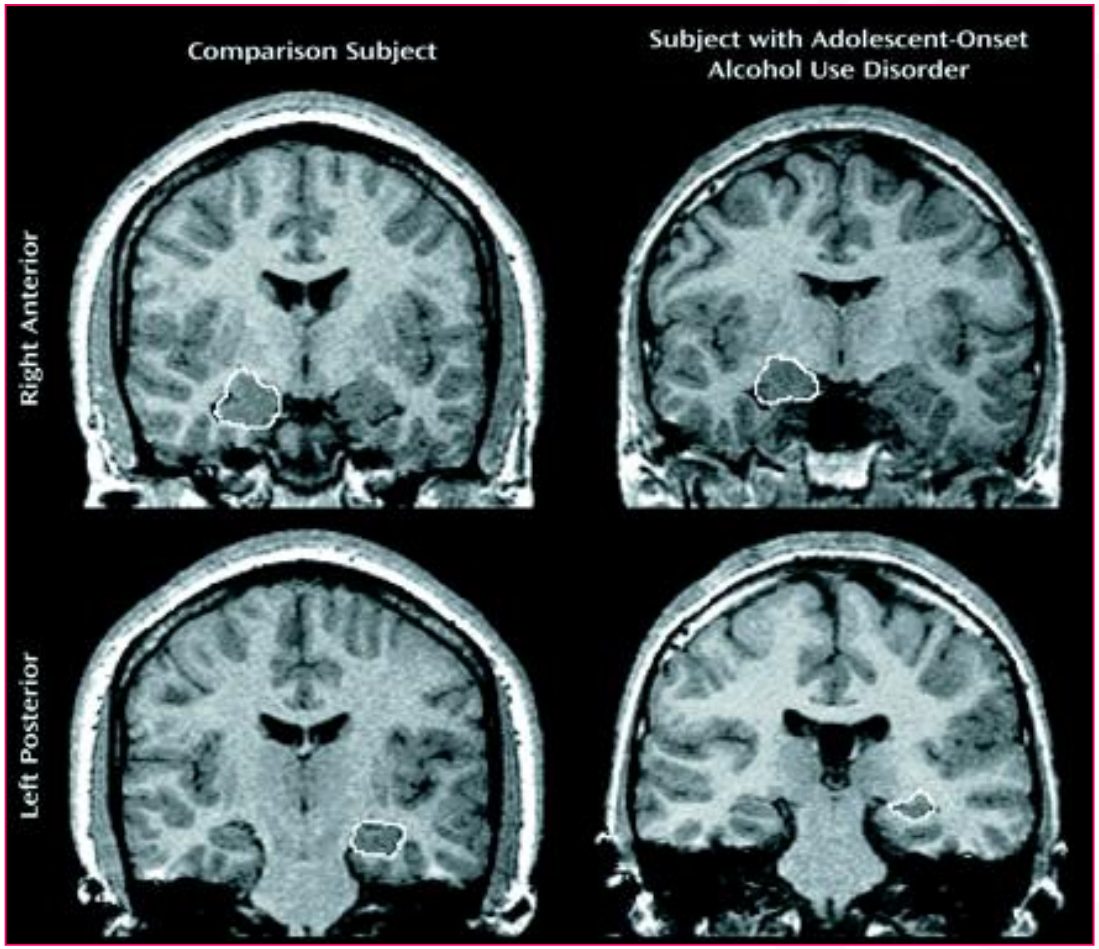
Binge drinking rat models find brain damage (black stain) in both adults and adolescents, but adolescent cortical neuronal death is far greater.

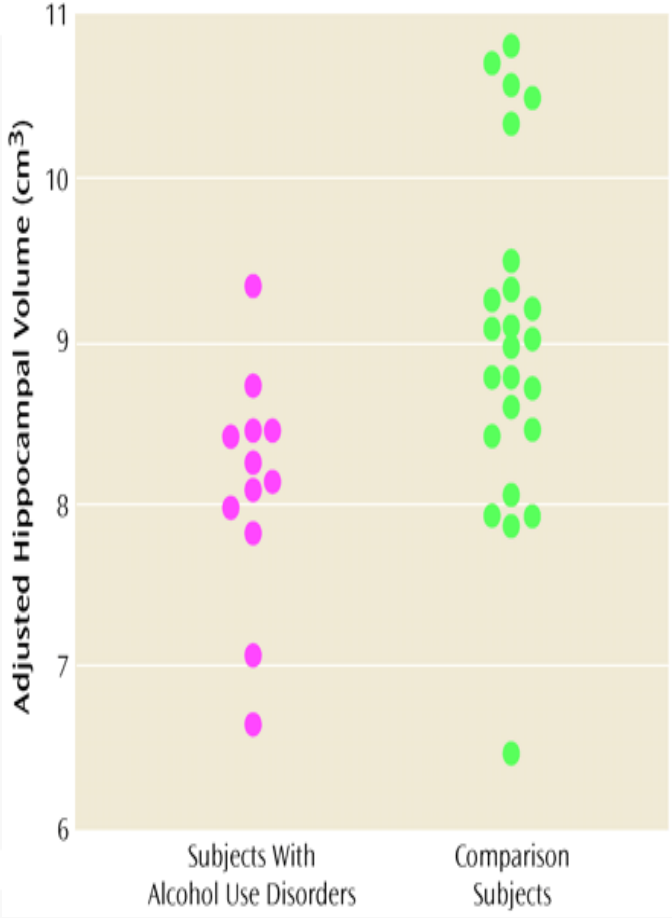


Crews et al., Alcoholism: Clin Exp Res 24:1712 (2000)

Hippocampal Volume Is Reduced in Adolescent-onset Alcohol Use Disorders

Adolescents with AUD show early loss of hippocampus volume.
The hippocampus is an essential brain region for memory formation.





De Bellis, Am J Psychiatry (2000)

Neurobiology of Adolescent Drinking in Adulthood

Defining The Persistent Effects Of Adolescent Binge Drinking On Adults

- Memory deficits, reduced problem-solving ability.
- Epigenetics-increases in DNA methylation and histone acetylation regulating gene expression.
- Persistent brain proinflammatory gene induction similar to AUD.
- Loss of adult brain stem cell regeneration.
- Loss of cholinergic and serotonergic neurons, altered myelin.
- Disrupted sleep.

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Adolescents' Drinking Takes Lasting Toll on Memory

Even moderate drinking by adolescents on a regular basis can cause potentially lasting changes to the

Exposure to alcohol up to the age of 25 can lead to changes in brain circuitry, resulting in poorer memory and slower learning. PHOTO: CORBIS

ADOLESCENT DRINKING NEUROBIOLOGY OF NADIA IN ADULTHOOD

Adolescent Alcohol Exposure Persistently Impacts Adult Neurobiology and Behavior. *Crews et al., Pharm Rev, (2016)*

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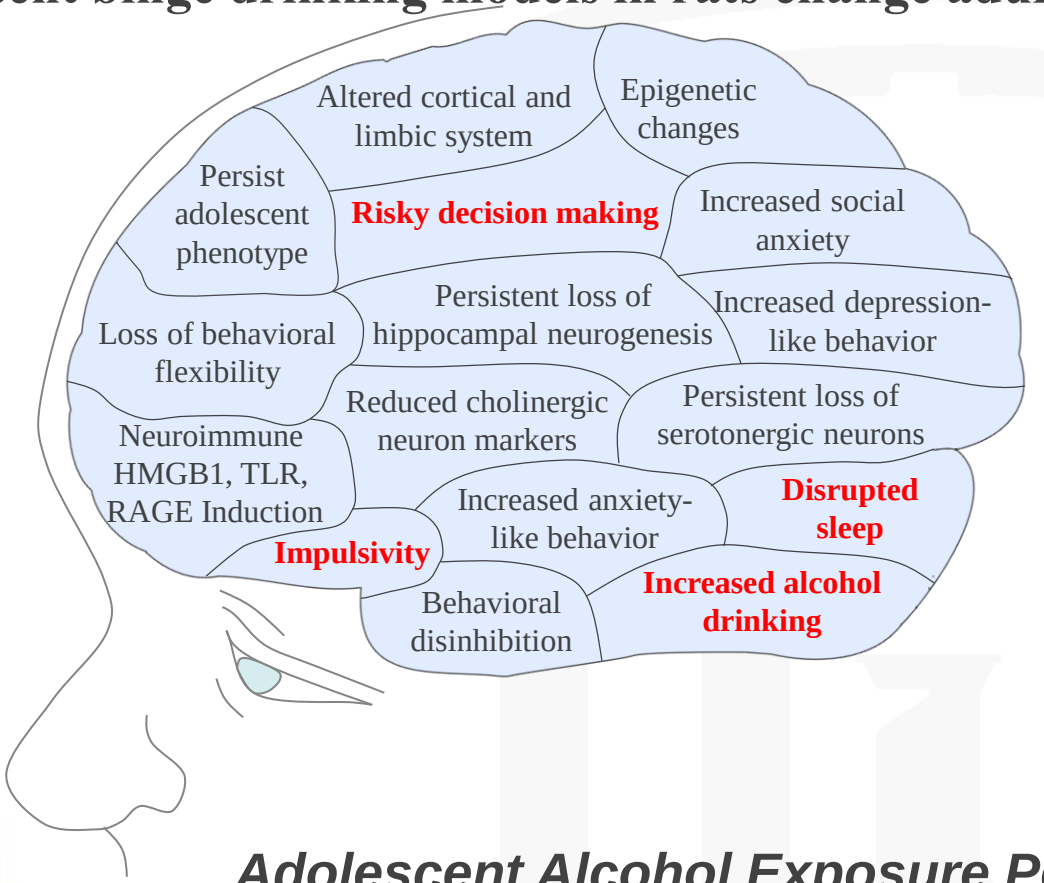
Lasting Consequences Of Adolescent Binge Drinking In Adulthood

Persisting Adult Neurobiology following Adolescent Binge Drinking

Adolescent binge drinking models in rats change adults.



Adolescent Alcohol Exposure Persistently Impacts Adult Neurobiology and Behavior.

Crews et al., Pharm Rev (2016)

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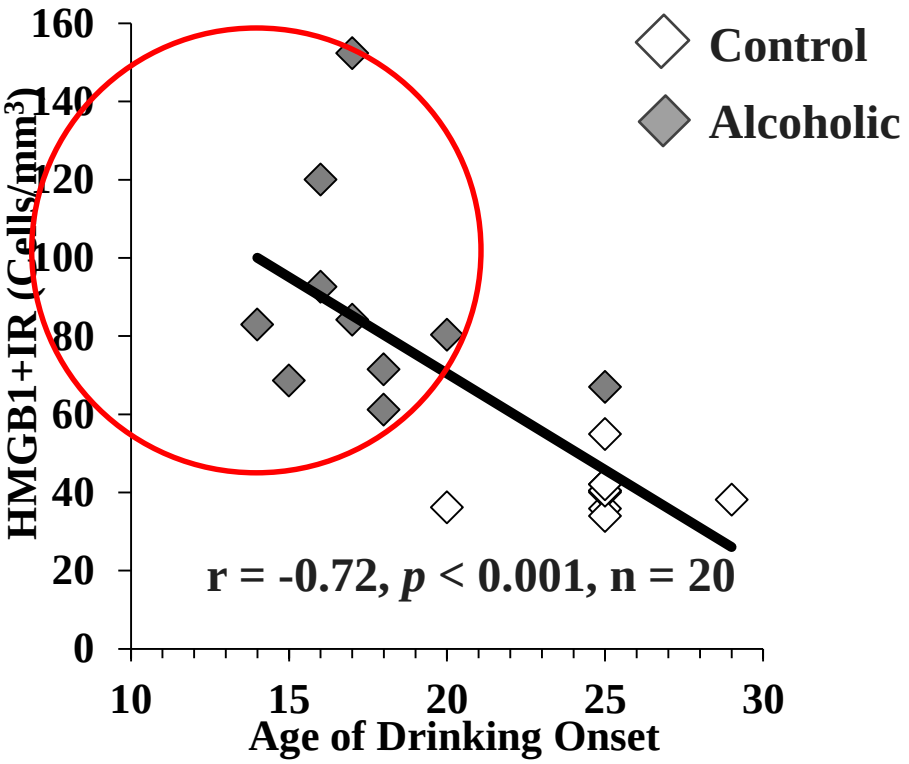
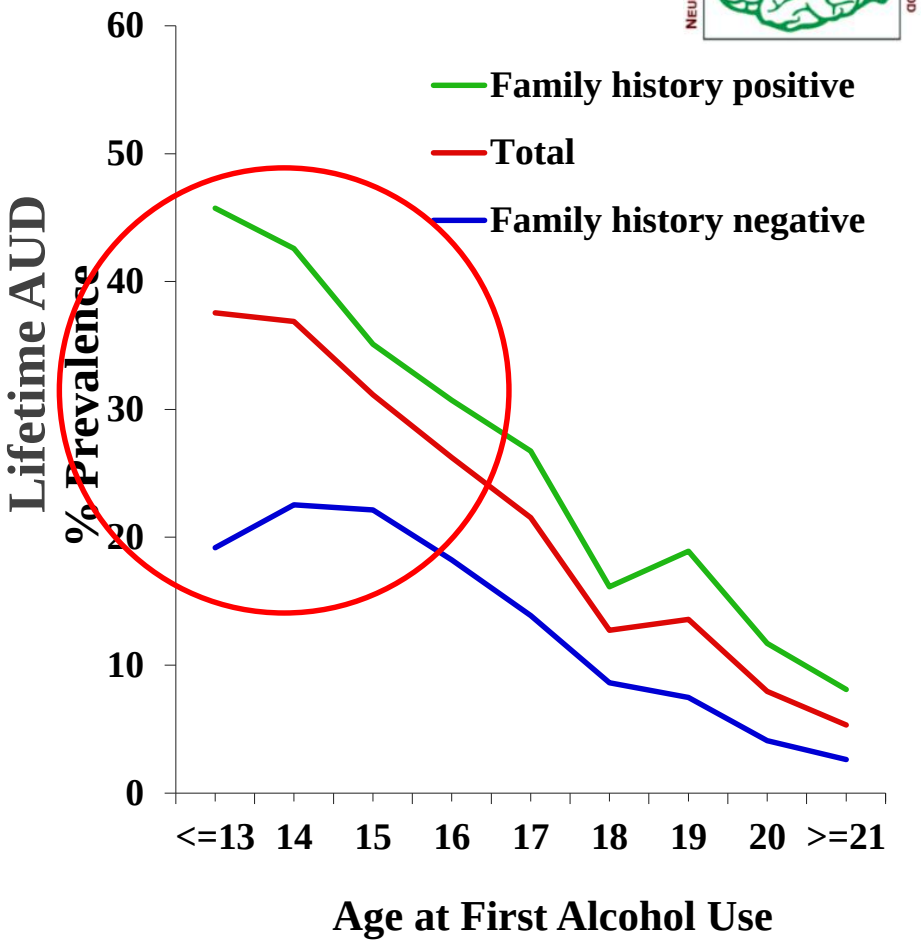
Age Of Drinking Onset and Lifetime AUD.





Vetreno and Crews, Neuroscience 226:475-88 (2012). **Earlier age of drinking onset correlates with increased HMGB1+IR in human post-mortem orbital frontal cortex.**

Also lifetime alcohol consumption correlates with increased HMGB1 expression.

Grant et. al. NIAAA NESARC (n = 43,093): **2001-2002. Earlier age of drinking onset is associated with increased risk of binge drinking, alcohol dependence, onset of dependence at a younger age, and adult injury after drinking.**

An early age of alcohol drinking is associated with alcohol-related violence both before and after age 21.

Lifetime Dependence by Age of First Use of Alcohol, Cigarettes, and Marijuana

(n=4,245 users of alcohol, cigarettes, and marijuana ages 24 to 32 participating in the nationally representative Add Health Survey*)

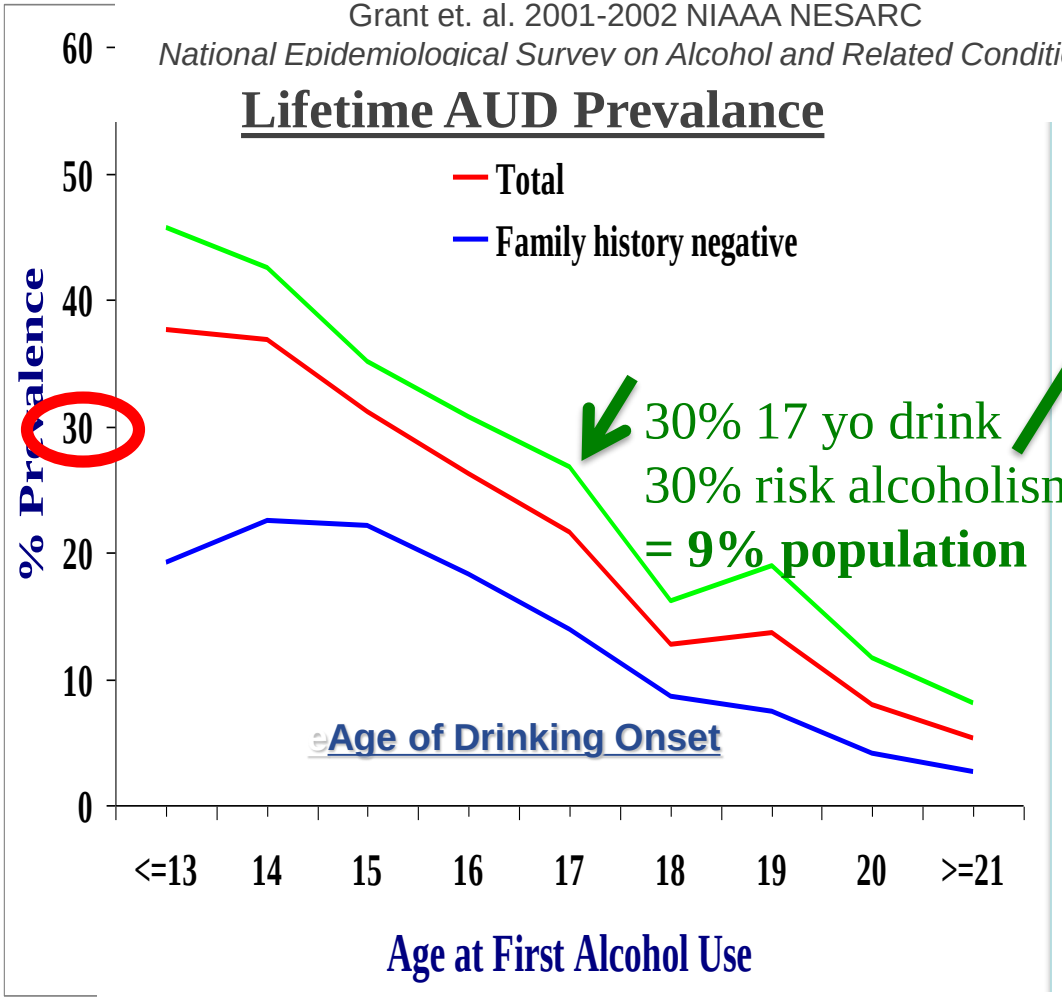
Ever Dependent† On:	Started Using All Three Drugs Before Age 16	Started Using All Three Drugs After Age 16
Alcohol	25%	16%
Nicotine	47%	27%
Marijuana	21%	8%
Other Illegal Drugs	20%	6%

Moss et al., Drug and Alcohol Dep. 136: 51, 2014

AUD Follows Underage Drinking

Grant et. al. 2001-2002 NIAAA NESARC

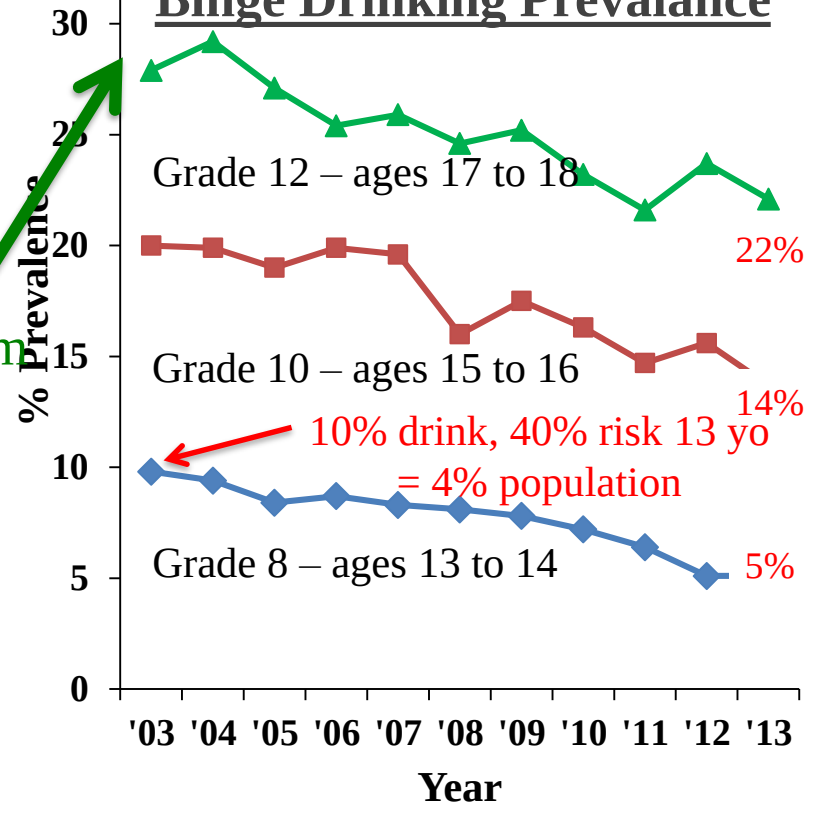
National Epidemiological Survey on Alcohol and Related Conditions



Johnston et al. 2013 NIAAA

Monitoring the Future Study 1975 – 2013

5 or more drinks in a row during a 2-week period



Does age of drinking onset underlie a significant proportion of alcohol drinking problems across the lifespan?

Adolescent Drinking Neurobiology of NADIA in Adulthood

UNC School of Medicine Bowles Center for Alcohol Studies

Natural History of Alcohol Dependence*

	Age
First drink	12-14
First intoxication	14-18
Minor alcohol problem	18-25
Age of onset (3+ DSM-IV criteria for dependence)	23-33
Age on entering treatment	40
Age of deaths (heart disease, cancer, accident, suicide)	55-60

*Chronic relapsing: In any one year, abstinence alternates with active drinking in 1/4 to 1/3

Shuckit MA (2006). Drug and Alcohol Abuse: A Clinical Guide to Diagnosis and Treatment.

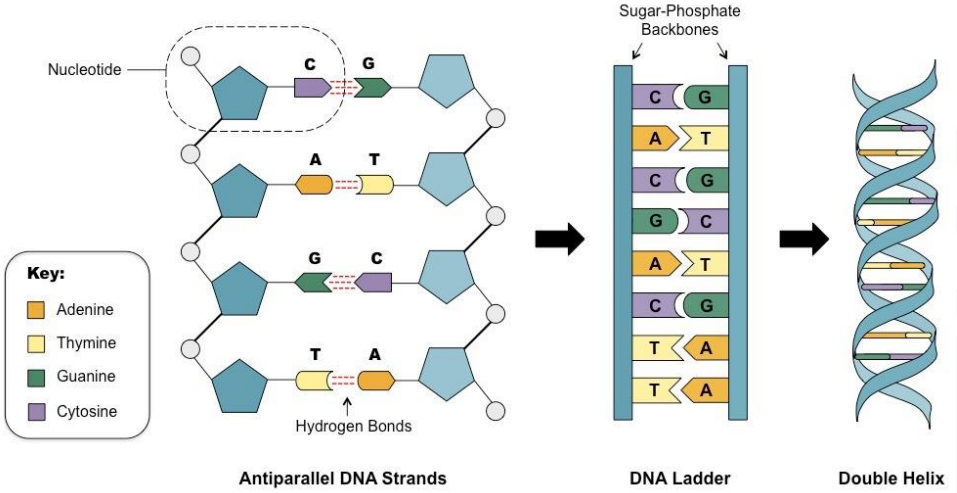
Why Do People Become Addicted?

Alcoholism Runs in Families

Genetics play a significant role: having parents with alcoholism, for instance makes you four times more likely than other children to become alcoholics. More than 60% of alcoholics have family histories of alcoholism.

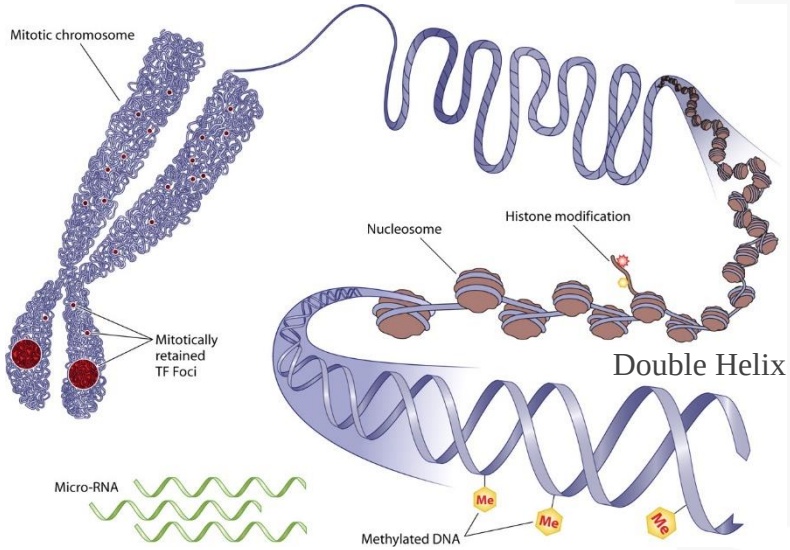
New genetics-epigenetics are inherited too!

Alcoholism Runs in Families



Old Genetics of AUD

- No single gene
- 40-50% genetic inherited risk
- twin studies support inheritance.



New Genetics?

- Epigenetics-environmental
- Alcohol induced
- Long lasting changes in gene expression.
- Inherited

Epigenetic changes in DNA, like methylated DNA, are increased by ethanol and inherited.

Alcoholics Have Increased DNA Methylation

Lowered DNA methyltransferase (DNMT-3b) mRNA expression is associated with genomic DNA hypermethylation in patients with chronic alcoholism

D. Bönsch, B. Lenz, R. Fiszer, H. Frieling, J. Kornhuber, and **S. Bleich**

Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nuremberg, Germany

J Neural Transm (2006) 113: 1299–1304

SCIENTIFIC REPORTS

Nature Scientific Reports, 2017

OPEN

DNA methylation signatures of chronic alcohol dependence in purified CD3$^+$ T-cells of patients undergoing alcohol treatment

eceived: 2 March 2017
ccepted: 19 June 2017

ORIGINAL ARTICLE

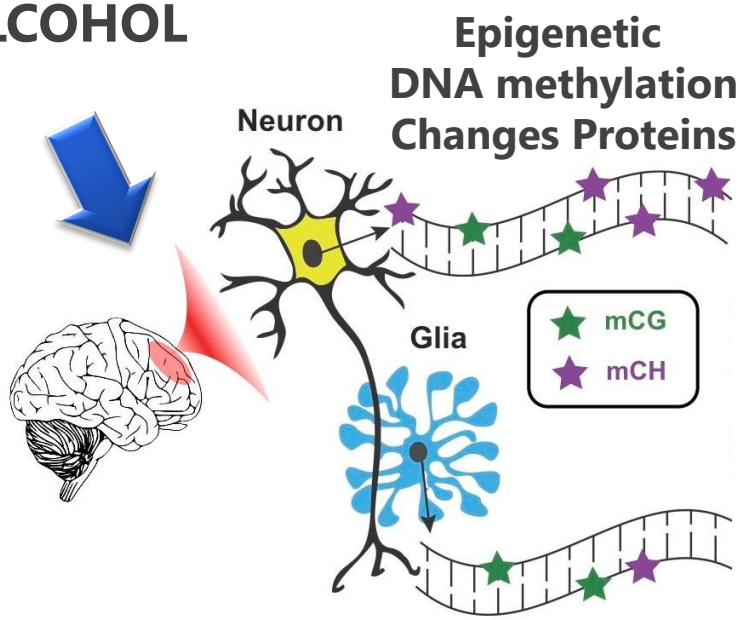
A DNA methylation biomarker of alcohol consumption

Molecular Psychiatry (2018) 23, 422–433

NEUROBIOLOGY OF ADOLESCENT DRINKING IN ADULTHOOD NADIA

Changes in the Adult Brain as a Result of Underage Drinking

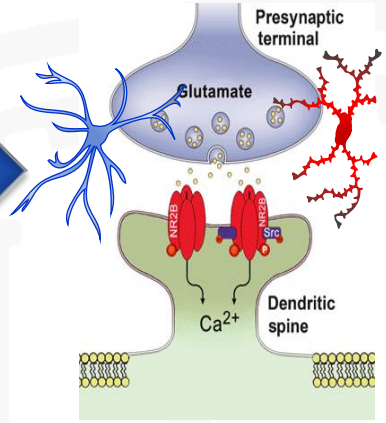
ALCOHOL

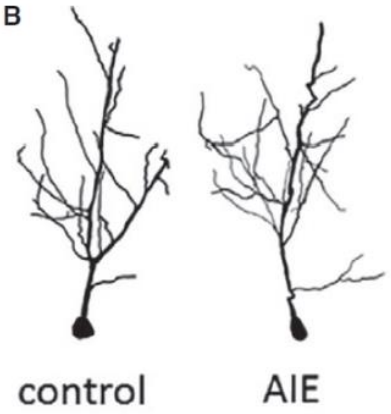


Risher et al., Alcol Clin Exp Res 39:989-997, 2015

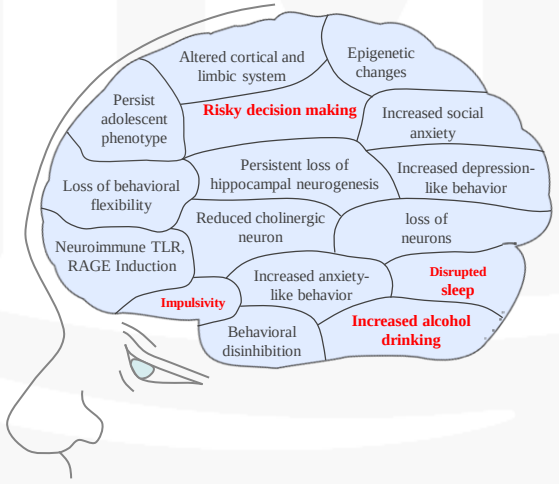
Epigenetic DNA methylation inherited by future generations.

Neuron-Glial-Synapse Changes





*Neuron*s Alters Adult Neurobiology



ADOLESCENT DRINKING NEUROBIOLOGY IN ADULTHOOD
NADIA

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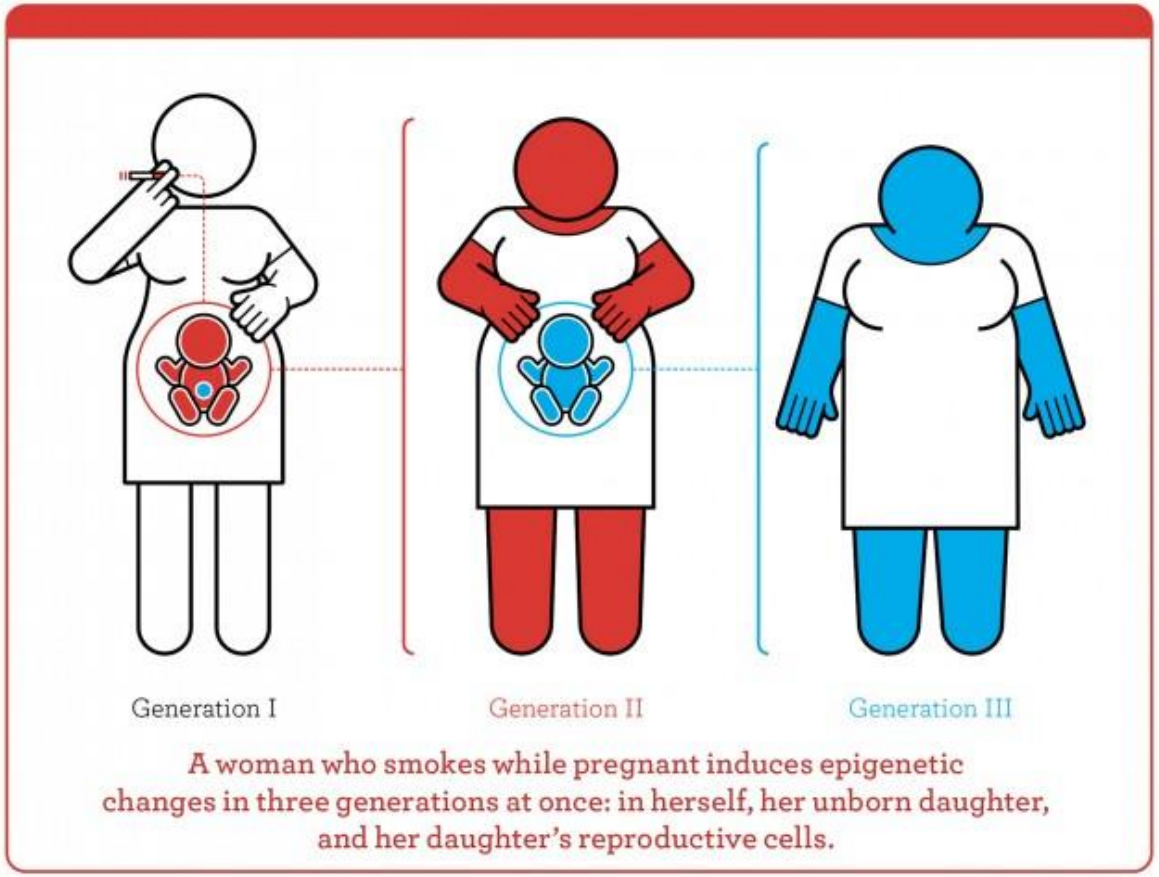
Alcohol Abuse and Families

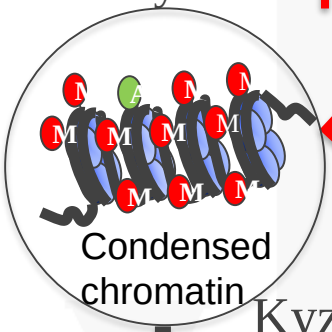
Epigenetic programing involves inherited and reversible DNA and histone modifications (Ac, Me, P,+) chromatin and chromosome structure.



Developmentally disrupted epigenetic programming

Binge ethanol exposure

DNA methylation
Histone acetylation ↑ HDAC2



Kyzar et al., 2016

Altered Adult Neurobiology

People who drink alcohol induce epigenetic changes that are inherited.

Can Parents Help?

YES!

Many parent behaviors can delay and decrease adolescent alcohol consumption

- Parent modeling of behavior
- Don't give them alcohol. (Lock up the alcohol.)
- Parent communication
- Disapproval of adolescent drinking
- Rules about alcohol
- Parental monitoring
- Parent-child relationship quality
- Limiting alcohol availability (Lock up the alcohol.)

So TALK IT OUT!

Can We Prevent These Brain Changes?

YES!

- Prevention is key
  - Abstinence or drinking in moderation
  - Harm reduction
- Current research studying how to repair the brain.
  - Exercise

So TALK IT OUT!

Summary

- Adolescent brain, particularly prefrontal cortex continues to develop in parallel with maturation of risk taking, impulsivity, goal setting and cognition.
- Adolescent binge drinking changes adult brain including reducing responses to alcohol and increased impulsivity, risk taking, and anxiety.
- Adolescent binge drinking causes long, lasting changes in adult brain physiology, structure and function through complex epigenetic mechanisms that may be inherited.

Understanding the consequences of underage drinking and adolescent binge drinking is important to guide public health decisions on drinking age, alcohol access, and other alcohol policies.

So TALK IT OUT!

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