Alcohol and the adolescent brain:
Why delaying the onset of drinking is so important

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Excessive drinking during adolescence is a global concern.
Alcohol is the drug of choice among youth in U.S.

Source: Monitoring the Future, 2010
Adolescents drink less often than adults but more per occasion

Source: SAMHSA Report to Congress on Prevention and Reduction of Underage Drinking, May 2011
Risk of alcohol abuse and dependence peaks in late adolescence/young adulthood

Percentages of Persons Aged 12 or Older Who Met the Criteria for Alcohol Dependence or Abuse in the Past Year, by Age Group: 2002, 2003, and 2004

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 to 17</td>
<td>5.9</td>
</tr>
<tr>
<td><strong>18 to 25</strong></td>
<td><strong>17.4</strong></td>
</tr>
<tr>
<td>26 to 34</td>
<td>11.1</td>
</tr>
<tr>
<td>35 to 49</td>
<td>7.5</td>
</tr>
<tr>
<td>50 or Older</td>
<td>3.0</td>
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</table>

Source: The NSDUH Report, Issue 16, 2006, SAMHSA
U.S. – Decrease in binge drinking

Binge (5+ drinks) past 30 days

See great risk in binge 1-2 per weekend

Source: Monitoring the Future (2010)
U.S. teens compared to other countries

Contrary to popular belief in the United States, American teenagers (15-16 year olds in this case) do NOT binge drink (5+ drinks) more often than kids in Europe. Compared to the 14 countries below, US teens only outpace teens in Turkey.

Sources: 2003 ESPAD and MTF surveys; 2005 publication by the US Dept of Justice and PIRE
Questions:

● What is it about adolescence that increases the likelihood of excessive drinking during this stage of life?

● How do the effects of alcohol on the adolescent brain help explain the short-term and long-term consequences of alcohol use?

● What do the findings suggest about the logic of a legal drinking age of 21?
Adolescence – What? Why?

- Transition from dependence to independence
- Period of biological, social and psychological changes that prepare us to survive in the adult world
- Tumult (e.g., risk taking, conflict, moodiness) is normal and can be adaptive
- Changes that occur in the brain during adolescence simultaneously get us out into the world to explore and then record experiences to prepare us for independence
Adolescent storm and stress is normal and often adaptive

“Teenage brains. Beautiful brains. Moody. Impulsive. Maddening. Why do teenagers act the way they do? Viewed through the eyes of evolution, their most exasperating traits may be the key to success as adults.”

David Dobbs
National Geographic Magazine
October, 2011
Adolescent brain development

Frontalization of function – Frontal lobes take on more and more organizational control over behavior as adolescence unfolds.
The amazing frontal lobes

- Planning, decision-making, impulse control, memory, language and more
- Remodeled during adolescence
Orbitofrontal and Ventrolateral Prefrontal Cortex Development

Schematic depiction of the ventrolateral prefrontal cortex (\textit{vlPFC in green}) and orbitofrontal cortex (\textit{OFC in red}) regions of the VPFC that contribute to the development of social flexibility. Inhibitory control and rule use are controlled by the \textit{vlPFC}, whereas computation of expected value of social stimuli is performed by the \textit{OFC}. All three of these functions mature slowly across development. (Adapted from Davidson, Putnam, and Larson (2000), and reprinted with permission.)

Frontal lobe development

Data from Jay Giedd, NIMH

Curve for frontal lobe energy demands follows a similar path. That is, as gray matter volumes go up so do energy needs, as gray matter volumes go down energy needs go down. In addition, frontal lobe circuits become more efficient once covered in myelin in late teens. The window for serious molding seems to close in early 20s.
FIGURE 3. Ventral striatal activity to reward and association with risk-taking. Note: Ventral striatum (left) is activated with reward (middle) and correlated with risk-taking (right) (adapted from Galvan et al.\textsuperscript{6} and Galvan et al.\textsuperscript{16}). Such findings could mean that adolescents are more motivated for reward and more reinforced by it.

Adolescent amygdala highly reactive to stressful stimuli
Stress hormone (cortisol) levels higher during adolescence
Adolescence is a time of high stress and uncertainty

**Amygdala**
- Volume knob for fear and anxiety
- Allows for learning to fear things
- Allows for learning not to fear things
How the brain records memories

- Hippocampus records facts and life events
- New brain cells born here throughout life
- Neurogenesis peaks in adolescence
Neurogenesis peaks during adolescence

Gray matter density age effect statistical maps showing gray matter density changes between childhood and adolescence (A) and between adolescence and adulthood (B).

Decreased DFC gray matter density but increased total DFC volume

“Close temporal linkage between dendritic arborization—synaptic density changes and increased myelination could be consistent with our in vivo findings of cortical gray matter density reduction spatially concomitant with late brain growth.”

White matter maturation during adolescent development

Relationship of network metrics and developmental age based on measurements of white matter

Hagmann et al. PNAS 2010;107:19067-19072

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Strengthening of circuits involving distant brain regions during adolescence based on white matter measurements

Hagmann et al. PNAS 2010;107:19067-19072 – supplemental materials
During adolescence strong drives and still developing cognitive control contributes to risk-taking

FIGURE 1. Cartoon model of ventral striatal cortex and prefrontal cortex (PFC) interactions across development. Note: Deeper color indicates greater regional signaling. Line represents functional connectivity, with solid line indicating mature connection and dotted line indicating immaturity.

Adolescence is risky business

Alcohol and drug use often begins here

Romer et al., 2010
Alcohol and other drugs can turn adaptive tendencies into maladaptive behaviors

- Adolescent brains built to learn with ease with an eye toward success during adulthood
- Adolescent brains learn particularly fast when behaviors are rewarded
- Frontal lobes (decision-making, impulse control) are not fully online during adolescence but emotional drive is in high gear
- Alcohol and other drugs produce reward leading to rapid learning and motivating further use
- Alcohol causes both short-term and long-term effects that are bad for adolescents
Two 20-year-old women take a memory test. One of them abuses alcohol. The MRI scan on the left is of her brain, the lack of color indicating a sluggish mind. In contrast, the scan on the right is of the woman who doesn’t have a drinking problem. The colors show areas of brain activity. Not surprisingly, she does better on the test.

Teen drinking, thinking don’t mix
Alcohol appears to damage young brains, early research finds

By Kathryn Sadler
USA TODAY

Teenagers who drink heavily face a host of hazards, ranging from accidental injuries to death by alcohol poisoning. It’s usually not a good idea to drink less than 4 hours after consuming alcohol. Preliminary studies indicate that heavy, regular drinking can damage the developing brains of teens and young adults and perhaps destroy critical cells involved in processing our memories.

Changing youths’ drinking habits, 93

call the teens to do well in school or at work. Critics say it’s not easy to change brain damage on alcohol abuse. They say that many teens who drink heavily also abuse other drugs and have other risk factors that could hurt the brain.

But researchers say that though the work is in the early stages, the evidence points toward a link between alcohol and damage to young brains.
Alcohol suppresses frontal lobes¹

- Teens already have problems with decision-making, attention, impulse control
- Alcohol makes the problems worse!

Alcohol – “Shot of courage”

- By suppressing the amygdala alcohol diminishes *psychological* experiences of stress (fear and anxiety)
- Does not help with the *physiological* effects of stress
- Makes it easier to do risky things

**Alcohol**
- Quiets the amygdala
- Temporary reduction in *experience* of stress
Alcohol suppresses amygdala response to threatening stimuli

**FIGURE.** Alcohol effects on amygdala activation to social signals of threat. **A)** Right lateral amygdala activation to Threat (> Non-threat) faces is present during the PBO session but absent during the ALC session. **B)** Mean BOLD Response (β weights ±SEM) extracted from amygdala ROIs showing activation to Threat (> Non-threat) faces in the PBO session but no activation during the ALC session. PBO, placebo; ALC, alcohol. **C)** Mean BOLD Response showing alcohol attenuates (PBO>ALC) activation to Threat (Angry, Fearful) faces but does not affect responses to Non-threat (Happy Faces).

Source: Sripada et al., 2011, Neuroimage, 55, 371-380.
Like virtually all drugs used for pleasure and relaxation, alcohol activates the reward system, thus tricking the brain into thinking that something important and worth repeating just happened. Each time the behavior is repeated and reinforced, the odds go up that alcohol will be consumed again. This is a tricky venture for adolescents, whose frontal lobes are still under construction and already have difficulty controlling impulses, and the behaviors they pick up tend to have staying power.
Alcohol blocks new memories

- Adolescent hippocampus more vulnerable to effects of alcohol on hippocampal function
- Effects on hippocampus lead to blackouts

Make it a night you won't forget, not one you can't remember.
Alcohol-induced memory blackouts
'Drunk and naked' in Cancun

By Gary Strauss, USA TODAY

CANCUN, Mexico — Shane Mahmood woke from a booze-induced fog with a half-inch stainless steel ring pierced through his lower lip.

Shane Mahmood doesn't remember getting his lip pierced.

"I don't know how I got it or if it hurt when I did," says Mahmood, who was partying at disco La Boom with University of Washington pals when the predawn procedure apparently occurred. "I just remember beer and tequila before waking up and seeing it in the mirror."
Memory blackouts are common

Prevalence of blackouts in a sample of U.S. college students (n = 772)

- 51% in lifetime
- 40% in year
- 9% in 2 weeks

12% of students who drank in two-week period over summer between HS graduation and college

Memory blackouts are common

An interview questionnaire was administered to subjects regarding a recent alcohol associated arrest with a documented BAC greater than 0.08 g/dL for either public intoxication, driving under the influence, or under age drinking.

The Association of Alcohol-Induced Blackouts and Grayouts to Blood Alcohol Concentrations


**FIG. 1** Probability of grayouts or blackouts as a function of the blood alcohol concentration (BAC) (g/dL) where probability = \(2.46(BAC) - 0.02\) \((R^2 = 0.27)\).

**FIG. 2** Probability of blackouts as a function of the blood alcohol concentration (BAC) (g/dL) where probability = \(2.21(BAC) - 0.18\) \((R^2 = 0.54)\).
Five binge-drinking deaths 'just the tip of the iceberg'

By Robert Davis, USA TODAY

This month has been deadly for binge-drinking college students.

Five underclassmen in four states appear to have drunk themselves to death, police say, after friends sent their pals to bed assuming that they would "sleep it off."
Death by overdose on alcohol/other drug combinations

- Excessive alcohol and/or other CNS depressants can shut down brainstem areas involved in vital reflexes like breathing, gagging, and heart rate.

**Alcohol**
- Suppresses respiratory areas and other vital reflex centers
- Causes death
Alcohol overdose/poisoning

- Alcohol has a very small therapeutic index (TD$_{50}$/ED$_{50}$)
- A toxic or deadly dose not much higher than a moderately intoxicating dose

Potentially fatal alcohol overdoses: How much alcohol?

If ED$_{50}$ = ~.08%
And TD$_{50}$ = ~.32%
Then TI = ~4

10 drinks in 2 hrs for a 140 lb female
BAC = 0.32

13 drinks in 2 hrs for a 160 lb male
BAC = 0.44

BAC = 0.43
BAC = 0.48
Officials say CU student died of alcohol poisoning also had drug in his system

A University of Colorado student who died after a night of partying during the first week of school in August had drugs and alcohol in his system, the Boulder County Coroner’s Office said Thursday.

A toxicology test found the narcotic painkiller oxymorphone, and alcohol poisoning caused the death of 21-year-old Michael Alexander Hoffman of Berkeley Heights, N.J.

Hoffman was found unconscious Aug. 26 on the porch of a home at 1429 10th St., two blocks west of the CU campus. The residents there did not know him, the Daily Camera reported at the time.

He never regained consciousness and died at a hospital four days later. A police report said messages on Hoffman's cellphone indicated he had been drinking heavily the night he died.
Trends in Emergency Department Visits Involving Underage Alcohol Use: 2005 to 2009

Figure 4 Table. Number of Underage Drinking-Related Emergency Department (ED) Visits, by Age group and Type of Alcohol-Related Visit: 2005 to 2009*

<table>
<thead>
<tr>
<th>Age Group and Type of ED Visit</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged 18 to 20, Alcohol Only</td>
<td>67,382</td>
<td>73,973</td>
<td>80,255</td>
<td>77,018</td>
<td>82,786</td>
</tr>
<tr>
<td>Aged 12 to 17, Alcohol Only</td>
<td>42,739</td>
<td>52,342</td>
<td>55,960</td>
<td>55,236</td>
<td>54,726</td>
</tr>
<tr>
<td>Aged 18 to 20, Alcohol in Combination with Other Drugs</td>
<td>27,784</td>
<td>31,702</td>
<td>32,308</td>
<td>36,975</td>
<td>38,067</td>
</tr>
<tr>
<td>Aged 12 to 17, Alcohol in Combination with Other Drugs</td>
<td>19,720</td>
<td>24,418</td>
<td>26,403</td>
<td>19,752</td>
<td>22,192</td>
</tr>
</tbody>
</table>

*ED visits for which age is unknown have been excluded from analysis.
Changes in rates of alcohol, drug and combined overdoses among 18-24 year olds between 1999-2008

A. Alcohol overdoses  ↑ 25%
B. Drug overdoses  ↑ 56%
C. Combined alcohol + drug overdoses  ↑ 76%

Overdose defined as excessive consumption and/or poisoning based on ICD-9-CM codes
Long-term effects: Starting young is bad news

- Starting early increases risk of dependence
- Brain seems to pick up alcohol habits quickly
- Increased risk of negative outcomes
- Lingering cognitive deficits
### Age of drinking onset and dependence: Risk goes up as age goes down

<table>
<thead>
<tr>
<th>AGE</th>
<th>FHP (%)</th>
<th>FHN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 13</td>
<td>57</td>
<td>26</td>
</tr>
<tr>
<td>14-15</td>
<td>48</td>
<td>32</td>
</tr>
<tr>
<td>16-17</td>
<td>35</td>
<td>21</td>
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<tr>
<td>18-19</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>20</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>≥ 21</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

Source: Grant and Dawson, 1997
Adolescent alcohol abusers show strong reactions to alcohol-related cues reflecting strong associative learning

Functional magnetic resonance imaging (fMRI) results during alcoholic beverage picture trials relative to non-alcoholic beverage picture trials

Greater activation in AUD subjects (red color) in the ventral anterior cingulate and subcallosal, prefrontal, orbital, and limbic regions, areas previously associated with reward and drug craving.

AUD group (N = 15) 6 girls 9 boys average age of 16, DSM abuse or dependence

Control group (N = 15) 6 girls 9 boys average age 16, low levels of previous use

Amount of brain activation in response to alcohol-related cues increases with drinking levels

Blood oxygen level-dependent (BOLD) response signal contrast in the right precuneus/posterior cingulate region during exposure to alcoholic beverage pictures relative to nonalcoholic beverage pictures plotted as a function of drinks consumed per month for adolescents with alcohol use disorder (n = 15).

Are strong associations between alcohol and cues part of why adolescents are at such high risk of developing dependence and of relapsing?

Smaller frontal lobes

Ventral Prefrontal Volume

Source: Squeglia et al., 2009
Decreased frontal lobe activation during working memory tasks in young males with AUD

![Brain activation areas in the control group (n = 10, left) and the AUD group (n = 11, right).](image)

Significantly decreased activation was identified in the left frontal circuit including Broca’s region (BA 44) and the premotor cortex (BA 6). The left frontal circuit is known to be responsible for the articulatory rehearsal process.

Binge drinkers show less prefrontal lobe activity during visual working memory

**Subjects**
- 53 controls
- 42 binge drinkers (BD)
- 18-20 years old

**Average binge episodes last 2 weeks**
- Controls = 0.2
- Binge drinkers = 2

**Technique**
Low resolution brain electromagnetic tomography

**SOURCE:** Crego et al. (2010) Reduced anterior prefrontal cortex activation in young binge drinkers during a visual working memory task. Drug and Alcohol Dependence, 109, 45-56.
Amount of frontal lobe volume reduction in alcohol dependent adults predicts shorter time to relapse.

~ Adolescents have under-developed frontal lobes and alcohol abuse seems to produce damage here – do these factors increase odds of relapse for teens? ~

FIGURE 2. Significant clusters of gray matter volume deficit in alcohol-dependent patients (35 men, 10 women, aged 18-50, current DSM-IV alcohol dependence) relative to healthy comparison subjects (28 men, 22 women, aged 18-50)

Smaller hippocampus

Sources: Nagel et al., 2005; Medina et al., 2007
Alcohol suppresses hippocampal neurogenesis

- Alcohol suppresses neurogenesis much more so than it kills cells
- Cells born during intoxication abnormal (Nixon et al, 2010)
- Similar amount of suppression of neurogenesis in adolescents and adults but adolescents make more cells, so effect is greater (Nixon et al, 2010)
- In adolescent rats, exercise increases neurogenesis after binge exposure but cells tend to die (Helfer et al, 2009)
- Primates who binge daily for 11 months show impaired neurogenesis 2 months later (Taffe et al, 2010)
- Partial explanation for link between adolescent AUD and memory? depression?
4-day binge alcohol exposure activates microglia in the hippocampus of adolescent rats and activation persists into adulthood.

Microglia in control animals had morphological characteristics consistent with resting microglia, while binge ethanol-exposed rats had swollen cell bodies with thicker, less ramified processes, consistent with activation.

Relationship between levels of alcohol and marijuana use and measures of cognitive function in adolescents

As the number of drinks consumed per day goes up performance on tests of attention, executive function and memory go down. More days smoking marijuana equals poorer memory.

SUBJECTS: 48 adolescents (ages 12 to 18), recruited in 3 groups: a healthy control group (HC, n = 15), a group diagnosed with substance abuse or dependence (SUD, n = 19), and a group with a family history positive for alcohol use disorder (AUD) but no personal substance use disorder (FHP, n = 14).

RESULTS: More DPDD predicted poorer performance on Attention and Executive Function composites, and more frequent use of marijuana was associated with poorer Memory performance. In separate analyses, adolescents in the SUD group had lower scores on Attention, Memory, and Processing Speed composites, and FHP adolescents had poorer Visuospatial Ability.

Summary

- Alcohol risky for adolescents in part because brain is still developing.
- Alcohol causes direct effects on adolescent brain that increase risk of accidents and bad decision-making.
- Long-term lingering effects on brain including heightened risk of alcoholism and cognitive deficits.
- Goal should be to delay onset and model/promote moderate use.