'Striking' Impact of Adolescent Drinking on the Brain

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Drinking during adolescence interrupts normal brain development and results in gray matter loss, new research shows.

A team of investigators associated with five US universities used MRI to analyze the brains of 483 youth and young adults (age, 12 to 21 years) before initiation of drinking and again 1 and 2 years later.

At the 2-year assessment, study participants who initiated heavy drinking were found to have an accelerated decline in their frontal cortical gray matter trajectories that was divergent from the norm.

Lead researcher Edith V. Sullivan, PhD, professor, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, California, called the findings "striking."

"It may be particularly relevant that the alcohol's influence on brain structural development was significant for frontal regions, which are among the last to mature," she told Medscape Medical News.

"Damage to these regions can result in difficulties with problem solving, decision making, good judgment, appropriate social behavior, inhibition of inappropriate behaviors, and other actions associated with maturity," she said.

The study was published online October 31 in the American Journal of Psychiatry.

Gray Matter Loss

In normal brain maturation, cortical gray matter volume increases during the first decade of life and declines continuously thereafter. Supratentorial white matter volume increases throughout adolescence, slowing only during the third decade, the authors note.

These "significant and predictable changes in normal neurodevelopment" have contributed to the speculation that "the evolution of the adolescent brain is especially vulnerable to environmental insult."

Engaging in consumption of "potentially deleterious agents," such as alcohol, might therefore result in "accelerated gray matter loss, attenuated white matter growth, or both," the authors write.

Previous research has identified abnormal growth patterns in youths who initiated and continued heavy drinking. However, moderate drinkers were excluded from these reports, "leaving unaddressed the question of whether highly prevalent, moderate drinking levels could interfere with normal developmental trajectories."

To investigate this question as well as the impact of heavy drinking on the developing adolescent brain, the researchers conducted a longitudinal analysis of structural MRI data on 483 youth and young adults. Data were collected at baseline, then 1 and 2 years later.

The participants were in the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA) study, "a longitudinal project to examine brain structural and functional development and to track deviations from normal growth patterns related to initiation of appreciable alcohol or drug consumption," reported Dr Sullivan, who is a member of the NCANDA scientific team.

Participants were required to never have engaged in alcohol or drug consumption or to have done so only at minimal levels prior to the study. However, during the study period, a proportion of the participants (n = 127) initiated drinking to levels that exceeded the study entry criteria, "thereby enabling pursuit of a naturalistic study on the effects of drinking on the adolescent brain," the investigators write.

"We predicted that prospective longitudinal analysis would provide novel insight into the role of alcohol consumption for the developing adolescent brain and its functions," Dr Sullivan said.

The researchers sought to "establish normal growth trajectories" - ie, decline in regional gray matter volume concurrent with growth of white matter volume in participants who continued to meet the no or low age-dependent criteria (no/low).
The investigation was also designed to identify potential differences related to family history of alcoholism, as well as the "compounding effects of marijuana and alcohol co-use on brain volume trajectories."

**Two Drinking Criteria**

The researchers began with 483 persons aged 12 to 21 years at study entry who had usable baseline and 2-year follow-up data (n = 457). Twenty-six had missed their first follow-up visit, but 2-year data were still available.

Past and current alcohol and substance use were determined through completion of the Customary Drinking and Drug Use Record.

Participants were then divided into two sets on the basis of drinking criteria. For the first group, inclusion criteria were the same as for the study: "no/low" drinking in their lifetime prior to the study, as defined by National Institute on Alcohol Abuse and Alcoholism guidelines for risky drinking. Determination was based on maximum drinking days and maximum drinks consumed on an occasion.

The maximum allowable drinks per occasion was three for female participants of any age. Maximum drinking by male participants was categorized by age: three for participants aged 12 to 13.9 years, four for those aged 14 to 19.9 years, and five for those aged 20 years or older.

In the second set of criteria, "heavy," "moderate," and "no/low" drinkers were defined by a classification inventory developed by Prof Don Cahalan and colleagues, in which individuals’ past-year drinking levels were classified with respect to quality (average and maximum consumption) and frequency.

At the 2-year follow-up, 356 youths remained in the no/low double criterion group, and 127 had transitioned from the no/low group to moderate (n = 65) or heavy (n = 62) drinkers.

The researchers analyzed potential additive effects of alcohol and marijuana consumption by applying a marijuana-use criterion at the 2-year follow-up. They regarded >50 lifetime uses as a "dichotomous variable" of concomitant marijuana use in the 127 heavy (n = 17) and moderate (n = 10) drinkers and 100 non-marijuana-using alcohol users.

A "stepwise difference in use occasions" emerged: no/low drinkers < moderate drinkers (t = 3.42, df = 58.7, \( P = .001 \)), moderate drinkers < heavy drinkers (t = 2.52, df = 76.2, \( P = .014 \)).

To be included, each participant had to meet the both sets of inclusion criteria. In addition, imaging data had to be of adequate quality and meet FreeSurfer signal-to-noise criteria, and MRI and Customary Drinking and Drug Use Record data had to be available at the 2-year follow-up. For most participants, 1-year follow-up data were available.

**Dose-Dependent Effect**

On average, all six regional neocortical and cortical gray matter regions (frontal, temporal, parietal, occipital, cingulate, and insular) exhibited negative slopes when tested against 0, with t values ranging from -11.466 to -27.158, (\( P < 10^{-8} \) to 10^{-87}).

Older age brought monotonic decelerating trajectories in all regions of interest. Although the annual rate of decline was greater in female than in male participants, no age-by-sex interaction was considered significant.

Unlike the cortical regions, the three white matter volumes displayed growth, with t values ranging from 30.656 to 44.134 (\( P < 10^{-100} \)). With advancing age, however, this growth slowed; t values ranged from -8.173 to -13.617 (\( P < .001 \)).

With regard to age-by-sex interactions, there were significantly more rapid declines in growth across age in males vs females.

In paired analyses of 65 moderate vs 356 no/low drinkers and 62 heavy vs 356 no/low drinkers, significant group effects were found only in the heavy drinkers, who displayed more rapid declines in volumes of frontal, cingulate, and total gray matter.

White matter also expanded more slowly in the heavy drinkers than in the no/low drinkers.

Because the heavy drinkers tended to be in the older age range, the researchers wanted to see whether the decline may be age-related, so they conducted a follow-up test on a subset of 62 control persons who were matched to the heavy drinkers with respect to age, sex, and ethnicity.

They found that frontal gray matter volume continued to show a steeper decline in the heavy vs the no/low drinking group.

When the researchers expanded their analysis to seek potential local effects from in-group differences, they found that 12 cortical regions showed faster declines in volume in the heavy drinkers vs the no/low drinkers. In particular, the caudal middle frontal, the superior frontal, and the posterior cingulate cortices met the false discovery rate (corrected \( P \) threshold of \( \geq .025 \)).
Faster tissue loss correlated with more maximum drinks per occasion. But there were no significant differences between baseline volumes of any regions of interest for either the heavy or the no/low groups.

Family history of alcoholism did play a role. The researchers found no significant differences in family history within the no/low or moderate-drinking group.

But within the heavy drinking group, for the 21 participants who had a positive family history, steeper slopes were noted in the parietal, occipital, and total gray matter than for the 41 participants with a negative family history (W = 231, P = .003; W = 255, P = .008; and W = 274, P = .019, respectively).

The researchers compared slopes of 10 persons who were older than 17 years, were moderate or heavy drinkers, and for whom there were >50 marijuana occasions to the slopes of the remaining 100 drinkers who did not meet the marijuana criterion. Only the insular gray matter slopes were less negative in the alcohol and marijuana co-use group than in the alcohol-only group (t = 2.551, P = .014).

The researchers note that the "dynamic growth pattern" in which gray matter volume declined and white matter volume grew in healthy participants through adolescence "formed the context for addressing whether and how initiation of moderate or heavy drinking altered components of these developmental trajectories."

Dr Sullivan noted that research suggests that the normal trajectory of loss of gray matter throughout adolescence "represents pruning of brain cells that we do not need or use." Youth who engaged in heavy drinking displayed an acceleration of this normal process.

"Importantly, through having a comparison group of no-to-low drinking youth, which enabled a quantitative measure of the expected normal rate of brain structural change, we could measure deviations from the norm in the drinking groups," she added.

**Interrupted Brain Development**

Commenting on the study for *Medscape Medical News*, Lindsay M. Squeglia, PhD, assistant professor, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, said that the study, which was "run at five different sites across the US, ensured a large representative sample."

The findings have important implications, she said.

"These interesting findings suggest that alcohol use, even infrequent use, during the teen years interrupts the way the brain matures, and it's particularly interesting that they found a dose-dependent effect, meaning that the more someone drank, the more they saw an effect on the brain."

The findings have immediately applicable take-home messages, she said.

"It's important to educate youth, parents, educators, and healthcare providers that alcohol use during the teen years can negatively affect and alter the way the brain is developing. Our brains are developing until about age 25, so any insults during this important developmental period could have long-term effects."

It is not surprising that youth are "likely to initiate underage drinking," Dr Sullivan observed. She noted that parents and professionals interacting with young persons should be aware of this.

"Youth and overseers can be helped through education about the problems associated with excessive drinking or drug use," she said.

"Don't ask, don't tell" is not an option for a responsible response to youthful drinking or drug abuse. Friends and adult leaders and overseers should know how to ask about alcohol and drug use and know what to do when youthful — or adult — abuse is suspected or detected."

She stated that further research is needed to address the "critical question" of whether damage done to the adolescent brain by drinking can be undone through abstinence or lifestyle changes later in life.

"We know from studies of adults who developed an alcohol use disorder or alcohol dependence that they can enjoy at least some recovery of cognitive and motor functioning and improvement in brain structural status with prolonged abstinence, leading us to predict that heavy-drinking youth who reduce drinking might show recovery and return to a normal developmental trajectory."

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