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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Institute on Alcohol Abuse and Alcoholism

FEATURE

ALCOHOL AND THE AGING BRAIN

Double trouble for the prefrontal cortex

There's really no way around it. Like all other organs and tissues of the human body, the brain is subject to the aging process and the typical structural and functional changes that go along with it. With normal aging, the brain begins to shrink in middle age, losing volume primarily in the frontal lobes and the hippocampus, which leads to a decline in cognitive function and memory as people grow older.

It is also well-established that alcohol misuse over time can have harmful effects on brain structure and function. NIAAA is keenly interested in how alcohol misuse and normal brain aging might interact, particularly as the nexus between alcohol and aging becomes increasingly apparent.

"The evidence indicates that Americans are getting older and drinking more," says NIAAA Director George F. Koob, Ph.D.

Currently, 26 percent of men and 30 percent of women in the United States are age 55 or older, compared with 21 percent of men and 24 percent of women 10 years ago. Experts estimate that by 2050, nearly 1 in 5 people in the United States will be age 65 or older, compared with 1 in 7 now. And alcohol researchers have reported significant increases in alcohol use and misuse among older individuals. For example, recent years have seen an increase in alcohol use among men and women age 60 or older and an increase in binge drinking among women age 60 or older.

A new study supported by NIAAA provides important information about the effects of aging and alcohol on the brain. As reported in the May 2018 issue of *JAMA Psychiatry*, researchers led by Edith V. Sullivan, Ph.D., of Stanford University School of Medicine examined brain changes in individuals ages 25–75 with and without alcohol use disorder (AUD) who also received one or more magnetic resonance imaging scans over a 14-year period (222 subjects with AUD vs. 199 age-matched control subjects without AUD). The investigators also examined data collected over time from 116 participants with AUD and 96 age-matched control subjects, who were subsets of the whole group, to see how factors such as other substance use disorders and hepatitis C virus infection comorbidities might also interact with alcohol misuse and aging to affect brain structure.

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FEATURE

ALCOHOL POLICY RESEARCH AT NIAAA

Alcohol policies are the statutes and regulations that govern a wide range of alcohol issues—from beverage pricing and taxation to the availability of alcohol to rules about underage drinking—and are established at the federal, state, and local levels. A large body of evidence has shown that alcohol policies can be effective in reducing alcohol misuse and related problems among youth and adults. For example, studies consistently show that higher alcohol prices and taxes and raising the minimum legal drinking age are linked to reductions in alcohol consumption and alcohol-related problems, including alcohol-impaired driving.

An authoritative resource for alcohol policy researchers is NIAAA's Alcohol Policy Information System (APIS), a database containing detailed information on a wide variety of alcohol-related policies in the United States at both state and federal levels. Designed to facilitate research on the effects and effectiveness of alcohol-related policies, APIS is a tool for both researchers and policymakers; it also contains a wealth of information relevant to others interested in alcohol policy issues.

APIS includes state-by-state policy information on:

- Alcoholic beverage control
- Taxation and pricing
- Transportation, crime, and public safety
- Health care services and financing
- Alcohol and pregnancy

The database tracks policy changes over time and includes maps that provide graphic information about policy differences across the country. Recently, APIS was expanded to include policies related to the recreational use of cannabis (marijuana) and drugged-driving laws, as well.

This new policy information about cannabis is timely, as the proportion of youth (ages 12–21) that uses cannabis before alcohol or other drugs has jumped dramatically—increasing from 4.8 percent in 2004 to 8.8 percent in 2014, according to data from the National Survey on Drug Use and Health. Meanwhile, teen drinking has gradually declined over the past decade, with the percentage of teens who drink decreasing by one-third (30.1 percent in 2007 compared to 19.9 percent in 2017, based on data from the Monitoring the Future study—see the By the Numbers story "Percentage of Teens Who Drink Decreased by One-Third in the Past Decade"). Concurrent use of alcohol and cannabis among youth and adults is an emerging concern. Research is needed to understand the effects of simultaneous use of these substances and to design effective prevention and treatment strategies.

"Policy research is an important component of NIAAA's diverse research portfolio. The Institute continues to encourage innovative research to examine policies that have the potential to lead to meaningful changes in public health," says NIAAA Director George F. Koob, Ph.D. In addition to investigator-initiated policy research, NIAAA encourages studies to better understand the effects of alcohol and drug policy on public health through the funding opportunity announcement, "Public Policy Effects on Alcohol-, Marijuana-, and Other Substance-Related Behaviors and Outcomes" (PA-17-135, PA-17-132, and PA-17-134). The National Institute on Drug Abuse and the National Cancer Institute also participate in these funding opportunities.

To learn more about the NIAAA staff who help facilitate policy research, see "5 Questions With Mike Hilton, Ph.D."

The NIAAA APIS is available at https://alcoholpolicy.niaaa.nih.gov.

APIS | Alcohol Policy Information System

References:

Office of the Surgeon General. *Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health*. Washington, D.C.: U.S. Department of Health and Human Services, November 2016.

Fairman, B.J.; Furr-Holden, C.D.; and Johnson, R.M. When marijuana is used before cigarettes or alcohol: Demographic predictors and associations with heavy use, cannabis use disorder, and other drug-related outcomes. *Prevention Science* May 17, 2018. PMID: 29770947

Miech, R.A.; Schulenberg, J.E.; Johnston, L.D.; et al. *Monitoring the Future National Survey: Trends in 30-Day Prevalence of Use of Various Drugs in Grades 8, 10, and 12, 2017*. Ann Arbor, MI: Institute for Social Research, University of Michigan, 2018.

FEATURE: *Alcohol and the Aging Brain . . . Continued from page 1*

Analyses revealed that adults with AUD had brain volume reductions, independent of sex, in a number of areas, including the frontal, temporal, parietal, cingulate, and insular cortices. These effects were particularly pronounced in adults age 65 or older. Accelerated aging was seen in some brain areas, including the frontal cortex. Notably, the accelerated aging was also seen in subjects who had developed AUD later in life.

"What was particularly striking about our study was accelerated aging of brain structure that was especially prominent in the frontal cortex. Even those individuals who developed severe AUD at an older age showed accelerated loss," says Dr. Sullivan. "Although both substance use and hepatitis C infection may have exacerbated brain volume loss, these factors did not fully account for the AUD-aging interaction we identified. A take-home message of our results is that old age is not protective against developing AUD-related brain volume deficits."

A Spectrum of Concerns for Older Drinkers

In addition to the specific brain-related issues that confront older people who misuse alcohol, it is important to remember that aging introduces a spectrum of other concerns for people who drink alcohol. Aging slows the body's ability to break down alcohol, so alcohol remains in a person's system longer. Alcohol may act differently in older people than in younger people, so some older people can feel increased effects from the same amount of alcohol they drank when younger. This can make accidents, including falls and fractures and car crashes, more likely. Also, for biological reasons, older women are more sensitive than men to the effects of alcohol.

Many medicines—including prescription, over-the-counter, or herbal remedies—can be dangerous or even deadly when mixed with alcohol. A lot of older people take medications every day and are more likely to take one or more medications that interact with alcohol, increasing their risk for harmful alcohol–medication interactions.

Finally, alcohol misuse by older people can contribute to, or complicate, other health problems, such as liver damage, immune system disorders, osteoporosis, diabetes, and high blood pressure.

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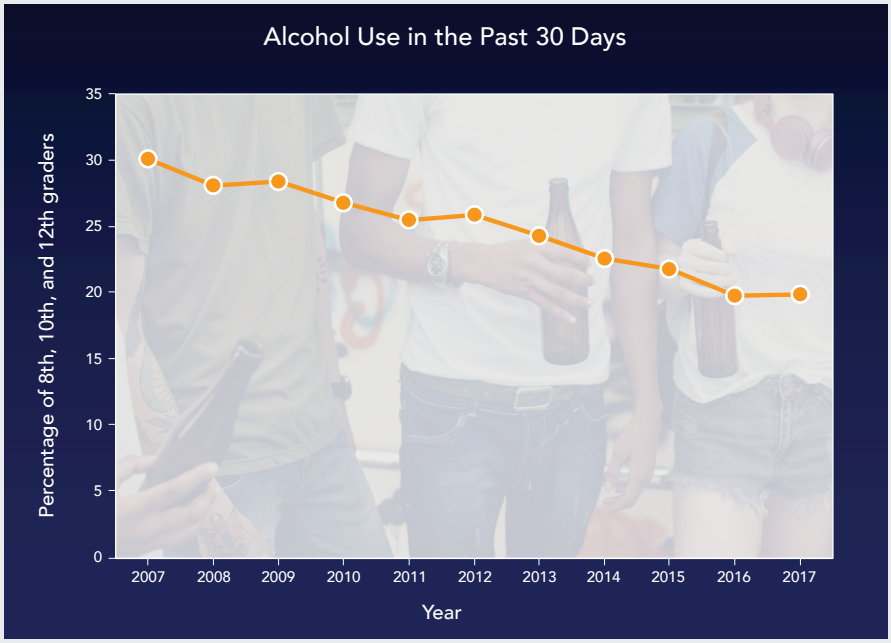
BY THE NUMBERS

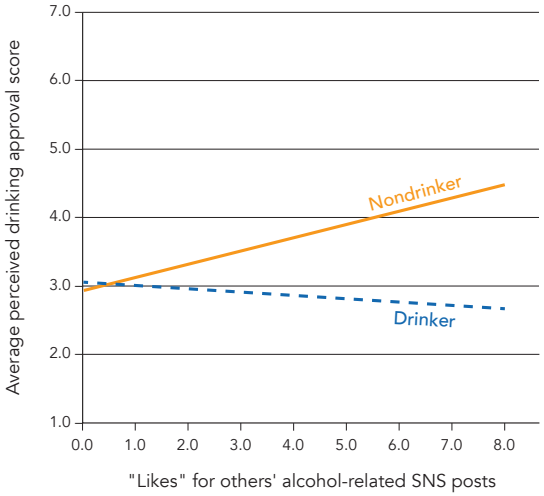


Source: Miech, R.A.; Schulenberg, J.E.; Johnston, L.D.; et al. *Monitoring the Future National Survey: Trends in 30-Day Prevalence of Use of Various Drugs in Grades 8, 10, and 12, 2017*. Ann Arbor, MI: Institute for Social Research, University of Michigan, 2018.

PERCENTAGE OF TEENS WHO DRINK DECREASED BY ONE-THIRD IN THE PAST DECADE

Recent research shows progress in reducing underage drinking, a major focus at NIAAA. The percentage of teens who drink decreased by one-third in the past decade, according to data from Monitoring the Future, an ongoing survey of 8th, 10th, and 12th graders.

BY THE NUMBERS



Nondrinkers' and drinkers' perceptions of typical student approval for underage drinking as a function of relative "likes" received by others' alcohol-related social networking site (SNS) posts. Source: Adapted from Boyle, S.C.; Smith, D.J.; Earle, A.M.; and LaBrie, J.W. What "likes" have got to do with it: Exposure to peers' alcohol-related posts and perceptions of injunctive drinking norms. *Journal of American College Health* 66(4):252–258, 2018. PMID: 29405864

ALCOHOL AND SOCIAL MEDIA

Social media can influence how college students view risky drinking. For those who have not yet started drinking, seeing friends "like" alcohol-related posts may increase perception of peer approval for the behavior. "Likes" did not affect perceived approval among students who had already started drinking.

NIAAA has just launched a new Instagram account (@NIAAAnews) to help spread science-based information about alcohol and health.

NIAAA@WORK

MAINTAINING NIAAA FACILITIES

Bob Ward, an NIAAA Administrative Officer, serves as an Institute liaison to the National Institutes of Health Office of Research Facilities and the real estate property management companies that manage NIAAA's office buildings. In this capacity, he handles all matters relating to NIAAA facilities, including parking, access, and maintenance. Ward, who has been with NIAAA for 12 years, holds the additional responsibilities of Green Team Leader, Occupant Emergency Coordinator, Property Custodial Officer, Chairman of Feds Feed Families, and Purchase Card Holder.

NEWS FROM THE FIELD

ADVANCED ANALYTIC METHODS COULD PROVIDE INSIGHT INTO MECHANISMS OF BEHAVIOR CHANGE

Numerous evidence-based behavioral interventions for alcohol use disorder (AUD) are available, including cognitive behavioral therapy, couples therapy, 12-step facilitation, and motivational interviewing. A current focus of research on behavioral interventions for AUD is identifying the processes through which evidence-based interventions work. Known as mechanisms of behavior change (MOBCs), such as increased readiness to change, increased social support for abstinence, and reduced craving, these processes partly explain why some treatments for AUD help people reduce or stop their alcohol use. A more comprehensive understanding of MOBCs, particularly of when they exert their effects, could inform clinicians' efforts in evaluating patient progress and making treatment decisions. In addition, identifying how specific events, actions, and processes contribute to MOBCs could provide clues into how these mechanisms develop, which would assist clinicians in targeting treatments more effectively.

Research on MOBCs has traditionally relied on mediation analysis frameworks, which are methods that help researchers assess the pathways that link a specific factor, like an MOBC, to an outcome, such as abstinence. To help move this area of research forward, Kevin Hallgren, Ph.D., of the University of Washington, and colleagues undertook an analysis of some statistical approaches beyond mediation analysis frameworks that may enhance understanding of how MOBCs work.

Sophisticated analytic techniques that consider behavioral change processes that occur during AUD treatment could provide a broader picture of how MOBCs operate. For example, an approach known as growth-curve modeling can shed light on the timing of MOBCs, such as when alcohol craving changes after abstinence. Other advanced analytical approaches can provide much-needed information about the complex relationships between factors that impact treatment, such as how a clinician's behavior during treatment sessions influences a patient's voicing of reasons to change, and vice versa.

In their study, Dr. Hallgren and colleagues note that a greater diversity of analytic methods to study MOBCs will lead to a better understanding of how patients successfully change and can improve the translational value of MOBCs research.

Reference:

Hallgren, K.A.; Wilson, A.D.; and Witkiewitz, K. Advancing analytic approaches to address key questions in mechanisms of behavior change research. *Journal of Studies on Alcohol and Drugs* 79(2):182–189, 2018. PMID: 29553344

NEWS FROM THE FIELD

BRAIN TRAINING MAY HELP PEOPLE WITH ALCOHOL USE DISORDER DELAY GRATIFICATION

Previous research has shown that people with alcohol use disorder (AUD) have more difficulty with working memory (WM) tasks and in planning for the future, compared with people without AUD. Individuals with AUD also overvalue immediate rewards, such as consuming an alcoholic drink offered to them, and devalue potentially larger future rewards, such as better health. The devaluation of delayed rewards is also known as "delay discounting." A new NIAAA-funded study has shown that WM training, along with episodic future thinking (EFT), may improve the ability of some people with AUD to value delayed rewards. WM training uses tasks or games to enhance brain functions such as short-term memory and attention, whereas EFT involves visualizing positive future events or rewards.

In the current study, led by Warren K. Bickel, Ph.D., of the Virginia Tech Carilion Research Institute, 50 people with AUD participated in either 20 active WM training sessions or control sessions. Before and after each session,

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NEWS FROM THE FIELD

MATERNAL CYTOKINE BALANCE MAY PLAY ROLE IN FASD RISK

A study done in conjunction with the NIAAA-supported Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) reports that disruptions in levels of certain immune system molecules during pregnancy can alter the risk for fetal alcohol spectrum disorders (FASD).

The effects of alcohol consumption on the immune system are well-documented. For example, chronic alcohol consumption has been shown to significantly increase levels of pro-inflammatory cytokines during pregnancy. Cytokines are small proteins that act as messengers between the immune system and the rest of the body. Some can promote and others can dampen inflammation, as well as regulate myriad other aspects of immune responses. Cytokines also have a broad range of functions outside the immune system, including roles that are important for the development and function of the brain. However, animal studies have shown that excessive levels of certain cytokines can pose harm to the fetal central nervous system.

Maternal immune activation and elevated cytokines during pregnancy have been linked to disorders such as autism and schizophrenia in offspring, and research has shown that alcohol misuse increases levels of numerous immune cytokines. In the new CIFASD study, researchers investigated whether elevated cytokines during pregnancy were a risk factor in women who gave birth to a child with FASD or a child with neurobehavioral impairment. A report of the study, led by Christina Chambers, Ph.D., of the University of California San Diego, and senior author Carl L. Keen, Ph.D., of the University of California Davis, appears in the May 2018 issue of *Alcohol*.

The investigators recruited women who reported "moderate to heavy" alcohol use during pregnancy, as well as women who reported low or no alcohol use during pregnancy. The women provided blood samples during the second and third trimesters of pregnancy that were used to measure cytokine levels. Infants born to women in the study were examined during the first year after birth for neurodevelopmental and physical features of FASD.

Researchers found that maternal alcohol consumption was associated with an increase in cytokine levels during pregnancy. However, subjects who did not have elevated levels of a specific anti-inflammatory cytokine known as interleukin 10 in the third trimester had an elevated risk of having a child with an FASD. The findings suggest that disrupting the levels of pro- and anti-inflammatory cytokines could adversely affect neurobehavioral development and influence the risk of FASD.

Note: In the CIFASD study, moderate to heavy alcohol use was defined as at least weekly binge-drinking episodes (5 or more drinks), at least 5 episodes of 3–4 drinks, or at least 10 episodes of 1–2 drinks, either in the month around conception or during the most recent month of pregnancy. Low to no alcohol use was defined as no binge episodes, minimal or no alcohol in the month around conception, and no drinking in the most recent month of pregnancy.

Reference:

Sowell, K.D.; Uriu-Adams, J.Y.; Van de Water, J.; Chambers, C.D.; Coles, C.D.; Kable, J.A.; Yevtushok, L.; Zymak-Zakutnya, N.; Wertelecki, W.; Keen, C.L.; and Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD). Implications of altered maternal cytokine concentrations on infant outcomes in children with prenatal alcohol exposure. *Alcohol* 68:49–58, 2018. PMID: 29453023

NEWS FROM THE FIELD: *Brain Training May Help . . .* *Continued from page 5*

participants also completed novel WM tasks, delay discounting tasks, and tasks that combined delay discounting and EFT. The researchers found that WM training enhanced the effectiveness of EFT in participants who had the highest delay discounting rates when the study began. These findings suggest that WM training may exert its effect on EFT by strengthening the ability of people with AUD to reconstruct the episodic cues during the tasks. The researchers note that this study is one of the first to show that WM training enhances EFT, and that more research is warranted to investigate this relationship.

Reference:

Snider, S.E.; Deshpande, H.U.; Lisinski, J.M.; Koffarnus, M.N.; LaConte, S.M.; and Bickel, W.K. Working memory training improves alcohol users' episodic future thinking: A rate-dependent analysis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 3(2):160–167, 2018. PMID: 29529411

5 QUESTIONS WITH . . .

MIKE HILTON, PH.D.

Deputy Director of the Division of Epidemiology and Prevention Research and Project Officer for the Alcohol Policy Information System

1 You are the Deputy Director of the Division of Epidemiology and Prevention Research (DEPR). Could you describe the Division's mission and priorities?

Our mission is to support, stimulate, and guide research on the epidemiology of alcohol use and on the prevention of alcohol-related problems. In practical terms, the program officials in the Division are like a membrane between the scientific community and the government community. We help the scientists navigate the maze of applying for government funding, and we help the government and citizens understand what is coming out of the science.

2 What have been some milestones for DEPR's research portfolio in recent years?

Recent research has marshaled the evidence that screening and brief interventions are effective among adolescents and young adults. Unfortunately, there are also findings that these interventions are vastly underutilized. Another recent milestone is more definitive evidence supporting the positive impact of setting the minimum legal drinking age at 21 years. Finally, some recent trials focused on underage alcohol use have shown that large-scale, comprehensive, community interventions produce positive outcomes. These community studies are very expensive to conduct, so the result of each rigorous community trial is quite valuable.

3 Looking ahead, where do you see the DEPR research program moving?

I can see three areas that will be of emerging research interest. First, the Institute is very concerned about the prevalence of extreme binge drinking—occasions where twice or more of the "binge drinking" amounts are consumed. Second, the convergence between males' and females' drinking patterns is fascinating. It runs counter to some very long-standing sex differences. Third, we anticipate that there may be increases in the simultaneous use of alcohol and cannabis, so we will need to know more about potential synergistic effects of the substances.

4 You are also Project Officer for the Alcohol Policy Information System (APIS), which was launched in 2003. How has the website evolved to remain relevant for the research community?

The website was designed primarily as a tool for researchers and policymakers, providing user-searchable access to authoritative, detailed, and comparable information on alcohol public policies in the United States, at both state and federal levels. The most important development, of course, is that APIS has started to track state policies allowing recreational use of cannabis. I firmly believe that the tools, methodologies, and traditions of studying policy impacts, which have been a part of the alcohol field since the repeal of Prohibition, provide a model for how to study the impact of cannabis policies.

5 If your career path had taken you in a different direction, what might you be doing now?

Answer 1: I'd probably be teaching history at some small, obscure, liberal arts college. Ever since seeing Kenneth Clark's *Civilisation* in 1969, I have had a deep interest in the kind of things you studied in your freshman introduction to humanities course. I have continued ever since to read and explore these things. Answer 2: A lion tamer. (I borrowed that from Monty Python.)

NOTEWORTHY

NIAAA Director Receives Jellinek Award

At the 41st Annual Research Society on Alcoholism Scientific Meeting held in June, NIAAA Director George F. Koob, Ph.D., received the Jellinek Memorial Fund Award for his outstanding contribution to the advancement of knowledge in the alcohol research field.

NIAAA on the Move

In July, the NIAAA offices moved to a new location at 6700B Rockledge Drive, Bethesda, Maryland, 20892. NIAAA laboratories and clinical spaces remain in Rockville, Maryland, and on the main National Institutes of Health campus in Bethesda, Maryland.

FEATURE: *Alcohol and the Aging Brain . . .* *Continued from page 3*

"These findings," notes Dr. Koob, "provide compelling evidence that alcohol misuse during later adulthood could confer a greater risk of deficits in frontal lobe function beyond the deficits that typically occur with aging."

In an editorial that accompanied the report by Dr. Sullivan and colleagues, Dr. Koob cites the "prominent alteration of frontal cortex volumes" as the most compelling aspect of the study.

"The frontal cortex controls executive function," says Dr. Koob, "and the prefrontal area has prominent projections to the basal ganglia and amygdala, controlling impulsivity and compulsivity. Disruption of this frontal cortex control is part of the causative mechanism of AUD."

Dr. Koob explains that frontal cortex control is underdeveloped during adolescence and compromised during the aging process, thus opening the possibility of greater vulnerability to AUD early and later in life. He describes how alcohol misuse could contribute to the aging process, and that the aging process may contribute to the development of AUD.

"Particularly with alcohol, the negative emotional states associated with aging may converge with the negative emotional states of alcohol withdrawal, which drives many individuals with AUD to self-medicate to avoid experiencing negative effects," says Dr. Koob. "This convergence, in turn, could also drive the need to self-medicate. In short, alcohol misuse in the elderly population may tap into misdirected attempts at emotional self-regulation, in which an individual consumes alcohol to fix the problem that alcohol helped cause."

References:

Sullivan, E.V.; Zahr, N.M.; Sassoon, S.A.; Thompson, W.K.; Kwon, D.; Pohl, K.M.; and Pfefferbaum, A. The role of aging, drug dependence, and hepatitis C comorbidity in alcoholism cortical compromise. *JAMA Psychiatry* 75(5):474–483, 2018. PMID: 29541774

Koob, G.F. Age, alcohol use, and brain function: Yoda says, "with age and alcohol, confused is the force." *JAMA Psychiatry* 75(5):422, 2018. PMID: 29541767

ABOUT US

NIAAA Spectrum is NIAAA's triannual webzine. With engaging feature articles, short news updates, and colorful graphics, *NIAAA Spectrum* offers accessible and relevant information on NIAAA and the alcohol research field.

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