NIAA consortium further knowledge of alcohol’s effects on brain development in adolescents

Two years ago, NIAAA launched the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA), a multisite longitudinal study to address alcohol’s potential effects on normal brain development. The NCANDA consortium consists of five research centers that collectively will enroll more than 800 participants ages 12 to 21, and will capture brain images and other data on these youth beginning before they start to drink. NCANDA’s overall objectives are to elucidate the short- and long-term effects of alcohol exposure on the developing brain and to identify brain characteristics that may predict alcohol use disorder. The NCANDA project is currently scheduled to run through June of 2017.

NCANDA precipitated and now can inform a larger proposed trans-NIH collaborative initiative: A national longitudinal study of the neurodevelopmental consequences of substance use, referred to as the Adolescent Brain Cognitive Development Study, or ABCD study. (See next story for more information on the ABCD study.)

NCANDA was initially funded in 2012, but it has its roots in NIAAA’s longstanding research portfolio on adolescent neuroscience and in the Institute’s Underage Drinking Research Initiative (UDRI) begun under former NIAAA director Ting-Kai Li, M.D. Vivian Faden, Ph.D., who co-chaired UDRI and is now NIAAA’s Associate Director for Behavioral Research, said: “NCANDA’s investigators have laid an important foundation for a more extensive research undertaking to assess the effects of drugs and alcohol, alone and in combination, on the adolescent brain.”

In recent decades, researchers have established that neuroplasticity—changes in functional and structural properties of brain cells, neural pathways, and synapses resulting from changes in behavior, environment, and neural processes—plays a fundamental role in brain development and disease. During childhood and into early adulthood, neuroplastic processes drive brain development as maturing connections between brain cells enable increasingly complex communication among brain regions. Researchers also have shown that repeated exposure to alcohol leads to adaptations that ultimately may result in alcohol use disorders. Thus, studies conducted by the NCANDA advance our understanding of alcohol’s effects on neuroplasticity at multiple levels.

Considerable evidence shows that drinking at early ages can increase the likelihood of developing alcohol-related problems and suggests that early exposure to alcohol sensitizes the neurocircuitry of addiction. These areas have long been NIAAA research priorities. NIAAA helped lay the foundation for NCANDA in late 2006, when it solicited pilot studies of the effects of child and adolescent alcohol use on the developing human brain.

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FEATURE

NIAAA AND OTHER NIH INSTITUTES PROPOSE MAJOR STUDY OF SUBSTANCE USE ON ADOLESCENT BRAIN DEVELOPMENT

In May 2014, leaders from several Institutes of the National Institutes of Health proposed an historic scientific initiative: a national longitudinal study of the neurodevelopmental consequences of substance use. Referred to as the Adolescent Brain Cognitive Development (ABCD) Study, the project will be unique in its size and duration, as it calls for 10,000 youths to be followed and studied for 10 years. And, importantly, like NCANDA, it will recruit participants before they have started using substances.

In a joint statement, NIAAA Director George Koob, Ph.D., and the directors of the National Institute on Drug Abuse (NIDA), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Cancer Institute’s (NCI) Division of Cancer Control and Population Sciences, explained: “We have evidence (from both animal and human studies) that exposure to marijuana, alcohol, tobacco, and other drugs can affect the adolescent brain, possibly in a lasting way. But there are many gaps in our knowledge, and no large prospective study has yet been conducted that has followed participants all the way from childhood—i.e., before the first use of substances—through to adulthood, employing neuroimaging tools to assess the effects of substance exposure on brain development while measuring a broad range of behavioral antecedents and outcomes. The good news is, with the combined resources and ingenuity of multiple NIH Institutes and other partners, we now have the capability to conduct such a study with a very large sample—one that would help us more confidently establish the effects of occasional or regular use of alcohol, tobacco, and other drugs on the brains and lives of young Americans.”

Following the announcement, NIH convened a panel of scientific experts on May 27–28, 2014, to discuss how

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BY THE NUMBERS

BINGE DRINKING: WHO’S WASTING TIME GETTING WASTED?

NIAAA defines binge drinking as a pattern of drinking that brings blood alcohol concentration levels to the legal limit for driving in the United States—what many people know as “.08.” This typically occurs after 4 drinks for women and 5 drinks for men—in about 2 hours.¹

Many people associate binge drinking with young people, particularly those in college. Studies show that this stereotype isn’t just based on what we see in movies and on television. In fact, college-aged drinkers are the age group most likely to binge drink. About 15 percent of people ages 12–20 are binge drinkers.² Nearly 25 percent of people ages 18 or older reported that they engaged in binge drinking in the past month.³ However 40.1 percent of college students ages 18–22 engaged in binge drinking (5 or more drinks on an occasion) in the past month compared with 35 percent of same-age peers not in college.⁴

Researchers estimate that each year among college students between the ages of 18 and 24, there are 1,825 deaths from alcohol-related unintentional injuries, including motor-vehicle crashes; 696,000 assaults by another student who has been drinking; 97,000 reports of alcohol-related sexual assault or date rape.⁵ Additionally, roughly 20 percent of college students meet

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to move the project forward. The panel, which included four renowned imaging experts, considered a range of design elements and measures that could be used in the new study. An important focus of the discussion was the collection of neuroimaging data which will be central to the project’s success. Key recommendations came from several experts currently involved in the National Consortium on Alcohol and Neurodevelopment in Adolescence, or NCANDA. (See previous article for more details about NCANDA.)

The ABCD study will follow participants beginning in late childhood. Investigators will collect mental health, genetic, and behavioral data on substance use, school achievement, IQ, and cognition. Brain imaging will be a key component. As outlined in NIH’s statement announcing the initiative: “The array of neuroimaging and genetic tools now available enables us to study the nature of the brain changes that arise from substance use and shed light on causal mechanisms, to a degree never before possible. Among its many goals, the study should illuminate interactions between substances, identify neurodevelopmental pathways that link drug abuse with mental illnesses, and disentangle the effects of individual substances as well as characterize their combined effects.”

As a followup to the May meeting, NIH released a Request for Information (closing date: August 31; see grants.nih.gov/grants/guide/notice-files/NOT-DA-14-014.html) seeking input on the proposed study. In the fall, NIH will host an open satellite event about the project at Neuroscience 2014, the annual meeting of the Society for Neuroscience. The satellite event is scheduled for Monday, November 17 in Washington, DC (view more details at http://addictionresearch.nih.gov/news-events/nov-17-sfn-satellite-event-planned). According to the Collaborative Research on Addiction at NIH initiative (CRAN) Web site, NIH anticipates that a Funding Opportunity Announcement for the project will be issued in 2015.

Importantly, the proposed ABCD study also fits the goals of the recently established CRAN perfectly. NIAAA, NIDA, and NCI’s Division of Tobacco Control play the largest roles in CRAN. Key staff from each of these Institutes and NICHD met several times to plan the May meeting of the expert panel to discuss the National Longitudinal Study of Neurodevelopmental Consequences of Substance Use. In addition, scientific program staff from the National Institute of Mental Health provided technical consultation and attended the meeting. The official meeting summary and other related news and announcements can be found at the CRAN Web site: addictionresearch.nih.gov.

**NEWS FROM THE FIELD**

**Repeated cycles of alcohol intoxication and withdrawal take a toll on the brain**

Repeated cycles of excessive alcohol use reflect a pattern of compulsive-like responding known to alter functioning of brain systems involved in incentive salience and habit formation particularly in the dorsolateral striatum (DLS) and prefrontal cortex areas of the brain. Such compulsive-like responding can be mimicked in mice with chronic intermittent ethanol exposure (CIE) in which mice are exposed to repeated bouts of alcohol intoxication and withdrawal. In a recent study, David Lovinger, Ph.D., of NIAAA’s Laboratory for Integrative Neuroscience; Andrew Holmes, Ph.D., of NIAAA’s Laboratory for Behavioral and Genomic Neuroscience, and colleagues explored the effects in mice of prolonged CIE on plasticity, the adaptive changes in functional and structural properties of brain cells and synapses, in the DLS. The researchers also examined CIE effects on DLS-mediated behaviors, such as seeking alcohol. For this study, prolonged CIE consisted of 16 hours of continuous exposure to alcohol vapor followed by 8 hours of withdrawal, repeated for 16 days, whereas the typical CIE cycle lasts for 8 days. Recordings of brain activity revealed evidence of impaired plasticity in the DLS of the CIE-exposed mice. In addition, CIE-exposed mice showed significantly higher ethanol consumption and preference for alcohol compared with controls. CIE-exposed mice also showed deficiencies in a behavioral task involving reward-associated cue learning. The study opens the door to further examinations of how chronic alcohol exposure changes the way the brain regulates rewarded behavior.

**Source:**
**NEWS FROM THE FIELD**

**DRINKING IN THE DARK SHEDS LIGHT ON THE MECHANISMS UNDERLYING BINGE DRINKING**

DID is a research procedure that capitalizes on a mouse’s tendency to drink more during the dark phase of its circadian rhythm cycle. It promotes voluntary, binge-like drinking in mice, resulting in high blood ethanol concentrations (BEC). In this study, mice first acclimated to a reversed light/dark cycle over the course of a week. Then, 3 hours into the dark cycle, mice had their water bottles replaced with either water or ethanol for four consecutive days. On the first 3 days, mice had access to these bottles for 2 hours. On the fourth day, access was increased to four hours. These “drinking” days were followed by three days of abstinence. Researchers repeated this 7-day cycle for 6 weeks.

Researchers observed that all mice drank more when the bottles were replaced with either water or ethanol. Mice with ethanol bottles had the highest drinking rates during the first 15 minutes of when they were given access to the alcohol, and this drinking rate increased over the 6 weeks. BEC levels also increased over the weeks of exposure, as did preference for ethanol. The study also examined DID’s effect on changes in synaptic transmission (the process nerve cells use to communicate information using chemicals called neurotransmitters) in the dorsal lateral striatum (DLS), an area of the brain that controls motor movement—and which is particularly vulnerable to the effects of ethanol. Previous studies have shown that prolonged access to alcohol over 3 years changed synaptic transmission in the DLS of non-human primates at synapses that use the excitatory neurotransmitter glutamate or the inhibitory neurotransmitter GABA. In contrast to these previous studies, researchers found that drinking in the dark did not change spontaneous excitatory transmission or the density of inhibitory neurons of the DLS. However, it did show that inhibitory GABA-using synapses are depressed, or resistant to transmission, in the striatum after DID. This reduced transmission of inhibitory synapses may have contributed to the mice’s increased tendency to seek out and consume ethanol.

**Source:**

**FEATURE: NIAAA Consortium. . . Continued from page 1**

Through a Request for Applications (RFA) entitled “Impact of Adolescent Drinking on the Developing Brain,” NIAAA sought to determine the feasibility of, and broaden the research base for, the longitudinal study now being conducted by NCANDA investigators. In 2007, NIAAA made 5 grant awards from this RFA. Brief descriptions of key findings from those studies follow.

**Adolescent Neurocognitive Recovery Following Abstinence from Alcohol.** Researchers led by Sandra Brown, Ph.D., of the University of California-San Diego, reported that adolescents with recent histories of heavy episodic drinking have poorer performance on a number of neuropsychological tests compared with their nondrinking peers. They also found that these cognitive differences persist even after 4 to 6 weeks of abstinence from alcohol. These findings suggest a possible alcohol-induced impact to underlying brain systems, particularly given that drinkers and nondrinkers in this study had comparable academic test scores before the onset of drinking.

**Neurodevelopmental Maturation and Alcohol Use in Adolescents.** In brain imaging studies, Duncan Clark, M.D., Ph.D. of the University of Pittsburgh, and his colleagues found that adolescents who have alcohol or other substance use disorders have significantly greater difficulty with tasks that measure cognition, behavior, and affect, compared with controls. Brain images showed that substance-using adolescents had disorganized white matter in the prefrontal and...
ALCOHOL-INDUCED DEPLETION OF “BRAIN FERTILIZER” PROTEIN MAY INFLUENCE HIV TREATMENT RESPONSE

Hazardous alcohol use by people with HIV may deplete a protein that stimulates nerve cell growth, according to a new study supported by NIAAA. The study also suggests that the protein, called brain-derived neurotrophic factor (BDNF), plays an important role in the immune systems of people receiving anti-retroviral therapy for HIV.

Scientists measured BDNF—sometimes referred to as “fertilizer for the brain” for its ability to stimulate nerve cell growth—in 400 people receiving antiretroviral therapy for HIV infection. They found that people who drank at “hazardous” levels tended to have lower blood levels of BDNF than people who drank less. Hazardous alcohol use was defined for men as more than 4 drinks on any day or more than 14 drinks per week and for women as more than 3 drinks on any day or more than 7 drinks per week.

People with lower BDNF levels were less likely to have healthy blood counts of a key infection fighter, the CD4 immune cell, and, in turn, less suppression of the virus over a 6-month follow-up period. Previous studies have shown that BDNF improves CD4 cell survival, but its role in depleting or replenishing these immune cells in HIV patients receiving anti-retroviral therapy has been unknown.

Although the study’s design cannot establish causality, the findings may help explain the commonly observed poor response to anti-retroviral therapy among people with HIV who drink heavily. In addition, the findings suggest that BDNF helps keep HIV under control and thus may lead to new strategies for stimulating the immune system in the many people who do not fully respond to anti-retroviral therapy.

Source:
The+Role+of+Brain+Derived+Neurotrophic+Factor+in+Viroimmune+Responses+to+Antiretroviral+Therapy+among+People+Living+with+and+without+Alcohol+Use

NOTEWORTHY

NIAAA LEADERSHIP RECOGNIZED

The Fondation Ipsen’s Neuronal Plasticity Prize recognizes outstanding contributions in the field of neuronal plasticity. Dr. Koob was cited for his pioneering work in the domain of “Neuropsychology of Drug Addiction,” particularly for his contribution to our understanding of the neurocircuitry associated with the acute reinforcing effects of alcohol and drugs of abuse and the neuroadaptations of the reward and stress circuits associated with the transition to dependence.

The Research Society on Alcoholism (RSA) presented longtime NIAAA Deputy Director (and former Acting Director), Kenneth R. Warren, Ph.D., with the RSA Lifetime Achievement Award at its annual meeting on June 25, 2014. The award recognizes a person with a long, balanced career whose contributions to alcohol research, training, service, and advocacy have had a lasting impact on the field.

Dr. Warren is a distinguished scientific administrator and a foremost expert on the effects of alcohol use during pregnancy. He joined NIAAA in 1976, and more than 30 years ago, he initiated NIAAA’s research program on fetal alcohol syndrome. For his work on the development of the first Surgeon General’s Advisory on Alcohol Use in Pregnancy, Dr. Warren received a Superior Service Award from the Public Health Service in 1982. Currently, Dr. Warren chairs the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders.
A CLOSER LOOK

ALCOHOL MONITORING TECHNOLOGY

Recognize this fashion accessory? The Secure Continuous Remote Alcohol Monitoring (SCRAM) bracelet is among the most well-known alcohol biosensors, making high-profile appearances on celebrity ankles. SCRAM bracelets are increasingly being used by the justice system to ensure that people with alcohol-related arrests, most often drunk driving, abstain from drinking as part of their sentencing or probation. The manufacturer, Alcohol Monitoring Systems, reports that SCRAM technology is used by more than 200 service providers in 1,800 courts and agencies across the United States. And the Mayor of London, England, recently announced that SCRAM bracelets would be used in a pilot project aimed at getting repeat alcohol offenders to remain abstinent.

So how does it work? The bracelet is secured to the ankle and tests for alcohol consumption every 30 minutes. Alcohol is excreted through sweat, so measurements can be taken as ethanol vapor is emitted through the skin (called “transdermal monitoring”). A violation is reported if an individual’s blood alcohol level rises above 0.02 g/dL. The bracelet cannot be removed and an infrared beam measuring the distance between the leg and bracelet prevents tampering. The bracelet also can be used to collect data about the wearer’s location. On average, the device is worn for about 90 days.

Are SCRAM bracelets effective? The National Highway Traffic Safety Administration collected data from six U.S. programs using alcohol monitoring devices and found that, in general, people using the devices remained abstinent. Among offenders in the six selected programs, 1.4 percent had a confirmed drinking event and 16.9 percent had tamper violations. These compliance rates are slightly higher than a 2004–2009 study of 9,100 offenders monitored using SCRAM bracelets. Among this group, 75 percent remained alcohol-free and did not attempt to tamper with the device.

The case study from the National Highway Traffic Safety Administration concluded that the six programs using alcohol monitoring were satisfied with the technology and would recommend its use to others. NHTSA recommends that those interested in using SCRAM bracelets familiarize themselves with the equipment first-hand, if possible, and work closely with vendors to obtain information and training.

Sources:

Alcohol, Sleep and Brain Development.
Ian Michael Colrain, Ph.D., of SRI International, and colleagues used studies of sleep physiology and brain EEG activity to examine the effects of alcohol on the developing nervous system. In mature adults, alcohol is known to initially decrease the time to sleep onset, but also to decrease the quality of sleep, and increase wakefulness after sleep onset. Alcohol’s effect on sleep during late adolescence is of interest given that this age group shows both dramatic increases in alcohol consumption and significant developmental changes in the central nervous system. In a study of 18 to 21-year-olds, Dr. Colrain’s group found that alcohol’s effects on sleep were broadly consistent with findings in adults. One difference, however, is that alcohol’s physiological and EEG effects on this group’s half-night sleep could not be attributed to changes in sleep length. The results suggest that the effects of alcohol on sleep depends on a person’s developmental level.

Alcohol Effects on the Adolescent Brain: A Study of Monozygotic Twin Differences. In a study of adolescent identical twins with different drinking levels, in which one twin served as the control for the other, researchers led by Stephen Matthew Malone, Ph.D., of the University of Minnesota, found that alcohol use was associated with poorer performance on a task that measured decision-making. MRI scans showed that gray matter volumes for brain regions involved in performing the task were reduced in adolescents with problematic alcohol use. The researchers note that the association between alcohol use and poorer performance likely reflects a causal effect of alcohol exposure on the processes utilized during performance of the task, and suggests that normative levels of alcohol use may diminish the quality of adolescent decisionmaking and thus have potentially important public health implications.

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TRISH POWELL, PH.D.
Associate Director for Scientific Initiatives at NIAAA

1 Your new title is Associate Director for Scientific Initiatives. What does that involve?

With Dr. Koob coming on board as our new director this year, NIAAA is putting additional emphasis on certain research areas. In my new position, I will be trying to jump-start or expand projects that reflect Dr. Koob’s priorities. Along the way, I will be consulting with experts here at NIAAA and seeking input from the research community. One of my responsibilities is to try to find opportunities for NIAAA to become more involved in existing activities and initiatives across the National Institutes of Health and beyond and then hand these initiatives off to a lead person here to further develop.

2 Can you give us an example?

PTSD and alcohol is a prime example. In 2012 President Obama issued an executive order that called for development of the National Research Action Plan (NRAP) for Improving Access to Mental Health Services for Veterans, Service Members, and Military Families. As NIAAA’s representative on this project, I worked with colleagues across Federal agencies to develop and implement the NRAP. Given the intersection of problem alcohol use and PTSD, as well as the potential overlap in mechanisms underlying the two disorders, it makes sense for us to expand our research in this area. The goal is to identify effective treatments for these co-occurring disorders; NIAAA’s Dr. Lindsey Grandison is now overseeing this effort.

A second area of interest to the White House is protecting students against sexual assault. Dr. Koob has interacted with the White House task force and we are exploring how NIAAA’s research expertise on college drinking and its consequences can inform the work of the task force.

3 Dr. Koob has expressed an interest in biosensor technology. What can you tell us about that area of research?

Biosensors measure alcohol in the body in various ways: in breath, expiration through the skin, in the blood, and in the fluid in the eye. There are many applications for alcohol sensors including research, treatment, self-awareness of one’s drinking levels, and patterns. NIAAA is interested in developing a small, unobtrusive sensor that could be used for multiple applications. NIAAA’s Dr. Kathy Jung is now leading this effort.

4 You’ve been at NIAAA for almost 20 years. What has been one of your favorite projects?

While I’m interested in NIAAA’s entire portfolio, I have my favorite areas, one of which is our research on underage drinking. I have worked closely with NIAAA’s underage research initiative since its inception and served as a senior editor on the Surgeon General’s Call To Action to Prevent and Reduce Underage Drinking.

I’m also fascinated by human development and especially the changes occurring in the adolescent brain. Having a high school senior and an 8th grader, I get to watch this unfold on a daily basis. Fortunately, this is also a priority area for Dr. Koob, so I won’t be giving it up anytime soon.

5 How did your career path lead you to NIAAA?

I took a very circuitous career path, which I have thoroughly enjoyed.

I am a molecular and cellular biologist by training and my Ph.D. work was on generating viral resistance in plants by genetically modifying them. This was in the early days of genetically modified organisms (GMOs) and gave me my first taste of contentious science policy issues.

I subsequently switched fields and worked with fruit flies looking at pattern formation in the fly eye and peripheral nervous system. In that position, I gained a deep appreciation for the elegance of fly genetics and the development of organs and systems.

Prior to joining NIAAA, I was an American Association for the Advancement of Science (AAAS) science and technology policy fellow at the National Science Foundation. In working with experts in science museums, television, and IMAX films, I gained an admiration for those who communicate cutting-edge science accurately and engagingly.

When NIH joined the AAAS program the following year I had the good fortune to come to NIAAA as an NIH/AAAS fellow and prior to my current position I served as NIAAA’s Chief of the Science Policy Branch.
References:
3 SAMHSA. 2012 National Survey on Drug Use and Health (NSDUH). Available at: http://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/DetTabs/NSDUH-DetTabsSection2peTabs43to84-2012.htm#Tab2.46B.

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When choosing to drink at any level, individuals among all age groups should consider the very real possibility of harm—for themselves and those around them—associated with misusing alcohol.

To evaluate your drinking patterns, visit Rethinking Drinking: Alcohol and Your Health (RethinkingDrinking.niaaa.nih.gov).

FEATURE: NIAAA Consortium . . . Continued from page 6

Adolescent Neurodevelopment and Alcohol. Robert Thoma, Ph.D., of the University of New Mexico, and colleagues conducted brain imaging studies to compare white matter changes in young people with current or past alcohol use disorders (AUDs). The researchers took MRI scans of people with current alcohol use disorders, people with alcohol use disorders in remission for at least 1 year, and healthy non-drinkers as controls. The brain scans showed that the AUD remission group had white matter damage in brain regions involved in processing visuospatial information and self-awareness, whereas current drinkers had abnormal white matter distribution in areas that regulate impulsivity, attention, and memory. As a combined group, AUD individuals had abnormalities in areas associated with sensory processing and memory. The researchers note that the pattern of white matter abnormality across groups suggests that they may result from alcohol use. They caution, however, that their findings should be considered preliminary, and that longitudinal studies are necessary to establish causality and extend the present findings and to test their functional consequences.

ABOUT US
NIAAA Spectrum is NIAAA’s first-ever 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 for a wide range of audiences. Each issue includes feature-length stories, new research findings from the field, image and data analyses, and an interview with an NIAAA staff member or alcohol researcher. NIAAA Spectrum is published three times a year.

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the criteria for an AUD and about 1 in 4 college students report academic consequences from drinking, including missing class, falling behind in class, doing poorly on exams or papers, and receiving lower grades overall. When choosing to drink at any level, individuals among all age groups should consider the very real possibility of harm—for themselves and those around them—associated with misusing alcohol.

To evaluate your drinking patterns, visit Rethinking Drinking: Alcohol and Your Health (RethinkingDrinking.niaaa.nih.gov).