U.S. Department of Health and Human Services
National Institutes of Health
Minutes of the 12th Joint Meeting of the
National Advisory Council on Alcohol Abuse and Alcoholism,
National Advisory Council on Drug Abuse, and
National Cancer Advisory Board
May 8, 2024

Members of the National Advisory Council on Alcohol Abuse and Alcoholism (NIAAA), National Advisory Council on Drug Abuse (NIDA), and the National Cancer Advisory Board of the National Cancer Institute (NCI) convened for their 12th joint meeting on May 8, 2024, in hybrid format. Chaired by Nora Volkow, M.D., Director of NIDA and George Koob, Ph.D., Director of NIAAA, the open session convened at 10:00 a.m.

National Advisory Council on Alcohol Abuse and Alcoholism Members Present:

Nancy Barnett, Ph.D.
Andrew M. Cameron, M.D., Ph.D.
Christina Chambers, Ph.D.
Haiden A. Huskamp, Ph.D.
Rhonda J. Jones-Webb, Dr.P.H.
David Kareken, Ph.D.
Michael J. Lewis, Ph.D.
Dayne Mayfield, Ph.D.
Katie Witkiewitz, Ph.D.

National Advisory Council on Drug Abuse (NACDA) Members Present:

Arpana Agarwal, Ph.D.
Katherine L. Beebe Devarney, Ph.D.
Deborah Chassler, M.S.
Charles Chavkin, Ph.D.
Anna Rose Childress, Ph.D.
Christiane S. Duarte, M.P.H., Ph.D.
Shelley F. Greenfield, M.D.
Regina M. LaBelle, J.D.
Angela R. Laird, Ph.D.
Rajita Sinha, Ph.D.
Mark E. Von Zastrow, M.D., Ph.D.

National Cancer Advisory Board Members Present:

Nilofer S. Azad, M.D.
Richard J. Boxer, M.D.
John D. Carpten, Ph.D.
Luis Alberto Diaz, Jr., M.D.
Ysabel Duron
Howard J. Fingert, M.D., F.A.C.P.
Julie Papanek Grant, M.B.A.
Amy B. Heimberger, M.D.
Ana Navas-Acien, M.D., Ph.D., M.P.H.
Fred K. Tabung, Ph.D., M.S.P.H.
Karen M. Winkfield, M.D., Ph.D.

Chairs: George Koob, Ph.D., and Nora Volkow, M.D.
National Institute on Drug Abuse (NIDA) Director: Nora Volkow, M.D.
National Institute of Alcohol Abuse and Alcoholism (NIAAA) Director: George Koob, Ph.D.
National Cancer Institute/Behavioral Research Associate Director: William Klein, Ph.D.
NIAAA Deputy Director: Patricia Powell, Ph.D.

NIDA Deputy Director: Wilson Compton, M.P.E., M.D.
NIAAA, Director, Office of Extramural Activities: Philippe Marmillot, Ph.D.
NIDA, Director, Division of Extramural Research: Susan B. Weiss, Ph.D.
NCI, Director, Division of Extramural Activities: Paulette S. Gray, Ph.D.
NIDA Senior Staff: Gayathri J. Dowling, Ph.D.
NIAAA Senior Staff: Vicki Buckley, M.B.A.; Ralph Hingson, Sc.D.; M. Katherine Jung, Ph.D.; Raye Litten, Ph.D.; David Lovinger, Ph.D.; Antonio Noronha, Ph.D.; and Bridget Williams-Simmons, Ph.D.

NCI Senior Staff: William Klein, Ph.D.

Additional Participants

Approximately 295 observers joined the meeting, including representatives of constituent groups, liaison organizations, and members of the general public.

Call to Order

Dr. Volkow called to order the twelfth meeting of the National Advisory Councils of NIAAA, NIDA, and NCI in open session at 10:00 a.m. on Wednesday, May 8, 2024. Members of the three respective Councils introduced themselves.

NIDA Director's Presentation

Dr. Volkow announced the appointment of Iván D. Montoya, M.D., M.P.H., as the new director of NIDA's Division of Therapeutics and Medical Consequences.

2023 Monitoring the Future Study. The annual survey of 8th, 10th, and 12th graders is important because this is the stage at which adolescents experiment with drugs, potentially leading to escalating use and sometimes to severe outcomes. The 2023 findings are consistently positive, with significant reductions in both legal and illegal drug use, compared to the previous year. The reductions in use among 12th graders are the most important because this grade engages in the highest level of consumption. These findings also represent good news: During the COVID pandemic, consumption among teens dropped most likely because they were isolated from their peers and more closely supervised by parents who were often working from home. Researchers feared this pandemic-related decrease in adolescent drug consumption would rebound as normal life resumed, but that has not happened.

Alcohol. There have been significant reductions in alcohol consumption, including patterns of harmful consumption, over the past five years. Nonetheless, alcohol has remained the most widely used substance (45.7 percent) among 12th graders.

Vaping. In past years, marijuana use (29 percent in 2023) was the next most widely used substance among 12th graders; in 2023, its position was challenged by vaping (28.8 percent) of any type. Both nicotine (23 percent) and marijuana (19.6 percent) are vaped. Nicotine vaping is of particular concern because vaping delivers a high content of nicotine that can lead to nicotine dependence and ultimately to the use of combustible tobacco.

Cannabis. The increase in cannabis consumption among adults is not reflected among teens, despite legalization of cannabis in many states. Both illicit drug use in the past year and daily use of marijuana have remained stable across all three grades. It is important to distinguish between these two behaviors because marijuana is the indicator substance of illicit drug use.

Hallucinogens. Hallucinogens (4.3 percent among 12th graders) are another area of particular concern because hallucinogens have not appeared in the "top 10" list of drugs consumed by teens in the past 20 years. Hallucinogens have been in the media a lot ; and such news coverage generates curiosity among teens. Hence, the use of hallucinogens among teens is a trend that needs to be monitored.
Psychotherapeutic Drugs. Dr. Volkow also pointed to a variety of psychotherapeutic drugs (cough medicine, amphetamines, sedatives/tranquilizers, Adderall, and narcotics other than heroin). While these drugs are all at levels lower than they were in previous years, they are consequential because one way fentanyl is getting into the United States is disguised as prescription pills. A single pill with fentanyl can lead to a fatal overdose.
Adult Substance Use. Reports from the National Survey on Drug Use and Health from the Substance Abuse and Mental Health Services Administration (SAMHSA) indicate that adult substance use does not parallel trends among adolescents. For example, marijuana use is increasing among adults but not among teens. Nicotine vaping is higher in teens than adults, despite an increase in adult use. In both age groups, alcohol remains the most widely-used substance. The second most prevalent substance used by adults is tobacco products, followed by marijuana. One striking finding of the survey is the almost 50 percent ratio between new initiates of hallucinogens (1.4 million) and their adult past month prevalence (2.3 million), suggesting a rise in prevalence can be expected in the future. Similarly, the proportion of new initiates to vaping (6 million) is approximately one quarter of its past month prevalence (23.5 million), anticipating a rise in nicotine vaping.
Research programs: NIDA, NIAAA, and NCI are all funders of the Adolescent Brain and Cognitive Development (ABCD) study that started in 2016 to monitor the development of 12,000 youngsters recruited at age 9-10 who are now in their teens. ABCD study inspired the HEALthy Brain and Child Development (HBCD) study that is currently recruiting over 7,000 pregnant women and babies to understand normative neurodevelopment of children from infancy to ages 9-10 and to assess the impact of in-utero exposures to drugs and harmful environments. HBCD study poses more challenges than ABCD study because the goal is to recruit a sample in which 25 percent of mothers were exposed to substances during pregnancy, such as opioids, alcohol, and marijuana.
The Opioid Overdose Crisis. Data from the National Center for Health Statistics identified a first-ever decrease in overdose deaths (0.49 percent), driven primarily by reductions in the use of heroin and opioid analgesics. Increases continue to be seen, in the use of cocaine, stimulants such as methamphetamines, and synthetic opioids (illicit fentanyl). The primary culprit in drug overdose deaths is fentanyl. Most overdose deaths involve multiple drugs; thus, clinicians and first responders may find it difficult to reverse overdoses and treatment becomes more complex. Therefore, it makes sense to develop medications that treat addiction across drugs.
Therapeutics for Polysubstance Use. Needed therapeutics for polysubstance use include overdose reversal agents, pharmacological and biological agents, and device-based therapeutics. Neuromodulation therapies, such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and low intensity ultrasound, promise to revolutionize the treatment of psychiatric diseases by tailoring treatments to the individual. Other promising approaches include psychedelics that expand neuroplasticity and GLP1-R agonists (e.g., semaglutide-Wegovy) that may be reducing substance use.
Drug Overdose Deaths by Race/Ethnicity. Native American/Alaska Native individuals have the highest rate of drug overdose deaths across all racial/ethnic groups in the U.S., almost twice as high as the general population. To ameliorate this significant health disparity, the Helping to End Addiction Long-term (HEAL) initiative at NIH, engaging multiple Institutes and Centers (ICs), launched the Native Collective Research Effort to Enhance Wellness (N CREW) Addressing Overdose, Substance Use, and Pain in June 2023. Two Research Opportunity Announcements (ROAs) to Tribes and Native American Serving

Organizations (T/NASOs) were issued for research and development of culturally appropriate models of care. Currently in Phase I (FY24-FY26), N CREW's overall planned budget is approximately $268 million.

Drug Overdose Deaths by Age. Drug overdose deaths have increased among all age groups. Those aged 35-44 have the highest overdose mortality rate, followed by those 45-54 years old. Older Americans (65-74) and younger Americans (15-24) have lower rates of overdose deaths; nonetheless, deaths in these age groups have increased over time. Thus, effectively addressing the opioid overdose crisis means not just intervening among those with an opioid use disorder (OUD) but also emphasizing prevention. Accordingly, NIDA supports a cascade of care for substance use disorders (SUDs) from prevention to harm reduction to treatment to long-term recovery. Dr. Volkow said that more research is particularly needed in the areas of harm reduction and recovery. She concluded her presentation by inviting everyone to celebrate NIDA's 50th anniversary on May 14, 2024.

Discussion. Dr. Koob asked if vaping of marijuana is increasing. Dr. Volkow reported that nicotine vaping is the most widely used followed by marijuana vaping. Overall patterns of vaping were extremely high when vaping was first introduced, but prevalence has now stabilized. Dr. Jones-Webb inquired about potential explanations for the stabilization of cannabis use among teens, given its increasing legalization across states. Dr. Volkow cited the entire landscape of declining substance use (even as mental health issues among teens have increased) and the role of drugs as reinforcers. One can speculate that the decline may be due to students using cell phone-based technologies to interact and meet their social needs without the presence of face-to-face peer pressure. The ABCD and HBCD studies are poised to provide insight into some of these dynamics. Dr. Navas-Acien asked if NIDA has data linking vaping with depression. Dr. Volkow replied that she has seen no clear-cut data on this, but it has been established that teens self-medicate with substances and nicotine is known to have anti-depressant effects.

NIAAA Director's Presentation

Dr. Koob shared statistics about alcohol use to emphasize the scope of the problems posed by this substance. There has been a dramatic increase in annual deaths from excessive alcohol over the past 20 years. During the first year of the pandemic, the mention of alcohol on death certificates increased by 25 percent with an additional 10 percent rise in the second year and no decrease in the third year. The U.S. Centers for Disease Control and Prevention (CDC) estimates that about 180,000 American lives are lost each year due to alcohol.

Alcohol and Women's Health. For all age groups, differences between females and males in the prevalence of drinking and binge drinking are narrowing. People under the age of 21 are drinking less but the declines are bigger for males than females. As a result, females in this age group are now more likely than males to drink and to binge drink each month. A similar pattern occurred for people aged 18-25. For adults 26+, alcohol use is increasing for women but not for men. These trends are concerning for several reasons: 1) There is a risk-severity paradox for women in that women tend to experience a range of alcohol-related harms at lower doses of alcohol over shorter periods of time than men. 2) Studies suggest women are more likely to experience hangovers, blackouts, liver disease, brain atrophy, cognitive deficits, cardiomyopathy, and certain cancers. Women also have a faster progression of AUD severity. 3) Women are less likely than men to receive treatment for AUD. 4) In the past two decades, there have been larger increases in alcohol-related emergency department visits, hospitalizations, and deaths for women compared to men. 5) Alcohol use during pregnancy is still prevalent – 11 percent of pregnant people report past month drinking and 5 percent report binge drinking. 7) Women are about twice as likely to develop anxiety disorders, PTSD, and depression, which can motivate drinking to cope.

Examples of NIAAA Research in Women's Health. NIAAA-supported studies include studying sex differences in neurobiological mechanisms underlying alcohol misuse, including the impact of trauma; understanding the neurobiology of negative reinforcement drinking (e.g., drinking to cope), which is

more common in women; tracking gender differences and norms in alcohol use across the life course; and developing interventions for pregnant and postpartum women. New activities include:

- The Model Continuums of Care Initiative (MCCI) to Advance Health Equity and End Health Disparities Among Women and Girls in Racial/Ethnic Minority and Other Underserved Communities (RFA-AA-24-006) (U34) to support the planning phase of MCCI. The goal of MCCI is to reduce the prevalence and impact of multi-morbidity among racial/ethnic minority women and girls of reproductive age who are at risk of and living with mental health disorders, substance use disorders, and common co-occurring physical conditions. Using implementation and dissemination science, the initiative proposes a continuum of care approach that integrates preventive health services, primary care, behavioral health, integrative care, and cardiopulmonary and endocrine specialties to fully address health care needs.
- In coordination with the White House Initiative on Women's Health Research, NIH issued a Notice of Special Interest (NOSI) (NOT-OD-24-079) to highlight its interest in applications focused on diseases and health conditions that predominantly affect women, that present and progress differently in women, or that are female-specific. NIAAA's specific areas of interest within this NOSI are: 1) research focused on the mental health of women, including alcohol and other substance use disorders; 2) research on health issues that affect young women, including the etiology, prevention, and treatment of alcohol misuse; and 3) research to understand the mechanisms through which common environmental factors influence resilience and disease among women across the lifespan.

Alcohol and Older Adult Health. The size of the population aged 65+ is growing rapidly and both the percentage and number of older drinkers are increasing. The *percentage* of people 65+ who drank alcohol in the past month increased 15 percent overall from 2002-2022, with an increase for women (37 percent) but not men (-1.7 percent). Due to the rapid increase in the size of the population 65+, the *number* of people that drink alcohol increased 91 percent overall between 2002-2022. Concerns about alcohol and the health of older adults include the following factors: 1) The health consequences of alcohol tend to shift from acute causes (injuries) to chronic causes (e.g., cancer, heart disease) with age. 2) Older adults are more sensitive to the sedative effects of alcohol, take more medications that may interact with alcohol, and are more likely to have problems with sleep, which is worsened by alcohol. 3) The risk of falls increases with age and alcohol impairs balance and coordination more as we get older. 4) Alcohol misuse has been associated with faster cognitive decline, and alcohol may contribute to and worsen Alzheimer's disease and other forms of dementia

Examples of NIAAA Research Related to Alcohol and Older Adult Health. In collaboration with the National Institute on Aging, NIAAA is supporting research into the mechanisms by which alcohol affects brain aging processes and influences dementias and Alzheimer's disease. Other research projects are focused on cognitive decline, behavioral consequences, and functional impairment in older adults, including those with HIV; mechanisms through which alcohol contributes to inflammation and increases risk of infections; and factors that influence alcohol use and associated harms in older adults. Additional priorities include basic, translational, and clinical research on the effects of alcohol on the "health span" of older adults, age-related diseases, and improving alcohol screening, prevention, and treatment for older adults.

Whole Person Health. Alcohol affects the whole body. In fact, alcohol misuse is associated with more than 200 diseases and injury-related conditions, such as liver diseases, cancer, diabetes, cardiac diseases, and injuries from falls, car accidents, etc.

Cancer. Alcohol is a carcinogen. In the US, about 5.6 percent of cancer cases and 4 percent of deaths from cancer can be attributed to alcohol. Alcohol is the third largest contributor to all cancer cases for women (6.4 percent, about 50,110 cases per year) and the fourth largest contributor for men (4.8

percent; about 37,410 cases per year). For women, it appears the risk of breast cancer—the second leading cause of cancer death in women-- increases by around 5-15 percent with a single standard U.S. serving per day. Unfortunately, awareness of the link between alcohol and cancer is low. A survey by NCI found that about 70 percent of people are unaware that alcohol can cause cancer and about 10 percent incorrectly believe that wine reduces the risk of cancer. In fact,the positive health effects attributed to red wine touted in earlier studies in European nations are more likely due to the Mediterranean diet and a more healthy lifestyle in general.

A Whole Person Approach to Alcohol. NIAAA has adopted a whole person approach that looks across different domains of health and integrates the care of alcohol-related problems to improve prevention, diagnosis, treatment, and recovery strategies. For example, integrating treatment for alcohol use disorder and alcohol-associated liver disease has the potential to promote recovery from both conditions and enhance the long-term survival of patients. Further, alcohol screening, brief intervention, and referral to treatment in primary care can help clinicians identify other physical and mental health-related issues affected by alcohol misuse. Collaborative research across NIAAA, NIDA, NCI, and other ICs holds promise for understanding of whole person health and improving substance misuse-related health outcomes.

New NIAAA Strategic Plan. The new NIAAA Strategic Plan, Fiscal Years 2024-202, "Research to Promote Whole Person Health and Well-Being," charts a course for alcohol research over the next five years. The new strategic plan seeks to advance many long-held NIAAA research and research training priorities, and highlights key areas such as diversity, equity, inclusion, and access (DEIA) in the alcohol research enterprise; women's health research; whole person health and integrated health approaches; data science and data management; translation and back translation of research findings; social determinants of health (SDoH) in the context of risk and resilience; social media impact on alcohol-related behaviors and outcomes, and social media as a tool for innovating interventions.

NIAAA Resources. Dr. Koob reviewed NIAAA resources for public and healthcare professionals. These include: 1) Rethinking Drinking is a website and print publication for a general audience to help individuals assess their drinking habits and find ways to make a change; 2) CollegeAIM provides acomprehensive information on prevention approaches found to be effective in college environments; 3) The Alcohol Treatment Navigator provides a resource that helps individuals understand treatment options and search for nearby treatment, including telehealth services. It also includes a portal to assist health care providers in making referrals for their patients; 4) The Healthcare Professional's Core Resource on Alcohol is an online resource that covers the basics of what every healthcare professional needs to know about alcohol, including how alcohol can impact a patient's health, and provides strategies for alcohol screening and interventions. Dr. Koob also noted web-based resources for youth: 1) NIAAA for Middle School contains interactive activities to help parents, caregivers, and teachers introduce and reinforce key messages about peer pressure, resistance skills and other topics related to underage drinking; and 2) NIAAA for Teens provides a research-based online resource for teens about how alcohol affects one's health, warning signs and symptoms, and where to get help for alcohol-related problems.

Discussion: Dr. Fingert inquired if there is any objective information from other regions where lifespan is prolonged (e.g., Blue Zones, such as Okinawa)--other than the "Mediterranean diet"--that might provide the basis for further actionable research and intervention? Dr. Koob responded that the J-shaped curve that suggested a benefit to alcohol consumption disappears when sick abstinent people are removed from the sample. These data suggest that there are no health benefits to alcohol.

Dr. Greenfield thanked Dr. Koob for NIAAA's attention to women's health. She noted the critical role that social determinants of health (SDoH) play in women's health and the importance of implementation

research. However, the medical community remains largely unaware of these issues. Dr. Koob responded that NIAAA's National Advisory Council concurs with her comments and that NIAAA is continuing to work on advancing implementation research. Dr. Kareken inquired about the trends in alcohol use among women, noting that the chart presented by Dr. Koob appeared to show men's consumption declining more rapidly than women's use is increasing. Dr. Koob responded that Dr. Kareken's observation was valid but emphasized that women have greater pathology related to alcohol use. Parity between the sexes in alcohol consumption is an issue that the field needs to address.

Dr. Volkow observed that although there is a significant focus on SDoH, commercial determinants of health from the pharmaceutical industry should also be emphasized. Commercial interests are disrupting health behaviors (e.g., obesity, alcohol and drug use), which leads to questions about appropriate policy strategies for better regulation of products. Dr. Koob concurred, observing that research clearly indicates that increased alcohol advertising targeting young people leads to increased consumption and that an increase in alcohol outlets in a neighborhood leads to an increase in consumption there. He believes it will be challenging to address this issue. Dr. Volkow agreed, suggesting that citing the link between alcohol, tobacco, obesity, and cancers might be persuasive since so many people are unaware of the relationship. In the chat, Dr. Winkfield suggested that further research is also needed to address political determinants of health research, including insurance policies for coverage of behavioral health care.

Through the online chat, Ms. Duron stated that she appreciates the concept of whole person health. Noting the challenges of addressing a patient from a whole person perspective, she suggested that a whole person record be built, beginning in pediatric care, based on family history, SDoH, and input from parents to present clinicians with a clear picture of the patient throughout his or her life.

CRAN-related NCI Activities and Priorities

Dr. William Klein, Associate Director, NCI Behavioral Research Program in the Division of Cancer Control and Population Sciences (DCCPS), reported on CRAN-related activities at NCI. Dr. Klein provided updates on NIH and NCI leadership, noting that Dr. Monica Bertagnolli , previously NCI Director, has been appointed the new Director of NIH and Dr. Kimryn Rathmell, the new Director of NCI. DCCPS is led by Dr. Katrina Goddard. There are four programs within DCCPS, including Epidemiology and Genomics Research, Surveillance Research, Behavioral Research, and Healthcare Delivery Research. Cross-cutting themes across all programs include health equity, data strategies, modifiable risk factors, climate change, evidence-based policy, and digital health.

Recent NCI activities have included 1) the integral participation of BRP Program Directors in the development of the HHS Framework to Support and Accelerate Smoking Cessation, as part of recent details to the Office of the Assistant Secretary for Health (OASH); 2) implementation of the 2022-2023 Tobacco Use Supplement to the Current Population Survey (TUS-CPS) with September 2022 data now publicly available; 3) BRP presentations on alcohol and cancer messaging at Alcohol Policy 20 and the World Cancer Congress; 4) the addition of cannabis questions (timing and mode of cannabis use; whether use is medical, non-medical or both; and perceived harm/benefit of using cannabis) to the Health Information National Trends Survey (HINTS); 5) establishment of a collaboration with the French National Cancer Institute (INCa) to address shared priorities for advancing tobacco cessation research, particularly among persons who use multiple tobacco products, persons with co-occurring conditions, and subpopulations that experience other social and health disparities; 6) the December 2023 launch of SmokefreeNATIVE, a free text messaging resource to help American Indian and Alaska Native adults and adolescents quit smoking commercial tobacco, representing a partnership between Smokefree.gov and the Indian Health Service; and 7) a recent tobacco policy and health equity grantee workshop.

Dr. Klein reviewed selected current CRAN-relevant funding opportunity announcements (FOAs), including 1) Notice of Special Interest: Public Policy Effects on Alcohol-, Cannabis-, Tobacco-, and Other Drug-Related Behaviors and Outcomes (NOT-AA-21-028); 2) Population Approaches to Reducing Alcohol-related Cancer Risk (PAR-23-244), noting the need for effective communication strategies; 3) Screening, Brief Intervention and Referral to Treatment or Prevention (SBIRT/P) for alcohol, tobacco, and other drugs (ATOD) use and misuse in adult populations that experience health disparities (PAR-23-270); and 4) Notice of Special Interest: Basic Mechanisms of Cannabis and Cannabinoid Action in Cancer (NOT-CA-22-085).

Tobacco. Dr. Klein provided an update on the U.S. Food and Drug Administration (FDA)'s policy on menthol-flavored cigarettes. The FDA had earlier announced proposed product standards to prohibit menthol as a characterizing flavor in cigarettes and prohibit all characterizing flavors (other than tobacco) in cigars and sent the proposed rules to the White House Office of Management and Budget for review. The evidence is clear that such a ban will reduce smoking, because menthol makes it more difficult to quit smoking. African American smokers are more likely than other groups to smoke menthol-flavored cigarettes, raising social-cultural issues regarding the proposed ban. In a recent statement, HHS Secretary Xavier Becerra gave no timeline for issuing the rule, saying only that the Administration would take more time to consider feedback, including from civil rights groups.

Tobacco Corrective Statements. On December 6, 2022, the U.S. Department of Justice (DOJ) and HHS announced a court order that resolves the civil racketeering lawsuit first brought against four U.S. tobacco companies more than 20 years ago. As part of the lawsuit, the companies were required to issue a series of "corrective statements" about the harms of cigarettes. DOJ asked NCI to evaluate potential wording for the corrective statements to help the court determine how the proposed statements would affect consumers. The order went into effect on July 1, 2023, and gave defendants three months to post the required corrective statements. Retailers will display the signs at point of sale for 21 months thereafter.

Cannabis. There is now a trans-NCI Cannabis and Cancer Research Interest Group (CCRIG) that is interested in cannabis at the population level, but also focused on cannabis as pain medication for cancer patients. CCRIG's goals include: 1) develop a trans-NCI research agenda related to cannabis and cancer; 2) coordinate activities related to cannabis and cancer research across NCI; 3) develop communication materials for various audiences about cannabis and cancer; and 4) coordinate with ICs and other federal agencies on matters related to cannabis and cancer.

Changes in the Cannabis Landscape. With contributions from NCI, NIDA, the National Center for Complementary and Integrative Health (NCCIH), and CDC, the National Academies of Sciences, Engineering, and Medicine (NASEM) is developing a report that will provide an objective and authoritative account of the experiences in states and localities in the United States that permit medical or non-medical (adult) use of cannabis and cannabinoids; this report is anticipated in the spring/summer 2024. The first public meeting of the Committee on the Public Health Consequences of Changes in the Cannabis Policy Landscape was held in September 2023.

Alcohol and Cancer. Dr. Klein reviewed selected NCI activities relating to alcohol and cancer. These included: 1) Promoting Healthy Lifestyles to OPTImize Cancer Survivorship (OPTICS) project on alcohol, where Dr. Klein noted, among other issues, the "pink washing" by the alcohol beverage industry when it hands out pink ribbons for breast cancer awareness, not acknowledging that alcohol is a leading contributor to breast cancer 2) participating in the Congressionally-mandated NASEM "Review of Evidence on Alcohol and Health;" 3) contributing to the 2025 Dietary Guidelines Alcohol Recommendations which will be informed by a NASEM evidence review; 4) serving on the Interagency Coordinating Committee on Prevention of Underage Drinking (ICCPUD/SAMHSA), a commissioned group

of experts to assess health impacts; and 5) contributing to efforts to address alcohol labeling. The NASEM and ICCPUD reports should be released in late 2024.

New Data: A Working Group of the International Agency for Research on Cancer published a review of the evidence on cessation of alcohol use and cancer risk. It concluded that alcohol reduction or cessation decreases the risk of oral cancer and esophageal cancer; more data is needed to determine the risk for breast, colorectal, and other cancers. The review also revealed scientific gaps on some or all alcohol-related cancers, including the duration of cessation necessary to observe a reduced risk, reduction in consumption, and patterns of consumption over the life course.

Resources. Dr. Klein shared many of NCI's resources that are relevant to CRAN, including the HINTS survey; Smokefree.gov; Tobacco Use Supplement to the Current Population Survey (TUS-CPS); Classification of Laws Associated with School Students (CLASS); Automated Self-Administered 24-Hour (ASA24) Dietary Assessment Tool; Activities Completed over Time in 24 Hours (ACT24) Previous Day Recall Tool; and a library of webinars about alcohol, tobacco, and funding opportunities.

Training. In FY 2023, DCCPS hosted over 50 fellows from various training mechanisms, including Cancer Research Training Awardees, Cancer Prevention Fellows, summer interns, University of Maryland semester interns, iCURE Fellows, Presidential Management Fellows, and Management Interns.

Discussion. Dr. Volkow inquired if the risks from alcohol, tobacco, obesity, and other factors were additive or interactive. Dr. Klein replied that the field understands some of the mechanisms, e.g., acetaldehyde in alcohol increases cancer risk and interacts with estrogen in the development of breast cancer. More research is needed, however. There is a modest interaction effect between tobacco and alcohol on cancer risk, although the demographic profiles of the users of each substance tend not to overlap. Understanding the synergistic effects is difficult because the effects are generally not large. Adding cannabis to the mix makes the pool of users even smaller. Dr. Volkow asked if using more than one substance increases the toxicity of alcohol, even if the effects are small. Dr. Klein responded affirmatively, noting that it is the ethanol in alcohol that has an impact. In response to a question about the differential effects of policies on substance use and cancer risk, Dr. Klein said that NIH does not develop policies but does inform their development through its research. For example, NCI has worked with the FDA Center for Tobacco Products to investigate topics such as the identification of cognitive and emotional effects of different types of warning label messages.

HEALthy Brain and Child Development (HBCD) Update

Dr. Volkow introduced Kathy Cole, Ph.D., Chloe Jordan, Ph.D, and Janani Prabhhakar, Ph.D., who presented an update on the HBCD study. Dr. Cole began with an overview of longitudinal HBCD study that will follow pregnant women and their children for ten years. Study participants are enrolled in the study starting in the second trimester of the mother's pregnancy. HBCD study will deploy multi-modal assessments of brain, cognitive, and emotional development from birth through childhood to characterize neurodevelopmental trajectories from a large sample (~7,000) to determine how substance exposure and other environmental factors affect these developmental trajectories. The Study will release data annually beginning in late 2024/early 2025. HBCD study is funded in part by the NIH HEAL Initiative® and 12 ICs, including NIDA, NIAAA, NCI, and NIMH.

The HBCD consortium consists of 27 recruitment sites across 24 U01 awards and 20 states. Coordinating centers are located at the University of California San Diego (UCSD) and Boston Children's Hospital. Data coordinating centers are located at Washington University in St. Louis, the University of Minnesota, and UCSD.

Objectives. The HBCD study seeks answers to these questions:

- What are typical neurodevelopmental trajectories and what is the normal range of variability in brain development from birth through childhood? How do biological and other environmental exposures affect these developmental trajectories?
- How do genetic influences interact with environmental factors to influence neurodevelopment and cognitive, emotional, and social behavior?
- How does early life exposure to opioids, other substances, and/or other adverse environmental circumstances affect developmental trajectories?
- Are there key developmental windows during which the impact of adverse exposures (e.g., stress, COVID 19) influence later neurodevelopmental outcomes?
- Are there key developmental windows during which ameliorating influences (e.g., substance use disorder treatment; social/economic support) are protective against the potential neurodevelopmental insults of early adverse exposures?
- What is the impact of early parent/caretaker interactions with their children on later health and other outcomes?

To address these questions, the Study will assess four domains: 1) pre-pregnancy factors (e.g., prenatal health, substance use, etc.); 2) social and environmental determinants (e.g., early life stress, environmental exposures, poverty, etc.); 3) biological factors (e.g., physical health, genetics and epigenetics, etc.); and 4) parent/child factors (e.g., child-caregiver relationship, behavioral regulation, mental health, etc.).

The structure of HBCD study relies on multiple workgroups comprised of Principal Investigators (PIs), co-PIs, and study staff across the 27 sites. Workgroups include those focusing on assessment domains, social and ethical oversight, neuroimaging and technology, study design and monitoring, participant experience, and communications. The chairs of each work group meet weekly.

Timeline of Events. Eight visits are anticipated for each Study participant through the first 5 years of life, including five face-to-face visits, including a prenatal assessment of the mother (Visit 1) and four child assessments at 0-1 month (Visit 2), 3 to 9 months (Visit 3), 9-15 months (Visit 4), and 15-48 months (Visit 6). Three remote visits are expected at 10-17 months (Visit 5), 16-50 months (Visit 7), and 36-60 months (Visit 8). Future visits from 5 years of age are still being planned. Biospecimens will be obtained from mothers and children at all face-to-face visits. Child participants will participate in magnetic resonance imaging (MRI) at all face-to-face visits, and electroencephalograms (EEGs) during all face-to-face visits starting at Visit 3. Infants will be asked to wear heart rate and movement sensors during Visits 2 and 3.

As of May 1, 2024, 1,330 participants have been recruited. Of these, approximately 50 percent are White, 20 percent are Black, and 18 percent are Hispanic. The current rate of substance use among participants is 25 percent, which meets the Study sampling goals. Across the sample, 12 percent report having used alcohol, 12 percent marijuana, 11 percent tobacco, and 4 percent opioids.

Neuroimaging. The MRI scans used in the study include structural scans (T1 and T2); diffusion MRI; quantitative MRI; functional MRI; and spectroscopy. EEG domains include resting state/baseline; response to faces; visual evoked potentials; and auditory oddball/ MMN.

Substance Use Measures. Dr. Jordan reported that substance use is assessed before, during, and after pregnancy via self-report as well by analysis of biospecimens. Substance use self-report criteria are based on specified frequency of use criteria, e.g., more than seven drinks per week for two or more weeks or three or more standards drinks/occasion on two or more occasions. Lifetime use is assessed at Visit 1. Thresholds are used for enrollment targets for opioids, alcohol, nicotine and cannabis.

Biospecimens. Biospecimens include nails, blood, urine, and saliva from the mother and urine, stool, and saliva for the child at every face-to-face visit. Currently, nails from Visit 2, as well as dried blood spot cards and urine from Visit 1, are being sent to the U.S. Drug Testing Laboratory to test for exposure to

substances. The remaining biospecimens are sent to a biorepository for future use. Sites are storing nails from Visit 1 for analysis in the near future.

A very preliminary first analysis of biospecimens as of May 1, 2024, revealed that 753 of the mothers were positive for some substance (mostly nicotine and cannabinoids) per the urine analysis (detection window 2-4 days) at Visit 1. The Study workgroups are currently matching this data with the self-report data. Overall, the opioid positive specimens add up to about 4.8 percent, closely approximately the self-reported 4 percent use. Examining 982 dried blood spot cards for the alcohol biomarker phosphatidylethanol (PEth), 82 percent were negative and 18 percent positive (detection window approximately 2-4 weeks), higher than the 12 percent that self-reports indicated. PETH does not detect light or casual drinking, but there are many individual differences in how much alcohol needs to be consumed to generate a positive result.

Accountability: Dr. Prabhhakar reported on how the program is monitoring the study using real-time data from multiple sources to assure that study objectives are met via results-based accountability. (RSA). The Metrics Monitoring workgroup (that includes NIH) oversees monitoring of site progress and works with investigators to identify and solve problems, providing resources as needed. Two dashboards using real-time data allow for additional monitoring. One is an enrollment dashboard that not only provides current enrollment statistics but also allows sites to titrate their rates of enrollment and project their results forward, while the other is a metrics dashboard that shows completion of study measures and visits.

Discussion. Dr. Sinha commented that the preliminary substance use results were quite high for pregnant women. Noting that the investigators have a responsibility toward participants, she asked how HBCD study is imparting health recommendations to them. Dr. Cole responded that the Consortium members had extensive conversations about what resources to provide to participants without becoming interventional. The study created a pregnancy health flyer that includes substance use in pregnancy recommendations, as well as an associated web page. The information provided is taken from many national resources, but not specifically targeted to the study population. One concern was encouraging participants to be honest and to not stigmatize them for their substance use, while still being informative. Dr. Cole responded to a question about whether study analyses distinguish between methadone prescribed for pain versus methadone as a treatment for opioid use disorder by explaining that all opioids, whether prescribed or not, are currently combined for analytic purposes. When data is released, that information will be differentiated. For enrollment goals, the study is looking at opioid use in general. Dr. Jordan noted that the biospecimens don't distinguish between different types of drugs.

Adolescent Brain and Cognitive Development (ABCD) Study Update

Dr. Volkow introduced Gaya Dowling, Ph.D., Director of the ABCD study, who provided an update on the status of the ABCD study. Dr. Dowling introduced ABCD study staff members Elizabeth Hoffman, Ph.D., and Kim LeBlanc, Ph.D., as well as new additions to the ABCD study team: Diana Alkire, Ph.D., Program Analyst, and Lieutenant Commander (LCDR) Traci M. Murray, Scientific Advisor for Justice, Equity, Diversity, and Inclusion (JEDI) for the ABCD and HBCD studies.

Overview of ABCD, Cohort Diversity, and Retention. ABCD study is a longitudinal study of approximately 12,000 diverse children from 21 research sites across the country beginning at ages 9-10 and continuing through adolescence into early adulthood to assess factors that influence individual brain development trajectories and functional outcomes. Data sources include questionnaires regarding physical and mental health, substance use, and culture and environment; biospecimens; Fitbit records of sleep and heart rate; neurocognition and structural and functional MRIs, each administered bi-annually on alternating years; and geocodes that reveal contextual environmental and policy information about where the participants live.

Diversity. Approximately seven in ten youth participants in ABCD study (71 percent) are from groups traditionally underrepresented in biomedical research, with more than a third represented in 2 or more groups. Almost one-half (48 percent) are non-White and non-Hispanic. Over one-quarter (28 percent) come from families in which the household income is equal or below 200 percent of the Federal Poverty level. Almost one-quarter (23 percent) reported a sexual orientation other than straight in the fourth year of the Study. Smaller percentages of other diversity categories used by the NIH *All of Us* program intersect with other ABCD study categories to contribute to the proportion of diversity in the sample.

Retention. ABCD study is currently in its eighth year of assessments and has retained 96 percent of its participants. There are some missing data from Years 2-5 due to the COVID pandemic, but sites are catching up. Approximately 7,800 participants have never missed a visit. Approximately 750 participants are in the "extended absence" category (i.e., not completing an annual visit since baseline, 1-yr, or 2-yr follow-up) as of March 2023, but that number is now down to 550. To accomplish this reduction, the HBCD study turned to sites that had been highly successful in retaining participants for advice on how to retain hard-to-reach participants, e.g., providing bonus payments for a prompt response, providing transportation and childcare, etc.

ABCD JEDI Initiative: To improve efforts to enhance justice, equity, diversity, and inclusion (JEDI), ABCD study reset its JEDI initiative to reach beyond racial discrimination and improve transparency and accountability. The JEDI Advisory Council was expanded. An internal climate survey was conducted by an external consultant, revealing that 92 percent of staff agreed that ABCD study has a strong commitment to JEDI values. Finally, to reengage staff, ABCD study has scheduled quarterly JEDI all-hands meetings, provided short trainings by LCDR Murray, and fostered greater integration and collaboration with non-JEDI Work Groups.

Leveraging ABCD. ABCD study is participating in the NIH Researching COVID to Enhance Recovery (RECOVER) initiative that addresses Long COVID. ABCD study's participants constitute 45 percent (6429 participants) of the total RECOVER Pediatric Cohort (N=14,195). ABCD study was approached by NIDA's HIV program about how it could help them research HIV. An exploratory meeting with ABCD study investigators, outside investigators, and some young adults who contracted HIV as teens was held on November 18, 2023.

Resource Sharing. Dr. Hoffman reported on the current ABCD study data release 5.0/5.1 that includes 3-year follow-up and 24-month follow-up for the full cohort, as well as interim 4-year follow-up data. All ABCD study data is available on the NIMH Data Archive. Data resources to support investigators using ABCD study data include an online data dictionary, release notes, and a discussion forum. Questions posted on the forum may be included on the ABCD study Wiki page that contains release notes on a wide range of topics and descriptions of instruments from the ABCD study data dictionary.

A new data sharing platform, the NIH Brain Development Cohorts (NBDC) Data Sharing Platform, will be launched in the summer of 2024. ABCD study Data Release 6.0 will be posted on the new platform and all existing ABCD study data currently on the NIMH Data Archive will be transferred. The NBDC Platform is optimized for large datasets, including neuroimaging and genomics data; provides scalable data ingestion, integrated data analytics, and a customized user experience; and provides a homogenous solution for harmonizing with planned data from the HBCD study. A mandatory Responsible Data and Biospecimen Use module will be part of the new data release. Researchers must complete the module with a 90 percent pass rate before they can access the data.

Biospecimen Access Program. Dr. LeBlanc addressed the NBDC biospecimen access program. Its purpose is to allow internal and external investigators to apply to use residual biospecimens from the ABCD study through an Access Award (X01) (PAR-23-229) for studies that are consistent with ABCD study objectives, or which expand the knowledge of child or adolescent health more broadly. No funds

are associated with the award; applicants need to obtain outside funding for analyses and sample shipment prior to submitting their X01 application. Successful applicants are required to deposit the results of their analyses into the ABCD study Data Repository.
The NBDC portal will be available on the NIDA website. Dr. LeBlanc conducted a brief tour of the portal, pointing to the Biospecimen Explorer that researchers can use to see which biospecimens are available; information on how biospecimens are collected/stored; and the biospecimen access application process.

ABCD Study Outcomes and Dissemination. Dr. Dowling reported that more than 200 grants using ABCD study data or methods have been funded. Most of these are Research Program Grants (RPG) or individual training grants. About one-half of the RPGs have been awarded to non-ABCD study investigators, while the majority (65 percent) of training grants have been awarded to individuals currently or previously affiliated with ABCD. Ten ICs support the ABCD study consortium, but 15 ICs have supported these grant awards, along with some non-NIH organizations. The ABCD study data domains most frequently used by these grants are neuroimaging and mental health (NIMH is the largest funder) with smaller numbers addressing neurocognition, substance use, culture and environment, and physical health.

To date, 972 empirical publications using ABCD study data have been published; of these, 60 percent are by individuals who are not affiliated with the Consortium. ABCD study is tracking other metrics of its research impact, e.g., the relative citation ratio (RCR). For ABCD studies, the average ABCD study paper is cited 2.5 to 7 times that of the average NIH-funded research paper. Another measure of impact is Altmetric, a weighted count of attention a research output has received in public sources. As of April 2024, ABCD study research has garnered over 35,000 mentions, primarily on Twitter/X (29,000) but also in other venues.

To showcase its data, ABCD study sponsored the first ABCD study Insights and Innovations meeting on March 4-5, 2024. Over 400 people attended, 90 percent of whom were from outside the Consortium. Meeting organizers received 170 proposals for presentations and mentoring opportunities were provided for early-stage investigators.

ABCD study has made it a priority to synthesize its key findings in infographics targeting non-researchers, including ABCD study families. Infographics have been created on screen use, sleep, and the pandemic. The sleep infographic won a Plain Language award. Webinars have been conducted in conjunction with each infographic with the main researchers on the topic presenting their findings. Approximately 500 participants attended each webinar. ABCD study papers are also increasingly being cited in policy documents, including those from the Urban Institute and the World Health Organization.

Discussion. In the chat, Dr. Fingert suggested that it could be useful to expand on the ABCD study program efforts to measure and analyze follow-up/missing data/retention as these remain ongoing problems in oncology trials and could be informed by the ABCD study experience. Dr. Kareken inquired about the percentage of time that ABCD study participants spend in face-to-face contact with their peers because that may impact development of depression or anxiety. Dr. Dowling responded that the ABCD study collects data on what the youth are doing (e.g., sports) but not how much time they're spending on each one. As the Consortium members think about the next phase, the social interaction component will be at the center of ABCD study concerns, especially as the youth age out of high school. Dr. Duarte commented that HBCD and ABCD studies provide an opportunity to examine intergenerational influences on adolescent pregnancy that will be showing up very soon among ABCD study's participants. She cited the experiences of the Boricua Youth Study of 2,500 children in Puerto Rico. Investigators interviewed the youth about sexual risk behaviors that then facilitated a discussion of pregnancy and led to regular pregnancy screenings. Dr. Dowling noted that there have been a couple of pregnancies already among ABCD study's participants. The Consortium has discussed how it could follow

current ABCD study's participants over the next ten years to determine what youth factors influenced their trajectories in adulthood. Dr. Volkow interjected that the HBCD study would like to do this if it makes sense, but the decision is funding-dependent.

START Program Overview

Dr. Volkow introduced Micah Johnson, Ph.D., an epidemiologist at the University of South Florida who created the Scientific Training in Addiction Research Techniques (START) program supported by NIDA that uses ABCD study data as a resource.

Overview of START. START began in 2021 as a collaborative effort between Dr. Johnson and two colleagues at the University of Vermont to overcome the barriers that result in some groups being grossly underrepresented in academia, thereby limiting the potential of biomedical research to equitably serve all people. Specifically, START seeks to recruit scholars from among Black, Indigenous, and People of Color (BIPOC) communities; train them to access, analyze, and disseminate ABCD study data; and facilitate mentored independent research studies. START is built on five pillars that are aligned with NIH goals: recruitment, enrichment, training, effective mentoring, and nourishing environments.

Recruitment. START collaborates with organizations serving underrepresented communities to recruit trainees and uses Fortune 500 talent acquisition techniques. The pilot cohort of 12 individuals successfully accomplished many of its members' goals. Thirty percent of the pilot cohort have published in peer-reviewed journals.

Training. In four years, START will train 60 scholars using a three-phase program. Phase I consists of a one-week intensive orientation and training conference at the University of Vermont where scholars participate in data collection techniques and tour data collection facilities. Phase II consists of monthly virtual two-hour group sessions that build community. These sessions include individual presentations, group open discussions, and 60 minutes of protected one-on-one time with mentors. Each of the 8-month sessions has a specific learning objective with a way to demonstrate mastery of the objective. Phase III is a three-day dissemination and professional development conference, where scholars present their research. They may also present at professional meetings.

Mentoring. The core of the START program is mentorship, including the facilitation of mentor-mentee relationships on research project development. START employs a multi-mentoring model that includes both mentor and mentee panels so that trainees can lead sessions about what mentoring strategies work for them. Interest in serving as a mentor has been high so that there has been a surplus of mentors over the past two years. Thus, the program can match mentors and mentees based on people's preferences; surveys and anecdotal data show that this approach has been very successful. In addition, START fosters community mentoring, flipped mentorships, and peer mentoring.

Evaluation: Ongoing evaluation is a key part of the program, including informal feedback as part of a continuous improvement plan. Evaluation addresses not only enhanced knowledge and skills but also internal and social barriers that scholars face as they pursue their careers. One strategy was for trainees to create reflection notes about the program; trainees mentioned mentorship and a sense of safety for underrepresented people as important aspects of the program.

Next Steps: START will be refining and expanding its training and helping scholars publish their research. Dr. Johnson is hoping to start similar programs in other NIH consortia.

Impact The START founders did not anticipate the deeply profound sense of connection and community among the scholars. Dr. Johnson is committed to creating a world class science training program for future generations. He believes that compassion and humanity are the key aspects of the START program and may also provide the key to unlocking health disparities and promoting equity since these scholars can support the communities that look like them in the future.

Discussion. Ms. LaBelle asked how the first cohort of scholars might contribute to the next or future cohorts. Dr. Johnson responded that 100 percent of the first cohort signed up to be informal peer mentors to the next cohort. Dr. Sinha inquired about follow-up for the scholars' career development. Dr. Johnson responded that some are entering T32 training programs and others are applying for K awards. The program is also trying to integrate its scholars into ABCD study workgroups.

Advancing the Prediction of Adolescent Alcohol Use Onset by Deriving PolyeXposure Alcohol Risk Scores Using the ABCD Study

Dr. Koob introduced Faith Adams, an alumna of the START program and a fourth-year Ph.D. candidate at the Icahn School of Medicine at Mount Sinai, who reported on her research using ABCD study data to predict adolescent substance use. Ms. Adams began by reviewing past month substance use in adolescents from the 2022 Monitoring the Future study, noting patterns of alcohol, cannabis, and nicotine vaping. A small percentage of students who use substances transition to substance use disorders. Research indicates that earlier onset of substance use is linked to a higher risk of developing an SUD and later life dependence. Therefore, it is important to learn more about how to delay the onset of substance use.

Ms. Adams noted that extensive research indicates that risk factors for adolescent substance use includes a genetic predisposition (i.e., family history of substance use, and polygenic liability measured by polygenic risk scores), coupled with environmental risk factors that include low parental monitoring, school engagement, neighborhood stressors, and cultural norms. However, there are gaps in the field, including limited generalizability in genetics due to a focus on European participants; environmental studies that use a "pick and choose" approach; and existing analytical approaches that overlook co-occurring and interactive effects. To explore potential solutions to these limitations, Ms. Adams proposed creation of a non-genetic "exposome" risk score. The exposome is the totality of the environment i.e., all "non-genetic" factors. These can be approached via an Exposome-Wide Association Study (ExWAS), analogous to a genome-wide association study (GWAS), that captures the total contribution of several exposome variables while also accounting for inter-exposure correlations, i.e., it is akin to a polygenic risk score (PRS). ExWAS has been shown to improve the prediction accuracy of Type 2 Diabetes three-fold compared to that of PRS.

Thus, the objectives of Ms. Adams' research were to: 1) Conduct an Exposome-Wide Association Study (ExWAS) to evaluate the exposomic associations with substance onset in youth; and 2) Derive PolyExposure Risk Score (PXS) to assess the additive and cumulative exposomic risks on substance use onset.

To characterize the ABCD study Exposome, Ms. Adams first examined adolescent substance use behavior based on youth's self-report. She identified 609 participants who reported substance use, with a time of onset from about 4 to 15 years of age. Next, she reviewed ABCD study measures to identify non-genetic factors that might influence substance use, including lifestyle (e.g., screen time, sleep issues) , home (parental monitoring), parental health (psychopathology), culture (cultural identification, religious beliefs), neighborhood (based on geocode measures), and school (engagement, involvement). Then she conducted the ExWAS study, beginning with univariate analyses linking a single exposure to a substance use outcome rather than looking at all the variables simultaneously in one model. She employed a survival analysis approach, i.e., Cox regression, controlling in different iterations for sex, race/ethnicity, pubertal score, site identification, and family identification, and correcting for multiple comparisons. These analyses allowed identification of the most significant independent associations that were then used in a multivariate model to build a polyexposure risk score (PXS). The PXS is a weighted sum of the estimates of the variables that were significant within the final model.

The ExWAS revealed 74 exposomic features (out of 200+ variables) independently associated with time to substance use onset. Among the 74 features were both protective and risk factors. Different types of discrimination, R-rated movie exposure, and parental psychopathologies were most strongly associated with substance use onset. Youth from homes with no rules about cannabis were more likely to start using marijuana. Among the risk factors identified by geocodes were the percentage of the population in the neighborhood that had incomes below the Federal Poverty level and the percentage that had no telephones. Protective factors included a better school environment, greater parental monitoring, important religious values, and higher socio-economic status. The PXS included factors from ABCD's Lifestyle, Home and Neighborhood domains. Its power to predict substance naïve and substance exposed youth was about a 3 percent increase in prediction accuracy.

Among the limitations of the study are measurement error and recall bias, i.e., misreporting of actual events, including self-reported environmental variables and age of onset, as well as underreporting of alcohol use among youth. Future directions include comparing PXS to genetic risk factors (family history density [FHD] and PRS) and exploring the neurobiological correlates for substance onset in youth.

Discussion. Noting that some variables are inheritable, Dr. Agarwal asked Ms. Adams if she had considered correlating the exposomic features with genetic factors or looked at gene-environment interactions. Ms. Adams responded that some included variables have genetic aspects. She agreed it would be interesting to compare the exposome and the genetic. Dr. Navas-Ancien inquired about other factors within the environment, e.g., lead exposure, that could be included in these analyses. Ms. Adams replied that such variables are included in the geocode data. But the only two that were significant were the two indicators of poverty that she mentioned in her report.

Racial Inequities and Neuroimaging Findings in ABCD Study

Dr. Volkow introduced Nathaniel G. Harnett, Ph.D., Director of the Neurobiology of Affective and Traumatic Experiences at McLean Hospital and Assistant Professor of Psychiatry at Harvard Medical School, who presented on the potential impact of racial inequities on neuroimaging. He began by noting that his laboratory primarily studies the neural substrates that underlie threat learning, expression, and regulation. Such regions included the amygdala where threat learning occurs, the hippocampus that modulates perceived information about the environment and the emotional response of the amygdala, and parts of the prefrontal cortex that can facilitate or dampen the emotional response as needed. This circuit is transdiagnostic across psychiatric diseases, including post-traumatic stress disorder (PTSD).

PTSD provides a good example to illustrate how different types of stressors have a multifactorial impact on the brain. People often think that individuals move from "healthy" to "PTSD" following exposure to a discreet trauma. Dr. Harnett provided a more complex picture of the healthy to PTSD continuum. Iin addition to discreet trauma, there may also be pre-traumatic stressors that shape how the brain develops, and how the individual subsequently responds to stress and trauma, peri-traumatic stressors, and post-traumatic stressors. These stressors are not randomly distributed, but influenced by where they live and policies that influenced those physical and social environments. For example, a study conducted by the University of Alabama in Birmingham revealed that food deserts and neighborhood deprivation indices in that city lined up well with red-lined districts meant to ensure racial segregation that were created in the early 20th century. This is true nationally. For example, in a study mapping the percentage of children who had experienced an adverse childhood experience, it was clear that—independent of geographic location—those who come from racially/ethnically minoritized backgrounds are disproportionately exposed to early life stressors compared to White, non-Hispanic individuals. These factors influence health outcomes. For example, one study examined rates of premature death among individuals getting off the Boston subway at specific stops, revealing that those who exited at

stops in neighborhoods with high percentages of racial/ethnic minorities had a higher likelihood of dying prematurely than those exiting at stops in more affluent, non-minority neighborhoods.

The location from which samples are drawn from neuroimaging studies likely has downstream impacts on researchers' ability to generate different types of phenotypes of psychiatric disorders and the generalizability of findings. Dr. Harnett and his colleagues are using ABCD study data to identify how early the biological embedding of racial inequities is visible in neuroimaging and what the downstream impacts of these patterns may be. Early on, Natalie Dumornay, then a research assistant in Dr. Harnett's laboratory and now at the University of Minnesota, examined the impact of early life stressors on brain development in Black and White children, looking at indices of structural racism such as family conflict, family hardship, trauma load, family income, parent education, parent employment, and neighborhood disadvantage. Compared to White children, Black children in the ABCD study have caregivers with less education, are more likely to have unemployed parents and lower family income, come from more disadvantaged neighborhoods, experience more family conflict, experience more financial hardship, and have greater endorsement of traumatic events. In the study, there were small but significant differences in volume between White and Black youngsters' brains that might have important effects on how they develop into adulthood. The researchers believe these differences reflect the influences of early life inequities. Thus, it is important to contextualize racial difference in brains, i.e., differences are not due to skin color but to factors that influence brain development.

These early life inequities also contribute to PTSD, with family income, material hardship, and family conflict having a significant impact. Brain volume measurements are also correlated with PTSD. In analyses to normalize the drawbacks, about 50 percent of the differences in brain volume could be accounted for by these inequities. This suggests that structural racism changes the structure of brain regions that are important for responding to threat in young people. Using data from ABCD study release 4.0, Dr. Harnett and his colleagues are now examining the impact of inequities using both individual and neighborhood level metrics to project what happens to children as they continue to grow up in stressful environments. The study will leverage new computational techniques like population level normative modeling to account for inter-geographical differences beyond just accounting for site and also accounting for other types of global geography differences.

Regardless of how the data is modeled—e.g., via a general linear model (GLM) using age and sex, age and sex and site, or brainchart deviations—race-related differences in the brain, e.g., in cortical thickness and hippocampus volume, are evident, although modeling choices affects the extent of differences. There are also unique associations with variables such as level of income, nation-wide measures of resource availability, individual discrimination, and state-level racism. Differences in these variables account for a fair amount of the variability in cortical morphology.

The neural substrates related to threat neuroprocessing are connected both functionally and structurally by different anatomical tracks. Dr. Harnett and his team have been looking at these tracks in white matter, e.g., the dorsal cingulum and the uncinate fasciculus, that may support various cognitive and affective processes that may contribute to downstream differences between groups. While the previous discussion has indicated that Black individuals' brains may have lower volume or thickness than those of White individuals, the opposite appears to be true of white matter. This might be related to different coping strategies that individuals develop while living in more disadvantaged neighborhoods.

Adult brains also show race-related differences in emotional processing. For example, in one study of neurophysiological response to a Pavlovian fear conditioning task, investigators observed a blunted emotional response among young Black adults (18-23) compared to their White counterparts that could be almost completely mediated by differences in violence exposure, neighborhood disadvantage, and family income. In the Aurora Study, Dr. Harnett and his team have also observed resting state

connectivity differences between White, Black, and Hispanic individuals who are recent trauma survivors; the different connectivity profiles are predictive of PTSD symptoms within this group.

Dr. Harnett summarized his presentation about the impact of childhood exposures to stressors impacting downstream impacts on health by making the following key points: 1. Racial inequities contribute to altered structural morphology of threat neurocircuitry in children and adolescents.

2. Racial inequities during development contribute to blunted neural reactivity to threat in young adulthood. 3. Racial inequities contribute to differences in tonic arousal that are tied to PTSD susceptibility.

Discussion. Dr. Volkow observed that there are racial differences in the brain that cannot be accounted for by economic factors alone. She asked Dr. Harnett for his perspective on identifying the variables that researchers are unable to capture, particularly given the complex interactions among so many of the possible variables that need to be disentangled, e.g., stress and racial discrimination accelerate the development of puberty, thereby compressing the time the brain has to develop. Dr. Harnett responded that the field needs to be thinking about new models to study these relationships. Many of the current models are advanced, but not complex, e.g., they can look at unique associations by income but not by income and education interactions. Machine learning has been shown to be promising in disentangling multiple variables. Differences in terms of white and gray matter suggests a hypothesis such as: Differences in exposure prompts differences in emotional regulation and coping strategies. Researchers with the Grady Trauma Project showed that discrimination potentiates unexpected brain responses, e.g., fewer errors during cognitive-affective tasks, that appear related to lower white matter variability.

Dr. Koob inquired about the possibility that early life experience conveys resilience. Dr. Harnett agreed that it does, noting that despite the brain differences observed, one still needs to go to school and work and the ability to carry on with life functions may reflect resilience. Dr. Powell asked about the brain volume of non-minority children who face early adversities. Are the differences between Black and White children's brains due solely to discrimination or do stressed White children show similar brain characteristics? Dr. Harnett responded that race is usually the most predictive factor, but race is not simply biological. People from all groups are exposed to stressors, but Black children are disproportionately exposed to them due to inequities.

Round Table Discussion

Dr. Von Zastrow asked if it would make sense to analyze the large amounts of data collected in ABCD study via unbiased clustering and data reduction strategies rather than by hypothesis-driven questions. Dr. Dowling responded that there have been a couple of ABCD-related papers using cluster analysis that identified groups of variables that define specific phenotypes. Dr. Barnett inquired about the proposed reclassification of cannabis as a Schedule III controlled substance. Dr. Volkow replied that the proposed reclassification would make it easier to study cannabis, especially if medical and recreational use can be scaled and state laws made more consistent. Dr. Fingert asked Dr. Johnson if START has networked with other public and private organizations that are striving to achieve similar goals. He recommended collaborating across national borders. Dr. Johnson responded that START is going global with its sites and is studying organizations that achieve comparable goals well so that START can replicate their best practices. Dr. Witkiewitz expressed appreciation for today's discussion of SDoH and wondered if more back translation about environmental impacts could be included in preclinical studies. Dr. Koob agreed on the importance of doing so, suggesting studies of brain circuitry in primates such as marmosets that have more highly-developed brains than mice. Dr. Volkow commented that there has been substantial research in rodent studies on vulnerability for using drugs or for relapse.

Dr. Klein mentioned that the impact of the pandemic was a recurrent theme in the presentations. He said that as the pandemic recedes into the distance, research needs to continue to track the impact of

COVID on behaviors independent of the pandemic itself. Dr. Koob agreed, noting that NIAAA and NIDA are striving to do so. Dr. Volkow noted that the ABCD study is conducting a deep analysis to examine the downstream effects of COVID on its participants. Dr. Chambers commented to Dr. Harnett that the HBCD study presents a great opportunity to replicate his studies to determine whether the associations found in ABCD study are also seen at younger ages. She asked if the ABCD study database is large enough to allow examination of the impact of relocation to a neighborhood that is different from the previous one. Dr. Harnett responded that there was not much change in participant addresses between Years 1 and 2, but there may be an opportunity in the future for a closer look at the data. Dr. Greenfield concurred with Dr. Klein's comments about continuing to study COVID's impact beyond the pandemic. She inquired about the identification of resilience factors (e.g., neighborhood cohesion) and ways to increase resilience via implementation research. Dr. Volkow commented that research has shown that brain functioning improves when people receive basic income supplements; such efforts need to be scaled up.

Adjournment

Dr. Koob adjourned the meeting at 3:46 p.m.

CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

For NIAAA:

/s/
George Koob, Ph.D.
Director
National Institute on Alcohol Abuse and Alcoholism, and
Chairperson
National Advisory Council on Alcohol Abuse and Alcoholism

/s/
Philippe Marmillot, Ph.D.
Executive Secretary
National Advisory Council on Alcohol Abuse and Alcoholism
National Institute on Alcohol Abuse and Alcoholism

For NIDA:

/s/
Nora Volkow, M.D.
Director
National Institute on Drug Abuse, and
Chairperson
National Advisory Council on Drug Abuse

/s/
Susan Weiss, Ph.D.
Executive Secretary
National Advisory Council on Alcohol Abuse
National Institute on Drug Abuse

For NCI:

/s/
John D. Carpten, Ph.D.
Chair
National Cancer Advisory Board
National Cancer Institute

/s/
Paulette S. Gray, Ph.D.
Executive Secretary
National Cancer Advisory Board
National Cancer Institute