



National Institute on Alcohol  
Abuse and Alcoholism

# **NIAAA DIRECTOR’S REPORT ON INSTITUTE ACTIVITIES TO THE 158<sup>TH</sup> MEETING OF THE NATIONAL ADVISORY COUNCIL ON ALCOHOL ABUSE AND ALCOHOLISM**

Thursday, September 9, 2021  
Virtual Meeting

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## NIAAA BUDGET

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### Fiscal Year (FY) 2021

The Consolidated Appropriations Act, 2021 (H.R. 133), signed by the President in December 2020, provided the National Institutes of Health (NIH) \$42.9 billion, an increase of \$1.25 billion or 3 percent above the FY 2020 enacted level. This funding included allocations for the Helping to End Addiction Long-term (HEAL) Initiative, the 21<sup>st</sup> Century Cures Act, Brain Research Through Advancing Innovative Neurotechnologies (BRAIN), and research on influenza. The funding also provided a general increase to NIH Institutes and Centers and continued support of the Gabriella Miller Kids First Act pediatric research initiative. The NIH also received supplemental funding of \$1.25 billion through FY 2024 from the coronavirus supplemental appropriation included in H.R. 133.

The Consolidated Appropriations Act, 2021, provided the NIAAA \$554.9 million. This represents a \$8.2 million (1.8 percent) increase over the FY 2020 actual budget level. NIAAA estimates that it will support a total of 713 research project grants in FY 2021.

### FY 2022

The President released his FY 2022 President's Budget (PB) on May 28, 2021, requesting \$52.0 billion for NIH, a \$9.1 billion increase from the FY 2021 enacted budget. The NIAAA PB request is \$570.2 million, a \$15.3 million increase from FY 2021. The President included \$6.5 billion in the proposed NIH budget to create the [Advanced Research Projects Agency for Health \(ARPA-H\)](#), a new research entity within NIH that would be tasked with supporting high-risk, high-reward science to catalyze biomedical breakthroughs.

The House passed [H.R. 4502](#), a consolidation of several FY 2022 appropriations bills including Labor, Health and Human Services, on July 29, 2021. The House-proposed budget level increase is 5 percent or \$49.4 billion for NIH, and a 5 percent or \$27.5 million increase for NIAAA. The bill includes \$3 billion for ARPA-H.

## HONORS AND AWARDS

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**Dr. Shana Augustin**, Postdoctoral Fellow, received an American College of Neuropsychopharmacology 2021 Travel Award in May 2021.

**Dr. Raye Litten**, Acting Director of the Division of Treatment and Recovery, received the Research Society on Alcoholism (RSA) Lifetime Achievement Award in June 2021.

**Dr. Daria Piacentino**, Postdoctoral Visiting Fellow, received a Research Society on Alcoholism Junior Investigator Meeting Award in June 2021 and the College on Problems of Drug Dependence Early Career Investigator Travel Award in May 2021.

## STAFF TRANSITIONS

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### New Staff



**Dr. Ilse Alonso-Vazquez** joined the Laboratory for Integrative Neuroscience as a Postdoctoral Visiting Fellow in the Division of Intramural Clinical and Biological Research (DICBR). In this position, Dr. Alonso-Vazquez will perform studies examining effects of alcohol on sleep and cognitive function, and the neuronal and circuit mechanisms underlying these effects.



**Dr. Pinaki Bhattacharjee** joined the Section on Medicinal Chemistry as a Postdoctoral Visiting Fellow in DICBR. In this role, Dr. Bhattacharjee will conduct studies on the design, synthesis, and biological investigation of novel cannabinoid modulators for treatment of metabolic and fibrotic disorders.



**Dr. Biswajit Kundu** joined the Section on Medicinal Chemistry as a Postdoctoral Visiting Fellow in DICBR. In this role, Dr. Kundu will conduct studies on multi-target agents for treatment of inflammatory disorders.



**Dr. Nagaraja "Sethu" Balakathiresan** joined the Division of Neuroscience and Behavior as a program officer, where he will be responsible for the posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI) portfolios. Dr. Balakathiresan earned a Ph.D. in Biological Science from the Madurai Kamaraj University in India. Before joining NIAAA, he was an Assistant Professor of Pathology at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, where he studied the role of PTSD-related rapid eye movement (REM) sleep disturbances and microRNA-based biomarkers for repetitive chronic TBI-induced PTSD.



**Bonnie Hebb** joined the Administrative Services Branch as a Program Specialist providing procurement and purchasing support to both intramural and extramural areas within NIAAA. In her almost 20 years of federal service, she has served in many acquisition roles, most recently with the National Cancer Institute as a Purchasing Agent.



**Sarah Nelson** joined the Grants Management Branch (GMB) as a Grants Management Specialist. Previously, she was a contractor working with GMB, where her duties included managing a portfolio focused on National Research Service Awards (fellowships and institutional training grants), assisting in the grant closeout process, and tracking administrative supplements and co-funding. In her new position, she will be responsible for managing a more extensive grant portfolio.

## Internal Transitions



**Dr. Andrew Kesner** converted from a Postdoctoral Intramural Research Training Award (IRTA) Fellow to a Research Fellow in the Unit on Motivation and Arousal within the Laboratory for Integrative Neuroscience, DICBR. Dr. Kesner is the first NIAAA fellow to be named as an NIH Independent Research Scholar. Dr. Kesner will continue his work on the role of cannabinoids in sleep, affect, and cognitive function, as well as the neurobiological basis of these processes.



**Dr. Bradley Kerridge** joined the Division of Epidemiology and Prevention Research (DEPR) as a program officer. Prior to his new position, Dr. Kerridge served as an epidemiologist in the Epidemiology and Biometry Branch (EBB). In DEPR, Dr. Kerridge will oversee a portfolio of grants on college and college age drinking, sexual minorities, mobile platforms for prevention delivery, social media, and advertising.



**Dr. Jenica Patterson (née Tapocik)** joined the Division of Treatment and Recovery (DTR), Medications Development Branch. She previously served as a program officer in the Division of Neuroscience and Behavior, where she managed a research portfolio on stress, posttraumatic stress disorder, and alcohol use disorder (AUD) comorbidities. Dr. Patterson's research expertise includes behavior and molecular neuroscience, epigenetics, translational science, medications development, and psychiatric comorbidity. In DTR, she oversees a research portfolio that includes AUD-related translational research, medications development, and comorbidities.

## Departing Staff

**Dr. Miriam Bocarsley**, former Research Fellow for the Laboratory Neurobiology of Compulsive Behaviors, DICBR, has accepted an Assistant Professor position at the Rutgers New Jersey Medical School in the Department of Pharmacology, Physiology, and Neuroscience and as a Core Member of Rutgers Brain Health Institute.

**Patricia Brown** retired in April 2021 after more than 40 years of public service. Patricia joined NIAAA in 1989 as a Paralegal Specialist when the Institute was a part of the Alcohol, Drug Abuse and Mental Health

Administration (ADAMHA). Over the years, she has had numerous positions, including Legislative Analyst and Ethics Specialist. Patricia looks forward to a peaceful and relaxing time, moving forward.

**Dr. Chuck Chen**, former Postdoctoral Researcher in DICBR, joined the University of Toronto, Canada, as a Research Assistant Professor working on the genomics of nutrition.

**Dr. Patricia Chou** retired from federal service in April. She joined NIAAA in 1990 in the intramural Laboratory of Epidemiology and Biometry and later served as Acting Chief of the Epidemiology and Biometry Branch when the laboratory transitioned to NIAAA's extramural research program. During her time at NIAAA, Dr. Chou played a vital role in the design and analyses of all three National Epidemiologic Surveys on Alcohol and Related Conditions (NESARC). She will continue to advise the branch on working with the NESARC datasets and is currently serving as a contractor for the Laboratory of Membrane and Biochemistry and Biophysics in DICBR.

**Dr. Lucia Guerri** has departed the Laboratory of Neurogenetics, DICBR, and is presently focusing her efforts on a neurorobotics startup company.

**Dr. Yong He**, former Research Fellow in the Laboratory of Liver Disease, DICBR, has accepted a position as a Principal Investigator at the Shanghai Institute of Materia Medica in Shanghai, China.

**Dr. Ji Soo Lee**, former Postdoctoral Visiting Fellow in DICBR, accepted a job in the pharmaceutical industry in South Korea.

**Dr. Daniel Liput**, former Research Fellow in the Laboratory for Integrative Neuroscience, DICBR, has taken a position as a Scientist at Vigene Biosciences, Inc.

**Emily Wilkins**, former Program Specialist supporting the NIAAA Office of the Director, has departed the Institute for a position as a Management Analyst at the U.S. Food and Drug Administration.

**Dr. Troy Zarcone** departed the NIAAA Science Policy Branch to serve as Director of the Office of Extramural Policy and Review and the Acting Branch Chief for the Extramural Activities and Initiatives Development Branch at the National Institute on Drug Abuse.

## RECENTLY ISSUED FUNDING OPPORTUNITY ANNOUNCEMENTS

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### Funding Opportunity Announcements (FOAs) Issued by NIAAA:

**HIV Prevention and Alcohol:** The FOA seeks to expand the HIV/AIDS prevention toolkit among alcohol impacted populations with a range of patterns of episodic and long-term use and associated behavioral and biological risks for HIV acquisition. This includes integration of effective prevention and treatment interventions with an understanding of the overarching framework for reducing the incidence of new infections by facilitating cross-cutting informative research. (R01 Clinical Trials Optional [RFA-AA-21-016](#)); (R34 Clinical Trials Optional [RFA-AA-21-017](#)).

## **NIH-Wide FOAs with NIAAA Participation:**

Maximizing Opportunities for Scientific and Academic Independent Careers (MOSAIC) Postdoctoral Career Transition Award to Promote Diversity (K99/R00 Independent Clinical Trial Not Allowed, [PAR-21-271](#); Independent Clinical Trial Required [PAR-21-272](#); Independent Basic Experimental Studies with Humans Required (BESH) [PAR-21-273](#))

Chronic, Non-Communicable Diseases and Disorders Across the Lifespan: Fogarty International Research Training Award (NCD-LIFESPAN) (D43 Clinical Trial Optional) [PAR-21-230](#)

HEAL Initiative: Planning Studies for Initial Analgesic Development [Small Molecules and Biologics] (R61 Clinical Trial Not Allowed) [RFA-NS-21-029](#)

BRAIN Initiative: Research on the Ethical Implications of Advancements in Neurotechnology and Brain Science (R01 Clinical Trial Optional) [RFA-MH-21-205](#)

BRAIN Initiative Cell Atlas Network (BICAN): Comprehensive Center on Human and Non-human Primate Brain Cell Atlases (UM1 Clinical Trial Not Allowed) [RFA-MH-21-235](#)

BRAIN Initiative Cell Atlas Network (BICAN): Specialized Collaboratory on Human, Non-human Primate, and Mouse Brain Cell Atlases (U01 Clinical Trial Not Allowed) [RFA-MH-21-236](#)

BRAIN Initiative Cell Atlas Network (BICAN): Coordinating Unit for Biostatistics, Informatics, and Engagement (CUBIE) (U24 Clinical Trial Not Allowed) [RFA-MH-21-237](#)

BRAIN Initiative: New Technologies and Novel Approaches for Recording and Modulation in the Nervous System (R01 Clinical Trial Not Allowed) [RFA-NS-21-026](#)

BRAIN Initiative: Optimization of Transformative Technologies for Recording and Modulation in the Nervous System (U01 Clinical Trials Not Allowed) [RFA-NS-21-027](#)

Dyadic Interpersonal Processes and Biopsychosocial Outcomes (R01 - Basic Experimental Studies with Humans [PAR-21-280](#)); (R01 Clinical Trials Not Allowed [PAR-21-281](#))

American Women: Assessing Risk Epidemiologically (AWARE) (R01 Clinical Trial Optional) [RFA-AI-21-058](#)

Blueprint MedTech: Incubator Hubs (U54 Clinical Trial Not Allowed [PAR-21-314](#)); (UG3/UH3 - Clinical Trial Optional [PAR-21-315](#)); (U44 - Clinical Trial Optional [PAR-21-282](#))

## **NIH-Wide NOSIs with NIAAA Participation:**

Notice of Special Interest (NOSI): Navigating Pediatric to Adult Health Care: Lost in Transition [NOT-HD-21-027](#)

Notice of Special Interest: Alzheimers-Focused Administrative Supplements for NIH Grants that are Not Focused on Alzheimers Disease [NOT-AG-21-018](#)

HEAL Initiative: Notice of Special Interest (NOSI) regarding the Availability of Administrative Supplements to Support Strategies to Advance the Study of Chronic Overlapping Pain Conditions (COPCs) [NOT-NS-21-068](#)

Notice of Special Interest to Encourage Eligible NIH BRAIN Initiative Awardees to Apply for PA-21-071 Research Supplements to Promote Diversity in Health-Related Research (Admin Supp - Clinical Trial Not Allowed, [NOT-NS-22-012](#))

Notice of Special Interest (NOSI): Social, Behavioral, and Economic Impact of COVID-19 in Underserved and Vulnerable Populations [NOT-MH-21-330](#)

## **NIAAA DIRECTOR'S ACTIVITIES**

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NIAAA Director **George F. Koob, Ph.D.**, gave the following virtual presentations between April 1 and July 31, 2021:

- “Hyperalgesia and Hyperkatifeia” for the American Society of Addiction Medicine - Pain and Addiction: Common Threads Course on April 21, 2021
- “Diversity, COVID-19, and Telehealth at NIAAA” for the American Society of Addiction Medicine - Bridging Gaps between Science and Practice Session on April 23, 2021
- “Negative Emotional State Neuroadaptations in Addiction and How They Can Become Conditioned to Cues and Context,” a plenary lecture for the Third International Conference of the Society for Interdisciplinary Placebo Studies on May 27, 2021
- “Alcohol Use Disorder: Evidence-based Science as a Framework for Diagnosis, Prevention, and Treatment” for the CREATE Hope: Carilion Research and Experience in Addiction Treatment and Education conference on June 4, 2021
- “Alcohol Use Disorder as a Coping Response: Hyperkatifeia, Deaths of Despair, and COVID-19” for the American Society of Clinical Psychopharmacology Federal Agency Updates Plenary on June 4, 2021
- “Congratulations to the Class of 2021” for the American College of Academic Addiction Medicine Fellowship Graduation on June 9, 2021
- “Alcohol Misuse Science, COVID-19, and Challenges for the Future” for the American Psychiatric Nurses Association Clinical Psychopharmacology Institute (keynote speaker) on June 11, 2021
- “Alcohol and Opioid Addiction: The Gain in the Brain is in the Pain” for the Dell Medical School, University of Texas, Austin, Department of Psychiatry Grand Rounds on June 15, 2021
- “NIAAA State of the Science: Update” for the Friends of NIAAA Annual Membership meeting on June 16, 2021
- “NIAAA Update” for the Research Society on Alcoholism/International Society for Biological Research on Alcoholism Plenary on June 20, 2021
- “Rising from the Depths of Despair: Understanding Hyperkatifeia to Inform AUD Treatment Strategies” for the Research Society on Alcoholism/International Society for Biological Research on Alcoholism Symposium (Discussant) on June 21, 2021
- “NIAAA State of the Science: Update” for the College on the Problems of Drug Dependence 83<sup>rd</sup> Annual Scientific Meeting on June 21, 2021

- “The Neurocircuitry of Alcohol Use Disorder” for the Research Society on Alcoholism Lecture Series on June 26, 2021
- “NIAAA Update” for the NIAAA Liaison Meeting on June 30, 2021
- “Conversation with General Barrye Price, President and CEO of Community Anti-Drug Coalitions of America (CADCA), about youth underage drinking and the impact of the COVID-19 pandemic on alcohol policy” for the CADCA 20<sup>th</sup> Annual Mid-Year Training Institute Plenary on July 13, 2021
- “Conversation on Health Aspects of Alcohol Use: Question and Answer Session” for the United Nations Division of Healthcare Management and Occupational Safety and Health Public Health Monthly Conversation Series on July 14, 2021
- “Alcohol and SARS-CoV-2 Infection” for the National Institute on Neurological Diseases Neurologic and Psychiatric Effects of SARS-CoV-2 Infection (Round Table with NIH Leadership on [Institute and Center] interests and Resources for Addressing Neurologic and Psychiatric Effects of SARS-CoV-2 Infection) on July 15, 2021
- “Central Sensitization and Hypersensitization to Pain Due to Chronic Opioid Use” for the National Institute of Diabetes and Digestive and Kidney Diseases Workshop on Pancreatic Pain: Knowledge Gaps and Research, Symposium on July 21, 2021

## NOTABLE NIAAA STAFF ACTIVITIES

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**Dr. Brett Hagman** served as a co-guest editor for a 14-article topic series on [Recovery from Alcohol Use Disorder](#) for *Alcohol Research: Current Reviews*, the peer-reviewed scientific journal published by NIAAA.

**Dr. Kathy Jung** is representing NIAAA on the NIH-wide Post-Acute Sequelae of COVID-19 (PASC) Task Force, which advises on the establishment of a meta-cohort to study the prevalence, pathobiology, etiology, and symptomatology of a long or unremitting course of COVID-19 disease, with the goal of finding treatment and means of prevention.

**Dr. Raye Litten** presented “Update on NIAAA’s Medications Development Program to Treat Alcohol Use Disorder” to the Department of Defense Alcohol and Substance Abuse Disorders Research Program virtual meeting in April 2021.

**Dr. Bill Dunty** served as a scientific expert for the American College of Obstetricians and Gynecologists Twitter Chat for Alcohol Awareness Month on April 7, 2021.

**Dr. Changhai Cui** presented at the Society on NeuroImmune Pharmacology COVID-19 Virtual Workshop and co-chaired a symposium on “Molecular approaches to COVID-19 pathogenesis and underlying mechanisms” on April 9, 2021.

**Dr. Bill Dunty** participated in a roundtable discussion on child development research at the NIH during the 2021 Development Society for Research in Child Development biennial meeting on April 9, 2021.

**Dr. Ivana Grakalic** participated in the Young Investigator Research Forum 2021: NIH National Institutes of Health – Meet and Greet sponsored by the American Academy of Sleep Medicine Foundation on April 16, 2021.



**Dr. Trish Powell** and **Dr. Tatiana Balachova** organized and led the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders 2021 Annual Public Meeting on April 23, 2021. The meeting included a Special Panel titled “Prevention of Fetal Alcohol Spectrum Disorders (FASD) and Services During the COVID-19 Pandemic: Focus on Women and Individuals Living with FASD.”

**Dr. Robert Freeman** served on the Conference Organizing Committee for the “Scientific Workshop on Violence and Related Health Outcomes in Sexual and Gender Minority Communities” on May 6, 2021.

**Dr. Deidra Roach**, **Dr. Ivana Grakalic**, and **Deb Langer** organized a webinar titled “Innovations in Treating Stress and Trauma in Women with Alcohol Use Disorder” held July 28, 2021.

**Dr. Jenica Patterson** served as an organizer for a virtual Diversity Supplement Professional Development Workshop held on August 26 and 27, 2021.

**NIAAA Staff Activities at the 2021 Research Society on Alcoholism (RSA) Virtual Annual Meeting, June 19–23, 2021:**

**Dr. Rachel Anderson** and **Dr. Jenica Patterson** organized and chaired a symposium, “Rising from the Depths of Despair: Understanding Hyperkatifeia to Inform AUD Treatment Strategies.”

**Dr. Changhai Cui** provided introductory remarks for the symposium on “Involvement of Microglia, Astrocytes and Extracellular Vesicular Signaling in AUD Pathology” and served as the discussant for the symposium on “Astrocyte-Ethanol Interactions: What Cutting-edge Tools Have Revealed.”

**Dr. Bill Dunty** co-chaired and provided introductory remarks in the symposium titled “Health Outcomes of Adults with FASD: A Fetal Basis to Adult Disease.”

**Dr. Daniel Falk** presented a talk titled, “NIAAA Data Archive: Data Sharing Policy and Resources towards Open Science.”

**Dr. Robert Freeman** served as a discussant for the symposium “Novel Social Media and Substance Use Research: From data collection to intervention.”

**Dr. Brett Hagman** organized and provided introductory remarks for a symposium titled “Recovery Version 2.0: Recent advances in the use of digital technology to assess and enhance recovery from alcohol use disorders.”

**Dr. Michael Hilton** and **Gregory Bloss** organized and chaired a symposium session on “Advances in Research on Alcohol-Related Policies.” Dr. Hilton also served as a discussant.

**Dr. Raye Litten** served as discussant for the session “New Anticonvulsants Clinical Trials in AUD- Predictors and Modifiers of Response.”

**Dr. Philippe Marmillot** presented an overview at the Grantsmanship Workshop, organized by the RSA Education Committee and the Office of Extramural Activities, NIAAA. The following NIAAA Staff also participated in this event: **Dr. Changhai Cui**, **Lauren Early**, **Dr. Luis Espinoza**, **Judy Fox**, **Dr. Robert Freeman**, **Dr. Anna Ghambaryan**, **Dr. Ivana Grakalic**, **Dr. Brett Hagman**, **Dr. Li Lin**, **Dr. Abbas Parsian**, **Dr. Jenica Patterson**, **Dr. Mariela Shirley**, **Dr. RV Srinivas**, and **Jeff Thurston**.

**Dr. Antonio Noronha** co-organized and gave the introduction to the symposium “Emerging Genetic and Epigenetic Mechanisms Underlying Alcohol Use Disorders.”

**Dr. Andras Orosz** co-organized, co-chaired, and introduced the symposium titled “Alcohol Consumption, Longevity, and Age-Related Disease.”

**Dr. Abbas Parsian** organized a symposium titled, “From Variant to Function: Using Multi-Omics Approaches to Understand Genetics of Alcohol Use Disorder (AUD).”

**Dr. Jenica Patterson** provided introductory remarks for the symposium, “Leveraging Human Laboratory Data to Inform Novel Intervention Targets in Comorbid Post-traumatic Stress Disorder and Alcohol Use Disorder.”

#### **Fetal Alcohol Spectrum Disorder (FASD) Study Group at RSA:**

- **Dr. Tatiana Balachova** presented the Federal Agency Updates on the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD)
- **Dr. Bill Dunty** gave the “NIAAA Update” presentation

## **WHAT’S AHEAD?**

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The Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD) Executive Committee Meeting will be held virtually on November 15, 2021. The meeting will be organized and led by Dr. Trish Powell, Chair, and Dr. Tatiana Balachova, ICCFASD Scientific Coordinator and Executive Secretary of the ICCFASD. Dr. Bill Dunty is the NIAAA representative to the ICCFASD, and Dr. Deidra Roach is the alternate member.

The Gordon Research Conference (GRC), “Alcohol-Induced End Organ Disease,” will be held in Ventura, California, October 24–29, 2021.

The National Institute on Drug Abuse-NIAAA Frontiers in Addiction Research Mini-Convention will be held this year in a virtual format on November 1 and 2, 2021. Dr. John Matochik is the program contact.

## **NIAAA RESEARCH HIGHLIGHTS**

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### **Intercalated Amygdala Clusters Orchestrate a Switch in Fear State**

*Significance:* Effective extinction of fear memories prevents persistent, excessive reactions to threats that are associated with anxiety or trauma-related disorders. Researchers identified two clusters of neurons in the amygdala, ventral and dorsal intercalated cell masses (ITCs), that differentially mediate the acquisition and retrieval of fear extinction memory in mice. Inhibition of the ventral ITCs impaired both extinction memory formation and retrieval, whereas inhibition of the dorsal ITCs strengthened retrieval of extinction. Investigators also demonstrated that the two clusters have direct, selective access to major cortex-

amygdala loops that regulate fear extinction. Collectively, the results suggest aberrant ITC function could contribute to susceptibility to various psychiatric conditions and may have implications for understanding the neuropathological basis for post-traumatic stress disorder.

Adaptive behaviour necessitates the formation of memories for fearful events, but also that these memories can be extinguished. Effective extinction prevents excessive and persistent reactions to perceived threat, as can occur in anxiety and 'trauma- and stressor-related' disorders<sup>1</sup>. However, although there is evidence that fear learning and extinction are mediated by distinct neural circuits, the nature of the interaction between these circuits remains poorly understood<sup>2-6</sup>. Here, through a combination of in vivo calcium imaging, functional manipulations, and slice physiology, we show that distinct inhibitory clusters of intercalated neurons (ITCs) in the mouse amygdala exert diametrically opposed roles during the acquisition and retrieval of fear extinction memory. Furthermore, we find that the ITC clusters antagonize one another through mutual synaptic inhibition and differentially access functionally distinct cortical- and midbrain-projecting amygdala output pathways. Our findings show that the balance of activity between ITC clusters represents a unique regulatory motif that orchestrates a distributed neural circuitry, which in turn regulates the switch between high- and low-fear states. These findings suggest that the ITCs have a broader role in a range of amygdala functions and associated brain states that underpins the capacity to adapt to salient environmental demands. (Hagihara KM, Bukalo O, Zeller M, Aksoy-Aksel A, Karalis N, Limoges A, Rigg T, Campbell T, Mendez A, Weinholtz C, Mahn M, Zweifel LS, Palmiter RD, Ehrlich I, Lüthi A, Holmes A. *Nature*. 2021 Jun;594(7863):403-407. doi: 10.1038/s41586-021-03593-1. Epub 2021 May 26.)

### **Ketogenic Diet Reduces Alcohol Withdrawal Symptoms in Humans and Alcohol Intake in Rodents**

**Significance:** Acetate plasma levels fall during alcohol withdrawal, causing an energy deficient state. To test the hypothesis that a deficit in energy from acetate in the brain contributes to symptoms of alcohol withdrawal and increased alcohol drinking, investigators assessed the impact of a high-fat, low-carbohydrate “ketogenic diet” intervention in patients with alcohol use disorder (AUD) undergoing alcohol detoxification. Patients on the ketogenic diet needed fewer benzodiazepines to treat alcohol withdrawal and showed less alcohol craving compared with patients who consumed a standard American diet. Rats with a history of a ketogenic diet drank significantly less alcohol compared to those on a regular chow diet. The study provides clinical and preclinical evidence that a ketogenic diet may offer a unique AUD treatment option to alleviate withdrawal symptoms and to lower alcohol craving and consumption.

Individuals with alcohol use disorder (AUD) show elevated brain metabolism of acetate at the expense of glucose. We hypothesized that a shift in energy substrates during withdrawal may contribute to withdrawal severity and neurotoxicity in AUD and that a ketogenic diet (KD) may mitigate these effects. We found that inpatients with AUD randomized to receive KD (n = 19) required fewer benzodiazepines during the first week of detoxification, in comparison to those receiving a standard American (SA) diet (n = 14). Over a 3-week treatment, KD compared to SA showed lower "wanting" and increased dorsal anterior cingulate cortex (dACC) reactivity to alcohol cues and altered dACC bioenergetics (i.e., elevated ketones and glutamate and lower neuroinflammatory markers). In a rat model of alcohol dependence, a history of KD reduced alcohol consumption. We provide clinical and preclinical evidence for beneficial effects of KD on managing alcohol withdrawal and on reducing alcohol drinking. (Wiers CE, Vendruscolo LF, van der Veen JW, Manza P, Shokri-Kojori E, Kroll DS, Feldman DE, McPherson KL, Biesecker CL, Zhang R, Herman K, Elvig SK, Vendruscolo JCM, Turner SA, Yang S, Schwandt M, Tomasi D, Cervenka MC, Fink-Jensen A,

Benveniste H, Diazgranados N, Wang GJ, Koob GF, Volkow ND. *Sci Adv.* 2021 Apr 9;7(15):eabf6780. doi: 10.1126/sciadv.abf6780.)

### **Alcohol Consumption Is Associated with Poor Prognosis in Obese Patients with COVID-19: A Mendelian Randomization Study Using UK Biobank**

**Significance:** Using the UK Biobank cohort, this study examined the association between alcohol consumption and odds of SARS-CoV-2 infection and risk of death, using both traditional regression analyses (of self-reported alcohol consumption data) and Mendelian randomization analyses (of relevant genetic variants as a proxy for alcohol consumption). Alcohol consumption was not associated with either increased or decreased risk of SARS-CoV-2 infection. However, in white patients with obesity, frequent alcohol consumption, especially heavy drinking, was associated with greater risk for worse COVID-19 clinical outcomes (intensive care unit admission and death). The findings suggest that alcohol can worsen the prognosis in patients with other risk factors for dying from COVID-19, such as obesity.

**Background:** Acute and chronic alcohol abuse has adverse impacts on both the innate and adaptive immune response, which may result in reduced resistance to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and promote the progression of coronavirus disease 2019 (COVID-19). However, there are no large population-based data evaluating potential causal associations between alcohol consumption and COVID-19. **Methods:** We conducted a Mendelian randomization study using data from UK Biobank to explore the association between alcohol consumption and risk of SARS-CoV-2 infection and serious clinical outcomes in patients with COVID-19. A total of 12,937 participants aged 50-83 who tested for SARS-CoV-2 between 16 March to 27 July 2020 (12.1% tested positive) were included in the analysis. The exposure factor was alcohol consumption. Main outcomes were SARS-CoV-2 positivity and death in COVID-19 patients. We generated allele scores using three genetic variants (rs1229984 (Alcohol Dehydrogenase 1B, ADH1B), rs1260326 (Glucokinase Regulator, GCKR), and rs13107325 (Solute Carrier Family 39 Member 8, SLC39A8)) and applied the allele scores as the instrumental variables to assess the effect of alcohol consumption on outcomes. Analyses were conducted separately for white participants with and without obesity. **Results:** Of the 12,937 participants, 4496 were never or infrequent drinkers and 8441 were frequent drinkers. Both logistic regression and Mendelian randomization analyses found no evidence that alcohol consumption was associated with risk of SARS-CoV-2 infection in participants either with or without obesity (All  $q > 0.10$ ). However, frequent drinking, especially heavy drinking (HR = 2.07, 95%CI 1.24-3.47;  $q = 0.054$ ), was associated with higher risk of death in patients with obesity and COVID-19, but not in patients without obesity. Notably, the risk of death in frequent drinkers with obesity increased slightly with the average amount of alcohol consumed weekly (All  $q < 0.10$ ). **Conclusions:** Our findings suggest that alcohol consumption has adverse effects on the progression of COVID-19 in white participants with obesity, but was not associated with susceptibility to SARS-CoV-2 infection. (Fan X, Liu Z, Poulsen KL\*\*, Wu X, Miyata T, Dasarathy S, Rotroff DM, Nagy LE. *Nutrients.* 2021 May 10;13(5):1592. Doi: 10.3390/nu13051592.)

\*\*K99/R00 awardee from NIAAA

### **Transcriptomics Identifies STAT3 as a Key Regulator of Hippocampal Gene Expression and Anhedonia During Withdrawal from Chronic Alcohol Exposure**

**Significance:** Investigators collected hippocampal tissue from rats during withdrawal from chronic alcohol exposure. RNA sequencing followed by network analysis identified the transcription factor STAT3 gene as

a central node in a cluster of genes. *Stat3* was not only elevated in rat hippocampus during withdrawal, but increased expression of pSTAT3-labeled cells was also observed in the post-mortem hippocampus of humans with alcohol use disorder (AUD). Inhibition of STAT3 reversed the post-withdrawal anhedonia phenotype in rats, suggesting that STAT3 signaling in the hippocampus may contribute to negative affect associated with AUD.

Alcohol use disorder (AUD) is highly comorbid with depression. Withdrawal from chronic alcohol drinking results in depression and understanding brain molecular mechanisms that drive withdrawal-related depression is important for finding new drug targets to treat these comorbid conditions. Here, we performed RNA sequencing of the rat hippocampus during withdrawal from chronic alcohol drinking to discover key signaling pathways involved in alcohol withdrawal-related depressive-like behavior. Data were analyzed by weighted gene co-expression network analysis to identify several modules of co-expressed genes that could have a common underlying regulatory mechanism. One of the hub, or highly interconnected, genes in module 1 that increased during alcohol withdrawal was the transcription factor, signal transducer and activator of transcription 3 (Stat3), a known regulator of immune gene expression. Total and phosphorylated (p)STAT3 protein levels were also increased in the hippocampus during withdrawal after chronic alcohol exposure. Further, pSTAT3 binding was enriched at the module 1 genes *Gfap*, *Tnfrsf1a*, and *Socs3* during alcohol withdrawal. Notably, pSTAT3 and its target genes were elevated in the postmortem hippocampus of human subjects with AUD when compared with control subjects. To determine the behavioral relevance of STAT3 activation during alcohol withdrawal, we treated rats with the STAT3 inhibitor stattic and tested for sucrose preference as a measure of anhedonia. STAT3 inhibition alleviated alcohol withdrawal-induced anhedonia. These results demonstrate activation of STAT3 signaling in the hippocampus during alcohol withdrawal in rats and in human AUD subjects, and suggest that STAT3 could be a therapeutic target for reducing comorbid AUD and depression. (Chen WY, Chen H, Hamada K, Gatta E, Chen Y, Zhang H, Drnevich J, Krishnan HR, Maienschein-Cline M, Grayson DR, Pandey SC, Lasek AW. *Transl Psychiatry*. 2021 May 20;11(1):298. Doi: 10.1038/s41398-021-01421-8.)

### **Effectiveness of Spironolactone Dispensation in Reducing Weekly Alcohol Use: A Retrospective High-Dimensional Propensity Score-Matched Cohort Study**

***Significance:*** Spironolactone is mineralocorticoid receptor (MR) antagonist that is widely used in primary and specialty care settings to treat a variety of health conditions, including hypertension, heart failure, primary hypoaldosteronism, hypokalemia, and nephrotic syndrome. To test the hypothesis that MRs may represent a novel pharmacological treatment for alcohol use disorder (AUD), investigators conducted a pharmacoepidemiologic retrospective cohort study to examine whether dispensation of spironolactone ( $\geq 90$  continuous days), for any indication, was associated with changes in weekly alcohol use about 6 months later. For patients who drank  $>7$  drinks/week at baseline, those treated with spironolactone (vs untreated patients) reported a reduction in weekly alcohol use by around four drinks. No significant difference was observed among patients who drank less at baseline. Spironolactone (or other MR antagonists) may hold promise as a pharmacotherapy for AUD.

There is a need to increase the armamentarium of pharmacotherapies for alcohol use disorder (AUD). Recent research suggests that mineralocorticoid receptor (MR) antagonism via spironolactone may represent a novel pharmacological treatment for AUD. We conducted a pharmacoepidemiologic retrospective cohort study (June 1, 2014 to May 31, 2018) to examine whether spironolactone dispensation ( $\geq 90$  continuous days), for any indication, is associated with changes in weekly alcohol use

about 6 months later. We compared 523 spironolactone-treated adults and 2305 untreated adults, matched on high-dimensional propensity scores created from a set of predefined (sociodemographic and health characteristics, diagnoses, and service utilization) and empirical electronic health record-derived covariates. The sample was 57% female and 27% non-White with a mean age of 59.2 years (SD = 19.3). Treated patients reduced their weekly alcohol use by 3.50 drinks (95% CI = -4.22, -2.79), while untreated patients reduced by 2.74 drinks (95% CI = -3.22, -2.26), yielding a significant difference of 0.76 fewer drinks (95% CI = -1.43, -0.11). Among those who drank >7 drinks/week at baseline, treated patients, compared to untreated patients, reported a greater reduction in weekly alcohol use by 4.18 drinks (95% CI = -5.38, -2.97), while there was no significant difference among those who drank less. There was a significant dose-response relationship between spironolactone dosage and change in drinks/week. Pending additional evidence on its safety and efficacy in individuals with AUD, spironolactone (and MR blockade, at large) may hold promise as a pharmacotherapy for AUD. (Palzes VA, Farokhnia M, Kline-Simon AH, Elson J, Sterling S, Leggio L, Weisner C, Chi FW. *Neuropsychopharmacology*. 2021 Aug 2. doi: 10.1038/s41386-021-01117-z. Epub ahead of print.)

### **Alcohol Use Disorder and Non-Fatal Suicide Attempt: Findings from a Swedish National Cohort Study**

*Significance:* Analysis of longitudinal nationwide Swedish registry data showed that alcohol use disorder (AUD) was robustly associated with suicide attempt after adjusting for sociodemographic factors and psychiatric comorbidity. Sex differences and age-of-onset effects were observed, with early-onset AUD more strongly associated with suicide attempt. AUD appears to be an important predictor of suicide attempt even in the context of other psychiatric disorders, results that have clinical implications for screening for suicidality risk on AUD diagnosis.

Background and aims: Alcohol use disorder (AUD) is associated with increased risk of non-fatal suicide attempt. We aimed to measure the strength and mechanistic nature of the association between AUD and increased suicide attempt and determine any causal pathways and/or shared risk factors. Design: We used Cox proportional hazards models in population-level and co-relative analyses to evaluate the risk of first non-fatal suicide attempt as a function of previous AUD. Setting and participants: We used continuously updated longitudinal nationwide Swedish registry data on native Swedes born from 1950 to 1970 (n = 2 229 619) and followed from age 15 until 2012. Measurements: AUD and suicide attempt were identified using International Classification of Diseases (ICD)-8, ICD-9, and ICD-10 codes. AUD was also identified using pharmacy and criminal records. Genetic and family environmental risks were derived based on relatedness via the Multi-Generation Register and shared residency via the Population and Housing Census and the Total Population Register. Findings: AUD was robustly associated with suicide attempt in crude models (hazard ratio [HR] = 15.24 [95% CI: 14.92, 15.56]). In models adjusted for sociodemographic factors and psychiatric comorbidity, the association was attenuated: for women, HRs declined gradually across time, ranging from 5.55 (3.72, 8.29) during the observation period that ranged from age 15 to 19 years to 1.77 (1.65, 1.90) at age 40 or older. For men, the corresponding figures were 6.12 (4.07, 9.19) and 1.83 (1.72, 1.94); in contrast to women, risk of suicide attempt among men increased from age 15 to 29 before declining. In co-relative models, a residual association remained, consistent with a causal path from AUD to suicide attempt. Conclusions: In Sweden, alcohol use disorder appears to be an important predictor of suicide attempt even in the context of other psychiatric disorders. The observed association is likely the result of features that jointly impact risk of alcohol use disorder and suicide attempts (genetic liability, psychiatric illness, and childhood stressors) and a potentially causal

pathway, acting independently or in conjunction with one another. (Edwards AC, Ohlsson H, Mościcki E, Crump C, Sundquist J, Kendler KS, Sundquist K. *Addiction*. 2021 Jun 22. doi: 10.1111/add.15621.)

## NIAAA COMMUNICATIONS AND PUBLIC LIAISON ACTIVITIES

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### Press and Publication Activities

#### Media Interviews:

Dr. Koob and other NIAAA staff continue to speak with national and international news outlets about NIAAA's research. Interviews since May 2021 include: *The New York Times*, *The New Yorker*, *The Washington Post*, *Radio Health Journal*, and *Harper's Magazine*. Topics covered in these interviews included:

- the impact of the pandemic on alcohol consumption
- drinking to cope with stress and anxiety
- dangers that nonalcoholic versions of alcoholic drinks may pose to people with alcohol use disorder
- prenatal alcohol exposure
- how language choices can reduce mental health and addiction stigma

#### NIAAA News Items:

- [Words matter: language can reduce mental health and addiction stigma, NIH Leaders say](#) (July 18)
- [Life achievements linked to sustained recovery in nationally representative survey](#) (June 25)
- [Scientists discover brain cells that compete to sustain or suppress traumatic memories](#) (May 26)
- [NESARC-III genetic data now available to researchers](#) (May 5)

#### NIAAA Director's Blog Posts:

- [Want to Reduce Stigma? Choose Your Words Wisely](#) (July)
- [National Institute on Alcohol Abuse and Alcoholism Invites Input on 2022-2026 Strategic Plan Outline](#) (July)
- [Mourning the Loss of a Great Addiction Pioneer](#) (April)

#### Major Events:

*NIAAA Liaison Group Virtual Roundtable*: NIAAA held its second virtual liaison group roundtable on June 30. Dr. Koob and liaison contacts—including Beth Bagwell (International Town and Gown Association), Rick Birt (Students Against Destructive Decisions), and Relja Ugrinic (Community Anti-Drug Coalitions of America)—provided updates. An informal discussion and additional updates concluded the meeting.

*CollegeAIM Webinar Series*: NIAAA and the International Town and Gown Association continued with the webinar series, "The Updated College Alcohol Intervention Matrix (*CollegeAIM*): What Colleges and Communities Need to Know Now," with webinars in April, May, and August. Panelists included Jason

Kilmer, Ph.D. (University of Washington), Jessica Cronce, Ph.D. (University of Oregon), and Alicia Baker (University of Florida).

*Innovations in Treating Stress and Trauma in Women with Alcohol Use Disorder Webinar:* Held on July 28, the webinar featured a panel discussion on the link between recent increases in rates of alcohol use disorder among women and stress and trauma, focusing on vulnerable populations of women and presenting advances in treatment. Presenters included Geetanjali Chander, M.D., M.P.H.; Tracy Simpson, Ph.D.; and Sherry McKee, Ph.D.



*Students Against Destructive Decisions (SADD) Summer Video Challenge:* With support from NIAAA, SADD challenged students to create short videos focused on underage drinking and based on NIAAA factsheets. More than 50 students in 12 states submitted entries.

### Publications:

Since April, NIAAA publications elicited about 700,000 pageviews, 12,000 downloads, and almost 4,000 print copies ordered. The most viewed NIAAA publications were [Alcohol Facts and Statistics](#), [Alcohol Overdose](#), and [Underage Drinking](#), and the most frequently downloaded publication was [Alcohol Facts and Statistics](#). The most ordered NIAAA publications were [Treatment for Alcohol Problems: Finding and Getting Help](#) – English version, [Harmful Interactions: Mixing Alcohol with Medications](#) – English version, and [Make A Difference: Talk to Your Child About Alcohol](#) – English version.

NIAAA recently created Spanish-language translations of: [Alcohol and the Hispanic Community](#), [Alcohol Facts and Statistics](#), [Fetal Alcohol Exposure](#), [Parenting to Prevent Childhood Alcohol Use](#), [Parents: Talk With Your High School Grads About Celebrating Safely](#), and [Using Alcohol to Relieve Your Pain: What Are the Risks?](#) NIAAA also translated the following factsheets into fifteen additional languages: [Interrupted Memories: Alcohol-Induced Blackouts](#), [Hangovers](#), and [Alcohol Use Disorder: A Comparison Between DSM-IV and DSM-5](#).



### Social Media Highlights:

NIAAA's Twitter account ([@NIAAnews](#)) currently has almost 27,000 followers, which is an increase of about 1.4 percent since April. NIAAA's Instagram account ([@NIAAnews](#)) now has almost 2000 followers, which is an increase of about 10 percent. Facebook ([@NIAAAgov](#)), NIAAA's newest social media account, currently has more than 760 followers, more than doubling the number of followers since April.

A social media post with a blue background. On the left, a silhouette of a person in a graduation cap and gown is shown from behind, throwing their cap. On the right, the text reads "Celebrate Graduation Safely" in large white font. Below this is the NIH logo and the text "National Institute on Alcohol Abuse and Alcoholism". At the bottom right, it says "7 Total Engagements". On the left side of the post, there is a block of text: "Twitter: Graduation is a time to celebrate! Be sure to talk with your new #graduates about keeping events #alcohol-free—it just may save a life. No amount of #underagedrinking is legal or safe."



Sample social posts:

 <p><b>Instagram:</b> <a href="#">@alexa_gracias</a> is a postbaccalaureate scholar in NIAAA's Laboratory for Integrative Neuroscience (LIN). She studies the effects of alcohol on the endocannabinoid system in the brain using advanced optical imaging techniques. . .</p> <p>47 Total Engagements</p>	<p><b>Facebook:</b> #Hangover symptoms peak when the blood alcohol concentration in the body returns to about zero. The symptoms can last 24 hours or longer. Learn more about hangover causes and remedies.</p>  <p>NIAAA.NIH.GOV <b>Hangovers   National Institute on Alcohol Abuse and Alcoholism (NIAAA)</b> A hangover refers to a set of...</p> <p>58 Total Engagements</p>
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In recent months NIAAA also utilized social media to promote the following:

- Interagency Work Group on Drinking and Drug Use in Women and Girls Webinar
- Juneteenth recognition
- #NIHCopeWithStress campaign—Dr. Koob discussing gardening
- White House/NIH ARPA-H Listening Session