NIAAA Director's Report on Institute Activities to the 151st Meeting of the National Advisory Council on Alcohol Abuse and Alcoholism

May 14, 2019
Bethesda, MD

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Director
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health

NIH National Institute on Alcohol Abuse and Alcoholism

Welcome to New NIAAA Staff

Dr. Yoo Sun Kim joined the Laboratory of Molecular Signaling (LMS) as a Visiting Fellow in February 2019. Dr. Kim received her Ph.D. in Nutritional Science from Ewha Woman's University, in Seoul, Republic of Korea

Nyamer Koat joined the Division of Medications Development (DMD) as a Health Research Associate. Ms. Koat completed her B.S. in Biology from Iowa State University.

NIAAA Budget

- NIH received a total of $39.3 billion for FY 2019
  - NIAAA received a total of $525.6 million for FY 2019
- The FY 2020 budget is under development.

NIAAA Funding Opportunity Announcements (FOAs)

Recently Issued FOAs and Notices:

- Mechanistic studies on chronic alcohol use and sleep homeostasis (R01)
- Alcohol and Other Substance Use Research Education Programs for Health Professionals (R25)
- Notices of Special Interest:
  - Methodological Advances to Improve Alcohol Measurement and its Consequences for People Living with HIV who have Comorbidities, Coinfections, and Complications
  - Supporting Administrative Supplements for Fetal Alcohol Spectrum Disorders (FASD)
  - Development and Dissemination of Behavioral Treatments for Alcohol Use Disorder

NIAAA participation in NIH-wide FOAs

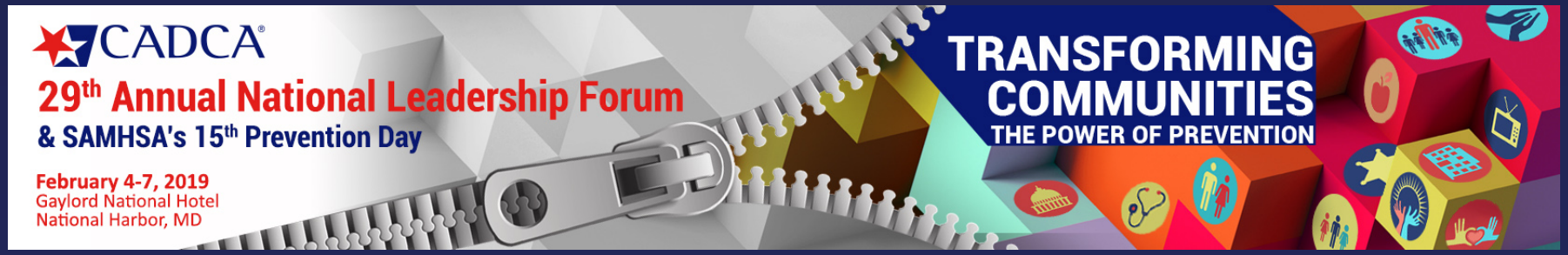
Recently issued NIH-wide FOAs include:

- BRAIN Initiative
  - Secondary Analysis and Archiving of BRAIN Initiative Data (R01)
  - Tools to Facilitate High-Throughput Microconnectivity Analysis (R01)
- ABCD Study (Limited Competition)
  - Data Analysis, Informatics and Resource Center (U24)
  - Linked Research Project Sites (U01)
  - Coordinating Center (U24)
- A full list is provided in the Director's Report

NIAAA Outreach:
Community Anti-Drug Coalitions of America

- In February, the CADCA Leadership Forum was held in National Harbor, Maryland.

- Several NIAAA staff members participated in this annual event:
  - **Dr. George Koob** gave a presentation describing NIAAA priorities, research advances, and resources for prevention and treatment of alcohol use disorder.
  - **Dr. Ralph Hingson** presented "Trends and Interventions that Work to Prevent Underage Drinking."
  - **Dr. Aaron White** presented "Alcohol and Opioids – A Deadly Combination."



NIAAA Receives CADCA National Leadership Award

NIAAA, along with NIDA and SAMHSA, received the **National Leadership Award** from CADCA.

This annual award recognizes significant contributions to the field of substance abuse prevention.

Advancing Technology for the Treatment and Prevention of Alcohol Use Disorder

- In April, NIAAA hosted a workshop titled "Taking Stock of Advancing Technology for the Treatment and Prevention of Alcohol Use Disorder."

- The event was organized by Drs. Anita Bechtholt and Mike Hilton and included a panel of experts discussing topics such as applications of technology for research and clinical use, privacy and ethical issues, and barriers to adoption.

NIAAA Priorities for 2019

- **Clinician's Navigator** (companion to Alcohol Treatment Navigator)
- Resource Development:
  - Clinician's Core Resource
  - Core Prevention Resource
  - Core Liver Resource
- FASD research guidelines
- Research on:
  - High intensity drinking
  - Alcohol and aging
  - Recovery from alcohol use disorder
- Mentor training to support diversity in NIAAA's biomedical workforce

NIAAA Outreach: Social Media Highlights

- For one week in April, NIAAA participated in a takeover of NIH's social media accounts (Twitter, Instagram, and Facebook), posting alcohol-related messages on the main NIH accounts. The expanded audience resulted in increased reach for NIAAA's messages.

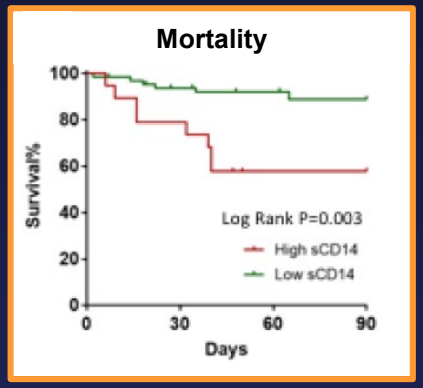
- For Alcohol Awareness Month, NIAAA participated in Twitter chats on the topics of adolescent alcohol screening and fetal alcohol spectrum disorders in April.

Research Highlights

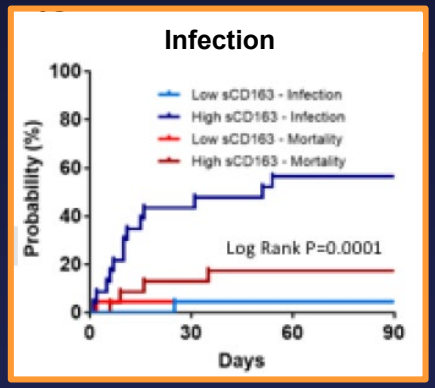
Biomarkers of Macrophage Activation and Immune Danger Signals Predict Clinical Outcomes in Alcoholic Hepatitis

This study assessed a panel of recently identified potential biomarkers of tissue injury and immune cell activation as predictors of mortality and other clinical outcomes in alcoholic hepatitis.

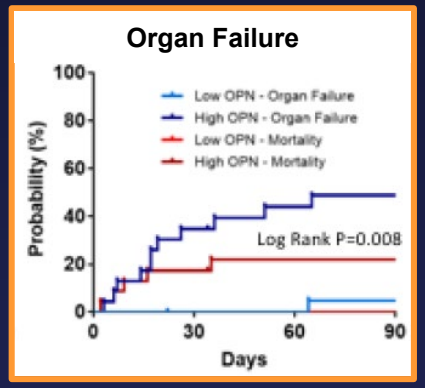
High plasma sCD14 predicts mortality.



High plasma sCD163 predicts infection.



High plasma OPN predicts organ failure.



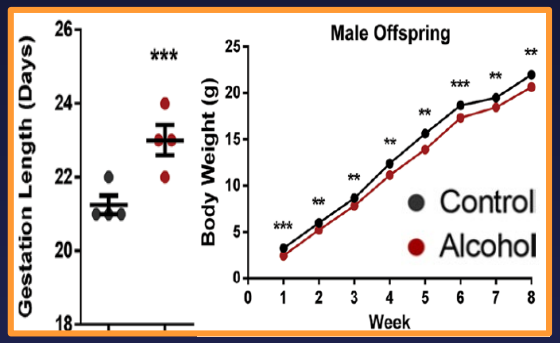
Results revealed multiple new biomarkers to indicate severity and outcomes in alcoholic hepatitis. Specifically, plasma levels of soluble cluster of differentiation 14 (sCD14; a host response indicator), soluble cluster of differentiation 163 (sCD163; a macrophage activation marker), and osteopontin (OPN; a phosphoprotein involved in neutrophil activation) were independent predictors of 90-day alcoholic hepatitis mortality, infection, and organ failure, respectively.

Citation: Saha B, Tornai D, Kodys K, Adejumo A, Lowe P, McClain C, Mitchell M, McCullough A, Srinivasan D, Kroll-Desrosiers A, Barton B, Radaeva S, and Szabo G. *Hepatology*. Epub 2019 Mar 19.

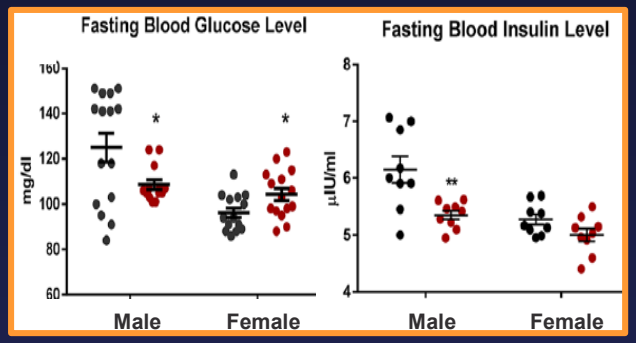
Preconception Paternal Alcohol Exposure Exerts Sex-Specific Effects on Offspring Growth and Long-Term Metabolic Programming

This study revealed multiple effects of chronic paternal alcohol exposure (prior to conception) on offspring that persisted into adulthood, including:

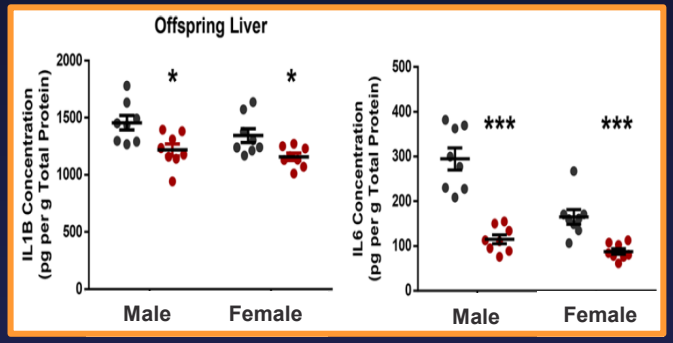
Prolonged fetal gestation and growth deficits in males



Sex-specific alterations in metabolic function

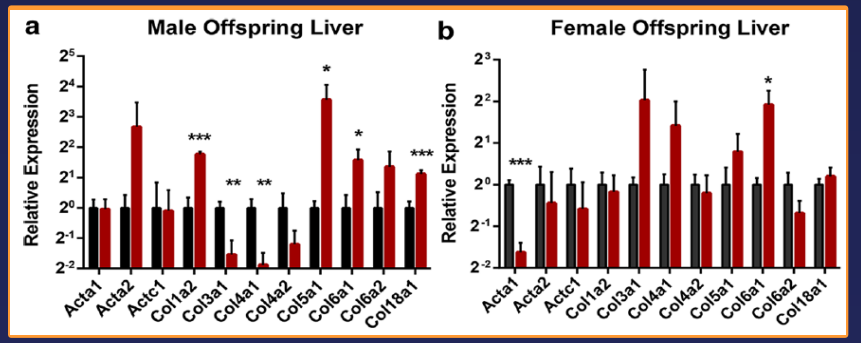


Alterations in immune signaling



These abnormalities may suggest alterations in a sperm-inherited epigenetic program that influences the formation and function of the placenta. Importantly, these findings suggest that preconception lifestyle choices of biological fathers may impact offspring.

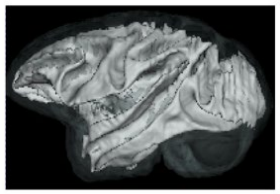
Increased pro-fibrotic structural proteins (markers of hepatic fibrosis) in adult male offspring



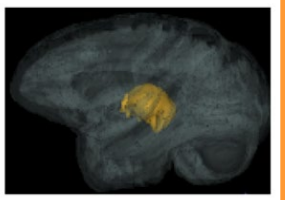
Citation: Chang RC, Wang H, Bedi Y, and Golding MC. Epigenetics Chromatin. 2019 Jan 22;12(1):9.

Chronic Alcohol Drinking Slows Brain Development in Adolescent and Young Adult Nonhuman Primates

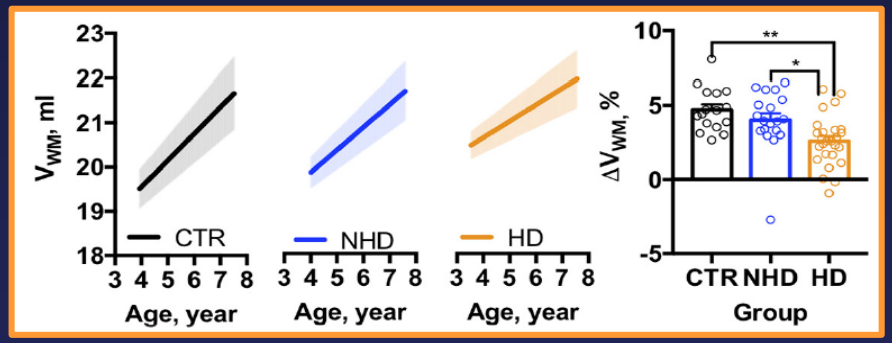
Alcohol misuse during late adolescence and early adulthood is a risk factor for the development of alcohol use disorder. This study used a macaque model of daily alcohol self-administration and *in vivo* imaging to quantify the impact of chronic alcohol exposure on neural alterations that occur during this developmental period.

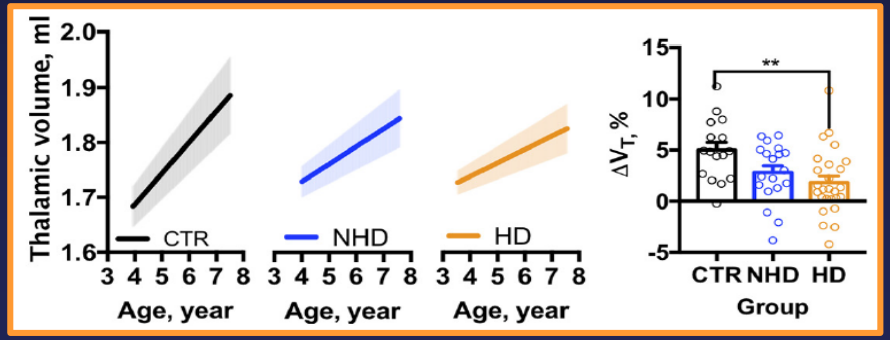


Brain white matter growth is reduced in macaques identified as heavy drinkers (HD) in late adolescence.



Heavy ethanol consumption attenuates thalamic growth in the developing brain.

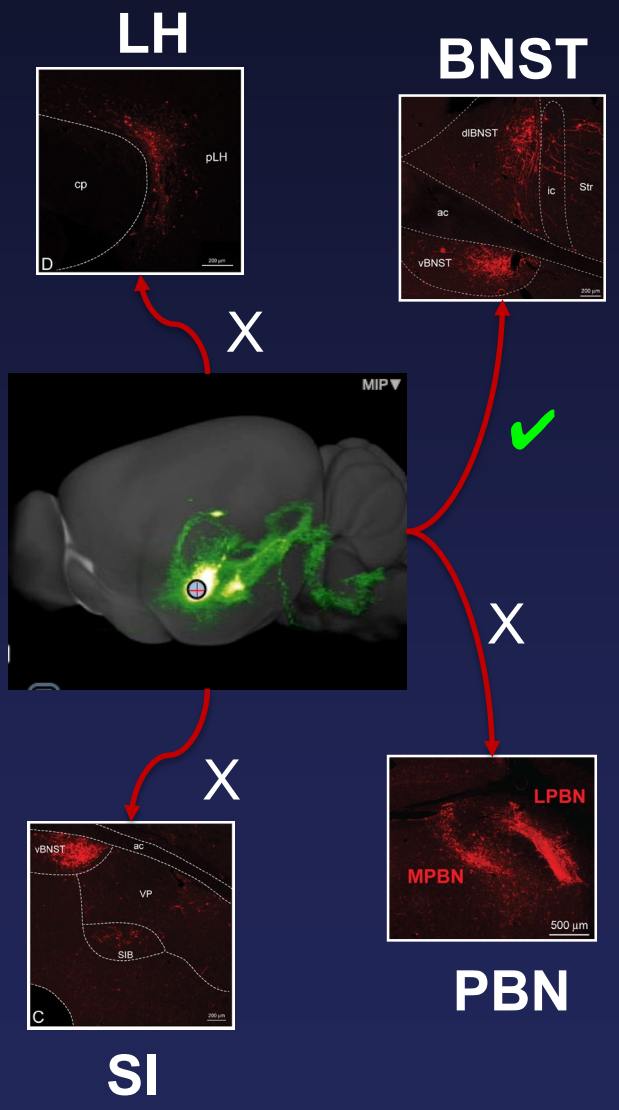




These results demonstrate that heavy alcohol exposure during the transition to young adulthood significantly impacts brain development, an insult that may lead to the continuation of heavy drinking throughout later adult life.

Citation: Shnitko TA, Liu Z, Wang X, Grant KA, and Kroenke CD. *eNeuro*. 2019 Apr 9;6(2).

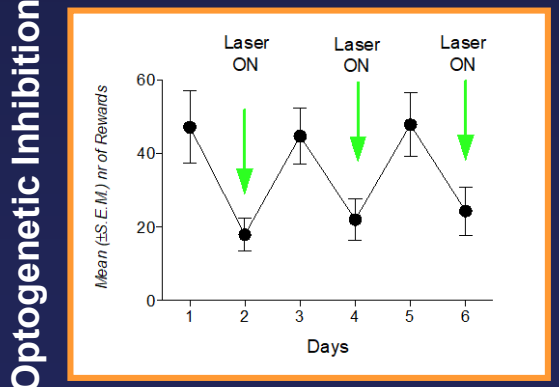
Inactivation of a CRF-Dependent Amygdalofugal Pathway Reverses Addiction-Like Behaviors in Alcohol-Dependent Rats



CRF-containing projections from the CeA to four different brain regions were optogenetically inhibited.

Only inhibition of the CeA-BNST projection replicated previous findings obtained with Daun02 (decreased drinking in dependent rats).

Alcohol drinking ✔



Inhibition of CeA^{CRF} neurons projecting to the BNST reverses:

Excessive Alcohol Intake

Negative Emotional States

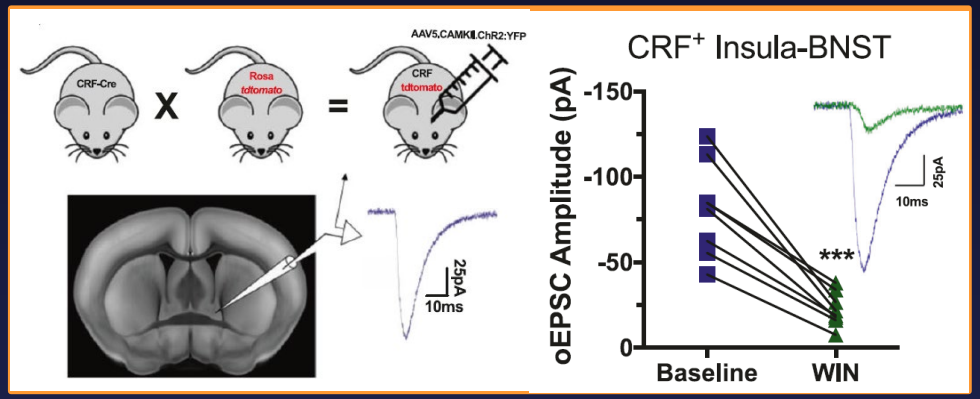
Citation: de Guglielmo G, Kallupi M, Pomrenze, MB, Crawford E, Sierra Simpson S, Schweitzer P, Koob, GF, Messing, RO, George O, 2019 Nat Commun., 2019 Mar 18;10(1):1238.

Endocannabinoid Control of the Insular-Bed Nucleus of the Stria Terminalis Circuit Regulates Negative Affective Behavior Associated with Alcohol Abstinence

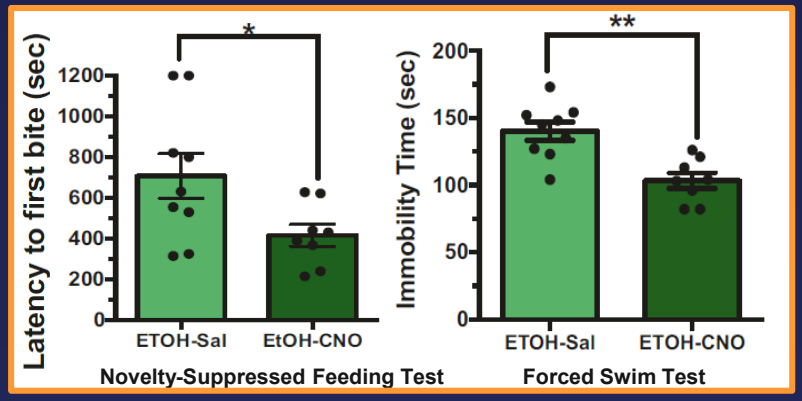
Using a mouse model of chronic alcohol consumption followed by forced abstinence, this study demonstrates that the endocannabinoid-sensitive projection from the insular cortex to the dorsal bed nucleus of the stria terminalis (dBNST) plays a key role in regulating negative affective behavior.

These results establish the insula-dBNST neurocircuit as a promising target for endocannabinoid-based pharmacotherapy to alleviate negative affective symptoms associated with abstinence in AUD.

Insula inputs onto dBNST CRF neurons are suppressed by CB1R activation.



CNO-induced inhibition of the insula-dBNST pathway reduced measures of negative affect in the novelty-suppressed feeding test and forced swim test.



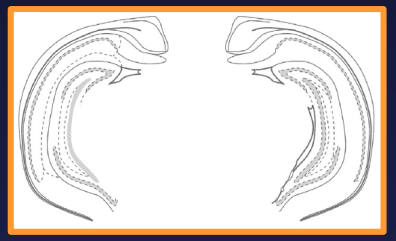
Citation: Centanni SW, Morris BD, Luchsinger JR, Bedse G, Fetterly TL, Patel S, and Winder DG. *Neuropsychopharmacology.* 2019 Feb; 44(3): 526-537.

Chronic Intermittent Ethanol Exposure Selectively Increases Synaptic Excitability in the Ventral Domain of the Rat Hippocampus

Despite evidence for distinct functional roles of hippocampal subregions, the discrete effects of chronic alcohol on synaptic transmission in the ventral (vHC) compared to the dorsal hippocampus (dHC) have not been characterized.

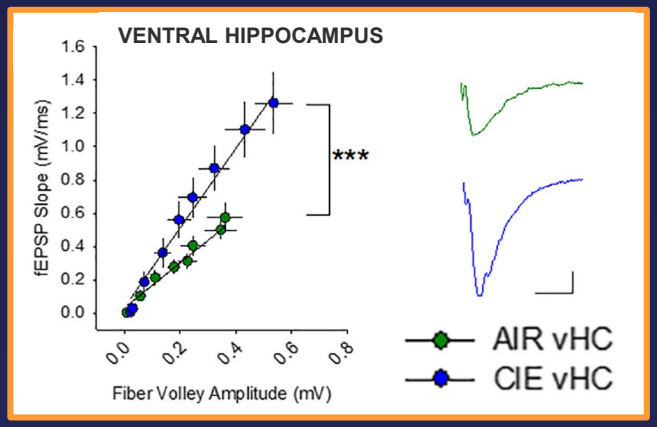
This study demonstrated that withdrawal from chronic intermittent alcohol exposure enhances synaptic excitability specifically in the vHC, providing insight into a neural mechanism that may contribute to the negative affect observed during abstinence in AUD.

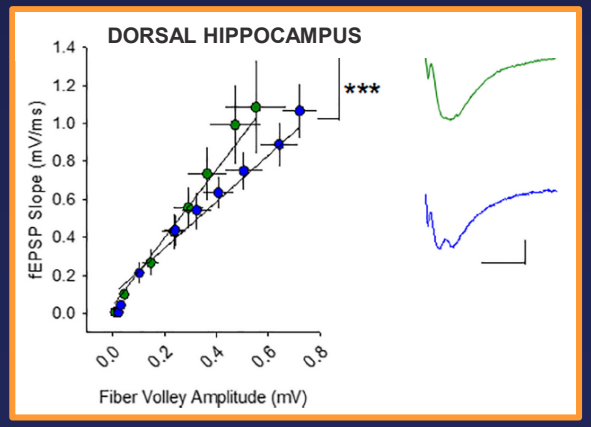
Dorsal hippocampus:
spatial learning and memory



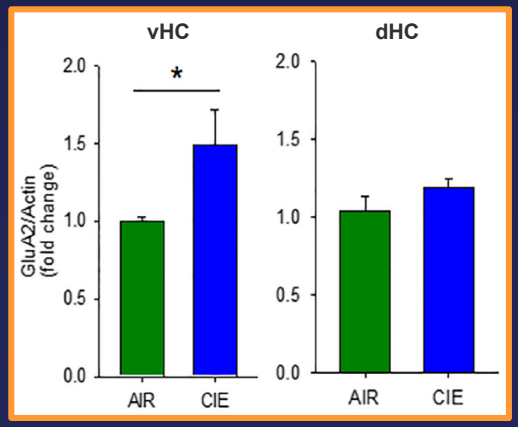
Ventral hippocampus:
negative affect

Withdrawal from CIE increases synaptic excitability in vHC and decreased excitability in dHC.





CIE increases GluA2 expression in the vHC but not the dHC.

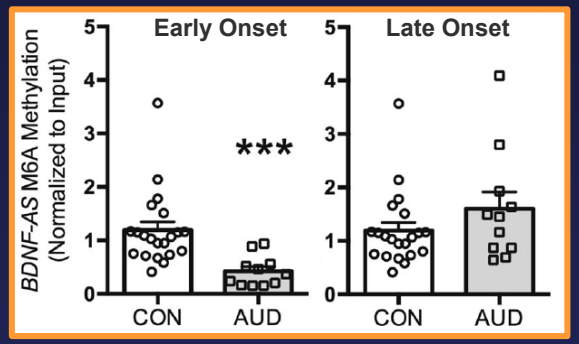


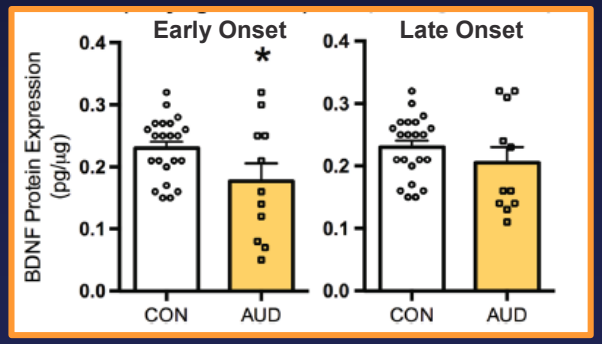
Citation: Ewin SE*, Morgan JW, Niere F, McMullen NP, Barth SH, Almonte AG, Raab-Graham KF, and Weiner JL. *Neuroscience*. 2019 Feb 1;398:144-157. *NIAAA trainee

The lncRNA BDNF-AS is an Epigenetic Regulator in the Human Amygdala in Early Onset Alcohol Use Disorders

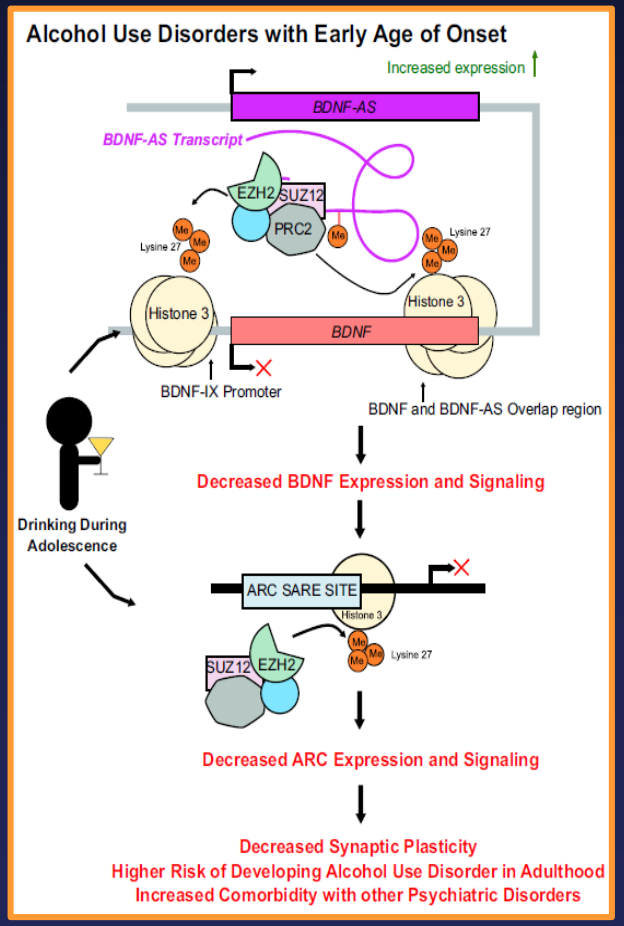
The current study compared brain-derived neurotropic factor antisense (*BDNF-AS),* a long non-coding RNA that negatively regulates BDNF expression, and associated epigenetic mechanisms in the postmortem human amygdala in individuals with AUD who began drinking either before ("early onset") or after ("late onset") age 21 to age-matched control samples.

In amygdala tissue from humans with early (but not late) onset AUD, a reduction in BDNF-AS methylation, corresponding with reduced expression of BDNF, was observed.





The alcohol-induced epigenetic modifications of amygdala *BDNF-AS* impact BDNF expression and suggest a possible role for developmentally-sensitive lncRNAs in early onset AUD. These results suggest that regulation of BDNF may prove useful in the treatment of adult psychopathology after adolescent alcohol drinking.



Citation: Bohnsack JP, Teppen T, Kyzar EJ, Dzitoyeva S, and Pandey SC. *Transl Psychiatry.* 2019 Feb 6;9(1):34.

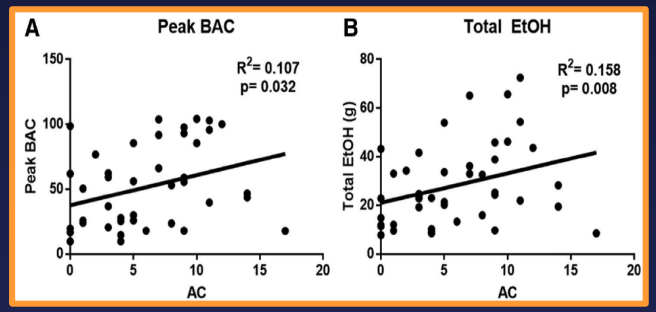
The Relationship Between Impaired Control, Impulsivity, and Alcohol Self-Administration in Nondependent Drinkers

Loss of control over drinking and impulsivity are key features of alcohol use disorder (AUD). This study examined the relationship between **impaired control** over drinking and alcohol consumption and the modulation of this relationship by impulsive personality traits in drinkers without AUD in a human laboratory paradigm.

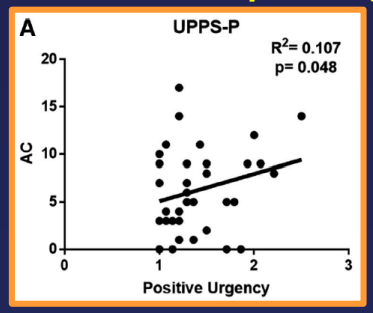
Impaired control was associated with higher alcohol self-administration and **positive urgency** (the tendency to act rashly during positive mood states). These findings highlight the critical role of impaired control as a mediator of the relationship between impulsivity, alcohol consumption, and subjective responses in drinkers without AUD.

The **Impaired Control Scale** measures Attempted Control (attempts to control drinking) and Failed Control (failures to control drinking) within past 6 months

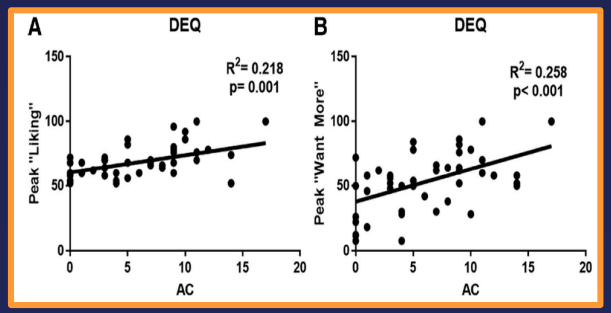
Attempted Control (AC) predicted peak blood alcohol concentrations (BAC) and total ethanol consumed.

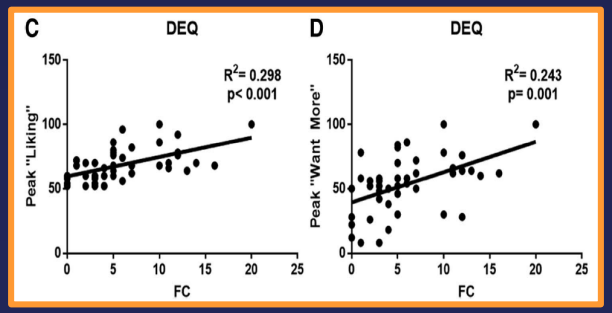


Attempted Control (AC) was predicted by Positive Urgency (a measure of impulsivity)



Both Attempted Control (AC) and Failed Control (FC) predicted greater hedonic subjective responses to alcohol (measured Drug Effects Questionnaire; DEQ).





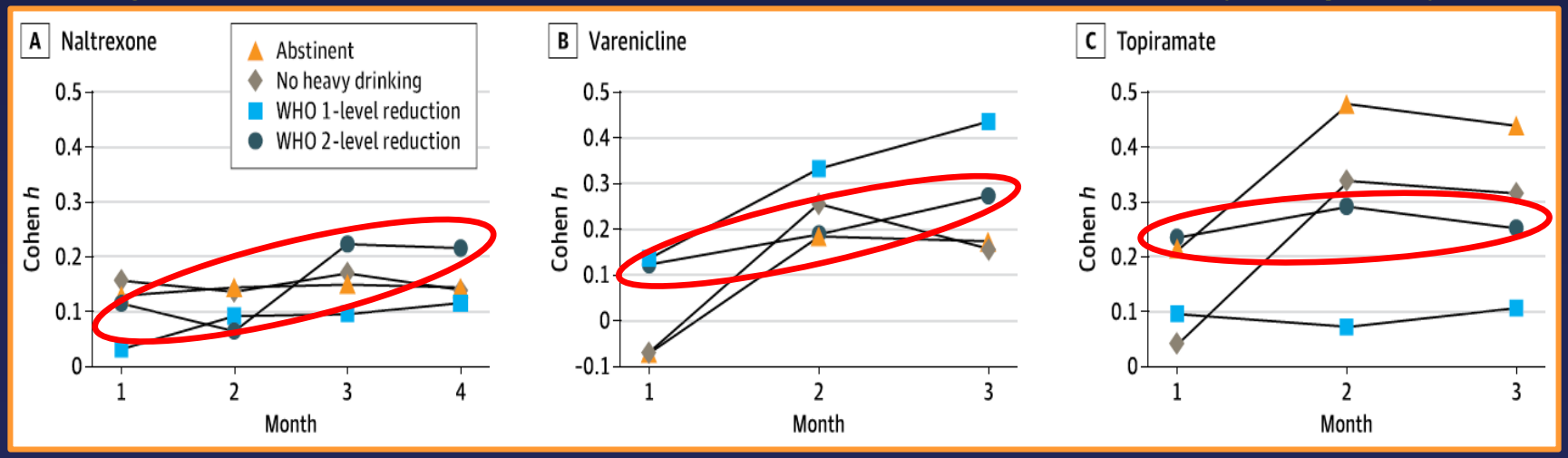
Citation: Vaughan CL, Stangl BL, Schwandt ML, Corey KM, Hendershot CS, and Ramchandani VA. *Exp Clin Psychopharmacol*. Epub 2019 Jan 28.

Evaluation of Drinking Risk Levels as Outcomes in Alcohol Pharmacotherapy Trials: a Secondary Analysis of 3 Randomized Clinical Trials

This study conducted secondary analyses of data from three multi-site AUD pharmacotherapy trials to evaluate 1- and 2-level reductions in World Health Organization (WHO) drinking risk level as AUD treatment outcome measures.

These measures capture reduction in drinking, an outcome which is more often achieved than outcomes currently accepted by FDA (total abstinence or no heavy drinking days). Results suggest that WHO drinking risk level reduction is equally or more sensitive to treatment compared to FDA-accepted outcomes, demonstrating that this measure is an indicator of treatment efficacy that could be included as an additional outcome for AUD pharmacotherapy trials.

Across three AUD pharmacotherapy trials, the size of treatment effects for WHO 1- and 2-level reductions in drinking risk were as sensitive as or more sensitive than outcomes currently accepted by the FDA.



Citation: Falk DE, O'Malley SS, Witkiewitz K, Anton RF, Litten RZ, Slater M, Kranzler HR, Mann KF, Hasin DS, Johnson B, Meulien D, Ryan M, and Fertig J; Alcohol Clinical Trials Initiative [ACTIVE] Workgroup. *JAMA Psychiatry*. Epub 2019 Mar 13.

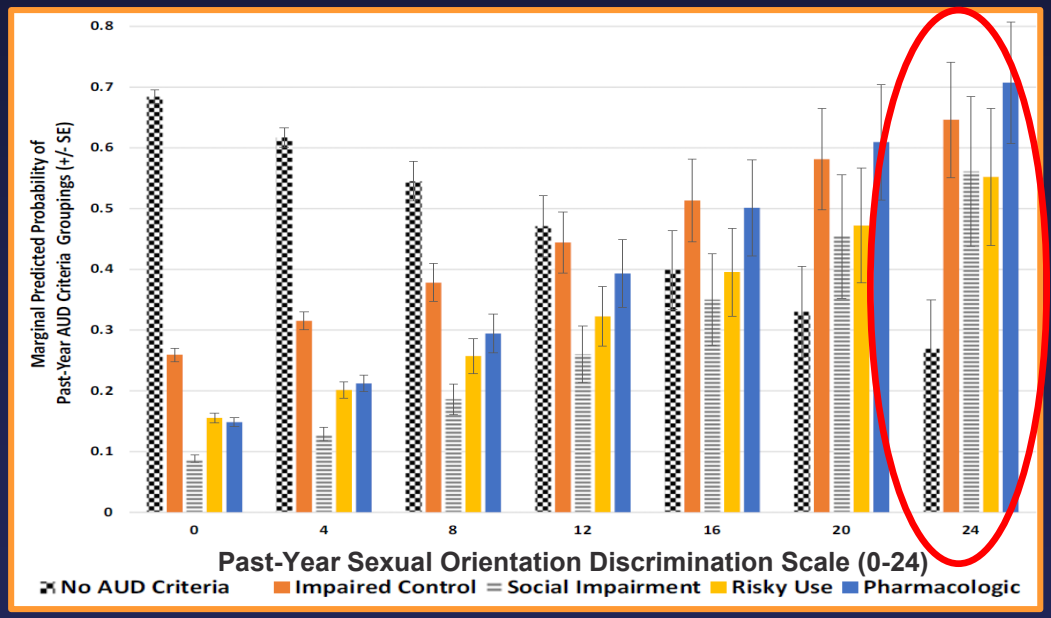
DSM-5 Alcohol Use Disorder Severity as a Function of Sexual Orientation Discrimination: A National Study

This study examined the association between DSM-5 AUD severity and sexual orientation discrimination using a nationally representative sample.

Discrimination associated with sexual orientation was associated with significantly higher levels of AUD severity, with proximal (past-year) experiences of discrimination more salient than more distal experiences.

These findings provide new evidence that sexual minorities who experience high levels of discrimination are at an increased risk of severe AUD.

AUD criteria increase as a function of past-year sexual orientation discrimination



Citation: McCabe SE, Hughes TL, West BT, Veliz P, and Boyd CJ. Alcohol Clin Exp Res. 2019 Mar;43(3):497-508.

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