NIAAA Director's Report on Institute Activities to the 154th Meeting of the National Advisory Council on Alcohol Abuse and Alcoholism

May 12, 2020
Virtual Meeting

George F. Koob, Ph.D.
Director
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health

https://www.niaaa.nih.gov/about-niaaa/advisory-council

Welcome to New NIAAA Staff

Dr. Elma Aflaki joined the Laboratory of Molecular Signaling in the Division of Intramural Clinical and Biological Research as a Staff Scientist. She earned her Ph.D. from the Medical University of Graz, Austria, where she studied the role of adipose triglyceride lipase in macrophage inflammation, cytoskeleton rearrangement, and cell survival.

Dr. Michelle Antoine joined the Division of Intramural Clinical and Biological Research as a Basic Tenure-Track investigator and 2019 NIH Distinguished Scholar. She earned her Ph.D. from the Albert Einstein College of Medicine. Dr. Antoine's research focuses on deciphering the genetic and environmental factors that impair neurocircuit activity and contribute to neurodevelopmental disorders.

Dr. Salma Majid joined the Laboratory of Neurogenetics in the Division of Intramural Clinical and Biological Research as a Staff Scientist. Dr. Majid received her Ph.D. in Toxicology from Hamdard University National Institute of Immunology in New Delhi, India.

Commander (CDR) LaToya Sewell of the United States Public Health Service joined the Office of the Clinical Director in the Division of Intramural Clinical and Biological Research. CDR Sewell is a board-certified Family Nurse Practitioner with over 14 years of experience.

Staff Transitions

INTERNAL TRANSITIONS

Dr. Raouf Kechrid has been appointed as Facility Head of the Office of Laboratory Animal Science in the Division of Intramural Clinical and Biological Research.

Dr. Peter Menza has been converted from a Post-Doctoral Intramural Research Training Award (IRTA) to a Research Fellow in the Laboratory of Neuroimaging, Division of Intramural Clinical and Biological Research.

Dr. Vijay Ramchandani was promoted to tenured Senior Investigator. Dr. Ramchandani is Chief of the Section on Human Psychopharmacology in the Division of Intramural Clinical and Biological Research.

DEPARTING STAFF

Gabriela Coello, former Administrative Officer, accepted a new position at the National Cancer Institute where she will now serve as the Administrative Officer for the Surgery Branch.

FY 2020 Budget

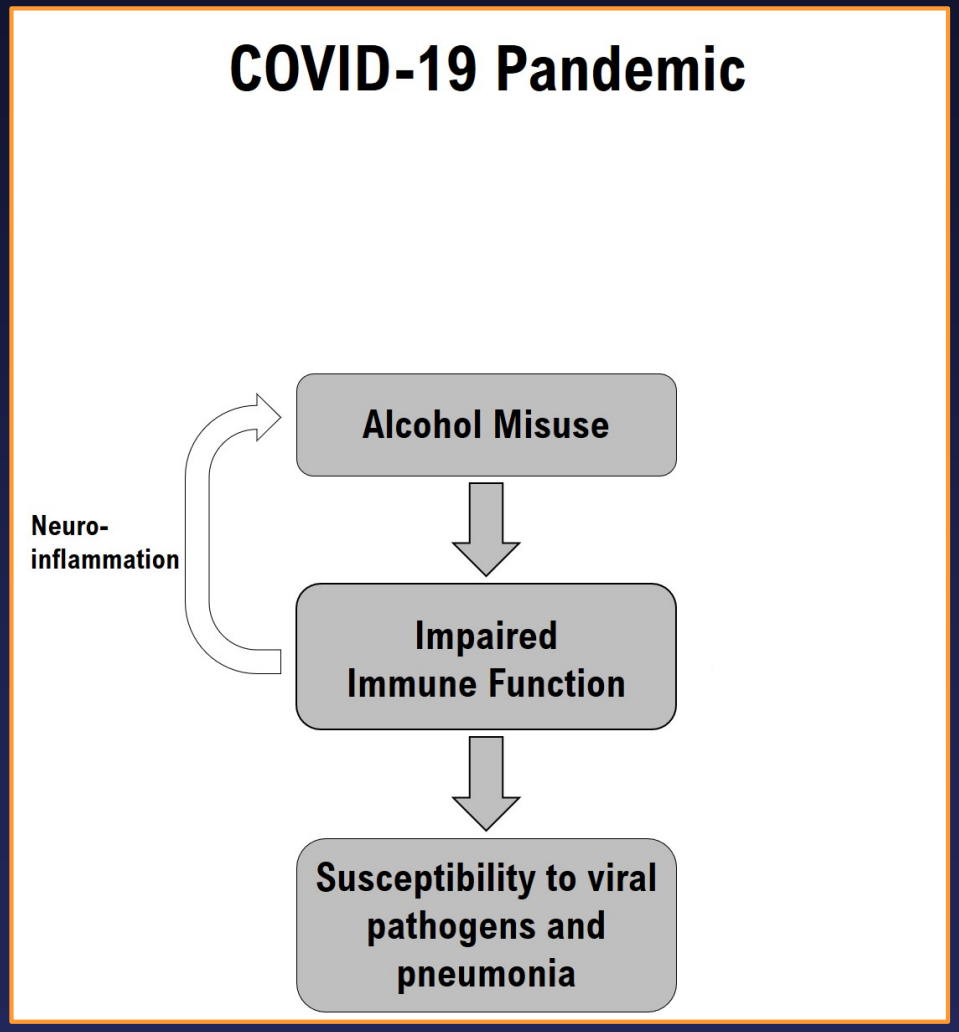
- NIH received $41.6 billion ($2.3 B increase from FY19)
  - This funding includes allocations for:
    - Helping to End Addiction Long-term (HEAL) Initiative
    - 21st Century Cures Act
    - BRAIN Initiative
    - Research on influenza
  - Continues support for Gabriella Miller Kids First Act Pediatric Research Initiative
- NIAAA received $545.4 million ($19.8 M increase from FY19)
- FY21 budget is under development.

Role of Alcohol in the COVID-19 Pandemic

Impact of alcohol use on COVID pandemic

Biological effects: Alcohol effects on immune function

Chronic alcohol consumption increases the risk for Acute Respiratory Distress Syndrome (ARDS), with increased need for mechanical ventilation, prolonged intensive care unit stay, and higher incidence of mortality



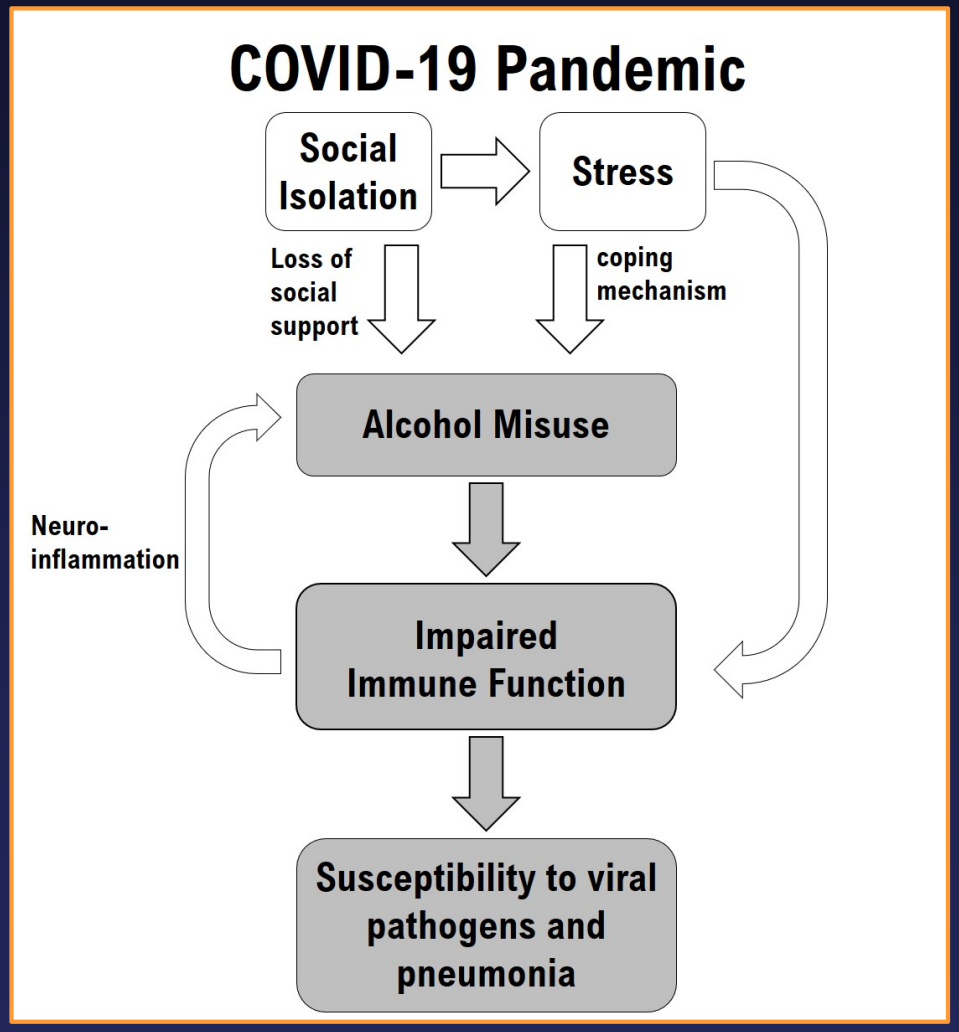
Role of Alcohol in the COVID-19 Pandemic

Impact of COVID pandemic on alcohol use and treatment

Isolation: Physical distancing can lead to social isolation or loss of social support, which can lead to stress

Stress: Drinking to cope with the stress of the pandemic

Treatment and Recovery: Physical distancing poses challenges for those with alcohol use disorder and emphasizes the need for telehealth and virtual meeting options for individuals seeking treatment or in recovery from AUD



NIAAA Response to COVID-19 Pandemic

- New landing page on NIAAA website that links to:
  - Updates to the NIAAA Treatment Navigator that include COVID-19 telehealth messages and links in banners
  - Updates to the Alcohol Policy Information System (APIS) that include new information about state level alcohol-related COVID-19 policies
  - Fact sheet: "Alcohol and Physical Distancing"
  - Director's blog: "Alcohol poses different challenges during the COVID-19 pandemic"
- Ongoing press engagement and social media outreach (including Twitter chats with ASAM and APA)
- In progress: Collecting data on apparent per capita alcohol consumption during the pandemic

COVID-19 Funding Opportunities: Notices of Special Interest (NOSIs)

- **Availability of Administrative Supplements and Competitive Revision Supplements on Coronavirus Disease 2019 (COVID-19) within the Mission of NIAAA** NOT-AA-20-011

NIH-wide NOSIs with NIAAA participation

- **Availability of Administrative Supplements and Urgent Competitive Revisions for Research on the 2019 Novel Coronavirus and the Behavioral and Social Sciences** NOT-OD-20-097
- **Availability of Administrative Supplements and Urgent Competitive Revisions for Research on Stress Management in Relation to Coronavirus Disease 2019 (COVID-19)** NOT-AT-20-011
- **Availability of Administrative Supplements and Urgent Competitive Revisions for Mental Health Research on the 2019 Novel Coronavirus** NOT-MG-20-047
- **Availability of Administrative Supplements and Revision Supplements on Coronavirus Disease 2019 (COVID-19)** NOT-AG-20-022

COVID-19 Funding Opportunities: Notices of Special Interest (NOSIs)

- Administrative Supplements for NIH grants to Add or Expand Research Focused on Maternal Mortality NOT-OD-20-104
- Competitive and Administrative Supplements for the Impact of COVID-19 Outbreak on Minority Health and Health Disparities NOT-MD-20-019
- Availability of Urgent Competitive Revisions and Administrative Supplements For Research on Biological Effects of the 2019 Novel Coronavirus on the Nervous System NOT-NS-20-051

COVID-19 Funding Opportunities: Notices of Special Interest (NOSIs)

COVID-19 science-focused NOSIs (including NOT-AA-20-011) are linked to:

- **PA-18-591 - Administrative Supplements to Existing NIH Grants and Cooperative Agreements *to request additional funding to increase or preserve the parent award's overall impact within the original scope of award or expand one of the existing specific aims***
- **PA-18-935 - Urgent Competitive Revision to Existing NIH Grants and Cooperative Agreements *to request additional funds during the current project period for new or additional activities (e.g., new specific aim) that reflect an expansion of the scope of the grant-approved activities***

Administrative Supplements for Activities Disrupted by COVID-19

- Covers unexpected increases in cost and hardships due to the COVID-19 pandemic
- All Administrative Supplement applications for activities disrupted by COVID-19 must be submitted through the parent administrative supplement FOA PA-18-591

NIAAA-specific instructions for Administrative Supplements are available on our website.

NIAAA Funding Opportunity Announcements

- **Consortium on the Neurobiology of Adolescent Drinking in Adulthood (U01 Clinical Trial Not Allowed; U24 Clinical Trial Not Allowed): RFA-AA-20-003; RFA AA 20-004; RFA AA-20-005**
- **Impact of Alcohol on the Onset and Progression of Alzheimer's Disease and Its Related Dementias (R01 - Clinical Trial Optional): RFA-AA-20-006**
- **Medications Development for the Treatment of Alcohol Use Disorder (AUD) or Alcohol-Related Organ Damage (AROD), or the Combination of AUD and AROD (U01 Clinical Trial Optional): RFA-AA-20-007**

NIAAA participation in NIH-wide FOAs

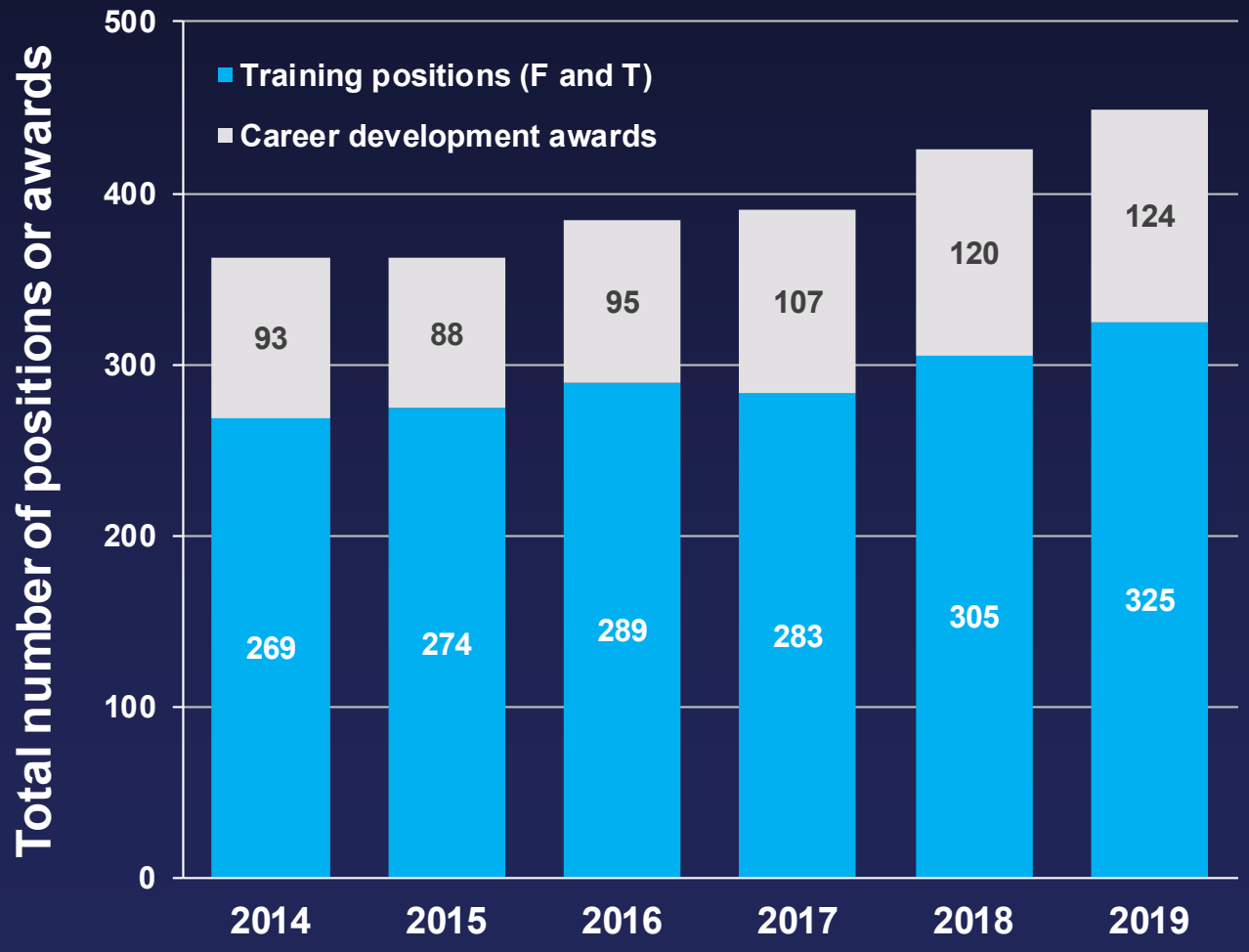
NIAAA is currently participating in over 20 FOAs and NOSIs, including:

- **BRAIN Initiative: Exploratory Team-Research BRAIN Circuit Programs (U01 - Clinical Trials Optional)** RFA-NS-20-029
- **HEAL Supplements to Improve the Treatment and Management of Common Co-occurring Conditions and Suicide Risk in People Affected by the Opioid Crisis** NOT-MH-20-025
- **National Cooperative Drug/Device Discovery/Development Groups for the Treatment of Mental or Substance Use Disorders or Alcohol Disorder (U19 - Clinical Trial Optional)** PAR-20-119
- **For full listing, please refer to the Director's Report.**

Examples of NIAAA Collaborations with other NIH Institutes

- Research on health effects
  - Fatty liver disease (NIDDK)
  - Alcohol and cancer (NCI)
- Aging research
  - Alcohol and progression of dementias (NIA)
- Pain research
  - HEAL Initiative
- Neuroscience research across NIH
  - NIH Blueprint for Neuroscience Research
  - BRAIN Initiative
  - Intramural collaboration: NIH Center for Compulsive Behavior
- Collaborative Research on Addiction at NIH (CRAN)
  - ABCD study (longitudinal study on brain development)
- HEALthy Brain and Child Development Study

Supporting the Next Generation of Alcohol Researchers:
Increases in NIAAA Training and Career Development Awards



Research Highlights

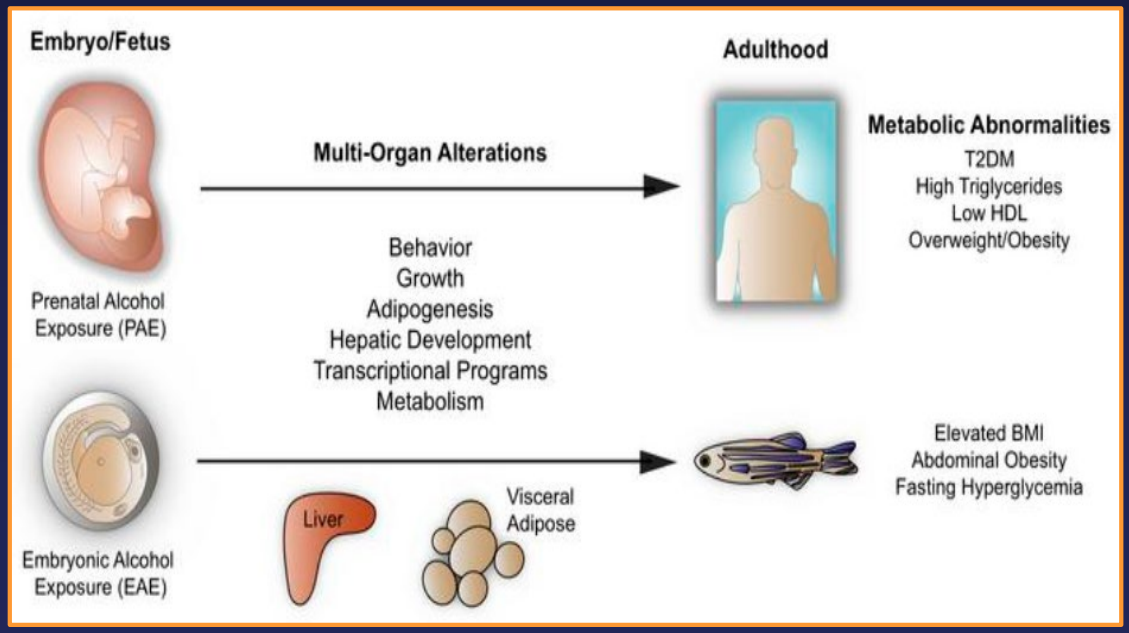
Fetal Alcohol Spectrum Disorder Predisposes to Metabolic Abnormalities in Adulthood

Analysis of patient health data revealed that prenatal alcohol exposure (PAE) is a risk factor for developing features of metabolic syndrome in adulthood. Using a zebrafish model of PAE, researchers examined the biological and molecular connections between these metabolic abnormalities and PAE.

PAE was associated with obesity, fasting hyperglycemia, increased abdominal fat, and abnormal liver development in adult fish challenged with a high-fat, high-cholesterol diet.

This study has implications for prevention strategies among individuals with prenatal alcohol exposure.

In humans, reductions in adult activity, alterations in visceral adipose tissue and hepatic development, and persistent diet-responsive transcriptional changes are consequences of PAE that may contribute to metabolic abnormalities in adulthood.



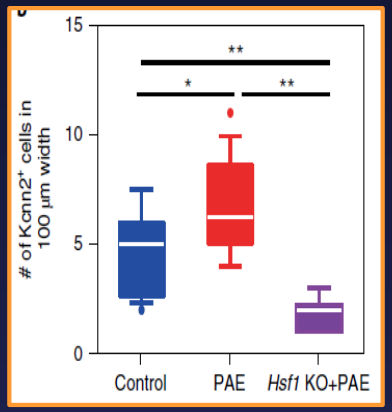
Citation: Weeks O*, Bossé GD, Oderberg IM**, Akle S, Houvras Y, Wrighton PJ**, LaBella K, Iversen I, Tavakoli , Adatto I, Schwartz A, Kloosterman D, Tsomides A, Charness ME, Peterson RT, Steinhauser ML, Fazeli PK, and Goessling W. *J Clin Invest.* 2020 Mar 23.
*NIAAA F31 trainee; **NIAAA F32 trainee

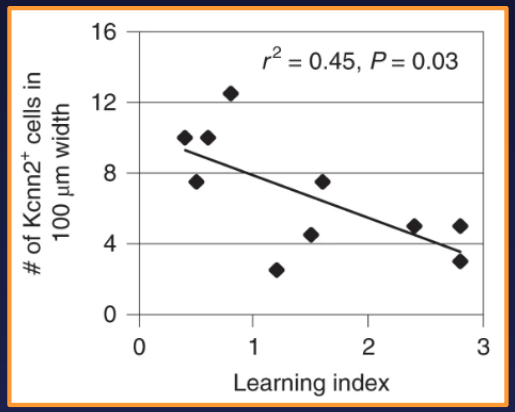
Kcnn2 Blockade Reverses Learning Deficits in a Mouse Model of Fetal Alcohol Spectrum Disorders

Alcohol-induced activation of heat shock factor 1 (HSF1) leads to epigenetic changes in nearly 100 genes. This study tested one change, increased expression of a small-conductance calcium-activated potassium channel, Kcnn2, in the motor area of the cerebral cortex.

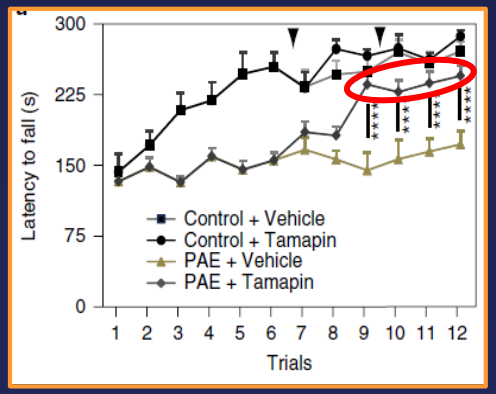
The study demonstrated that increased Kcnn2 expression correlated with deficits in motor skill learning caused by prenatal alcohol exposure that were mitigated by pharmacological blockade of Kcnn2. These results provide early evidence for Kcnn2 blockade as a potential pharmacotherapy for FASD-related learning disabilities.

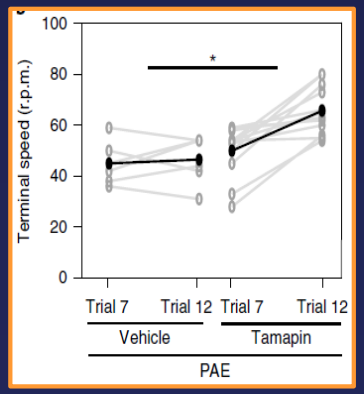
Kcnn2+ cells in the motor cortex are increased in PAE mice compared to control mice, an effect not observed in Hsf1 KO mice. Number of Kcnn2+ cells is negatively correlated with learning.

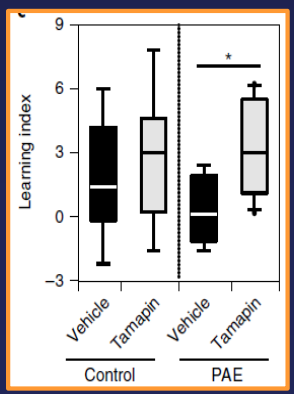




The Kcnn2 channel blocker tamapin increased latency to fall, increased speed, and improved learning in a motor learning task for PAE but not control mice.







Citation: Mohammad S, Page SJ, Wang L, Ishii S, Li, P, Sasaki T, Basha A, Salzberg A, Quezado Z, Imamura F, Nishi H, Isaka K, Corbin JG, Liu JS, Imamura Kawasawa Y, Torii M, and Hashimoto-Torii K. *Nat Neurosci*. 2020 Mar 16.

Concurrent Prenatal Drinking and Smoking Increases Risk for SIDS: Safe Passage Study report

A network of researchers conducted a large-scale study of the outcomes of nearly 12,000 pregnancies among women across multiple study sites with high rates of prenatal alcohol use and SIDS.

Researchers found that infants prenatally exposed to both alcohol and cigarettes beyond the first trimester have a substantially higher risk for SIDS compared to those unexposed, exposed to alcohol or cigarettes alone, or when the mother reported quitting early in pregnancy. These findings further emphasize the role of the early prenatal environment for healthy postnatal outcomes and suggest that screening for substance use early in pregnancy and intervening as soon as possible may help address this public health concern.

Adjusted associations between infant demise and exposures.

	% of alive at1 Year n = 10,727[1]	SIDS and alive at 1 Year n = 10,755		
		SIDS n = 28[2]	RR (CI)[3]	p-value
2-level drinking measure and 2-level smoking measure (in model together, 95% Confidence Intervals)[5]				
Drink (None, quit early)	7752 (73·8%)	11 (0·14%)	1·0	
Drink (Continuous, quit late)	2752 (26·2%)	17 (0·61%)	2·59 (1·14, 5·90)	0·02
Smoke (None, quit early)	6387 (60·8%)	5 (0·08%)	1·0	
Smoke (Continuous, quit late)	4117 (39·2%)	23 (0·56%)	3·84 (1·42, 10·42)	0·008
Primary exposure measure: 4-level drinking and smoking measure				
None, Quit Early	5574 (52·1%)	3 (0·05%)	1·0	
Drink only (Continuous, Quit Late)	913 (8·7%)	2 (0·22%)	3·95 (0·44, 35·83)	0·14
Smoke only (Continuous, Quit Late)	2278 (21·7%)	8 (0·35%)	4·86 (0·97, 24·27)	0·02
Dual (Continuous, Quit Late)	1839 (17·5%)	15 (0·81%)	11·79 (2·59.53·70)	<0·001

RR: Relative risk, CI: confidence interval

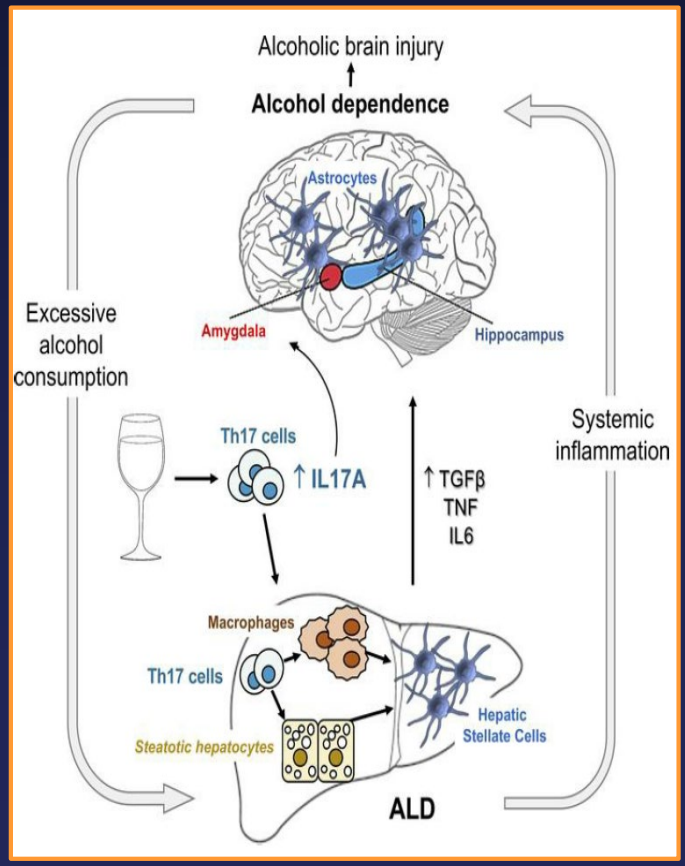
Citation: Elliott AJ, Kinney HC, Haynes RL, Dempers JD, Wright C, Fifer WP, Angal J, Boyd TK, Burd L, Burger E, Folkerth RD, Groenewald C, Hankins G, Hereld D, Hoffman HJ, Holm IA, Myers MM, Nelsen LL, Odendaal HJ, Petersen J, Randall BB, Roberts DJ, Robinson F, Schubert P, Sens MA, Sullivan LM, Tripp T, Van Eerden P, Wadee S, Willinger M, Zaharie D, and Dukes KA. *EClinicalMedicine.* 2020 Jan 20;19:100247

Blockade of IL-17 Signaling Reverses Alcohol-Induced Liver Injury and Excessive Alcohol Drinking in Mice

Using mouse models, this study demonstrated that the pro-inflammatory cytokine IL-17 is involved in both alcohol-induced liver and brain injury and in voluntary drinking behavior. The study also found that IL-17 levels are elevated in both humans who drink alcohol excessively and in alcohol-dependent mice.

Most significantly, results demonstrated that **pharmacological blockade of IL-17 effectively reduces the alcohol-induced liver/brain damage and voluntary drinking in mice**, supporting the translational potential of this approach for treatment of alcohol-related pathology.

IL-17–dependent reactive astrogliosis is a common neuropathology in mice chronically exposed to alcohol. Alcohol-induced liver injury further facilitates systemic inflammation and release of IL-17.



Citation: Xu J et al., Brenner DA, Koob GF, and Kisseleva T. *JCI Insight*. 2020 Feb 13;5(3).

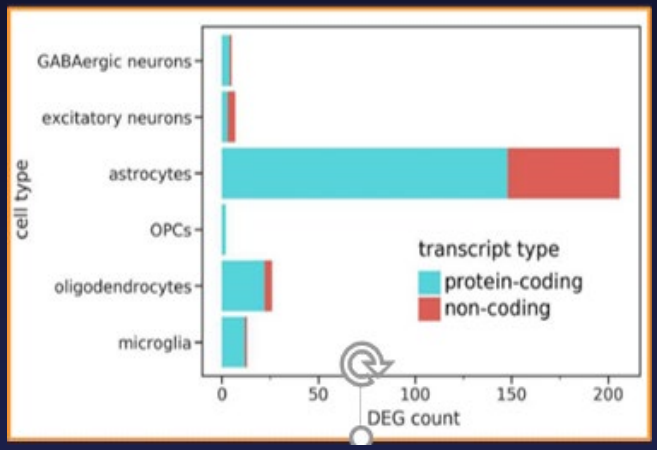
Single Cell Transcriptome Profiling of the Human Alcohol-Dependent Brain

Investigators applied single-cell RNA sequencing to examine gene expression changes in cells of the prefrontal cortex from postmortem brains of people with alcohol use disorder (AUD) and controls.

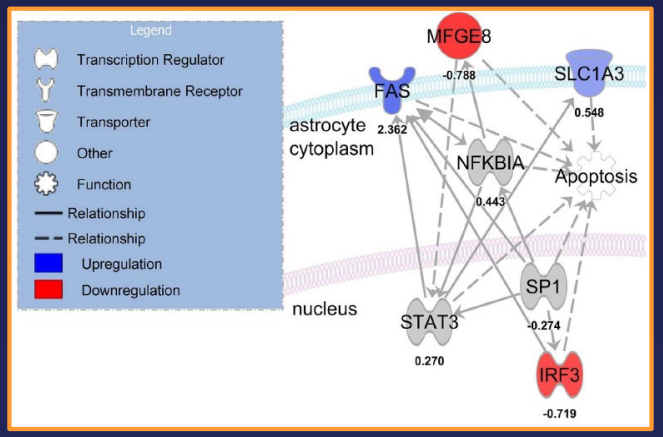
Chronic alcohol exposure altered the expression of multiple genes (coding and non-coding) in all neuronal cell types. The most pronounced expression changes were identified in non-neuronal cells, including astrocytes, oligodendrocytes, and microglia. **Each cell type displayed an increase in the expression of genes linked to neuroinflammation**, a process associated with excessive alcohol use.

This study demonstrates the capacity of single-cell sequencing technology to dissect the complex cell types and gene networks altered in the brains of individuals with AUD.

Differentially expressed genes (DEGs) by cell and transcript type



Four DEGs involved in neuro-inflammation (SLC1A3, FAS, MFGE8, IRF3) were found in astrocytes



Citation: Brenner E, Tiwari GR, Kapoor M, Liu Y, Brock A, and Mayfield RD. *Hum Mol Genet*. 2020;ddaa038.

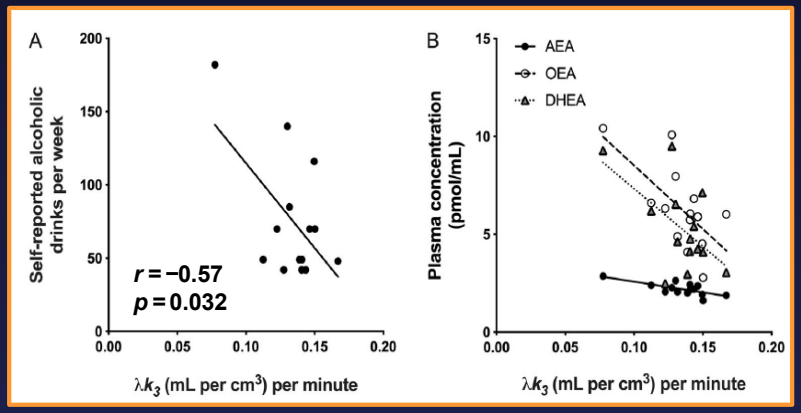
Lower Brain Fatty Acid Amide Hydrolase in Treatment-Seeking Patients with Alcohol Use Disorder: A Positron Emission Tomography Study with [C-11]CURB

Fatty acid amide hydrolase (FAAH), an enzyme that metabolizes the endogenous cannabinoid anandamide, has been implicated in alcohol use disorder (AUD). This study used positron emission tomography with a carbon-11 radiotracer to measure FAAH binding in the brains of individuals with AUD during early and protracted abstinence from alcohol compared to healthy controls.

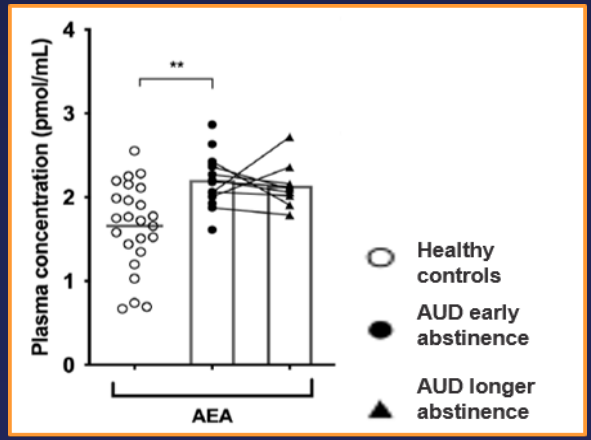
Brain levels of FAAH were lower during early abstinence (3-7 days) in individuals with AUD and were correlated with elevated anandamide levels and a higher number of drinks per week prior to abstinence. FAAH levels appeared to normalize after 2-4 weeks of monitored abstinence.

These findings suggest that an endocannabinoid-elevating process may be associated with heavy drinking in AUD, implying a unique target for therapeutic intervention in the brain.

During early abstinence, FAAH levels negatively correlated with drinks per week and plasma concentrations of the three FAAH substrates



Anandamide (AEA) is significantly elevated in AUD patients in early abstinence.



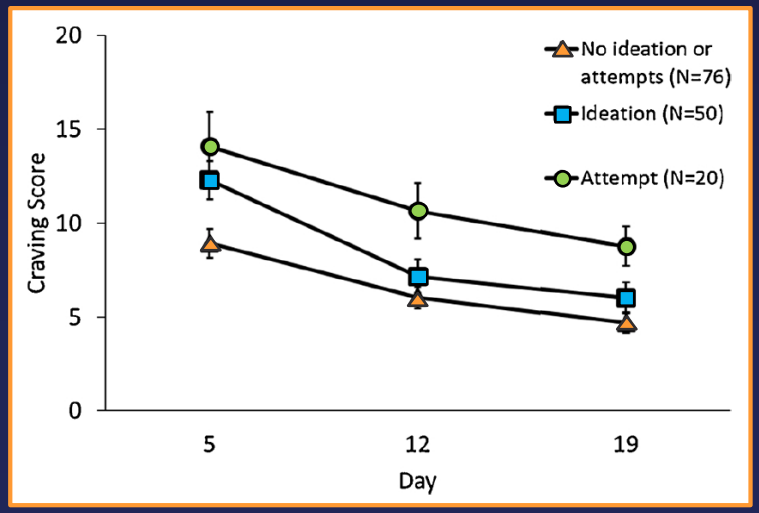
Citation: Best LM, Williams B, Le Foll B, Mansouri E, Bazinet RP, Lin L, De Luca V, Lagzdins D, Rusjan P, Tyndale RF, Wilson AA, Hendershot CS, Heilig M, Houle S, Tong J, Kish SJ, and Boileau I. *Neuropsychopharmacology.* 2020 Jan 7.

History of Suicidality and Alcohol Craving Trajectories During Inpatient Treatment for Alcohol Use Disorder

To determine whether past suicidality affects the course of alcohol use disorder (AUD), researchers examined whether previous suicidal ideation or attempts are associated with treatment response in individuals with AUD. Participants undergoing detoxification and residential treatment for AUD were assessed for history of suicidal ideation with or without suicide attempts, and alcohol craving was measured weekly during treatment.

Individuals with a history of suicide attempts showed higher levels of craving throughout treatment compared to those without a history of suicidality. These results support current guidelines on assessing suicidal ideation in patients with substance use disorders.

Craving over time during inpatient treatment for AUD based on history of suicidal ideation or attempts

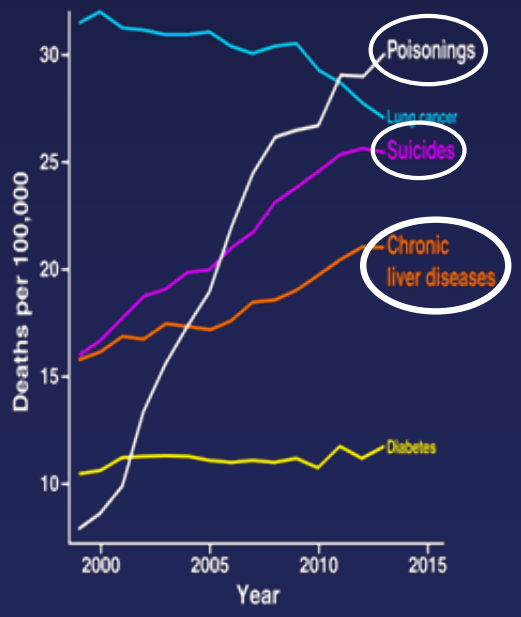


Citation: Janakiraman R, Gowin JL, Sloan ME, Schwandt ML, Diazgranados N, Ramchandani VA and Kwako LE. *Drug Alcohol Depend.* 2020 Apr 1;209:107918.

A New Report Highlights Changes in Alcohol-Related Deaths in the United States

- Alcohol-related deaths **doubled** from 1999 to 2017
  - Death rates were highest among men and middle-aged and older adults (ages 45-74)
  - Death rates increased over time across all age groups except 16-20 and 75+
  - Increase in death rate over time was greater in women than men
- These statistics align with other recent reports that have highlighted changing trends in drinking patterns and increased consequences of alcohol in **women** and the **aging population**
- Alcohol plays a prominent role in **"deaths of despair"**, contributing to:
  - 15-20% of all drug overdoses
  - 26% of suicides
  - 50% of liver disease deaths

Mortality by cause among White non-Hispanics (age 45-54)



Case and Deaton, 2015

Citation: White AM, Castle IP, Hingson RW, and Powell PA. 2020. *ACER*. 44 (1):178-187

Alcoholics Anonymous and Other 12-Step Programs for Alcohol Use Disorder

This systematic review examined outcomes of over 10,000 participants from 27 studies that compared peer-led Alcoholics Anonymous (AA) or professionally delivered Twelve-Step Facilitation (TSF) with other behavioral interventions such as motivational enhancement therapy or cognitive-behavioral therapy, TSF treatment variants, or no treatment.

Across a variety of measures, **AA performed at least as well as other behavioral treatments for AUD**, and AA was more effective in increasing abstinence. These results suggest that AA and TSF can offer a low-cost, effective treatment option for maintaining abstinence among those with AUD.

Comparison of AA/TSF to other behavioral interventions

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		Risk with other clinical interventions	Risk with AA/TSF			
Abstinence	Proportion of participants (%) completely abstinent Follow-up: 12 months	Study population 345 per 1000	418 per 1000 (356 to 490)	RR 1.21 (1.03 to 1.42)	1936 (2 RCTs)	⊕⊕⊕⊕ High
	PDA Follow-up: 12 months	The mean PDA in the comparison group ranged from 62.3% to 84.0%	MD 3.03 higher (4.36 lower to 10.43 higher)	-	1999 (4 RCTs)	⊕⊝⊝⊝ Very low [a, b, c]
	LPA Follow-up: 6 months	The mean LPA in the comparison group ranged from 0.47 to 1.71 months	MD 0.60 higher (0.30 lower to 1.50 higher)	-	136 (2 RCTs)	⊕⊕⊝⊝ Low [d, e]
Drinking Intensity	Drinks per drinking day Follow-up: 12 months	The mean DDD in the comparison group ranged from 4.66 to 5.38	MD 0.17 lower (1.11 lower to 0.77 higher)	-	1516 (1 RCT)	⊕⊕⊕⊝ Moderate [c]
	PDHD Follow-up: 12 months	The mean PDHD in the comparison group was 13.4%	MD 5.51 lower (14.15 lower to 3.13 higher)	-	91 (1 RCT)	⊕⊕⊝⊝ Low [f]
Alcohol-related consequences (assessed with DrInC) Follow-up: 12 months		The mean DrInC in the comparison group ranged from 21.8% to 72.9%	MD 2.88 lower (6.81 lower to 1.04 higher)	-	1762 (3 RCT)	⊕⊕⊕⊝ Moderate [c]
Alcohol addiction severity (assessed with ASI) Follow-up: 12 months		One study found an advantage for the AA/TSF intervention relative to the comparison intervention in the slope for improvement over a 12-month follow-up period (Brooks 2003), as measured by the ASI alcohol composite score ($P < 0.05$).			112 (1 quasi-RCT)	⊕⊕⊝⊝ Low [a, g]

Citation: Kelly J, Humphreys K, and Ferri M. *Cochrane Database Syst Rev*. 3(3) CD012880 2020 Mar 11.

THANK YOU!

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