Institute of Medical Science
UNIVERSITY OF TORONTO

camh Centre for Addiction and Mental Health

Can Molecular Imaging Help Move Forward Endocannabinoid-focused Treatments For Psychiatric Illness?

THE PENN-YALE PET ADDICTION CENTER OF EXCELLENCE

23RD OF NOVEMBER, 2020

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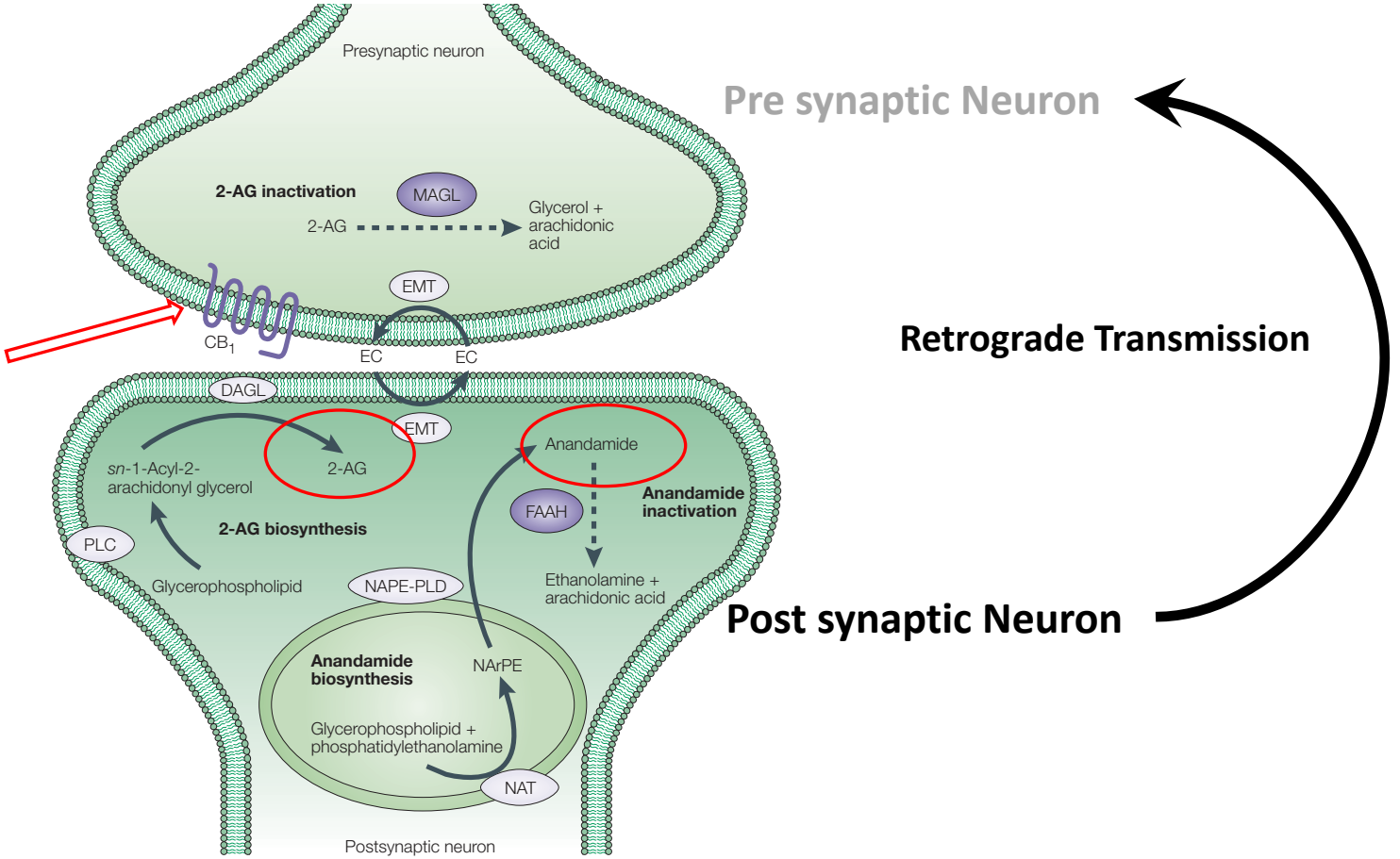
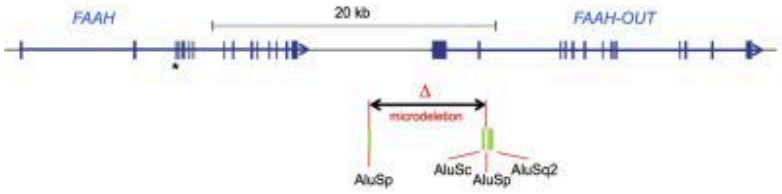
The Endocannabinoid System and FAAH

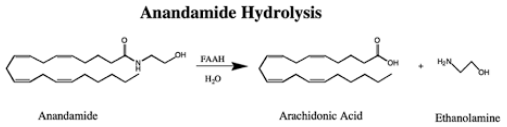


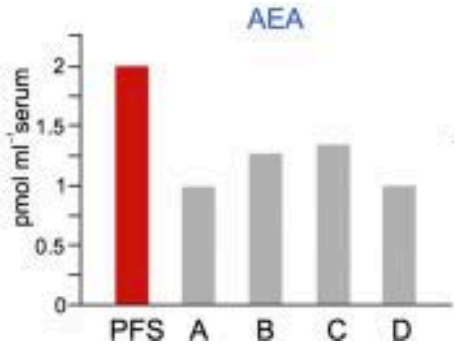
Joanne Cameron's "World without Pain": the coinheritance of two FAAH mutations

Microdeletion in a *FAAH* pseudogene identified in a patient with high anandamide concentrations and pain insensitivity

Abdella M. Habib[1,2], Andrei L. Okorokov[1], Matthew N. Hill[3], Jose T. Bras[4,5], Man-Cheung Lee[1,6,7], Shengnan Li[1], Samuel J. Gossage[1], Marie van Drimmelen[8], Maria Morena[3], Henry Houlden[5], Juan D. Ramirez[9], David L. H. Bennett[9], Devjit Srivastava[10,*] and James J. Cox[1,*]

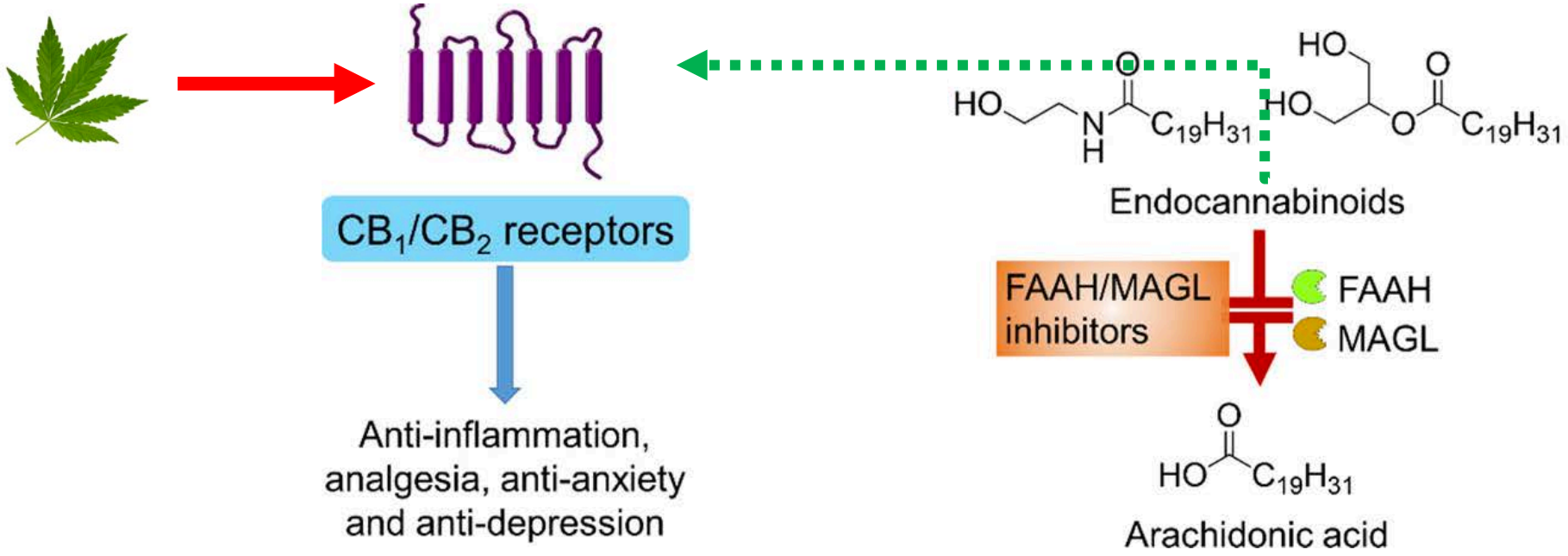






Photograph by Kamila Lozinska for The New Yorker

ECS Enzyme Inhibitors : Inspired By The Medicinal Properties Of Cannabis



J. Med. Chem. 2017, 60, 1, 4–46

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Development of CNS Disorders Drugs: Can PET help?

REQUIREMENTS FOR SUCCESSFUL NEW TREATMENTS:

1. **The disease / condition must be well understood**
2. **A molecular target linked with the disease process must be identified**
3. Develop synthetically feasible, stable, drug-like molecule (desired potency, selectivity, PK / PD and toxicity properties).
4. Advance to IND-enabling studies and Phase 1-III

PET CAN SUPPORT: KEY DECISIONS

1. Providing proof of concept (proof of biology) CNS imaging in humans
2. Detect and measure expression of molecular target
3. Measure and track drug engagement with molecular target (Target occupancy relationship) and
4. Establish evidence of treatment response

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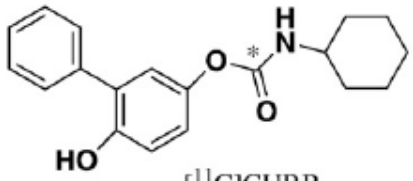
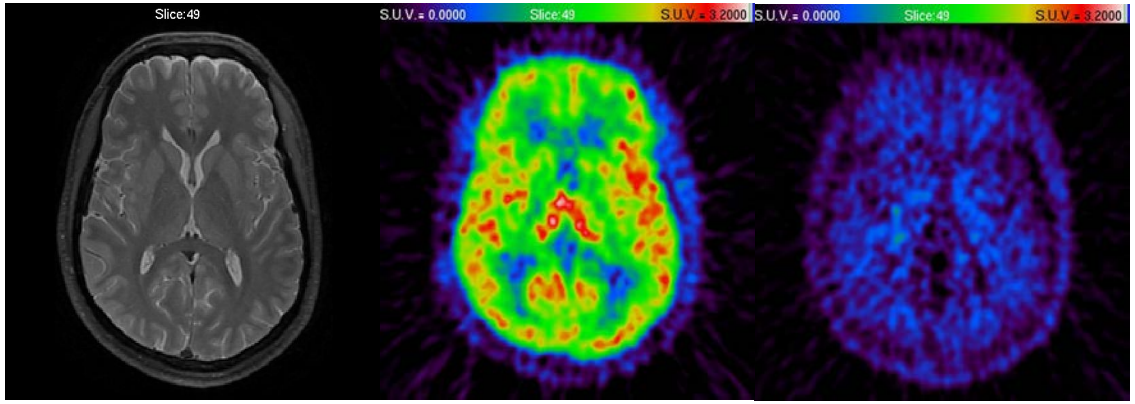
[^{11}C]CURB: PET Tracer for Fatty Acid Amide Hydrolase



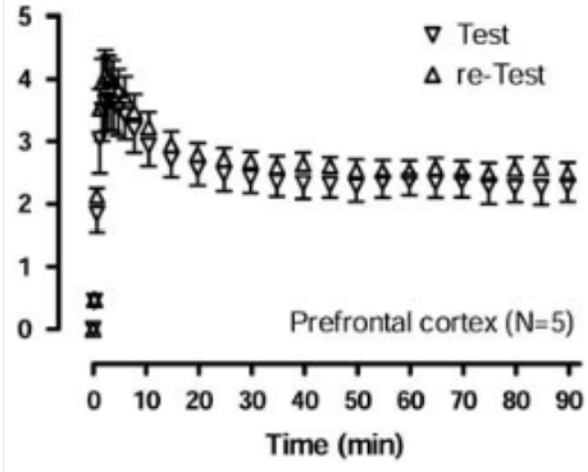
[^{11}C]CURB

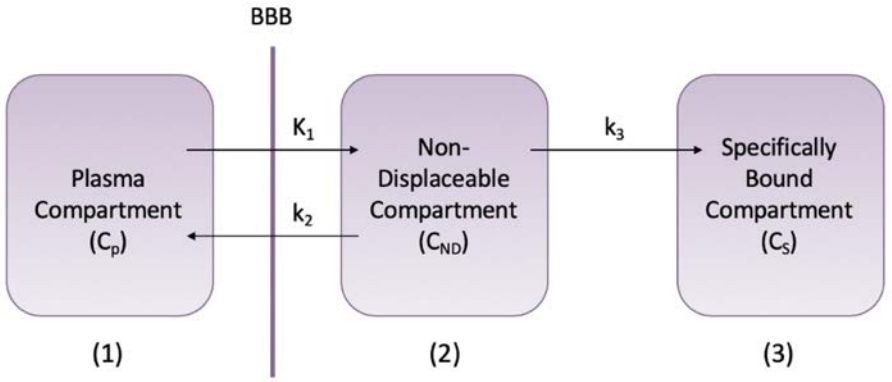
* denotes position of the ^{11}C radiolabel



Baseline [^{11}C]CURB

PF-04457845 (4 mg)





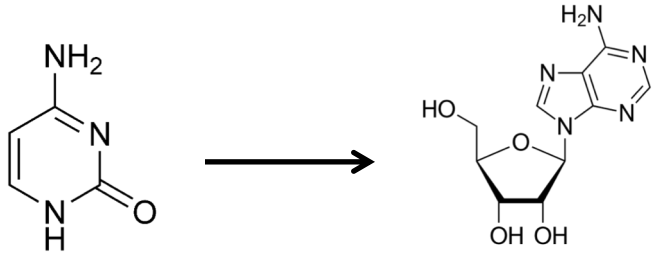
Objective

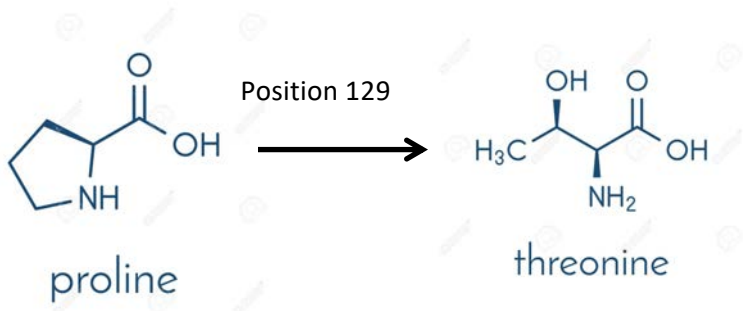
To use brain PET imaging of FAAH with [^{11}C]CURB to gain a better understanding of whether endocannabinoid metabolism in humans relates to:

- Psychiatric illnesses (substance use disorders, PTSD and anxiety disorder)
- Risk phenotypes

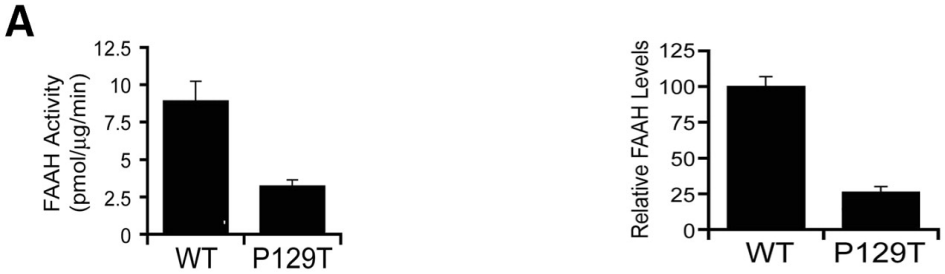
FAAH C385A polymorphism: loss-of-function mutation

A functional non-synonymous missense mutation → ↑ sensitivity to proteolytic degradation





FAAH expression and activity in human peripheral blood T-lymphocytes.



(Sipe et al., 2002; Chiang et al. 2004)

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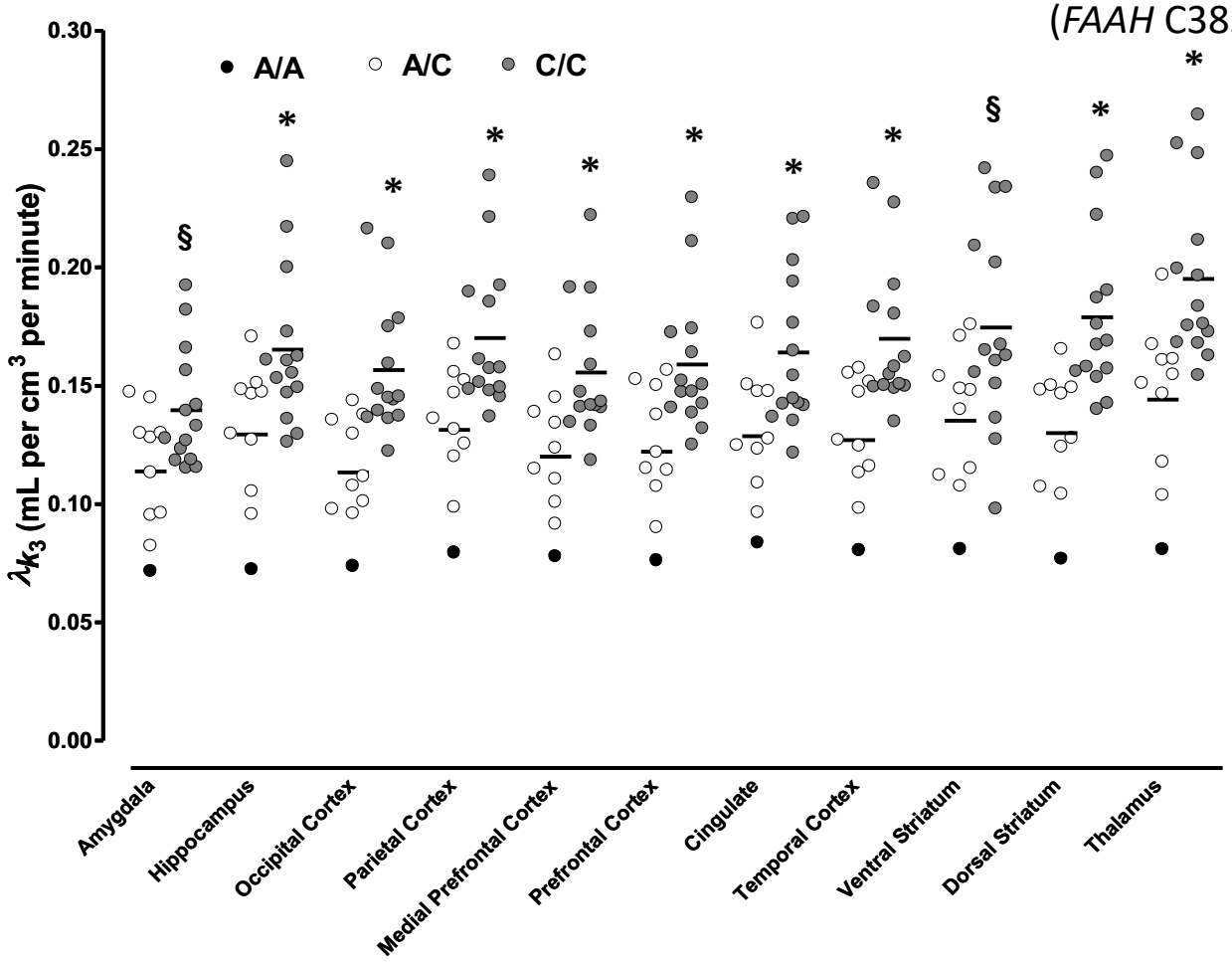
BRIEF COMMUNICATION

The fatty acid amide hydrolase C385A variant affects brain binding of the positron emission tomography tracer [^{11}C]CURB

Isabelle Boileau[1,2,3,4,5,6], Rachel F Tyndale[3,5,7], Belinda Williams[1,2,3,4], Esmaeil Mansouri[1,2,3,4], Duncan J Westwood[1,2,3,4,6], Bernard Le Foll[3,5,6,7], Pablo M Rusjan[4,5], Romina Mizrahi[3,4,5,6], Vincenzo De Luca[3,5,6], Qian Zhou[7], Alan A Wilson[3,4], Sylvain Houle[3,4], Stephen J Kish[2,3,4,5,6,7] and Junchao Tong[2,3,4,5]

Evidence that a SNP affecting FAAH (*FAAH* C385A) is functional in brain .



FAAH C385A Behavioral phenotype: Human

AVOIDANCE BEHAVIOR

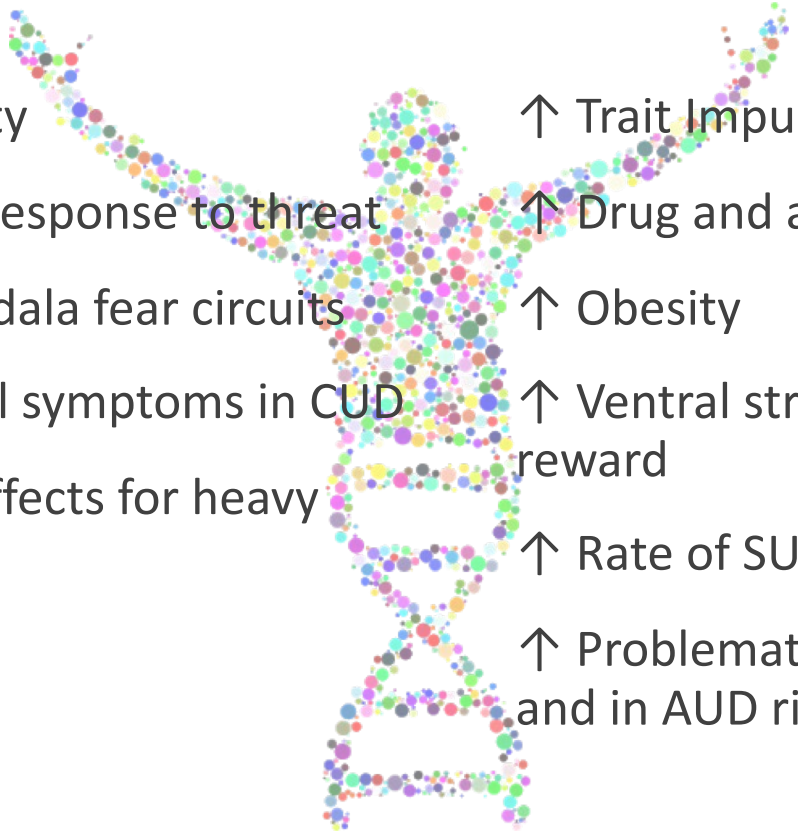
↓Trait Anxiety

↓Amygdala response to threat

↑FC in amygdala fear circuits

↓Withdrawal symptoms in CUD

↓Negative effects for heavy drinking



REWARD / APPROACH BEHAVIOR

↑ Trait Impulsivity

↑ Drug and alcohol use

↑ Obesity

↑ Ventral striatum response to reward

↑ Rate of SUD (sedative drugs)

↑ Problematic drinking in AUD and in AUD risk

FAAH KO & C385A KI Behavioral phenotype: Mice

↓Fear avoidance

↑ Pain threshold

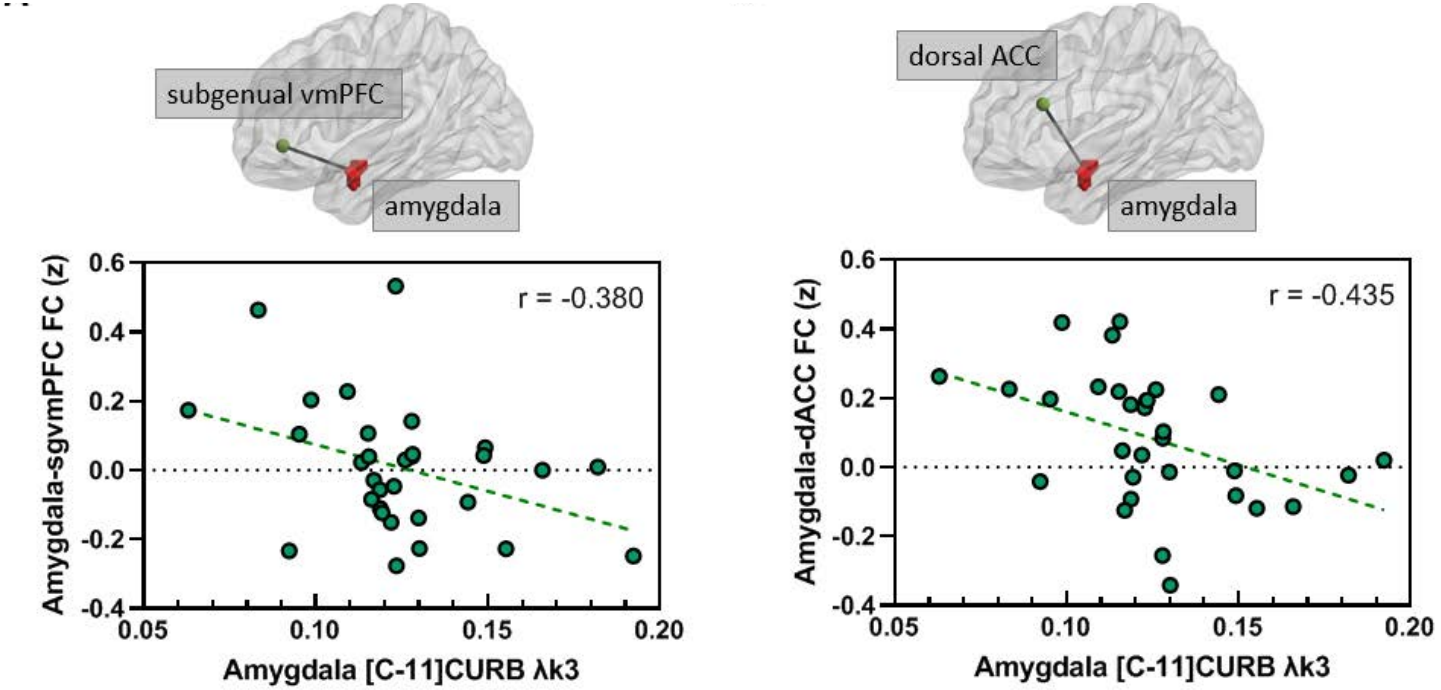
↑FC in amygdala fear circuits

↑ Alcohol intake

↓Acute effects of alcohol

Is FAAH elevated in “fear” related conditions (PSTD and Social anxiety) and associated with ”fear” circuits ?

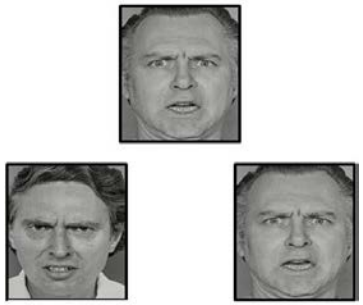
FAAH is negatively associated with amygdala functional connectivity in HC (N = 31)

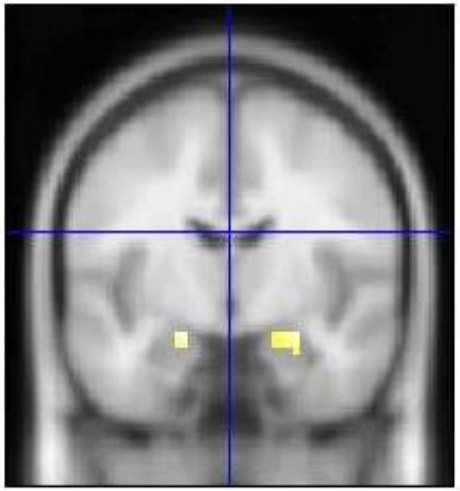


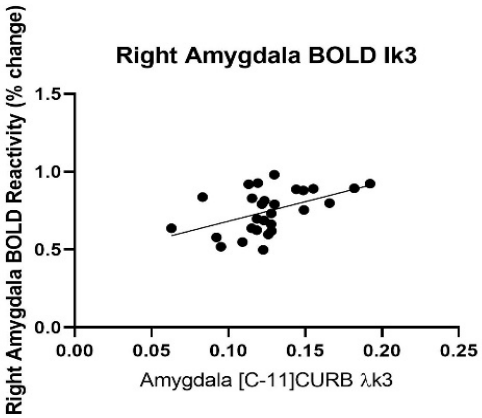
- FAAH affects amygdala circuitry involved in fear and emotion processing
- Drug that inhibit FAAH may regulate this circuit know to be abnormally functioning in PTSD, anxiety and mood disorder.

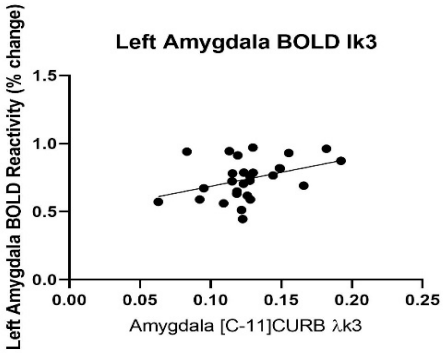
Green et al. 2020, JNP

FAAH is positively associated with amygdala reactivity to threat in HC (N = 28)









- Higher FAAH levels is associated with amygdala hyper reactivity to threat
- FAAH inhibitors may decrease hyper-reactivity to threat

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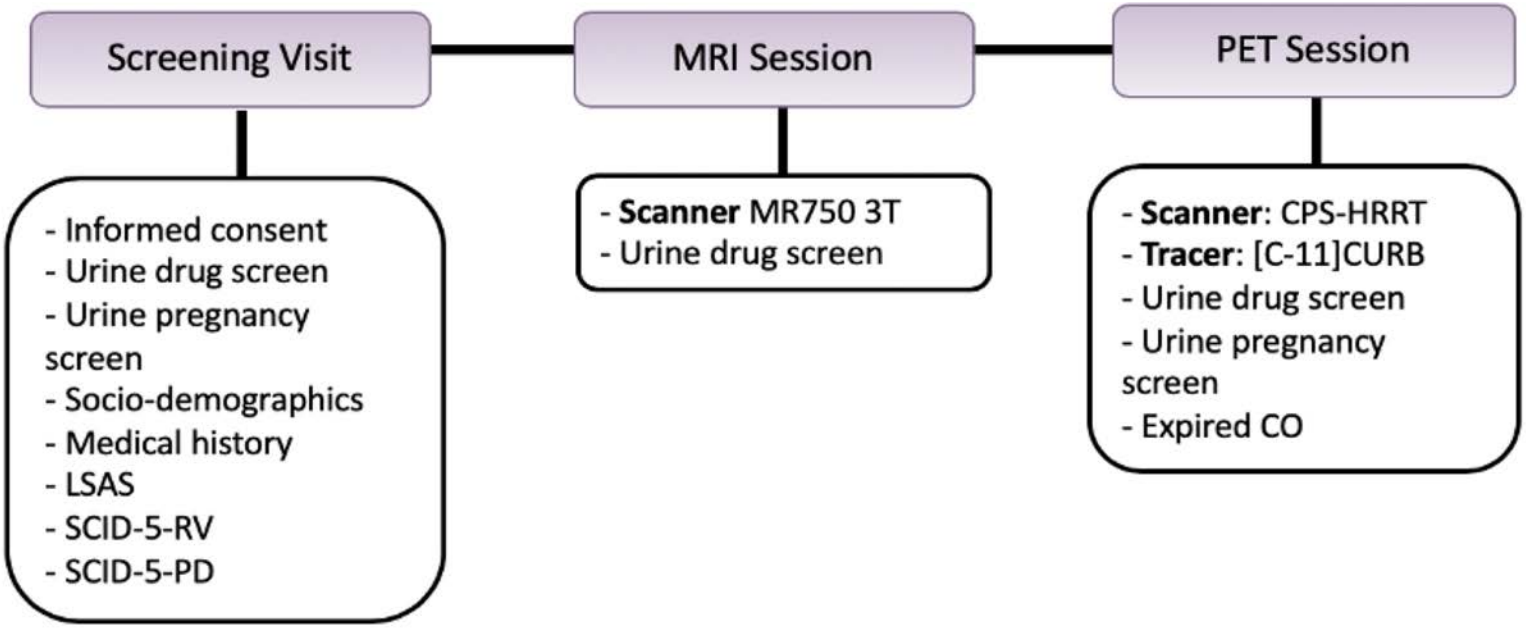
Elevated Anandamide, Enhanced Recall of Fear Extinction, and Attenuated Stress Responses Following Inhibition of Fatty Acid Amide Hydrolase: A Randomized, Controlled Experimental Medicine Trial

Leah M. Mayo, Anna Asratian, Johan Lindé, Maria Morena, Roosa Haataja, Valter Hammar, Gaëlle Augier, Matthew N. Hill, and Markus Heilig

FAAH inhibitor PF-04457845

- ↑levels of AEA (10 fold)
- ↓fear learning (startle)
- ↓autonomic stress reactivity (EDR)
- ↓ stress-induced affective responses (facial EMG)
- FAAH inhibition = ↓ response to fear and anxiogenic effects of stress.

Cross-sectional study design



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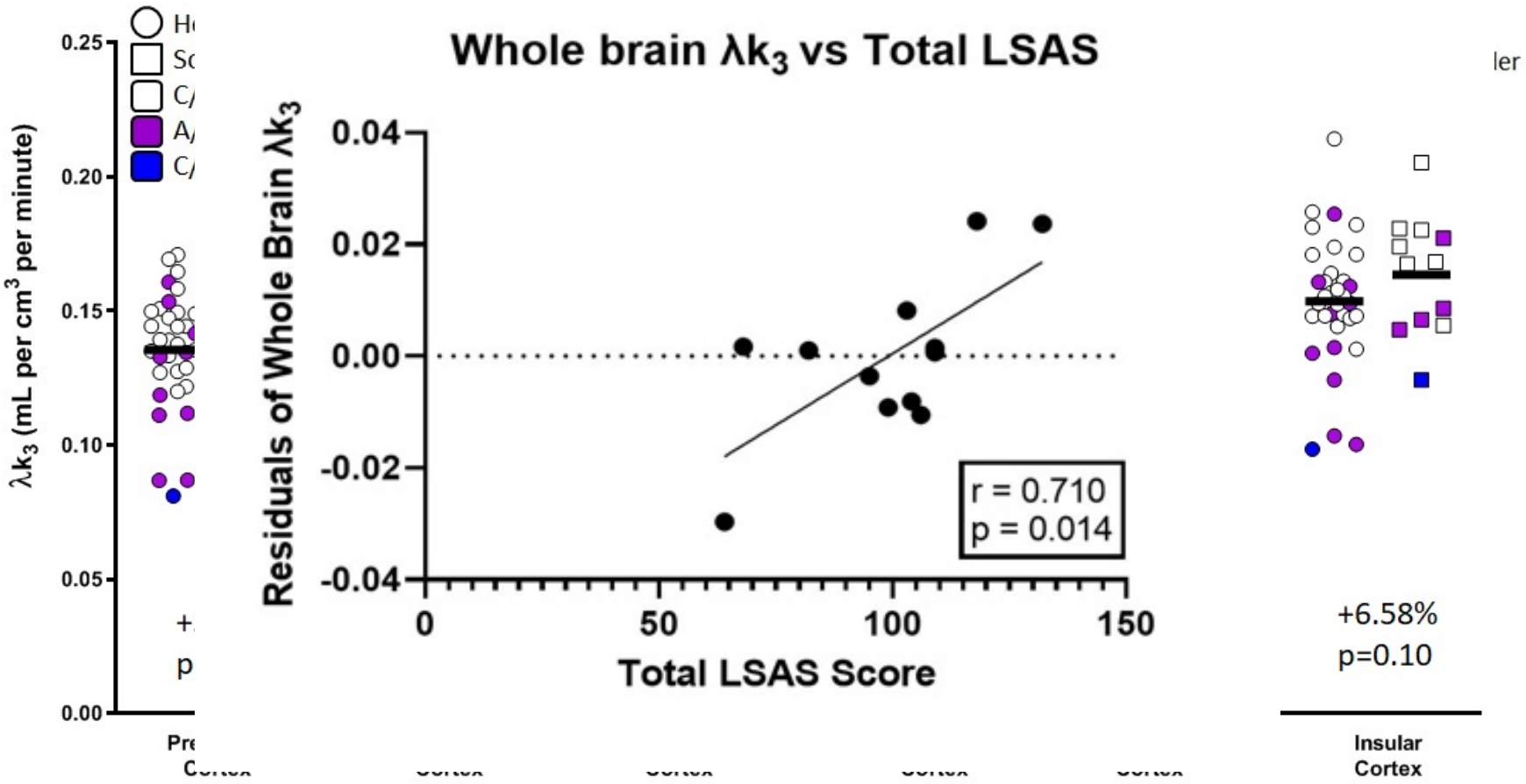
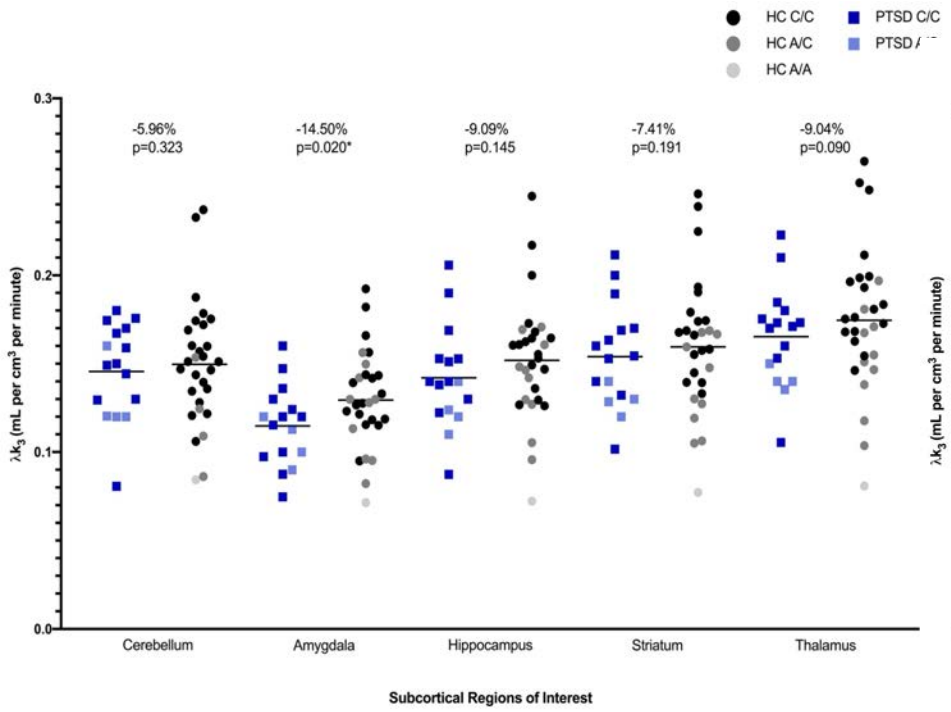
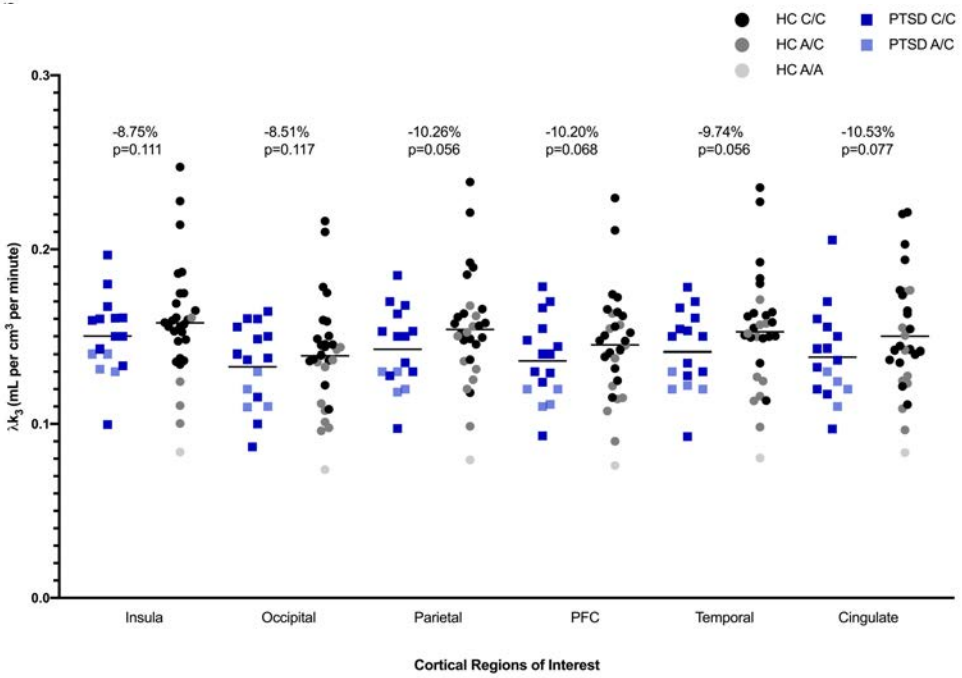
FAAH is marginally elevated in Social Anxiety (N = 12 SAD vs 34 HC)



FAAH is NOT elevated in PTSD (N = 16 PTSD vs 29 HC)





Summary

- Multimodal imaging data in HC are in line with models suggesting that up regulated FAAH may contribute to abnormal fronto-amygdala circuit function.
- These findings support use of FAAH inhibitors in disorders in which abnormalities in these circuits are suspected.
- Our finding in SAD support the view that upregulated FAAH may contribute to the pathology
- Our findings in PTSD are not in line with “imperfect” animal models of PTSD in which differences in timeline or acute state may explain discrepant findings

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Is FAAH lower in substance use disorders?

Testing the hypothesis that SUD would be associated with of lower levels of FAAH

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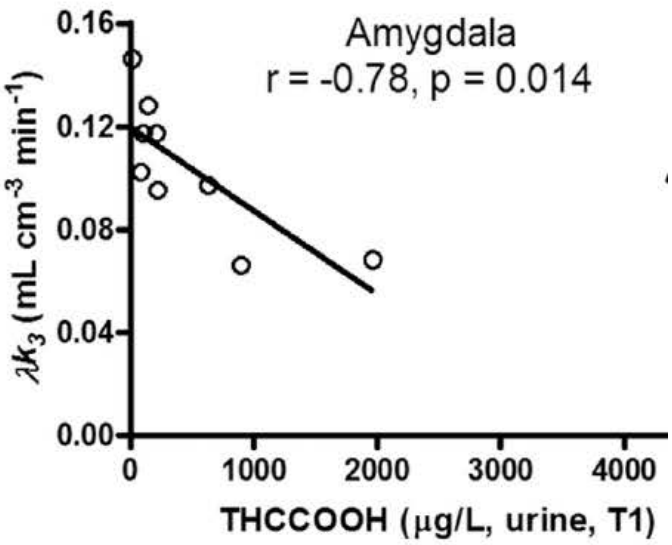
FAAH Inhibitors as a Substitution Therapy in CUD(?)

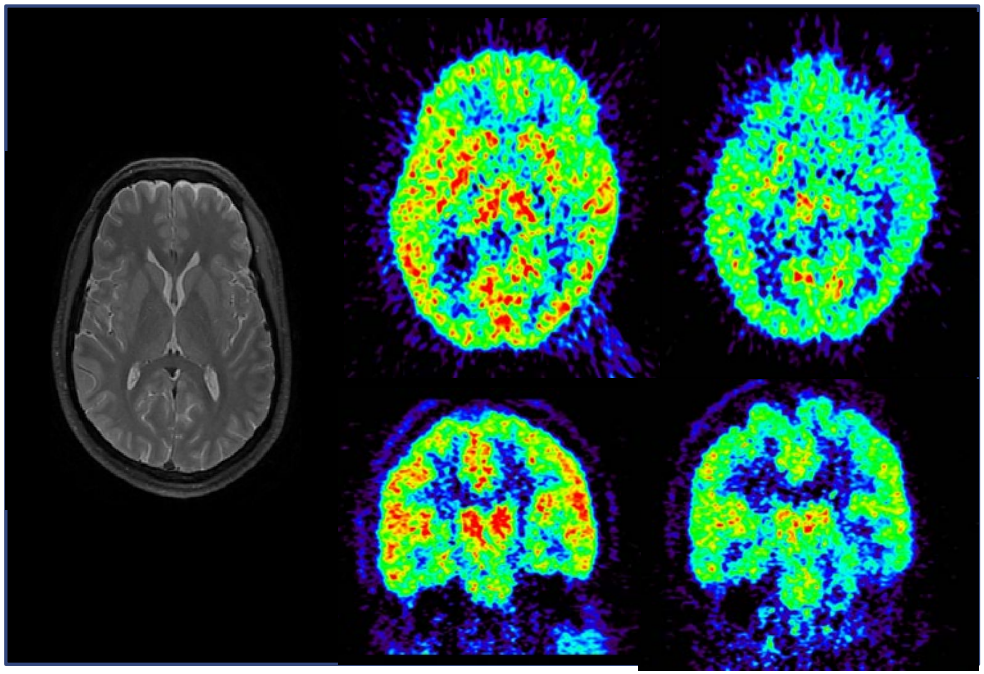
Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence in men: a double-blind, placebo-controlled, parallel group, phase 2a single-site randomised controlled trial

Deepak Cyril D'Souza, Jose Cortes-Briones, Gina Creatura, Grai Bluez*, Halle Thurnauer*, Emma Deaso, Kim Bielen, Toral Surti, Rajiv Radhakrishnan, Aarti Gupta, Swapnil Gupta, John Cahill, Mohamed A Sherif, Alexandros Makriyannis, Peter T Morgan, Mohini Ranganathan†, Patrick D Skosnik†*

FAAH is lower in CUD in early abstinence and correlated with THC metabolites

Heavier more recent use of cannabis ↓ FAAH





HC CUD

Alcohol-induced changes in brain FAAH levels in preclinical studies and clinical investigations of AUD

FAAH KO/KI ↑ DRINKING AND AUD SEVERITY

FAAH IN PMB – INCONSISTENT FINDINGS

Involvement of Endocannabinoids in Alcohol "Binge" Drinking: Studies of Mice with Human Fatty Acid Amide Hydrolase Genetic Variation and After CB1 Receptor Antagonists

Yan Zhou, Ted Huang, Francis Lee, and Mary Jeanne Kreek

Selective alterations of the CB1 receptors and the fatty acid amide hydrolase in the ventral striatum of alcoholics and suicides

K. Yaragudri Vinod[a,b,c,*], Suham A. Kassir[d], Basalingappa L. Hungund[a,c,e], Thomas B. Cooper[a,c,e], J. John Mann[d,e], and Victoria Arango[d,e]

Addiction Biology
SSA
ORIGINAL ARTICLE
doi:10.1111/adb.12491

Severity of alcohol dependence is associated with the fatty acid amide hydrolase Pro129Thr missense variant

Matthew E. Sloan[1], Joshua L. Gowin[1], Jia Yan[1], Melanie L. Schwandt[2], Primavera A. Spagnolo[2], Hui Sun[2], Colin A. Hodgkinson[3], David Goldman[2,3] & Vijay A. Ramchandani[1]

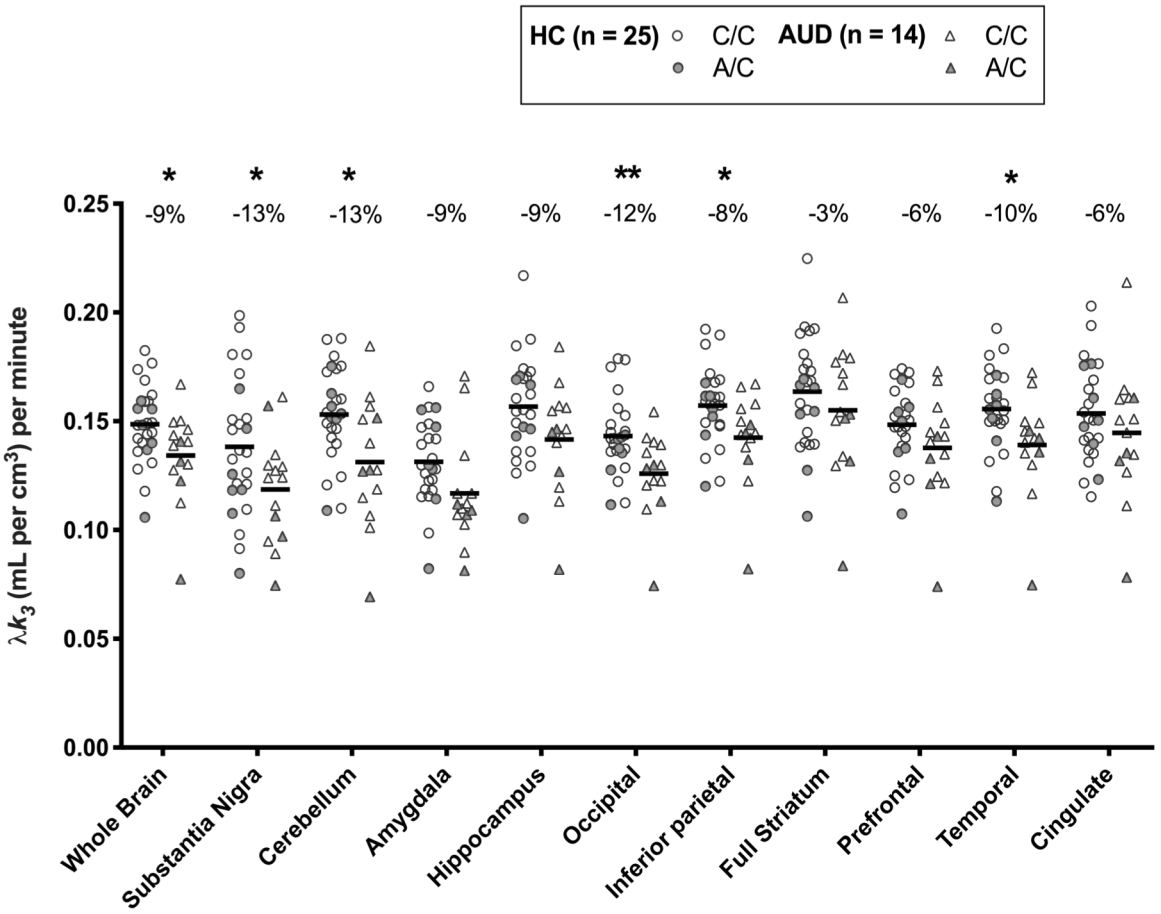
Section on Human Psychopharmacology, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD USA[1], Office of the Clinical Director, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD USA[2] and Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, Rockville, MD USA[3]

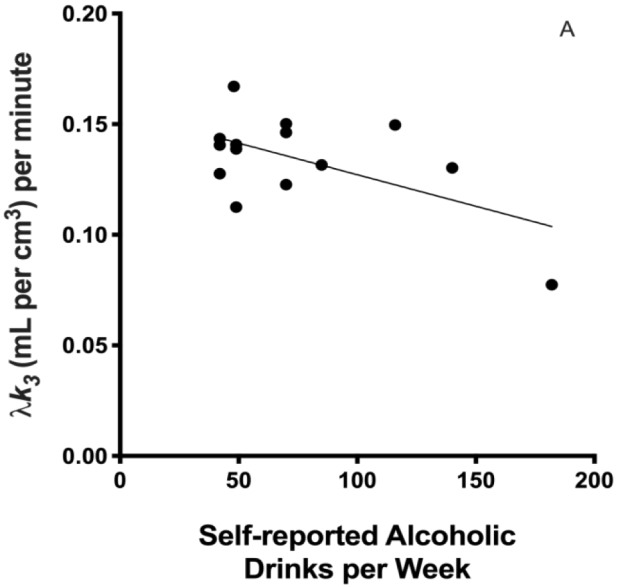
Addiction Biology
SSA
CLINICAL STUDY
doi:10.1111/adb.12160

The endocannabinoid system is altered in the post-mortem prefrontal cortex of alcoholic subjects

Amaia M. Erdozain[1,2†], Marina Rubio[3], Elsa M. Valdizan[2,4], Angel Pazos[2,4], J Javier Meana[1,2,5], Javier Fernández-Ruiz[3,6,7], Stephen P. H. Alexander[8] & Luis F. Callado[1,2,5]

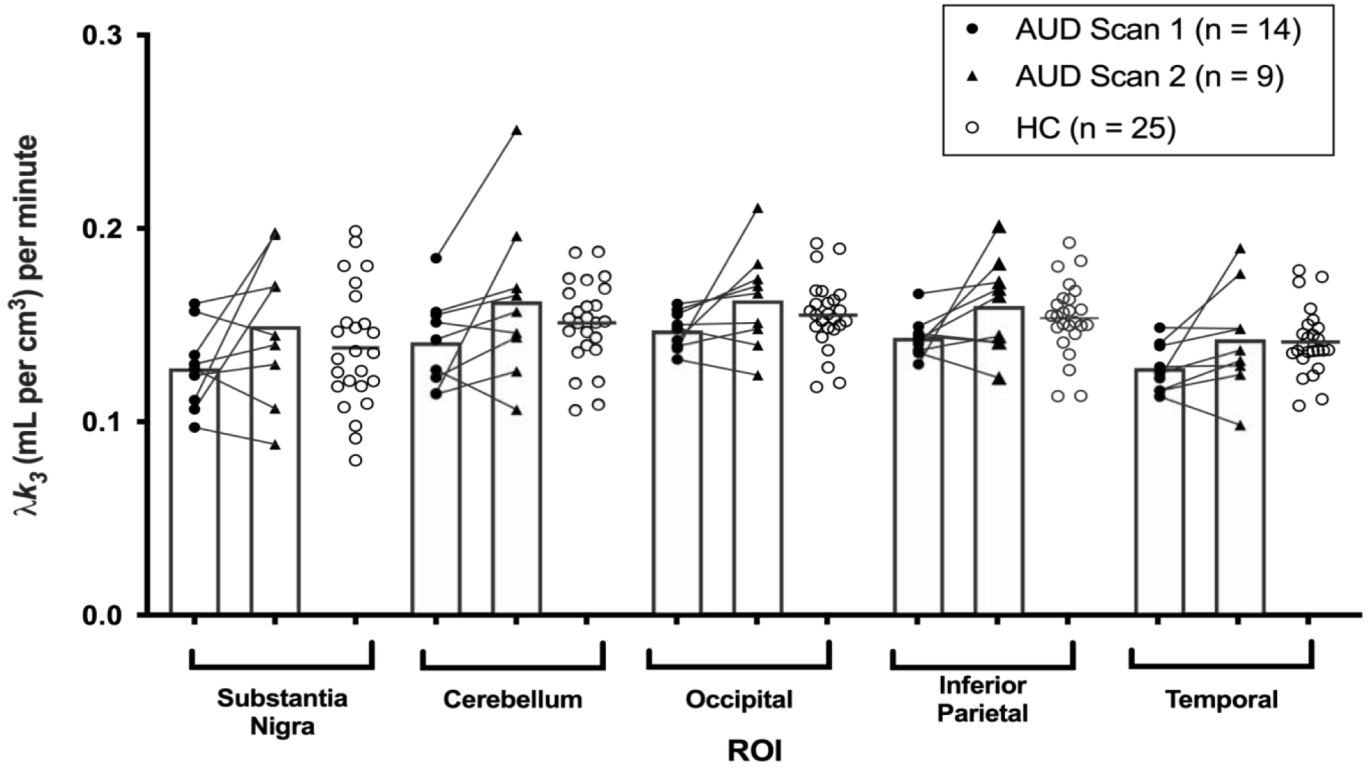
FAAH is lower in AUD in early abstinence and correlated with drinks a week (N = 14 AUD vs 25 HC)





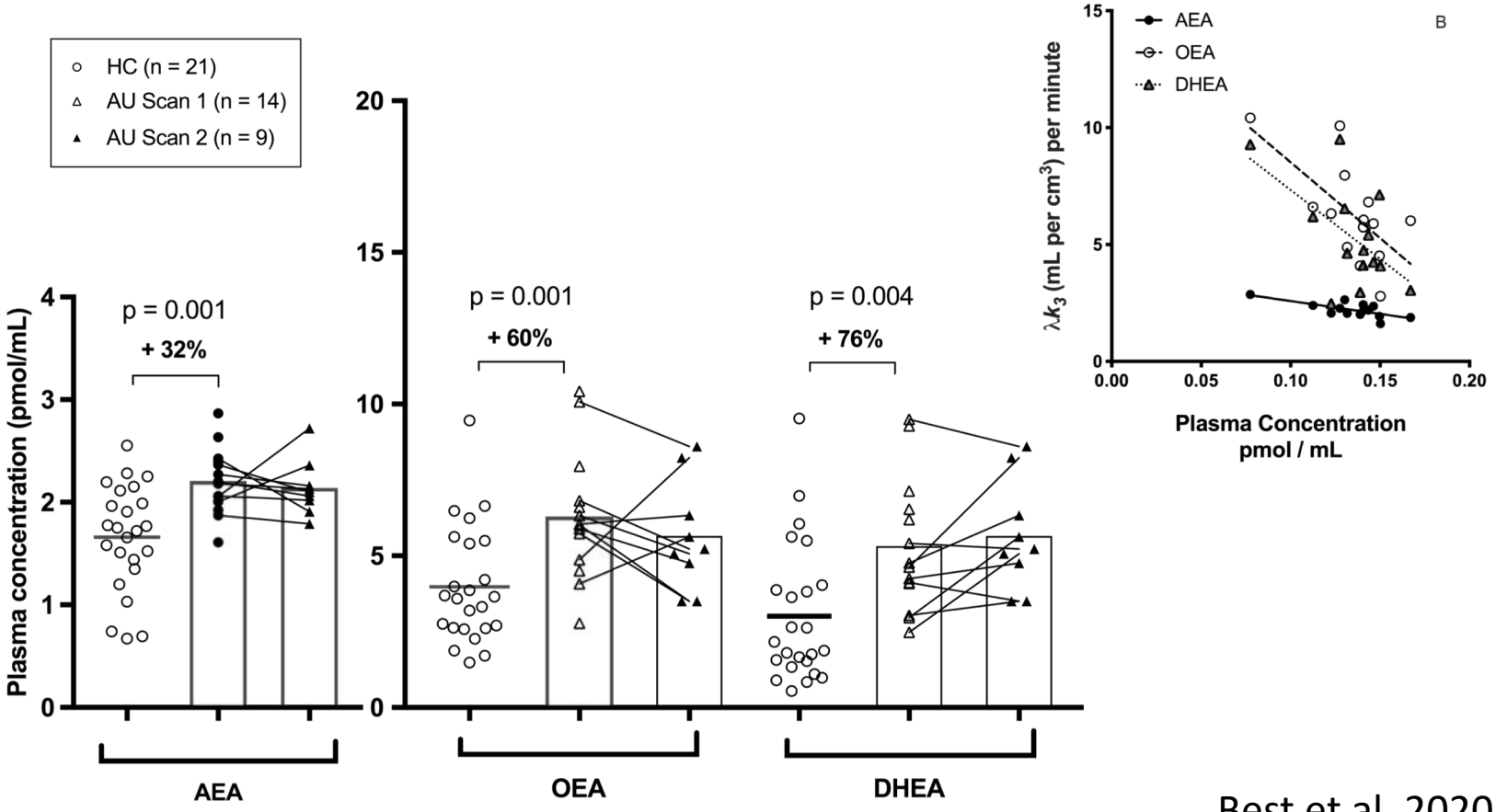
Best et al. 2020 NPP

Low FAAH may be transient



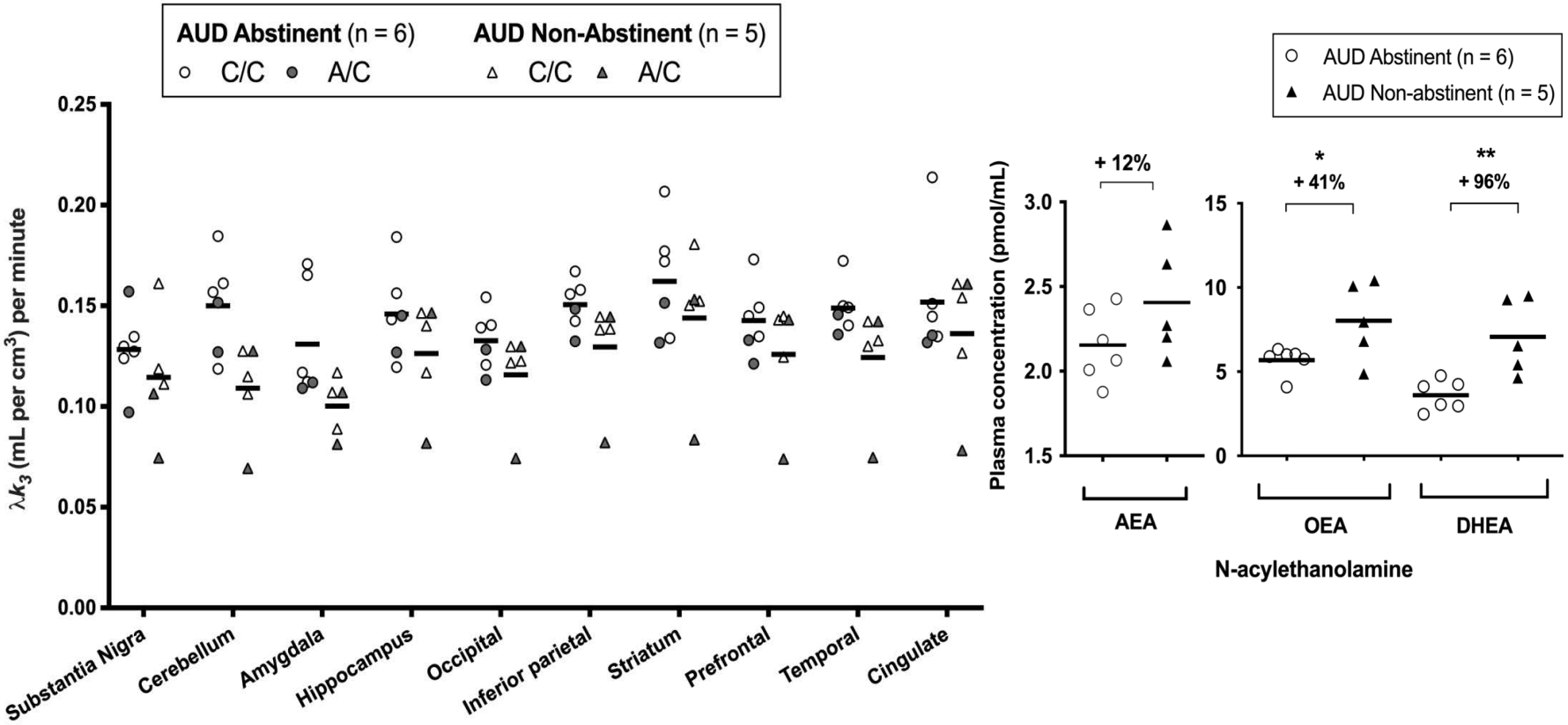
Best et al. 2020 NPP

FAAH substrates are elevated in AUD in early abstinence



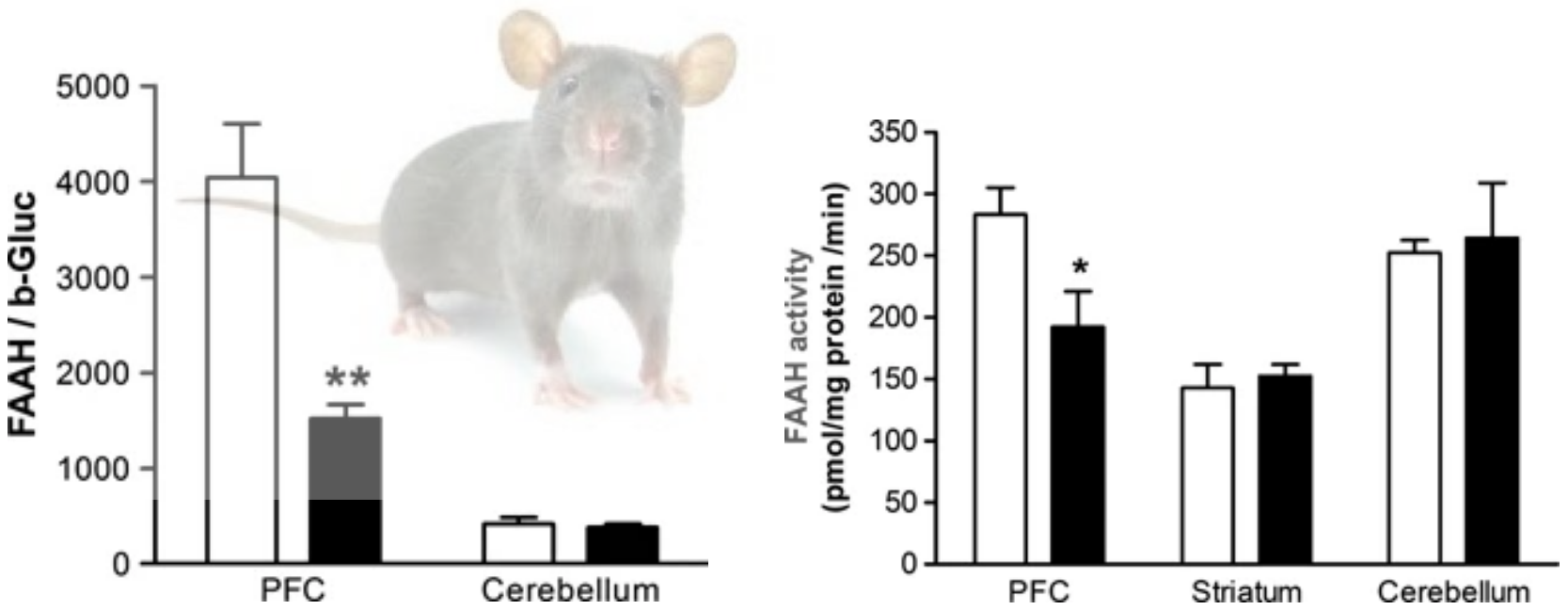
Best et al. 2020 NPP

Brain FAAH is marginally lower in people that relapse



Best et al. 2020 NPP

Impaired FAAH function : Phenotype for high alcohol intake and potential vulnerability factor



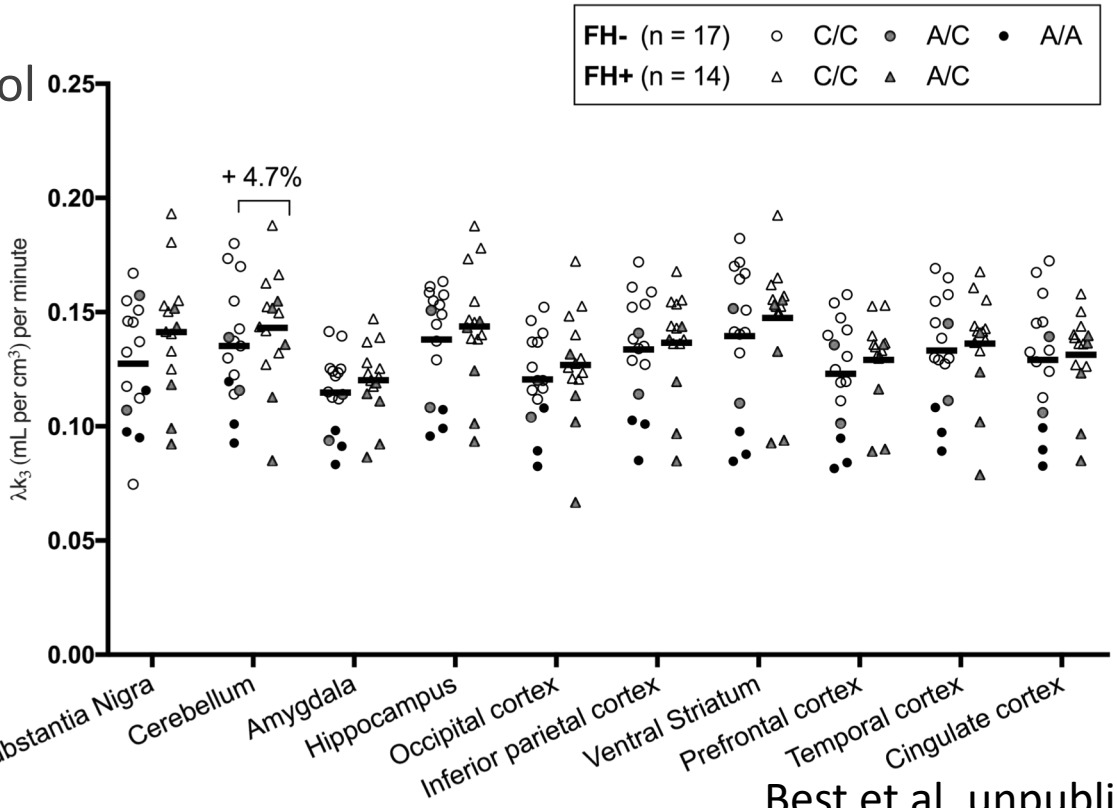
Hansson 2007

Do FAAH levels vary with risk for AUD?

Family history

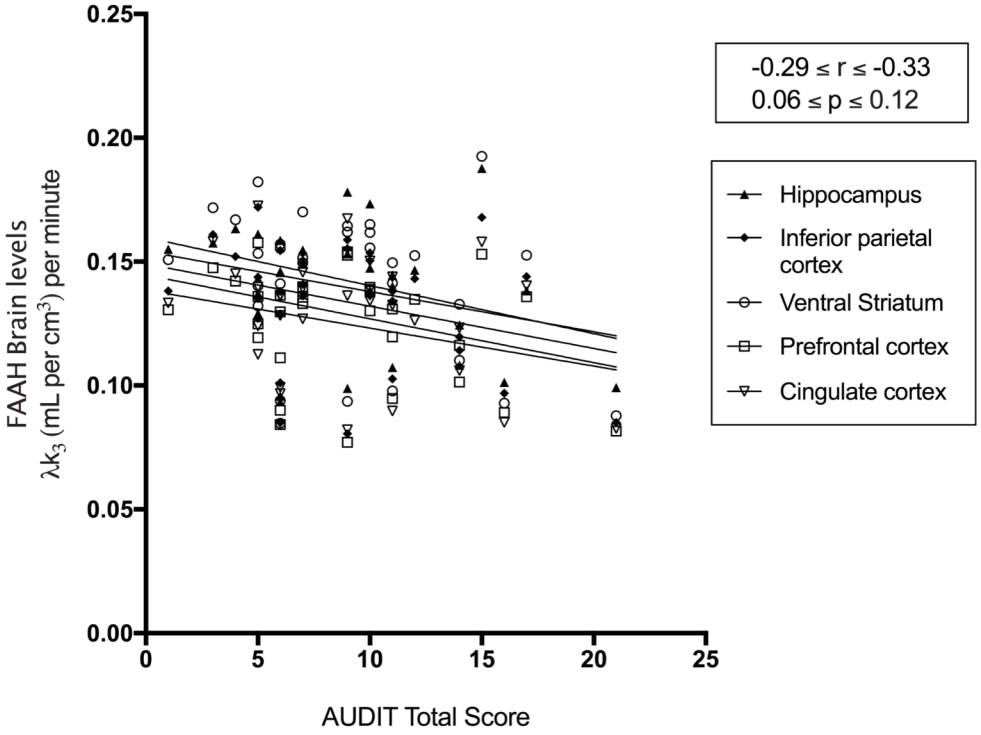
Self-reported effects of alcohol during alcohol infusion

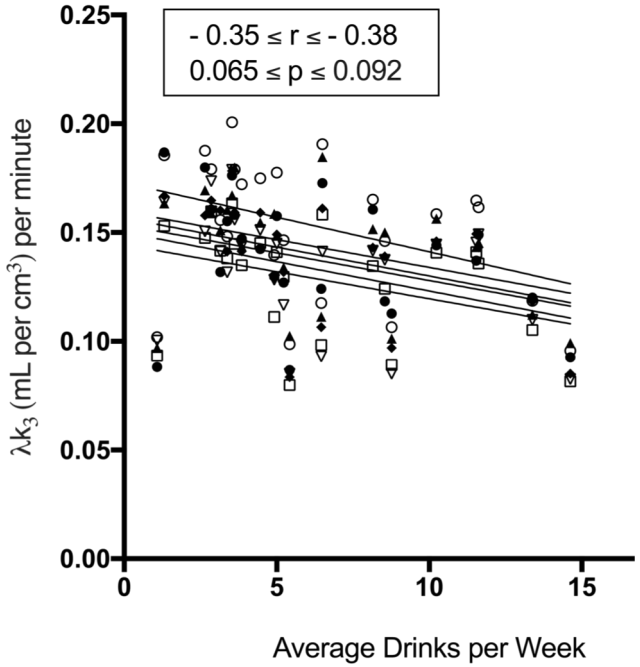
HRV during alcohol infusion



Best et al. unpublished

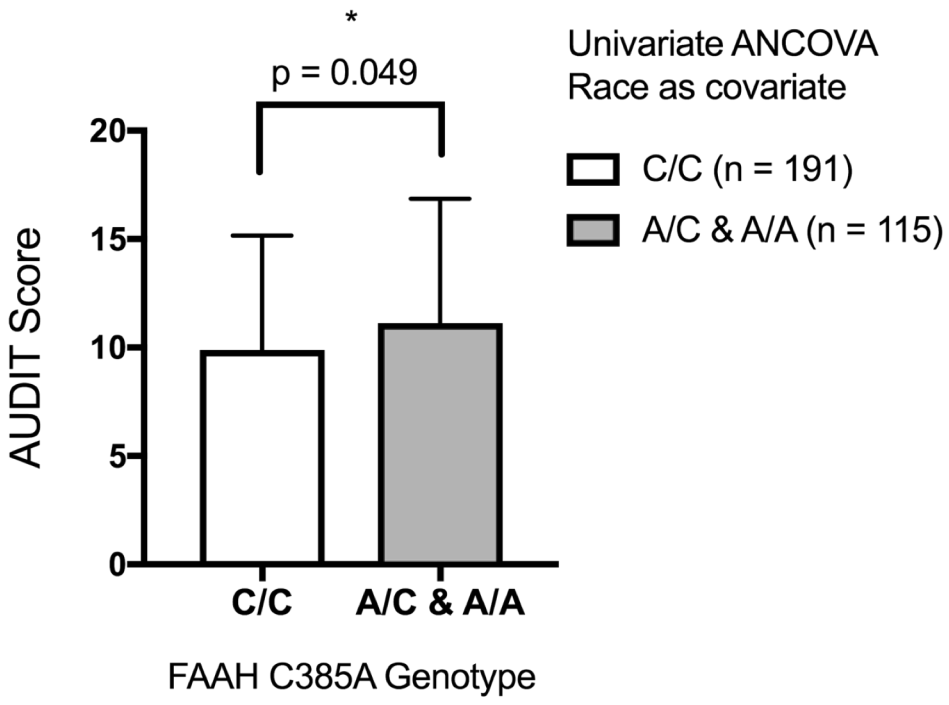
FAAH in brain marginally related to AUDIT Scores and drinks/week

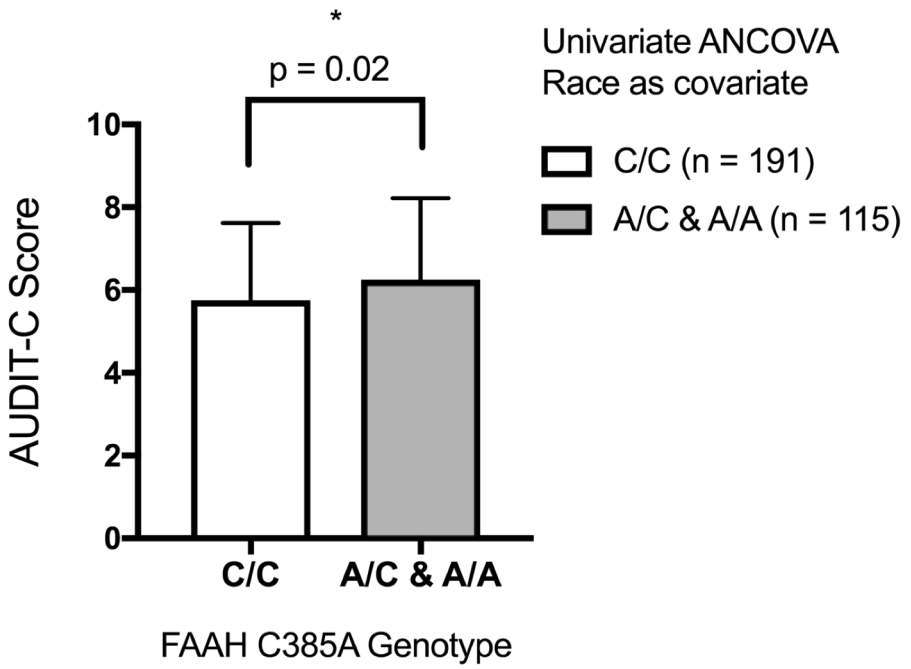




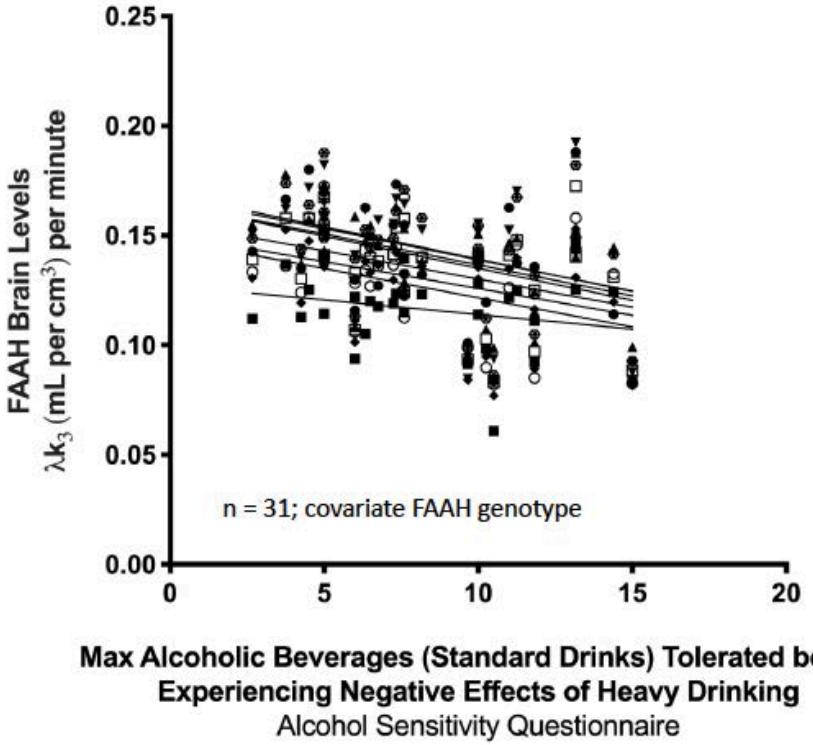
Best et al. unpublished

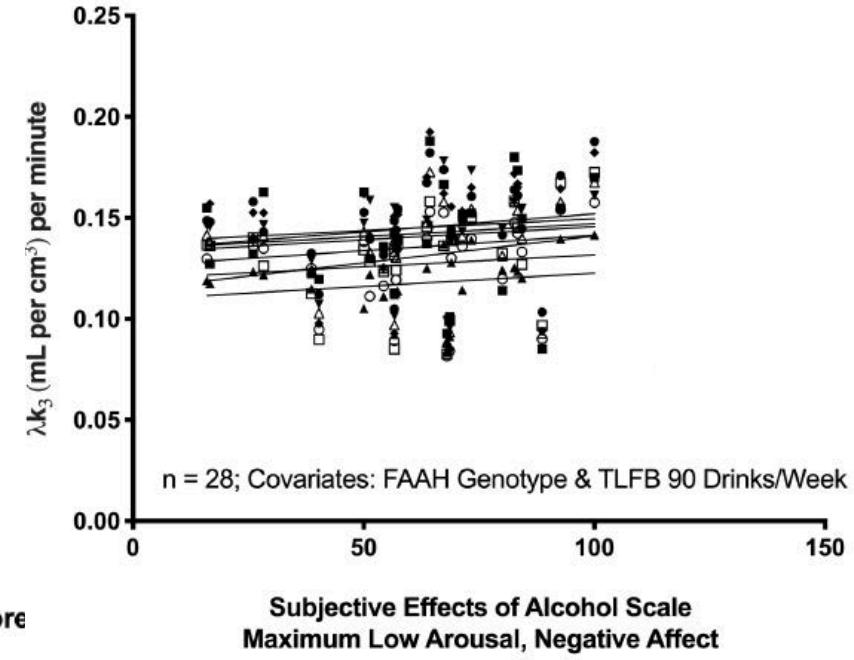
FAAH polymorphism related to higher AUDIT scores in heavy drinking youth





Low FAAH: Less negative Effects of Heavy Drinking





Best et al. unpublished

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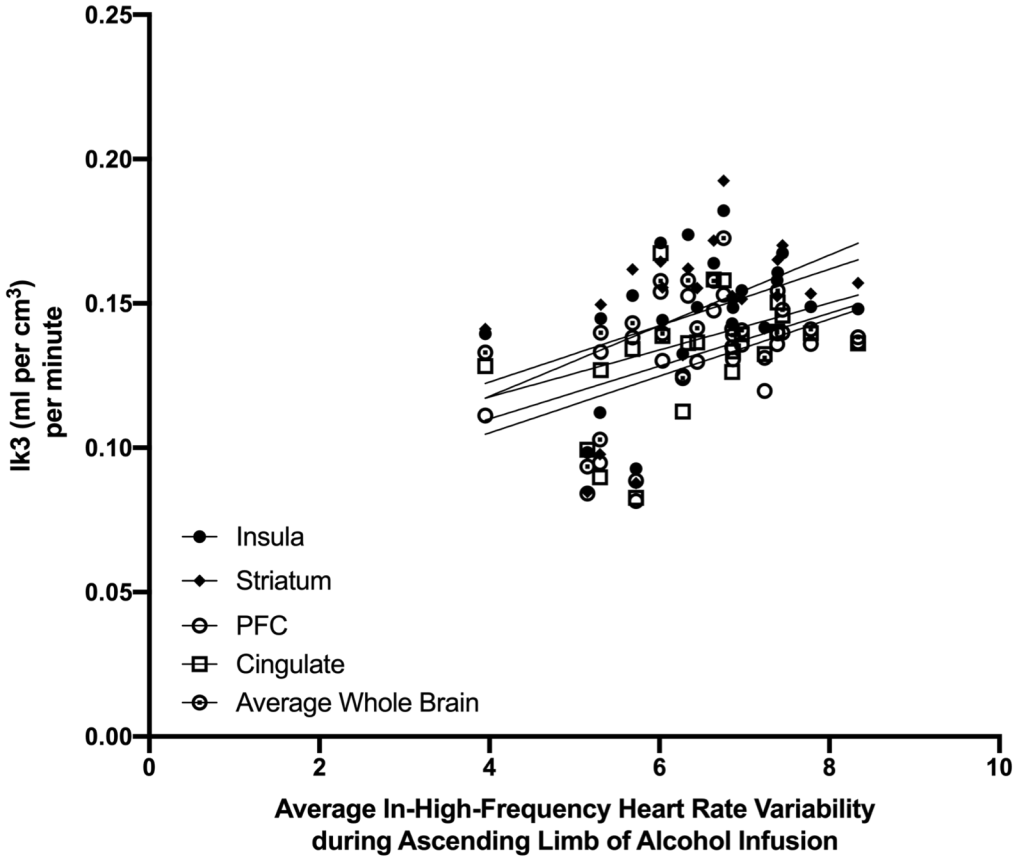
Low FAAH related to low HRV during alcohol infusion



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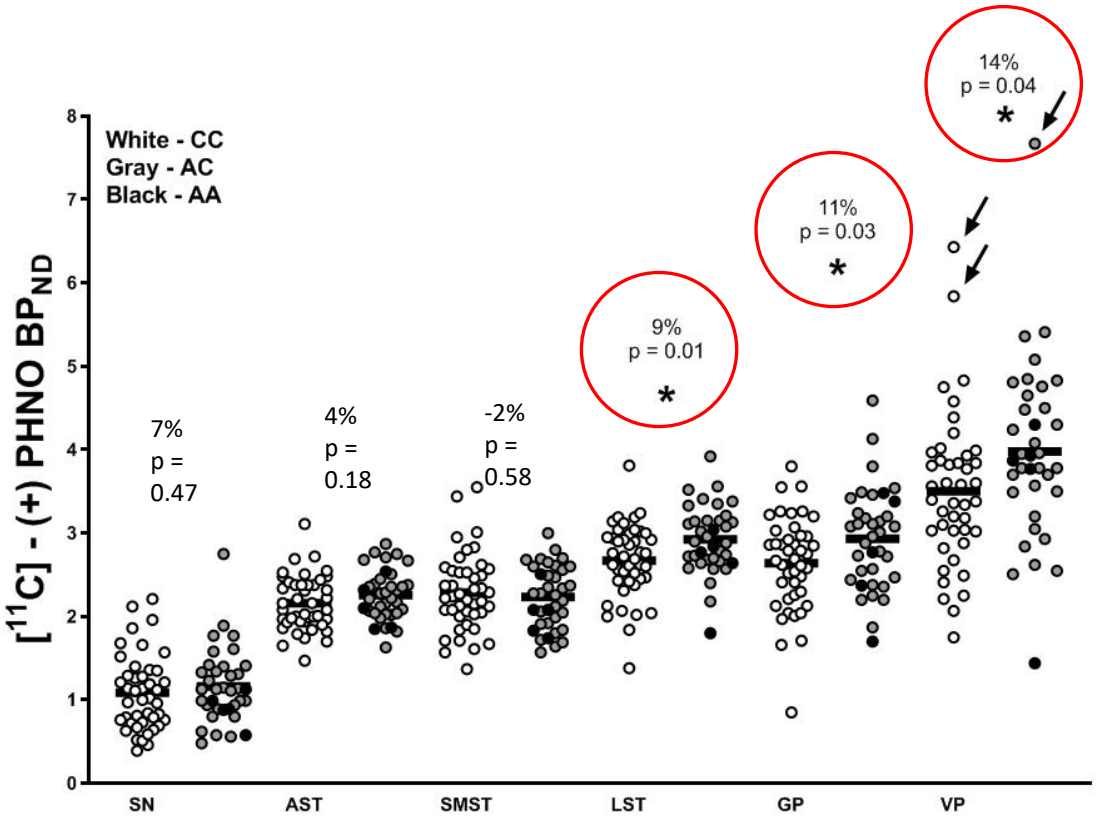
Summary

- FAAH levels are lower in CUD and related to heavier use / could mask withdrawal
- FAAH levels are transiently lower / peripheral AEA is higher in recently-abstinent subjects with AUD compared to controls and related to heavier recent alcohol use and relapse
- Family history of AUD is not related to brain levels of FAAH
- Low FAAH is associated with greater rates of drinking (AUDIT), decreased self-reported negative effects of alcohol and lower HRV during alcohol infusion.

Lower FAAH (C385A) is associated with D3 receptor in mice and men



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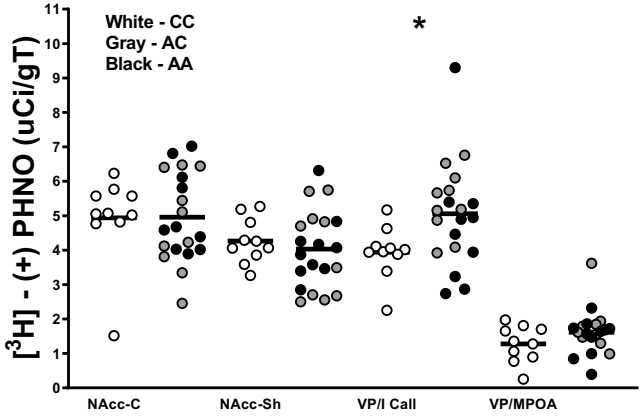

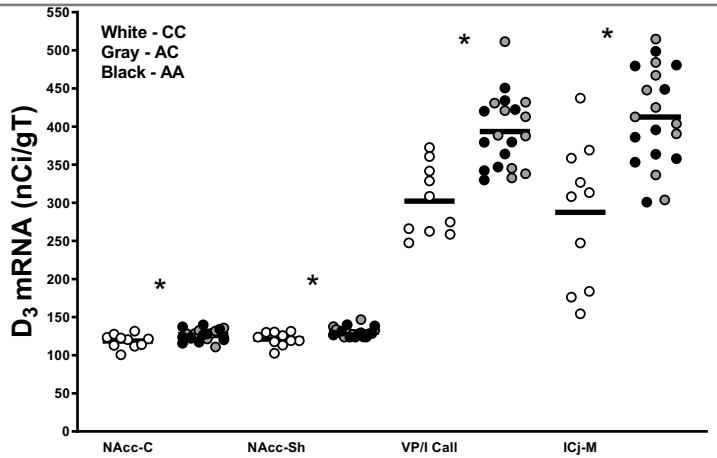

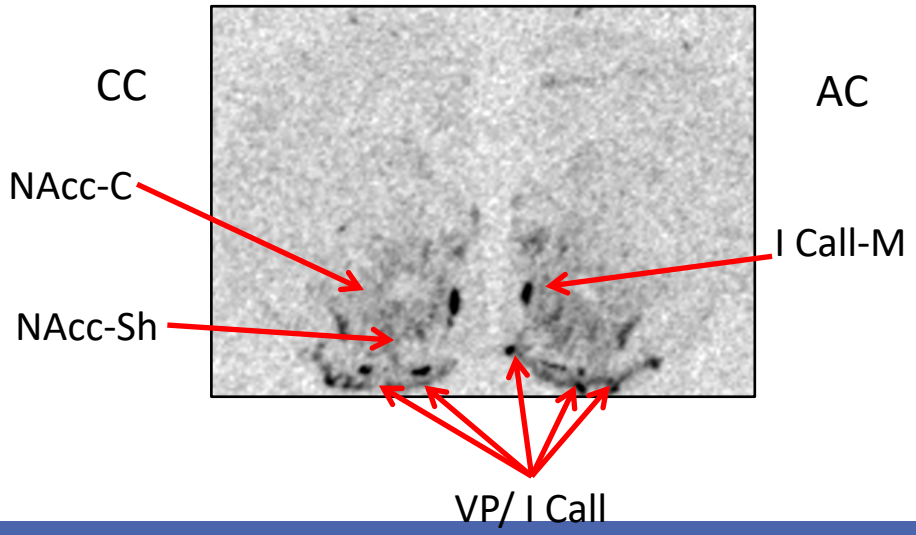

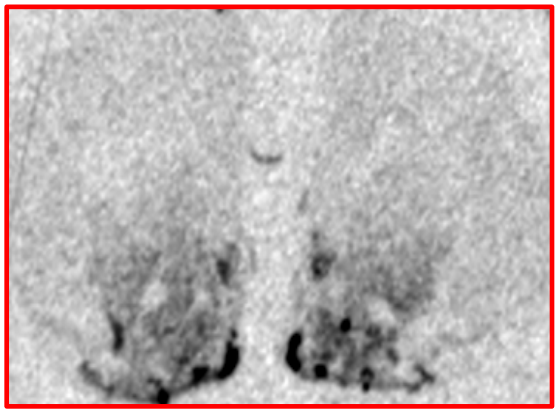

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Conclusion

- Low FAAH and increased endocannabinoid tone may be related to motivation to use drugs or increased tolerance
- Whether low FAAH is an acute compensatory response or an inherited or acquired biological vulnerability is not known
- The exact mechanism linking low FAAH with more drinking or greater tolerance is not know but may involve decreased GABA / increased mesolimbic dopamine signaling
- Longitudinal studies comparing FAAH vs. clinical symptoms should help in understanding whether FAAH might represent a useful therapeutic target.

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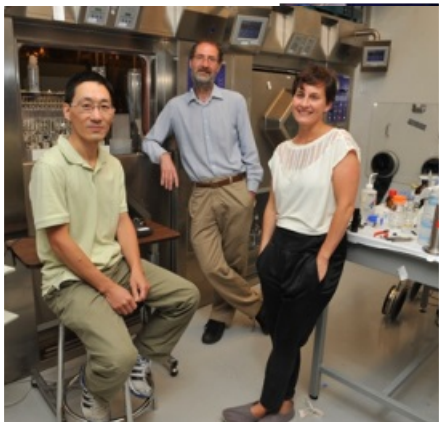

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