Perelman School of Medicine
UNIVERSITY of PENNSYLVANIA

Metabolic ketosis as a potential treatment for alcohol use disorder

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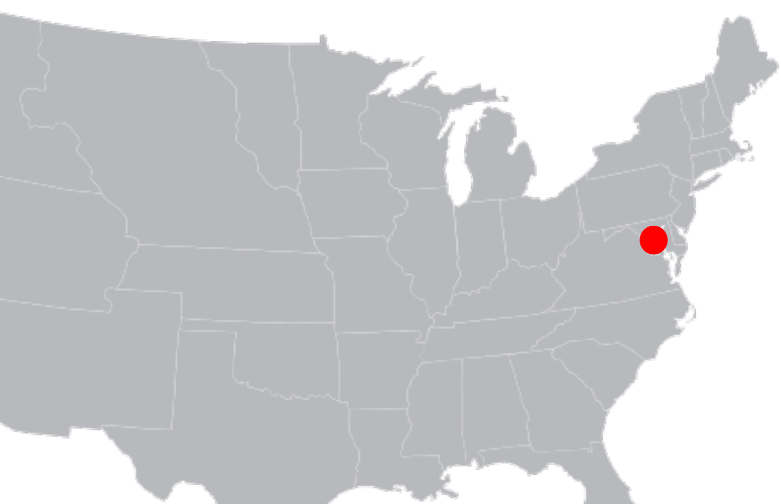
Short CV

BSc PsychoBiology, BSc MSc Psychology (2010)
University of Amsterdam, Sussex University
Mentors: Dr. Duka, Dr. Stephens

PhD Psychology (2014)
Berlin School of Mind and Brain
Mentors: Dr. Bermpohl, Dr. Heinz



Postdoctoral Fellow (2014-2020)
NIH/NIAAA Bethesda
Mentor: Dr. Volkow

Alcohol Use Disorder

- Worldwide, 3 million deaths every year result from harmful alcohol use (5.3 %) WHO, 2018
- Over 1 in 7 Americans are estimated to develop an AUD in their life Grant, 2015 JAMA
- 31.4% increase in alcohol sales during COVID19 lockdown in UK The Lancet Gastroenterology Hepatology, July 2020

- There is an urgent need for interventions that can promote long-term abstinence and reduce alcohol craving

Research Objectives

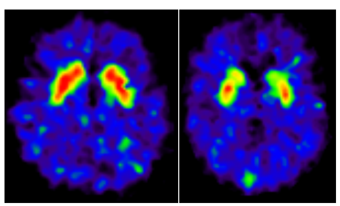
- Study neurobiological basis of AUD using neuroimaging to explore targets for treatment
- Utilize neuroimaging to capture treatment effects in AUD

Research Overview

Dopaminergic system

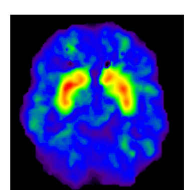
Alcohol Cue reactivity, fMRI

Dopamine D2/D3: PET ^{11}C Raclopride

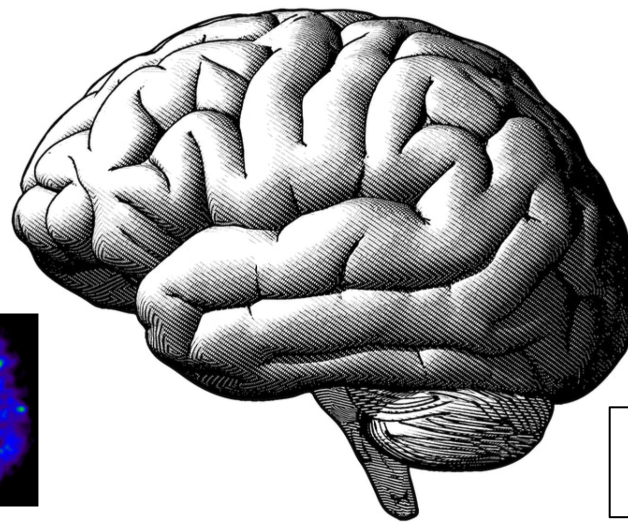


Neurogenetics

***DAT1* methylation, PET ^{11}C Cocaine**

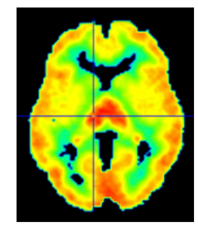


Genetic ancestry



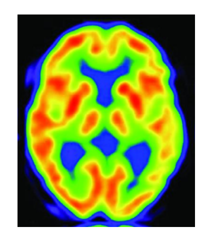
Neuroinflammation

TSPO: PET ^{11}C PBR28



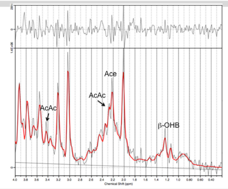
Metabolism

Glucose metabolism (FDG)



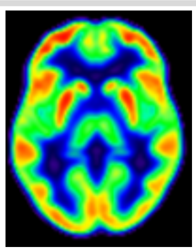
^{11}C Acetate, MRS

Talk Outline



Part 1: *K99*
Brain metabolism and alcohol withdrawal

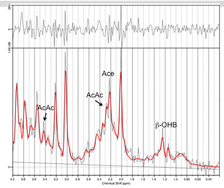
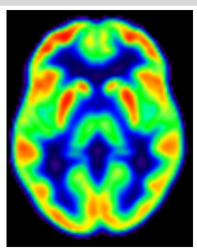
Part 2: *R00*
Brain metabolism and alcohol consumption



Part 3: *B2B proposal*
Brain metabolism and alcohol tolerance

Part 4:
Future Directions

Talk Outline

	**Part 1:** *K99* Brain metabolism and alcohol withdrawal
	**Part 2:** *R00* Brain metabolism and alcohol consumption
	**Part 3:** *B2B proposal* Brain metabolism and alcohol tolerance
	Part 4: Future Directions

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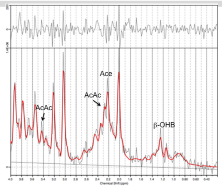	**Part 1:** ***K99*** Brain metabolism and alcohol withdrawal
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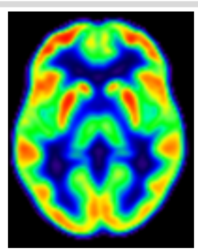	**Part 3:** ***B2B proposal*** Brain metabolism and alcohol tolerance
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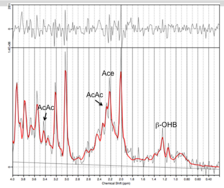

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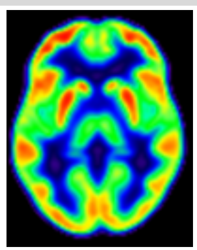

Part 3: *B2B proposal*
Brain metabolism and alcohol tolerance

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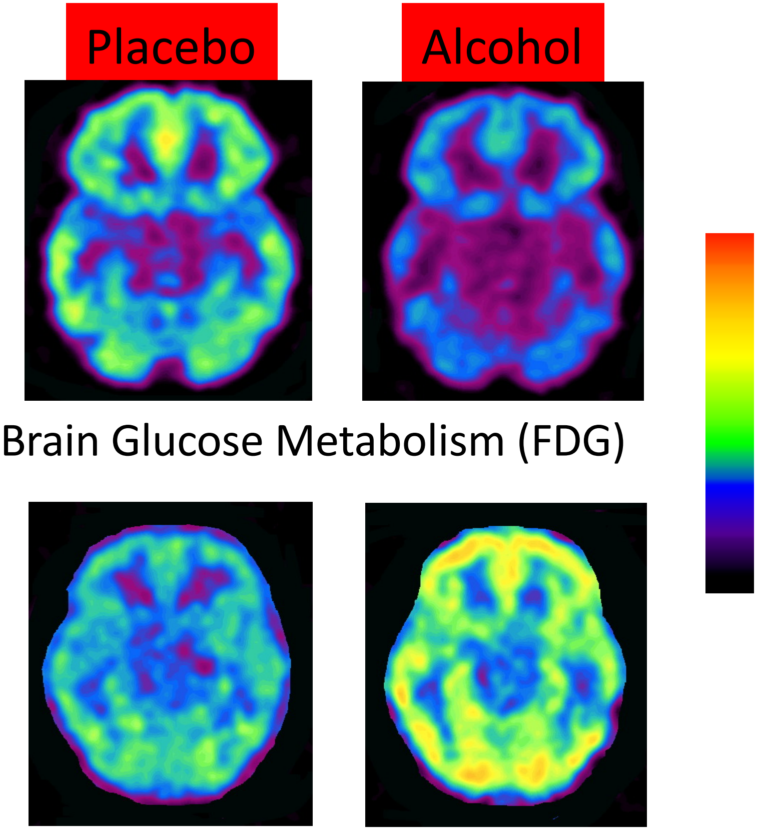
1. Brain metabolism and alcohol withdrawal

Effects of a ketogenic diet on alcohol withdrawal in AUD - *K99*

Wiers, Vendruscolo …. Koob, Volkow, under review

Effects of acute alcohol on **brain glucose metabolism** and **brain acetate** uptake



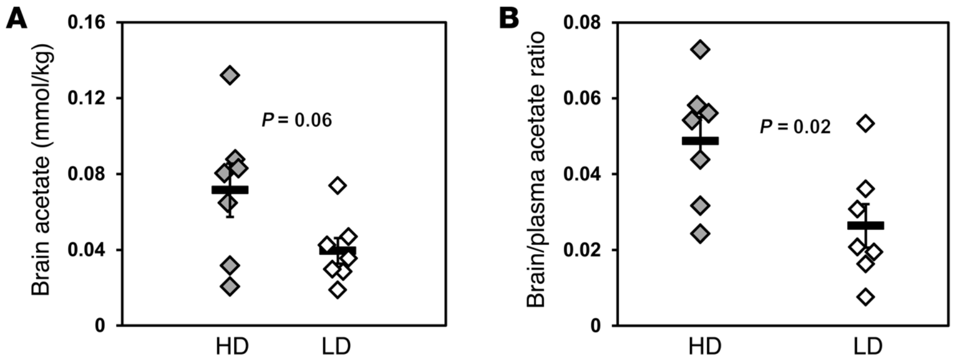
Brain Glucose Metabolism (FDG)

Brain Acetate Uptake (^{11}C Acetate)

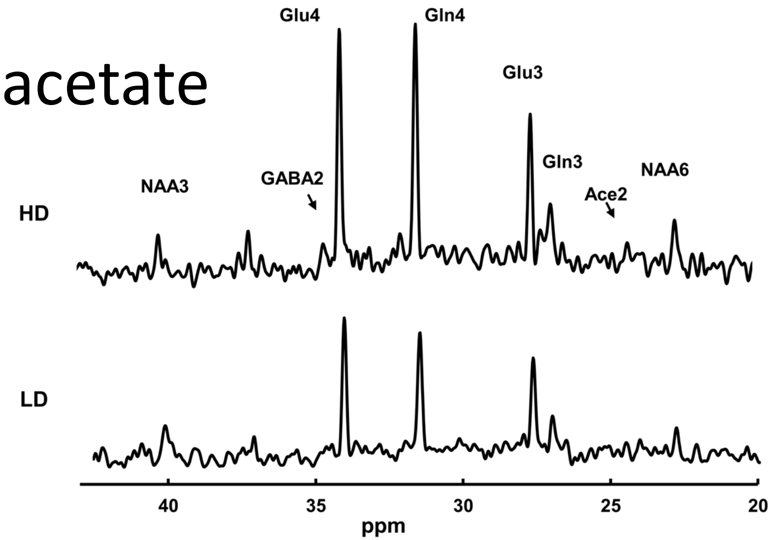
- **Alcohol decreases glucose metabolism, increases acetate**
- **Acetate metabolism was higher in heavy drinkers than controls**

Volkow et al., NeuroImage 2013; Shokri-Kojori et al., 2019

During sobriety, heavy drinkers show **higher acetate uptake** compared to social drinkers

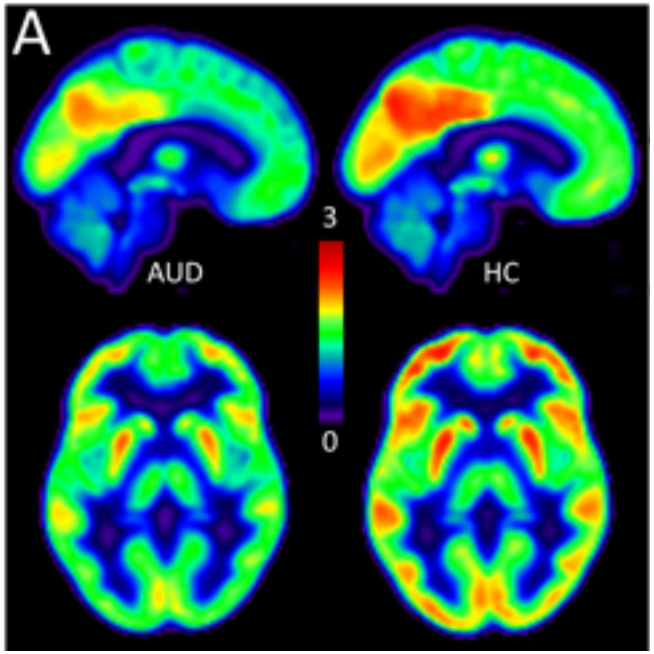


^{13}C acetate



Jiang L, et al, 2013 J Clin Investigation

During sobriety, heavy drinkers show **lower brain glucose metabolism**

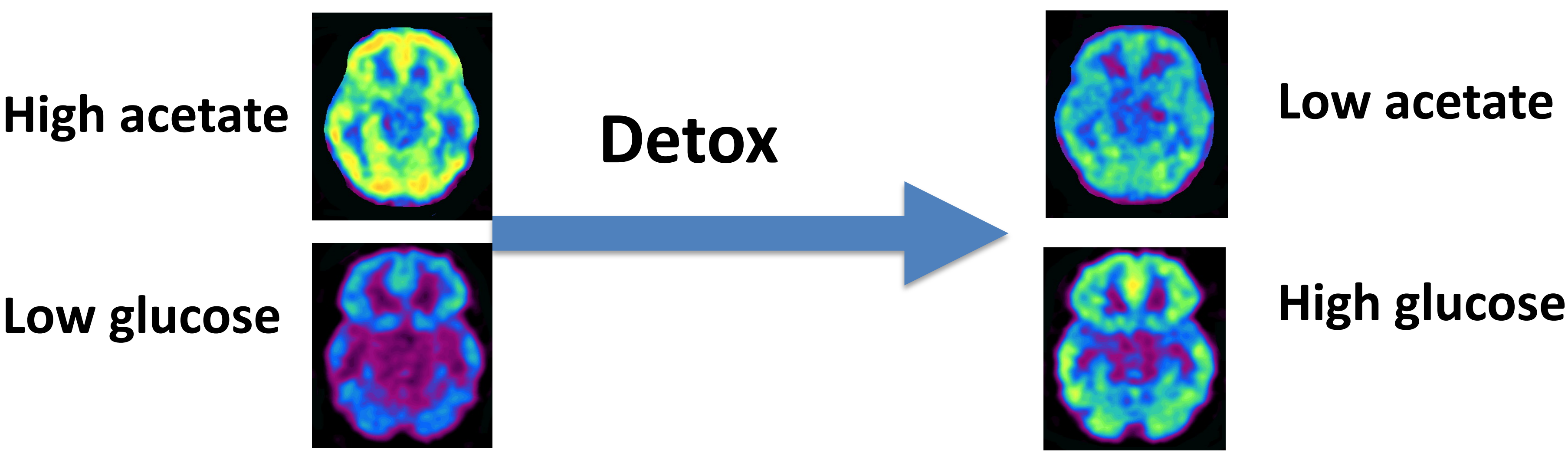


AUD < Control

Volkow, Wiers et al, 2017
Tomasi, Wiers et al, 2019

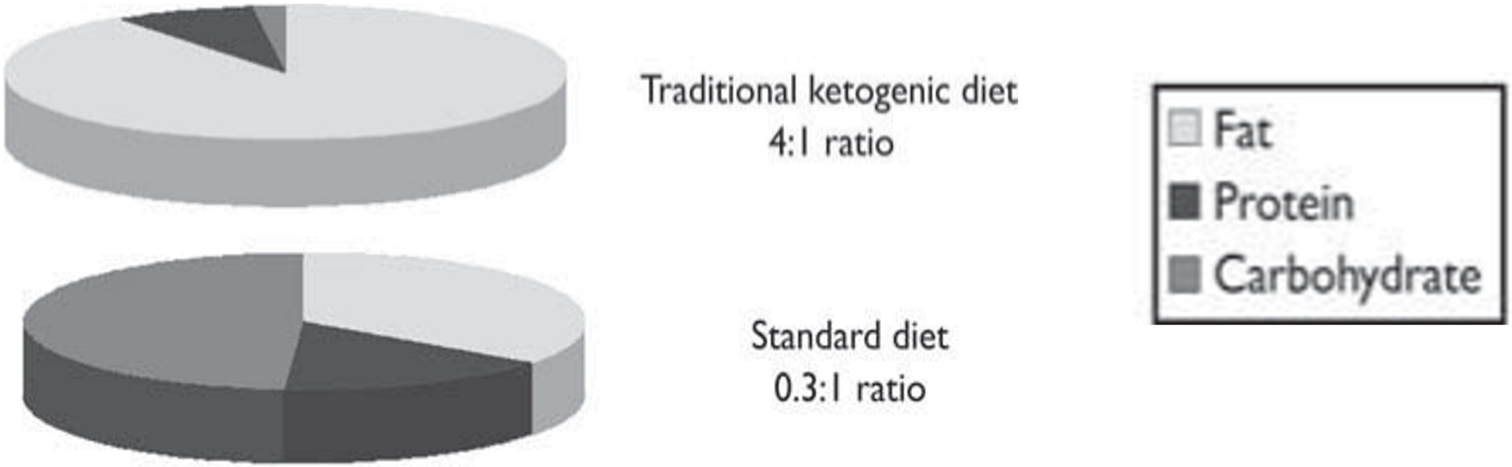
Relevance to AUD treatment

During prolonged detoxification, decrease in acetate may result in an energy-deficient state in the brain that could contribute to neurotoxicity and enhanced neuronal excitability in AUD



Ketogenic Diet

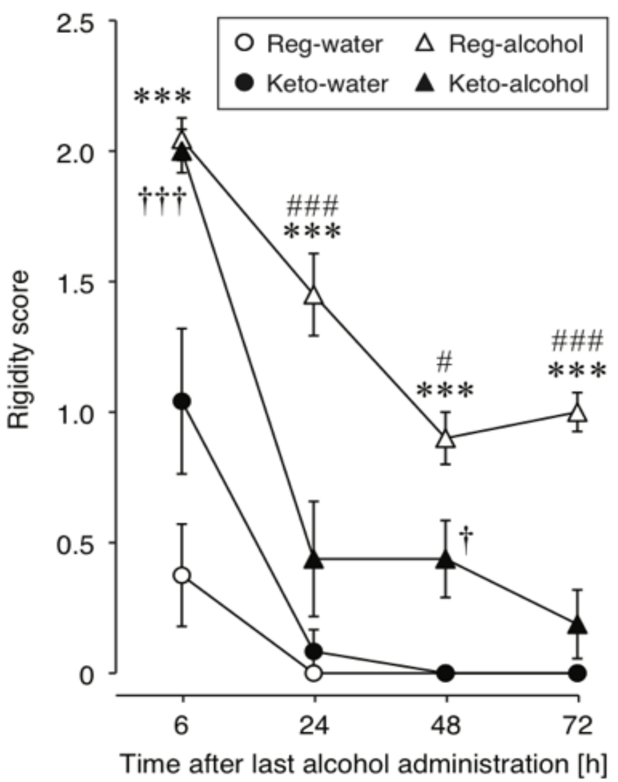
- **High fat, low carbohydrate** diet
- Frequently used for reducing seizures in epilepsy
- **Metabolic Ketosis:** cells are using ketone bodies for fuel rather than glucose: **aceto-acetate, β-hydroxybutyrate and acetone**

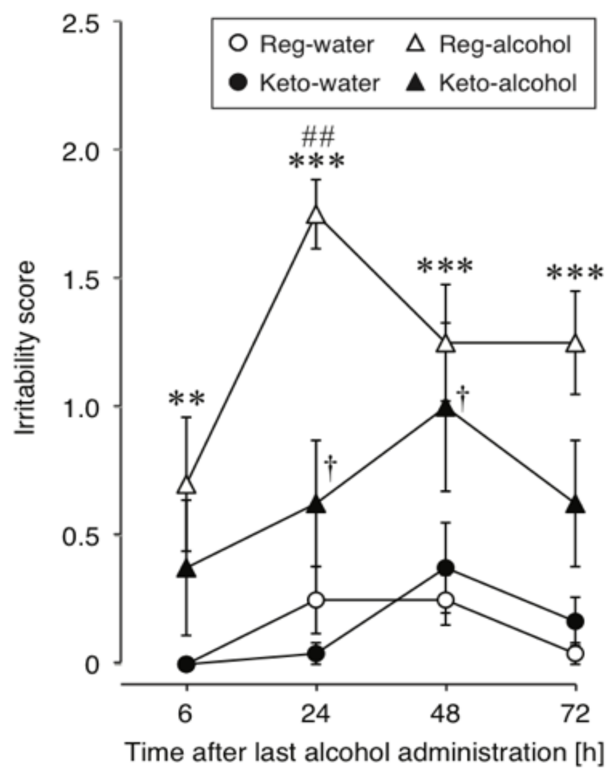


Diet compositions **Grams of fat: protein+carbohydrates**

Ketogenic diet and alcohol withdrawal

- KD reduces withdrawal in rats Derr, 1981
- KD lowers **body rigidity** and **irritability** during detox:





Dencker, Fink-Jenssen et al ACER, 2018

n=48, 12 per group

Aims and Hypotheses

- To assess effects of KD in human AUD on:

Aim 1 Withdrawal symptoms (CIWA), benzodiazepine use and alcohol craving

H: KD reduces withdrawal symptoms, need for benzodiazepines, and craving

Aim 2 Ketone bodies in brain using ^{1}H-MRS

H: Ketones in brain mediate effects of KD on withdrawal and craving

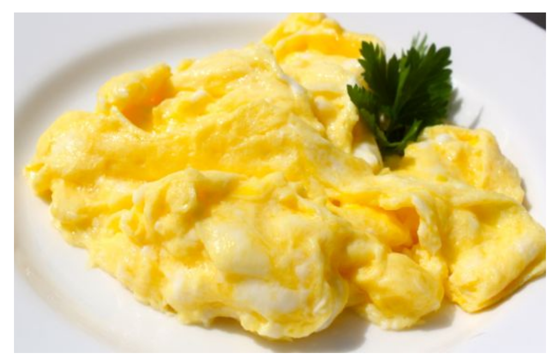
Methods

- Patients with AUD undergoing detoxification and inpatient treatment (N=33)
- Within 2 days: randomly assigned to **KD** or **Standard American** (double blind) for 3 weeks
- Daily withdrawal and craving ratings
- Weekly ^{1}H-MRS scans, fMRI Alcohol Cue Reactivity

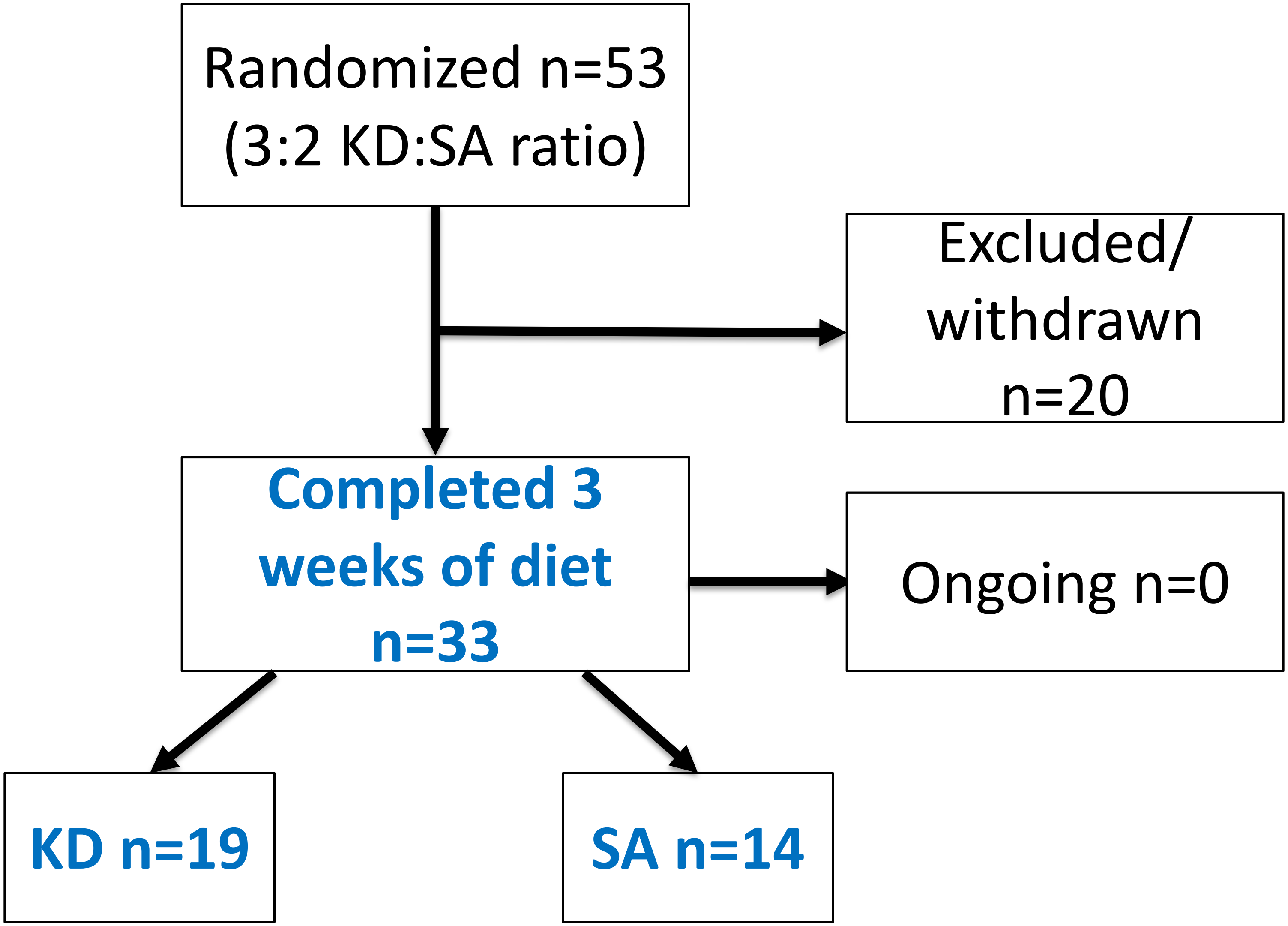
Anterior Cingulate Cortex

Methods: KD/SA diet (isocaloric)

- **Shakes:** chocolate, blueberry, raspberry, strawberry, and peanut butter
- **Snacks:**
  - Avocado Dip with Veggies
  - Beef Broth
  - Cauliflower and Cheese (low carb version of mac and cheese)
  - Buffalo Chicken Dip
  - Chicken Broth
  - Chocolate Mousse
  - Salad
  - Scrambled Eggs
  - Tuna and Celery
  - Vegetable Broth
  - Yogurt and Pecans



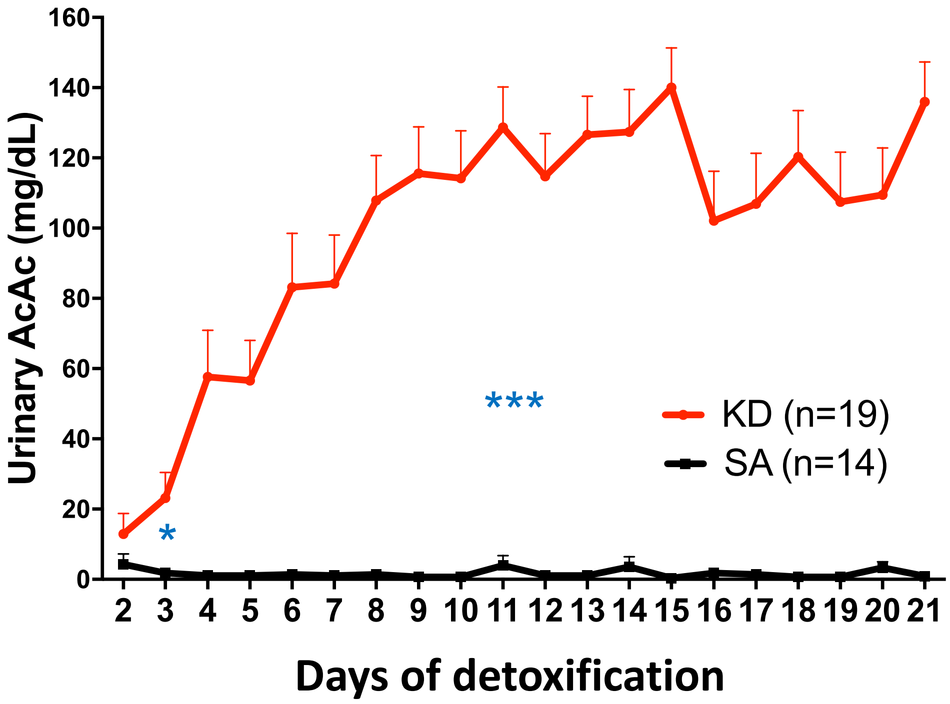
Current sample

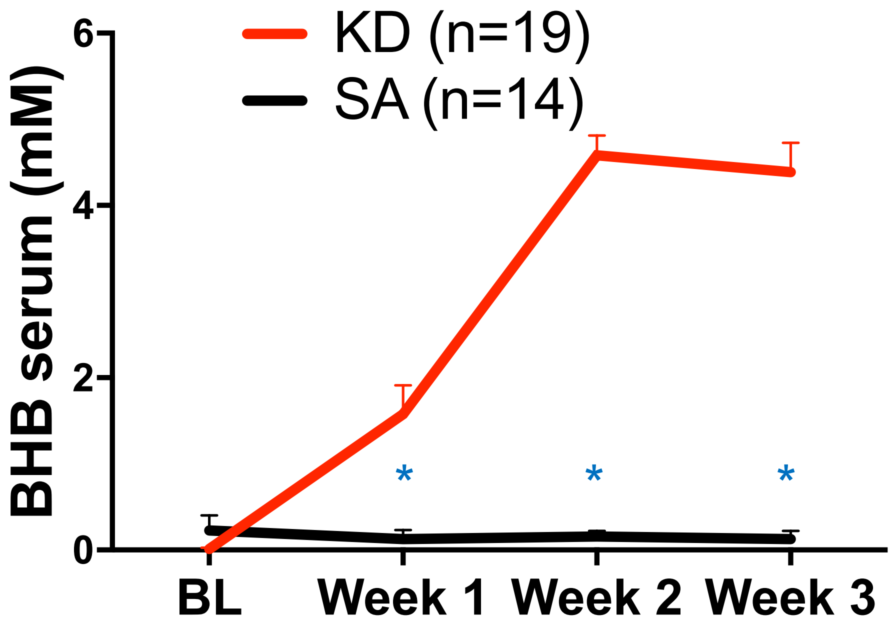


Sample characteristics

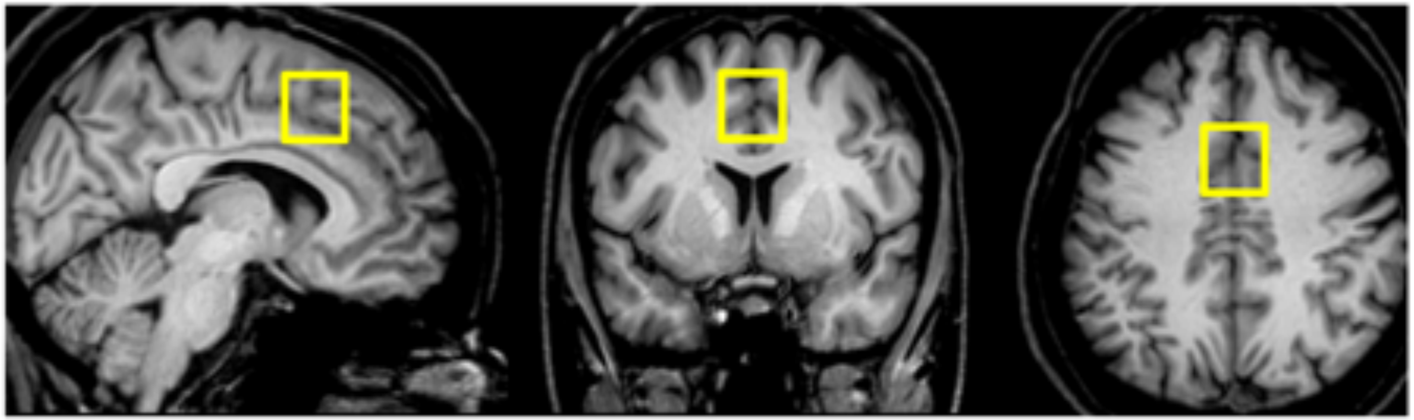
	KD *n*=19	SA *n*=14	*p*-value
Age	39.3 ± 11	44.2 ± 16	.31
Sex	7 F, 12 M	3 F, 11 M	.34
BMI	24.5 ± 3	27.5 ± 5	.051
Weight loss during 3-week study (kg)	1.4 ± 3	1.8 ± 2	0.69
Max CIWA withdrawal at admission	9.9 ± 6	7.9 ± 4	.23
Drinks/day	15.2 ± (8)	17.0 ± (10)	.58
Heavy Drinking years	12.5 ± 8	15.9 ± 8	.24
Days since last drink at admission	0.2 ± 0.2	0.4 ± 0.3	.49

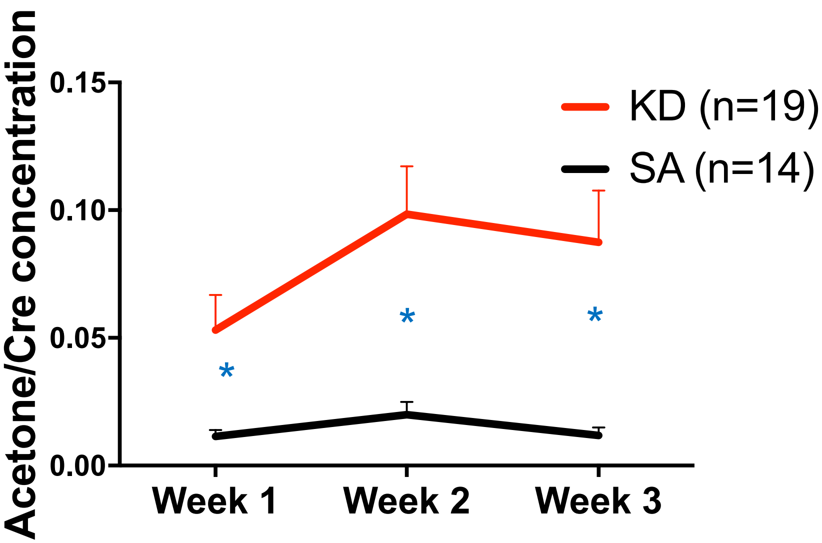
Urine and blood ketones

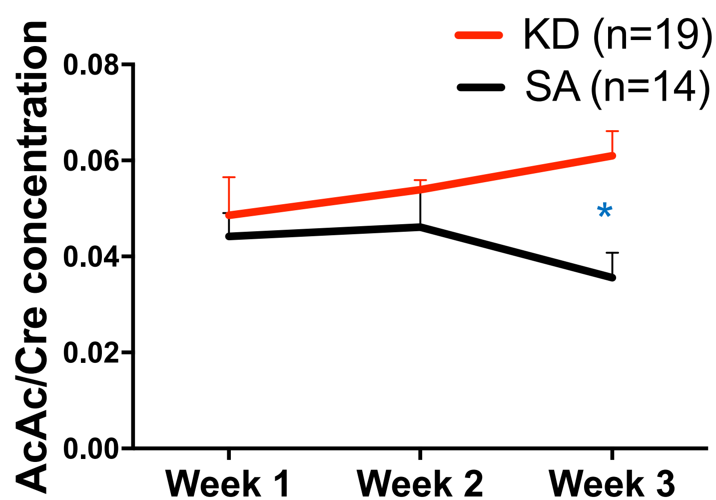




[1]H-MRS brain ketones

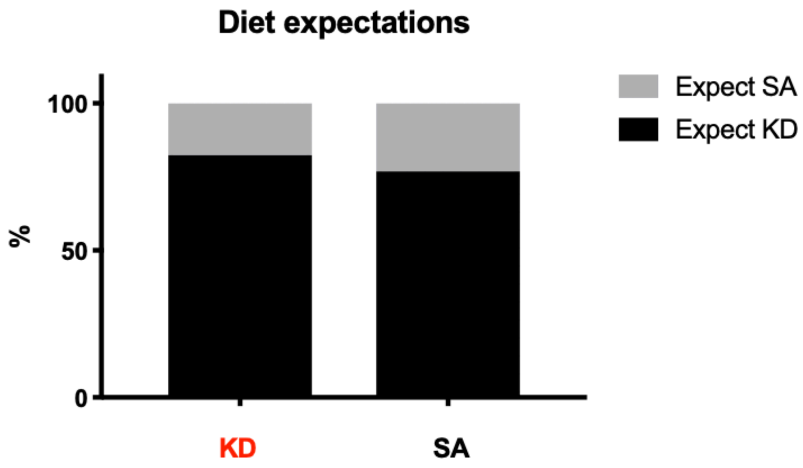






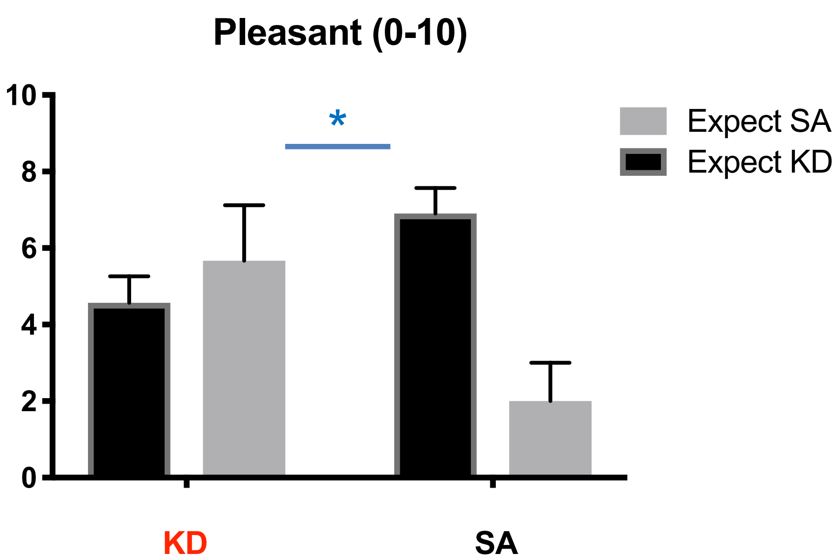
However, no reliable measures of BHB with standard PRESS sequence

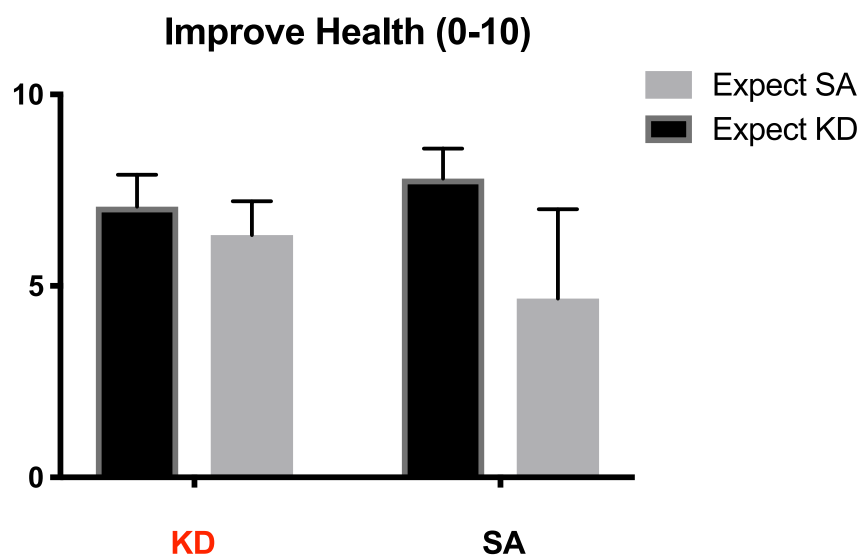
End of diet evaluation



No effect of diet expectation

X^2=0.14, p=0.71

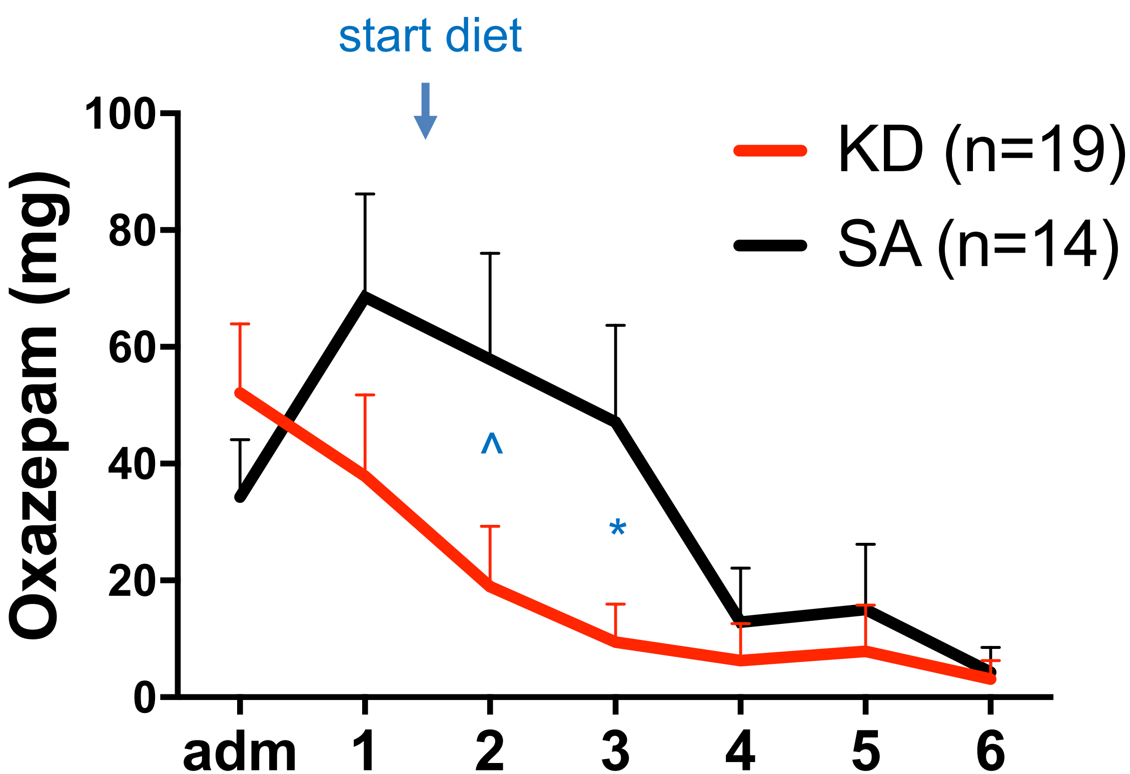


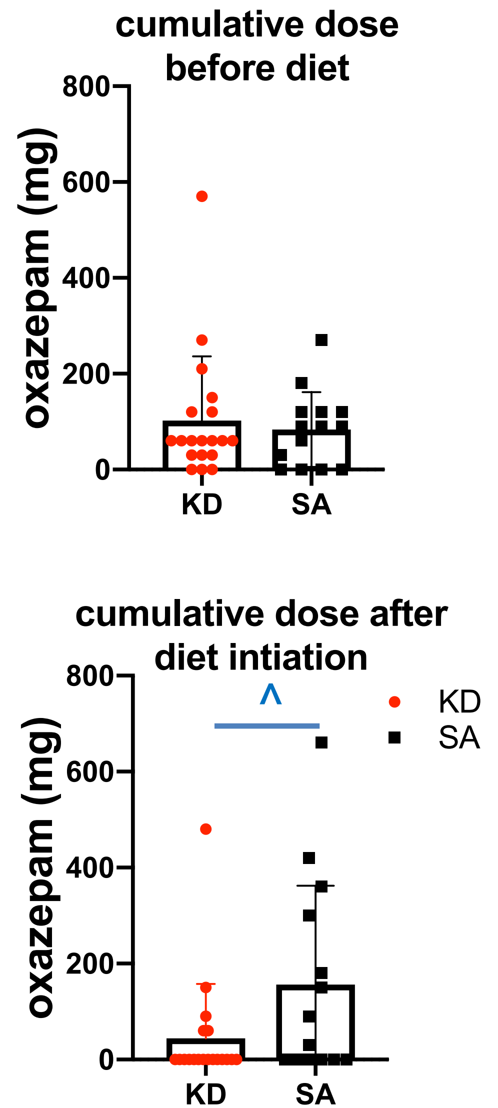


* Interaction diet x diet expectation for pleasantness (F=7.6, p=0.01)

Benzodiazepine intake: dose

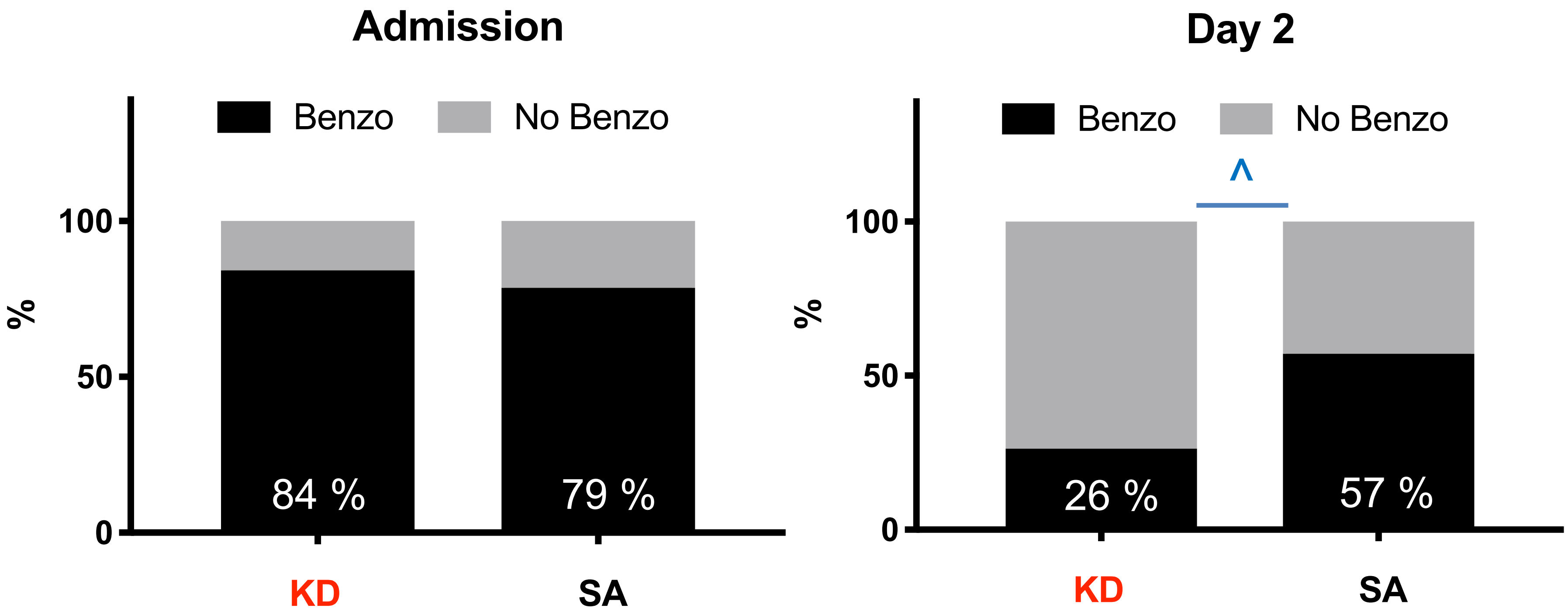
Diazepam: Oxazepam 1:3





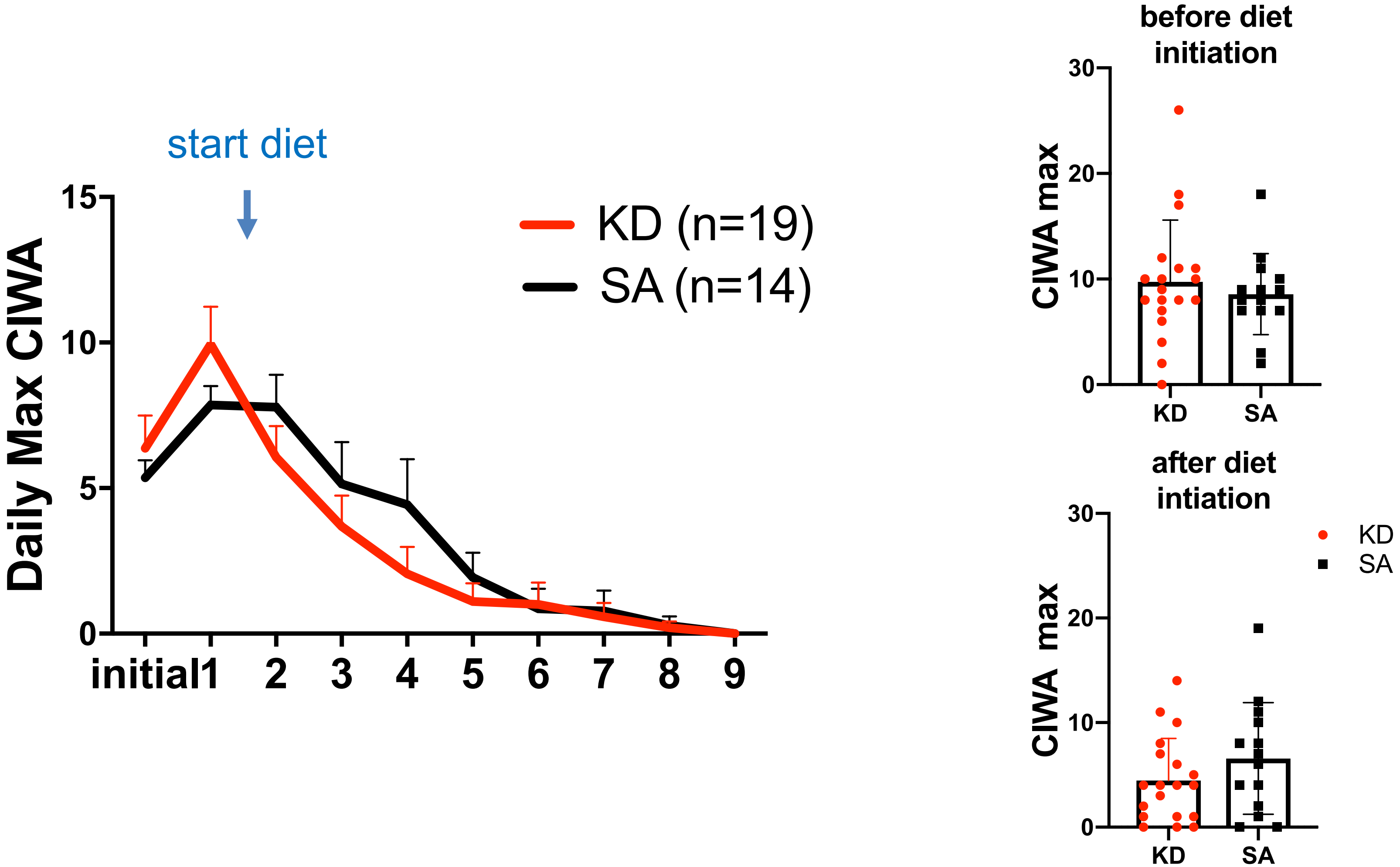
Significant effect of diet x time ($F=2.6$, $p=0.01$), with KD showing lower benzodiazepine use after diet initiation

Benzodiazepine intake



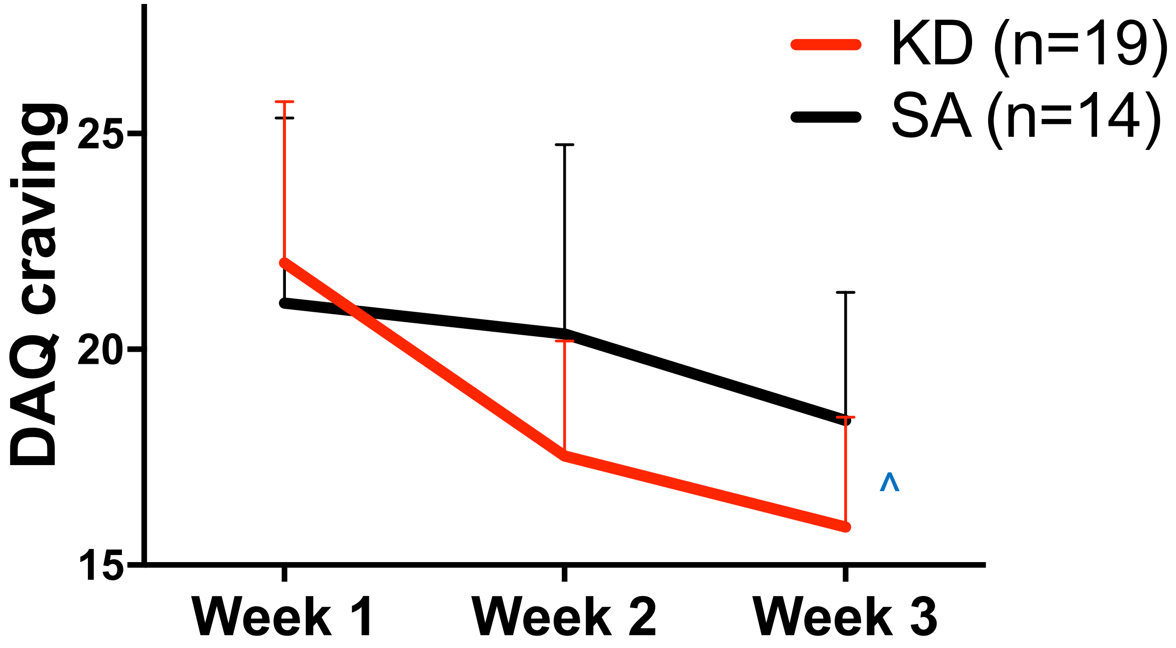
After diet initiation, there was a trend effect of fewer AUD inpatients needing benzodiazepines in the KD group compared to SA (X^2=3.2, p=0.073)

Alcohol withdrawal: CIWA score



Benzodiazepines are prescribed when CIWA is =>8, which may explain lack of effect of KD on withdrawal

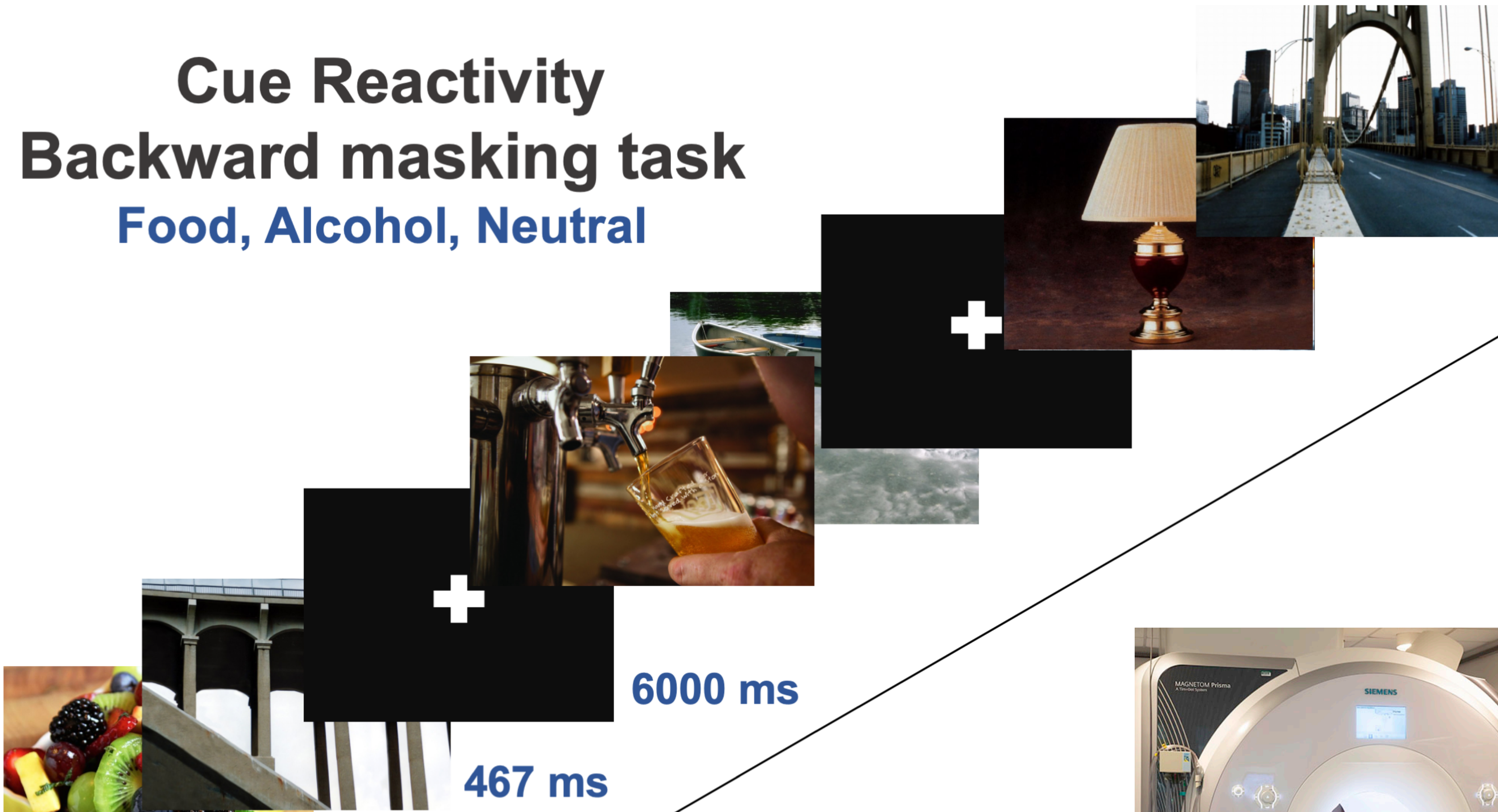
Desire for Alcohol Questionnaire (craving)



^ Self-reported alcohol craving on the Desire for Alcohol Questionnaire reduced in KD at trend level ($t=1.9$, $p=0.07$) but not in the SA group ($t=.9$, $p=0.4$)

Alcohol cue-induced brain reactivity

Cue Reactivity
Backward masking task
Food, Alcohol, Neutral

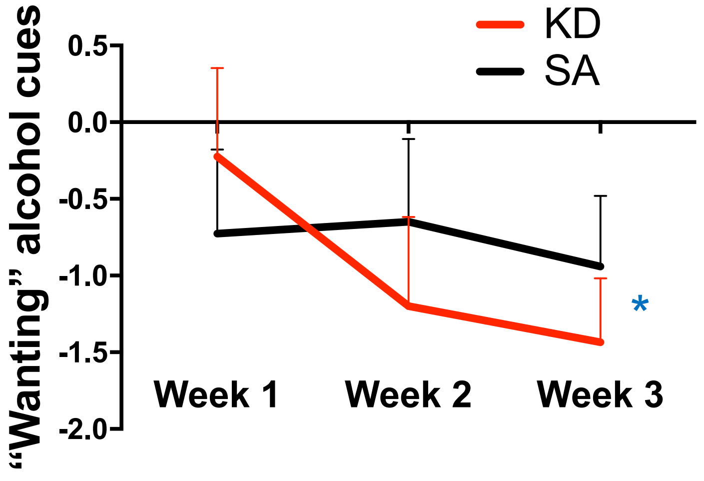


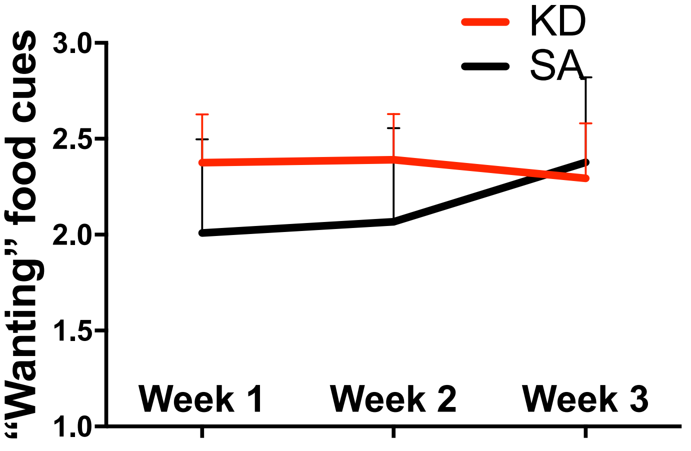
3T fMRI

Subjective ratings: How much do you want this right now? (-3 – 3)

40 alcohol cues

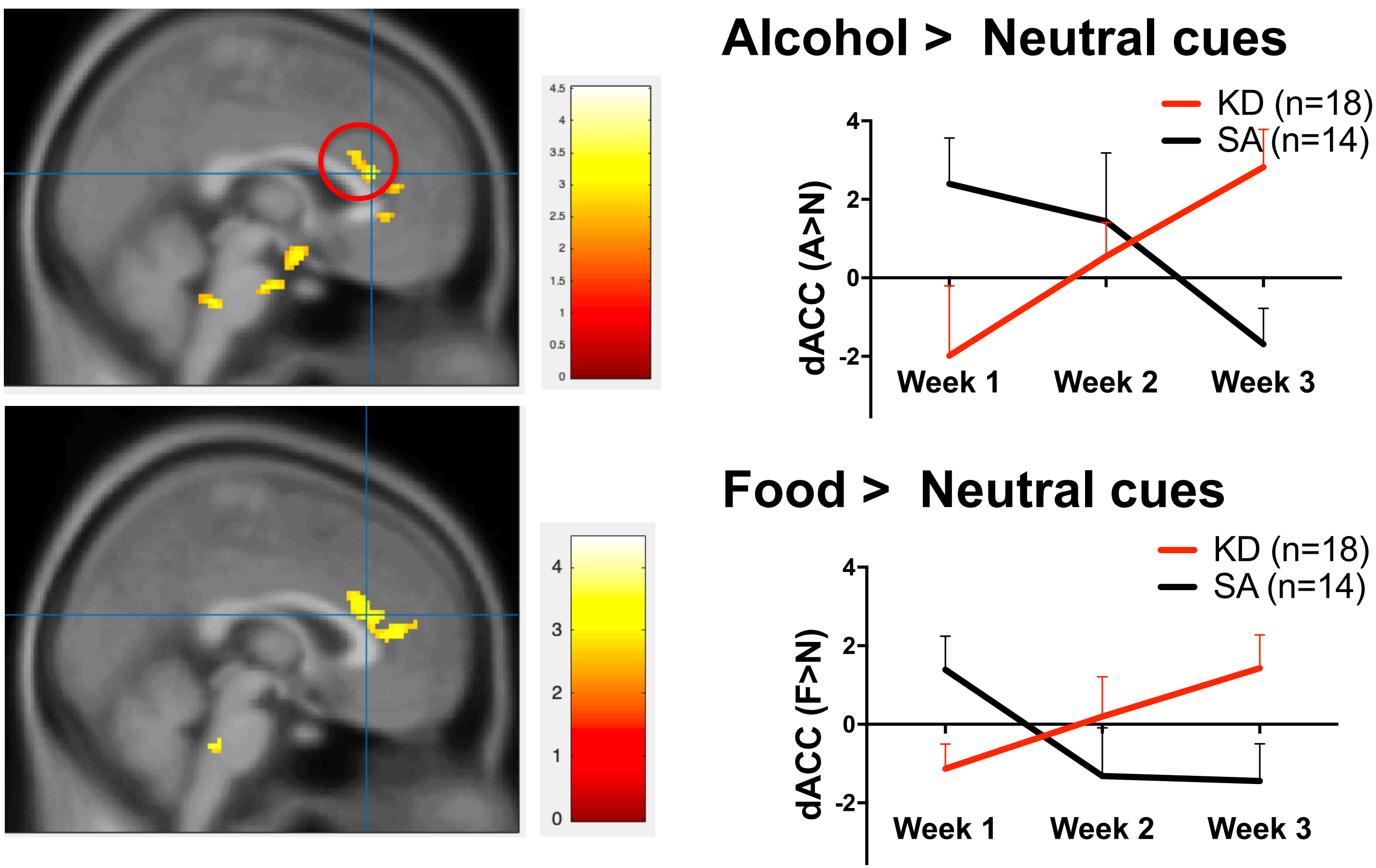
40 food cues





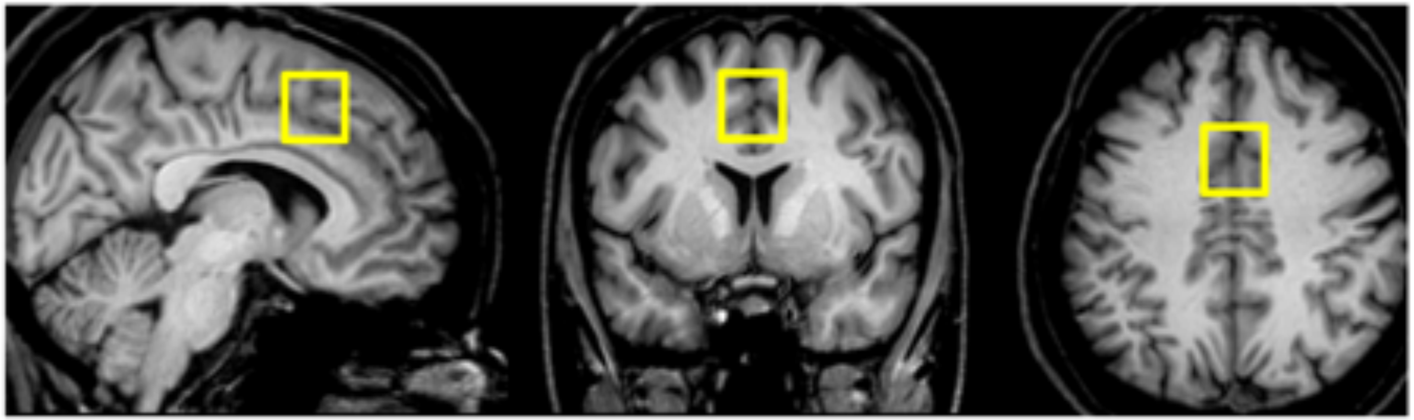
* "Wanting" ratings of alcohol > neutral cues used in the fMRI cue reactivity task reduced in the KD group (t=3.4, p=0.003) but not in SA (t=.84, p=0.42), and the interaction effect of time x group was significant (F=4.9, p=0.048). No effects for food cues.

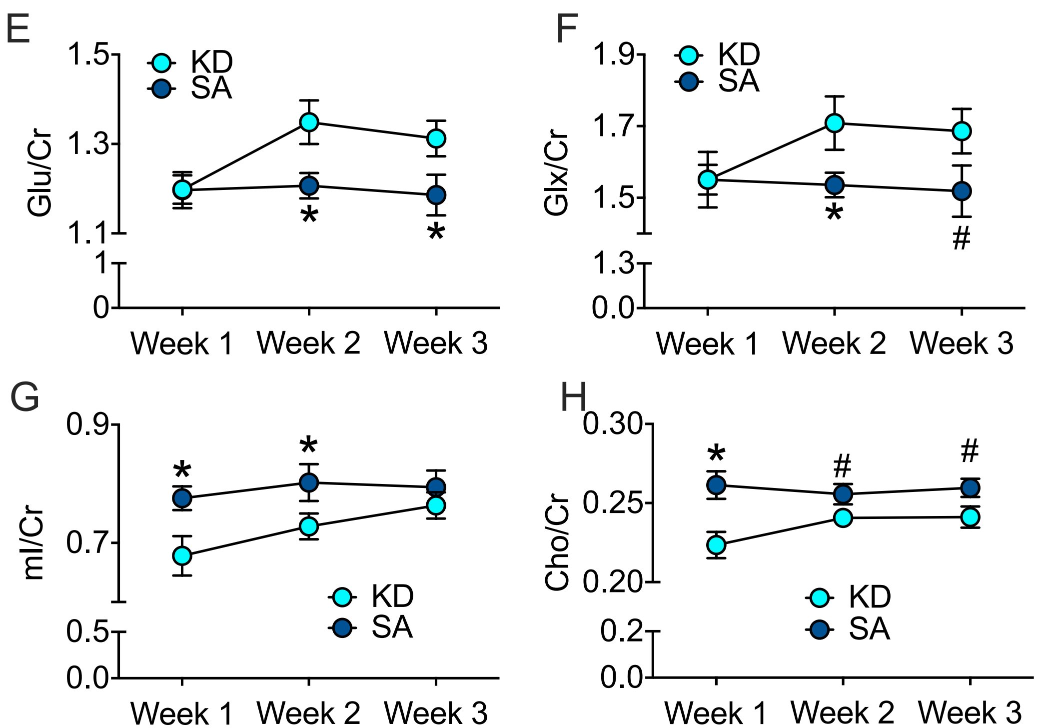
Group x time interaction in dorsal ACC



dACC responses to both alcohol and food cues increased in KD versus SA. Region implicated in self-control and processing salience attribution.

KD's effect on other metabolites





KD increased Glutamate and Glutamine – alternative energy source?

KD decreased myo-inositol and Choline – markers of neuroinflammation?

Summary

- First KD intervention study in human AUD: 4:1 KD diet well tolerated
- KD lowers benzodiazepine intake and (hence) no effect on withdrawal
- KD reduced “wanting” of alcohol cues, and alcohol craving at trend level
- KD increased Acetone and AcAc in dACC, and elevated reactivity to alcohol cues may indicate enhanced control over alcohol

National Institute on Alcohol Abuse and Alcoholism

Many thanks to:

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Dana Feldman
Erin Biesecker
Katherine McPherson
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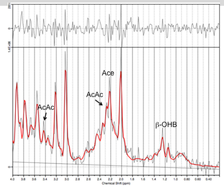
Shanna Yang
Richard Veech

Nancy Diazgranados
Kimberly Herman
Ted George
Yvonne Horneffer
Mackenzie Cervenka
Melanie Schwandt
George Koob
Leandro Vendruscolo

Perelman School of Medicine
University of Pennsylvania

Talk Outline

	**Part 1:** ***K99*** Brain metabolism and alcohol withdrawal
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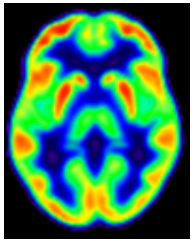	**Part 3:** ***B2B proposal*** Brain metabolism and alcohol tolerance
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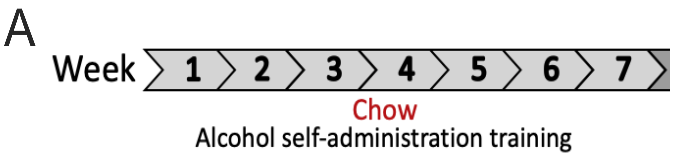
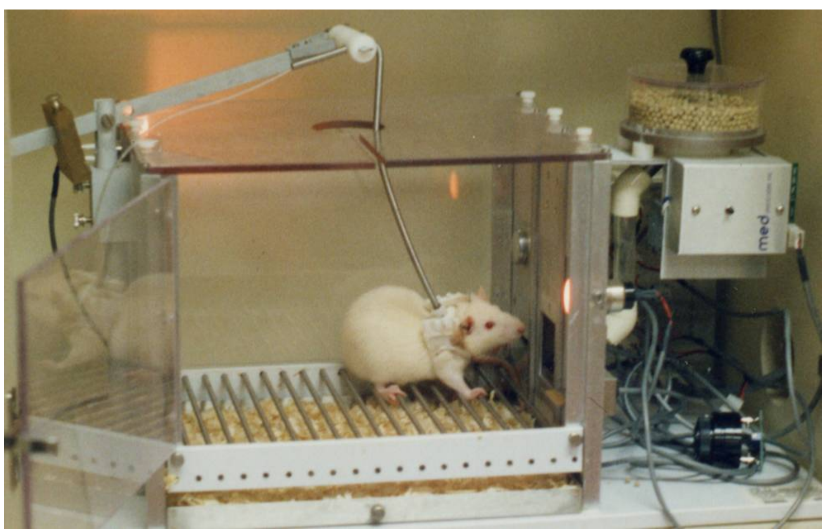
Does ketosis influence alcohol consumption?



n=36 Wistar rats



Wiers, Vendruscolo …. Koob, Volkow, under review

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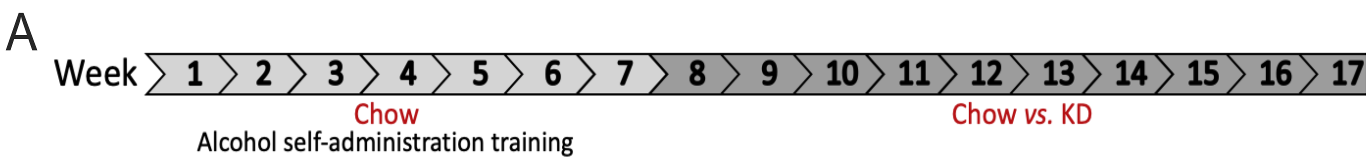
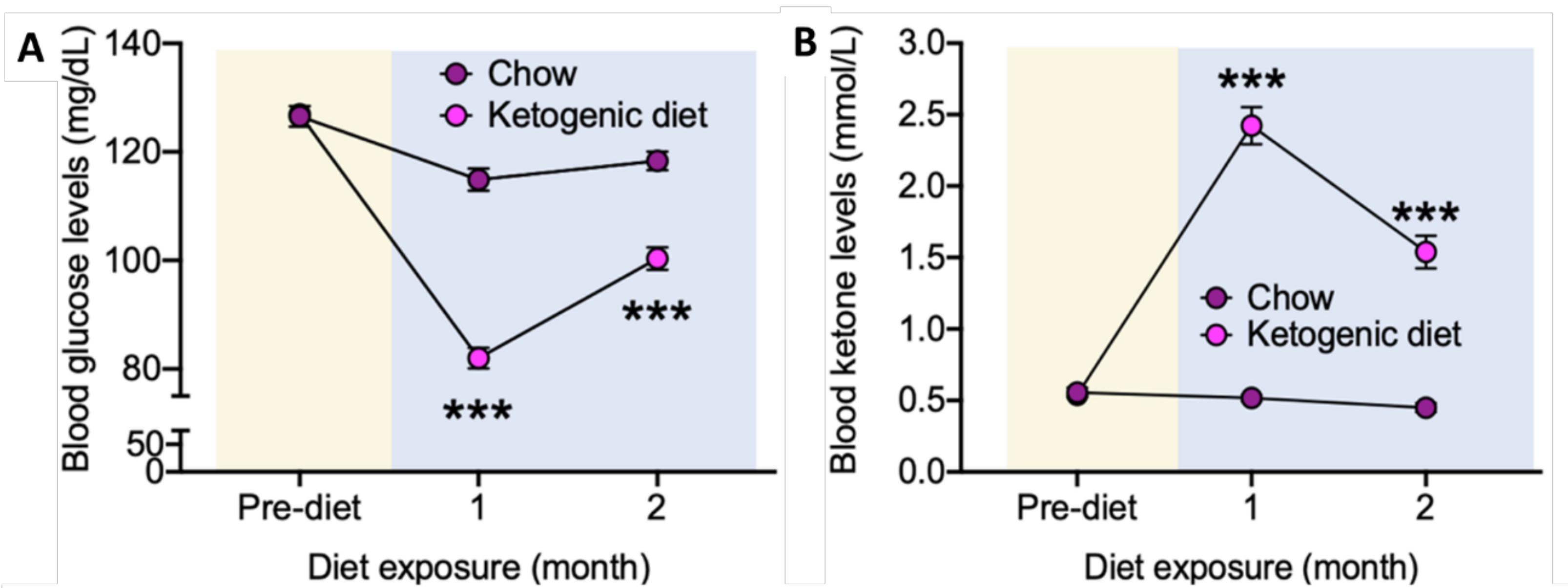


n=18 KD
n=18 Chow
for 2 months



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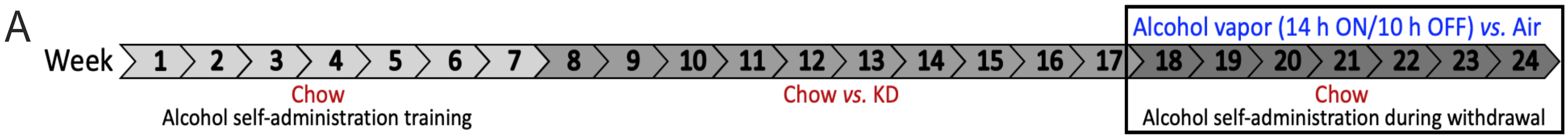
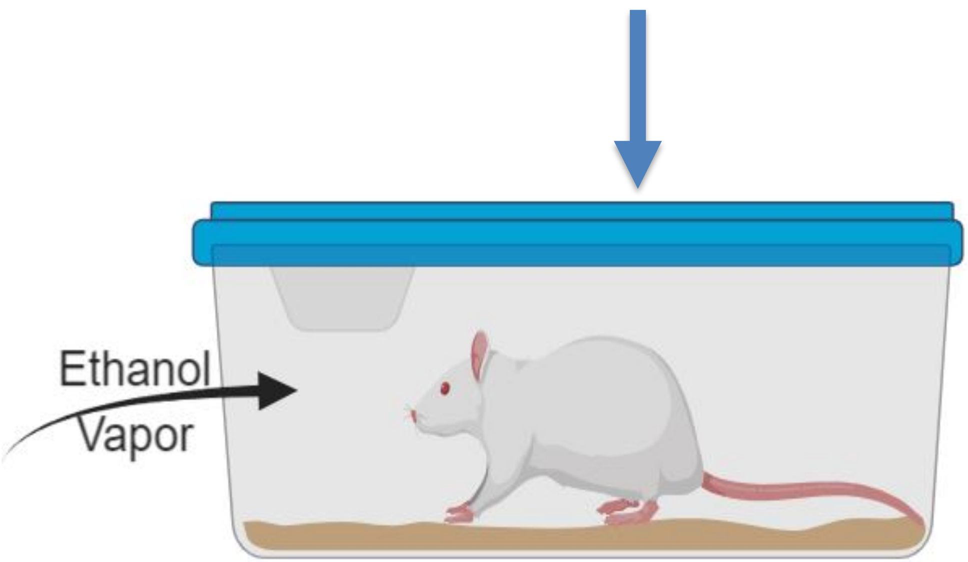


Alcohol or air for 7 weeks



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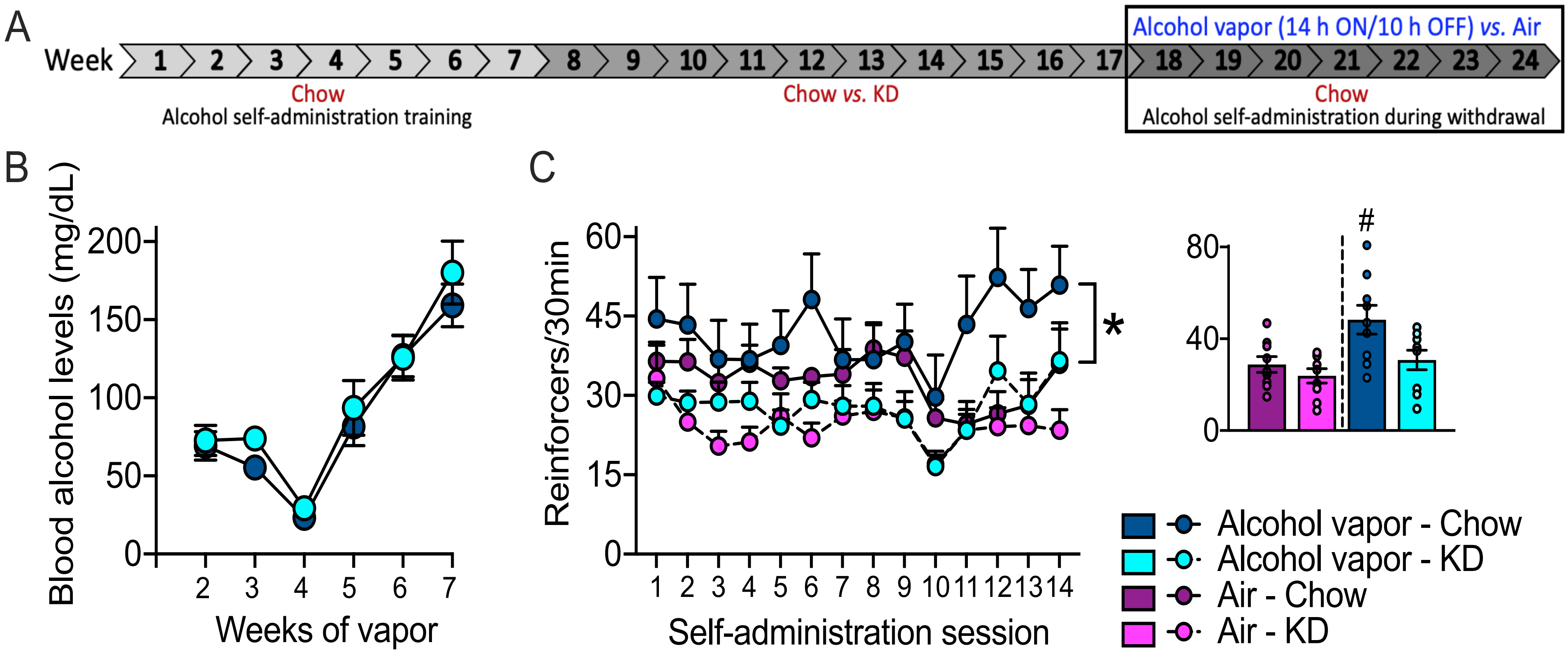

***History of* KD lowers alcohol consumption**

Wiers, Vendruscolo …. Koob, Volkow, under review

National Institute on Alcohol Abuse and Alcoholism

R00 proposal

Perelman School of Medicine
University of Pennsylvania

Aim 1: to test whether metabolic ketosis decreases alcohol consumption in AUD outpatients

H: ***ketosis lowers alcohol consumption***

Aim 2: to measure effects of metabolic ketosis on brain ketone bodies

H: ***Ketones in brain mediate effects of ketosis on alcohol consumption***

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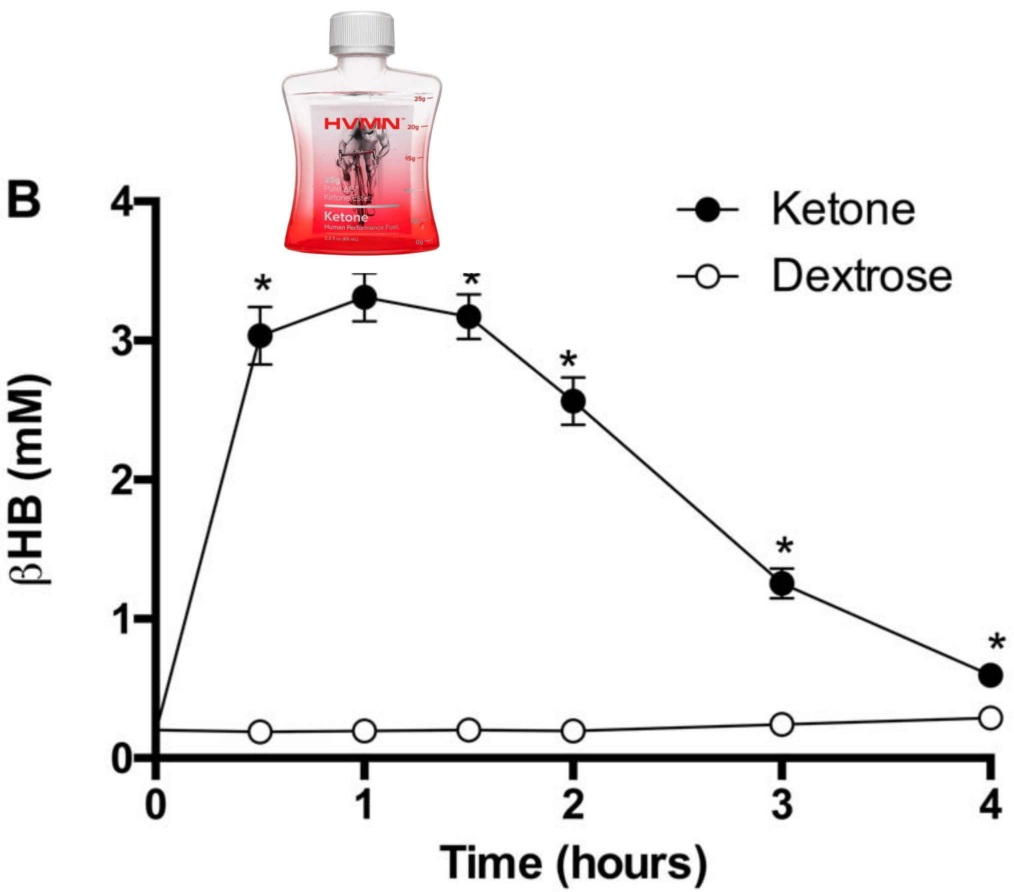
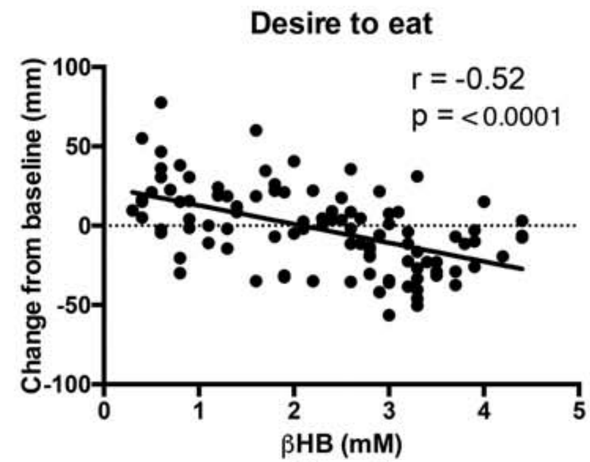
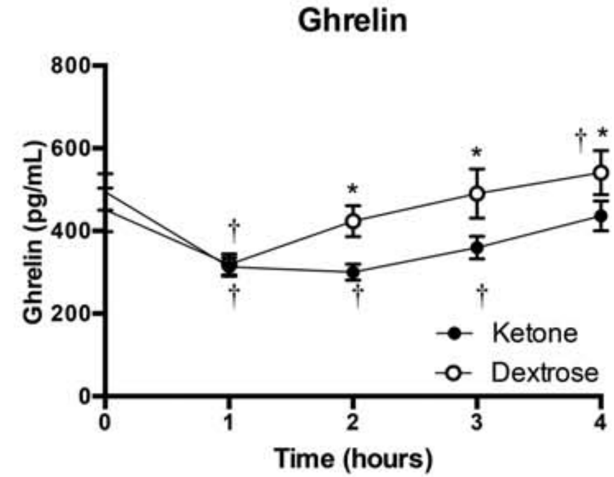
A Ketone Ester Drink Lowers Human Ghrelin and Appetite

Brianna J. Stubbs, Pete J. Cox, Rhys D. Evans, Malgorzata Cyranka, Kieran Clarke, Heidi de Wet

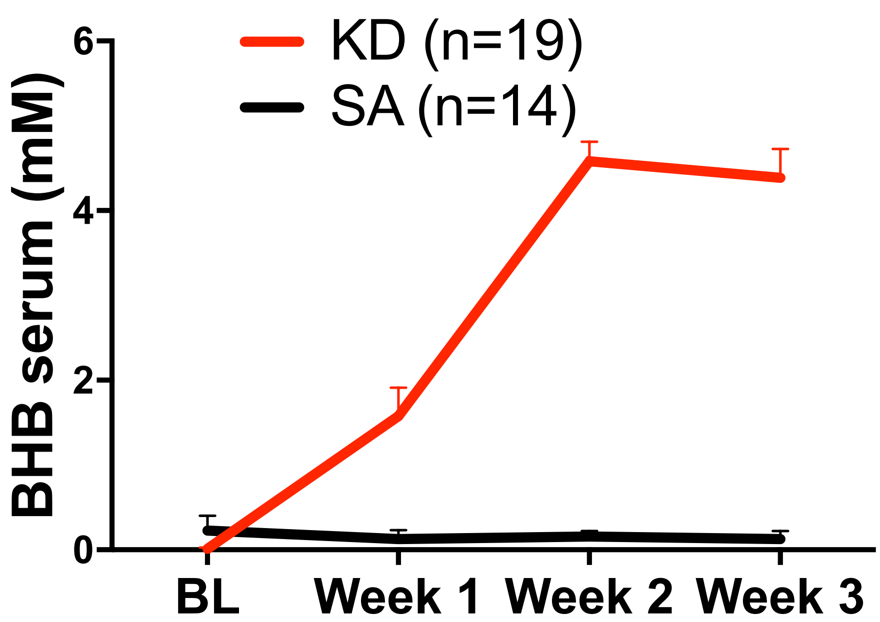




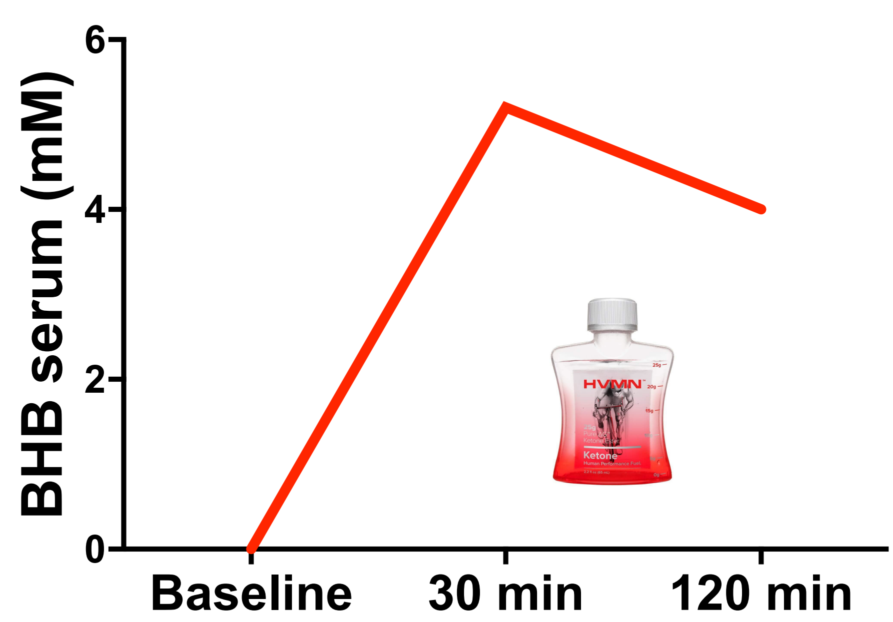


Blood ketones in KD vs **Ketone Ester**

K99: Ketogenic Diet in AUD



N=1 Ketone Ester "pilot" data



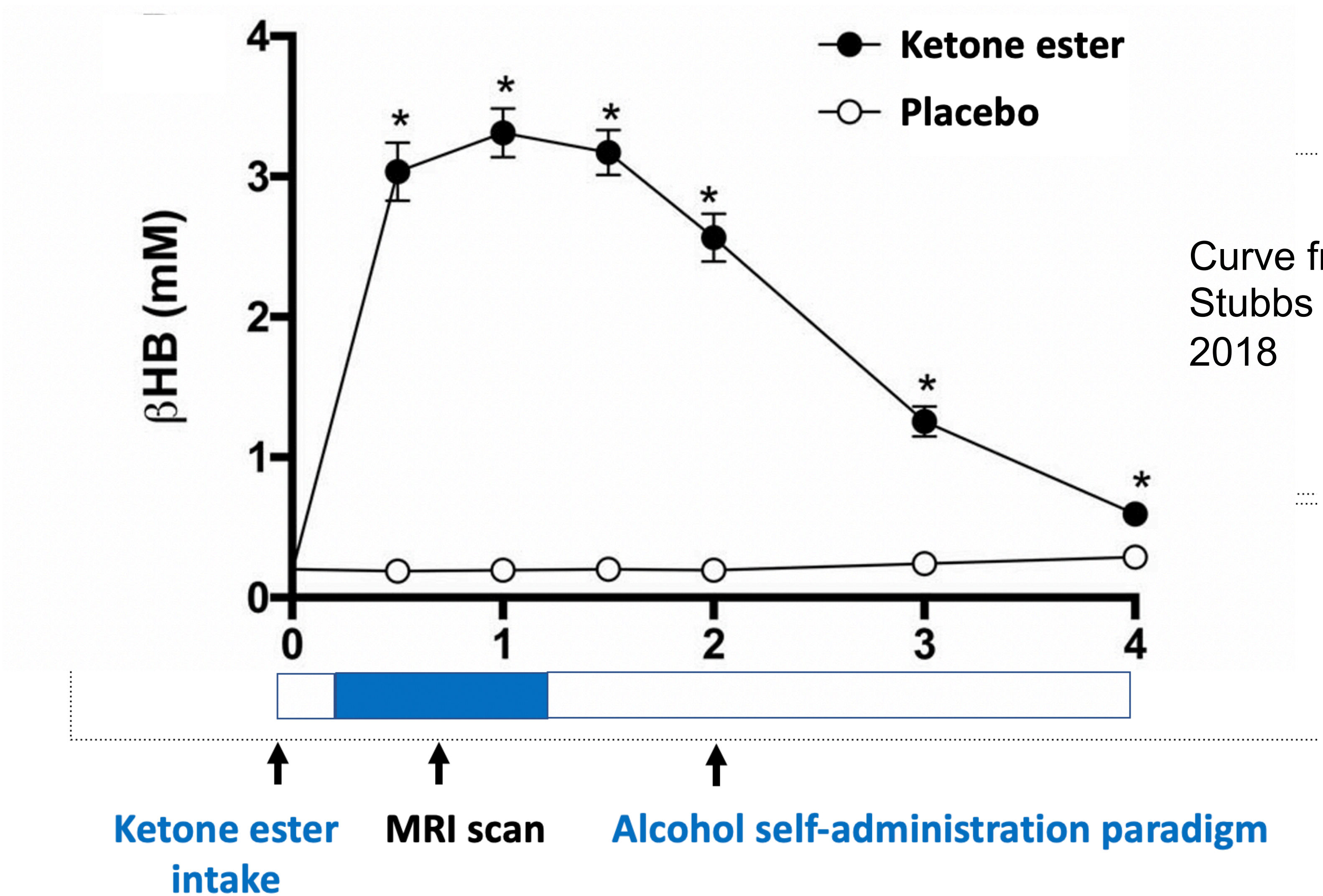
Comparable BHB levels 2-weeks diet versus 30 mins after HVMN ketone ester

Proposed R00 Design at Penn

n = 20 AUD patients (non-treatment seeking)
n = 20 Healthy volunteers

Visit 1	**Ketone Ester**	Random order: 2-way crossover
Visit 2	**Placebo**	

R00 Design: study visits



Curve from Stubbs et al, 2018

1-hr MRI scan (3T Prisma - Hup6)

- T1/T2
- fMRI Alcohol Cue Reactivity

  H: Ketone Ester normalizes cue-induced craving and brain reactivity

- MRS: BHB edited sequence
- H: Faster elevation of BHB in AUD patients than controls

Alcohol self administration: Bar lab

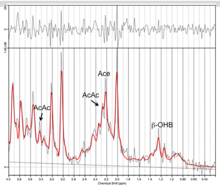
Priming drink

BrAC to 0.02-0.03 g/dL

Each participant received 16$ with which they could purchase 8 alcoholic mini-drinks (2$ each) over the course of 2 hours (max BrAC .1g/dL) OR keep the money

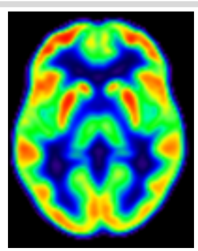
O'Malley, 2002

Talk Outline



Part 1: *K99*
Brain metabolism and alcohol withdrawal

Part 2: *R00*
Brain metabolism and alcohol consumption



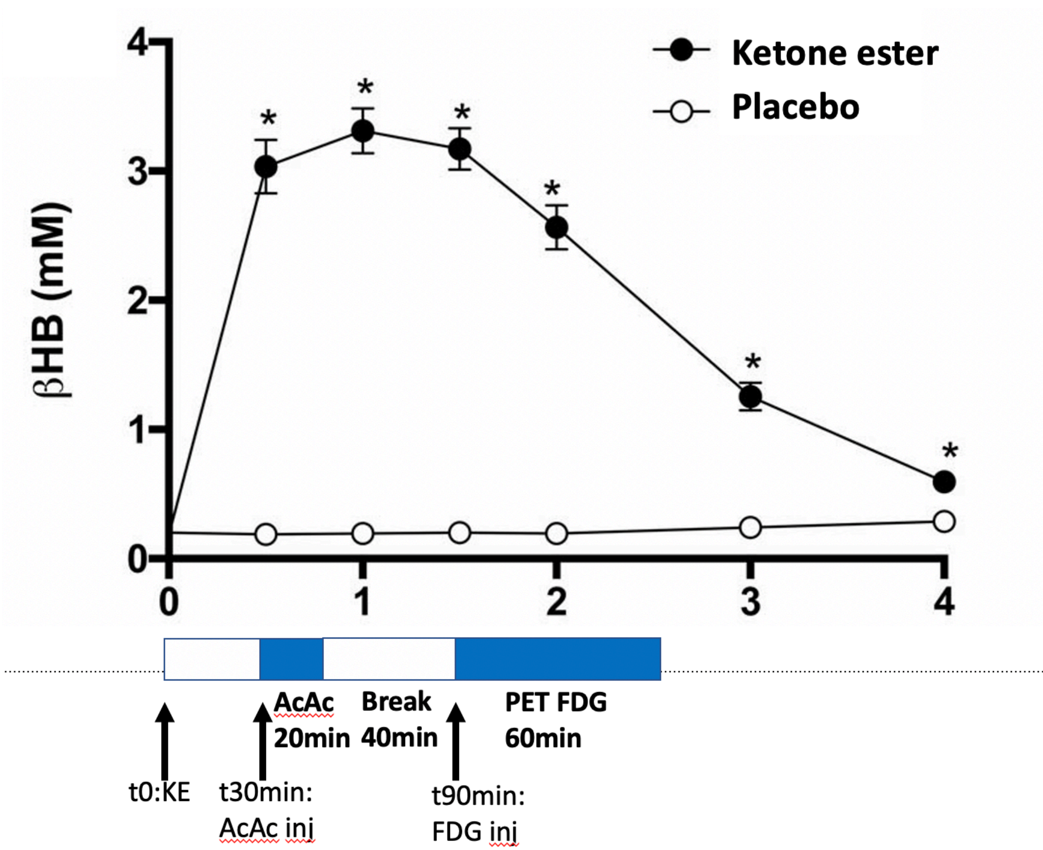
Part 3: *B2B proposal*
Brain metabolism and alcohol tolerance

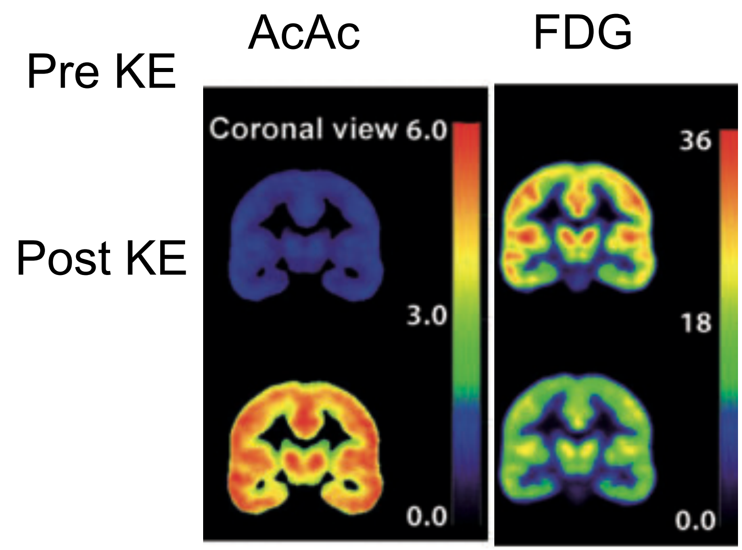
Part 4:
Future Directions

Bench to Bedside proposal (pending)

To test the effect of metabolic ketosis on
(1) brain Acetoacetate ([^{11}C]AcAc) in AUD
H: KE-induced uptake of [^{11}C]AcAc will be faster in AUD than controls, reflecting enhanced brain uptake of AcAc as an alternative to glucose as an energy source in alcohol dependence
(2): alcohol tolerance in AUD
H: Individuals with AUD will be more sensitive to the effects of alcohol

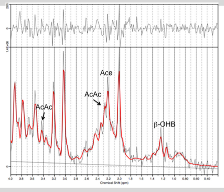
PET scan design





Courchesne-Loyer 2017

Talk Outline



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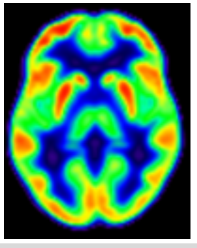

Part 3: *B2B proposal*
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Part 4:
Future Directions

Future Directions

- Collaboration with Paco Bravo: effects of Ketone Ester on Glucose/AcAc metabolism in heart and liver etc (whole body PET scan)
- Larger clinical trial of KD or KE on alcohol consumption in AUD patients
- Effects of metabolic ketosis on NAD+/NADH (brain energy) in AUD (31P-MRS)

Perelman School of Medicine
University of Pennsylvania

Thank you!

National Institute on Drug Abuse

National Institute on Alcohol Abuse and Alcoholism

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