DIFFERENTIAL BRAIN RESPONSES TO ALCOHOL-RELATED AND NATURAL REWARDS ARE ASSOCIATED WITH ALCOHOL USE AND PROBLEMS: EVIDENCE FOR REWARD DYSREGULATION

Jorge S. Martins[1] Ph.D., Keanan J. Joyner[3] M.A., David H. Morris[4] Ph.D., Denis M. McCarthy[2] Ph.D., Christopher J. Patrick[3] Ph.D., & Bruce D. Bartholow[2] Ph.D.
[1] Yale University [2] University of Missouri [3] Florida State University [4] Washington University in St. Louis

BACKGROUND

Multiple theories posit that repeated use of drugs can alter the neurocircuitry of reward processing in ways that bias motivational systems toward drug pursuit[1], at the expense of naturally-occurring rewarding activities[2].

- The **incentive-sensitization theory of addiction**[3,4] posits that cues signaling drug availability take on incentive value of the drugs themselves.
- **Reward-deficit models** posit that risk for drug use is conferred by blunted incentive-motivational value of natural (i.e., nondrug) reinforcers[5,6].
- **Behavioral economic and value-based decision-making models**[7,8] assert that the ratio of drug-free and drug reward is critical to addiction.

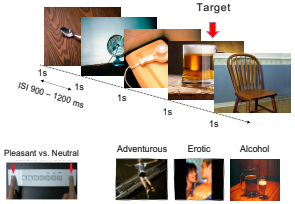
The current study examined **reward dysregulation P3**–a neurophysiological response representing differential value of alcohol vs. natural reinforcers–as a **neurobiological marker** of **problematic drinking** and **AUD risk**.

Primary Hypotheses: The difference in the brain responses to alcohol relative to naturals rewards (i.e., *reward dysregulation* brain index) would be more strongly associated with alcohol use and problems (**Hi**) and would better differentiate problem from nonproblem drinkers than either of its constituents (**Hii**).

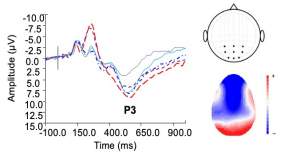
METHOD

Participants were **156 healthy young adults** (61% female; 88% White; M_{age} = 21.9 years). They reported on their past-year alcohol use, binge drinking, and heavy drinking using items from NIAAA Task Force[9]. Participants also reported alcohol problems using the Young Adult Alcohol Consequences Questionnaire (YAACQ[10]) and completed a picture-viewing task[11] while ERPs were recorded.

Picture-Viewing "Oddball" Task



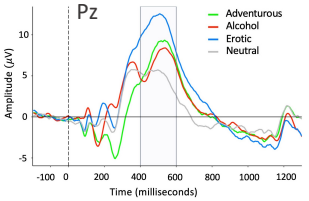
What is the P3 (or P300) of the ERP?



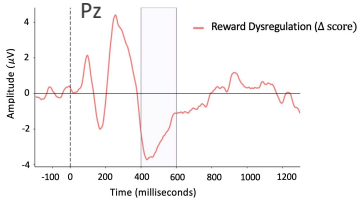
Predictors: P3 ERP response elicited by alcohol cues (ACR-P3) and natural rewards (Reward-P3) and their difference score (i.e., reward dysregulation P3)
Outcomes: Quantity/frequency of alcohol use, binge drinking [4+(women)/5+(men)], the largest number of drinks, and risk for problematic drinking, defined by applying cut-scores suggested previously[10]: low/moderate risk (YAACQ score ≤ 15) vs. high risk (YAACQ total score ≥ 16).

RESULTS

Waveforms as a Function of Image Type



Grand-averaged, stimulus-locked waveforms at channel Pz as a function of image type.



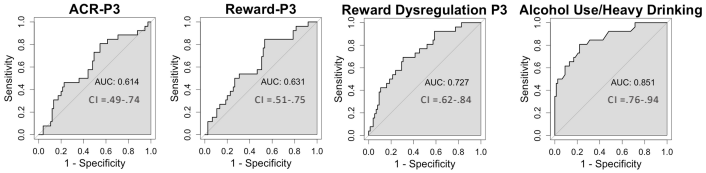
Difference waveform or reward dysregulation waveform (Alcohol minus Natural Rewards).

Summary of Regression Models Predicting Drinking Outcomes

Model	Alcohol Use				Binge Drinking				Heavy Drinking				Alcohol Problems			
	Adj. R^2	*b*	*SE b*	*p*	Adj. R^2	*b*	*SE b*	*p*	Adj. R^2	*b*	*SE b*	*p*	Adj. pseudo-R^2	*b*	*SE b*	*p*
Model 1: ACR-P3	.11				.09				.07				.15			
ACR-P3		0.53	0.34	.115		**0.11**	**0.04**	**.004**		0.09	0.12	.422		**0.03**	**0.01**	**.014**
Model 2: Reward-P3	.09				.03				.09				.14			
Reward-P3		-1.71	2.01	.398		-0.12	0.24	.619		-1.33	0.68	.051		0.01	0.08	.855
Model 3: ACR-P3 + Reward-P3	.12				.12				.11				.16			
ACR-P3		**0.90**	**0.38**	**.021**		**0.16**	**0.04**	**<.001**		**0.27**	**0.13**	**.040**		**0.05**	**0.02**	**.004**
Reward-P3		-4.33	2.28	.059		**-0.59**	**0.26**	**.024**		**-2.12**	**0.77**	**<.001**		-0.13	0.09	.150
Model 4: Reward Dysregulation P3	.13				.11				.11				.15			
Reward Dysregulation P3		**4.15**	**1.68**	**.015**		**0.68**	**0.19**	**<.001**		**1.58**	**0.57**	**<.001**		**0.17**	**0.07**	**.018**

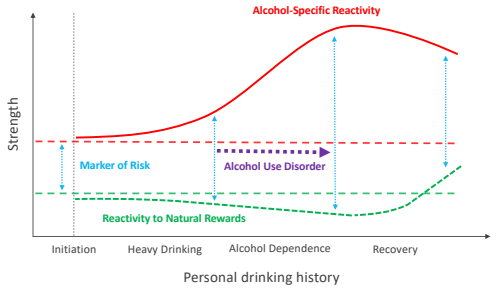
Note. All OLS regression models were estimated controlling for age, sex, race/ethnicity, and an alcohol use/heavy drinking composite (including alcohol use, binge drinking and heavy drinking).

ROC Curves Summarizing Classification Performance in Discriminating Risk



Reward dysregulation P3 successfully differentiated high-risk from low/moderate-risk drinkers (AUC = .73, 95% CI = .62-.84), and did so nearly as well as a composite alcohol use/heavy drinking measure (AUC = .85, 95% CI = .76-.94): AUCs = .73 vs. .85; Z = -1.83, p = .067.

Theoretical Model of Vulnerability for Alcohol Dependance



CONCLUSIONS

Take Home Message: The current results provide the first evidence that alcohol-related reward dysregulation is associated with risk for problematic drinking.

Impact/Significance: Our study suggests the utility of neurophysiological measures for **clinical diagnosis** and **vulnerability assessment** beyond that provided by self-report measures. Our results can contribute to the **development of intervention efforts** aimed at reducing the burden of alcohol misuse.

Limitations:

- The inability to resolve the **etiology** of the reward dysregulation P3 response.
- The inability to resolve whether the Reward-P3 and ACR-P3 **share sources** in the reward processing brain circuits.
- The **sample homogeneity** in terms of demographic characteristics.

Future directions:

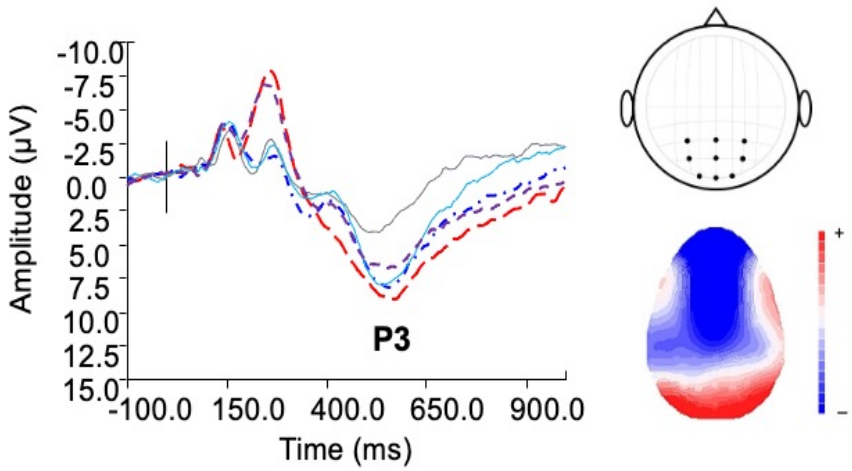
- To examine reward dysregulation P3 and its relation to drinking outcomes in **more diverse populations** and **expand the types of reward-relevant cues** used (e.g., food, money, and social intimacy).
- To clarify the **ontogeny** of the reward dysregulation phenotype using **longitudinal and/or genetically informed designs**.
- To evaluate the **specificity vs. generality** of its effects–in particular, whether reward dysregulation P3 indexes risk for problematic drinking specifically or is associated with broader, transdiagnostic traits (e.g., externalizing proneness) that also increase risk for alcohol problems.

jorge.martins@yale.edu

This work was supported by R01-AA019546 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and NIH Office of Behavioral and Social Sciences Research and R01-AA025451 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

What is the P3 (or P300) of the ERP

Individual differences in reactivity to stimuli: **P3 amplitude of the event-related potentials (ERPs)**



Source: http://www.hanix.net/En/Products/info/id/100.html

Neurophysiological marker of the **incentive salience** or **motivational significance** of a stimulus (e.g., Begleiter, Porjesz, Chou, & Aunon, 1983; Franken, Van Strien, Bocanegra & Huijding, 2011; see also Nieuwenhuis et al., 2005)

Participants and Materials

Participants

156 emerging and young adults – MU community

- 18 to 30 years-old
- Mean age = 21.91 (*SD* = 2.97)
- 61% female
- 88% White

Eligibility criteria:

- Fluent in English
- Aged between **18 to 30 years** old
- No current or past attempts to quit drinking
- No alcohol withdrawal symptoms
- No history of head trauma or neurological disorder

Compensated with **$10 per hour**

Materials and Measures

Picture-viewing oddball task (e.g., Bartholow et al., 2010)

Alcohol-related self-report measures :

Alcohol use (NIAAA, 2003):

- Past 12 mo. drinking quantity and frequency

Binge drinking (NIAAA, 2003):

- Past 12 mo. binge-drinking frequency

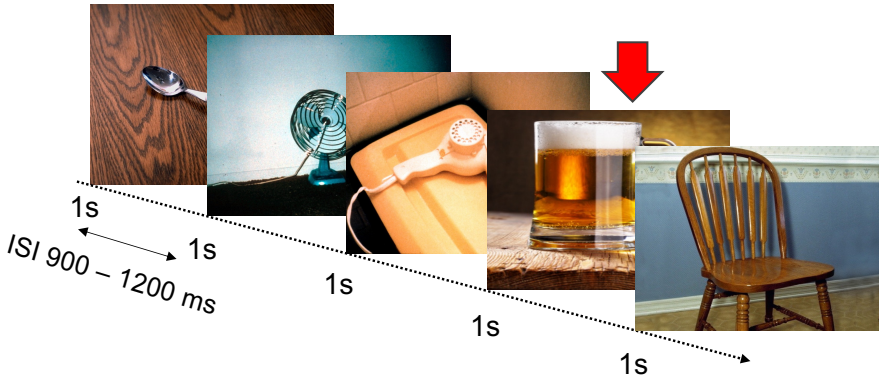
Heavy drinking (NIAAA, 2003):

- Past 12. mo. max. drinks in 24 hours

Alcohol problems (YAACQ; Kahler et al. 2005)

- Young Adult Alcohol Consequences Questionnaire
- Levels of risk for harmful and hazardous drinking.
  - **Low/Moderate risk**: *n* = 77; **High risk**: *n* =26

Picture-Viewing Oddball Task

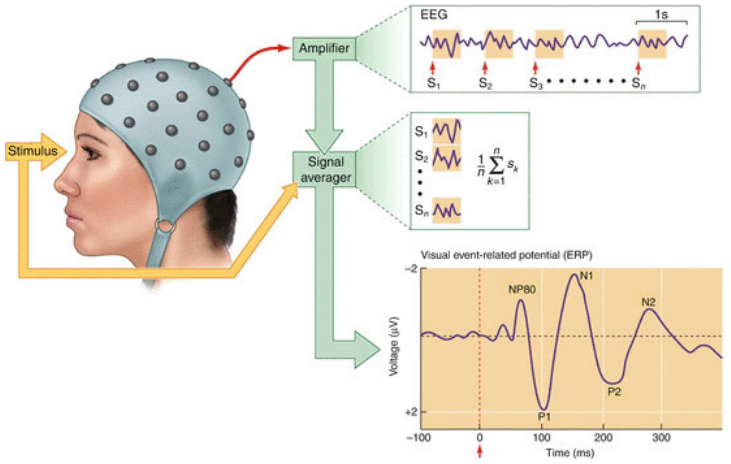


Pleasant vs. Neutral

Adventurous

Erotic

Alcohol



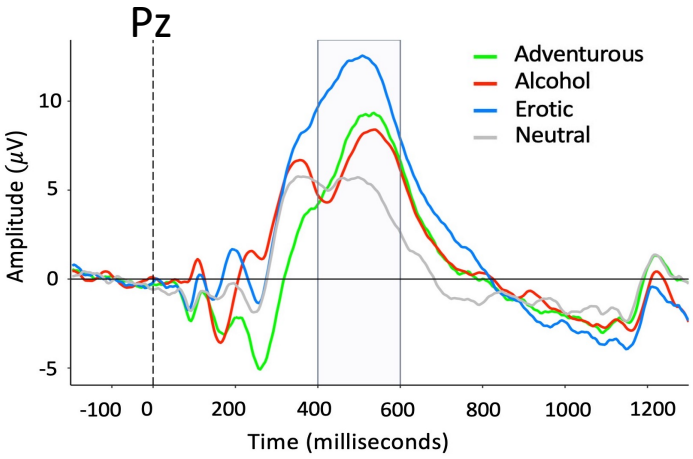
Source: https://sciencebeam.com/accessories-fnirs-bci-erp-sleep-mobo/

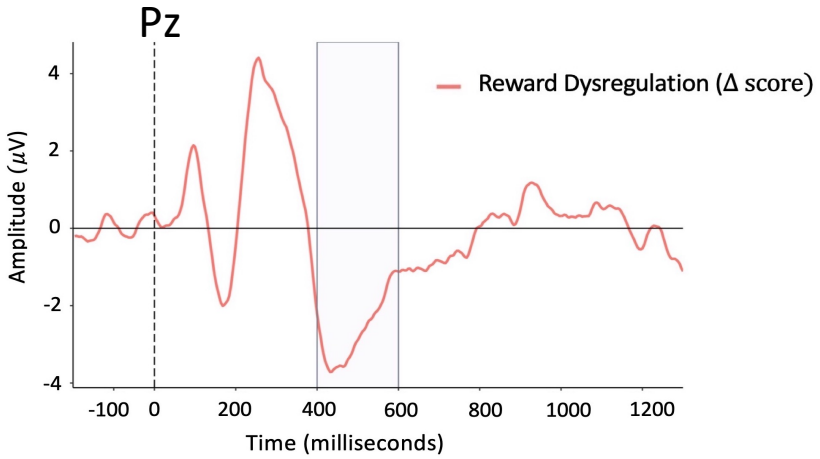
Martins et al. (2019) *Alcohol Clin Exp Res*

Bartholow et al. (2010) *Psychol Addict Behav*

Waveforms as a Function of Image Type

Grand-averaged, stimulus-locked waveforms at **channel Pz**:





P3-ERP amplitude measures:

- P3 amplitude elicited by **alcohol cues** (ACR-P3)
- P3 amplitude elicited by **naturals rewards = erotic + adventurous scenes** (Reward-P3)
- P3 amplitude elicited by **alcohol cues –** P3 amplitude elicited by **naturals rewards** (Reward dysregulation P3)

Results

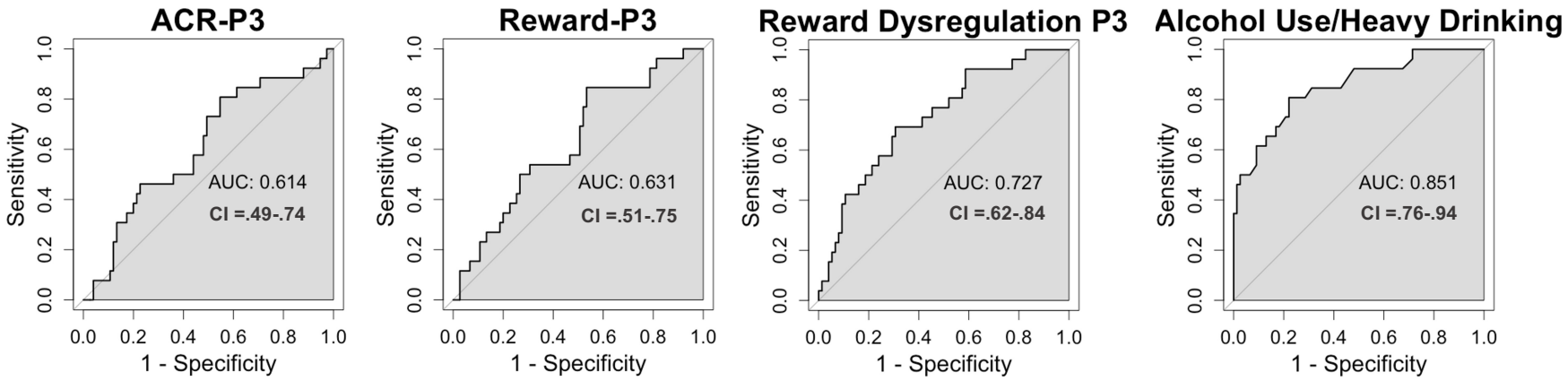
Summary of **regression models** predicting **drinking outcomes**:

Model	Alcohol Use				Binge Drinking				Heavy Drinking				Alcohol Problems			
	Adj. R^2	*b*	*SE b*	*p*	Adj. R^2	*b*	*SE b*	*p*	Adj. R^2	*b*	*SE b*	*p*	Adj. pseudo-R^2	*b*	*SE b*	*p*
Model 1: ACR-P3	.11				.09				.07				.15			
ACR-P3		0.53	0.34	.115		**0.11**	**0.04**	**.004**		0.09	0.12	.422		**0.03**	**0.01**	**.014**
Model 2: Reward-P3	.09				.03				.09				.14			
Reward-P3		-1.71	2.01	.398		-0.12	0.24	.619		-1.33	0.68	.051		0.01	0.08	.855
Model 3: ACR-P3 + Reward-P3	.12				.12				.11				.16			
ACR-P3		**0.90**	**0.38**	**.021**		**0.16**	**0.04**	**<.001**		**0.27**	**0.13**	**.040**		**0.05**	**0.02**	**.004**
Reward-P3		-4.33	2.28	.059		**-0.59**	**0.26**	**.024**		**-2.12**	**0.77**	**<.001**		-0.13	0.09	.150
Model 4: Reward Dysregulation P3	.13				.11				.11				.15			
Reward Dysregulation P3		**4.15**	**1.68**	**.015**		**0.68**	**0.19**	**<.001**		**1.58**	**0.57**	**<.001**		**0.17**	**0.07**	**.018**

Note. All regression models were estimated controlling for age, gender, and race/ethnicity. In addition, regression models predicting alcohol problems also controlled for an alcohol use/heavy drinking composite measure (including alcohol use, binge drinking and heavy drinking).

Results (Cont.)

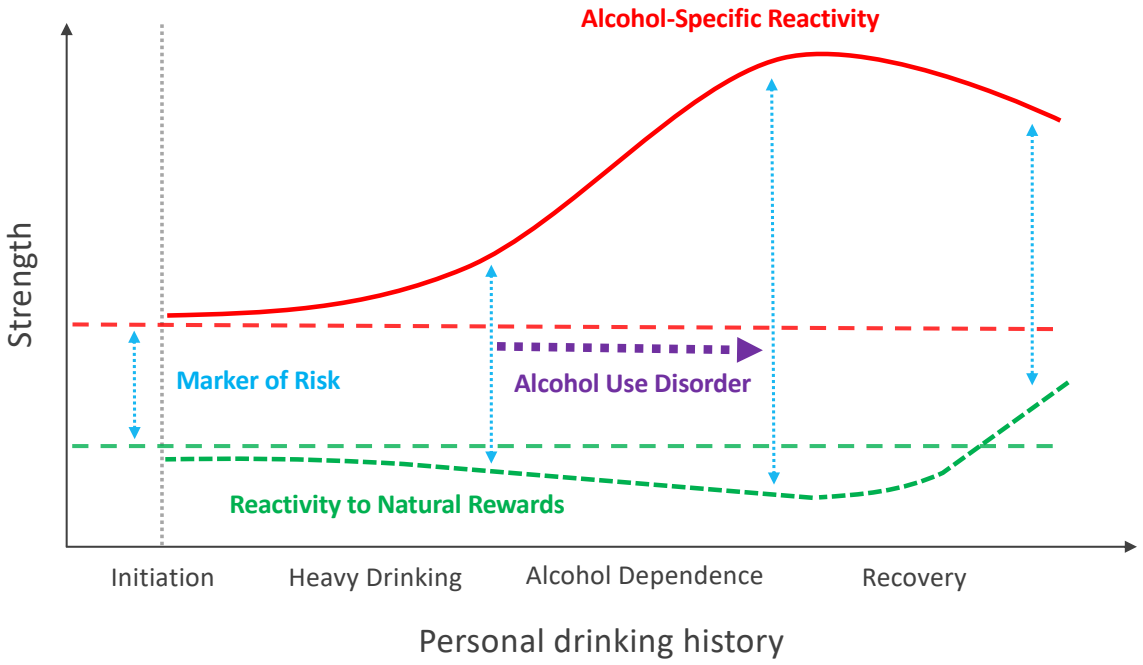
ROC curves summarizing **classification performance** in discriminating **risk**:



Reward dysregulation P3 successfully differentiated high-risk from low/moderate-risk drinkers (AUC = .73, 95% CI = .62-.84), and did so nearly as well as a composite alcohol use/heavy drinking measure (AUC = .85, 95% CI = .76-.94): AUCs = .73 vs. .85; Z = -1.83, p = .067.

Theoretical Implications

Integrative Theoretical Model of Vulnerability for Alcohol Dependence



DIFFERENTIAL BRAIN RESPONSES TO ALCOHOL-RELATED AND NATURAL REWARDS ARE ASSOCIATED WITH ALCOHOL USE AND PROBLEMS: EVIDENCE FOR REWARD DYSREGULATION

Jorge S. Martins[1] Ph.D., Keanan J. Joyner[3] M.A., David H. Morris[4] Ph.D., Denis M. McCarthy[2] Ph.D., Christopher J. Patrick[3] Ph.D., & Bruce D. Bartholow[2] Ph.D.
[1] Yale University [2] University of Missouri [3] Florida State University [4] Washington University in St. Louis

BACKGROUND

Multiple theories posit that repeated use of drugs can alter the neurocircuitry of reward processing in ways that bias motivational systems toward drug pursuit[1], at the expense of naturally-occurring rewarding activities[2].

- The **incentive-sensitization theory of addiction**[3,4] posits that cues signaling drug availability take on incentive value of the drugs themselves.
- **Reward-deficit models** posit that risk for drug use is conferred by blunted incentive-motivational value of natural (i.e., nondrug) reinforcers[5,6].
- **Behavioral economic and value-based decision-making models**[7,8] assert that the ratio of drug-free and drug reward is critical to addiction.

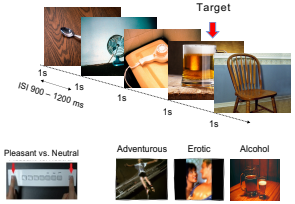
The current study examined **reward dysregulation P3**–a neurophysiological response representing differential value of alcohol vs. natural reinforcers–as a **neurobiological marker** of **problematic drinking** and **AUD risk**.

Primary Hypotheses: The difference in the brain responses to alcohol relative to naturals rewards (i.e., *reward dysregulation* brain index) would be more strongly associated with alcohol use and problems (**Hi**) and would better differentiate problem from nonproblem drinkers than either of its constituents (**Hii**).

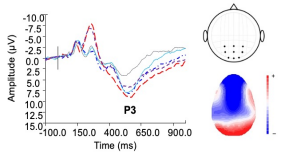
METHOD

Participants were **156 healthy young adults** (61% female; 88% White; M_{age} = 21.9 years). They reported on their past-year alcohol use, binge drinking, and heavy drinking using items from NIAAA Task Force[9]. Participants also reported alcohol problems using the Young Adult Alcohol Consequences Questionnaire (YAACQ[10]) and completed a picture-viewing task[11] while ERPs were recorded.

Picture-Viewing "Oddball" Task



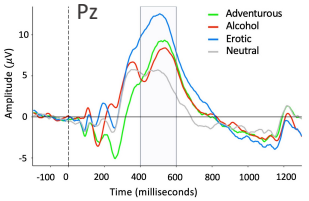
What is the P3 (or P300) of the ERP?



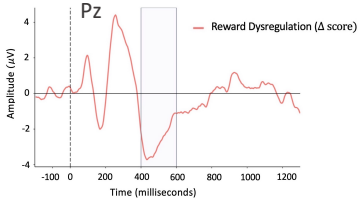
Predictors: P3 ERP response elicited by alcohol cues (ACR-P3) and natural rewards (Reward-P3) and their difference score (i.e., reward dysregulation P3)
Outcomes: Quantity/frequency of alcohol use, binge drinking [4+(women)/5+(men)], the largest number of drinks, and risk for problematic drinking, defined by applying cut-scores suggested previously[10]: low/moderate risk (YAACQ score ≤ 15) vs. high risk (YAACQ total score ≥ 16).

RESULTS

Waveforms as a Function of Image Type



Grand-averaged, stimulus-locked waveforms at channel Pz as a function of image type.



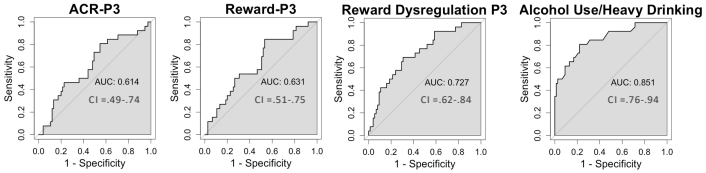
Difference waveform or reward dysregulation waveform (Alcohol minus Natural Rewards).

Summary of Regression Models Predicting Drinking Outcomes

Model	Alcohol Use				Binge Drinking				Heavy Drinking				Alcohol Problems			
	Adj. R^2	*b*	*SE b*	*p*	Adj. R^2	*b*	*SE b*	*p*	Adj. R^2	*b*	*SE b*	*p*	Adj. pseudo-R^2	*b*	*SE b*	*p*
Model 1: ACR-P3	.11				.09				.07				.15			
ACR-P3		0.53	0.34	.115		**0.11**	**0.04**	**.004**		0.09	0.12	.422		**0.03**	**0.01**	**.014**
Model 2: Reward-P3	.09				.03				.09				.14			
Reward-P3		-1.71	2.01	.398		-0.12	0.24	.619		-1.33	0.68	.051		0.01	0.08	.855
Model 3: ACR-P3 + Reward-P3	.12				.12				.11				.16			
ACR-P3		**0.90**	**0.38**	**.021**		**0.16**	**0.04**	**<.001**		**0.27**	**0.13**	**.040**		**0.05**	**0.02**	**.004**
Reward-P3		-4.33	2.28	.059		**-0.59**	**0.26**	**.024**		**-2.12**	**0.77**	**<.001**		-0.13	0.09	.150
Model 4: Reward Dysregulation P3	.13				.11				.11				.15			
Reward Dysregulation P3		**4.15**	**1.68**	**.015**		**0.68**	**0.19**	**<.001**		**1.58**	**0.57**	**<.001**		**0.17**	**0.07**	**.018**

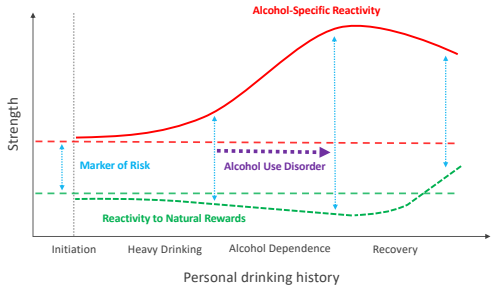
Note. All OLS regression models were estimated controlling for age, sex, race/ethnicity, and an alcohol use/heavy drinking composite (including alcohol use, binge drinking and heavy drinking).

ROC Curves Summarizing Classification Performance in Discriminating Risk



Reward dysregulation P3 successfully differentiated high-risk from low/moderate-risk drinkers (AUC = .73, 95% CI = .62-.84), and did so nearly as well as a composite alcohol use/heavy drinking measure (AUC = .85, 95% CI = .76-.94): AUCs = .73 vs. .85; Z = -1.83, p = .067.

Theoretical Model of Vulnerability for Alcohol Dependance



CONCLUSIONS

Take Home Message: The current results provide the first evidence that alcohol-related reward dysregulation is associated with risk for problematic drinking.

Impact/Significance: Our study suggests the utility of neurophysiological measures for **clinical diagnosis** and **vulnerability assessment** beyond that provided by self-report measures. Our results can contribute to the **development of intervention efforts** aimed at reducing the burden of alcohol misuse.

Limitations:

- The inability to resolve the **etiology** of the reward dysregulation P3 response.
- The inability to resolve whether the Reward-P3 and ACR-P3 **share sources** in the reward processing brain circuits.
- The **sample homogeneity** in terms of demographic characteristics.

Future directions:

- To examine reward dysregulation P3 and its relation to drinking outcomes in **more diverse populations** and **expand the types of reward-relevant cues** used (e.g., food, money, and social intimacy).
- To clarify the **ontogeny** of the reward dysregulation phenotype using **longitudinal and/or genetically informed designs**.
- To evaluate the **specificity vs. generality** of its effects–in particular, whether reward dysregulation P3 indexes risk for problematic drinking specifically or is associated with broader, transdiagnostic traits (e.g., externalizing proneness) that also increase risk for alcohol problems.

jorge.martins@yale.edu

This work was supported by R01-AA019546 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and NIH Office of Behavioral and Social Sciences Research and R01-AA025451 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

References

[1] Berridge KC, Robinson TE. Liking, wanting, and the incentive-sensitization theory of addiction. *Am Psychol*. 2016;71:670-9.

[2] Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. *Nat Rev Neurosci*. 2011;12:652-69.

[3] Robinson TE, Berridge KC. The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Res Rev*. 1993;18:247-91.

[4] Koob GF, Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*. 2001;24:97-129.

[5] Blum K, Cull JG, Braverman ER, Comings DE. Reward deficiency syndrome. *Am Sci*. 1996;84:132-45.

[6] Bickel WK et al. The behavioral economics of substance use disorders: Reinforcement pathologies and their repair. *Annu Rev Clin Psychol*. 2014;10:641-77.

[7] Field M et al. Recovery from addiction: Behavioral economics and value-based decision making. *Psychol Addict Behav*. 2020;34:182-93.

[8] Littel M et al. Electrophysiological indices of biased cognitive processing of substance-related cues: A meta-analysis. *Neurosci Biobehav Rev*. 2012;36:1803-16.

[9] NIAAA. Task Force on Recommended Alcohol Questions. 2003. Available from: https://www.niaaa.nih.gov/research/guidelines-and-resources

[10] Read JP et al. Development and preliminary validation of the young adult alcohol consequences questionnaire. *J Stud Alcohol*. 2006;67:169-77.

[11] Bartholow BD et a. Specificity of P3 Event-related potential reactivity to alcohol cues in individuals low in alcohol sensitivity. *Psychol Addict Behav*. 2010;24:220-8.