ALCOHOL DEPENDENCE
AS A *REWARD DYSREGULATION* BRAIN DISORDER

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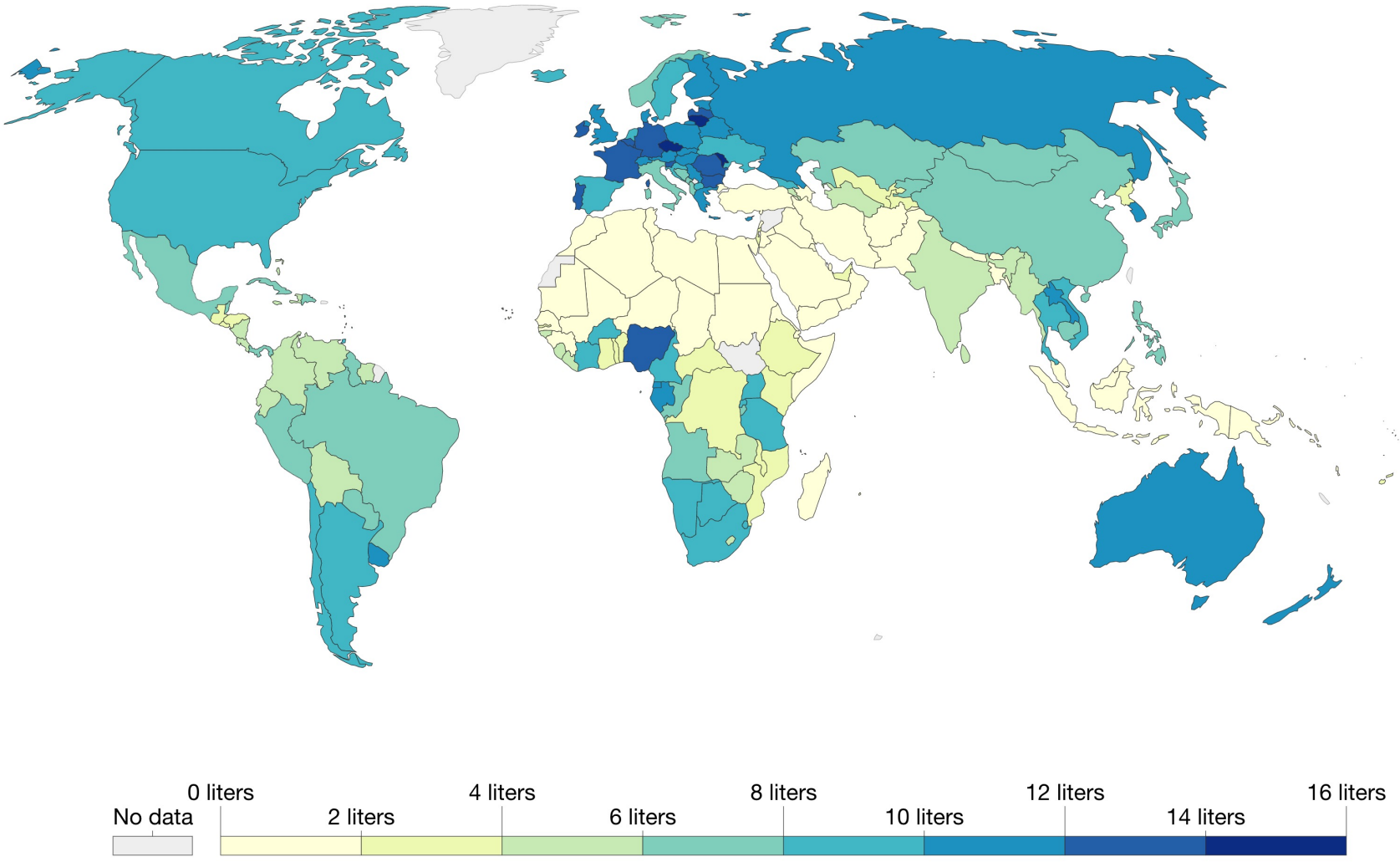
ALCOHOL DEPENDENCE: EPIDIMIOLOGY

- Lifetime prevalence of Alcohol Use Disorder or AUD: 20-30%
- Men > Women
- Globally, nearly 1.4 percent of the population has AUD (107 Million)
- AUD prevalence: 15 million (US), 23 million (EU)
- Earlier age of onset increases risk of AUD later in life
- Most common during young adulthood: 18–35 years
- AUD runs in families: 50% genetics
- High co-morbidity in individuals with AUD

ALCOHOL «EPIDEMIC»



Source: World Bank

OurWorldInData.org/alcohol-consumption • CC BY

ALCOHOL USE AND COVID-19

Business | Health

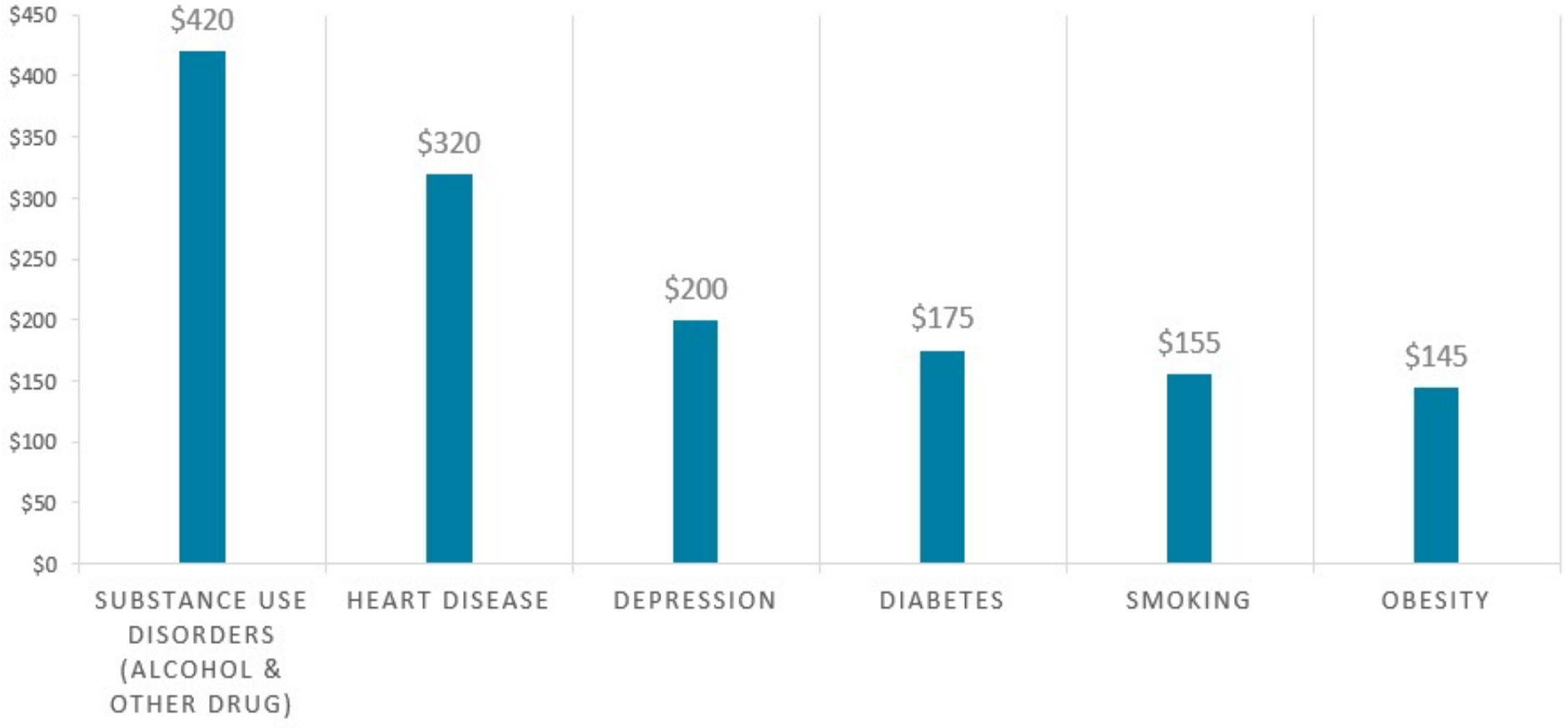
Pandemic drives alcohol sales — and raises concerns about substance abuse

As people stay at home and alcohol sales skyrocket, USC experts examine the physical, emotional and mental risks of substance abuse amid the global outbreak.

BY **Gary Polakovic** • APRIL 14, 2020

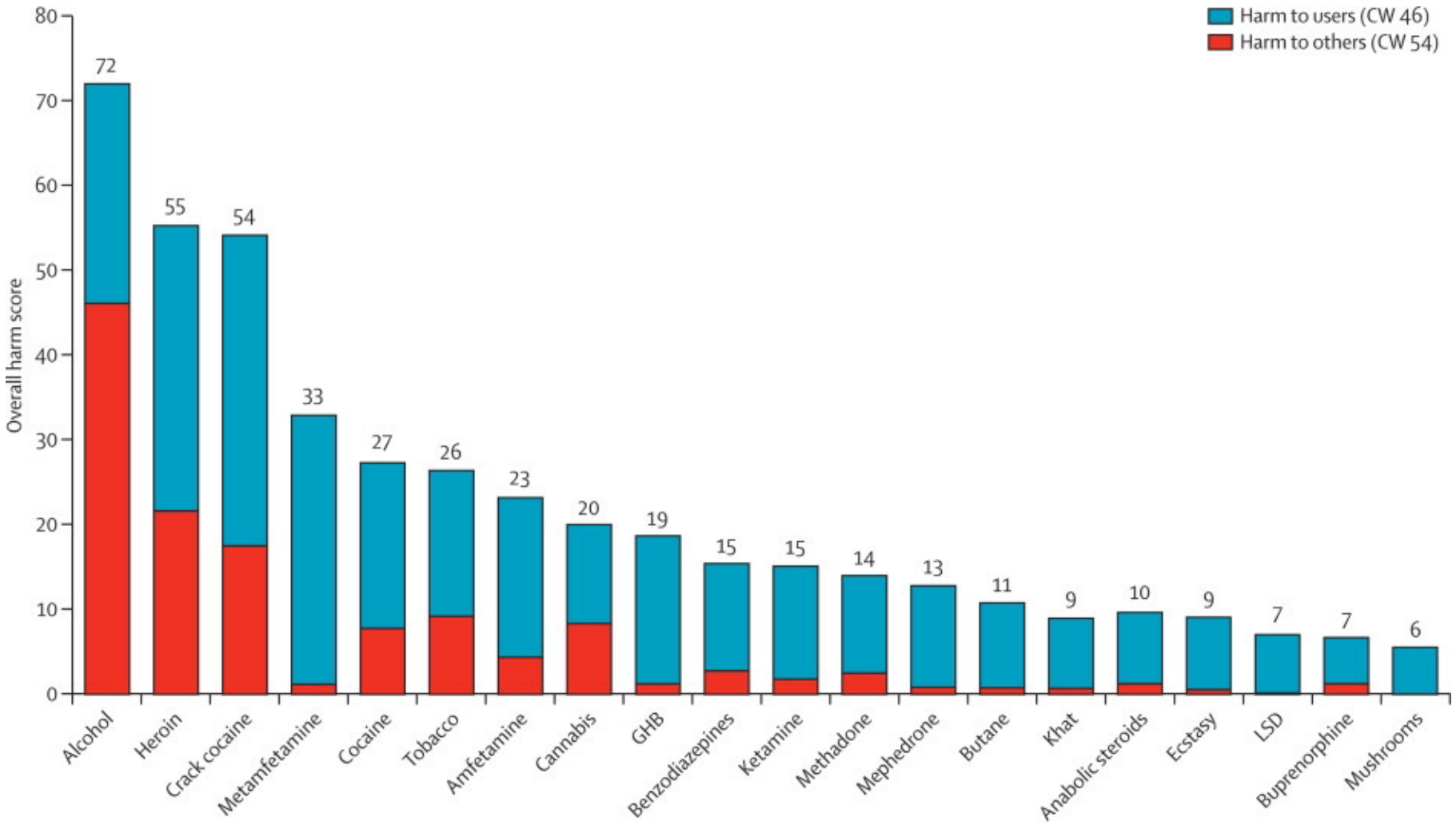
DISEASE BURDEN AND ECOMONIC COSTS

Economic Cost to society by disease (in Billions)



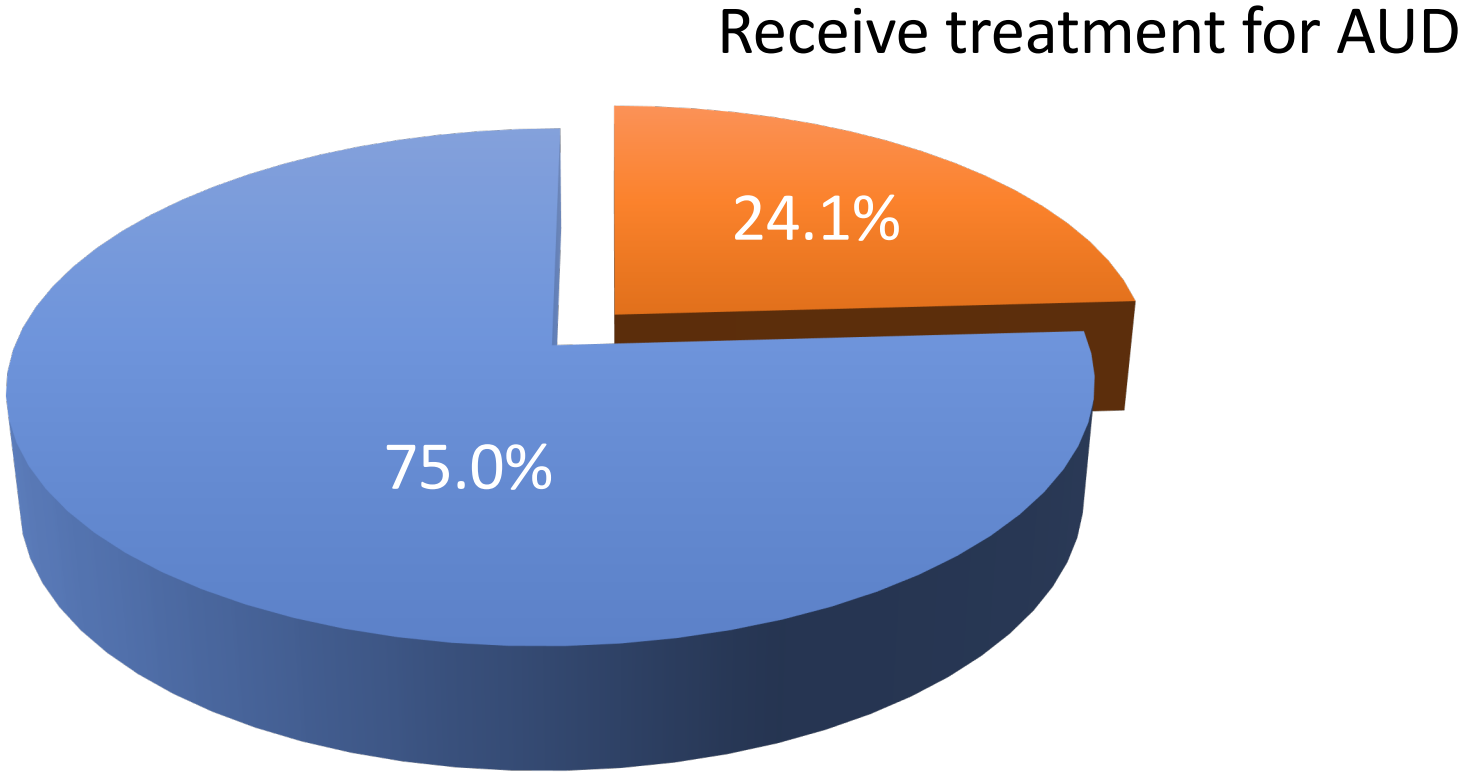
Bouchery et al. 2011 *American Journal of Preventive Medicine*

ALCOHOL MISUSE AND HARM

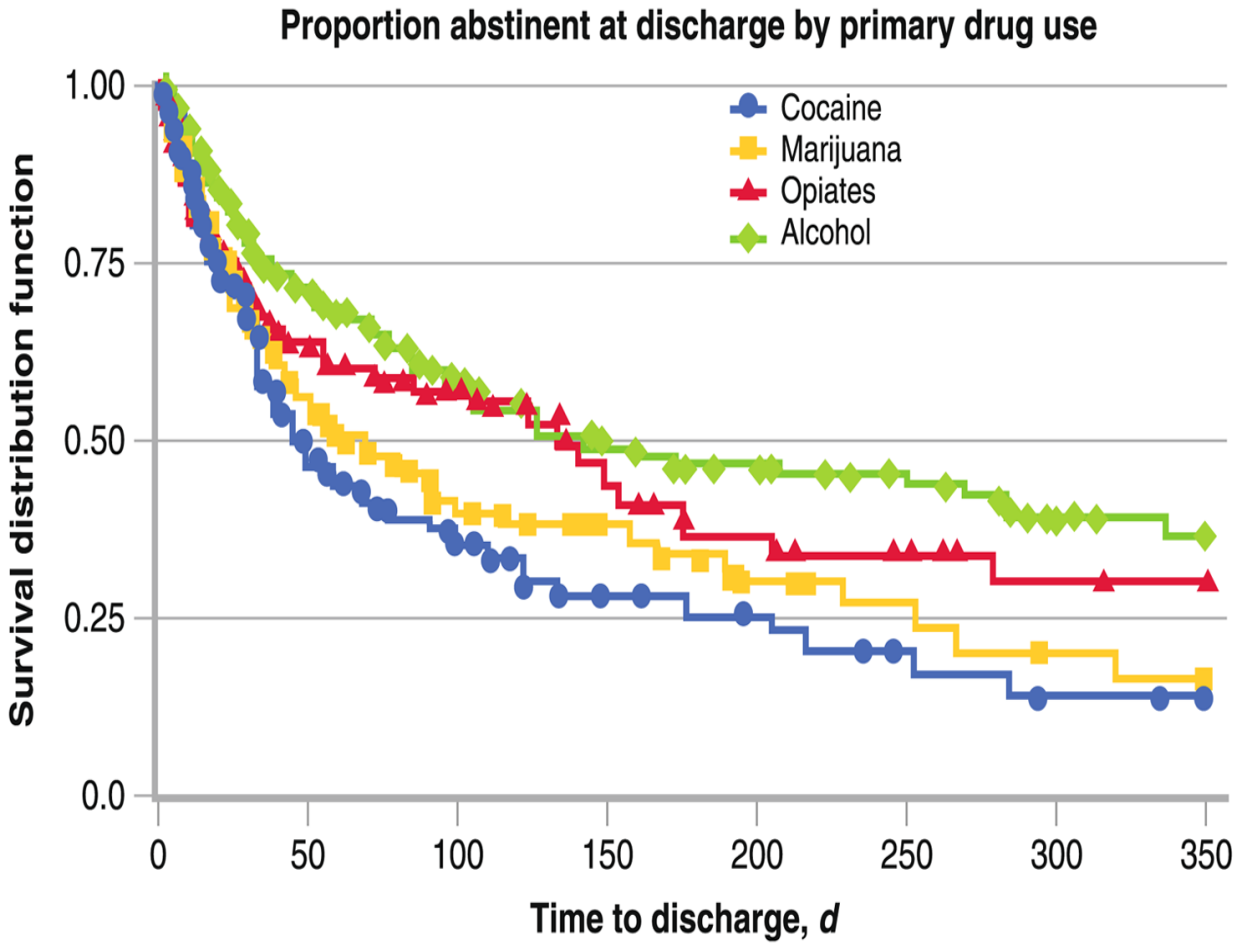


Nutt et al. 2010 *The Lancet*

ALCOHOL DEPENDENCE: TREATMENT GAP



ALCOHOL DEPENDENCE: TREATMENT (IN)EFFICACY



Sinha et al. 2011 *Current Psychiatry Reports*

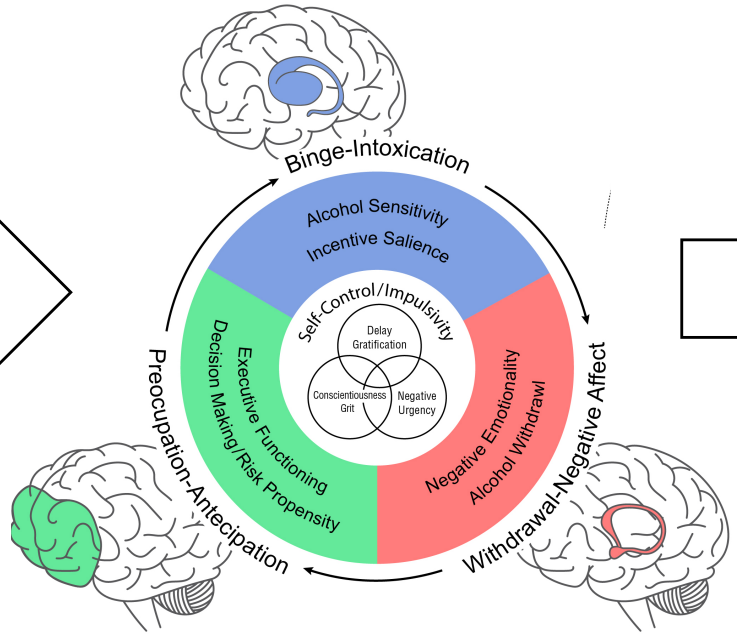
RESEARCH APPROACH

PREVENTION

TREATMENT

Risk Factors

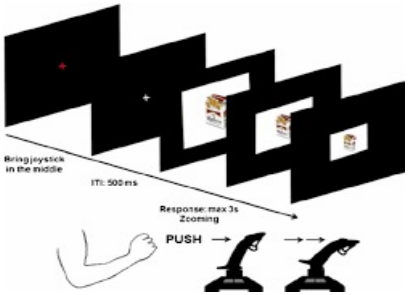
Prognostic

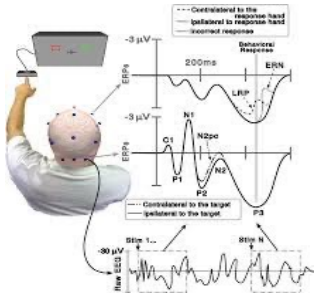


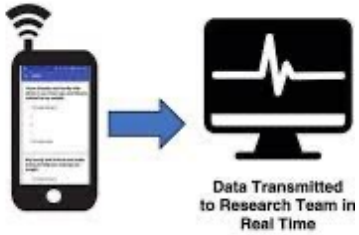
Vulnerability Exposure

Addiction Recovery

Behavioral **EEG/ERPs** **fMRI** **Daily Surveys**







STUDY 1 – PREVENTION

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

SUBSTANCE USE DISORDER AND REWARD CUES

- Individuals with SUDs and heavy users have *blunted* reactivity to non-drug-related rewards and *enhanced* reactivity to drug-related cues.

Natural Reinforcers

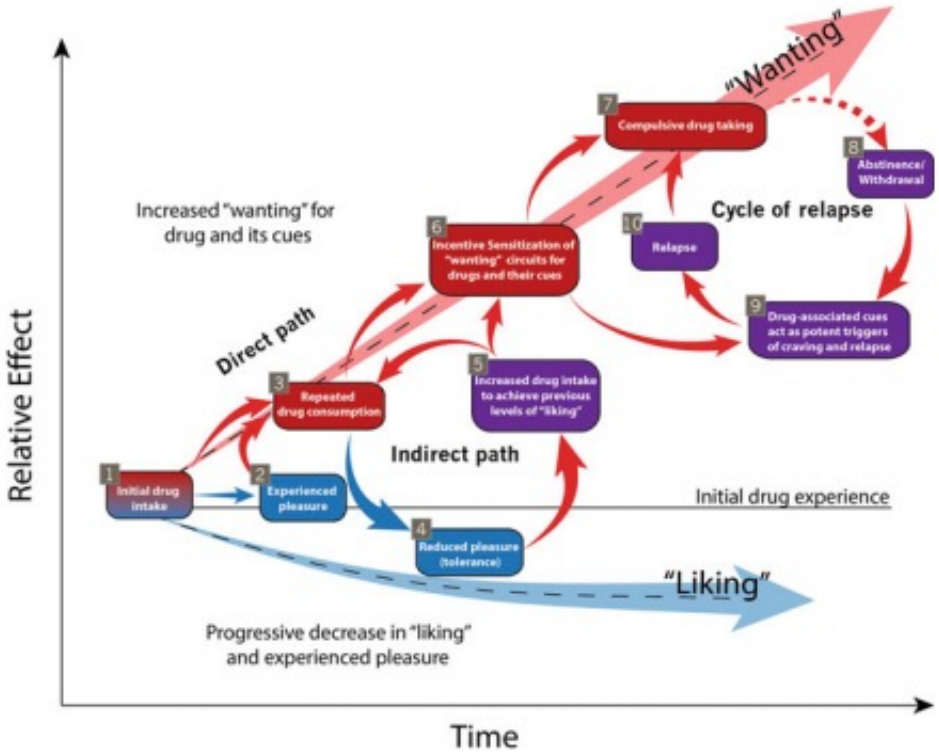
Drug-related cues

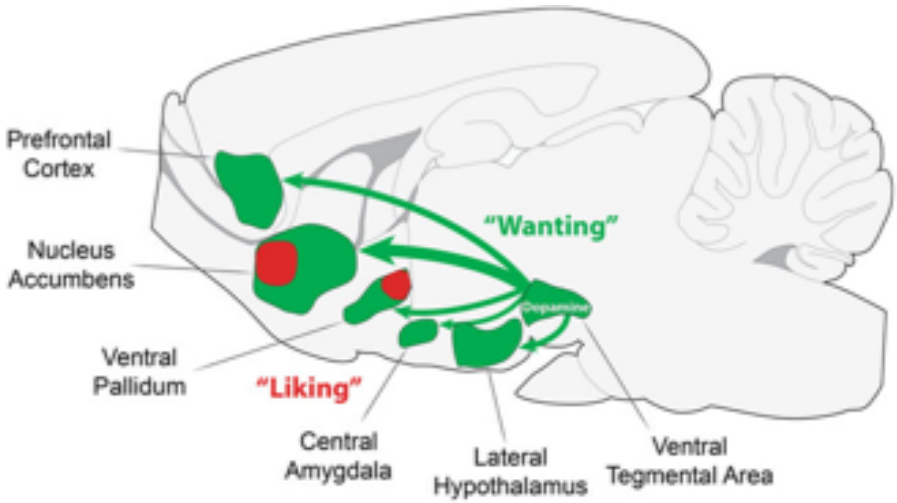
INCENTIVE-MOTIVATIONAL THEORIES OF ADDICTION

- Individuals with SUDs, including AUD, show an enhanced reactivity to substance-related cues (e.g., Little et al., 2012)
  - Behavioral paradigms: attentional bias (e.g., Field et al., 2006, 2008, 2009) and approach motivation bias (e.g., Wiers et al., 2016; Franken et al., 2003)
  - Neuroimaging studies (e.g., Heinz et al., 2007; Wrase et al., 2007, Greck et al., 2009)
  - Electrophysiological studies (e.g., Hermann et al., 2001; Namkoong et al., 2004)

INCENTIVE-SENSITIZATION THEORY OF ADDICTION

- Incentive-sensitization theory (Robinson & Berridge, 1993, 2000, 2003)





REWARD DEFICIT MODELS OF ADDICTION

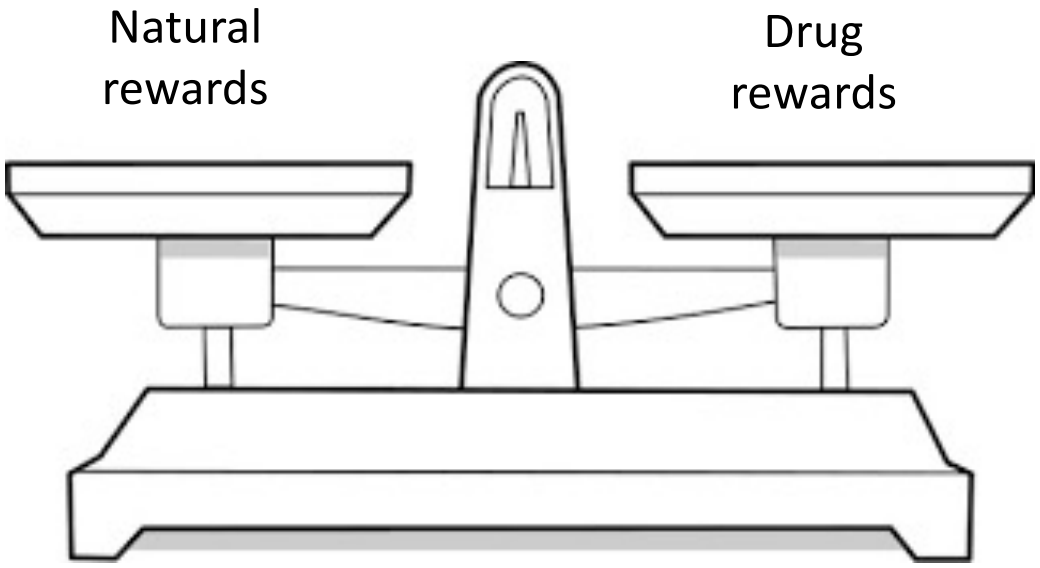
- Individuals with SUDs, including AUD, generally experience a hyposensitivity to non-substance-related or natural reinforcers (e.g., sex, food, money, etc.)
  - Neuroimaging studies (e.g., Heinz et al., 2007; Wrase et al., 2007, Greck et al., 2009)
  - Electrophysiological studies (e.g., Porjesz et al., 1987; Kamarajan et al., 2012)
- Two theoretical perspectives:
  - Reward-deficiency hypothesis (Blum, Cull, Braverman, & Comings, 1996; Blum et al., 2013; Bowirrat & Oscar-Berman, 2005)
  - Allostatic model (Koob & Le Moal, 2000, 2001, 2008a, 2008b; Koob, & Volkow, 2010, 2016)

LIMITATIONS OF PREVIOUS RESEARCH

Even though previous research demonstrates that individuals with SUDs and heavy users typically show enhanced reactivity to substance-related cues and blunted reactivity to natural reinforcers (e.g., sex, food, money, etc.), these indices show low predictive power and inconsistent associations with measures of intensity of use, craving, and likelihood of relapse.

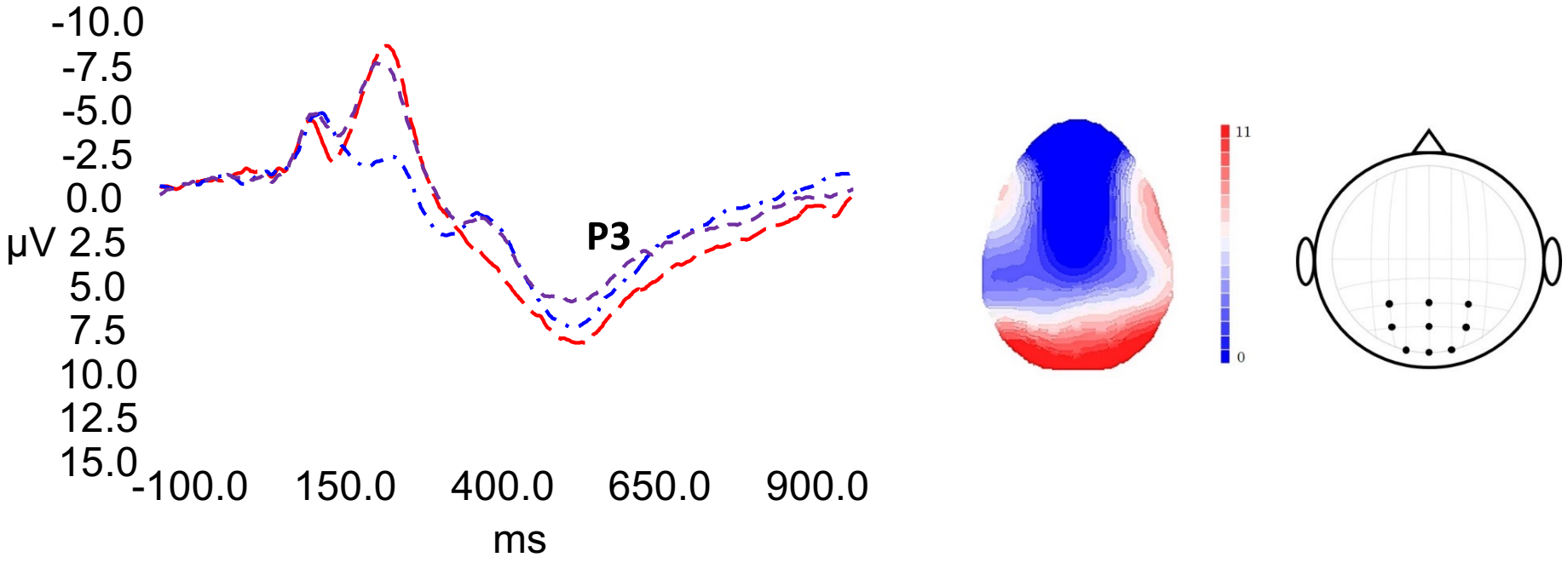
STUDY 1

The current study examined *reward dysregulation* (relative difference between reactivity to alcohol cues and reactivity to natural rewards) as a potential biobehavioral marker of harmful and hazardous drinking.



WHAT IS THE P3 (OR P300) OF THE ERP?

- Individual differences in neurophysiological reactivity to stimuli



- Neurophysiological marker of the motivational significance of a stimulus

  (e.g., Begleiter, Porjesz, Chou, & Aunon, 1983; Franken, Van Strien, Bocanegra & Huijding, 2011; Nieuwenhuis et al., 2005)

METHODS

PARTICIPANTS

- 156 emerging and young adults – MU and surrounding 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

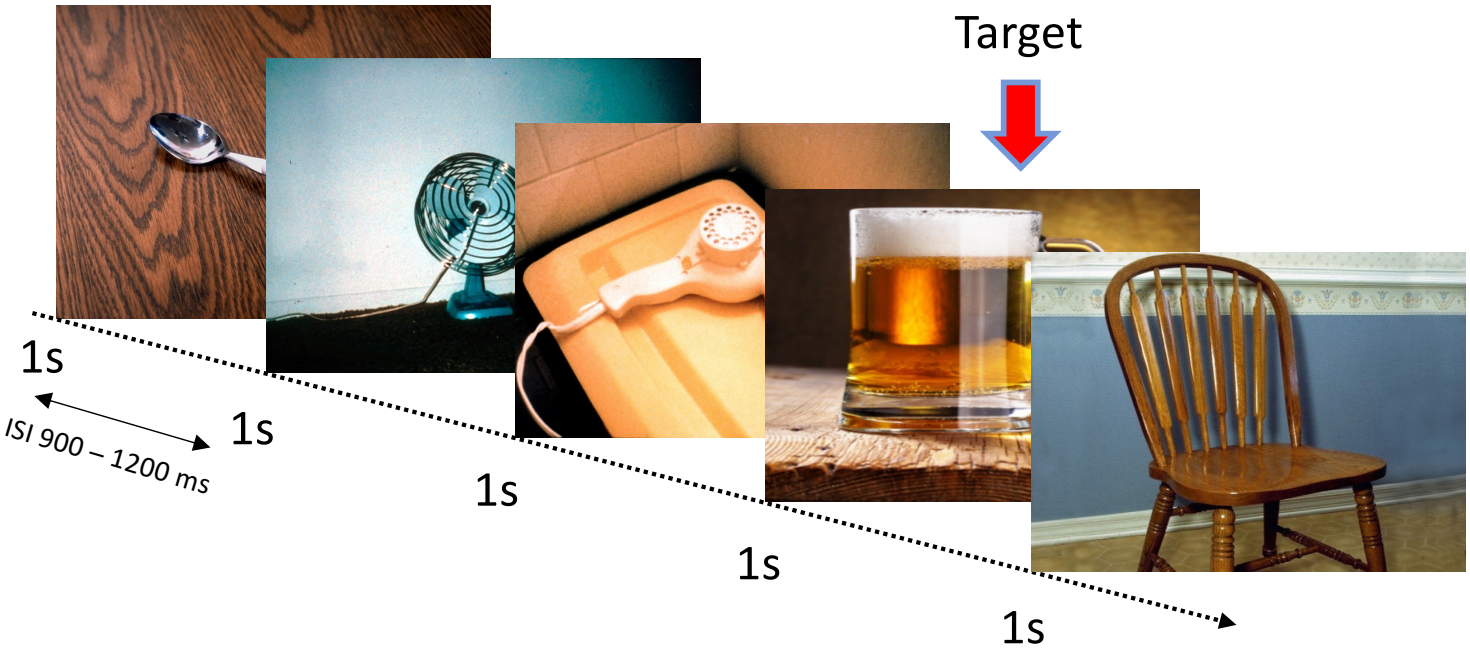
MATERIALS AND MEASURES

- Picture-viewing oddball task
- Alcohol-related self-report measures
  - Alcohol use (NIAAA, 2003)
    - Drinking quantity and frequency in the **past 30 days/past 12 months**
  - Binge drinking (NIAAA, 2003)
    - Binge-drinking frequency in the **past 30 days/past 12 months**
  - Heavy drinking (NIAAA, 2003)
    - Largest number of drinks consumed within 24 hours in the **past 30 days**
    - Largest number of drinks consumed within 24 hours in the **past 12 months**
    - **Lifetime** largest number of drinks consumed within 24 hours
  - Alcohol problems
    - Young Adult Alcohol Consequences Questionnaire (YAACQ; Kahler et al. 2005)

MATERIALS AND MEASURES

- Young Adult Alcohol Consequences Questionnaire (YAACQ):
  - Risky behavior
  - Poor self-care
  - Diminished self-perception
  - Physiological dependence
  - Blackout drinking
  - Social-Interpersonal
  - Academic-occupational
  - Impaired control
- Levels of risk for harmful and hazardous drinking (Read et al., 2016):
  - Low/Moderate risk: *n* = 77
  - High risk: *n* = 26

PICTURE-VIEWING «ODDBALL» TASK



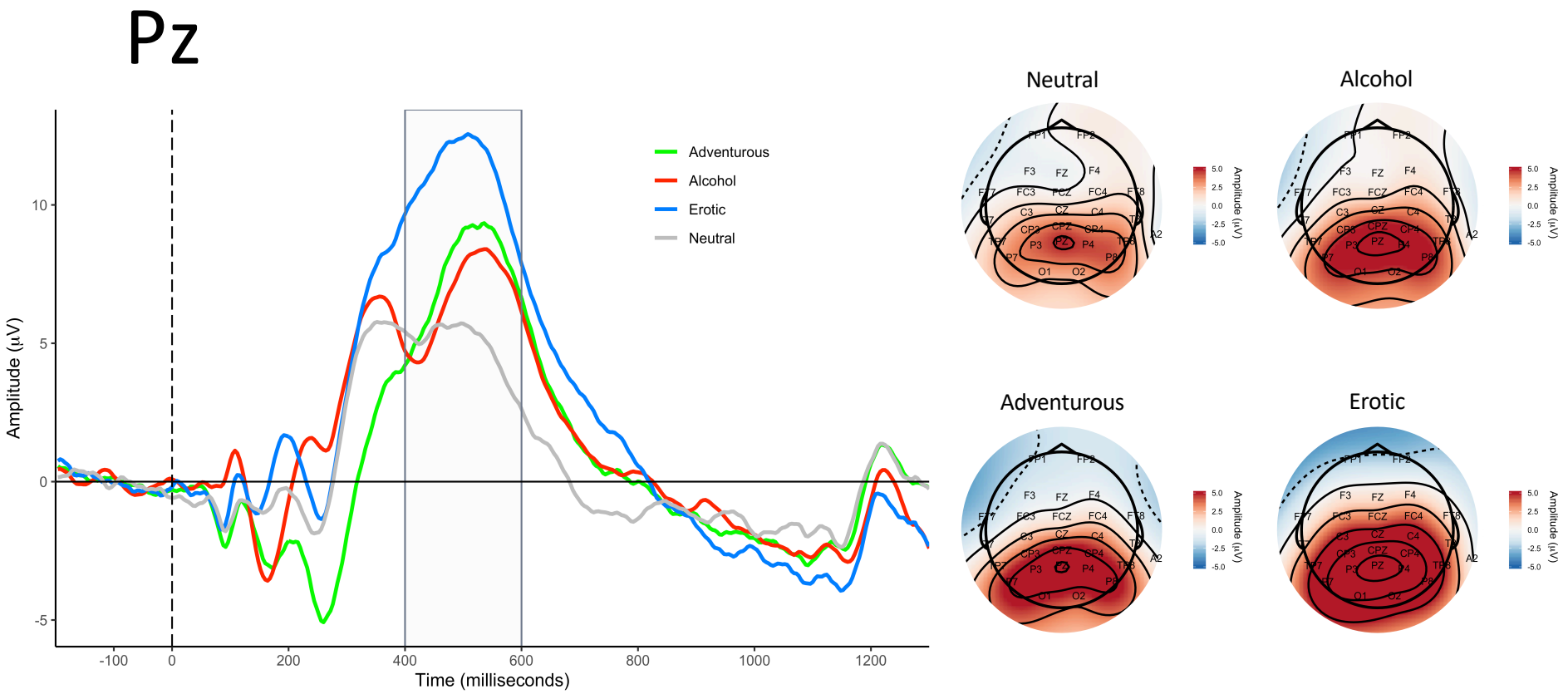
Pleasant vs. Neutral

Adventurous

Erotic

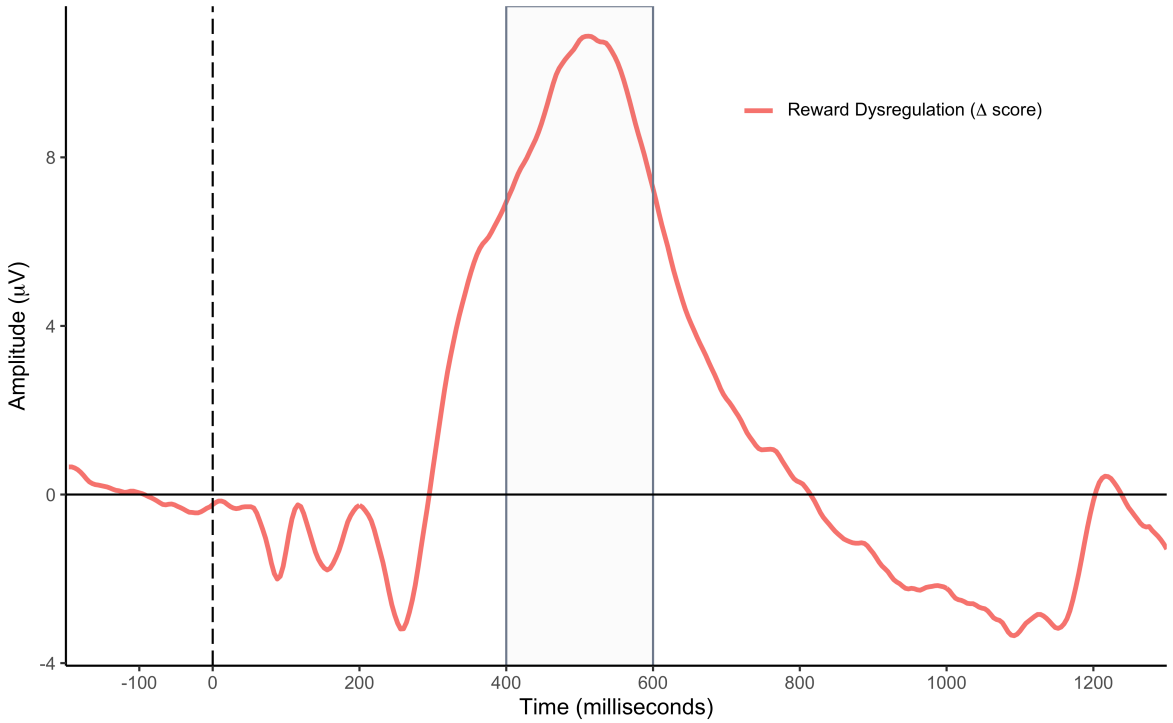
Alcohol

WAVEFORMS

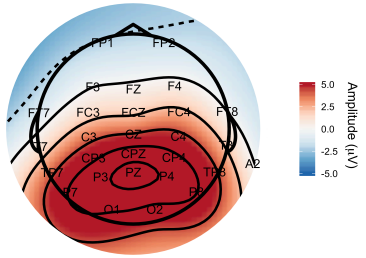

Pz
Adventurous
Alcohol
Erotic
Neutral
Amplitude (μV)
Time (milliseconds)
10
5
0
-5
-100
0
200
400
600
800
1000
1200
Neutral
Alcohol
Adventurous
Erotic
Amplitude (μV)
5.0
2.5
0.0
-2.5
-5.0

WAVEFORMS

Pz



Reward Dysregulation



RESULTS

REGRESSION MODELS PREDICTING ALCOHOL OUTCOMES

Model	Alcohol Use				Binge Drinking				Heavy Drinking				Alcohol Problems			
	b	*SE b*	*t*	*p*	*b*	*SE b*	*t*	*p*	*b*	*SE b*	*t*	*p*	*b*	*SE b*	*Z*	*p*
Model 1: Alcohol P3																
Age (in years)	0.59	0.658	0.899	.676	0.03	0.093	0.305	.761	0.04	0.200	0.202	.840	0.02	0.032	0.589	.556
Gender (0 = female, 1 = male)	4.93	4.406	1.120	.372	0.28	0.621	0.454	.651	**2.77**	**1.341**	**2.064**	**.042**	0.10	0.205	0.480	.631
Race (0 = non-White; 1 = White)	8.68	7.238	1.200	.266	1.40	0.971	1.445	.153	1.72	2.203	0.781	.437	-0.35	0.420	-0.827	.408
Alcohol Involvement													**0.05**	**0.012**	**4.546**	**< .001**
Alcohol P3	8.93	0.483	1.730	.234	**0.16**	**0.067**	**2.452**	**.016**	0.16	0.147	1.081	.283	0.02	0.021	1.177	.239
Model 2: Natural Rewards P3																
Age (in years)	0.30	0.659	0.452	.652	-0.02	0.095	-0.199	.843	-0.03	0.197	-0.169	.866	0.01	0.032	0.350	.726
Gender (0 = female, 1 = male)	1.17	4.676	0.250	.803	-0.39	0.670	-0.592	.555	1.63	1.397	1.169	.246	-0.04	0.223	-0.213	.831
Race (0 = non-White; 1 = White)	8.16	7.334	1.112	.270	1.29	1.003	1.285	.203	1.61	2.191	0.737	.464	-0.41	0.426	-0.985	.324
Alcohol Involvement													**0.06**	**0.012**	**4.738**	**< .001**
Natural Rewards P3	-2.58	2.752	-0.938	.351	-0.32	0.393	-0.812	.419	-1.12	0.822	-1.362	.177	-0.13	0.129	-0.976	.329
Model 3: Reward Dysregulation P3																
Age (in years)	0.47	0.635	0.748	.457	0.01	0.090	0.069	.945	0.03	0.192	0.141	.888	0.01	0.031	0.456	.648
Gender (0 = female, 1 = male)	1.53	4.200	0.365	.716	-0.39	0.584	-0.662	.510	2.00	1.271	1.577	.119	-0.06	0.196	-0.316	.752
Race (0 = non-White; 1 = White)	8.73	7.101	1.231	.222	1.35	0.951	1.425	.158	1.78	2.149	0.828	.410	-0.43	0.401	-1.064	.288
Alcohol Involvement													**0.05**	**0.012**	**4.445**	**< .001**
Reward Dysregulation P3 (Δ score)	**5.11**	**2.094**	**2.442**	**.017**	**0.91**	**0.296**	**3.064**	**< .001**	**1.42**	**0.634**	**2.235**	**.028**	**0.26**	**0.102**	**2.520**	**.012**

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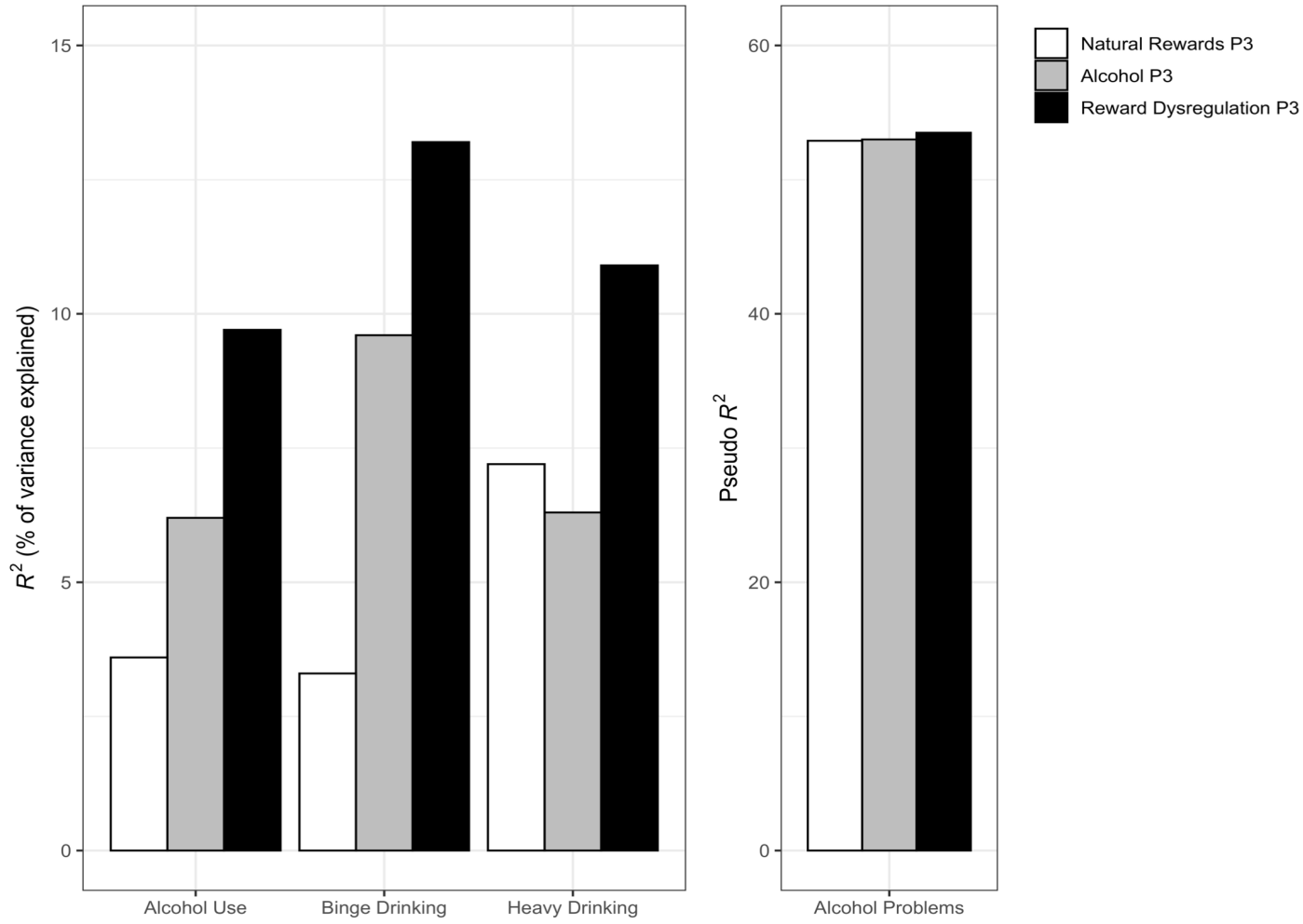
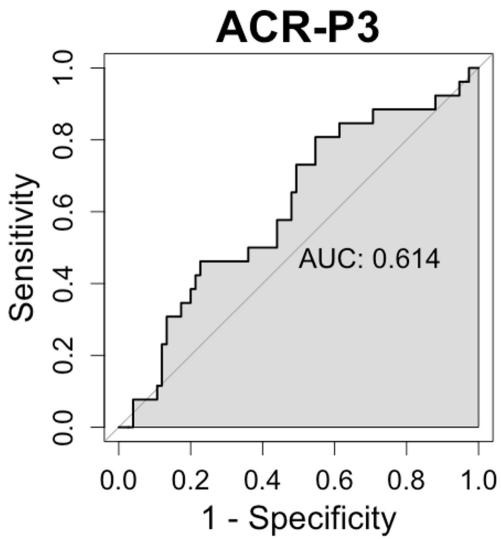
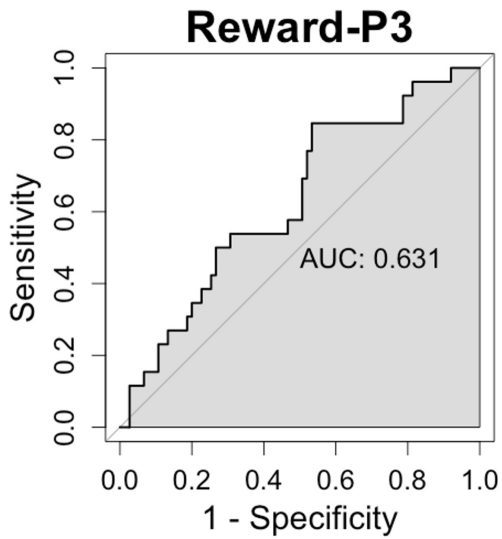
Model 2: Natural Rewards P3																
Age (in years)	0.30	0.659	0.452	.652	-0.02	0.095	-0.199	.843	-0.03	0.197	-0.169	.866	0.01	0.032	0.350	.726
Gender (0 = female, 1 = male)	1.17	4.676	0.250	.803	-0.39	0.670	-0.592	.555	1.63	1.397	1.169	.246	-0.04	0.223	-0.213	.831
Race (0 = non-White; 1 = White)	8.16	7.334	1.112	.270	1.29	1.003	1.285	.203	1.61	2.191	0.737	.464	-0.41	0.426	-0.985	.324
Alcohol Involvement													**0.06**	**0.012**	**4.738**	**< .001**
Natural Rewards P3	-2.58	2.752	-0.938	.351	-0.32	0.393	-0.812	.419	-1.12	0.822	-1.362	.177	-0.13	0.129	-0.976	.329
Model 3: Reward Dysregulation P3																
Age (in years)	0.47	0.635	0.748	.457	0.01	0.090	0.069	.945	0.03	0.192	0.141	.888	0.01	0.031	0.456	.648
Gender (0 = female, 1 = male)	1.53	4.200	0.365	.716	-0.39	0.584	-0.662	.510	2.00	1.271	1.577	.119	-0.06	0.196	-0.316	.752
Race (0 = non-White; 1 = White)	8.73	7.101	1.231	.222	1.35	0.951	1.425	.158	1.78	2.149	0.828	.410	-0.43	0.401	-1.064	.288
Alcohol Involvement													**0.05**	**0.012**	**4.445**	**< .001**
Reward Dysregulation P3 (Δ score)	**5.11**	**2.094**	**2.442**	**.017**	**0.91**	**0.296**	**3.064**	**< .001**	**1.42**	**0.634**	**2.235**	**.028**	**0.26**	**0.102**	**2.520**	**.012**

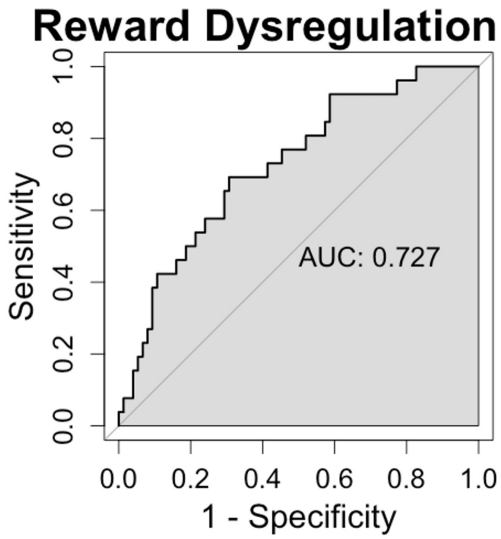
REGRESSION MODELS PREDICTING ALCOHOL OUTCOMES

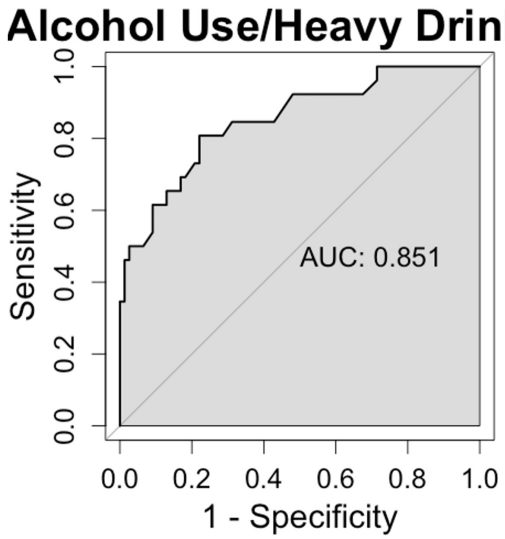


ROC CURVES PREDICTING HIGH RISK DRINKING



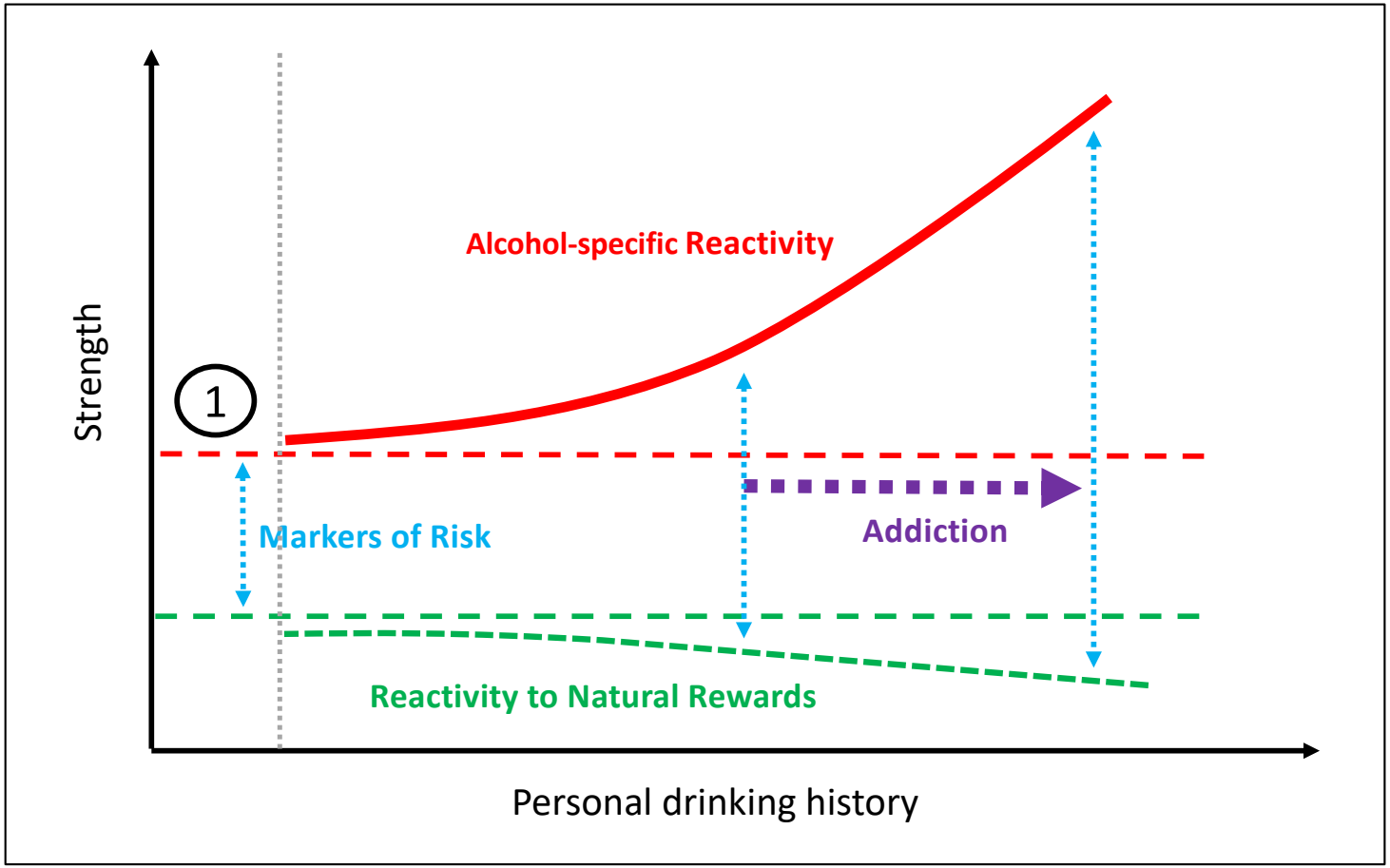




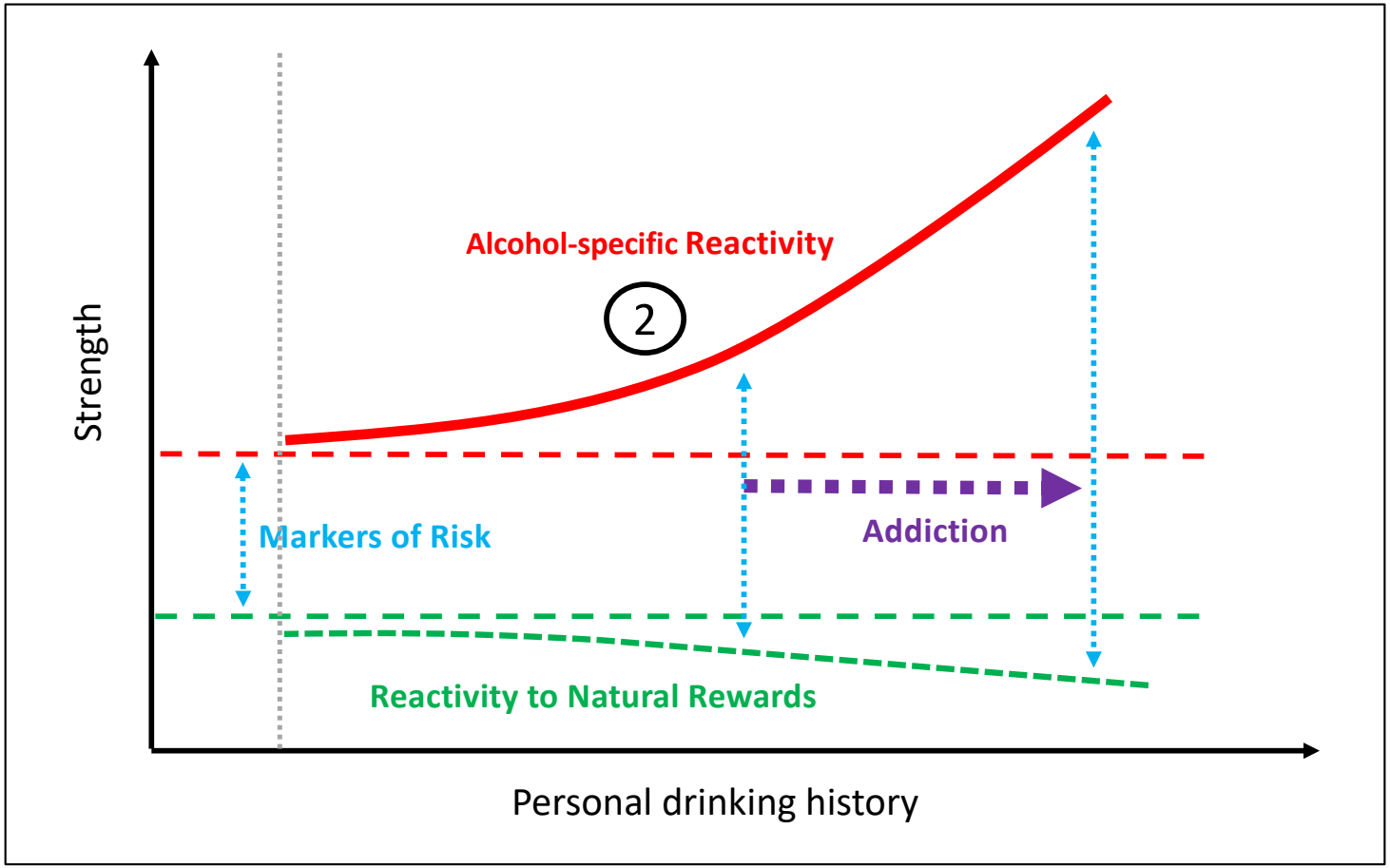


THEORETICAL IMPLICATIONS
&
FUTURE DIRECTIONS

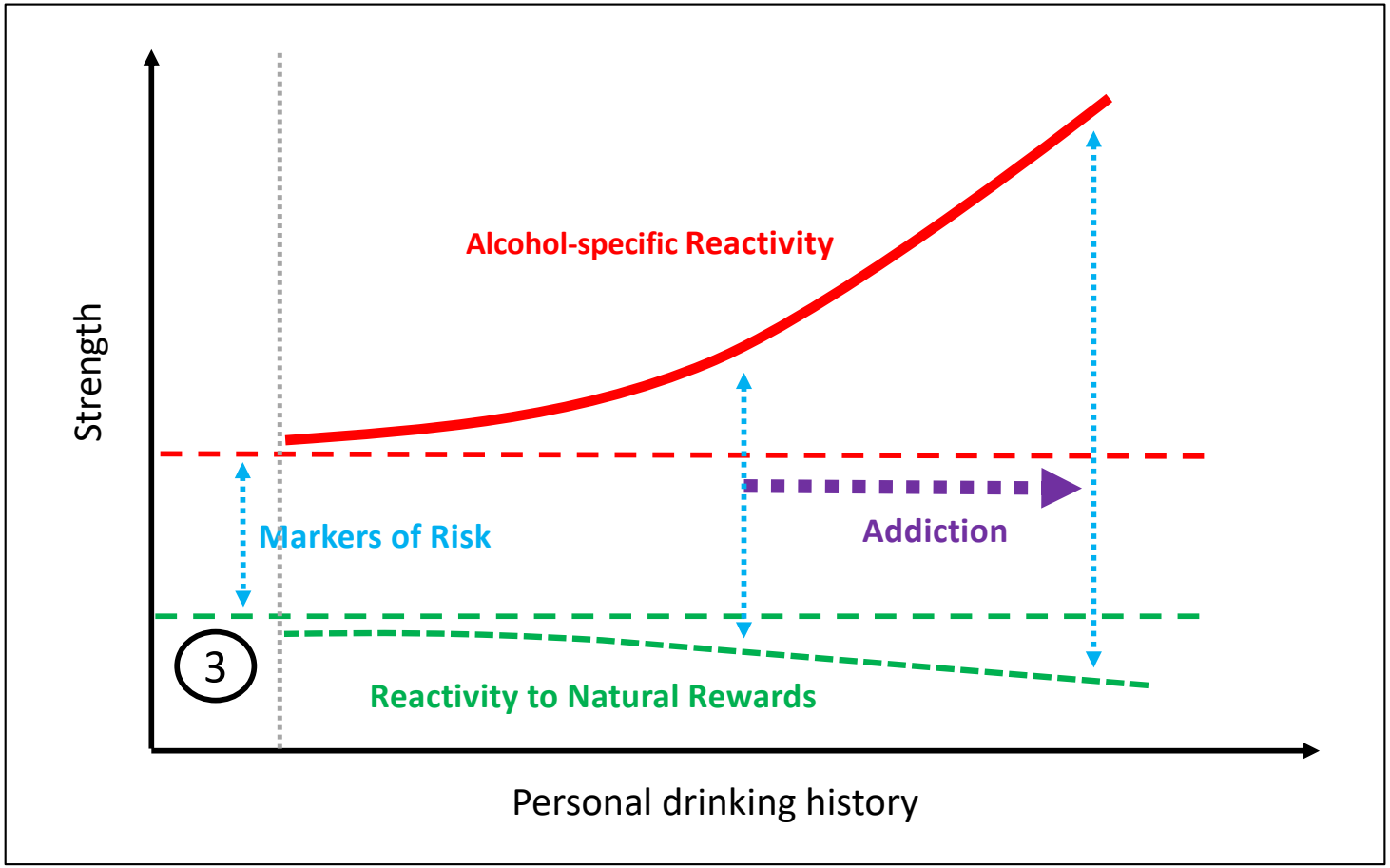
WORKING MODEL OF ALCOHOL DEPENDENCE



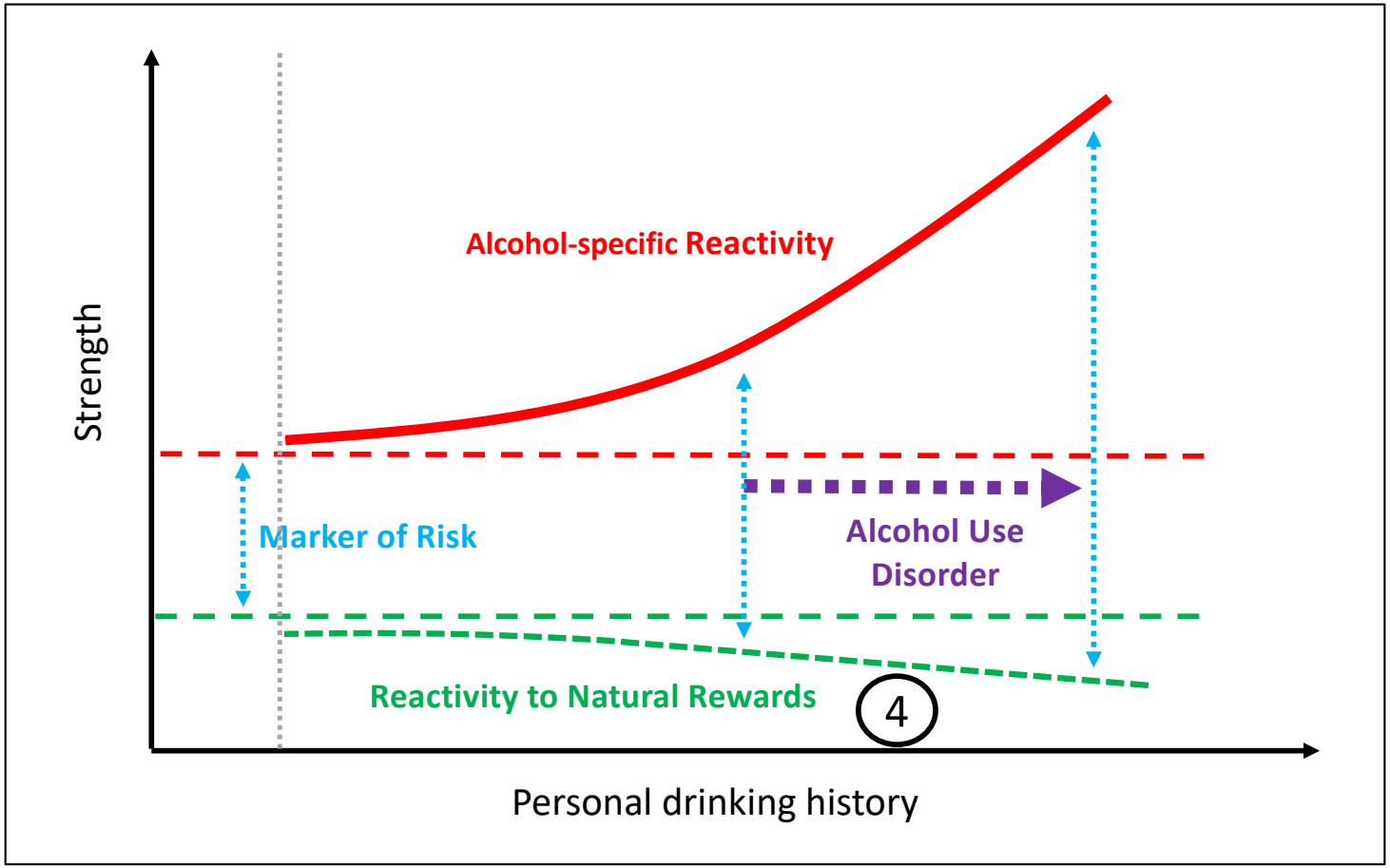
WORKING MODEL OF ALCOHOL DEPENDENCE



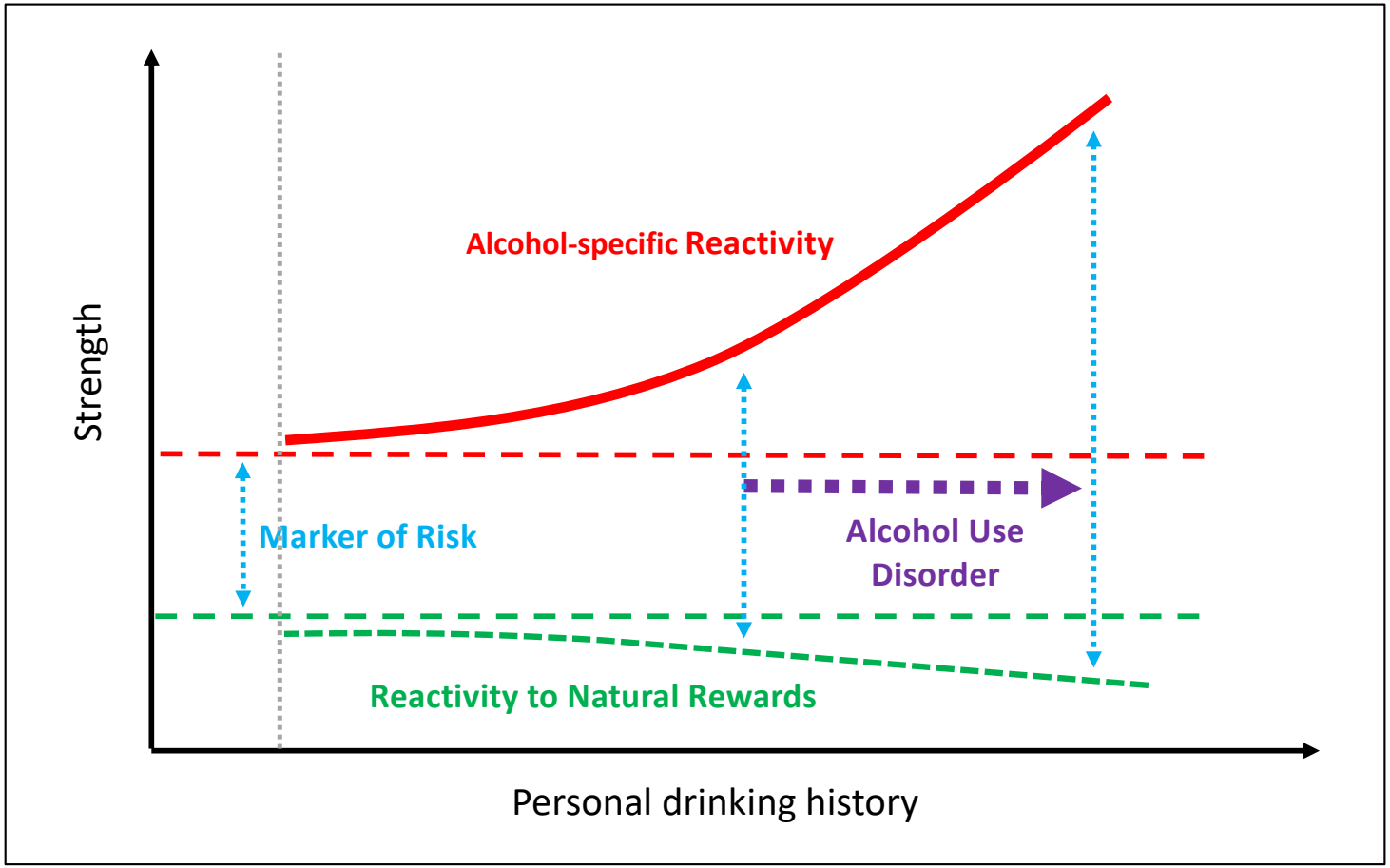
WORKING MODEL OF ALCOHOL DEPENDENCE



WORKING MODEL OF ALCOHOL DEPENDENCE



WORKING MODEL OF ALCOHOL DEPENDENCE



TAKE HOME MESSAGES

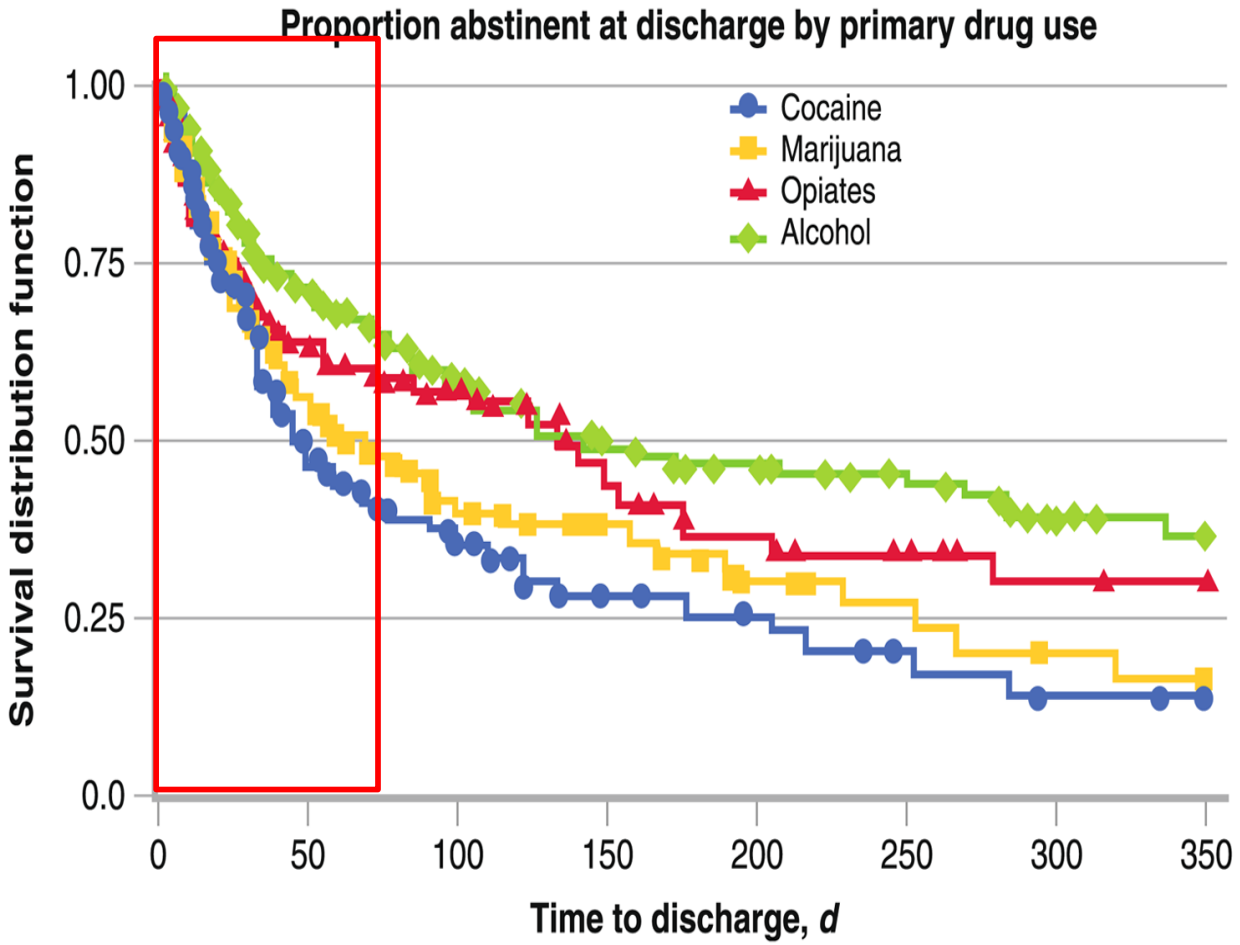
- Consistent with its conceptualization as a neurobiobehavioral marker of heavy and problematic drinking, the *Reward dysregulation P3* was quite robustly and consistently associated with all drinking outcomes.

- Reward dysregulation P3 showed some ability to discriminate individuals at risk for harmful drinking, and did so with similar accuracy as an alcohol use/heavy drinking composite, a "gold standard" measure of risky drinking.

STUDY 2 – TREATMENT

ALCOHOL WITHDRAWAL AND CRAVING AT TREATMENT ENTRY PROSPECTIVELY PREDICT ALCOHOL USE OUTCOMES DURING OUTPATIENT TREATMENT

ALCOHOL DEPENDENCE: TREATMENT (IN)EFFICACY

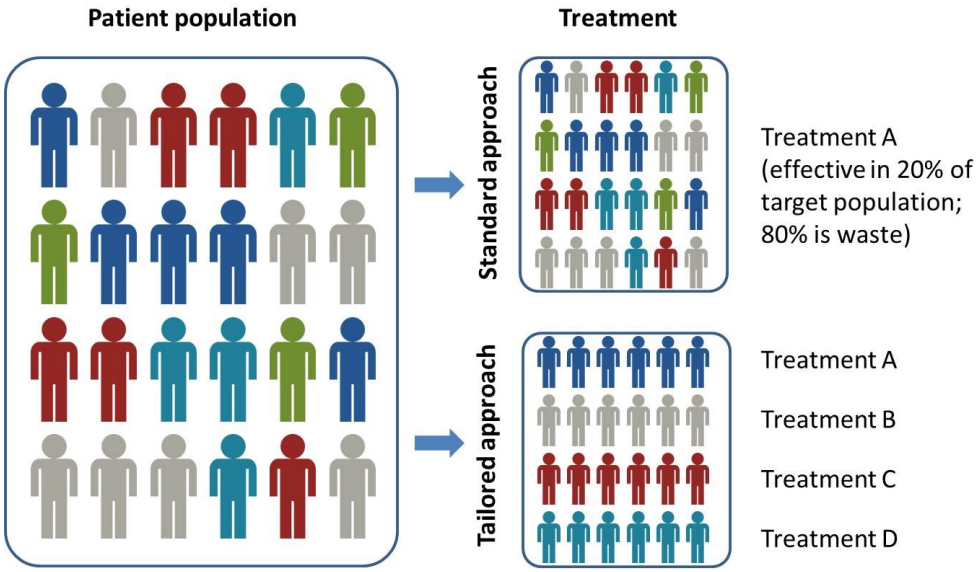


Sinha et al. 2011 *Current Psychiatry Reports*

PERSONALIZED TREATMENT OF AUD

Recent initiatives (e.g., Litten et al., 2015; Witkiewitz et al. 2019) aimed at improving **personalized treatment of AUD**:

1) The need to identify **AUD clinical features** that differentiate those at increased risk for relapse and treatment failure.
2) To develop **treatments** specifically targeted for those who are at risk.



AUD-RELATED DISRUPTIONS IN THE STRESS PATHOPHYSIOLOGY

Early alcohol abstinence in AUD:

- Altered stress and reward brain neurocircuitry (Koob, 2003; Seo, 2013)
- Disrupted prefrontal-striatal and HPA axis function (Blaine et al., 2020)
- Clinical symptoms: AW, craving, depression, anxiety, sleep difficulties

Stress

+

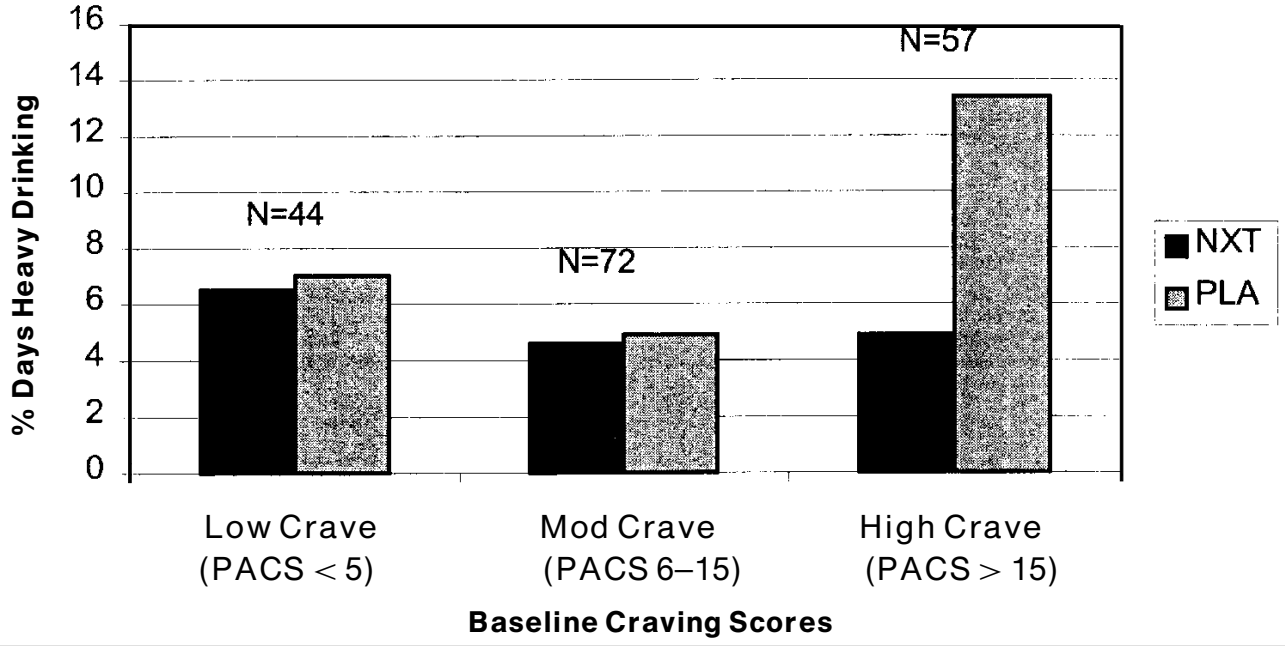
Contextual Cues

=

Relapse

MODERATORS OF MEDICATION EFFICACY

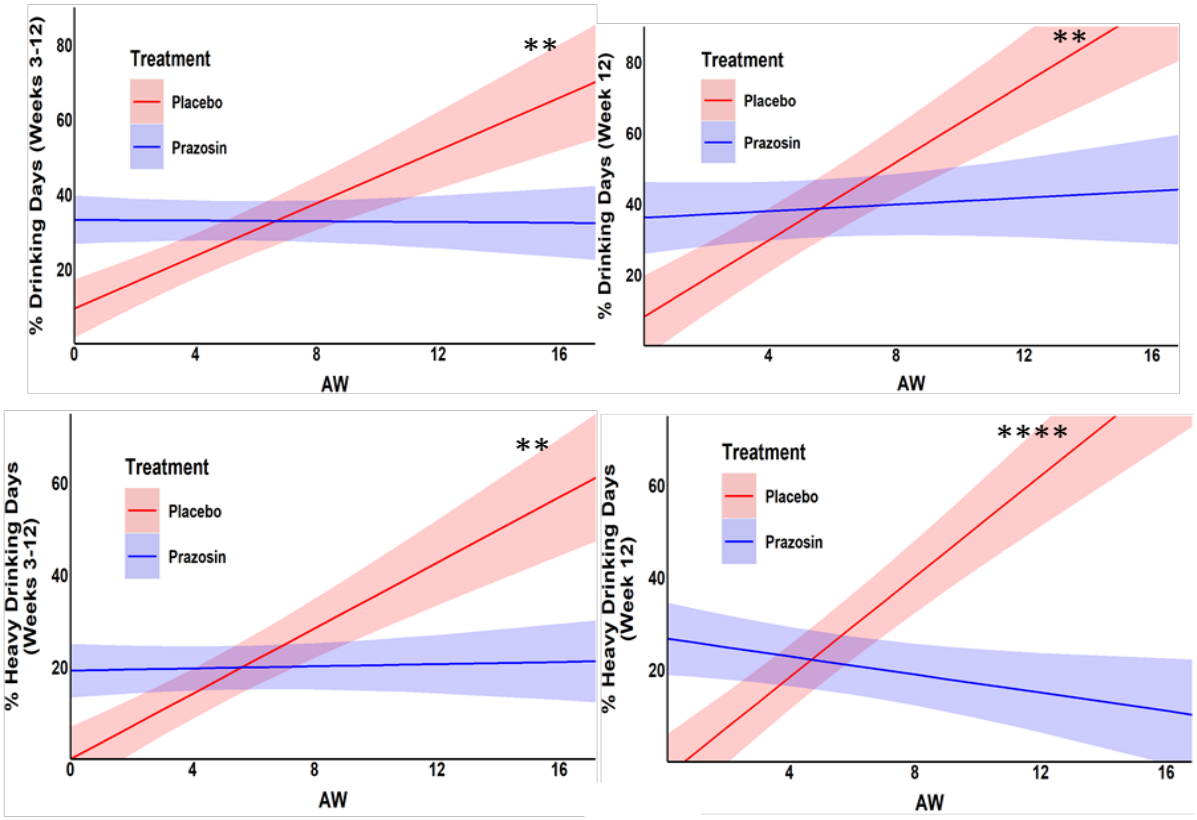
Medication efficacy of **naltrexone** for AUD treatment may be moderated by **alcohol craving** (Monterosso et al., 2001).



Monterosso et al., 2001 AJA

MODERATORS OF MEDICATION EFFICACY

Medication efficacy of **prazosin** for AUD treatment may be moderated by **alcohol withdrawal (AW) symptoms** (Sinha et al., 2020).



Sinha et al., 2020 AJP

CLINICAL PROGNOSTIC INDICATORS OF TREATMENT RESPONSE

Despite this evidence of relapse and treatment failure risk in those showing such stress pathophysiology of AUD, research to specifically assess whether these clinical features of AUD significantly impact alcohol use outcomes in outpatient treatment has lagged behind.

METHODS

PARTICIPANTS

- **80 AUD treatment-seeking community adults** with current DSM-5 moderate to severe AUD – Greater New Haven area
  - 20 to 60 years-old
  - Mean age = 36.6 (*SD* = 11.24)
  - 39.8% Female
  - 42.5% White
- **Eligibility criteria:**
  - Aged between 18 and 60
  - DSM-5 diagnosis for AUD
  - Positive alcohol urine toxicology screen at admission
- **Exclusion criteria:**
  - Current DSM-5 diagnosis for SUD
  - Severe psychiatric disorder
  - Acute untreated medical condition

STUDY DESIGN & PROTOCOL

PROTOCOL

- **Initial visits and baseline assessments at intake**
  - Demographic information (sex, age, race, and SES)
  - Clinical Institute of Withdrawal Assessment for Alcohol-revised (CIWA-Ar)
  - Alcohol Urge Questionnaire (AUQ)
  - Hamilton Anxiety Scale (HAS)
  - Beck Depression Inventory (BDI)
  - The Pittsburgh Sleep Quality Index (PSQI)
  - 90-day Substance Use Calendar
  - The Structured Clinical Interview for DSM-5 (SCID-5)

PROTOCOL

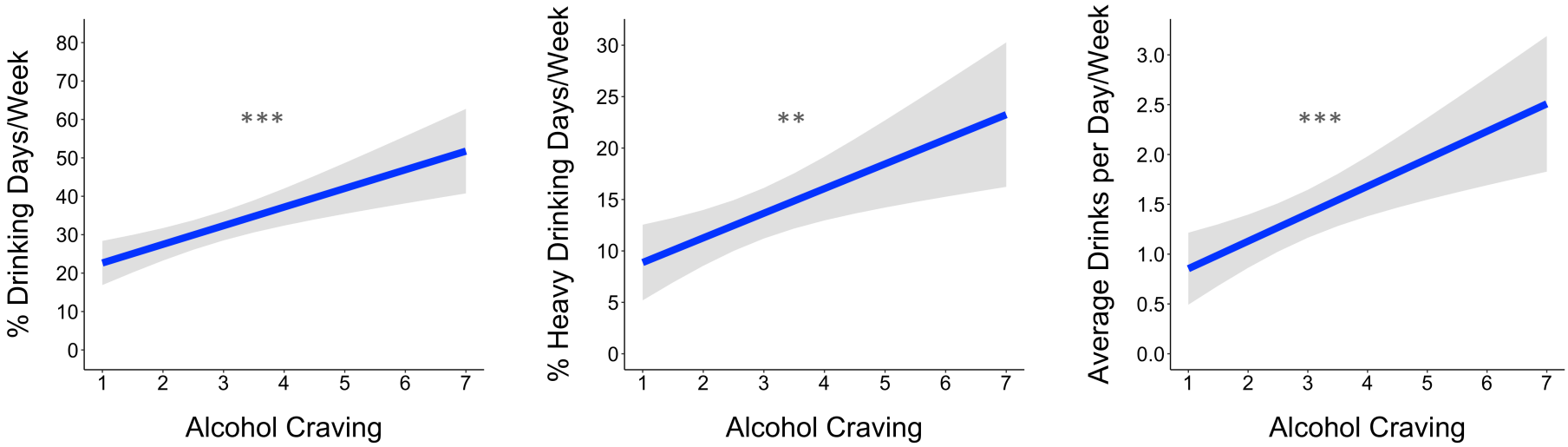
- **Weekly behavioral counseling and assessments:**
  - 1x week treatment sessions using standardized 12-Step and relapse prevention approach as outlined in the NIAAA Project MATCH manuals
  - Timeline follow-back assessments using the 7-day SUC
- **Daily ecological momentary assessment (EMA):**
  - Brief surveys administered in a smartphone application (MetricWire, Inc.)
    - Daily morning and evening prompts (and random prompts)
    - total number of drinks consumed (beer, wine, and liquor)
  - Acceptable compliance rate (approx. 69%)

CLINICAL PREDICTORS & DRINKING OUTCOMES

- **Clinical predictors:**
  - Alcohol Withdrawal (AW)
  - Alcohol Craving
  - Depression
  - Anxiety
  - Sleep Problems
- **Drinking outcomes:**
  - Percent drinking days/week (DD)
  - Percent heavy drinking days/week (HDD)
  - Average drinks per day/week (AvgD)
  - Time to dropout (i.e., time to withdraw from the study)
  - Time to lapse (i.e., time to first drink),
  - Time to relapse (i.e., time to first heavy drinking day).

RESULTS

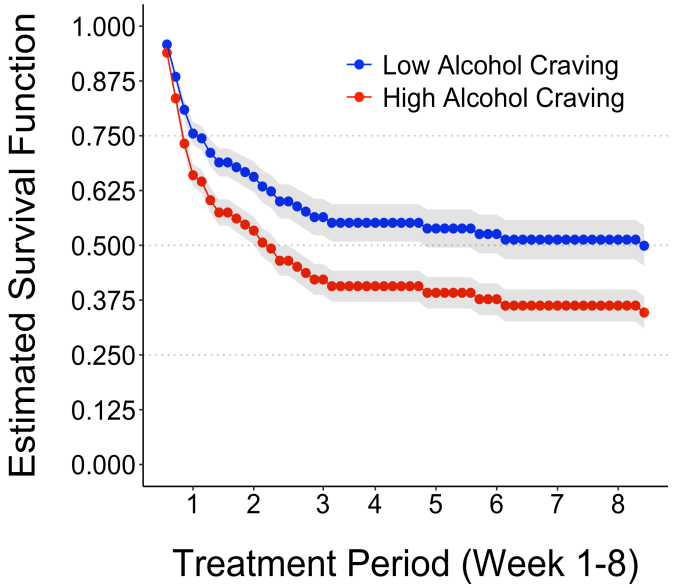
ALCOHOL CRAVING PREDICTING TREATMENT RESPONSE



Significant main effects of craving on DD ($p < .001$), HDD ($p < .009$), and AvgD ($p < .001$) during treatment.
Covariate Adjustment: # abstinence days, past 90-day alcohol use, age, sex, race, and SES

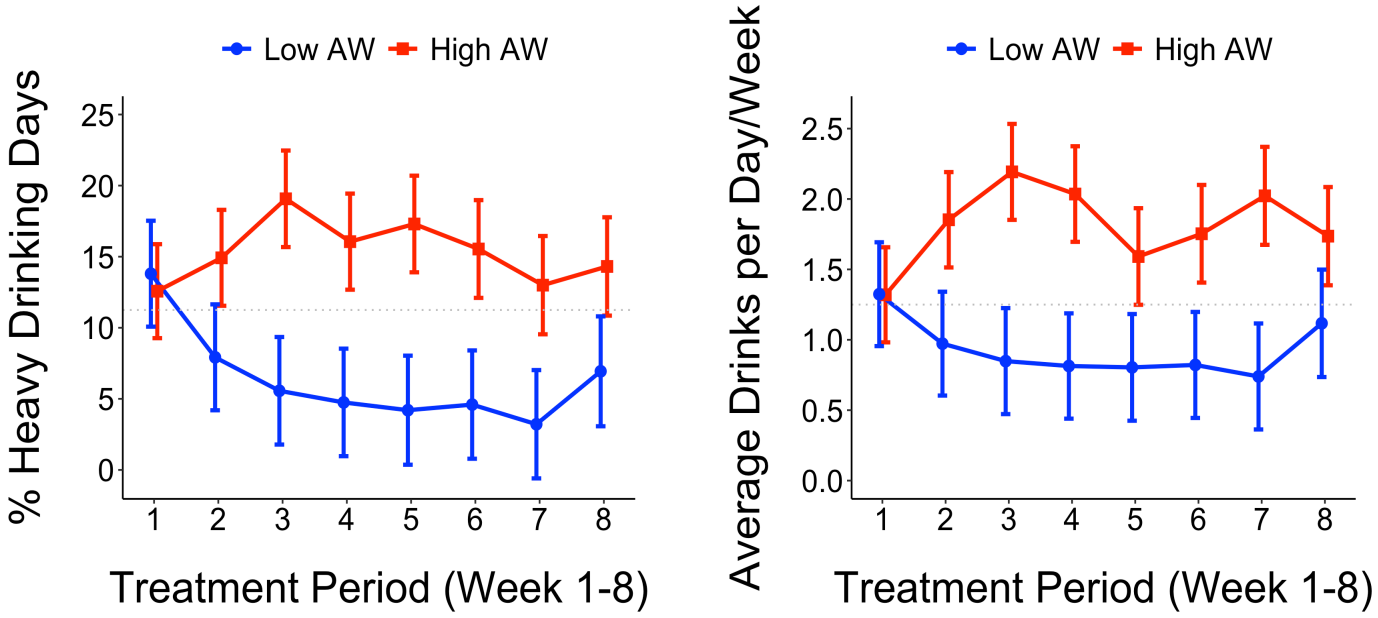
ALCOHOL CRAVING PREDICTING RELAPSE

HR: 1.20; 95% CI [1.00-1.44], *p* = .049



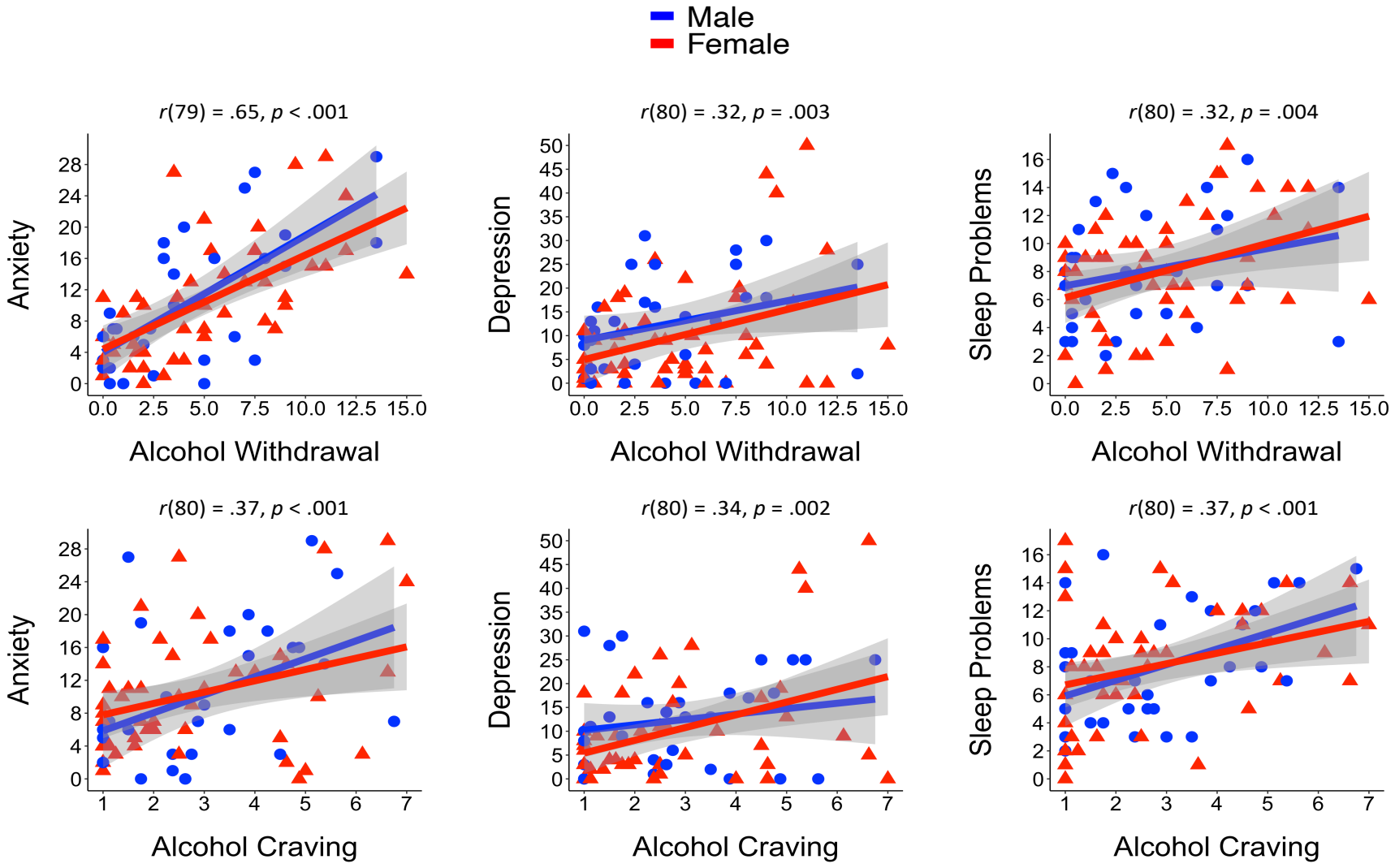
Baseline alcohol craving (continuous scores) predicted risk of relapse to heavy drinking during treatment.
Covariate Adjustment: # abstinence days, past 90-day alcohol use, age, sex, race, and SES

ALCOHOL WITHDRAWAL PREDICTING TREATMENT RESPONSE



Significant interaction effects of baseline AW with treatment week on HDD ($p < .018$) and AvgD ($p < .004$)
Covariate Adjustment: # abstinence days, past 90-day alcohol use, age, sex, race, and SES

ALCOHOL ABSTINENCE-RELATED SYMPTOMS



CONCLUSION

TAKE HOME MESSAGES

- Higher levels of craving *consistently* predicted higher levels of alcohol intake during treatment (Schlauch et al., 2019; Mchugh et al. 2017) and risk of relapse to heavy drinking (Sinha et al., 2011; Higley et al., 2011).
- Pretreatment levels of AW predict different trajectories in treatment response throughout the treatment period.
- Pretreatment symptoms of depression, anxiety, and sleep difficulties did not predict any drinking-related outcome during treatment.
- Predictive effects of AW and craving on treatment response hold up after controlling for drinking levels prior to treatment entry.

TAKE HOME MESSAGE

Pretreatment AW and alcohol craving, as assessed via Clinical Institute of Withdrawal Assessment for Alcohol (CIWA-Ar) and Alcohol Urge Questionnaire (AUQ), may serve as clinical prognostic indicators of alcohol use outcomes and AUD treatment response.

- Growing evidence suggesting that manifestations of **AUD-related disruptions** reflect manifestations of **stress pathophysiology**.
- Critical for understanding the wide **heterogeneity** of AUD treatment responses to improve AUD treatment outcomes.
- Treatments targeted **normalizing** and **stabilizing** AUD disruptions.

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NIH National Institute on Alcohol Abuse and Alcoholism

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THANK YOU!