Mapping Neuroimaging Pathways of Drug Addiction

Vulnerabilities, Causal Mechanisms, and Avenues for Recovery

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ISPA–Instituto Universitário

Disclosures

I declare no conflicts of interest in relation to this presentation.

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Definition

- Addiction: "Drug addiction is a chronically relapsing disorder that has been characterized by compulsion to seek and take the drug, loss of control in limiting intake, and emergence of a negative emotional state (…) reflecting a motivational withdrawal syndrome when access to the drug is prevented (defined as Substance Dependence by the Diagnostic and Statistical Manual of Mental Disorders [DSM] of the American Psychiatric Association." (Koob & Volkow, 2010)

The cycle of drug addiction

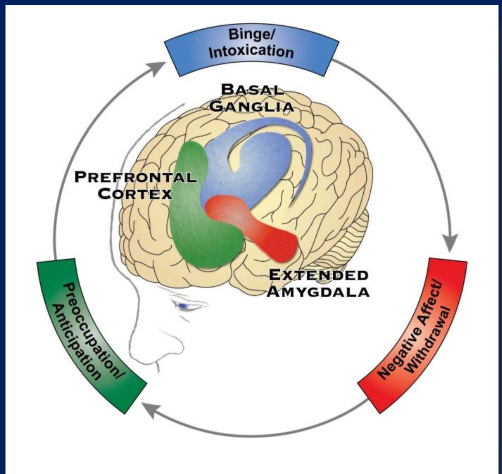


Image from Koob, G. F. & Volkow, N. D. (2010) Neurocircuitry of addiction. *Neuropsychopharmacology*, 35, 217-238

Recent advances in the neurobiology of addiction led to the identification of three stages of the addiction cycle:

- 'Binge/intoxication' stage
  - loss of control, compulsive use, risk taking
- 'Withdrawal/negative affect' stage
  - negative emotional states, withdrawal, craving
- 'Preoccupation/anticipation' stage
  - craving/obsessions, preoccupations, relapse

Multimodal neuroimaging approach:
Across the translational spectrum

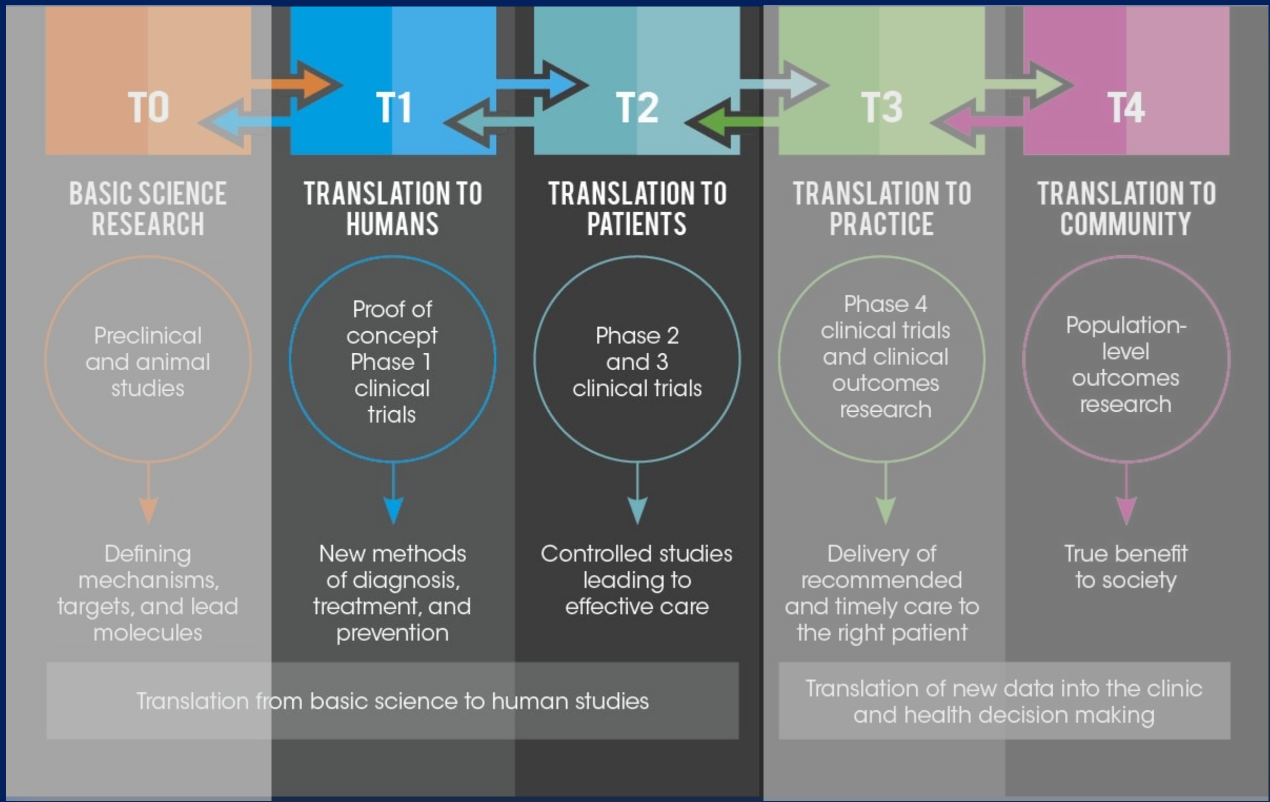


Image from website: https://tri.uams.edu/about-tri/what-is-translational-research/

64-channel EEG system

3T MRI scanner

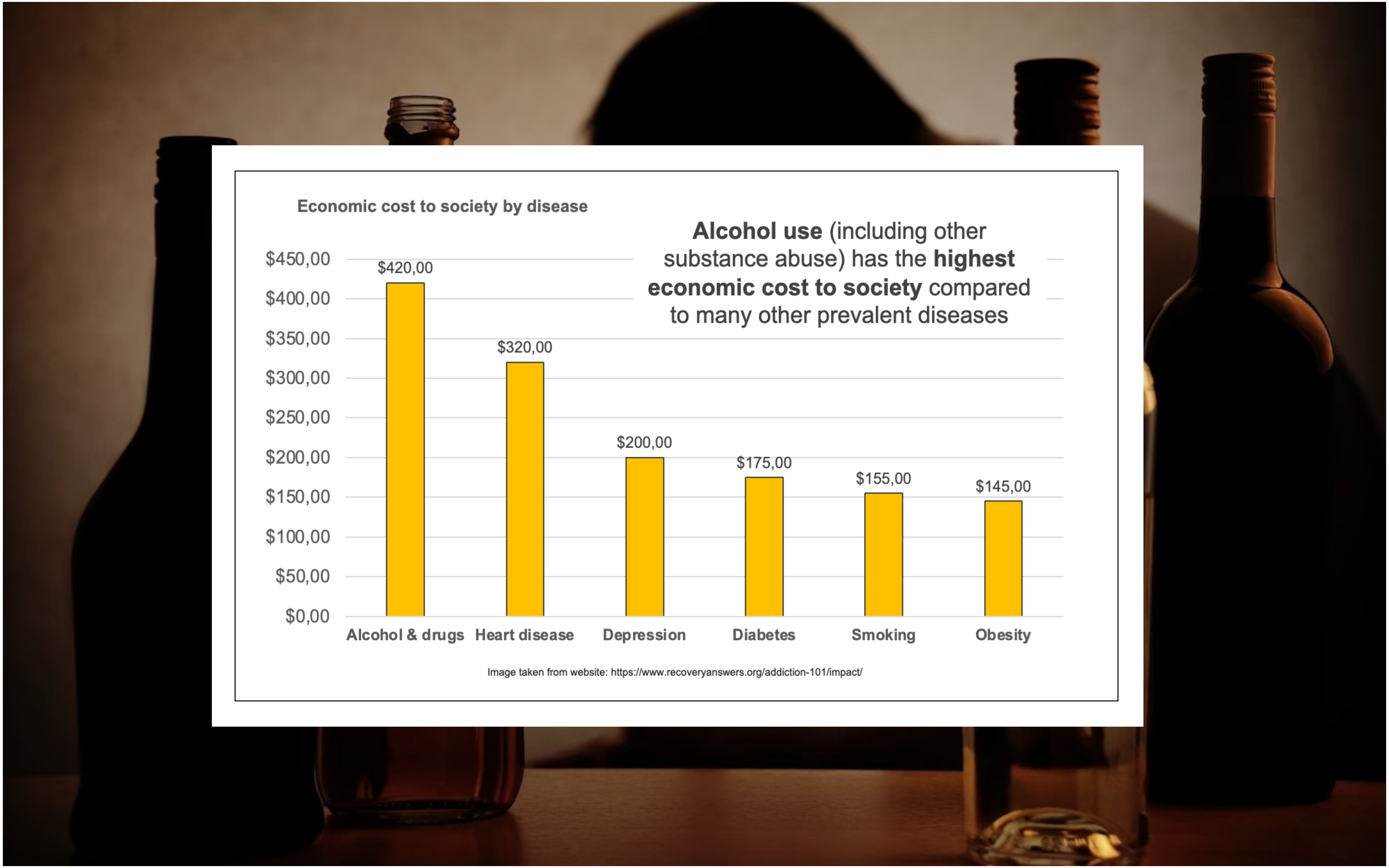
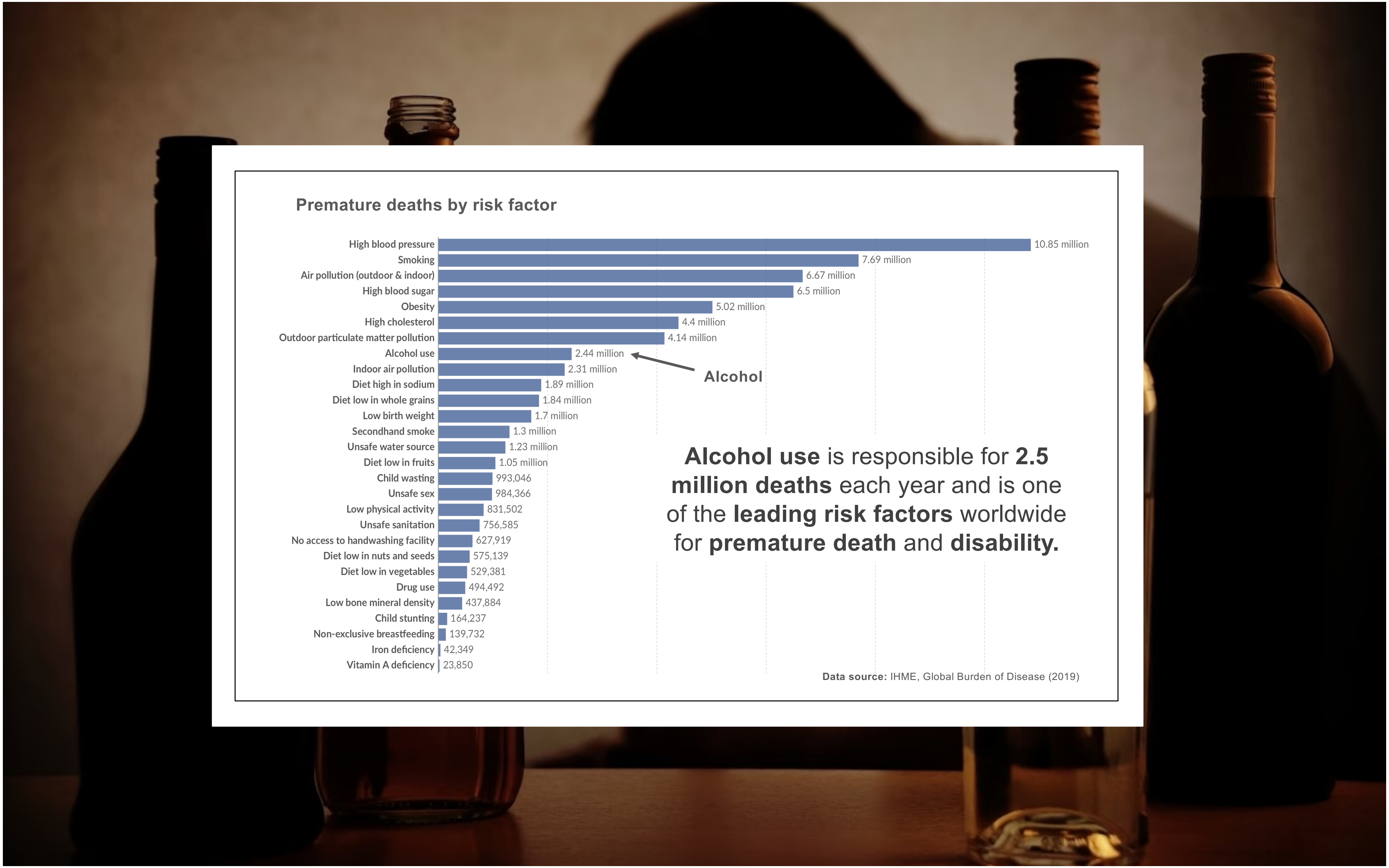
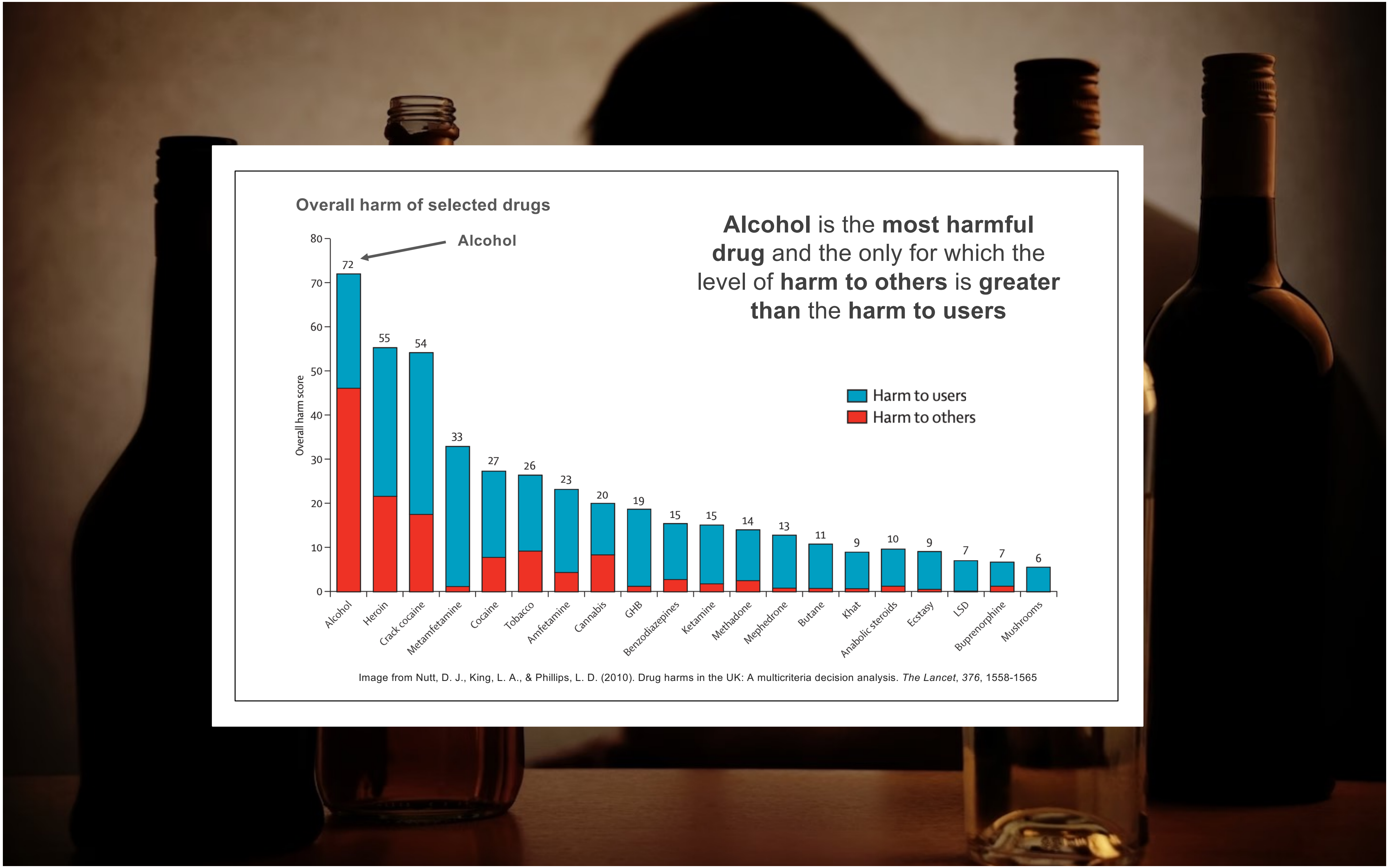


Image taken from website: https://www.recoveryanswers.org/addiction-101/impact/


Premature deaths by risk factor
High blood pressure 10.85 million
Smoking 7.69 million
Air pollution (outdoor & indoor) 6.67 million
High blood sugar 6.5 million
Obesity 5.02 million
High cholesterol 4.4 million
Outdoor particulate matter pollution 4.14 million
Alcohol use 2.44 million
Indoor air pollution 2.31 million
Diet high in sodium 1.89 million
Diet low in whole grains 1.84 million
Low birth weight 1.7 million
Secondhand smoke 1.3 million
Unsafe water source 1.23 million
Diet low in fruits 1.05 million
Child wasting 993,046
Unsafe sex 984,366
Low physical activity 831,502
Unsafe sanitation 756,585
No access to handwashing facility 627,919
Diet low in nuts and seeds 575,139
Diet low in vegetables 529,381
Drug use 494,492
Low bone mineral density 437,884
Child stunting 164,237
Non-exclusive breastfeeding 139,732
Iron deficiency 42,349
Vitamin A deficiency 23,850
Alcohol
Alcohol use is responsible for **2.5 million deaths** each year and is one of the **leading risk factors** worldwide for **premature death** and **disability.**
Data source: IHME, Global Burden of Disease (2019)



Overall harm of selected drugs
Alcohol is the most harmful drug and the only for which the level of harm to others is greater than the harm to users
Alcohol
Overall harm score
80
70
60
50
40
30
20
10
0
72
55
54
33
27
26
23
20
19
15
15
14
13
11
9
10
9
7
7
6
Alcohol
Heroin
Crack cocaine
Metamfetamine
Cocaine
Tobacco
Amfetamine
Cannabis
GHB
Benzodiazepines
Ketamine
Methadone
Mephedrone
Butane
Khat
Anabolic steroids
Ecstasy
LSD
Buprenorphine
Mushrooms
Harm to users
Harm to others
Image from Nutt, D. J., King, L. A., & Phillips, L. D. (2010). Drug harms in the UK: A multicriteria decision analysis. The Lancet, 376, 1558-1565

SAÚDE

Dependência de álcool em Portugal aumentou quase 50% na última década

A prevalência da dependência de álcool aumentou de 3%, em 2012, para 4,2% em 2022, segundo a Sociedade Portuguesa de Alcoologia, que pede o reforço das estruturas de tratamento.

Lusa

25 de Outubro de 2023, 10:59

Receber alertas

Battling the unchosen struggle...

"I never chose to be an alcoholic, alcoholism, for some reason, chose me. It has no respect for age, gender, personal or financial circumstances - alcoholism is just a life sucking leech, which once it has taken hold is extremely powerful and very difficult to detach, but not impossible! It is very easy to say it takes courage, focus, determination and willpower to beat this illness but when I was drinking, I was a complete mess and (...) all I wanted to do was drink and drink some more. I was totally oblivious to the damage and hurt I was causing to myself, my husband, my children and my extended family. I was very rapidly killing myself (...) I will never know how I crossed that boundary from being a fun social drinker into a chronic alcoholic, but cross I did and initially from having one too many drinks at a party I descended into being a secretive dependent alcoholic at home. (...) I made promises time and time again to stop, and in my heart of hearts I meant it, I know what I was doing was wrong but by then I was completely powerless over alcohol - I was soon to become another fatal statistic."

–Anonymous

Addiction is a brain disease, not a moral failing, weak character, or lack of willpower.

Roadmap

Roadmap

1. Review of the most influential theoretical perspectives of addiction
2. “Why do some people become addicted to drugs while others do not?”
3. “What are the acute and prolonged effects of alcohol and drugs in the brain?”
4. “Why is it so difficult to change addictive behaviors and recover from addiction?”

Roadmap

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Incentive-sensitization theory of addiction

- The incentive-sensitization theory of addiction (Berridge & Robinson, 1993) posits that cues signalling drug availability take on the incentive value of the drugs themselves, transforming cues into “motivational magnets” that capture attention, elicit craving and approach tendencies, and compel consumption.

Kent Berridge
University of Michigan

Terry Robinson
University of Michigan

Distinction between "liking" vs "wanting"

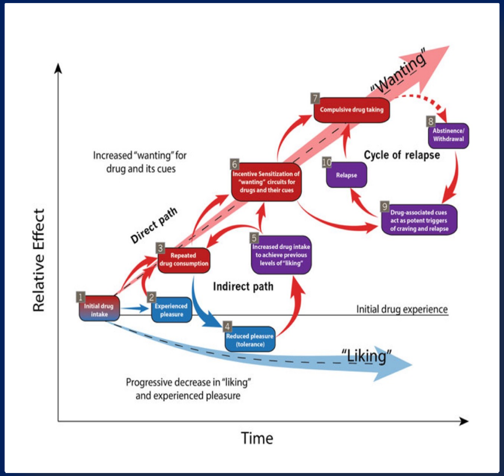


Image from Robinson et al. (2016). Roles of “wanting” and “liking” in motivating behavior. *Behavioral Neuroscience of Motivation*,105-136.

Three core assumptions of this theoretical perspective:

- Separation of “wanting” and ”liking” systems:
  - continue to crave drugs even if no longer pleasurable
- Sensitization of the brain’s "wanting" system:
  - increase in the motivational value of the drug or its cues
- Hypersensitivity to drug-related cues:
  - cues paired with drug use acquire rewarding properties

Reward deficiency hypothesis for addiction

- The reward deficiency hypothesis (Blum et al., 2019) posits that blunted sensitivity to nondrug-related rewards represents a premorbid liability factor for substance misuse (i.e., reward deficiency syndrome), prompting affected individuals to seek activities, such as drug use, that stimulate the reward system.

Kenneth Blum
University of Florida

Reward deficiency syndrome (RDS)

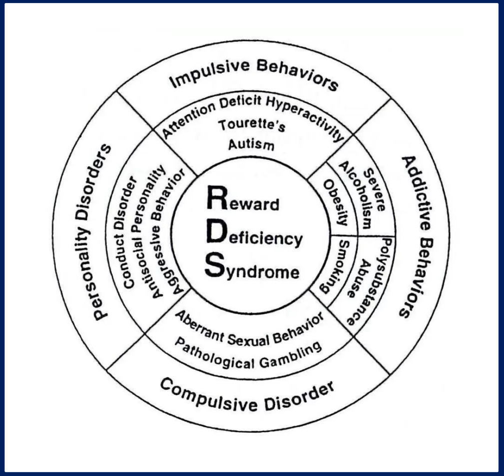


Image taken and adapted from website:
https://cruzlifecenter.com/reward-deficiency-syndrome/

Genetic predisposition for lower-than-normal levels of dopamine

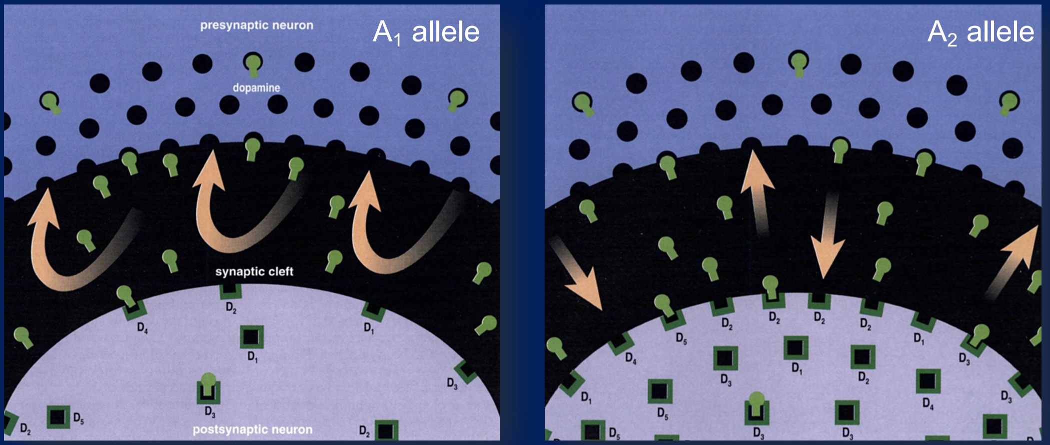


Image from Blum, K., Cull, J. G., Braverman, E. R., & Comings, D. E. (1996). Reward deficiency syndrome. *American Scientist*, *84*, 132-145.

Allostatic model of addiction

- The allostatic model of addiction (Koob & Le Moal , 2001) posits that, with chronic and repeated use of drugs of abuse, neural reward and anti-reward (or stress) pathways become sensitized and dysregulated such that incentive-motivational value of non-drug, naturally-occurring rewards is attenuated.

George Koob
Scripps Research Institute, NIAAA

Reward and anti-reward dysregulation

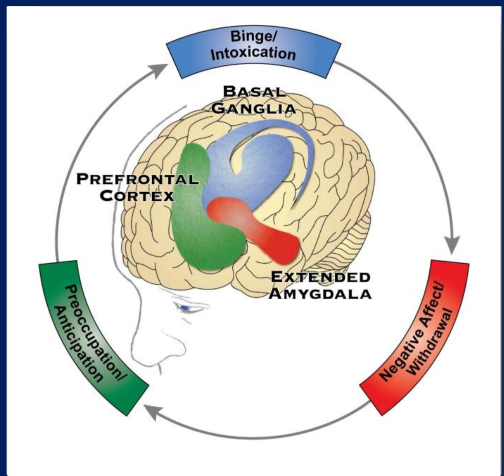
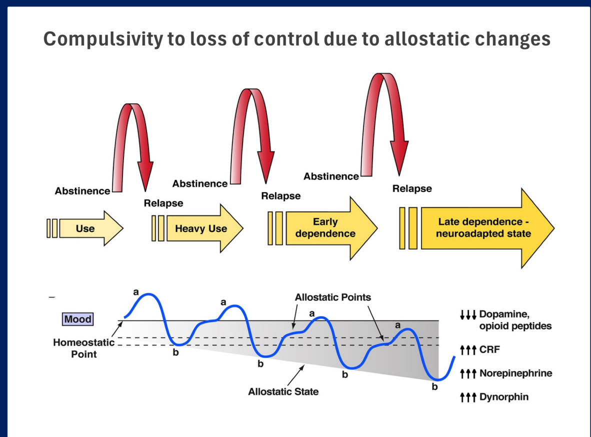
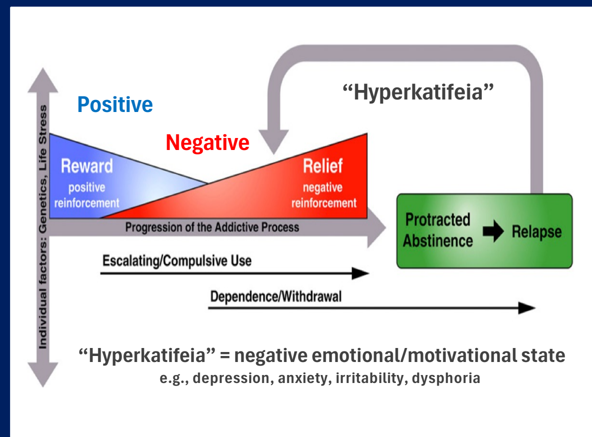


Image from Koob, G. F. & Volkow, N. D. (2010) Neurocircuitry of addiction. *Neuropsychopharmacology*, 35, 217-238

Hedonic dysregulation



The "dark side of addiction"



Images adapted from Koob, G. F. & Schulkin, J. (2019). Addiction and stress: An allostatic view. *Neuroscience & Biobehavioral Reviews*, *106*, 245-262.

Roadmap

1. Review of most influential theoretical perspectives of addiction

2. “Why do some people become addicted to drugs while others do not?”

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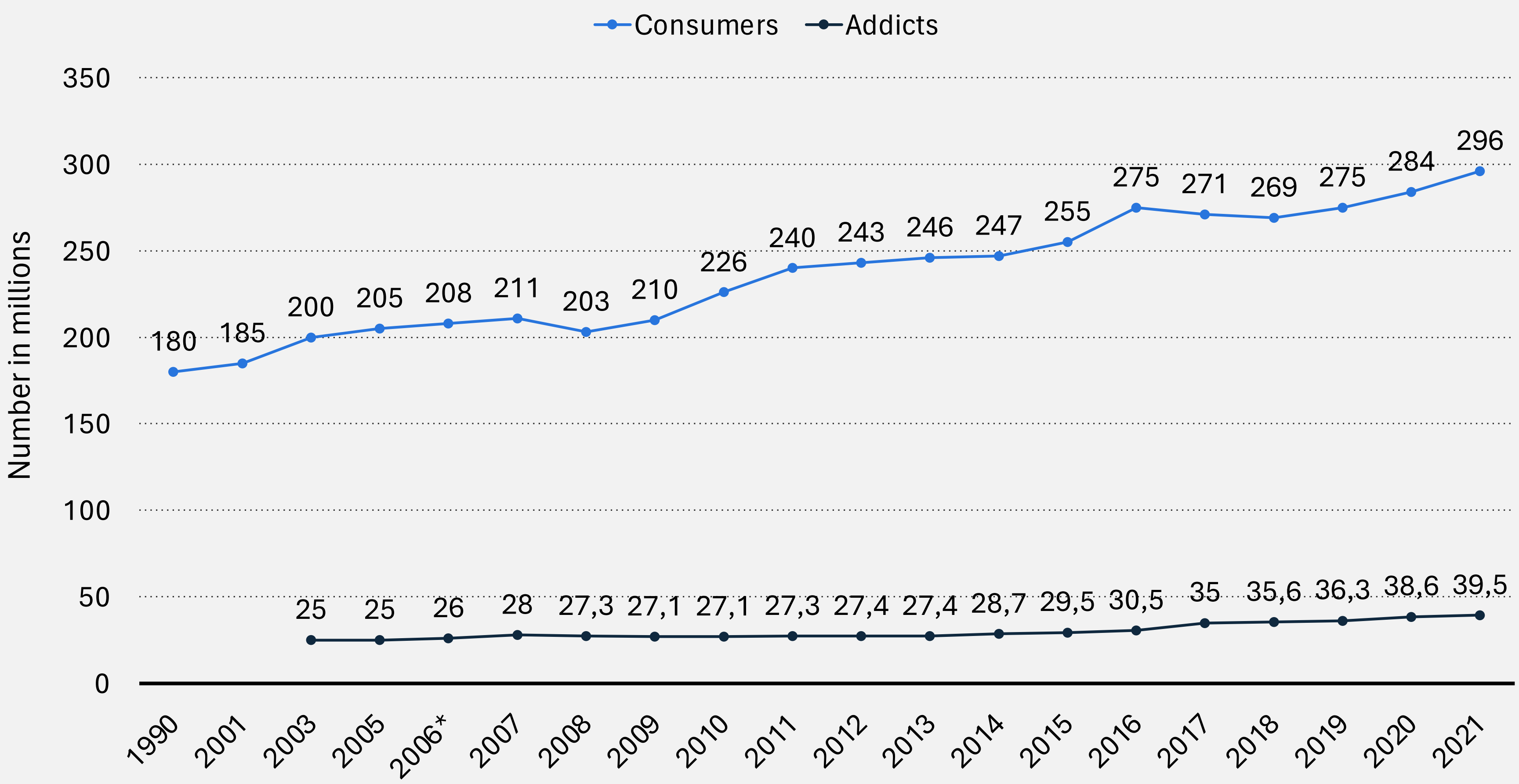
4. “Why is it so difficult to change addictive behaviors and recover from addiction?”

Addicts and consumers of illegal drugs worldwide from 1990 to 2021 (in millions)

Addicts and consumers of illegal drugs worldwide 1990-2021



Note(s): Worldwide; 15-64 years

Further information regarding this statistic can be found on page 8.

Source(s): UNODC; ID 274688

statista

Evolutionary wiring and rewards circuits

- Humans evolved to experience reward from activities that promote their survival, but...






Reward dysregulation in addiciton

- … hyposensitivity to non-drug rewards and blunted reactivity to natural reinforcers





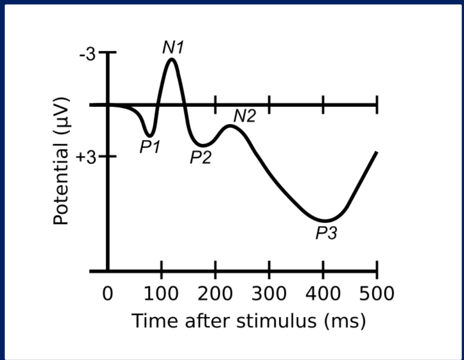

Reward dysregulation in addiciton

- … over-valuation of drug rewards and enhanced reactivity to drug rewards predictive-cues

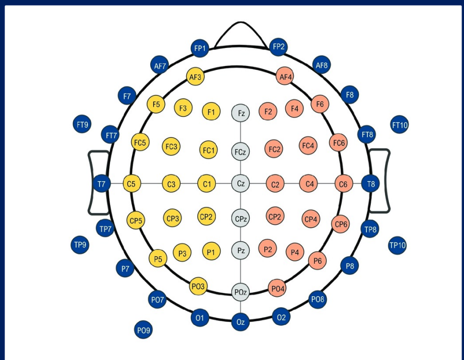
“Is this differential valuation also observed in nondependent individuals, or is it a specific clinical feature indicative of addiction as a disease?”

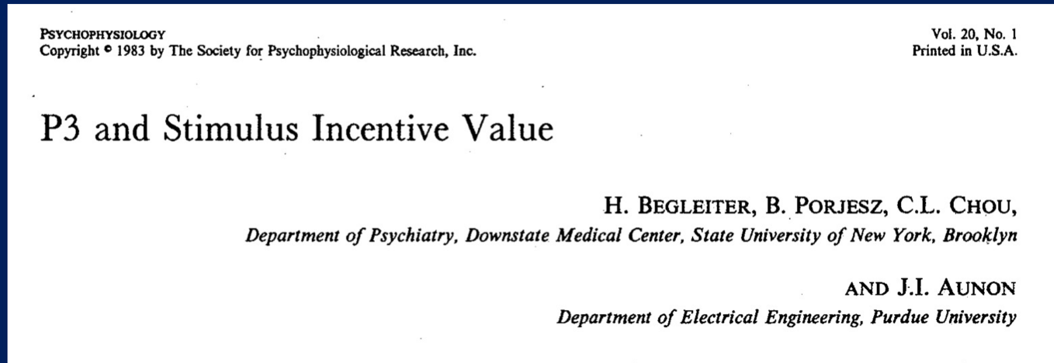
P3 as a bioelectrical signature of salience

P3 (or P300) amplitude



64-channel EEG system





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P3 and Stimulus Incentive Value

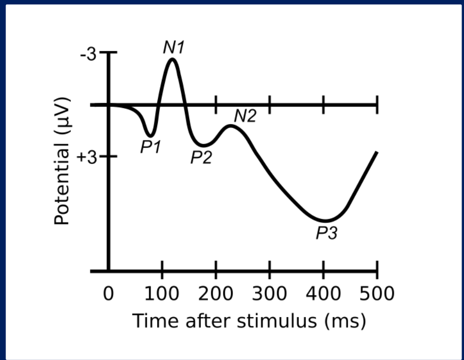
H. BEGLEITER, B. PORJESZ, C.L. CHOU,
Department of Psychiatry, Downstate Medical Center, State University of New York, Brooklyn

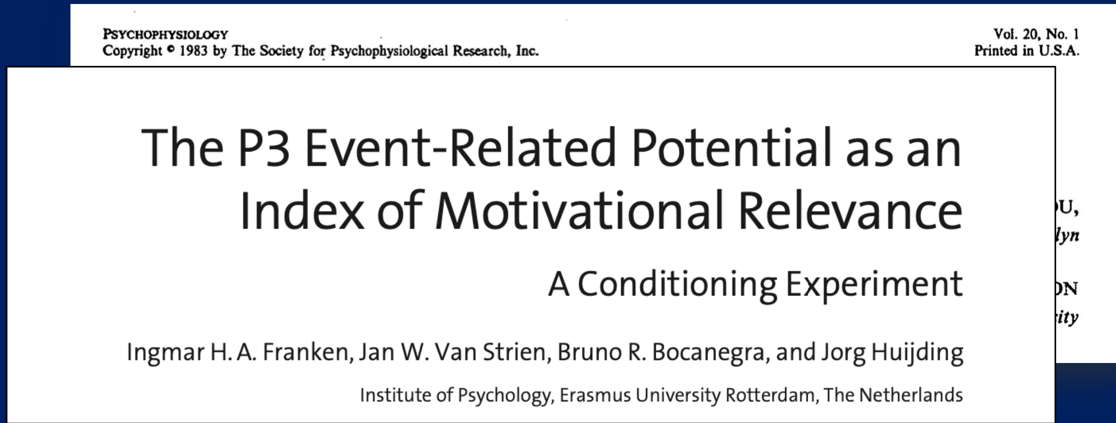
AND J.I. AUNON
Department of Electrical Engineering, Purdue University

"A myriad of cognitive processes have been invoked to explain the functional significance of the P3. Our findings suggest that the P3 component may well index the subjective motivational properties of environmental stimuli." (Begleiter et al. 1986)

P3 as a bioelectrical signature of salience

P3 (or P300) amplitude

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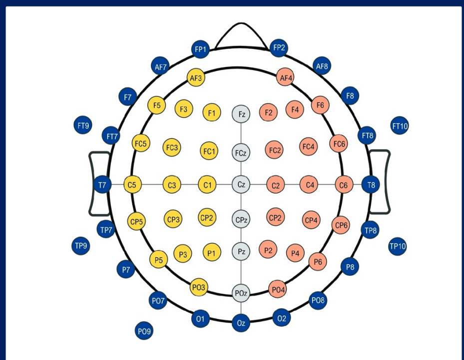
The P3 Event-Related Potential as an Index of Motivational Relevance

A Conditioning Experiment

Ingmar H. A. Franken, Jan W. Van Strien, Bruno R. Bocanegra, and Jorg Huijding
Institute of Psychology, Erasmus University Rotterdam, The Netherlands

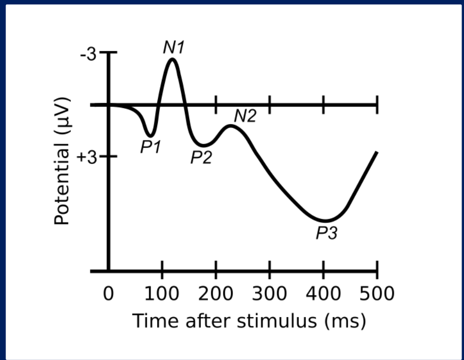
64-channel EEG system



"These results show that the P3 component is a suitable index of acquired motivational relevance and is not, at least not completely, dependent on task-irrelevant stimulus properties, such as complexity and contrast." (Franken et al. 2011)

P3 as a bioelectrical signature of salience

P3 (or P300) amplitude



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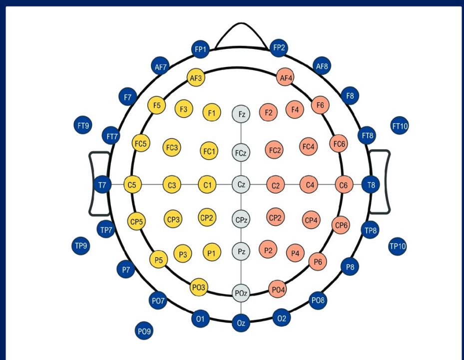

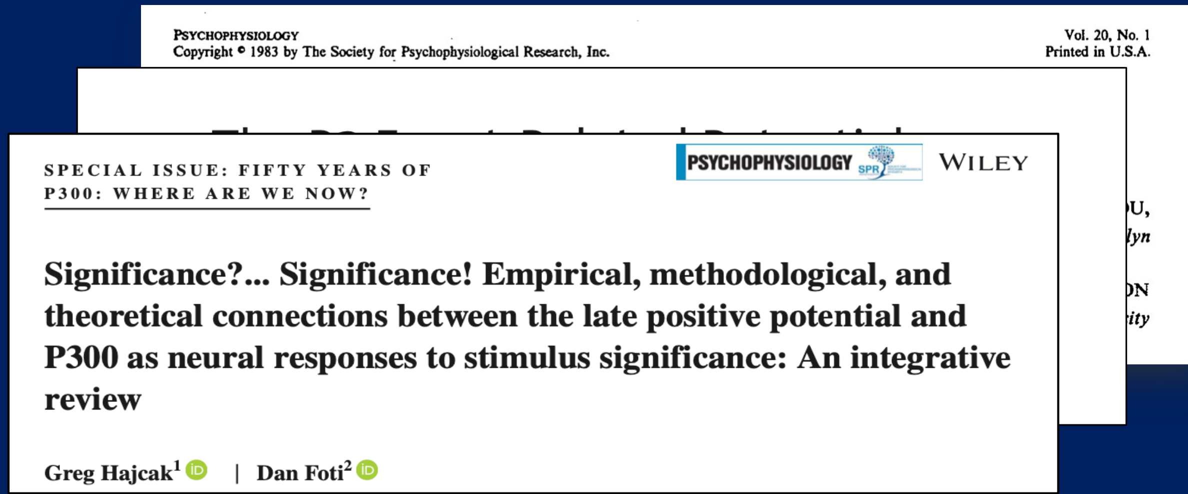
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SPECIAL ISSUE: FIFTY YEARS OF P300: WHERE ARE WE NOW?

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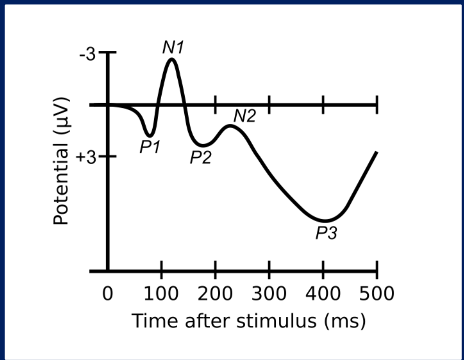
Significance?... Significance! Empirical, methodological, and theoretical connections between the late positive potential and P300 as neural responses to stimulus significance: An integrative review

Greg Hajcak[1] | Dan Foti[2]

"The most parsimonious account (...) is that [when] P300/LPP is elicited by motivationally significant stimuli (...) P300 and LPP may reflect output from a common system that tracks the time-course of stimulus significance." (Hajack & Foti, 2020)

P3 as a bioelectrical signature of salience

P3 (or P300) amplitude



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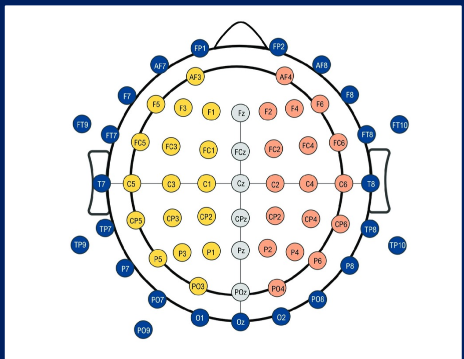

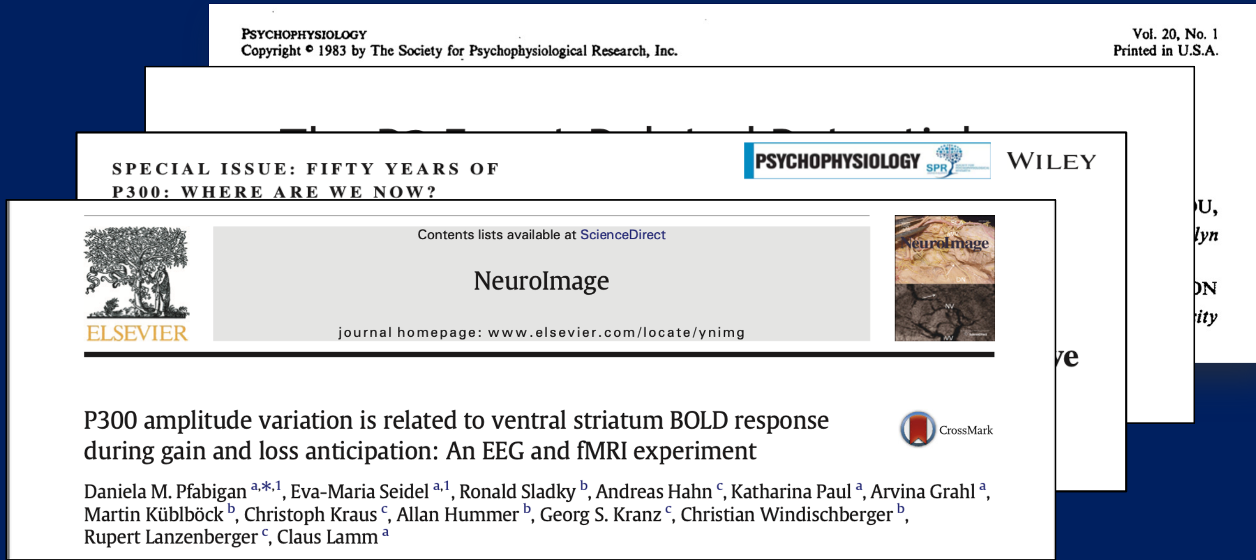

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SPECIAL ISSUE: FIFTY YEARS OF P300: WHERE ARE WE NOW?

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ELSEVIER

P300 amplitude variation is related to ventral striatum BOLD response during gain and loss anticipation: An EEG and fMRI experiment

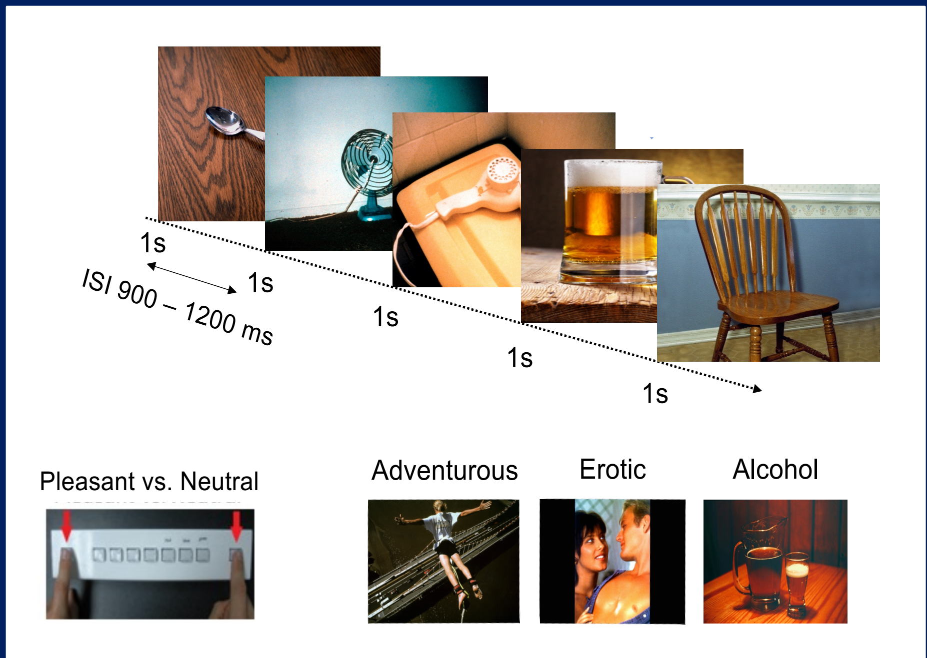
CrossMark

Daniela M. Pfabigan [a,*,1], Eva-Maria Seidel [a,1], Ronald Sladky [b], Andreas Hahn [c], Katharina Paul [a], Arvina Grahl [a], Martin Küblböck [b], Christoph Kraus [c], Allan Hummer [b], Georg S. Kranz [c], Christian Windischberger [b], Rupert Lanzenberger [c], Claus Lamm [a]

"Larger P300 amplitudes indicated higher ventral striatum blood oxygen level dependent (BOLD) responses (...), which are usually associated with reward processing." (Pfabigan et al., 2014)

Picture-viewing ‘oddball’ paradigm

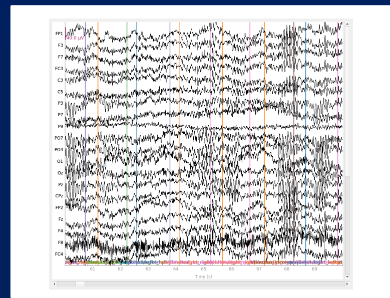
Picture-viewing ‘oddball’ task



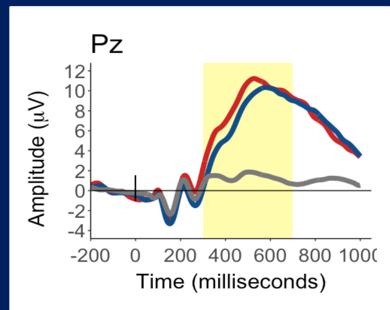
e.g., Bartholow et al., 2007, 2010; Cofresí et al., 2022; Martins et al., 2019, 2022

EEG/ERP system

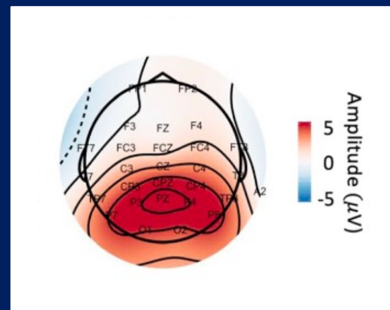
EEG signal



P3 (or P300) amplitude



Topographical scalp map



Reward pathology and AUD risk

AUD = Alcohol Use Disorder (diagnosis based on DSM-5 criteria)


Bruce Bartholow
The University of Iowa

Keanan Joyner
UC Berkeley

- Ps were *N*=143 young adults (ages 18-30; 62% women: ~4 binge episodes/past year)
- Picture-viewing 'oddball' task while EEG was recorded (~ 2 hrs per session)
  - Stimuli: alcohol beverages, nonalcohol beverages, adventure scenes, and erotic images
- Participants also completed measures of drinking and alcohol-related consequences

Alcohol

Nonalcohol

Neutral

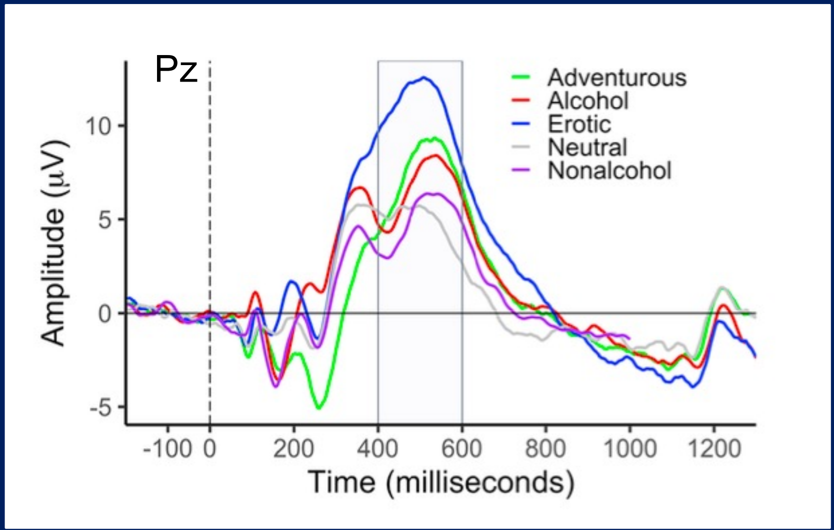
Adventure

Erotic

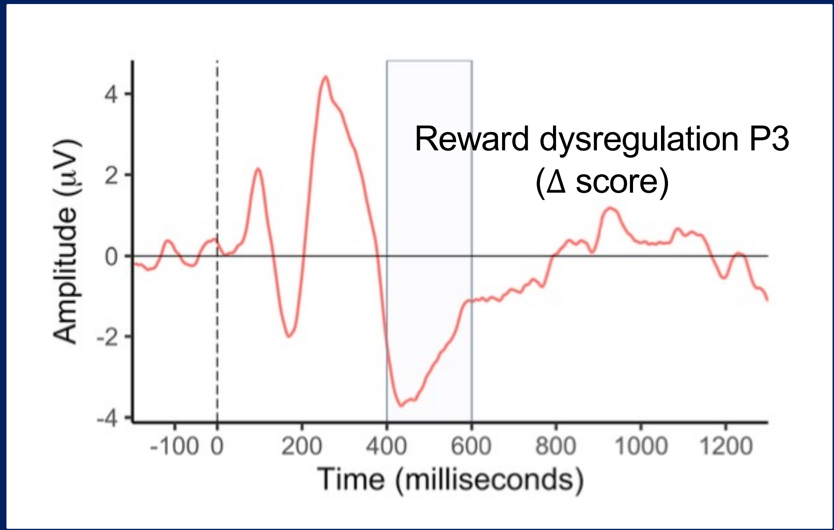
Reward dysregulation P3

- ACR-P3 = P3 amplitudes elicited by alcohol cues
- Reward-P3 = average of P3 amplitudes elicited by erotic and adventure images
- Reward dysregulation P3 = ACR-P3 – Reward-P3

Grand-averaged, stimulus-locked waveforms



Grand-averaged difference waveform



Predicting alcohol use and problems

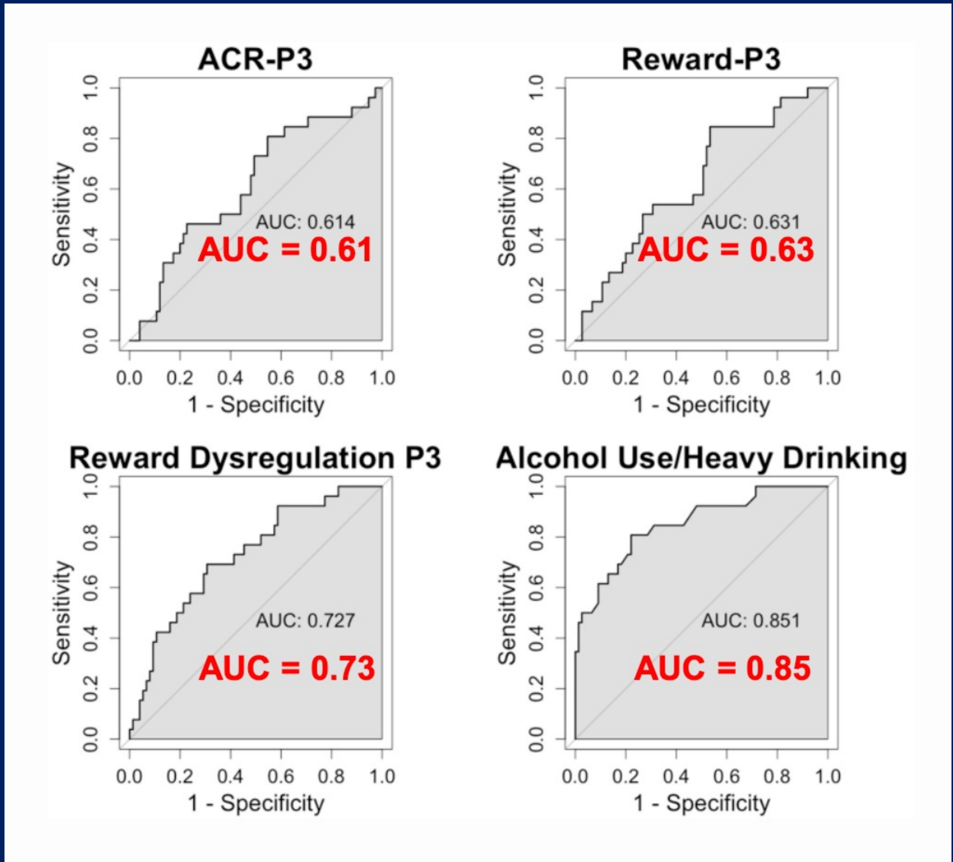
ACR-P3, Reward-P3, Reward dysregulation P3, & alcohol involvement and alcohol-related problems

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 ordinary least squares (OLS) regression models were estimated controlling for age (in years), sex (female/male), and race. In addition, all regression models predicting alcohol problems controlled for an alcohol use/heavy drinking composite (including average of alcohol use, binge drinking and heavy drinking).

Clinical utility: classification performance

Receiver Operating Characteristic (ROC) curves



Ps were categorized as "high" vs. "low" risk for AUD based on their frequency of alcohol-related problems (YAACQ score)

ROC curves:

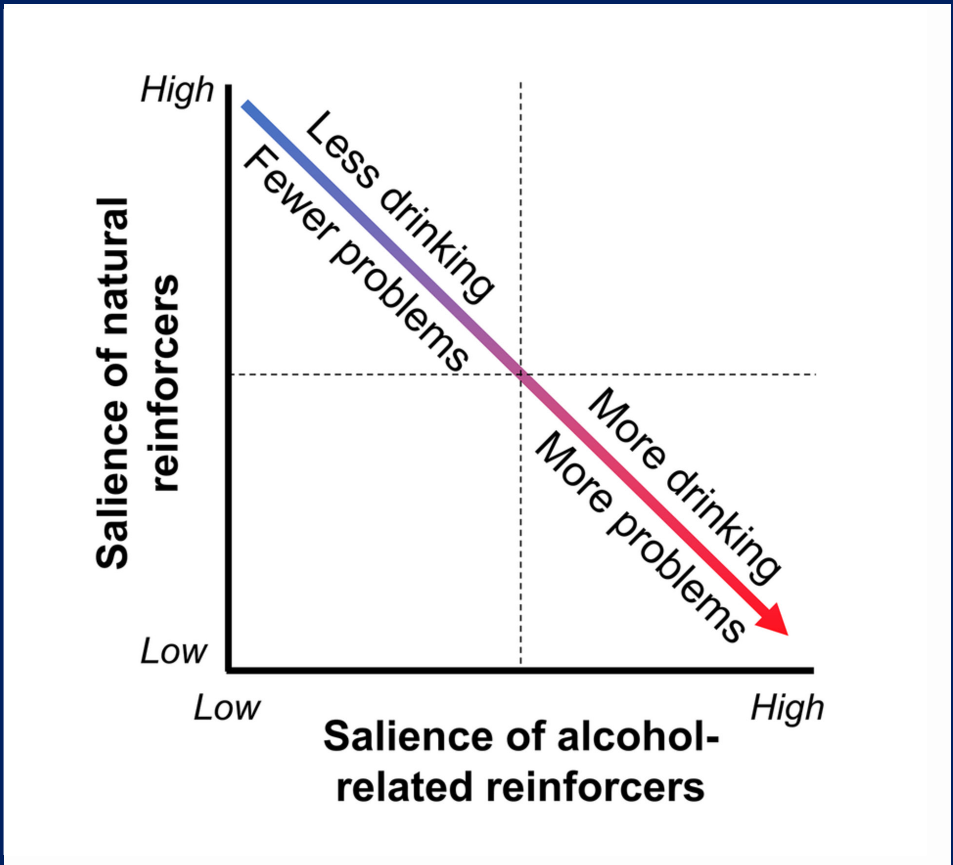
- quantify how well P3s differentiate Ps based on their predetermined classes

Reward Dysregulation P3 performed:

- better than either of its constituent P3s
- nearly as well as a heavy drinking scores

(Neuro)biomarker of risk for heavy drinking

Reward dysregulation and alcohol involvement



Reward dysregulation P3 as a *biomarker*…

Prediction:

- Reward dysregulation P3 was robustly associated with drinking outcomes

Classification:

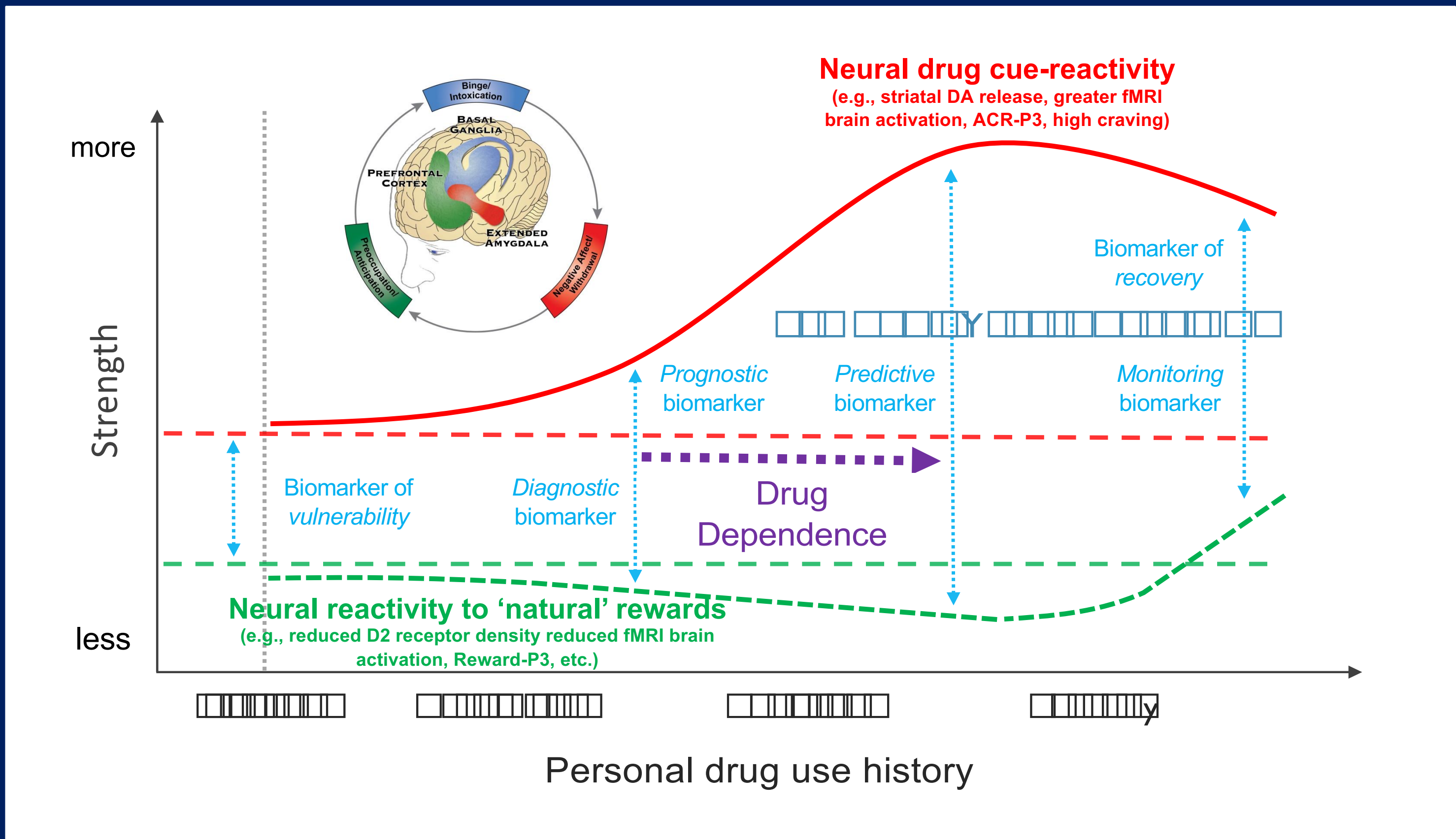
- Reward dysregulation P3 discriminated individuals at risk for problematic drinking

Diagnosis & *prognosis*:

- the utility of reward dysregulation P3 for both clinical diagnosis and vulnerability assessment beyond self-report measures

Integrative theoretical account of addiction

Transition from controlled alcohol or drug use to addiction and dependence



“Does neural drug cue-reactivity represent a preexisting liability or is it a result of prolonged drug use?”

Roadmap

1. Review of most influential theoretical perspectives of addiction
2. “Why do some people become addicted to drugs while others do not?”
3. “What are the acute and prolonged effects of alcohol and drugs in the brain?”
4. “Why is it so difficult to change addictive behaviors and recover from addiction?”

Causal inferences in observational data

4 key assumptions for inferring causality:

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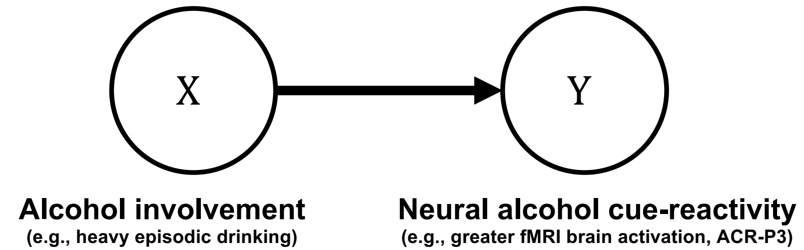
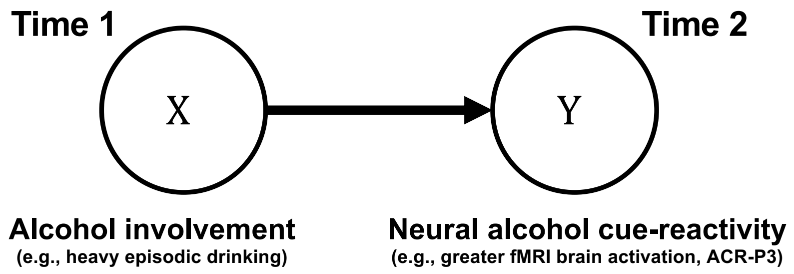
1. An observed association between the potential cause (IV) and the effect (DV)



Causal inferences in observational data

4 key assumptions for inferring causality:

1. An observed association between the potential cause (IV) and the effect (DV)
2. The cause (IV) must precede the effect (DV) in time (i.e., temporal precedence)



Causal inferences in observational data

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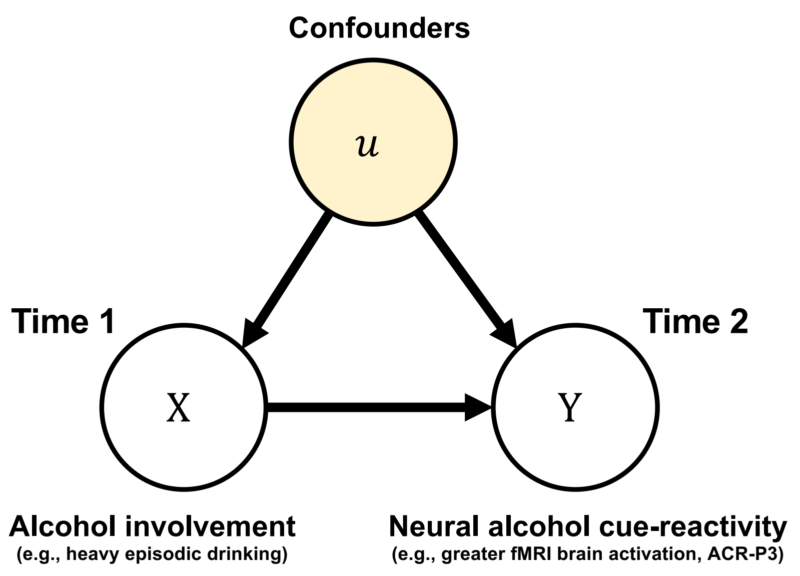

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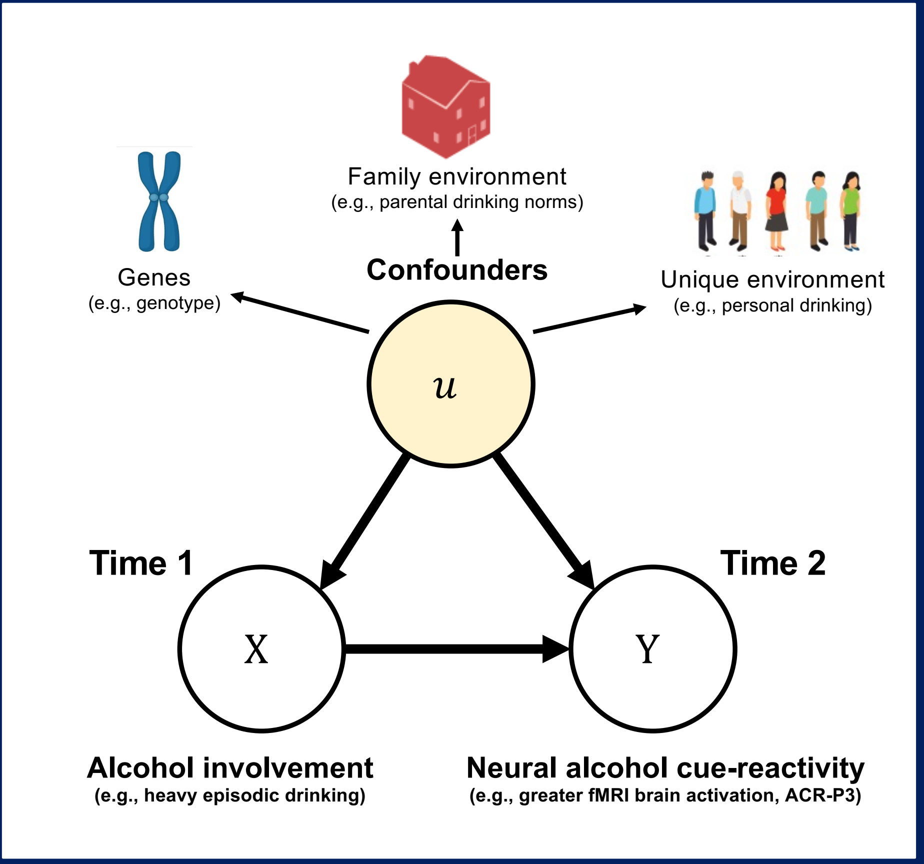

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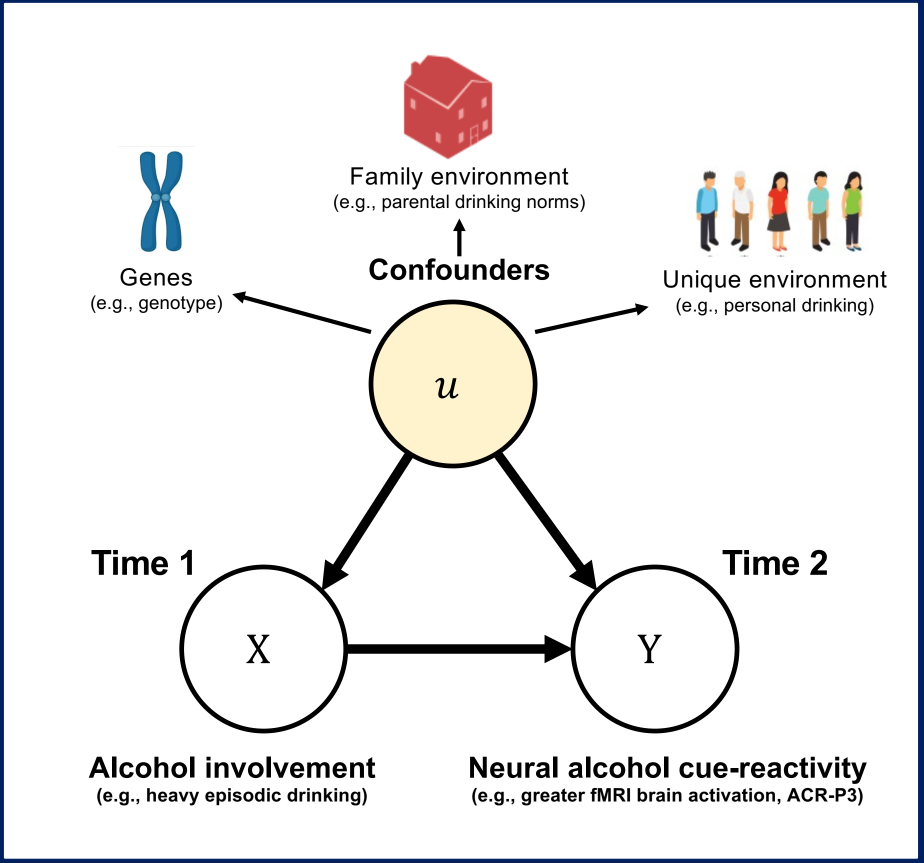

Causal inferences in observational data

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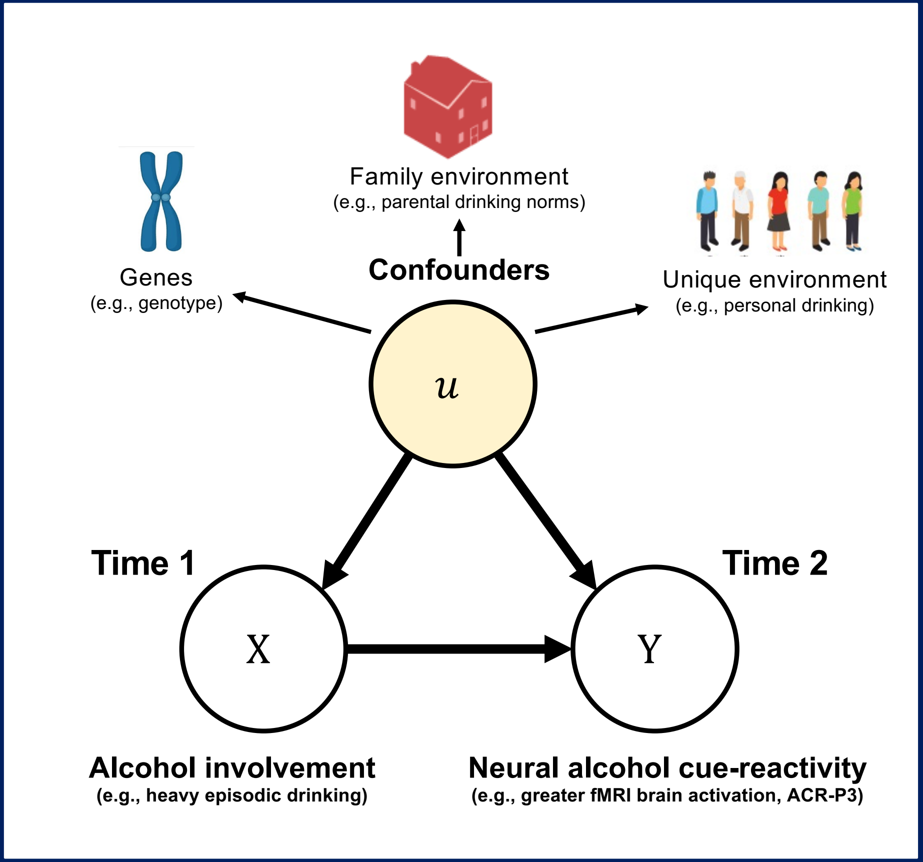
Fundamental problem of causal inference

(i.e., impossibility to observed the counterfactual scenario)



Monozygotic twins reared together

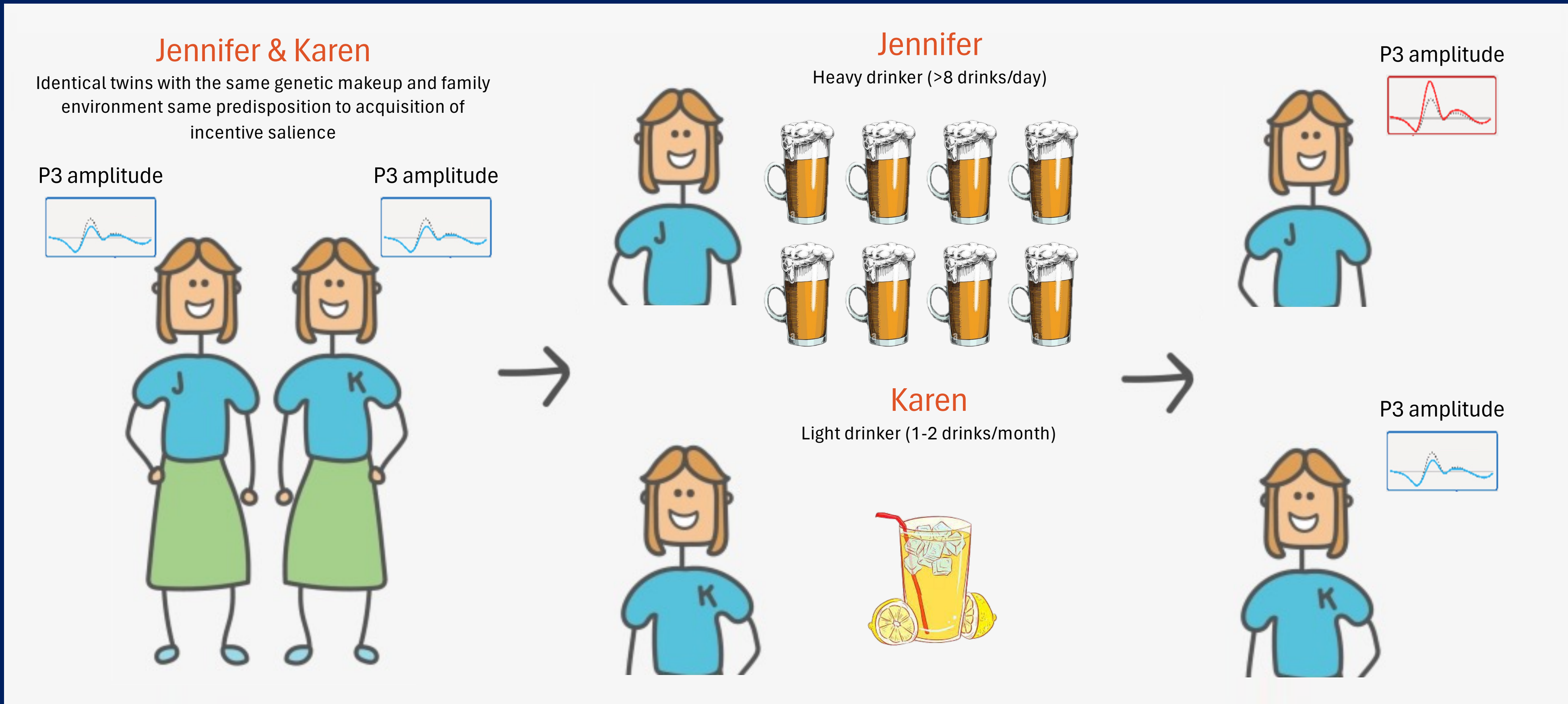
Monozygotic twins raised in the same household

Monozygotic (MZ) twins:

- share 100% their genetic makeup
- share all their family environment
- each twin has their own nonshared unique environmental experiences

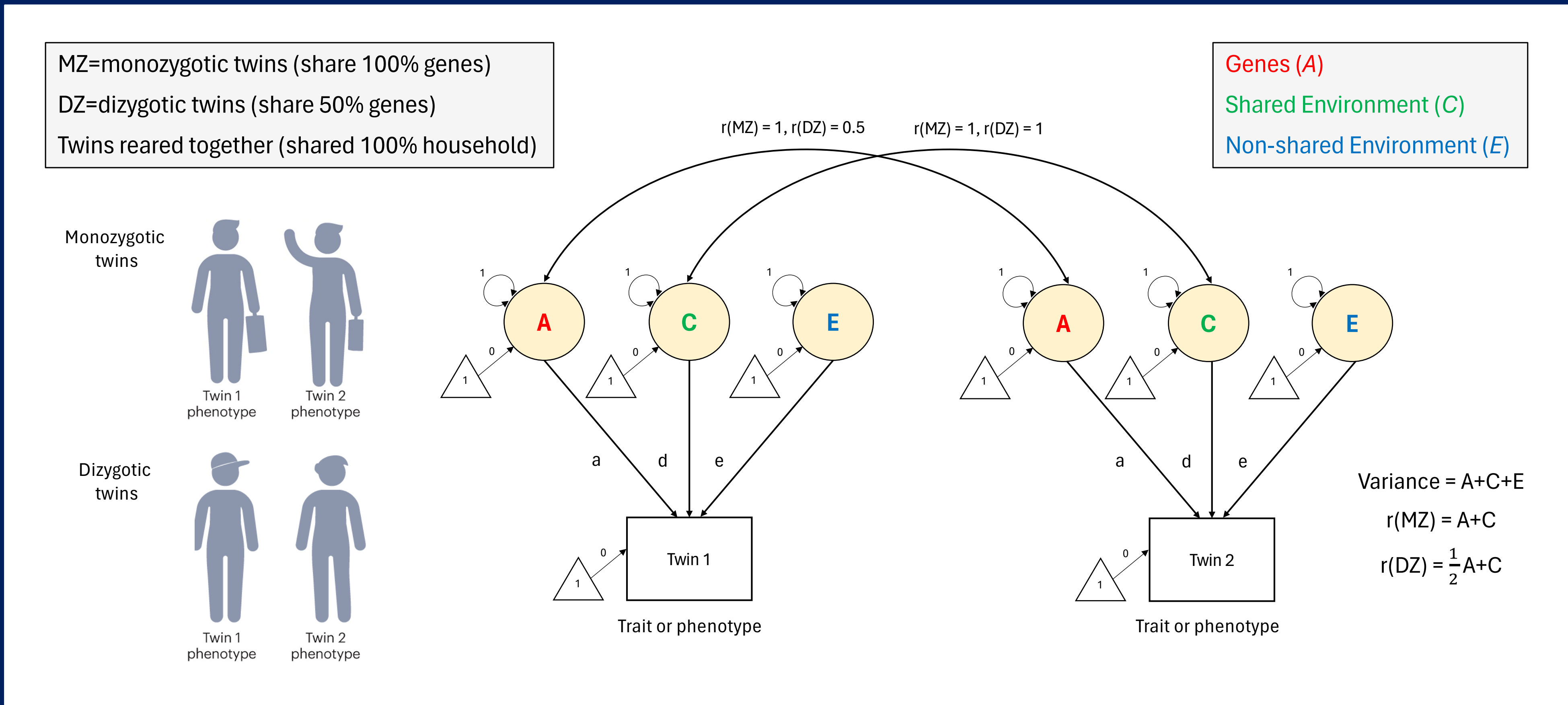
The Holy Grail of causality: A step forward

The discordant monozygotic (MZ) twin method and neural alcohol cue-reactivity



Classic Biometric Twin Model

Decompose phenotypic variance into genetic and environmental influences



ACR-P3 shaped by heavy drinking

Andrey Anokhin
Washington University

Bruce Bartholow
The University of Iowa

ACR-P3 = P3 amplitudes elicited by alcohol cues

- Ps were *N*=173 twins who were longitudinally followed from age 12 to 20
  - 44 MZ pairs/53 DZ pairs, 49% females and 86% White
- Alcohol use was assessed annually with structured clinical interviews
- Alcohol Image Task (AIT) while EEG was recorded (at age 18 or 20)
  - Stimuli: alcohol beverages, nonalcohol beverages, and neutral objects

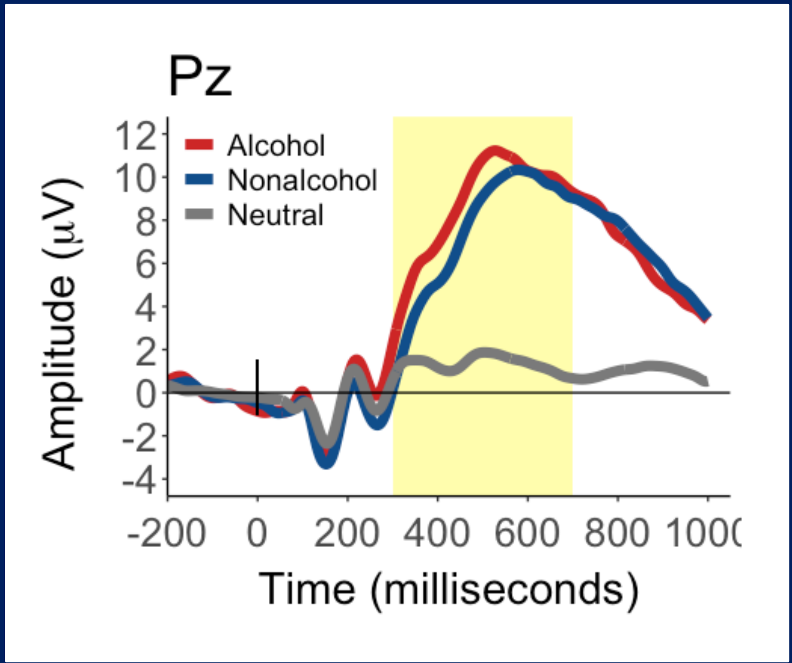
Alcohol

Nonalcohol

Neutral

ACR-P3, Nonalcohol-P3 and Neutral-P3

Grand-averaged, stimulus-locked waveforms

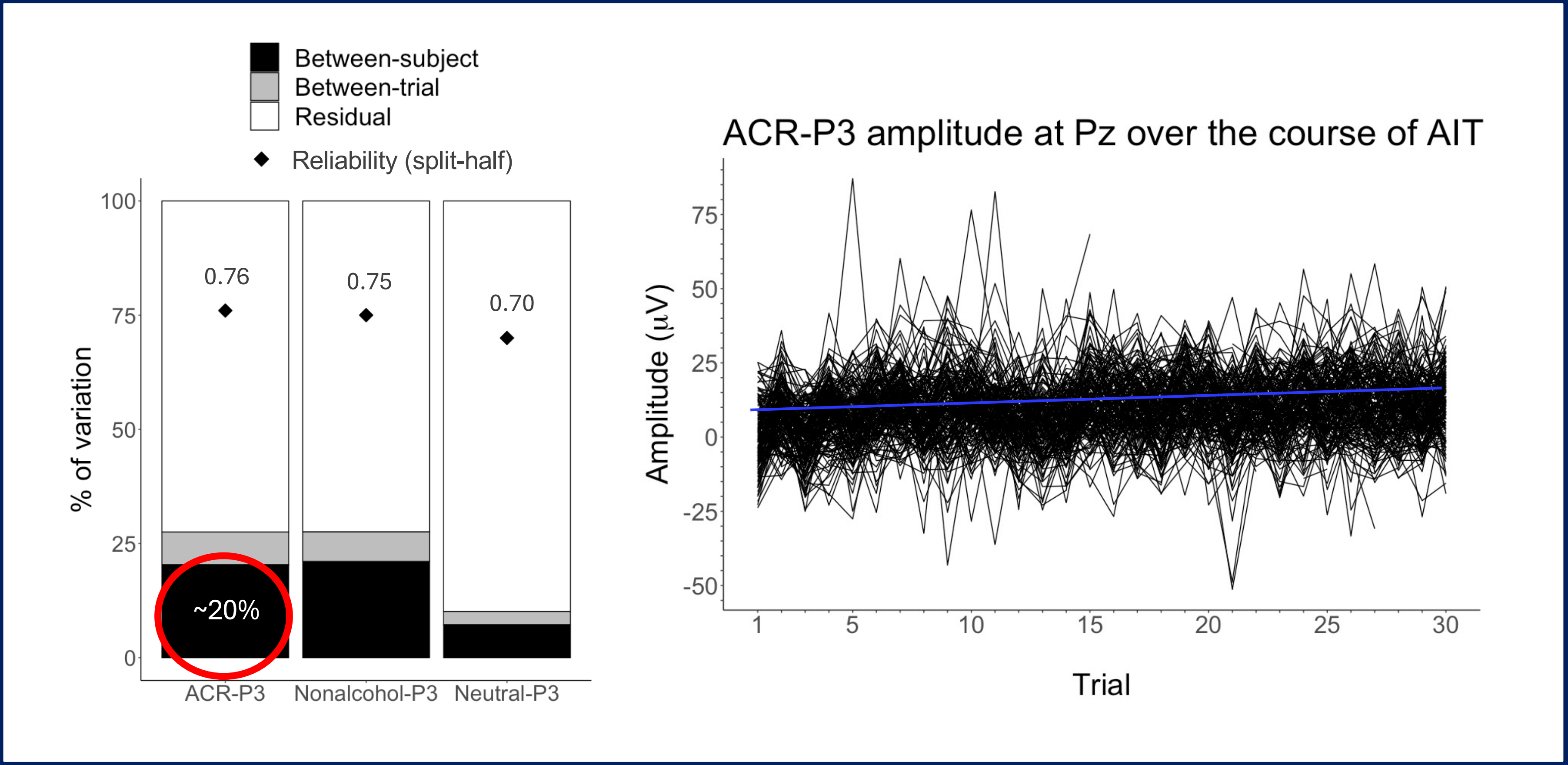


P3 amplitude ERP measures (at Pz channel):

- P3 elicited by alcohol cues => ACR-P3
- P3 elicited by nonalcohol cues => Nonalcohol-P3
- P3 elicited by neutral cues => Neutral-P3

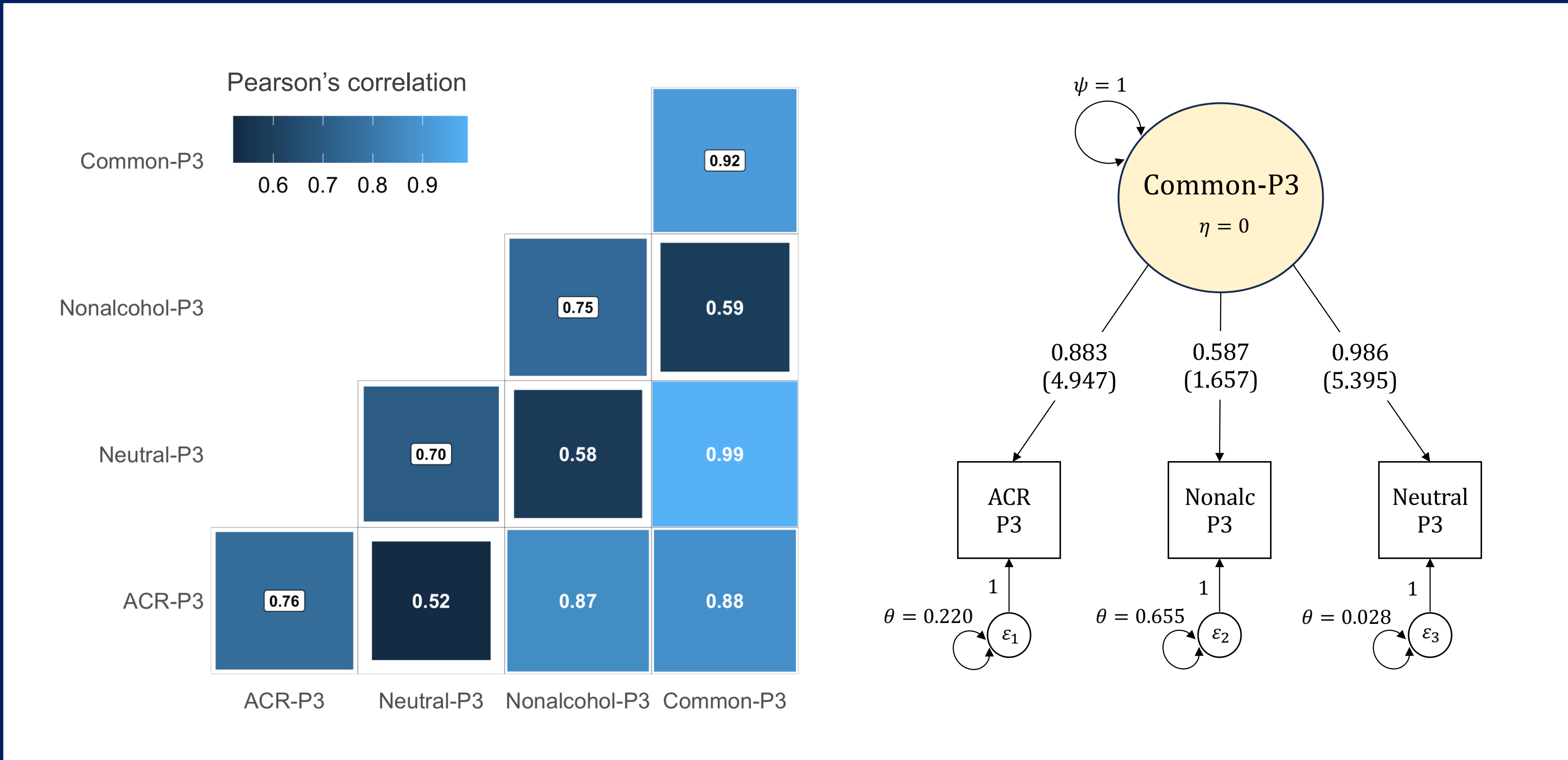
Quantifying individual differences in ACR-P3

Between-subject variability and individual differences in ACR-P3



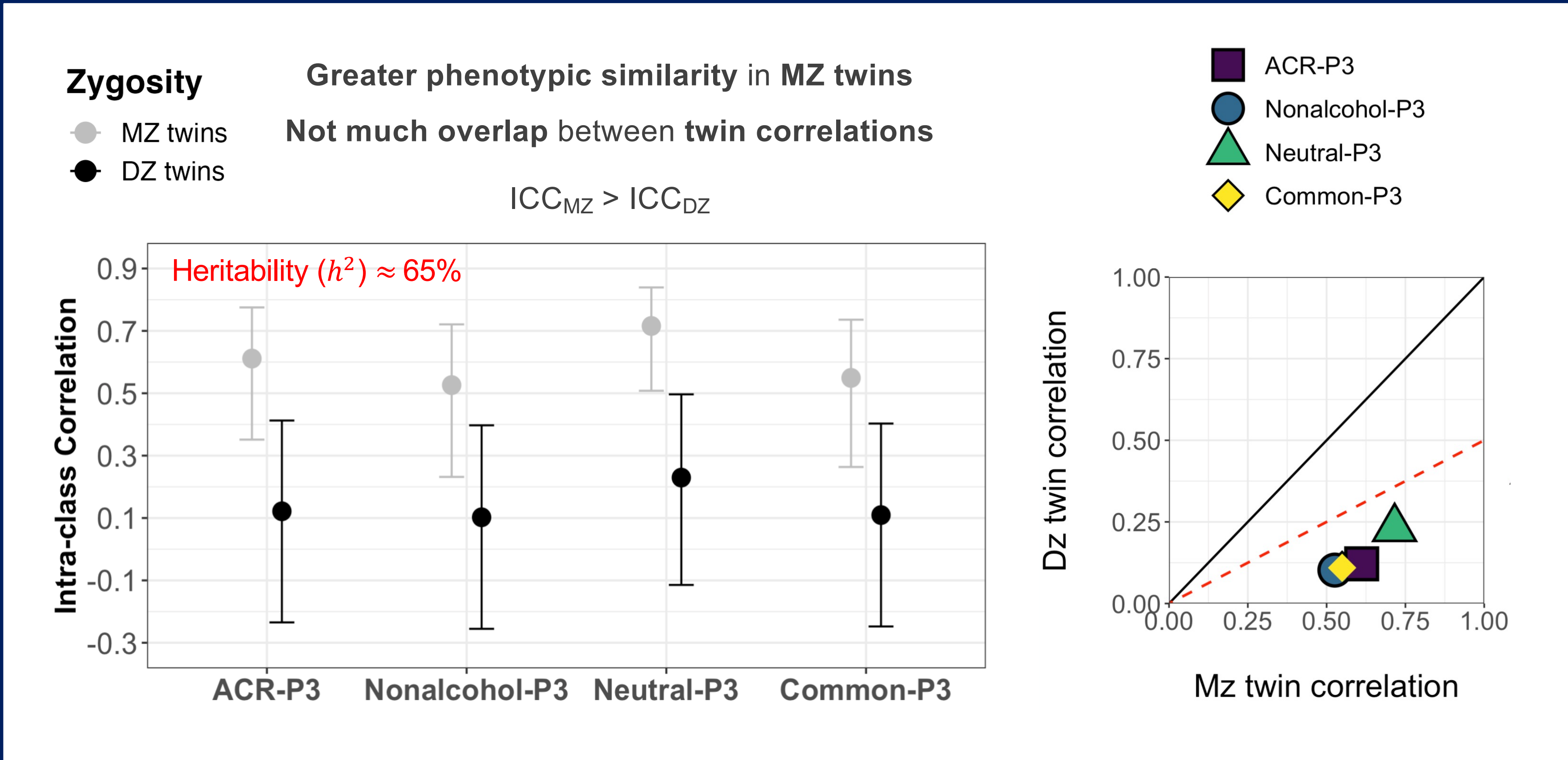
High commonality across P3 ERP measures

Reliable and highly correlated individual differences in P3 ERP reactivity

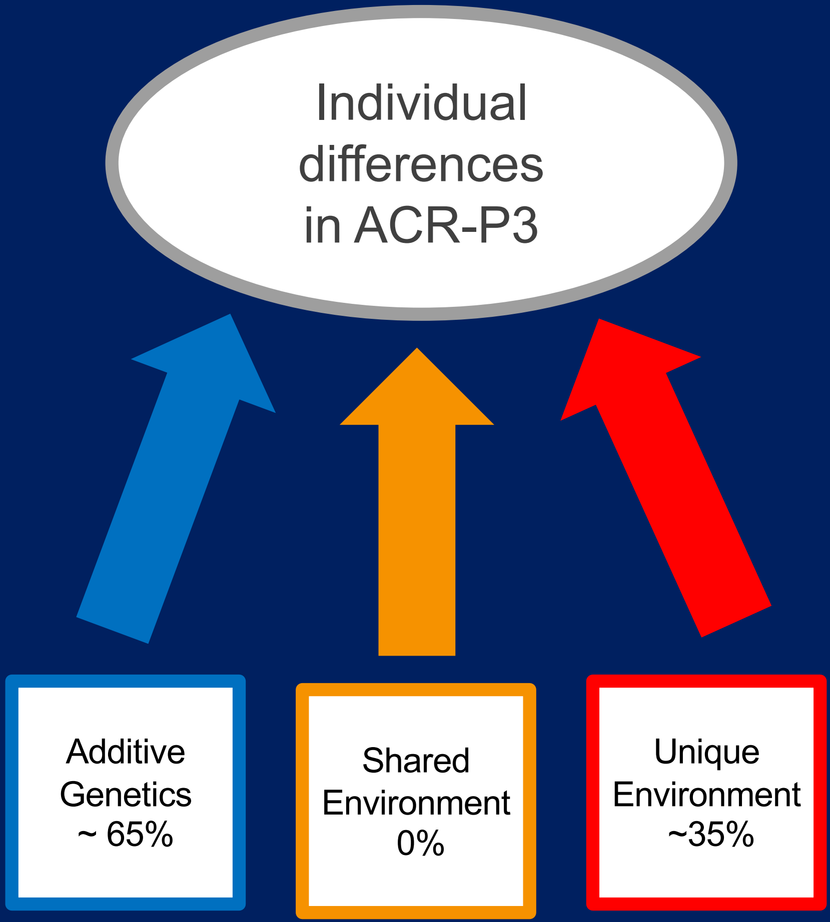


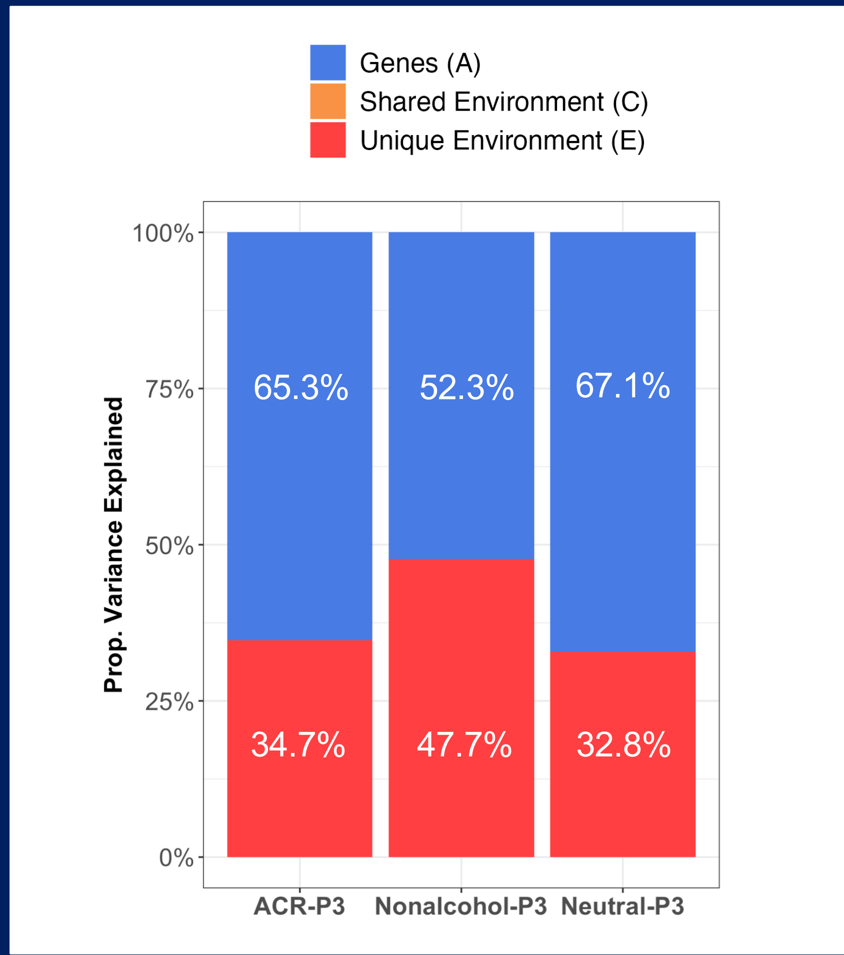
Nature vs. Nurture: Twin similarity in ACR-P3

Individual differences in ACR-P3 are highly heritable and strongly genetically determined



Genetic and environmental influences





Heavy drinking shapes ACR-P3

B_B = family-wide liability (shared genes & environment)

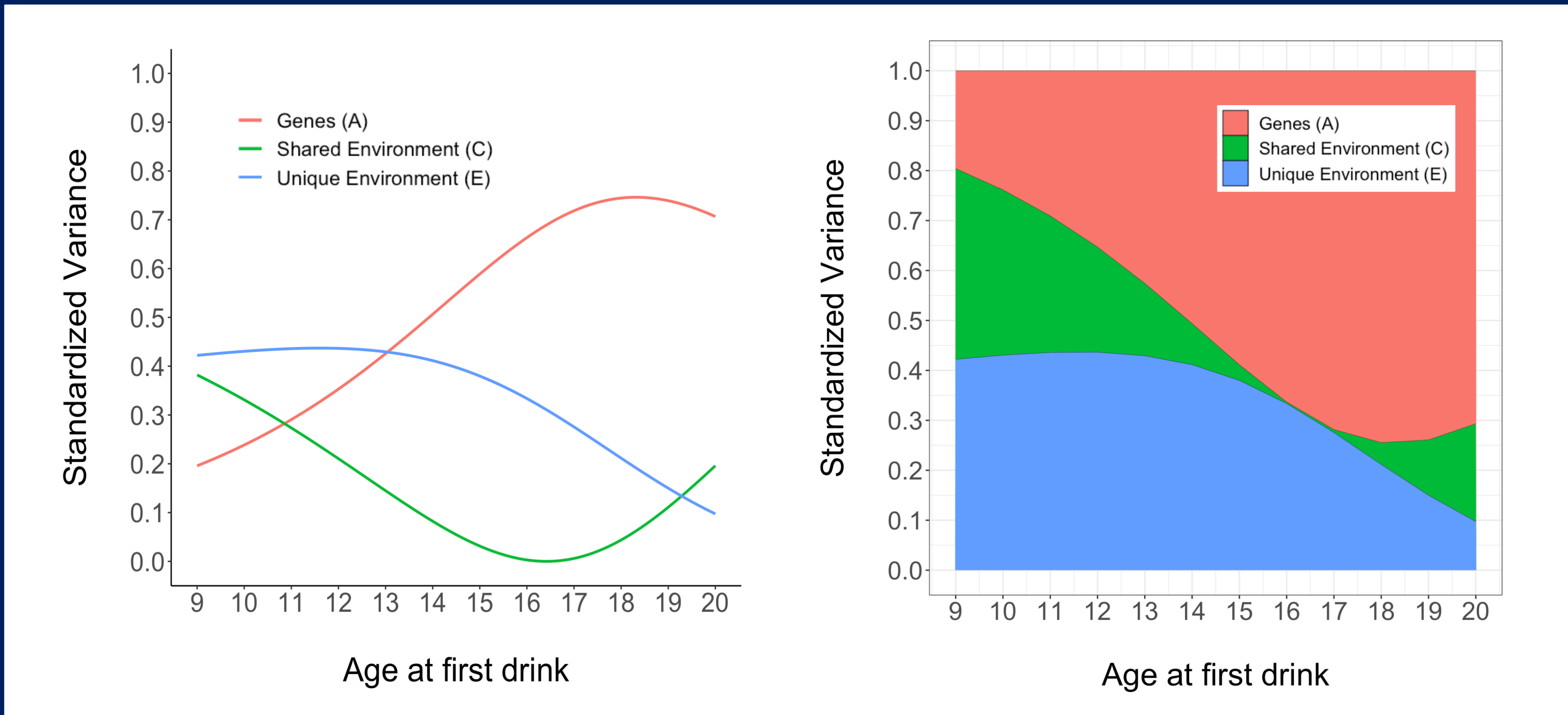
B_W = nonshared or unique environmental contribution

$$Y_{ij} = B_{00} + (B_B \times \bar{X}_{0j}) + \left(B_w \times (X_{ij} - \bar{X}_{0j})\right) + (B_{03} \times ZYG) + \left(B_{04} \times ZYG \times (X_{ij} - \bar{X}_{0j})\right) + u_{0j} + e_{ij}$$

	Age at first drink		Alcohol use		Heavy drinking	
DV: ACR-P3	B	P-value	B	P-value	B	P-value
Sex	2.74	0.0435	2.92	0.0416	2.42	0.0938
Within-twin (B_W)	0.12	0.6512	–0.02	0.2404	0.28	0.0335
Between-twin (B_B)	0.30	0.3389	0.005	0.2469	–0.06	0.6293
DV: Nonalcohol-P3						
Sex	2.98	0.028	2.93	0.0407	2.29	0.1203
Within-twin (B_W)	0.21	0.118	–0.03	0.0903	0.28	0.0698
Between-twin (B_B)	0.49	0.466	0.005	0.3080	–0.16	0.1940

Early initiation of drinking and ACR-P3

Early adolescence (ages 9-13) is a sensitive developmental period for incentive sensitization



“Can these altered neural brain responses caused by prolonged drug use be restored with treatment?”

Roadmap

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The cycle of chronic relapse

Relapse is highly prevalent in addiction

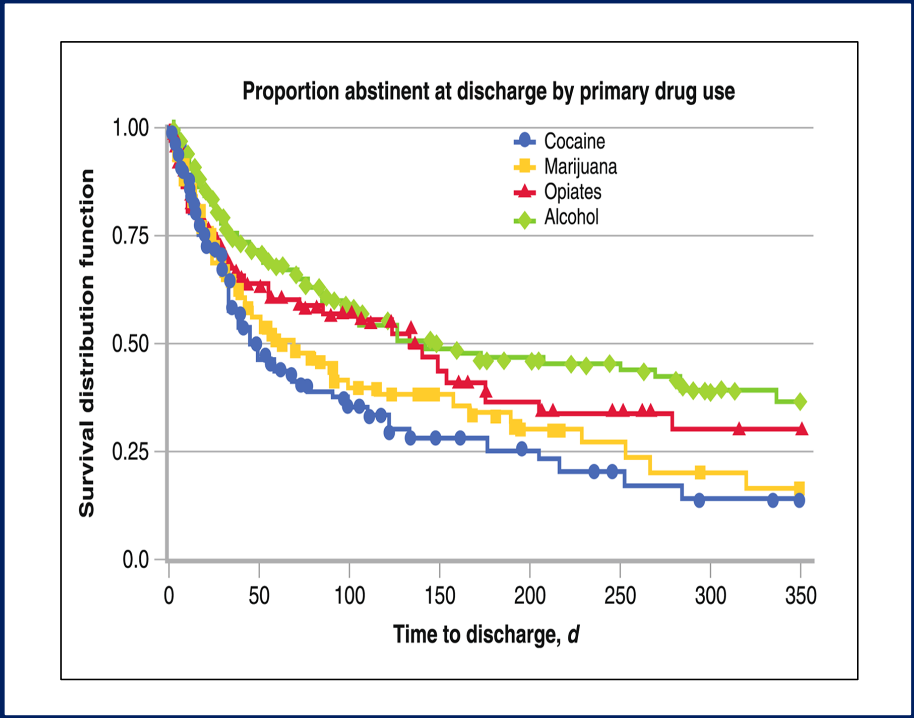


Image from Sinha, R. (2011). New findings on biological factors predicting addiction relapse vulnerability. *Current Psychiatry Reports*, *13*, 398-405.

Stress pathophysiology in addiction

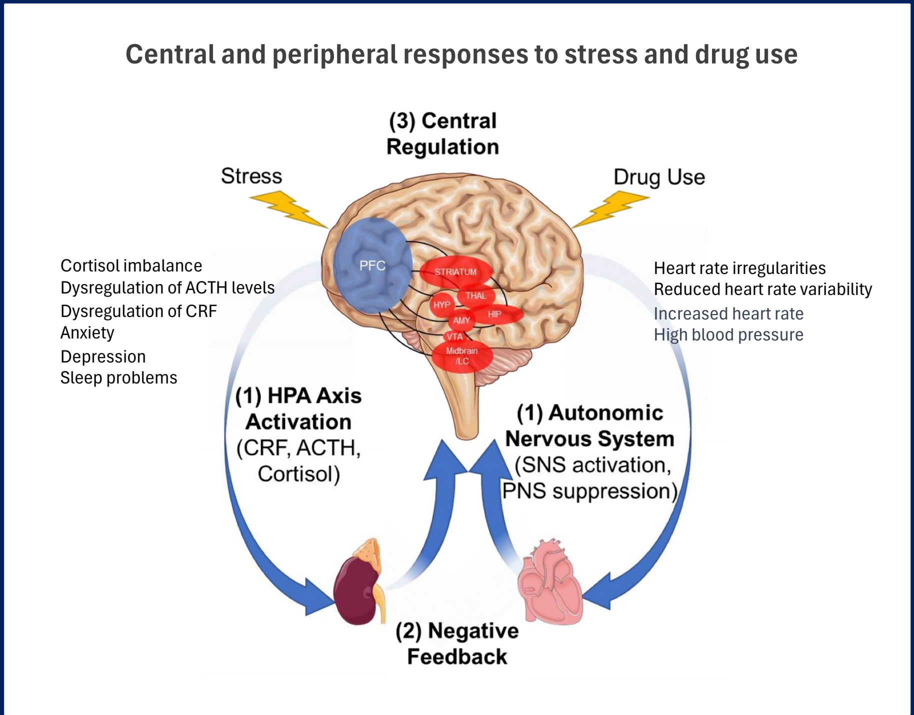


Image adapted from Wemm, S. E., & Sinha, R. (2019). Drug-induced stress responses and addiction risk and relapse. *Neurobiology of Stress*, *10*, 100148.

Altered neural responses in AUD

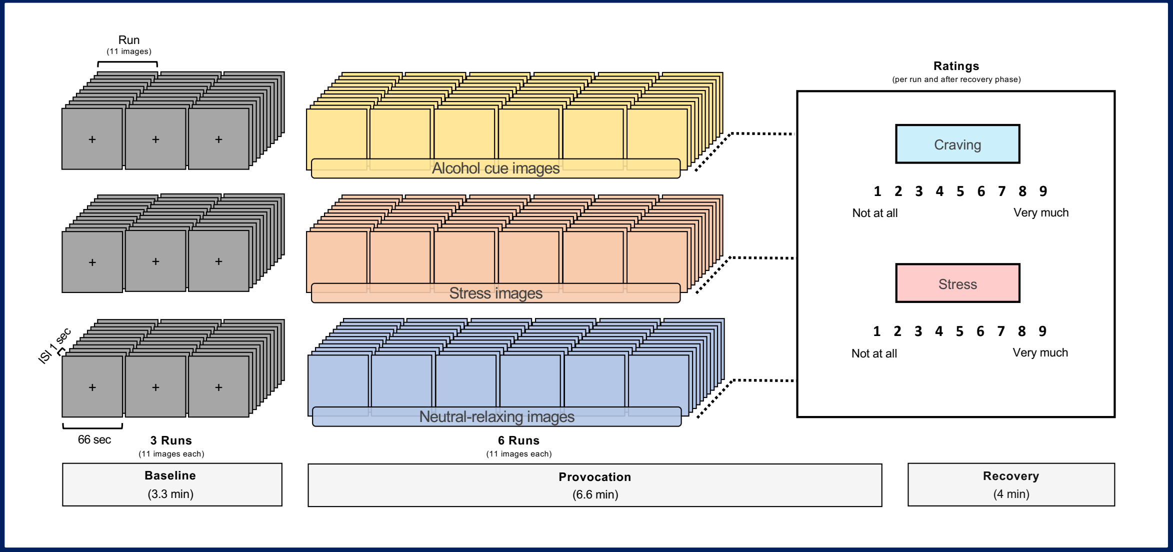
AUD = Alcohol Use Disorder (diagnosis based on DSM-5 criteria)

Dongju Seo
Yale University

Rajita Sinha
Yale University

- Ps were *N*=30 demographically matched AUD treatment-seeking patients (AUD) and 55 moderate drinkers (MD) who completed an fMRI task
- AUD patients completed treatment and a second fMRI task after treatment

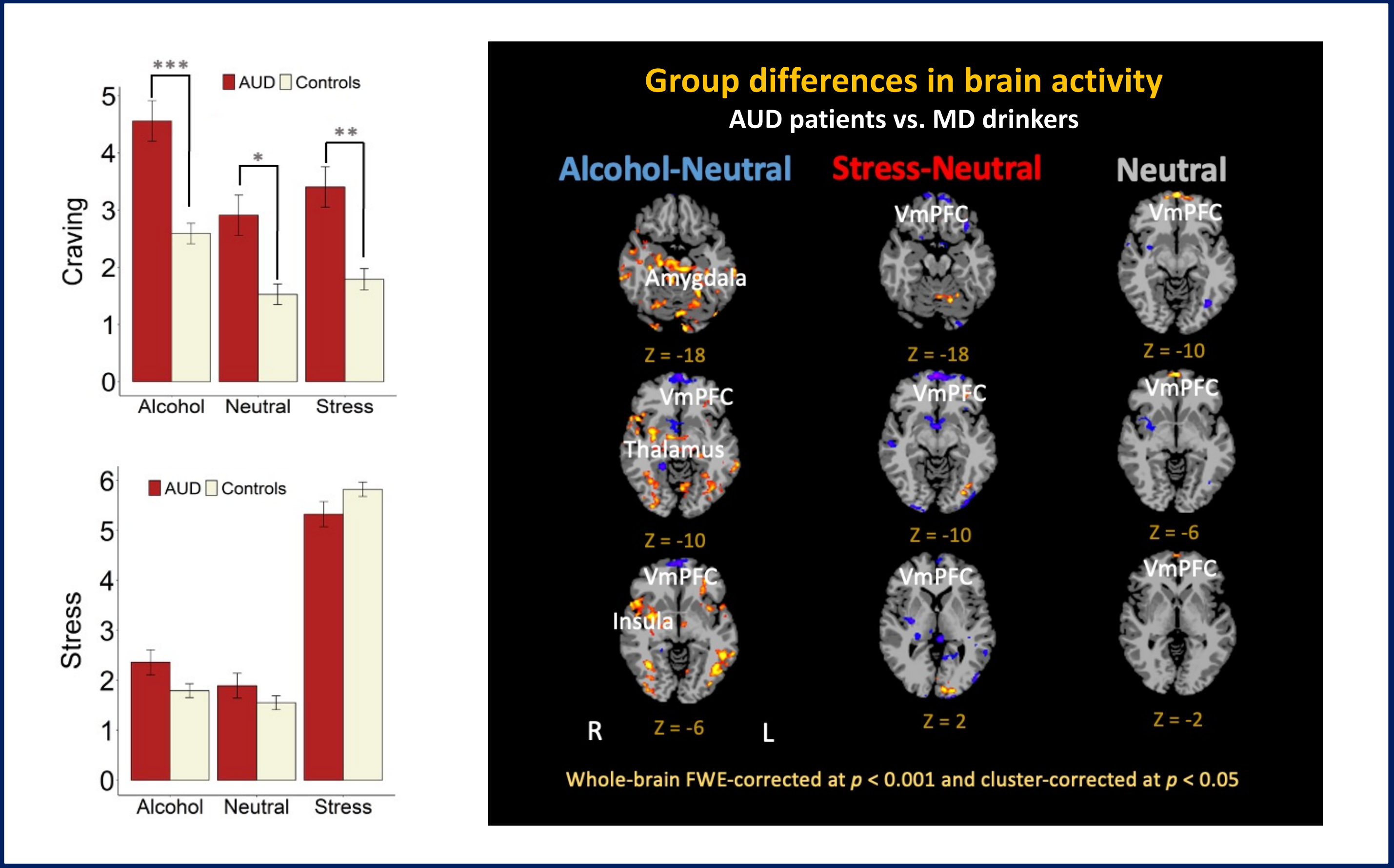
fMRI paradigm



3T Prisma MRI scanner

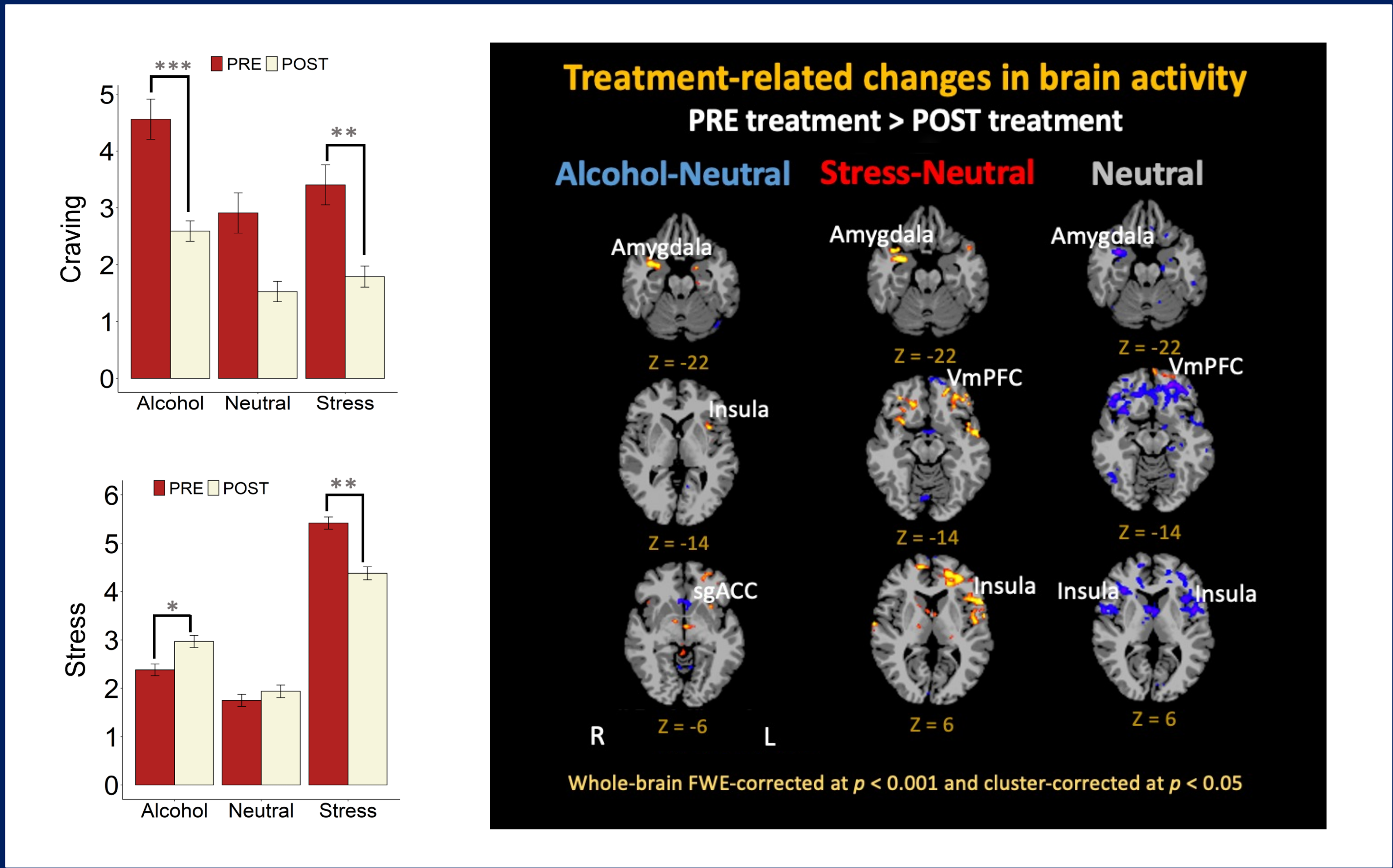
Altered neural circuits of reward and stress

Neural brain function in response to alcohol cues and stress in AUD patients



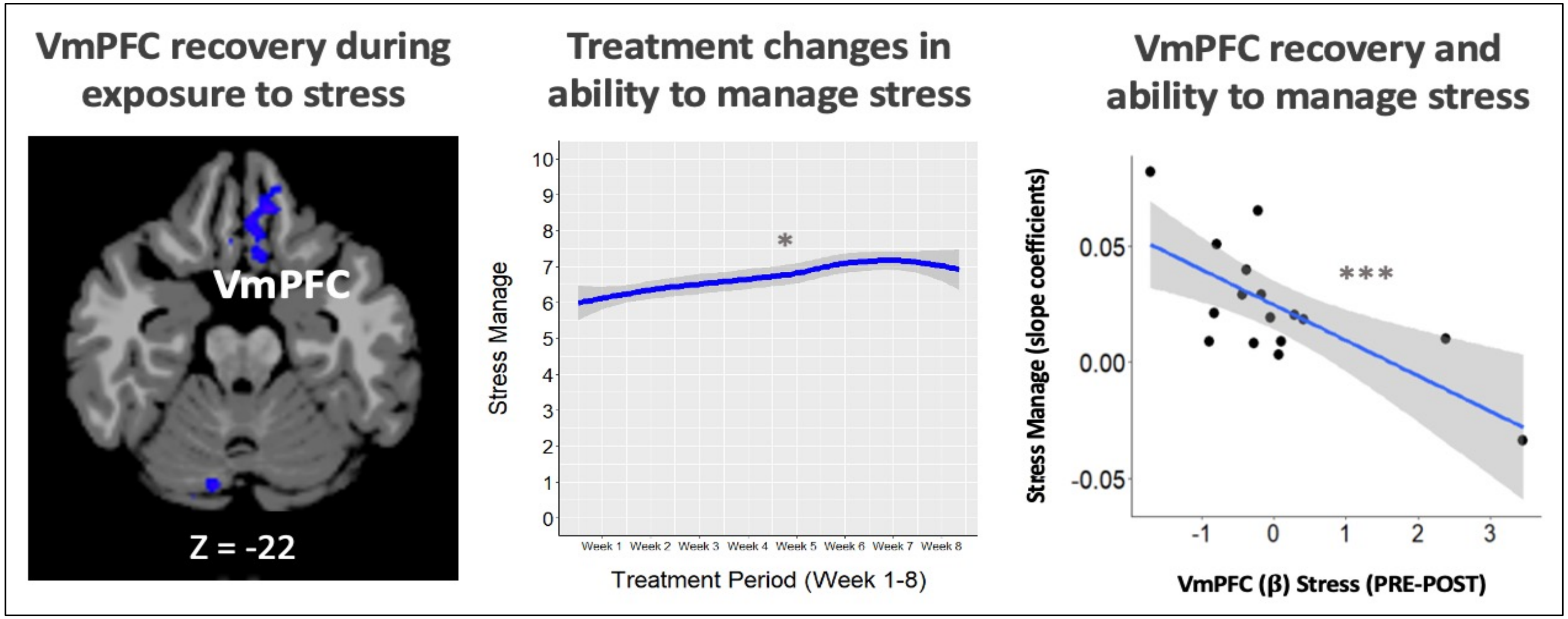
Neural correlates of AUD recovery

Treatment-related recovery of AUD dysfunctions in neural brain activity



VmPFC and ability to manage stress

VmPFC recovery is associated with greater improvements in ability to manage stress



Take home messages

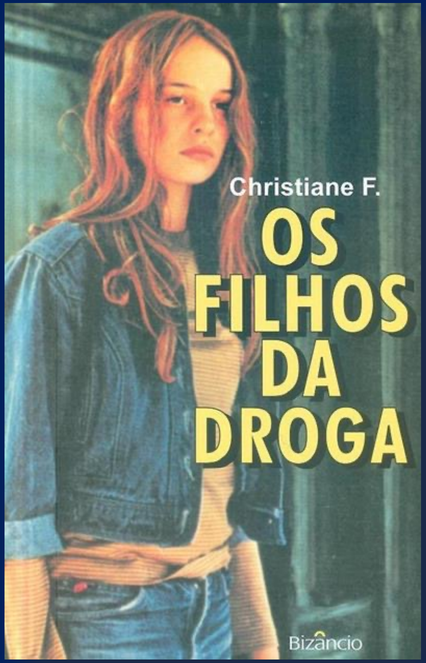
1. Differential brain valuation of alcohol-related and natural rewards (i.e., reward dysregulation) is a reliable and robust indicator of risk for heavy and problematic drinking.

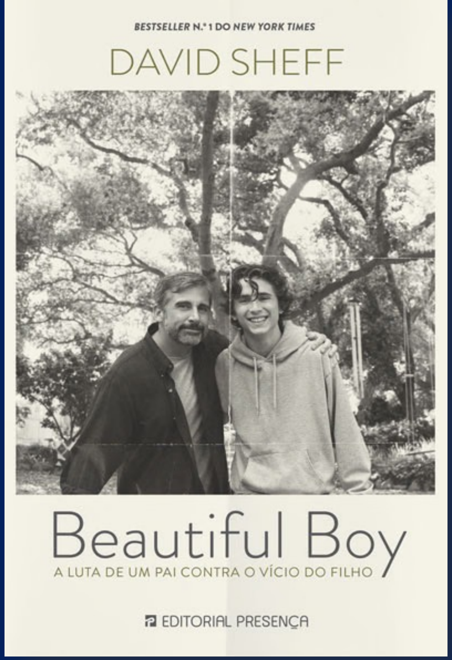
2. Individual differences in neural alcohol cue-reactivity are shaped by heavy episodic drinking:

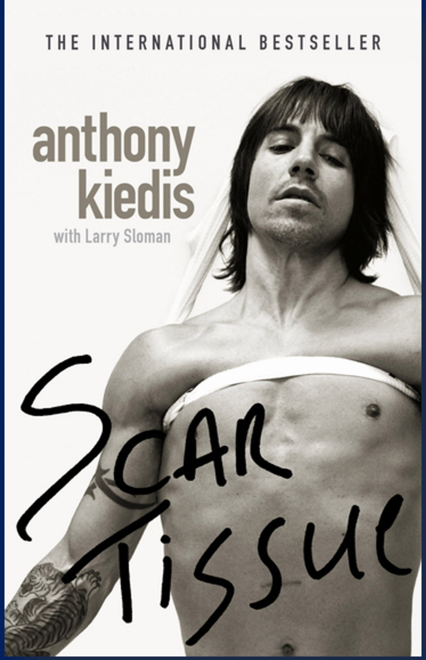
   - P3 amplitude elicited by alcohol cues (ACR-P3) is an acquired neuromarker of risk that likely reflects acquisition of incentive salience for alcohol cues due to heavy episodic drinking.
   - Early adolescence emerges as a sensitive period for incentive sensitization due to heavy episodic drinking with environmental influences playing a substantial role during this developmental phase.

3. Patients with alcohol use disorder (AUD) have altered neural circuits of stress and emotion regulation, a neural pattern that appear to improve significantly after treatment.

Addiction's harrowing realities







"Os fillhos da droga"
by Christiane F.

"Beautiful boy"
by David Sheff

"Scar tissue"
by Anthony Kiedis

Acknowledgments

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