Neuroimaging a Dopamine Pathway to Addiction

(Holy Grails and Other Tales)

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Psychiatry, Psychology, and Neurology & Neurosurgery

Montreal Neurological Institute

McGill University

Robert T. Malison Memorial Lecture
PET Addiction Center of Excellence
University of Pennsylvania
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October 5th
UNESCO World Teachers' Day

Acknowledgements

Psychiatry Dept, McGill Univ.

Marije aan het Rot, Ph.D.

Chawki Benkelfat, M.D., DERBH

Kevin Casey, Ph.D.

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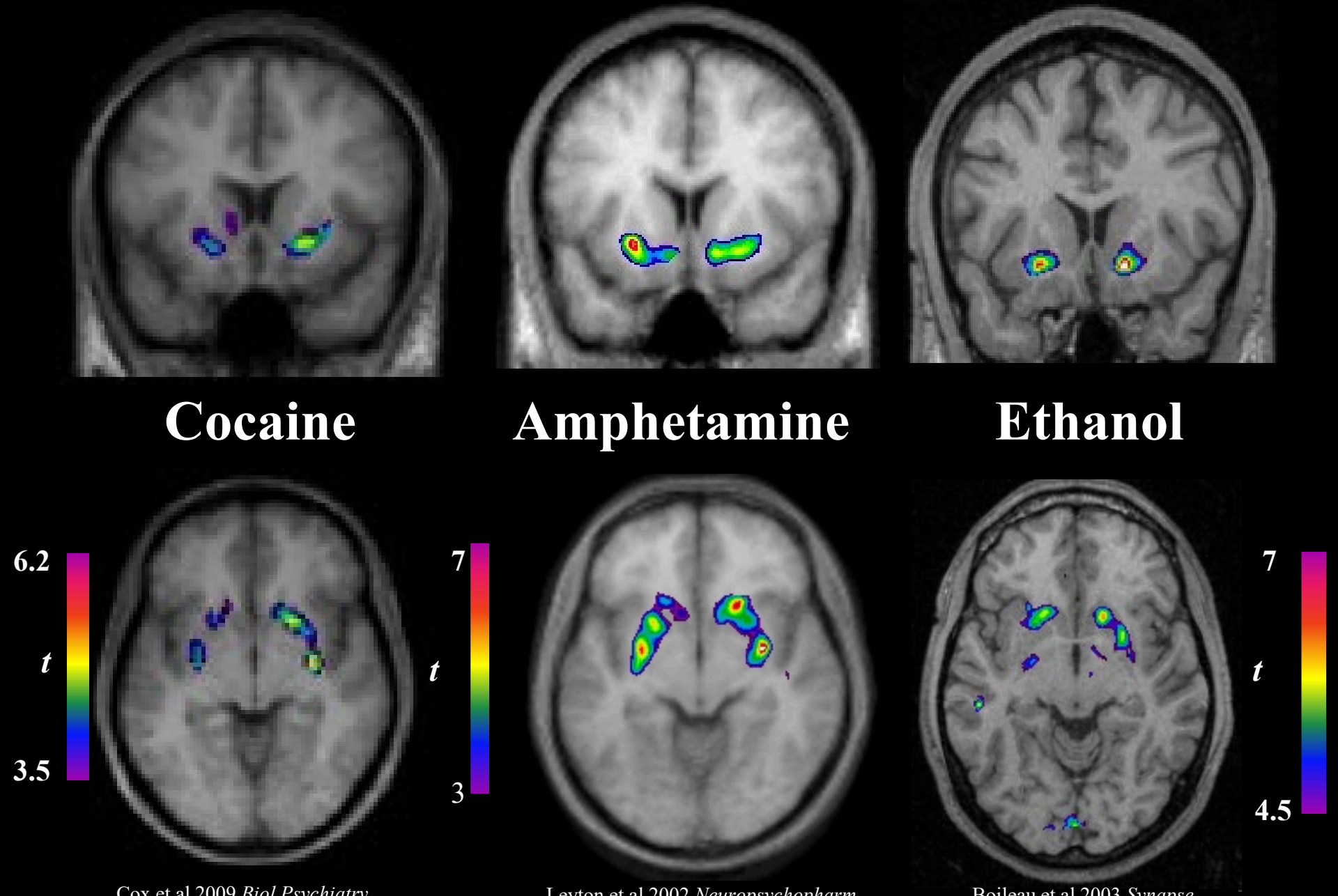
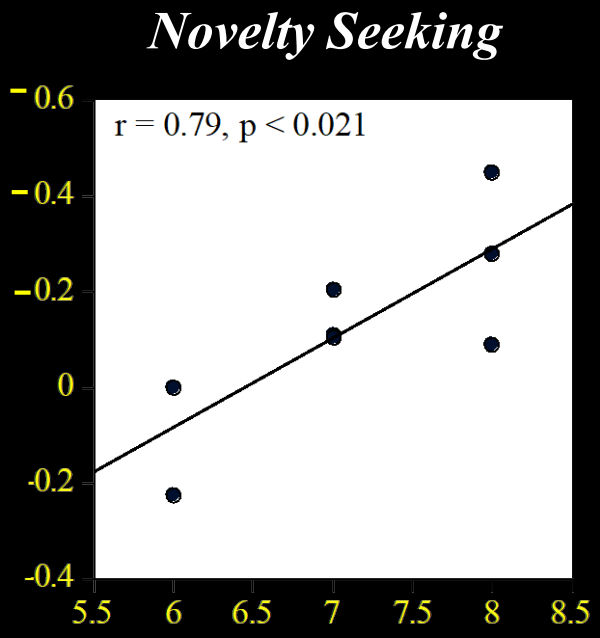
Why study addictions?

Drug-Induced [^{11}C]Raclopride Response



Dopamine

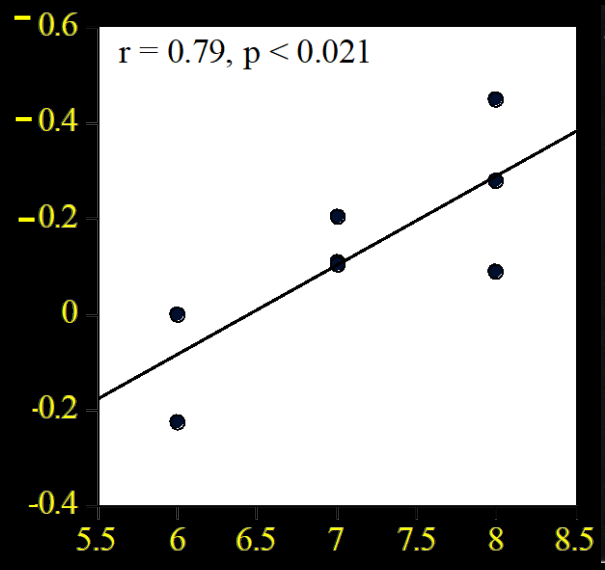


Leyton et al 2002
Neuropsychopharmacology

High striatal DA reactivity
=
higher novelty seeking

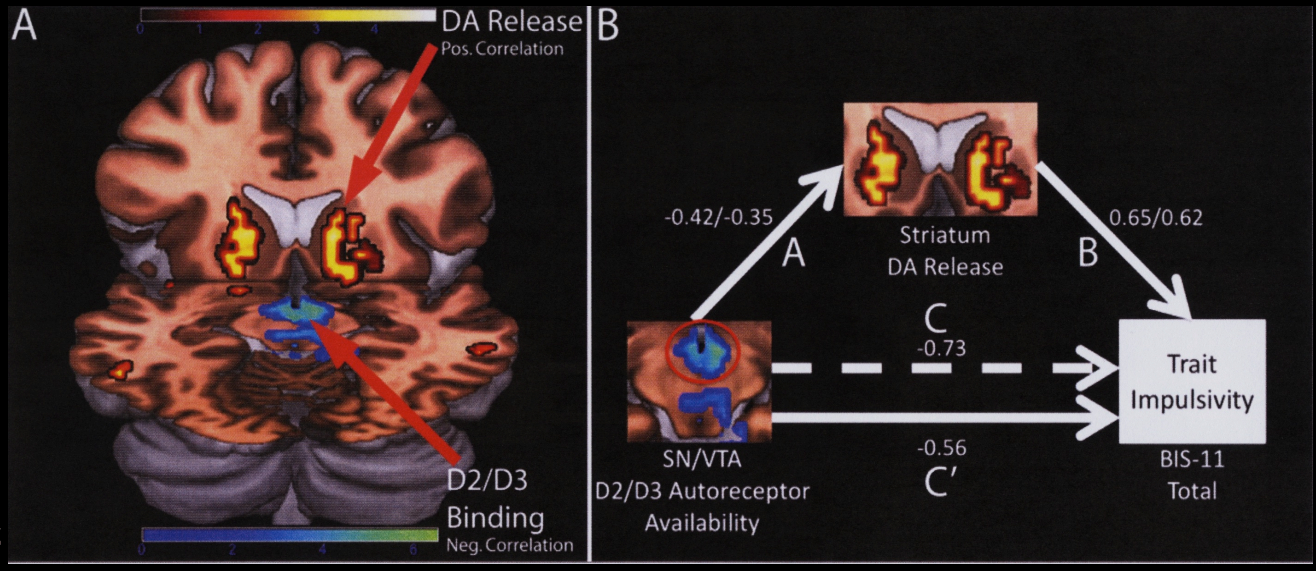
Dopamine

Novelty Seeking



Leyton et al 2002
Neuropsychopharmacology

Trait Impulsivity



Buckholtz et al 2010
Science

Acute Phenylalanine/Tyrosine Depletion (APTD)

Phenylalanine

PH

Tyrosine

TH

L-DOPA

AAAD

Dopamine

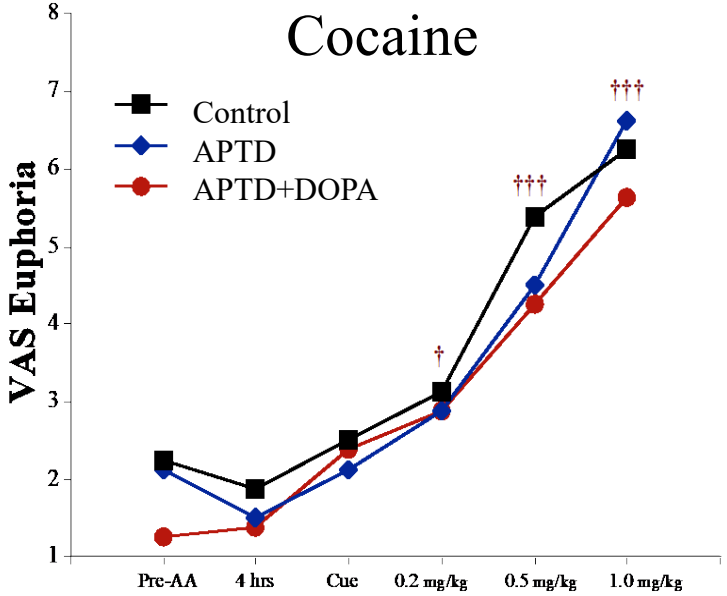
APTD decreases amphetamine-induced change in BPND

Leyton et al 2004
Neuropsychopharmacology

APTD changes resting BPND

Montgomery et al 2003
Am J Psychiatry

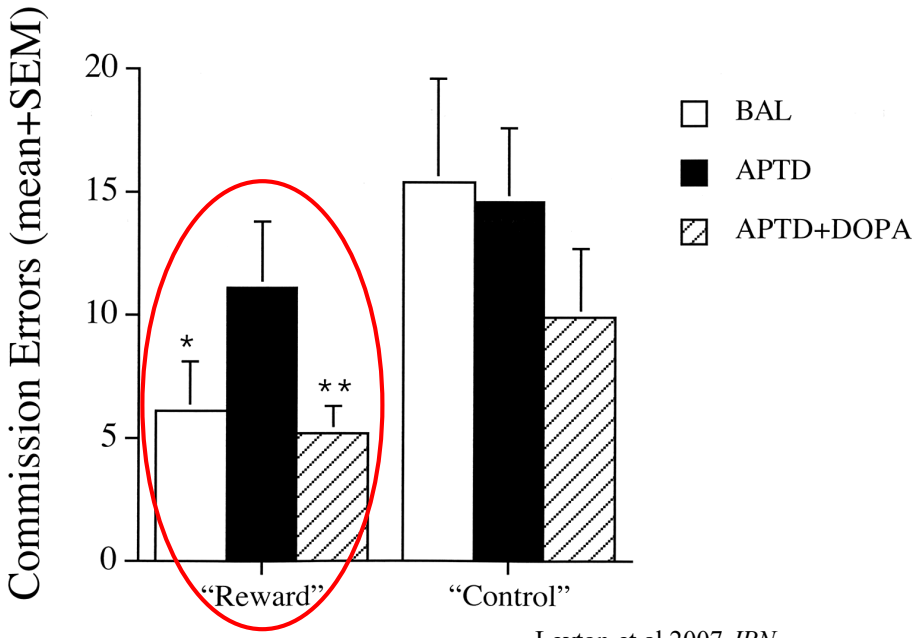
Pleasure



Leyton et al, 2005

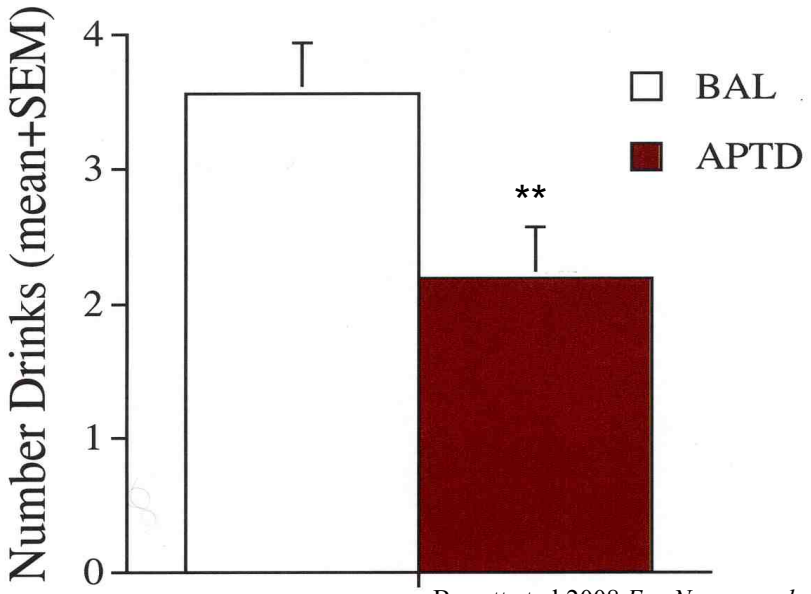
Cocaine Dose (mg/kg/line)

Incentive Salience / Reward Seeking



Leyton et al 2007 *JPN*

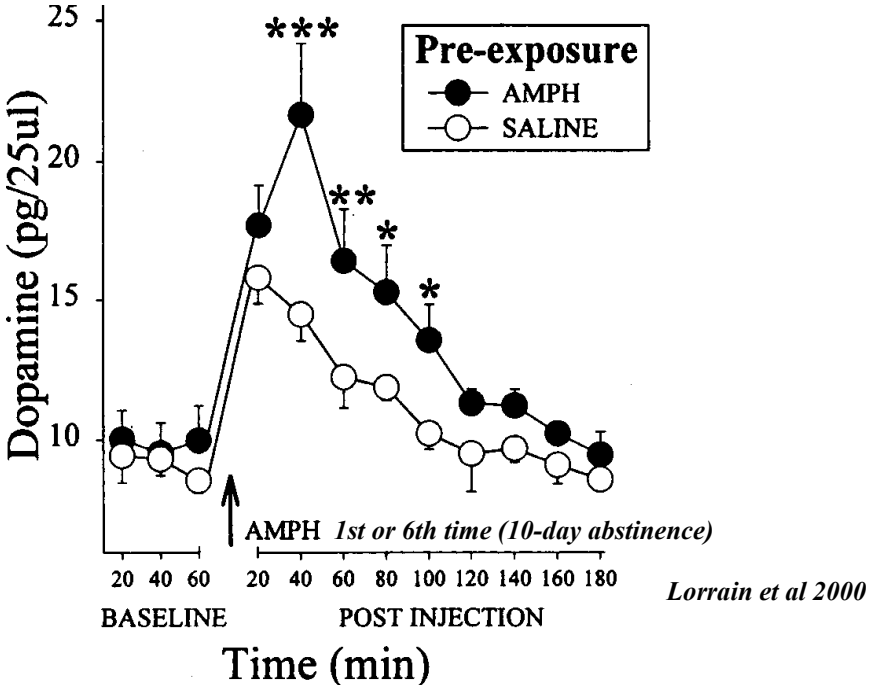
Alcohol PR Breakpoint



Barrett et al 2008 *Eur Neuropsychopharm*

Repeated Drug Effects

Sensitization



Lorrain et al 2000

Sensitization in Humans?

Authors	# of Doses	Amphetamine Dose	Sensitization?
Johanson & Uhlenhuth 1981	5 doses	5.0 mg, p.o.	No - mood, drug tablets chosen
Kelly et al 1991	6 doses	10.0 mg, p.o.	No - speech rate, smoking, stimulant effects, liking

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Kegeles et al 1999	2 doses	~ 20.0 mg, i.v.	No – euphoria, restless, anxiety
Wachtel & de Wit 1999	2 doses	20.0 mg, p.o.	No - subjective and psychomotor effects
Strakowski et al 1996	2 doses	~ 20 mg, p.o. (0.25 mg / kg)	Yes - energy, eye-blink, mood, speech rate
Strakowski & Sax 1998	3 doses	~ 20 mg, p.o. (0.25 mg / kg)	Yes - energy, eye-blink
Strakowski et al 2001	3 doses	~ 20 mg, p.o. (0.25 mg / kg)	Yes - energy, euphoria
Boileau et al 2006	4 doses	~ 20 mg, p.o. (0.30 mg / kg)	Yes - energy, eye-blink
O'Daly et al 2011	4 doses	~ 20 mg, p.o. (0.30 mg / kg)	Yes - energy, euphoria
Childs & de Wit 2013	2 doses	20 mg, p.o.	Yes - stimulation, craving
Weidenauer et al 2020	4 doses	~ 30 mg, p.o. (0.40 mg / kg)	Yes – lively, outgoing
Smart et al 2020	4 doses	~ 20 mg, p.o. (0.30 mg / kg)	Yes – mind-racing, speech

Adapted from: Leyton 2007 *PNPBP*
Leyton & Vezina 2013 *NBR*

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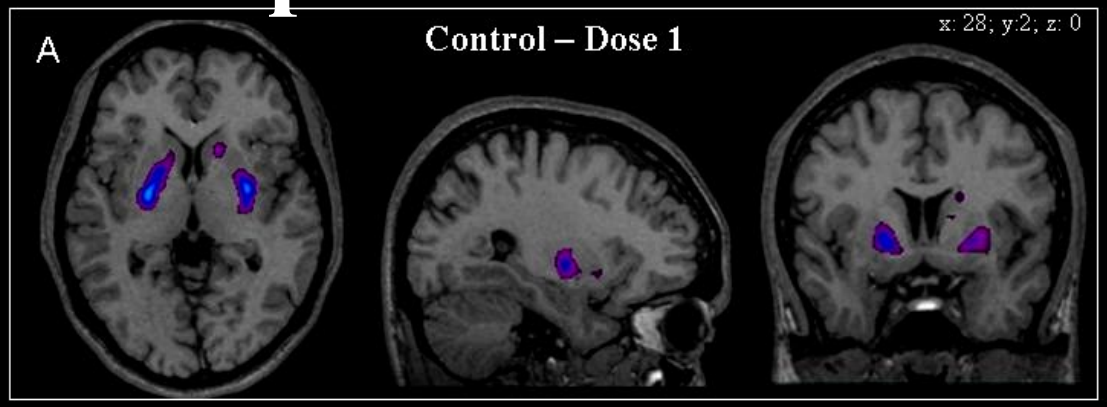
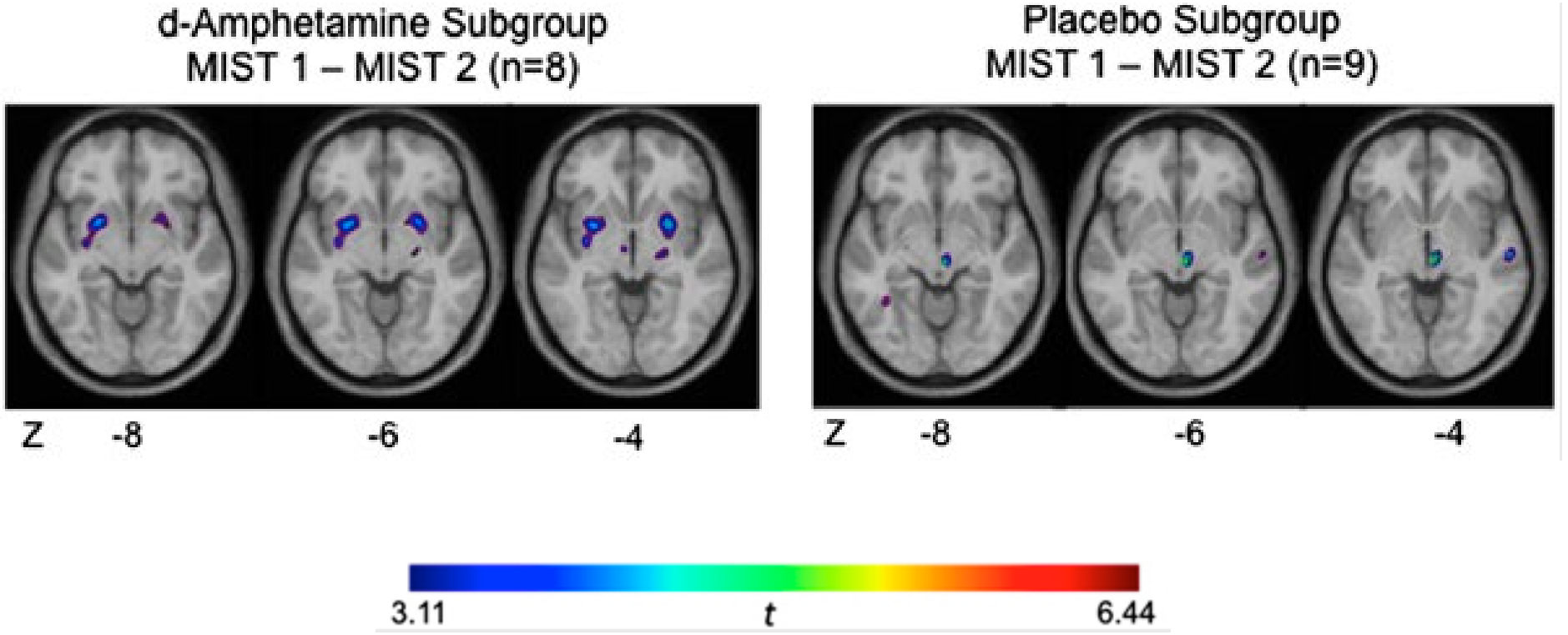
Repeat Amphetamine Administration Dopamine Sensitization



Boileau et al 2006
Arch Gen Psychiatry

Drug-Stress Cross-Sensitization



Booij et al 2016
Trans Psychiatry

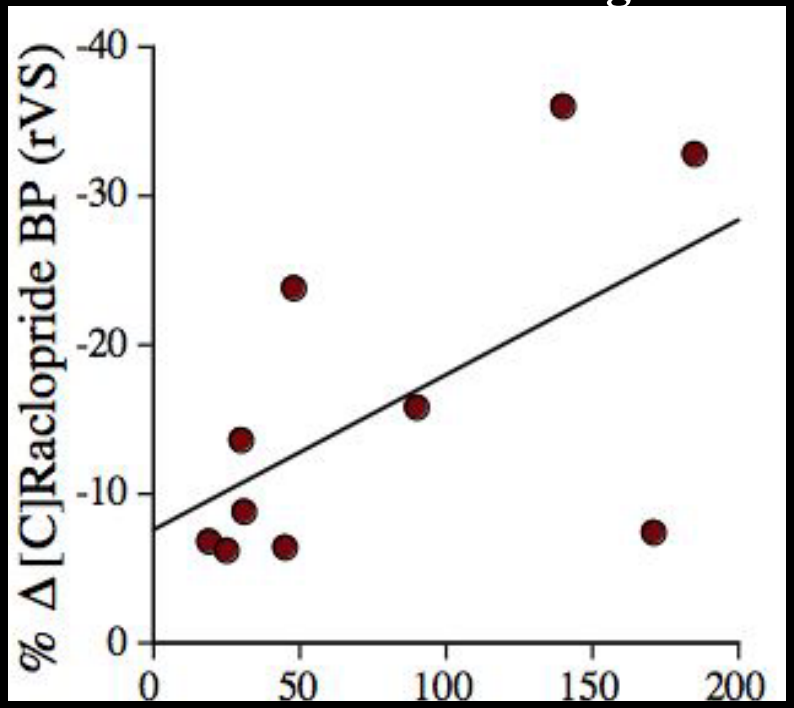
Repeated Drug Effects

Effects in Substance Users?

Effect of Past Drug Use

Cocaine Study

Lifetime Stimulant Drug Use



Drug cues:

Mirror Cocaine powder

Razor blade Straw

Cox et al 2009
Biol Psychiatry

Dopamine Transmission

Neuroimaging Risk for SUDs

PET [^{11}C]Raclopride

Subject Characteristics

	Healthy Ctl n=17	FH- n=15	FH+ n=16

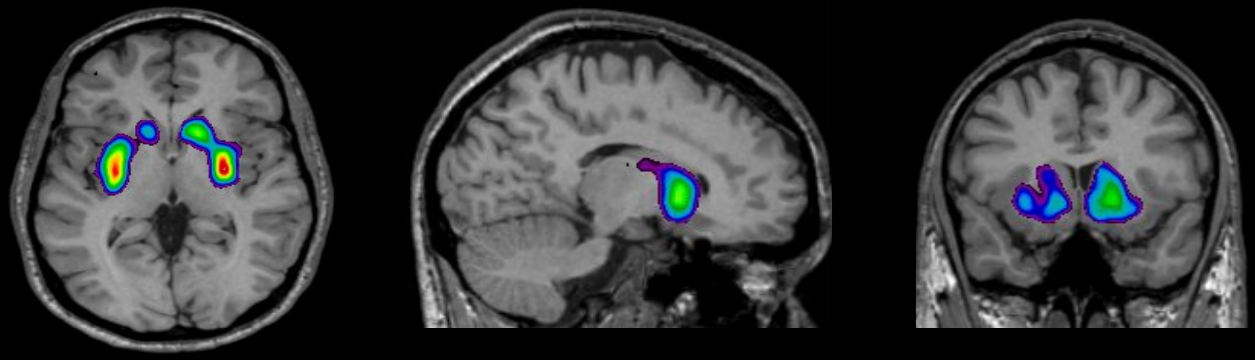
Casey et al, *Biol Psychiatry* 2014

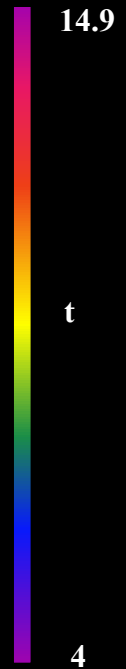
Amphetamine (no cues) **Induced Dopamine Release**

Casey et al, *Biol Psychiatry* 2014

Amphetamine (no cues) Induced Dopamine Release

Ctrl





Casey et al, *Biol Psychiatry* 2014

Risk for Alcohol Use Disorders

Behavioral Response to Alcohol

(cues present)

Subject Characteristics

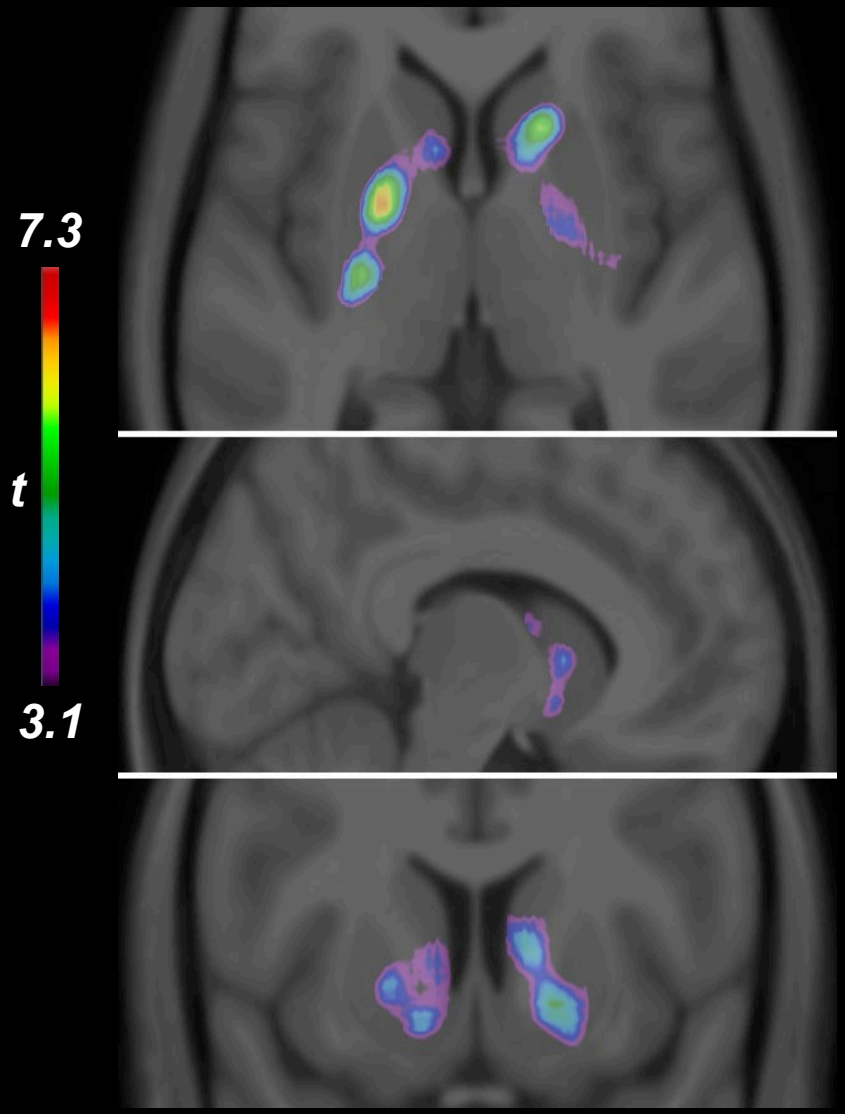
	Low Risk (13 {3F})	High Risk (13 {5F})	P
SHAS7 (alcohol response)	37.7±3.4	11.4±3.6	0.001
Age	21.5±0.9	21.1±0.8	0.75
Age first intoxication	15.5±0.6	15.2±0.6	0.78
Current Avg. Drinks/wk	8.4±2.4	13.0±2.4	0.19
Current Drinking Episodes/wk	1.5±0.4	2.7±0.3	0.026*
Current Heavy Episodes/wk	1.0±0.3	1.7±0.4	0.14
Lifetime Alcohol Intoxications	198±60	300±131	0.48
MAST	0.8±0.2	2.2±0.6	0.044*
FH+ (alcohol only)	3	8	0.055†
OCDS	3.8±0.6	6.1±1.1	0.076†
TPQ Impulsive NS	1.6±0.4	2.9±0.6	0.08†

Setiawan et al, *ACER,* 2014

Alcohol-Induced (cues present) DA Release

High-Risk

Low-Risk



Setiawan et al, *ACER,* 2014

Extra-Striatal Dopamine D2 Receptors

PET [^{18}F]Fallypride

Extra-Striatal D2 Study Predictions

1. Decreased midbrain cell body region D2 (auto)receptors, producing less inhibitory feedback on meso-striatal DA cells.

PET DRD2 Study Participants

Selected from top *vs*. bottom 30% of EXT risk traits in longitudinal cohort

Characteristic	Low Risk (n=31)	High Risk (n=27)
Age	18.4 ± 0.6 years	18.6 ± 0.6 years
Sex	20 females, 11 males	16 females, 11 males
Externalizing traits ¥	0.48 ± 0.29	2.4 ± 0.58*
AUDIT ¥	4.0 ± 2.6	6.0 ± 4.2*
Cigarette smokers	2/31	6/27*
Cannabis, occasions used lifetime ¥	19/31, 32.8±142.0	22/27, 309.2±542.4*
Other lifetime drug use (not THC), occasions used ¥	4/31, 1.06±4.4	11/27*, 27.11 ± 88.04
Likely current or past psychiatric disorder¥	1/31	14/27*
SURPS - Impulsivity	8.57±2.5	11.92±2.7*
SURPS - Hopelessness	11.23±2.7	13.12±3.7*
BIS - Total	54.45±7.8	63.36±8.1*
SPSRQ - Reward	8.17±2.81	11.08±4.5*
SPSRQ - Punishment	10.31±4.7	11.69±5.1
SPSRQ - Reward / Punishment ratio	1.04±0.8	1.20±0.89

*¥ = n, mean ± SD (range), * = significantly different from low risk individuals, $p < 0.05$*

Jaworska et al, 2020
Neuropsychopharm

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SURPS - Impulsivity	8.57±2.5	11.92±2.7*
SURPS - Hopelessness	11.23±2.7	13.12±3.7*
BIS - Total	54.45±7.8	63.36±8.1*
SPSRQ - Reward	8.17±2.81	11.08±4.5*
SPSRQ - Punishment	10.31±4.7	11.69±5.1
SPSRQ - Reward / Punishment ratio	1.04±0.8	1.20±0.89

*¥ = n, mean ± SD (range), * = significantly different from low risk individuals, $p < 0.05$*

Jaworska et al, 2020
Neuropsychopharm

PET DRD2 Study Participants

Selected from top *vs*. bottom 30% of EXT risk traits in longitudinal cohort

Characteristic	Low Risk (n=31)	High Risk (n=27)
Age	18.4 ± 0.6 years	18.6 ± 0.6 years
Sex	20 females, 11 males	16 females, 11 males
Externalizing traits ¥	0.48 ± 0.29	2.4 ± 0.58*
AUDIT ¥	4.0 ± 2.6	6.0 ± 4.2*
Cigarette smokers	2/31	6/27*
Cannabis, occasions used lifetime ¥	19/31, 32.8±142.0	22/27, 309.2±542.4*
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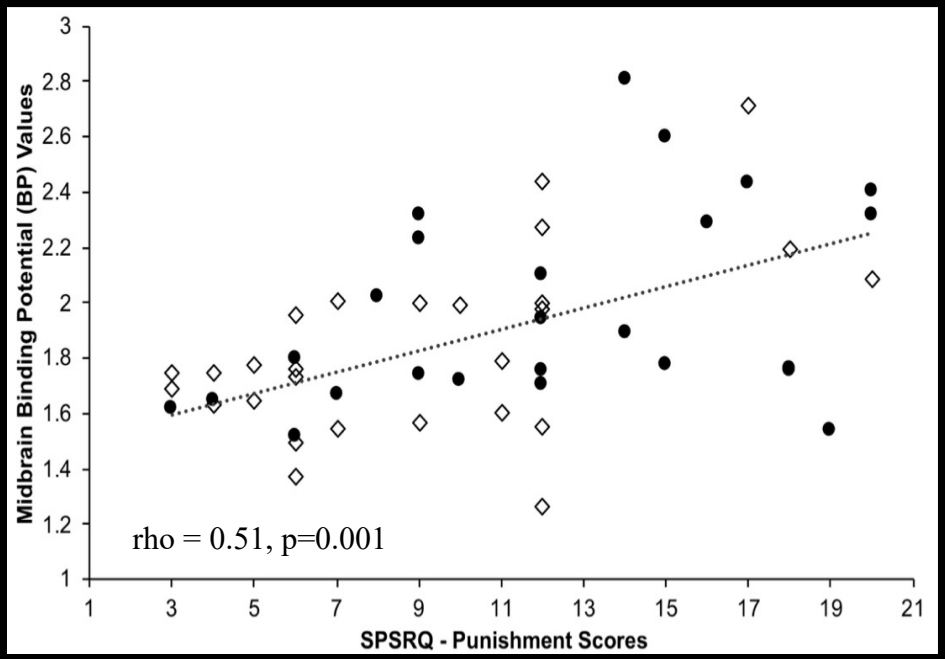
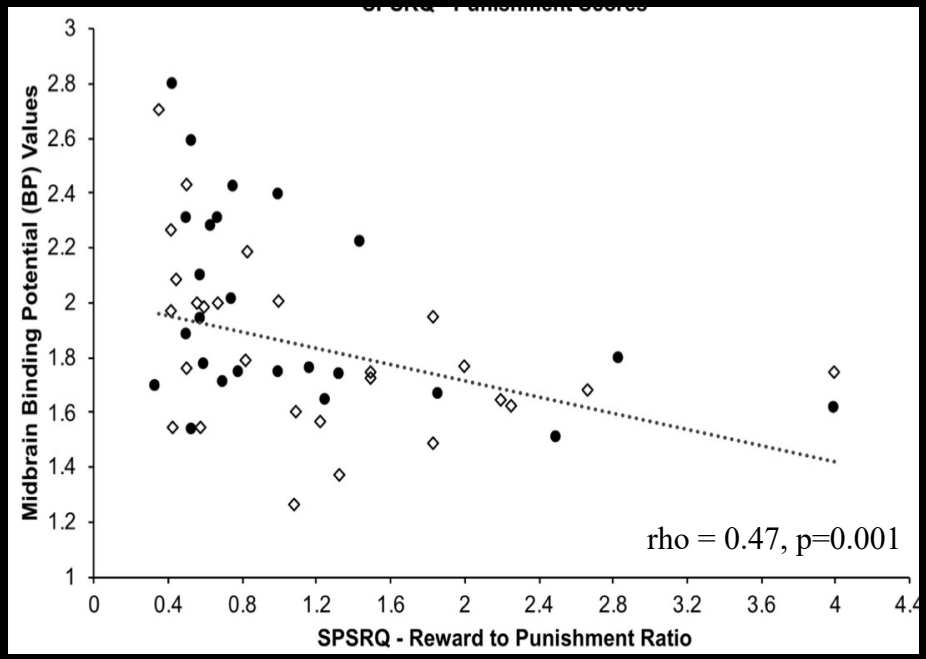
Jaworska et al, 2020
Neuropsychopharm

Sensitivity to Reward & Punishment Midbrain DRD2 Availability





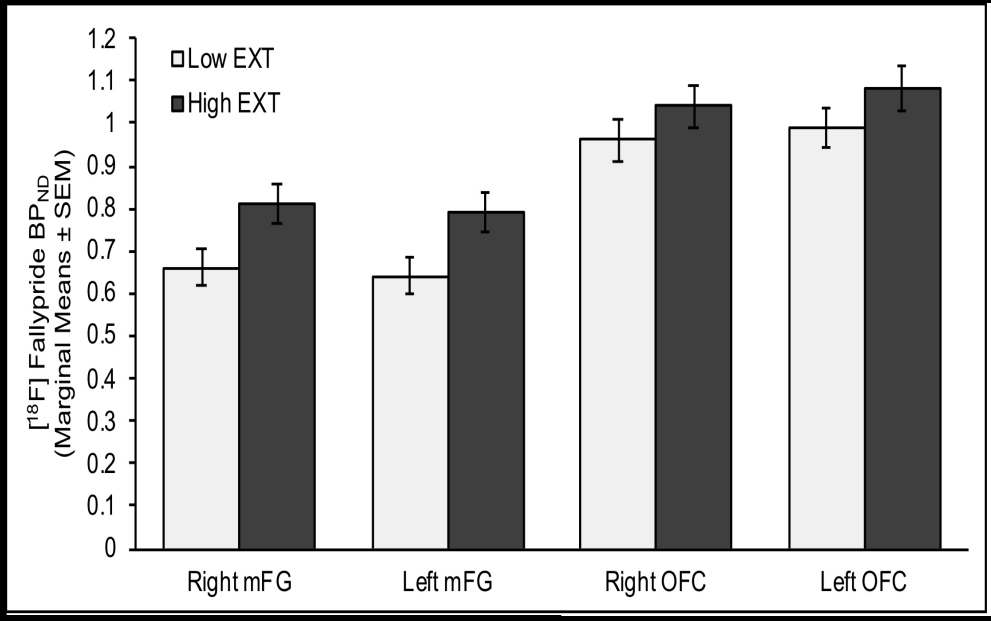
Low midbrain DRD2 associated with:

decreased punishment sensitivity, and

increased reward / punishment sensitivity ratio.

Jaworska et al 2020
Neuropsychopharmacology

Terminal Region DRD2 Availability



Main effect of Group.

No Group x Region interaction

Jaworska et al 2020
Neuropsychopharmacology

Integration

- Testing a three-factor model:
  1. Impulsive / EXT personality traits
  2. Early life adversity
  3. Midbrain DA autoreceptors

Binomial Logistic Regression

		Midbrain BP_{ND} (1.26 to 2.80)	EXT score (0 to 3.98)	CTQ total (25 to 61)
	Beta ± S.E.	-3.221 ± 1.6	2.14 ± 0.7	0.144 ± 0.1
	Wald	3.83	9.88	3.48
	p	0.050	0.002	0.062
	Odds Ratio	25.0	8.530	1.120
95% CI for Odds Ratio	Lower	1.00	2.241	0.994
	Upper	500	32.466	1.263
Chi squared		$\chi^2(3) = 24.116$, $p = 0.000024$		
Nagelkere R^2 & AUC		0.562 & 91.5%		
Classification predictive accuracy		90.4%		
Sensitivity & Specificity		75.0% & 95.0%		
Positive & Negative Predictive value		81.8% & 92.7%		

SUDs: 5
Mood: 5
ADHD: 4
Panic Dis: 4
GAD: 2
Adjust D: 2
Dyslexia: 1
Binge eat: 1
Conduct D: 1

First interview: 18.5±0.6 y.o.

Last interview: 21.0±0.9 y.o.

Iqbal et al, submitted

Binomial Logistic Regression

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Three-Factor Model Predicts Common Early Onset DSM-5 Disorders

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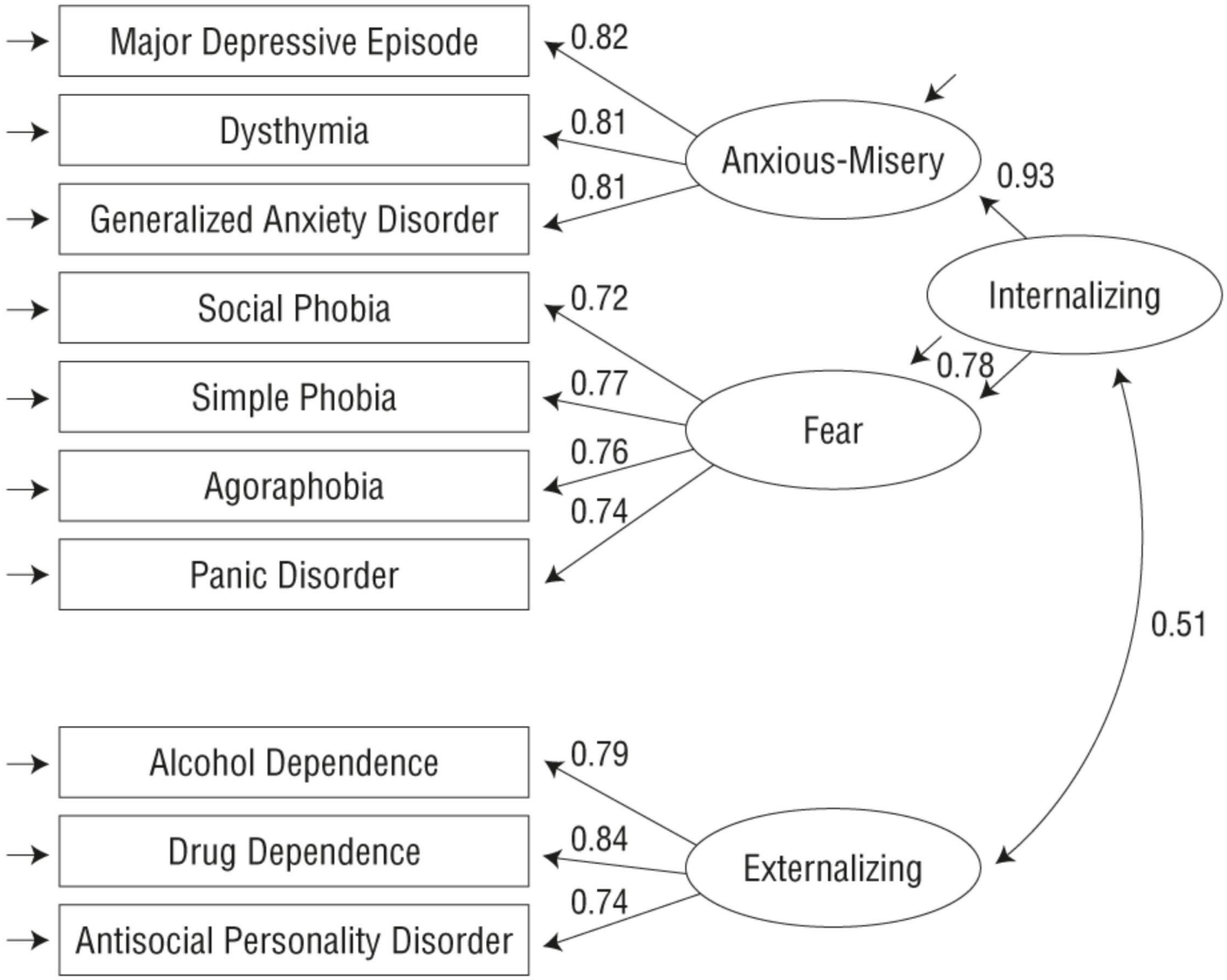
Model is reproduced at 2 to 3-year follow-up ($\chi^2(3)=23.333$, $p=0.000034$). Iqbal et al, submitted

Summary & Conclusions

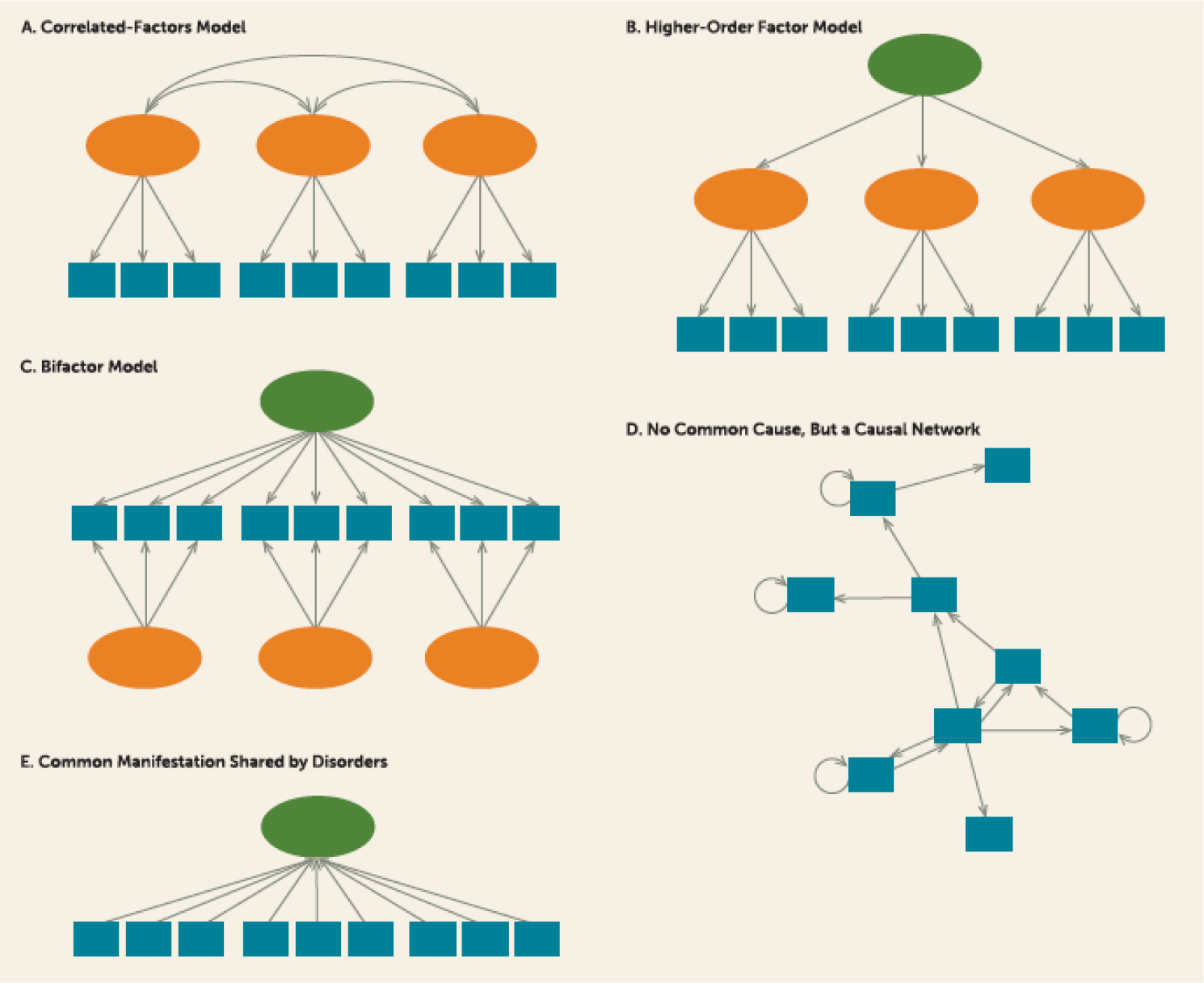
Pathways to Addictions



N=8,098
National Comorbidity Survey

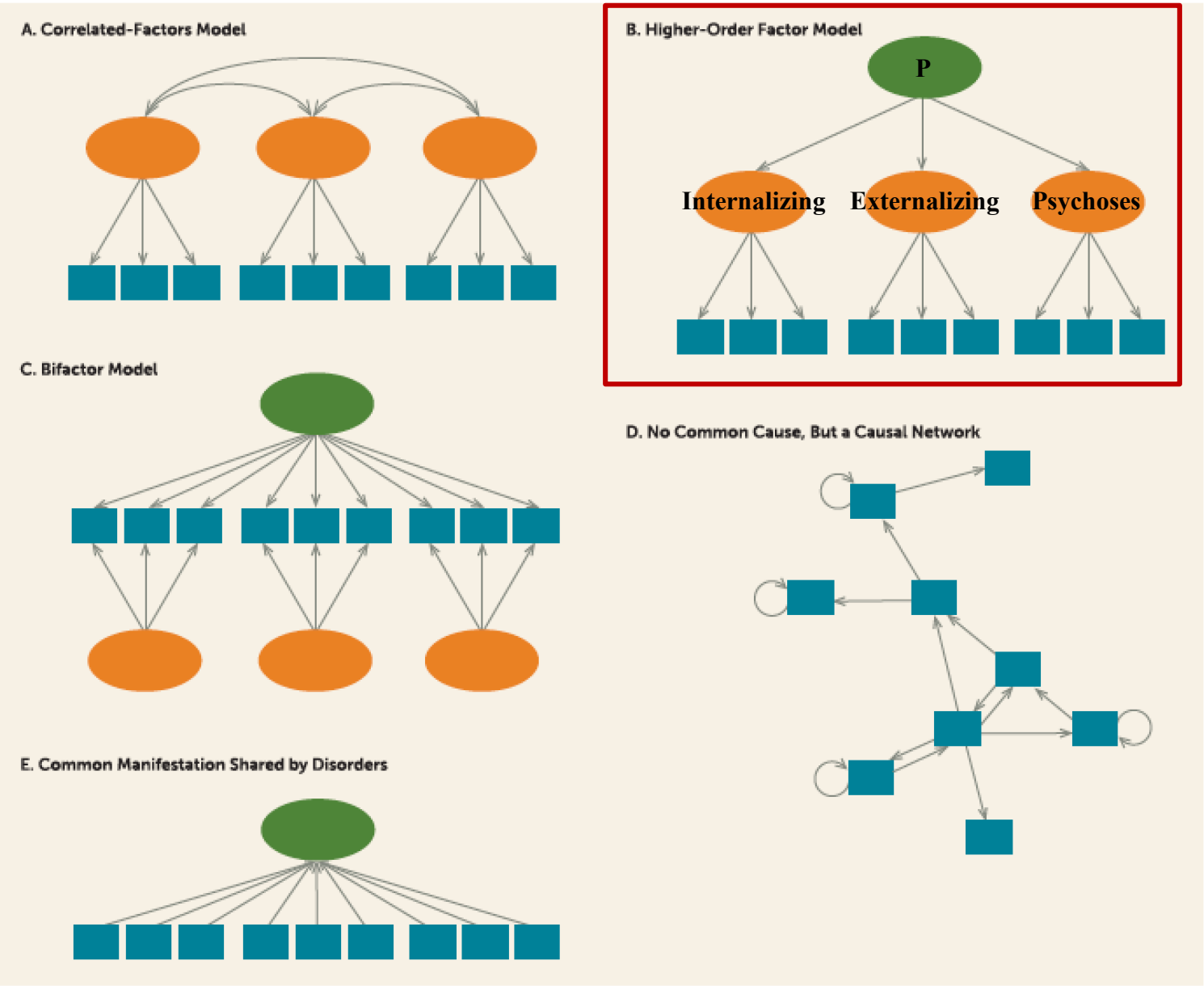
Krueger *Arch Gen Psychiatry* 1999

General P (Psychopathology) Factor



Caspi & Moffitt *Am J Psychiatry* 2018

General P (Psychopathology) Factor



Caspi & Moffitt *Am J Psychiatry* 2018

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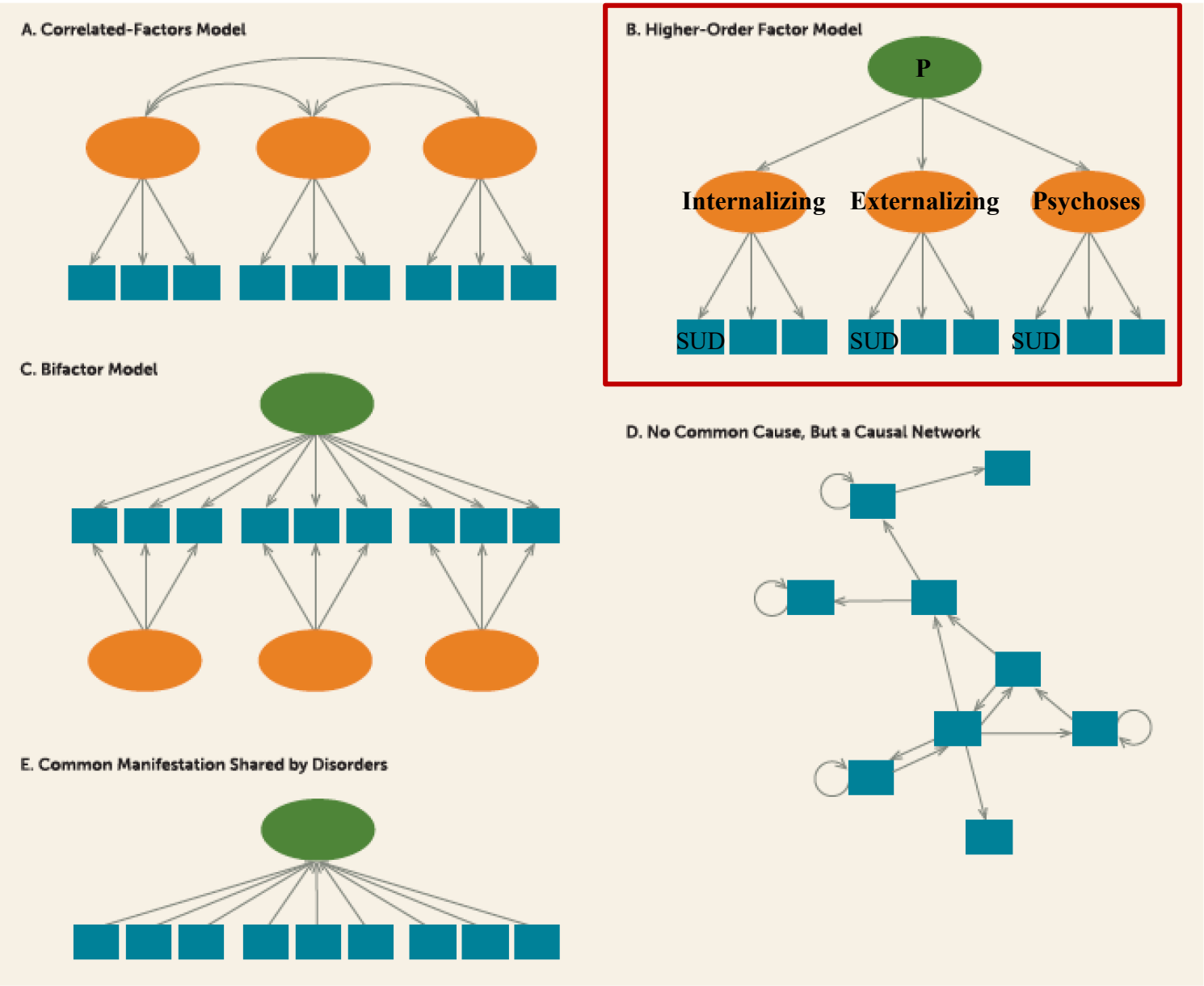
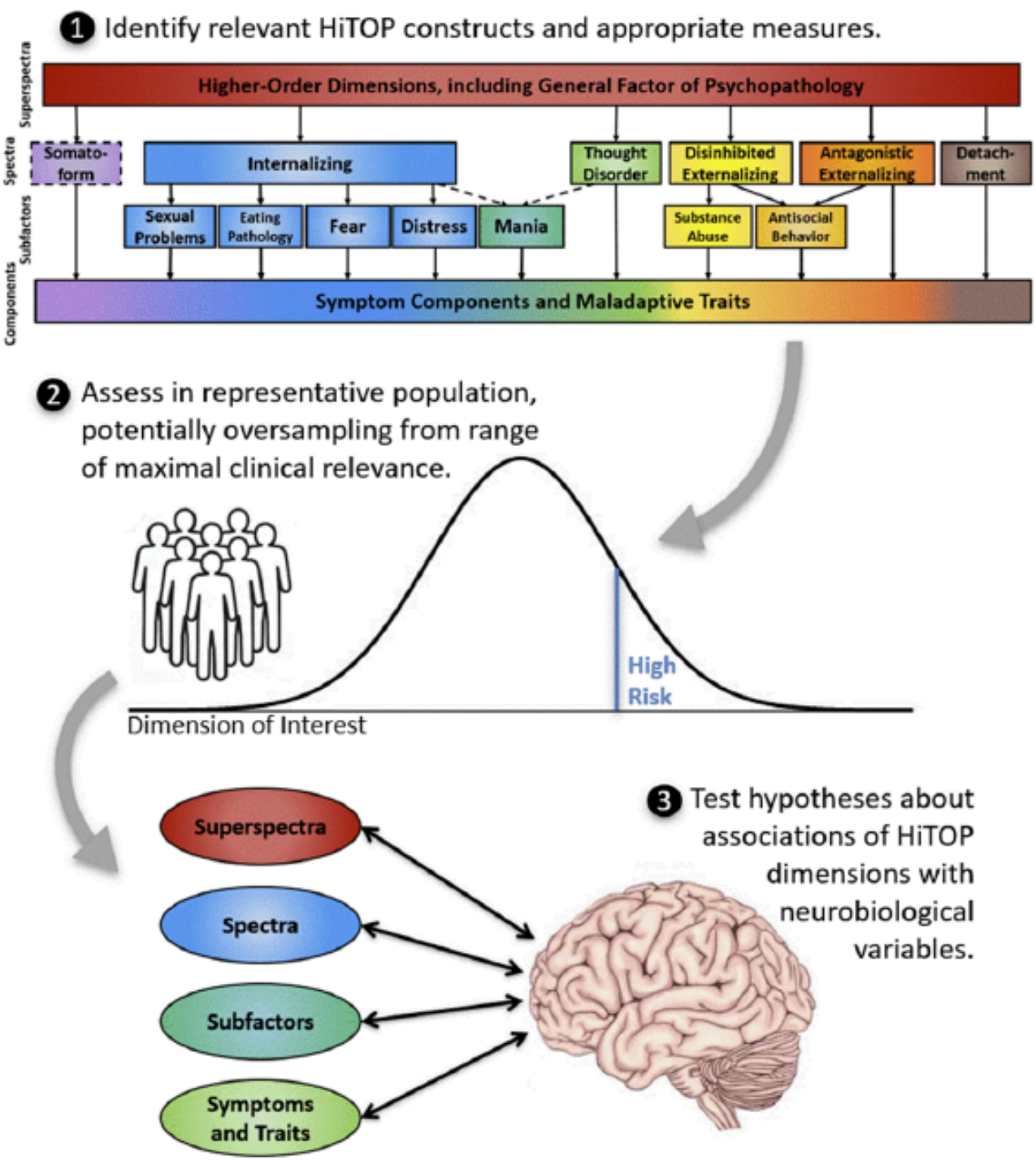


Caspi & Moffitt *Am J Psychiatry* 2018

HiTOP

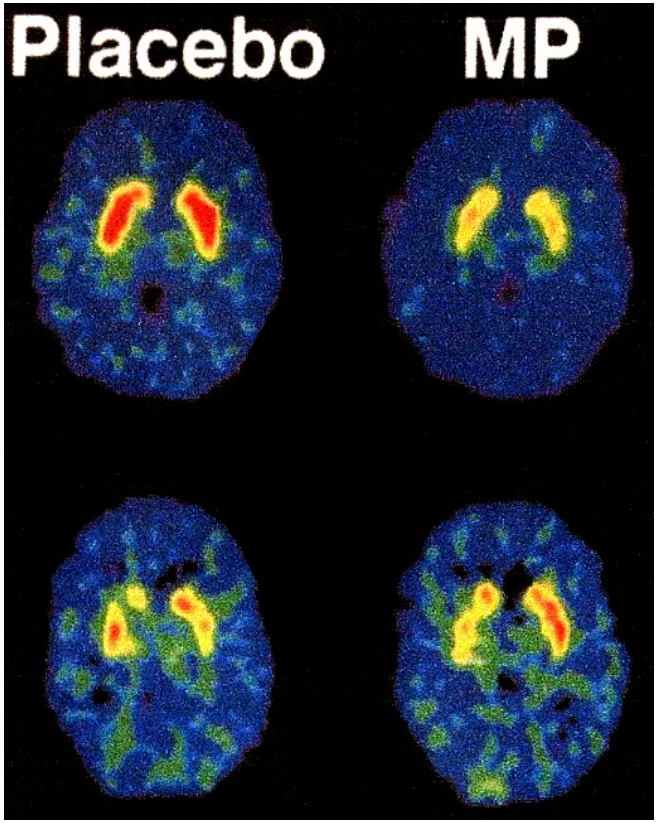
Hierarchical Taxonomy of Psychopathology



"Biological parameters …linked to higher levels influence a wider range of related behaviors than those linked to lower levels."

Krueger et al. 2018
World Psychiatry
Latzman et al. 2020
Neuropsychopharmacology

Current SUD
Drug-Induced Striatal DA Release



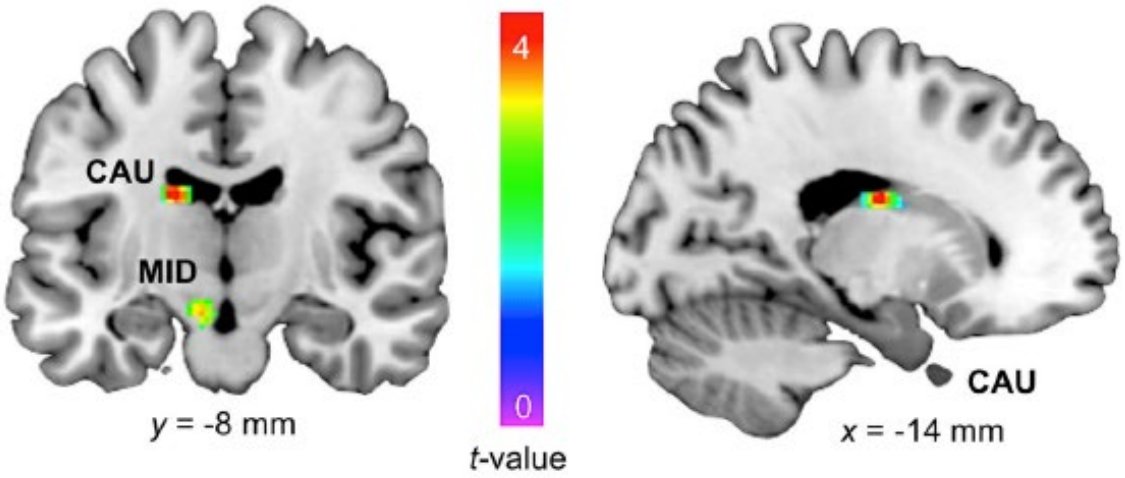
Healthy controls

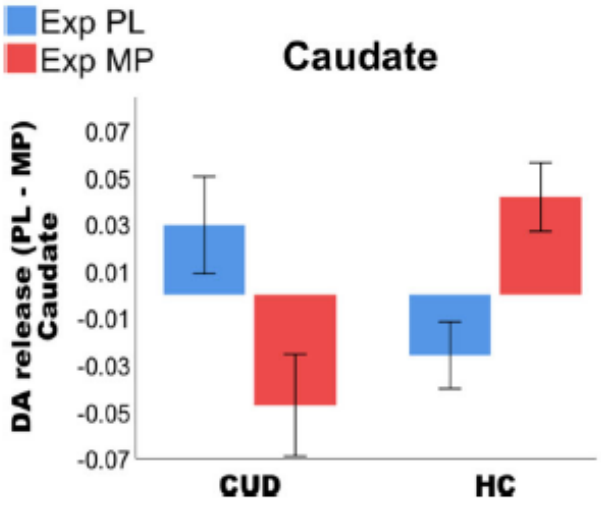
Cocaine dependent

Addiction	Low DA Release	No diff / increased
Cocaine	5 studies	1 study
Alcohol	2 studies	1 study
Opiates	1 study	0 studies
Amphetamines	2 studies	0 studies
Cannabis	1 study	2 studies
Total:	11	4

Volkow et al 1997
Nature

Expectation Effects?

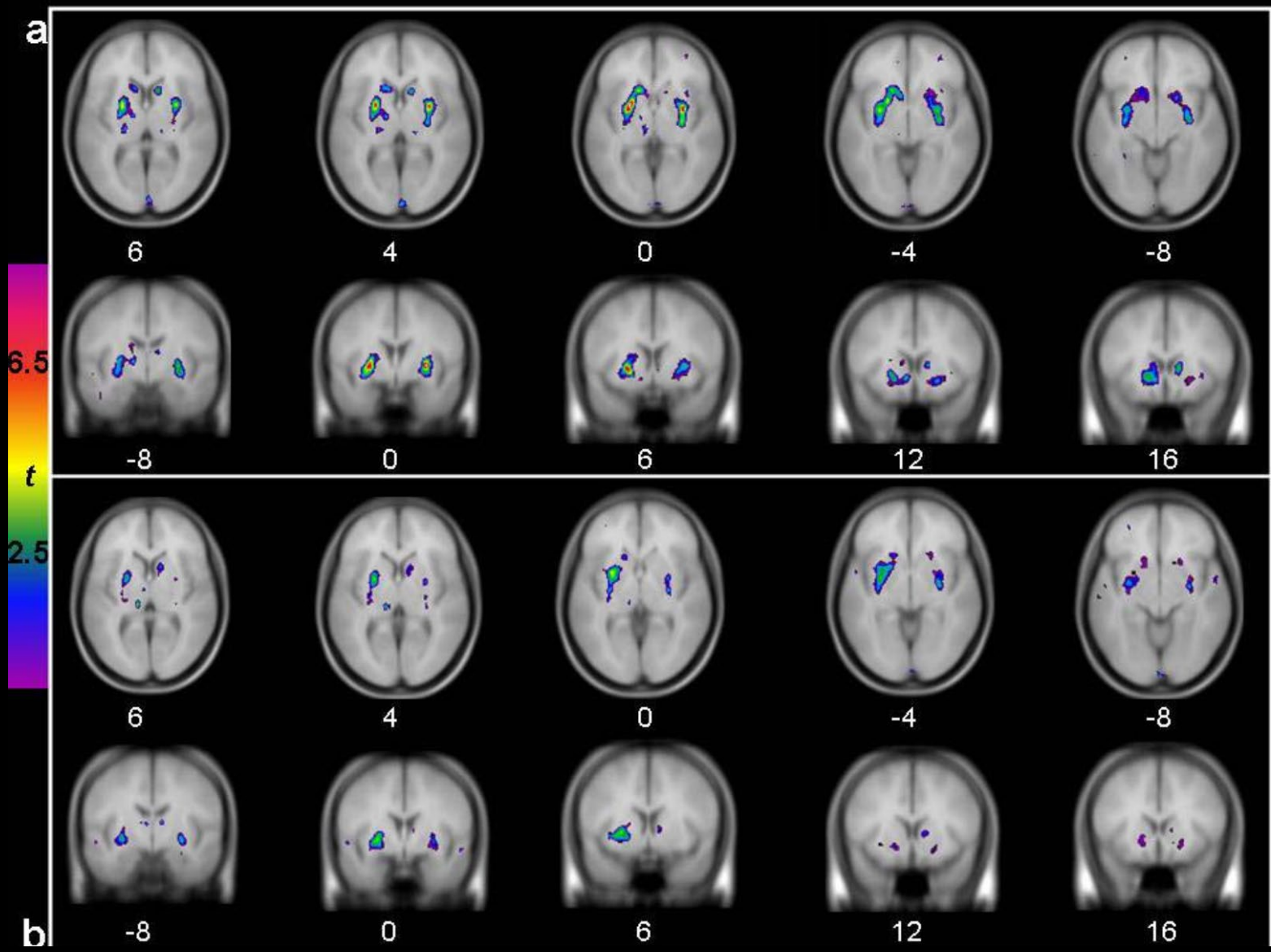




HC: Healthy control, n=23
CUD: Cocaine use disorder, n=23
MPH: 0.5 mg/kg iv

Wang et al 2019 *Trans Psychiatry*

Conditioned Dopamine Release



Amphetamine

CS+

Boileau et al 2007
J Neuroscience