The Neuroscience of Gambling: From Recreational Use to Gambling Disorder

T. Celeste Napier, Ph.D.

Department of Psychiatry and Behavioral Sciences

Rush University College of Medicine

Chicago, IL USA

For many people, gambling is harmless entertainment, but for some, it can become a problem.

Problem gambling is a progressive disorder

Initial motivation:

Rewarding

Repetitive engagement:

Learning & Memory

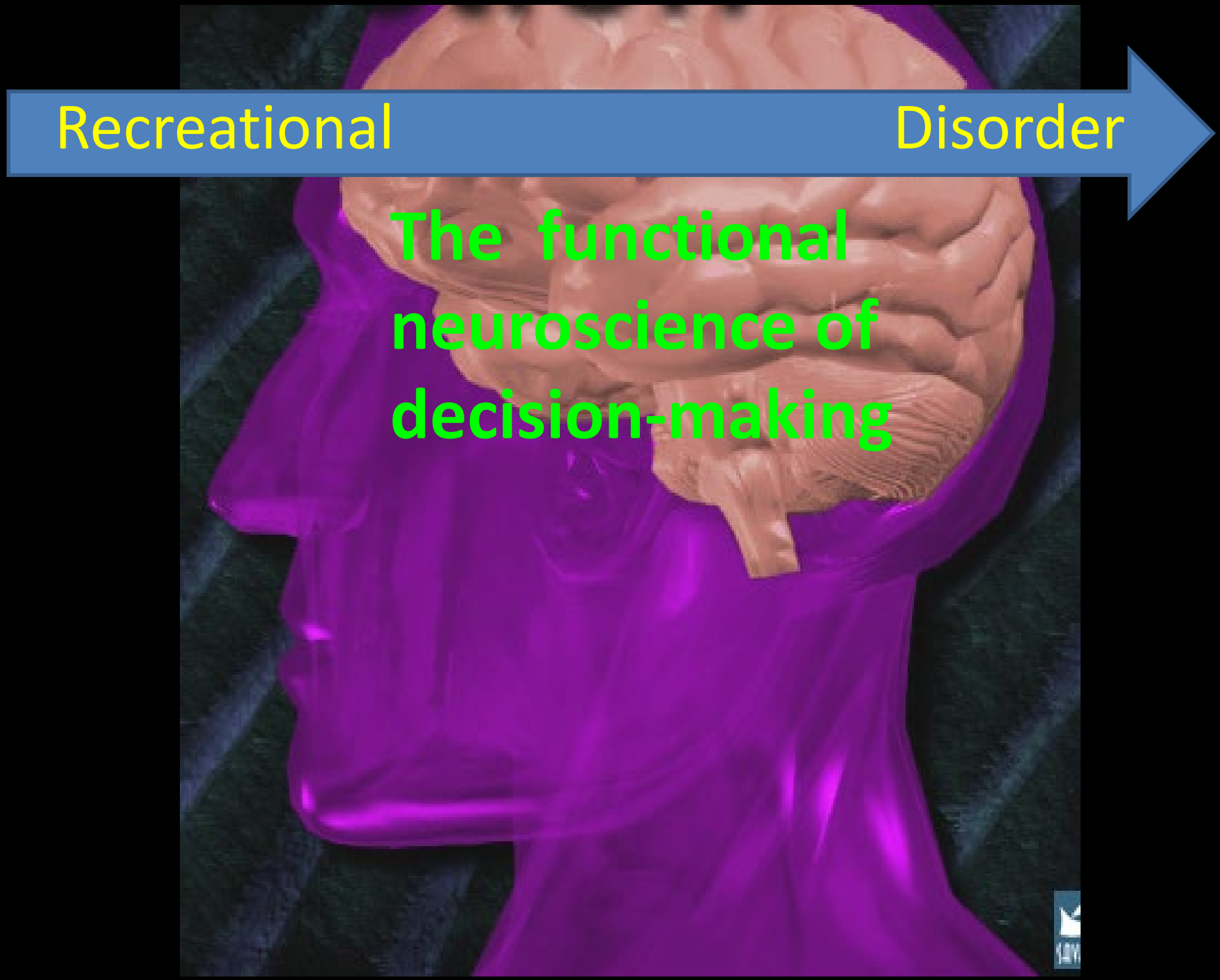
Impaired control

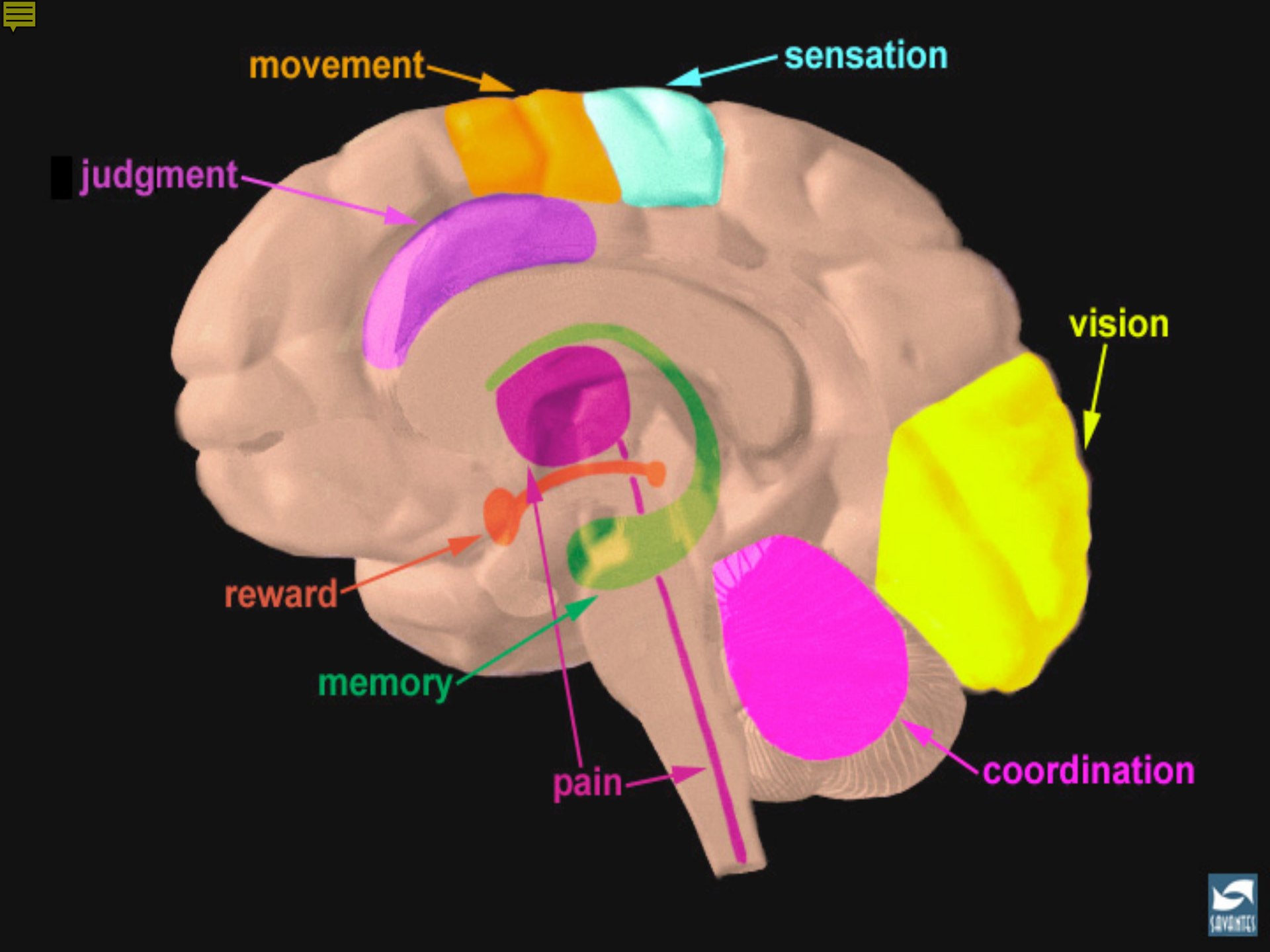
Persistence

Unsuccessful attempts to quit

Narrowing of interests

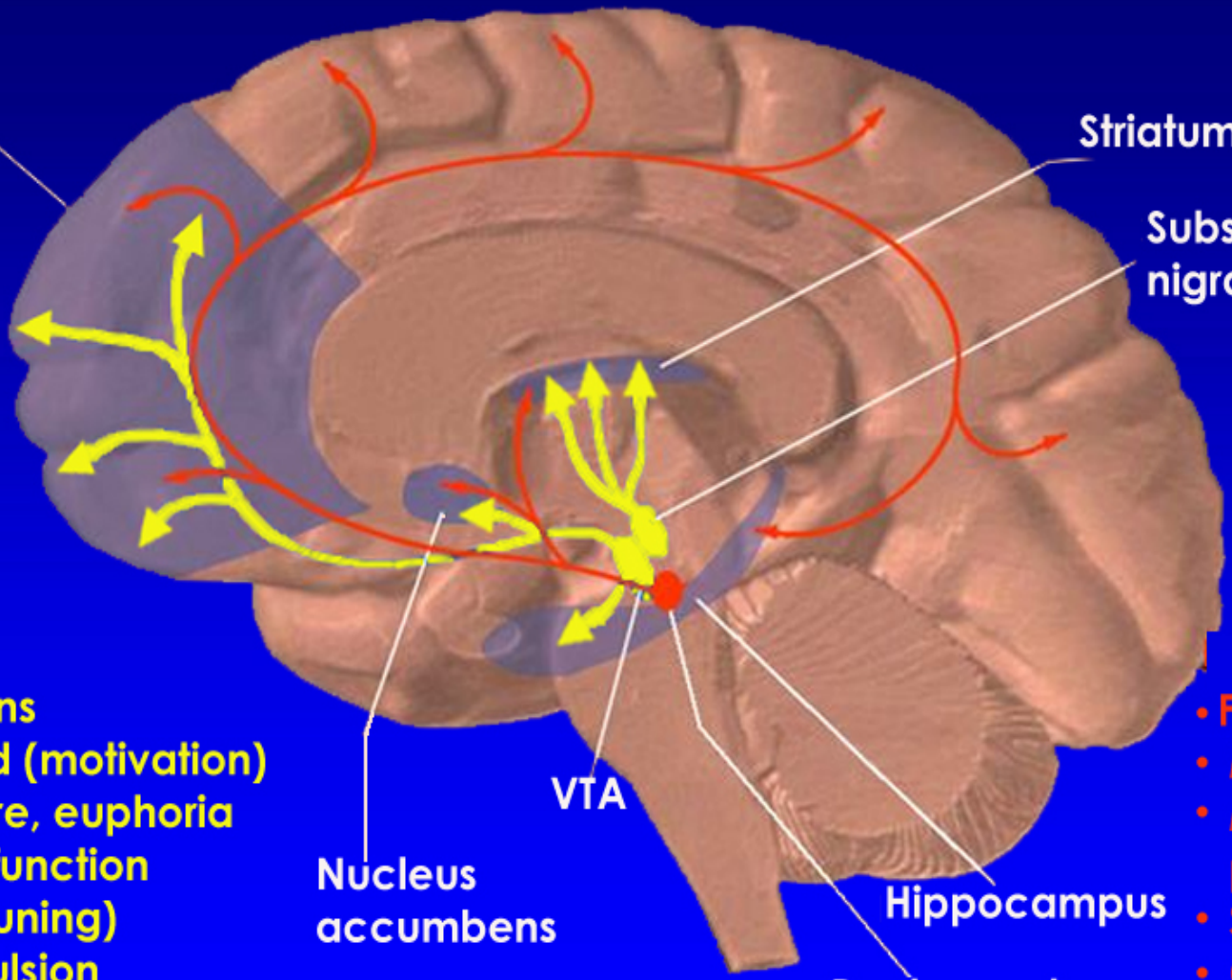
Neglect of other areas of life


Recreational
Disorder
The functional neuroscience of decision-making


movement
sensation
judgment
vision
reward
memory
pain
coordination

Dopamine Pathways

Serotonin Pathways



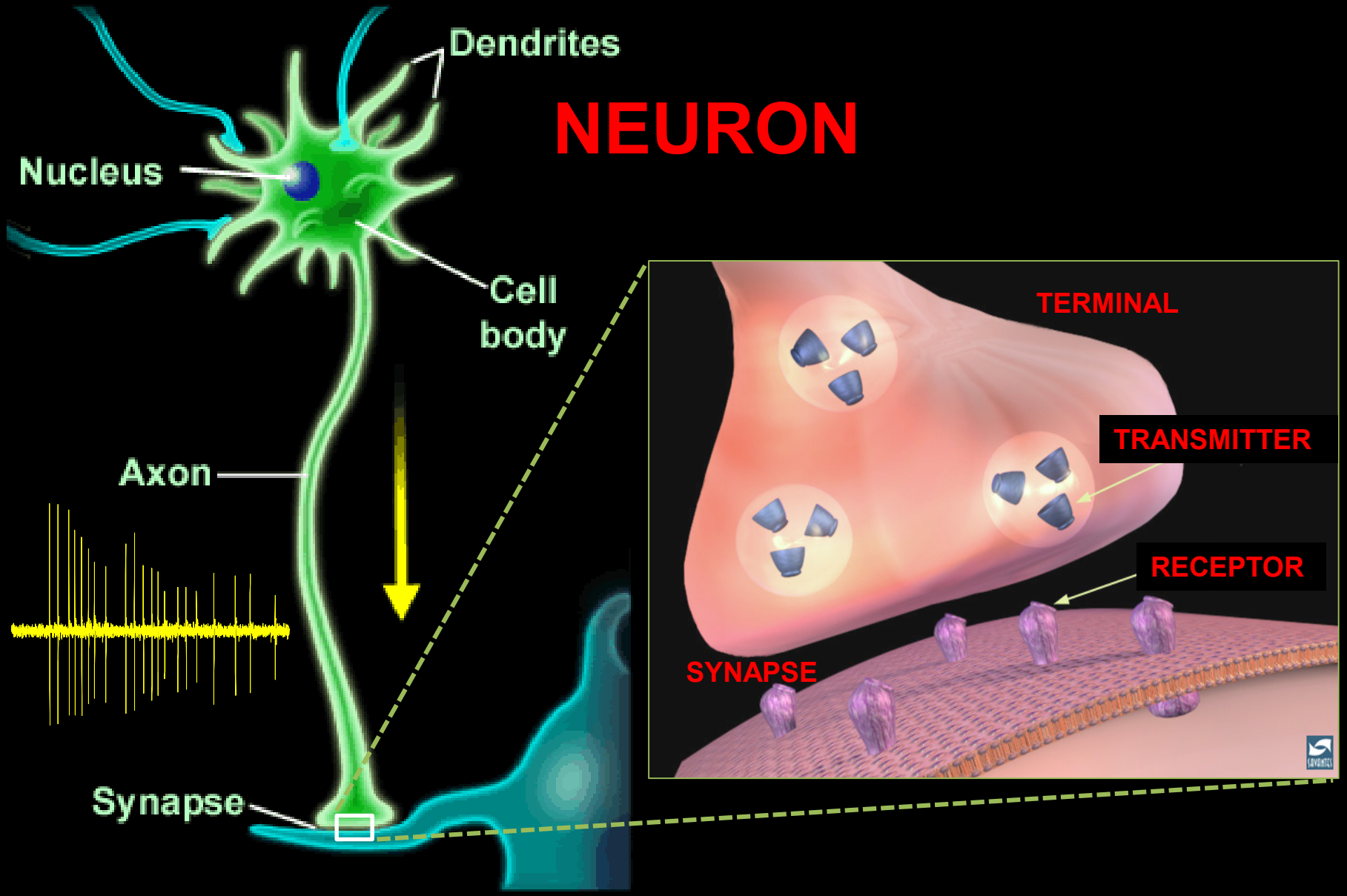
Functions

- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine-tuning)
- Compulsion
- Perseveration

- Functions
- Mood
- Memory processing
- Sleep
- Cognition

NIDA

NEURON


Dendrites
Nucleus
Cell body
Axon
Synapse
TERMINAL
TRANSMITTER
RECEPTOR
SYNAPSE

Reward-Motivated Behaviors

Natural Rewards

food

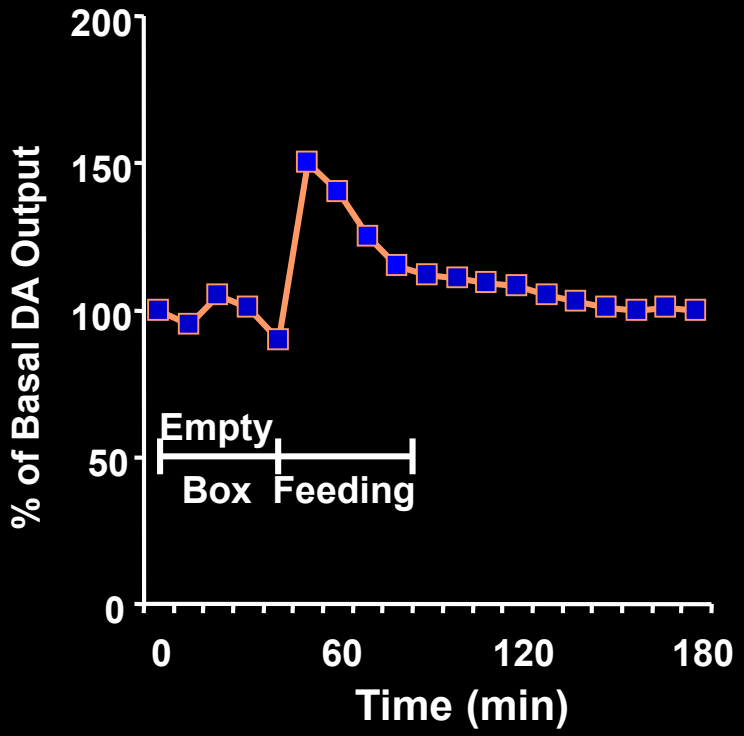
water

sex

nurturing

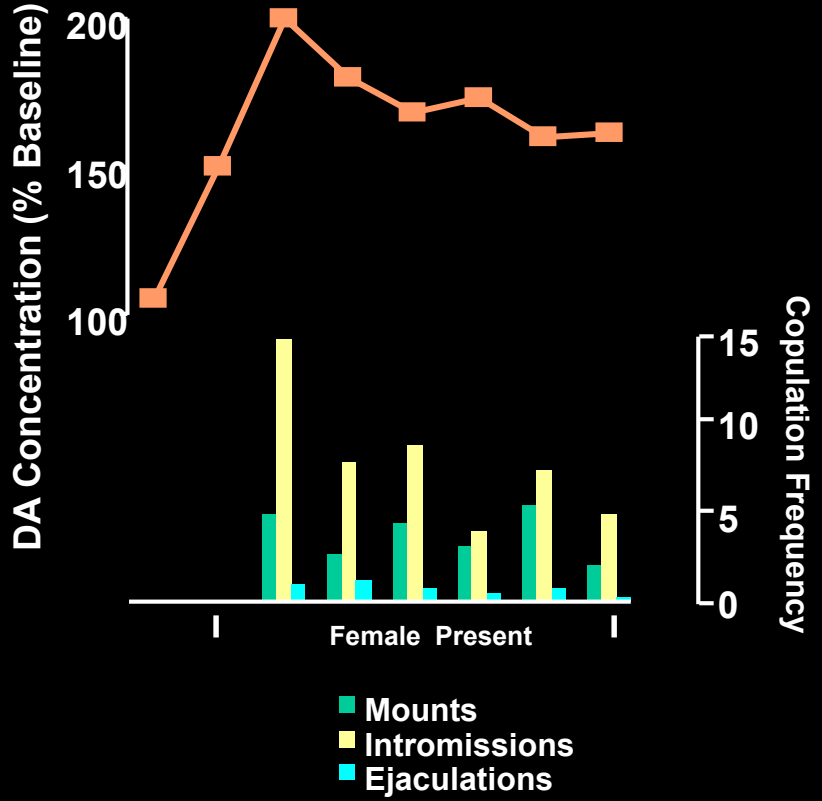
Natural Rewards Elevate Dopamine Levels

FOOD



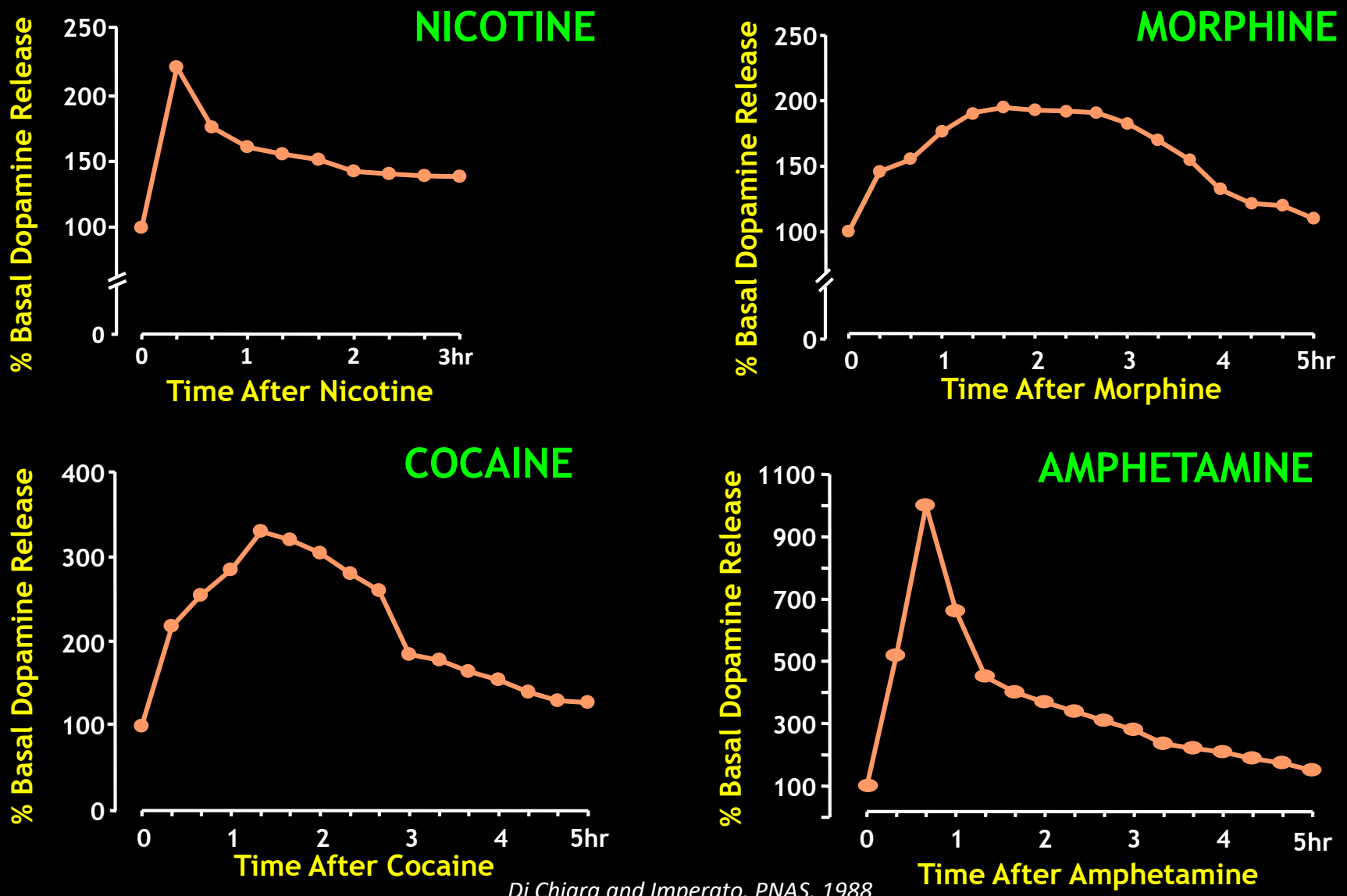
Di Chiara et al., Neuroscience, 1999.

SEX

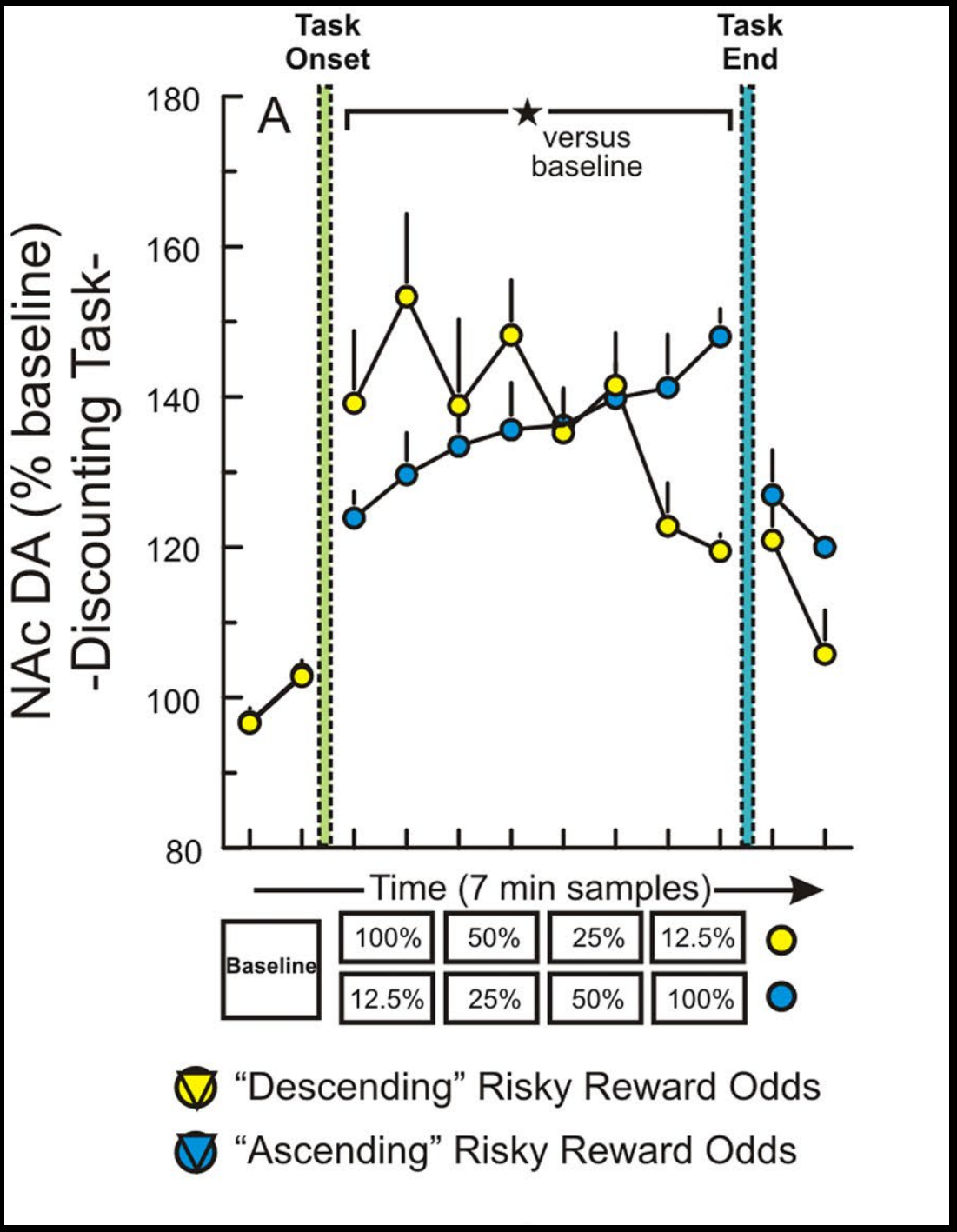


Fiorino and Phillips, J. Neuroscience, 1997.

Drugs of Abuse Increase Dopamine



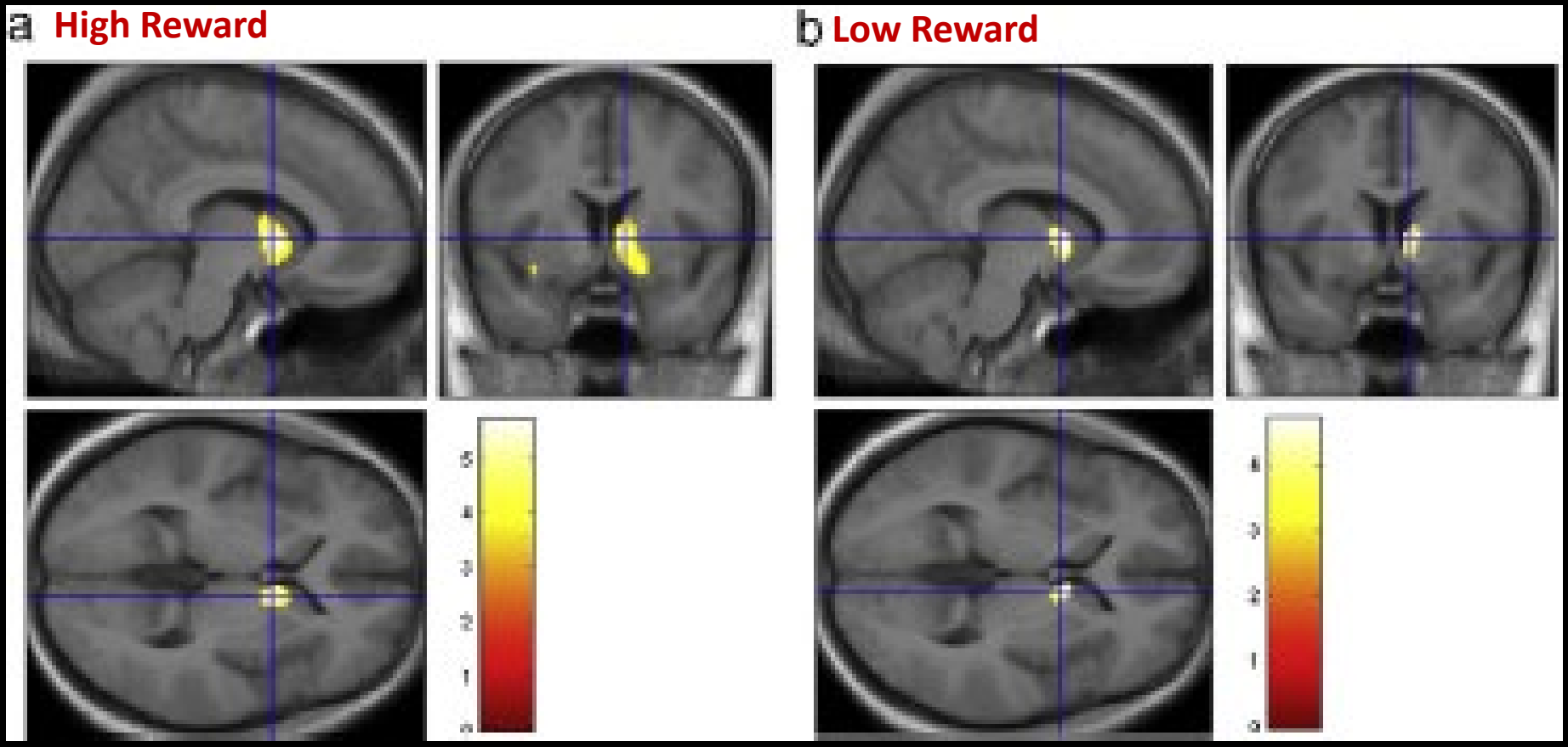
Di Chiara and Imperato. PNAS, 1988



Dopamine Increases During Gambling-Like Tasks in Laboratory Rats

St Onge, Ahn, Phillips and Floresco, J Neurosci 2012

Dopamine Increases During Gambling-Like Tasks in Humans



Joutsa et al.,
NeuroImage 2012

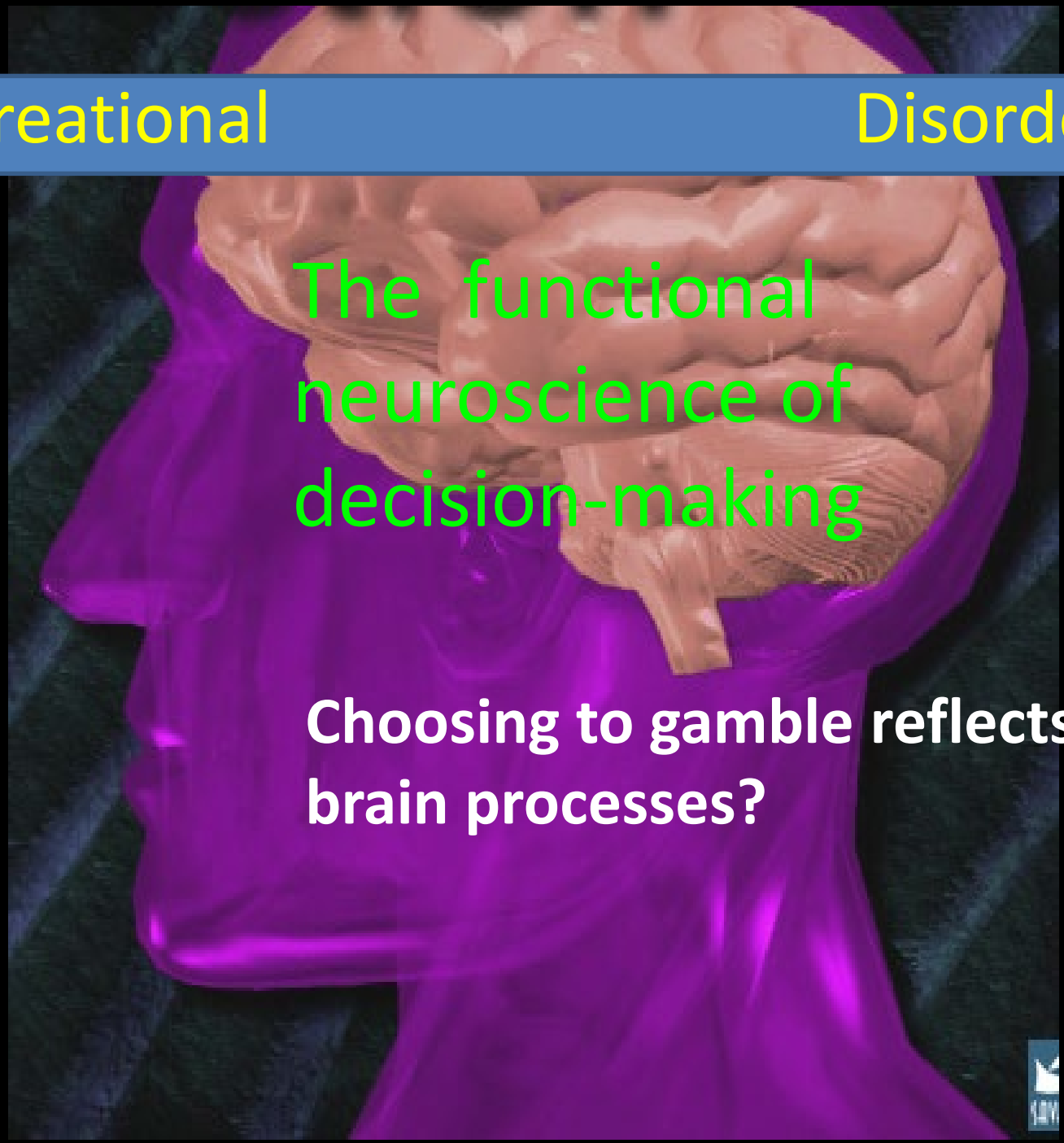
Psychology of Gambling

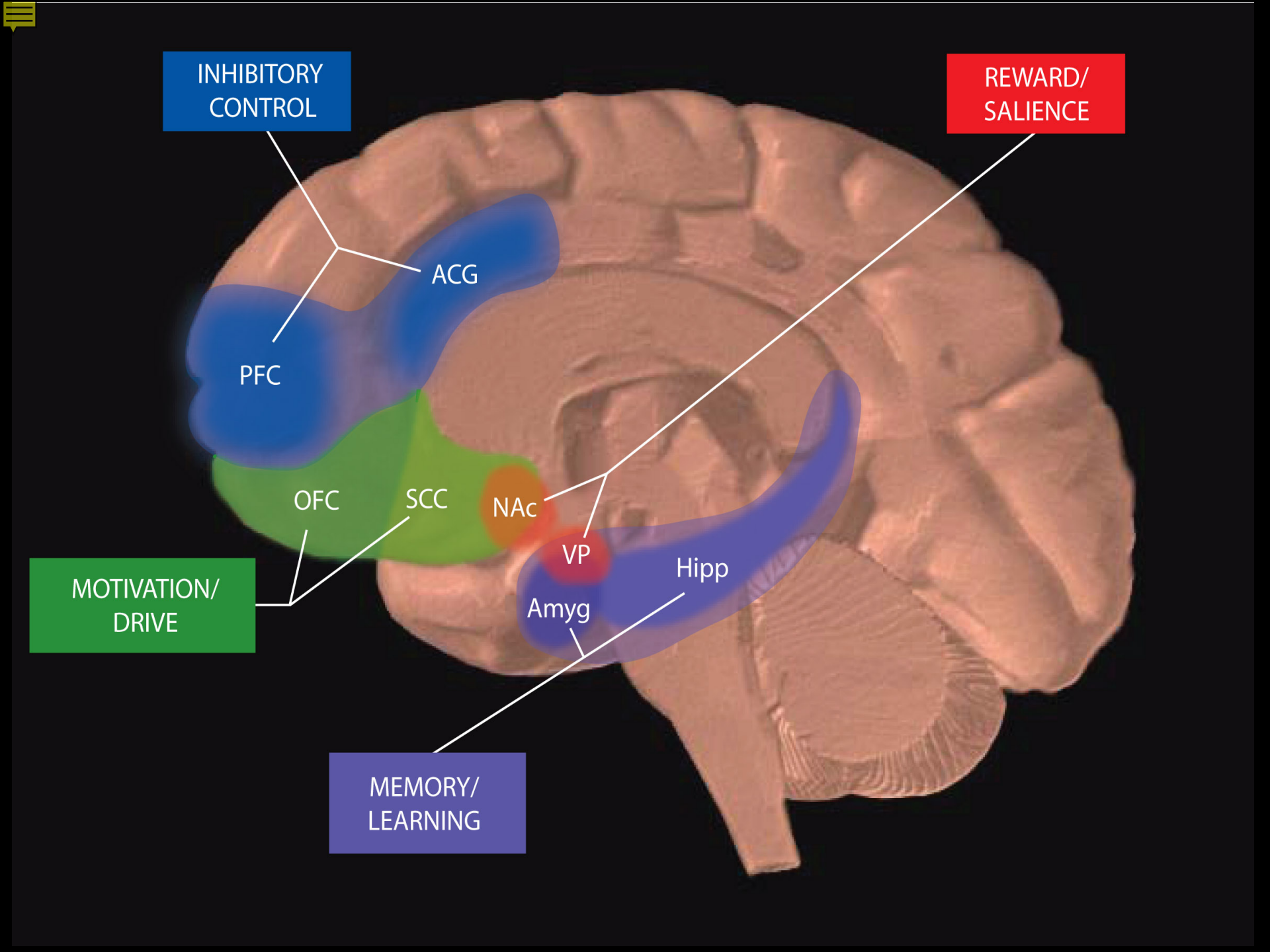
Risk-taking – it is human nature to fell excited when taking risks.

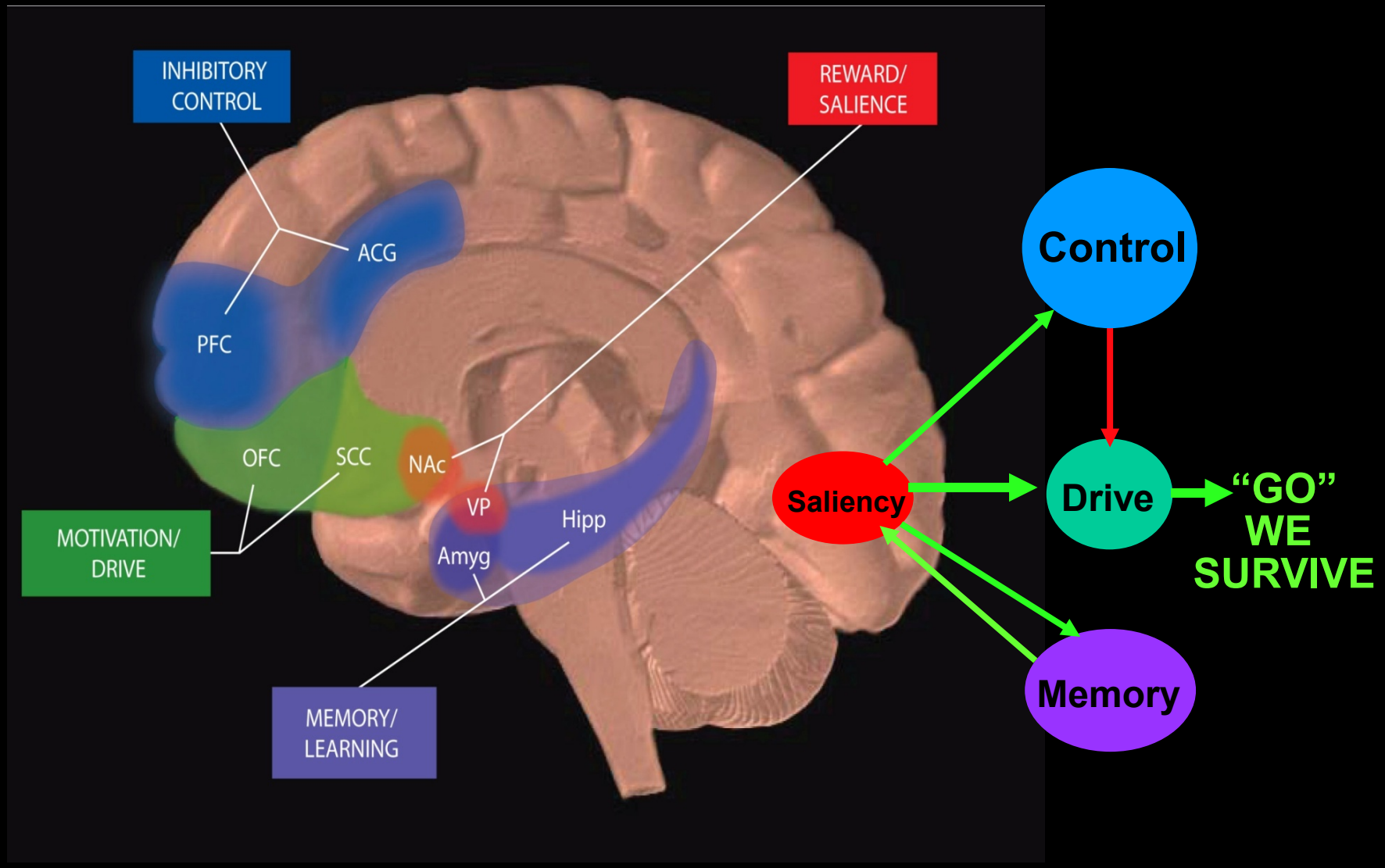
‘natural high’

- **adrenalin rush (PNS)**
- **dopamine elevation (CNS)**

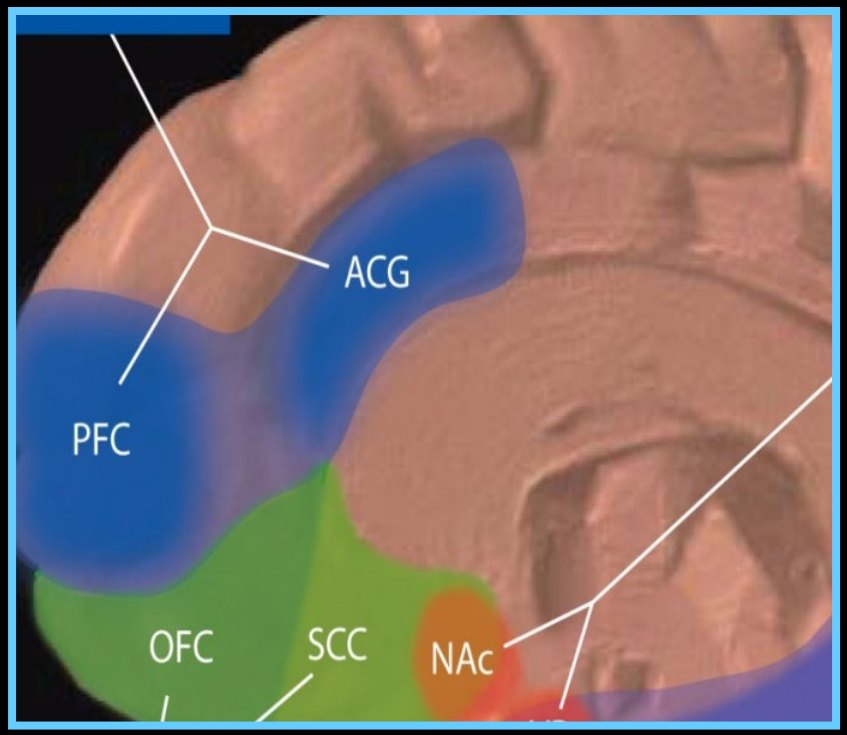
Activation of the reward pathway by addictive drugs and risk-taking

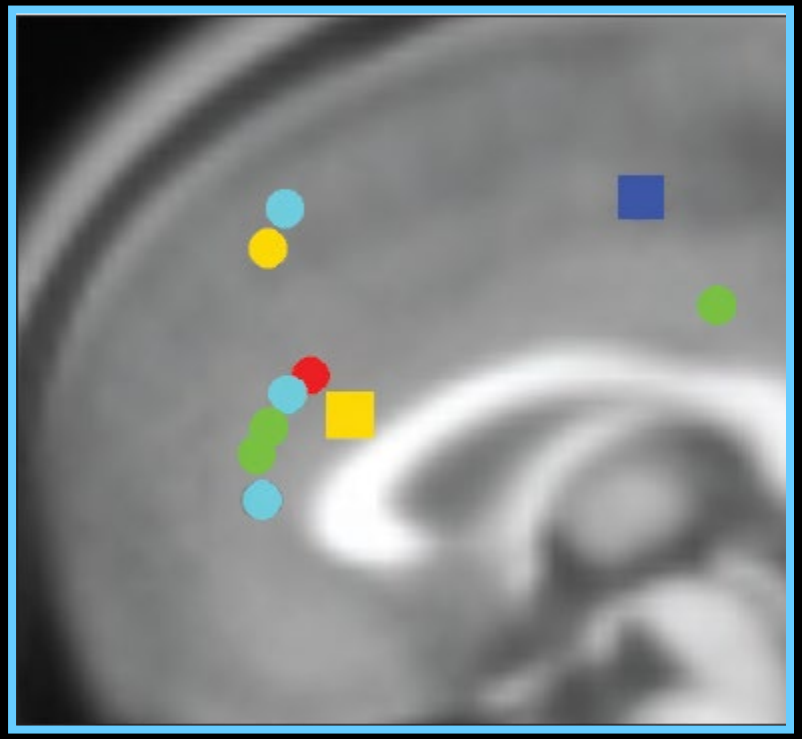

Recreational
Disorder
The functional neuroscience of decision-making
Choosing to gamble reflects what brain processes?


INHIBITORY CONTROL
REWARD/ SALIENCE
ACG
PFC
OFC
SCC
NAc
VP
Hipp
Amyg
MOTIVATION/ DRIVE
MEMORY/ LEARNING


INHIBITORY CONTROL
REWARD/ SALIENCE
ACG
PFC
OFC
SCC
NAc
VP
Hipp
Amyg
MOTIVATION/ DRIVE
MEMORY/ LEARNING
Control
Saliency
Drive
"GO" WE SURVIVE
Memory

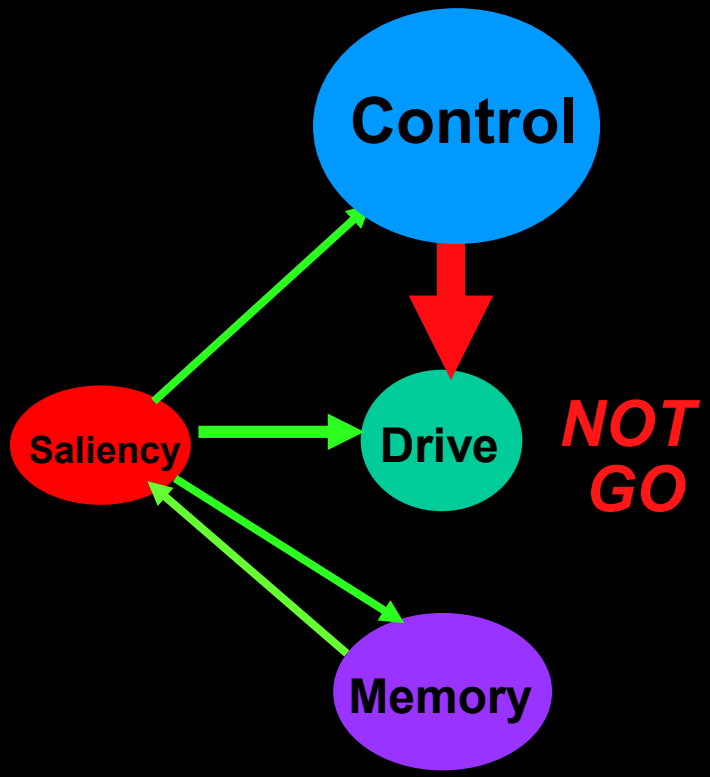
Inhibitory Control: Drug and Behavioral Addictions



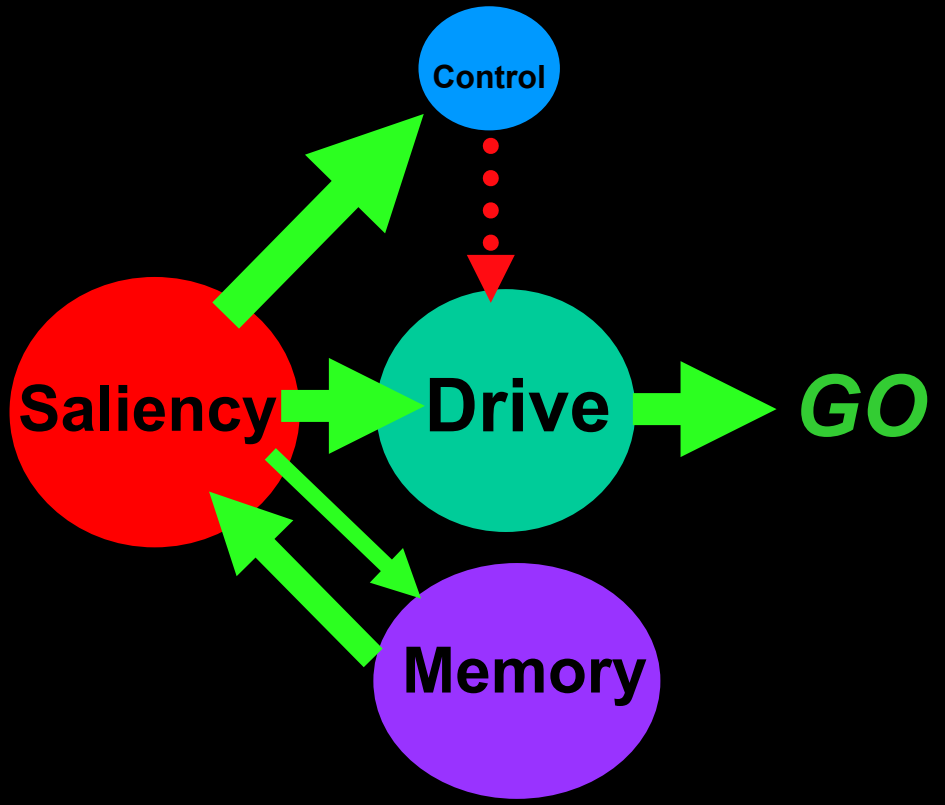


Luijten et al.,
J Psychiatry Neurosci, 2014.

Addictions Change Brain Circuits that Govern Decisions



NOT GO



GO

Adapted from Volkow et al., Neuropharmacology, 2004

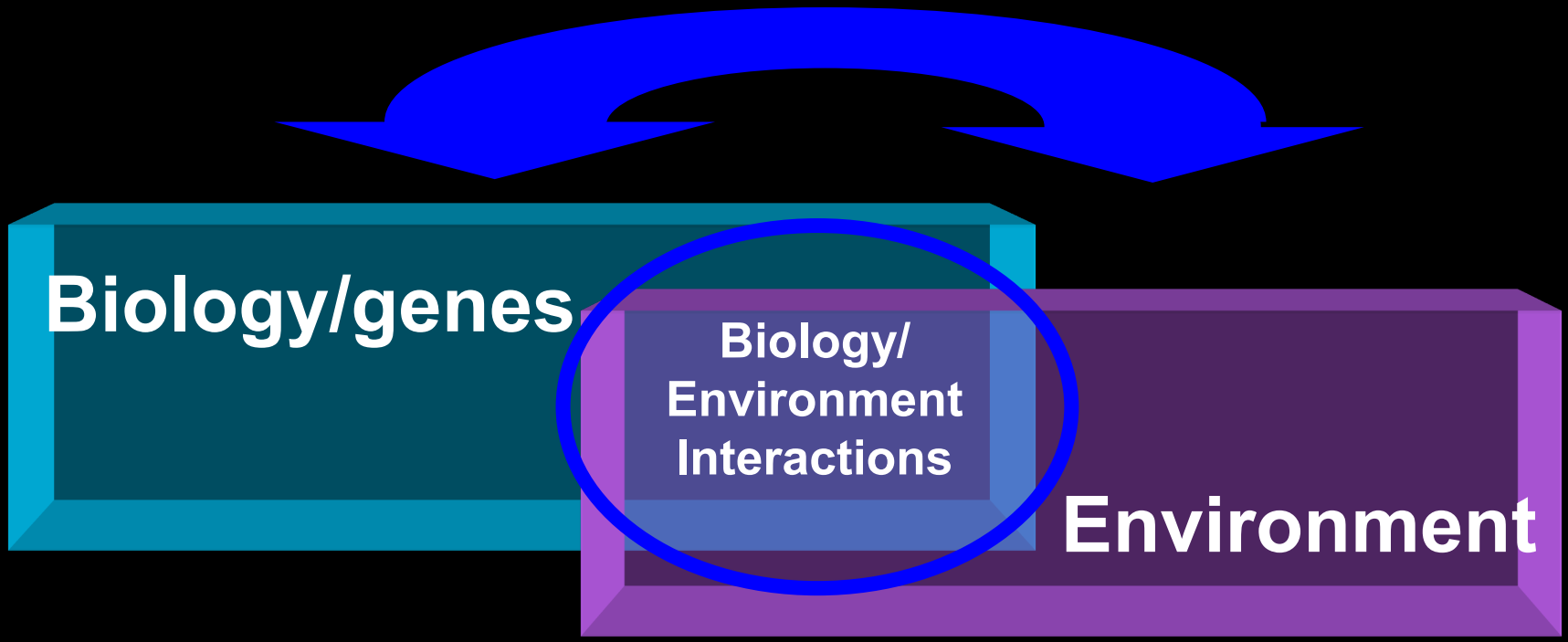
‘Psychology’ of Gambling

Risk-taking – it is human nature to fell excited when taking risks – ‘natural high’

Social – ‘game night’, sports, lottery, glamour

Escapism - the gambling environment can provide an escape from everyday life - glitzy casino, loud and exciting amusement arcade or online betting company - all of which stimulate and arouse our senses

‘Psychology’ of Gambling
Bio-Behavioral Factors



Why Do People Choose to Gamble?

To feel good

<u>To have new:</u>
feelings
sensations
experiences
and
to share them

To feel better

<u>Escapism</u>
anxiety
worries
fears
depression

Choosing to gamble

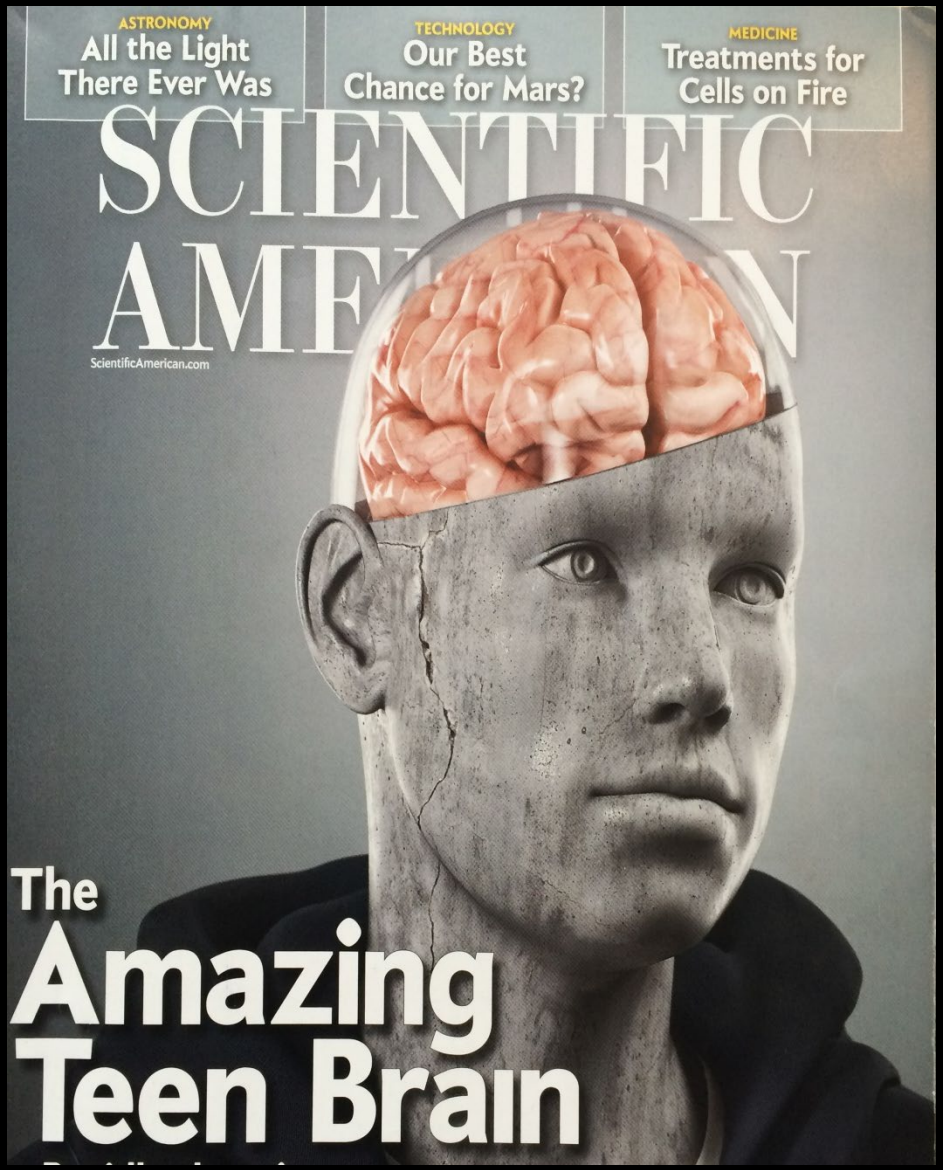
To feel good.

To have new feelings, sensations, experiences and to share them.

Genetic Predisposition

Developmental

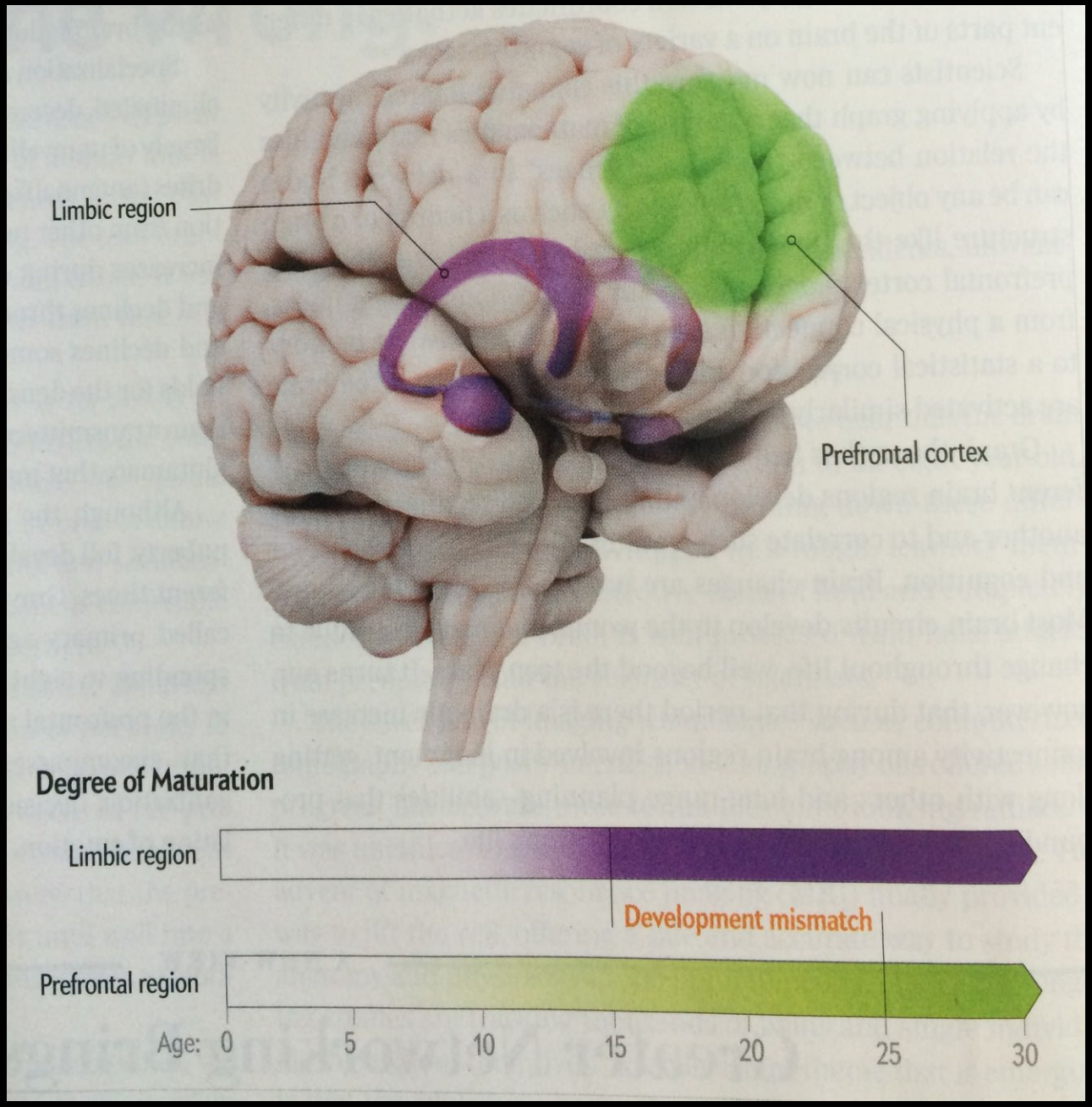
- Risk-taking, sensation-seeking
- Interacting with, and approval from peers



"Rapidly changing wiring leads to mental agility – and risky behavior"

By Jay N. Giedd

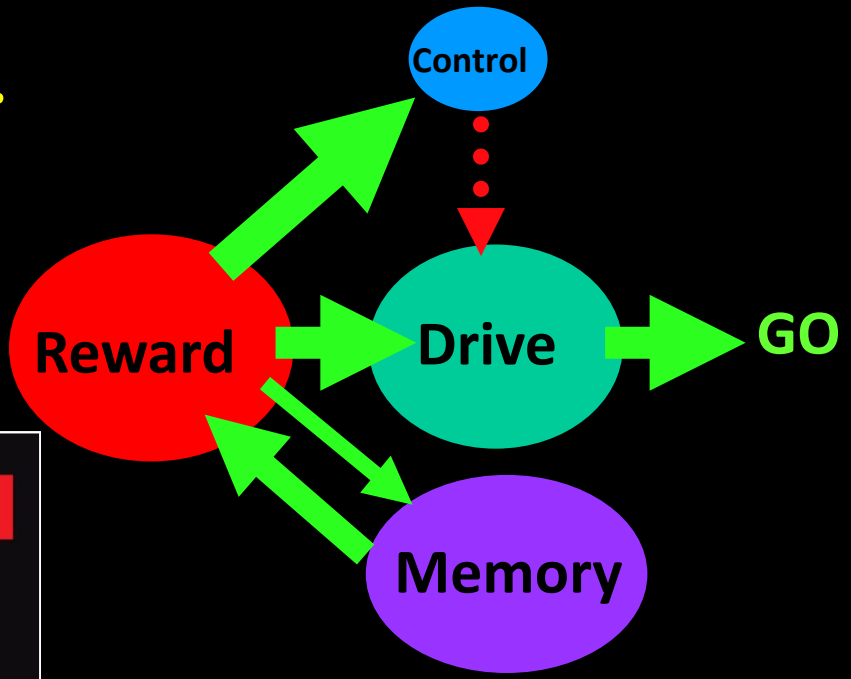
Time of high sensitivity to rewards, and increased vulnerability to developing addictions.
With potential for long-term consequences.

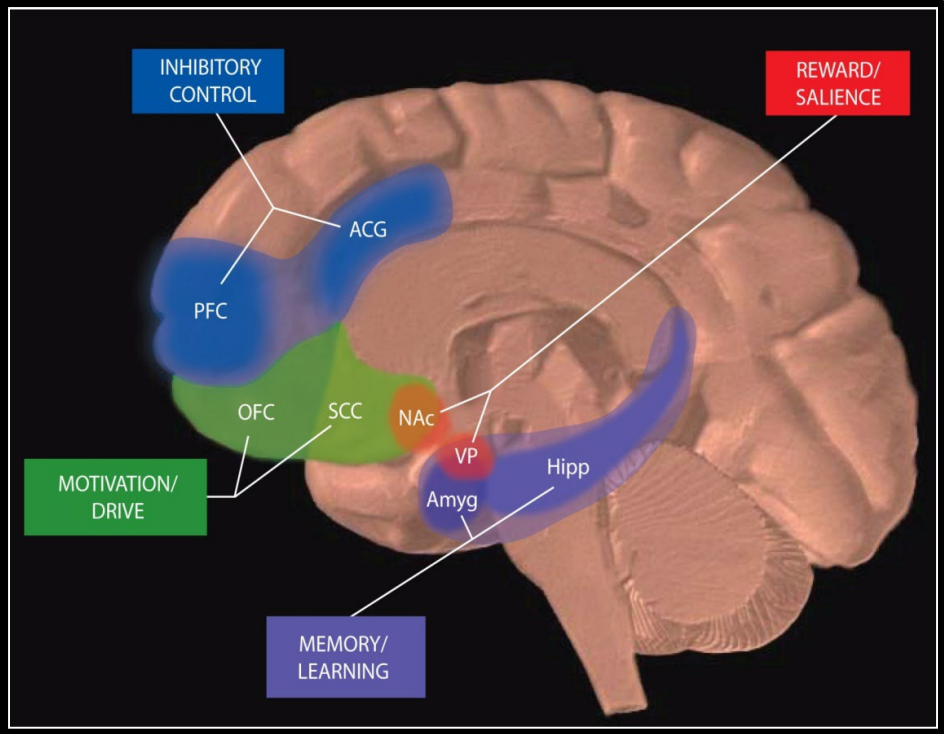


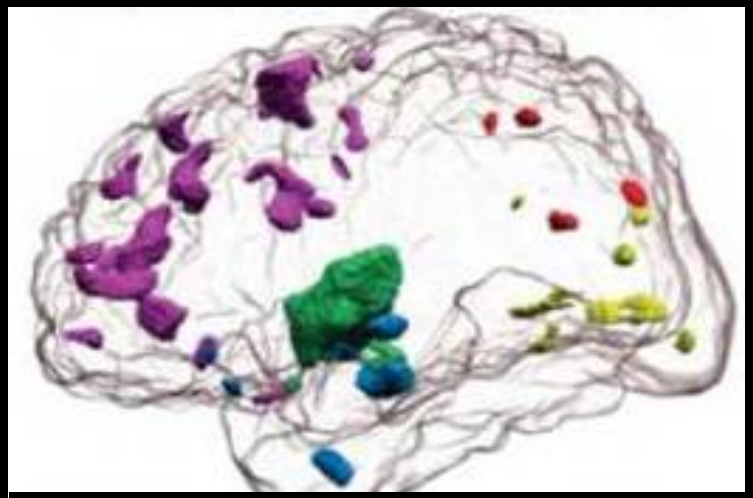
Miss match for development of brain regions that govern emotions and judgement.

Giedd.
Scientific American
312:32, 2015.

Cortical development and decision making







Adolescent to Adult

Sowell et al. The Neuroscientist, 2004.

Contents lists available at ScienceDirect

Hormones and Behavior

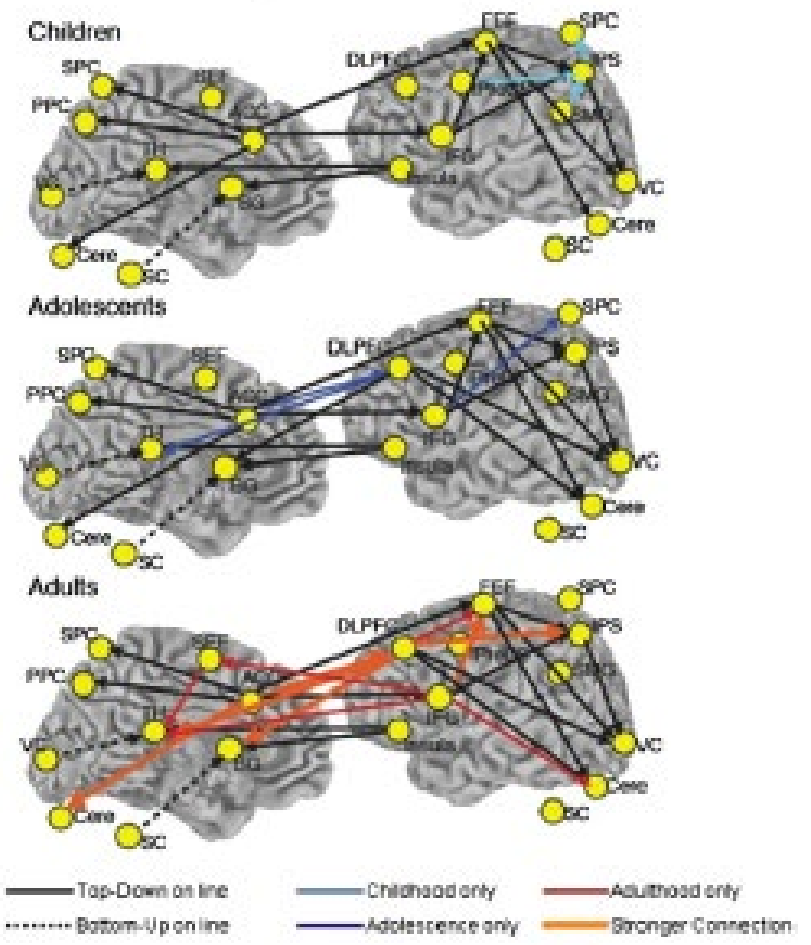
journal homepage: www.elsevier.com/locate/yhbeh

Review

Adolescent cognitive control and reward processing: Implications for risk taking and substance use

"Adolescence is marked by peaks in sensation, novelty, and reward seeking … stem from … increases in responsiveness in limbic and paralimbic brain structures".

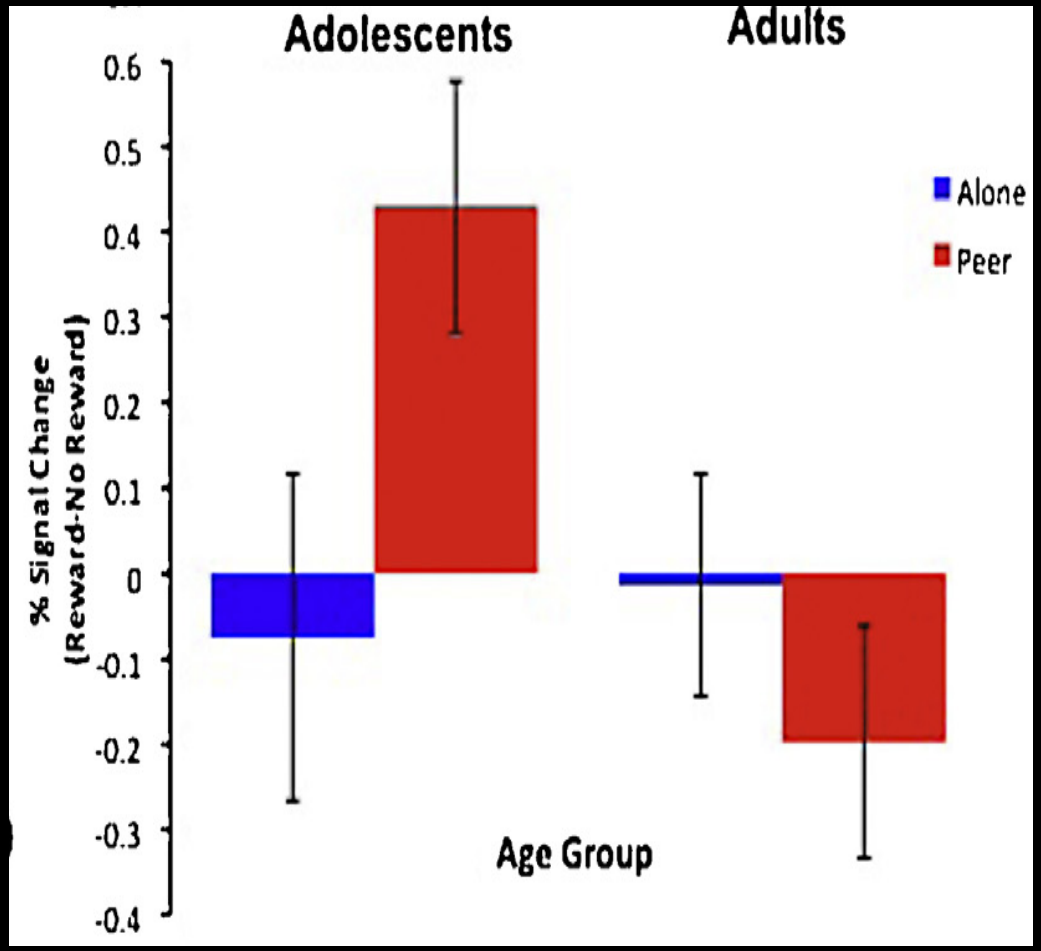
CF Geier.
Hormones and Behavior
64:333-342, 2013.
(Hwang et al., 2010)



Social Engagement Adolescent Risk-Taking

- Creates new friendships
- Safety in association as they leave parents

Increased adolescent risk-taking linked to the influence of peers on valuation of rewards



Smith et al., Dev Cog NeuroSci 11:75, 2015.

Choosing to gamble

To feel better (less studied).

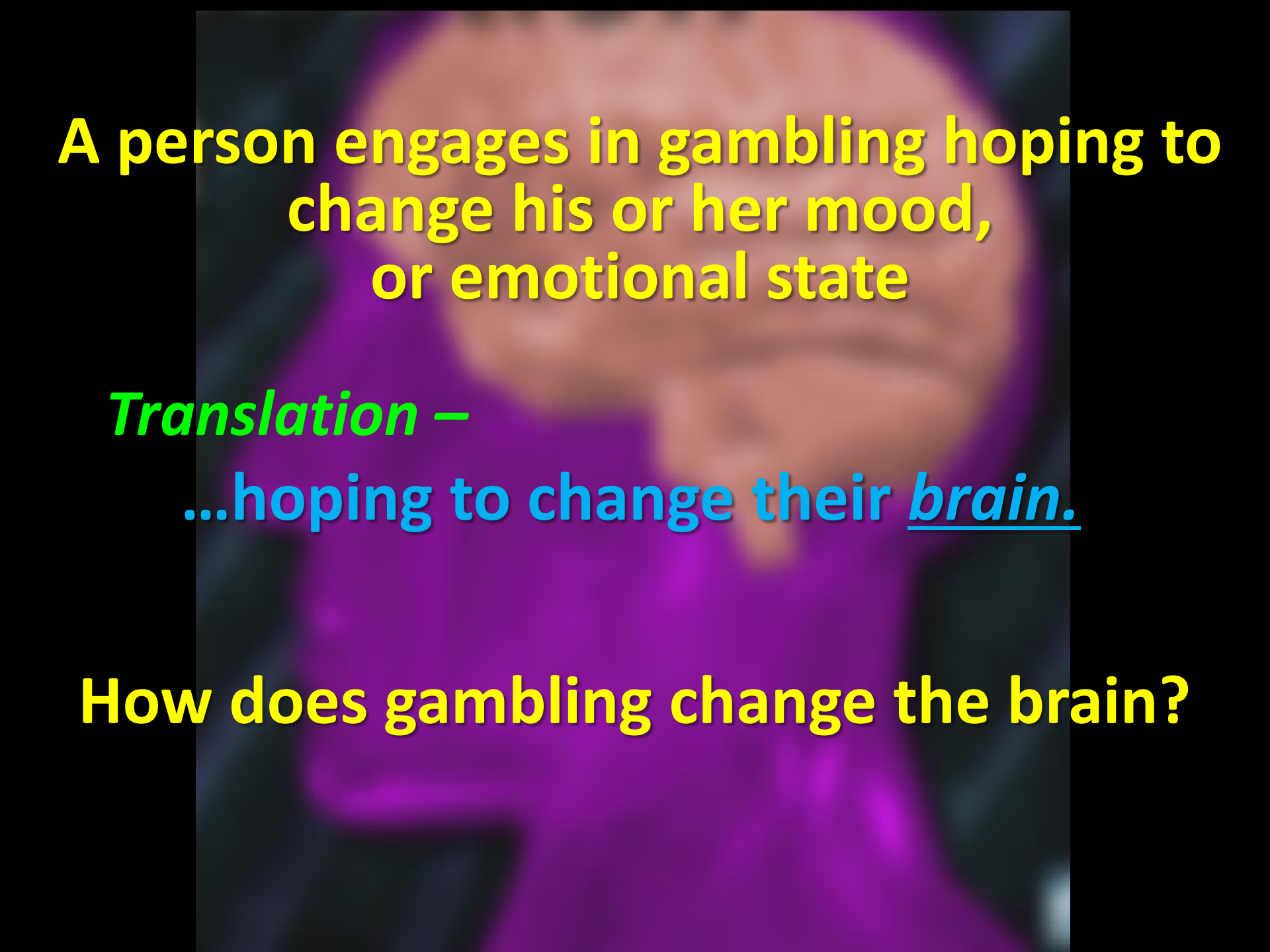
Escapism

- Co-morbidity w mental hlth disorders
  - esp substance use disorders
  - onset and persistence of GD predicted by prior diagnosis of mood disorders, anxiety, ICD, SUD (Kessler et al. Psychol Med, 2008)
- Environment
  - Life stresses
  - Brain trauma

Why Do People Choose to Gamble?

To feel good

To feel better

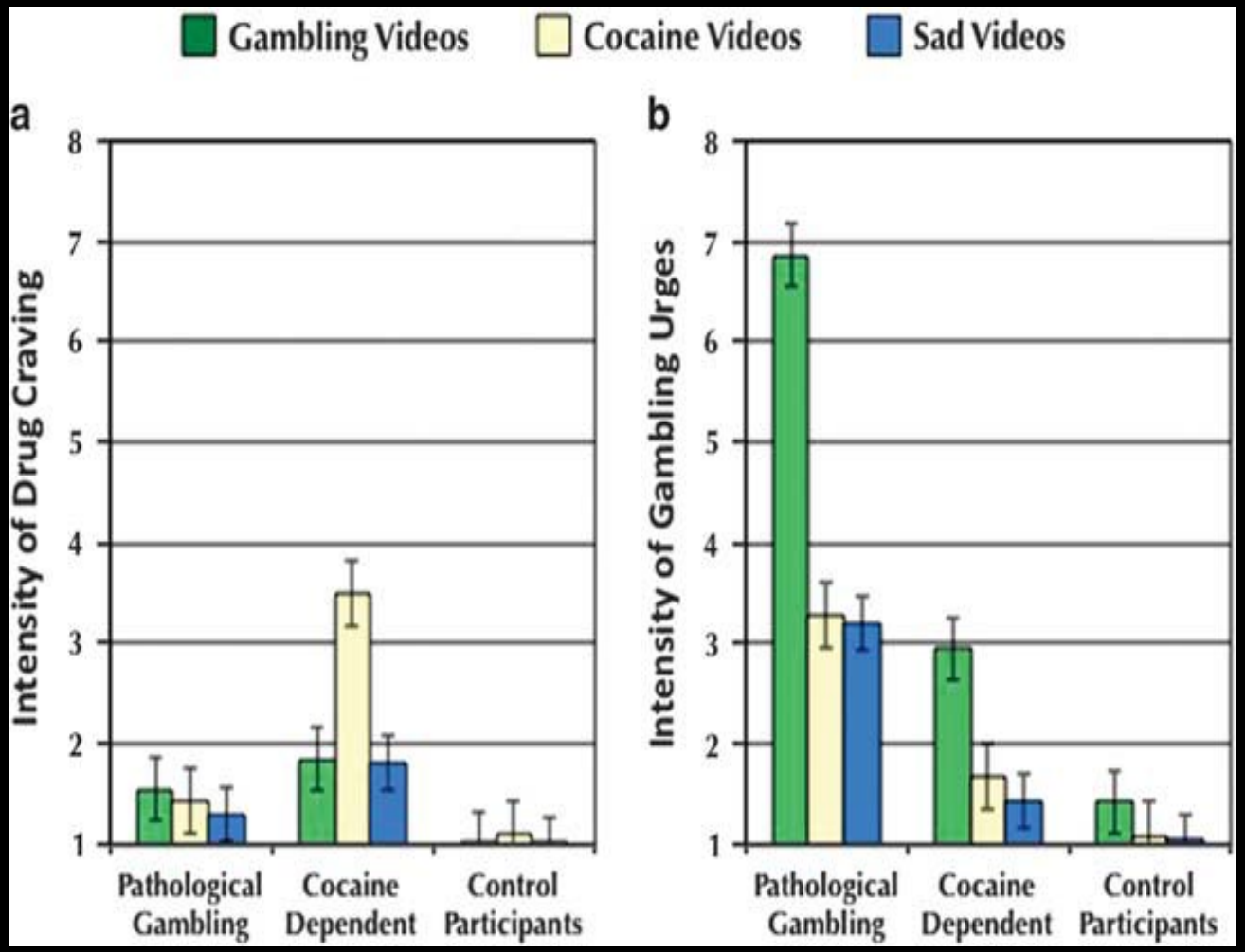

A person engages in gambling hoping to change his or her mood, or emotional state
Translation –
…hoping to change their *brain.*
How does gambling change the brain?

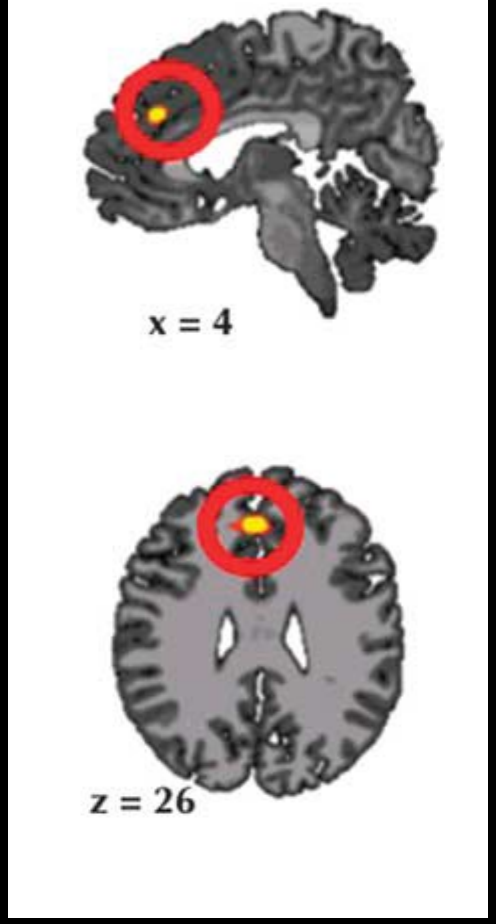
Memories are a Critical Aspect of Addiction Processes

It's about people, places, and things.


STARBUCKS
®

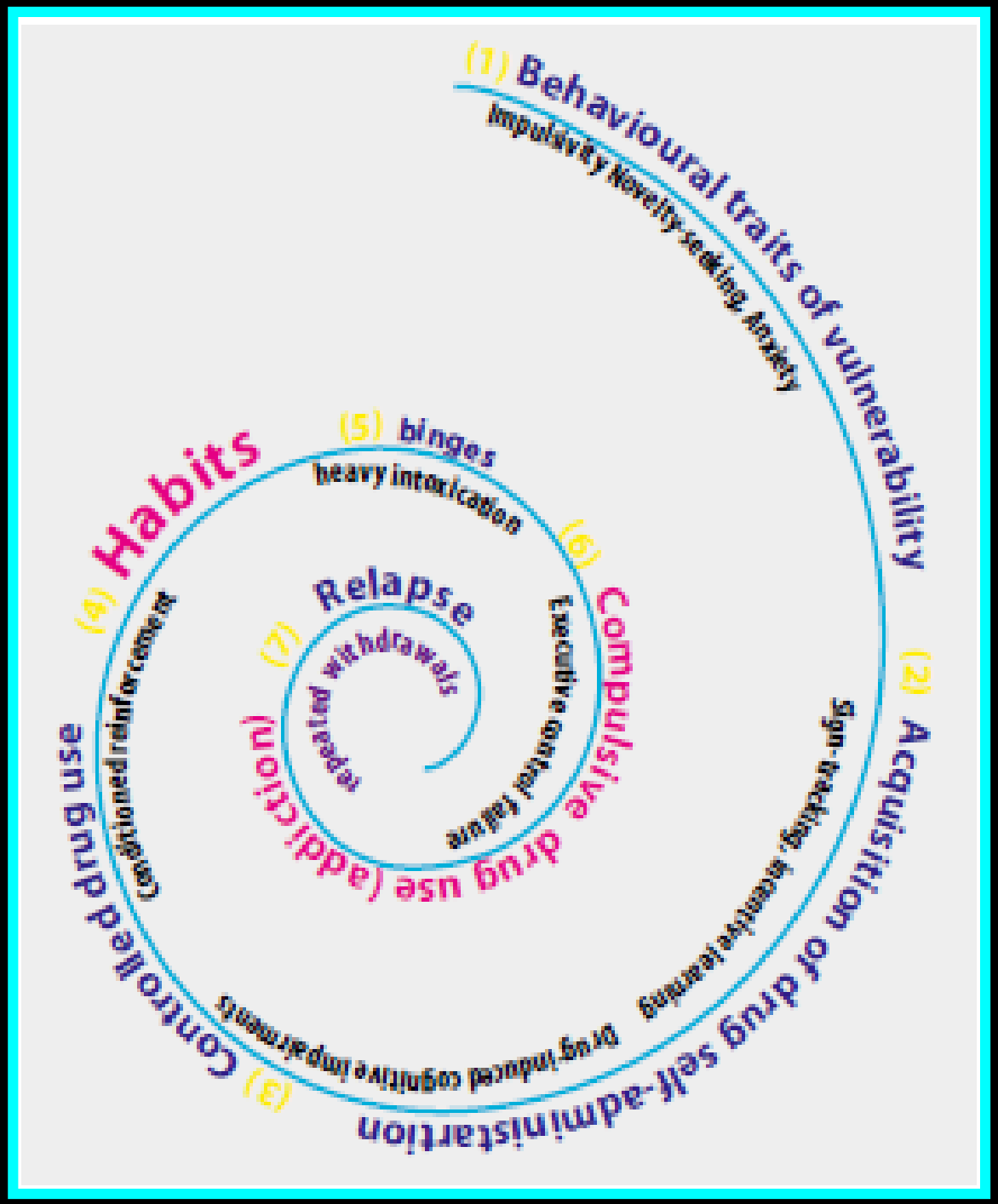
Remembering Causes Craving



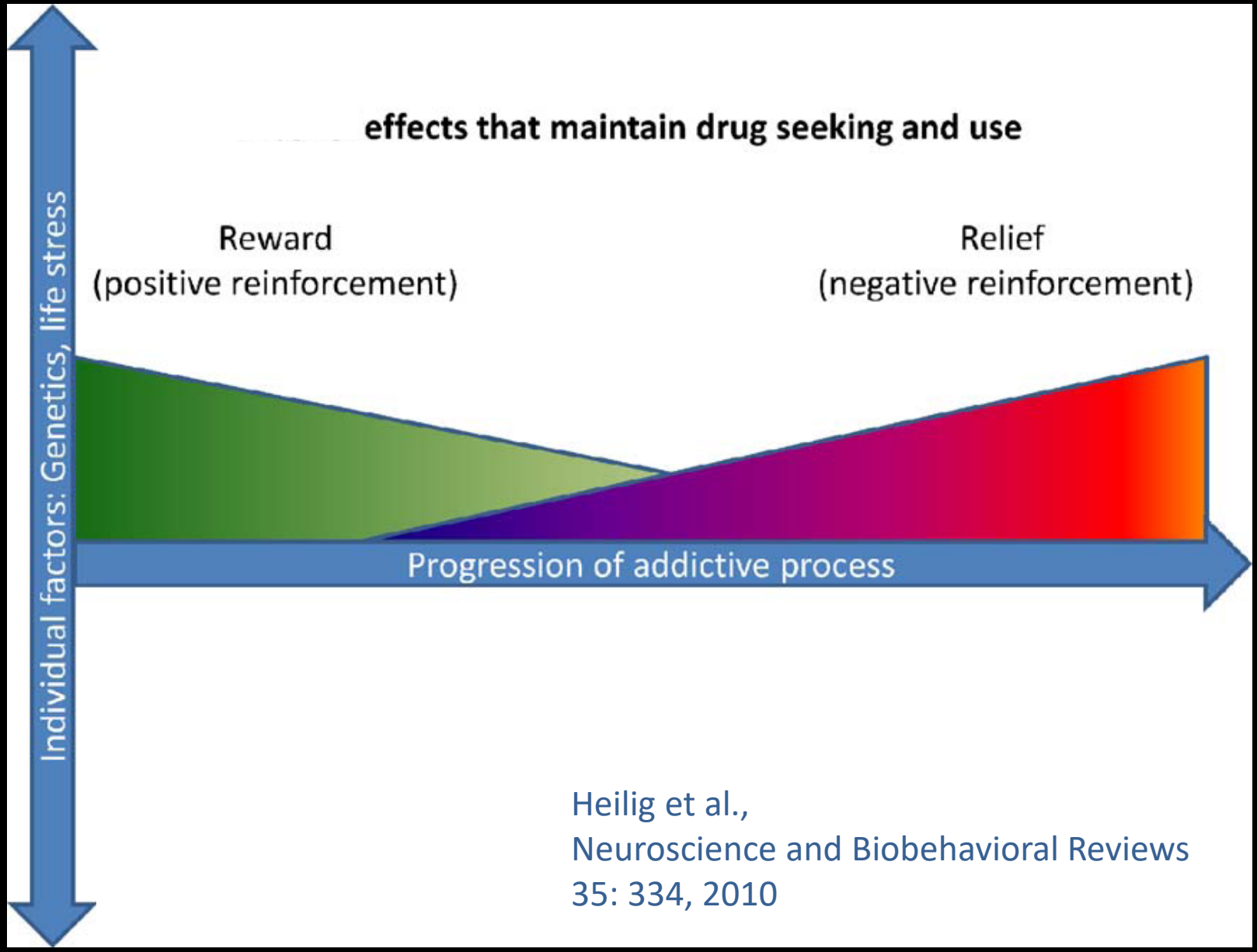


Kober et al., NPP 2016

The Addiction Process:

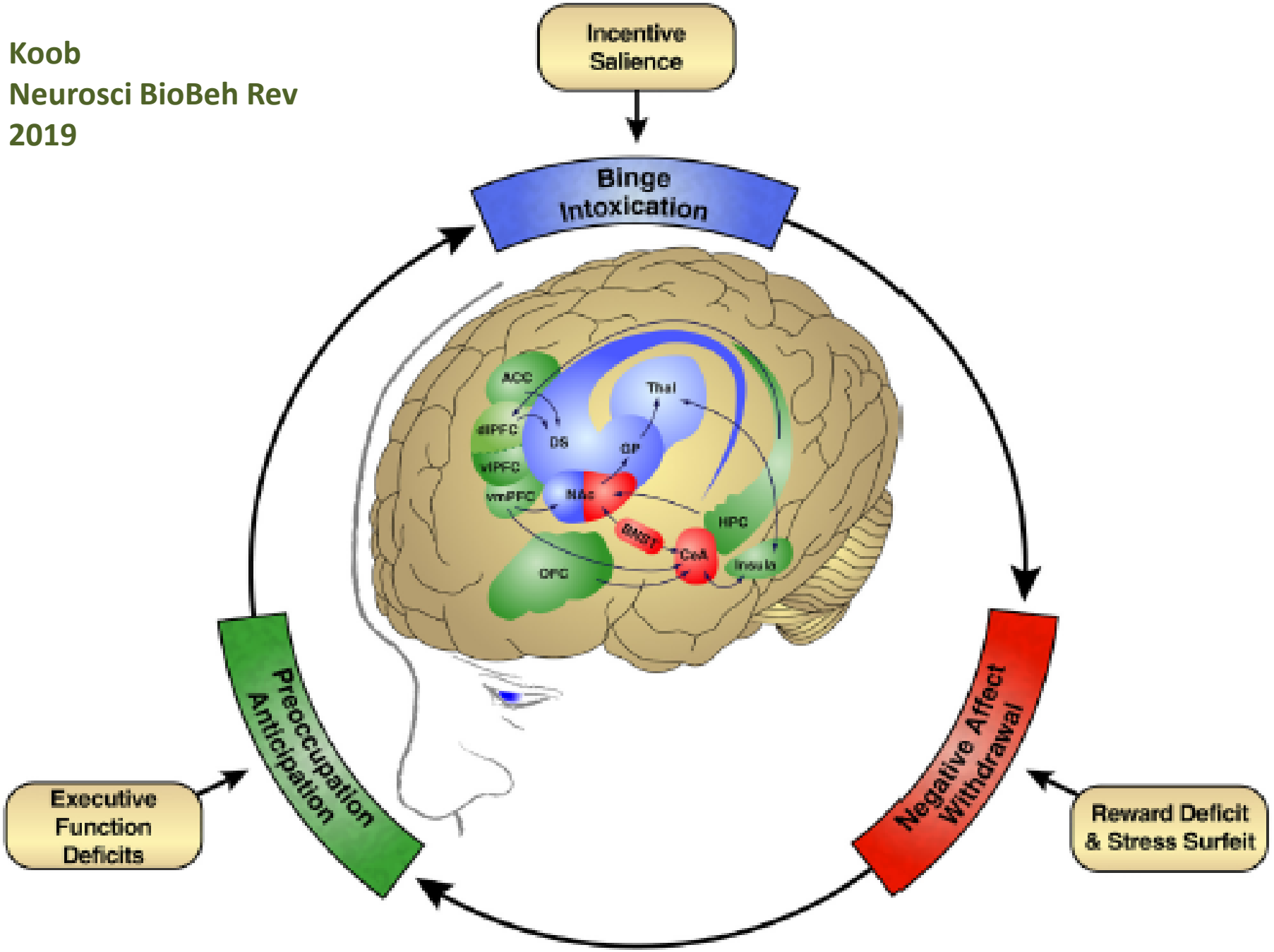


Everitt
Eur Jr Neurosci
40:2163, 2014.



Heilig et al.,
Neuroscience and Biobehavioral Reviews
35: 334, 2010

Koob
Neurosci BioBeh Rev
2019



Progression to Problem Gambling

Reframe concepts of

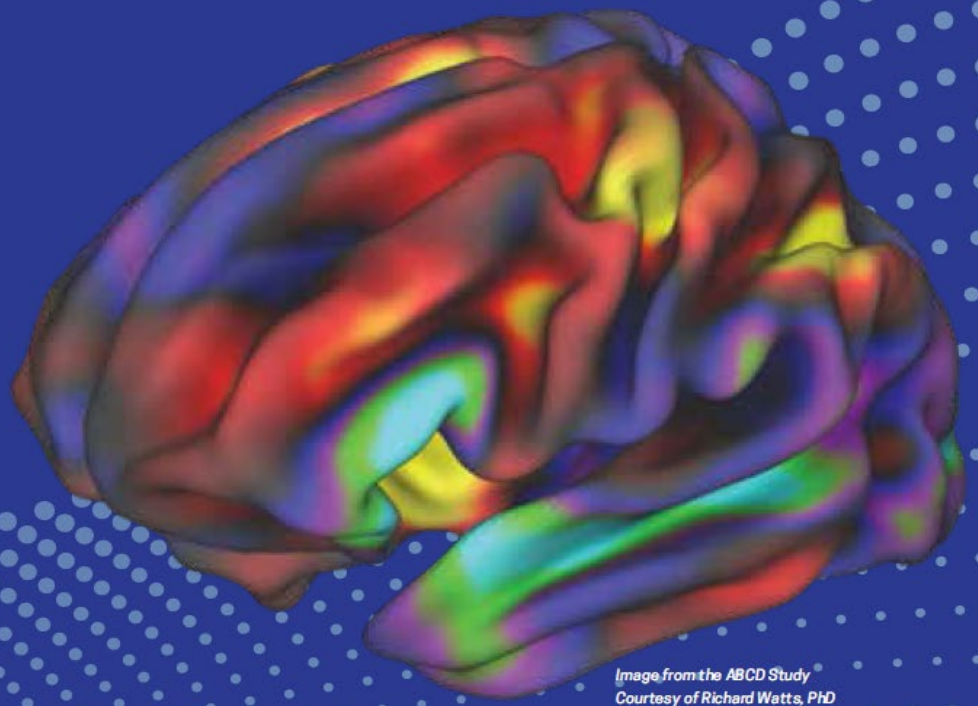
- stigma
- treatment expectations

GAMBLING DISORDERS ARE A *BEHAVIORAL ADDICTION*

In DSM-V, gambling disorder joins substance-related addictions in a renamed group called "Addiction and Related Disorders."

Addiction: A chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences.

Drugs, Brains, and Behavior:
The Science of Addiction

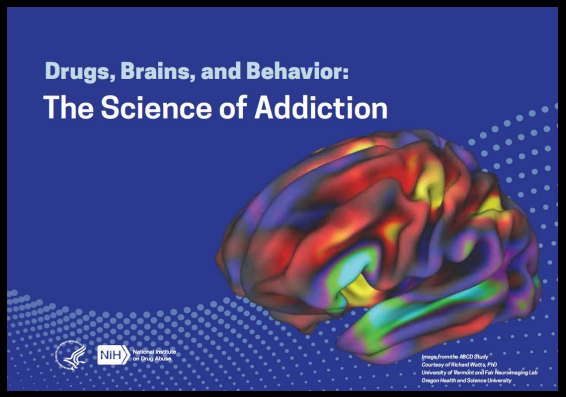


NIH National Institute on Drug Abuse

Image from the ABCD Study
Courtesy of Richard Watts, PhD
University of Vermont and Fair Neuroimaging Lab
Oregon Health and Science University

http://www.nida.nih.gov

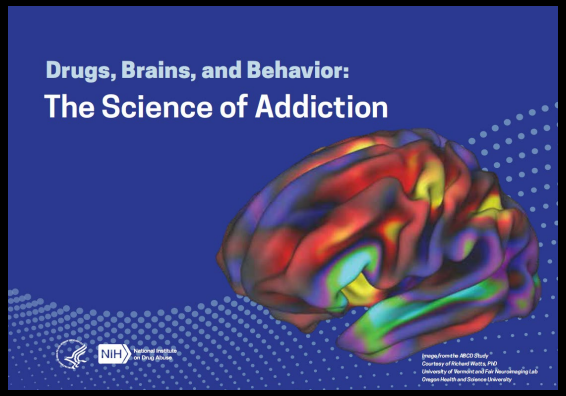
Is continued drug abuse a voluntary behavior?



"The initial decision to take drugs is mostly voluntary. However, when drug abuse takes over, a person's ability to exert self control can become seriously impaired."

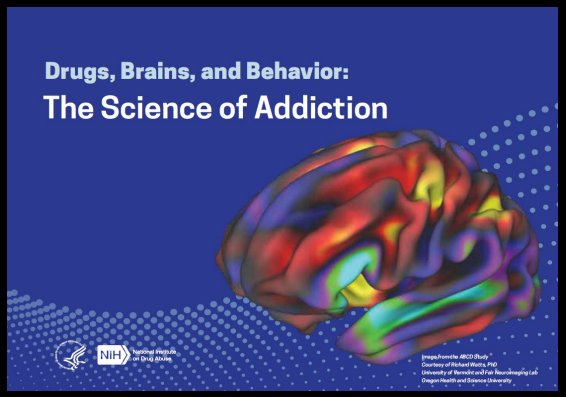
"Brain imaging studies from drug-addicted individuals show physical changes in areas of the brain that are critical to judgment, decision making, learning and memory, and behavior control."

addiction is a disease of the brain



"It is considered a brain disease because drugs change the brain - they change its structure and how it works. "

"Addiction is similar to other diseases, such as heart disease. Both disrupt the normal, healthy functioning of the underlying organ, have serious harmful consequences, are preventable, treatable, and if left untreated, can last a lifetime."



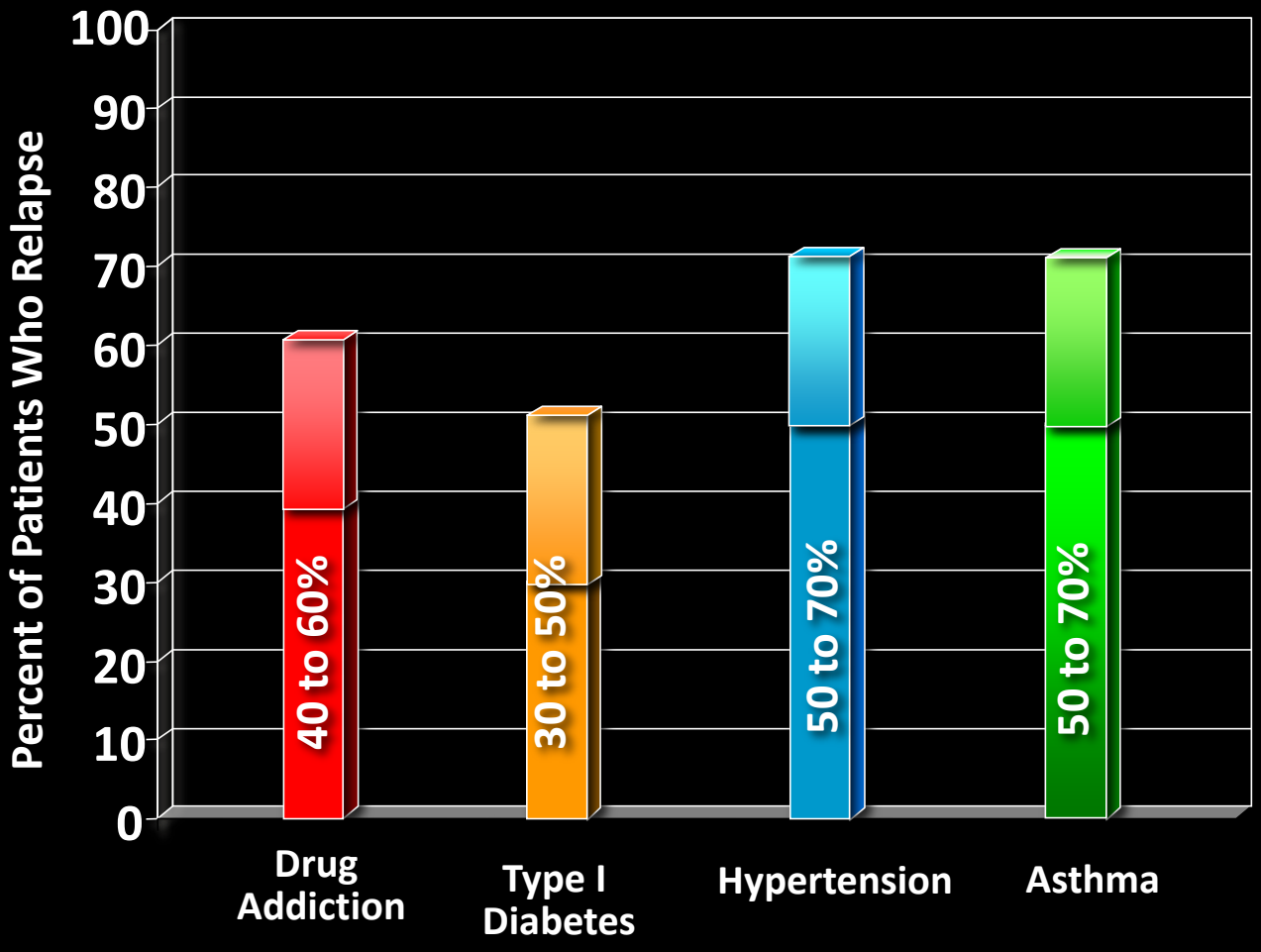
Does relapse to drug abuse mean treatment has failed?

"No. The chronic nature of the disease means that relapsing to drug abuse is not only possible, but likely.

Treatment of chronic diseases involves changing deeply imbedded behaviors, and relapse does not mean treatment failure. For the addicted patient, lapses back to drug abuse indicate that treatment needs to be reinstated or adjusted, or that alternate treatment is needed."

Addictions are chronic illnesses with relapse rates similar to those of other chronic illnesses.

Relapse Rates Are Similar for Drug Addiction and Other Chronic Illnesses



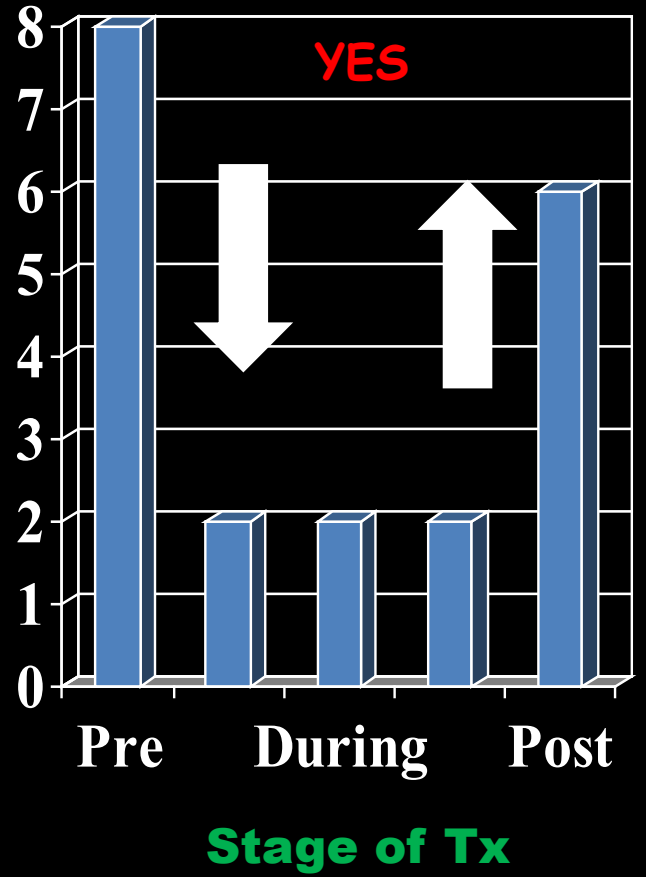
NIDA

McLellan et al., JAMA, 2000.

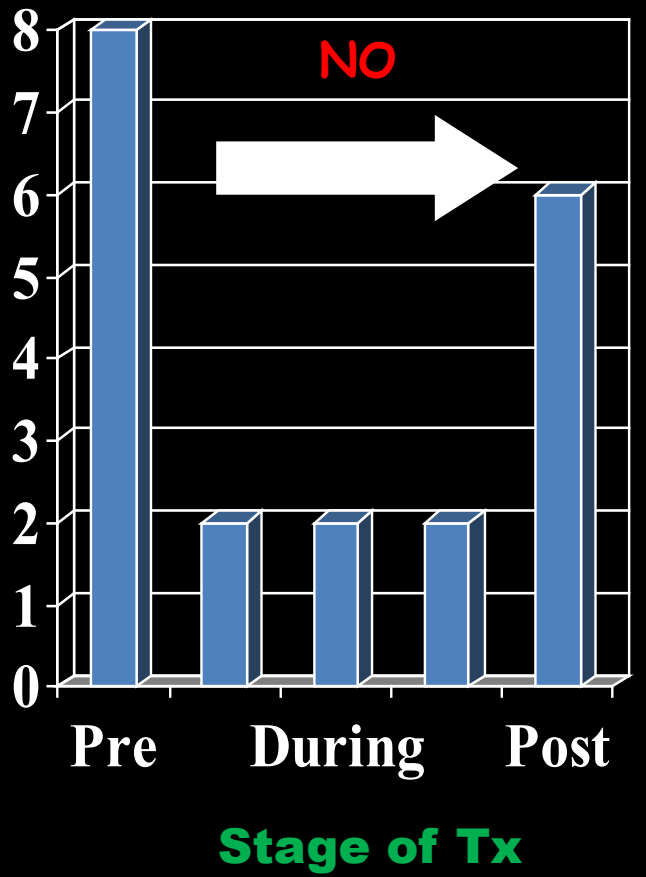
Addiction is similar to other chronic illnesses also because recovery is often a long-term process requiring repeated treatments

Measuring the Outcome of Treating Chronic Illnesses

Hypertension Tx



Addiction Tx



NIDA

Neuroscience Underpinnings of the Switch from Recreational to Problem Gambling

Initially hijacks normal reward pathways (especially in vulnerable individuals)

Reduces inhibitory control

Involves learning and memory – changes the brain

Reframe concepts of stigma and treatment outcomes.

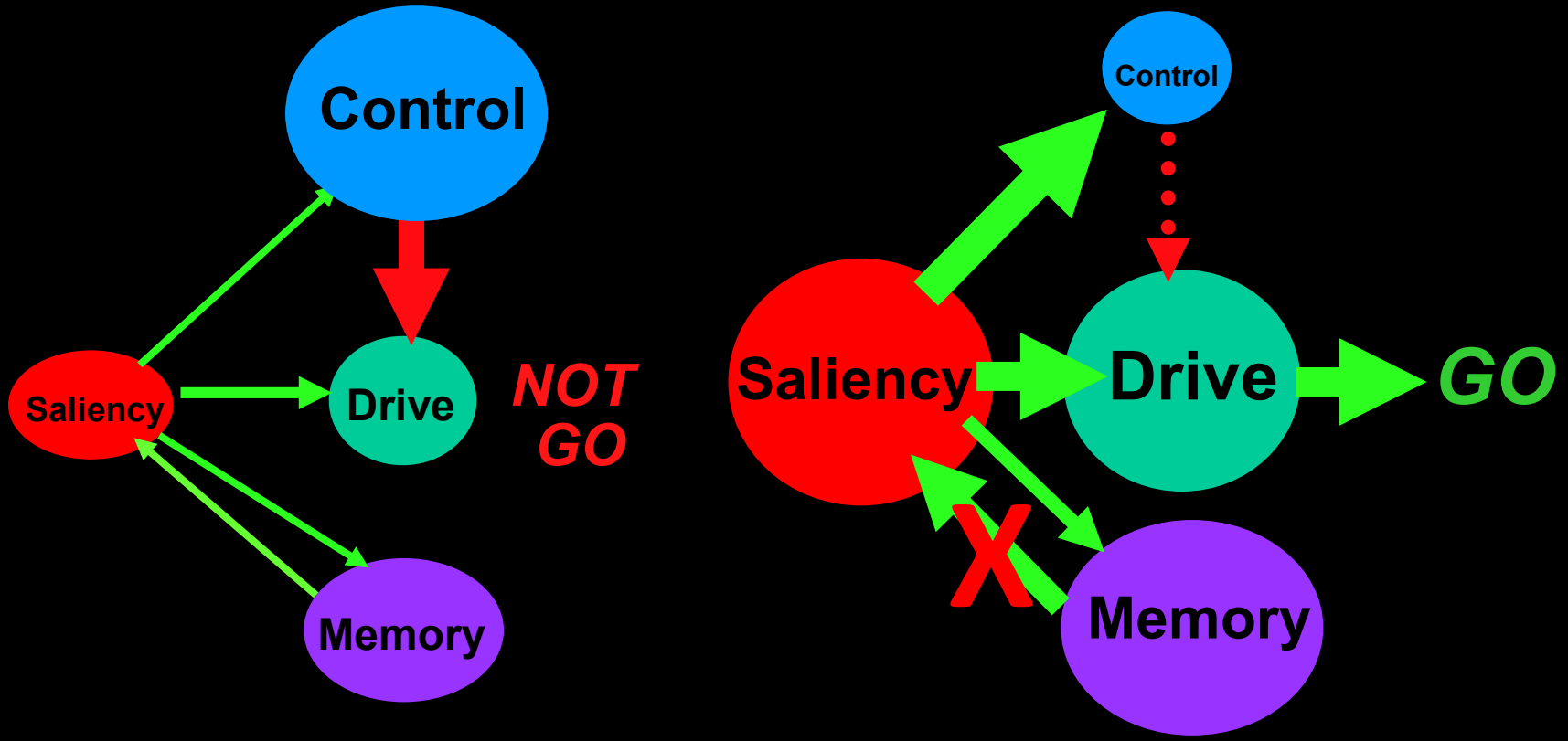
Medication Development

There is no FDA-approved pharmacotherapy.

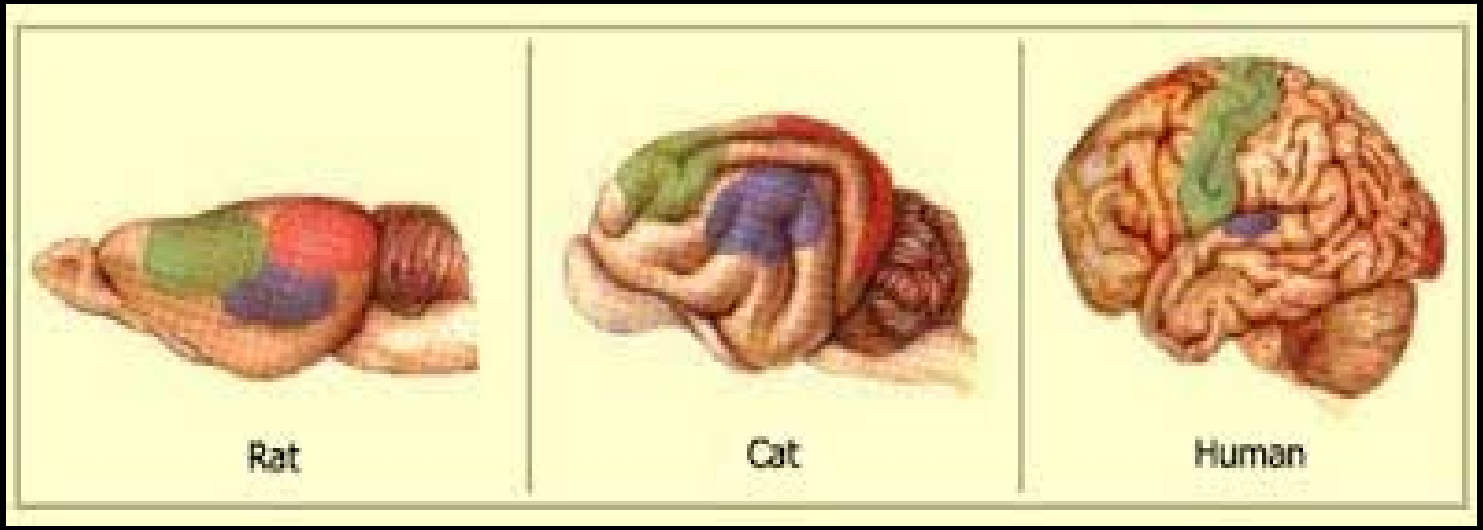
Using neuroscience to inform medication development for gambling disorders.

Development of effective preclinical models of particular aspects of the problem gambling process

Addiction Changes Brain Circuits that Govern Decisions



comparative functional neuroanatomy




JACKPOT

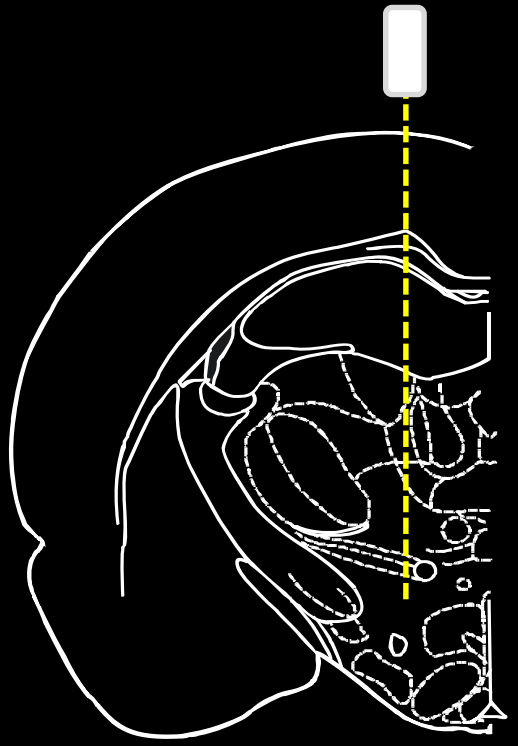
Features of Gambling: Humans versus Rats

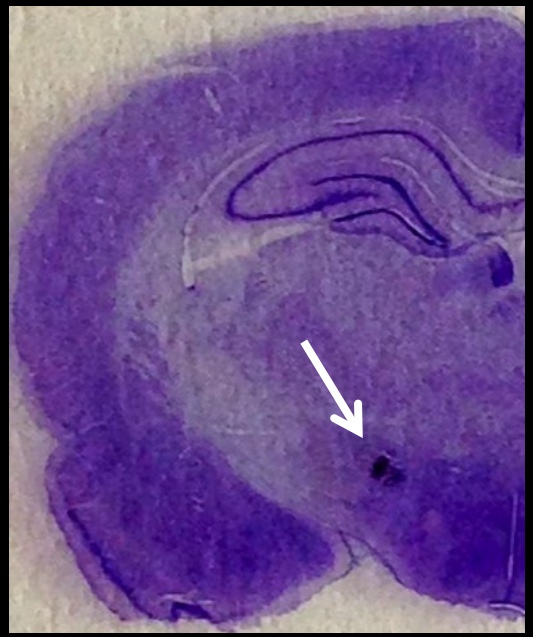
money → reward ← ICSS

$1	$1000	small reward	LARGE reward
more likely	less likely	more likely	less likely

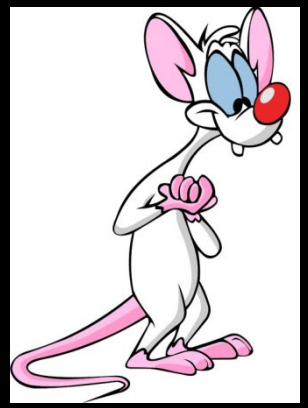
ICSS: Intra-Cranial Self-Stimulation

ICSS: Intra-Cranial Self-Stimulation



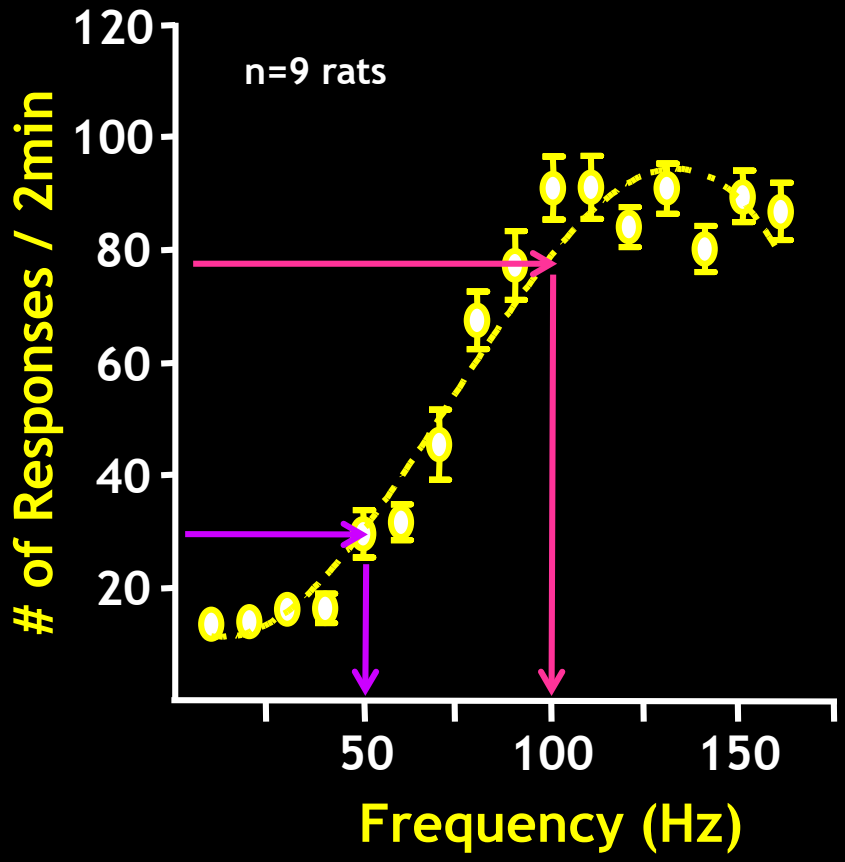


Determination of Small and Large Rewards Using ICSS

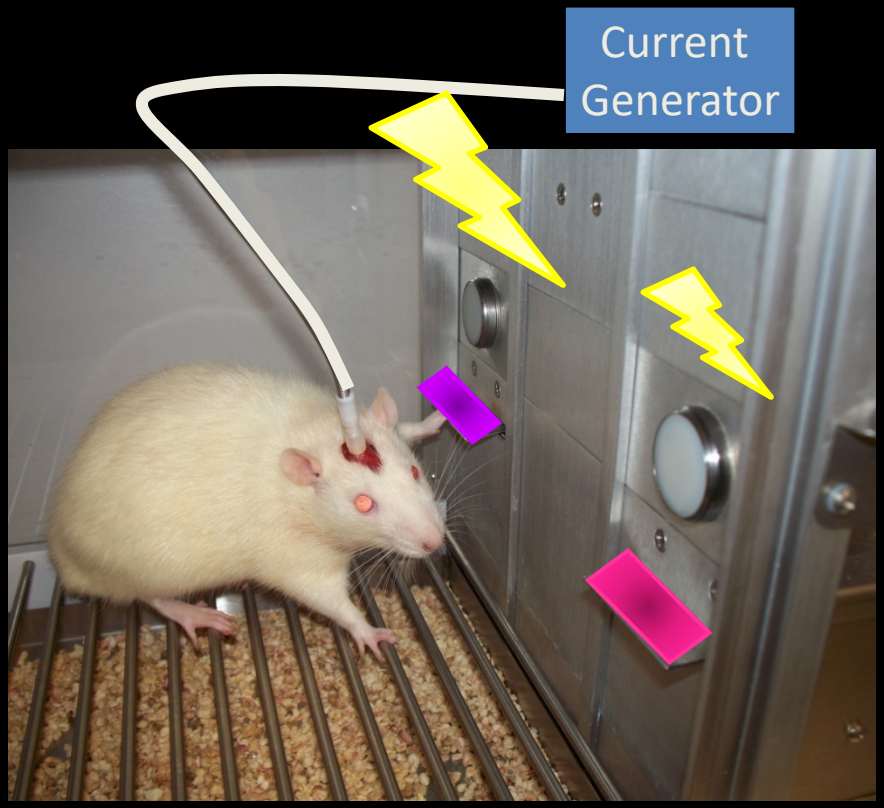


ICSS → reward

50-60Hz (small reward)	100Hz (LARGE reward)
more likely? "certain"	less likely? "risky"



Probability Discounting Task

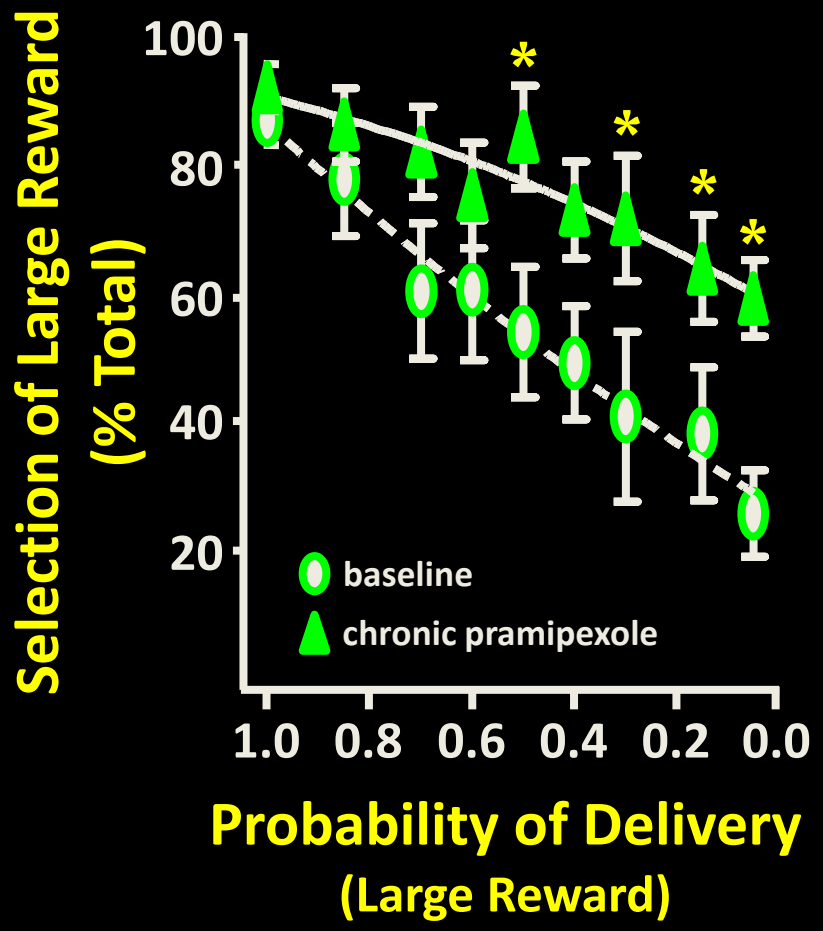


"CERTAIN" LEVER	"RISKY" LEVER
small reward (lower current) Probability of reward delivery is always 100%	LARGE reward (higher current) "risky" lever Probability of reward delivery = 100% 80% 70% 60% 50% 40% 30% 15% 5%

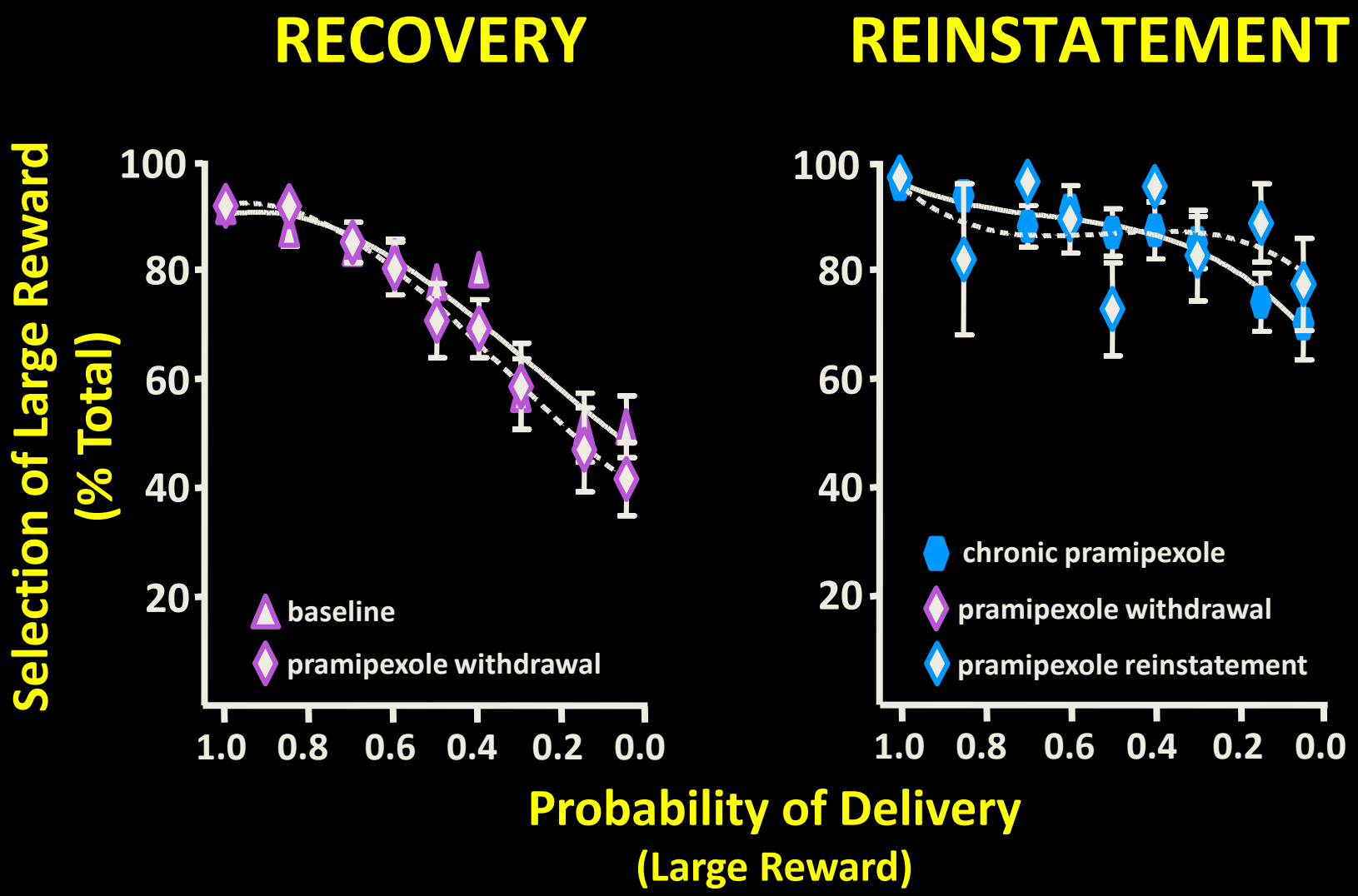
Risky Decision-Making

Rokosik and Napier, Journal of Neuroscience Methods, 2011

Activating Dopamine Receptors Increases Risk-Taking

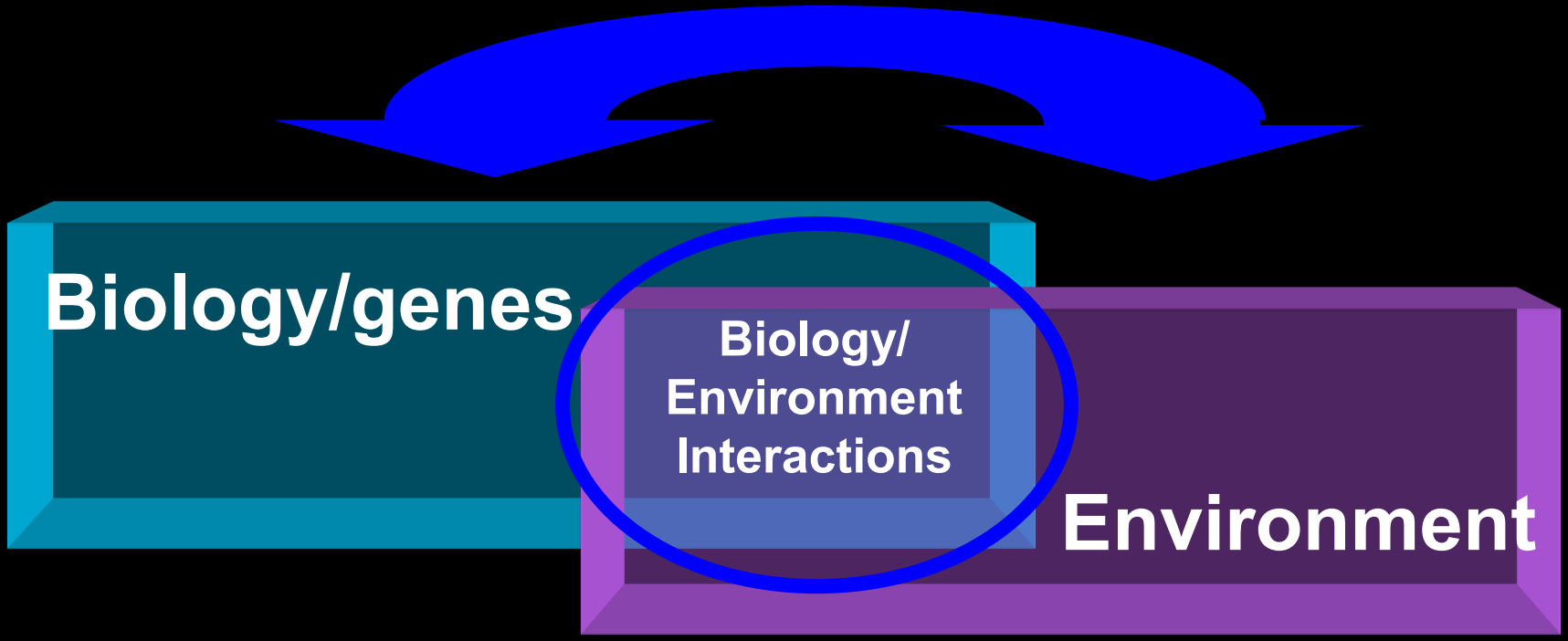


Rokosik & Napier. Neuropsychopharmacology, 2012

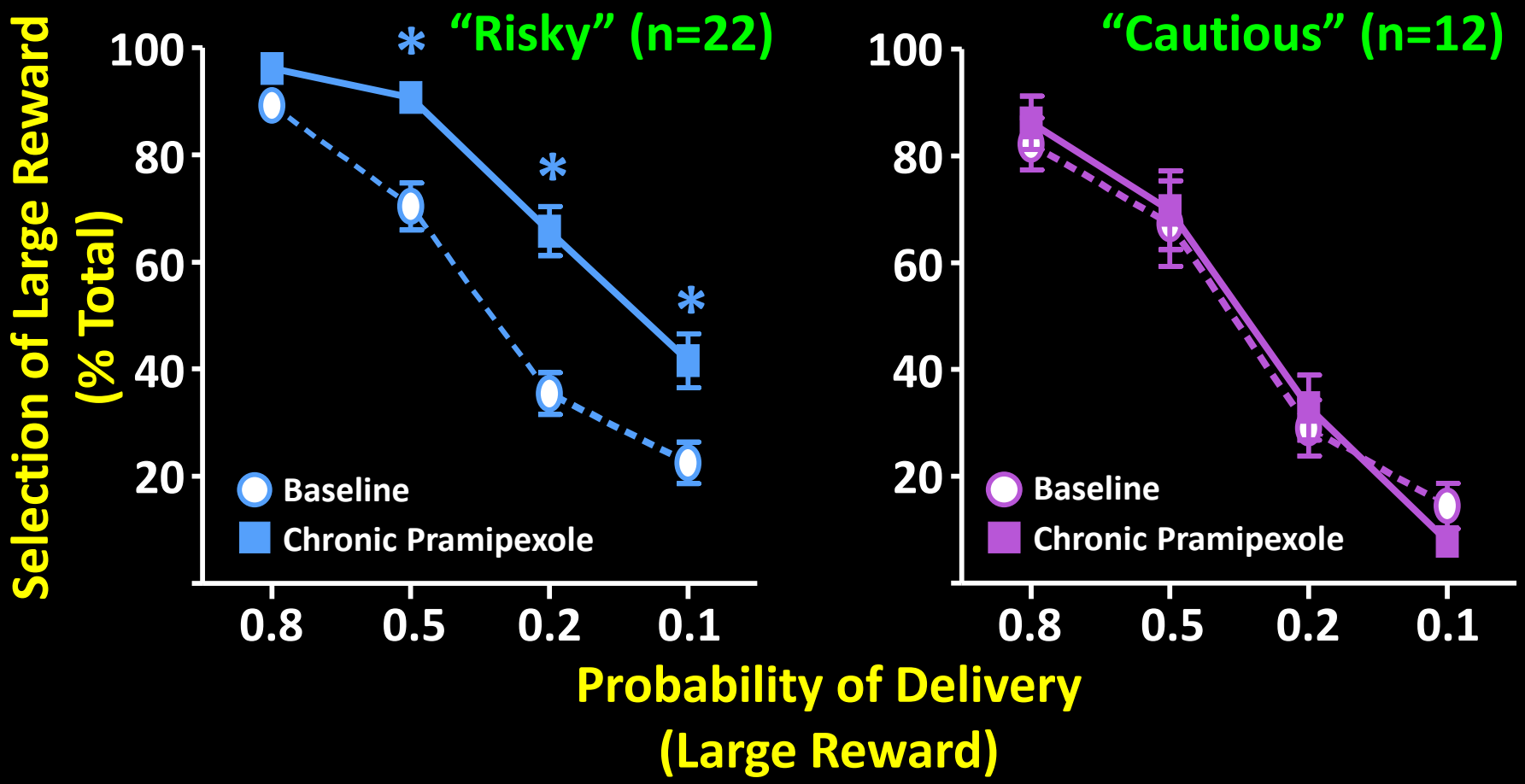


Rokosik & Napier. Neuropsychopharmacology, 2012

Addictions are the Quintessential Bio-Behavioral Disorders

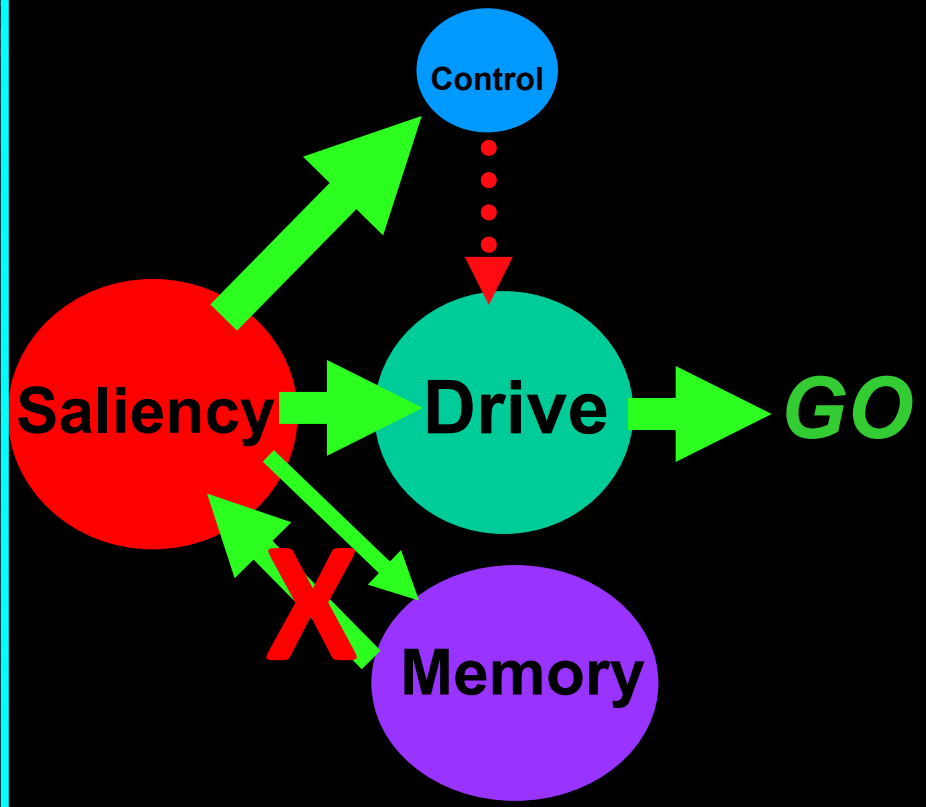


Pramipexole-Induced Risk-Taking: High and Low Responders



Holtz et al. Prog Neuropsychopharmacology Biol Psychiatry. 2016.

addiction changes brain circuits that govern decisions



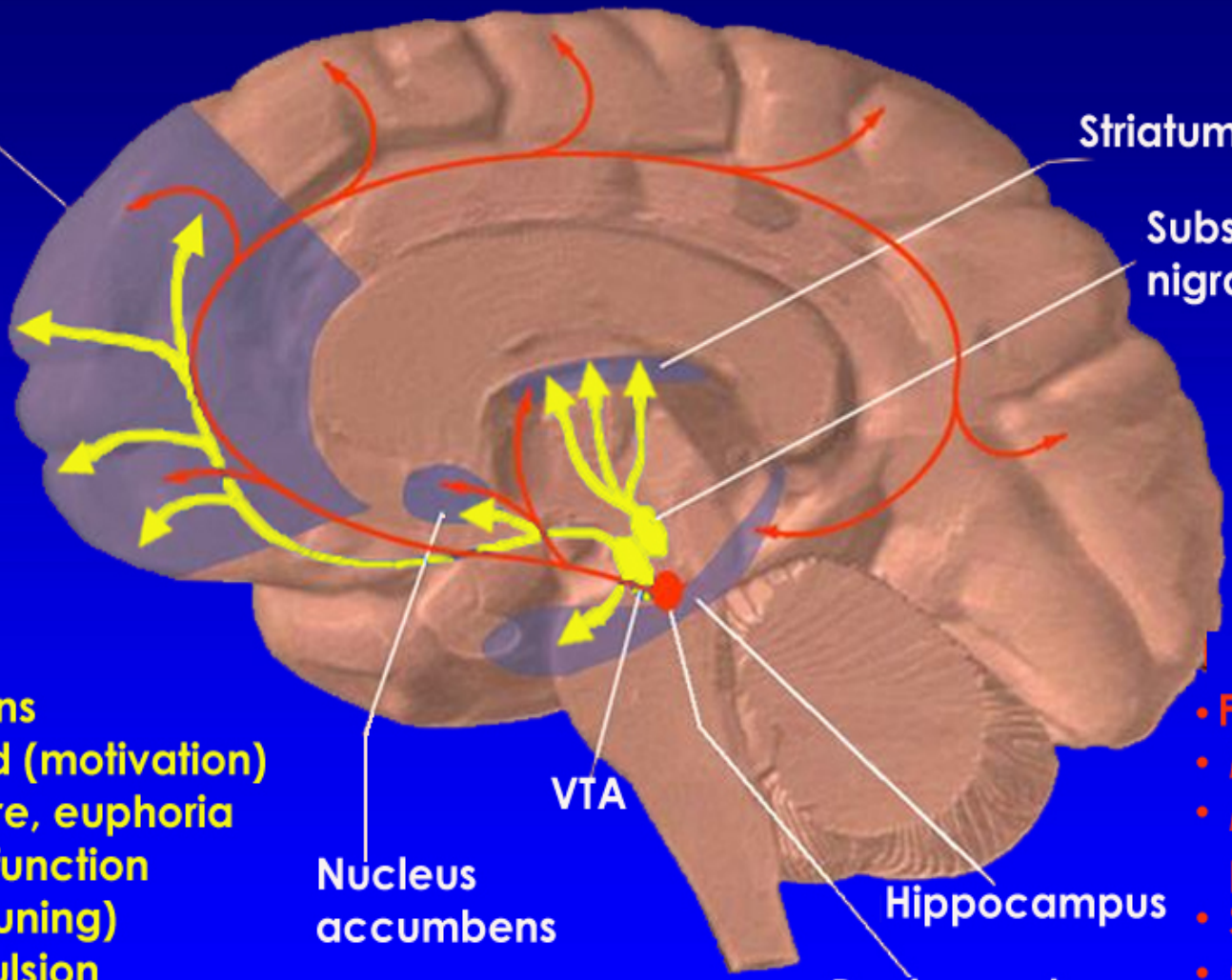
NEUROTRANSMITTERS IN GAMBLING

neurotransmitter	study modality	role
norepinephrine	CSF, blood, urine, drug, fMRI	arousal, excitement
serotonin	CSF, blood, drug, PET, randomized clinical trial	impulse control cognition, memory
dopamine	CSF, blood, urine, drug, PET	reward processing, reward-based learning reinforcement
opioid	randomized clinical trial	pleasure, urges
cortisol	blood	stress
glutamate	randomized clinical trial	compulsiveness, cognitive inflexibility

modified from Potenza MN. *Curr Opin Neurobiol*. 2013

Dopamine Pathways

Serotonin Pathways



Functions

- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine-tuning)
- Compulsion
- Perseveration

- Functions
- Mood
- Memory processing
- Sleep
- Cognition

NIDA

MIRTAZAPINE (REMERON®)

Available online at www.sciencedirect.com
ScienceDirect
Drug and Alcohol Dependence 86 (2007) 55–66
DRUG and ALCOHOL DEPENDENCE
www.elsevier.com/locate/drugalcdep

Nullifying drug-induced sensitization: Behavioral and electrophysiological evaluations of dopaminergic and serotonergic ligands in methamphetamine-sensitized rats

J. McDaid[a,1], C.E. Tedford[b], A.R. Mackie[a], J.E. Dallimore[a], A.L. Mickiewicz[a], F. Shen[a,c], J.M. Angle[b], T.C. Napier[a,c,*]

Available online at www.sciencedirect.com
ScienceDirect
Drug and Alcohol Dependence 99 (2009) 231–239

Mirtazapine treatment after conditioning with methamphetamine alters subsequent expression of place preference

Amy A. Herrold[a,c,d,*,1], Fei Shen[a,c,d,1], Martin P. Graham[c,d], Laura K. Harper[b], Sheila E. Specio[c,d], Clark E. Tedford[d,e], T. Celeste Napier[c,d]

Available online at www.sciencedirect.com
SciVerse ScienceDirect
www.elsevier.com/locate/brainres

Research Report

The atypical antidepressant mirtazapine attenuates expression of morphine-induced place preference and motor sensitization

Steven M. Graves, Amanda L. Persons[1], Jennifer L. Riddle, T. Celeste Napier*

Contents lists available at ScienceDirect
Behavioural Brain Research
journal homepage: www.elsevier.com/locate/bbr

Research report

Repeated mirtazapine nullifies the maintenance of previously established methamphetamine-induced conditioned place preference in rats

Robin M. Voigt[a,b,*], Amanda L. Mickiewicz[a,b,1], T. Celeste Napier[b]

frontiers in BEHAVIORAL NEUROSCIENCE
ORIGINAL RESEARCH ARTICLE
published: 13 January 2012
doi: 10.3389/fnbeh.2011.00092

Context-dependent effects of a single administration of mirtazapine on the expression of methamphetamine-induced conditioned place preference

Robin M. Voigt[1,2†] and T. Celeste Napier[1]*

KETANSERIN (SUFREXAL®)

Available online at www.sciencedirect.com
ScienceDirect
Drug and Alcohol Dependence 86 (2007) 55–66
DRUG and ALCOHOL DEPENDENCE
www.elsevier.com/locate/drugalcdep

Nullifying drug-induced sensitization: Behavioral and electrophysiological evaluations of dopaminergic and serotonergic ligands in methamphetamine-sensitized rats

J. McDaid[a,1], C.E. Tedford[b], A.R. Mackie[a], J.E. Dallimore[a], A.L. Mickiewicz[a], F. Shen[a,c], J.M. Angle[b], T.C. Napier[a,c,*]

Opposing effects of 5-HT_{2A} and 5-HT_{2C} receptor antagonists in the rat and mouse on premature responding in the five-choice serial reaction time test

Paul J. Fletcher · Maria Tampakeras · Judy Sinyard · Guy A. Higgins

A comparison of multiple 5-HT receptors in two tasks measuring impulsivity

John C. Talpos *Department of Experimental Psychology, University of Cambridge, Cambridge, CB2 3EB, UK.*
Lawrence S. Wilkinson *Laboratory of Cognitive and Behavioural Neuroscience, Babraham Institute, Cambridge, CB2 4AT, UK.*
Trevor W. Robbins *Department of Experimental Psychology, University of Cambridge, Cambridge, CB2 3EB, UK.*

Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg

Serotonin 2A receptors contribute to the regulation of risk-averse decisions

Julian Macoveanu[a,b,*], James B Rowe[b,c], Bettina Hornboll[a,b], Rebecca Elliott[d], Olaf B Paulson[a], Gitte M Knudsen[b,e], Hartwig R Siebner[a,b]

HYPOTHESIS

Treatment with mirtazapine or ketanserin will reduce aspects of gambling-like behavior in rodents

Cost/Benefit Decision-Making

money → reward ← ICSS

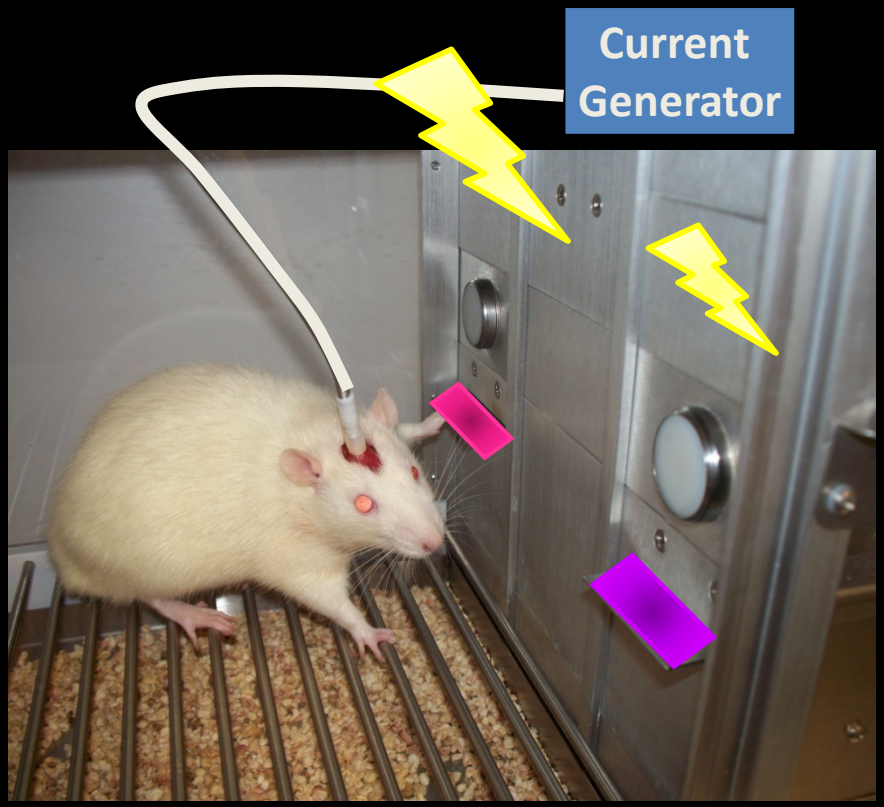
$1 — more likely

$1000 — less likely

small reward — low effort?

LARGE reward — high effort?

Cost/Benefit Decision-Making



Fixed Ratio

small reward (50-60Hz) "low effort" lever FR-3

Variable Ratio

LARGE reward (100Hz) "high effort" lever

VR-6 = 1, 3, 6, 9, 11

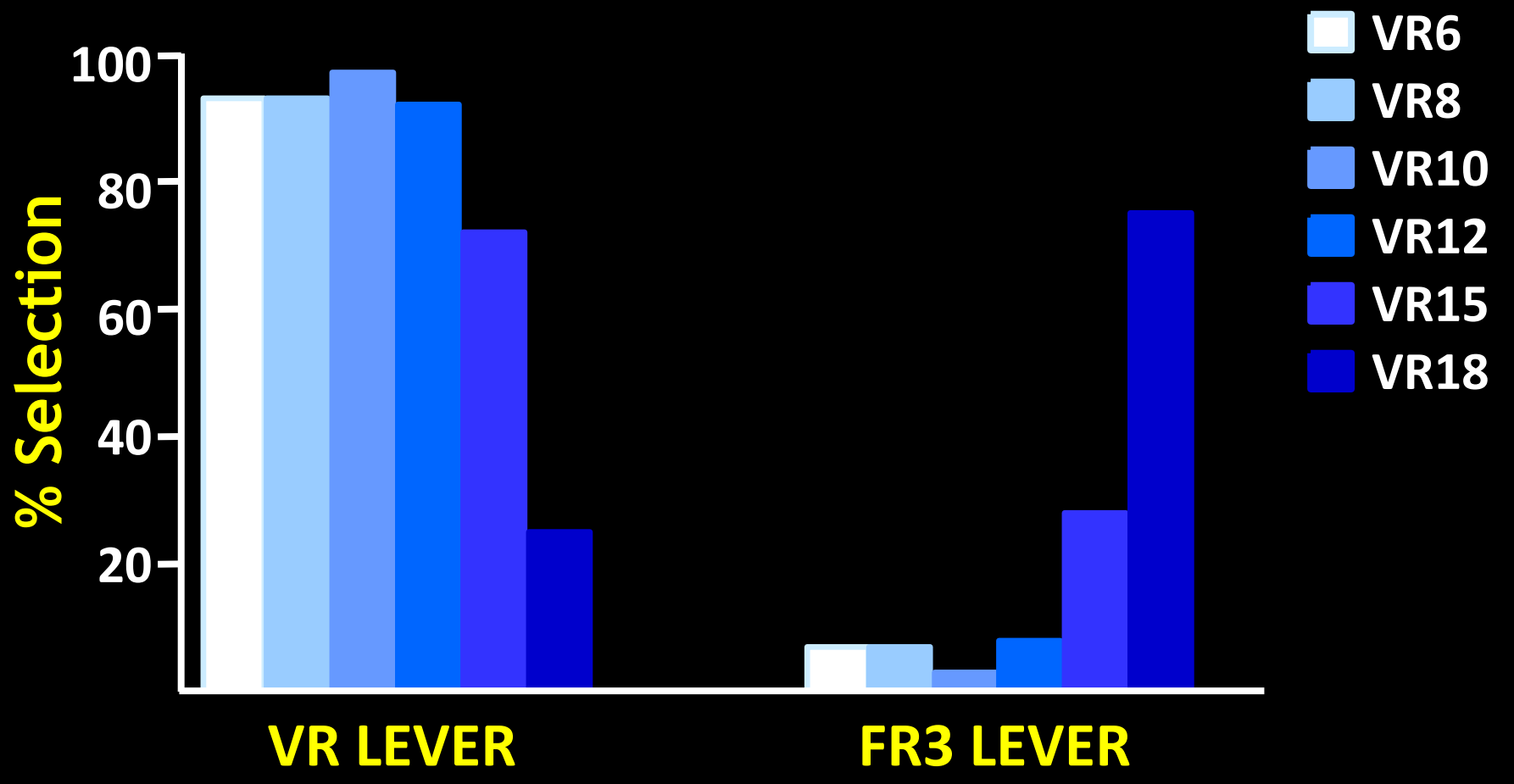
VR-8 = 1, 3, 8, 13, 15

VR-10 = 1, 5, 10, 15, 19

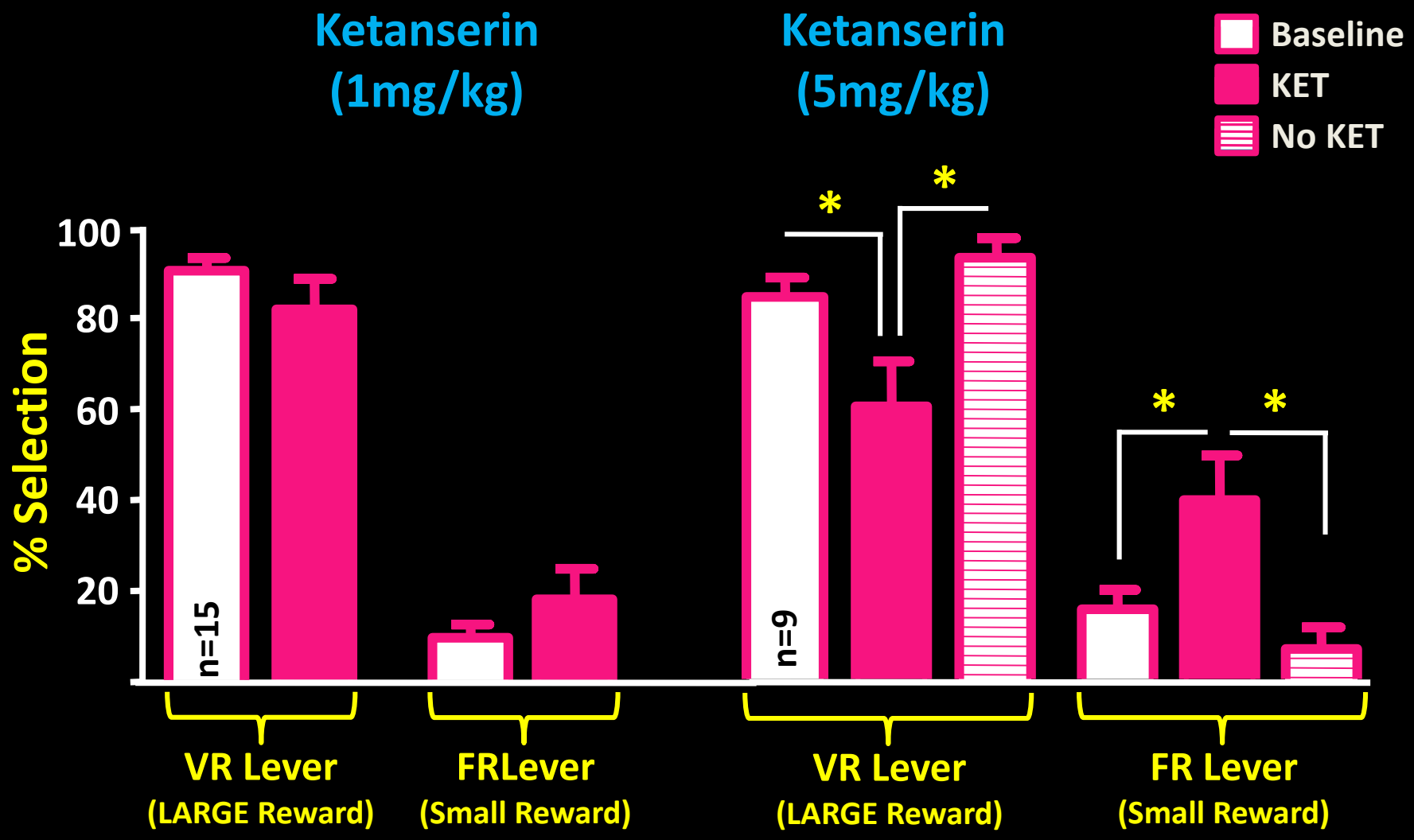
VR-12 = 1, 6, 12, 18, 23

VR-15 = 1, 8, 15, 23, 30

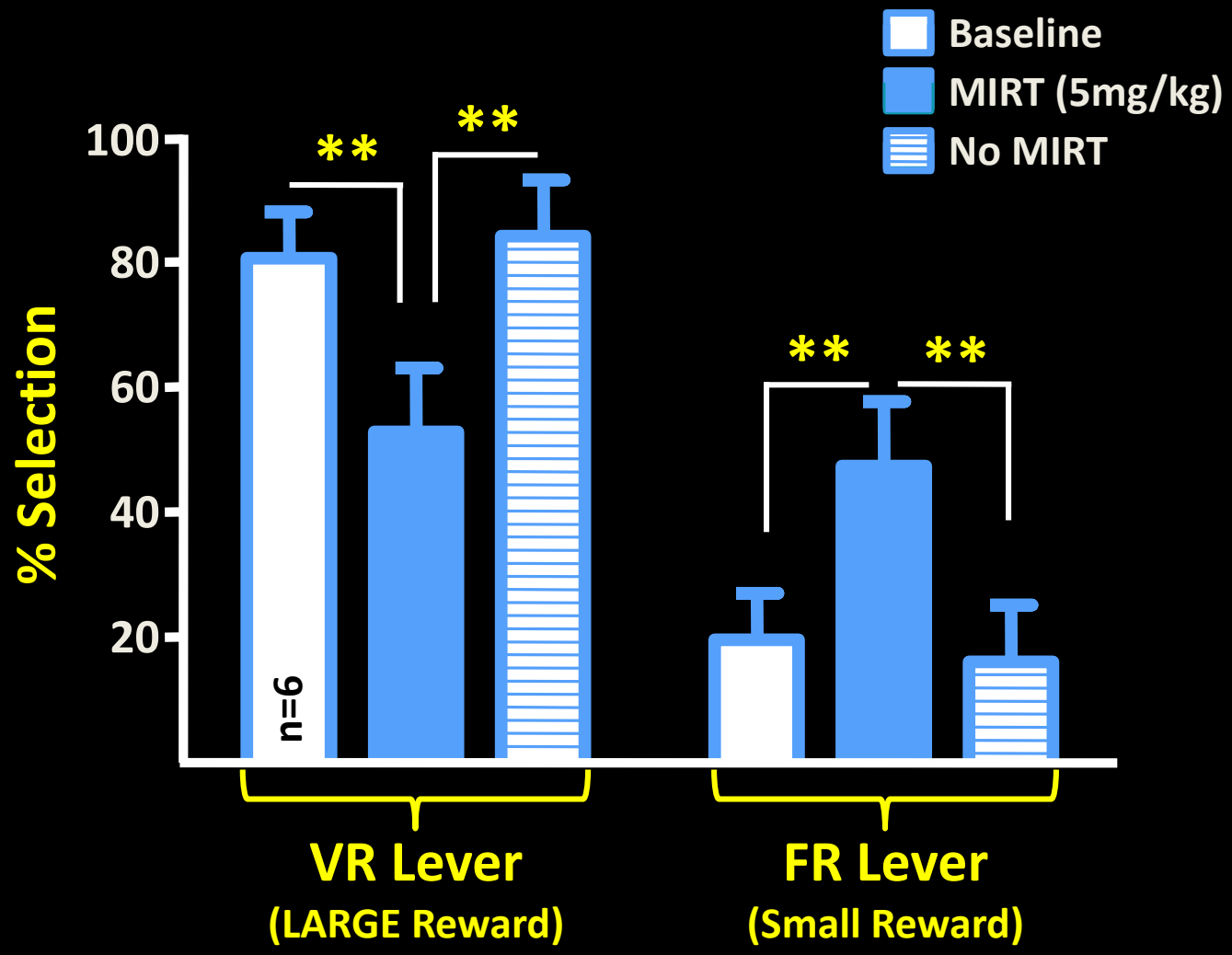
Cost/Benefit Task



Cost/Benefit Task: *Effects of Ketanserin*



Cost/Benefit Task: *Effects of Mirtazapine*



Summary and Conclusion

Rats will expend considerable effort to obtain the LARGE reward (i.e., VR-15; up to 30 lever presses).

Pretreatment with ketanserin or mirtazapine reduced behavioral readouts of risk-taking.

Thus, ketanserin and mirtazapine may be useful in reducing gambling-like behavior in humans that suffer from problem gambling.

ACKNOWLEDGEMENTS

Amanda L. Persons, PhD
Nathan Holtz, PhD

The Napier Lab:
Brinda Bradaric, PhD
Lihua Chen, PhD
Sandie Rokosik, PhD
Steve Graves, PhD
Stephanie Tedford, PhD
Wesley Wayman, PhD
Salvatore Grasso, BS

Financial Support:

NCRG
NATIONAL CENTER FOR RESPONSIBLE GAMING
Advancing Research, Education and Awareness

NIH National Institute on Drug Abuse
The Science of Drug Abuse & Addiction
NIH National Institute of Neurological Disorders and Stroke

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

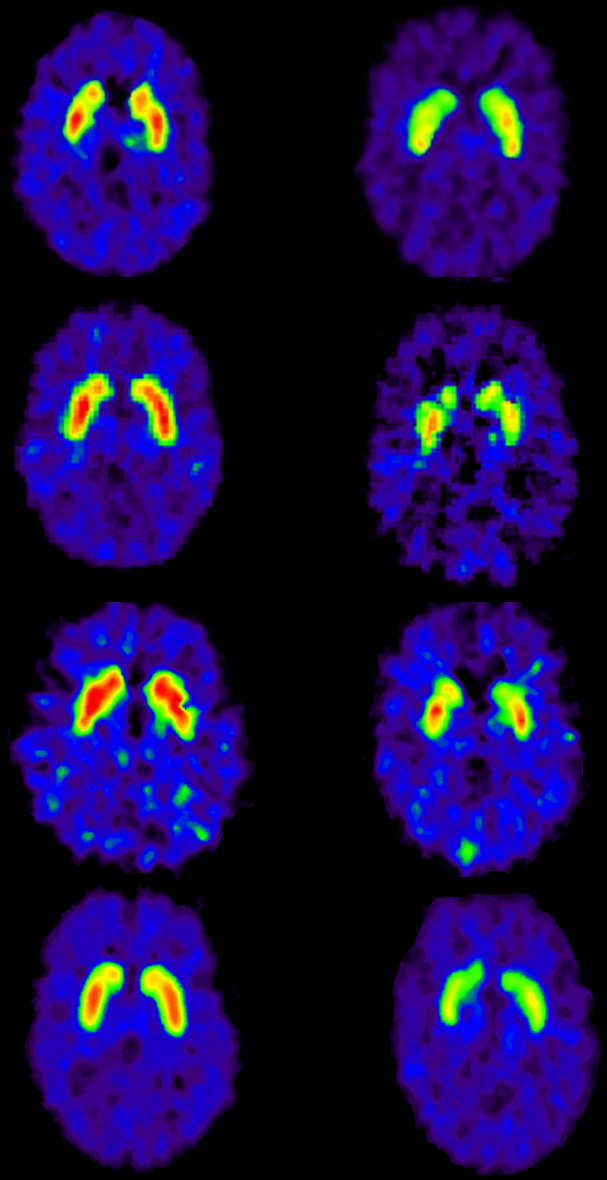
dopamine receptors are lower in addiction

Cocaine

Meth

Alcohol

Heroin

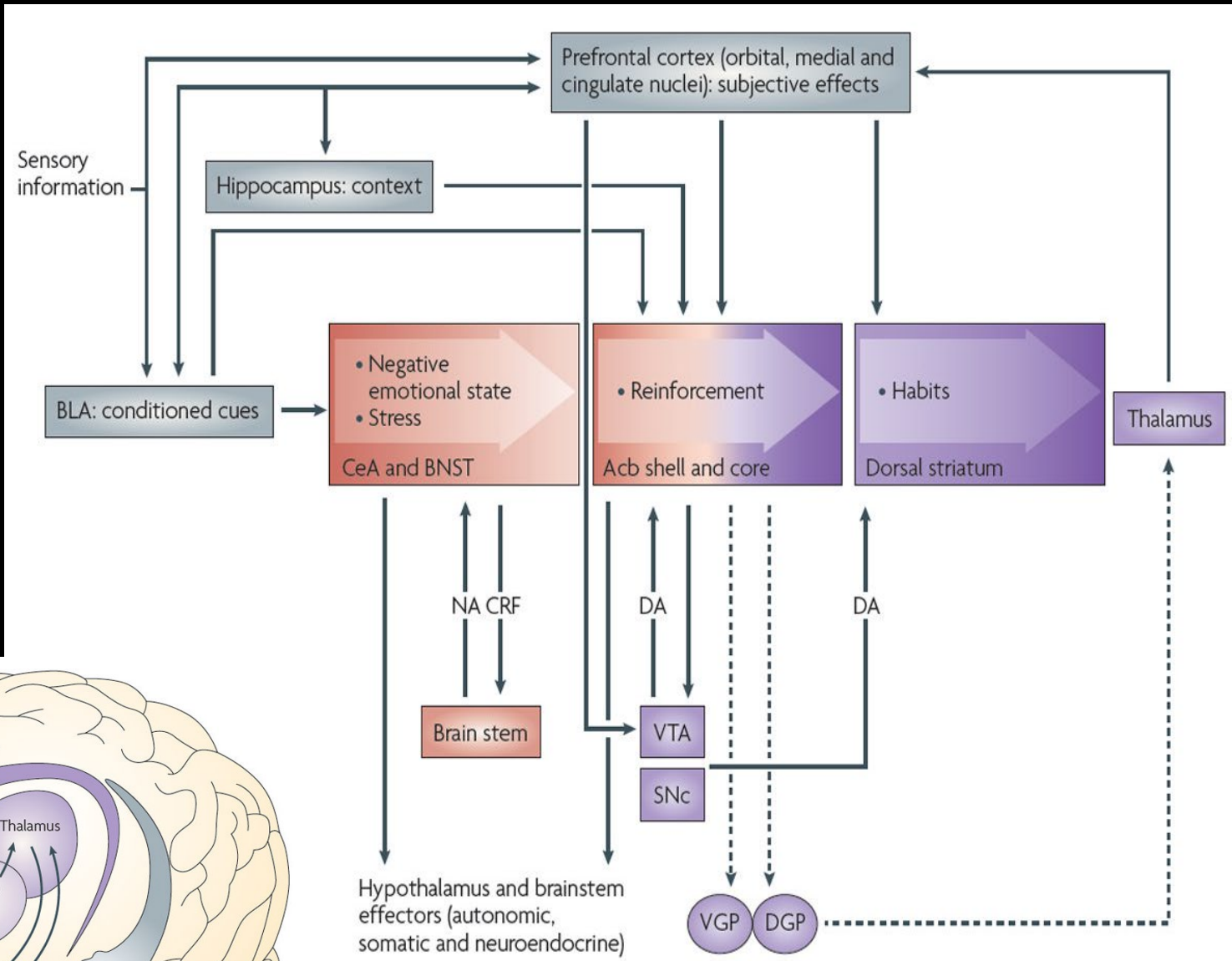


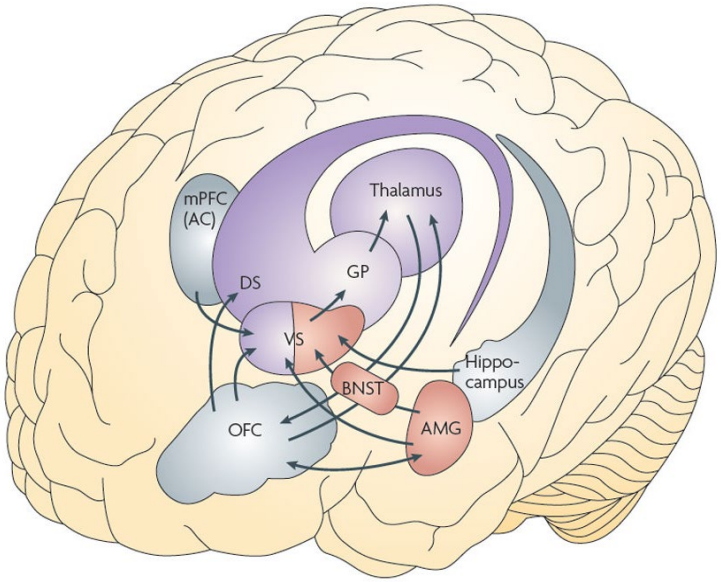
Control

Addicted

DA D2 Receptor Availability

Koob et al.,
Nat Rev Drug Discov.
8:500–515,2009.





Developing brain
Vulnerable brain