Drug addiction

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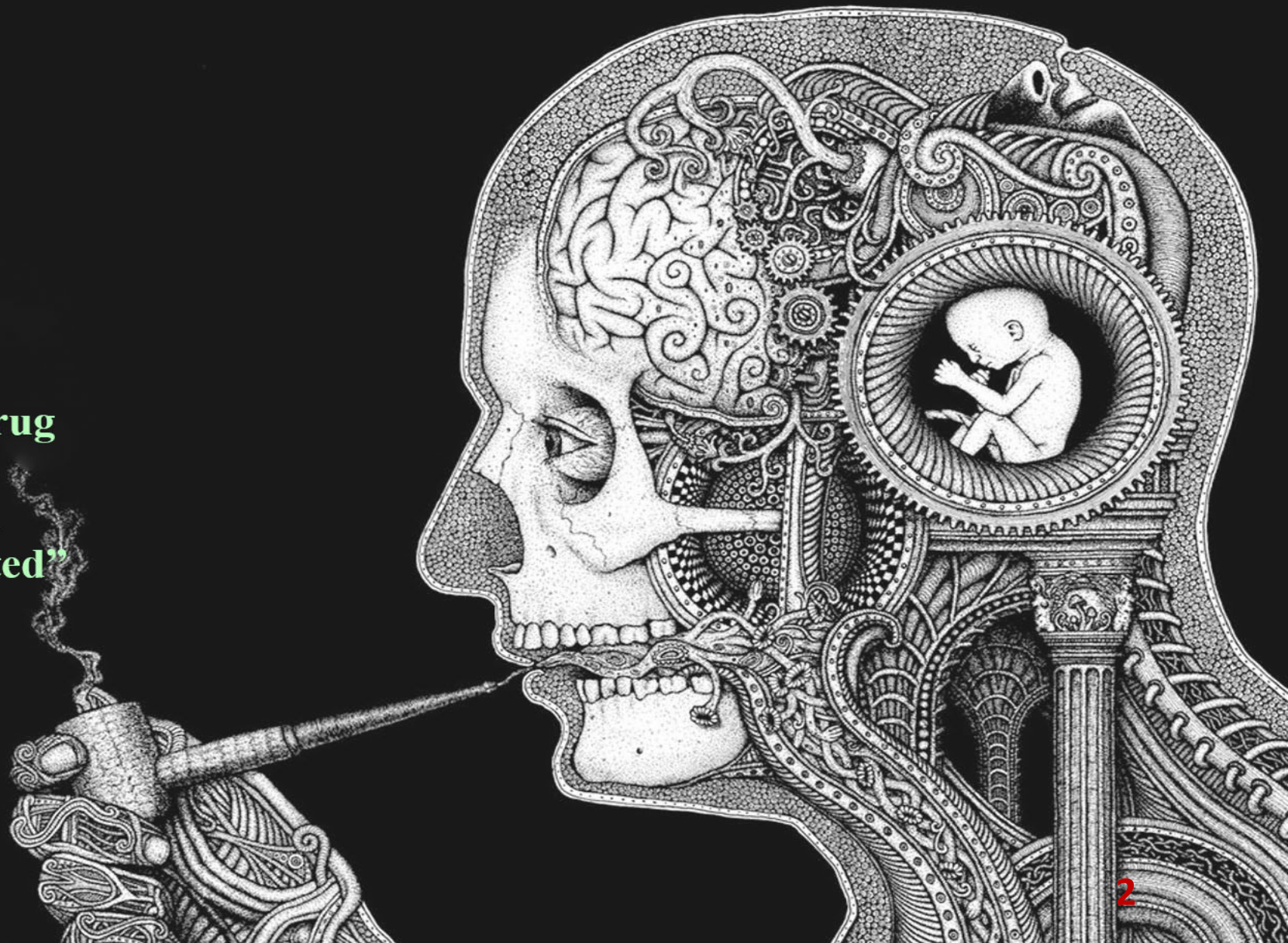
What is Addiction?
AS a Disease

.Biological view

Craving
Dependence
Withdrawal

.Psychological view

.Compulsion to seek and take the drug
.Loss of control in limiting intake
.Emergence of a negative emotional state when access to drug is prevented”




Kinds of addiction
SEX
ADDICTION

Factors initiated Drug Abuse

.Reward & Pleasure

.Diseases (Pain, Depression, Anxiety &….)

.Genetic

REWARD

A response to a stimulus

.Serotonergic

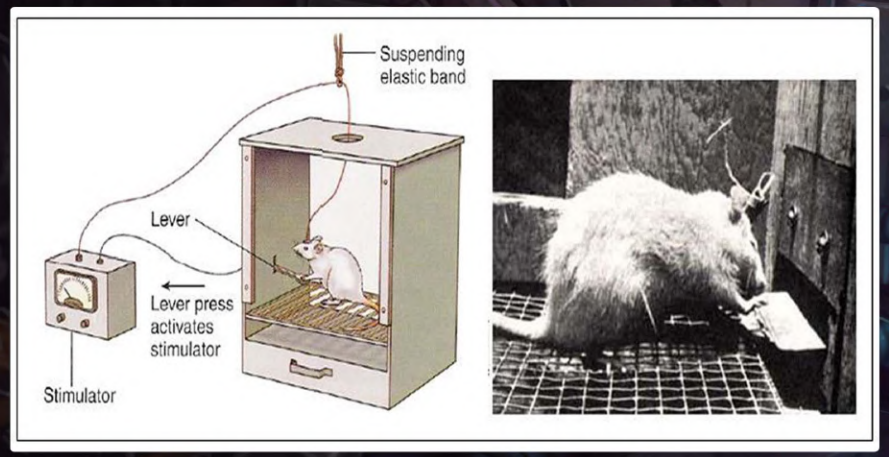
.Glutamatergic

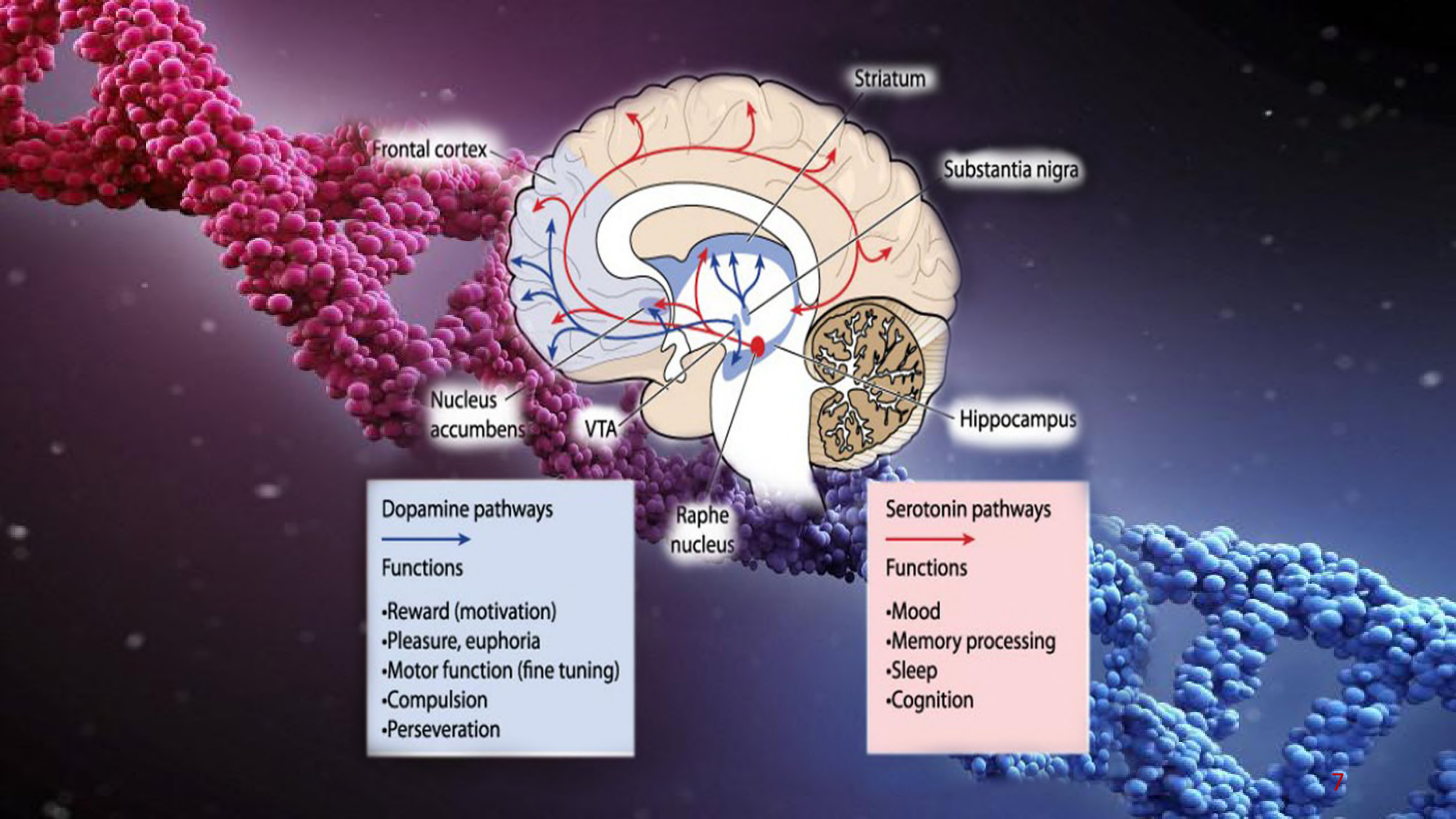
.Enkephalins

.Dopaminergic

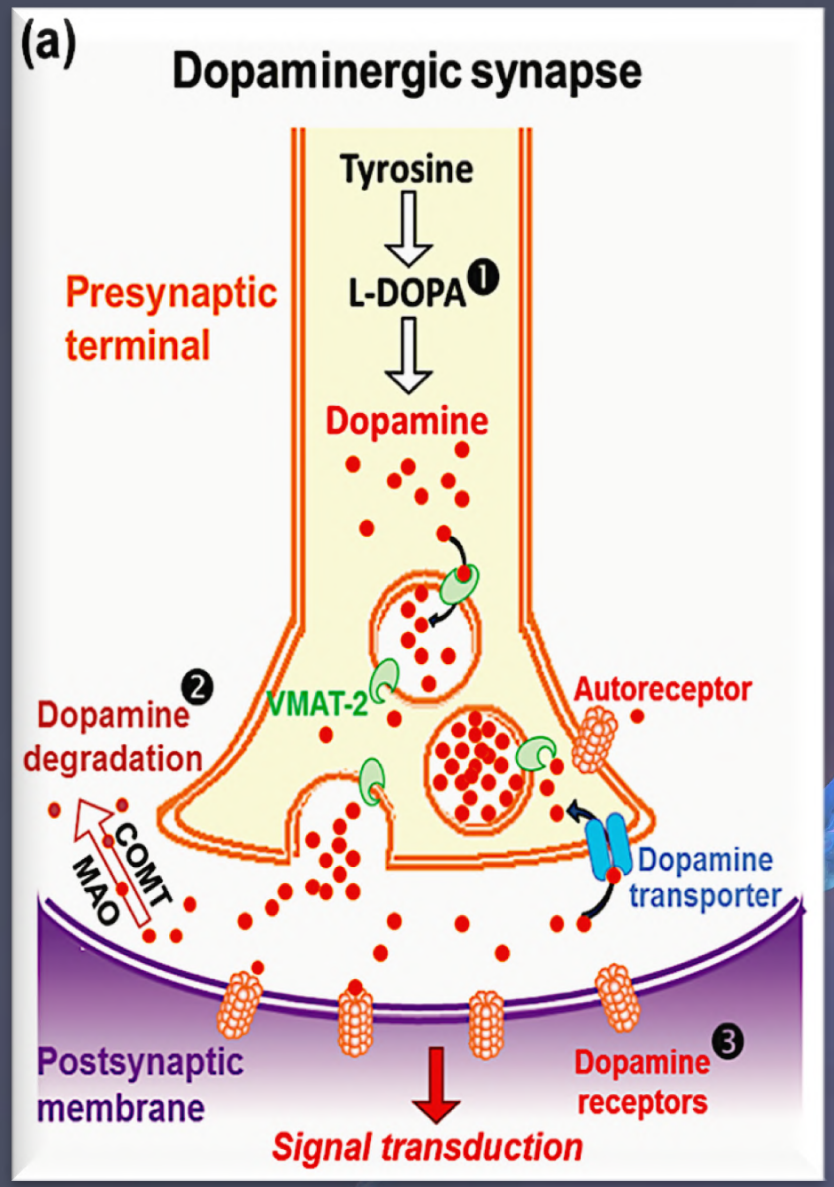
- .Mesolimbic pathway
- .Mesocortical pathway
- .Nigrostriatal pathway

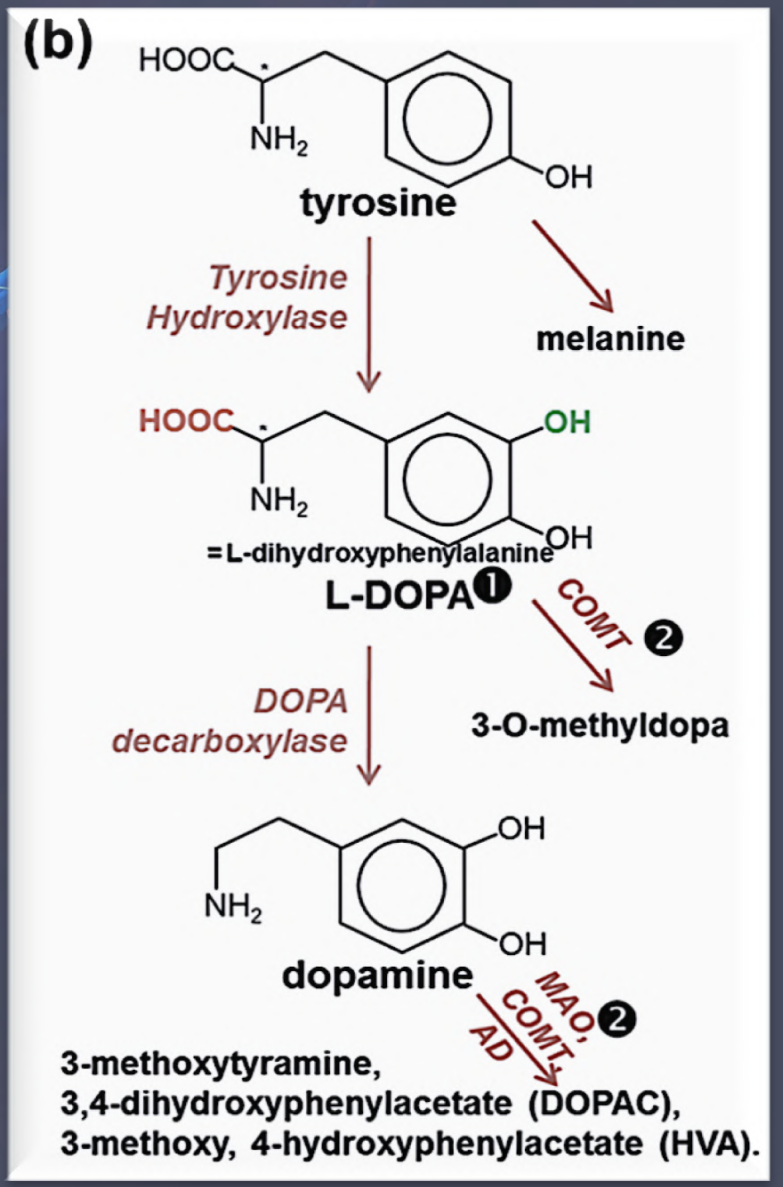
James olds

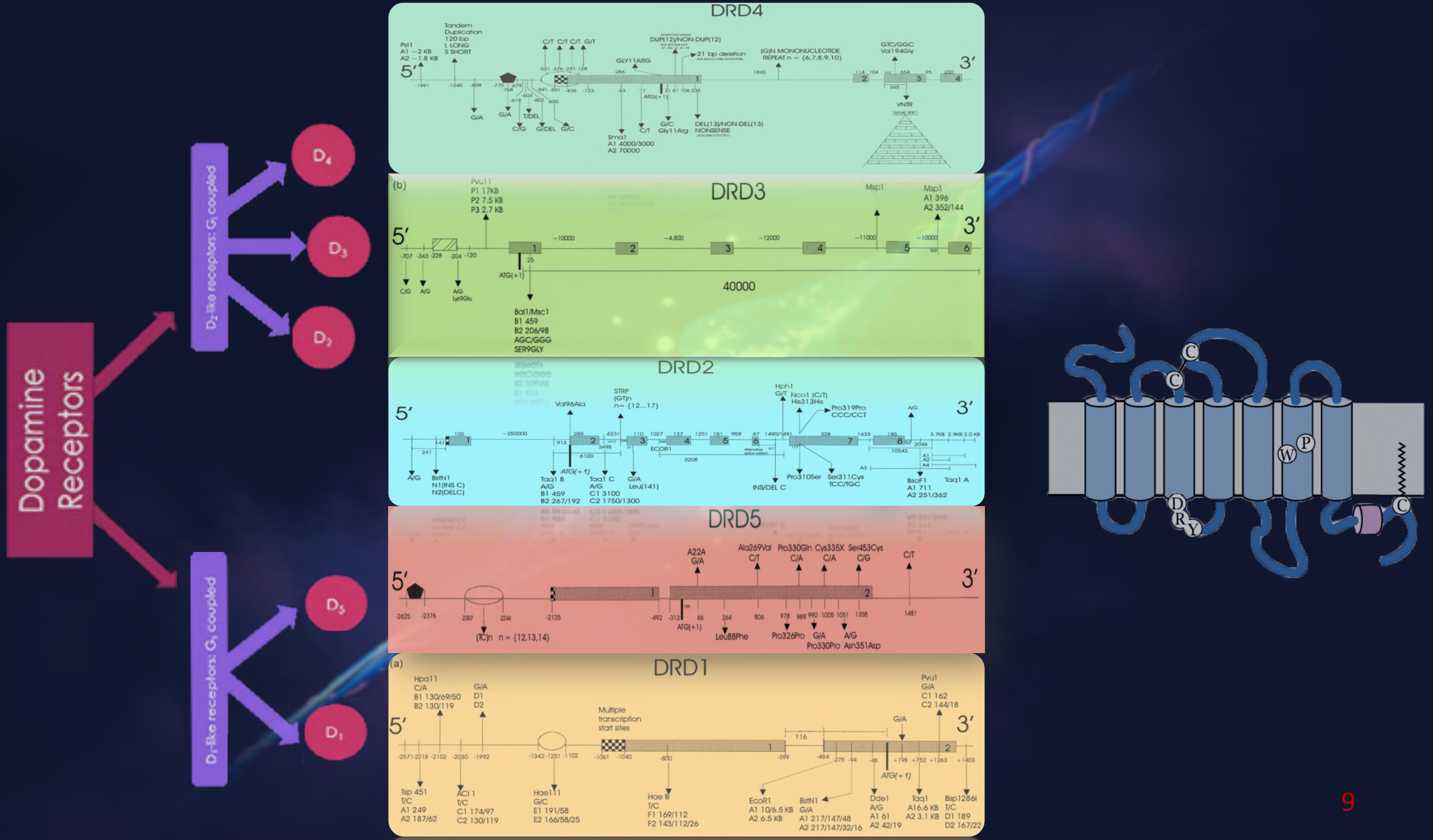

Suspending elastic band
Lever
Lever press activates stimulator
Stimulator


Striatum
Frontal cortex
Substantia nigra
Nucleus accumbens
VTA
Hippocampus
Raphe nucleus
Dopamine pathways
Functions
•Reward (motivation)
•Pleasure, euphoria
•Motor function (fine tuning)
•Compulsion
•Perseveration
Serotonin pathways
Functions
•Mood
•Memory processing
•Sleep
•Cognition

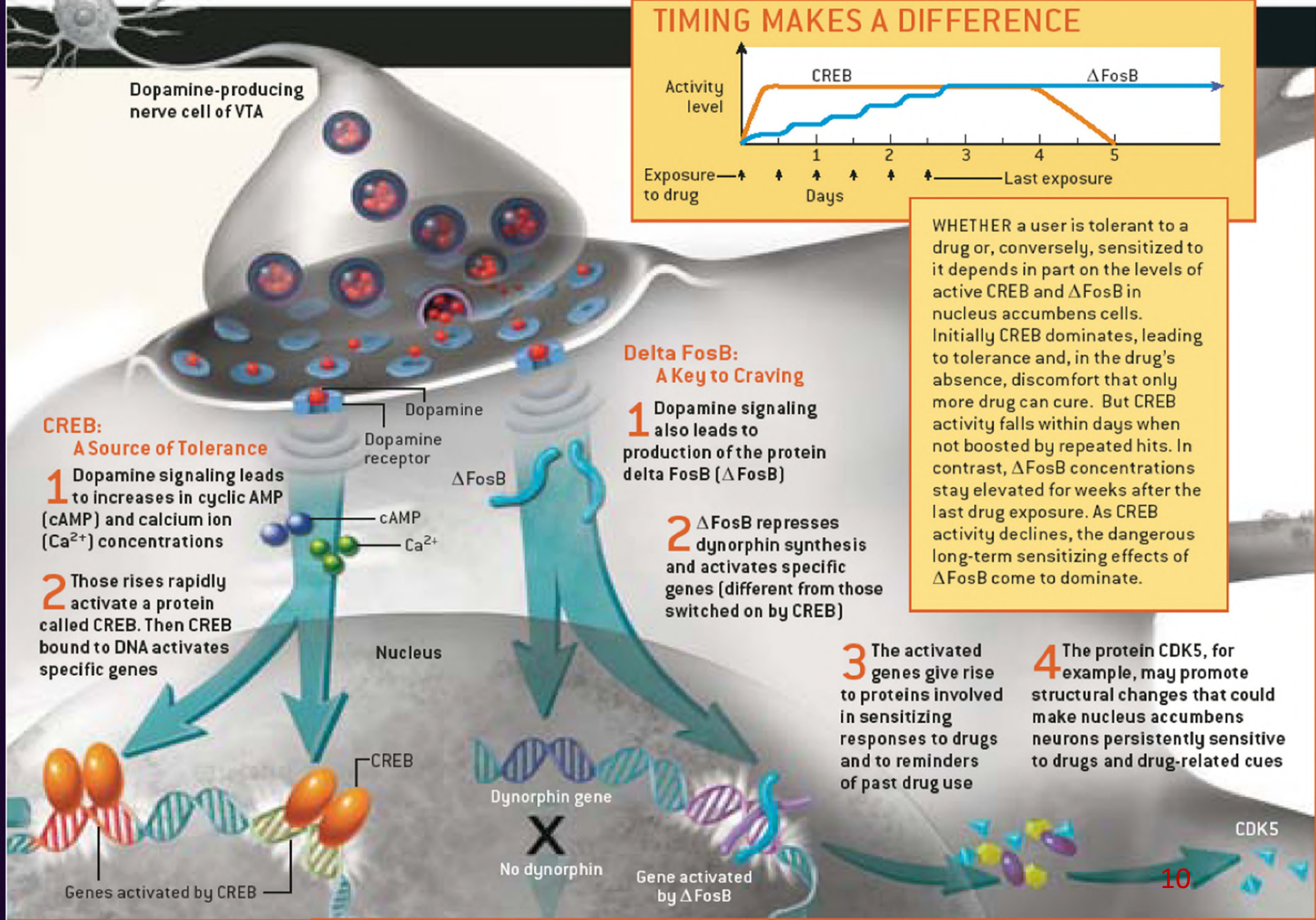
Dopamine


(a)
Dopaminergic synapse
Tyrosine
L-DOPA ❶
Dopamine
Presynaptic terminal
Dopamine ❷ degradation
VMAT-2
Autoreceptor
COMT
MAO
Dopamine transporter
Postsynaptic membrane
Dopamine ❸ receptors
Signal transduction

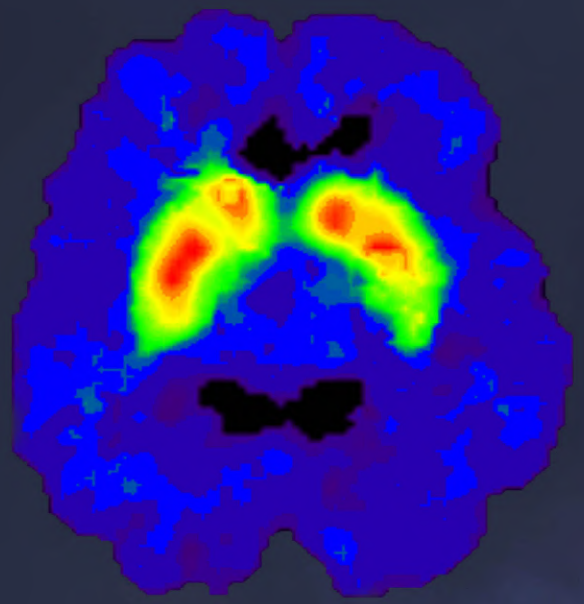

(b)
HOOC
NH2
OH
tyrosine
Tyrosine Hydroxylase
melanine
HOOC
NH2
OH
OH
=L-dihydroxyphenylalanine
L-DOPA ❶
COMT ❷
3-O-methyldopa
DOPA decarboxylase
NH2
OH
OH
dopamine
MAO, COMT, AD ❷
3-methoxytyramine,
3,4-dihydroxyphenylacetate (DOPAC),
3-methoxy, 4-hydroxyphenylacetate (HVA).


Dopamine Receptors
D2-like receptors: Gi coupled
D4
D3
D2
D1-like receptors: Gs coupled
D5
D1
DRD4
Tandem Duplication 120 bp L LONG S SHORT
Pst1 A1 ~2 KB A2 ~1.8 KB
5′
3′
C/T C/T C/T G/T
DUP(12)/NON-DUP(12)
21 bp deletion
GLY11ARG
(G)N MONONUCLEOTIDE REPEAT n = {6,7,8,9,10}
GTC/GGC Val194Gly
VNTR
ATG(+1)
G/A
T/DEL
C/G
G/DEL
G/C
Sma1 A1 4000/3000 A2 70000
C/T
G/C Gly11Arg
DEL(13)/NON-DEL(13) NONSENSE
DRD3
(b)
Pvu11 P1 17KB P2 7.5 KB P3 2.7 KB
Msp1
Msp1 A1 396 A2 352/144
40000
C/G
A/G
A/G Lys9Glu
Bal1/Msc1 B1 459 B2 206/98 AGC/GGG SER9GLY
DRD2
Val96Ala
STRP (GT)n n= {12...17}
Hph1 G/T
Nco1 (C/T) His313His
Pro319Pro CCC/CCT
ECOR1
A/G
BstN1 N1(INS C) N2(DELC)
Taq1 B A/G B1 459 B2 267/192
Taq1 C A/G C1 3100 C2 1750/1300
G/A Leu(141)
INS/DEL C
Pro310Ser
Ser311Cys TCC/TGC
BsoF1 A1 711 A2 251/362
Taq1 A
DRD5
A22A G/A
Ala269Val C/T
Pro330Gln C/A
Cys335X C/A
Ser453Cys C/G
C/T
(TC)n n = {12,13,14}
Leu88Phe
Pro326Pro
G/A Pro330Pro
A/G Asn351Asp
DRD1
(a)
Hpa11 C/A B1 130/69/50 B2 130/119
G/A D1 D2
Multiple transcription start sites
Pvu1 G/A C1 162 C2 144/18
Tsp 451 T/C A1 249 A2 187/62
ACI 1 T/C C1 174/97 C2 130/119
Hae111 G/C E1 191/58 E2 166/58/25
Hae III T/C F1 169/112 F2 143/112/26
EcoR1 A1 10/6.5 KB A2 6.5 KB
BstN1 G/A A1 217/147/48 A2 217/147/32/16
Dde1 A/G A1 61 A2 42/19
Taq1 A16.6 KB A2 3.1 KB
Bsp1286I T/C D1 189 D2 167/22
C
C
W
P
D
R
Y
C

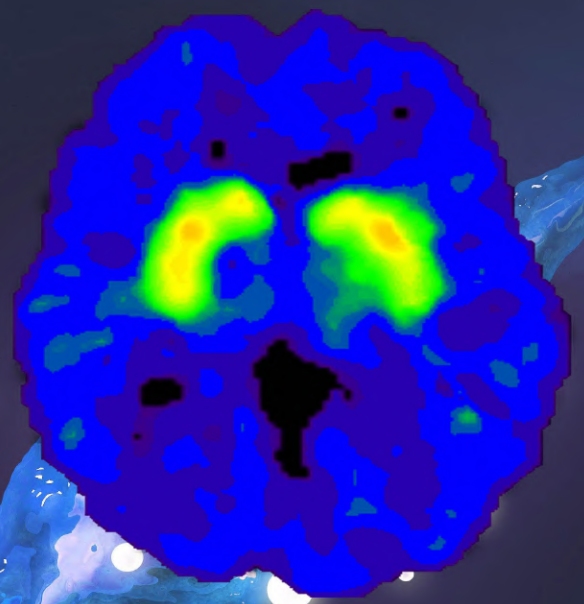
Transcription Factors



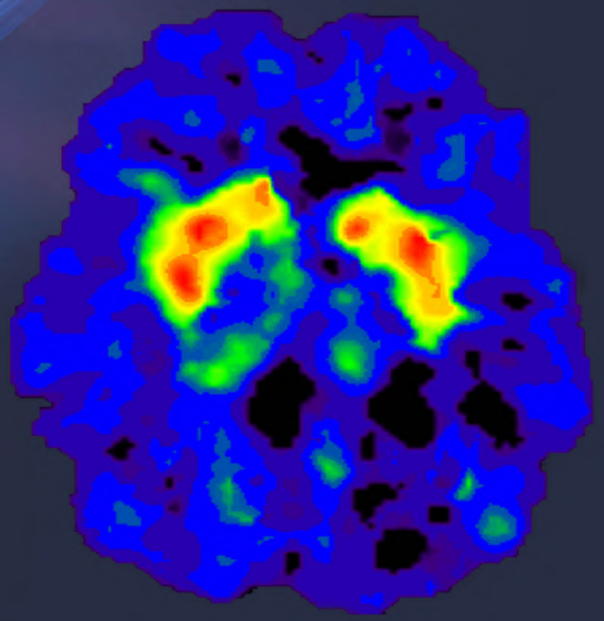
Why is Continued Treatment Critical?



Normal Control

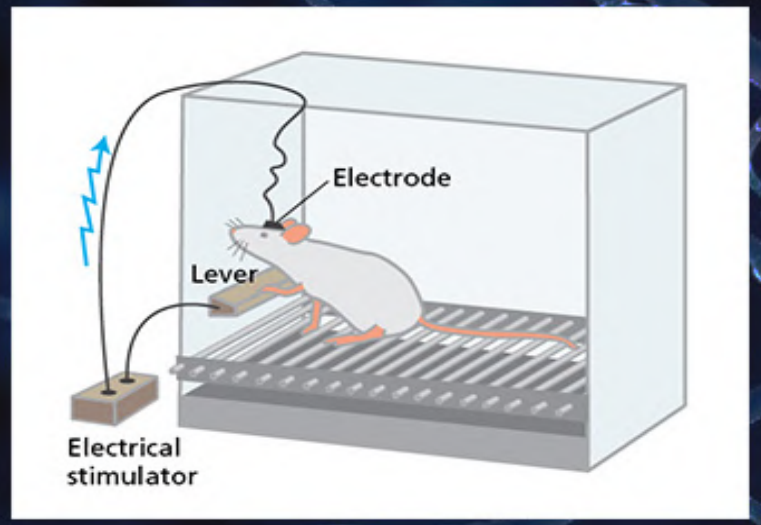


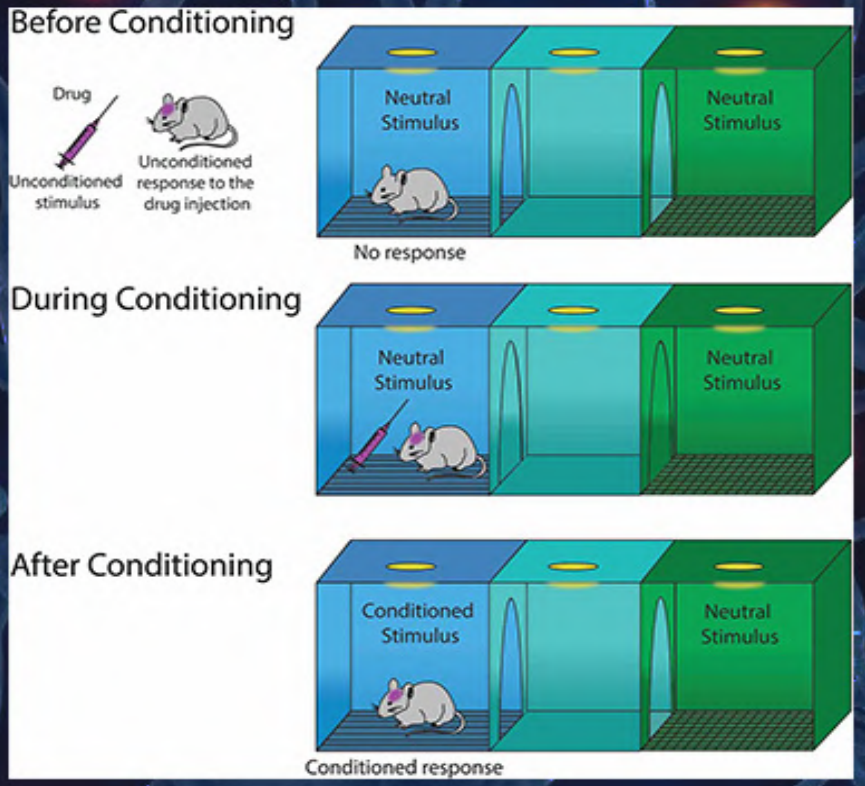
Meth user
(1 month abstinent)



Meth user
(14 months abstinent)

Animal Models (Based on Conditioning)



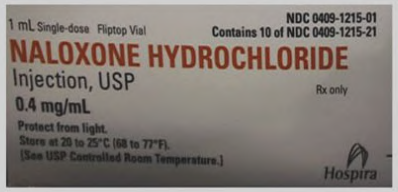


Intracranial Self-stimulation

Conditioning Place Preference

Drug Self-administration

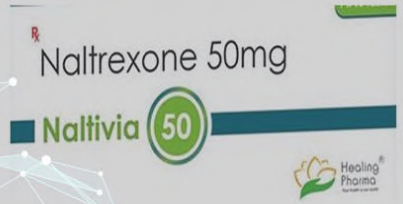
Treatment



opioid antagonist

treat alcohol use disorder

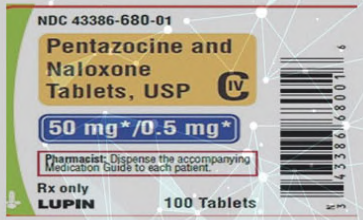
treatment of opiate addiction



Naltrexone

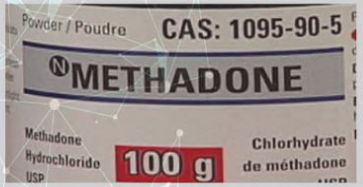
buprenorphine+naloxone

Researching



opioid pain medication

support smoking cessation



a synthetic opioid agonist

treatment of Opiate Withdrawal

IBOGAINE

Researching

BP-897

Researching

Vanoxerine

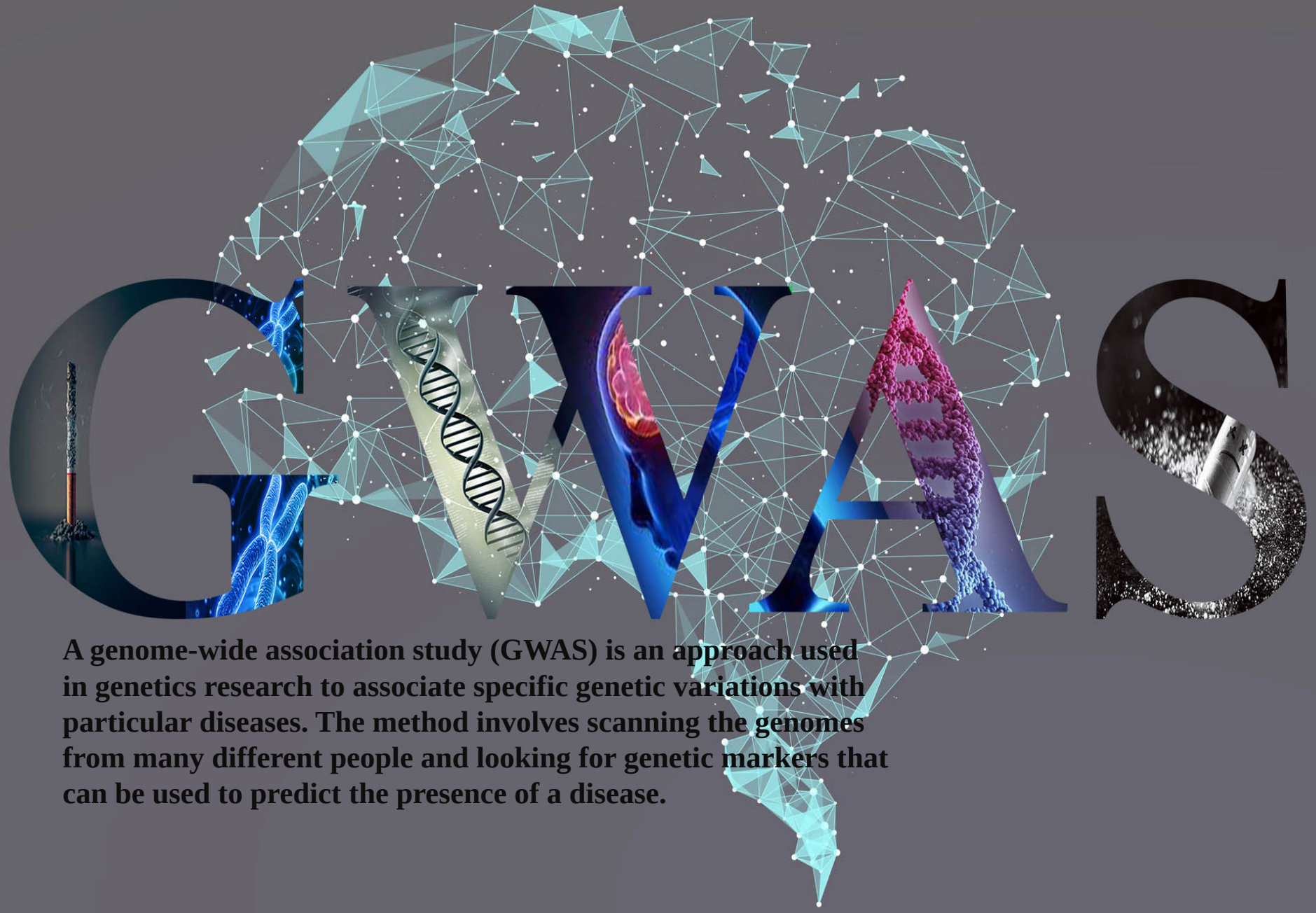
Researching

Monoclonal Antibodies

acts to “reduce the high” or the reward that a recovering addict may experience

	Gene Receptor	Description
Knockout	DAT/SERT	Conditioned place preference to cocaine is blocked
	mGluR5	Mice do not self-administer cocaine
	Alpha 1b adrenergic	Oral self-administration of cocaine and morphine decreased
	Substance P	Rewarding effects of opiates but not cocaine are absent
	Cannabinoid CB1	Self-administer cocaine but not morphine
deletion	Muscarinic M5	Mice show no preference for opioids

	Gene	Description
Mice	MPDZ increased expression	experience less severe withdrawal symptoms from sedative-hypnotic drugs such as barbiturates
	CNR1 without	less responsive to morphine
	HTR1B lacking	more attracted to cocaine and alcohol
	Lack of β2 subunit of nicotinic cholinergic receptors	reduced reward response to cocaine
	low levels of neuropeptide Y	drink more alcohol, whereas those with higher levels tend to abstain
	mutated defective PER2	drink three times more alcohol than normal
	CREB lacking	less likely to develop morphine dependence
Fruit flies mutated	unable to synthesize tyramine remain sedate even after repeated doses of cocaine	



A genome-wide association study (GWAS) is an approach used in genetics research to associate specific genetic variations with particular diseases. The method involves scanning the genomes from many different people and looking for genetic markers that can be used to predict the presence of a disease.

Ethanol	ALDH2 Glu504Lys (rs671)	decrease alcohol use
	ADH1B Arg48His (rs1229984)	slightly higher concentrations of acetaldehyde à deter alcohol use
	GABRA2 (rs279858, rs279826, rs279871)	SNPs are not functional but a2 subunit expression has been associated with binge drinking
	DRD2/ANKK1(Taq1A,rs1800497)	risk factor for alcoholism
	ADH1C (rs1693482 & rs698)	common in non-Asian population
	SLC6A4	serotonin transporter gene

Nicotine	CHRNA5/A3/B4 (rs16969968(Asp398Asn) /rs1051780)	in chromosome 15 association with cigarettes/ day
	CHRNB3-CHRNA6 (rs6474412)	-
	CYP2A6 (rs1801272)	protective allele
	CHRNA4	maximum cigarettes smoked in a 24-h period
	DRD2/ANKK1 Taq1A allele(Glu713Lys)	smoking initiation and current smoking but not for cigarettes/day

Opioid	mu-opioid receptor (OPRM1)
	Prodynorphin (PDYN)
	Proenkephalin (PENK)
	Kappa (OPRK1)
	Delta opioid receptors (OPRD1)
	(D4DR) exon III repeat polymorphism
	D2 (DRD2) SNP rs1076560
	VNTR-6R polymorphism of the gene SLC6A3
	ABCB1(rs1045642)

Epigenetic

- Histone acetylation and DNA methylation has been shown to occur in NAc and striatum after drug exposure

- Chronic morphine exposure correlated with global levels of histone 3 lysine 9 dimethylation (H3K9me2) in the mice NAc

- Chronic administration of morphine increases acetylation of histone H3 lysine 14 (aceH3K14) in the NAc

Patrick Melrose

This five-part limited series based on the acclaimed novels by Edward St. tracks Patrick from a privileged but deeply traumatic childhood in the South of France through severe substance abuse in his twenties in New York and, ultimately, toward recovery back home in Britain.

References

. Historical and cultural aspects of man's relationship with addictive drugs
. The Addicted Synapse: Mechanisms of Synaptic and Structural Plasticity.in Nucleus Accumbens
. A Review of Chemical Agents in the Pharmacotherapy of Addiction
. Transcriptional Mechanisms of Drug Addiction
. Underlying Susceptibility to Eating Disorders and Drug Abuse: Genetic and Pharmacological Aspects of Dopamine D4 Receptors
. Dopamine in Health and Disease: Much More Than a Neurotransmitter
. The dopamine theory of addiction: 40 years of highs and lows
. Genetics of dopamine receptors and drug addiction: a comprehensive review
. Polymorphisms in dopamine receptors: what do they tell us?
. Brain Change in Addiction as Learning, Not Disease
. Dopamine Receptors: From Structure to Function
. DRUG ADDICTION. *PART III.* PHARMACOTHERAPY OF ADDICTION
. Overexpression of CREB in the Nucleus Accumbens Shell Increases Cocaine Reinforcement in Self-Administering Rats
. Will we ever find the genes for addiction?
. DISTRIBUTION OF POLYMORPHIC VARIANTS OF CYP2A6 AND THEIR INVOLVEMENT IN NICOTINE ADDICTION
. Decoding Dopamine Signaling
. Targeting heat shock proteins to modulate -synuclein toxicity
. Structural insights into emergent signaling modes of G protein–coupled receptors
. Opiate addiction and cocaine addiction: underlying molecular neurobiology and genetics
. Mu Opioid Pharmacology: 40 Years to the Promised Land
. Genes and addiction Eric J. Nestler
. Neuroimaging of the dopamine/reward system in adolescent drug use
. Pharmacogenetic Treatments for Drug Addiction
. Neuroepigenetics and addiction
. OPRD1 Genetic Variation and Human Disease
. Neuroscience of Addiction: Relevance to Prevention and Treatment


There is always
HOPE