Neurobiology of Addiction

E. Mohandas, MD
Sun Medical & Research Centre,
Trichur, Kerala

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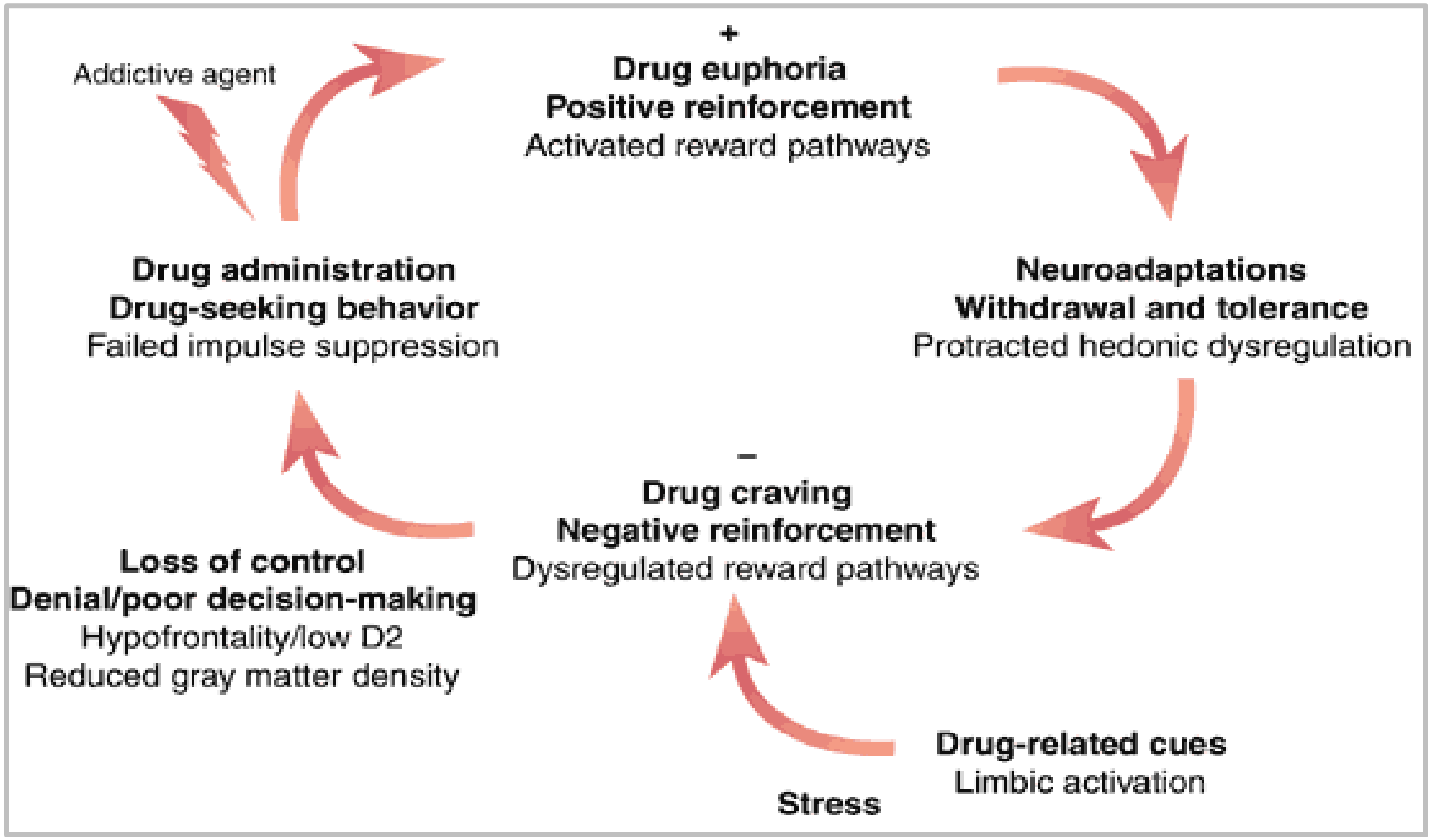
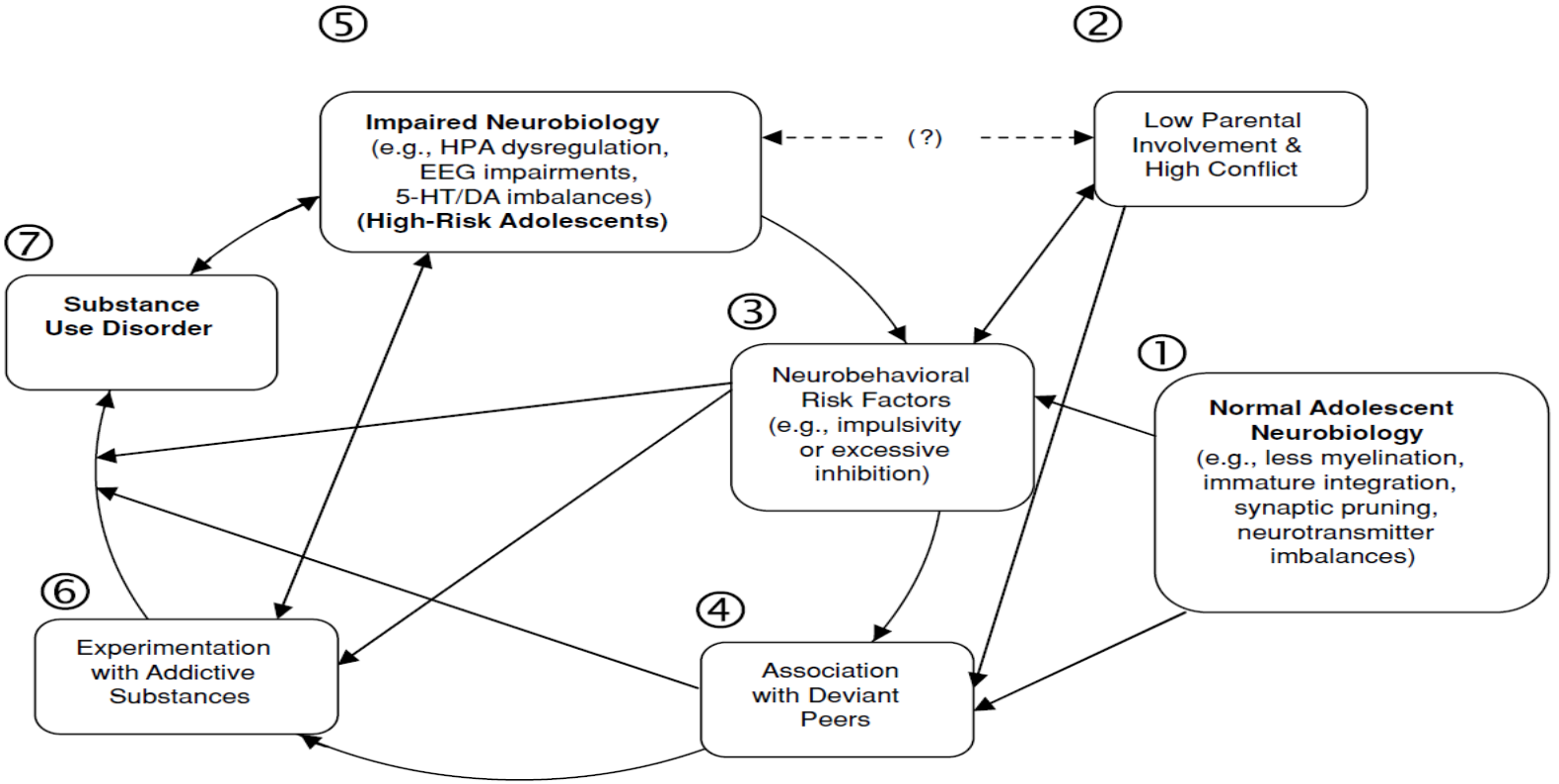
The Evolving Vicious Cycle

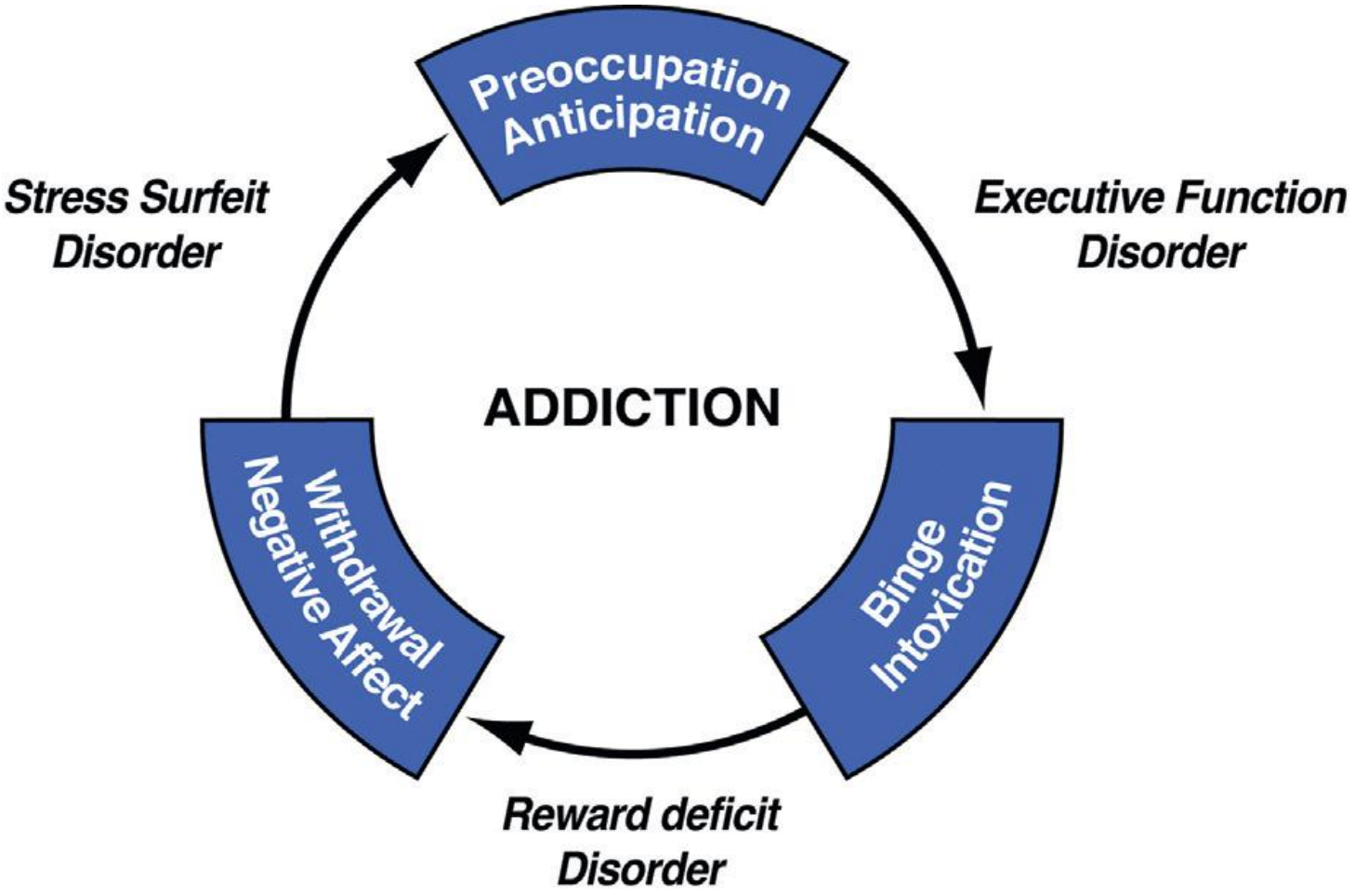


Entering the Mysterious Corridor



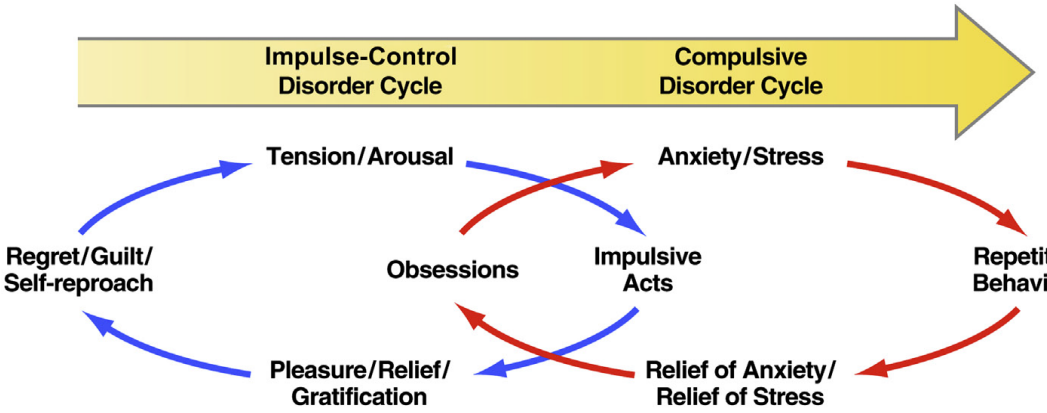
Labels for abbreviations
HPA = Hypothalamic-Pituitary-Adrenal Axis
EEG = Electroencephalogram
5-HT = Serotonergic
DA = Dopaminergic

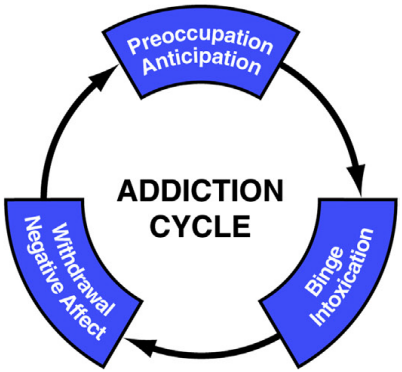
The Evolving Vicious Cycle

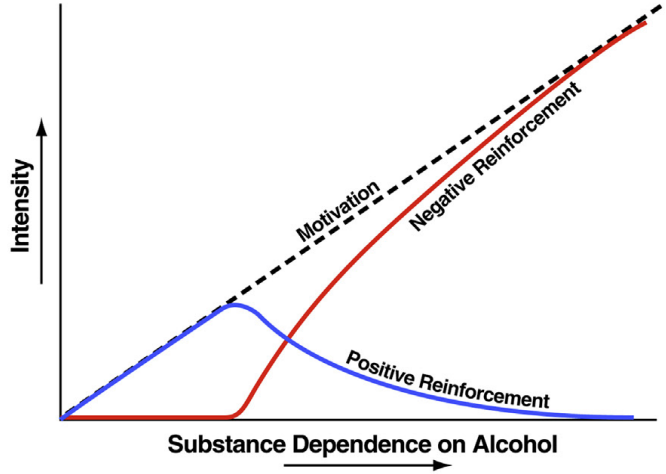


Koob GF (2014)

The Evolving Vicious Cycle







George F. Koob (2014) In: Neurobiology of Alcohol Dependence, Elsevier Inc

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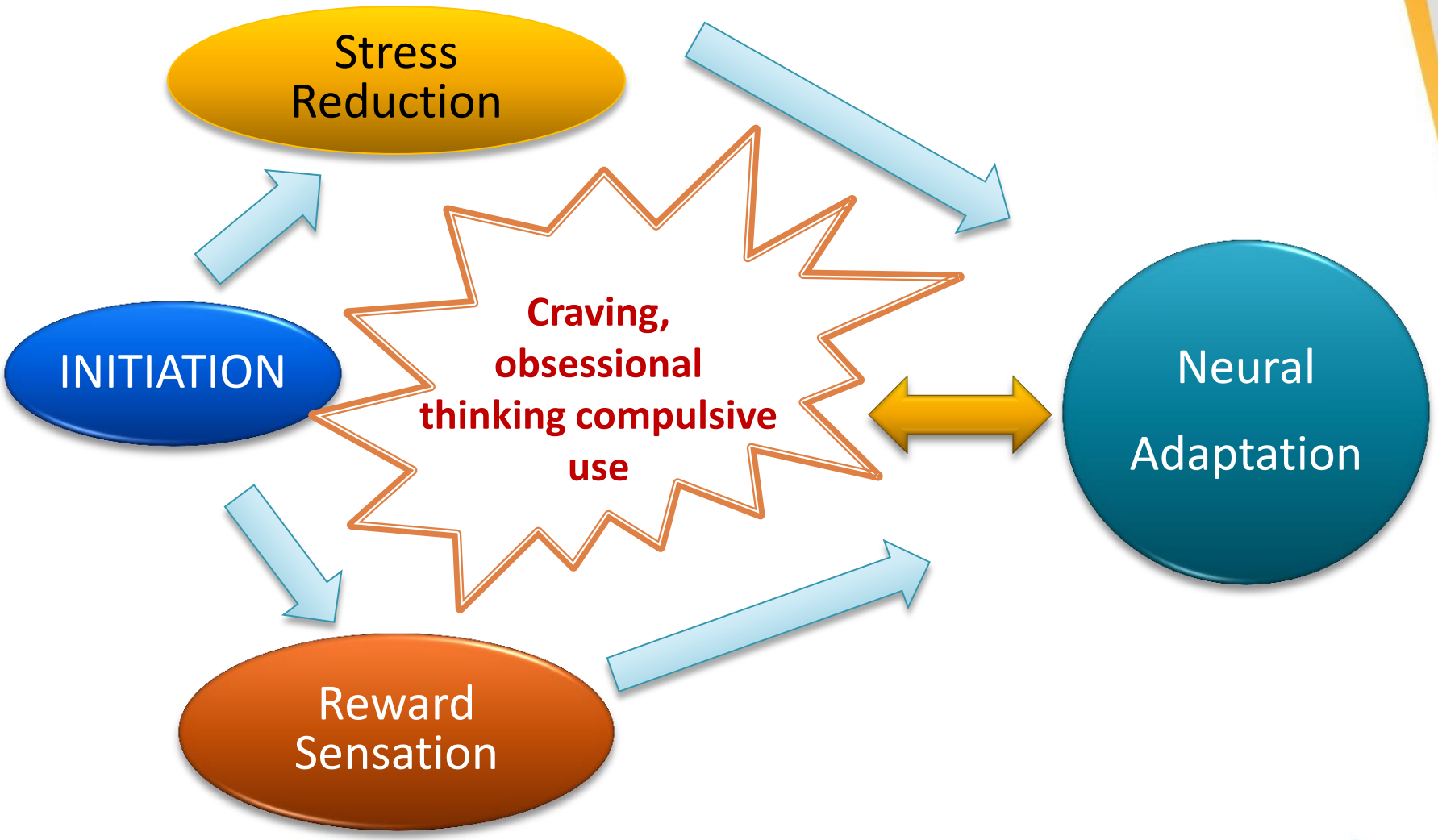
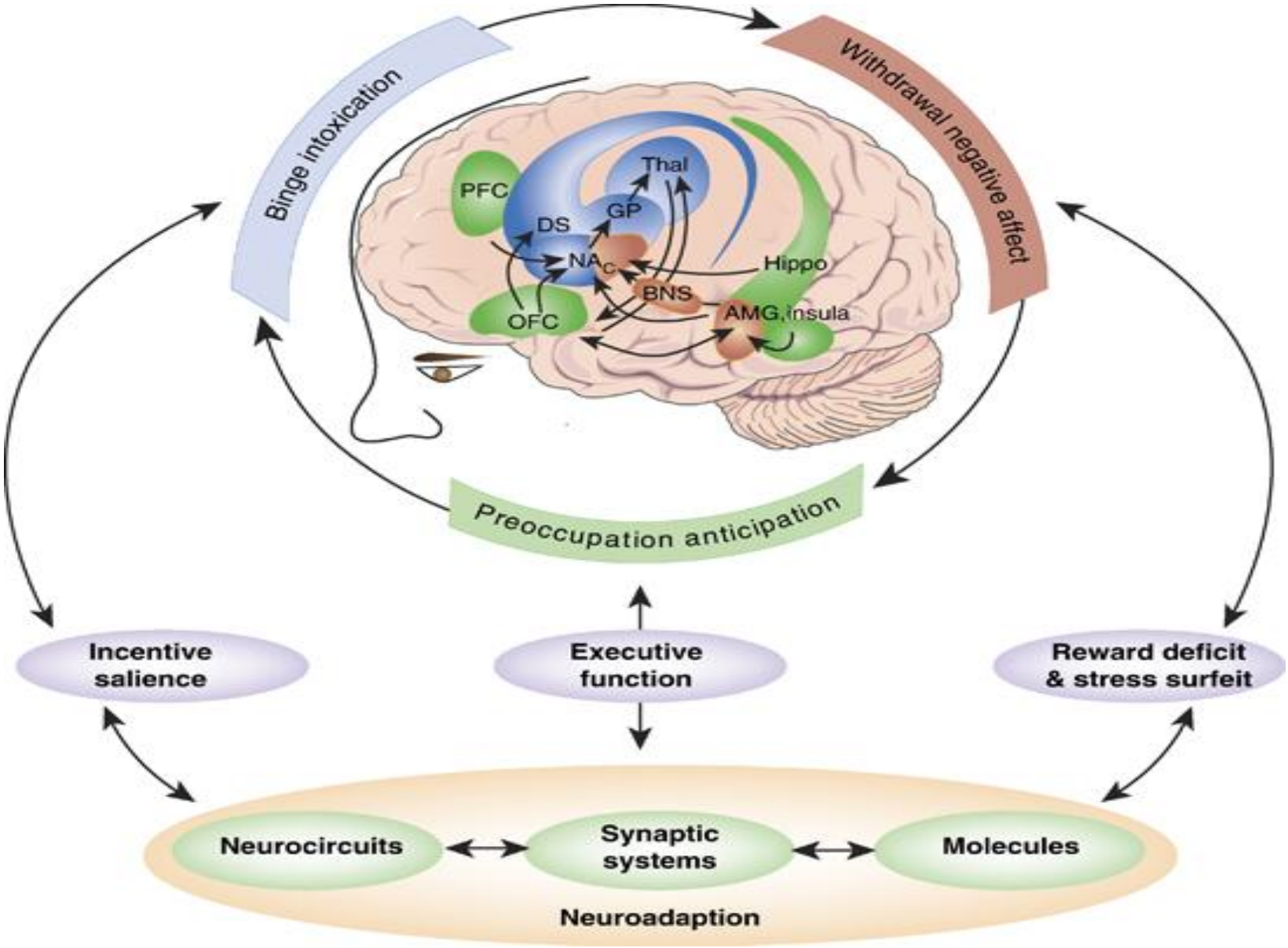
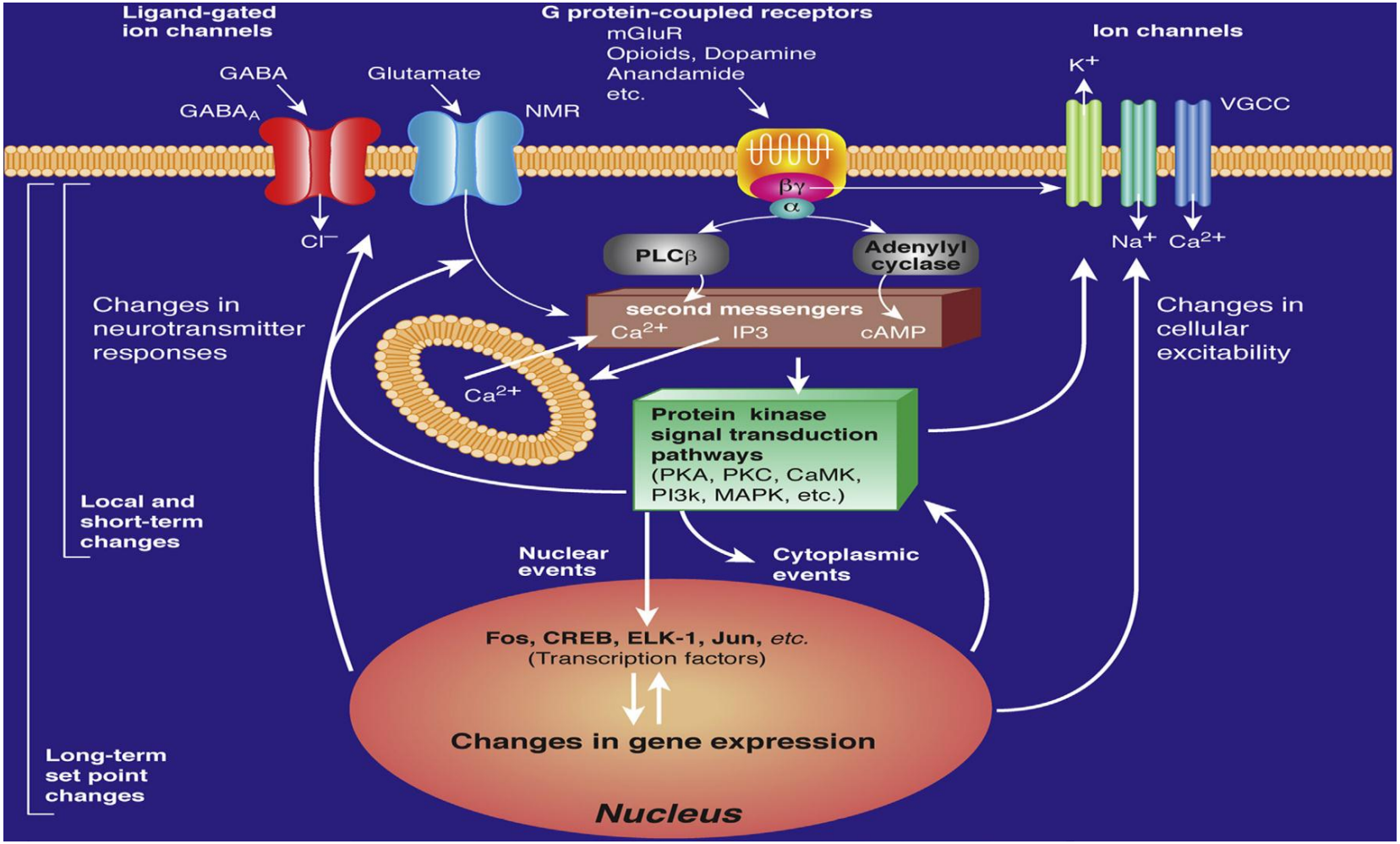
Metamorphosis



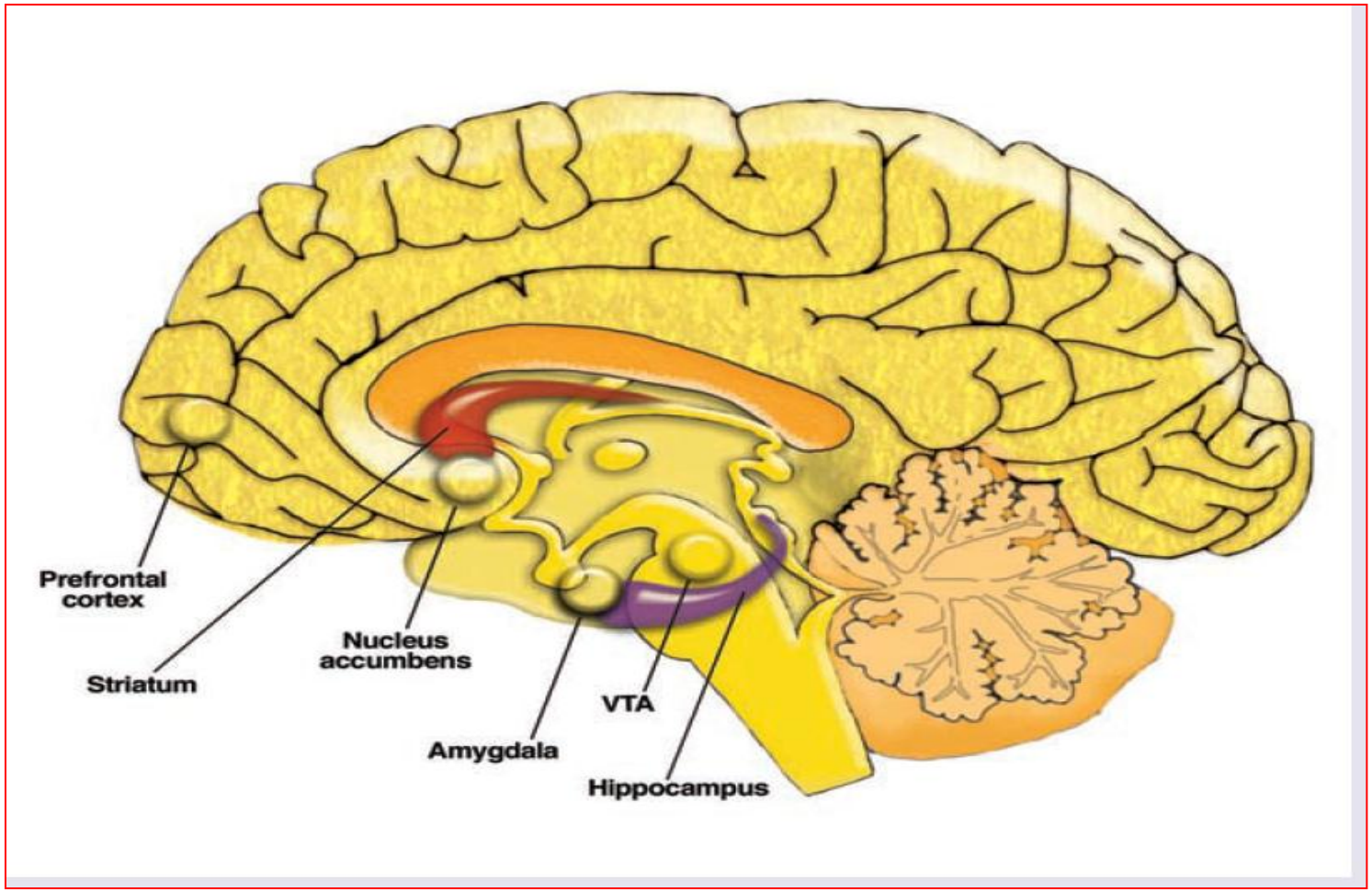

Binge intoxication
Withdrawal negative affect
Preoccupation anticipation
PFC
Thal
GP
DS
NAc
Hippo
BNS
OFC
AMG, insula
Incentive salience
Executive function
Reward deficit & stress surfeit
Neurocircuits
Synaptic systems
Molecules
Neuroadaption

Molecular mechanisms of neuroadaptation



Neuroanatomical System in Addiction

Neuroanatomical System in Addiction



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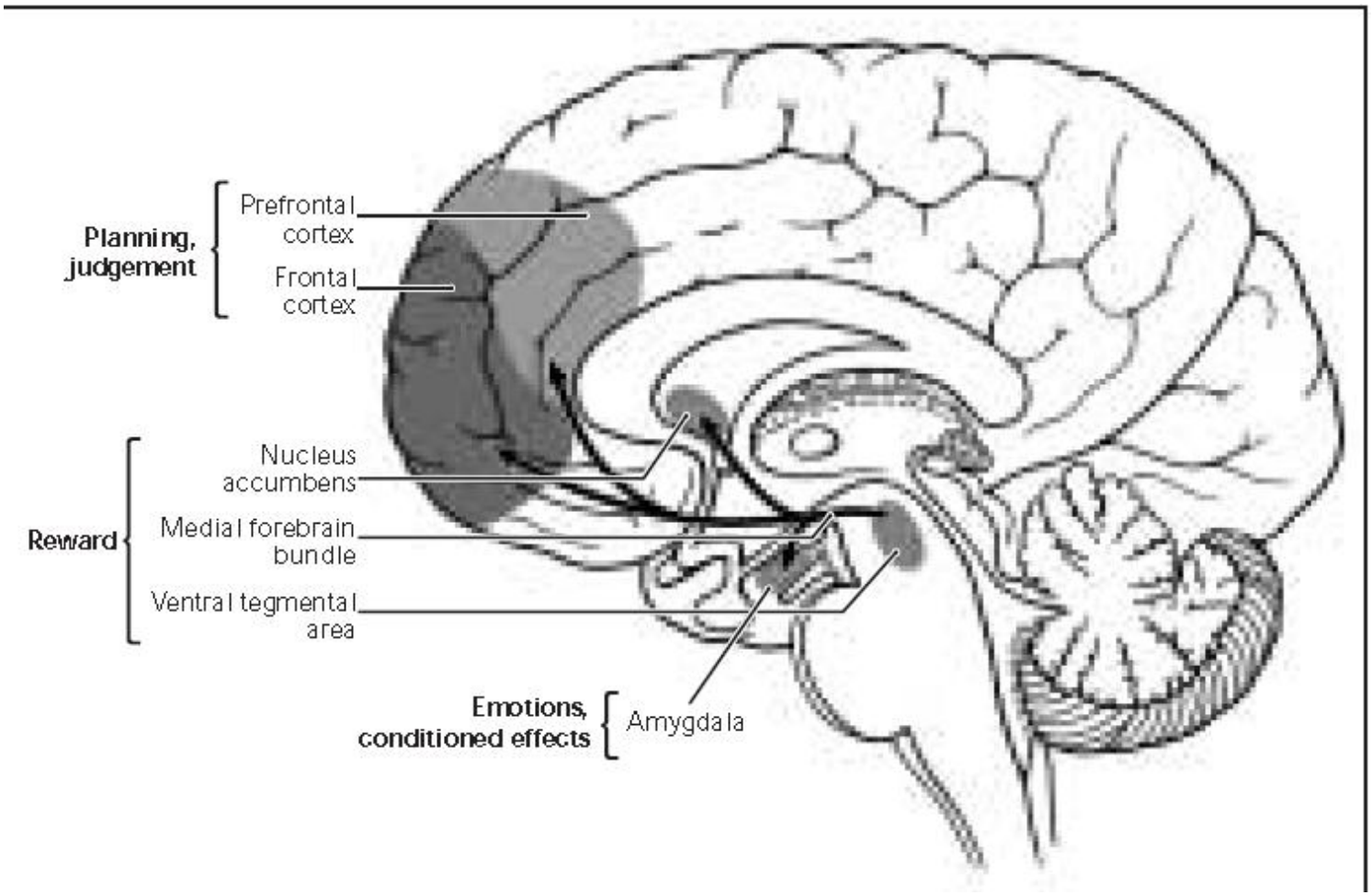

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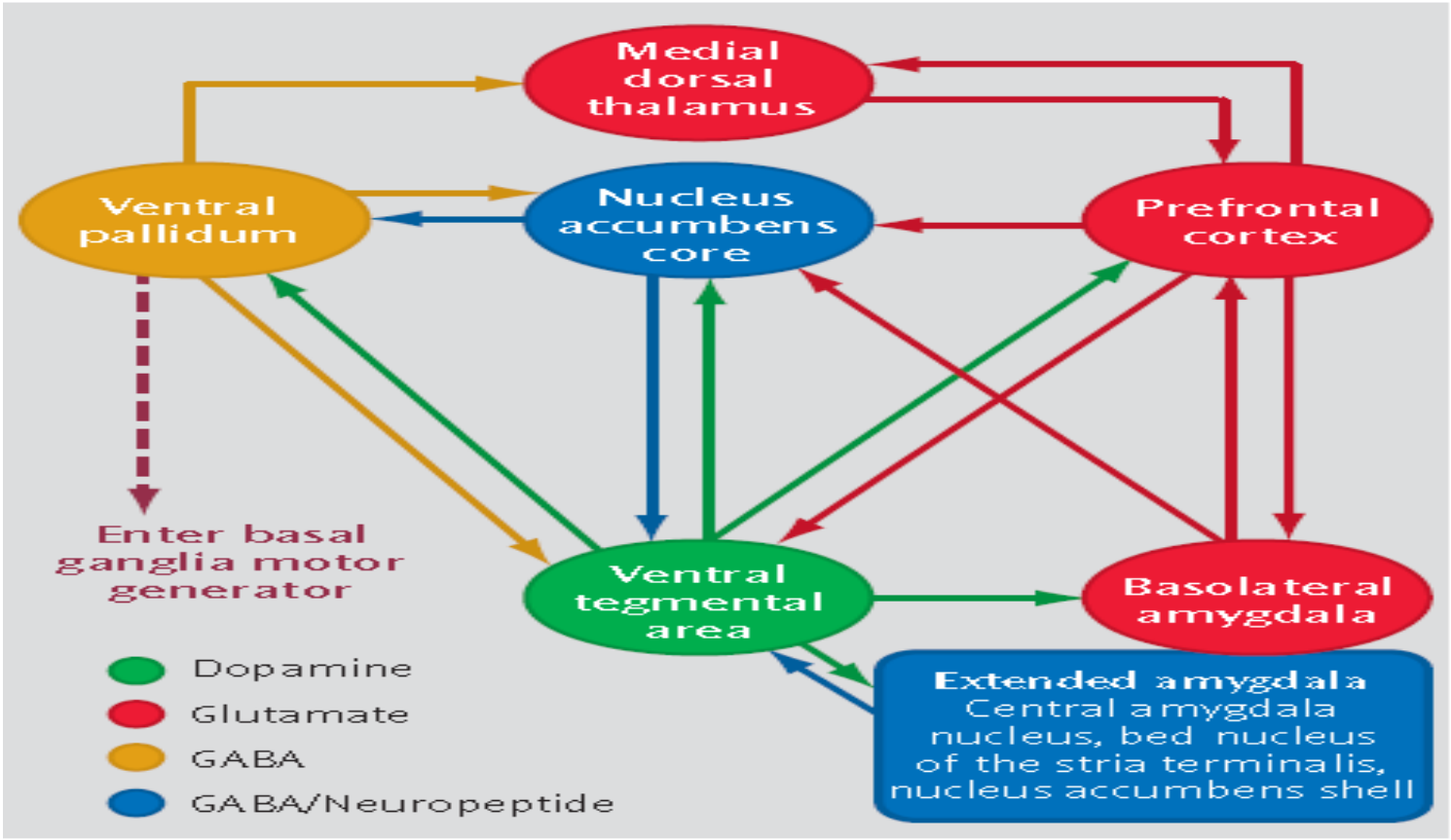
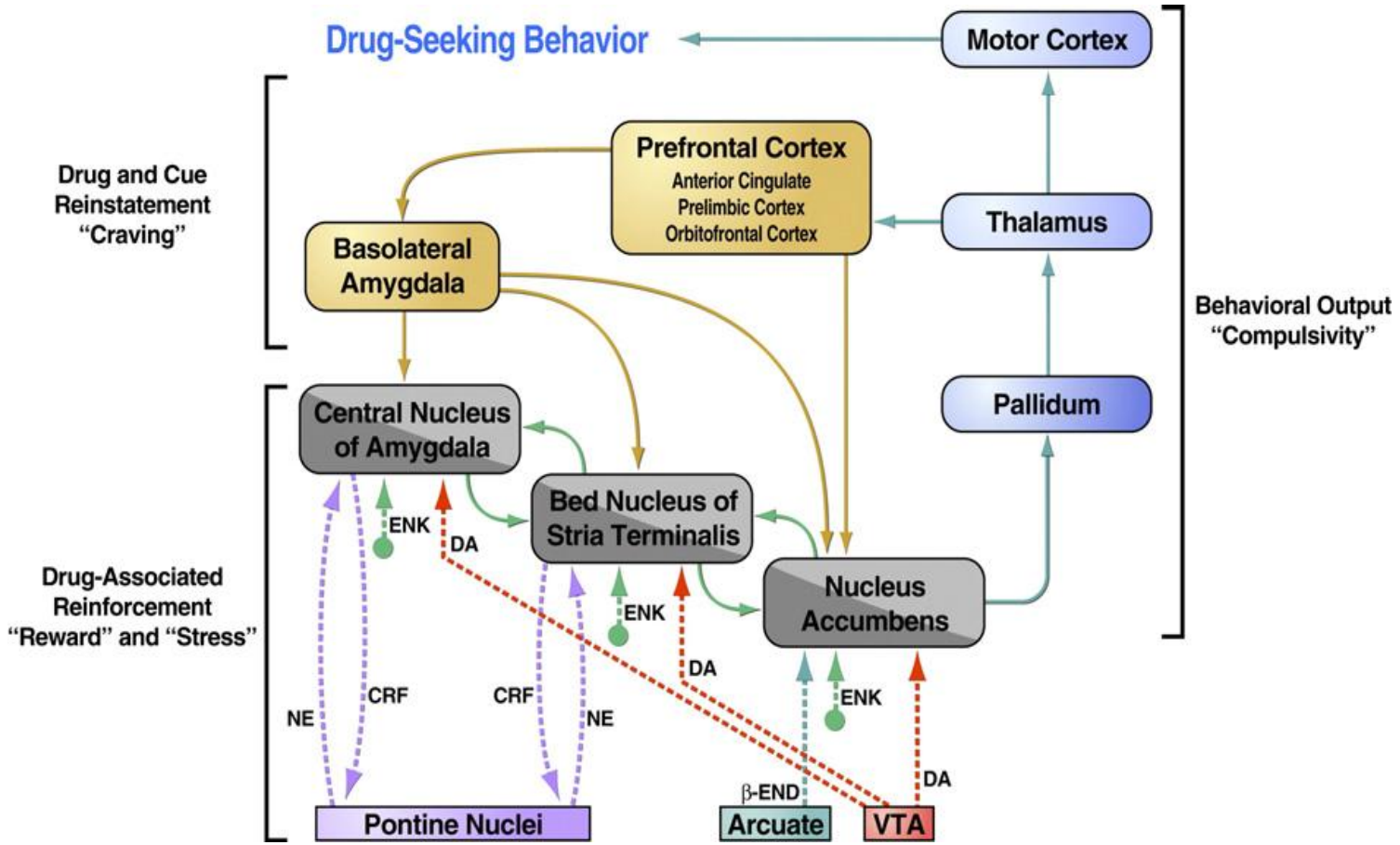
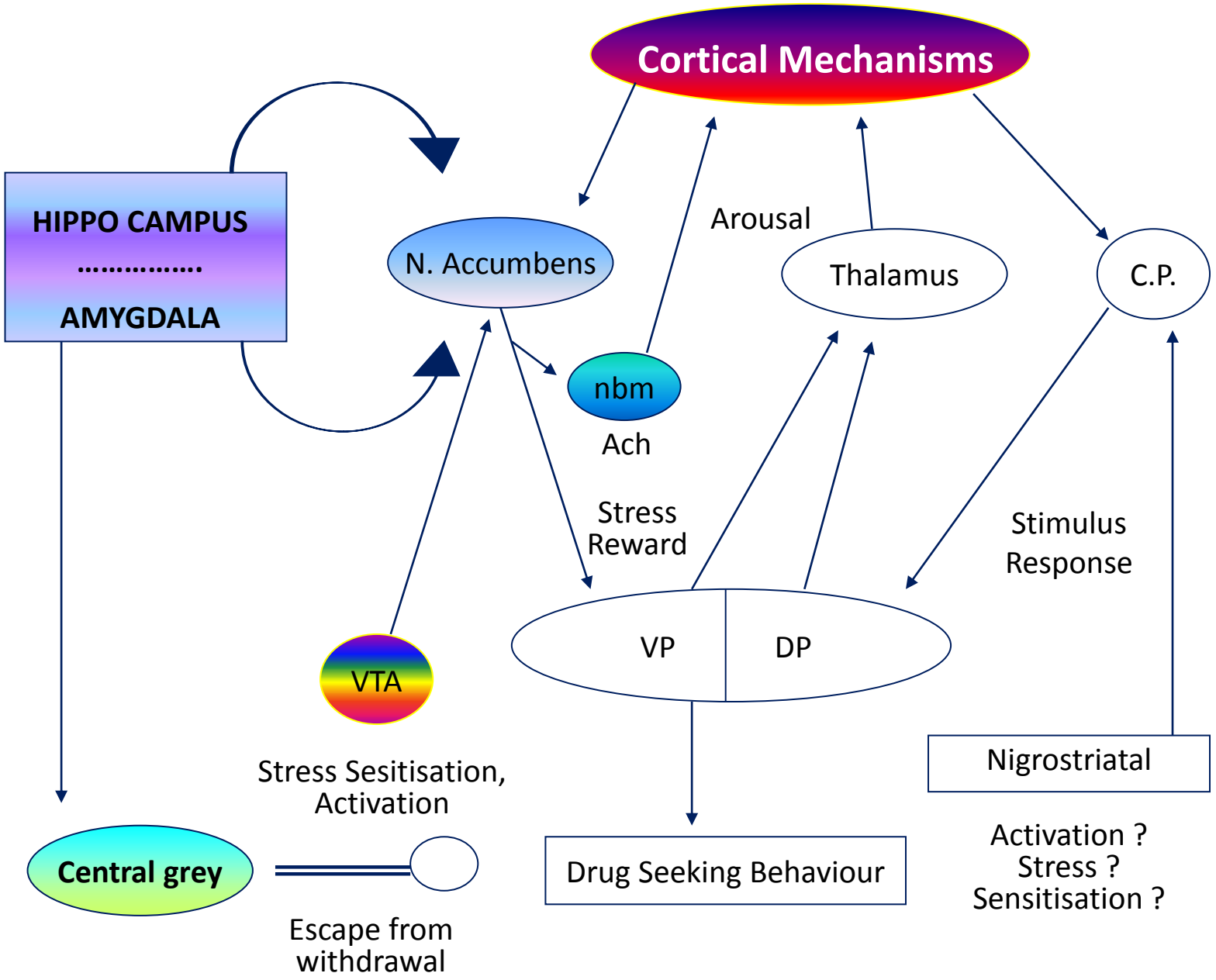


Kalivas, P. W., and Volkow, N. D. (2005).

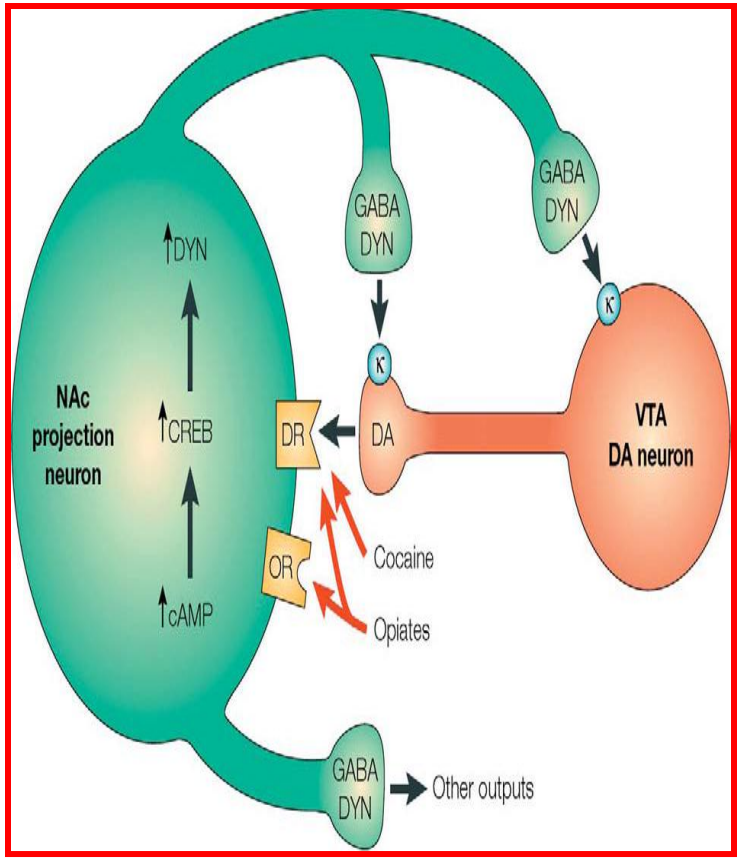
Neuroanatomical System in Addiction-Circuits



Le Moal M & Koob GF(2007) European Neuropsychopharmacology17: 377–393


Cortical Mechanisms
HIPPO CAMPUS
……
AMYGDALA
N. Accumbens
Arousal
Thalamus
C.P.
nbm
Ach
Stress
Reward
Stimulus
Response
VP
DP
VTA
Stress Sesitisation,
Activation
Nigrostriatal
Central grey
Drug Seeking Behaviour
Activation ?
Stress ?
Sensitisation ?
Escape from
withdrawal

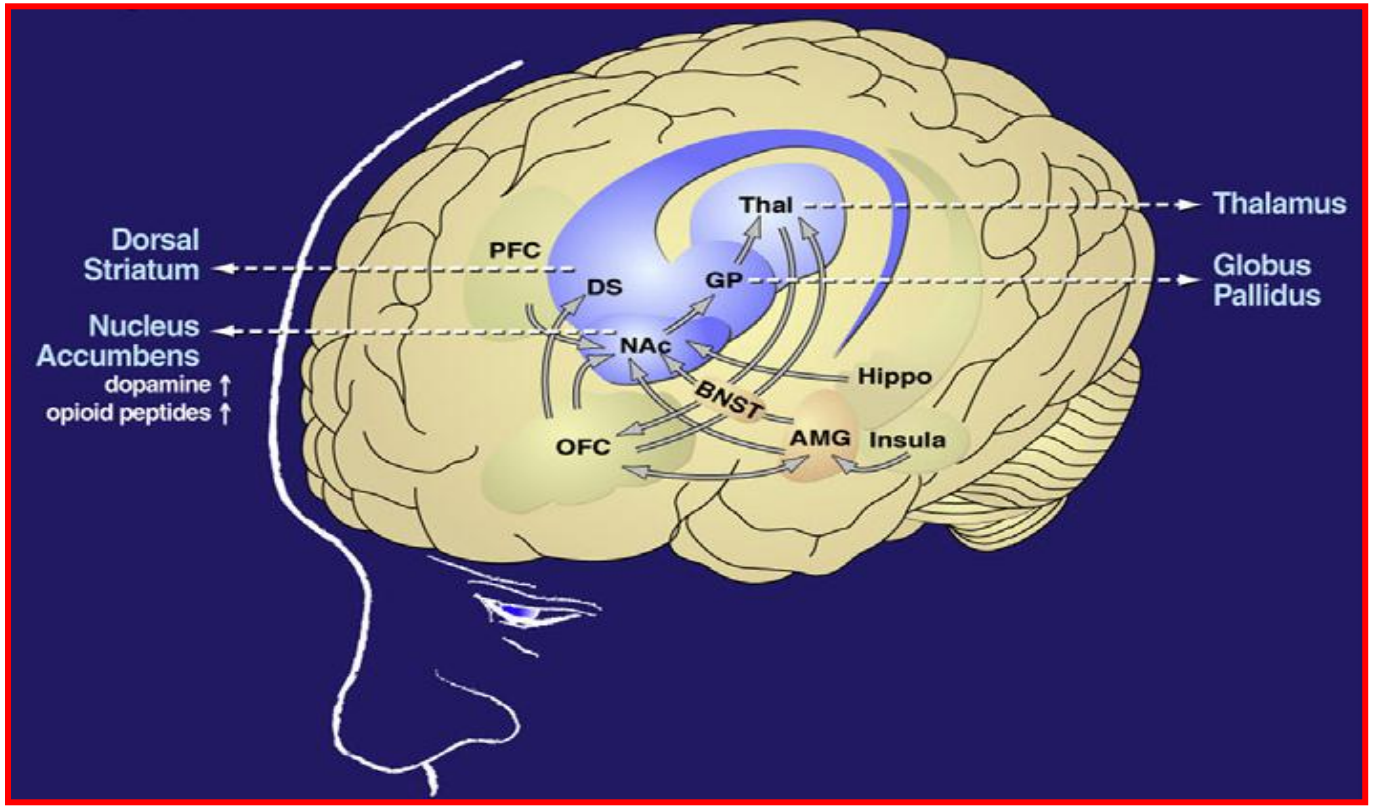
Feedback between the NAc and VTA via CREB activation



- Cocaine and amphetamine have been shown to activate pro-dynorphin gene expression in the NAc via D1 DA receptor stimulation, cAMP pathway, and the phosphorylation of CREB.
- Dynorphin peptides are transported to presynaptic terminals including terminals that feed back on VTA dopaminergic neurons.
- Dynorphin peptides are agonists at inhibitory -opioid receptors resulting in decreased dopamine release..

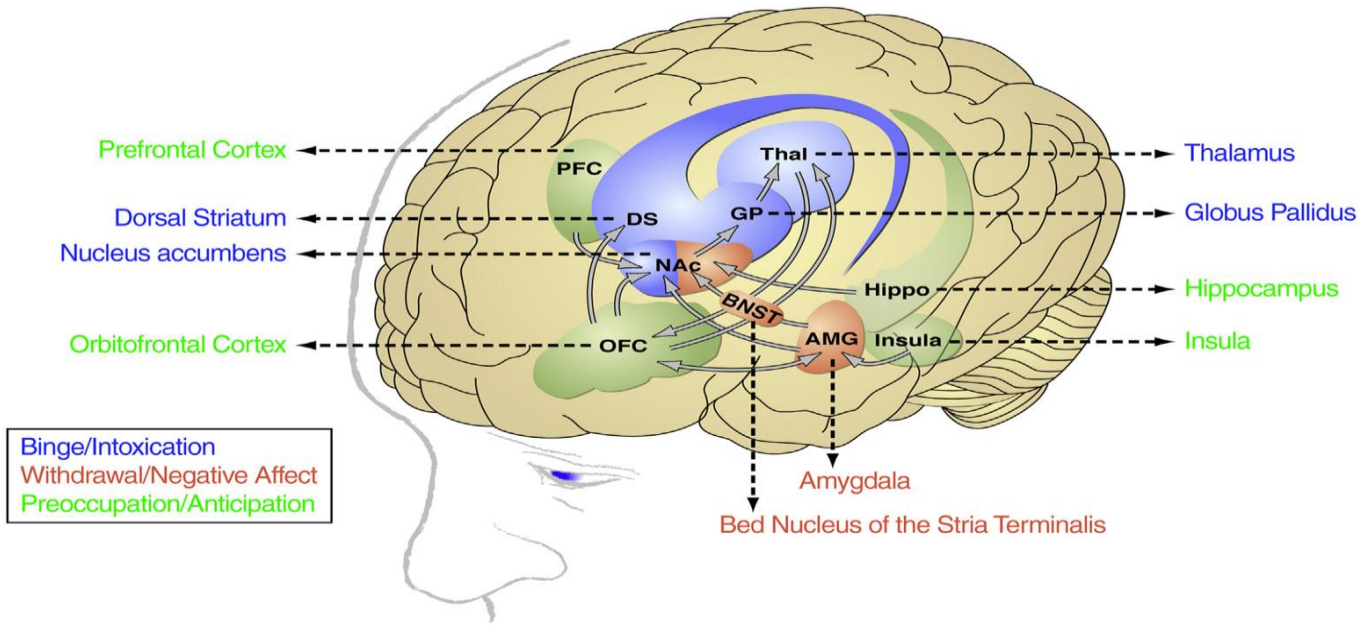
Nestler EJ (2001;2010)

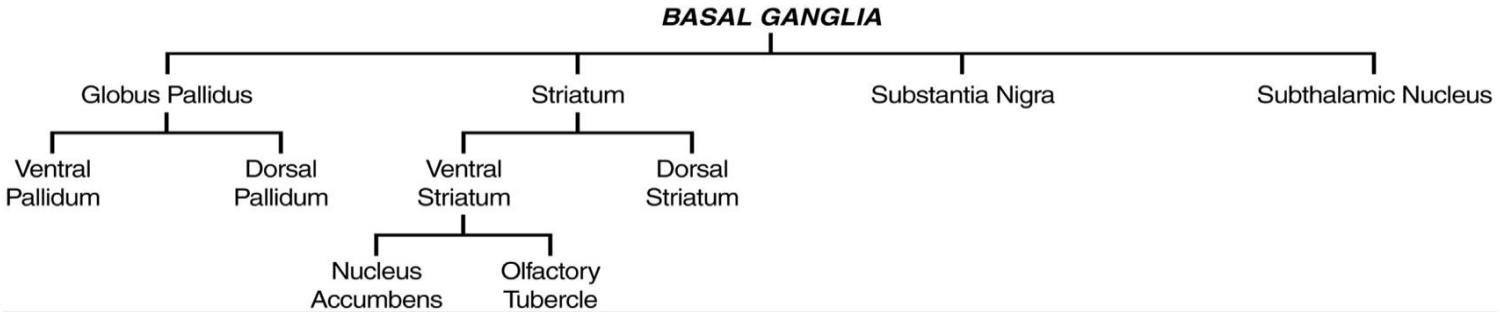
Binge/intoxication stage of the addiction cycle



Reinforcing effects of drugs may engage associative mechanisms and reward neurotransmitters in the NAc shell and core and engage stimulus-response habits that depend on the dorsal striatum.

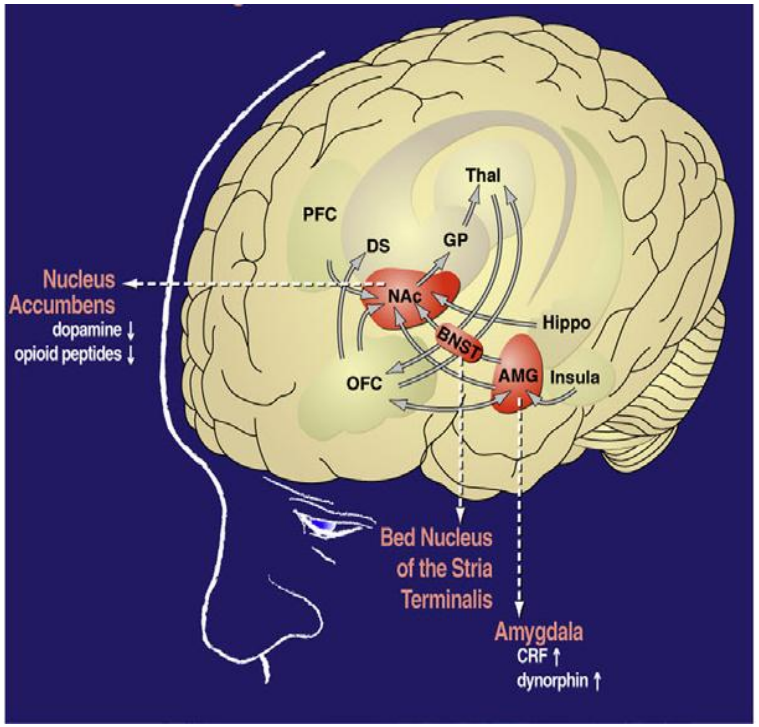
Binge/Intoxication Stage



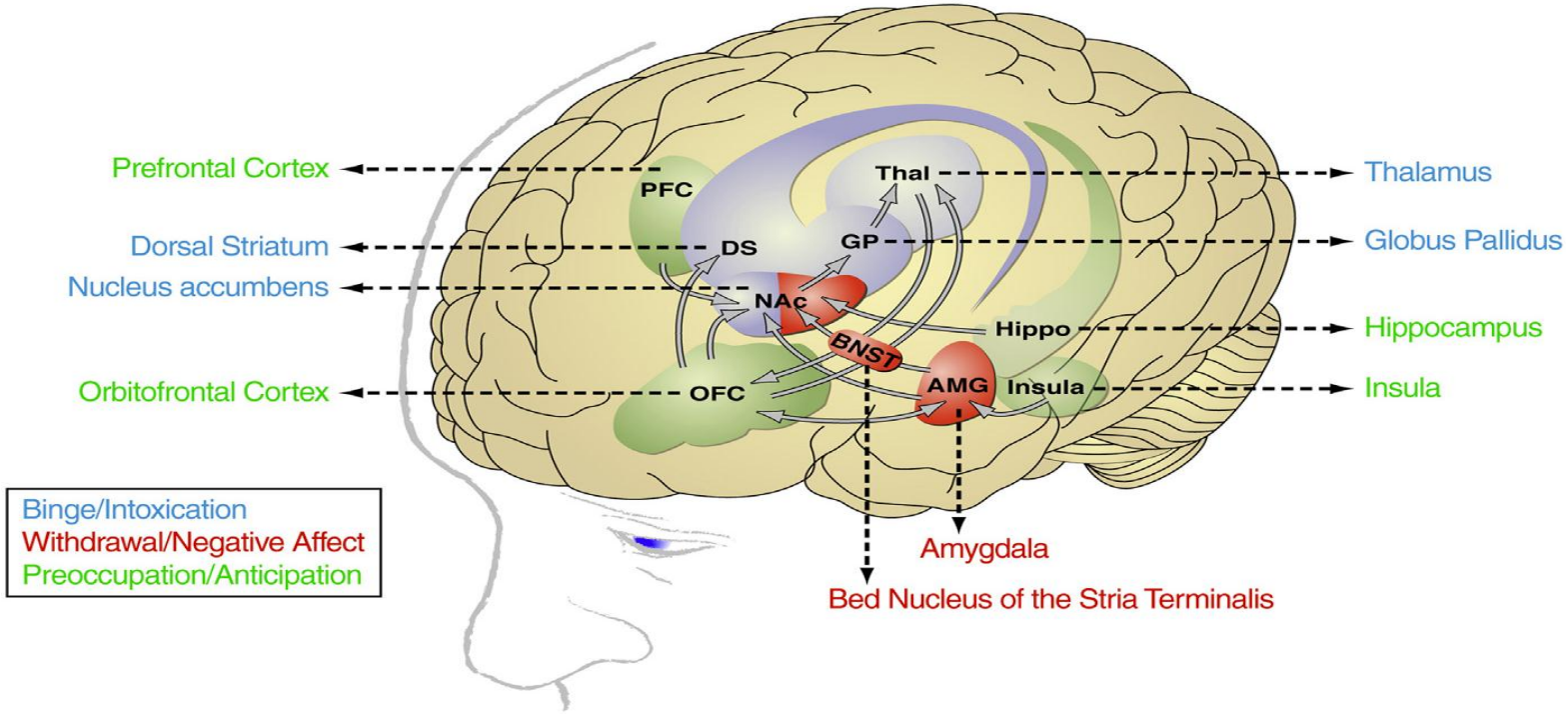


Withdrawal/negative affect stage of the addiction cycle

- Withdrawal/negative affect stage, the negative emotional state of withdrawal may engage the activation of the extended amygdala.
- The extended amygdala -several basal forebrain structures, including the bed nucleus of the stria terminalis, central nucleus of the amygdala, and possibly the medial portion (or shell) of the Nac
- CRF- major neurotransmitter in the extended amygdala



Withdrawal/Negative Affective Stage



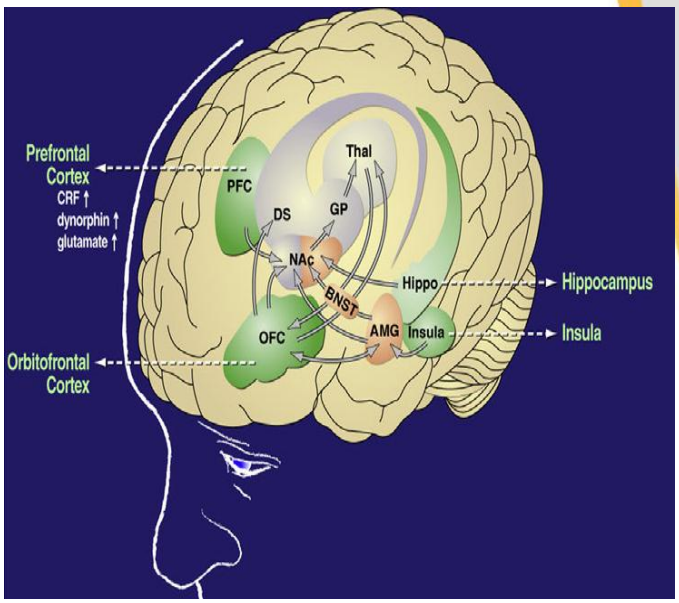
EXTENDED AMYGDALA

Central Nucleus of the Amygdala	Bed Nucleus of the Stria Terminalis	Nucleus Accumbens Shell

Koob GF, Volkow ND.(2010)

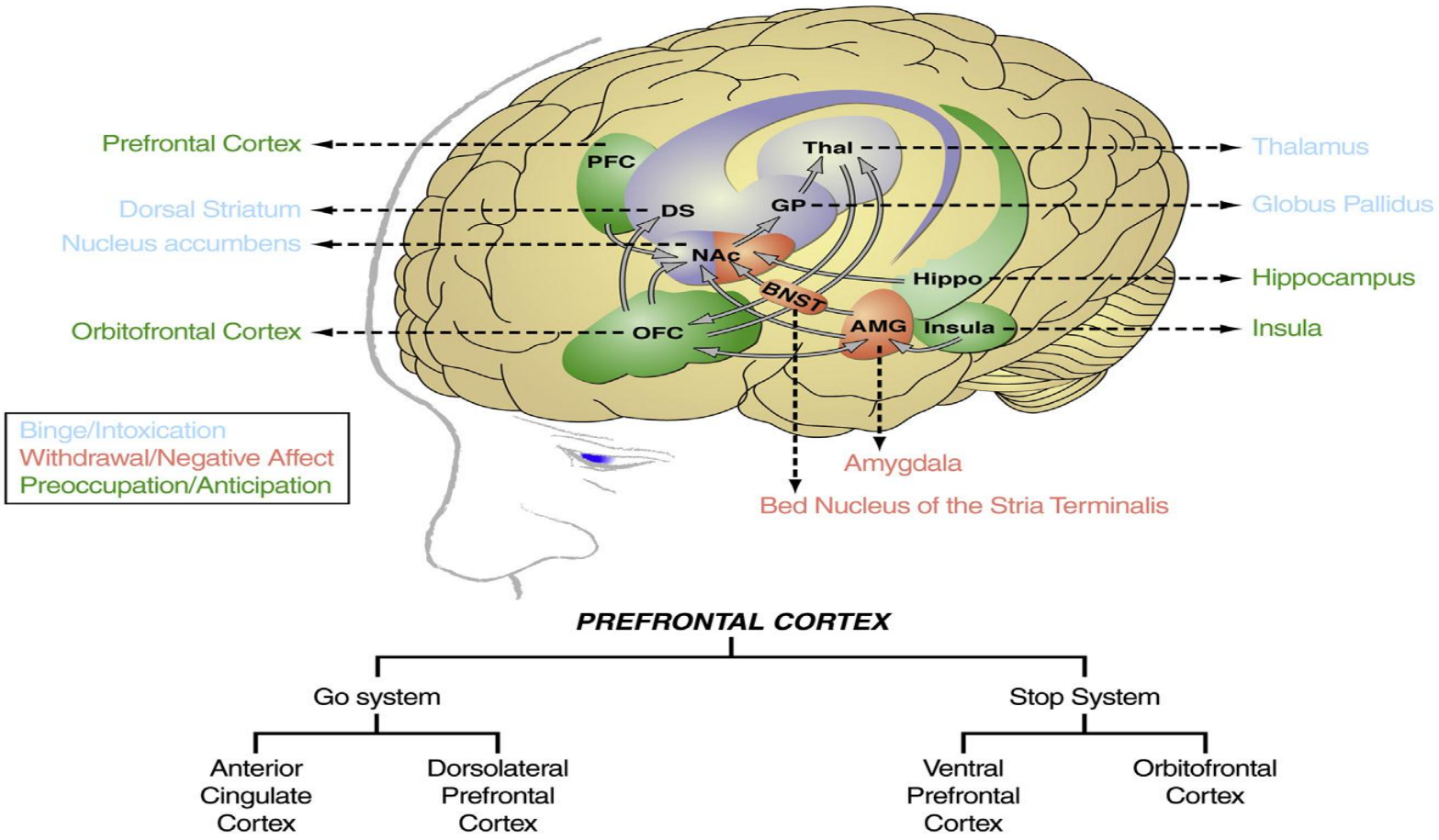
Preoccupation/Anticipation

- Processing of conditioned reinforcement in the BLA and the processing of contextual information by the HC.
- Executive control depends on the PFC and includes the representation of contingencies, the representation of outcomes, and their value and subjective states (i.e., craving and, presumably, feelings) associated with drugs.
- Drug craving in humans involves activation of the OFC and ACC and temporal lobe, including the amygdala, in functional imaging studies

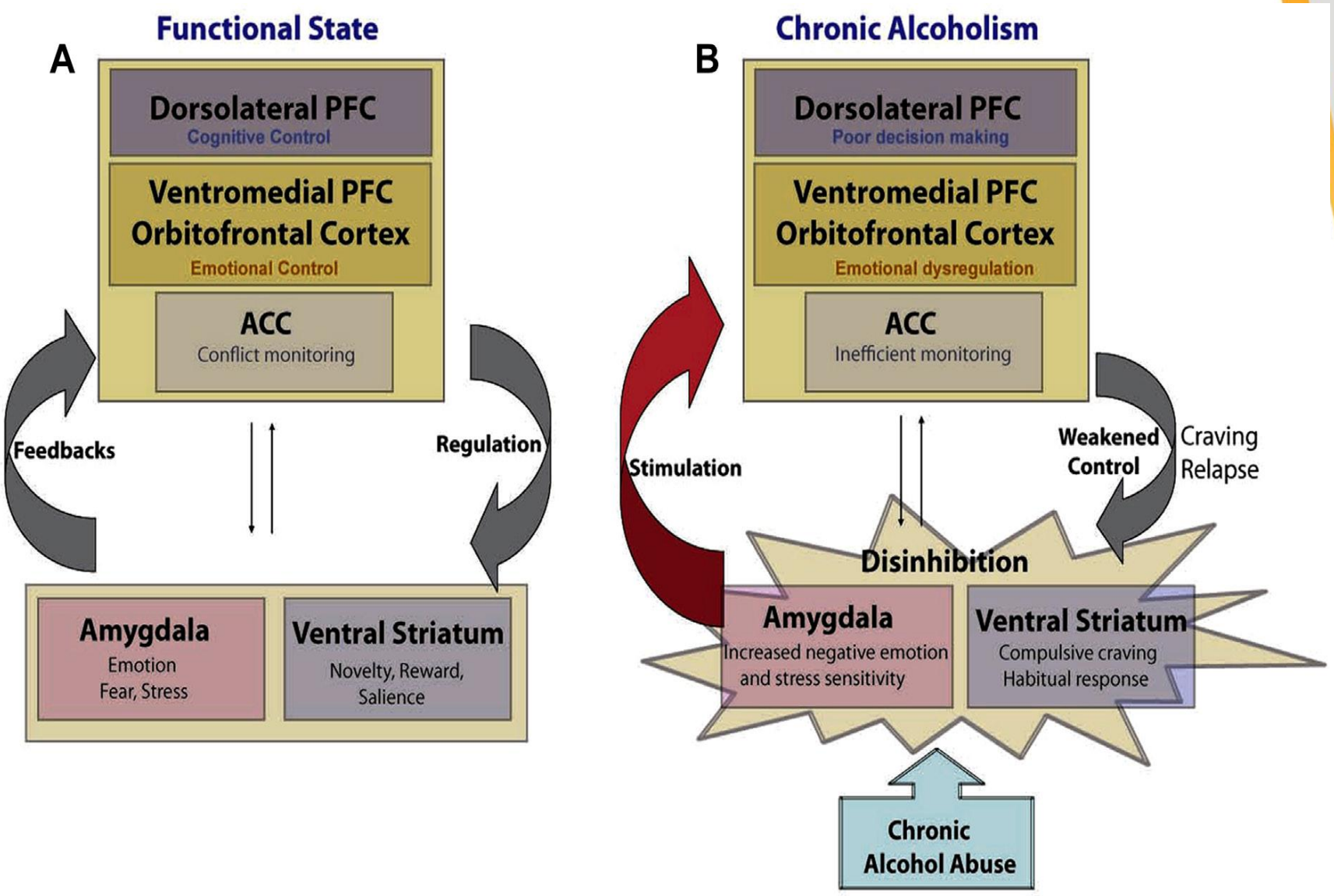


Drugs, Addiction, and the Brain (2014)

Preoccupation/Anticipation Stage



Neurobiology of Alcohol Dependence (2014)



Dongju Seo and Rajita Sinha (2014)

Neurotransmitter systems

Neurotransmitter systems

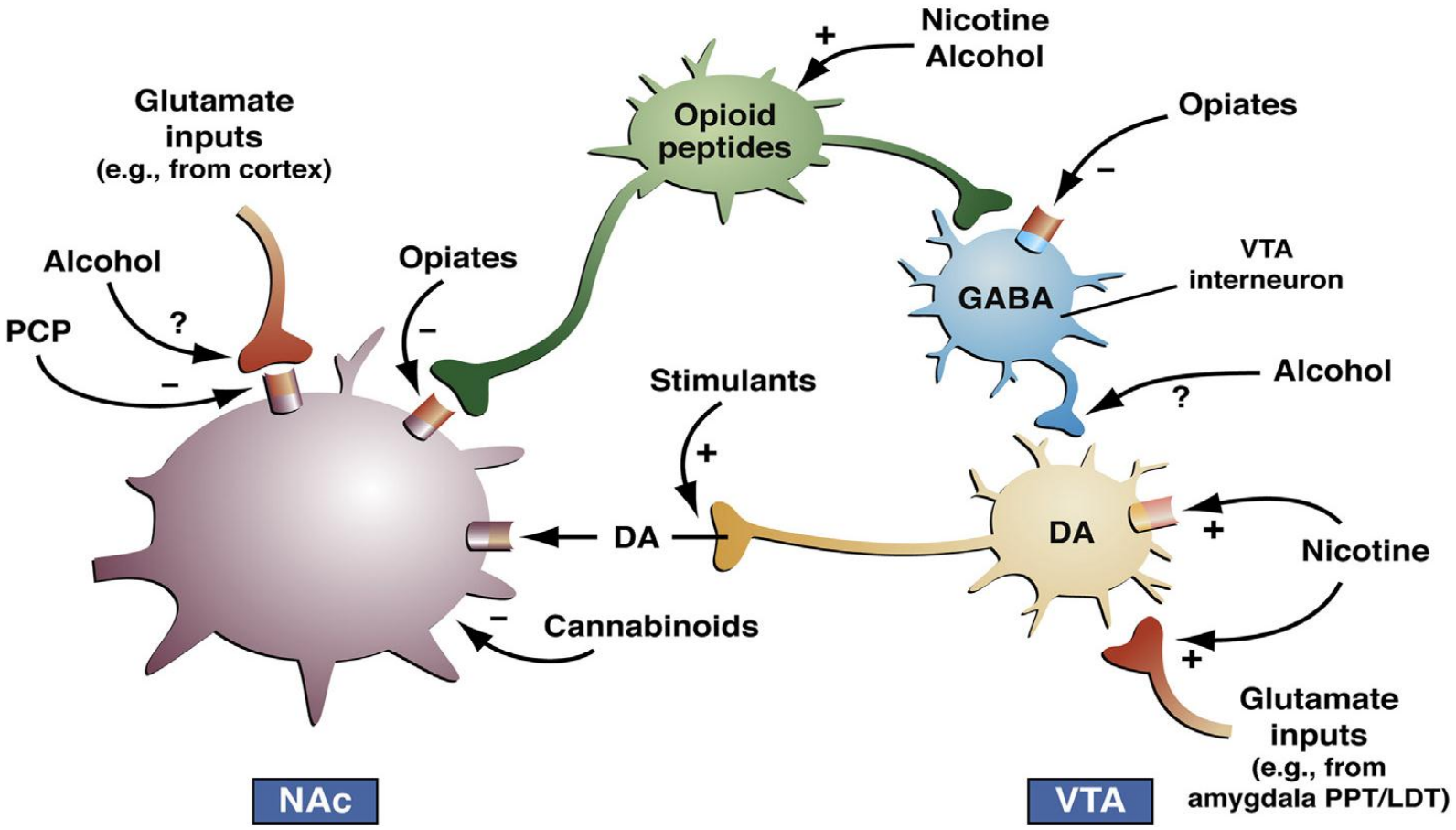
Neurotransmitters	Structures
GABA	Amygdala
Dopamine	VTA, Nucleus Accumbens
Opioids	VTA
Glutamate	Many areas esp. Hippocampus
CRF	PVN, CeA, BNST (Ext. Amygdala) (Hypo-Extrahypo)
Neuropeptide Y	Amygdala (CeA)
Norepinephrine	Locus Coeruleus
Serotonin	Raphae Nucleus

Adapted from: Koob GF & Le Moal M (2001) Neuropsychopharmacology 24:97–129

Acute pharmacologic actions of drugs of abuse

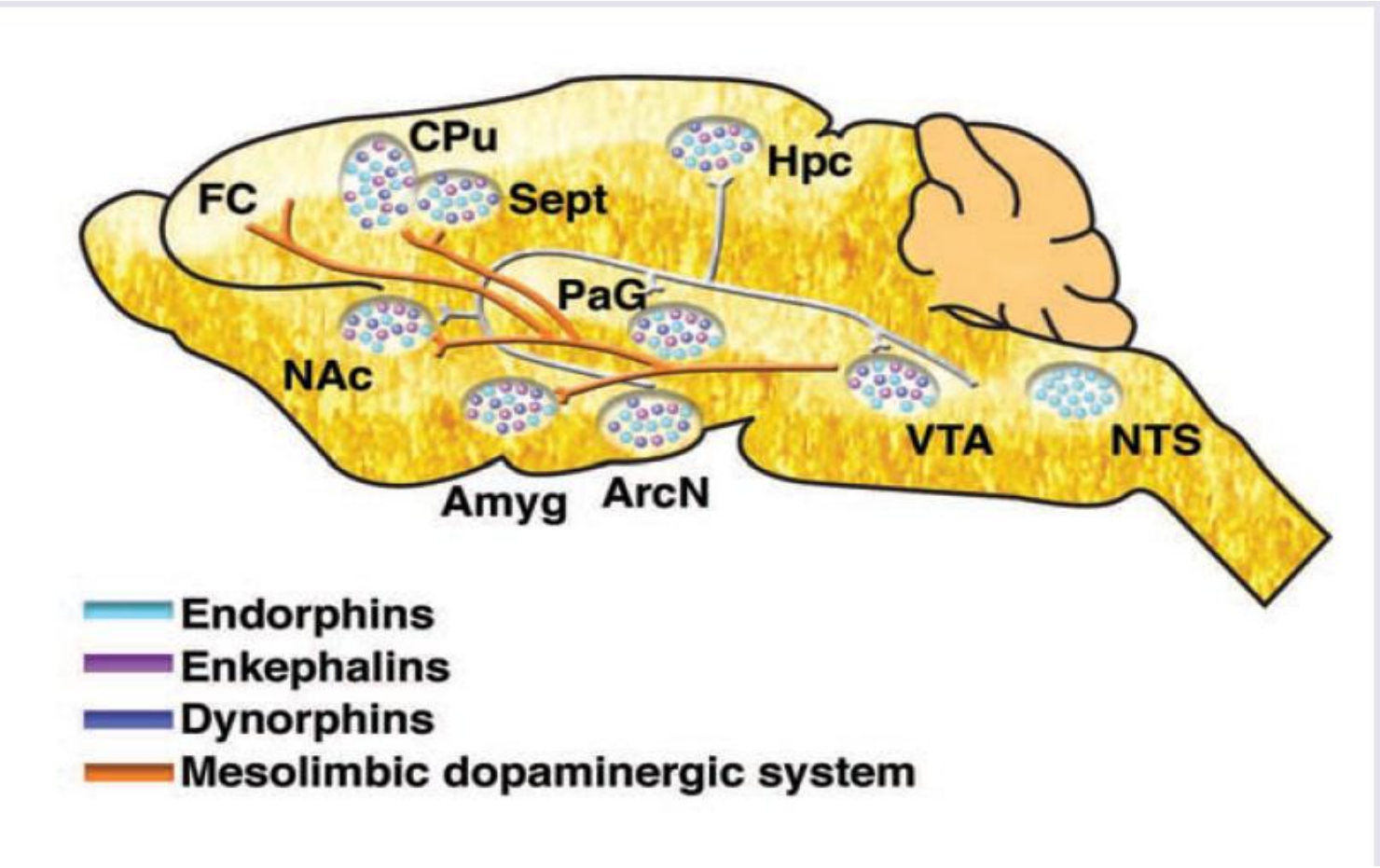
Opiates	Agonist at μ, and k opioid receptors
Cocaine	Inhibits monoamine reuptake transporters
Amphetamine	Stimulates monoamine release
Ethanol	Facilitates GABAA receptor function and inhibits NMDA glutamate receptor function
Nicotine	Agonist at nicotinic acetylcholine receptors
Cannabinoids	Agonist at CB1 Cannabinoids receptors
Hallucinogens	Partial agonist at 5HT2A serotonin receptors
Phencyclidine (PCP)	Antagonist at NMDA glutamate receptors

Neurotransmitter systems

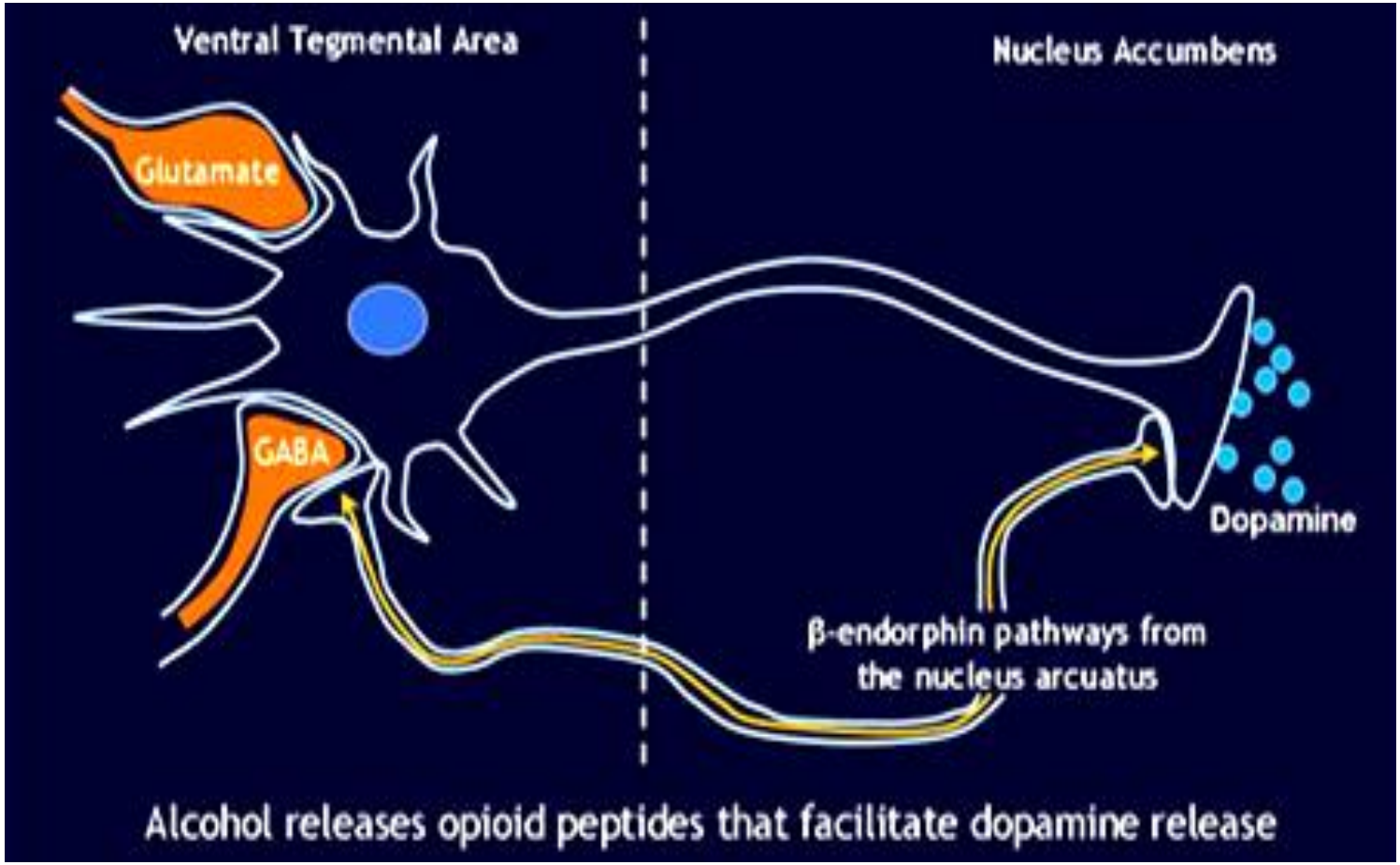


Nestler EJ.(2005)

Endogenous opioids and the mesolimbic dopamine system



Opioid System- Initiation

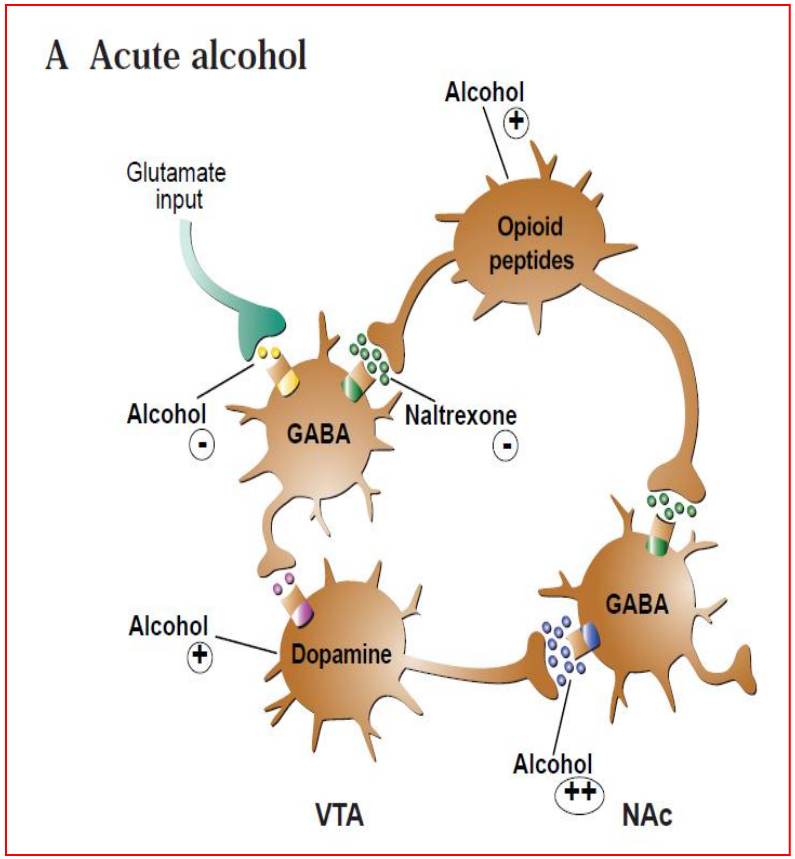


Sellers EM (2001) CMAJ 2001;164(6):817-21

Endogenous opioids and the mesolimbic dopamine system

- The activity of the DA-ergic neurons in the VTA is controlled by GABA releasing neurons. When these GABA neurons are activated (e.g., through the actions of the excitatory neurotransmitter glutamate), their signals decrease the firing of dopaminergic neurons
- Endogenous opioids can act on μ receptors on the GABA ergic neurons, thereby inhibiting GABA transmission, and ultimately leading to increased DA release.

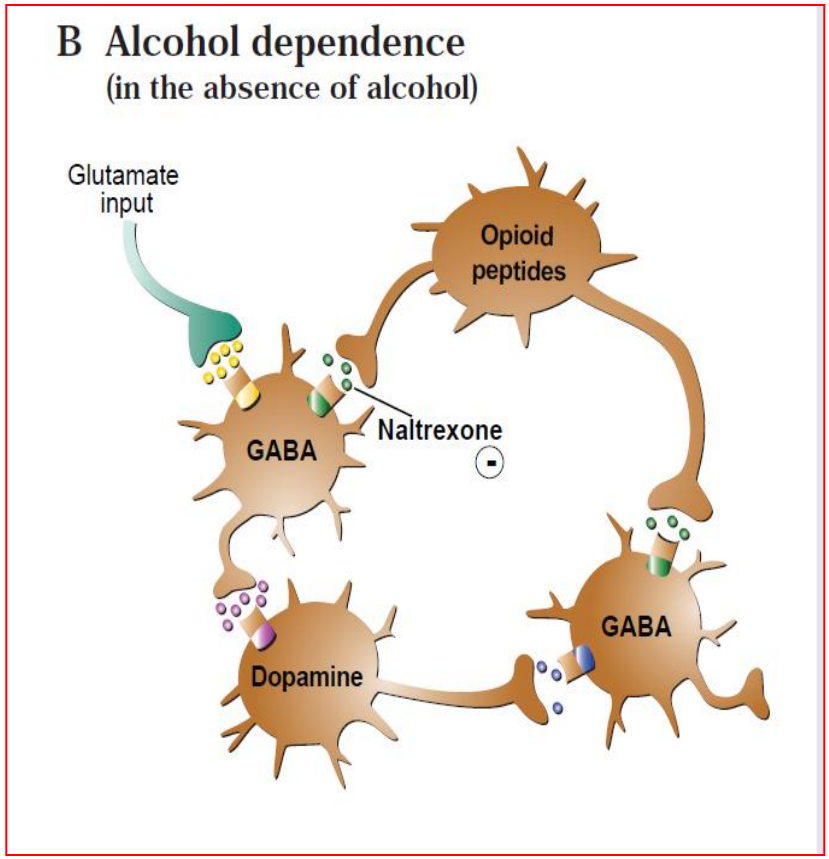
Endogenous opioids and the mesolimbic dopamine system



- β endorphin release
- Activation of μ receptors on the GABA ergic neurons in VTA
- Inhibition of glutamate effects on GABA neurons
- Decreased GABAergic activity in the VTA
- Increased firing of the dopaminergic neurons - increased DA in NAc.

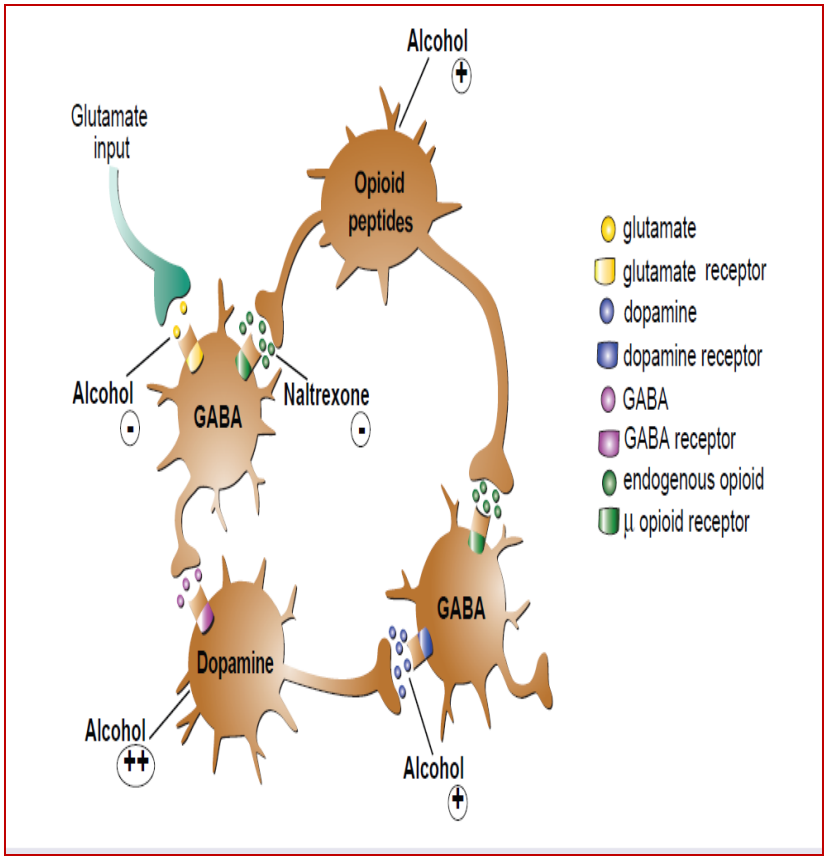
Endogenous opioids and the mesolimbic dopamine system

- Glutamate input to GABA neurons is increased, leading to decreased DA release. In addition, the activity of the VTA dopamine neurons is reduced.



Endogenous opioids and the mesolimbic dopamine system

- When alcohol is reintroduced, DA neurons are more sensitive to alcohol's direct effects
- Inhibits glutamate βendorphin release, thereby reversing the decreased DA release that occurs in the alcohol abstinent, alcohol dependent individual



Endogenous opioids

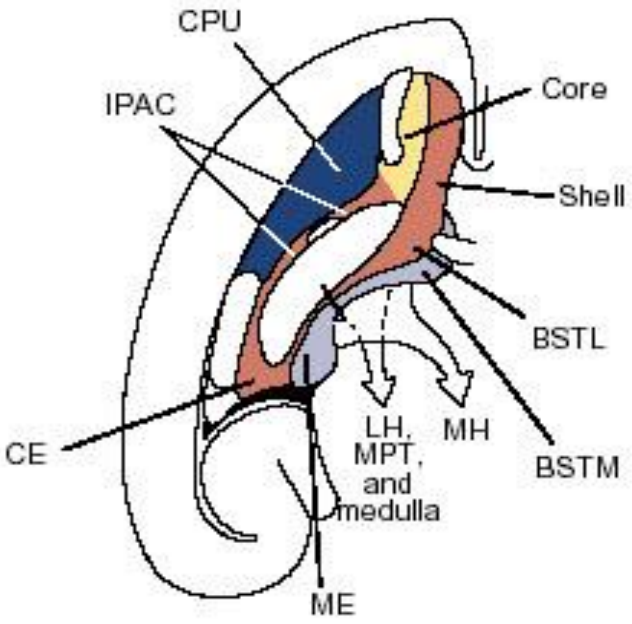
Opioid	Reinforcement, stress and emotional mechanisms
Release of β endorphin	Acute exposure to alcohol
Lower basal plasma β endorphin levels Pronounced β endorphin release on acute challenge of alcohol	High risk of alcohol dependence
μ and δ opioid receptors in VTA	Reinforcement
κ receptor KO (antagonism)	Greater preference for alcohol

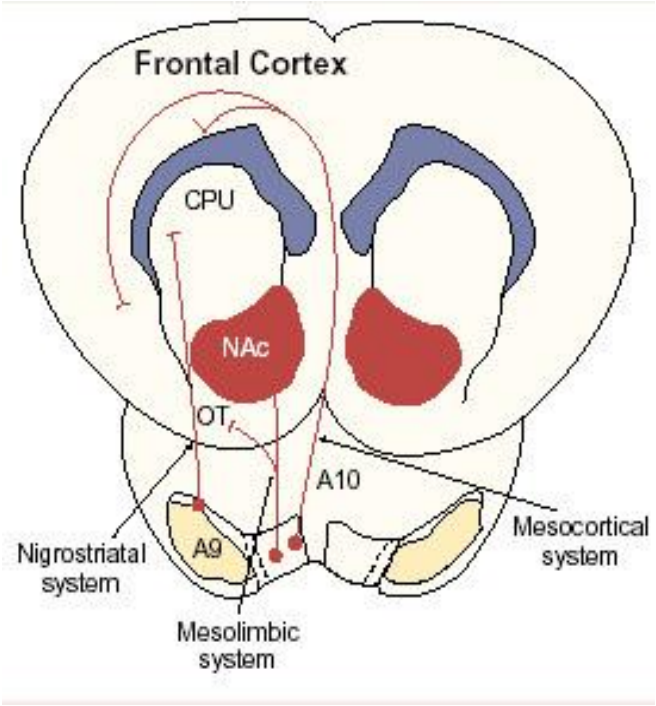
Dopamine in Addiction

- Alcohol on DA
  - Via GABA
  - Via Opioids
  - Direct
- Repeated administration of alcohol produces an initial facilitation of DA neurotransmission in NAc
- Chronic administration leads to decreases in DA neurotransmission in the NAc

Dopamine

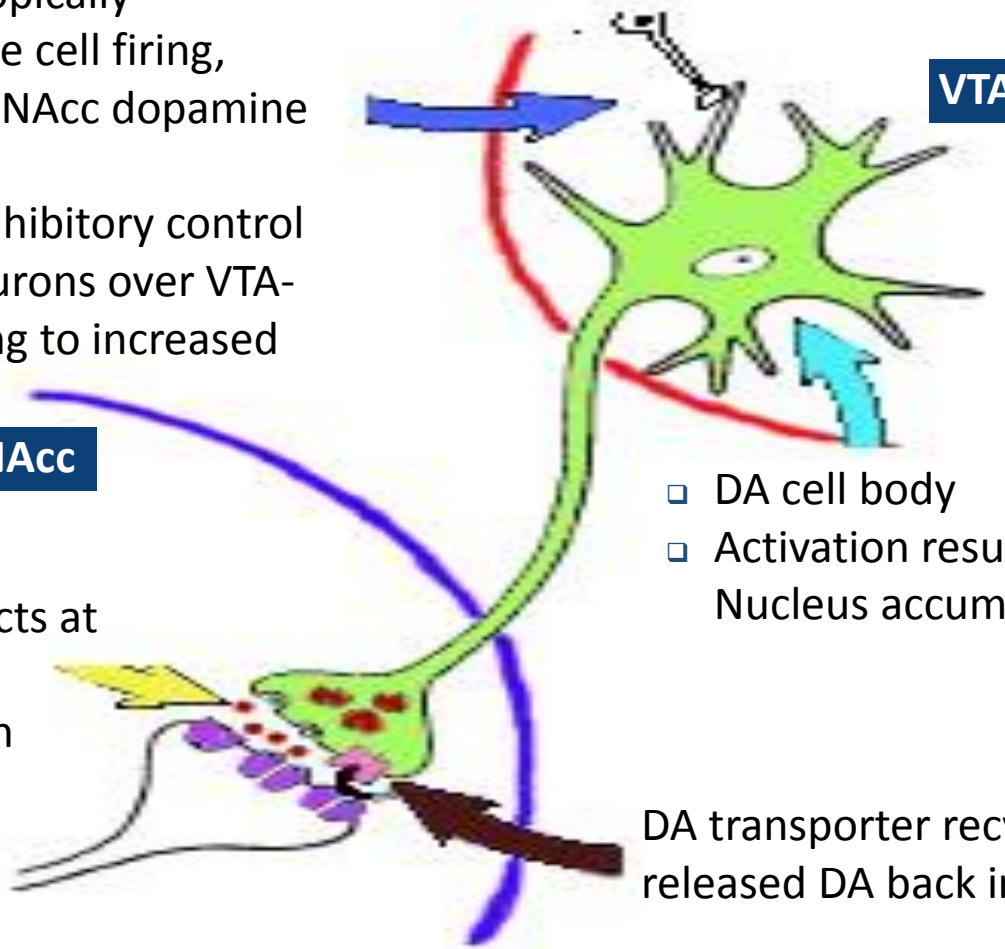
- Dopamine release in the Nucleus Accumbens shell





Dopamine

- GABA interneuron topically suppresses dopamine cell firing, resulting in reduced NAcc dopamine release.
- Alcohol blocks the inhibitory control exerted by these neurons over VTA-DA cell bodies leading to increased VTA – DA activity.



- DA cell body
- Activation results in DA release in Nucleus accumbens

- Release dopamine acts at postsynaptics DA receptors resulting in reward

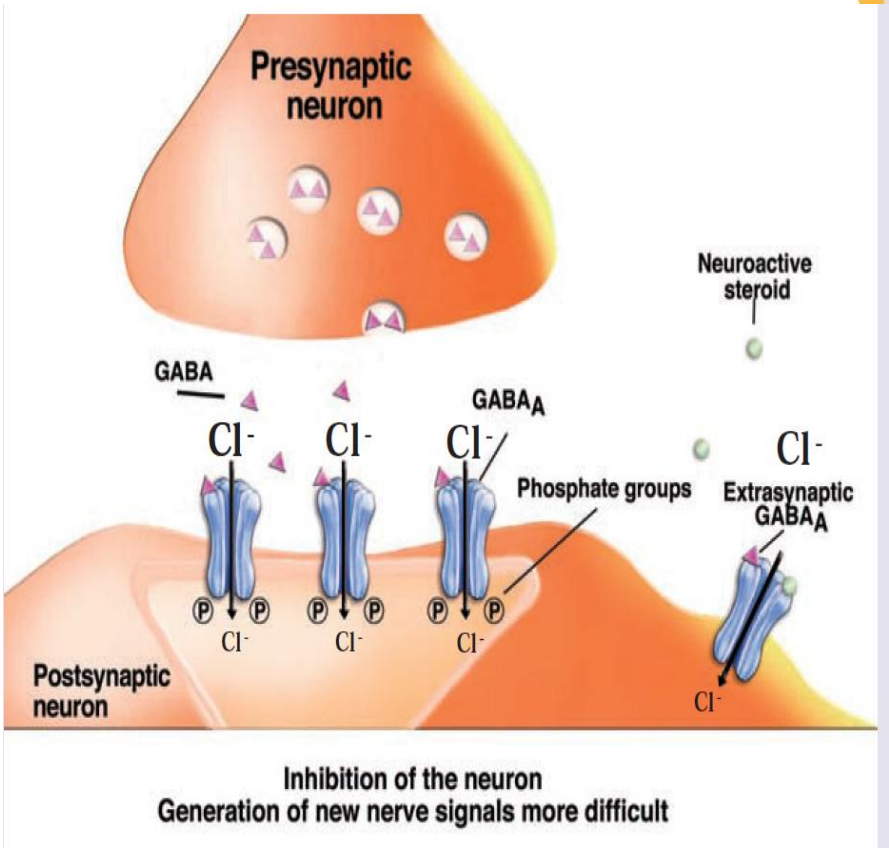
DA transporter recycles some of released DA back into nerve terminal

GABA

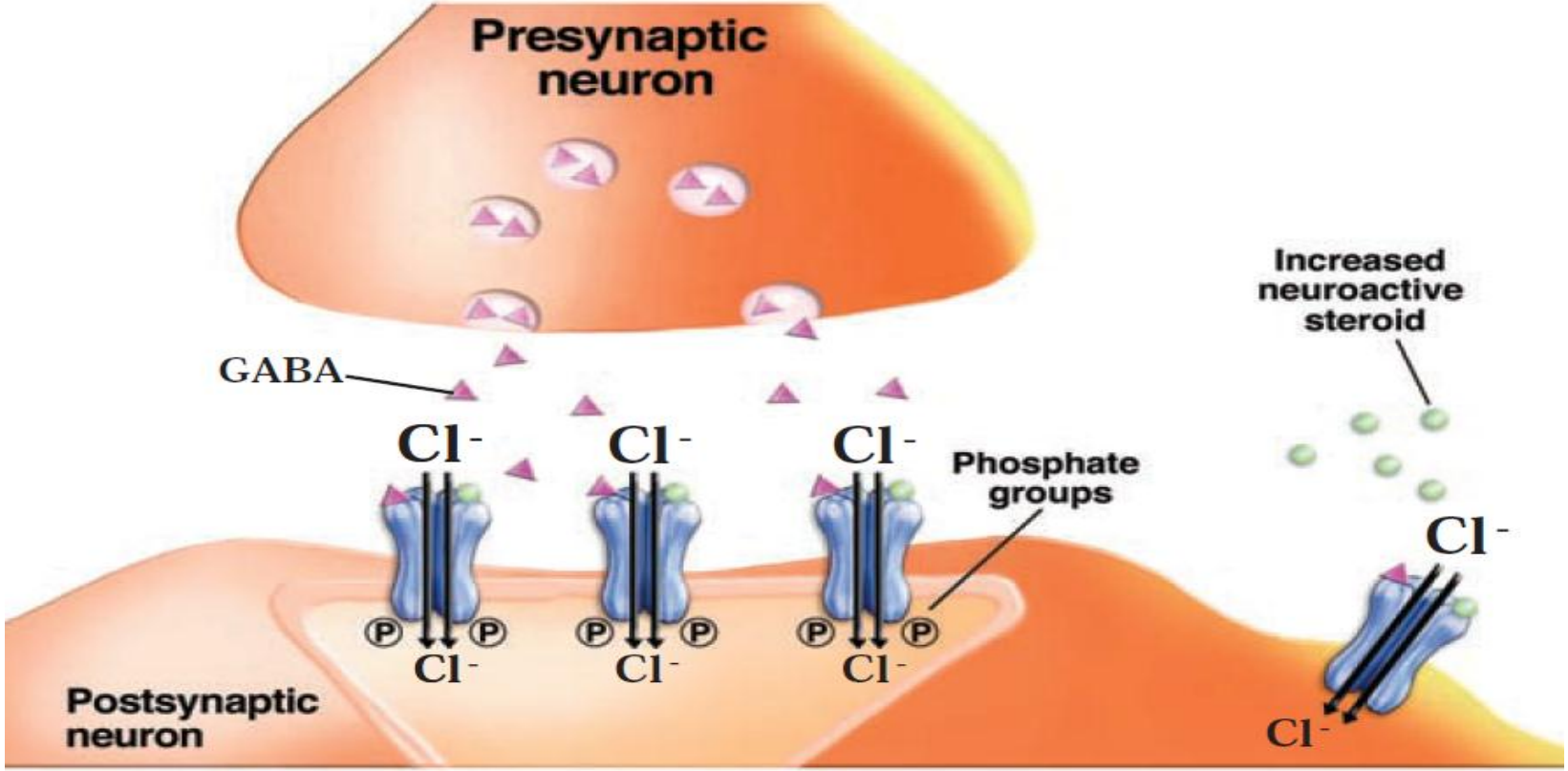
Effects	Mechanism
Sedation	Medial Septum ($GABA_A$)
AWS	Inferior Colliculus ($GABA_A$)
Reinforcement	VTA – NAc-DA ($GABA_A$)
Withdrawal	CeA GABA ↓ ($GABA_A$)
Neuroadaptation (Sensitization)	Reward, stress, emotional pathway interaction ($GABA_A$ -CRF)
↓Alcohol intake ↓Craving ↓Obsessive thinking about alcohol	$GABA_B$

GABA-Without Alcohol

- GABA acts in part through GABAA receptors, which serve as ion channels for chloride ions (Cl).
- Greater influx of Cl into the neuron makes it more difficult for the cell to generate a new nerve impulse.

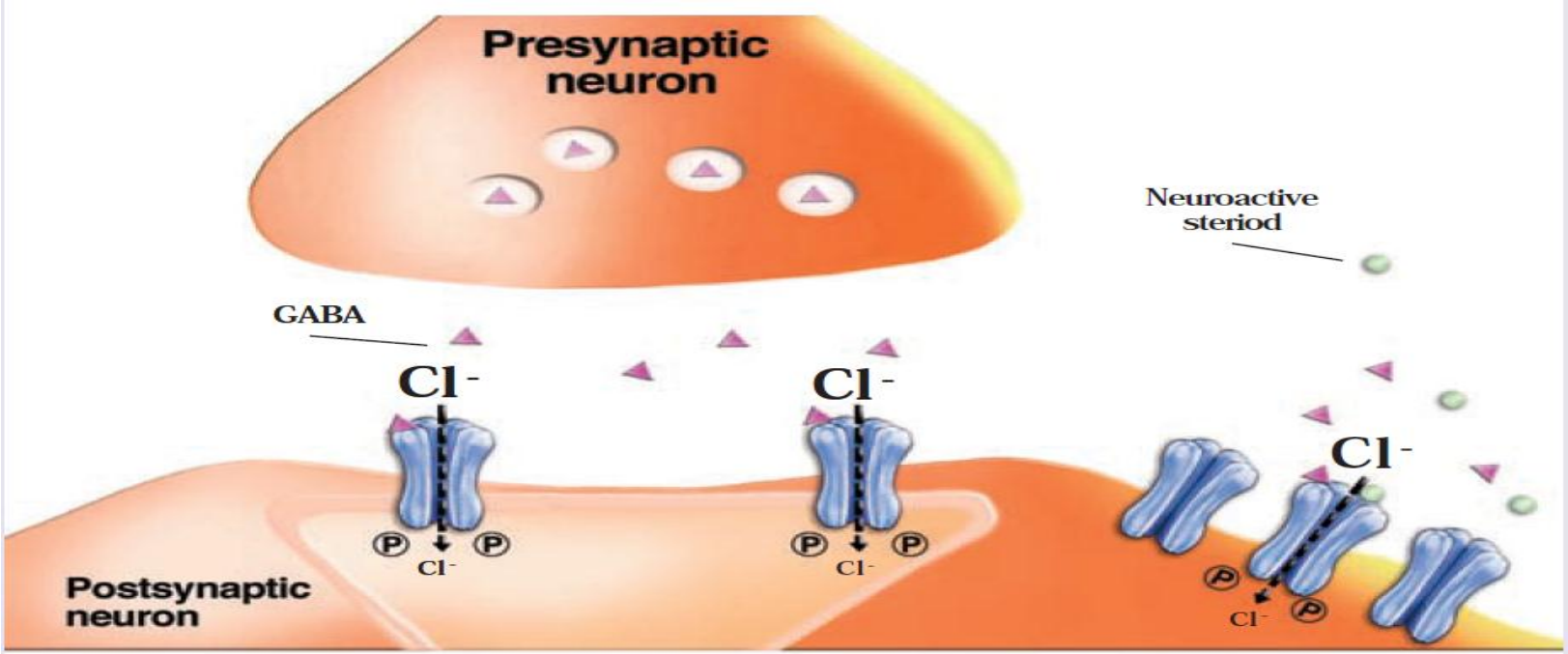


Acute Alcohol-GABA



Enhanced GABA activity
Greater Cl^- influx
Greater inhibition of neuron

Chronic Use - GABA



Reduced synaptic GABA activity
(due to changes in receptor properties)
Reduced Cl^- influx
Reduced inhibition of neuron

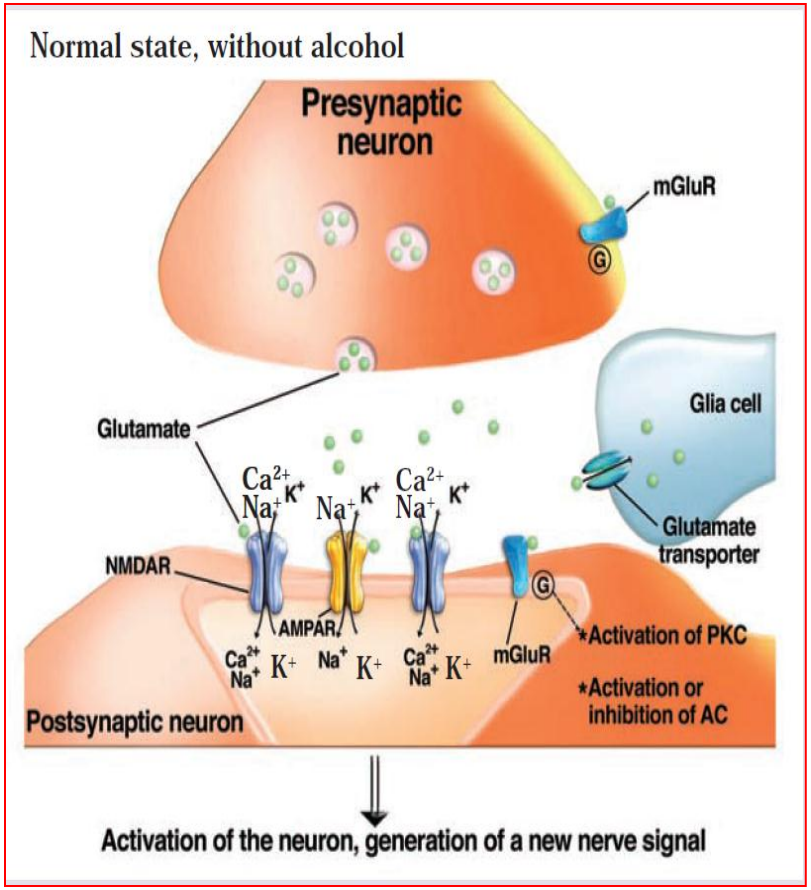
⇓

Anxiety, hyperexcitability

Glutamate

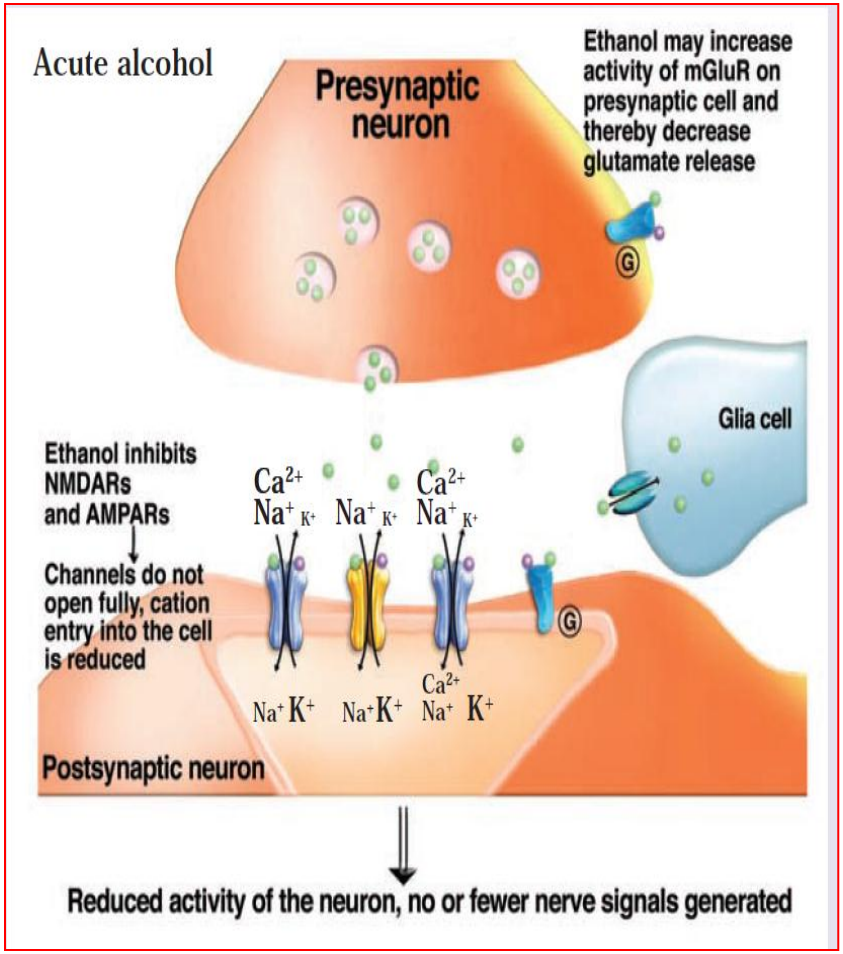
- Alcohol is an NMDA receptor antagonist
- NMDA involved in
  - Reinforcement (not robust)
  - Withdrawal
  - Neuroadaptation
  - Craving and cue, drug induced relapse
  - Seizures and neuronal degeneration
  - Cognitive dysfunction associated with intoxication

Glutamatergic System



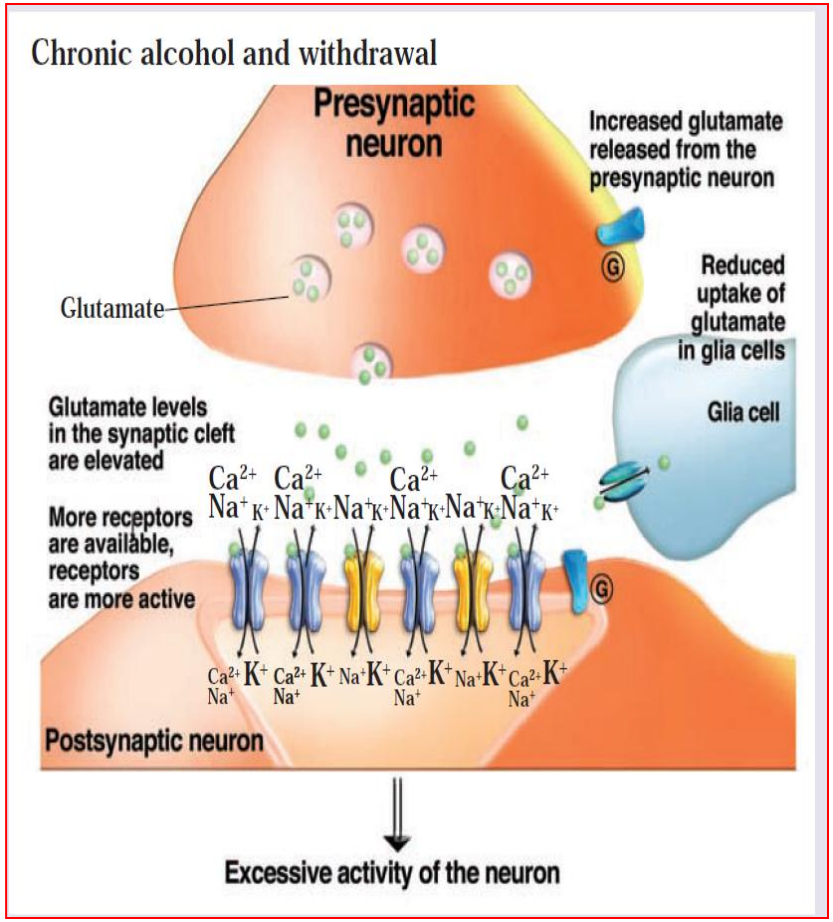
In the absence of alcohol, glutamate leads to the activation of the postsynaptic Neuron and the generation of a new nerve signal

Glutamate-Acute Alcohol



- Activity of the NMDARs and AMPARs is inhibited, reducing cation entry into the cell
- The activity of the neuron is reduced and no or fewer nerve signals are generated

Glutamate-Chronic Alcohol/Withdrawal



- Glutamate release at the synapse is enhanced and the number of synaptic NMDARs and AMPARs is increased.
- Glutamate induces excessive activity of the postsynaptic neuron

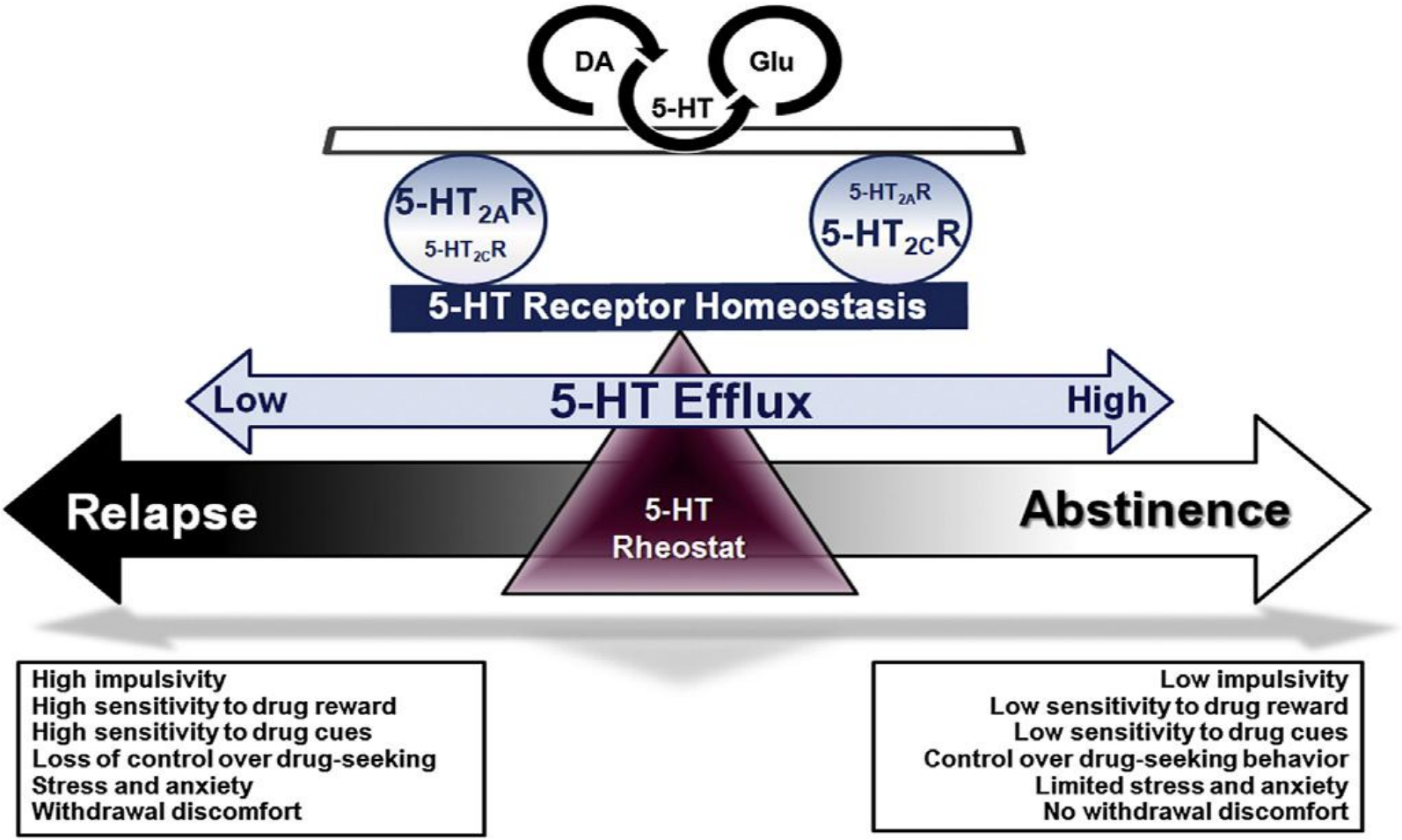
Serotonin in Addiction

- Midbrain DA under the tonic inhibitory control of serotonin
- Serotonin via interaction with the DA systems play a central role in the expression and appreciation of the rewarding effects of alcohol
- SSRI decrease voluntary ethanol consumption (mice)
- Type II or early onset alcoholism is related to a serotoninergic deficit

Serotonin in Addiction

Receptor	Action
5-HT_{1A} receptors partial agonism	Reduces ethanol consumption
5-HT_{1B} KO	Reduced intoxication
5-HT_2 & 5-HT_3 antagonists	Reduces ethanol consumption
5-HT_4 receptor antagonists	Reduced volitional ethanol intake

Serotonin in Addiction



Cunningham KA & Anastasio NC (2014) Neuropharmacology 76 : 460-478

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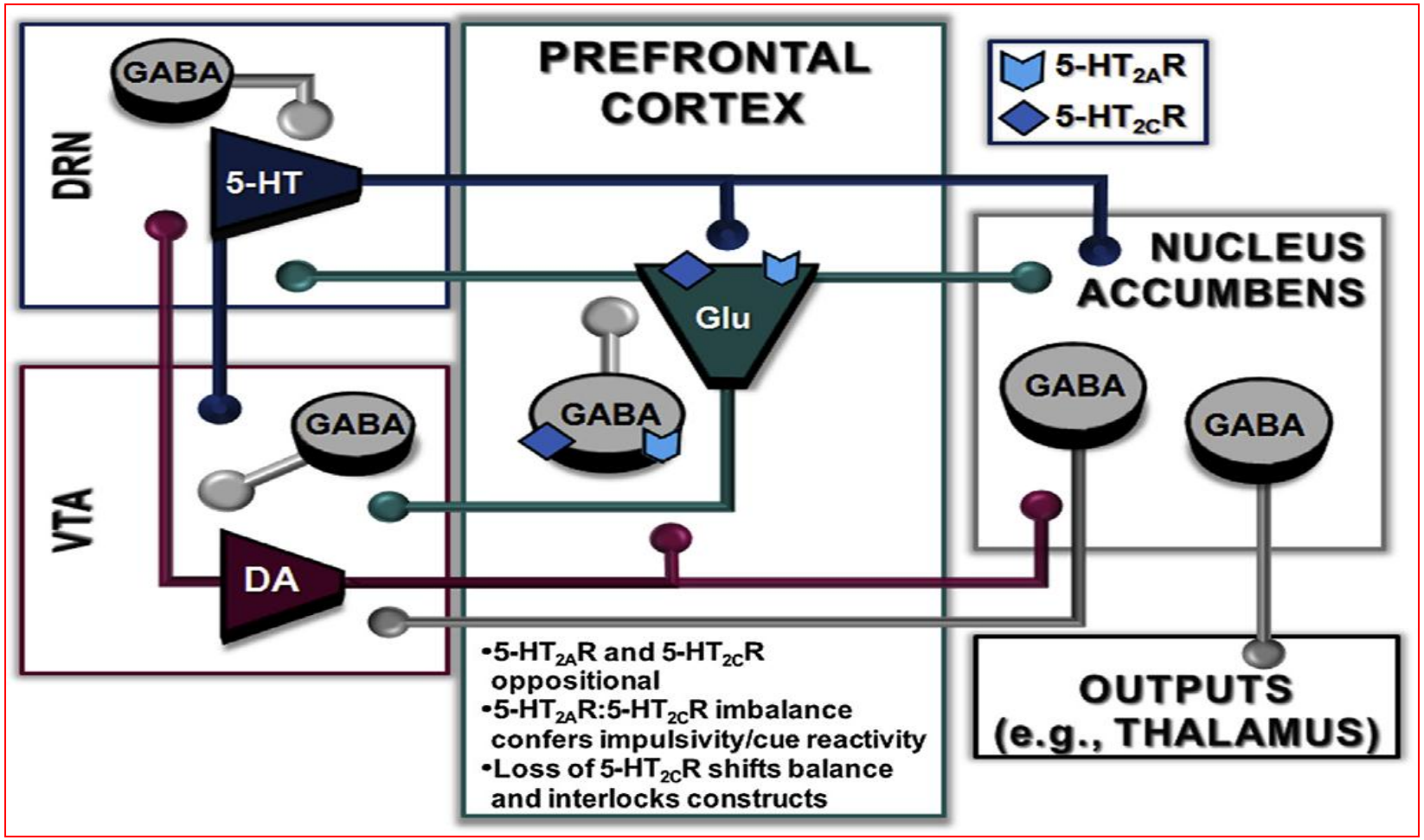
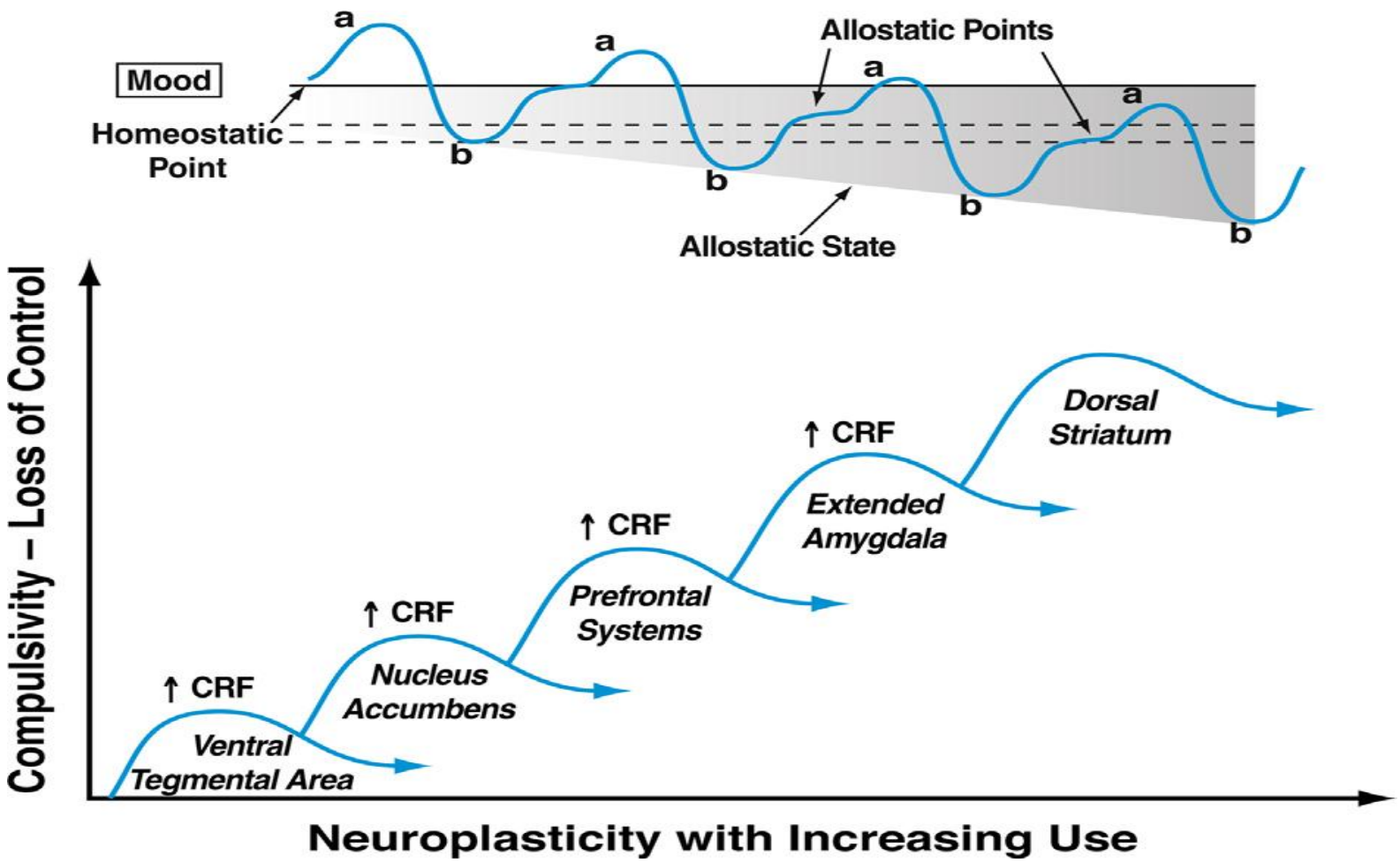
Serotonin in Addiction



CRF in Addiction



Zorrilla EP et al (2014) Frontiers in Neuroendocrinology 35: 234–244

CRF in Addiction

- Brain CRF mediates the facilitation of compulsive-like drug use
- Drug or alcohol withdrawal elevates CRF activity in the central extended amygdala, including the central nucleus of the amygdala (CeA), leading to a negative emotional state that motivates resumption of and maintenance of drug-taking

CRF in Addiction

- Withdrawal
  - Mediates negative affect during withdrawal
  - CRF receptor antagonist into CeA→ decrease anxiogenic effect
- Neuroadaptation
  - Antireward system leading to Neuroadaptation and transition to dependence
  - CRF antagonist - Prevents alcohol consumption and alcohol seeking behavior

CRF in Addiction

- Relapse
  - Mediates stress induced relapse
  - CRF antagonists blocks stress-induced relapse
  - CRF1 antagonists block
    - Ethanol withdrawal induced relapse
    - Anxiety related alcohol consumption

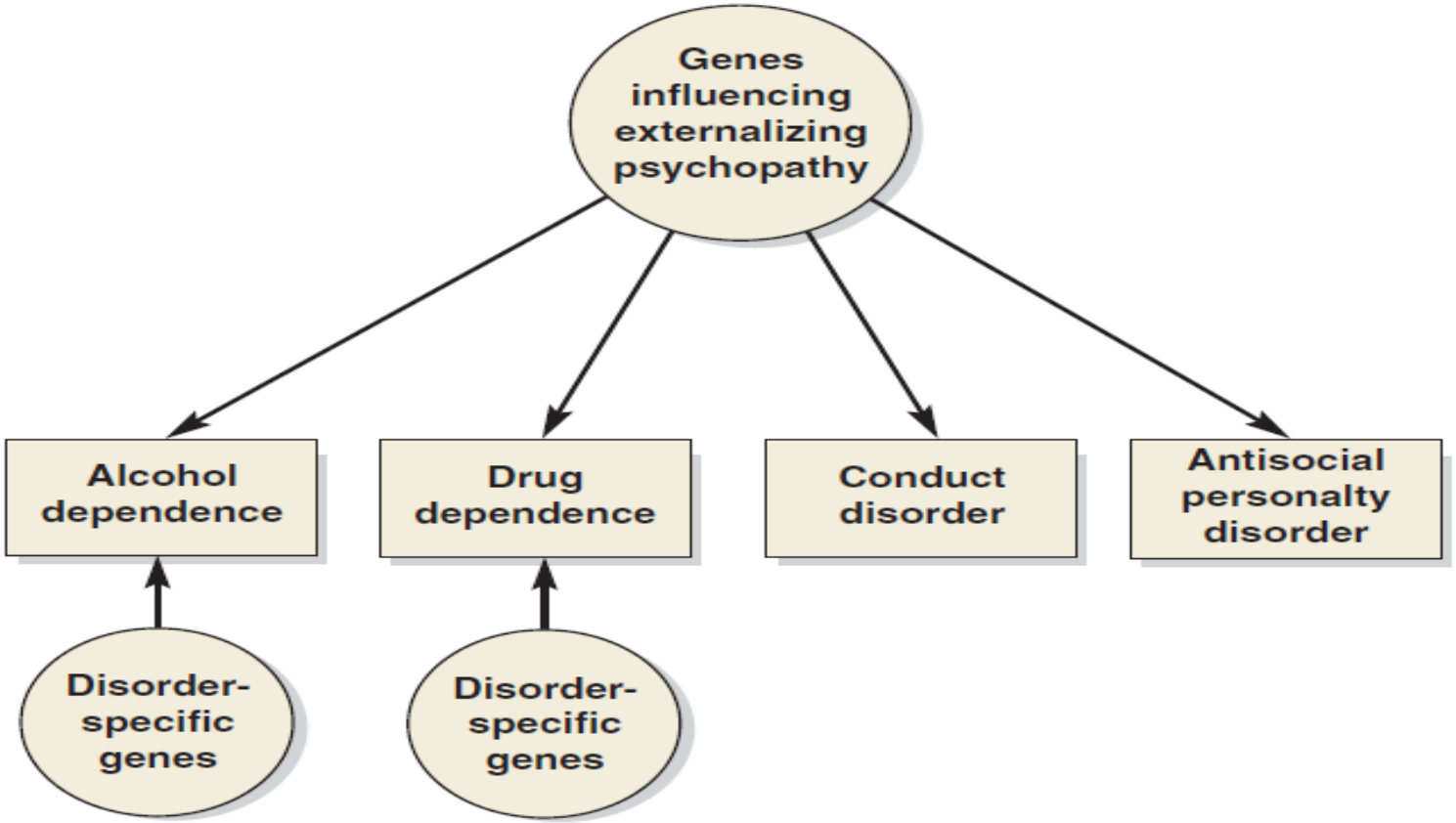
Endocannabinoids in Addiction

Phase	Function
Reinforcement	CB1 receptor agonism
Withdrawal	Upregulation of CB1 and ↓ AEA
Neuroadaptation	Downregulation of CB1 receptors
Stress induced alcohol use	CB 1 receptor involvement
Relapse	CB1 agonism and antagonists prevent relapse

Maldonado R et al (2006) TINS 29: 225-232

Addiction Genetics

Addiction Genetics



Dick DM & Agraval A (2008) Alcohol Research & Health 31:111-118

Addiction Genetics

- Polygenic, with vulnerability arising from the simultaneous impact of functional variations at several genes.
- Cocaine and opiates, among the most addictive of substances, are among the most heritable. On the other hand, hallucinogens are among the least addictive, and are also the least heritable.

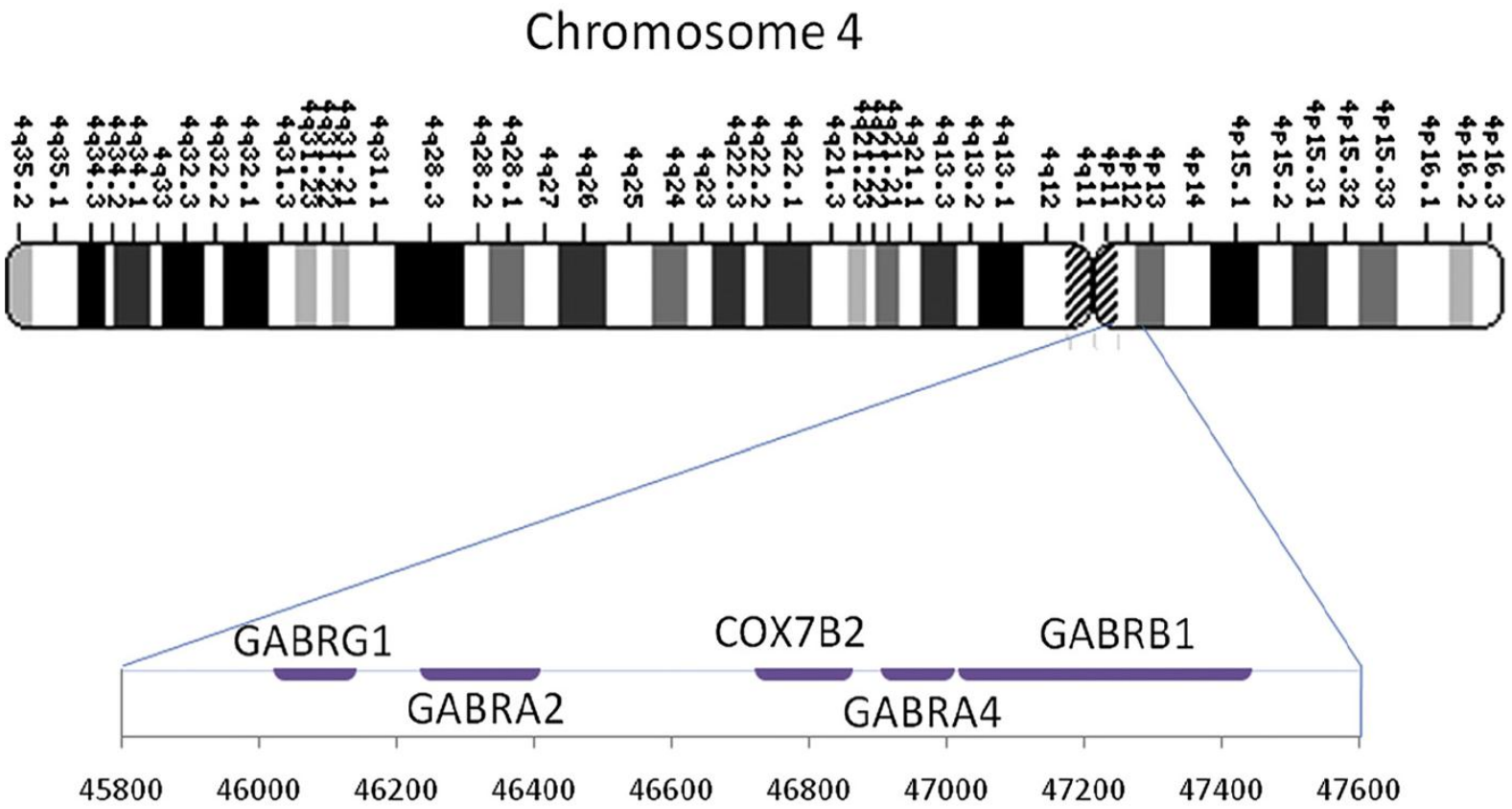
Addiction-Genetics

- Linkage mapping and association mapping have identified susceptibility loci for addiction-related phenotypes, especially for alcohol dependence (AD) and ND.
- However, few putative genome linkages have been replicated in independent studies, probably because of genetic heterogeneity

Addiction Genetics

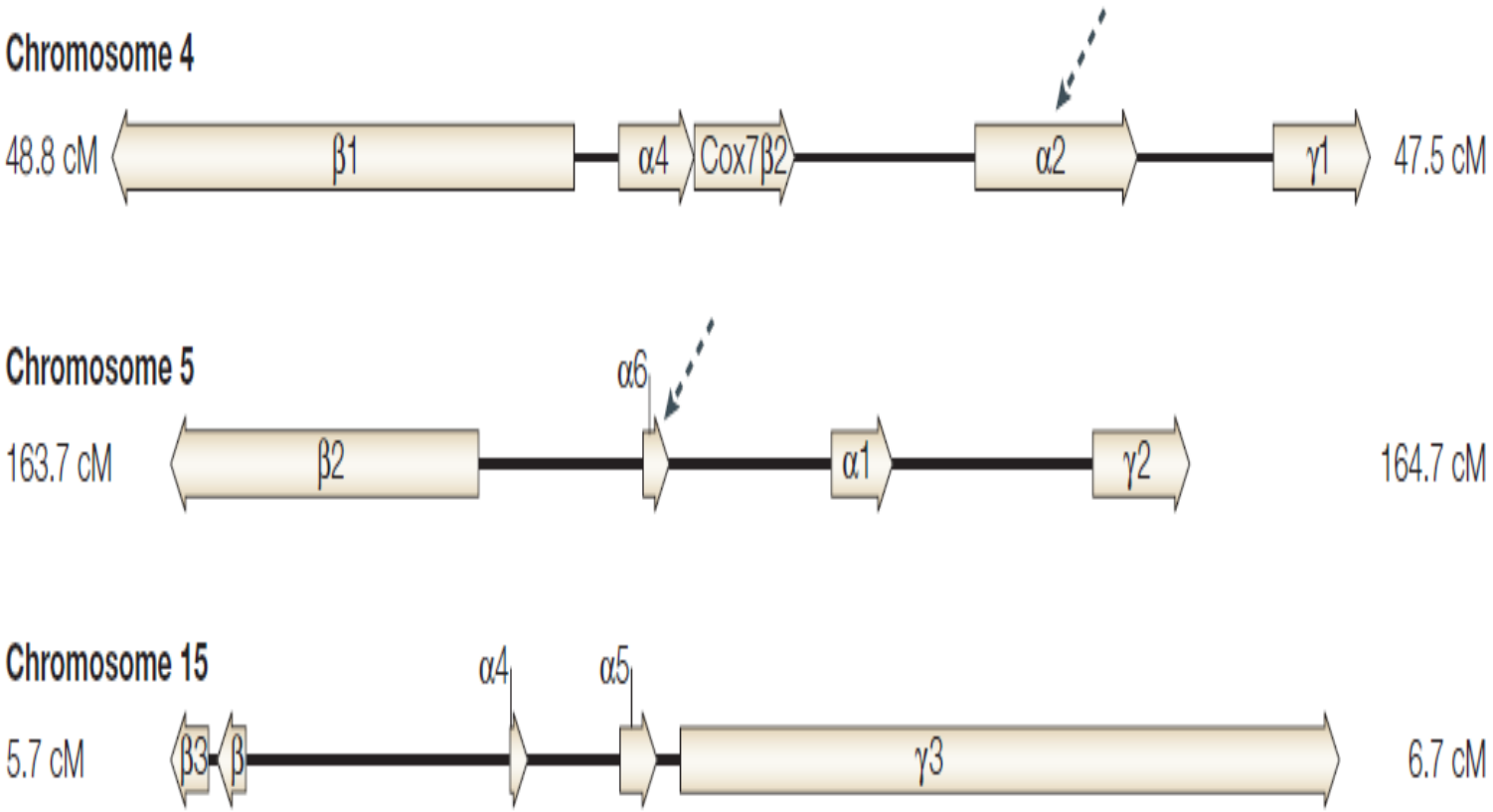
- Regions on chromosomes 2–5, 7, 9–11, 13, 14 and 17 have independent evidence of ‘suggestive’ or ‘significant’ linkage
- Regions on chromosomes 4, 5, 9, 10, 11 and 17 receiving the strongest support for harbouring susceptibility genes for addictions to multiple drugs

Addiction Genetics



Chromosome 4 region p12

Addiction Genetics



Addiction-Genetics

- Genes in the aldehyde dehydrogenase (ADH) gene cluster
- Genes encoding nicotinic acetylcholine receptor (nAChR) subunits
- GABAA receptor subunit 2 (GABRA2), Ankyrin repeat and kinase domain containing 1
- (ANKK1) and Neurexins

Addiction-Genetics

- Variants in CHRNA4, which encodes the α4 subunit, with ND
- CHRNA5–A3–B4 gene cluster with alcohol and cocaine addictions
- Variants in ANKK1, encoding a protein
- Kinase involved in signal transduction, associated with susceptibility to ND, AD, and co-morbid alcohol and drug dependence
- Neurexins 1 for ND and neurexin 3 for polysubstance, alcohol and opioid abuse

Addiction-Genetics

- Telomere of chromosome 11p,which contains the dopamine receptor D4 (DRD4)gene
- Chromosome 4q, contains the alcohol dehydrogenate (ADH) gene cluster
- Chromosome 4p region near the centromere contains GABAA gene cluster.
- Chromosome 15-CHRNA

Addiction-Genetics

Gene symbol	Gene name	Biological function	Chromosomal location	Drug (phenotype)	Evidence from knockout animal model
5HTT (also known as *SERT*)	5-hydroxytryptamine transporter	Neurotransmitter transport	17q11.1–q12	Alcohol (i, d, c), cocaine (d, c), heroin (d), methamphetamine (d), nicotine (d)	Increased sensitivity to alcohol-induced sedation and hypnosis; motor-coordination deficits in response to alcohol; reduced gross alcohol intake; altered behavioural responses to cocaine and alcohol
CYP2A6	Cytochrome P450, family 2, subfamily A, polypeptide 6	Oxidation reduction	19q13.2	Alcohol (d), nicotine (i, d, c)	None
DAT1	Dopamine transporter	Neurotransmitter transport	5p15.3	Alcohol (d, c), cocaine (d), heroin (d), methamphetamine (d), nicotine (i, d, c)	Reduced alcohol preference in female mice; cocaine-induced stereotypy (repetitive behaviour)
DRD2	Dopamine receptor 2	Synaptic transmission, dopaminergic	11q23.1–q23.2	Alcohol (d, c), cocaine (d), heroin (d), nicotine (i, d, c)	Alcohol preference and alcohol-induced ataxia; reduced rate of high-dose self-administration of cocaine
IL10	Interleukin-10	Cytokine activity	1q31–q32	Alcohol (d)	None
BDNF	Brain-derived neurotropic factor	Regulation of synaptic plasticity	11p13	Alcohol (i, d, c), nicotine (d), cocaine (d), methamphetamine (d)	Increased alcohol intake; increased preference for cocaine

Ming D. Li & Margit Burmeister (2009)Nature Reviews Genetics **10: 225-231**

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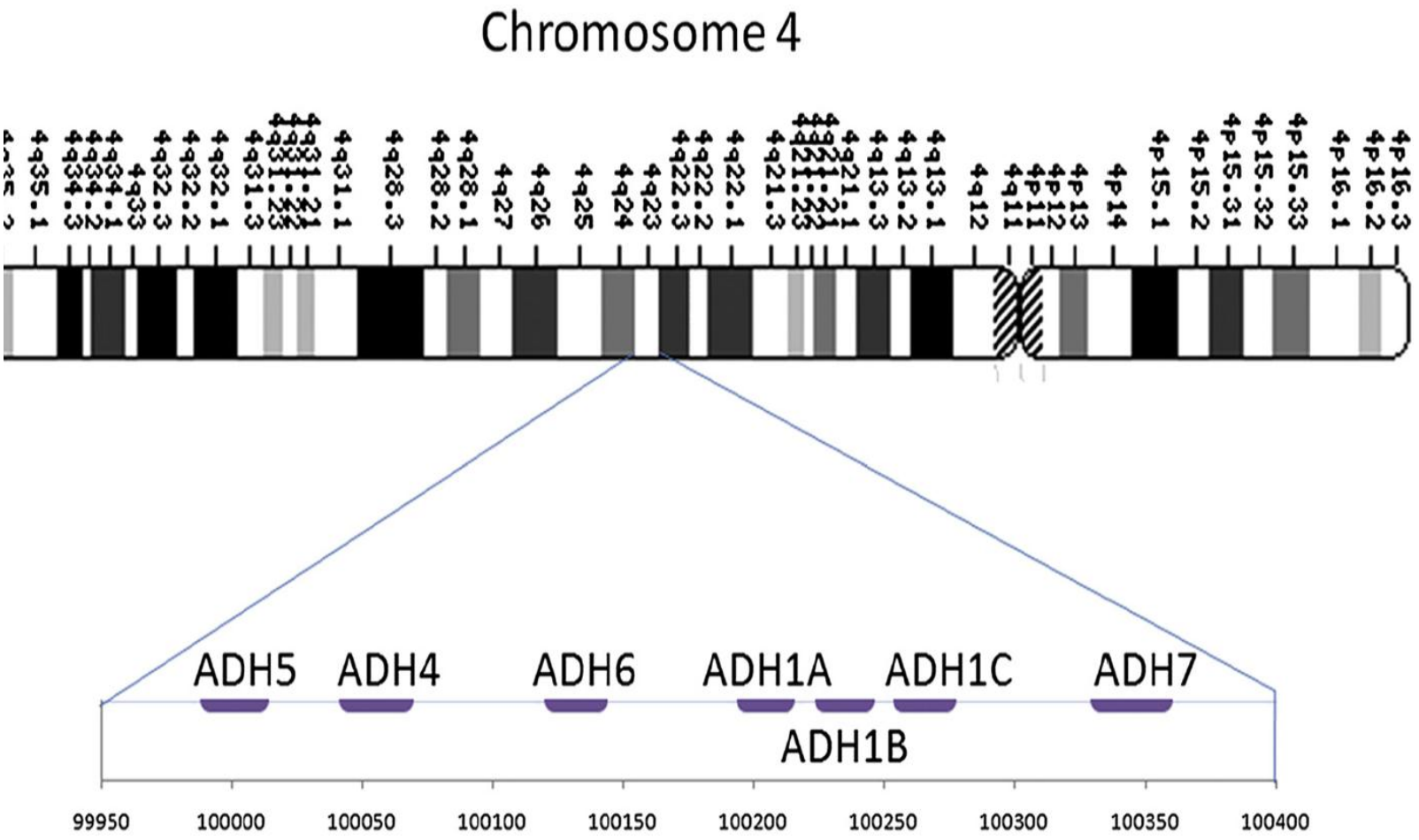
Alcohol

- Among first-degree relatives of alcohol-dependent individuals, the risk of alcohol dependence is 3 to 8 times the baseline population risk
- The ADH genes are located in a small region on chromosome 4
- The ALDH gene associated with alcohol dependence, ALDH2, is on chromosome 12q24.2.
- ALDH2 variant leading to decreased risk of alcohol dependence

Alcohol

- ADH locus contains a cluster of seven genes, of which ADH2 is the most important across populations, although functional variants in ADH4 and ADH7 might also be involved

Alcohol


Chromosome 4
ADH5
ADH4
ADH6
ADH1A
ADH1C
ADH7
ADH1B
99950
100000
100050
100100
100150
100200
100250
100300
100350
100400

Alcohol

- The odds ratio of alcohol dependence for subjects with 1 ALDH2*2 allele is 0.33, and there are almost no documented cases of people with alcohol dependence who are homozygous for ALDH2*2.
- This allele interacts with a nonsynonymous gene variant for the ADH1 enzyme, ADH1B*1, by further decreasing the odds ratio of alcohol dependence to 0.05 in the presence of both alleles

Alcohol

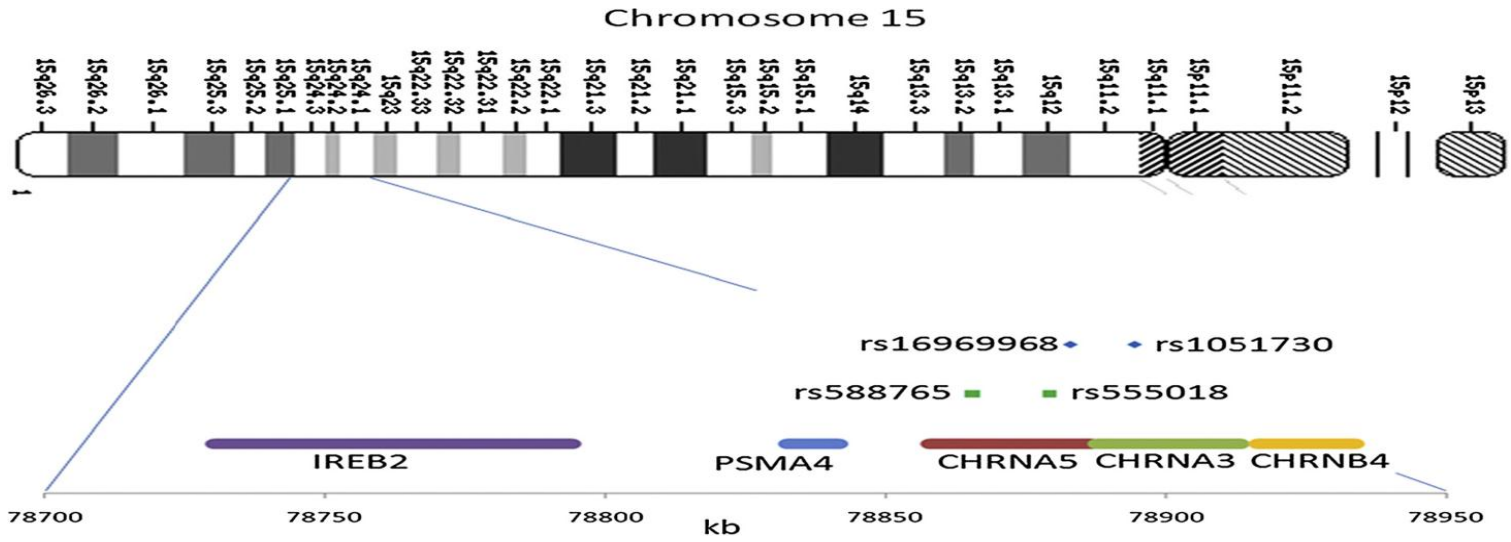
- ADH1B*2 allele (previously known as ADH2*2).
- This variant is in the ADH1B gene that encodes the b2 subunit of ADH, and results in histidine instead of arginine at position 48. protective against alcohol dependence, with an odds ratio of 0.12 in a Chinese population

Nicotine

- Smokers of European ancestry with the CYP2B6*6 genotype in the cytochrome p450 gene are more likely to relapse than smokers of other genotypes when on placebo, but they can be helped by bupropion treatment
- Linkage of chromosome 9 with smoking behaviour has been reported in several independent studies, and GABBR2 accounts for 28%–38% of this linkage signal

Nicotine

- Variants in CHRNA4, which encodes the α4 subunit, with ND



CHRNA5 gene may play a dual role in modulating susceptibility to addiction via the different mechanisms of action of cocaine and nicotine.

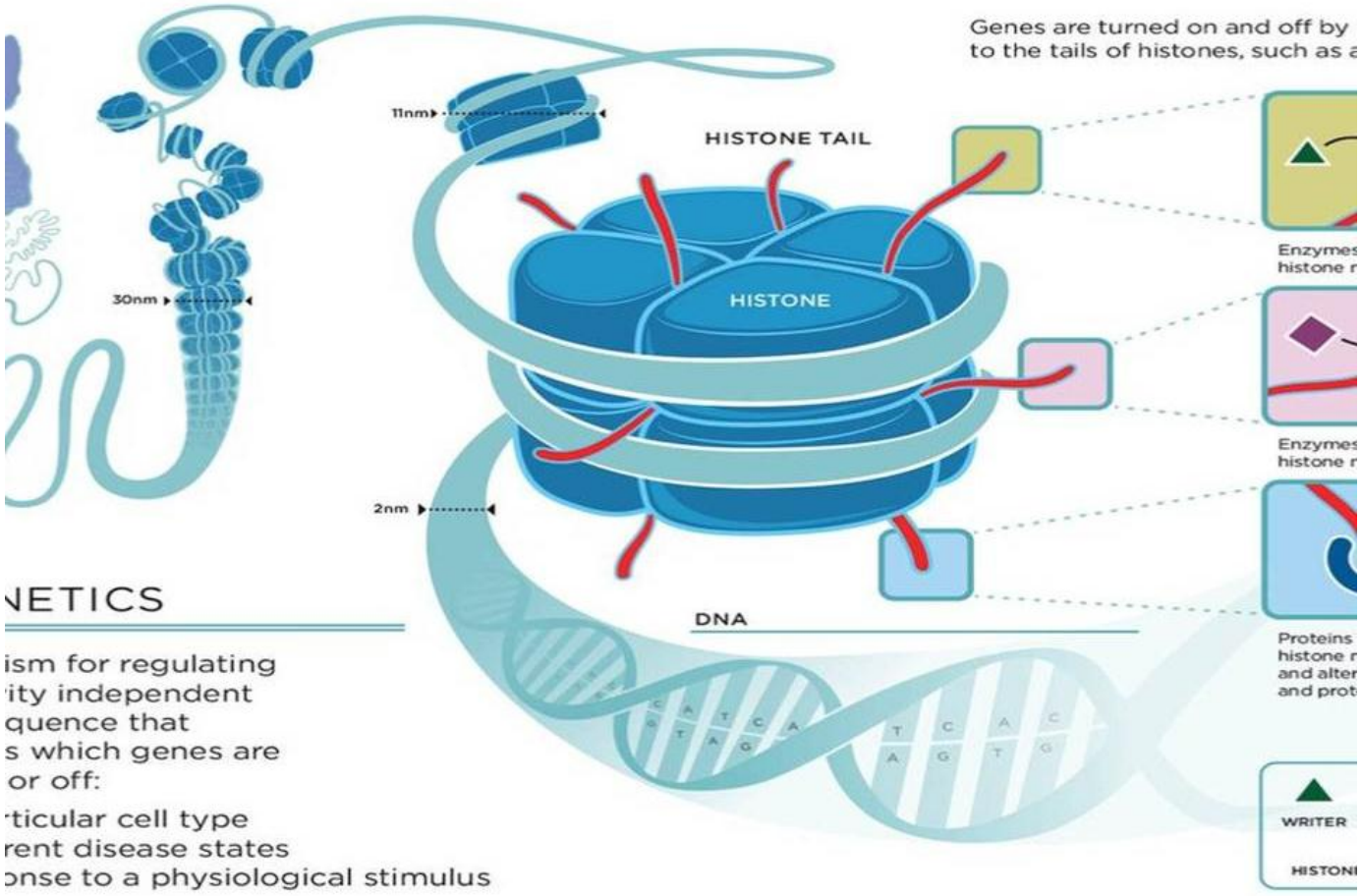
Addiction-Genetics

- CNIH3(association for cornichon family AMPA receptor auxiliary protein 3) polymorphisms involvement in the pathophysiology of opioid dependence, complementing prior studies implicating the α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA) glutamate system.

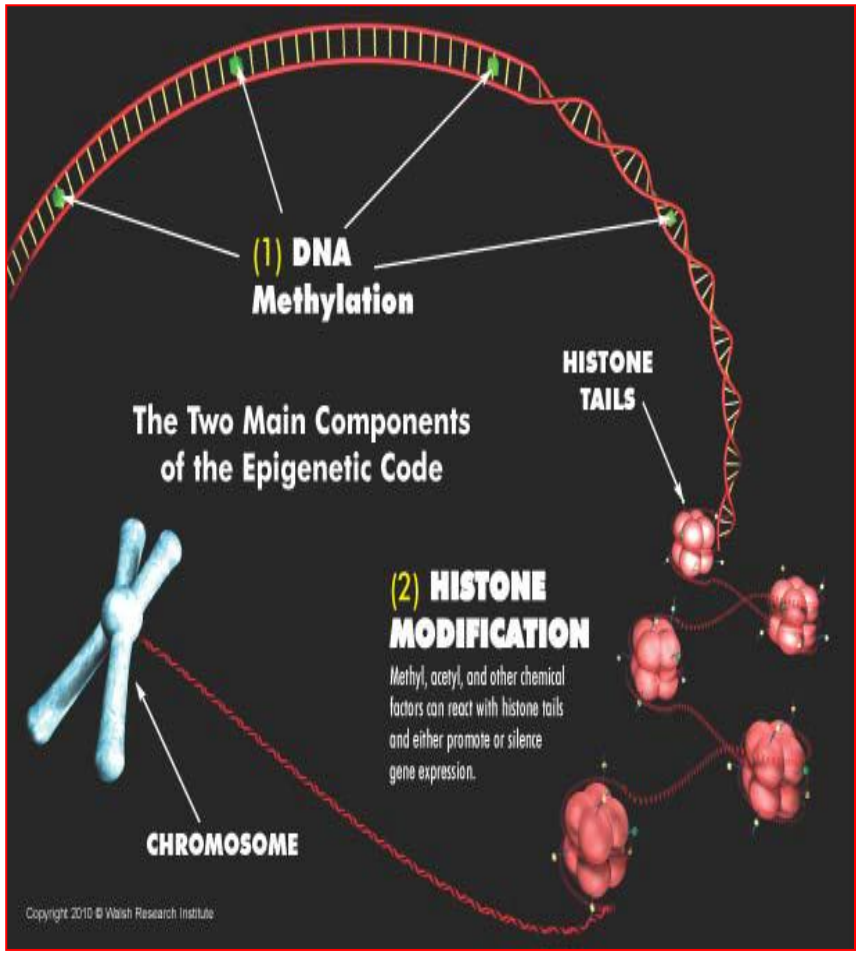
Nelson EC et al (2015) Molecular Psychiatry : 1–7

Epigenetics-Addiction

Altered gene expression without changes in DNA sequence

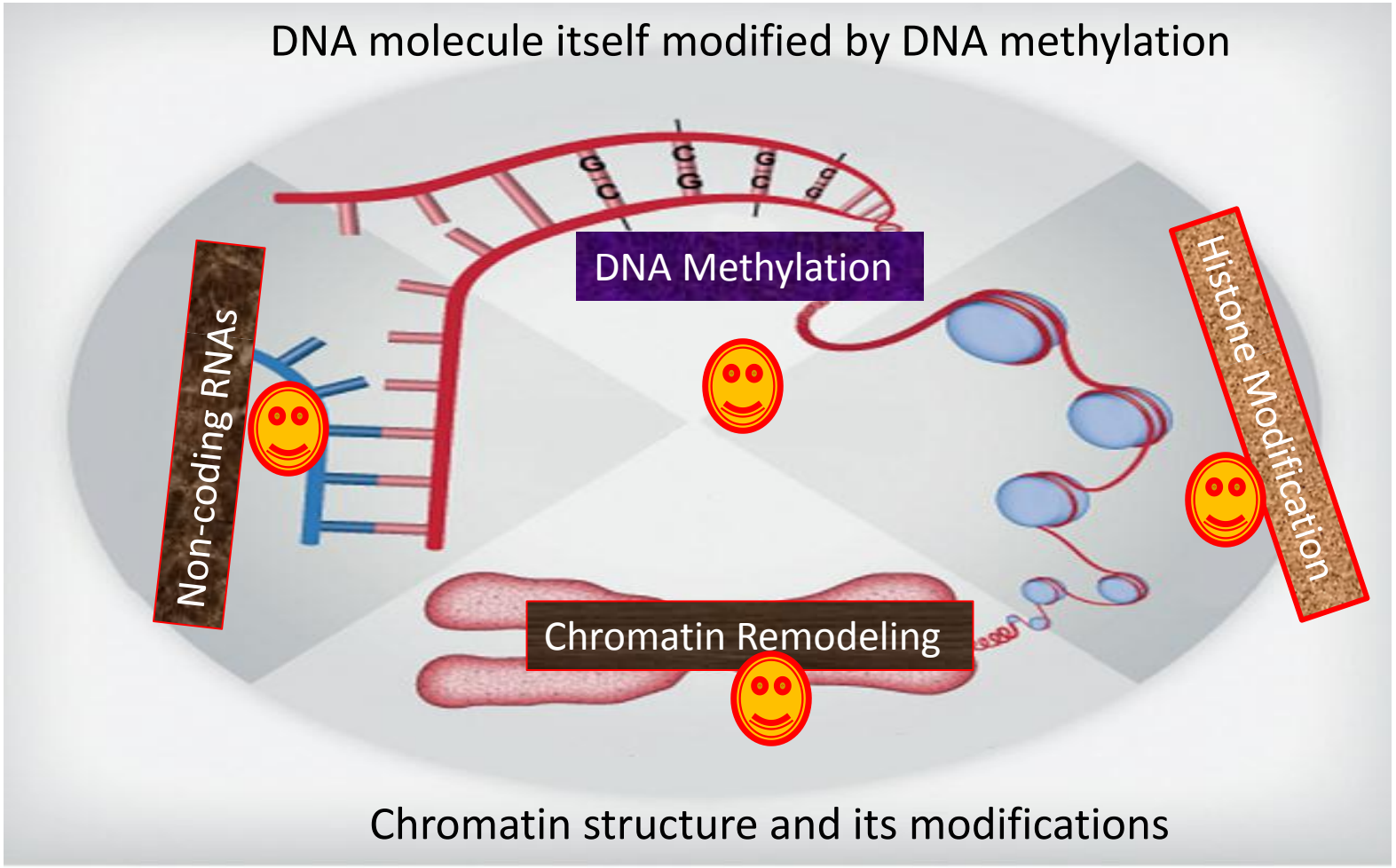


Epigenetic Mechanisms



- Two major epigenetic mechanisms:
  - Direct DNA Methylation
  - Histone Modification

Epigenetic Mechanisms

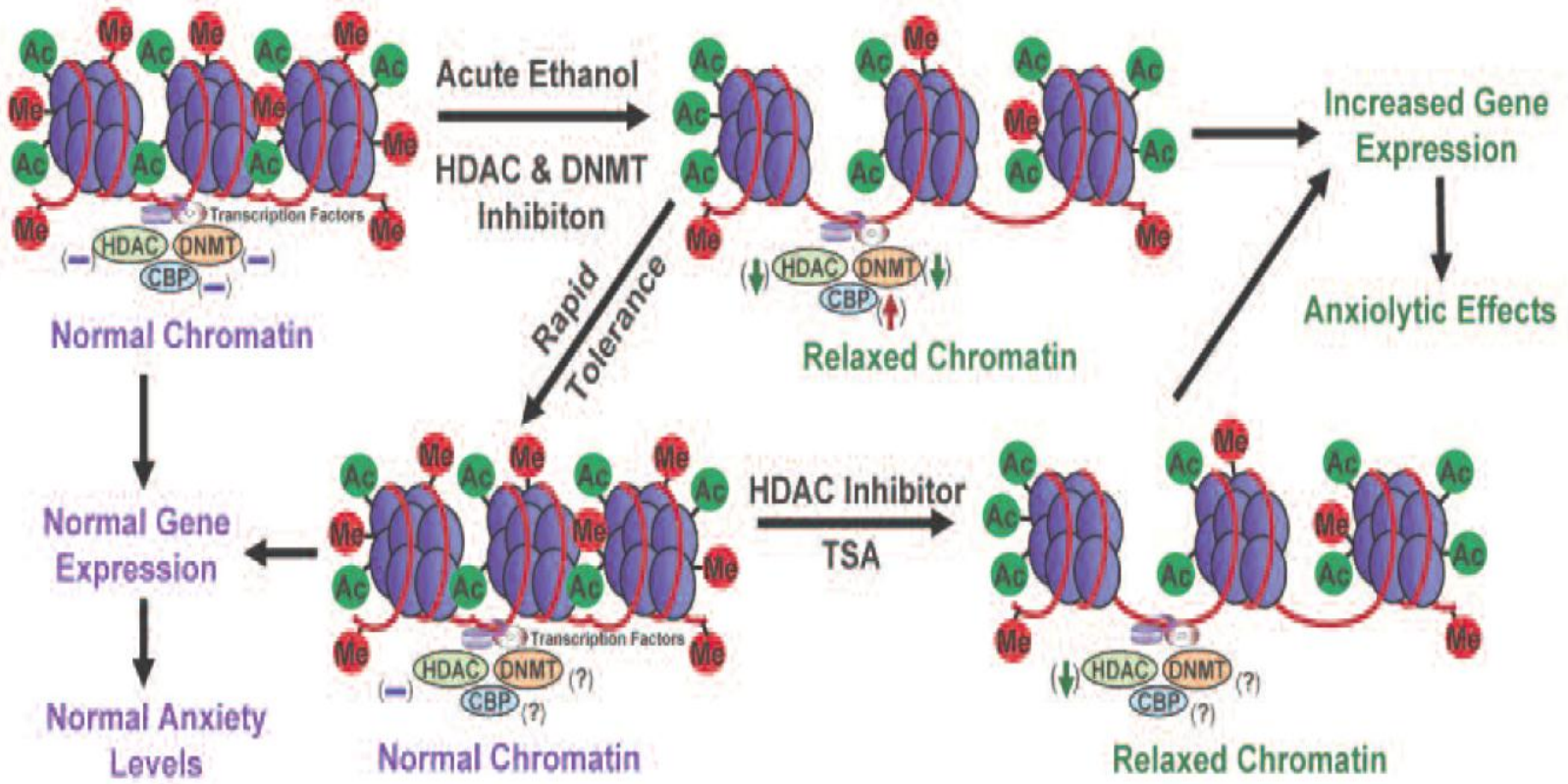


Hsieh J & Song H (2013)

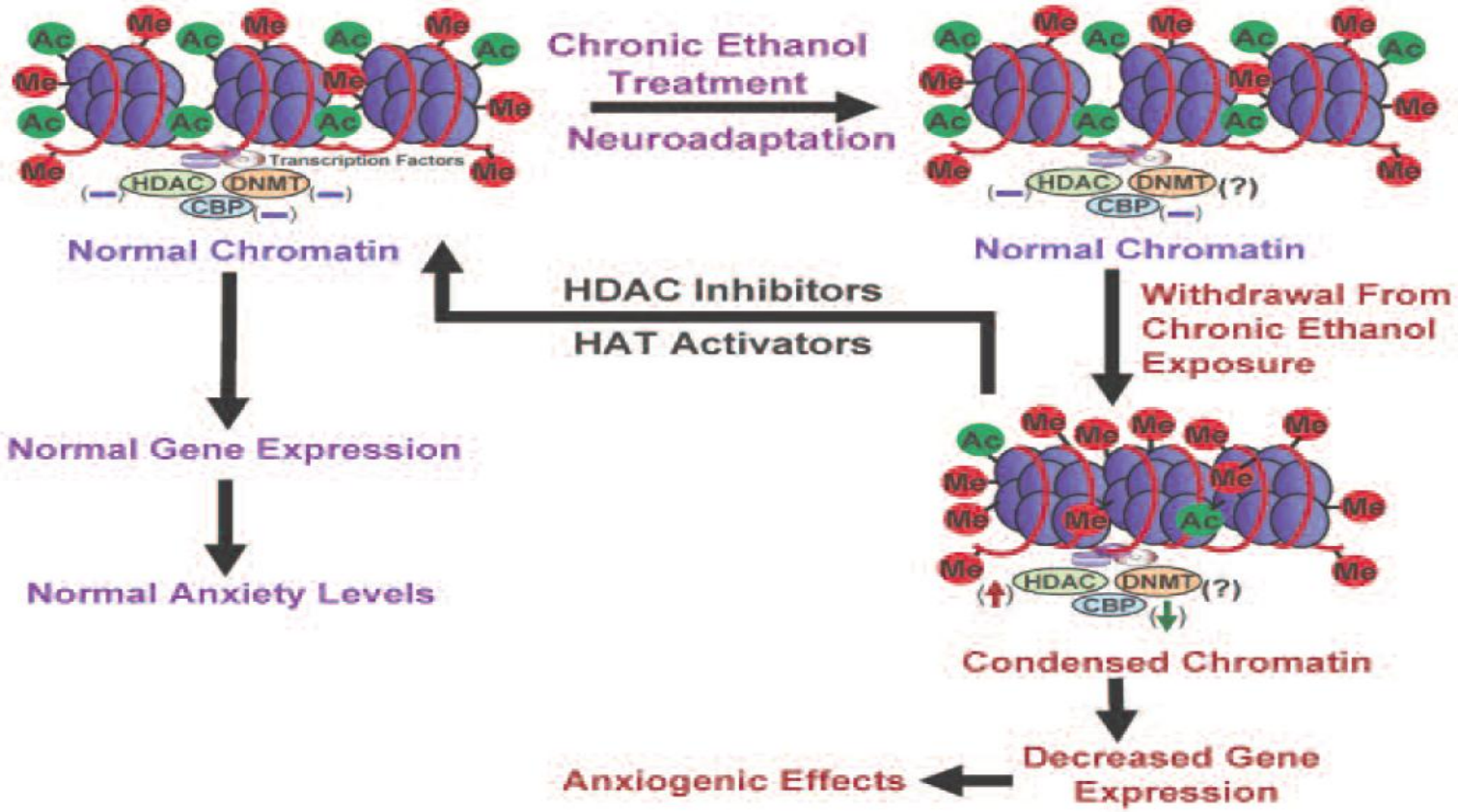
Epigenetics and Addiction

Treatment	Modification	Effect
Chronic cocaine exposure	↑ H3 Acetylation	↑ Induction of BDNF at promoter region
Acute cocaine exposure	↑ H4 acetyation	↓ fosB
Co-administration of sodium butyrate and cocaine	↑ H3 acetylation	↑ cFos mRNA in striatum
Chronic infusion of MS-275	↑ Global H3 acetylation	Blocks cocaine induced locomotor sensitization

Epigenetics of Alcohol Use



Epigenetics of Alcohol Use



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