Neuroscience of Addiction

A Brief Review

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What are we looking at?

- Importance of neuroscientific jargon
- Concept of addiction
- Stages of addiction
- Systems
- Progression

Importance of Neuroscientific Jargon

Importance of Neuroscientific Jargon

- Stigma
- Concept of disease – Lesion ?, Changes (Imaging data)
- Heritability

Heilig M et al. doi.org/10.1038/s41386-020-00950-y

Concept of Addiction

Addiction

- Risky (hazardous) substance use – quantity / frequency indicators of consumption
- SUD - criteria for a DSM-5 diagnosis (mild, moderate, or severe)
- Addiction - who exhibit persistent difficulties with self-regulation of drug consumption
- Among high risk individuals, a subgroup will meet criteria for SUD and, among those who have an SUD, a further subgroup would be considered to be addicted to the drug

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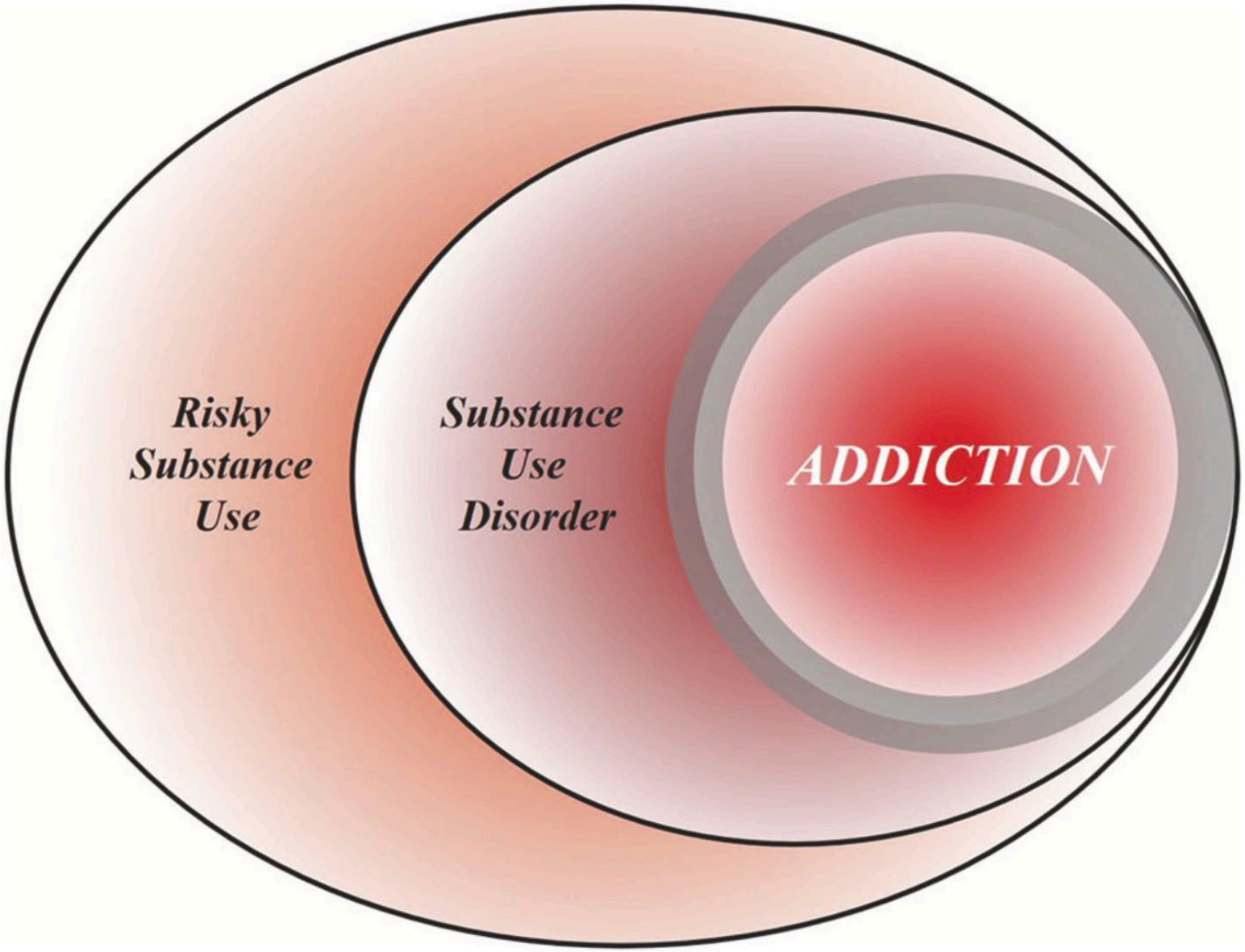

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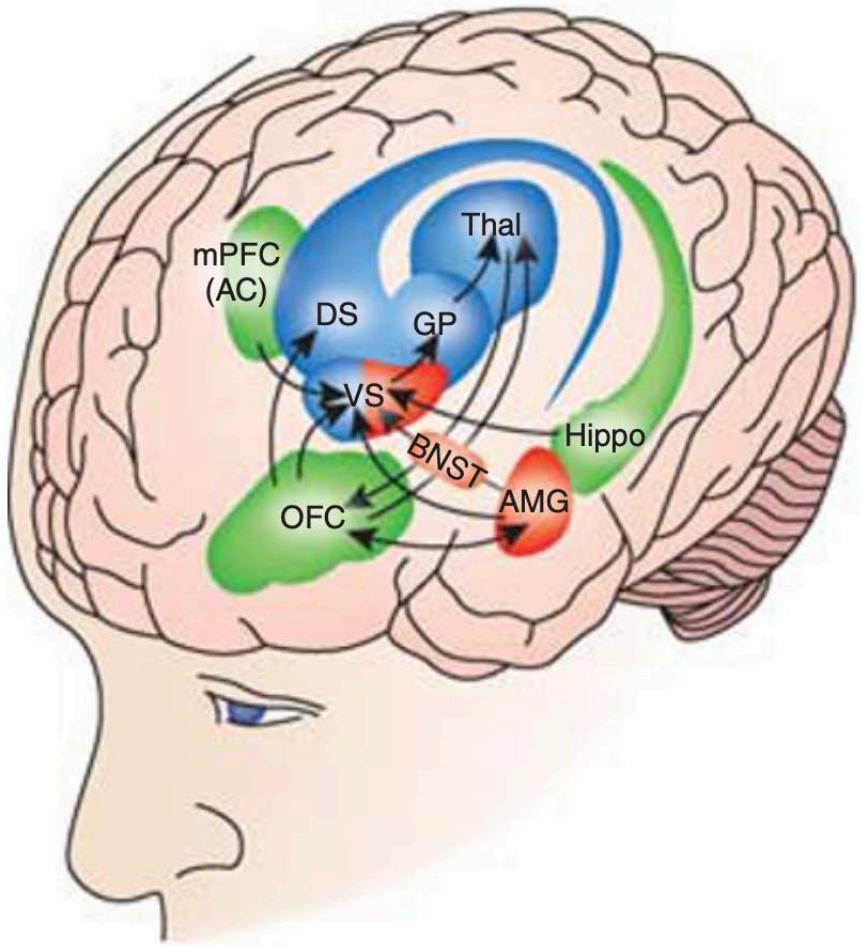
Addiction

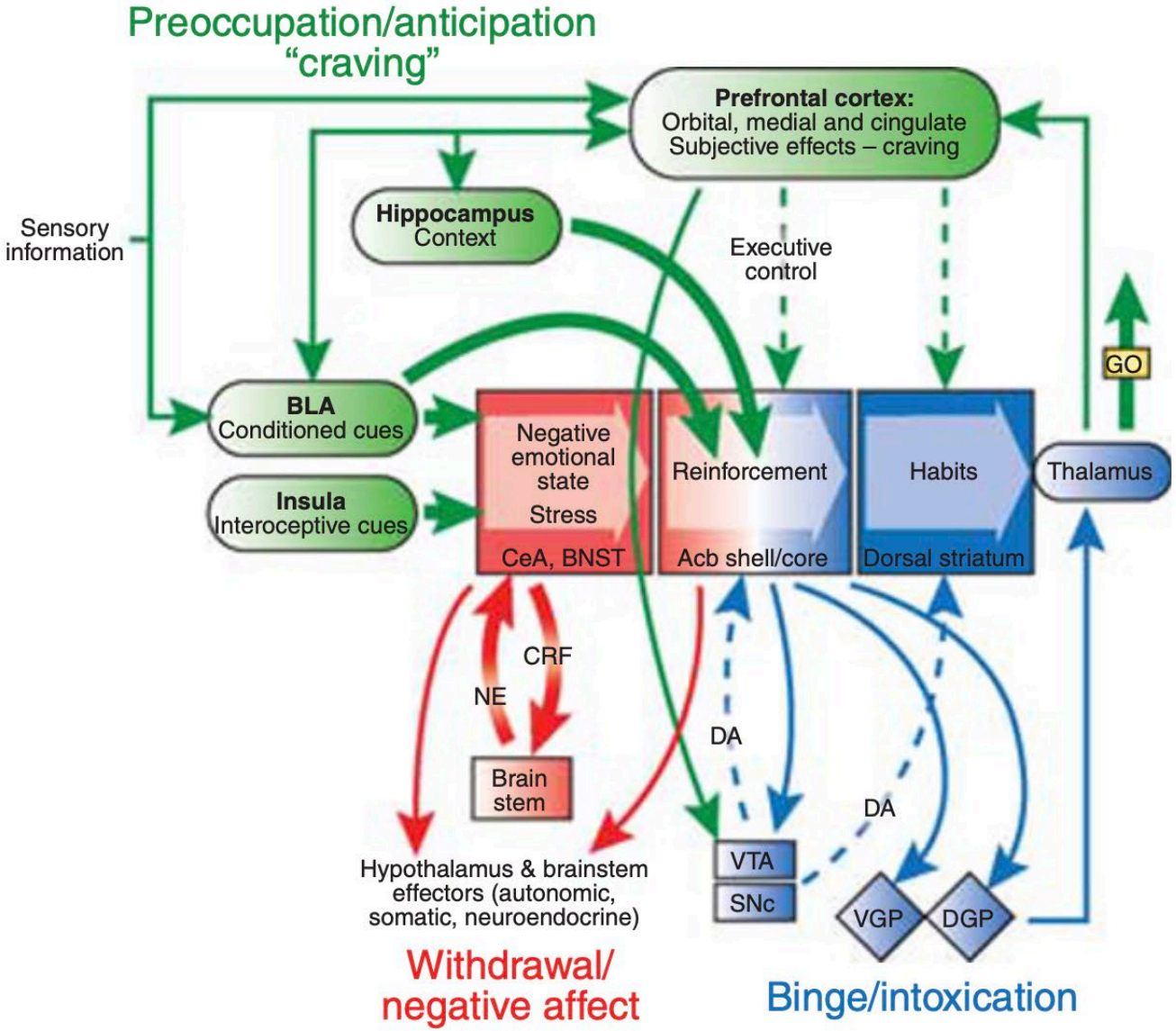
Chronically relapsing disorder

- compulsion to seek and take the drug
- loss of control in limiting intake
- emergence of a negative emotional state (eg. dysphoria, anxiety, irritability) when access to the drug is prevented
- **NOT LIMITED TO SUBSTANCES OR CHEMICALS**

Koob GF, Volkow N. Neuropsychopharmacology REVIEWS (2010) 35, 217–238

Stages of Addiction





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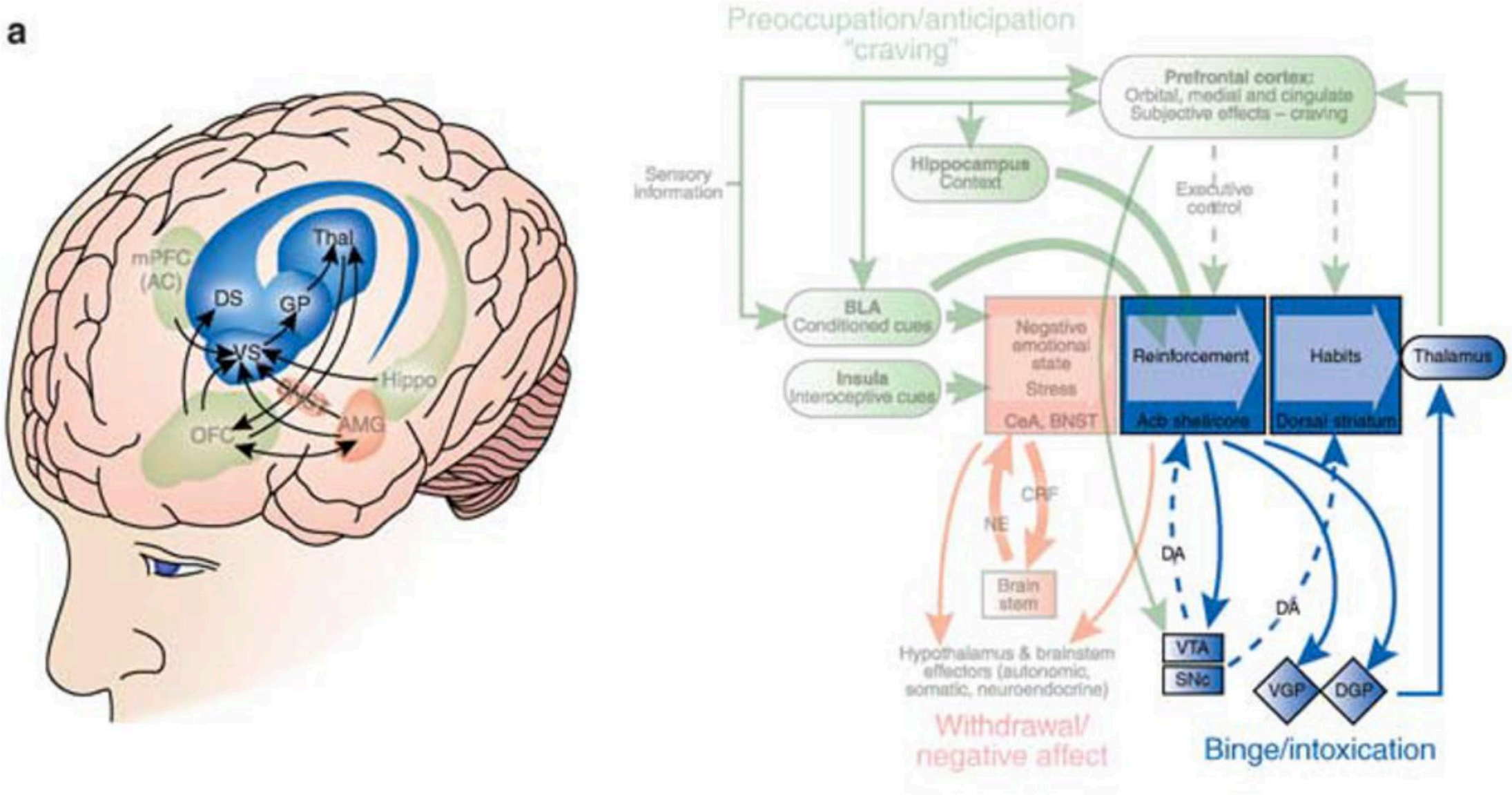

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The Binge / Intoxication stage

- Neutral stimuli become associated with drug availability
  - Incentive salience and promoting habit formation
  - Excessive drug seeking
  - Nucleus accumbens shell and core - dorsal striatum
  - Increase in dopamine, glutamate, opioid neuropeptide neurotransmission
  - Reinforcer in its own right

- Incentive salience - motivation for rewards derived from both one's physiological state and previously learned associations about a reward cue
  - Cue-induced drug seeking, self-administration behaviours
  - Transition to habit-like compulsive drug seeking

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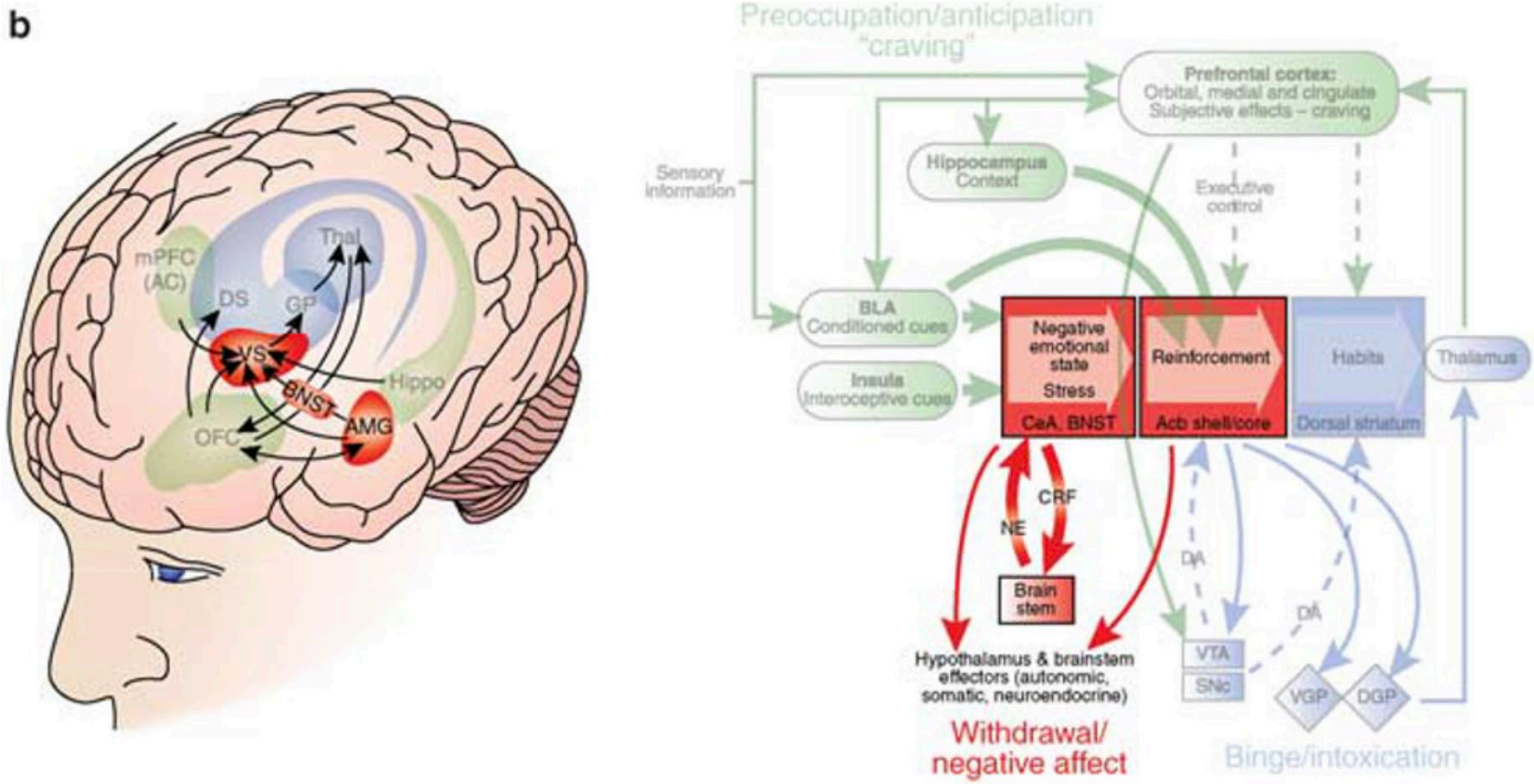

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The Withdrawal / Negative affect stage

- Chronic irritability, emotional pain, malaise, dysphoria, alexithymia, states of stress, and loss of motivation for natural rewards

Activation of the extended amygdala

- The extended amygdala - bed nucleus of the stria terminalis, central nucleus of the amygdala, and possibly a transition zone in the medial portion (or shell) of the NA
- Major projections of the extended amygdala are to the hypothalamus and brainstem
- Major neurotransmitters - corticotropin-releasing factor, norepinephrine, and dynorphin

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The binge / intoxication stage triggers

- Diminish reward function via dopamine and opioid peptide deficits
- Increased brain stress system activity - corticotropin-releasing factor and dynorphin
- Deficits in executive function via the dysregulation of glutamatergic, GABAergic, and dopaminergic neuronal networks in the prefrontal cortex - perpetuate the dysregulation of reward and stress function and induce compulsive drug use
- Increases in stress and anxiety-like responses

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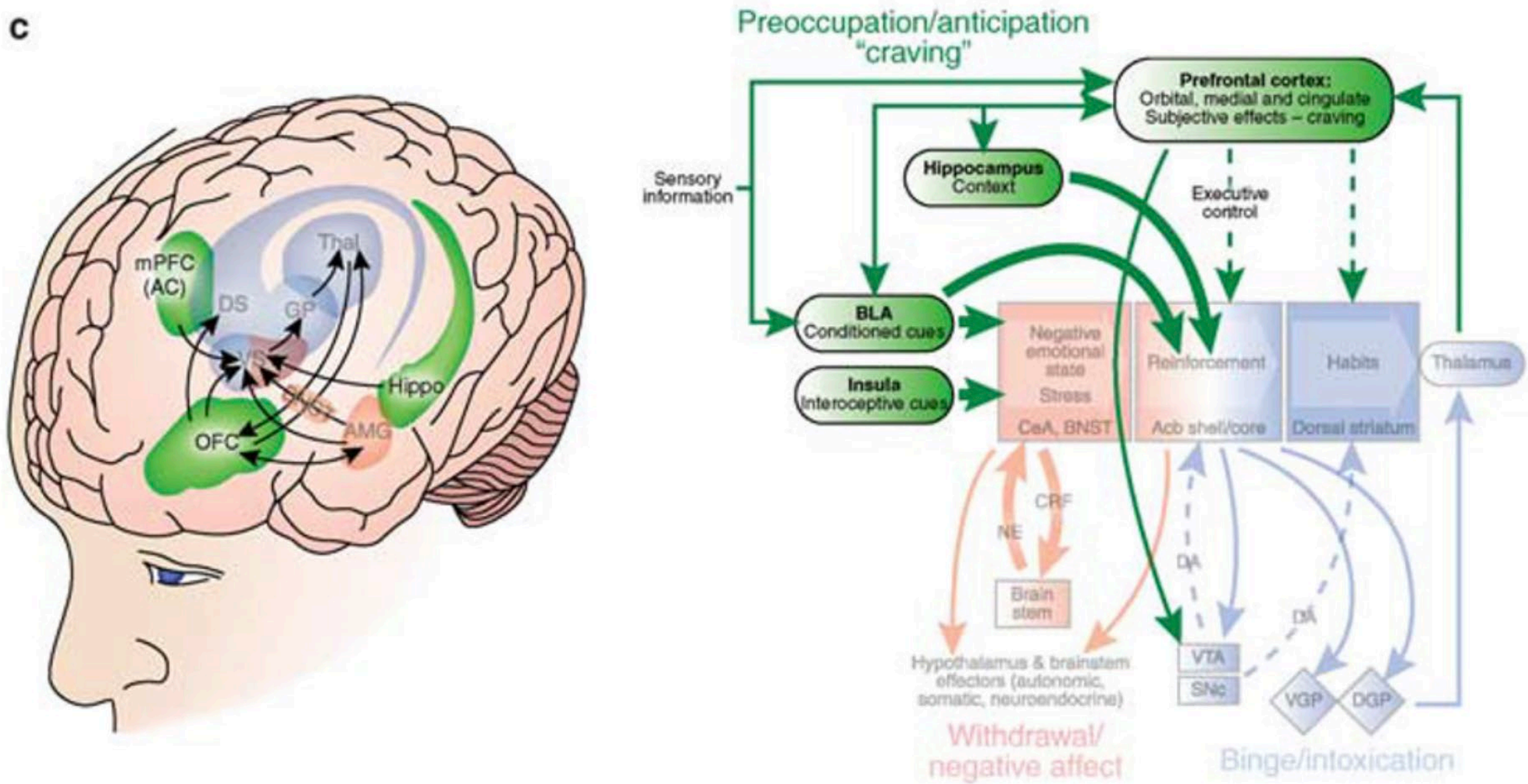

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The Preoccupation / Anticipation stage

Key to relapse

- Executive control over incentive salience is essential to maintain goal-directed behaviour and the flexibility of stimulus–response associations
- Cue-induced craving appears to involve activation of circuits, in which cues that are associated with drugs and elements of non-drug addictions produce activation of the prefrontal cortex
- Deficits in executive function that are reflected by decreases in frontal cortex activity that interfere with decision making, self-regulation, inhibitory control, and working memory

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- Processing of conditioned reinforcement in the BLA and the processing of contextual information by the hippocampus

- Executive control depends on the prefrontal cortex and includes representation of contingencies, representation of outcomes, and their value and subjective states (ie, craving and, presumably, feelings) associated with drugs

- Activation of the orbital and anterior cingulate cortices, temporal lobe, amygdala

- Glutamate, GABA, Norepinephrine, substance P, vasopressin, neuropeptide Y (NPY), endocannabinoids, nociceptin

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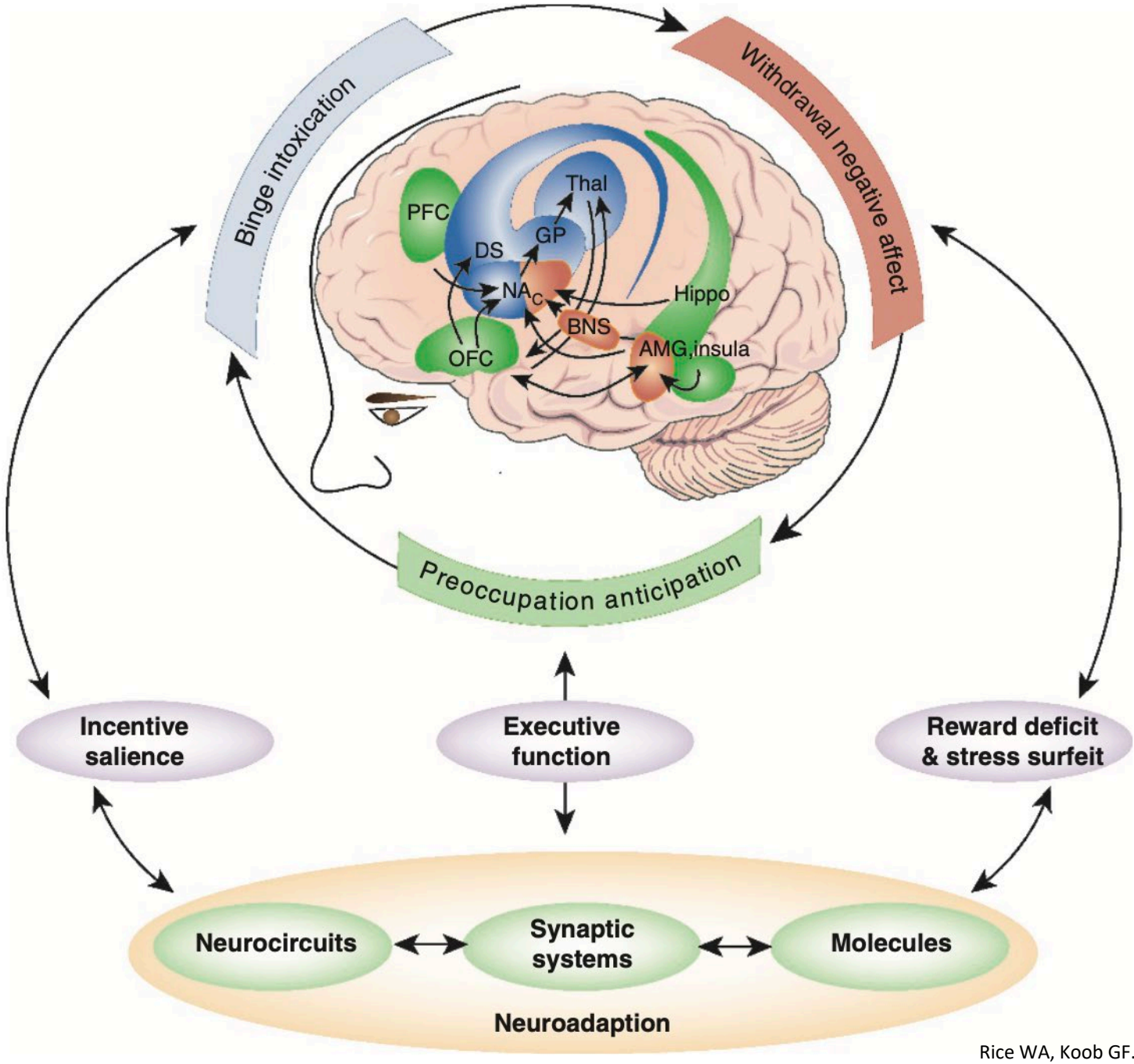

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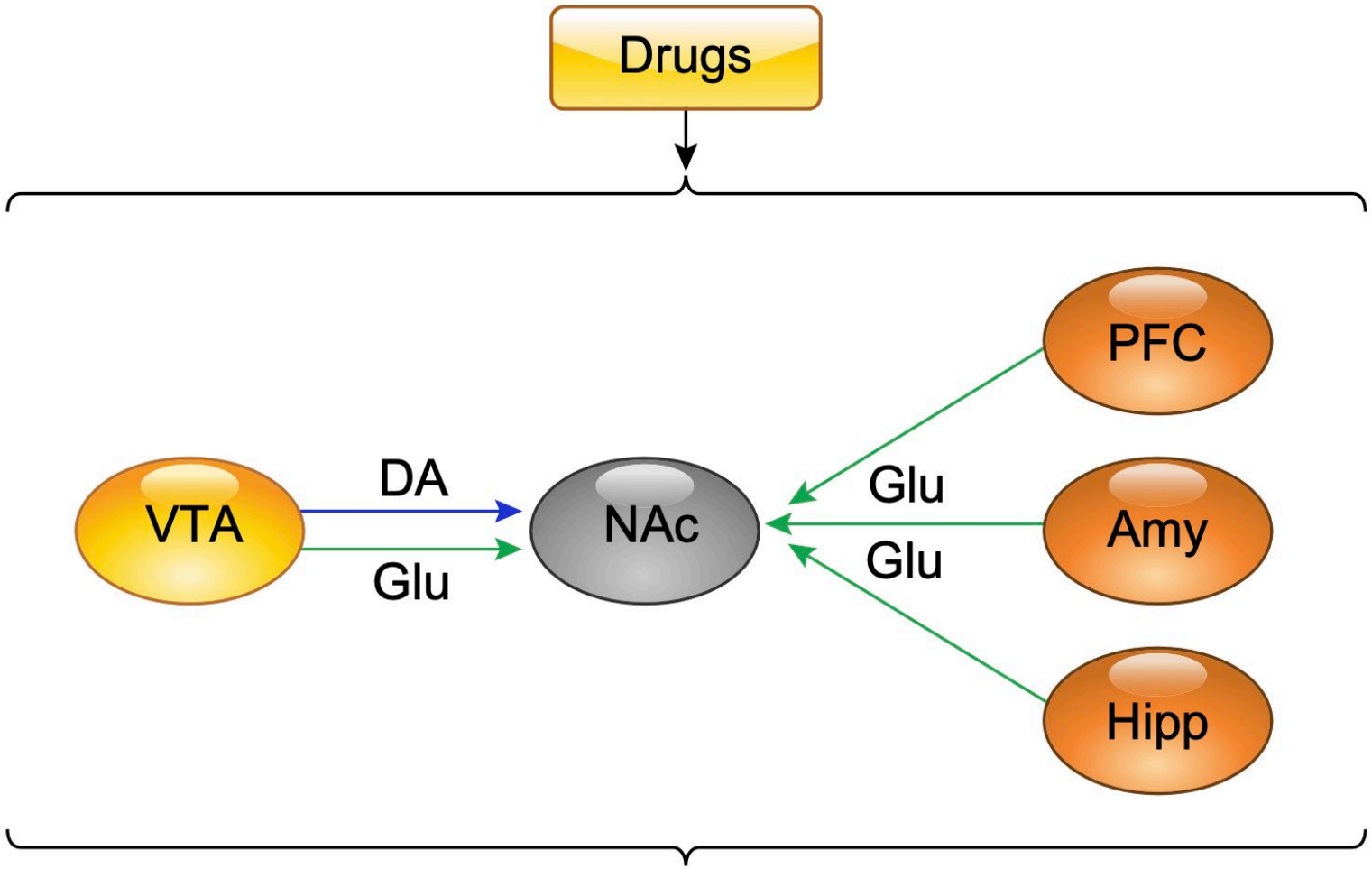
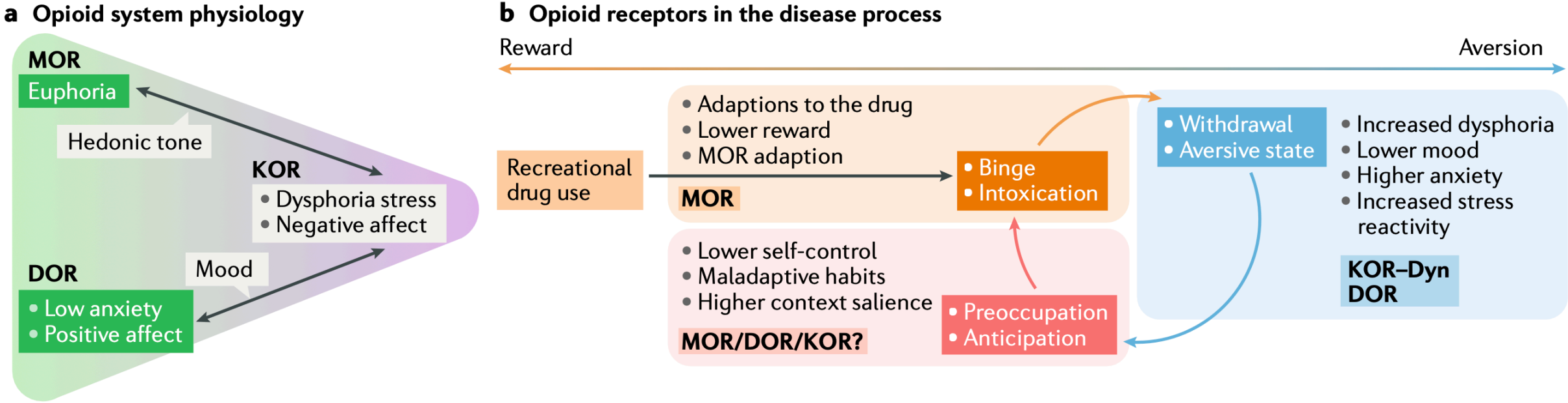
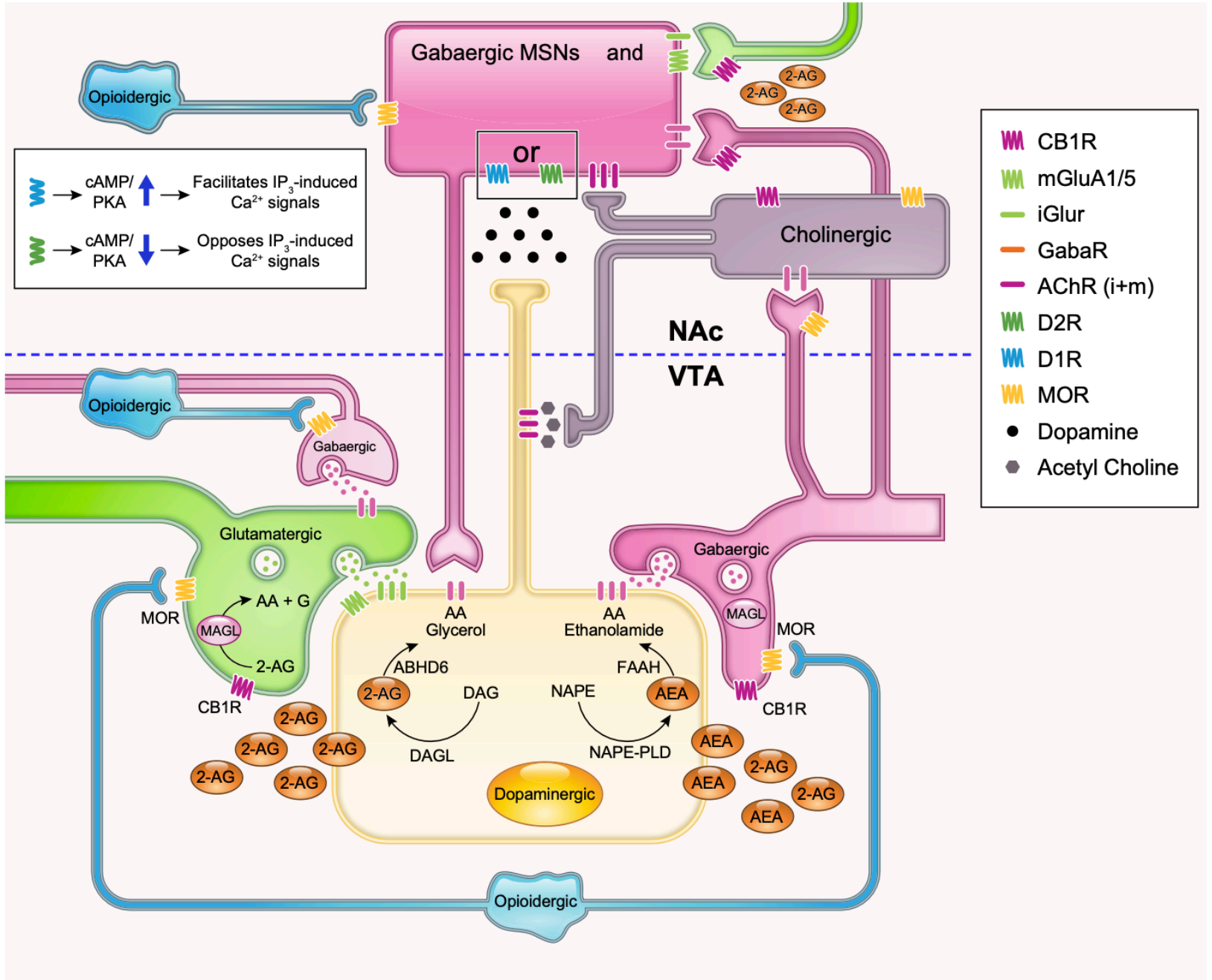
Systems in Addiction



Volkow N et al. doi:10.1152/physrev.00014.2018



Emmanuel Darcq, Brigitte Lina Kieffer. DOI: 10.1038/s41583-018-0028-x



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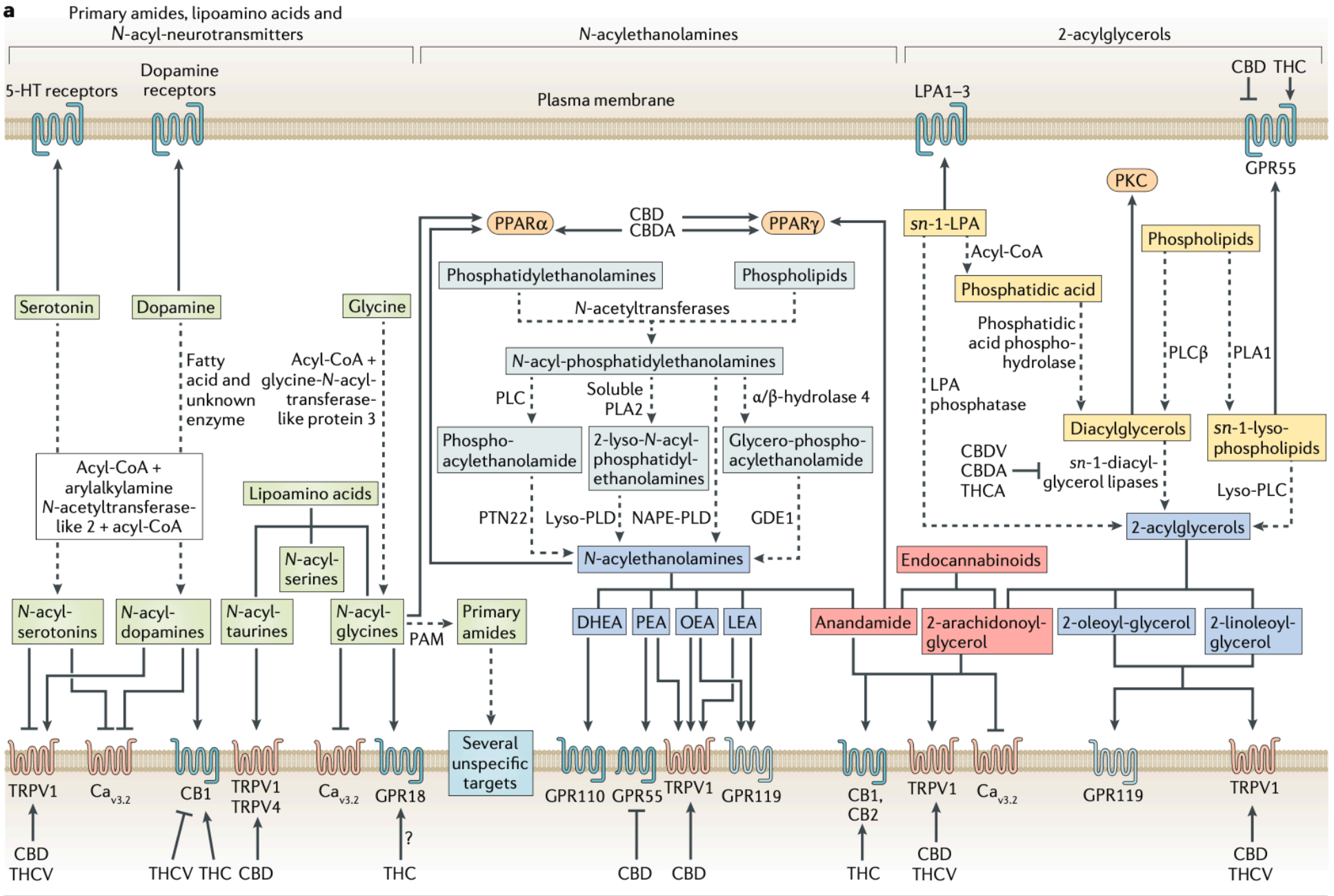

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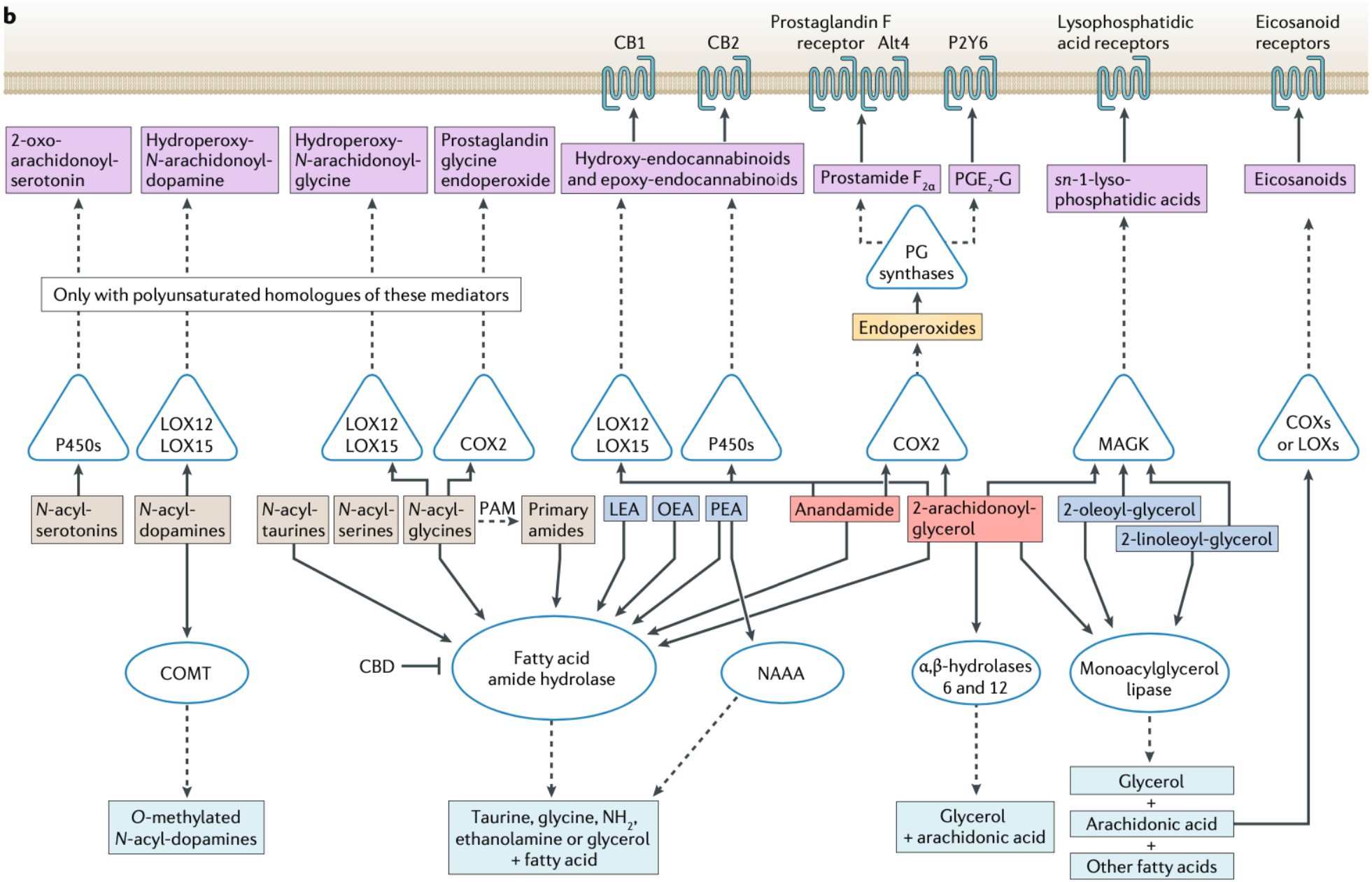

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Fig. 1 | **The expanded endocannabinoid system. a** | The endocannabinoids anandamide and 2-arachidonoylglycerol (red boxes) are often accompanied by their congeners, the *N*-acylethanolamines and the 2-acylglycerols (dark blue boxes). These congeners share biosynthetic pathways and enzymes with the endocannabinoids (pale blue for *N*-acylethanolamines and yellow for 2-acylglycerols) and modulate targets other than cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2), such as transient receptor potential cation channel subfamily V member 1 (TRPV1), peroxisome proliferator-activated nuclear receptor-α (PPARα) and PPARγ, T-type Ca^{2+} ($Ca_{v3.2}$) channels, and orphan G protein-coupled receptors such as GPR18, GPR55, GPR110 and GPR119. The biosynthetic precursors of 2-acylglycerols also have their own targets, such as protein kinase C (PKC), GPR55 and lysophosphatidic acid receptors 1–3 (LPA1–3). Other long-chain fatty acid amides, such as primary amides, lipoamino acids and some *N*-acyl-neurotransmitters have also been identified as elements of the expanded endocannabinoid system with promiscuous targets, whereas no receptor for *N*-acyl-serines has been identified. Distinct biosynthetic pathways exist for different lipoamino acids and *N*-acyl-neurotransmitters (pale green boxes). Intracellular targets are shown as orange rounded boxes. Plant cannabinoids modulate several targets of the expanded endocannabinoid system or endocannabinoidome. **b** | The endocannabinoids, their congeners and the various long-chain fatty acid amides often share inactivating enzymes, although these enzymes have different substrate selectivity. Fatty acid amide hydrolase breaks down long-chain *N*-acylethanolamines, *N*-acyltaurines and *N*-acylglycines; fatty acid amide hydrolase 2 (so far found only in human tissues) has a preference for oleoylethanolamide (OEA) and linoleoylethanolamide (LEA); *N*-acylethanolamine acid amidohydrolase (NAAA) recognizes saturated *N*-acylethanolamines, such as palmitoyl-ethanolamide (PEA); monoacylglycerol lipase is specific for long-chain 2-acylglycerols, especially those that are unsaturated; and α,β-hydrolases 6 and 12 also recognize long-chain 2-acylglycerols and have non-endocannabinoidome ester substrates. In addition, some oxidizing enzymes of the arachidonate cascade, such as cyclooxygenase 2 (COX2), and various lipoxygenases (LOX) recognize the polyunsaturated fatty acid-containing endocannabinoid congeners. Several metabolic products of these congeners have their own receptors, whereas the LOX and cytochrome P450 oxygenase (P450) derivatives of endocannabinoids can still activate CB1 and CB2 receptors. Solid arrows denote modulation or interaction with protein targets, dashed arrows denote metabolic transformation. 5-HT, 5-hydroxytryptamine; Alt4, splicing variant 4 of the FP receptor; CBD, cannabidiol; CBDA, cannabidiolic acid; CBDV, cannabidivarin; COMT, catechol *O*-methyltransferase; DHEA, *N*-docosahexaenoyl-ethanolamine; GDE1, glycero-phosphodiester phosphodiesterase 1; lyso-PLD, lysophospholipase D; MAGK, monoacylglycerol kinase; NAPE-PLD, *N*-acyl-phosphatidylethanolamine-specific phospholipase D; PAM, peptidyl-glycine α-amidating monooxygenase; P2Y6, P2Y purinoceptor 6; PG, prostaglandin; PLA, phospholipase A; PLC, phospholipase C; PTN22, tyrosine-protein phosphatase non-receptor type 22; THC, Δ^9-tetrahydrocannabinol; THCA, Δ^9-tetrahydrocannabinolic acid; THCV, Δ^9-tetrahydrocannabivarin. Adapted from REF.[340], Springer Nature Limited.

Cristino et al, 2019

Components – The Receptors

- **CB1R & CB2R – GPCRs**

- CB1R - presynaptically in excitatory and inhibitory neurons

- CB1R - retrograde activation of the receptor underlies short-term and long-term forms of synaptic plasticity, including depolarization-induced and metabotropic receptor-mediated suppression of excitatory and inhibitory neurotransmission, long-term depression of excitation or inhibition, and long-term potentiation

- CB1R - postsynaptic CB1 receptors mediate slow self-inhibition of neocortical interneurons and change expression of precursors of appetite-controlling peptides in the arcuate nucleus of the hypothalamus

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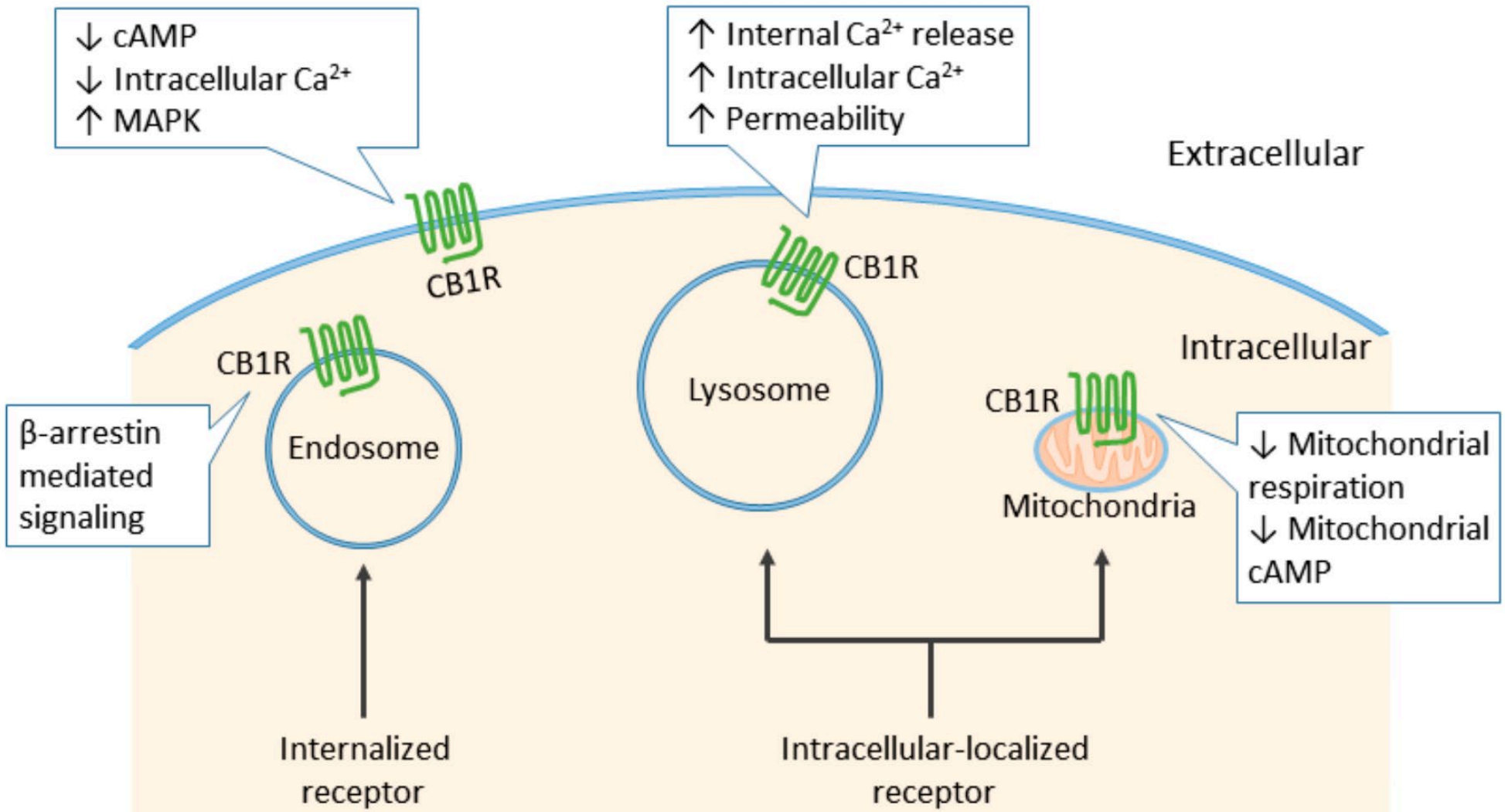
Components – The Receptors

- CB1R - small proportion of postsynaptic CB1 is located in the external membrane of mitochondria, where it inhibits electron transport and the respiratory chain, thereby affecting brain metabolism and memory formation

- CB1R - in astrocytes, CB1 is involved in the regulation of synaptic plasticity in the hippocampus and in leptin signalling in the hypothalamus

- CB1R - activation of CB1 also stimulates proliferation of adult progenitor stem cells and their differentiation into neurons or astrocytes, a role that could be relevant to neurodegenerative disorders

Cristino et al, 2019



Zhou & Kumar, 2018

Components – The Receptors

- CB2R - immune modulation
- CB2R - strongly and selectively expressed in microglia in diseases such as AD, MS and amyotrophic lateral sclerosis (ALS)
- CB2R - reduces pro-inflammatory cytokine release from activated microglia in AD
- CB2R - activation also stimulates adult neurogenesis, regulation of blood–brain barrier (BBB) permeability
- CB2R - expressed at very low levels in healthy neurons and that their activation has the opposite effects to CB1 activation
- CB2R - activation of postsynaptic CB2 reduces neuronal excitability in the CA3 and CA2 regions of the hippo- campus through functional coupling with the sodium-bicarbonate transporter

Cristino et al, 2019

Features of the Endocannabidiome

Endocannabinoid degradation

- Inhibition of increases levels of other endogenous FAAH substrates that activate other receptors, including peroxisome proliferator-activated receptor-α (PPARα), orphan GPCR 119 (GPR119), orphan GPCR 55 (GPR55) and the transient receptor potential cation channel subfamily V member 1 (TRPV1) - These receptors often have roles opposite to those of cannabinoid receptors.

- Substrates of MAGL include monoacylglycerols other than 2-AG that also target receptors other than CB1 and CB2, including TRPV1 and GPR119.

- AEA & 2AG are degraded by a number of enzymatic pathways

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Features of the Endocannabidiome

Endocannabinoid biosynthesis

- Redundancy and promiscuity
- Anandamide and 2-AG can be produced by several pathways and enzymes that are also involved in the biosynthesis of other *N*-acylethanolamines and monoacylglycerols
- Therefore, inhibition of the two main enzymes involved in endocannabinoid synthesis might not always selectively or effectively reduce tissue levels of the two endocannabinoids and could affect levels of other mediators.

Promiscuity of endocannabinoid targets

- Endocannabinoids act on other targets; for example, anandamide activates TRPV1 and PPARγ and inhibits Cav3.2 Ca^{2+} channels and transient receptor potential cation channel subfamily M member 8 (TRPM8) channels

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Features of the Endocannabidiome

Endocannabinoid-like mediators

- The complexity of endocannabinoid-related molecules extends to other long-chain *N*-acyl-amides, including *N*-acyl-taurines, *N*-acyl-serotonins, *N*-acyl-dopamines, fatty acid primary amides and a plethora of *N*-acyl-amino acids
- Each of these mediators has its own molecular targets and metabolic enzymes
- These receptors and enzymes are often shared with the endocannabinoids

Allosteric modulators of CB1 and CB2

- Allosteric modulators of CB1 and CB2 that have been identified include endogenous molecules, such as the haemopressins and related peptides

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Features of the Endocannabidiome

Other endocannabinoidome receptors

TRPV1 (Transient Receptor Potential Cation Channel Subfamily V Member 1)

- was thought not to have a function in the brain until it was found in GABAergic and glutamatergic terminals and neuronal somata in the hippocampus and cerebellum
- role in short-term and long-term synaptic plasticity - implications in the regulation of mood, fear, memory, food intake, visual development and locomotion, increase excitability of central neurons
- mediates long-term depression through upregulation of AMPA receptor reuptake
- increases glutamatergic neurotransmission via microvesicle release from microglia, particularly in neuroinflammatory conditions, although its activation inhibits release of inflammatory cytokines from activated microglia

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Features of the Endocannabidiome

PPARα and PPARγ (Peroxisome Proliferator-activated Receptor)

- Expressed in neurons, astrocytes and microglia in the brain, where they have anti-inflammatory and neuroprotective effects during acute and chronic neuroinflammatory insults, such as brain trauma, ischaemia, AD and MS
- Both isoforms have been associated with ethanol consumption, whereas PPARα activation by some *N*-acylethanolamines or *N*-oleoyl-glycine reduces nicotine preference. Additionally, strong evidence suggests that PPARα reduces food intake, whereas PPARγ is involved in neuronal differentiation

GPR55 (Orphan G-Protein Coupled Receptor)

- Activation stimulates excitatory hippocampal neurons
- Activation by endocannabinoidome mediators, such as anandamide, 2-AG and palmitoylethanol-amide, might be detrimental in epilepsy or conditions characterized by glutamate excitotoxicity

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Features of the Endocannabidiome

The endocannabinoidome and gut microbiota

- Major role in regulating myenteric neuron activity, vagal and sympathetic nerve function, and the release of gastrointestinal neuropeptides (ghrelin and cholecystokinin-8), which in turn modulate endocannabinoid levels
- CB1 has been implicated in dysbiosis-induced increases in intestinal permeability, the ensuing systemic inflammation, and modulation of the microbiota composition
- CB2 activation partly mediates the analgesic effects of probiotics against visceral pain
- TRPV1, GPR119 and PPARα, reduce intestinal permeability and altered levels of their endocannabinoidome ligands could mediate the negative effects of dysbiosis and the beneficial effects of the commensal microorganism *Akkermansia muciniphila* on increased intestinal permeability and the ensuing systemic inflammation

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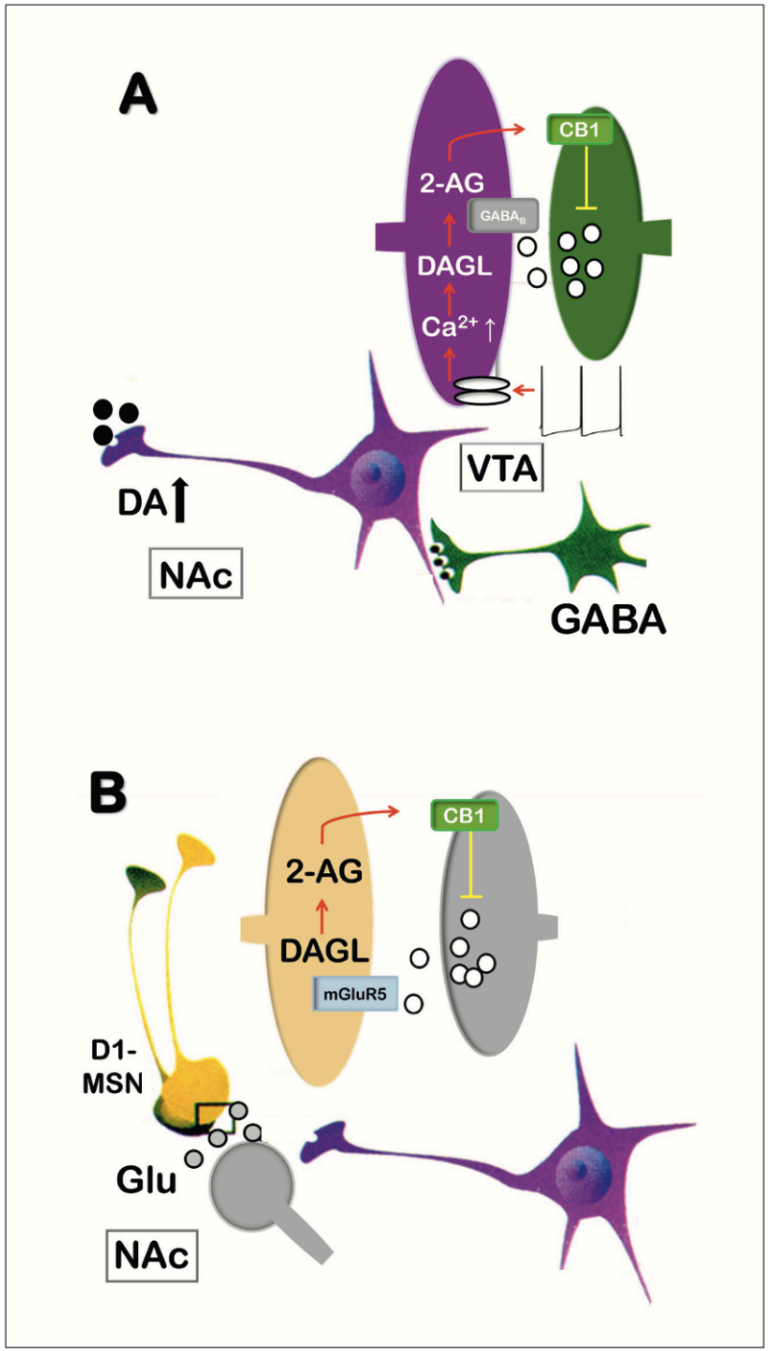
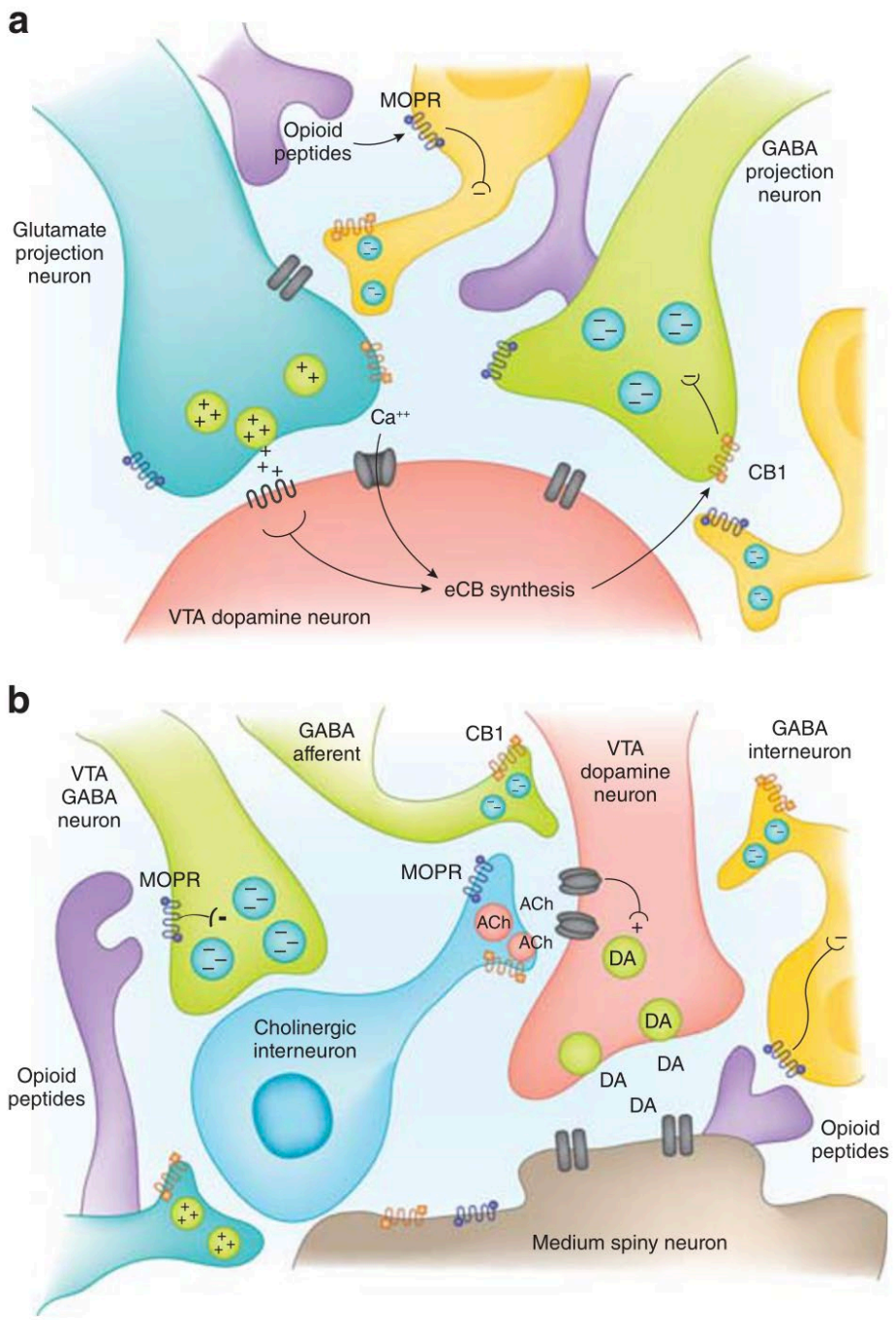


Figure 1. Two endocannabinoid-dependent mechanisms have been identified that are involved in mediating natural-reward and drug-seeking responses. A) One mechanism relates to disinhibition of ventral tegmental area (VTA) A10 dopamine neurons by cannabinoid type 1 (CB_1) receptor activation.[16] Under baseline conditions, dopamine neurons within the VTA are inhibited by GABA through activation of $GABA_B$ receptors. Following the presentation of drug-conditioned cues, dopamine neurons switch into phasic firing mode. Through this electrical event, intracellular calcium levels increase, which results in the activation of diacylglycerol lipase (DAGL) and the subsequent synthesis of 2-arachidonylglycerol (2-AG). 2-AG is then postsynaptically released and acts retrogradely at CB_1 receptors on GABAergic interneurons. CB_1-receptor activation leads to an inhibition of GABA release. This GABA suppression results in disinhibition of dopamine neurons, which further promotes burst firing. Blockade of either $GABA_B$ receptors[38,39] or CB_1 receptors can also inhibit reward-seeking responses through this mechanism.
B) The other mechanism relates to endocannabinoid/glutamate interactions within the nucleus accumbens (NAc) glutamatergic afferents from prefrontal regions impinging on D1-medium spiny neurons (D1-MSN). Glutamate-induced activation of metabotropic glutamate receptor 5 (mGluR5) leads to the induction of DAGL and 2-AG synthesis. 2-AG is then released and retrogradely activates Gi/o-coupled CB_1 receptors to inhibit further glutamate release. Blockade of either mGluR5[40-42] or CB_1 receptors[43,44] abolishes natural-reward– and drug-reward–seeking responses.[36] 2-AG, 2-arachidonylglycerol; Ca^{2+}, calcium; CB_1, cannabinoid type 1 receptor; DA, dopamine; DAGL, diacylglycerol lipase; mGluR5, metabotropic glutamate receptor 5; MSN, medium spiny neurons; NAc, nucleus accumbens; VTA, ventral tegmental area

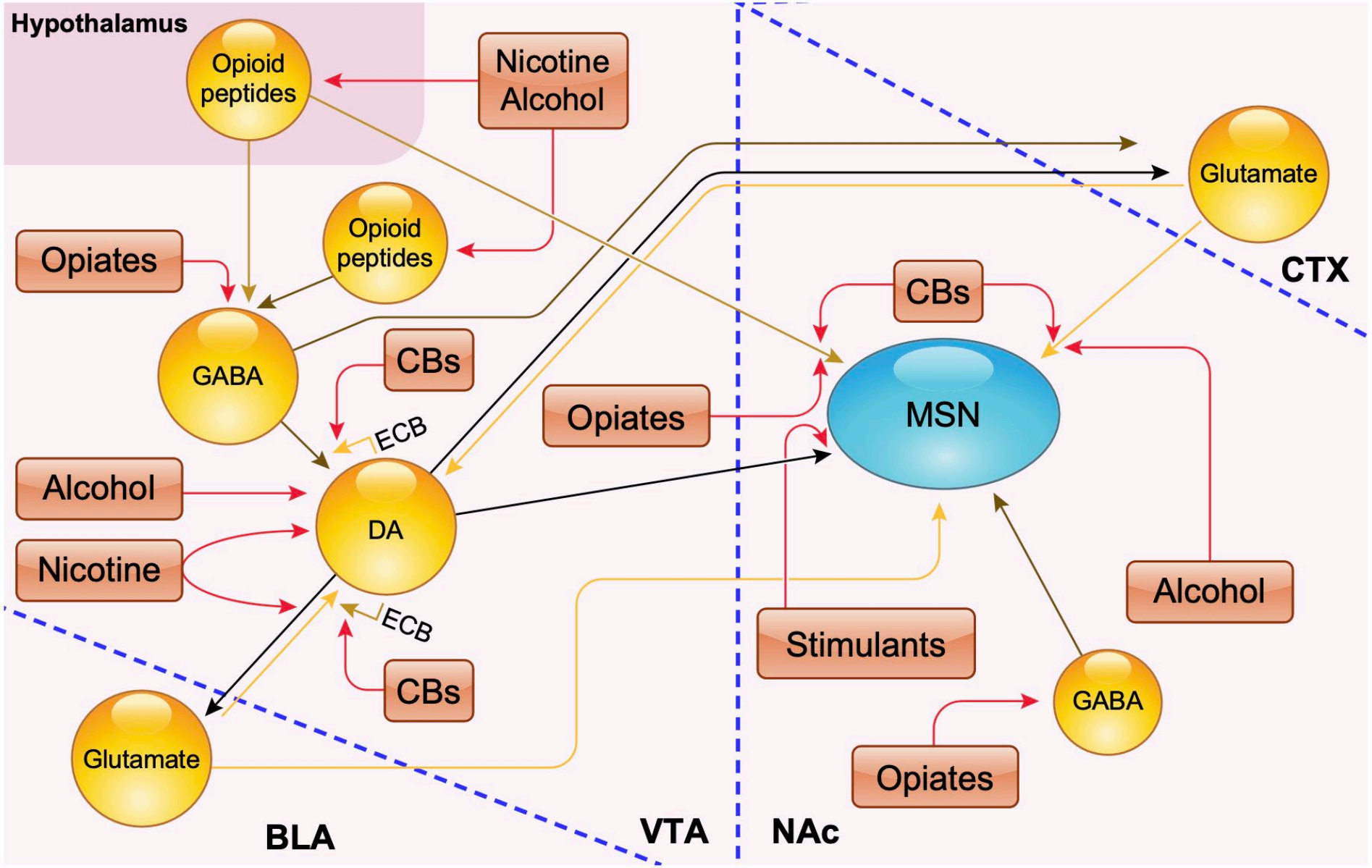
Rainer Spanagel (2020) Cannabinoids and the endocannabinoid system in reward processing and addiction: from mechanisms to interventions, Dialogues in Clinical Neuroscience, 22:3, 241-250, DOI: 10.31887/DCNS.2020.22.3/rspanagel



JM Wenzel and JF Cheer. Endocannabinoid Regulation of Reward and Reinforcement through Interaction with Dopamine and Endogenous Opioid Signaling Neuropsychopharmacology REVIEWS (2018) 43, 103–115

- ECS and opioid interaction - mesolimbic dopamine system in VTA & NA
- Glutamatergic and GABAergic terminals of the VTA express MOPR and CB1
- Glutamatergic activation of VTA dopamine (DA) neurons likely promotes synthesis and ‘on demand’ release of eCBs, which diffuse out of the post-synaptic cell and bind to CB1 to further disinhibit DA release via presynaptic GABA inhibition
- MOPR agonists (exogenous or endogenous opioid peptides) disinhibit VTA DA cells through inhibition of GABA neurons, which synapse on VTA DA cells or glutamate projections neurons
- NAc DA release can occur independently of VTA DA cell body excitation
- The VTA sends GABAergic projections to the NAc, which synapse on cholinergic interneurons, inhibiting excitatory cholinergic (ACh) input onto DA terminals
- CB1 or MOPR-mediated inhibition of these GABA cells may disinhibit ACh release, resulting in DA terminal stimulation
- ACh interneurons express MOPR and CB1, suggesting that direct opioid or eCB inhibition of these cells may decrease DA concentration in the Nac
- Glutamatergic and GABAergic terminals in the NAc may also directly modulate DA activity
- NAc Glutamate and GABA cells express MOPR and/or CB1
- CB1 or MOPR agonism of GABA inputs to NAc DA terminals could enhance DA release, while CB1 or MOPR-induced inhibition of glutamatergic inputs may dampen NAc DA release

JM Wenzel and JF Cheer. Endocannabinoid Regulation of Reward and Reinforcement through Interaction with Dopamine and Endogenous Opioid Signaling Neuropsychopharmacology REVIEWS (2018) 43, 103–115



Volkow N et al. doi:10.1152/physrev.00014.2018

Table 1. *Pharmacological targets of main classes of drugs of abuse*

Drug Class	NT Mediators	Mechanism
Opioids	MOR → GABA ↓ → DA ↑	Opioids, like morphine, heroin, or fentanyl, are agonists at MOR (214). Opioid stimulation of MOR in the VTA increases striatal DA release.
Alcohol	EtOH → MOR ↑, NMDA ↓, DA ↑, GABA ↑, ECS ↑	Unlike most addictive drugs that target specific receptors and transporters, EtOH affects a wide range of targets and indirectly increases DA in NAc (354).
Nicotine	nAChRs → DA ↑	Nicotine's interaction with specific nAChRs (i.e., $\alpha 4\beta 2$) leads to NAc DA release directly by increasing neuronal activity in VTA DA neurons (13, 24) or indirectly by activating modulatory (i.e., GABA or Glu) neurons in VTA (76, 114).
Stimulants	DAT/VMAT2 → DA ↑	Amphetamines block DAT and the VMAT2 (11, 96, 111), which increase synaptic levels of extracellular DA by DAT reversal and depletion of vesicular DA stores, which promotes DA release. Cocaine and methylphenidate block DAT inhibiting DA reuptake, thus increasing DA in NAc (171).
Cannabis	THC → Glu/GABA → DA ↑ ↓	THC activation of CB1 receptors regulates the presynaptic release of both GABA and glutamate, influencing the activity states of the mesolimbic DA system (92, 299) (see **FIGURE 1**)
Classic hallucinogens	5-HT_{2A}Rs > DA ↑; 5-HT_{2C}Rs > DA ↓	Indolamines (e.g., psilocybin, LSD, Mescaline) that display high-affinity agonist activity at serotonin 5-HT_2 G protein-coupled receptor subtypes (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}) (51). These drugs do not trigger compulsive drug taking and are therefore not considered addictive. Instead, these drugs are predominantly used to alter mental state.
Inhalants	Multiple agents and targets, including volatile substances like toluene, which modulates NMDA ↓, 5-HT_3 ↑, Gly ↑, $GABA_A$ ↑, nACh ↓, and DA ↑ (39, 119, 249)	Abused inhalants (other than nitrites) have a wide range of effects on neurotransmitter release and receptors, with a few similar actions as those of benzodiazepines, alcohol, and barbiturates (15) and have been shown to enhance striatal DA release and have direct reinforcing effects (166).
Benzodiazepines and barbiturates	GABA ↑ > DA ↑	Benzodiazepines and barbiturates enhance GABA by increasing the frequency or the duration of the chloride ion channel opening at the $GABA_A$ receptor, respectively. Both drugs can increase the firing rate of DA neurons in VTA through disinhibition (86, 318).

Progression

- What determines the transition from drug experimentation to addiction?
- Genetics – epigenetics
  - *transcription and epigenetic modulatory events include regulatory and signaling genes like fosB, FosB, NFB, CdK5, and MEF2*
- Several brain circuits including those involved with
  - *Conditioning*
  - *Reward sensitivity Incentive motivation*
  - *Self-monitoring / regulation*
  - *Mood*
  - *Interoception*

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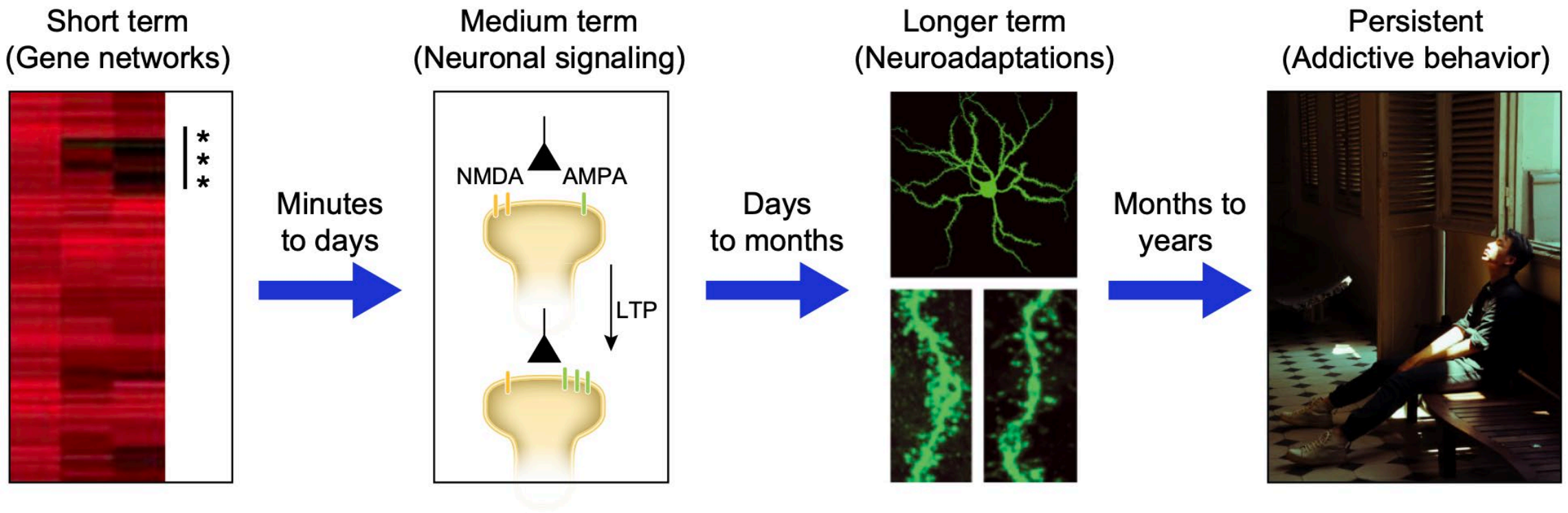

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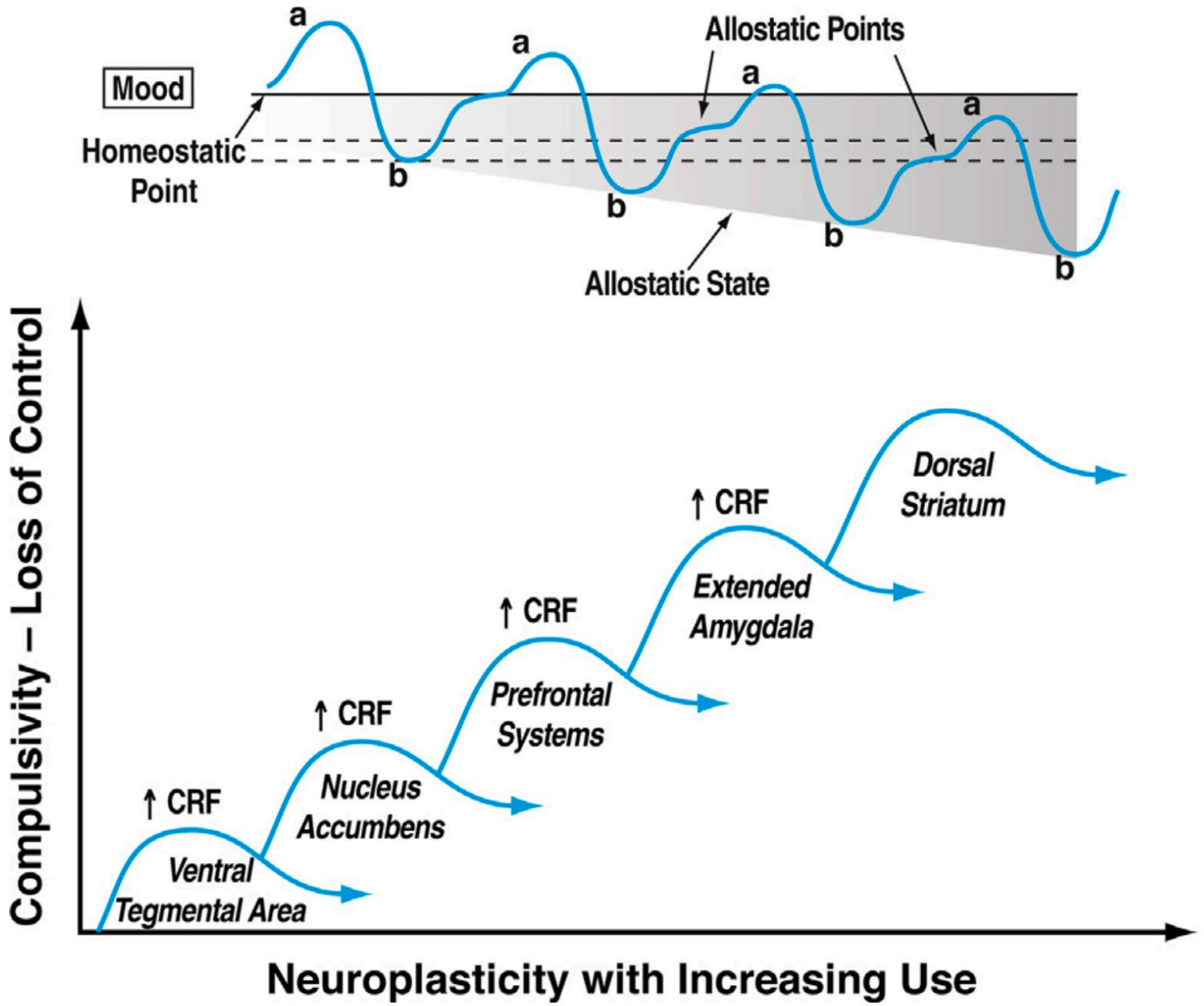

Zorrilla, E.P., et al. Corticotropin releasing factor: A key role in the neurobiology of addiction. Front. Neuroendocrinol. (2014), http://dx.doi.org/10.1016/j.yfrne.2014.01.001

- Progression – alteration in emotional homeostasis via opponent-process upregulation of CRF activity in multiple brain nuclei

- Acute drug use initially - positive shifts in mood (‘‘a’’ process)

- Countered by homeostatic decrements in mood (‘‘b’’ opponent-process)

- Repeated drug use - the ‘‘b’’ opponent-process manifests earlier and more prominently
  - *each drug experience elicits a smaller, briefer positive shift in mood*

- Alteration of emotional set points - allostatic states of decreased reward function and increased stress function

- Mood in a drug-free state does not return to the drug-naïve baseline (homeostatic point)
  - *new, stable allostatic states result, in which the drug-free baseline mood (allostatic points) becomes increasingly more negative, experienced as dysphoria in the absence of drug*

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- Continued use - no longer reattain the baseline, drug-naïve homeostatic set point, never the subjective positive ‘‘high’’
- Negative emotional allostatic state - negative reinforcement to reduce dysphoria and regain euthymia
- Initial phases - still effectively elicits positive mood states and maintained by positive reinforcement, brain regions central to reward processes (VTA, NA) are recruited
- Continued drug use - neuroadaptations in CRF systems in VTA and PFC
- Finally - activation of CRF systems in the extended amygdala and recruitment of circuitry linked to the dorsal striatum underlie the negative emotional state and habitual drug-seeking

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Thank You