20° Congresso Nazionale
Società Italiana di Tossicologia

Neurobiologia dell'addiction: focus su cannabis e sistema endocannabinoide.

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SITOX

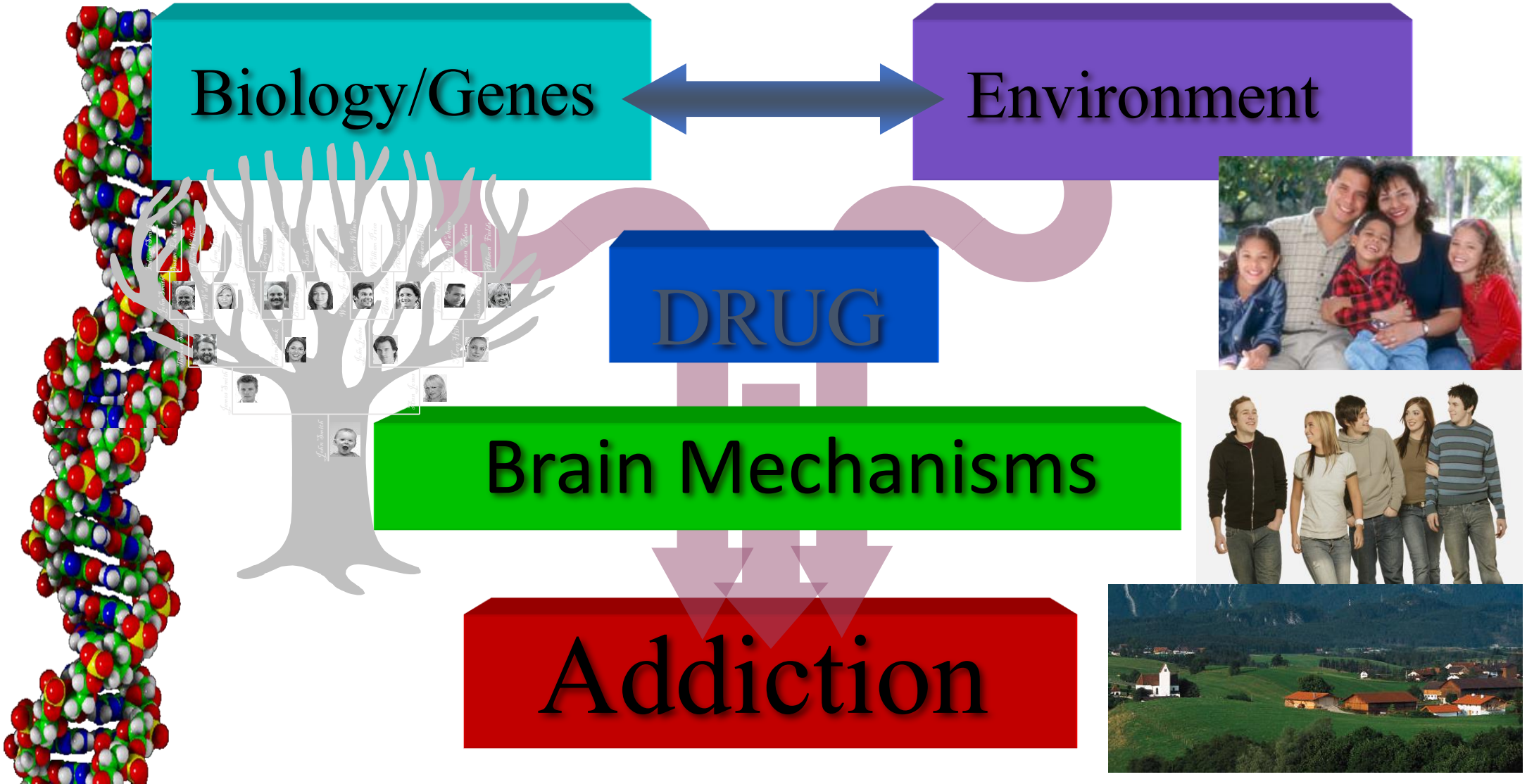
Sostanze di origine naturale: farmaci, veleni o entrambi
BOLOGNA 25-26-27 Ottobre 2021

A chronic relapsing disorder

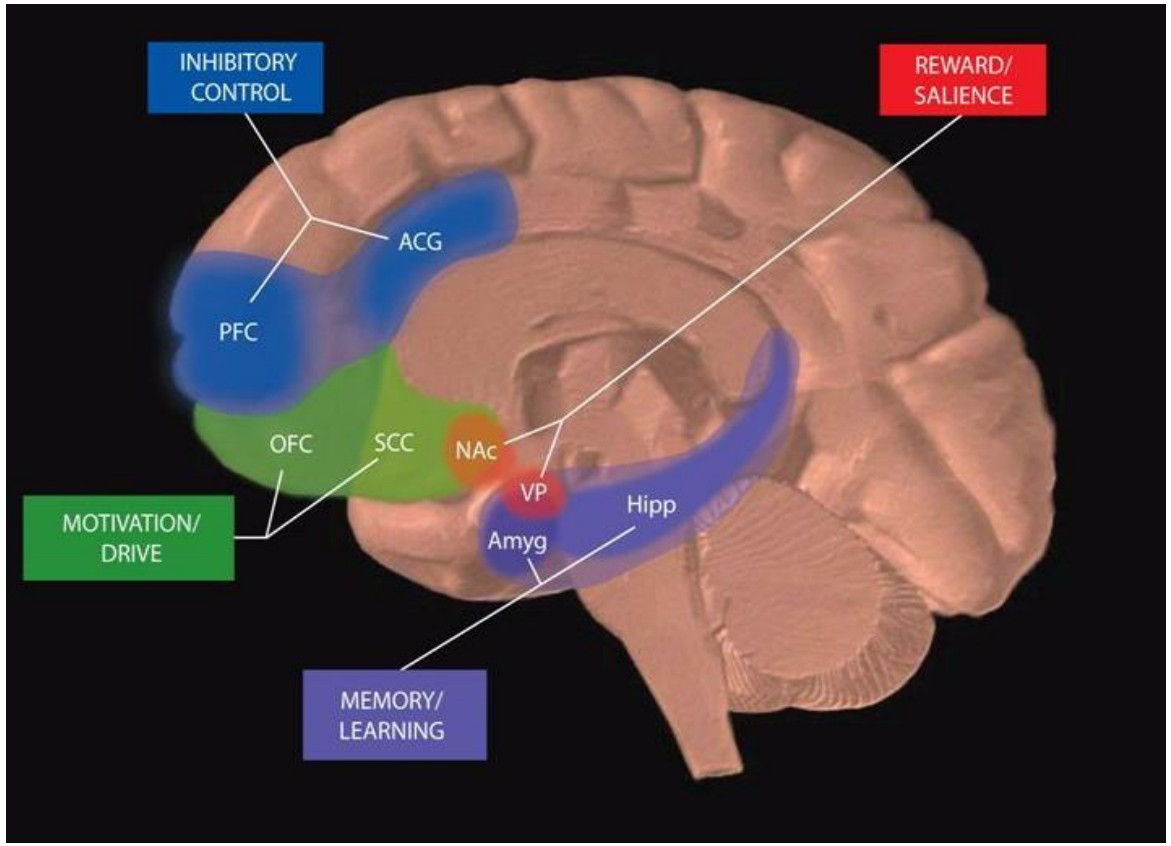
- "A chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences"[1]
- It is considered a brain disease because drugs change the brain; they change its structure and how it works[1]
- These brain changes can be long lasting and can lead to many harmful, often self-destructive, behaviours[1]

1. National Institute on Drug Abuse. The Science of Drug Abuse: the basics. www.drugabuse.gov/publications/media-guide/science-drug-abuse-addiction-basics (accessed September 2018).

ADDICTION INVOLVES MULTIPLE FACTORS

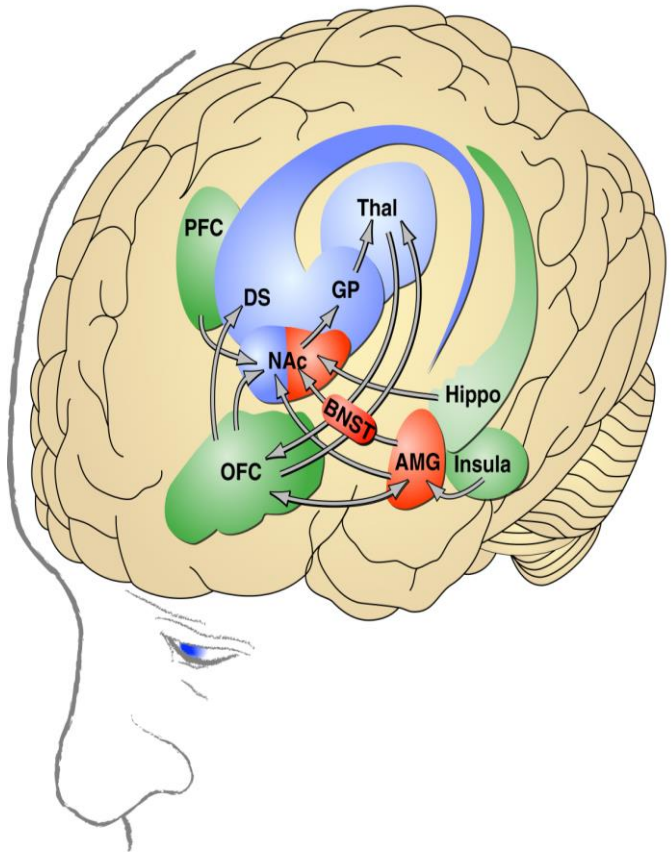


Circuits Involved In Drug Abuse and Addiction

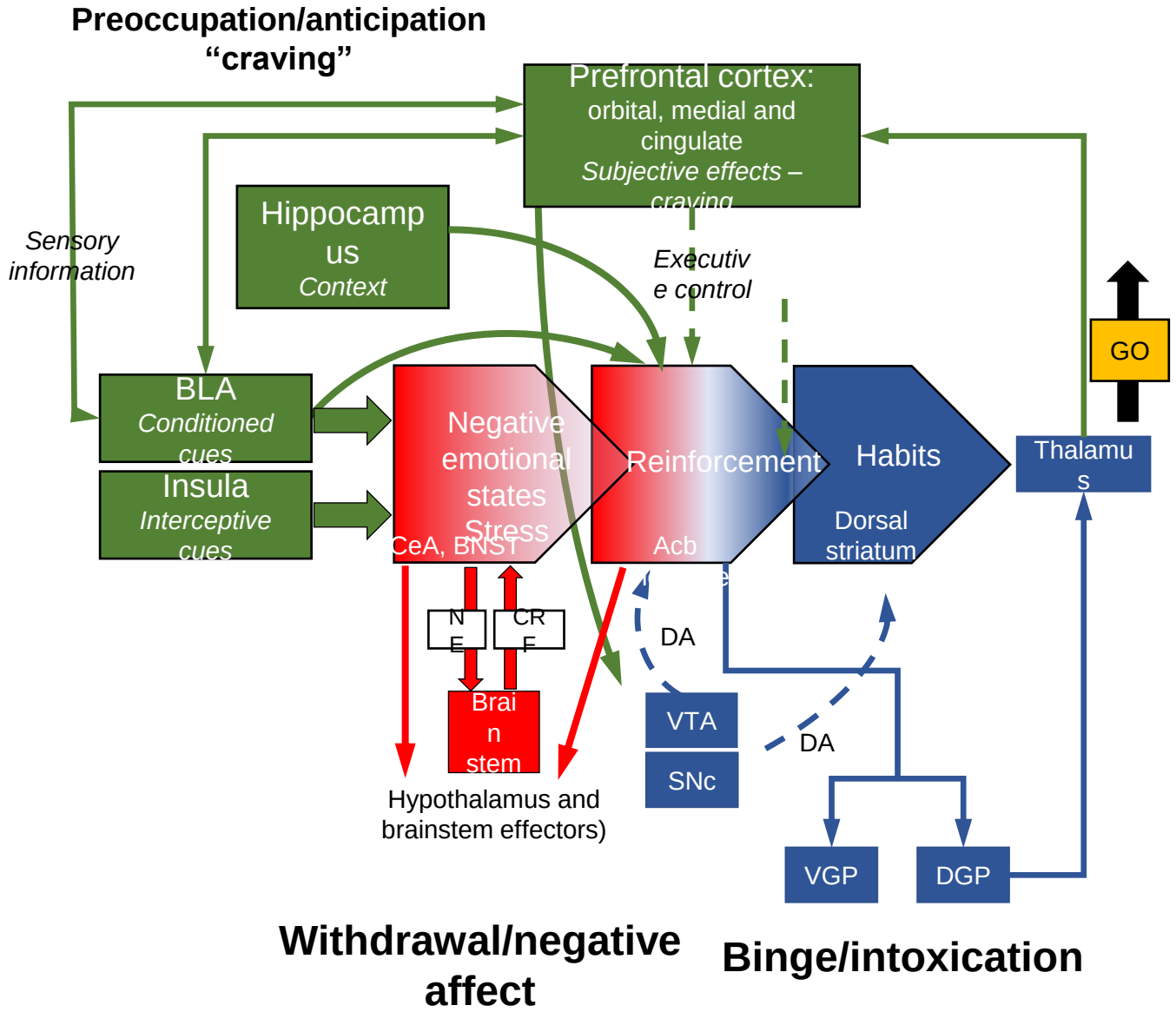


Uncontrollable compulsive behaviour

Conceptual framework: The three phases of addiction

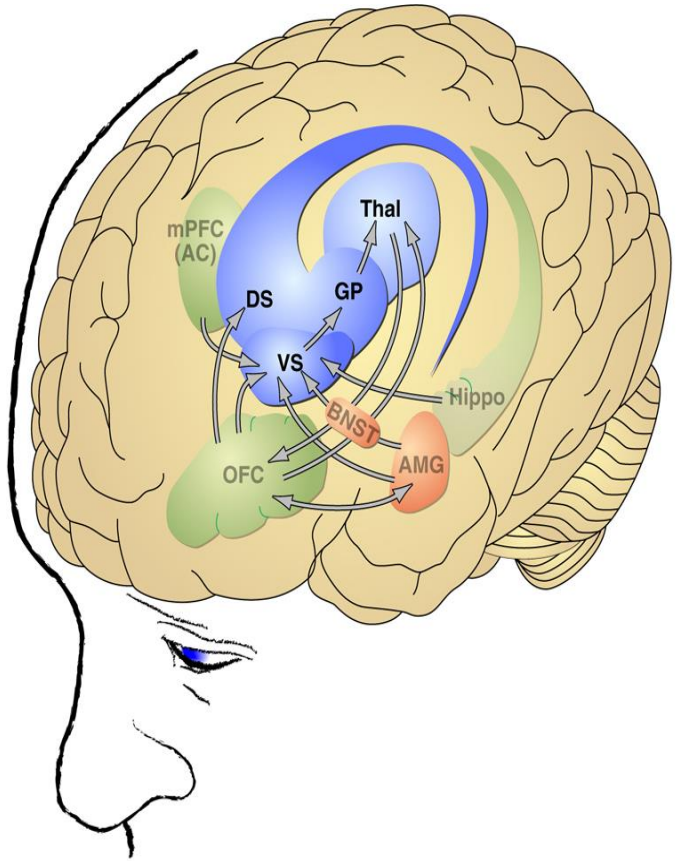


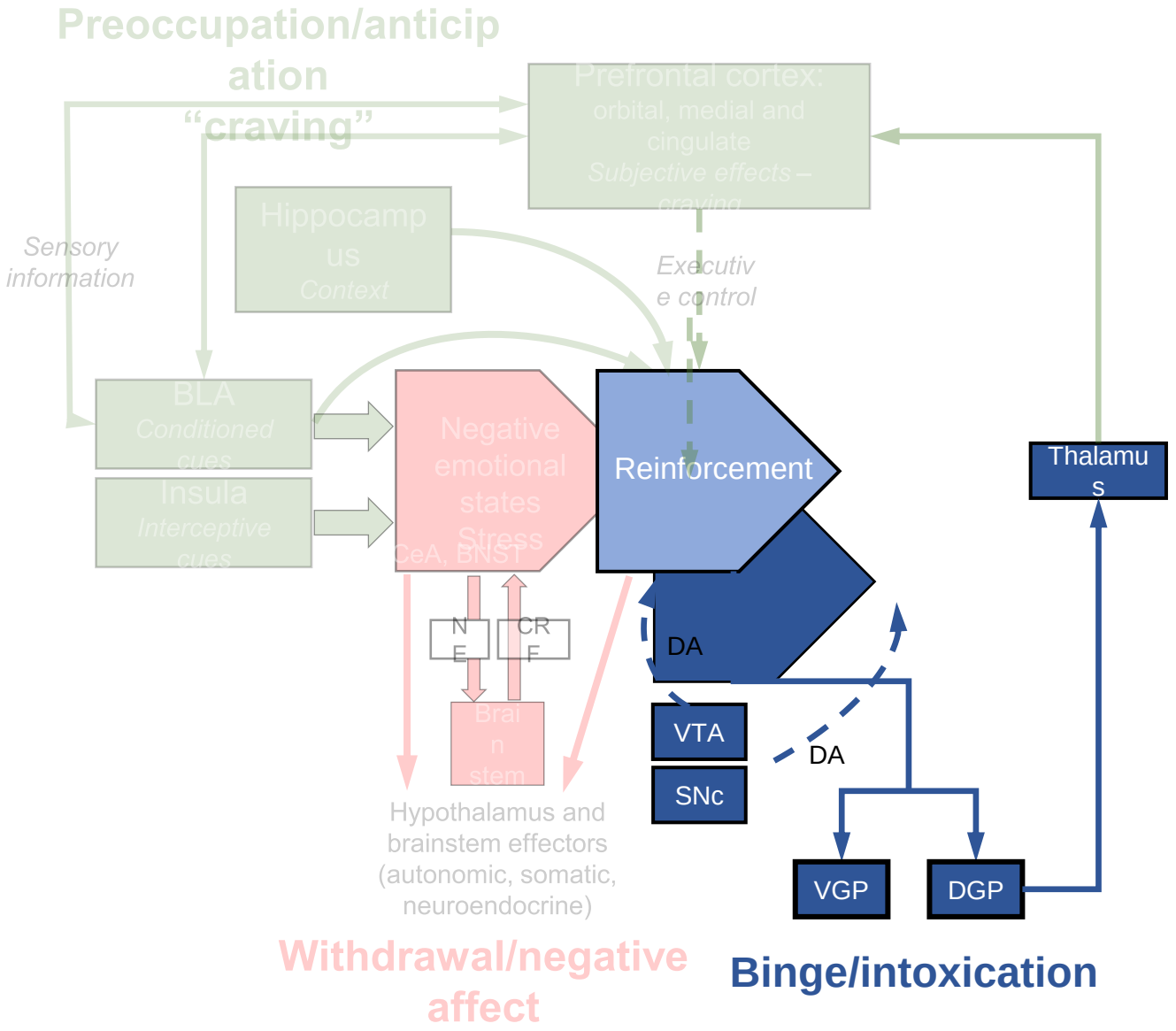
Koob GF, Volkow ND. *Neuropsychopharmacology* 2010;35:217–238.



Binge/intoxication phase

Koob GF, Volkow ND. 2010

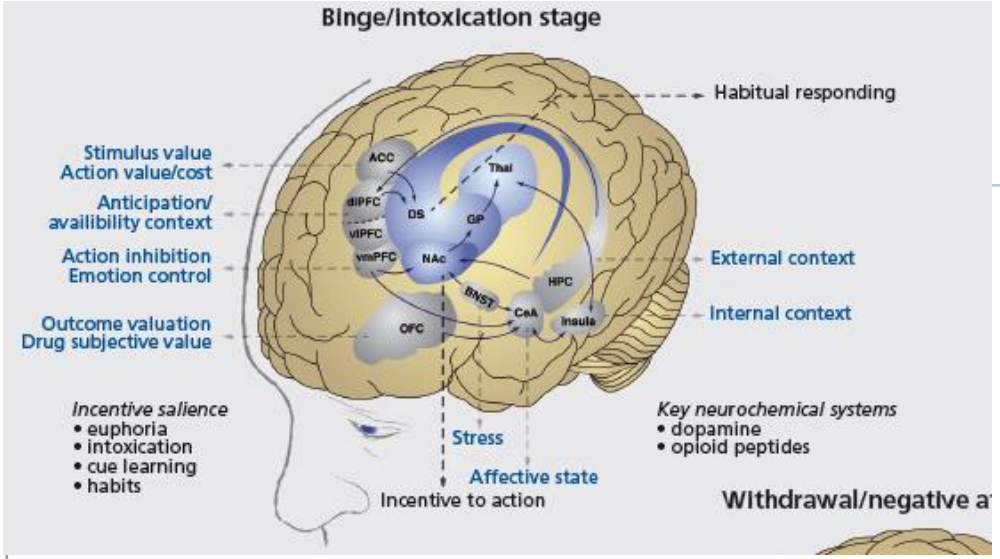




Binge/intoxication

- Basal Ganglia – Reward system
- Acute positive hedonic value
- Positive reinforcement
- Sensitization of incentive salience *(conditioned reinforcment)*
- Habit formation (d. striatum)

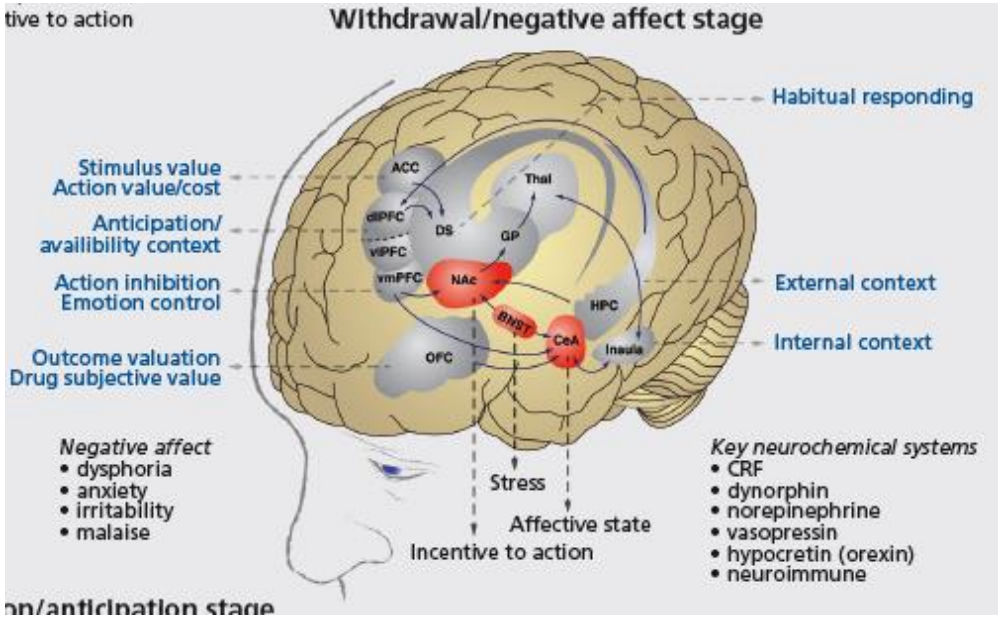
PFC ⟵ N.Acc ⟵ VTA



Drug Addiction: Hyperkatifeia/Negative Reinforcement as a Framework for Medications Development

George F. Koob 2021

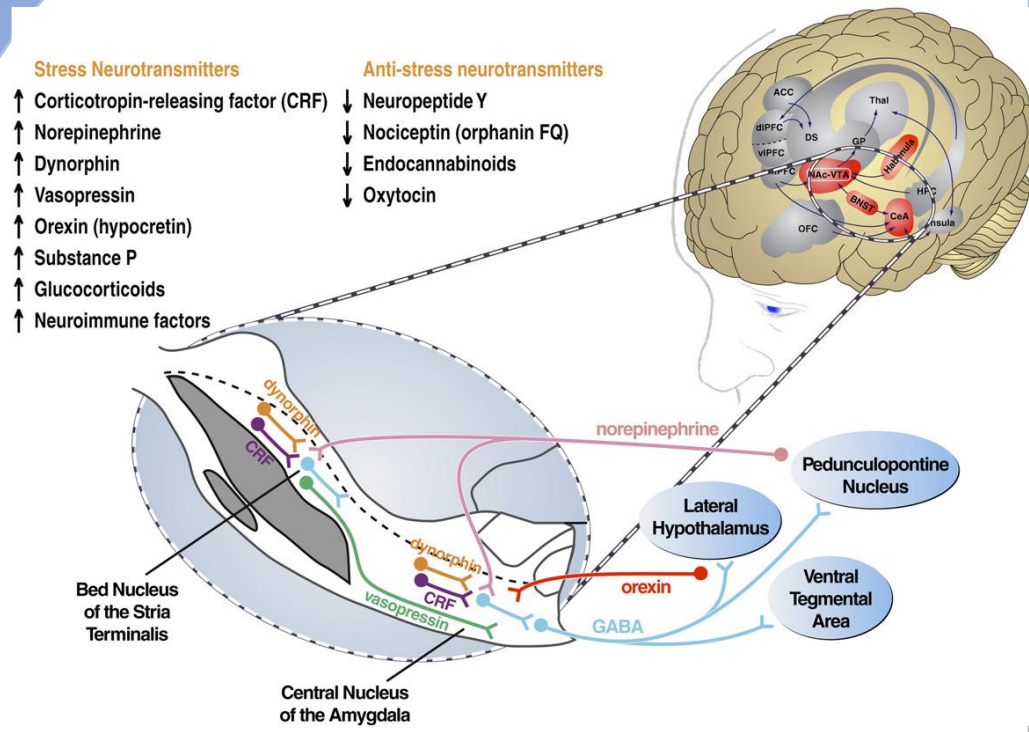
- **Extended Amygdala: Stress: Fight or flight, Negative Affect**
- **Negative feelings from**
- **Stress surfeit: activation of the stress systems, x-CRF (between system adaptation)**
- **Basal Ganglia**
- **Reward deficit: diminished activation in the reward circuitry (within system neuroadaptation)**



Drug Addiction: Hyperkatifeia/Negative Reinforcement as a Framework for Medications Development

George F. Koob 2021

- Reclutamento dei neurottrasmettitori dello stress
- Perdita di attività dei neurotrasmettitori ad effetto anti stress



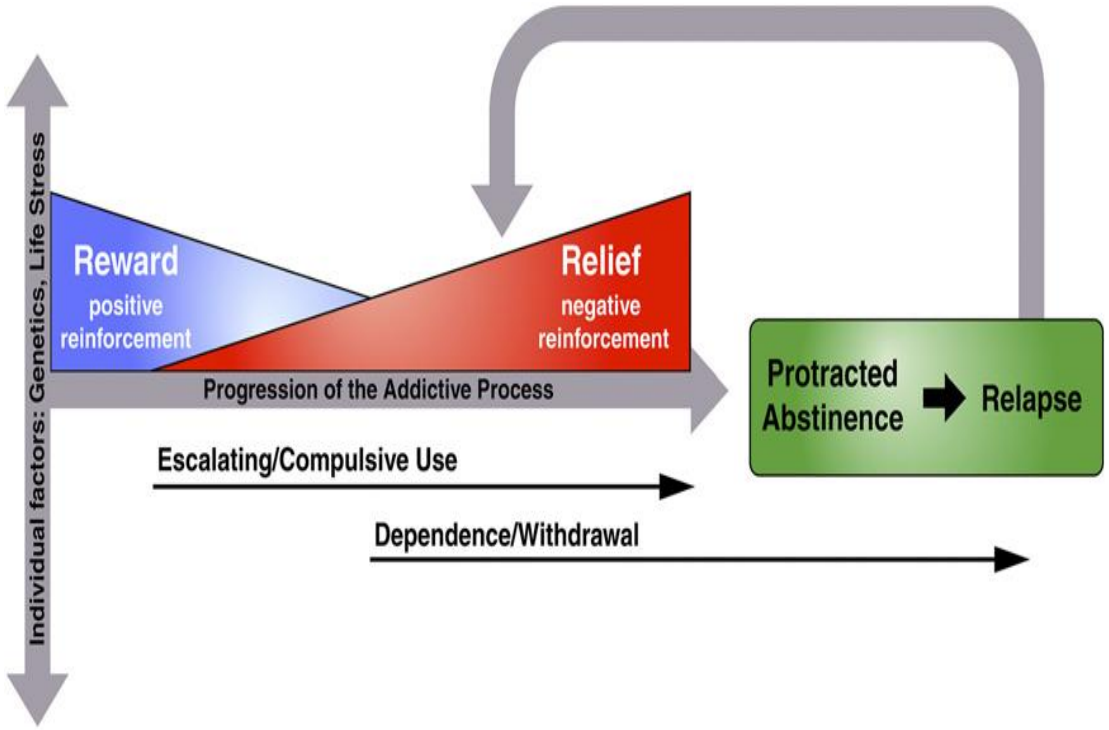
Drug Addiction: Hyperkatifeia/Negative Reinforcement as a Framework for Medications Development

George F. Koob 2021

PR e NR coesistono durante nel ciclo della addiction.

Il PR è associato alle fasi iniziali della malattied è correlabile con lo stato del Binge/intox.

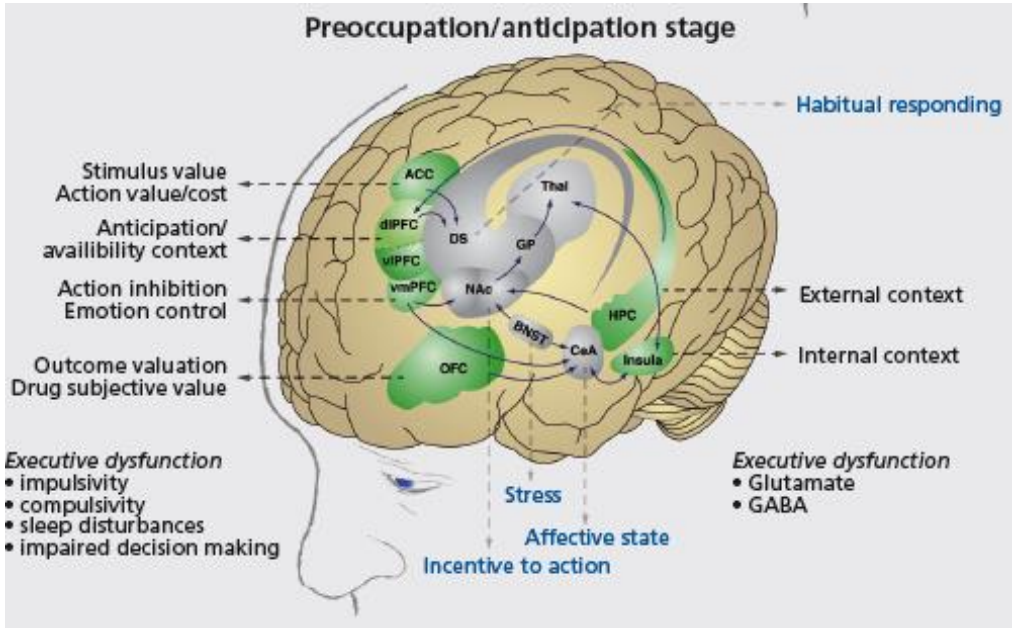
NR si sviluppa nel divenire della malattia e rappresneta il tentativo di fronteggiamntoallo stress o alla ipercatifeia



Preoccupation/anticipation – Executive function deficits

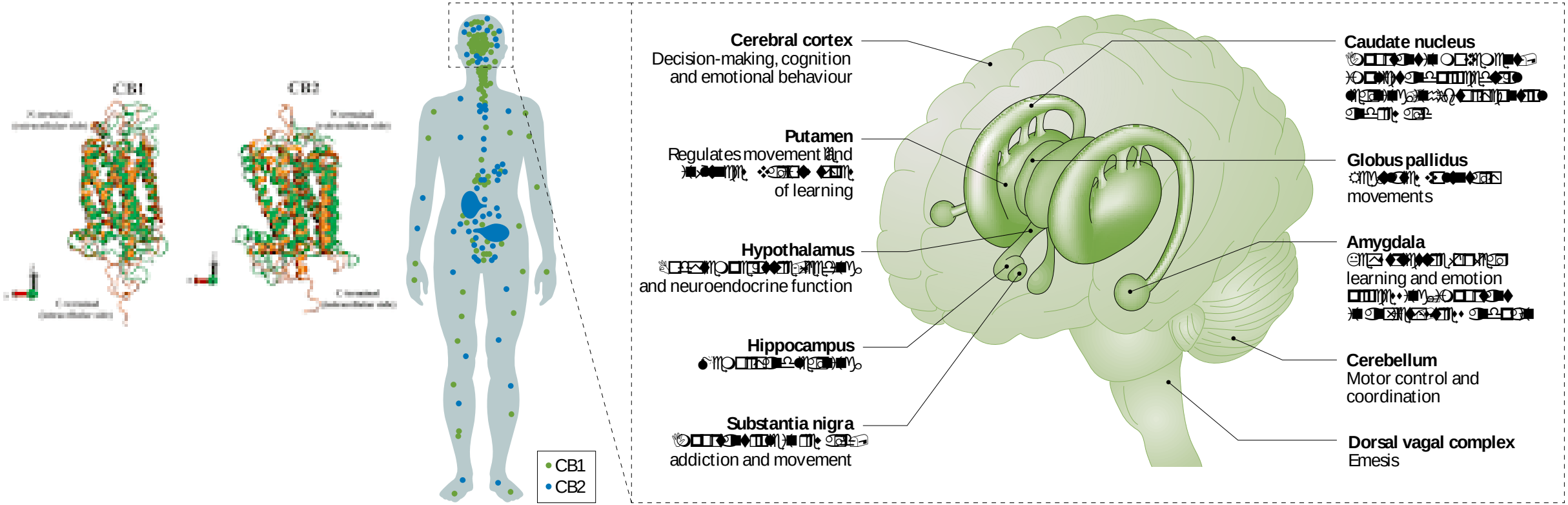
- Prefrontal cortex
- Complex cognitive processes: Organisation, priority of thoughts and feelings, planning, actions. Decision making.
- **Go system**: achieve goals, incentive salience, habits.
- Activation: Habit-like substance seeking

- **Stop system**: Inhibits Go system, incentive salience, impulsive behavior. Controls reward in basal ganglia & stress circuitry in ext amygdala.
- Inhibition: Increased craving, Incentive salinence and stress. Impulsive and compulsive substance seeking.

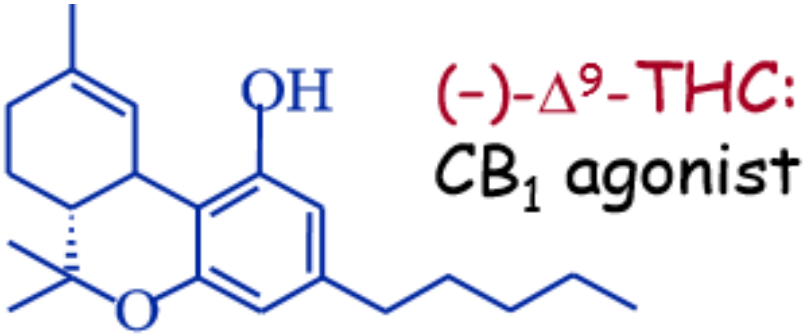


Cannabis use and cannabis use disorder

NATURE REVIEWS | DISEASE PRIMERS | Article citation ID: (2021) 7:16

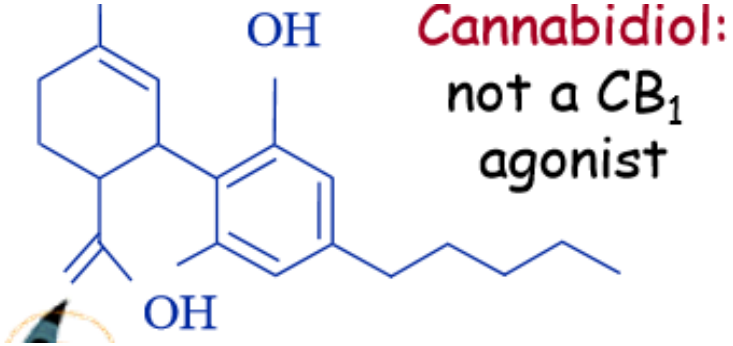


Pharmacology



(–)-Δ^9-THC:
CB_1 agonist

- Partial agonist on CB1 and CB2 receptors



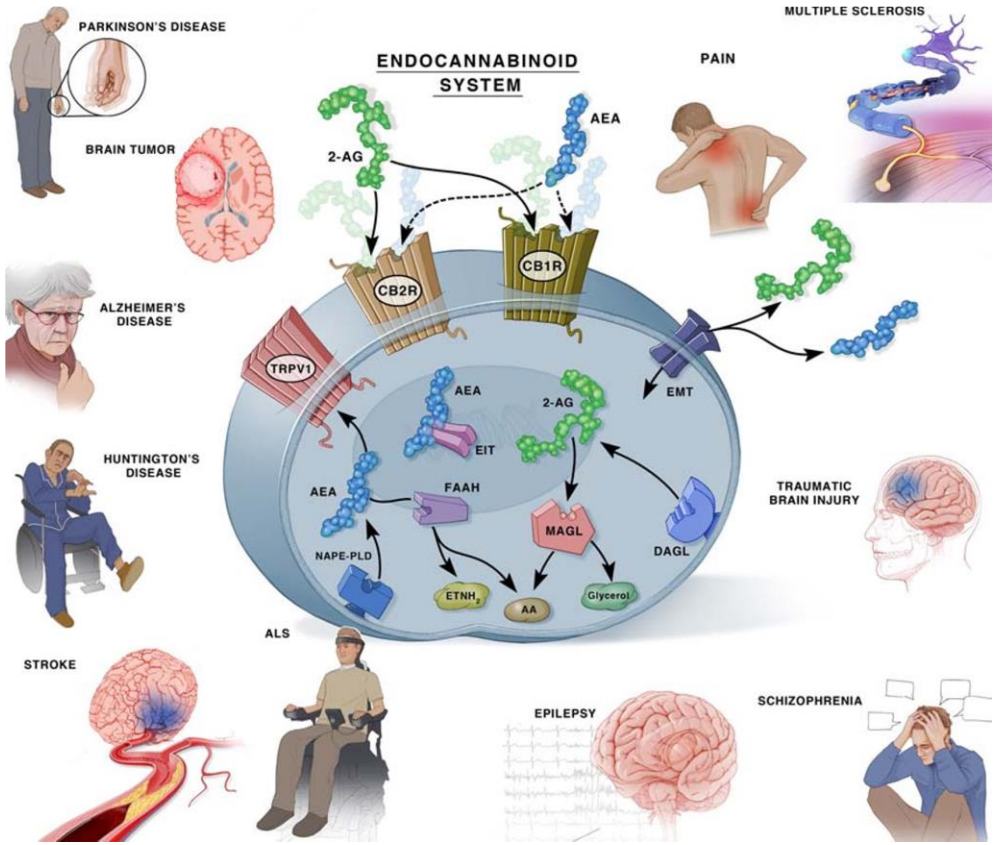
Cannabidiol:
not a CB_1
agonist

- Cannabindiol (CBD) – described as a specific or non-specific antagonist
- It does not activate CB1 or CB2 receptors - or mimic 2AG, anandamide or any known endocannabinoid.
- It may interact with the endocannabinoid system indirectly, e.g. antagonizes CBD1 receptors and inhibits FAAH (?).
- Effects of CBD are said to be “pleotropic”. It acts on many different receptors. (5HT-1A, opioids, adenosine ect)

Targeting the endocannabinoid system: a predictive, preventive, and personalized medicine-directed approach to the management of brain pathologies

EPMA Journal (2020) 11:217–250

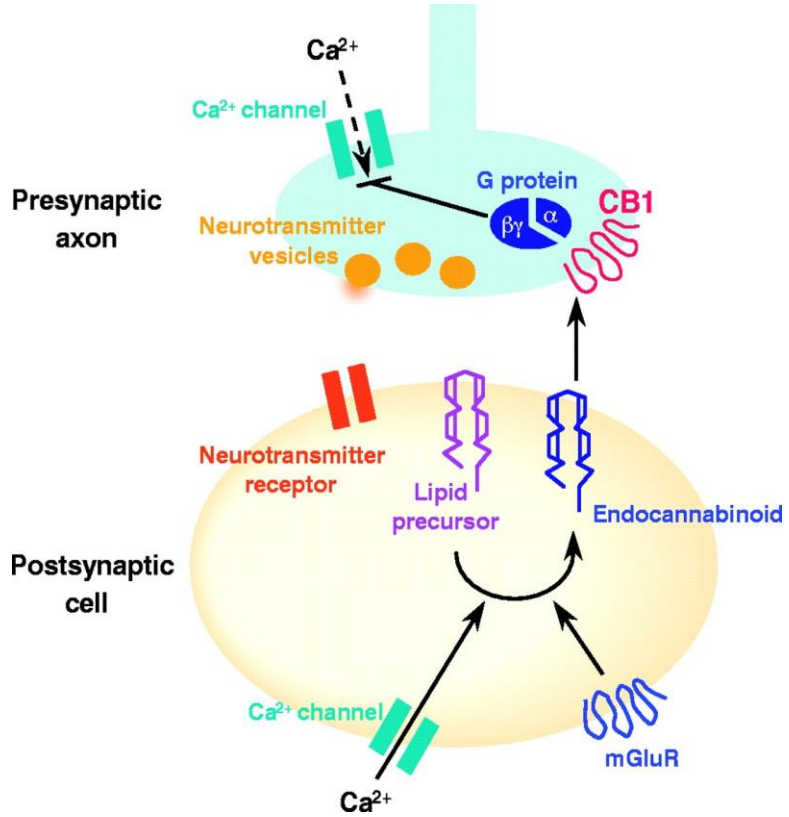
	CB1	CB2
Functions	a. Has psychoactive property [483, 484] b. Stimulates dopaminergic reward pathway [502] c. Motivates to eat, smoke or intake of drugs [502] d. Required for synaptic transmission [483, 484] e. CB1R signaling includes [58, 499, 503]: • Inhibition of forskolin-stimulated adenylyl cyclase • Inhibition of N-, P-, and Q-type calcium channels • Activation of inwardly rectifying potassium channels f. Plays an essential role in: • Fine-tuned motor control [504–506] • Central and peripheral regulation of food intake [504–506] • Fat accumulation [504–506] • Lipid and glucose metabolism [504–506]	a. Has immunological property [483, 484] • Regulates leukocytes adhesion and rolling on endothelium [70, 507–510] • Activation of CB2R improves microvascular circulation and protects BBB [70, 507–509, 511] • Regulates T cell differentiation [512, 513] • Inhibits melanoma cell transendothelial migration [514] b. CB2R may contribute to neuronal plasticity in mouse hippocampal CA3 and CA2 pyramidal neurons [64] c. CB2R signaling includes: • Phosphoinositide 3-kinase pathways [515] • Activation of de novo ceramide production or cyclooxygenase-2 (COX-2) induction [516]



THE ENDOCANNABINOID SYSTEM

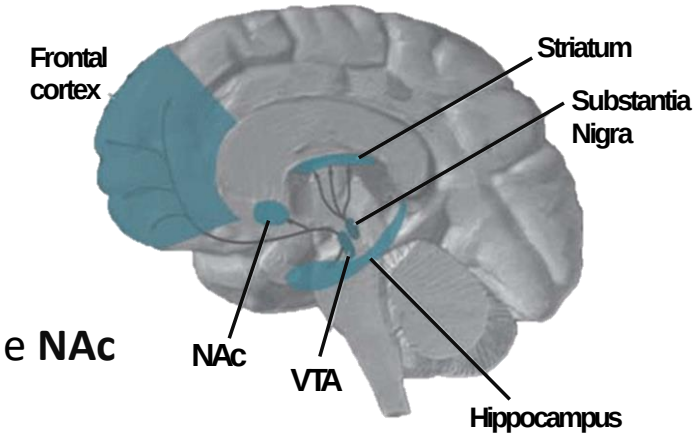
3 core elements

- **enzymes**
  - that synthesize endocannabinoid agonists (ECBs)
- **receptors**
- that respond to agonists by triggering intracellular signaling cascades
- **transporters and enzymes**
  - that remove ECBs from the receptor vicinity



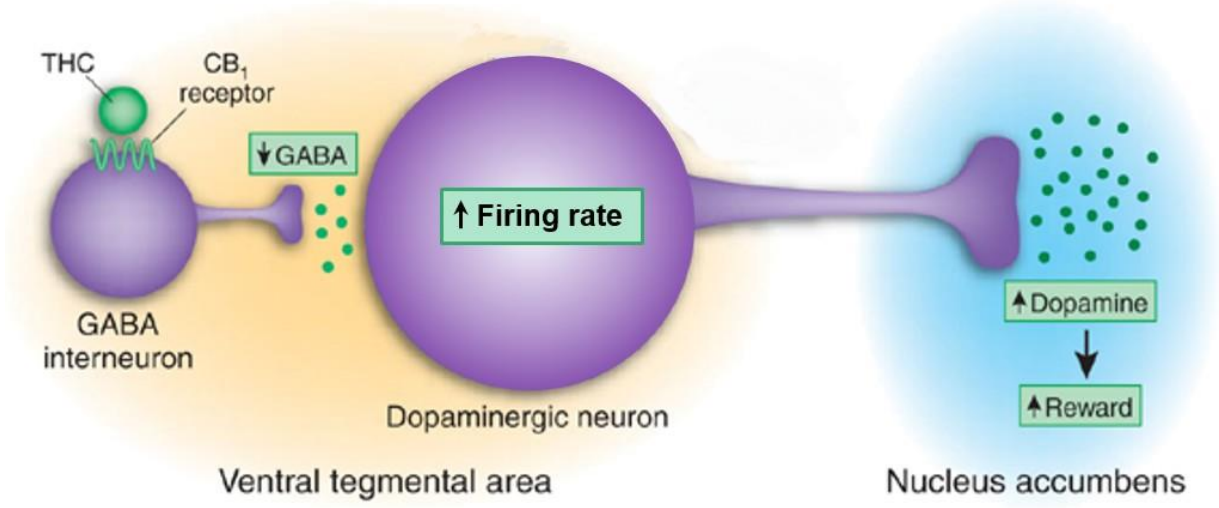
THE ENDOCANNABINOID SYSTEM

Endocannabinoid signaling in reward and addiction



Feelings of well being and euphoria →blocked by CB1 receptor antagonist
(Rinaldi-Carmona, 1994)

THC increases the firing rate of DA neurons in the **VTA** that project principally the **NAc**
(Kalivas & Volkow, 2005; Kalivas & Nakamura, 1999)



THC perturbs the proper balance between excitation and inhibition

Matyas et al., 2008; Thomas KL, 2006

Environment

- childhood maltreatment
- peers influence
- parental influence
- early life traumatic events

Genetics

Genetic variants related to
- Endocannabinoid system
- Neurogenesis synaptic
- Dopaminergic neurotransmission

Epigenetics

- Altered methylation enriched in genes implicated in synaptic plasticity, dopamine pathway, endocannabinoid system
- Altered miRNAs profile
- Genome-wide alterations in histone modifications

Cannabis Use Disorders

Marmet et al., *Addiction* 2021 Brosnan et al., *Addict Behav Rep.*

Addiction

Genetic and environmental influences on cannabis use initiation and problematic use:

a meta-analysis of twin studies.

Verweij et al., 2010

A systematic literature search

28 twin studies on cannabis use initiation

24 studies on problematic cannabis use

genes (A) shared environment (C) unshared environment (E)

cannabis use initiation:

A 48%, C 25%, E 27% in males

A 40%, C 39%, E 21% in females

problematic cannabis use:

A 51%, C 20%, E 29% for males

A 59%, C 15% , E26% for females.

Addiction

Candidate genes for cannabis use disorders: findings, challenges and directions.

Agrawal and Lynskey, 2009

Genes with specific influences
on cannabis use disorders:

Cannabinoid receptor gene (CNR1)

Cannabinoid receptor type 2 (CB2)

Fatty acid amide hydrolase (FAAH)

Monoglyceride lipase (*MGLL*),

Transient Receptor Potential Vanilloid 1 (*TRPV1*)

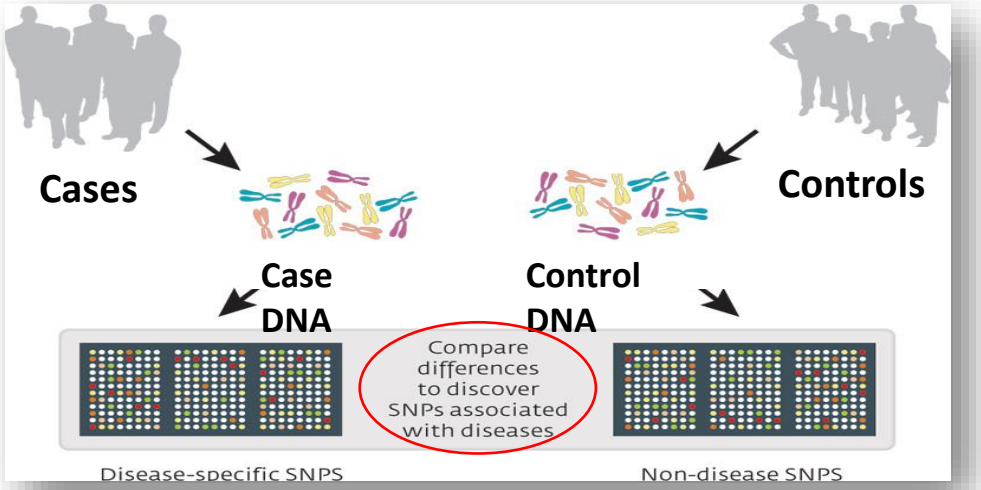
Orphan cannabinoid receptor (*GPR55*)

Genes with a non-specific influence
on risk of cannabis use disorders:

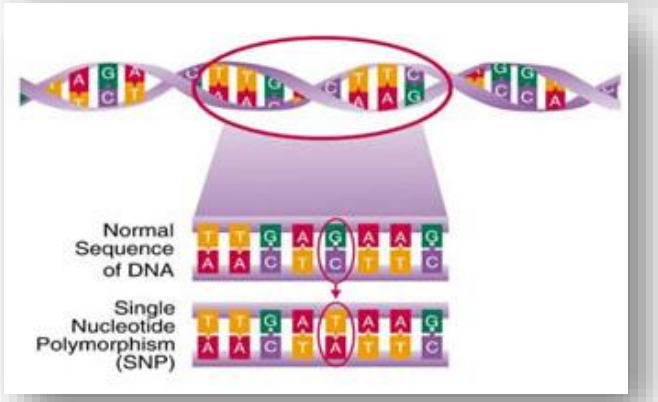
GABA Receptors 2 (GABRA 2)

Dopamine Receptors D2 (DRD2)

Opioid Receptors Mu 1 (OPRM1)



GWAS

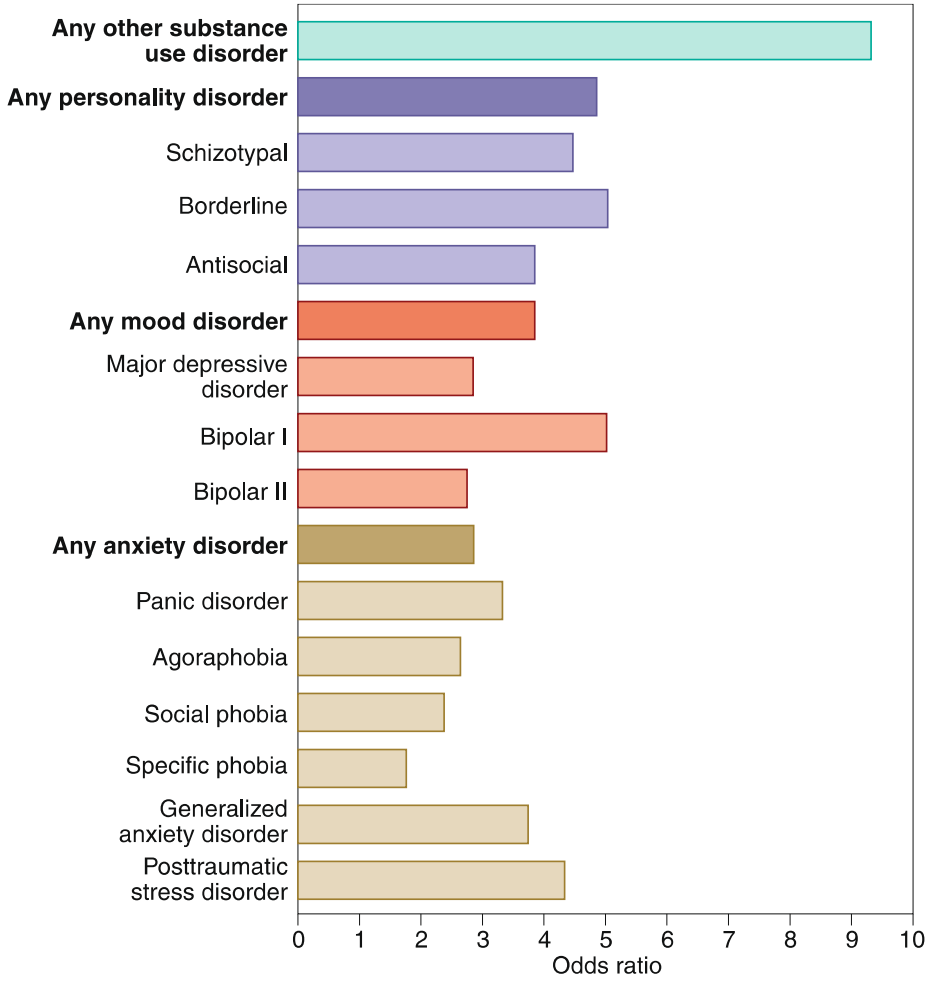


(SNPs)

Deconstructing the neurobiology of cannabis use disorder

Nature NeuroscieNce | VOL 23 | MAY 2020 | 600–610 | www.nature.com/natureneuroscience

- Monitoring individuals longitudinally suggest that frequent cannabis use and its abuse are associated with increased risk of a subsequent mental health disorder. Conversely, having any mood, anxiety or other substance-use pathology at baseline also predicts future cannabis use and dependence.
- Men have higher rates of CUD than women, a pattern that is present from childhood, when more boys than girls develop CUD2,35. Despite the high preva- lence of cannabis-dependent males, the escalation of use and sever- ity of CUD is greater in females, as with many substances of abuse36.



The endocannabinoid system

Essays in Biochemistry (2020) **64** 485–499
https://doi.org/10.1042/EBC20190086

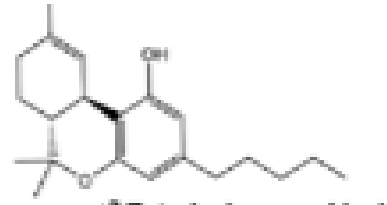
Cannabinoids	Category	Select Compounds
Phytocannabinoids	Psychoactive	Δ^9-Tetrahydrocannabinol Δ^8-Tetrahydrocannabivarin Cannabinol
	Non-psychoactive	Cannabidiol Cannabidivarin Cannabigerol Cannabichromene
Endocannabinoids	Major	Anandamide 2-arachidonyl glycerol
	Minor	Noladin ether Virodhamine *N*-Arachidonyl dopamine Oleamide
Cannabimimetics	*N*-Acylethanolamines	*N*-Palmitoylethanolamine *N*-Oleoylethanolamine *N*-Stearoylethanolamine
	Terpenoids & Phenolics	β-Caryophyllene Pristimerin Salvinorin A

2-Arachindonyl glycerol

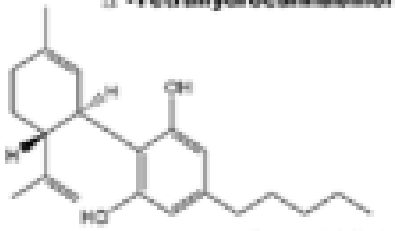
Anandamide

Noladin ether

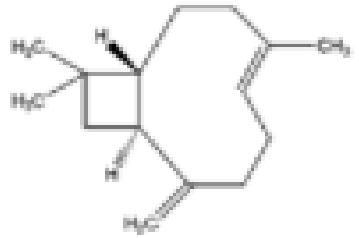
N-Palmitoylethanolamine



Δ^9-Tetrahydrocannabinol

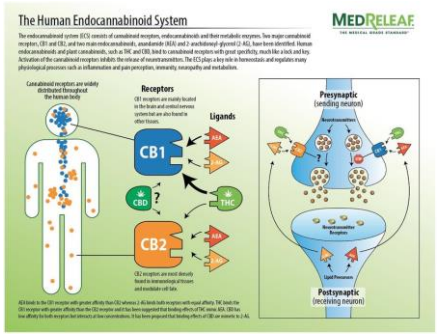


Cannabidiol



β-Caryophyllene

Endocannabinoid System - Function



In the brain, CB1 receptors are located in many different area and affect many different transmitters.

- They are perhaps not a “system”, but rather a series of local feedback mechanisms.
- **THC and congeners, however, activate these receptors all at once.**

In the brain, endocannabinoid feedback reduces transmitter release in many different systems.

These include: GABA, glutamate, DA, NE, 5HT, glycine, etc.

The endocannabinoid system

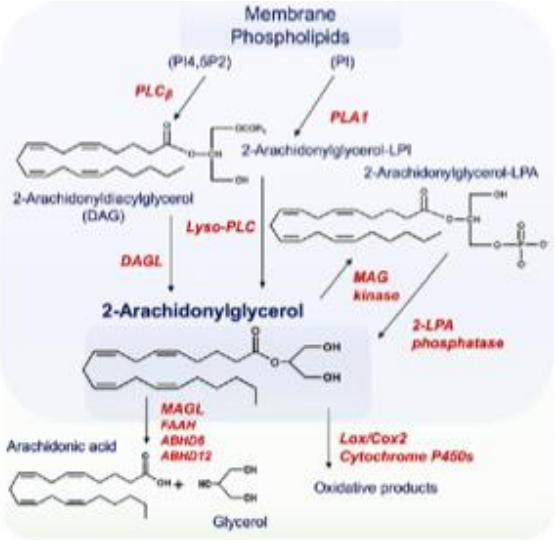
Essays in Biochemistry (2020) **64** 485–499
https://doi.org/10.1042/EBC20190086

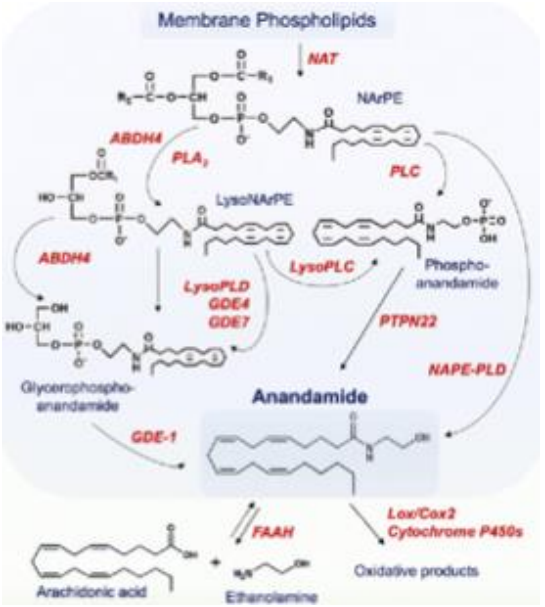
- **Anandamide and 2 AG are eicosanoids.**

- **They are formed** by the action of phospholipases on plasma membrane phospholipids.

- **They are broken down** by FAAH and other enzymes. Blockade of FAAH extends their half-lives.

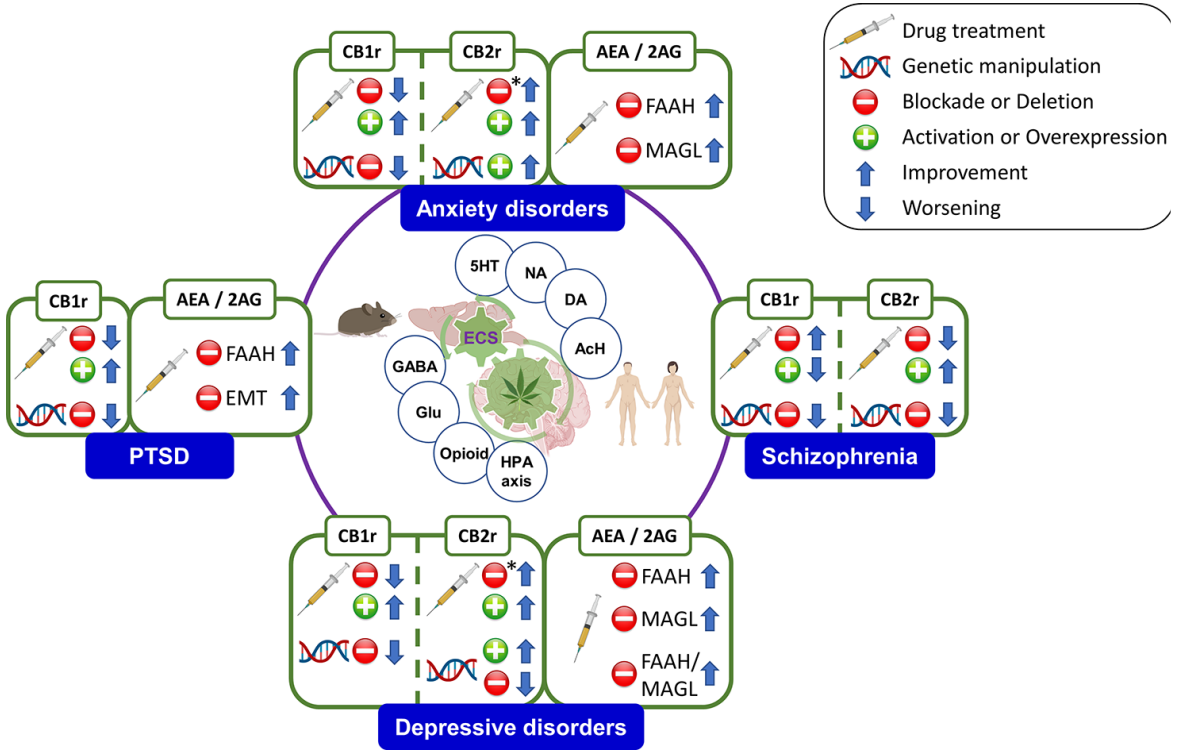
- **CB1** – 2 AG is a full agonist - anandamide is a partial agonist
- **CB2** – 2 AG binds with a higher affinity than anadamide





frontiers in Psychiatry

Endocannabinoid System Components as Potential Biomarkers in Psychiatry



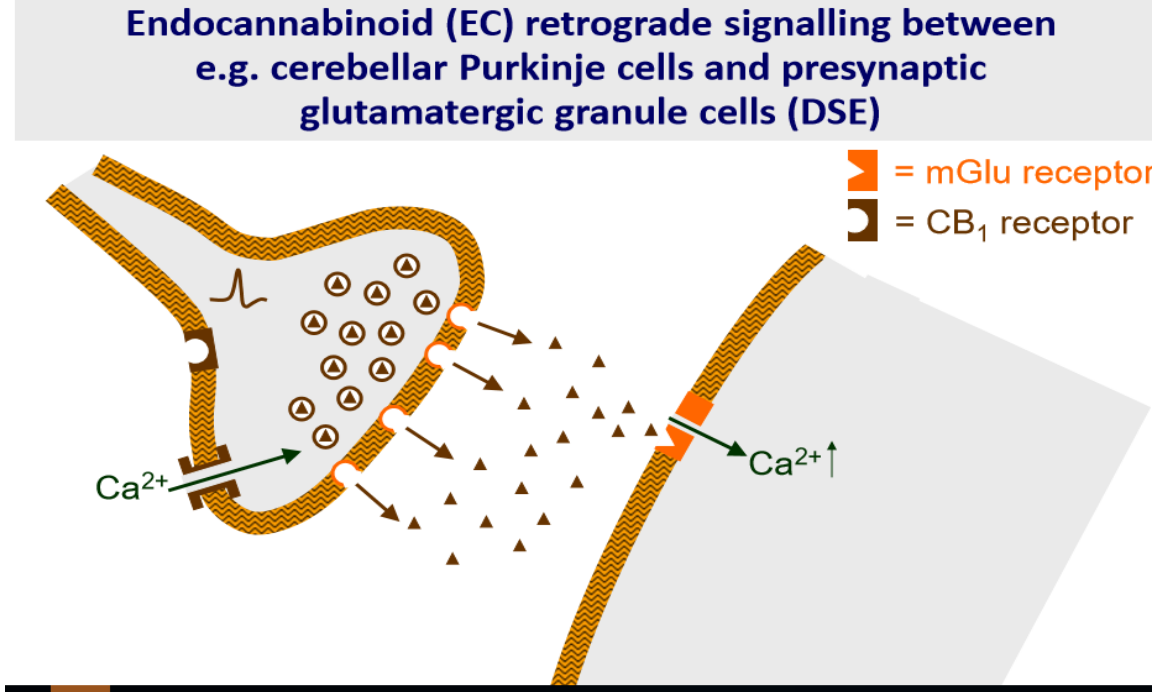
REVIEW

published: 27 April 2020

2 AG and anandamide are “retrograde inhibitors”.

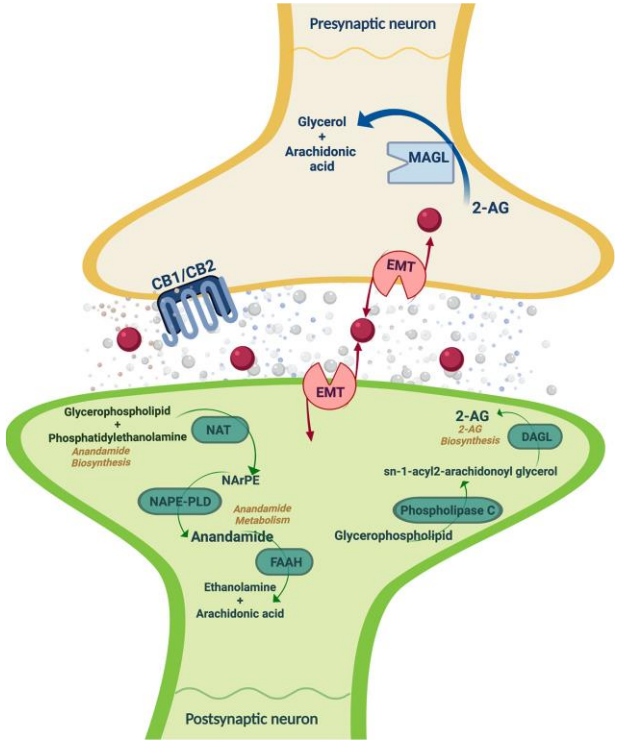
They are released post-synaptically following receptor activation.

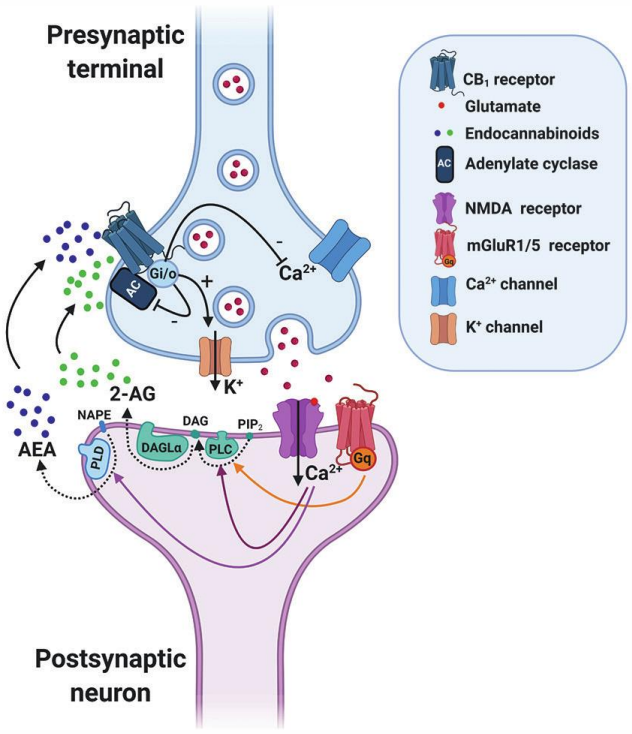
They then diffuse backwards to the presynaptic cell where they inhibit transmitter (CB1) or cytokine (CB2) release.



The endocannabinoid system in modulating fear, anxiety, and stress

DIALOGUES IN CLINICAL NEUROSCIENCE • Vol 22 • No. 3 • 2020 • **229**





They act by closing Ca++ channels and opening K+ channels via Gi/o.

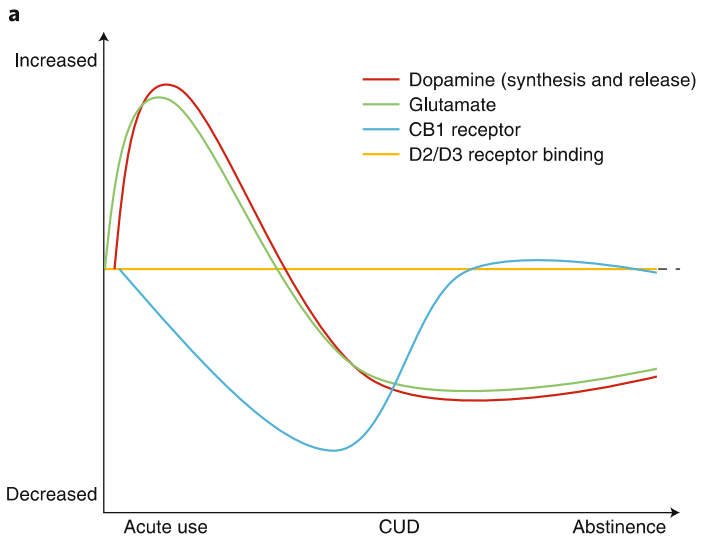
Deconstructing the neurobiology of cannabis use disorder

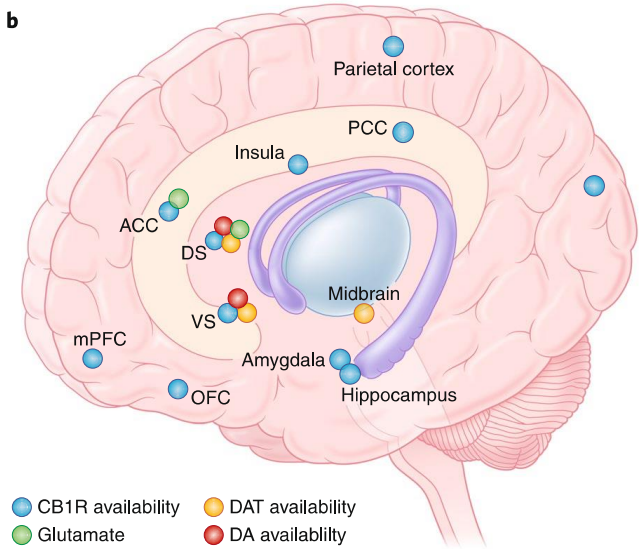
Nature NeuroscieNce | VOL 23 | MAY 2020 | 600–610 | www.nature.com/natureneuroscience

Hypodopaminergic state

↓

Amotivational syndrome





Hypoglutamatergic state

↓

Impaired decision making

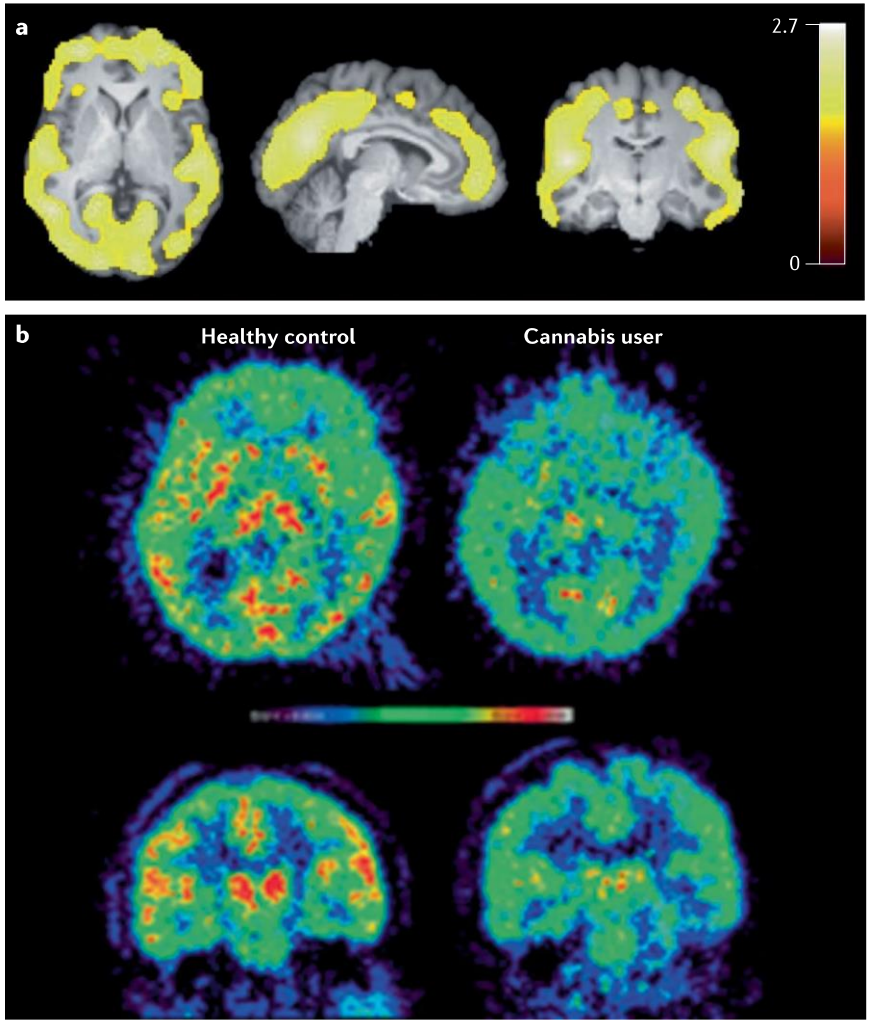
CB1Rs is downregulated in neocortex, limbic cortex and ventral stritum

↓

Alteration of cognition and emotional processing reward and goal-directed behavior

Cannabis use and cannabis use disorder

NATURE REVIEWS | DISEASE PRIMERS | Article citation ID: (2021) 7:16



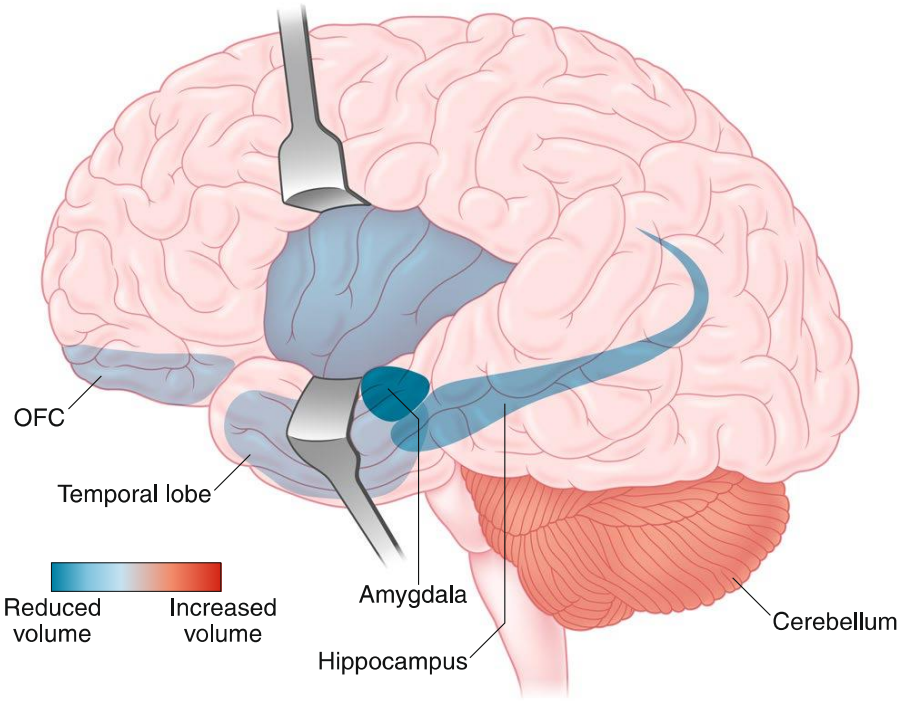
- Downregulation on CB1 receptor density;
- the endogenous cannabinoid anandamide is downregulated in striatal areas after repeated administration of THC in rodents Lower levels of anandamide have also been found in the cerebrospinal fluid of people who use cannabis;
- the activity of FAAH is lower in the brain of people who use cannabis

Deconstructing the neurobiology of cannabis use disorder

Nature NeuroscieNce | VOL 23 | MAY 2020 | 600–610 | www.nature.com/natureneuroscience

Table 1 | Alterations detected in specific brain regions of in vivo measures of gray matter volume and functional activity, associated with certain tasks and stimuli, in abstinent individuals with CUD

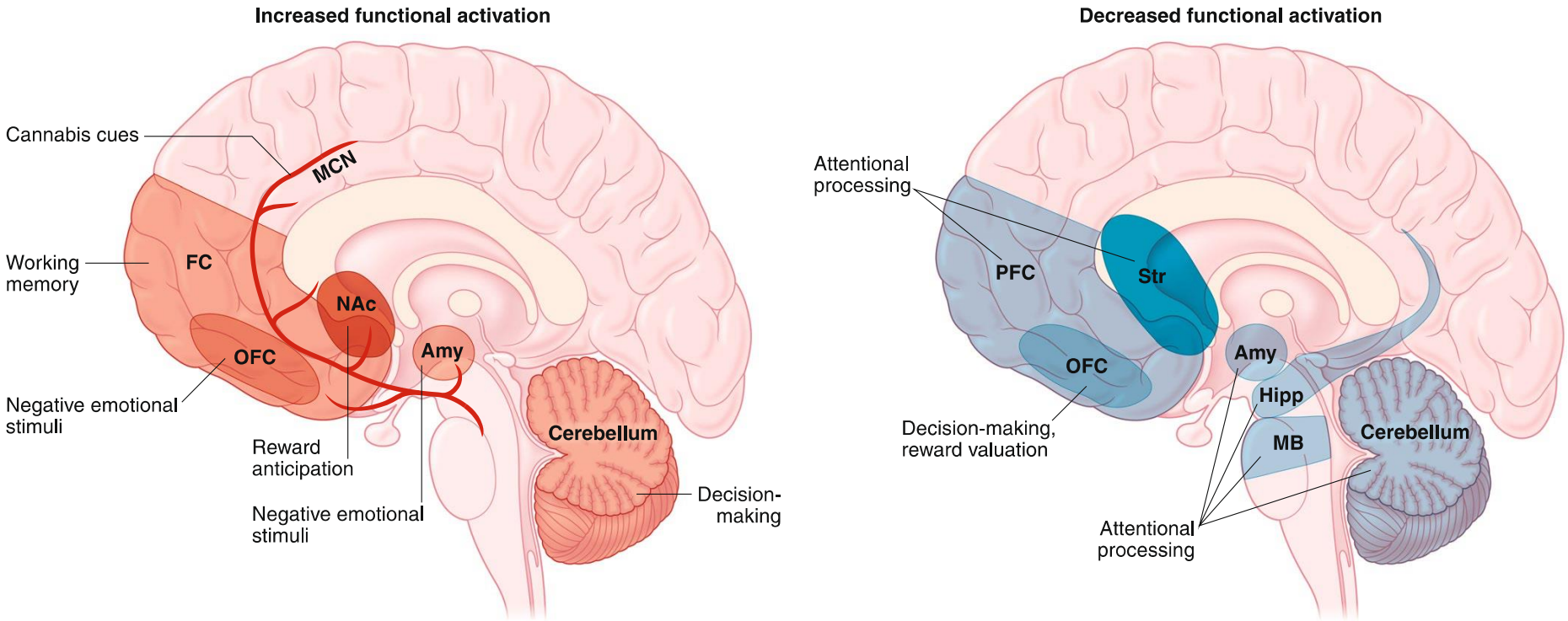
Region / circuit	Morphology	Neural activity	Association with function- or task-based activation
Frontal/ prefrontal cortex and insula	Decrease in volume (OFC[63,64,141] and insula[63])	Decrease[60,86,98,142] or increase[90–92,97] in activity based on task and absinence[85]	Decreased in decision-making[60]; decreased activity with uncertain reward[142]; decreased during cognitive appraisal of emotional stimuli[98]; decreased activity on attention task[85,86], but increased activity after 1 year of abstinence is associated with better treatment outcome[85]; increased activity on working memory tasks[90–92] and responsivity to negative emotional stimuli[97]
Ventral striatum	*[79]	Decrease[#,85] or increase in activity[143], based on task and abstinence	Decreased activity on an attentional task[85]; increased activity during reward anticipation[143]
Dorsal striatum	*[79]	Decrease in activity[85,#]	Decreased activity during attentional processing[85]
Hippocampus/ temporal lobe	Decrease in volume[63,66]	Decrease in activity (hipp)[85,#]	Attentional processing[85]
Amygdala	Decrease in volume[69,70,144]	Decrease[85,#] or increase[97] in activity based on task	Decreased functionality associated with attentional performance[85], increased activation in response to negative emotional stimuli[97]
Cerebellum	Increase in volume[63,69]	Decrease[86,#] or increase[60,#] in activity based on task	Increased activation during decision-making[60], decreased activity associated with attentional processing[86]
Mesocorticolimbic pathway		Increase in activity[93,94,145,146]	Cannabis cue reactivity[93,94,145,146]



- **Reduce OFC Volume predicts THC use**
- **A functional variant of the *CNR1* gene (rs2023239 G allele) linked with higher cortical CB1R is asso- ciated with smaller hippocampal volume in chronic cannabis users, but not healthy controls,**

Deconstructing the neurobiology of cannabis use disorder

Nature NeuroscieNce | VOL 23 | MAY 2020 | 600–610 | www.nature.com/natureneuroscience



Functional MRI studies also document differential brain activity during neurocognitive tasks in CUD individuals

Eur Arch Psychiatry Clin Neurosci (2012) 262:47–57
DOI 10.1007/s00406-011-0223-5

ORIGINAL PAPER

Psychobiological responses to unpleasant emotions in cannabis users

Lorenzo Somaini · Matteo Manfredini · Mario Amore · Amir Zaimovic · Maria Augusta Raggi · Claudio Leonardi · Maria Lidia Gerra · Claudia Donnini · Gilberto Gerra

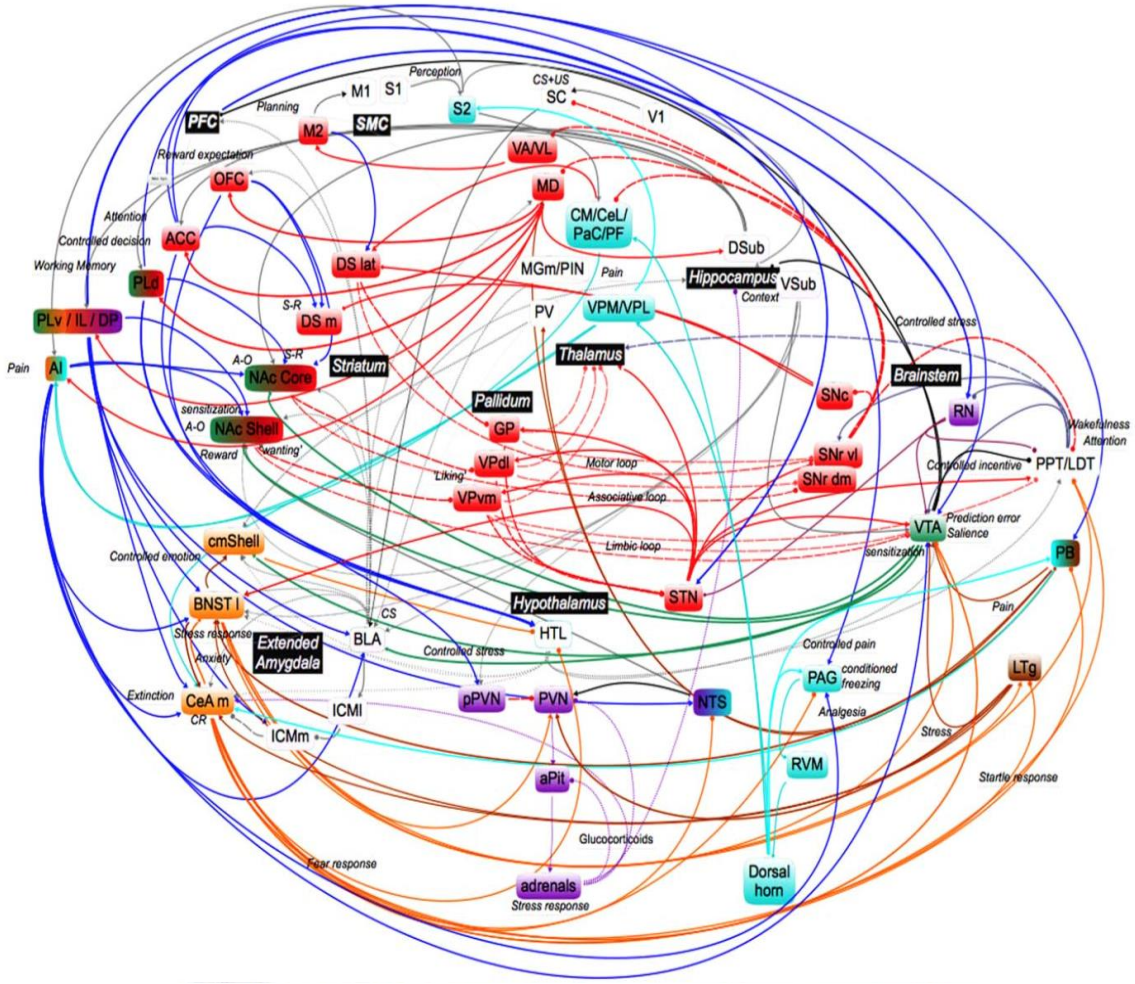
- association between active cannabis use, subjective
- reduced sensitivity to negative emotions and threat and
- HPA axis dysfunction

Addiction or multiple addictions?

George and Koob, Neurosci Biobehav Rev. 2010 Nov; 35(2): 232–247.

Six different modules:

- Decision making
- Negative affect
- Stress/HPA
- Habit
- Pain
- Incentive salience



Decision making
Prefrontal cortex

Negative affect
Extended amygdala

Stress
HPA axis

Habit formation
Basal ganglia

Pain
Spinomesothalamocortical

Incentive salience
Mesolimbic dopamine

Addiction or multiple addictions?

- Kwako LE, Momenan R, Litten RZ, Koob GF, Goldman D. Addictions Neuroclinical Assessment: A Neuroscience-Based Framework for Addictive Disorders. Biol Psychiatry. 2016;80(3):179-89.