Psychoneuroimmunology

Where Stress, Trauma and Addiction Intersect

Kevin McCauley, MD
Senior Fellow
The Meadows of Wickenburg

South Dakota Problem-Solving Courts Statewide Conference
November 2023

kevin.mccauley@meadowsbh.com

Pleasure Unwoven (Neuroscience of Addiction)

https://vimeo.com/347595250/df4ede31f7

Memo to Self (Recovery Management)

https://vimeo.com/347596435/deaf56bbea

Most recent epidemiology of the U.S. overdose epidemic …

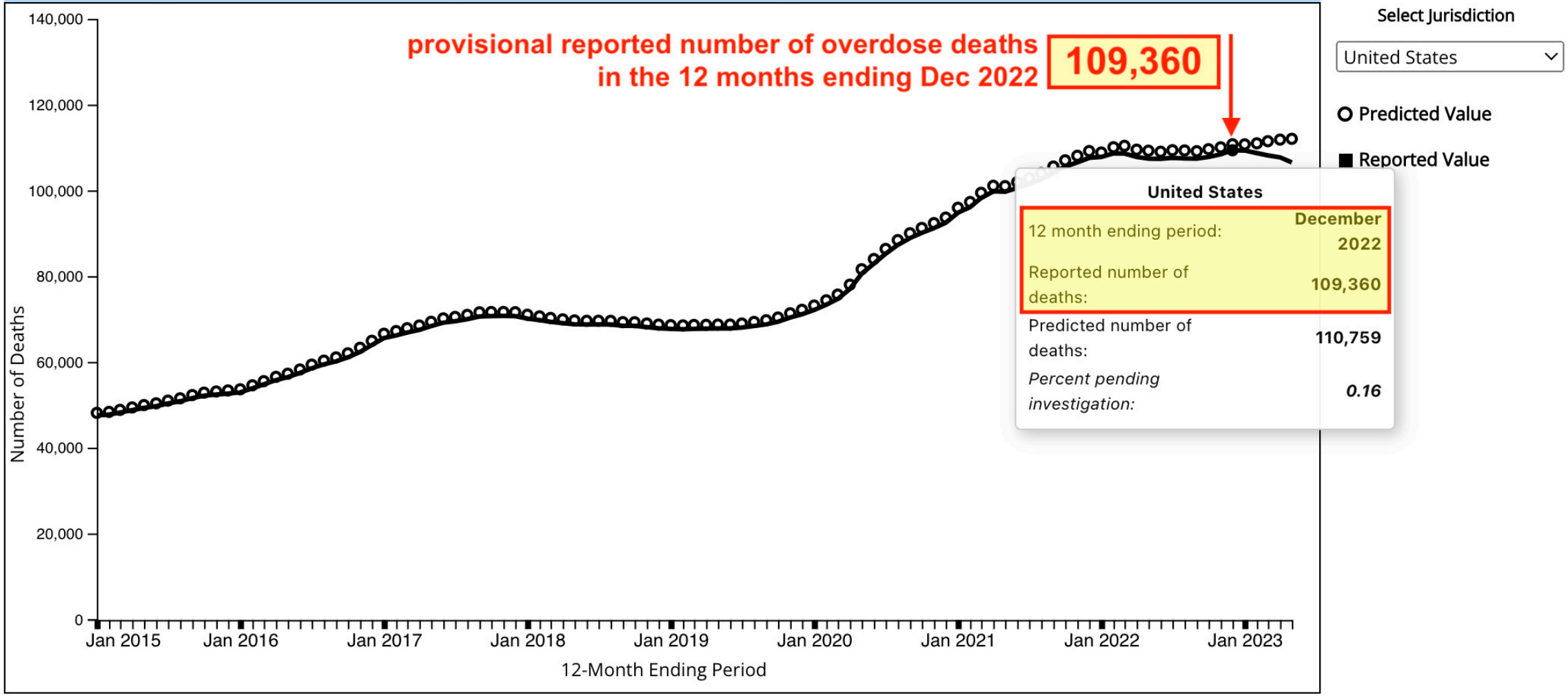
	Drug OD deaths	Opioid-involved deaths	age-adjusted mortality rate	% change from previous year
2019[1]	70,630	49,860 (70.6%)	21.6 / 10^5	+ 4.4%
2020[2]	91,799	68,630 (74.8%)	28.3 / 10^5	+ 31 %
2021[3,4]	106,699	80,411 (75.4%) SOOTM: 70,601 (66.2%)	32.4 / 10^5	+ 31.4%
	292 deaths/day 1 death / 5 minutes	220 deaths / day 1 death / 7 minutes		
Total deaths since 1999	1,039,063	644,933 (62.1%)		

1. Hedegaard, H., Miniño, A. M., & Warner, M. (2020). Drug Overdose Deaths in the United States, 1999-2019. NCHS data brief, (394), 1–8.
2. Hedegaard, H., Miniño, A., Spencer, M. R., & Warner, M. (2021). Drug overdose deaths in the United States, 1999–2020. NCHS Data Brief No. 428. https://doi.org/10.15620/cdc:112340
3. Spencer, M. R., Miniño, A. M., & Warner, M. (2022). Drug Overdose Deaths in the United States, 2001-2021. NCHS data brief, (457), 1–8.
4. https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

12 Month-ending Provisional Number and Percent Change of Drug Overdose Deaths

Based on data available for analysis on: October 1, 2023

Figure 1a. 12 Month-ending Provisional Counts of Drug Overdose Deaths: United States



Centers for Disease Control and Prevention. (2023, August 6). Vital statistics rapid release - provisional drug overdose data. National Vital Statistics System. Retrieved Aug 6, 2023, from https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

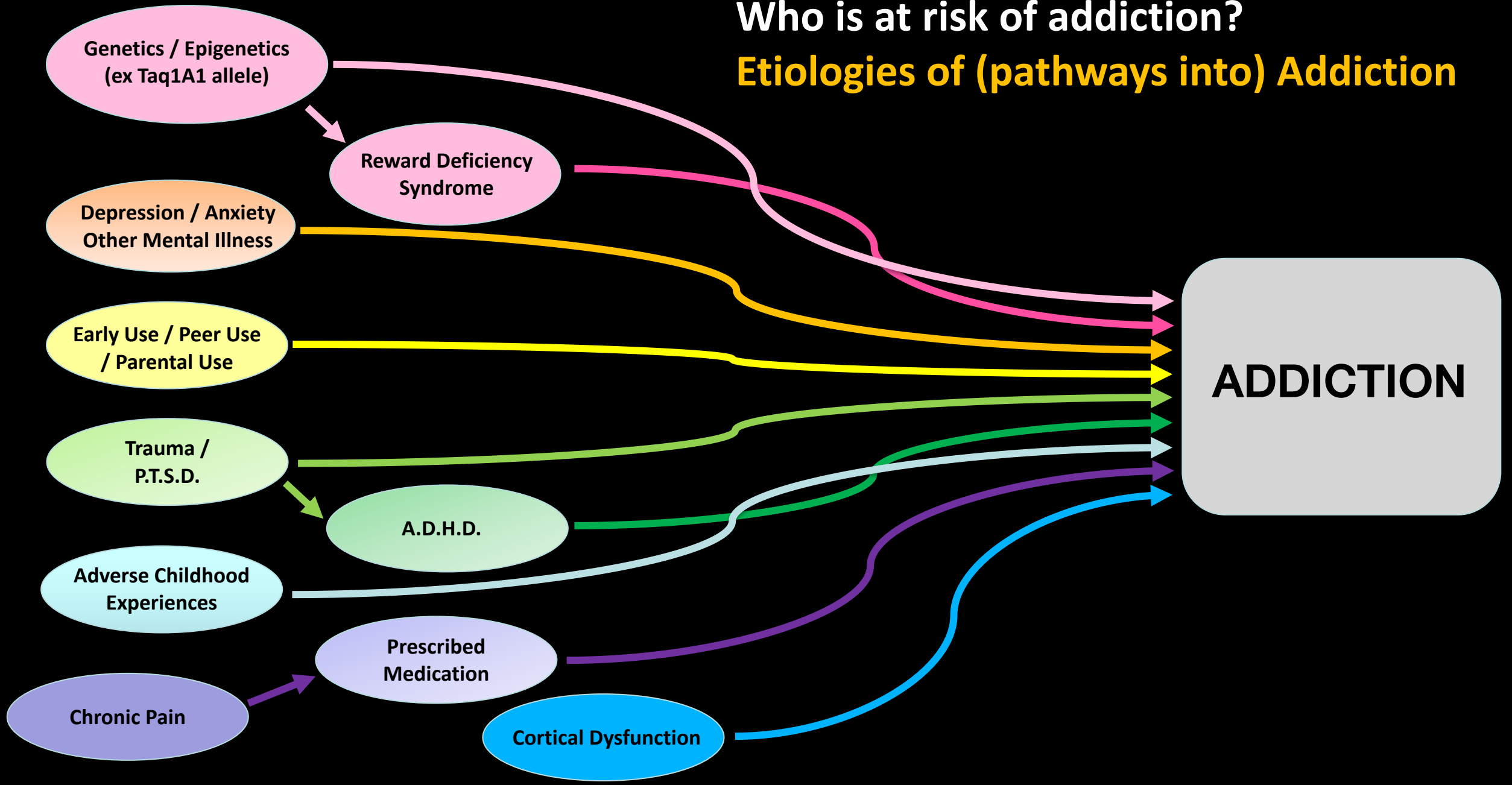
12-month ending **Dec 2022** (as of October 1, 2023) ...

	Drug OD deaths	Opioid-involved deaths	age-adjusted mortality rate	% change from previous year
2019[1]	70,630	49,860 (70.6%)	21.6 / 10^5	+ 4.4%
2020[2]	91,799	68,630 (74.8%)	28.3 / 10^5	+ 31 %
2021[3,4,5]	**106,699** (updated 1OOCT23: 107,573)	80,411 (75.4%) SOOTM: 70,601 (66.2%)	32.4 / 10^5	+ 31.4%
2022[5] (provisional)	**109,360** (300 deaths/day)	**82,472 (75.4% predicted)** 226 deaths/day		**+ 2.5%**

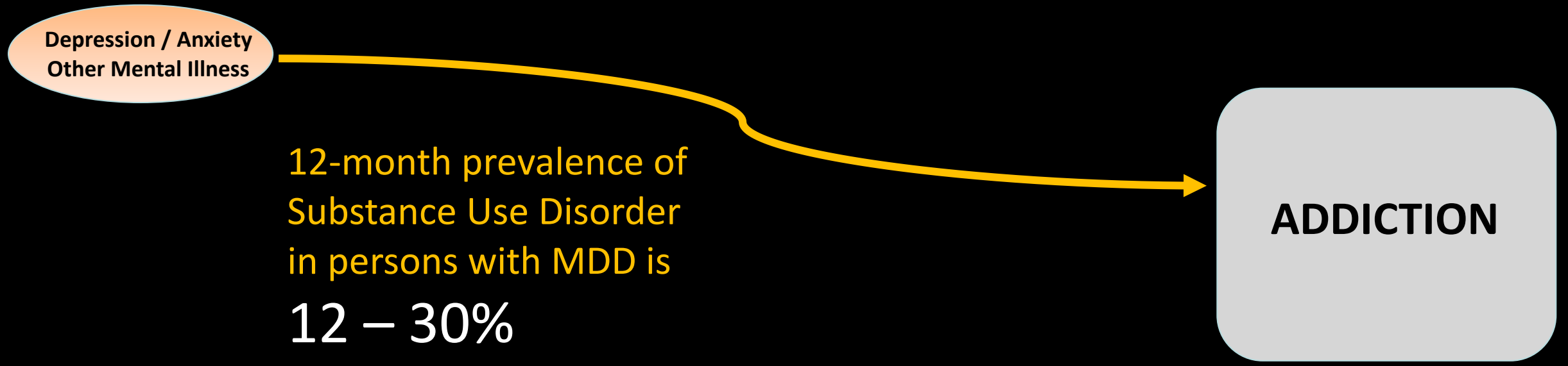
1. Hedegaard, H., Miniño, A. M., & Warner, M. (2020). Drug Overdose Deaths in the United States, 1999-2019. NCHS data brief, (394), 1–8.
2. Hedegaard, H., Miniño, A., Spencer, M. R., & Warner, M. (2021). Drug overdose deaths in the United States, 1999–2020. NCHS Data Brief No. 428. https://doi.org/10.15620/cdc:112340
3. Spencer, M. R., Miniño, A. M., & Warner, M. (2022). Drug Overdose Deaths in the United States, 2001-2021. NCHS data brief, (457), 1–8.
4. https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates
5. Centers for Disease Control and Prevention. (2023, October 1). Vital statistics rapid release - provisional drug overdose data. National Vital Statistics System. Retrieved Oct 1, 2023, from https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

Who is at risk of addiction?

Etiologies of (pathways into) Addiction



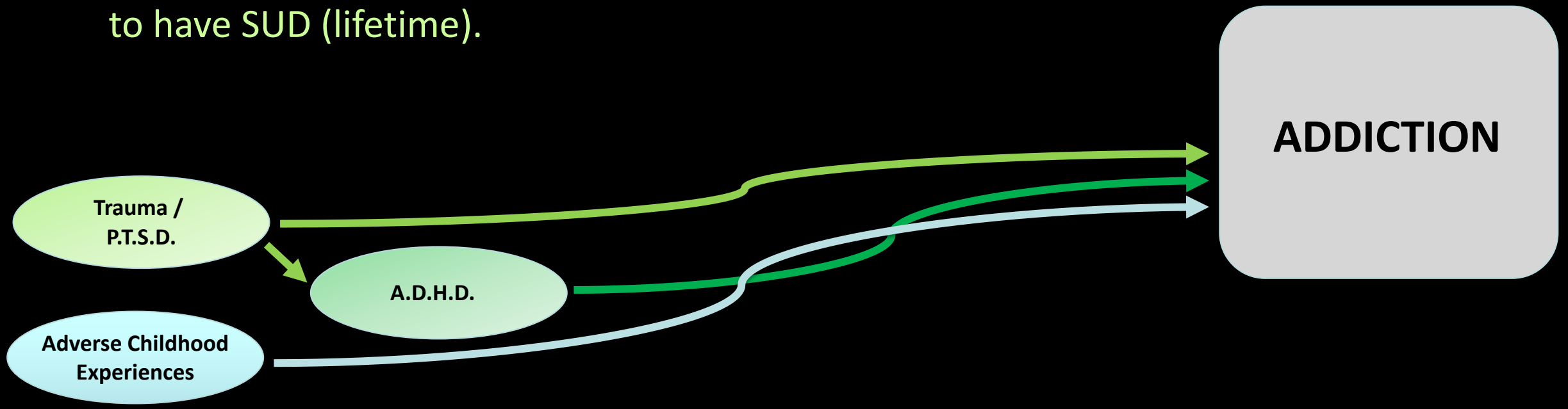
CO-OCCURRING DISORDERS: Self-Medication Pathways into Addiction



María-Ríos CE, Morrow JD. Mechanisms of Shared Vulnerability to Post-traumatic Stress Disorder and Substance Use Disorders. Front Behav Neurosci. 2020;14:6. Published 2020 Jan 31. doi:10.3389/fnbeh.2020.00006

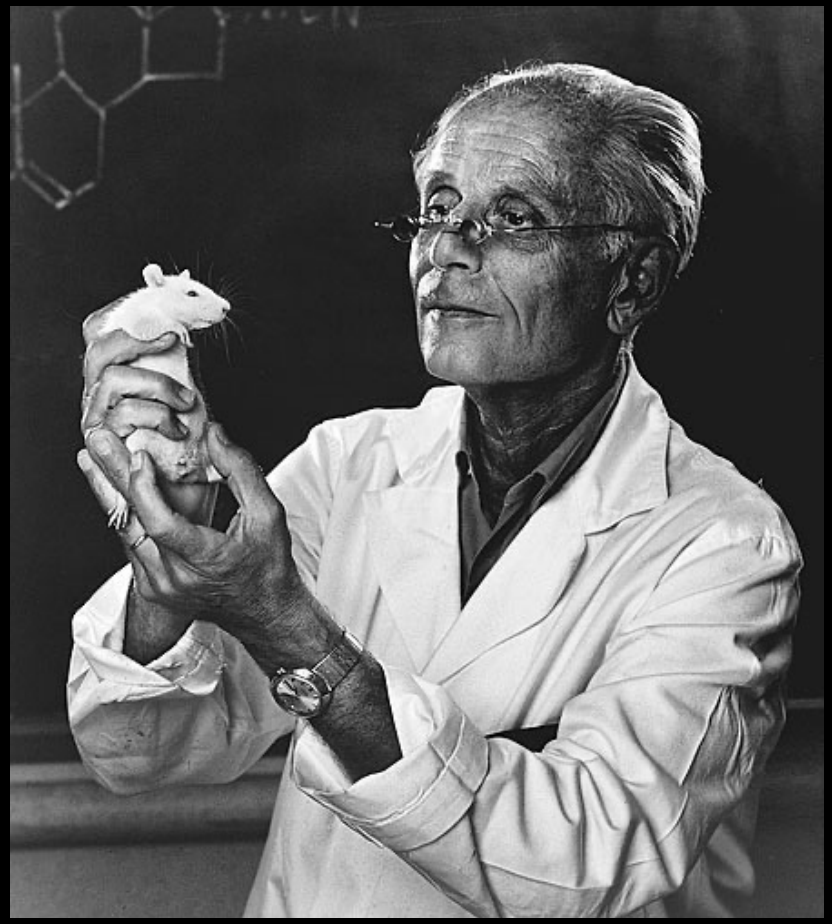
STRESS & Trauma pathways into Addiction

Among treatment-seeking persons with SUD,
30-50% also meet criteria for PTSD (lifetime),
and persons with PTSD are **4 to 5 times more likely**
to have SUD (lifetime).



Brady, K.T., McCauley, J.L., Back, S.E. (2021). The Comorbidity of Post-traumatic Stress Disorder (PTSD) and Substance Use Disorders.
In: el-Guebaly, N., Carrà, G., Galanter, M., Baldacchino, A.M. (eds) Textbook of Addiction Treatment. Springer, Cham. https://doi.org/10.1007/978-3-030-36391-8_93

What counts as “Stress?”



Janos “Hans” Selye, PhD (1907-1982)

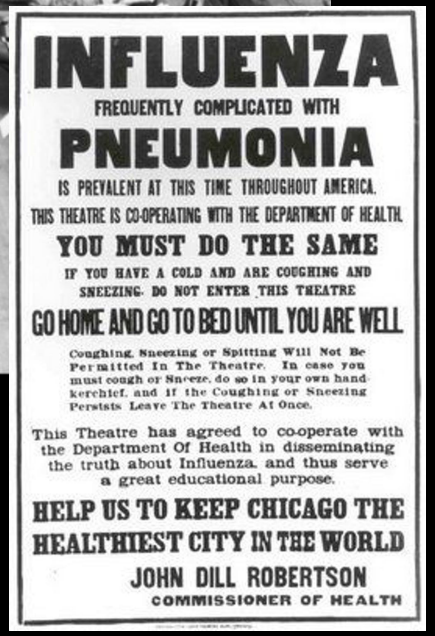
- Any unpredictable or uncontrollable event that exceeds the regulatory capacity of the organism, and that threatens or could threaten and organism’s physical or psychosocial integrity
- Eustress: healthy, “good” stress; perceived as a positive challenge, feelings of control/mastery, associated with meaning, hope and well-being; positive effect on healing and immunity
- Dystress: “bad” stress; sustained arousal that goes unresolved; failing performance; increasing anxiety; cumulatively taxing; hysteresis

What counts as “Trauma?”

Dr. Bessel VanDerKolk

- Anything less than nurturing
- “Trauma is an experience that overwhelms you, that leaves you bereft, paralyzed, and with no way out.”
- Being traumatized means continuing to organize your life as if the trauma were still going on – unchanged and immutable – as every new encounter or event is contaminated by the past.”
- ”People take drugs because they cannot stand the way they feel.”

1918 “Spanish” Influenza Pandemic



INFLUENZA

FREQUENTLY COMPLICATED WITH

PNEUMONIA

IS PREVALENT AT THIS TIME THROUGHOUT AMERICA.

THIS THEATRE IS CO-OPERATING WITH THE DEPARTMENT OF HEALTH.

YOU MUST DO THE SAME

IF YOU HAVE A COLD AND ARE COUGHING AND SNEEZING. DO NOT ENTER THIS THEATRE

GO HOME AND GO TO BED UNTIL YOU ARE WELL.

Coughing, Sneezing or Spitting Will Not Be Permitted In The Theatre. In case you must cough or Sneeze, do so in your own handkerchief, and if the Coughing or Sneezing Persists Leave The Theatre At Once.

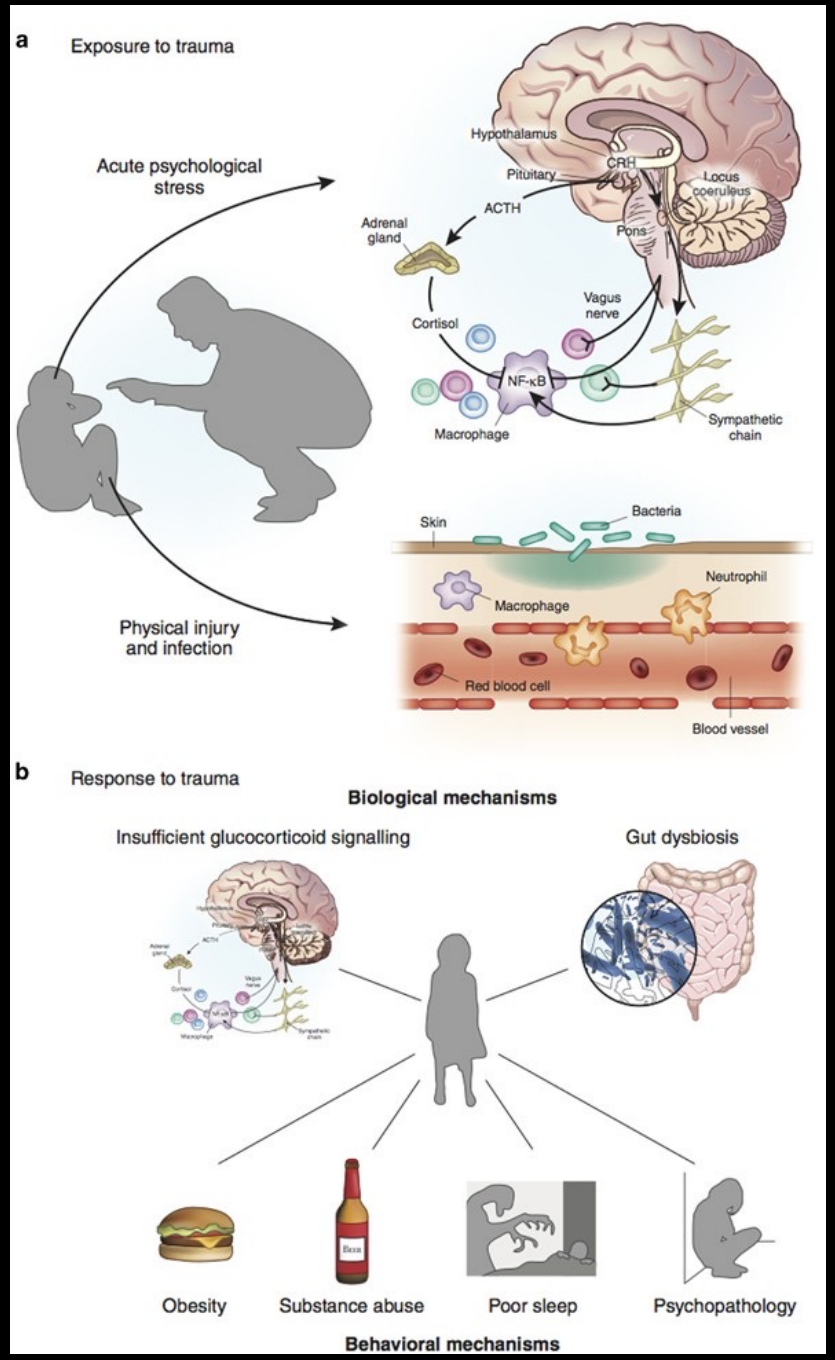
This Theatre has agreed to co-operate with the Department Of Health in disseminating the truth about Influenza, and thus serve a great educational purpose.

HELP US TO KEEP CHICAGO THE HEALTHIEST CITY IN THE WORLD

JOHN DILL ROBERTSON

COMMISSIONER OF HEALTH

- Lasted 3 years
- Infected 500 million people (a third of the world’s population)
- Killed 50 million people (maybe 100 million)
- Happened during WWI, censorship of newspapers except Spain = “Spanish” flu
- Struck otherwise healthy young adults
- Theory 1: world was at war, malnourishment, overcrowding, poor hygiene combined to ↓ resilience
- Theory 2: “cytokine storm” more likely in patients with strong immune response



Psycho-neuro-immunology

- A way to understand how stress and trauma cause mental illness through the immune system
- The Immune-Brain Loop: immune system is in constant communication with the brain; the immune system is a stress receptor for the brain
- CNS neurons terminate in thymus and spleen near clusters of lymphocytes and macrophages
- Adler & Cohen (1975): conditioned rats to drink saccharin water & Cytoxan (an immunosuppressant drug that tastes bad); later when they drank saccharin water the rats died of infection (immunosuppression in the absence of Cytoxan)
- Visintainer (1983): inescapable tail shock associated with decreased lymphocyte proliferation and decreased tumor rejection

Danese, A., & J Lewis, S. (2017). Psychoneuroimmunology of Early-Life Stress: The Hidden Wounds of Childhood Trauma?. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 42(1), 99–114. https://doi.org/10.1038/npp.2016.198

ASAM Addiction Definition (2011)

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry characterized by

1. inability to consistently abstain
2. impairment in behavioral control
3. craving
4. diminished recognition of significant problems with one's behaviors and interpersonal relationships,

and a

5. dysfunctional emotional response

ASAM Board of Directors. Definition of Addiction (Long Version). Chevy Chase, MD: American Society of Addiction Medicine; April 12, 2011.

ASAM Addiction Definition Updated (2019)

- Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences.
- People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences.
- Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.

American Society of Addiction Medicine Definition of Addiction. (2019, September 15). https://www.asam.org/Quality-Science/definition-of-addiction.

U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. Washington, DC: HHS, November 2016.

Addiction is a disorder in the brain's hedonic system (pleasure sense)

Shutterstock.com

… undermining the individual's decision-making capacity (choice) and self-awareness (insight).

shutterstock.com

1. Addiction is a disorder of **PLEASURE -** a broken “pleasure sense”
DOPAMINE – reward, expectation, trauma, the “Surprise!” chemical

2. Addiction is a disorder of **“CHOICE”**

3. Addiction is caused by . . .

DECISION-MAKING

JUDGEMENT

LIKELIHOOD/PROBABILITY

AGENCY

SELF-AWARENESS

SOCIAL COGNITION

EMOTIONAL REGULATION

1. Addiction is a disorder of **PLEASURE -** a broken “pleasure sense”
DOPAMINE – reward, expectation, trauma, the “Surprise!” chemical

2. Addiction is a disorder of **“CHOICE” –** impaired executive function
(decision-making, self-awareness, social cognition, emotional regulation)

3. Addiction is caused by . . .

GENES – not the cause of addiction but a powerful mediator

GENETICS / EPIGENETICS

1. Addiction is a disorder of **PLEASURE -** a broken "pleasure sense"

DOPAMINE – reward, expectation, trauma, the "Surprise!" chemical

2. Addiction is a disorder of **CHOICE –** impaired executive function

(decision-making, self-awareness, social cognition, emotional regulation)

3. Addiction is caused by . . .

GENES – not the cause of addiction but a powerful mediator

GENETICS / EPIGENETICS

1. Addiction is a disorder of **PLEASURE -** a broken "pleasure sense"

DOPAMINE – reward, expectation, trauma, the "Surprise!" chemical

2. Addiction is a disorder of **CHOICE –** impaired executive function

(decision-making, self-awareness, social cognition, emotional regulation)

3. Addiction is caused by **"STRESS"**

severe
repetitive
cumulative
unanticipated
early in life
inherited

Depression & Anxiety disorders
trauma / PTSD
Adverse Childhood Experiences
ADHD
Intergenerational Trauma
Intoxication disorders (SUD, Processes)

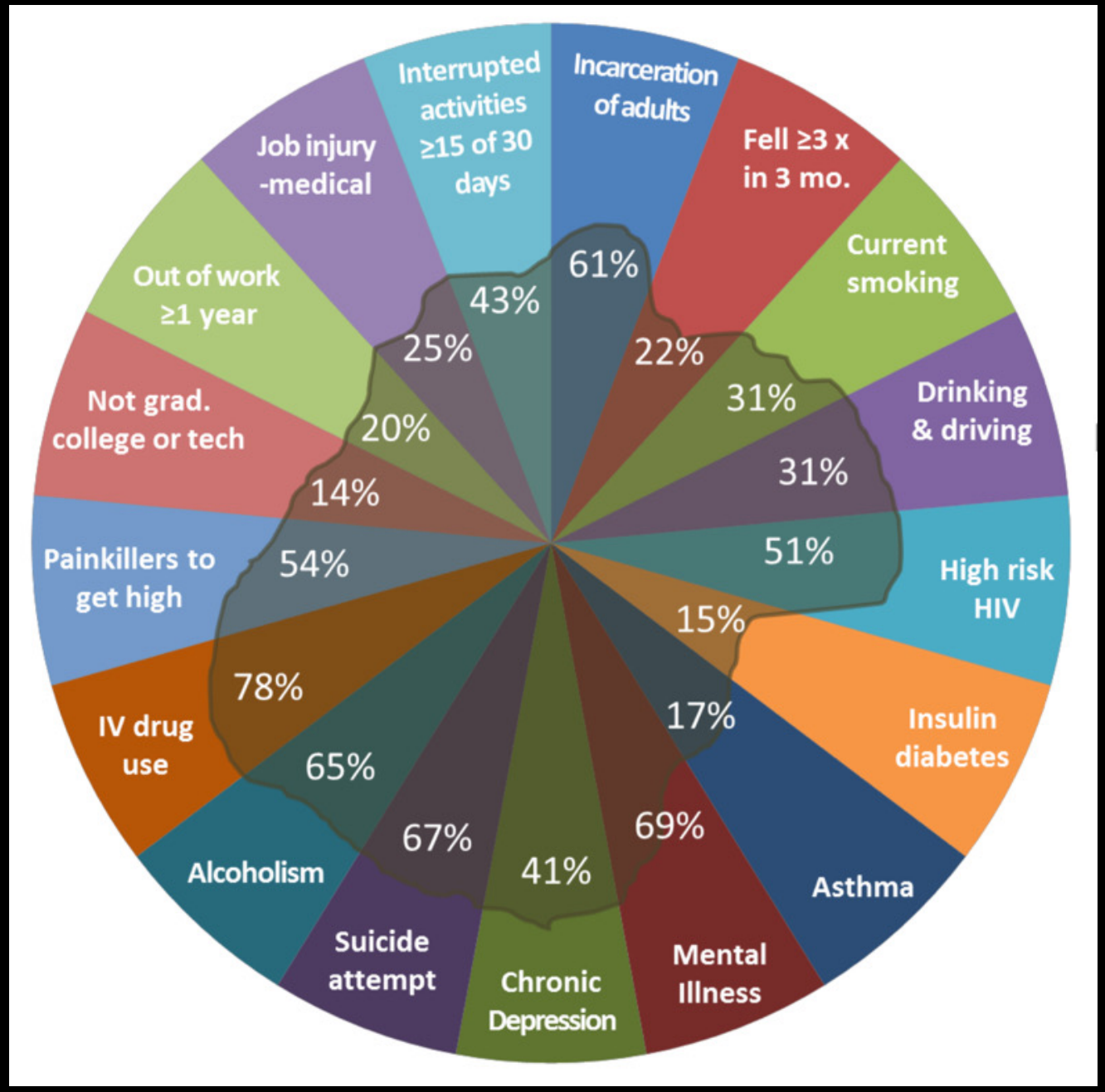
Adverse Childhood Experiences (ACEs) Study

- Dr Vincent Felitti and Dr Robert Anda
- Kaiser Permanente San Diego Obesity Clinic
- Felitti and Anda noticed a high number of patients were sexually abused in childhood
- ACEs Study: Kaiser employees (n = 17,337), 1995-1997 with long-term follow up
- Findings: early adversity can cause health and social problems across the lifespan
- ACEs alter neurodevelopment through the neuroendocrine system


Vincent Felitti, MD


Robert Anda, MD

Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C., Perry, B. D., . . . Giles, W. H. (2005). The enduring effects of abuse and related adverse experiences in childhood. *European Archives of Psychiatry and Clinical Neuroscience, 256*(3), 174-186. doi:10.1007/s00406-005-0624-4



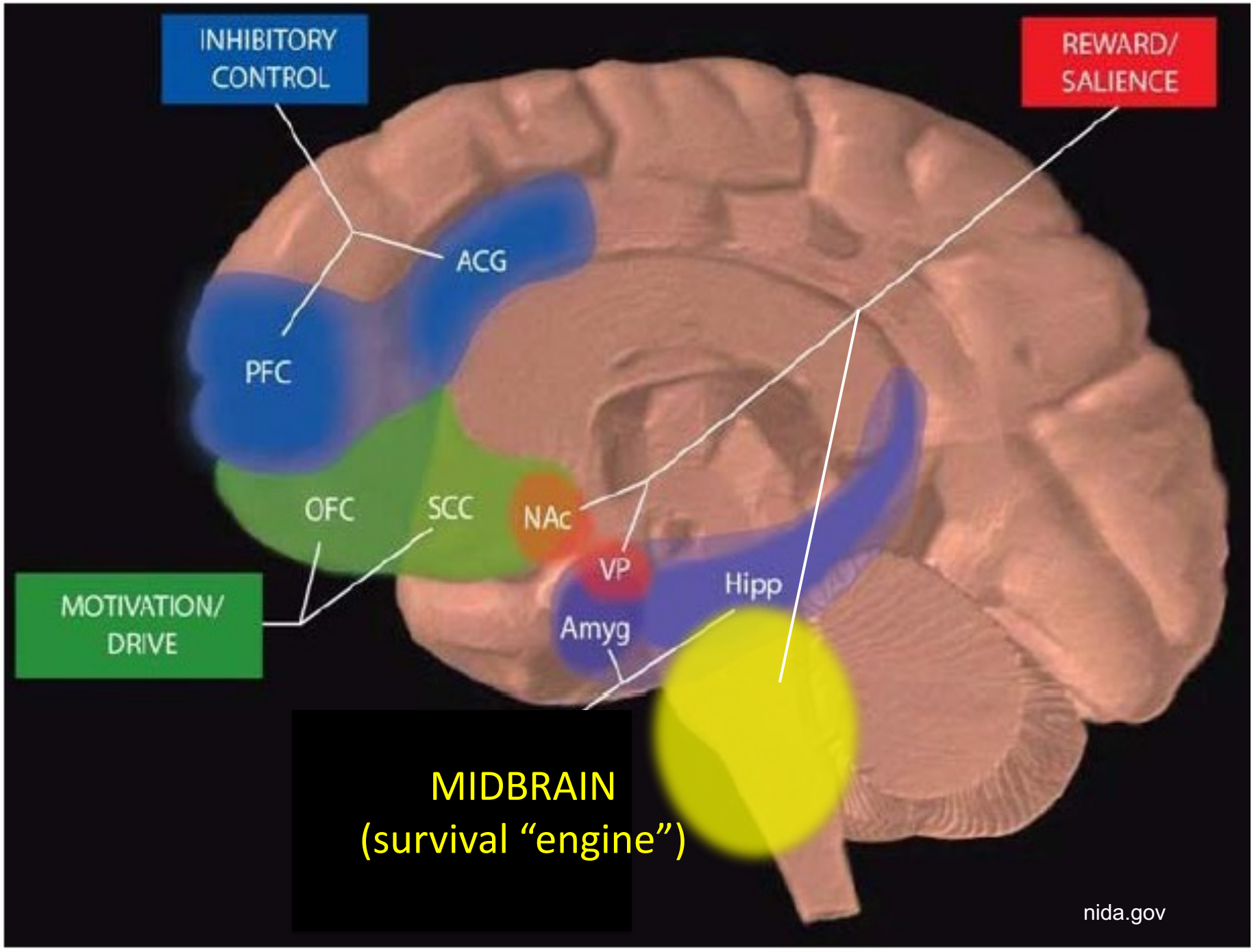
ACEs put people at risk for a wide range of health problems

- Population Attributable Risk: the portion of a disease caused by a particular agent
- The portion of each of these conditions attributable to ACEs

Health Safety and Resilience: Foundations for Health Equity. Foundation for Healthy Generations http://healthygen.webfactional.com/sites/default/files/Online%20Version_2014-2015%20Statewide_4-21-15.pdf

What goes into a pleasurable experience?

shutterstock.com



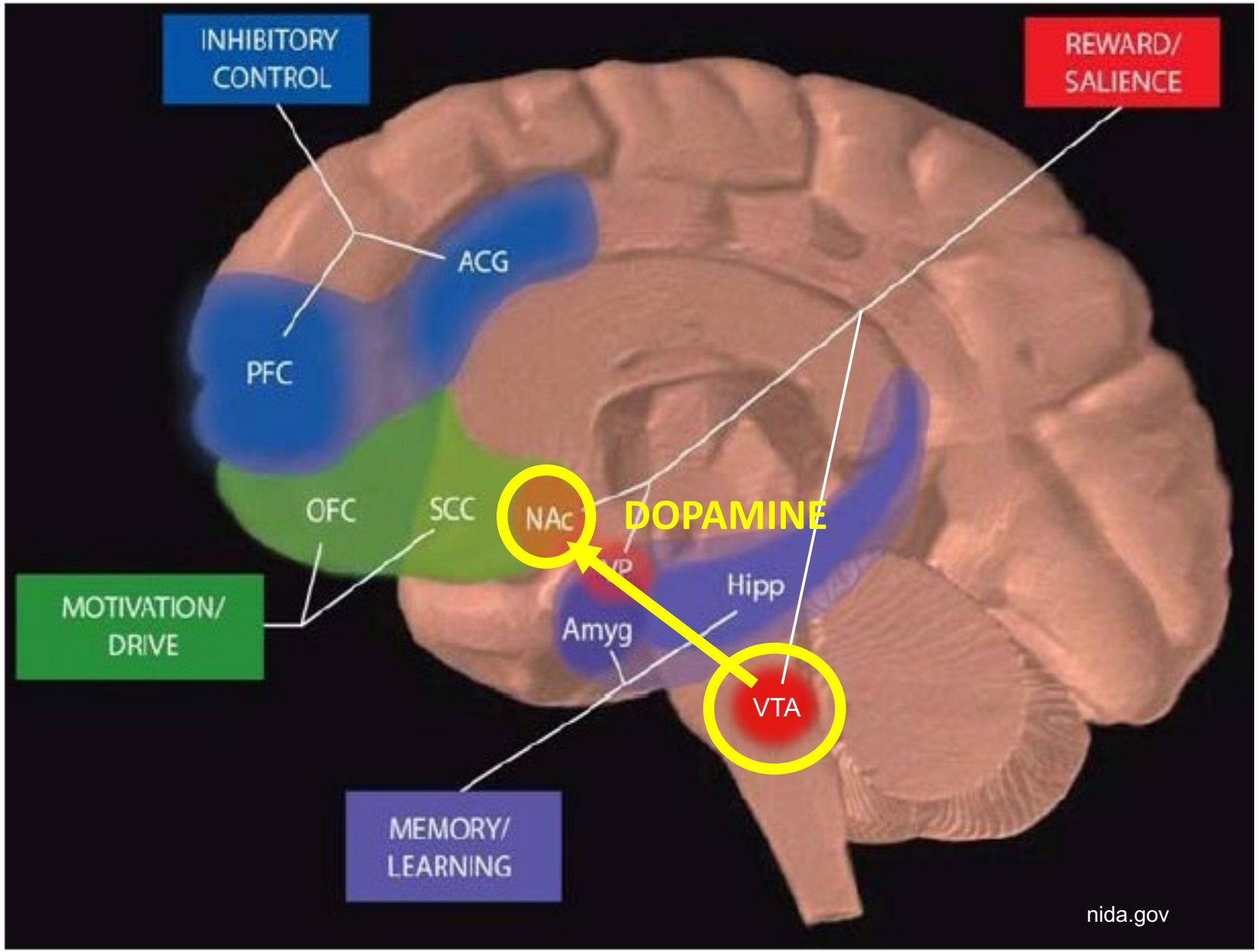
Reward/Salience Areas:

NAc: **Nucleus accumbens**
(ventral striatum)

VTA: **Ventral Tegmental Area**
(midbrain)

What goes into a pleasurable experience?

- Cake tastes good
- Cake ensures survival

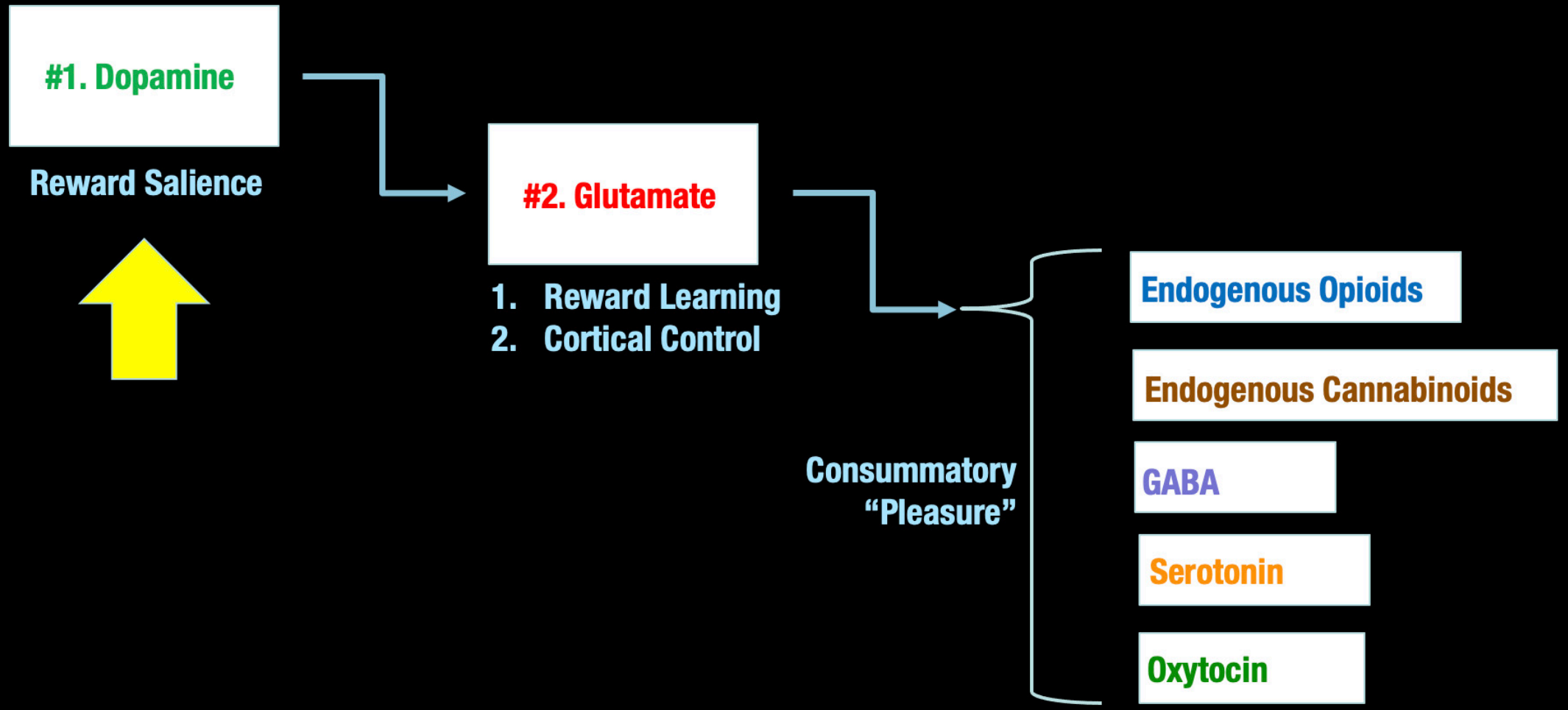


Reward/Salience Areas:

NAc: **Nucleus accumbens**
(ventral striatum)

VTA: **Ventral Tegmental Area**
(midbrain)

The "Brain Reward Cascade" (Blum)



Adapted from:
Blum K, Febo M, Badgaiyan RD. Fifty years in the development of a glutaminergic-dopaminergic optimization complex (KB220) to balance brain reward circuitry In reward deficiency syndrome: a pictorial. *Austin Addict Sci,* 2016;1(2).

What goes into a pleasurable experience?

- Memory of past cakes
- Memory of this cake
- Cake tastes good
- Cake ensures survival

The "Brain Reward Cascade" (Blum)

#1. Dopamine

Reward Salience

#2. Glutamate

1. Reward Learning
2. Cortical Control

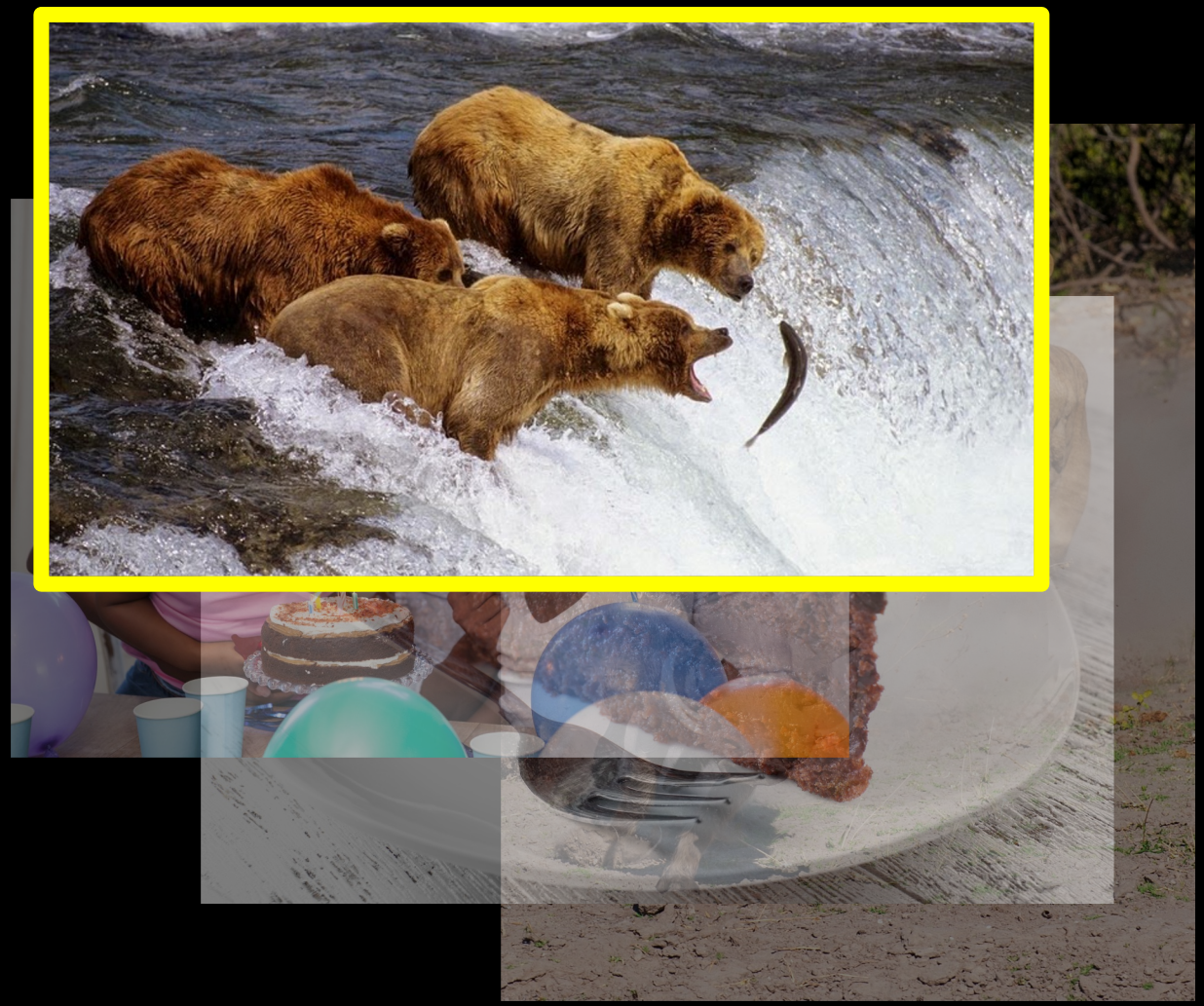
Consummatory "Pleasure"

- Endogenous Opioids
- Endogenous Cannabinoids
- GABA
- Serotonin
- Oxytocin

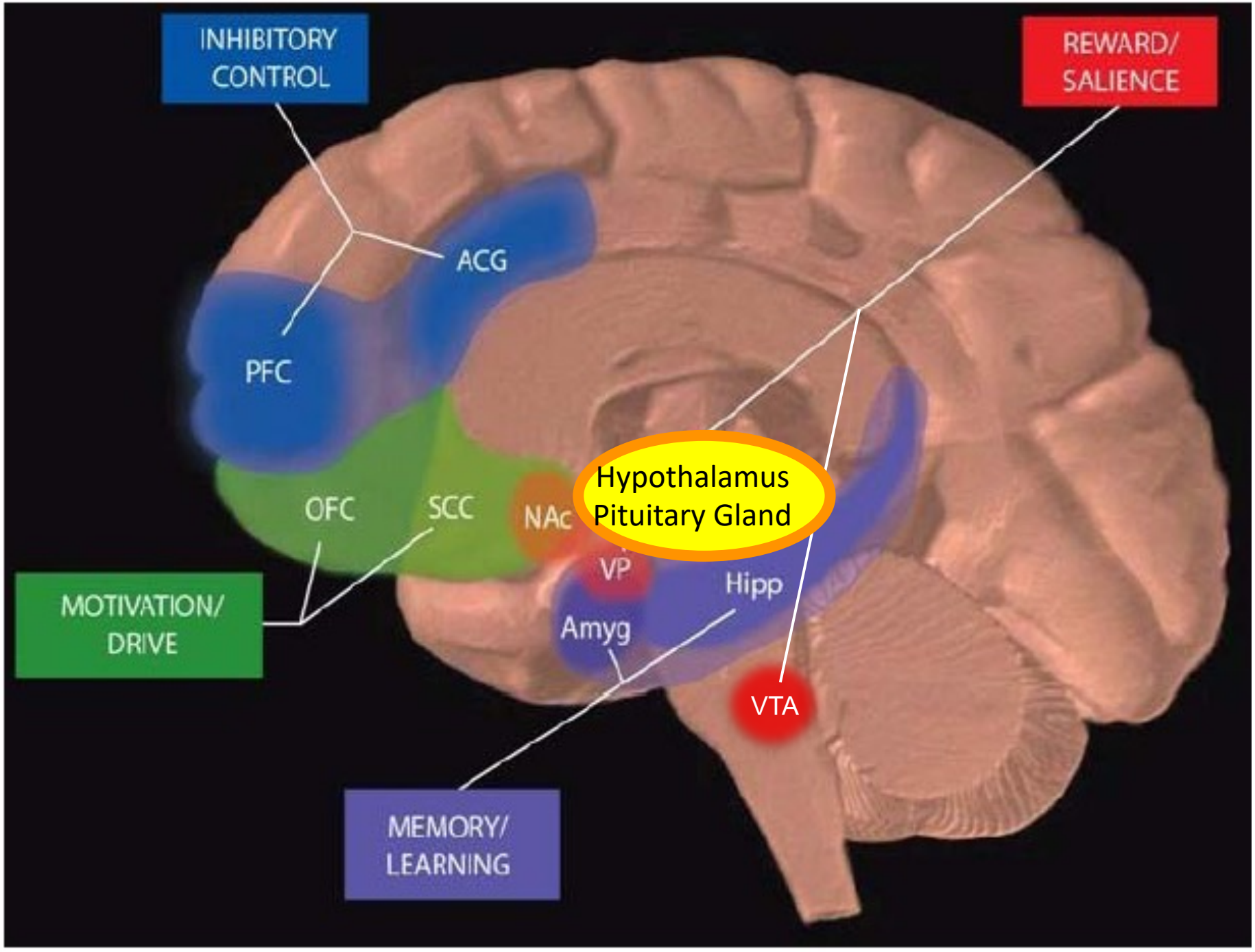
Adapted from:

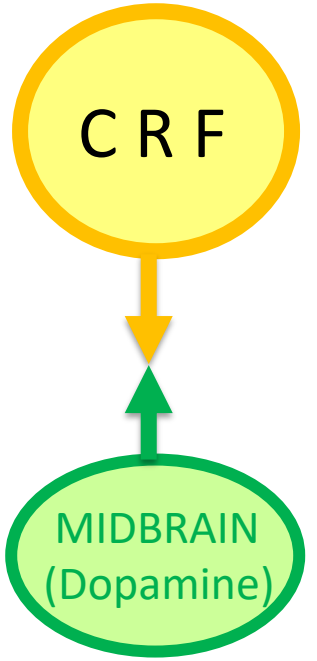
Blum K, Febo M, Badgaiyan RD. Fifty years in the development of a glutaminergic-dopaminergic optimization complex (KB220) to balance brain reward circuitry In reward deficiency syndrome: a pictorial. *Austin Addict Sci,* 2016;1(2).

What goes into a pleasurable experience?



- Cake stops hunger
- Memory of past cakes
- Memory of this cake
- Cake tastes good
- Cake ensures survival

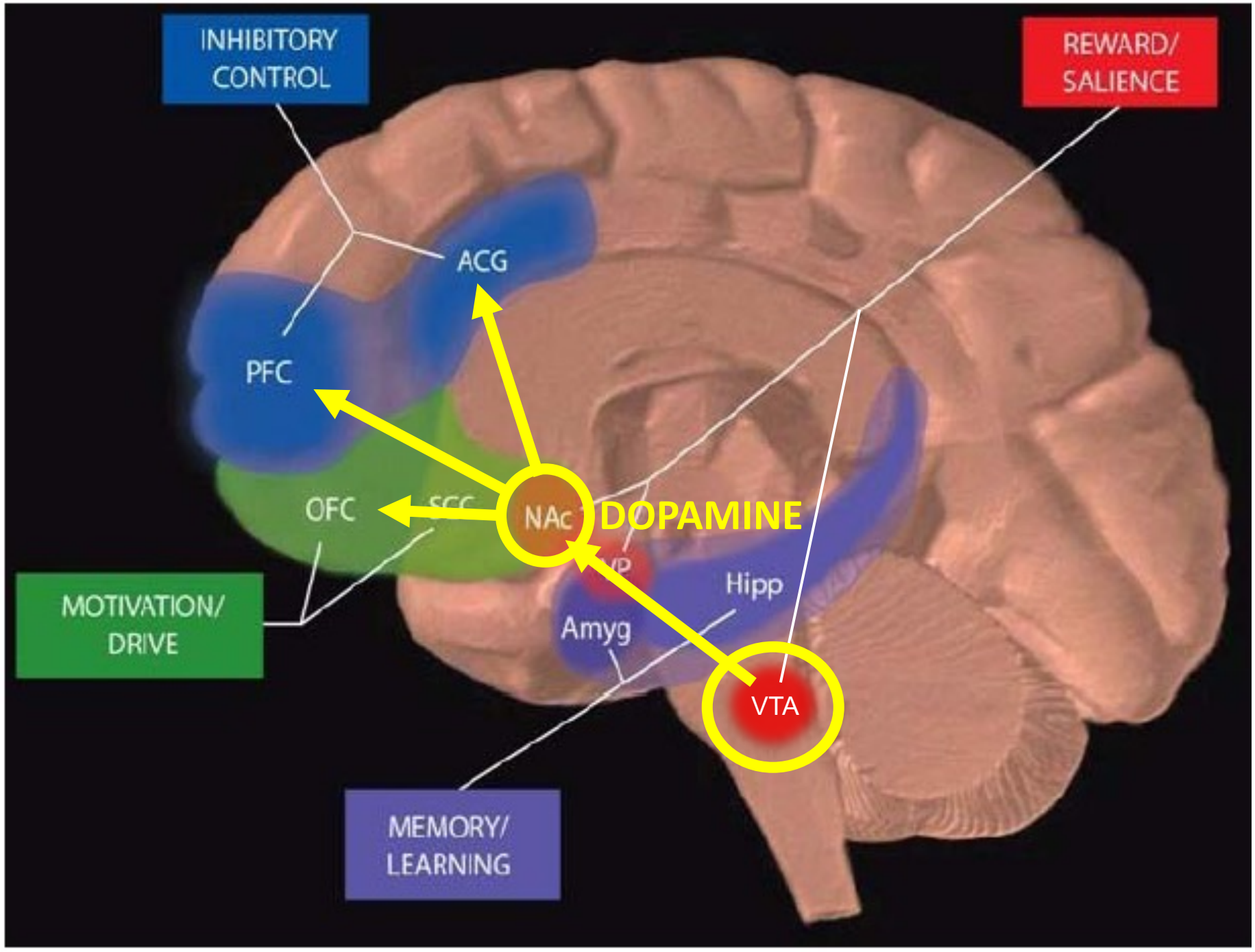




Stress Areas:
Hypothalamus
Pituitary
Adrenal
Axis

What goes into a pleasurable experience?

- Decision to have more cake
- Cake's impact on self
- Meaning of cake (Grandma's?)
- Emotions about cake
- Cake stops hunger
- Memory of past cakes
- Memory of this cake
- Cake tastes good
- Cake ensures survival



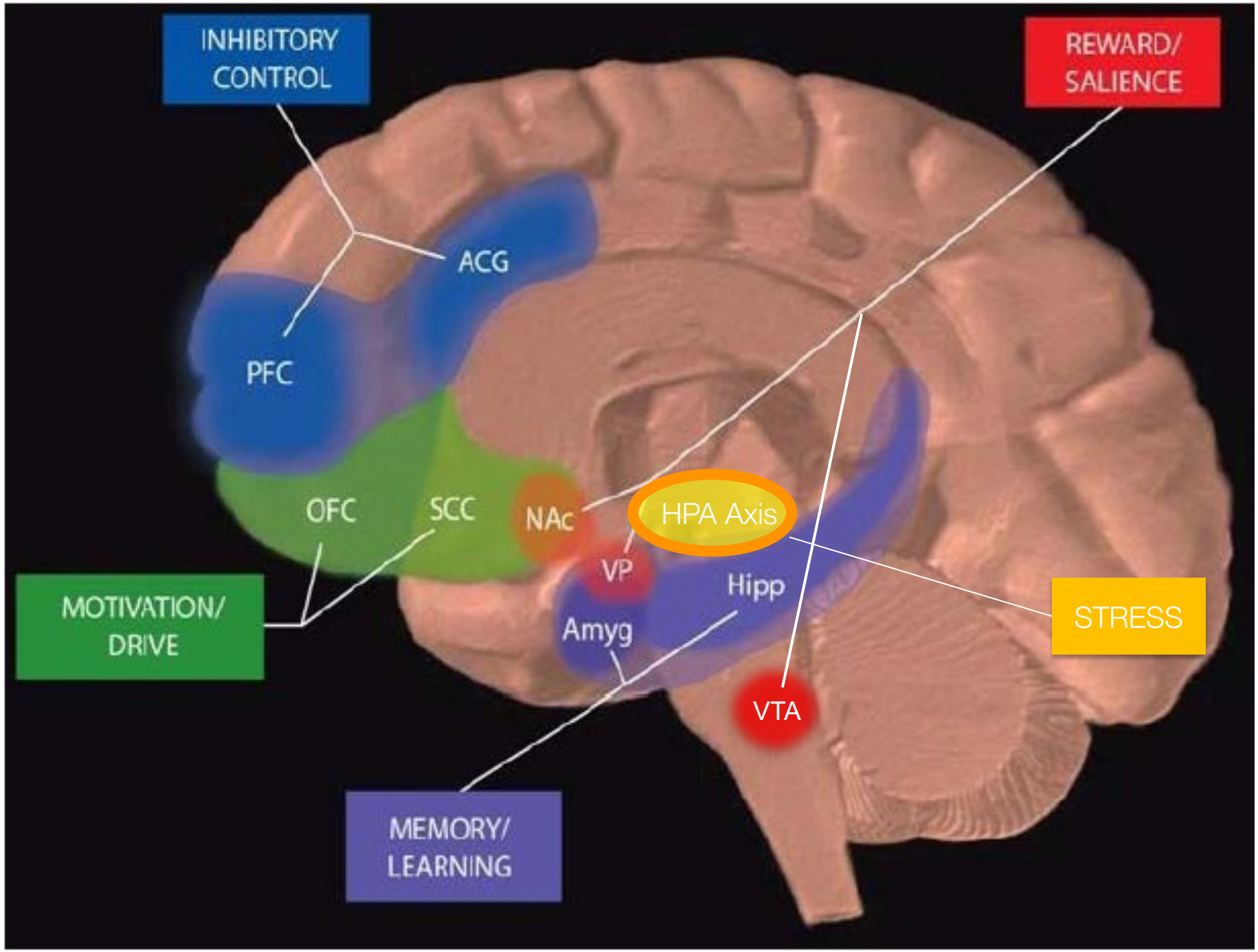
Frontal Cortex:

PFC: Prefrontal Cortex
- executive functioning
- behavioral inhibition

ACG: Anterior Cingulate Cortex
- social cognition
- error detection

OFC: Orbitofrontal Cortex
- valuation under shifting conditions of uncertainty

Insular Cortex – interoception



Frontal Cortex:

PFC: Prefrontal Cortex
- executive functioning
- behavioral inhibition

ACG: Anterior Cingulate Cortex
- social cognition
- error detection

OFC: Orbitofrontal Cortex
- valuation under shifting conditions of uncertainty

Stress Areas:

Hypothalamus (HPA Axis)
Pituitary Gland
Adrenal Glands

Memory/Learning Areas:

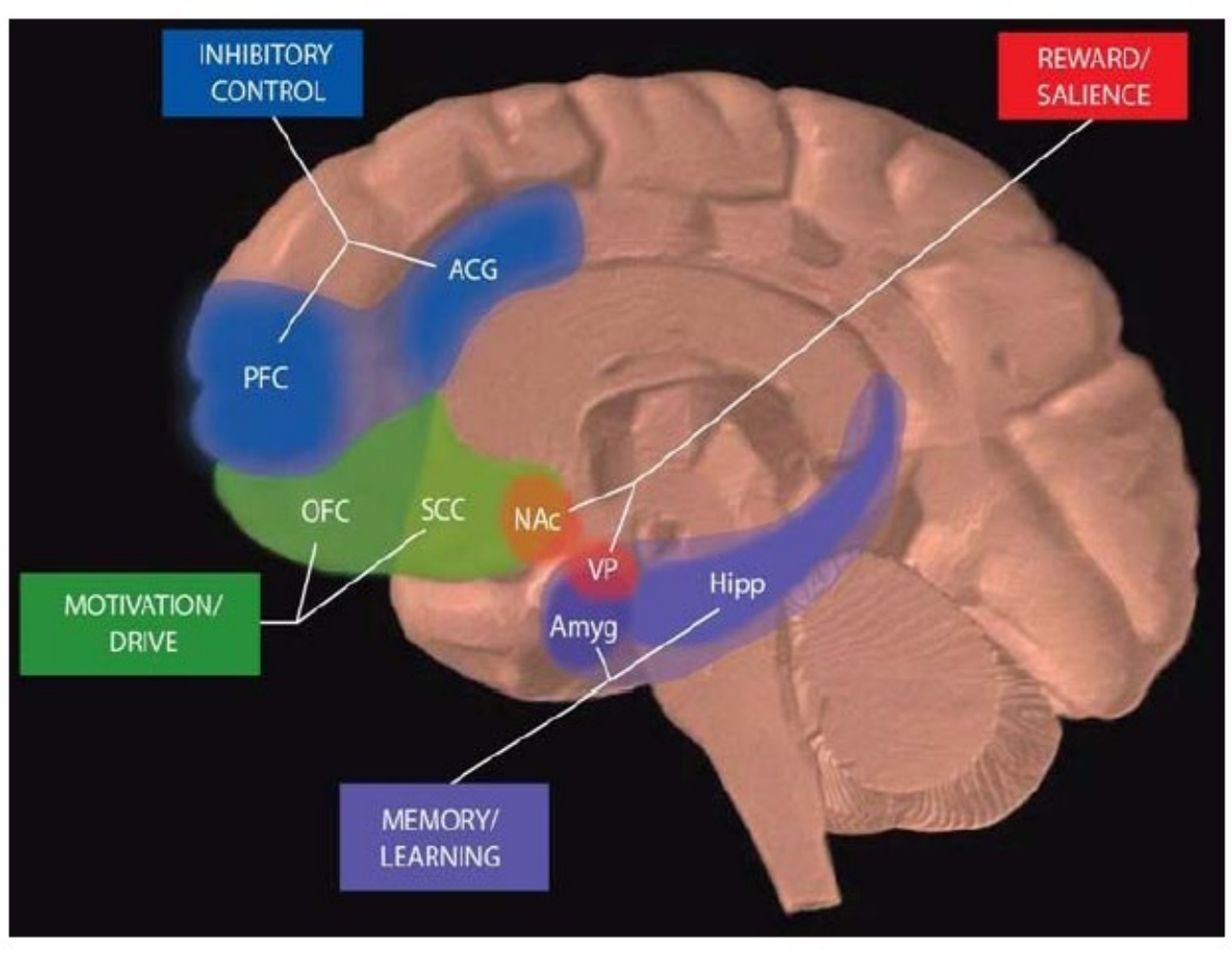
Hipp: Hippocampus
- memory formation

Amyg: Amygdala
- fear conditioning

Reward/Salience Areas:

NAc: Nucleus accumbens (ventral striatum)
VP: Ventral Pallidum
VTA: Ventral Tegmental Area (midbrain)

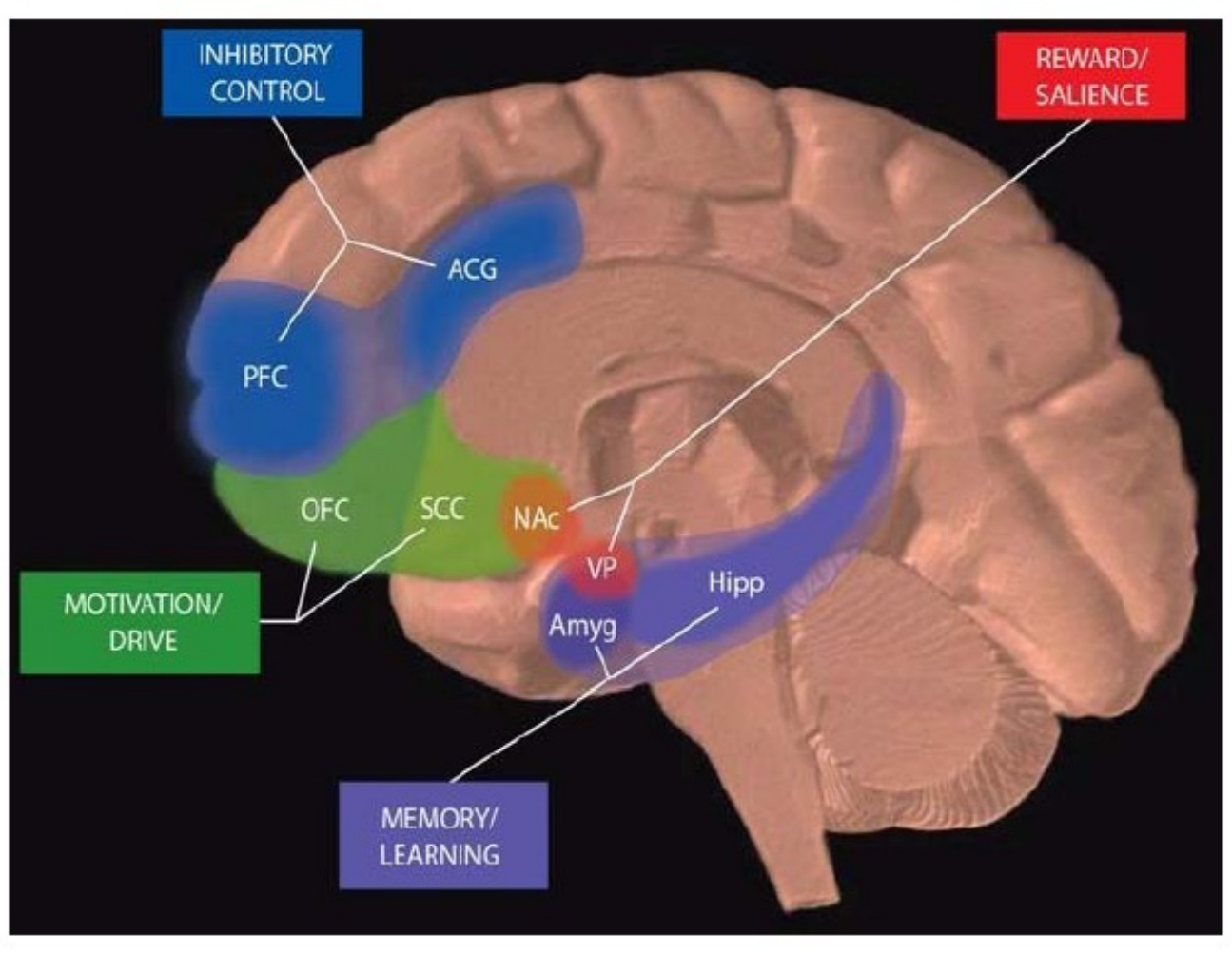
Addiction is a disorder of …



5. CHOICE	OFC, ACC, PFC, IC
	hypofrontality
4. STRESS	HPA axis
	allostatic load
3. MEMORY	dopamine + glutamate
	synaptic remodeling
2. REWARD	dopamine
	dopamine receptors
1. GENES	genome polymorphisms
	epigenetic changes

How does Addiction (SUD)
run in families?
What is the ***genetic component***
of Addiction (SUD)?

Addiction is a disorder of …



5. CHOICE	OFC, ACC, PFC, IC
4. STRESS	HPA axis
3. MEMORY	glutamate
	synaptic remodeling
2. REWARD	dopamine
	dopamine receptors
1. GENES	**polymorphisms**
	epigenetic changes

Heritability of Addiction

(from twin studies)

Alcohol: 48 – 66%

Cannabis: 51 – 59%

Cocaine: 42 – 79%

Opioids: 23 – 49%

Nicotine: 33 – 71%

shifts from adolescence (environment)
to young adulthood (genetics)

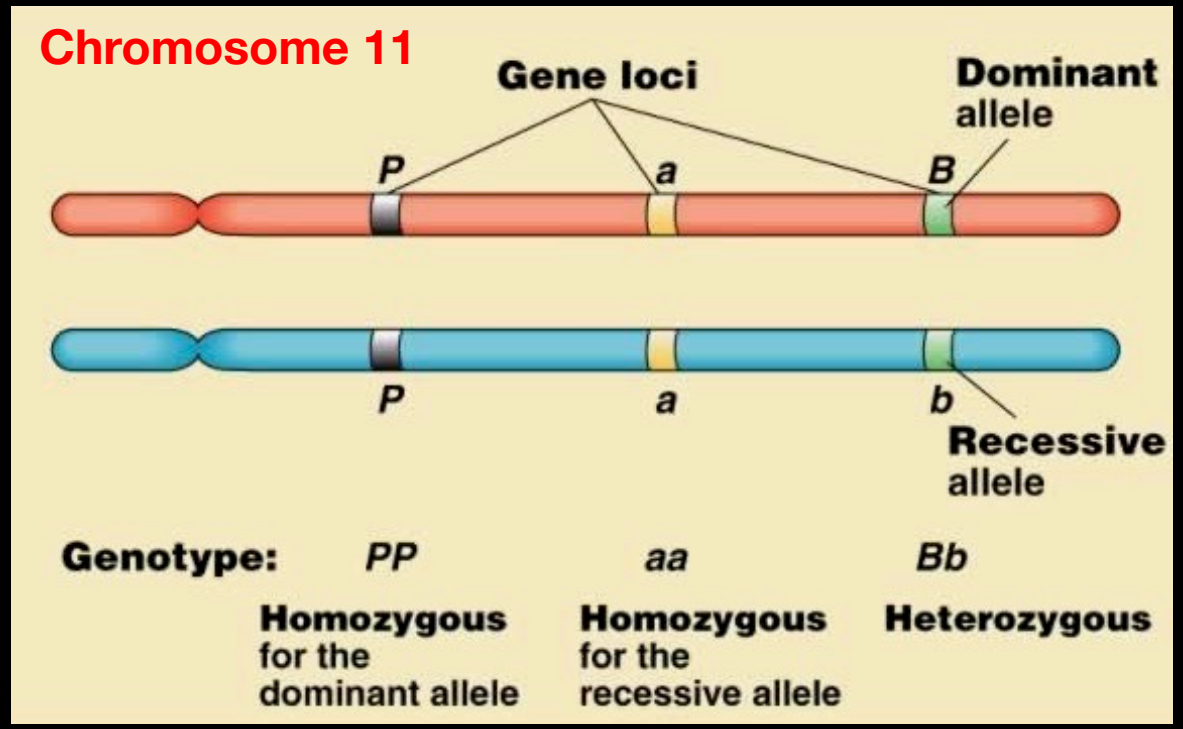
Gambling: 49%

- Heritability: an aggregate measure of the variability of a characteristic due to genetics vs environment (the risk due to genes – "risk genes")
- First-order family members of a person with SUD have a 4 – 8 x increased risk of developing SUD
- Applies to <u>populations</u>, not individuals (that would be *inheritance*)
- Probabalistic, not deterministic

Agrawal A, Verweij KJH, Gillespie NA, et al. The genetics of addiction – a translational perspective. *Translational Psychiatry* (2012), 2, 3140.

Taq1 A1 allele of the DRD2 gene

(Blum & Noble, 1990)

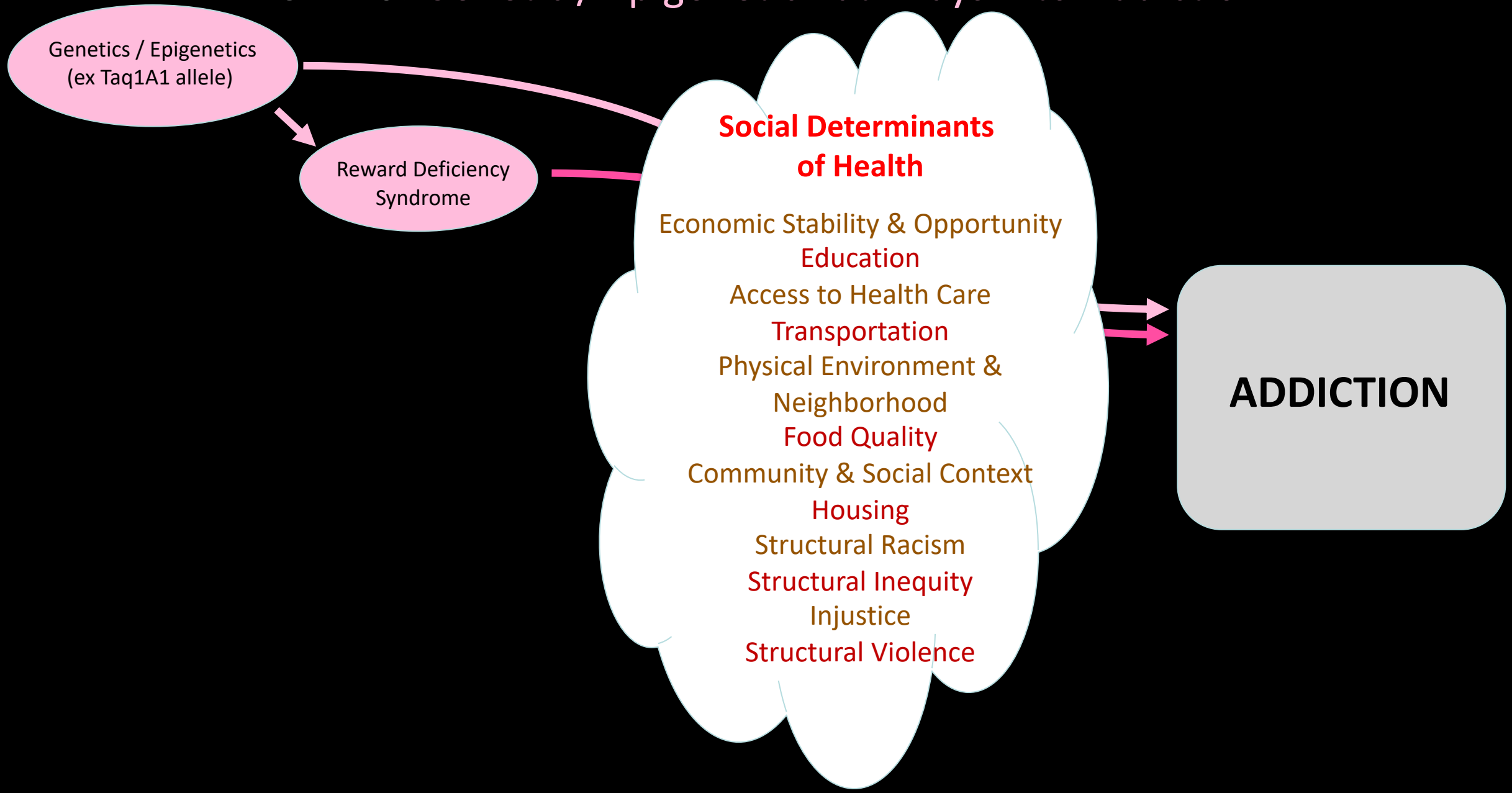


A single nucleotide polymorphism the carriers of which have 30-40% fewer DAD2 receptors and are at high risk for:

- Alcoholism and Addiction
- Repeated addiction treatment failures
- Increased mortality from alcoholism
- Lower striatal DAD2 receptor availability and lower striatal DA binding potential

Blum K, Noble EP, Sheridan PJ, *et al.* Allelic association of human dopamine D2 receptor gene in alcoholism. *JAMA.* 1990; 263(15):2055-60.

GENES: Genetic / Epigenetic Pathways into Addiction



Social Determinants of Health:

conditions in the environment in which people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning and quality of life outcomes and risks

Healthy People 2020 Approach to SDHs

Health Disparities:

systemic, avoidable health differences adversely affecting socially disadvantaged groups; different from health differences

Health Equity:

a commitment to reduce/eliminate health disparities; social justice with respect to health; equal opportunity to be healthy

https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health

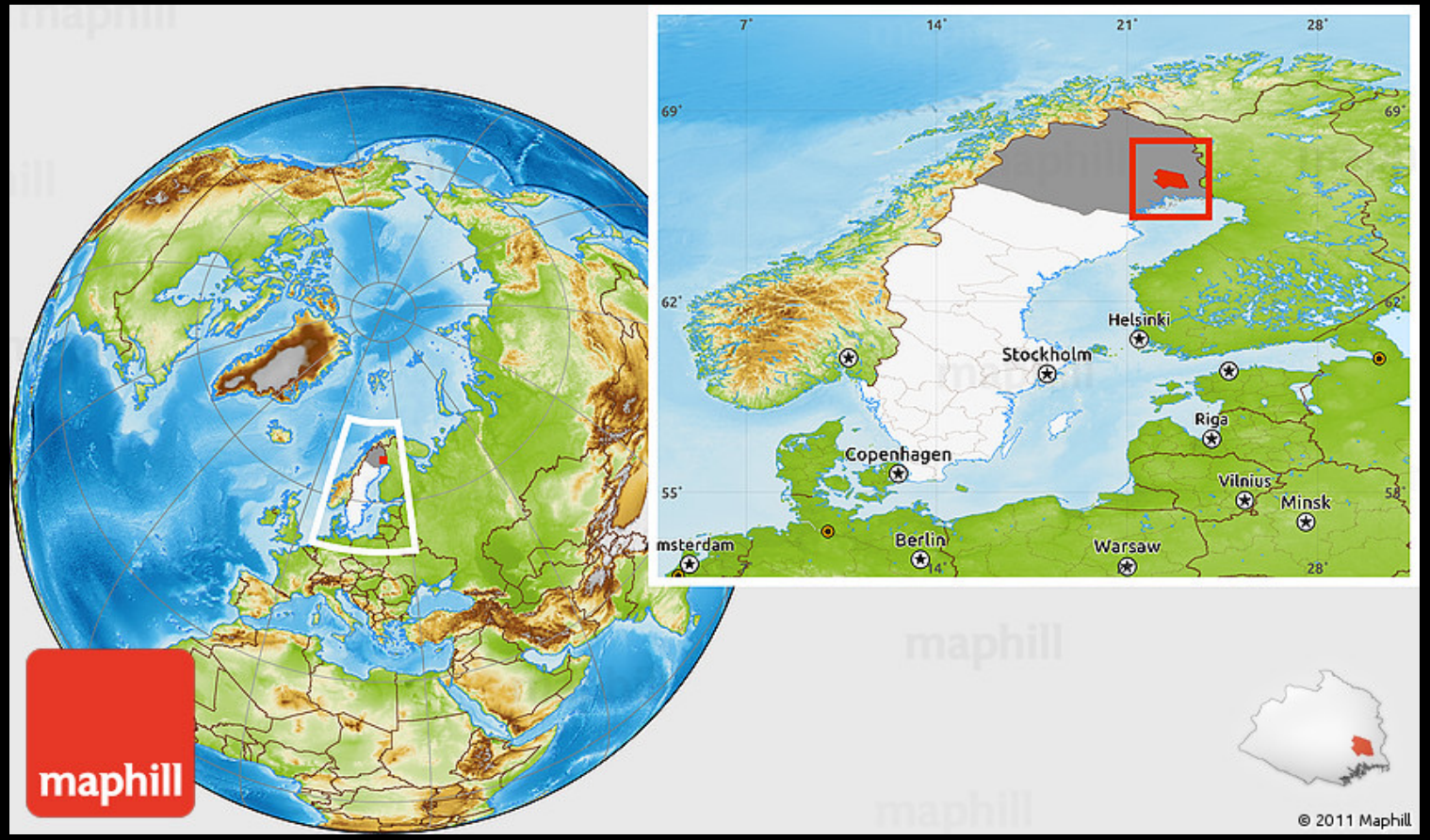
Social Determinants of Health

Social Determinant of Health	Health Disparity	Health Inequity
1. Safety	early life adversity (ACEs)	chronic disease, shorter lifespan
2. Healthy Food	low availability, food deserts	higher diabetes, obesity
3. Income Security	poverty, lack of social safety net	chronic disease, shorter lifespan
4. Housing	housing insecurity / rent as % of income	higher asthma, lead exposure
5. Education, Job Training	lower HS graduation rates	unhealthy behaviors (smoking)
6. Social / Family Support	isolation, intimate partner violence (IPV)	greater depression & suicide
7. Community	stigma, racism, discrimination	inaccessible services > chron dis.
8. Employment	unemployment, lack of opportunity	chronic disease, suicide, SUD
9. Access to Health Care	ineligibility / work requirements	ex. less cancer screening
10. Justice	disprop. policing / mass incarceration	chronic disease, shorter lifespan

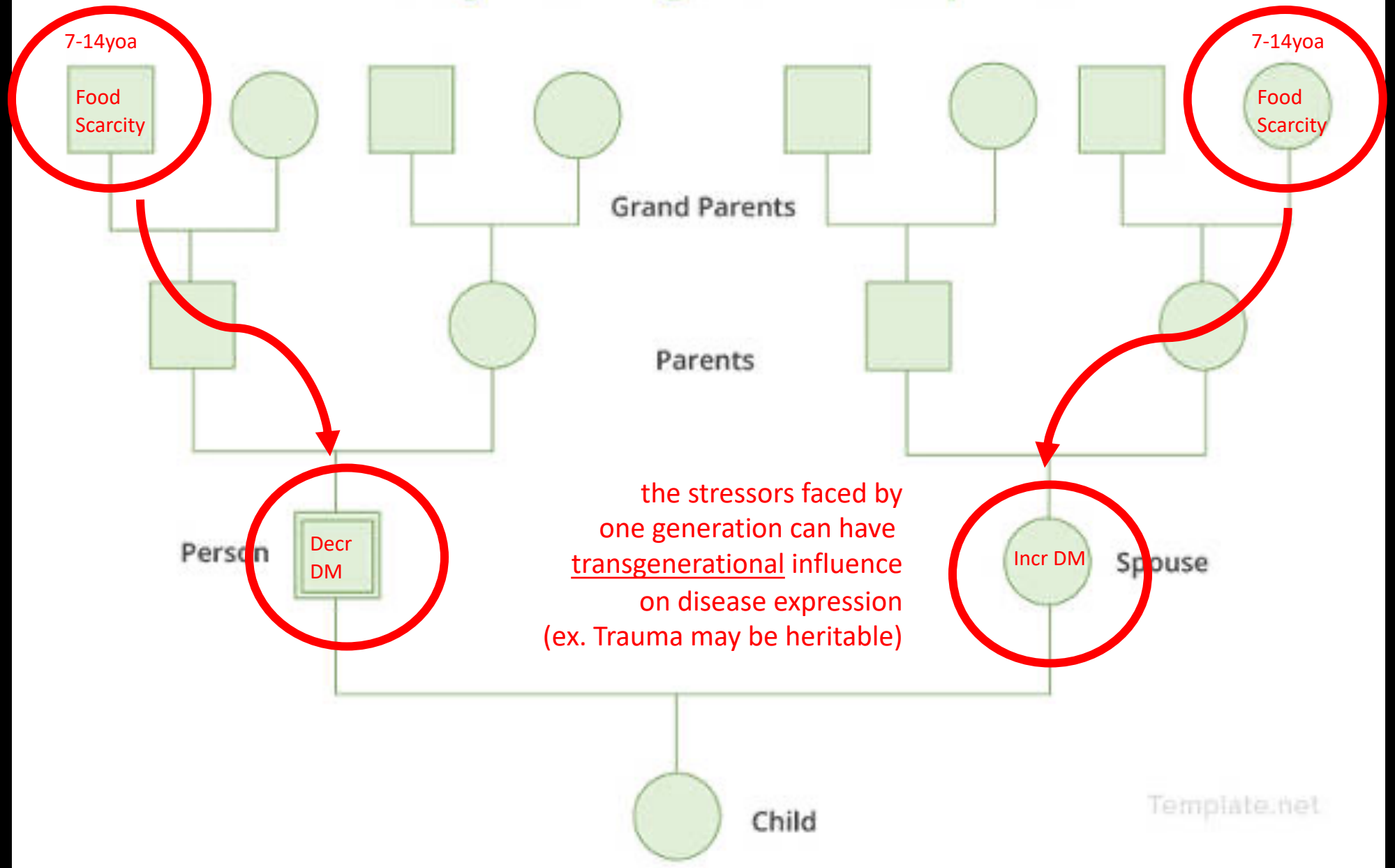
http://thenationshealth.aphapublications.org/content/infographics-social-determinants-health

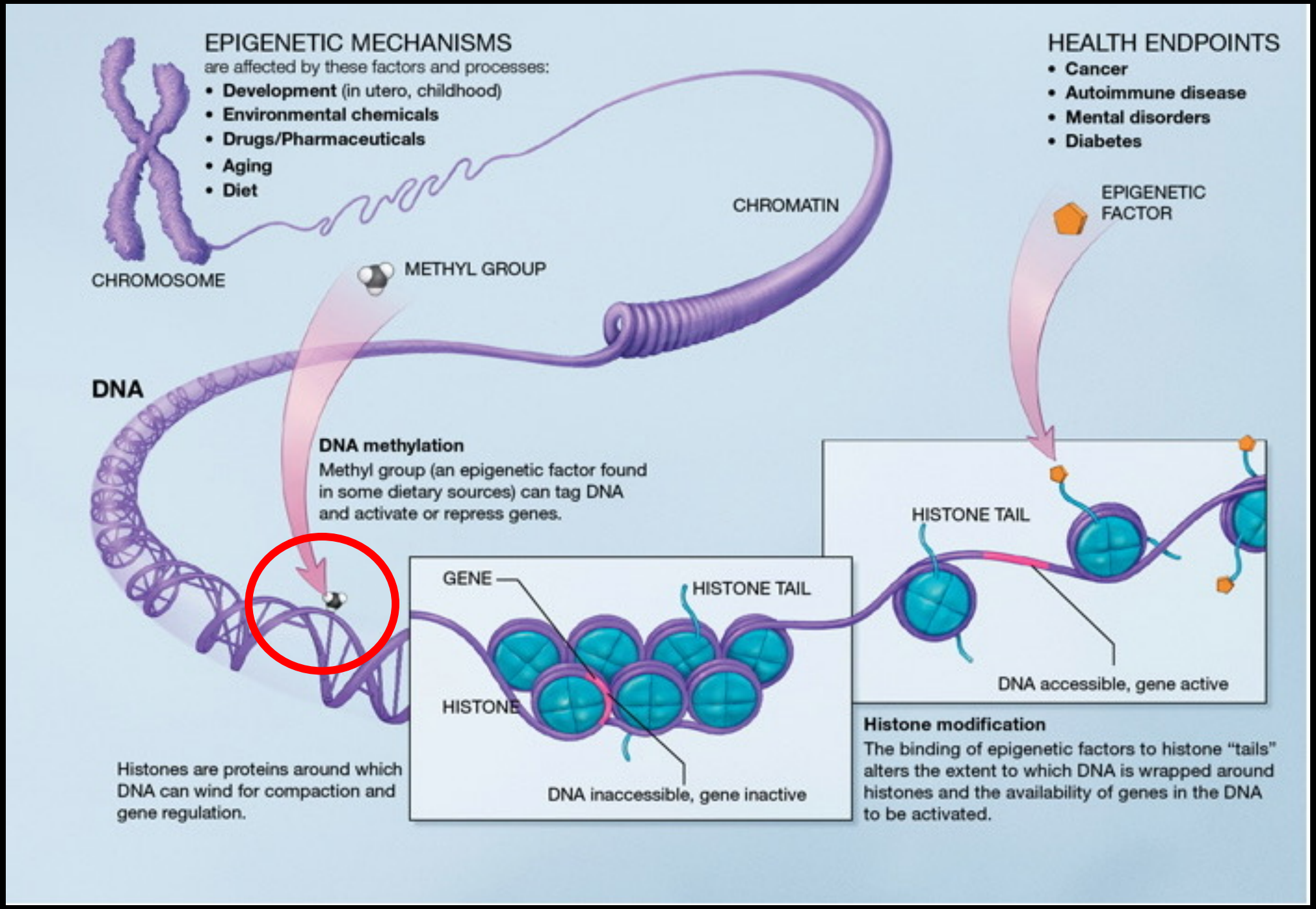
Epigenetics

- Overkalix study: Starvation during adolescence increased the prevalence of diabetes in *grandchildren*
- Holocaust survivors with PTSD: their children also had PTSD without having been exposed to trauma
- A mechanism exists to transmit environmental exposure information from one generation to the next to the next

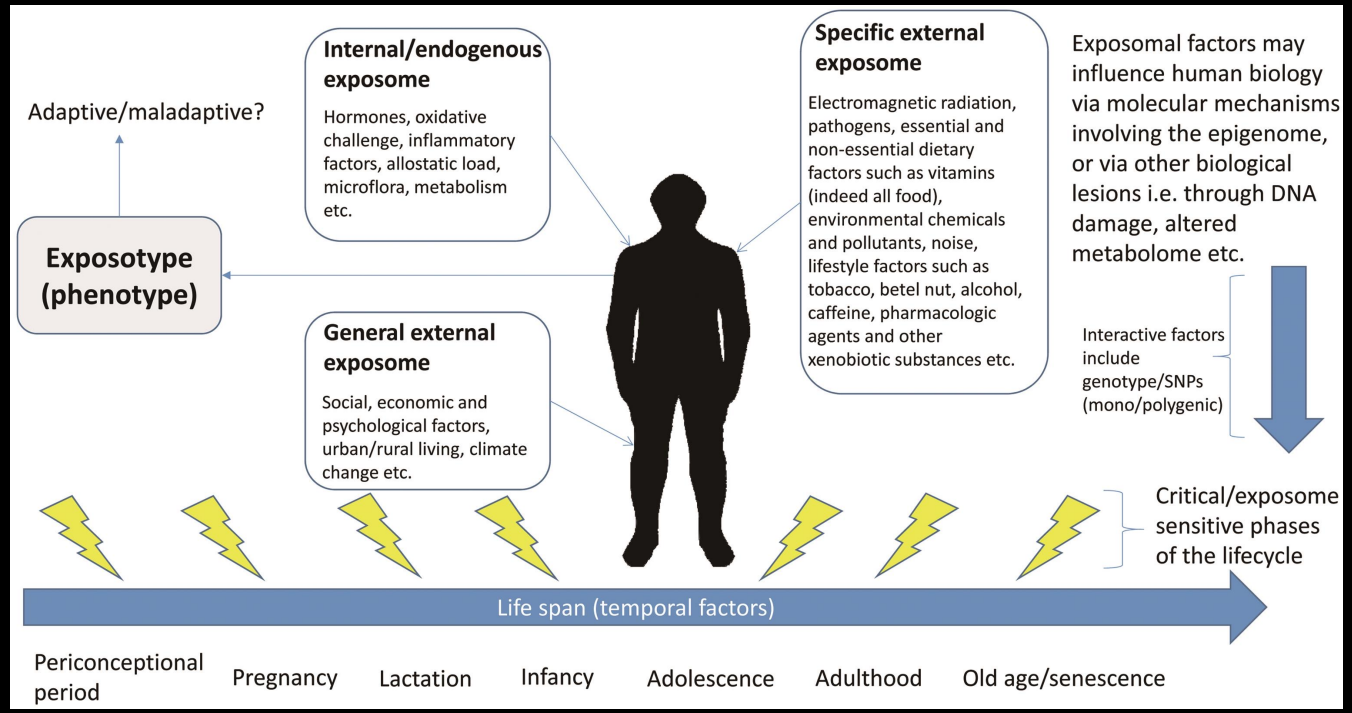


Family Genogram Template




EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Exposome & Exposomics



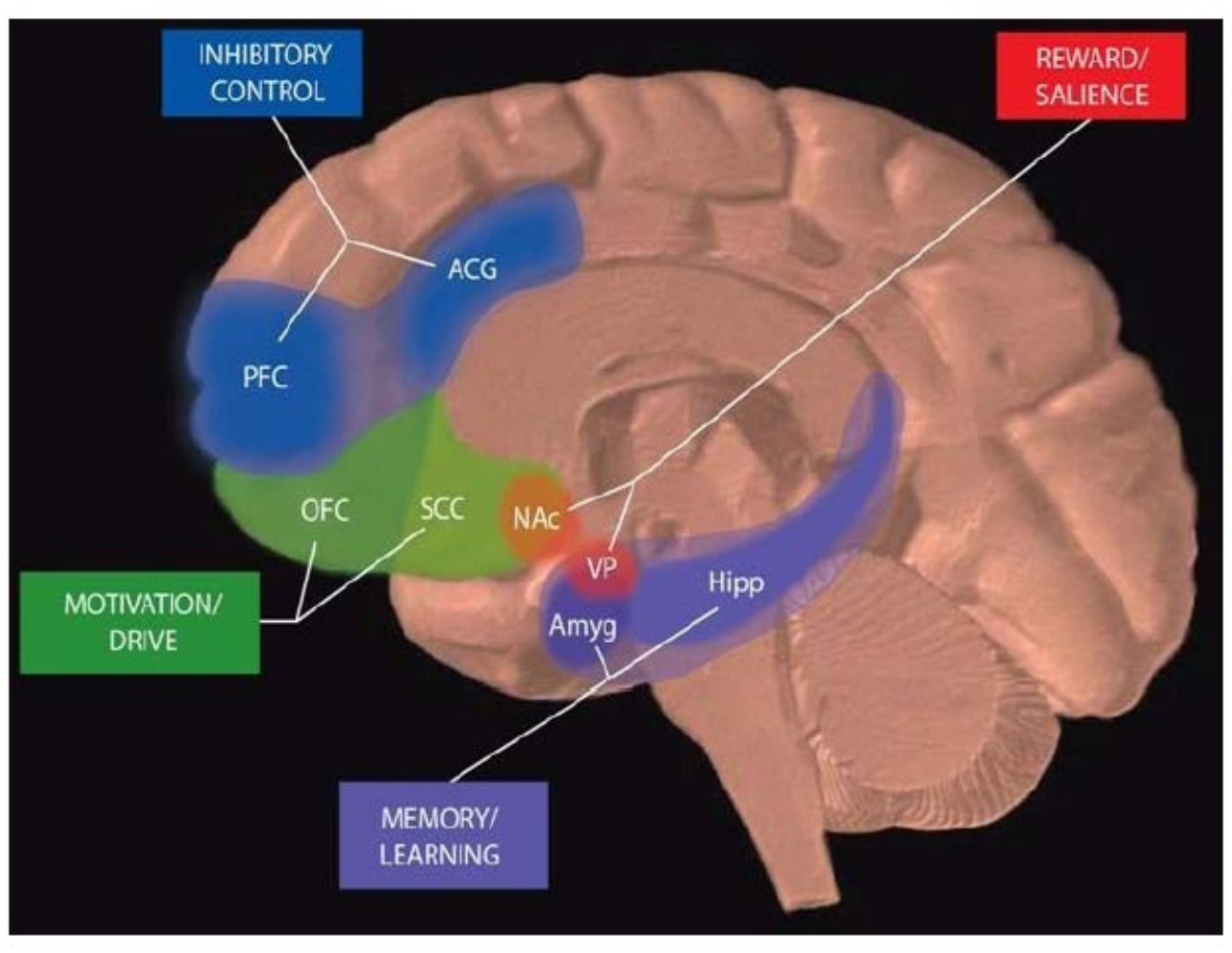
Fedan, J. (2022, August 19). Exposome and Exposomics. Workplace Safety and Health Topics. https://www.cdc.gov/niosh/topics/exposome/default.html

- Genetics has been found to account for only about 10% of diseases, and the remaining causes appear to be from **environmental causes**
- **Exposome** - all the exposures of an individual in a lifetime and how those exposures relate to health
- A key factor in describing the exposome is the ability to accurately measure **exposures** and effect of exposures
- The impact of exposures can also vary with the individual's **stage of life** (ex. exposure to lead in infants and early childhood can lead to cognitive deficiencies)

What goes into a pleasurable experience?

shutterstock.com

Addiction is a disorder of …

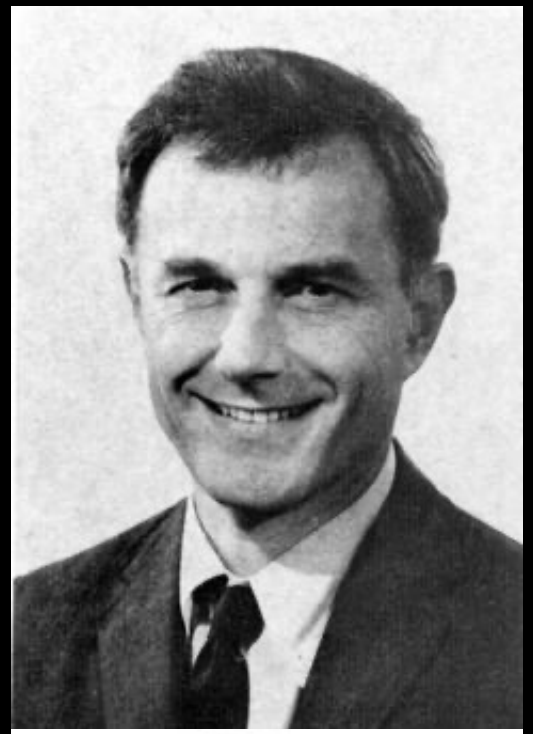


2. REWARD **dopamine**

reward salience

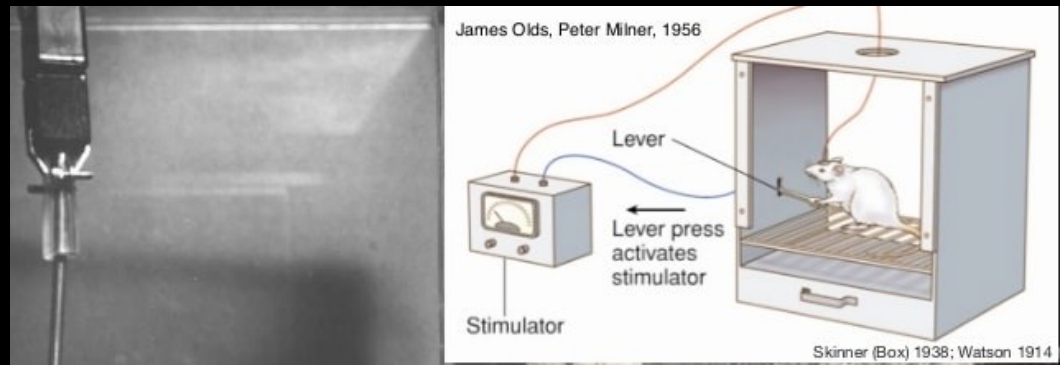
What goes into a pleasurable experience?

- Cake tastes good
- Cake ensures survival

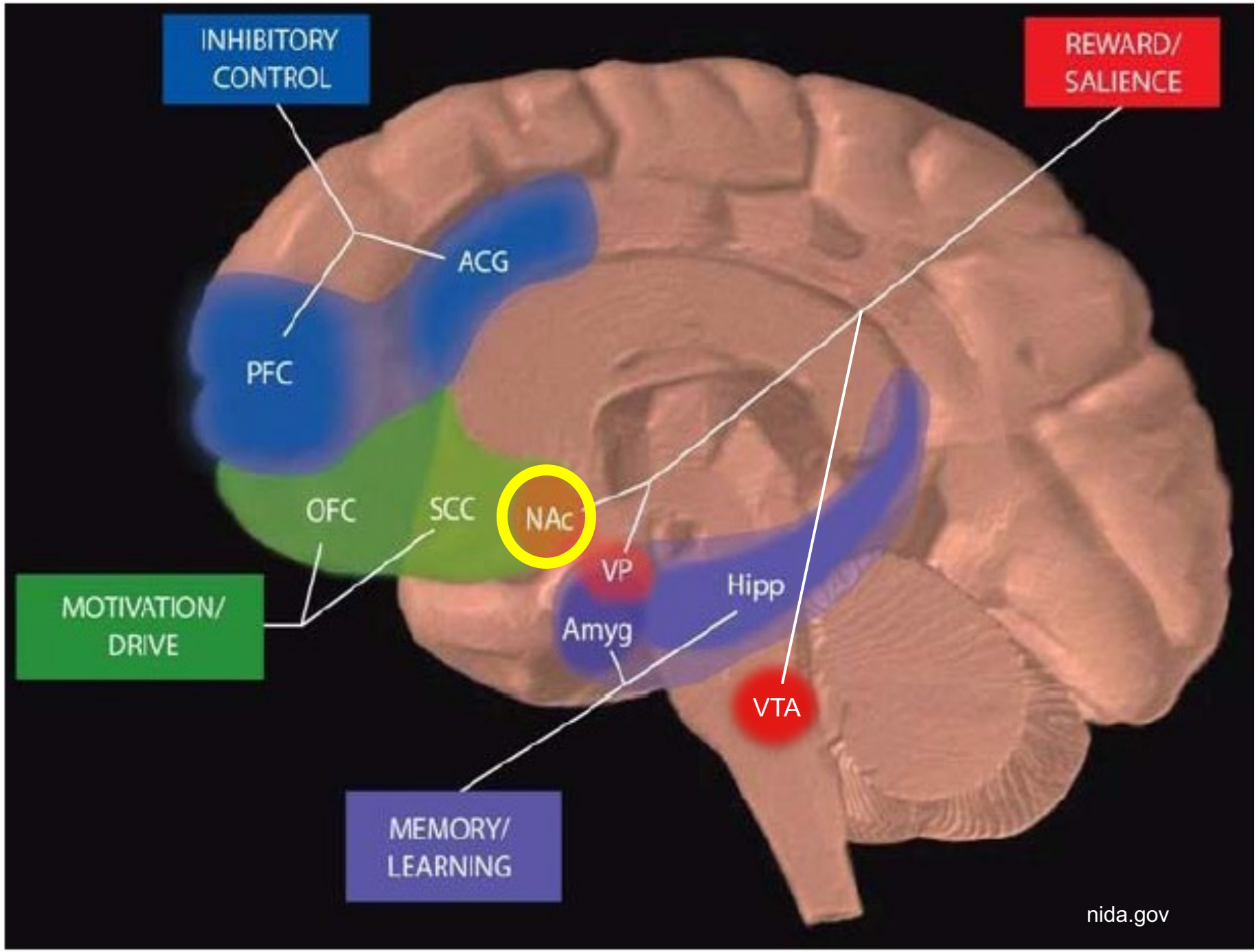


James Olds, PhD (1922 - 1976)
Peter Milner, PhD (1919 – 2018)

- Discovery of the reward system through intracranial self-stimulation in rats
- Mice will avidly self-administer electric currents to the Septal Areas
- They prefer the electrical stimulation over other survival rewards such as food (a drive state independent of other drive states such as hunger)



Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol. 1954 Dec;47(6):419-27.

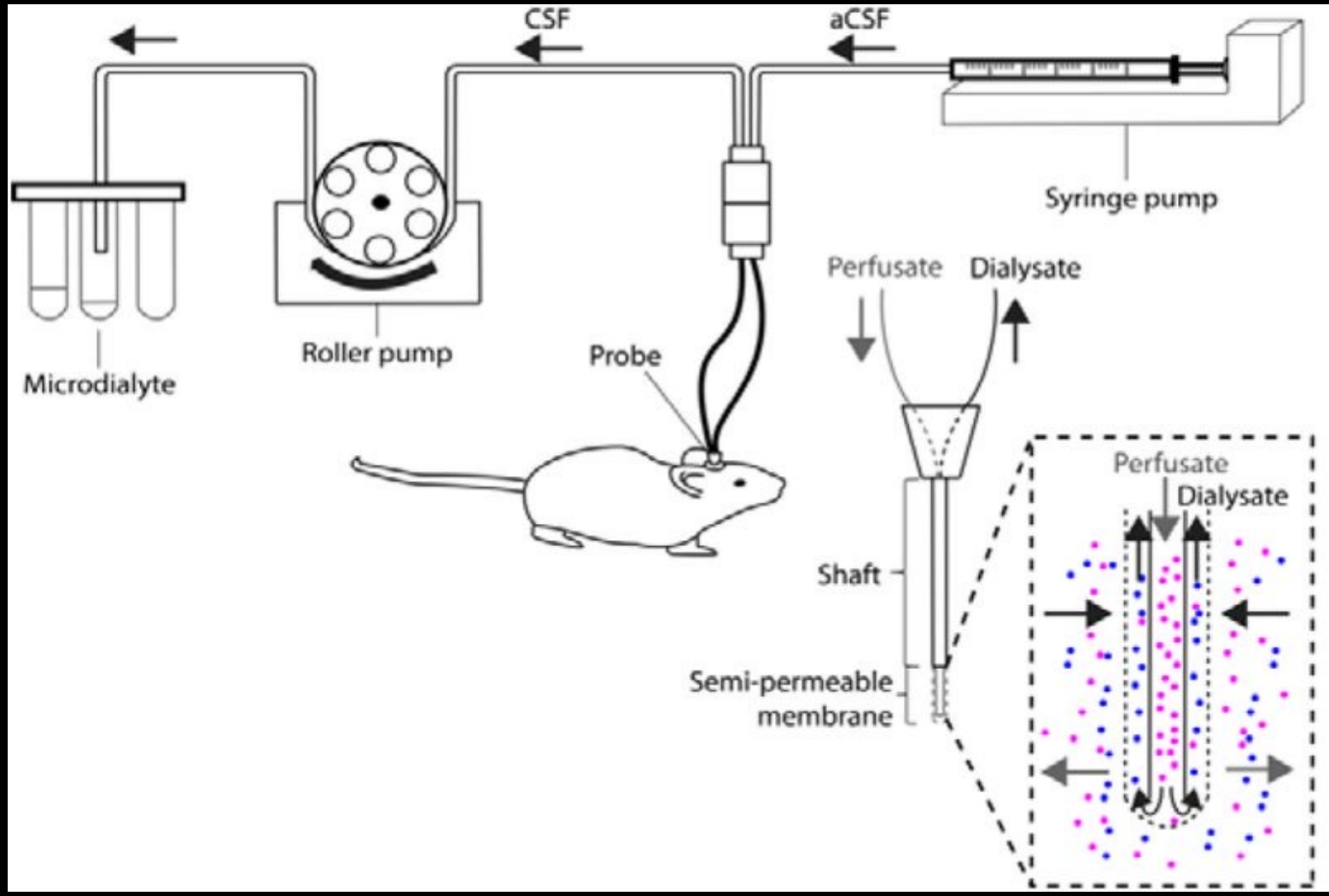


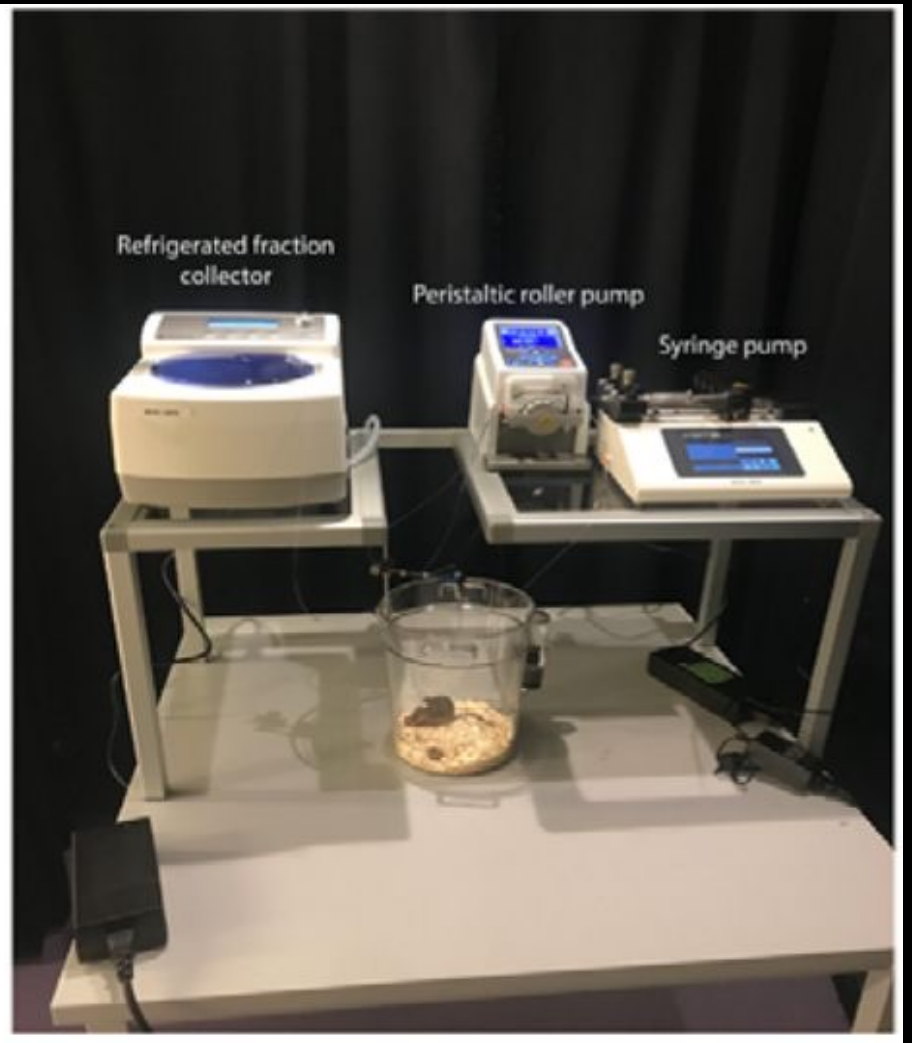
Reward/Salience Areas:

NAc: **Nucleus accumbens**
(ventral striatum)

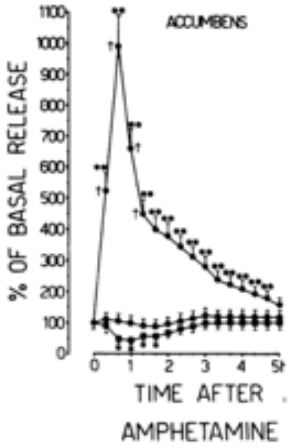
VTA: **Ventral Tegmental Area**
(midbrain)

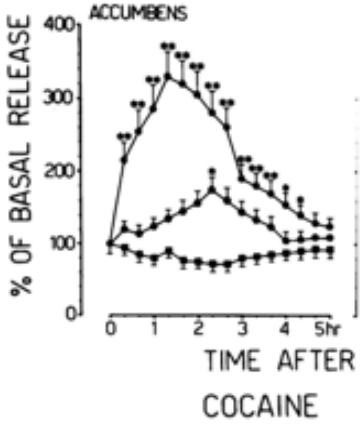
in vitro micro-dialysis

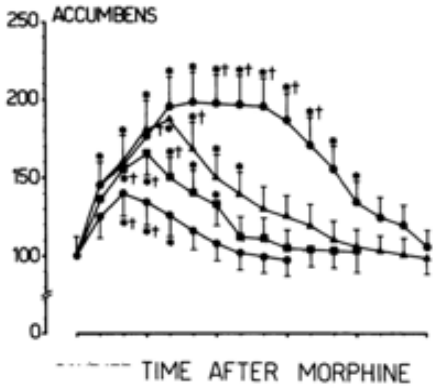


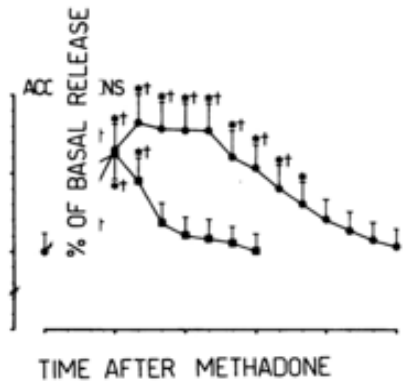


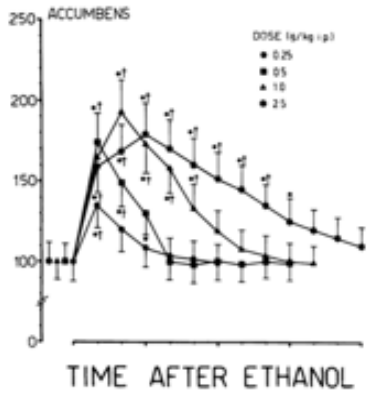
Drugs of abuse increase synaptic dopamine in the mesolimbic system of rats

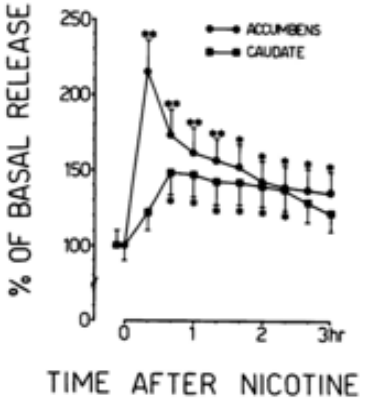












"The present results show that drugs belonging to different pharmacological classes but sharing the characteristic of being rewarding in animals and humans share the properties of preferentially increasing synaptic dopamine concentrations in the mesolimbic dopaminergic system and of stimulating behavior."

- DiChiara & Imperato, 1988

Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A. 1988;85(14):5274-5278. doi:10.1073/pnas.85.14.5274

The "Brain Reward Cascade" (Blum)

#1. Dopamine

Reward Salience

#2. Glutamate

1. Reward Learning
2. Cortical Control

Consummatory "Pleasure"

- Endogenous Opioids
- Endogenous Cannabinoids
- GABA
- Serotonin
- Oxytocin

Adapted from:

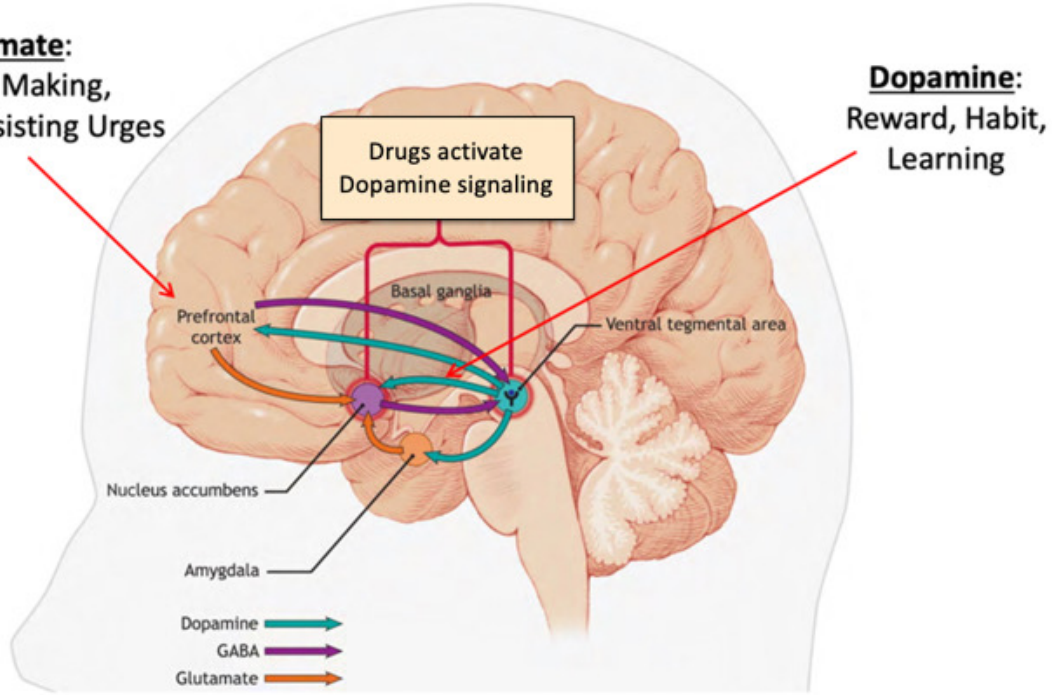
Blum K, Febo M, Badgaiyan RD. Fifty years in the development of a glutaminergic-dopaminergic optimization complex (KB220) to balance brain reward circuitry In reward deficiency syndrome: a pictorial. *Austin Addict Sci.* 2016;1(2).

Dopamine Neurotransmission

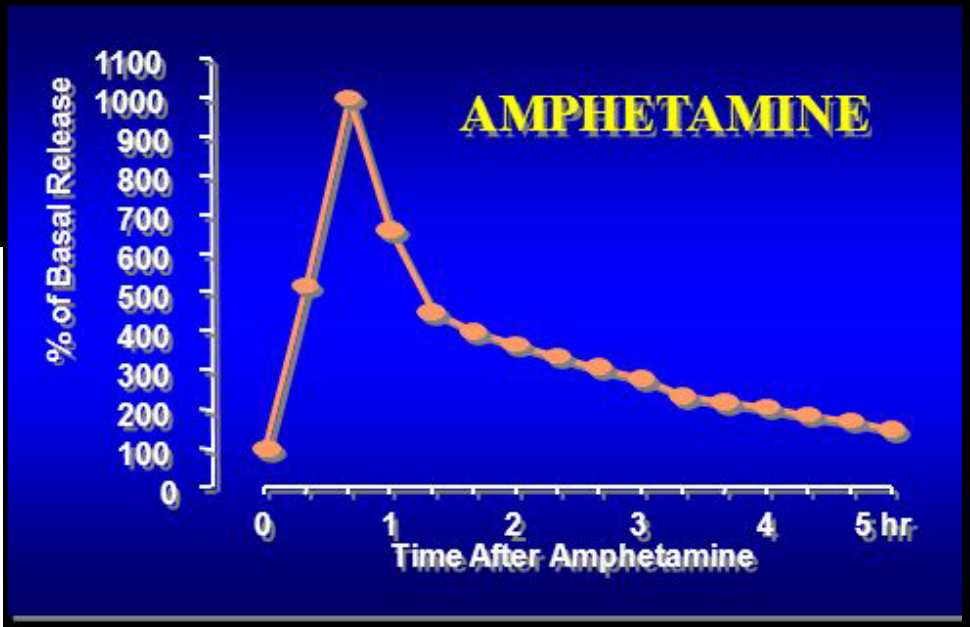
Brain circuits involved in addiction: Dopamine and glutamate

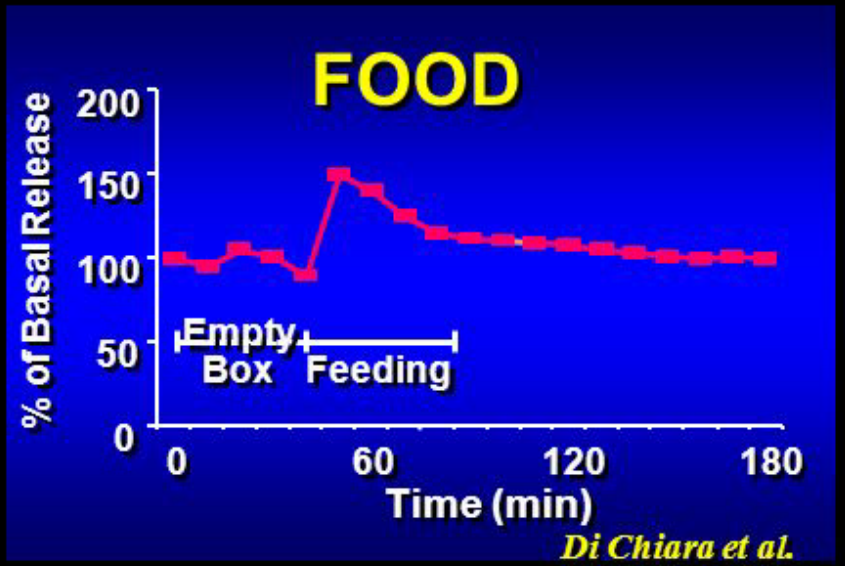
Glutamate: Decision Making, Planning, Resisting Urges

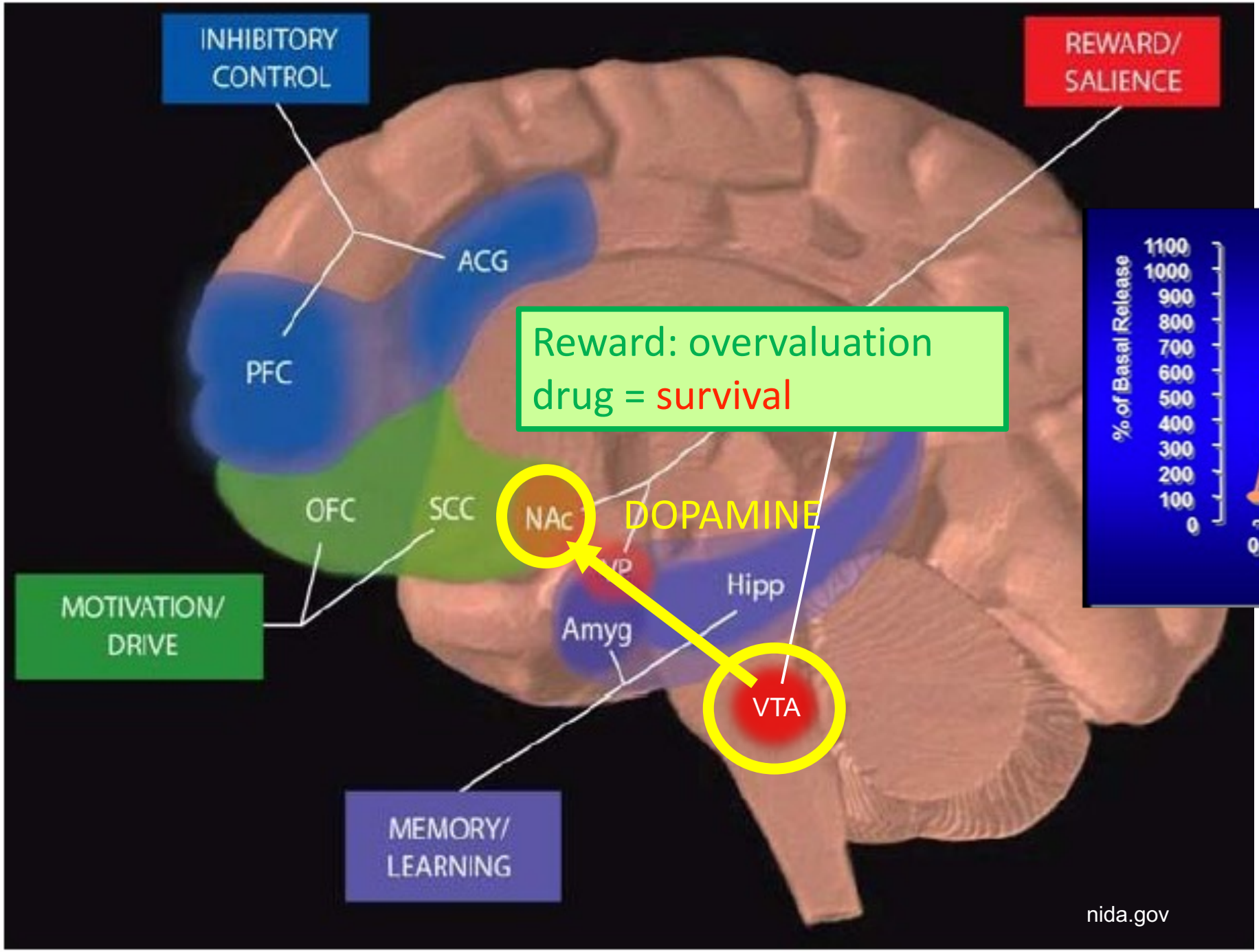
Dopamine: Reward, Habit, Learning



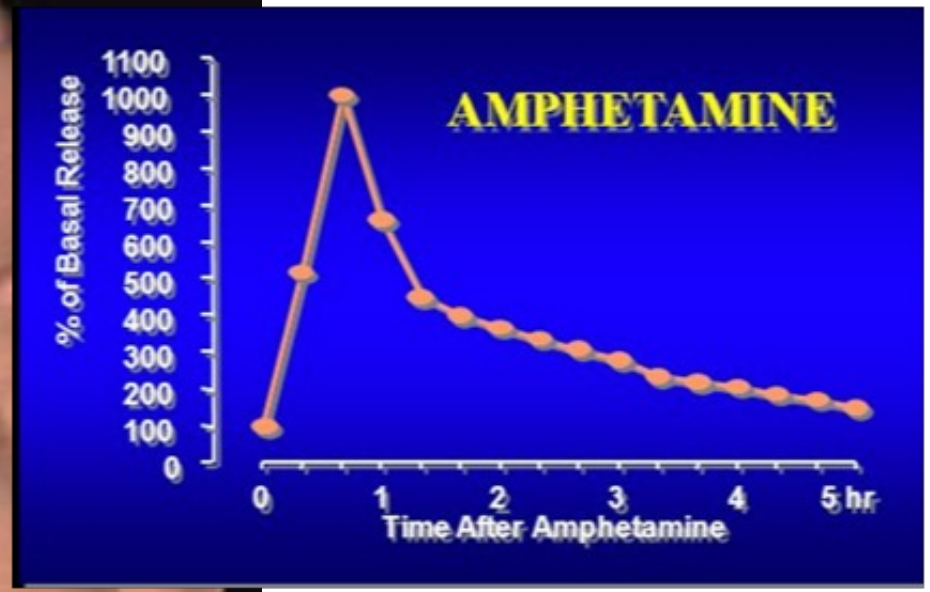
Le Foll B. CMAJ. 2007 Nov 20;177(11):1373-80.







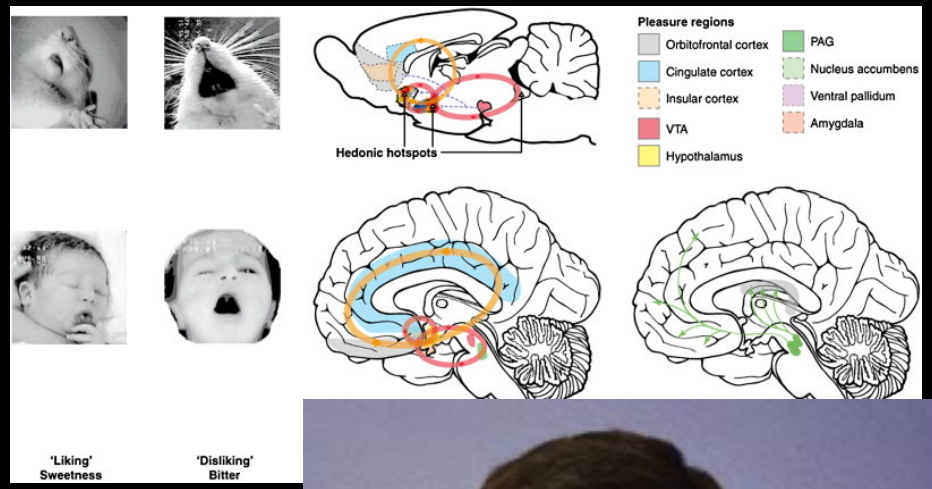
1. Survival Salience



Reward/Salience Areas:
NAc: **Nucleus accumbens**
(ventral striatum)
VTA: **Ventral Tegmental Area**
(midbrain)

Addiction Neurochemical #1: Dopamine

- All drugs of abuse and potential compulsive behaviors release Dopamine
- Dopamine is the first chemical in the cascade of chemicals that generate a rewarding experience
- DA is the chemical of incentive/reward salience (survival importance)



Incentive-Salience (Berridge & Robinson)

- Distinguished between a "liking" and a "wanting" role for Dopamine (it's more about "wanting")
- **Created hyper-dopaminergic Dopamine Transporter "knock-down" mice (mice with** increased synaptic Dopamine)
- Observed increased intake of reinforcing substances in these mice and greater thwarting of obstacles to get them (i.e. more "wanting")
- But did not observe greater "liking" of these substances by these mice

Kent Berridge, PhD
University of Michigan

Berridge, K. C., & Robinson, T. E. (2003). Parsing reward. *Trends in Neurosciences, 26*(9), 507-513. doi:10.1016/s0166-2236(03)00233-9

Addiction Neurochemical #1: Dopamine

- All drugs of abuse and potential compulsive behaviors release Dopamine
- Dopamine is the first chemical in the cascade of chemicals that generate a rewarding experience
- DA is the chemical of incentive/reward salience (survival importance)
- DA is more about “wanting” than “liking”

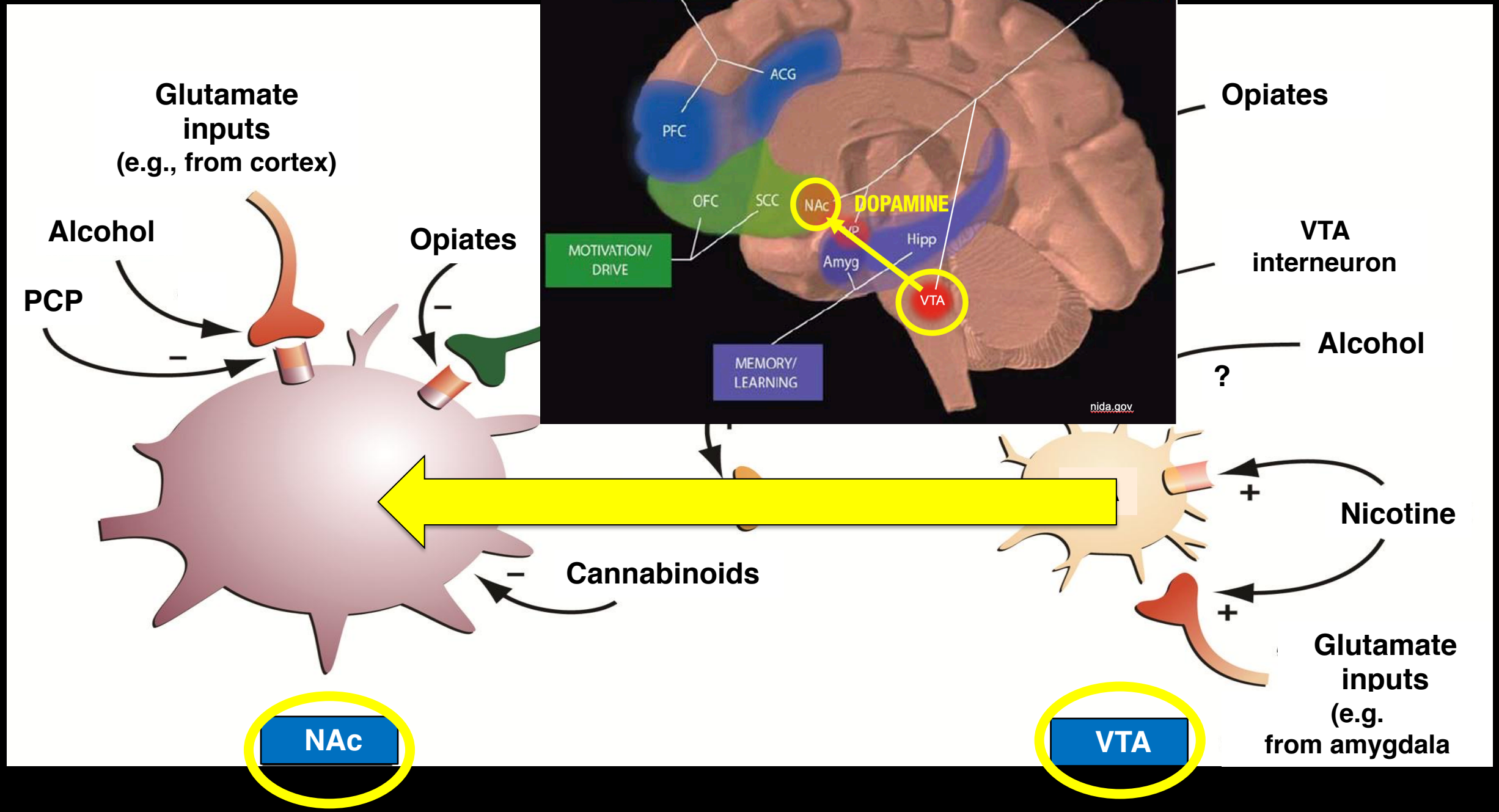
Addiction Neurochemical #1: Dopamine

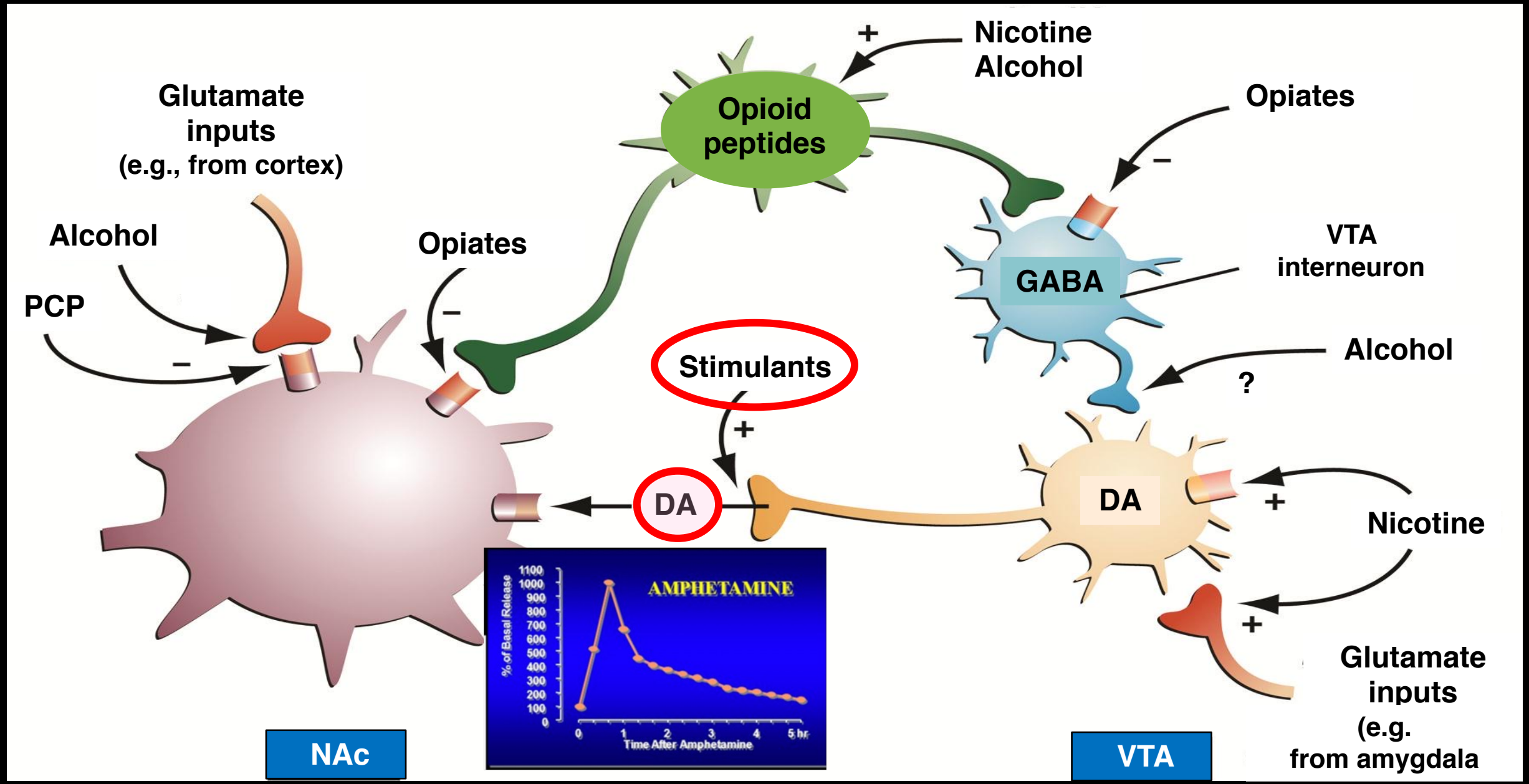
- All drugs of abuse and potential compulsive behaviors release Dopamine
- Dopamine is the first chemical in the cascade of chemicals that generate a rewarding experience
- DA is the chemical of incentive/reward salience (survival importance)
- DA is more about “wanting” than “liking”
- DA is more about expectation than consummation
- DA signals reward prediction error - it tells the brain when something is “better than expected”

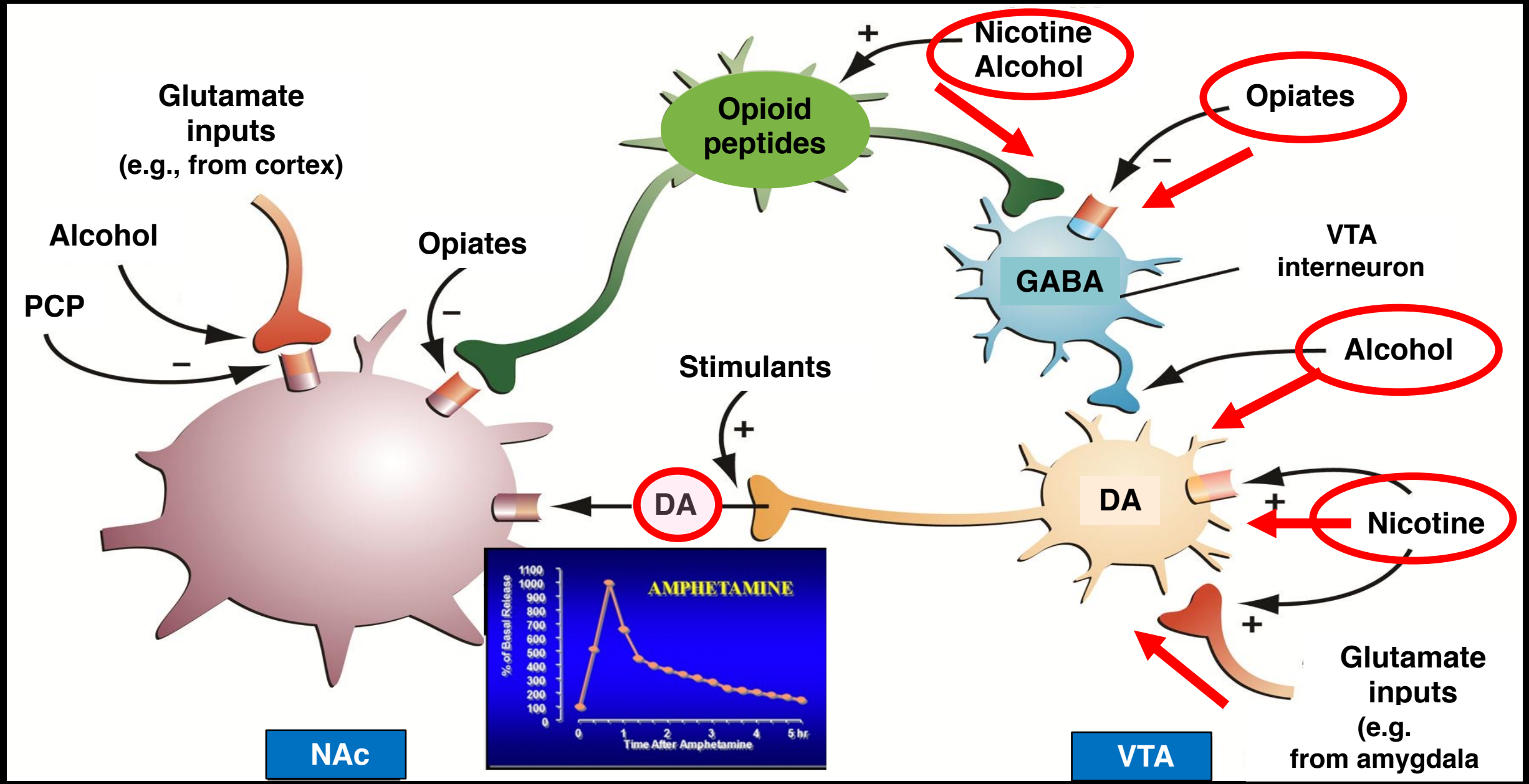
DA NAc neurons do more than encode receipt of reward

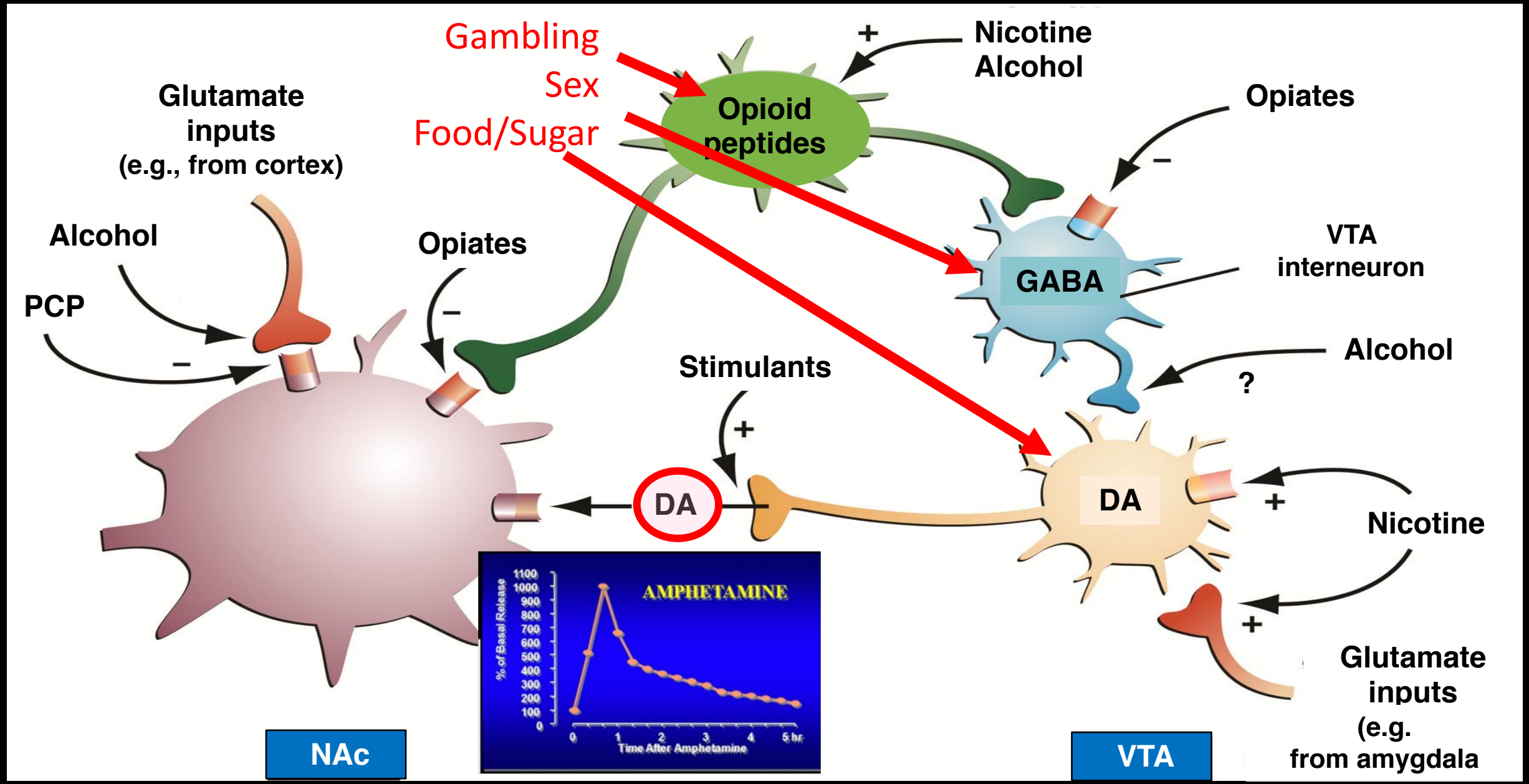
- Expectancy of reward
- Amount of reward
- Delay of reward
- Errors in reward prediction
- Motivation for drug seeking
- Contribute to synaptic neuroplasticity that underlies the acquisition of addictive behaviors

Gardner EL. Addiction and brain reward and antireward pathways. In: Clark, MR. Treisman GJ (eds): Chronic pain and addiction. Adv Psychosom Med. 30:22-60 (2011).

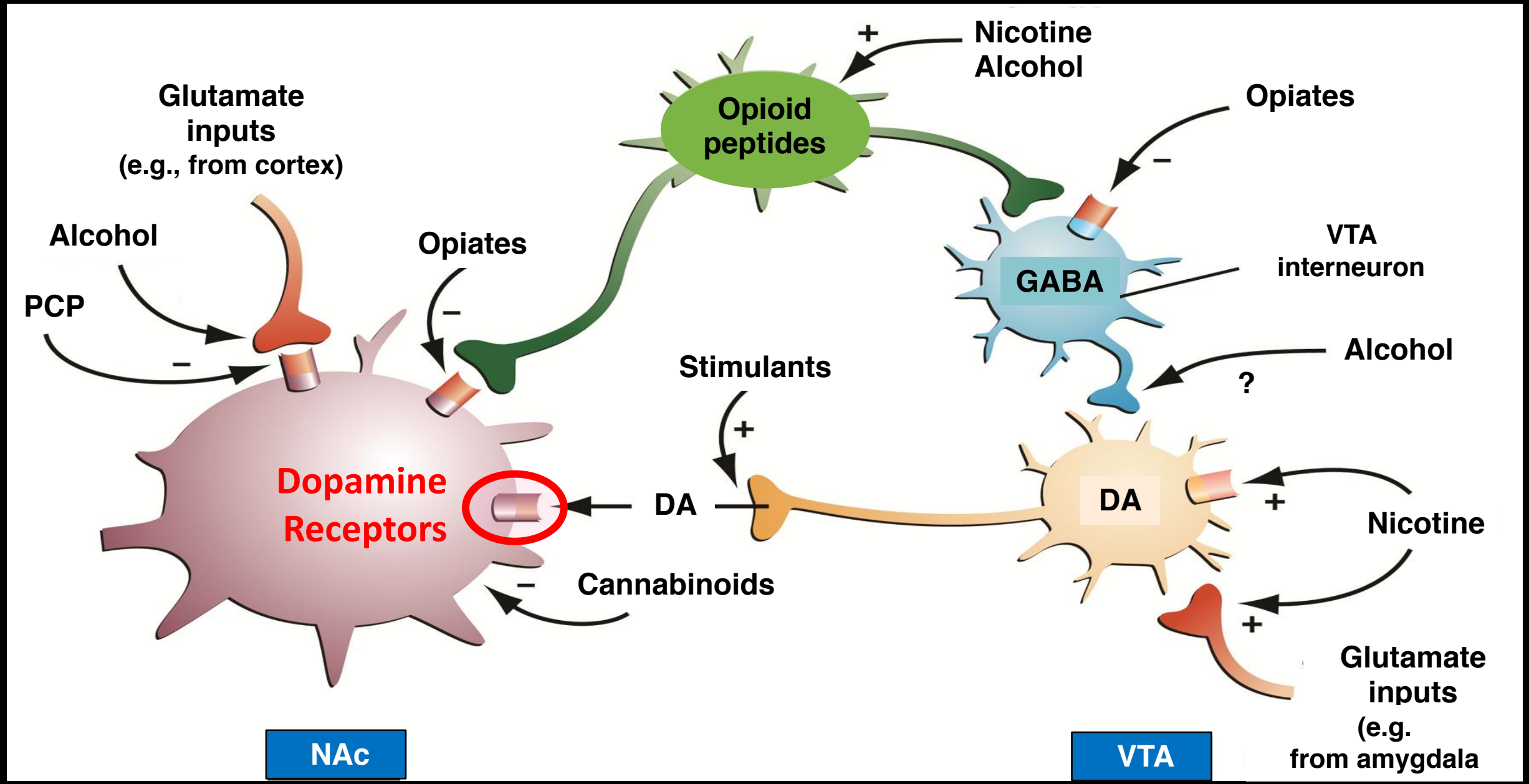

Glutamate inputs (e.g., from cortex)
Alcohol
PCP
Opiates
–
–
–
Cannabinoids
NAc
INHIBITORY CONTROL
REWARD/ SALIENCE
ACG
PFC
OFC
SCC
NAc
DOPAMINE
MOTIVATION/ DRIVE
Hipp
Amyg
VTA
MEMORY/ LEARNING
nida.gov
Opiates
VTA interneuron
Alcohol
?
+
Nicotine
+
Glutamate inputs (e.g. from amygdala
VTA

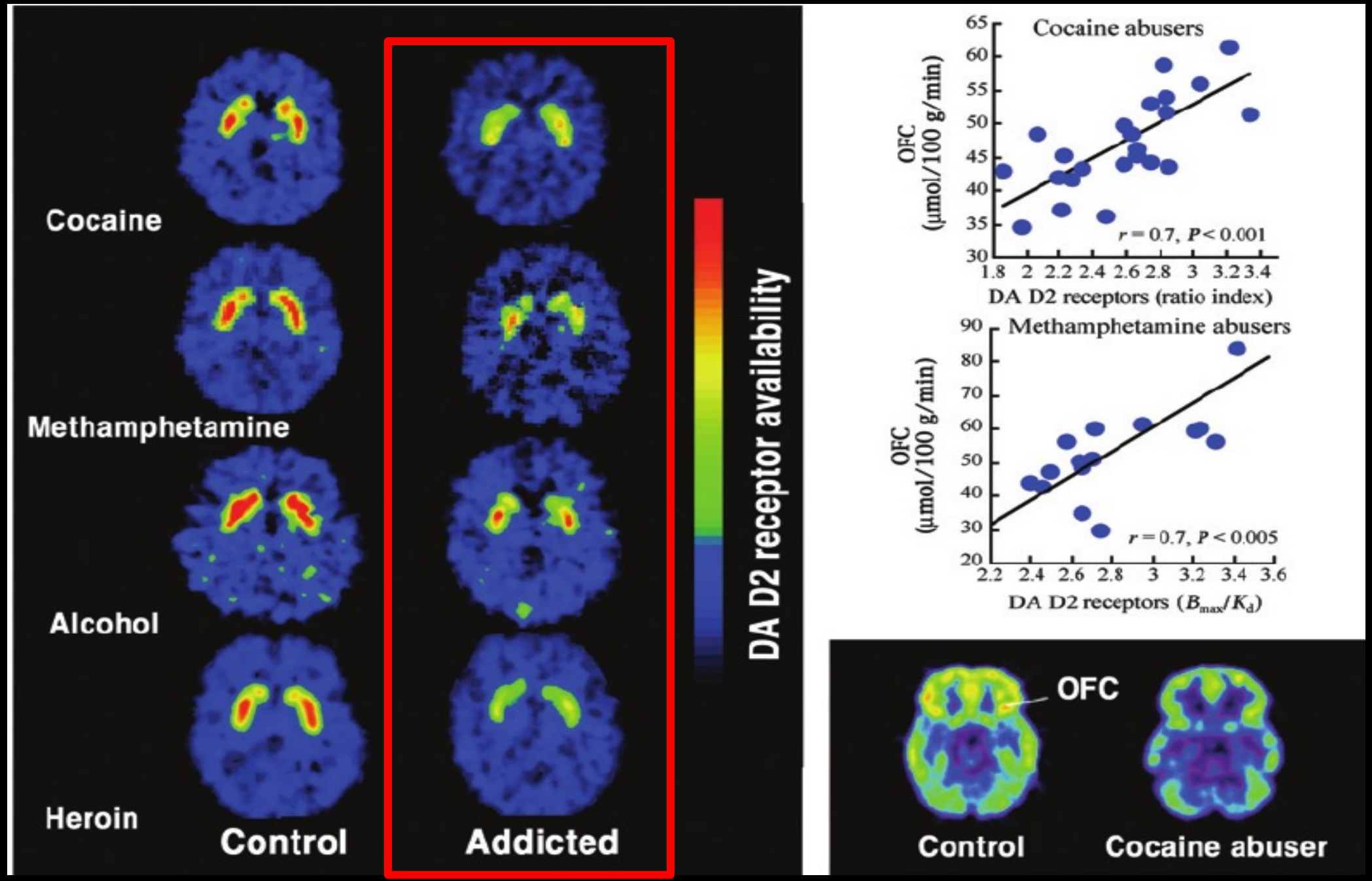

Glutamate inputs (e.g., from cortex)
Alcohol
PCP
Opiates
Nicotine
Alcohol
Opioid peptides
Opiates
VTA interneuron
GABA
Alcohol
?
Stimulants
DA
DA
Nicotine
Glutamate inputs (e.g. from amygdala
AMPHETAMINE
% of Basal Release
Time After Amphetamine
NAc
VTA


Glutamate inputs (e.g., from cortex)
Alcohol
PCP
Opiates
Opioid peptides
Nicotine
Alcohol
Opiates
GABA
VTA interneuron
Stimulants
DA
DA
Alcohol
Nicotine
Glutamate inputs (e.g. from amygdala
AMPHETAMINE
% of Basal Release
Time After Amphetamine
NAc
VTA



Frascella, J., Potenza, M. N., Brown, L. L., & Childress, A. R. (2010). Shared brain vulnerabilities open the way for nonsubstance addictions: carving addiction at a new joint?. Annals of the New York Academy of Sciences, 1187, 294–315. https://doi.org/10.1111/j.1749-6632.2009.05420.x


Glutamate
inputs
(e.g., from cortex)
Alcohol
PCP
Opiates
Nicotine
Alcohol
Opioid
peptides
Opiates
GABA
VTA
interneuron
Alcohol
?
Stimulants
Dopamine
Receptors
DA
DA
Nicotine
Cannabinoids
Glutamate
inputs
(e.g.
from amygdala
NAc
VTA



Volkow DN, Wise RA. How can drug addiction help us understand obesity? *Nat Neurosci. 2005; 8(5):555-60.*

Dopamine, Dopamine Receptors and Addiction

Nora D. Volkow, MD
Director, National Institute on Drug Abuse

- Drugs of abuse cause supraphysiologic increases in extracellular dopamine in the striatum that correlate with subjective feelings of being “high”
- PET scan studies: impaired striatal dopamine signaling due to decreased DAD2 receptors
- fMRI scan studies: brain activation abnormalities in striato-cortical pathways that regulate reward, self-control, and affect
- Overlap in brain circuitry underlying addiction and disorders such as binge eating and pathological gambling
- Other brain chemicals matter, too (glutamate, GABA, endogenous opioid and cannabinoids)

Volkow, N. D., & Morales, M. (2015). The Brain on Drugs: From Reward to Addiction. *Cell*, *162*(4), 712–725. https://doi.org/10.1016/j.cell.2015.07.046

Dopamine-Releasing Chemicals

- Alcohol & Sedative/Hypnotics
- Opiates/Opioids
- Cocaine
- Amphetamines
- Entactogens (MDMA)
- Entheogens/Hallucinogens
- Dissociants (PCP, Ketamine)
- Cannabinoids
- Inhalants
- Nicotine
- Caffeine
- Anabolic-Androgenic Steroids

Dopamine-Releasing Behaviors

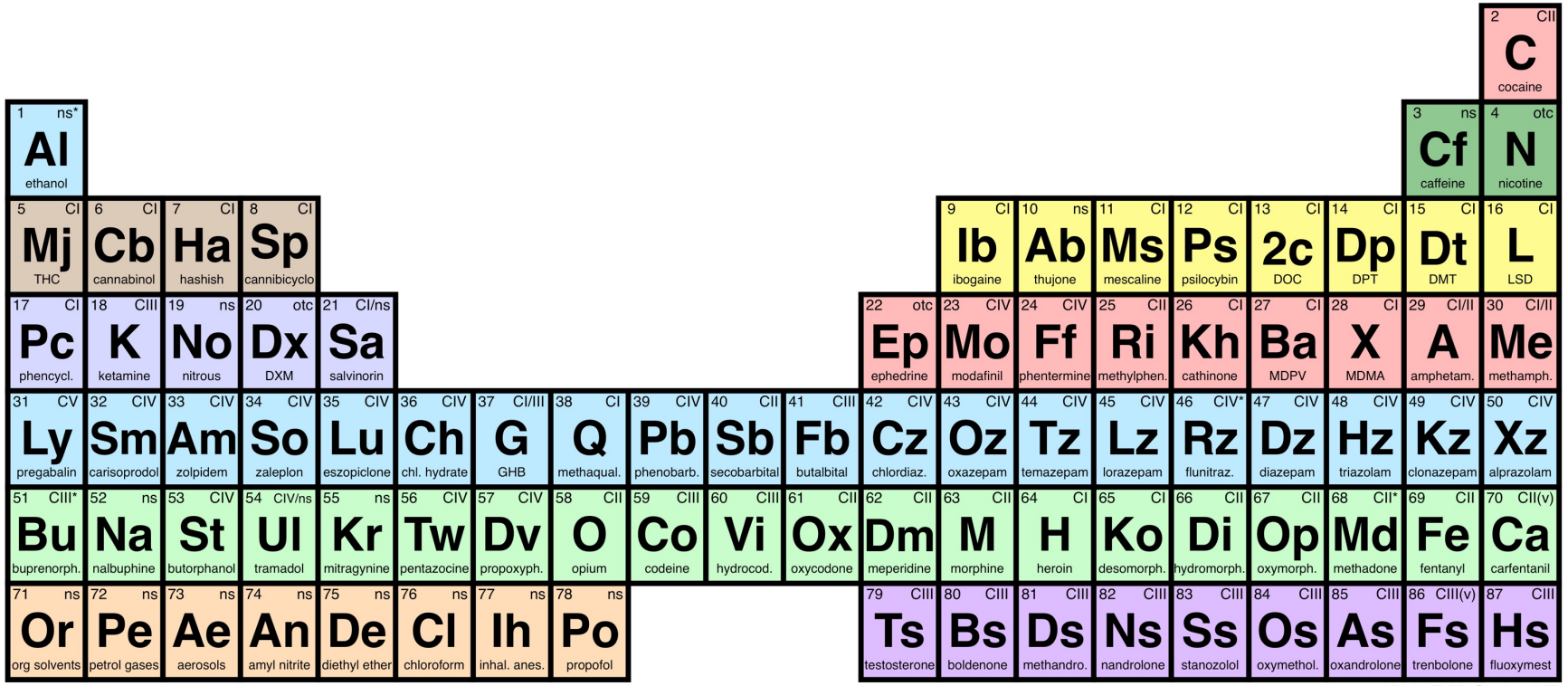
- Food (Bulimia & Binge Eating)
- Sex
- Relationships
- Other People
  ("Codependency," Control)
- Gambling
- Cults
- Performance
  ("Work-aholism")
- Collection/Accumulation
  ("Shop-aholism")
- Rage/Violence
- Media/Entertainment

The Full Spectrum of “Intoxication”

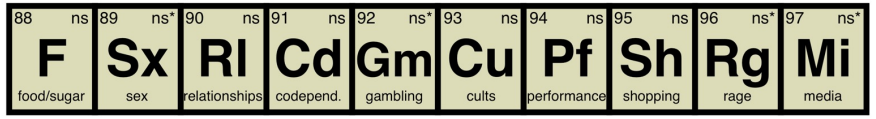
- Alcohol & Sedative/Hypnotics
- Opiates/Opioids
- Cocaine
- Amphetamines
- Entactogens (MDMA)
- Entheogens/Hallucinogens
- Dissociants (PCP, Ketamine)
- Cannabinoids
- Inhalants
- Nicotine
- Caffeine
- Anabolic-Androgenic Steroids

- Food (Bulimia & Binge Eating)
- Sex
- Relationships
- Other People
  (“Codependency,” Control)
- Gambling
- Cults
- Performance
  (“Work-aholism”)
- Collection/Accumulation
  (“Shop-aholism”)
- Rage/Violence
- Media/Entertainment

Periodic Table of the Intoxicants



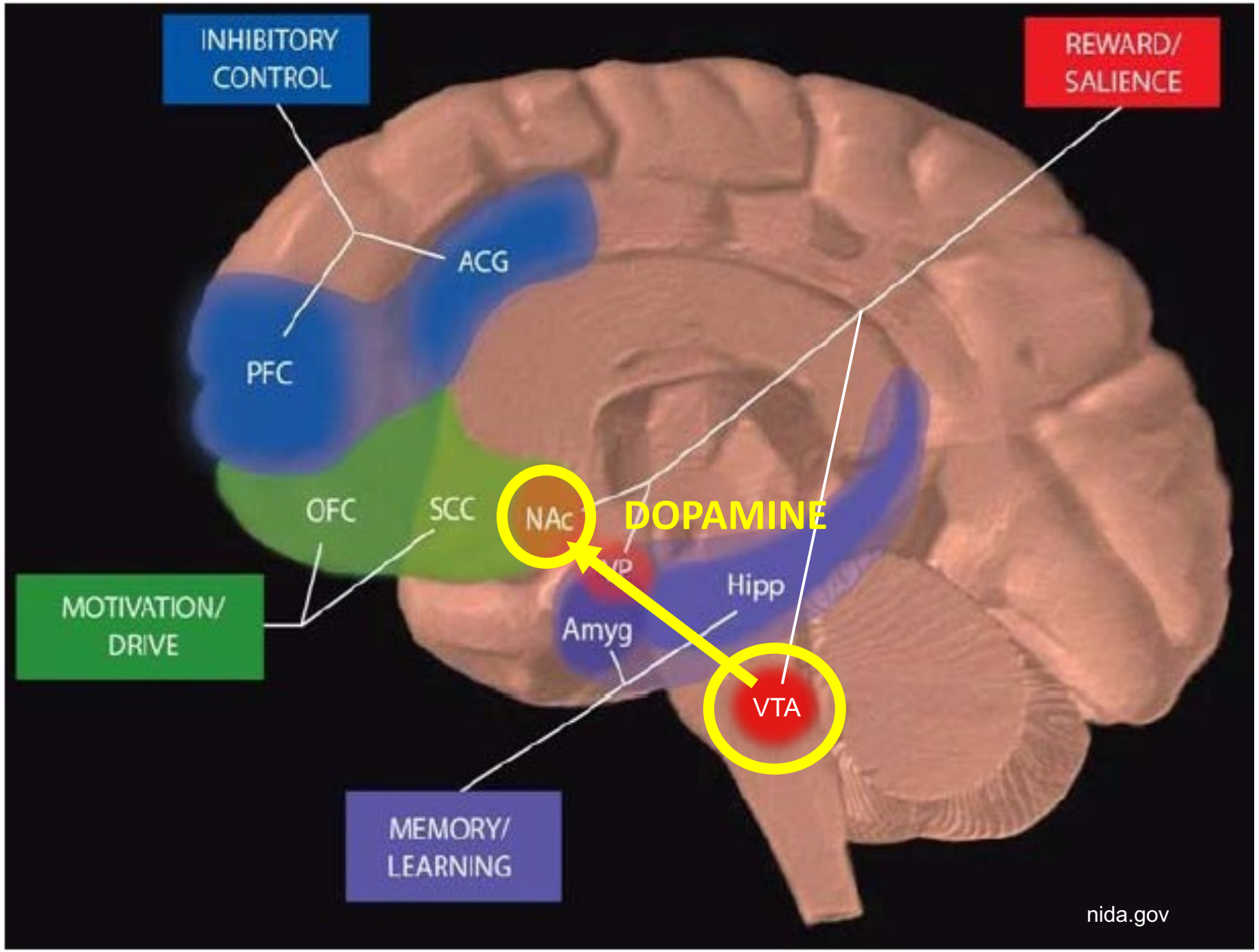
Kevin T. McCauley, MD



Dopamine: also for bad and neutral things

- Kutlu et al (2021): KCS Model – DA handles prediction error, association formation, attention, temporal dynamics
- Reward Prediction Error seen in specific reward learning contexts but not seen in aversive learning contexts
- Dopamine seen in neutral learning contexts, especially ones that are new (novel)
- Dopamine codes for a valence-independent perceived saliency (scaled physical intensity of a stimulus)

Kutlu MG, Zachry JE, Melugin PR, et al. Dopamine release in the nucleus accumbens core signals perceived saliency [published online ahead of print, 2021 Sep 8]. Curr Biol. 2021;S0960-9822(21)01188-X. doi:10.1016/j.cub.2021.08.052



Reward/Salience Areas:

NAc: **Nucleus accumbens**
(ventral striatum)

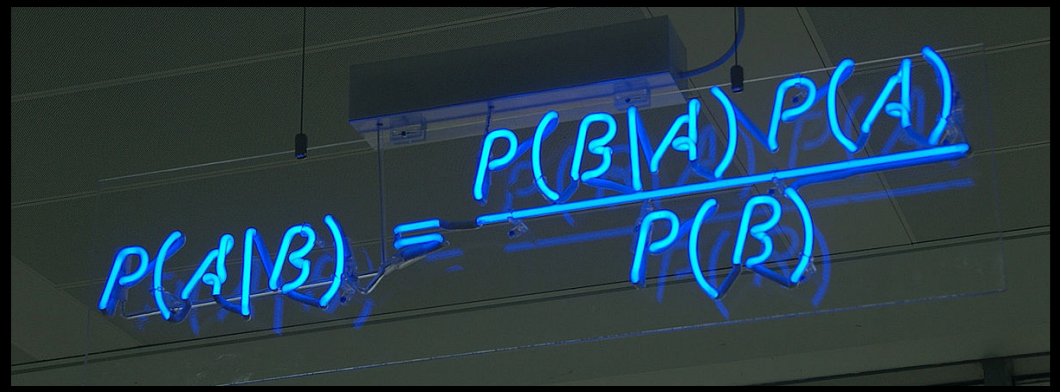
VTA: **Ventral Tegmental Area**
(midbrain)

The "Ns" of Dopamine

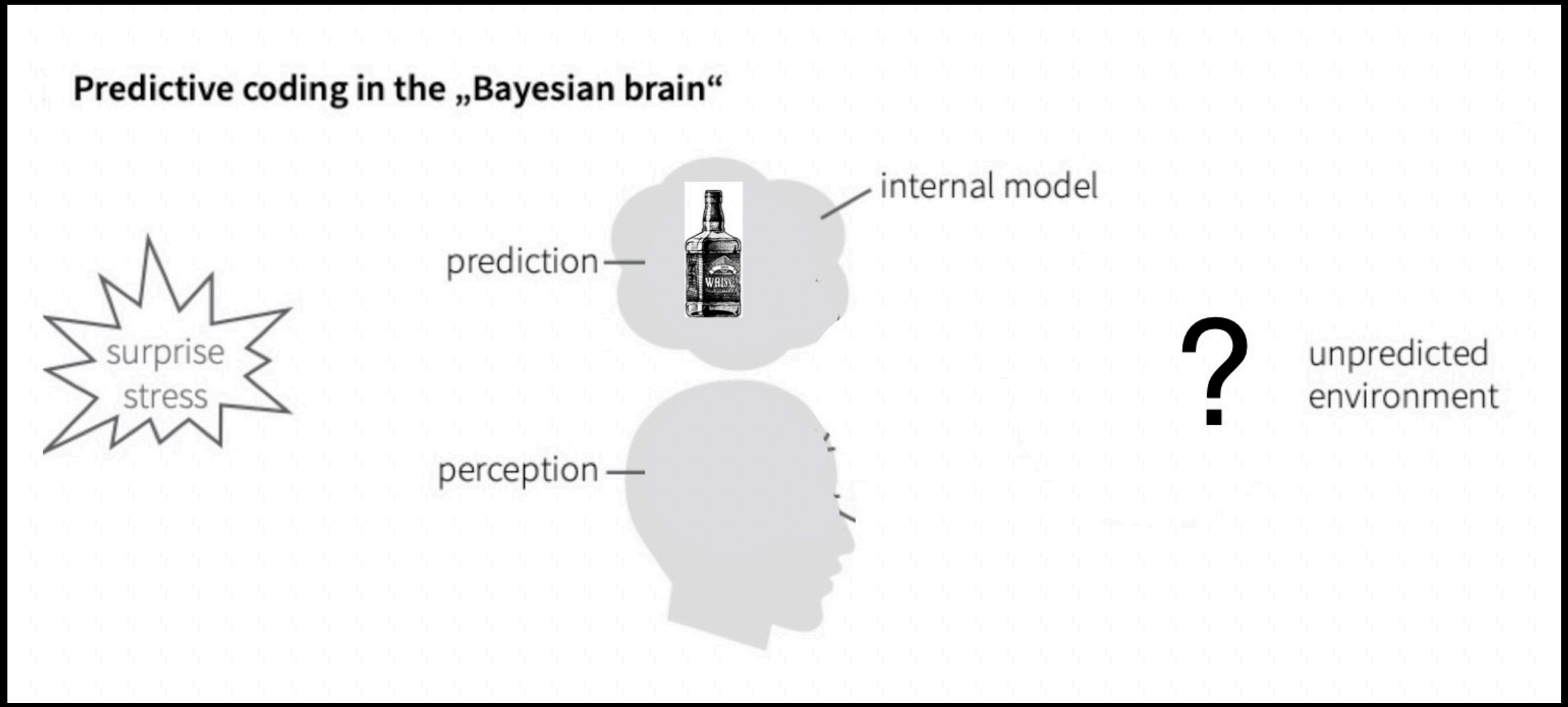
Dopamine encodes for things that are:	meaning	example
"N-Joyable"	rewarding stimuli	the core component of a hedonic (pleasurable) experience
"N-centivized"	incentive, motivational drive	wanting > liking
Novel	first exposure	magnification of learning of new & relevant experiences
Noxious	aversive stimuli	re-experiencing of traumatic events
Neutral	valence-independent stimuli	association with otherwise unrelated sensory & emotional cues, cunning/baffling/powerful nature of cue-induced relapse
Near-misses	reward prediction error	illusion of "better than expected" value, mis-remembering past intoxication episodes, chasing losses
Nearby	proximal, imminent	near in space and/or time; fantasy and fictive imagining; failure of delay discounting; craving
Numerated	number, amplitude, counts	social media "likes," hoarding (collection/accumulation addiction)

The Brain is a Bayesian Probability Calculator

Rev. Thomas Bayes (1701 – 1761)

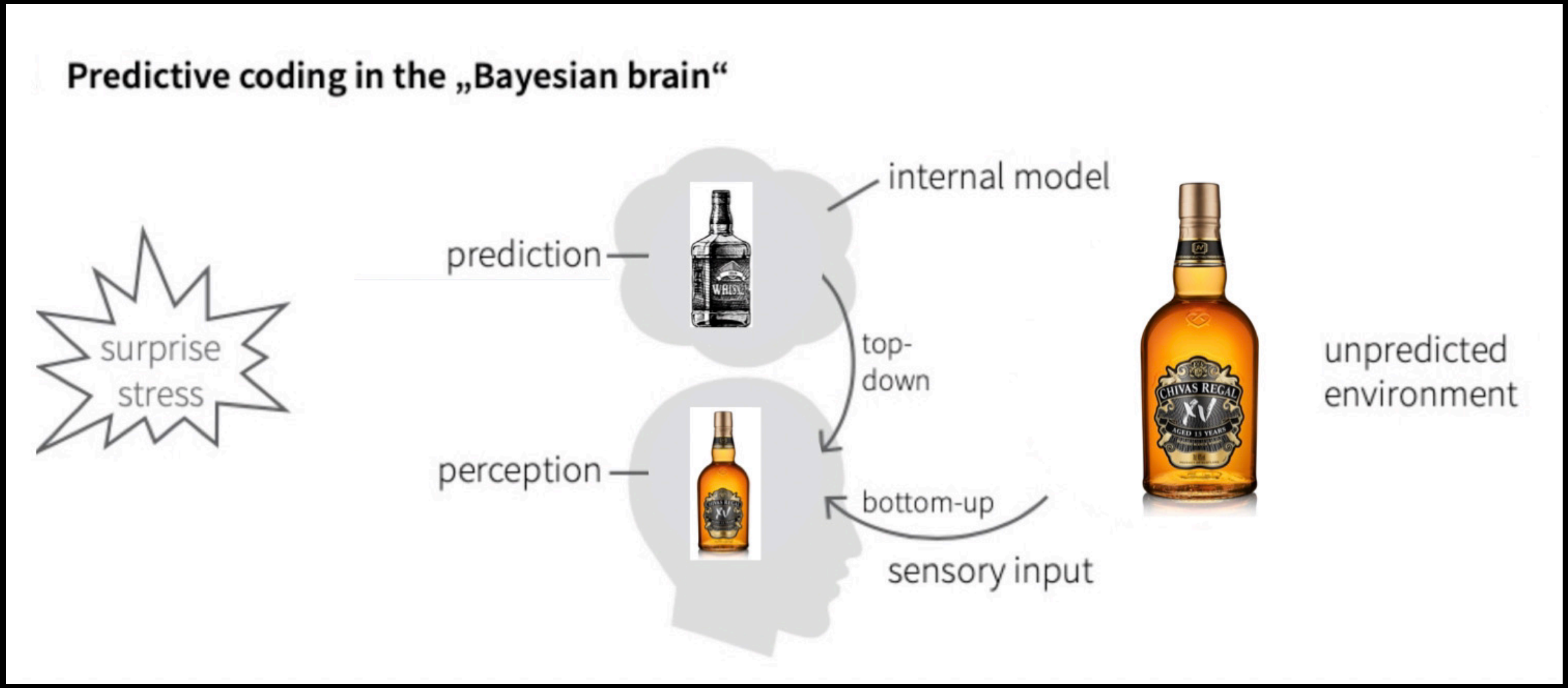


Predictive Processing/Coding (Clark)



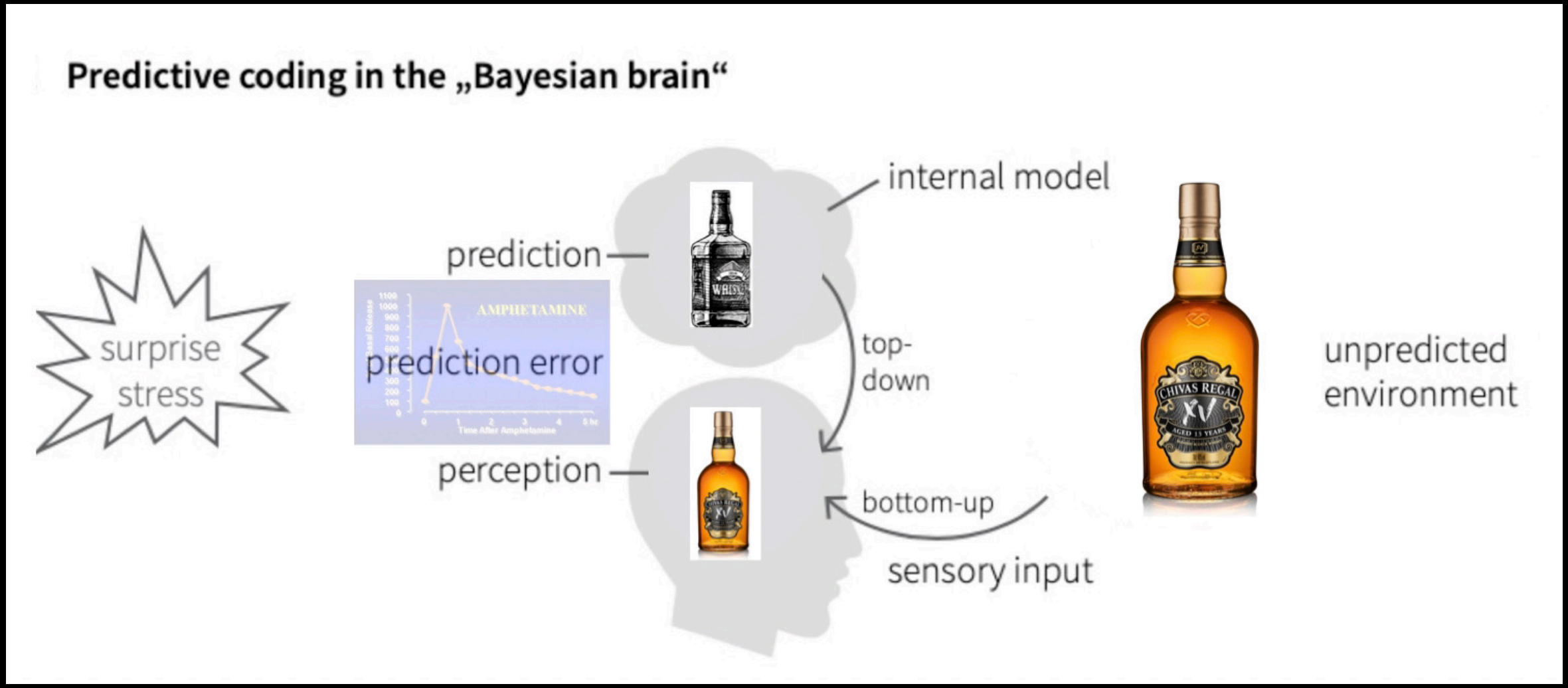
Clark, A. (2019). *Surfing uncertainty: Prediction, action, and the embodied mind*. Oxford University Press.

Predictive Processing/Coding (Clark)



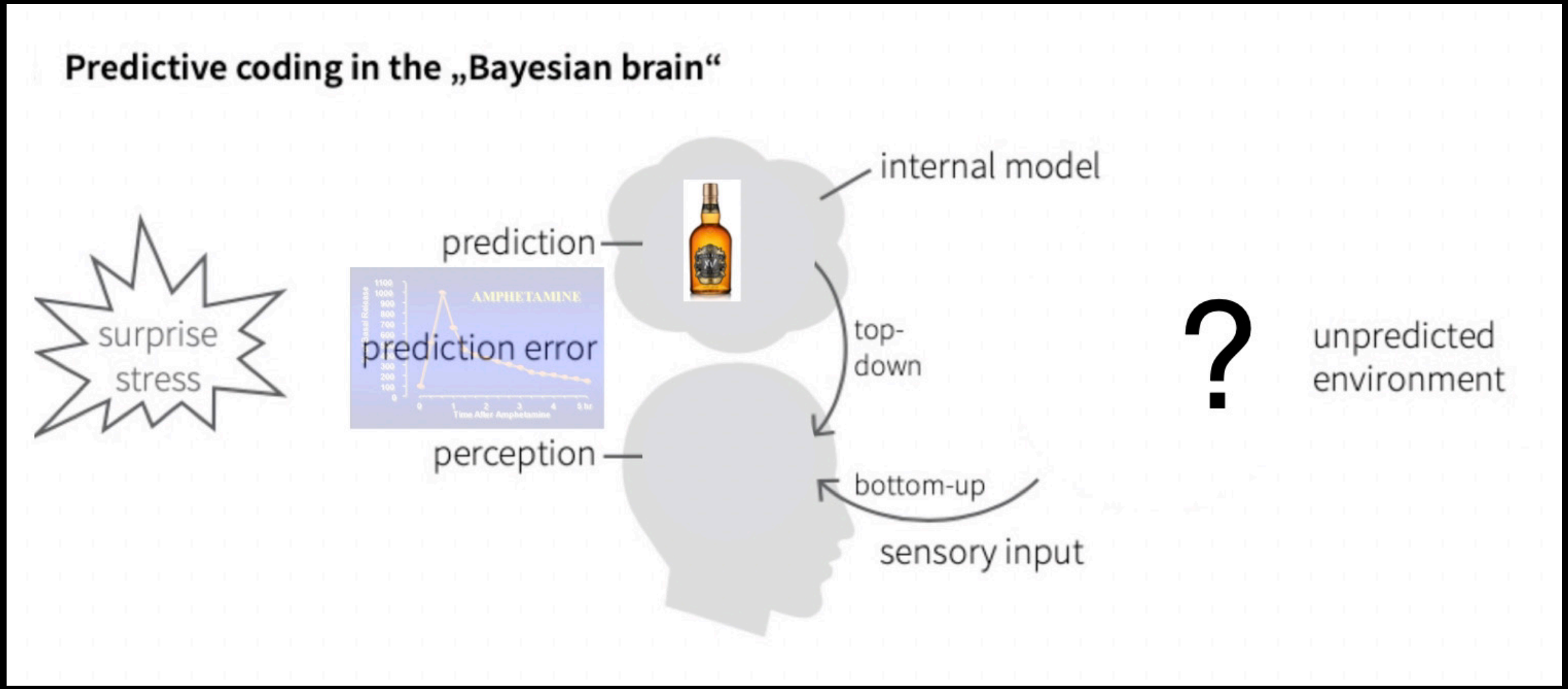
Clark, A. (2019). *Surfing uncertainty: Prediction, action, and the embodied mind*. Oxford University Press.

Predictive Processing/Coding (Clark)



Clark, A. (2019). *Surfing uncertainty: Prediction, action, and the embodied mind*. Oxford University Press.

Predictive Processing/Coding (Clark)

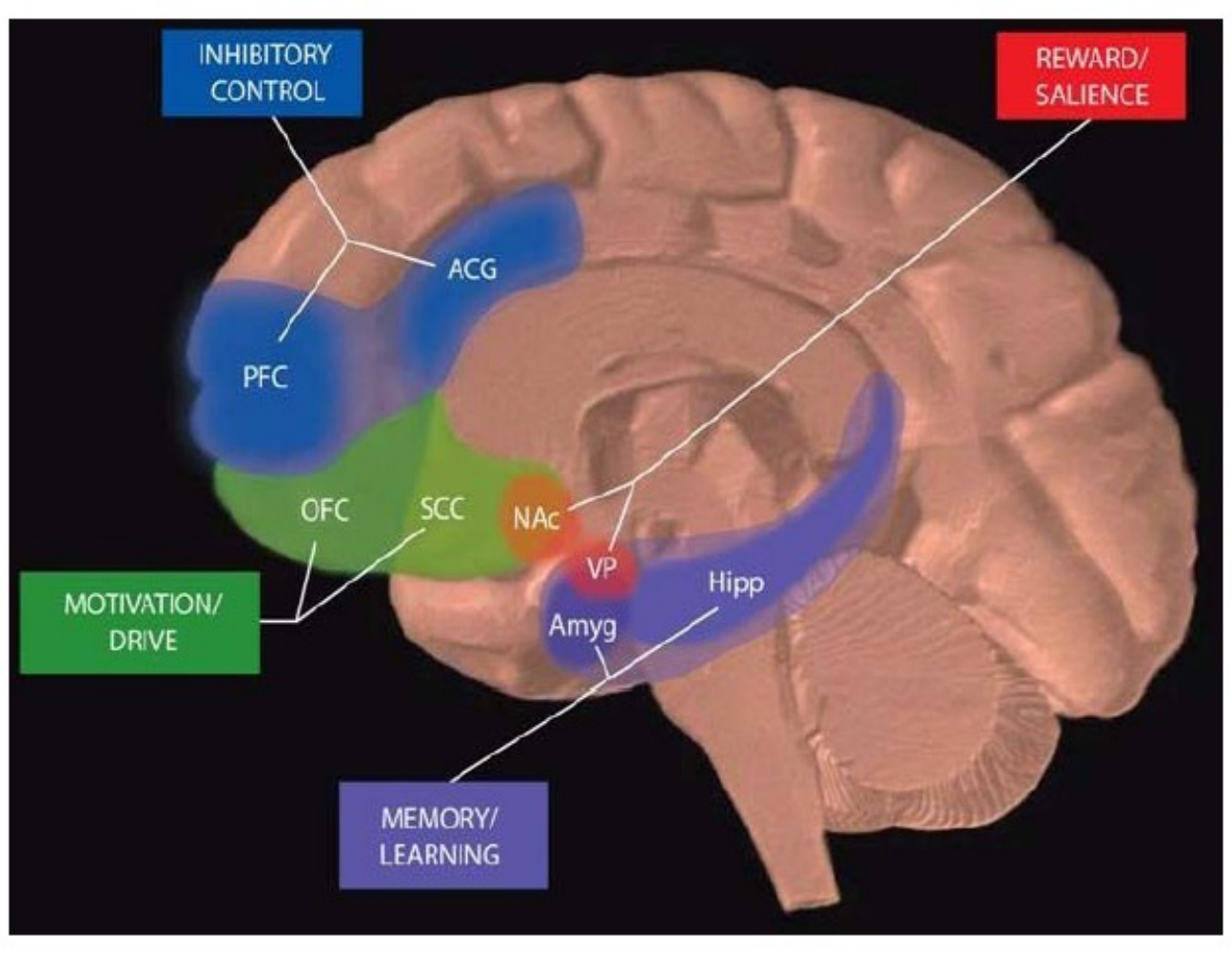


Clark, A. (2019). *Surfing uncertainty: Prediction, action, and the embodied mind*. Oxford University Press.

What goes into a pleasurable experience?

- Memory of past cakes
- Memory of this cake
- Cake tastes good
- Cake ensures survival

Addiction is a disorder of …



5. CHOICE	OFC, ACC, PFC, IC
4. STRESS	HPA axis
3. MEMORY	**glutamate**
	synaptic remodeling
2. REWARD	dopamine
	dopamine receptors
1. GENES	polymorphisms
	epigenetic changes

The "Brain Reward Cascade" (Blum)

#1.
Dopamine

Reward Salience

#2.
Glutamate

1. Reward Learning
2. Cortical Control

Consummatory "Pleasure"

Endogenous Opioids

Endogenous Cannabinoids

GABA

Serotonin

Oxytocin

Adapted from:
Blum K, Febo M, Badgaiyan RD. Fifty years in the development of a glutaminergic-dopaminergic optimization complex (KB220) to balance brain reward circuitry In reward deficiency syndrome: a pictorial. *Austin Addict Sci,* 2016;1(2).

Addiction Neurochemical #2: Glutamate

- The most abundant neurochemical in the brain
- Critical in memory formation & consolidation
- All drugs of abuse and many addicting behaviors effect Glutamate which preserves drug memories

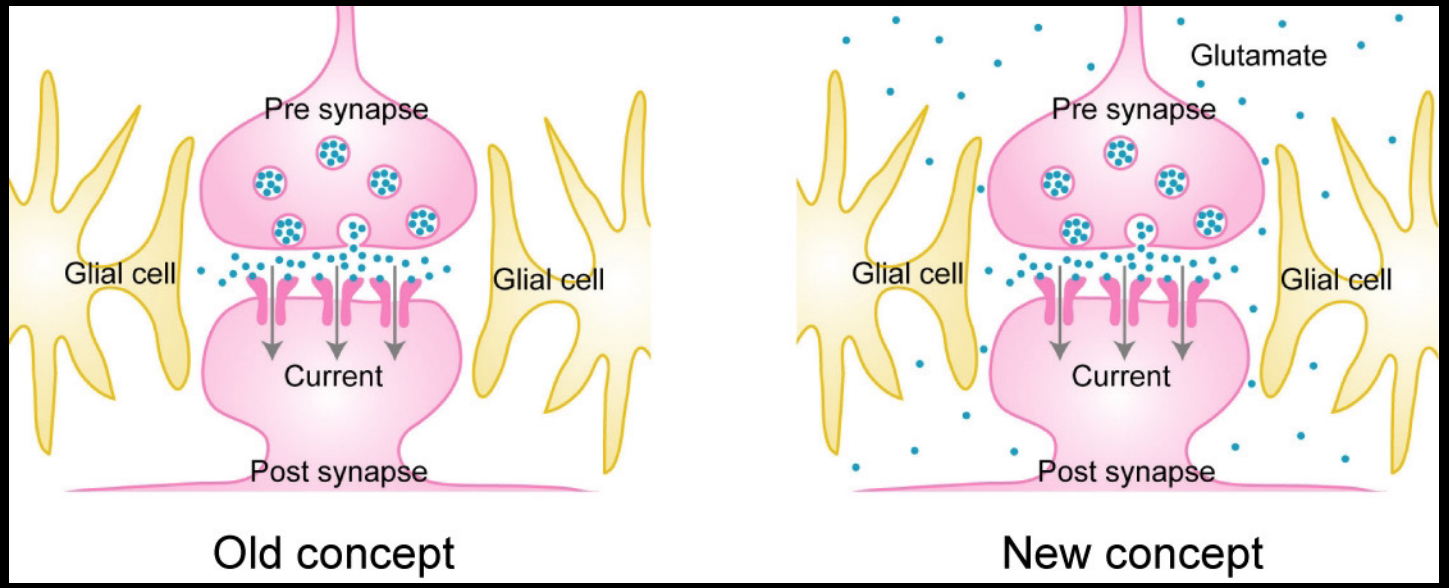
  and creates drug cues
- And … glutamate is the neurochemical of “motivation” (it initiates drug seeking)

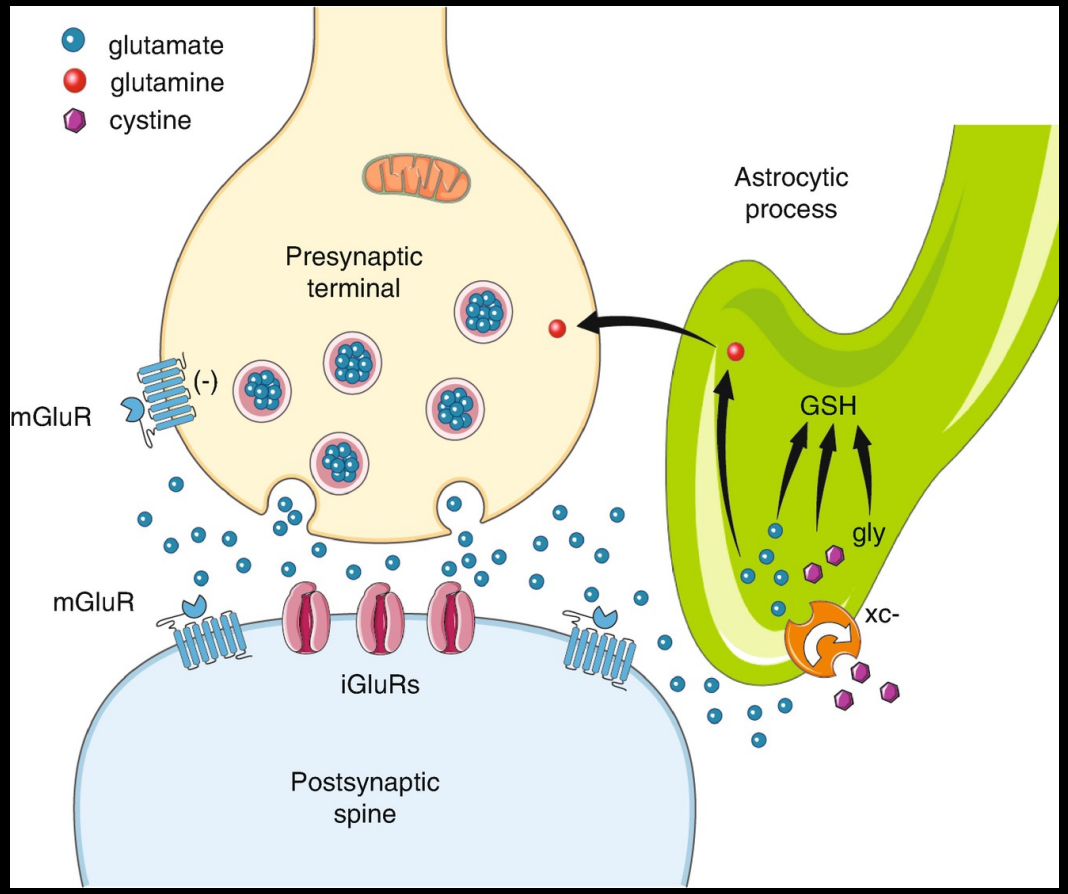
Glutamate “spillover”

- Enduring vulnerability to relapse due to recruitment of “corticofugal” GLU projections to striatum
- Excess GLU “spills” out of the synapse to bind to extra-synaptic GLU receptors
- Changes in synaptic plasticity leads to pathologic learning and memory
- Result: impairment of inhibition of drug seeking

Peter W. Kalivas, PhD
Department of Neurosciences
Medical University of South Carolina

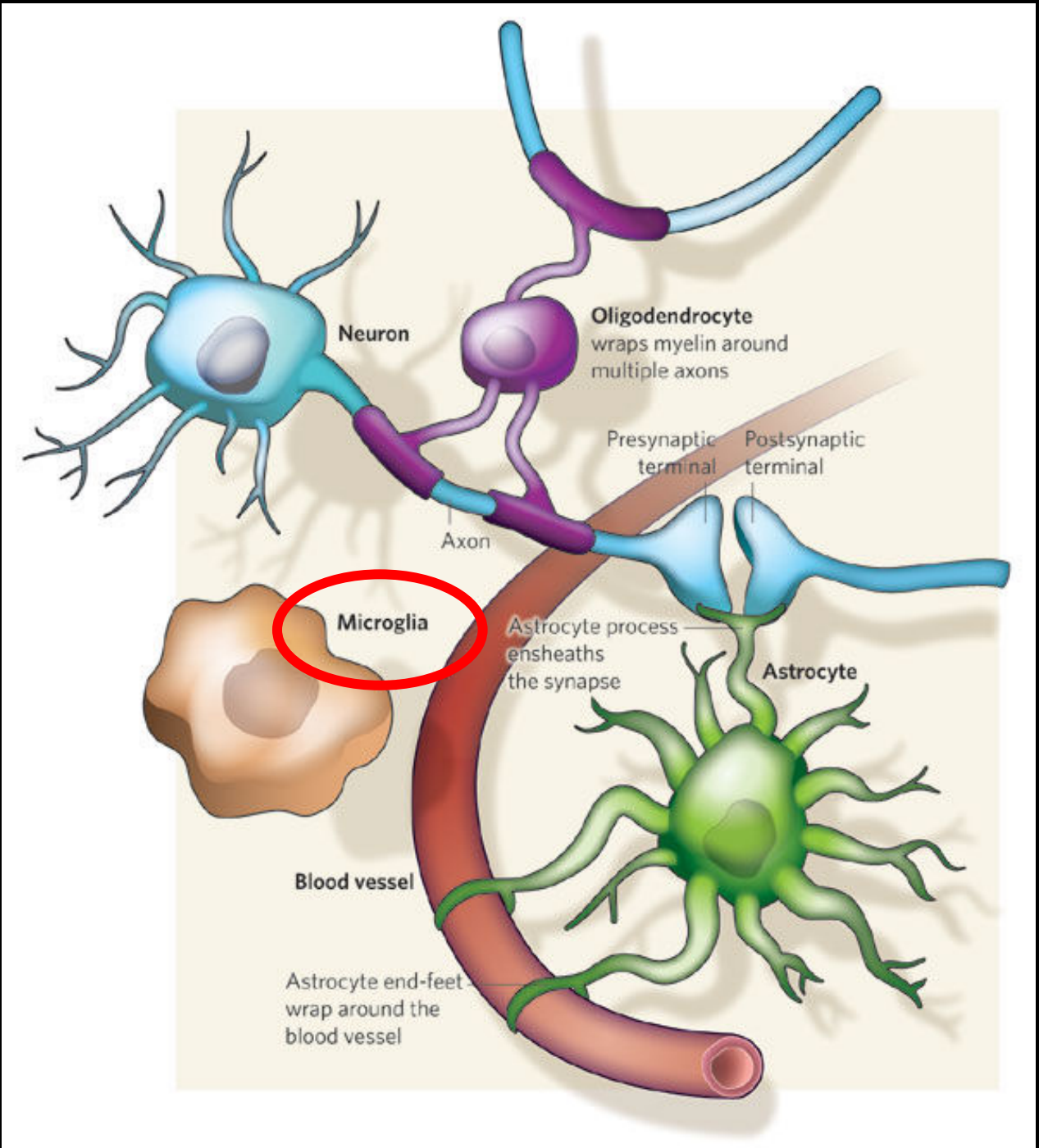
Glutamate “spillover”

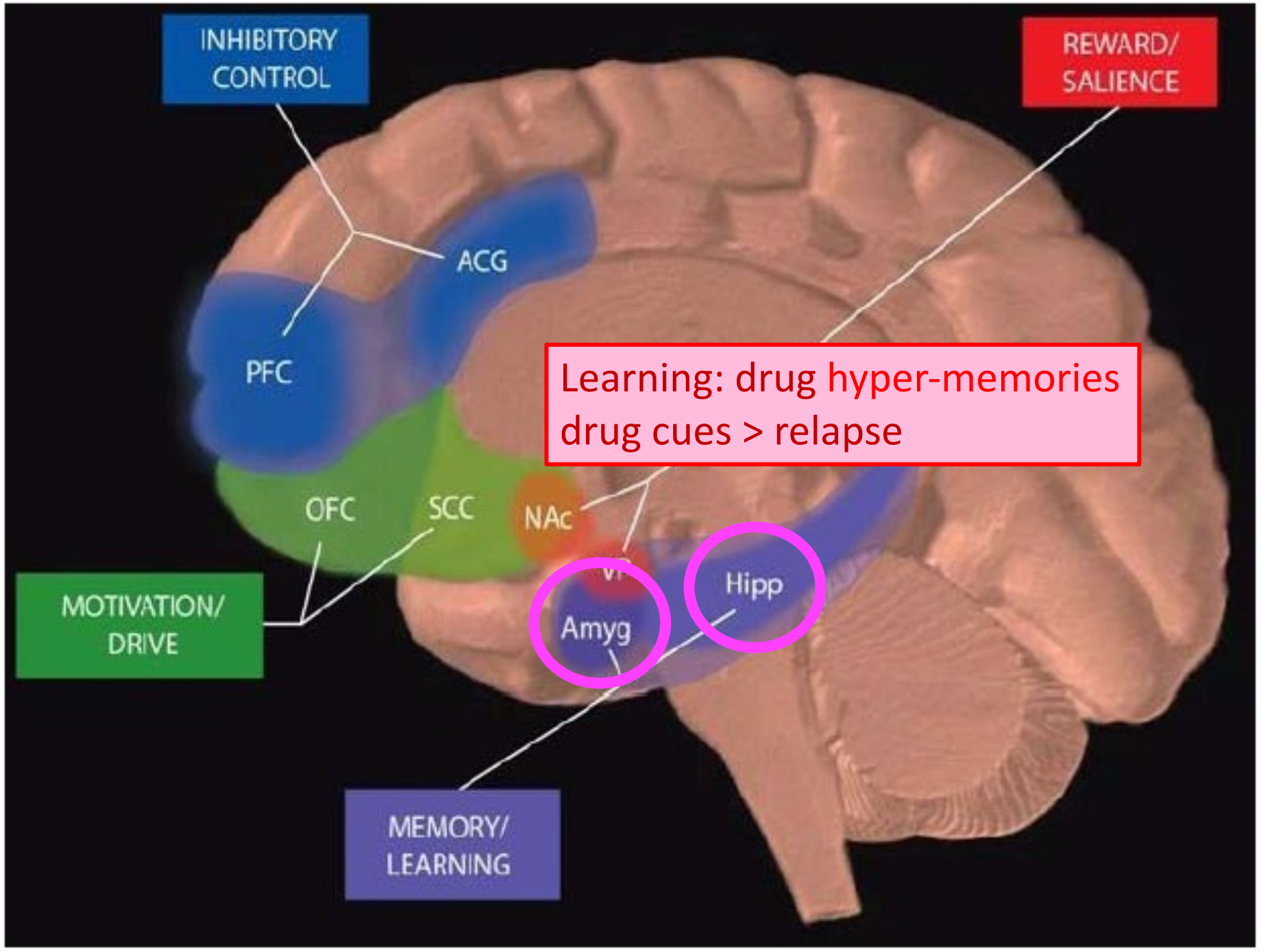




Glial Cells

- Caretaker cells of the CNS & PNS
- Half the total volume of the brain
- Equal number as neurons (in Cortex: 4 glial cells to each neuron)
- Can divide as adult cells





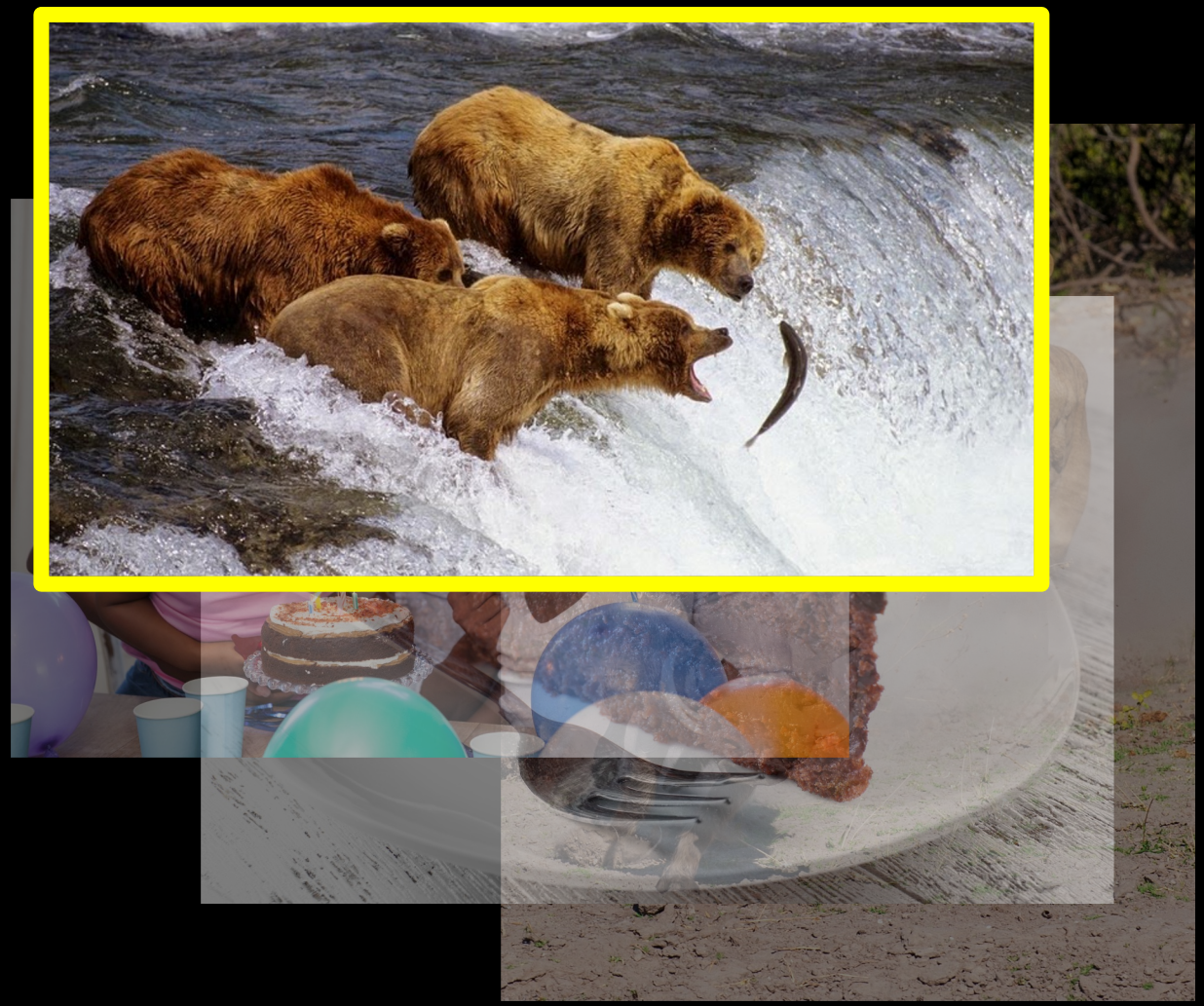
2. Hyper- Memorized

Memory/Learning Areas:

Hipp: **Hippocampus**
- memory formation

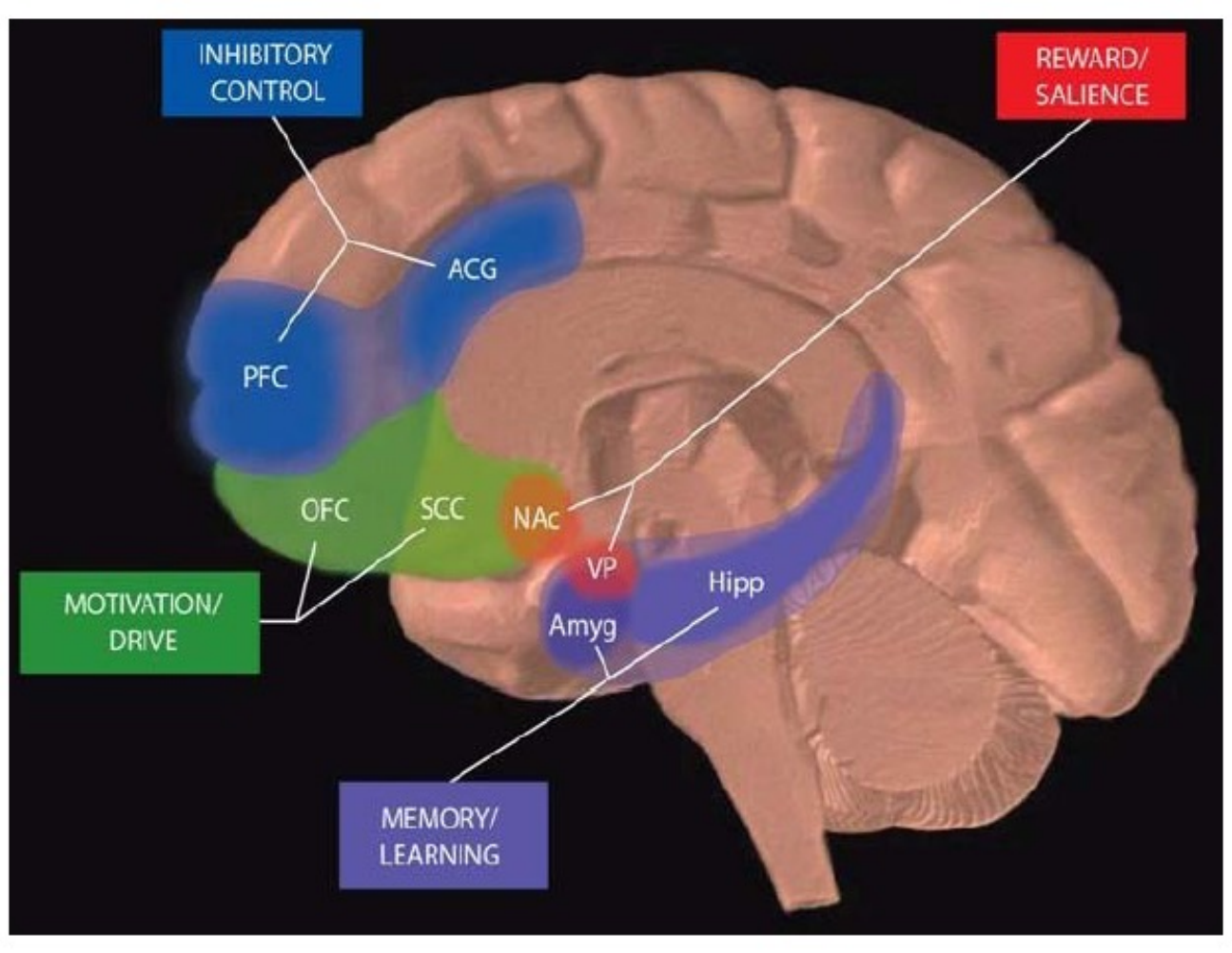
Amyg: **Amygdala**
- fear conditioning
- early emotion

What goes into a pleasurable experience?



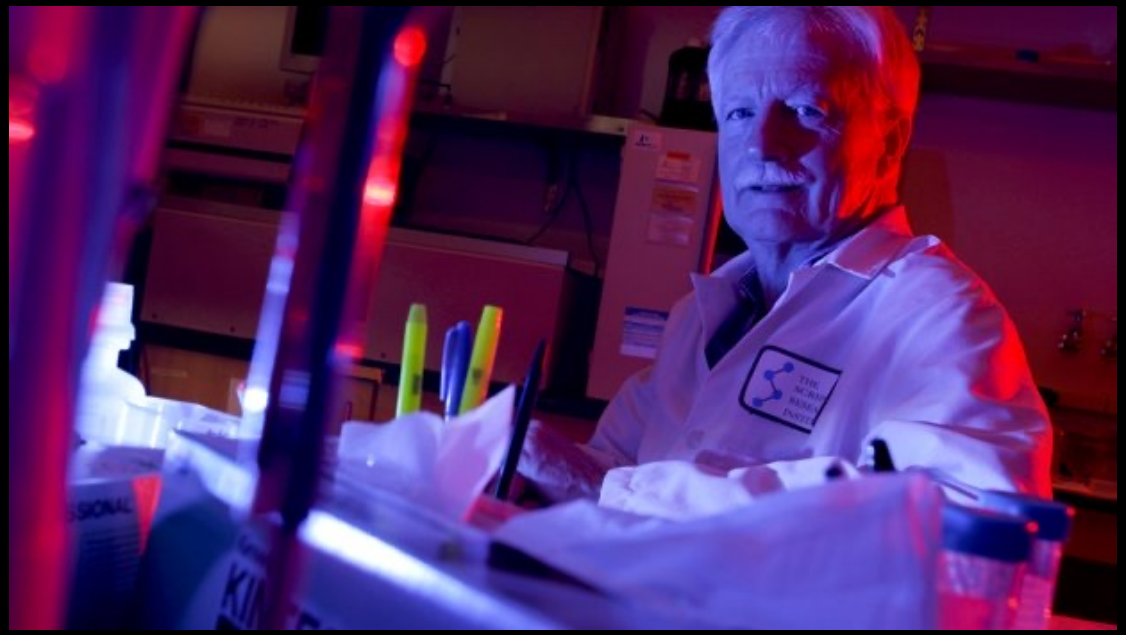
- Cake stops hunger
- Memory of past cakes
- Memory of this cake
- Cake tastes good
- Cake ensures survival

Addiction is a disorder of …



5. CHOICE	OFC, ACC, PFC, IC
4. STRESS	**HPA axis**
3. MEMORY	glutamate
	synaptic remodeling
2. REWARD	dopamine
	dopamine receptors
1. GENES	polymorphisms
	epigenetic changes

Hedonic Allostasis Theory (Koob & LeMoal)

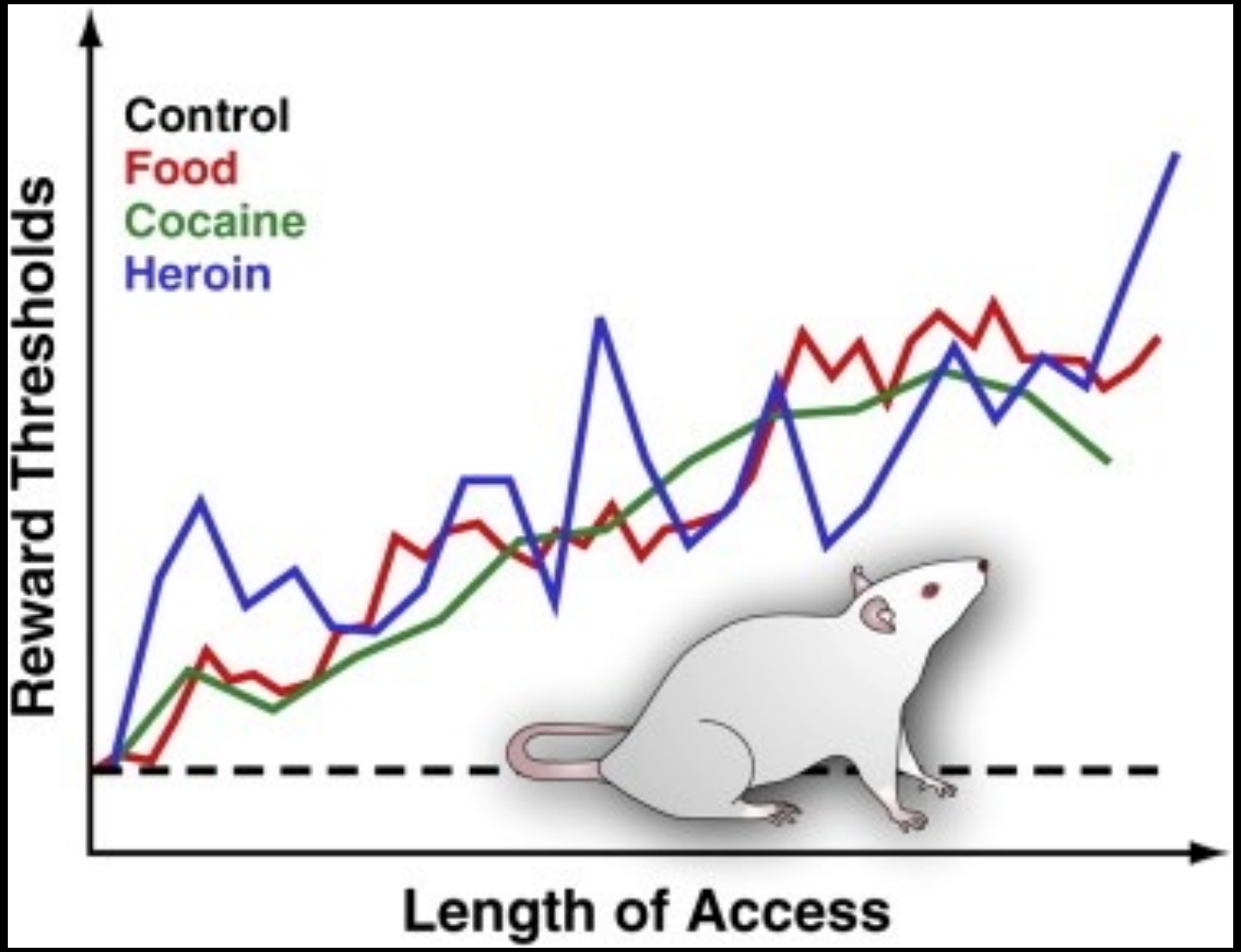


George Koob, PhD
Chair, Neurobiology of Addictive Disorders
Scripps Neurosciences Institute

- With continued drug use and withdrawal, the "anti-reward" system is recruited to counter-balance excess Dopamine using the stress hormone CRF
- Brain is unable to maintain normal "homeostasis"
- So the brain reverts to "allostasis" - change of the hedonic "set point" under stress in an attempt to maintain stability
- The result is anhedonia – an inability to find pleasure in normally pleasurable activities

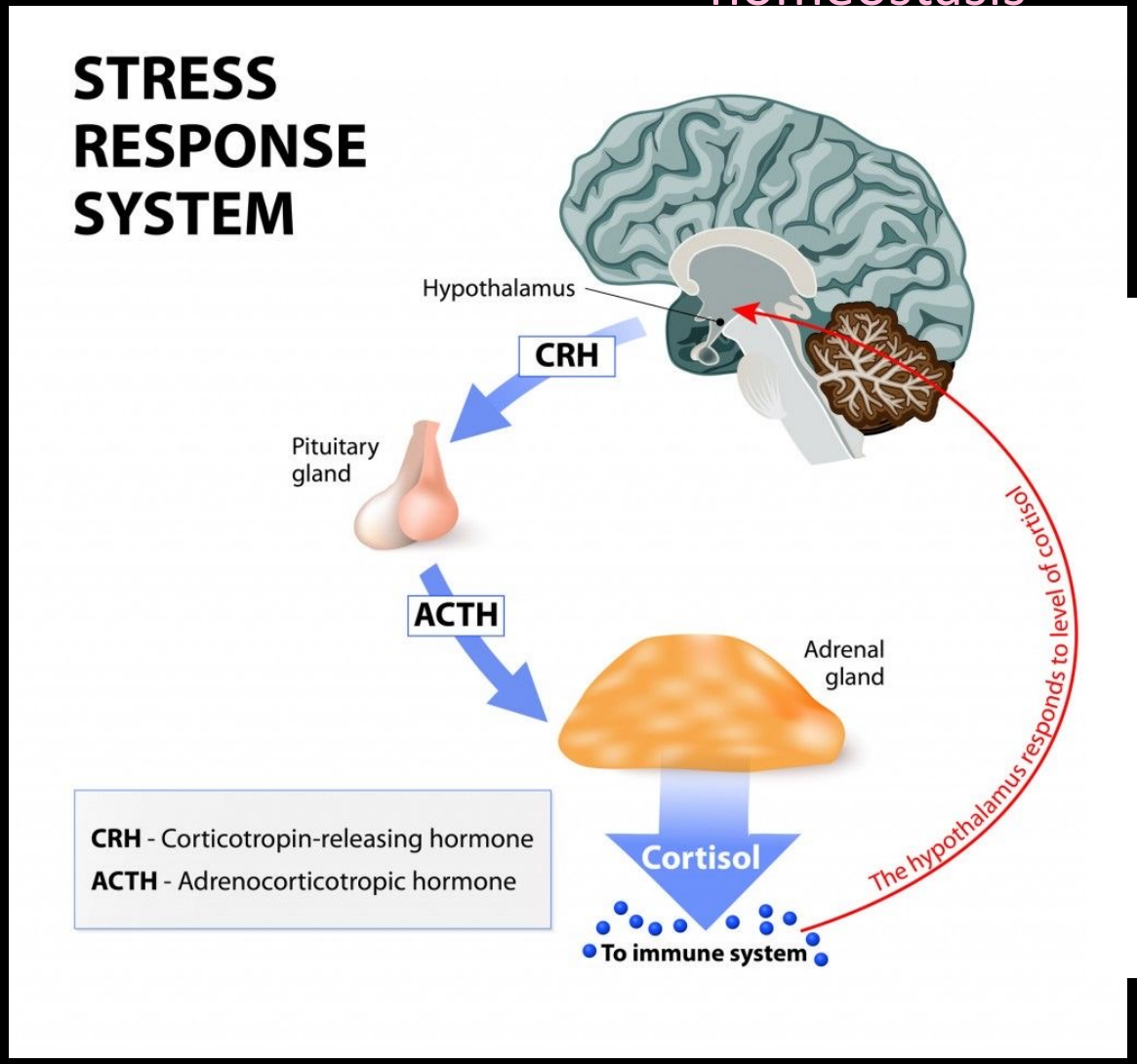
A-process:

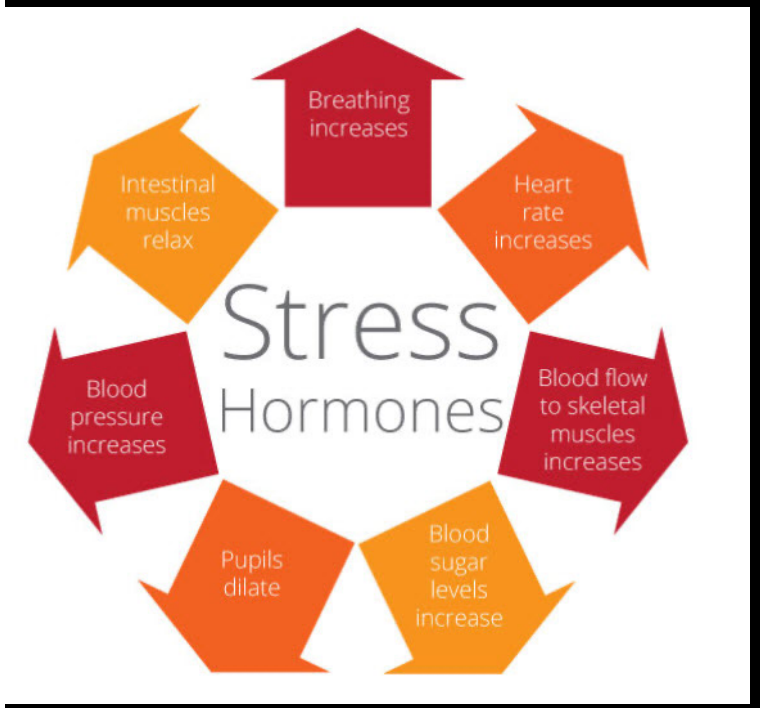
drugs activate brain circuits that elicit pleasurable emotional states (reward) …

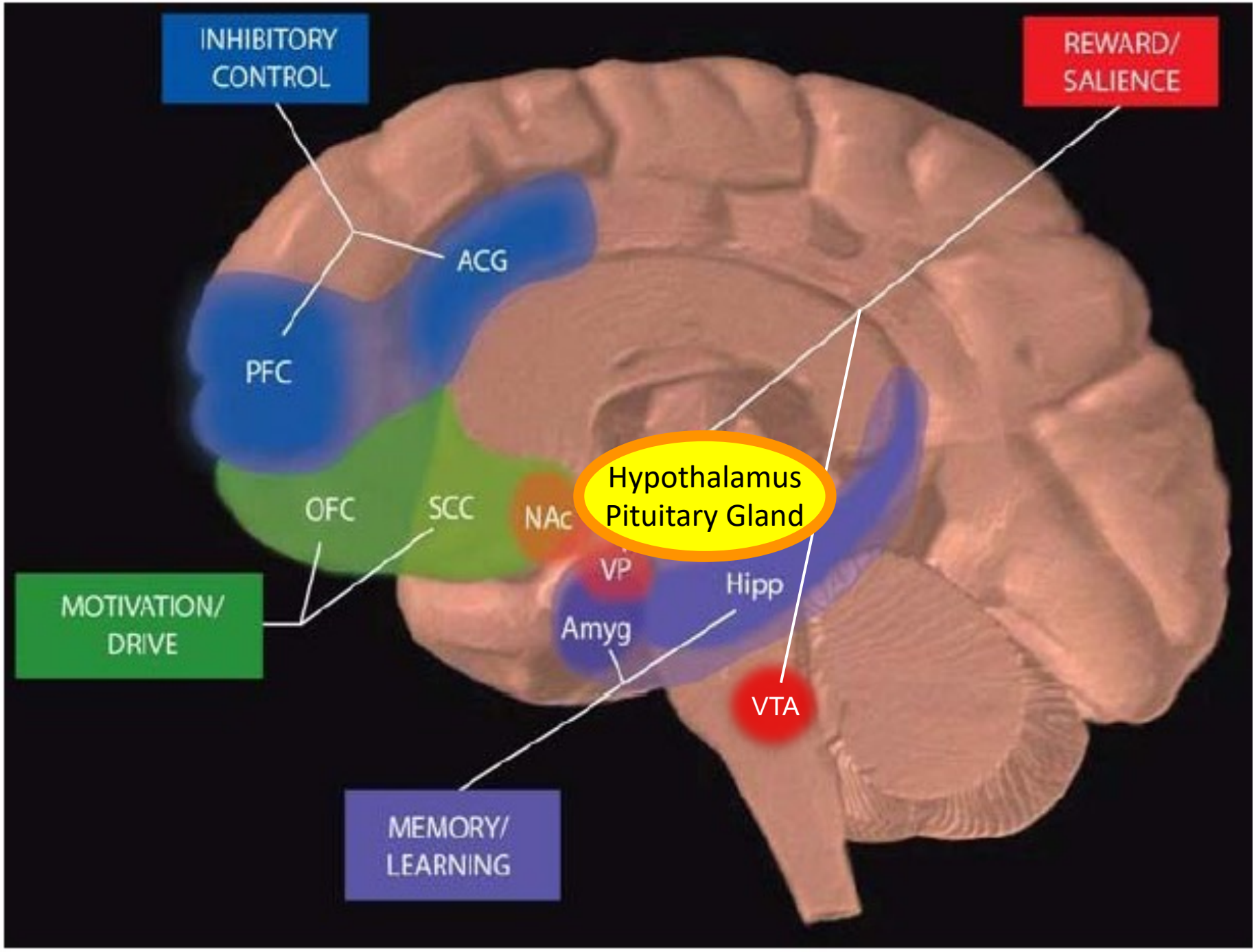


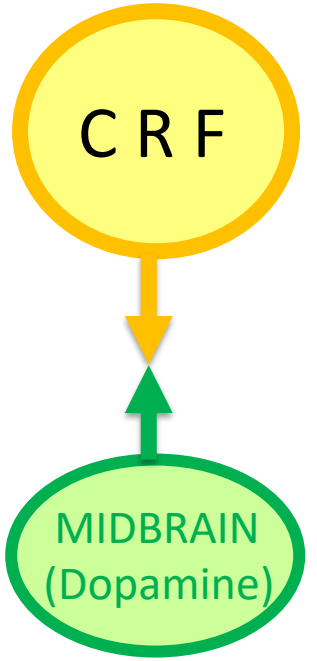
B-process:

… triggering counter-regulatory stress hormones to restore affective/emotional homeostasis

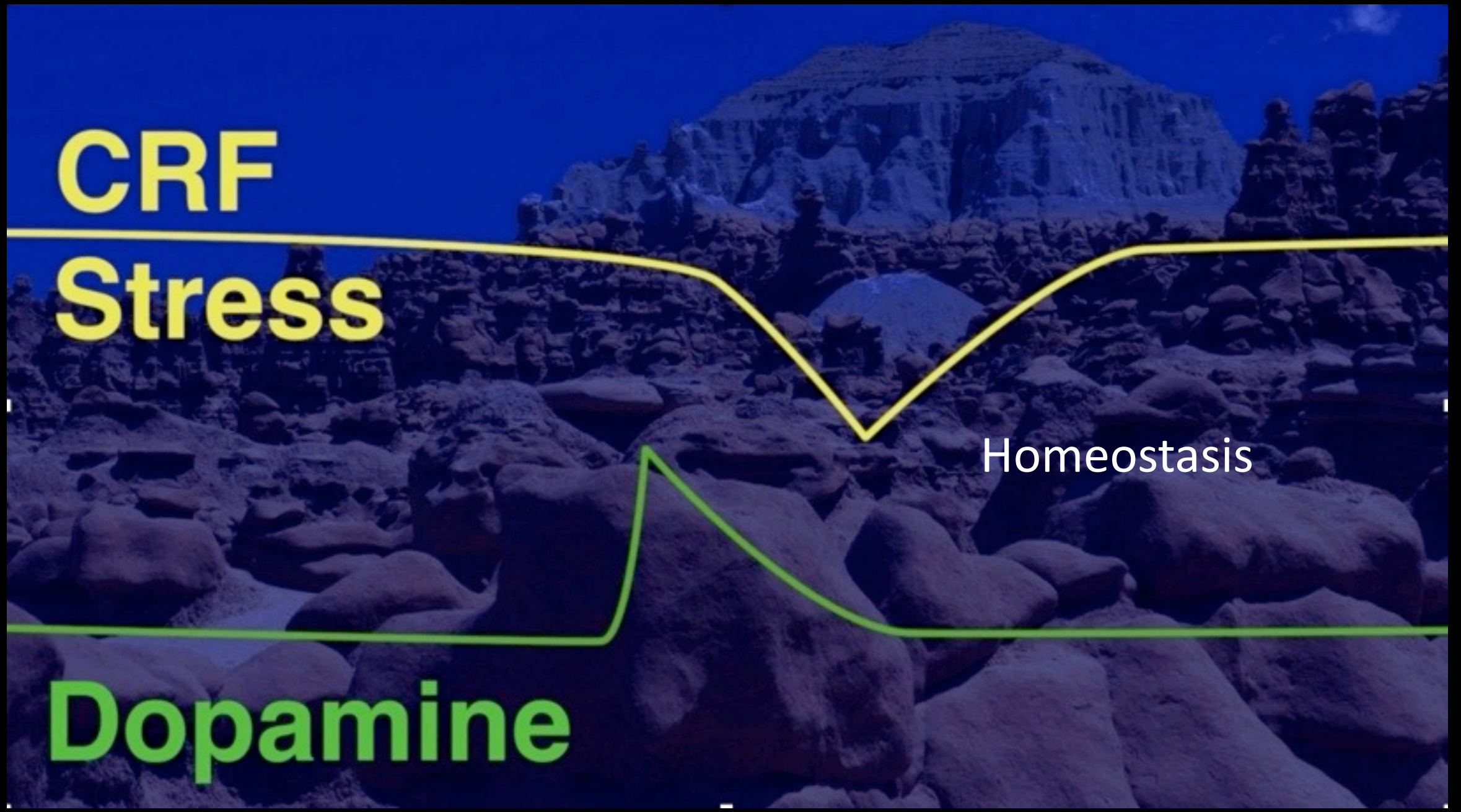


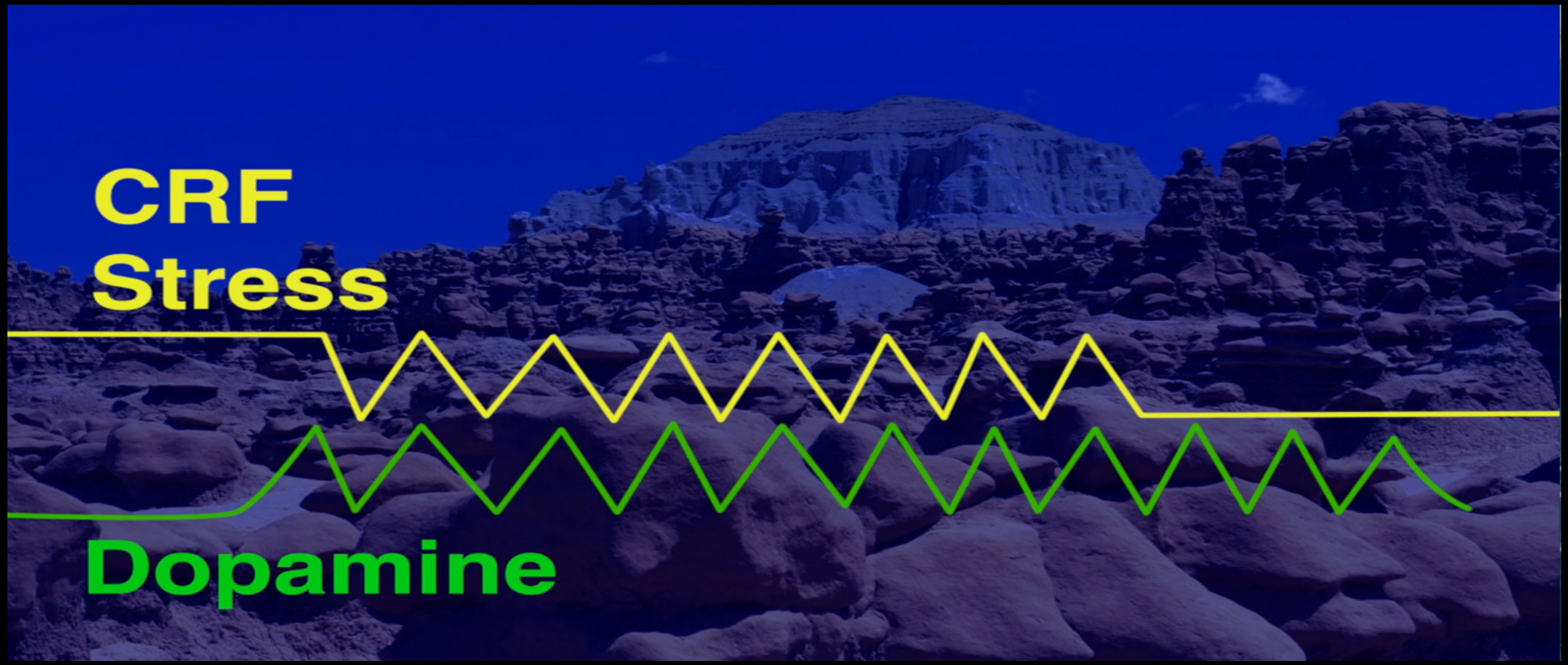




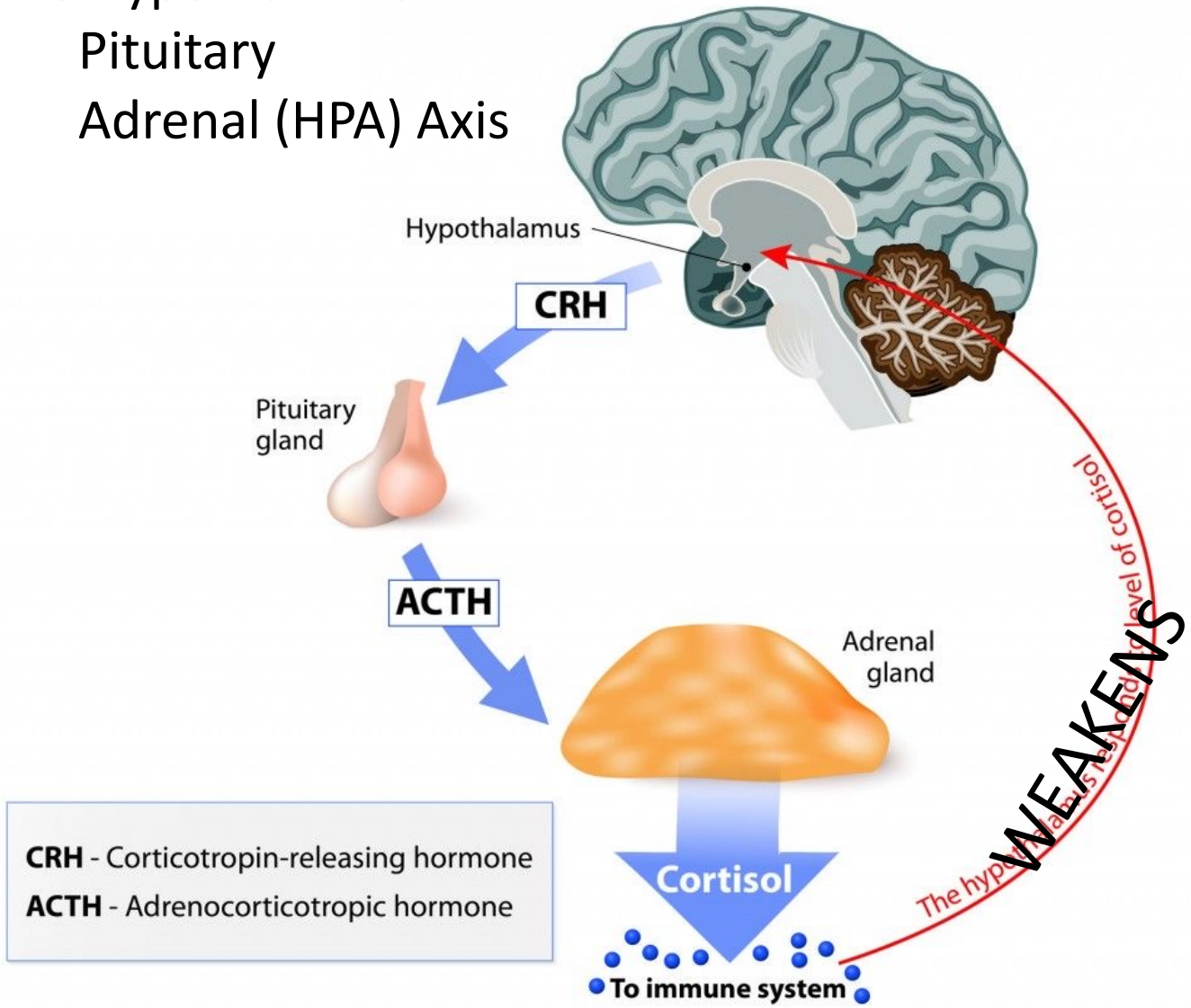


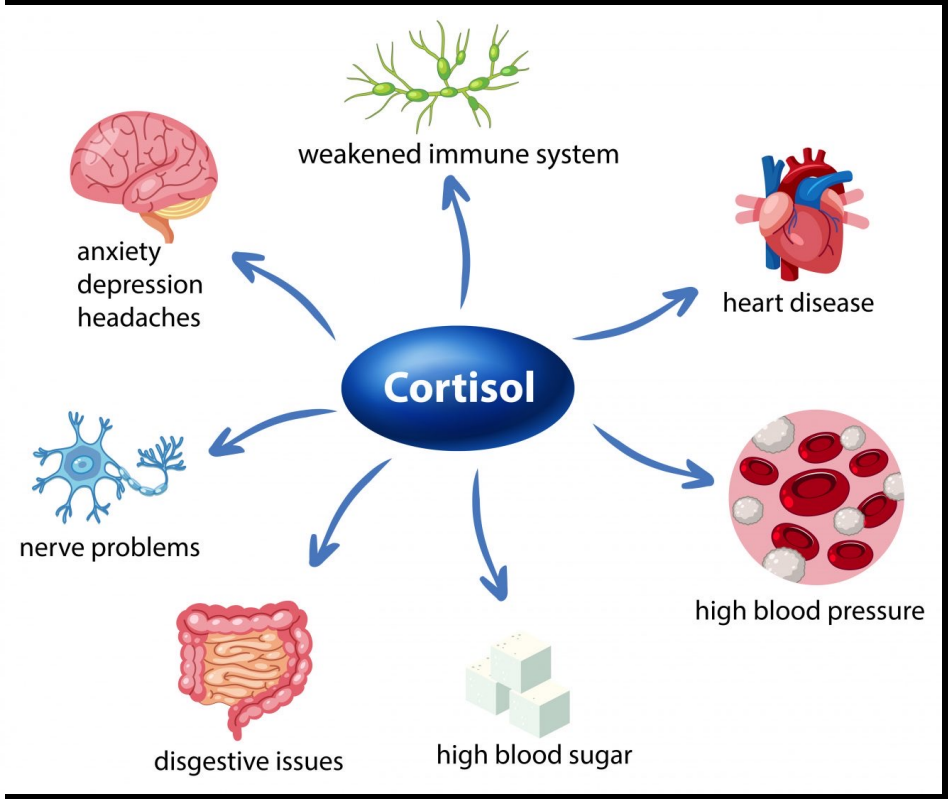
Stress Areas:
Hypothalamus
Pituitary
Adrenal
Axis

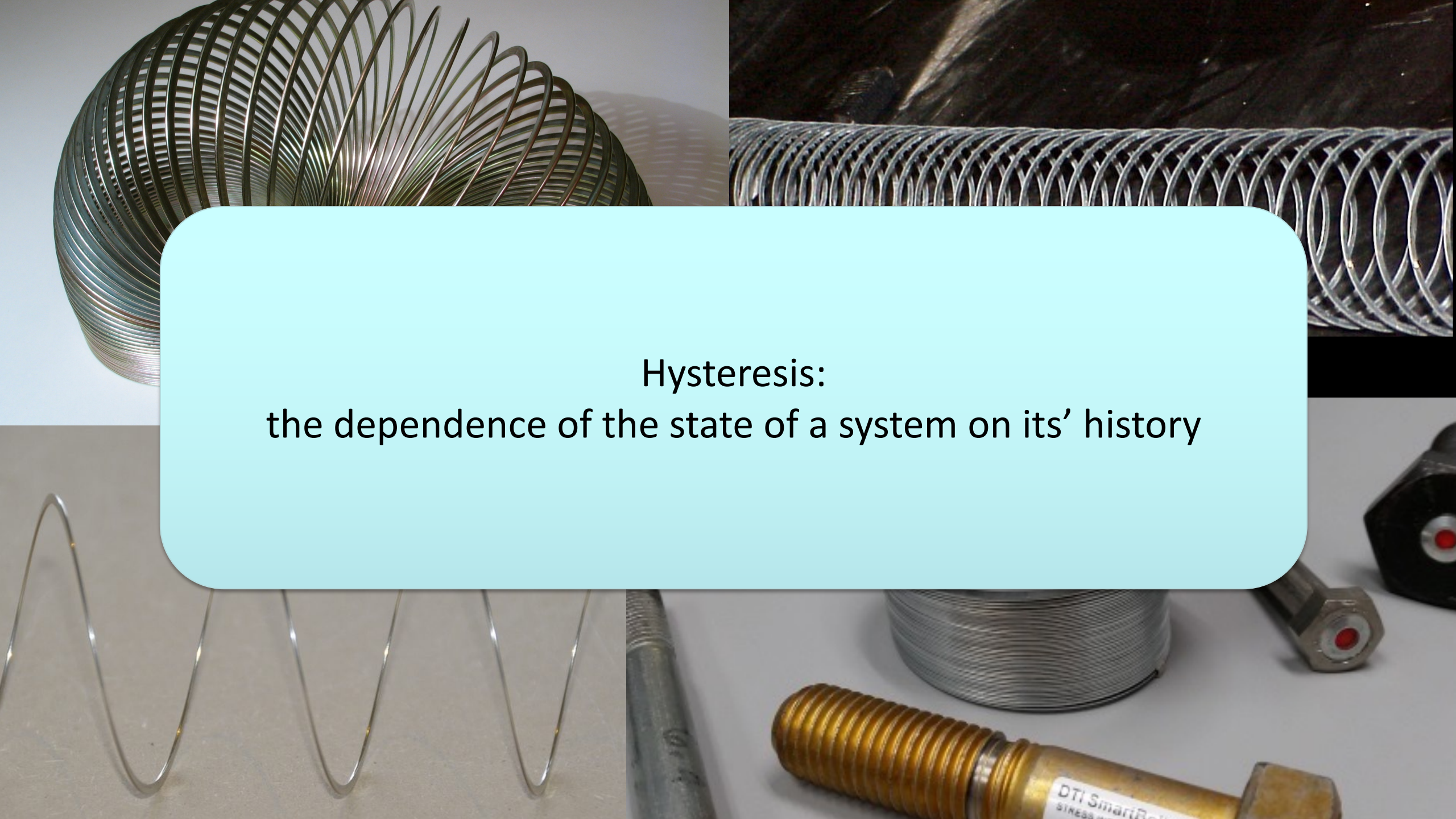

CRF
Stress
Homeostasis
Dopamine


CRF
Stress
Dopamine

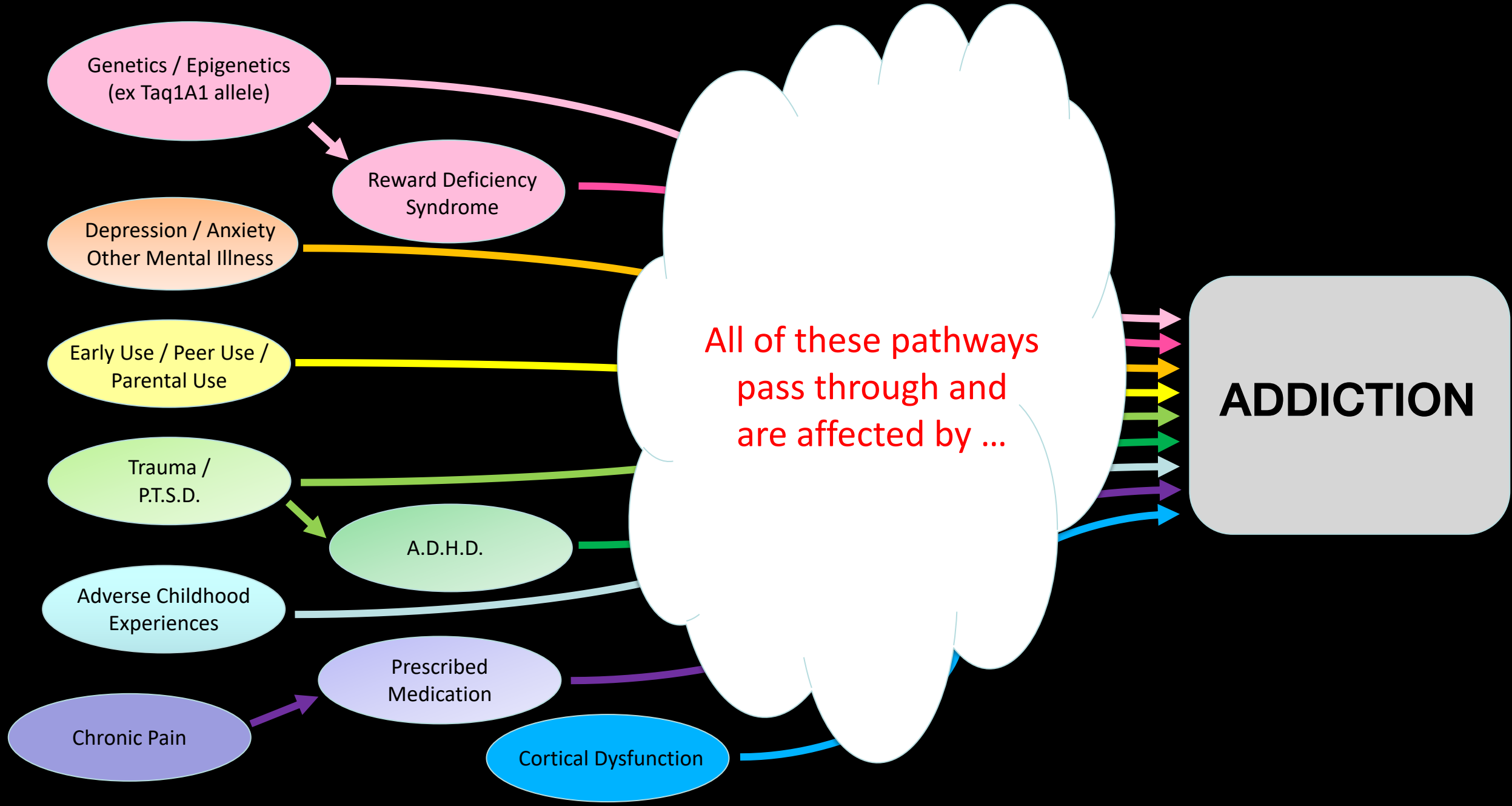
The Hypothalamic
Pituitary
Adrenal (HPA) Axis

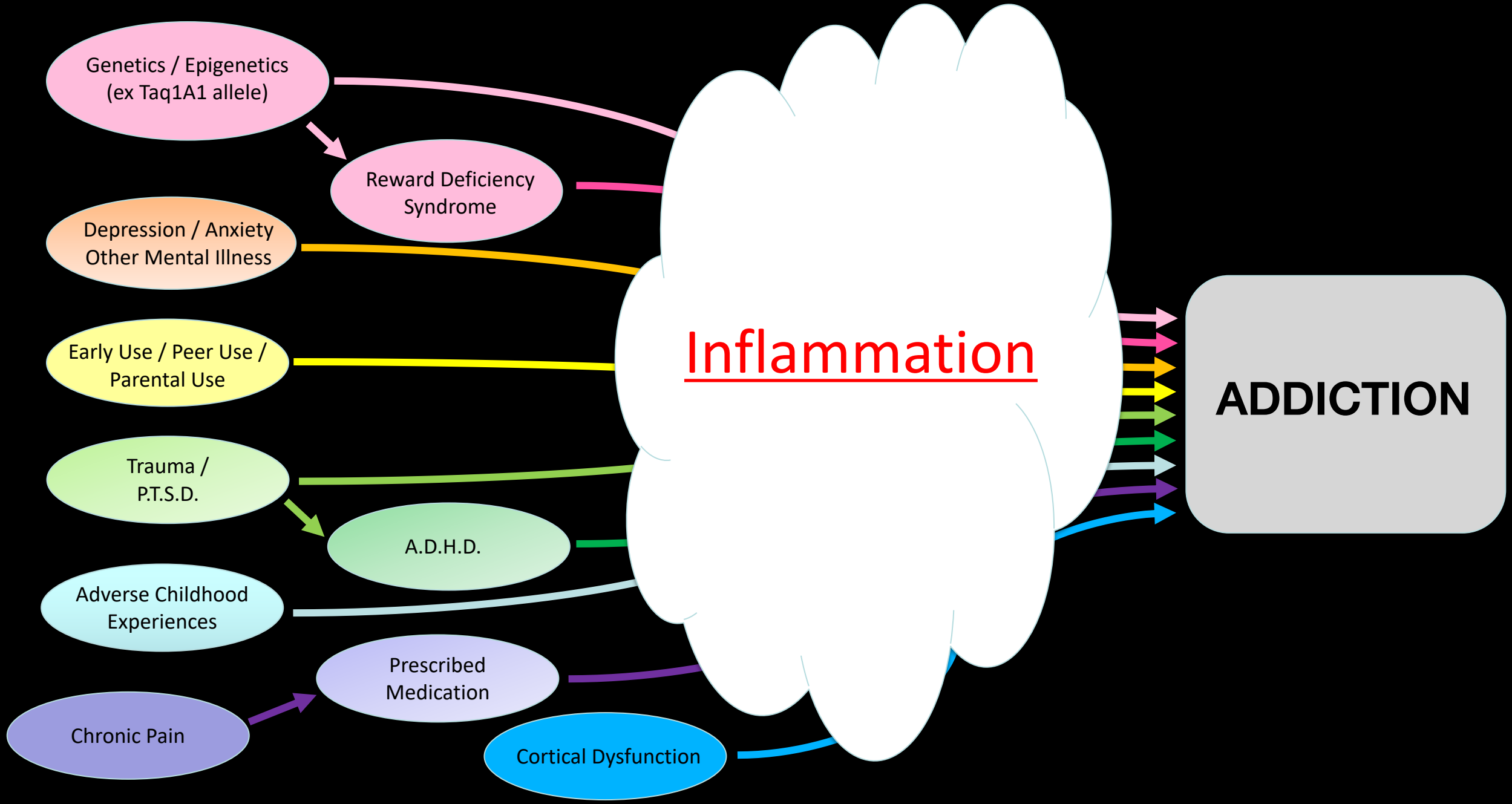


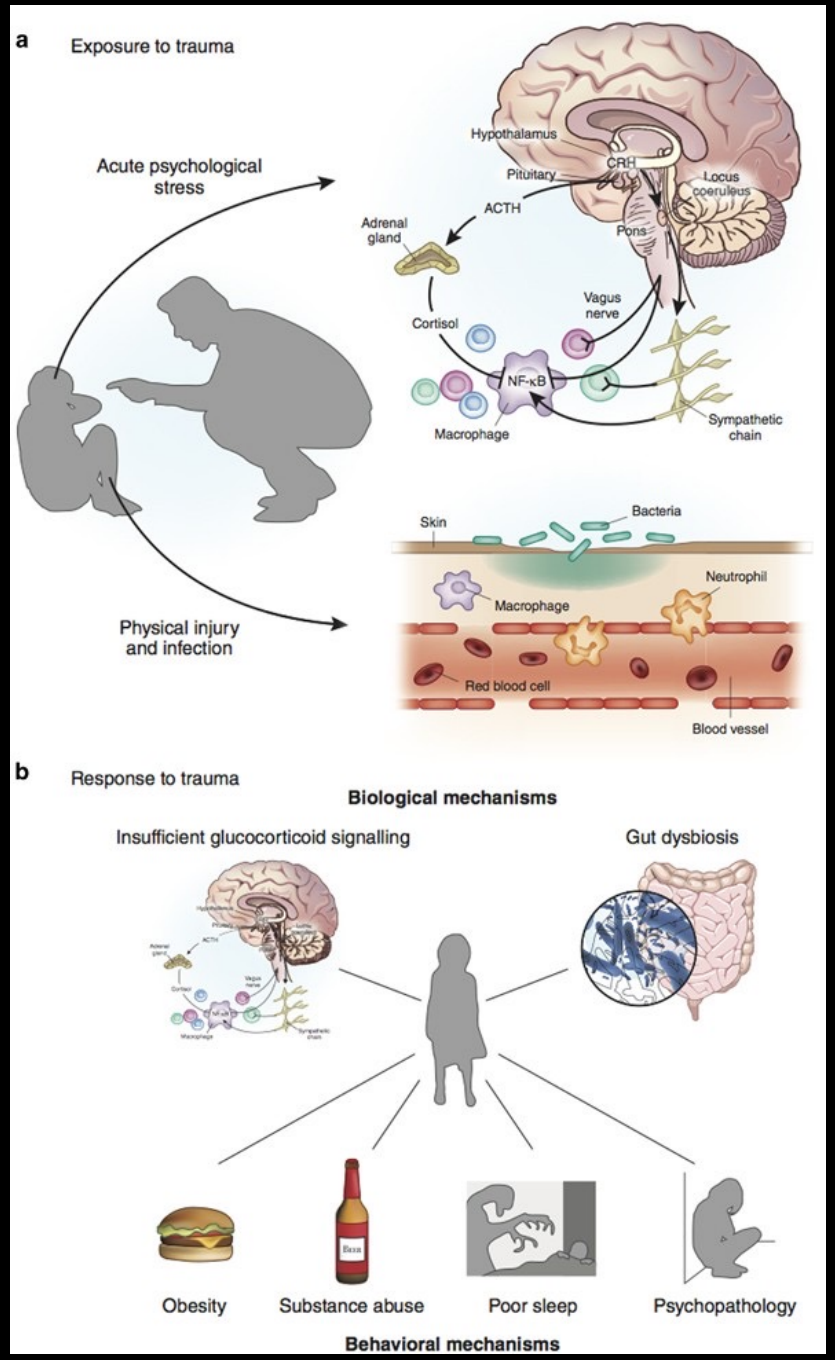




Hysteresis:
the dependence of the state of a system on its' history


Genetics / Epigenetics
(ex Taq1A1 allele)
Reward Deficiency
Syndrome
Depression / Anxiety
Other Mental Illness
Early Use / Peer Use /
Parental Use
Trauma /
P.T.S.D.
A.D.H.D.
Adverse Childhood
Experiences
Prescribed
Medication
Chronic Pain
Cortical Dysfunction
All of these pathways
pass through and
are affected by …
ADDICTION


Genetics / Epigenetics
(ex Taq1A1 allele)
Reward Deficiency
Syndrome
Depression / Anxiety
Other Mental Illness
Early Use / Peer Use /
Parental Use
Trauma /
P.T.S.D.
A.D.H.D.
Adverse Childhood
Experiences
Prescribed
Medication
Chronic Pain
Cortical Dysfunction
Inflammation
ADDICTION



Psycho-neuro-immunology

- A way to understand how stress and trauma cause mental illness through the immune system
- The Immune-Brain Loop: immune system is in constant communication with the brain; the immune system is a stress receptor for the brain
- CNS neurons terminate in thymus and spleen near clusters of lymphocytes and macrophages
- Adler & Cohen (1975): conditioned rats to drink saccharin water & Cytoxan (an immunosuppressant drug that tastes bad); later when they drank saccharin water the rats died of infection (immunosuppression in the absence of Cytoxan)
- Visintainer (1983): inescapable tail shock associated with decreased lymphocyte proliferation and decreased tumor rejection

Danese, A., & J Lewis, S. (2017). Psychoneuroimmunology of Early-Life Stress: The Hidden Wounds of Childhood Trauma?. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 42(1), 99–114. https://doi.org/10.1038/npp.2016.198

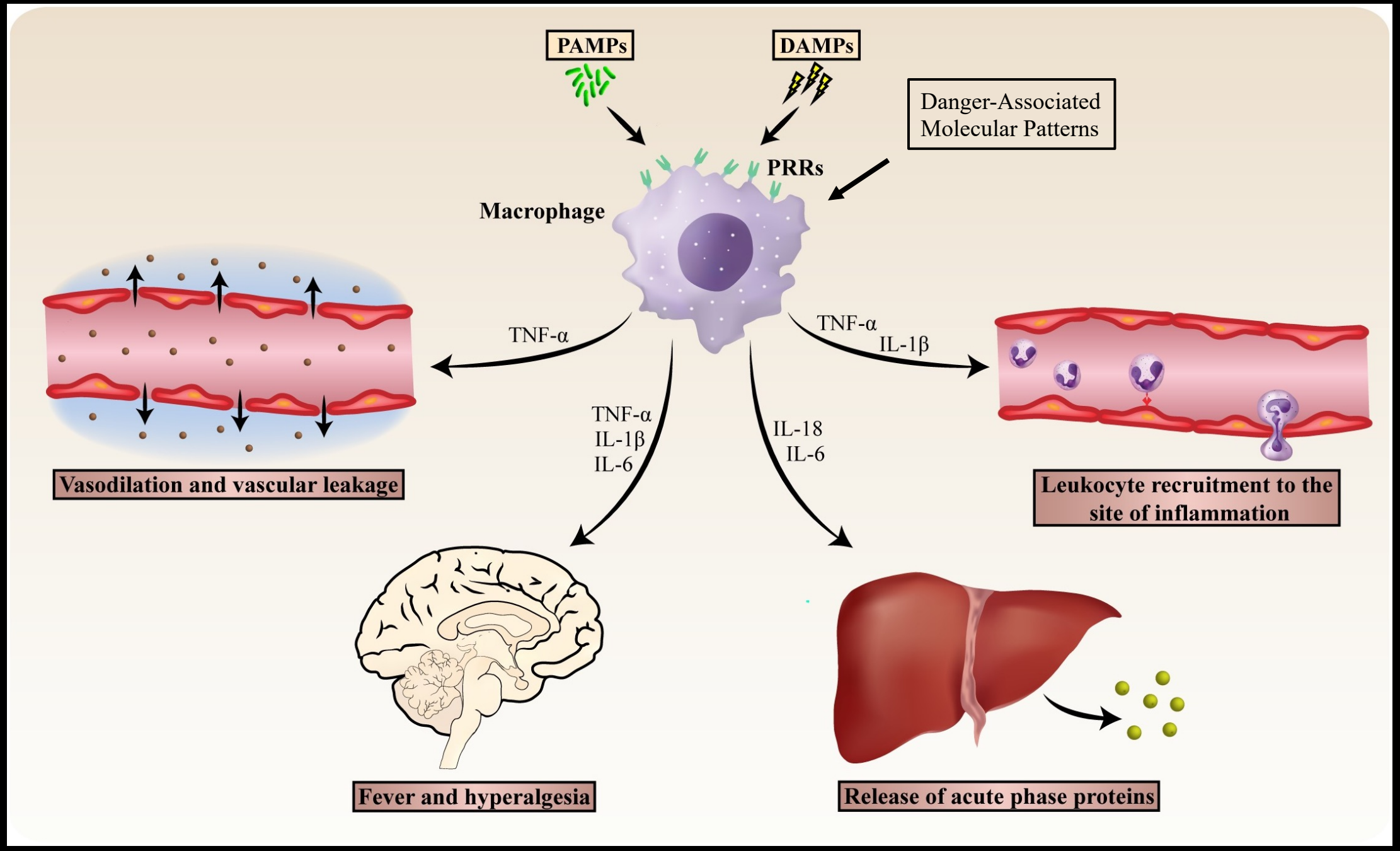
Two Parts of the Immune System

INNATE IMMUNE RESPONSE

- Present at birth
- Non-specific: just kills everything
- “Feverishly fast” (works in minutes)
- NO memory – reacts same way each time it encounters a specific threat
- Also includes barrier protection

  physical – epithelium, cilia

  chemical – low pH (stomach), lysosomes (tears)


PAMPs
DAMPs
Danger-Associated Molecular Patterns
PRRs
Macrophage
TNF-α
TNF-α
IL-1β
TNF-α
IL-1β
IL-6
IL-18
IL-6
Vasodilation and vascular leakage
Leukocyte recruitment to the site of inflammation
Fever and hyperalgesia
Release of acute phase proteins

Inflammation: Innate Immune Response

- Resident Immune Cells: macrophages, dendritic cells, mast cells, Kupfer Cells
- Pattern Recognition Receptors: Pathogen-Associated Molecular Patterns (PAMPs)
  Damage-Associated Molecular Patterns (DAMPs)
- Resident Immune Cells activate and release chemical mediators (cytokines)
- INFLAMMATION
- rubor (redness) - vasodilation (↑ blood flow)
- calor (heat) - ↑ metabolism (immune system works better at higher temps)
- tumor (swelling) - ↑ blood vessel permeability (more leaky) → exudation of plasma proteins → edema (WBCs follow)
- dolor (pain) – release of pain mediators: PGE2 and bradykinin → hyperalgesia (protection of further injury)

Two Parts of the Immune System

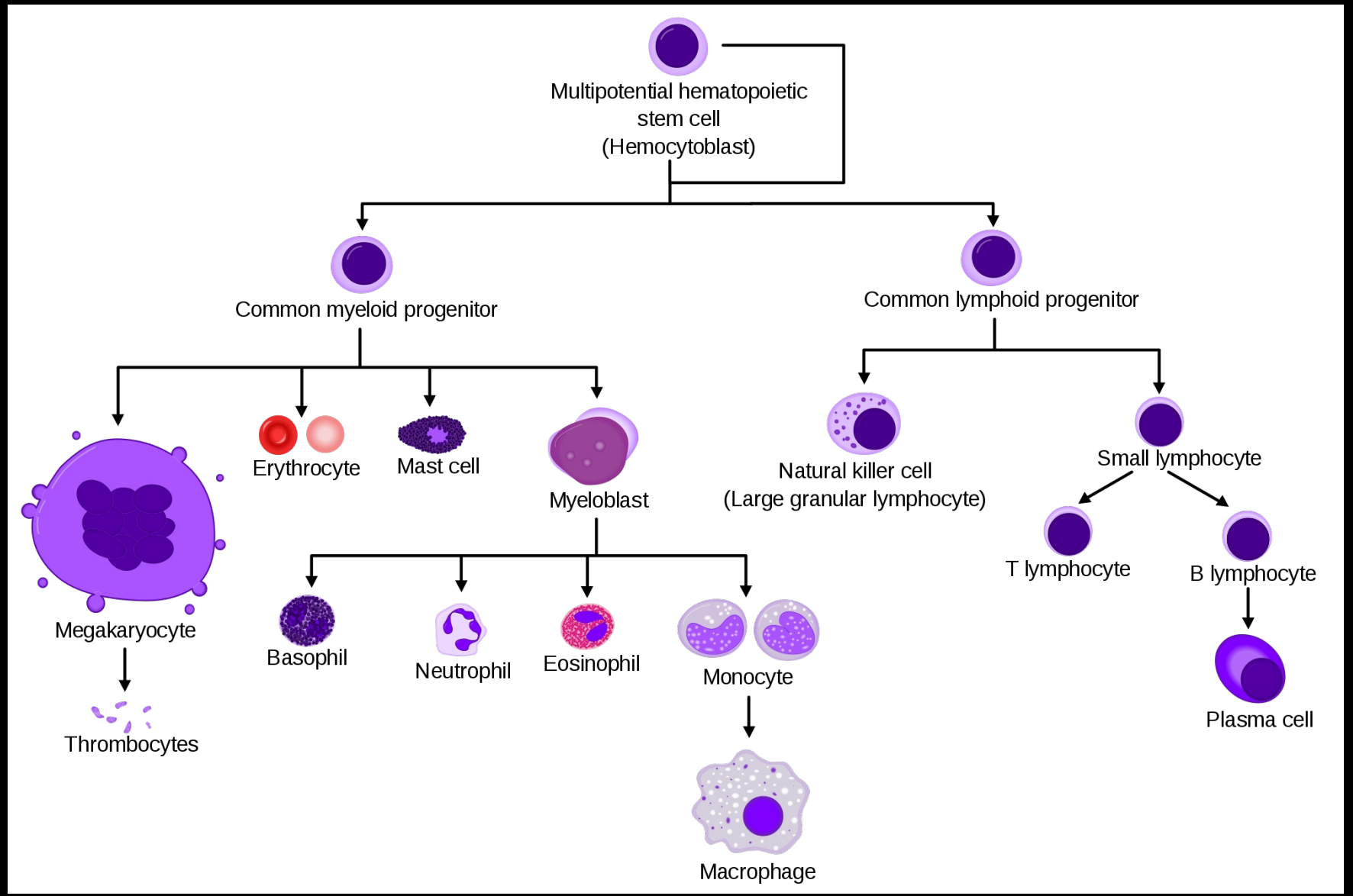
INNATE IMMUNE RESPONSE

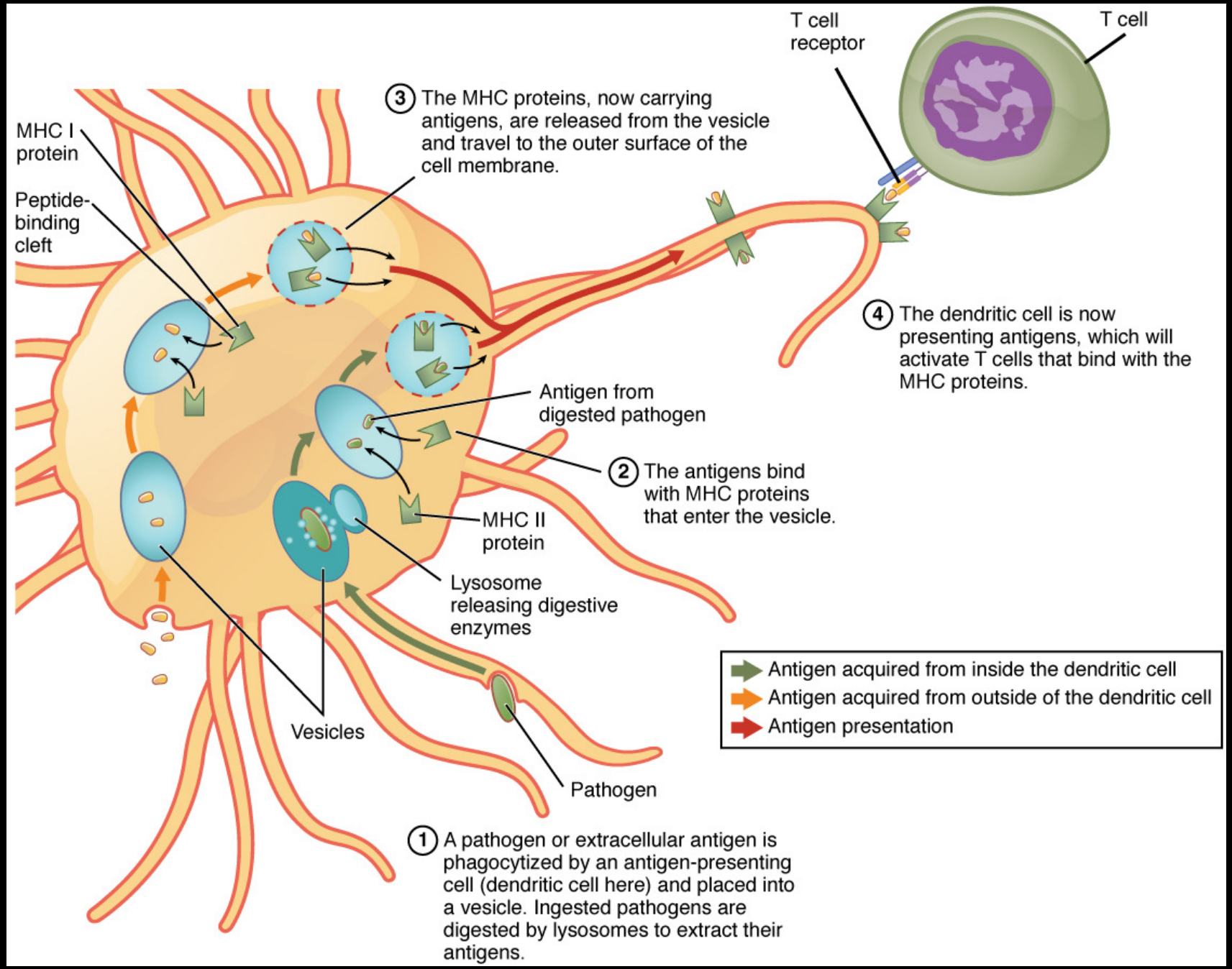
- Present at birth
- Non-specific: just kills everything
- “Feverishly fast” (works in minutes)
- NO memory – reacts same way each time it encounters a specific threat
- Also includes barrier protection
  - physical – epithelium, cilia
  - chemical – low pH (stomach), lysosomes (tears)

ADAPTIVE IMMUNE RESPONSE

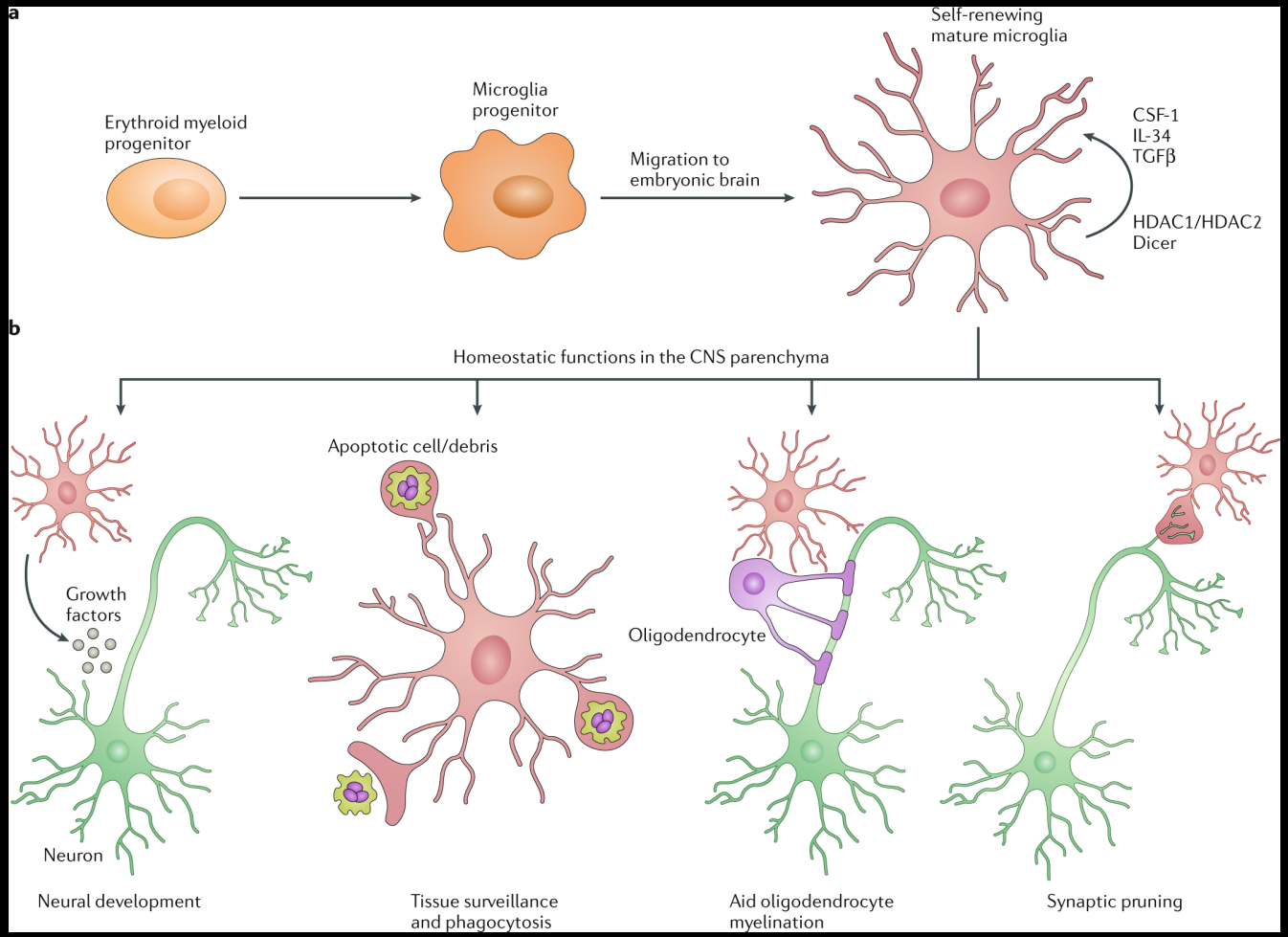
- Has to be “learned,” gains “maturity”
- Highly specific for each invader
- Takes weeks to respond
- Cells are activated and differentiate into needed forms
- Immunologic “memory” – once an adapted cell ”learns” an enemy it will remember it and undergo massive proliferation

Hematopoesis: making blood cells



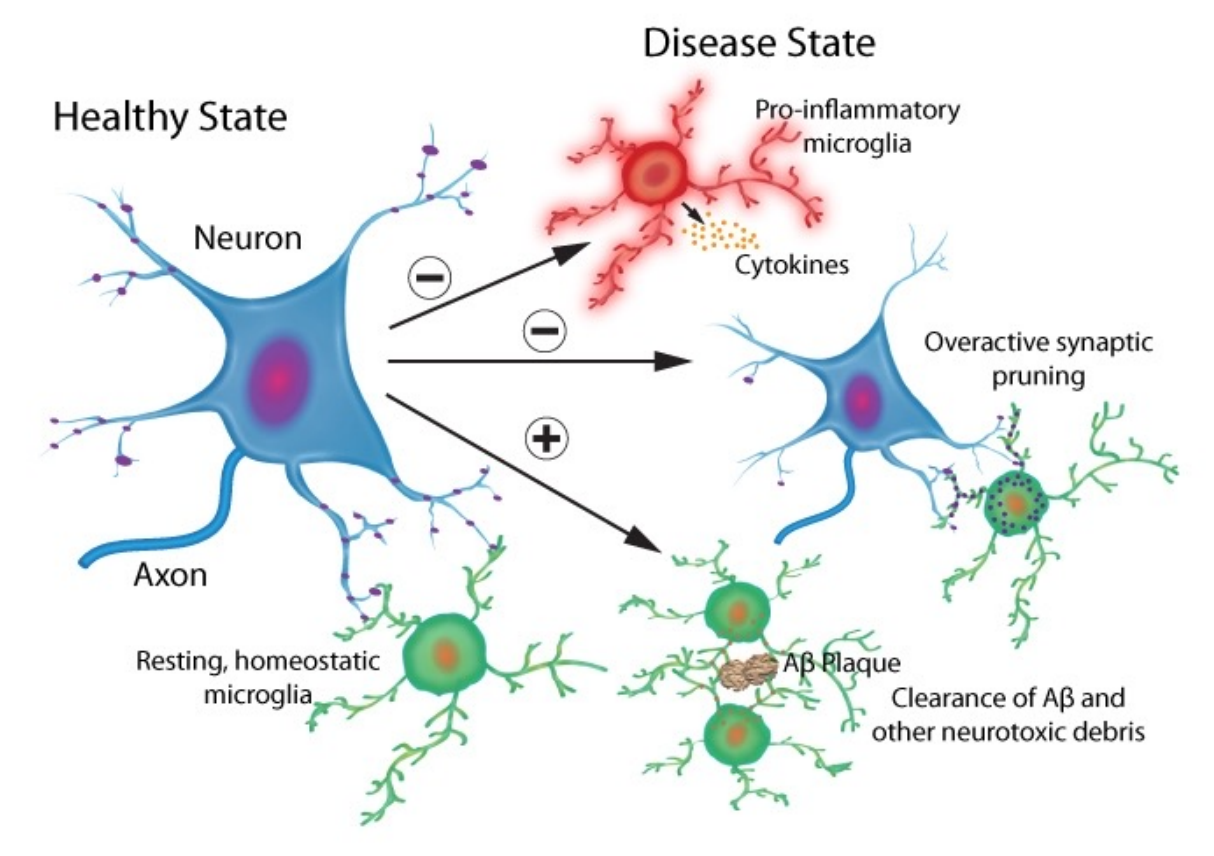

T cell receptor
T cell
3 The MHC proteins, now carrying antigens, are released from the vesicle and travel to the outer surface of the cell membrane.
MHC I protein
Peptide-binding cleft
4 The dendritic cell is now presenting antigens, which will activate T cells that bind with the MHC proteins.
Antigen from digested pathogen
2 The antigens bind with MHC proteins that enter the vesicle.
MHC II protein
Lysosome releasing digestive enzymes
Vesicles
Pathogen
Antigen acquired from inside the dendritic cell
Antigen acquired from outside of the dendritic cell
Antigen presentation
1 A pathogen or extracellular antigen is phagocytized by an antigen-presenting cell (dendritic cell here) and placed into a vesicle. Ingested pathogens are digested by lysosomes to extract their antigens.

Microglia

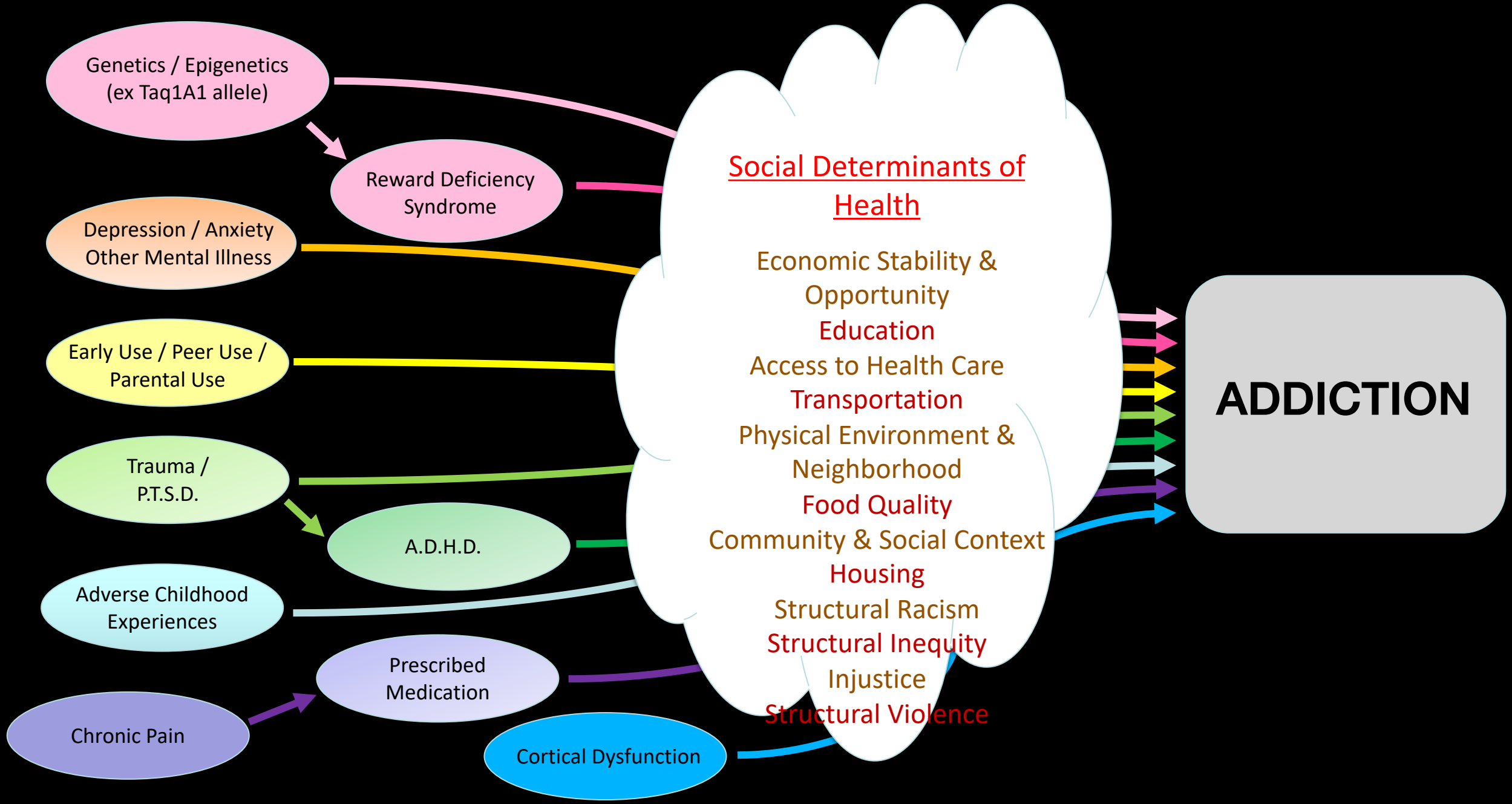


- Predominant immune cells of the CNS
- Cover a specific territory
- Usually in resting (ramified) state
- Secrete Brain-Derived Neurotrophic Factor (BDNF)
- Assist neuronal circuit remodeling across development (synaptic pruning)
- Responsible for CNS homeostasis and plasticity

Reactive Microgliosis: response to pathogen/injury



- Resting microglia: injury to brain > Reactive Microgliosis
- Microglia respond rapidly to stress and trauma
- Shift from ramified (resting) state to ameoboid (activated) state
- Microglia are very fast-moving cells (fastest in the brain: entire brain parenchyma scanned by microglia every few hours)
- Become macrophages > phagocytize pathogens and debris
- Antigen-presenting cell to T lymphocytes


Genetics / Epigenetics
(ex Taq1A1 allele)
Reward Deficiency Syndrome
Depression / Anxiety
Other Mental Illness
Early Use / Peer Use /
Parental Use
Trauma /
P.T.S.D.
A.D.H.D.
Adverse Childhood
Experiences
Prescribed
Medication
Chronic Pain
Cortical Dysfunction
Social Determinants of Health
Economic Stability &
Opportunity
Education
Access to Health Care
Transportation
Physical Environment &
Neighborhood
Food Quality
Community & Social Context
Housing
Structural Racism
Structural Inequity
Injustice
Structural Violence
ADDICTION

An Effective Recovery Management Plan

1. Treatment (Residential or IOP)	evidence-based treatment, enculturation
2. Therapist/Counselor/Coach	on-going f/u, advocacy, ROSC linkage
3. Recovery Residence	housing security, peer support
4. Mutual Support Groups	social connectedness, social narrative
5. Relapse Plan	contingency management
6. Testing	chronic disease monitoring, parity
7. Job/School/Future	educational / vocational opportunity
8. Addiction Medicine Specialist	access to longitudinal primary care
9. Medication	MAT, nicotine cessation, etc.
10. Hedonic Rehabilitation	community recreation & leisure activities

Cochrane Meta-analysis: Twelve-Step Facilitation for Alcohol Use Disorder

(Kelly, Abry, Ferri & Humphreys, 2020)

- Follow-up to Previous Cochrane publication
- AA/TSF was better than CBT and MET in facilitating continuous abstinence and AUD remission
- AA/TSF was at least as effective as CBT and MET in reducing intensity of drinking, alcohol-related consequences and severity of Alcohol Use Disorder
- AA/TSF reduced healthcare costs more than CBT, MET or IOP alone (by $10,000 per patient over two years)

John F Kelly, Alexandra Abry, Marica Ferri, Keith Humphreys, Alcoholics Anonymous and 12-Step Facilitation Treatments for Alcohol Use Disorder: A Distillation of a 2020 Cochrane Review for Clinicians and Policy Makers, Alcohol and Alcoholism, Volume 55, Issue 6, November 2020, Pages 641–651, https://doi.org/10.1093/alcalc/agaa050

Kevin McCauley, MD
kevin.mccauley@meadowsbh.com

The Meadows of Wickenburg
Meadows Behavioral Healthcare

www.protectingsobriety.com