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Wisconsin Collaborative of Treatment Professionals
FOR EDUCATION AND CAPACITY TRAINING

Weathering the Storm: The neurobiology of substance use and the maternal brain

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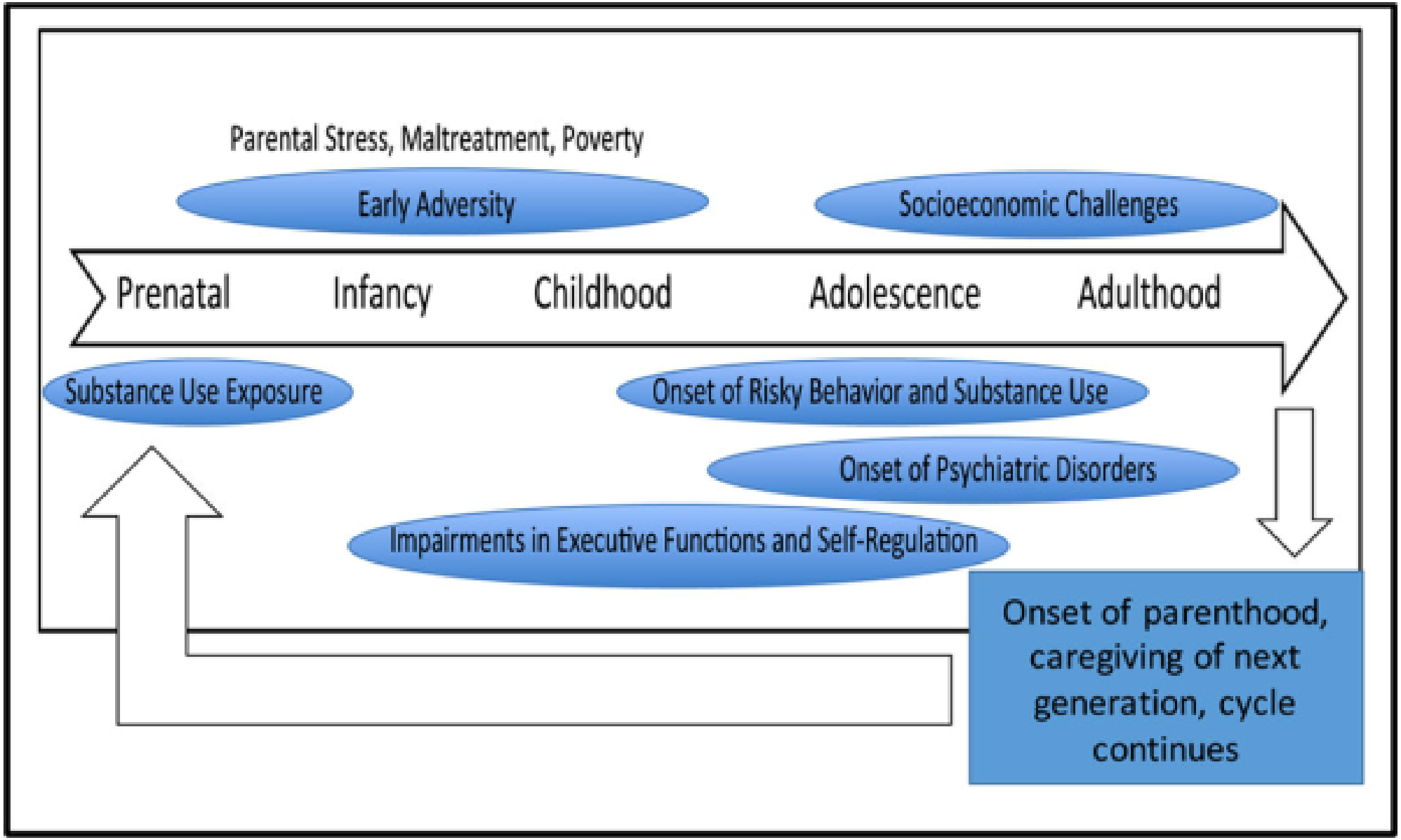
February 23, 2022

Objectives

- Describe the relationship between stress and substance use disorders.
- Describe two strategies for improving care of women with substance use disorders.

Introduction



Rutherford H and Mayes L, 2017

Addiction

Biology

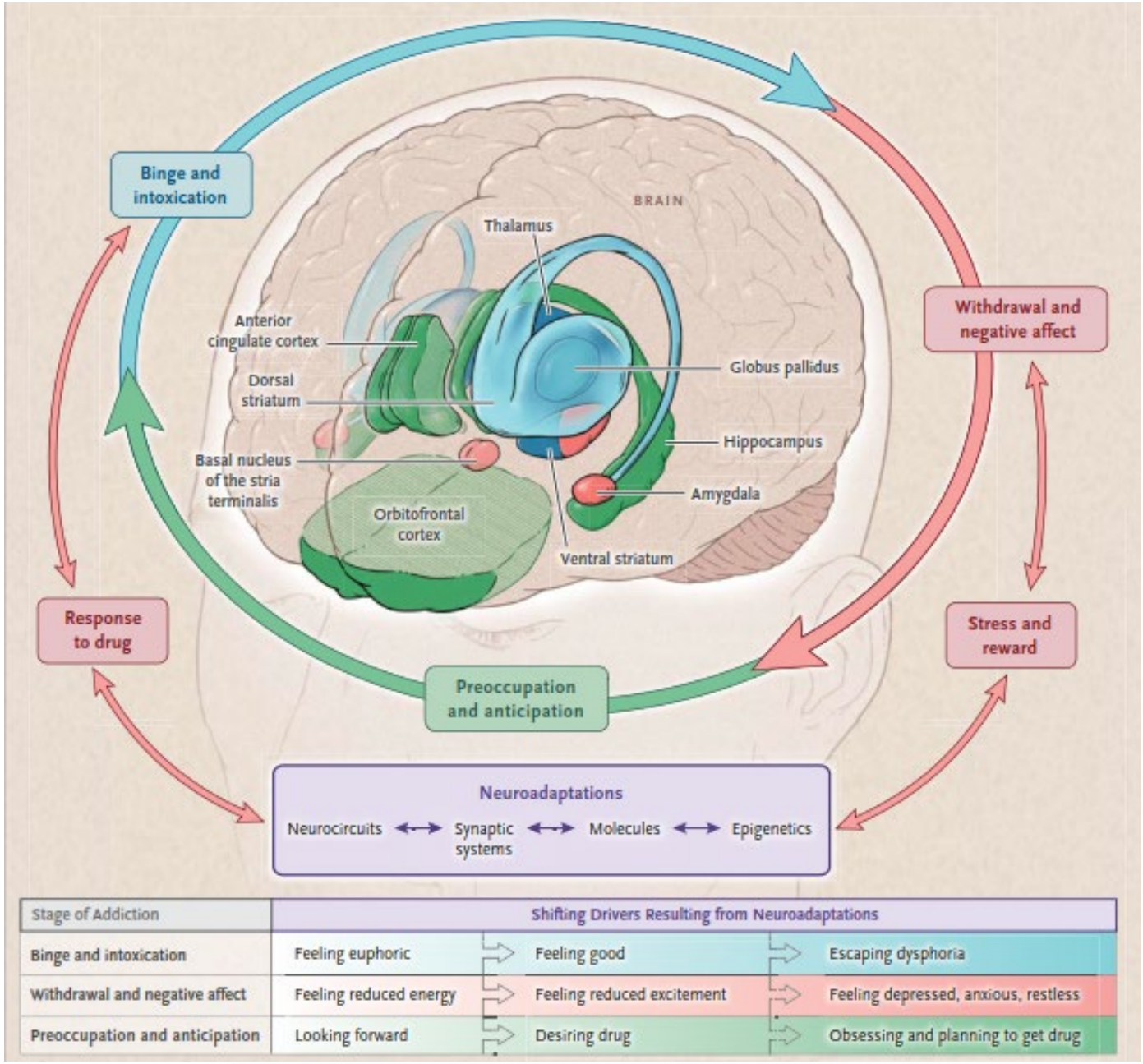
- Dopamine
  - Encodes motivation and reward
  - Other roles
    - Executive functioning
    - Motor planning
    - Sleep regulation
    - Food intake regulation
  - Addiction: a hypo-dopaminergic state with the reward circuit/pathway

Popescu et al. Exp Ther Med, 2021

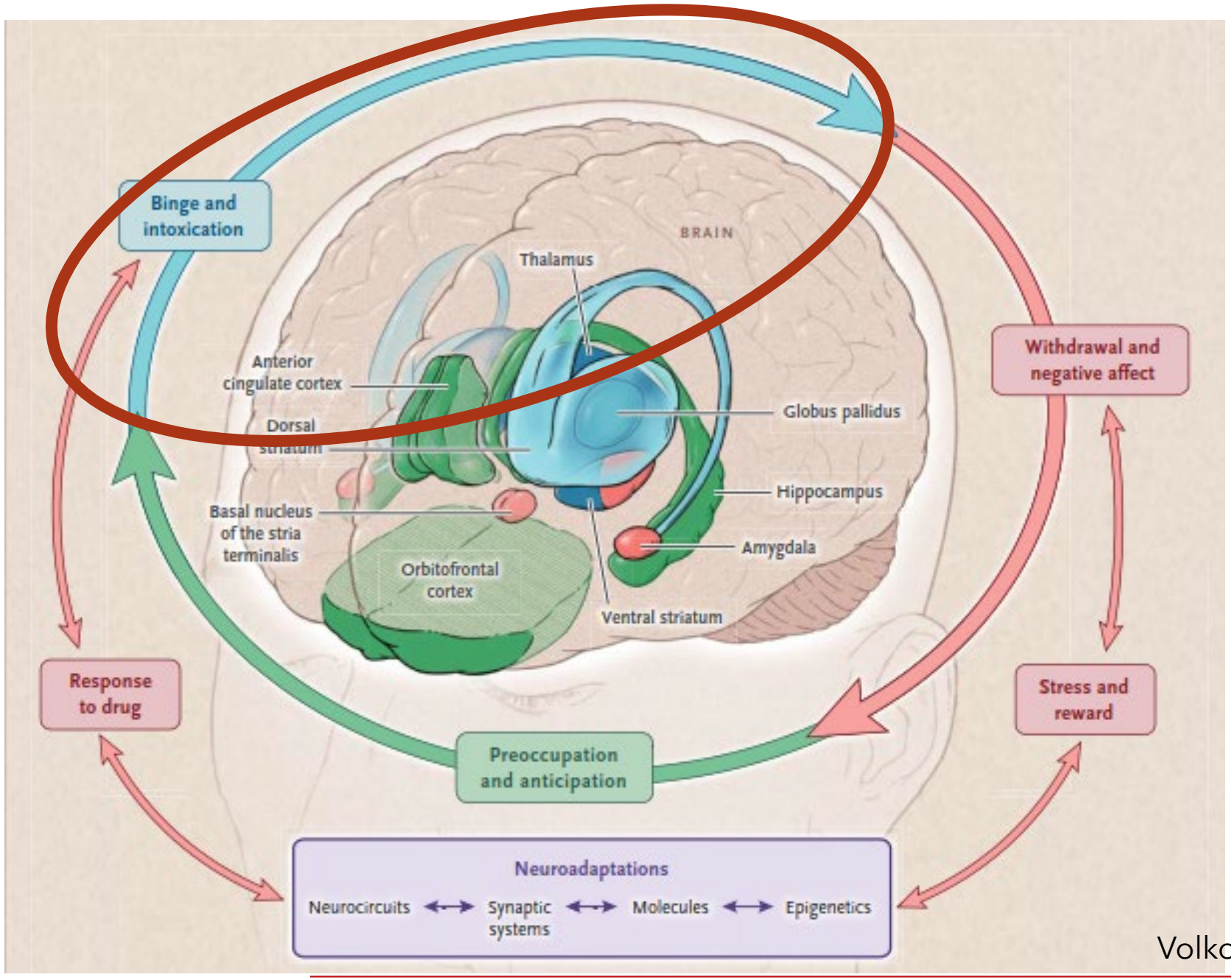
Biology

- Glutamate
  - The major mediator of excitatory signals and nervous system plasticity
  - Released extracellularly
  - Requires cellular uptake

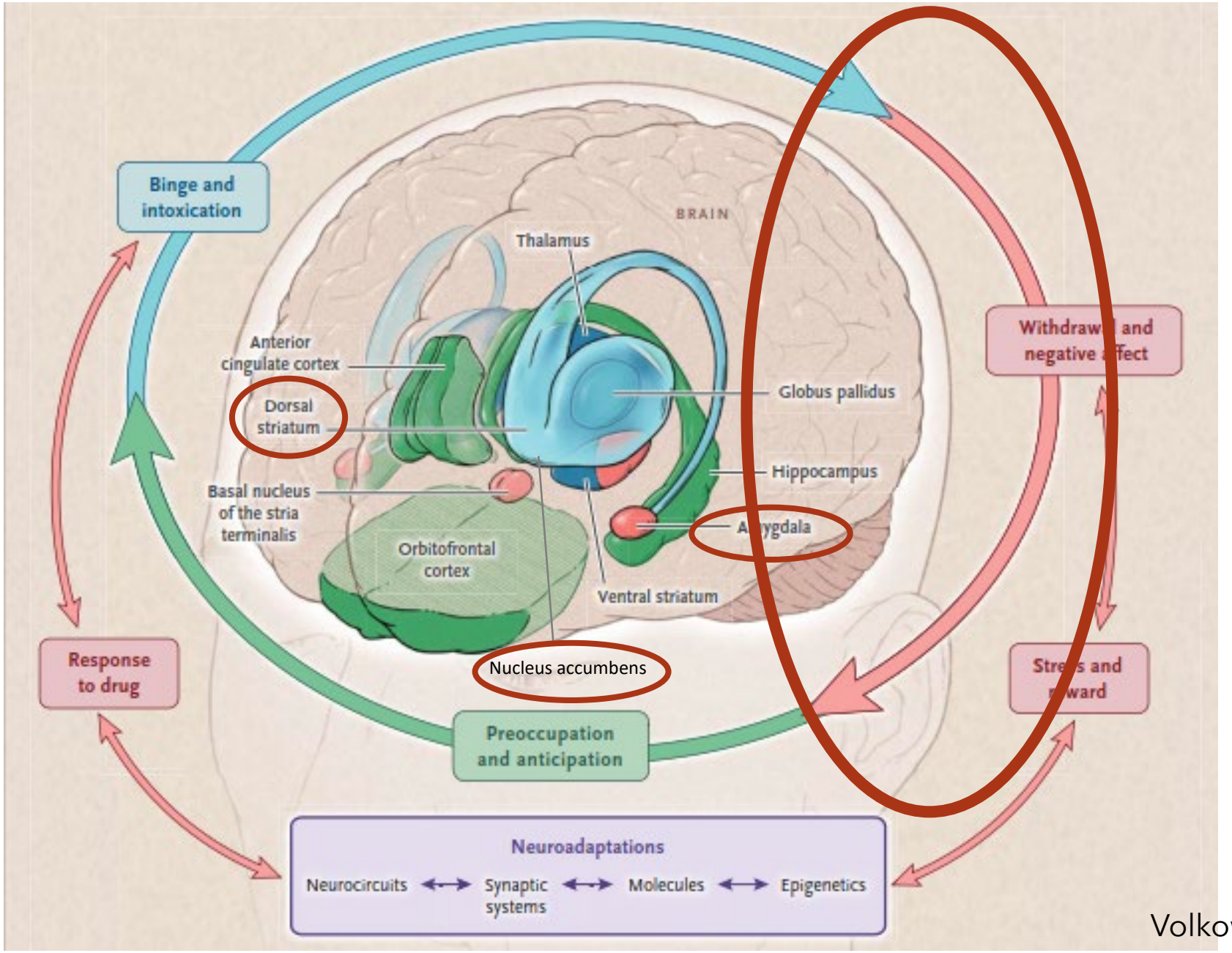
Zhou and Danbolt, 2014



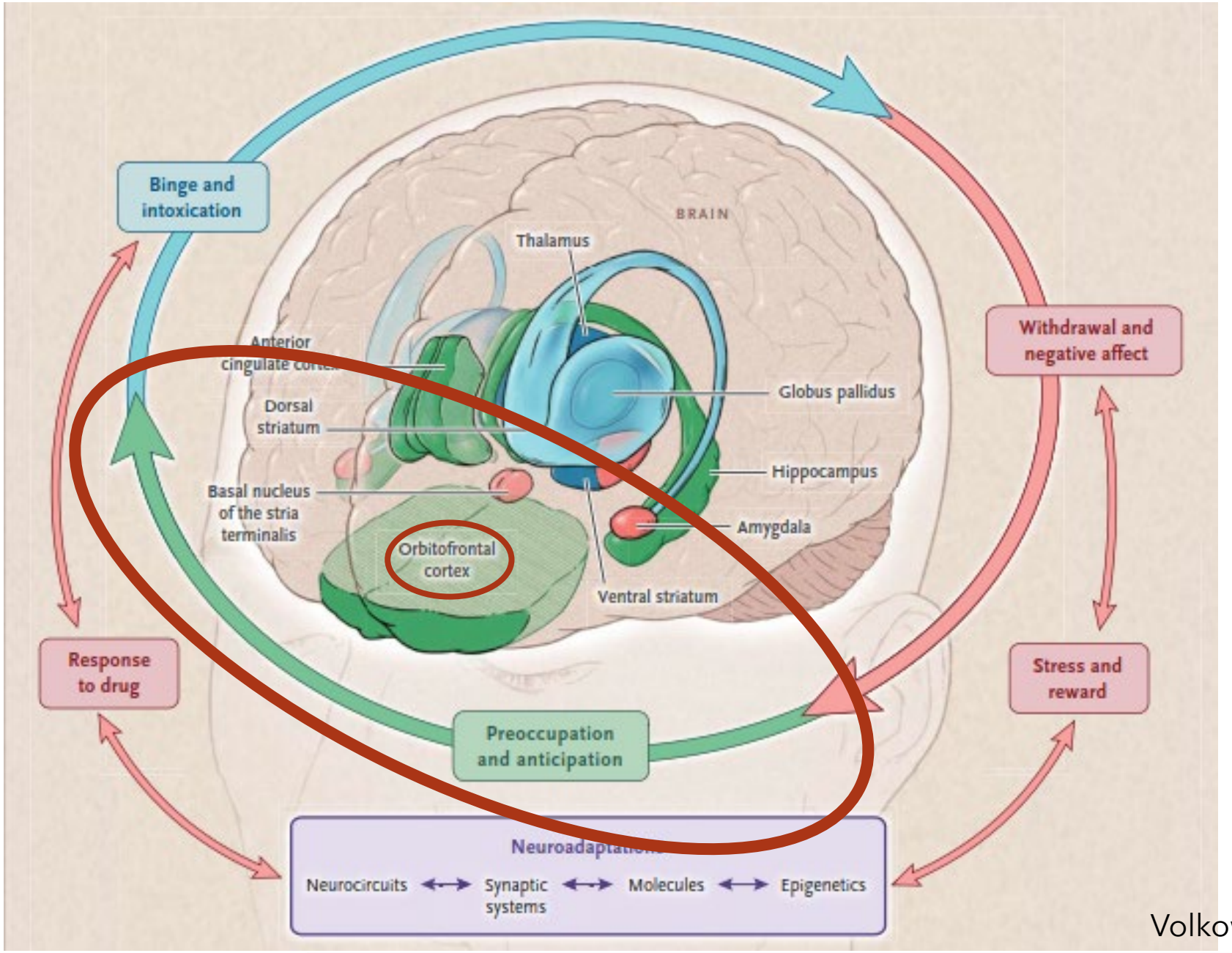
Volkow ND et al., 2016



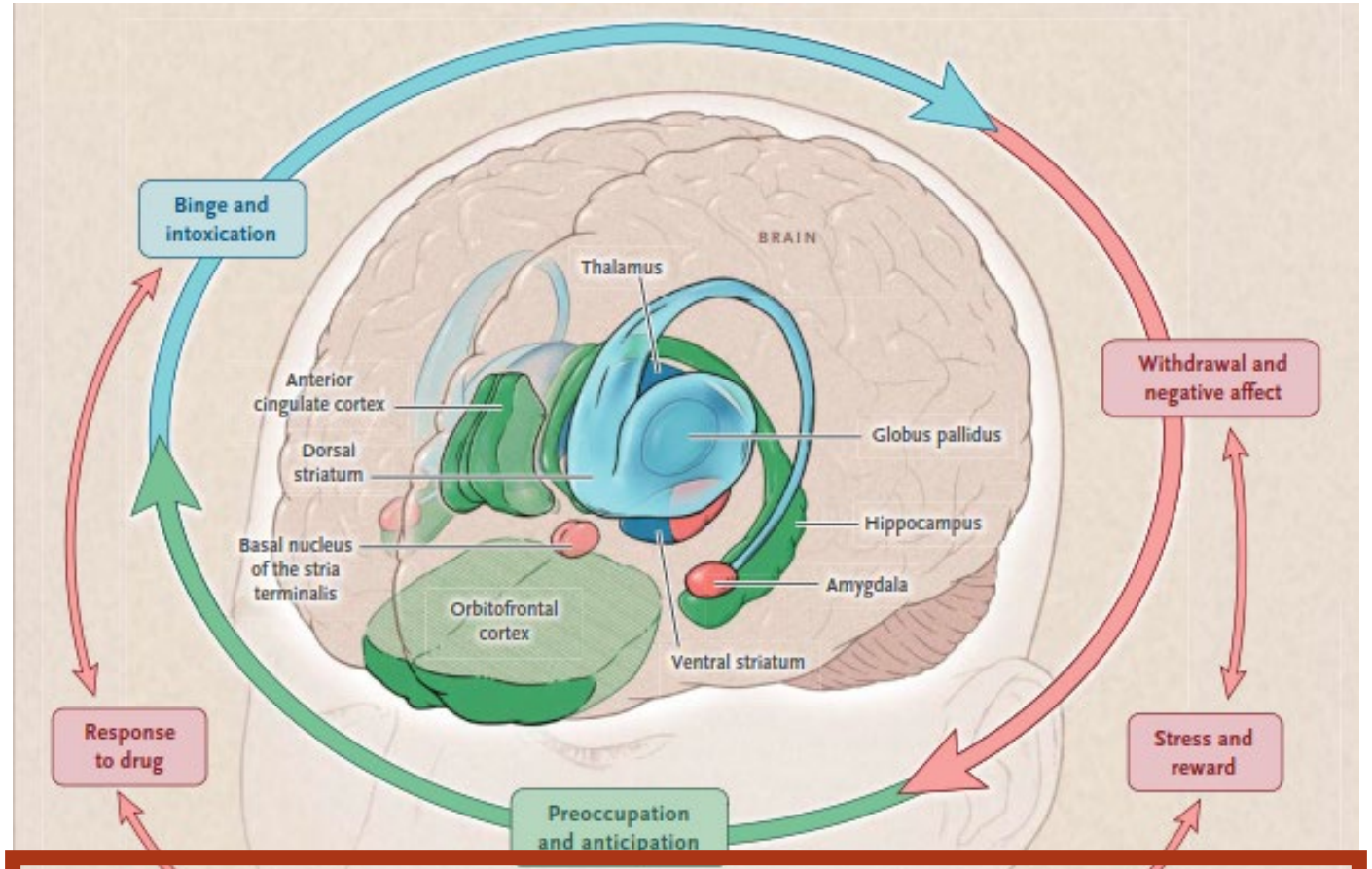
Volkow ND et al., 2016



Volkow ND et al., 2016



Volkow ND et al., 2016



Neuroadaptations

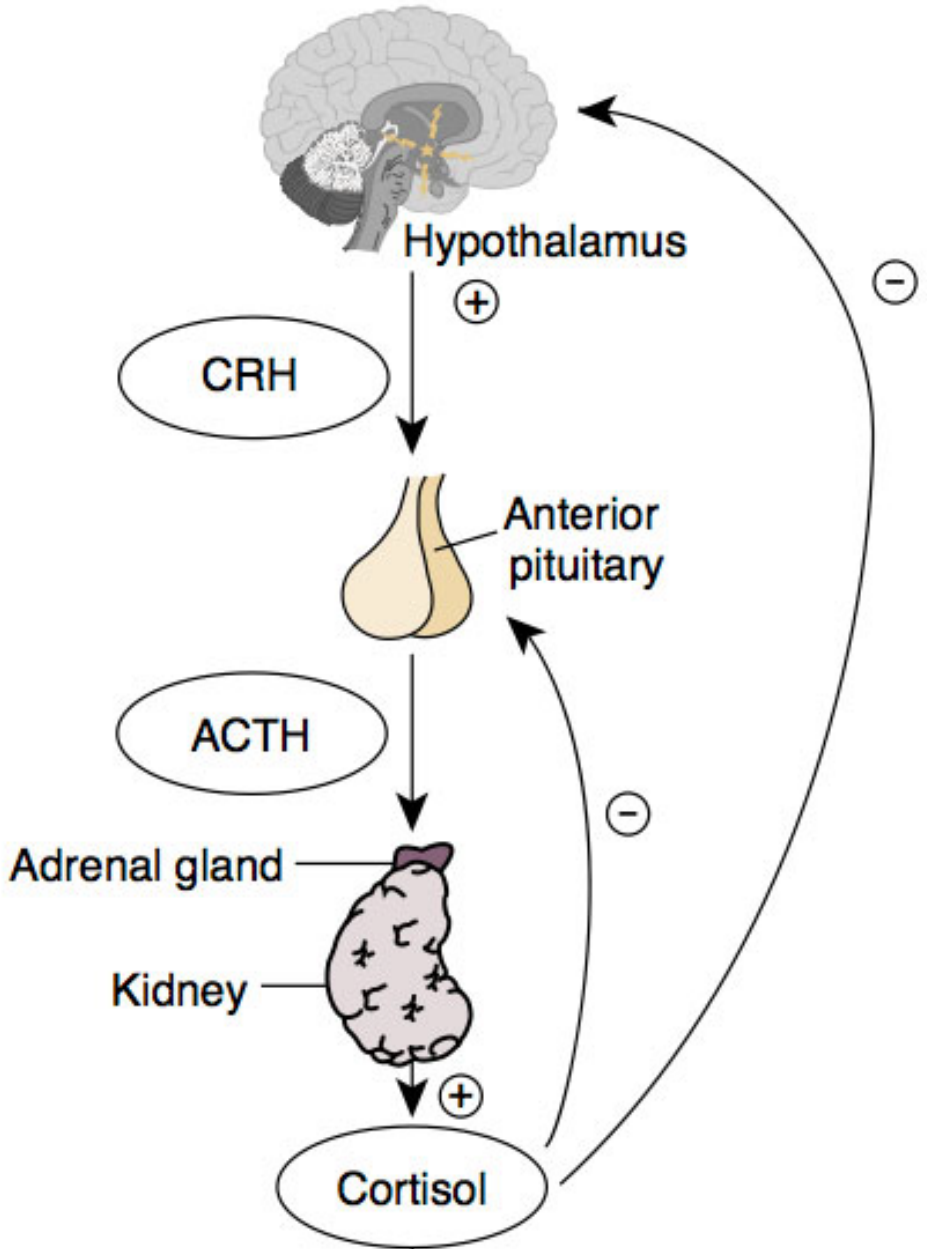
Neurocircuits ↔ Synaptic systems ↔ Molecules ↔ Epigenetics

Stage of Addiction	Shifting Drivers Resulting from Neuroadaptations		
Binge and intoxication	Feeling euphoric	Feeling good	Escaping dysphoria
Withdrawal and negative affect	Feeling reduced energy	Feeling reduced excitement	Feeling depressed, anxious, restless
Preoccupation and anticipation	Looking forward	Desiring drug	Obsessing and planning to get drug

Volkow ND et al., 2016

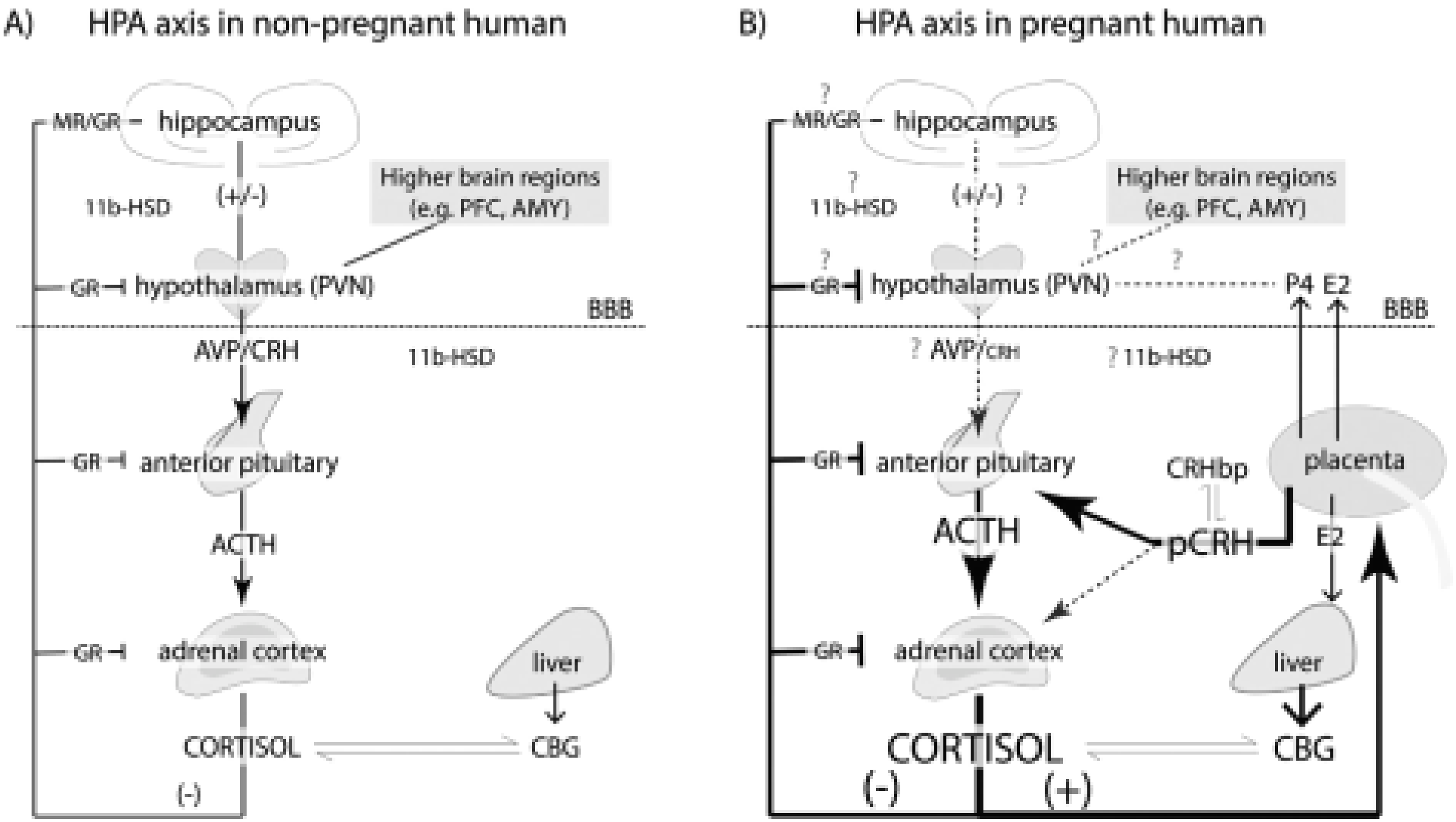
The Hypothalamic-Pituitary-Adrenal (HPA) Axis

HPA Axis


Hypothalamus
CRH
Anterior pituitary
ACTH
Adrenal gland
Kidney
Cortisol

Biology

- Cortisol
  - Glucocorticoid produced by the adrenal glands
  - Systemic effects
    - Nervous
    - Immune
    - Cardiovascular
    - Respiratory
    - Reproductive
    - Musculoskeletal
    - Integumentary


A) HPA axis in non-pregnant human
MR/GR
hippocampus
11b-HSD
(+/-)
Higher brain regions
(e.g. PFC, AMY)
GR
hypothalamus (PVN)
BBB
AVP/CRH
11b-HSD
GR
anterior pituitary
ACTH
GR
adrenal cortex
liver
CORTISOL
CBG
(-)
B) HPA axis in pregnant human
MR/GR
hippocampus
11b-HSD
(+/-)
Higher brain regions
(e.g. PFC, AMY)
GR
hypothalamus (PVN)
P4
E2
BBB
AVP/CRH
11b-HSD
GR
anterior pituitary
CRHbp
placenta
ACTH
pCRH
E2
GR
adrenal cortex
liver
CORTISOL
CBG
(-)
(+)

Stress

What is stress?

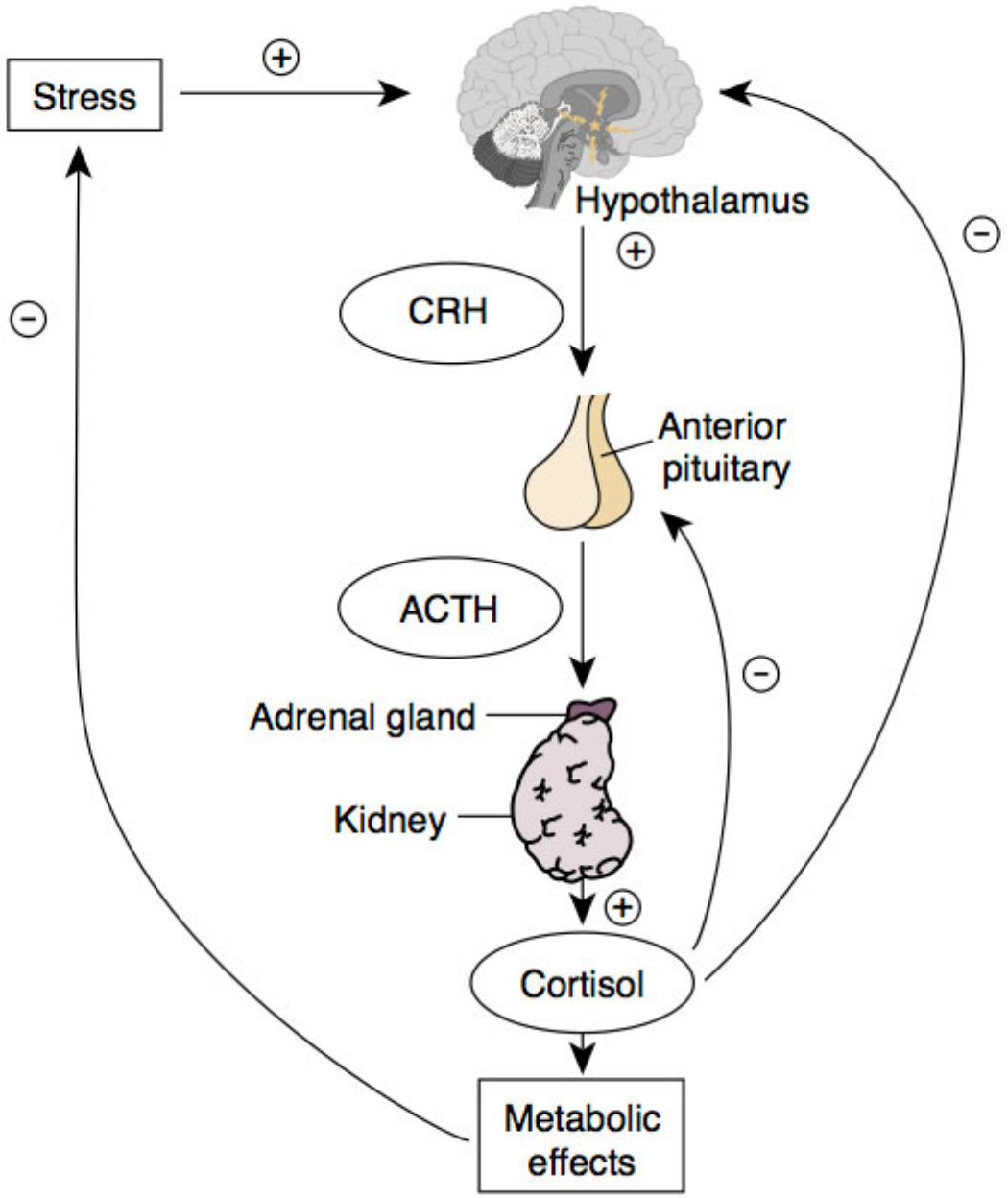
Stress

A real or interpreted threat to the physiological or psychological integrity of an individual that impacts behavior, subjective experience, and cognitive function.

The term "stress" refers to a disruption in equilibrium resulting in a cascade of physiological and behavioral responses to reinstate allostasis (e.g., achieving stability through change).

Sahani et al. Curr Topics Beh Neurosci, 2021

HPA axis under stress



Stress and Vulnerability to Addiction

PERINATAL STRESS

Social Determinants

Parental Psychopathology

Teratogenic Exposures

Environmental

Physiological Response

HPA Axis ⟷ Immune

Domain Vulnerabilities

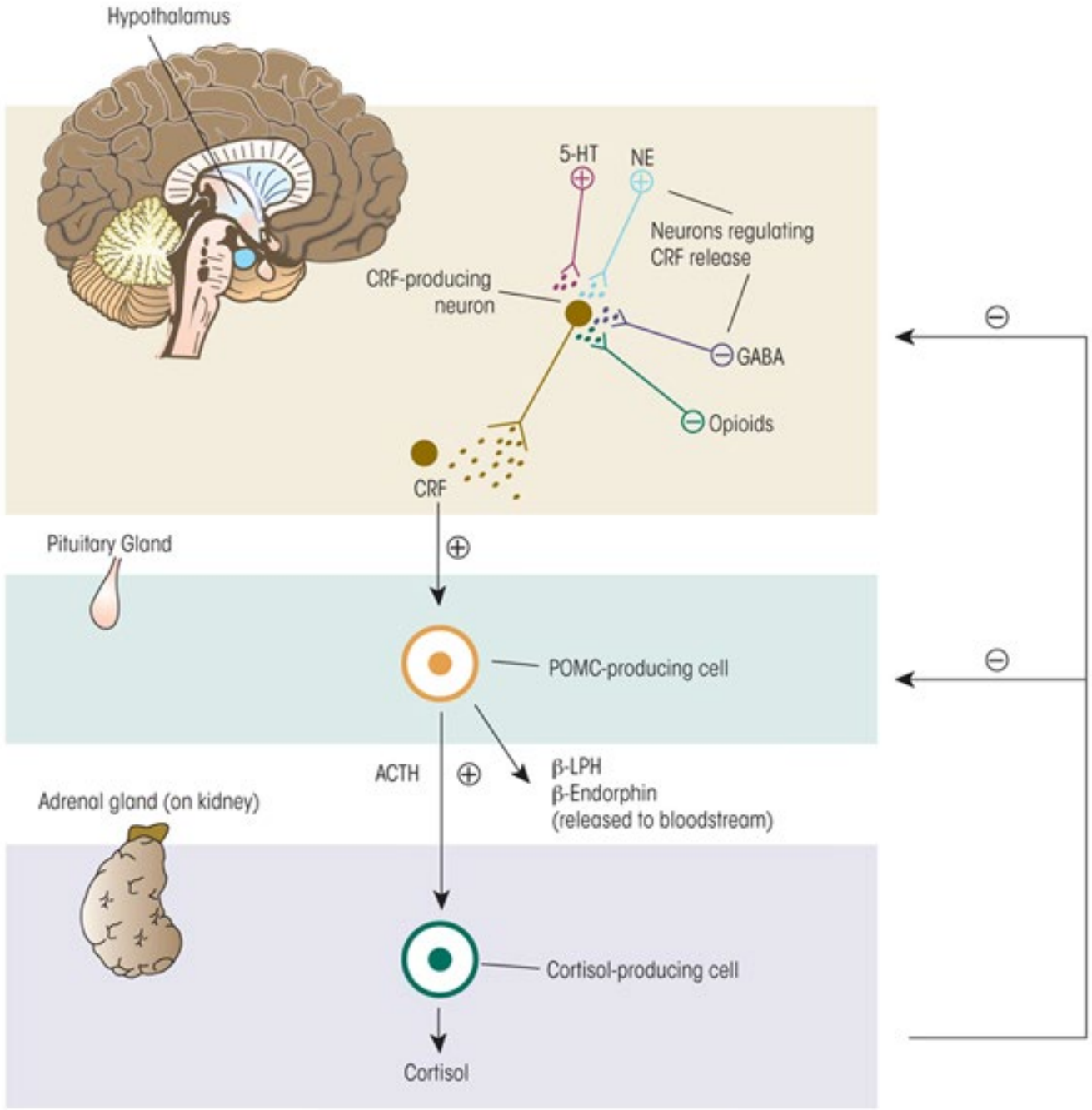
Cognitive

Psychosocial

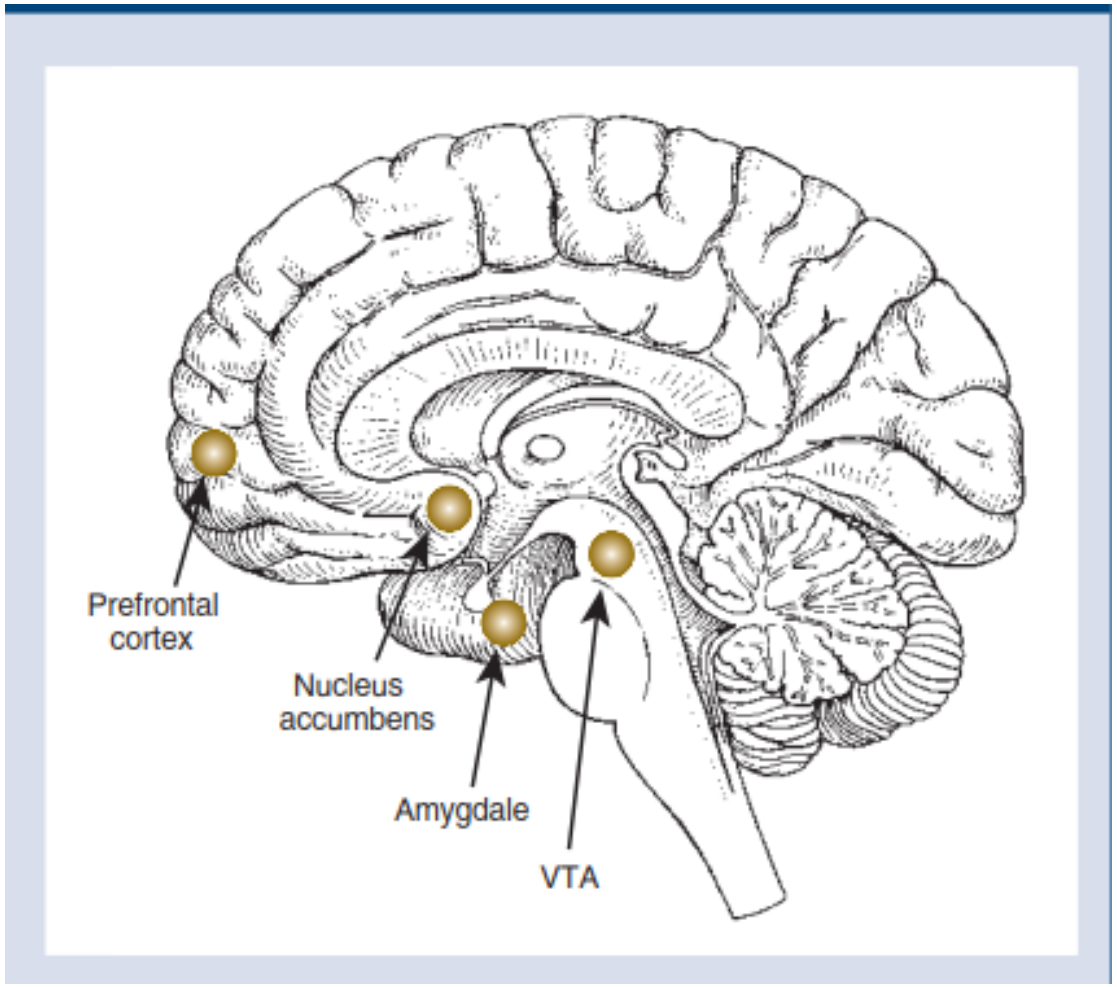
Neurobiological

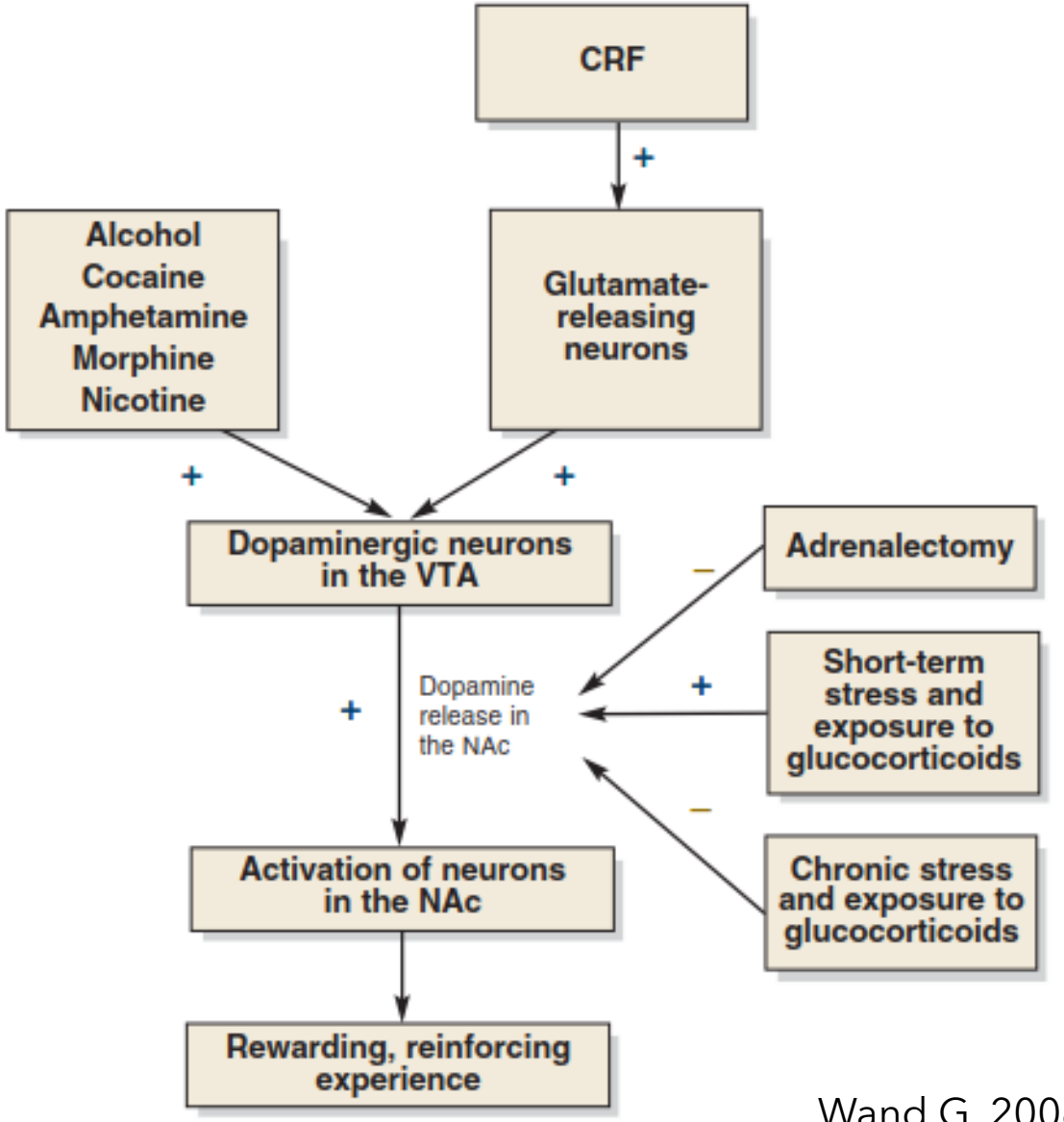
SUBSTANCE USE/ABUSE VULNERABILITY

From Horn et al., 2018


Hypothalamus
5-HT
NE
Neurons regulating CRF release
CRF-producing neuron
GABA
Opioids
CRF
Pituitary Gland
POMC-producing cell
ACTH
β-LPH
β-Endorphin
(released to bloodstream)
Adrenal gland (on kidney)
Cortisol-producing cell
Cortisol

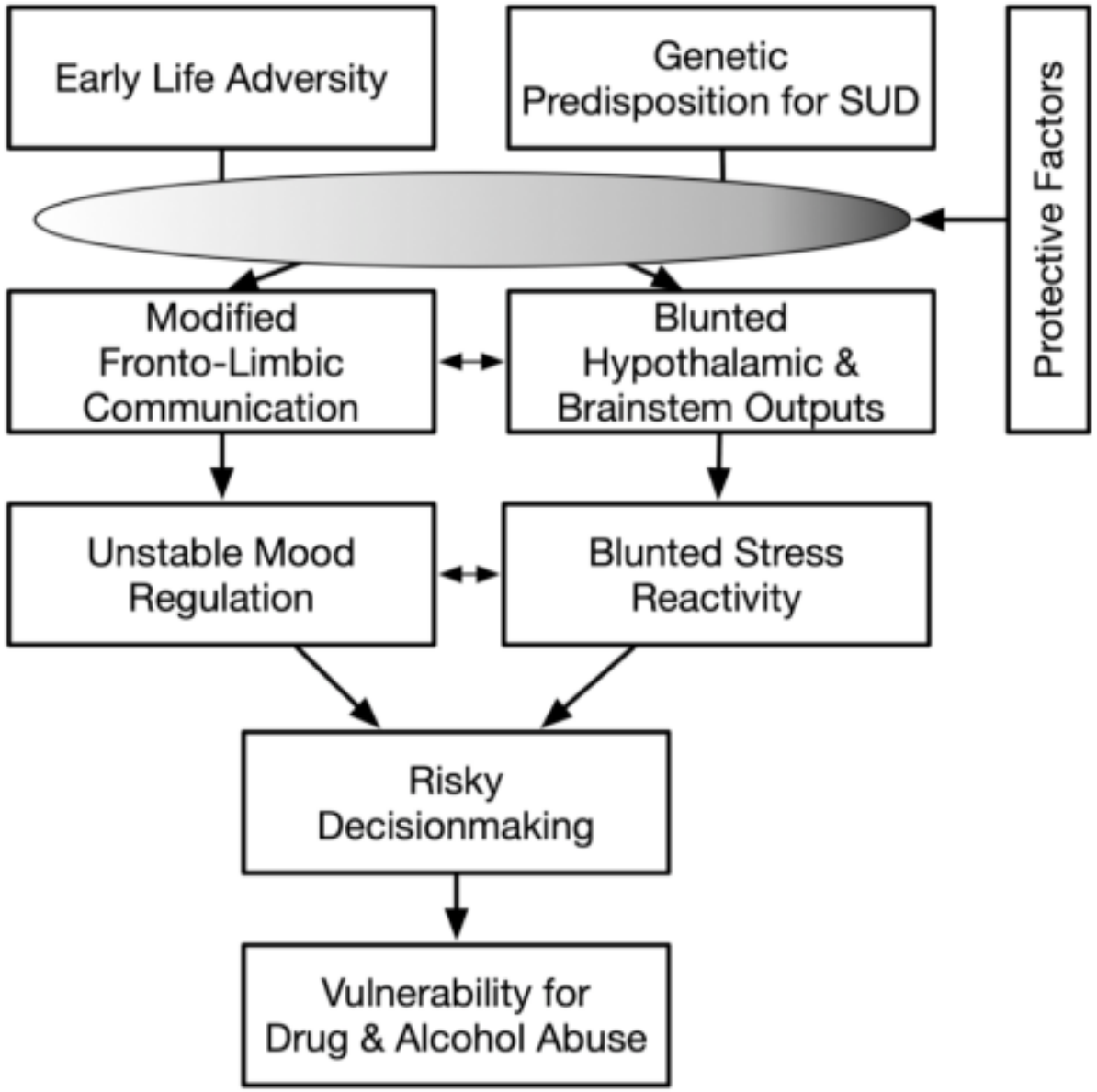
Wand G, 2008


Prefrontal cortex
Nucleus accumbens
Amygdale
VTA


CRF
+
Alcohol
Cocaine
Amphetamine
Morphine
Nicotine
Glutamate-releasing neurons
+
+
Dopaminergic neurons in the VTA
Adrenalectomy
–
Short-term stress and exposure to glucocorticoids
+
+
Dopamine release in the NAc
–
Chronic stress and exposure to glucocorticoids
Activation of neurons in the NAc
Rewarding, reinforcing experience

Wand G, 2008

Synthesis



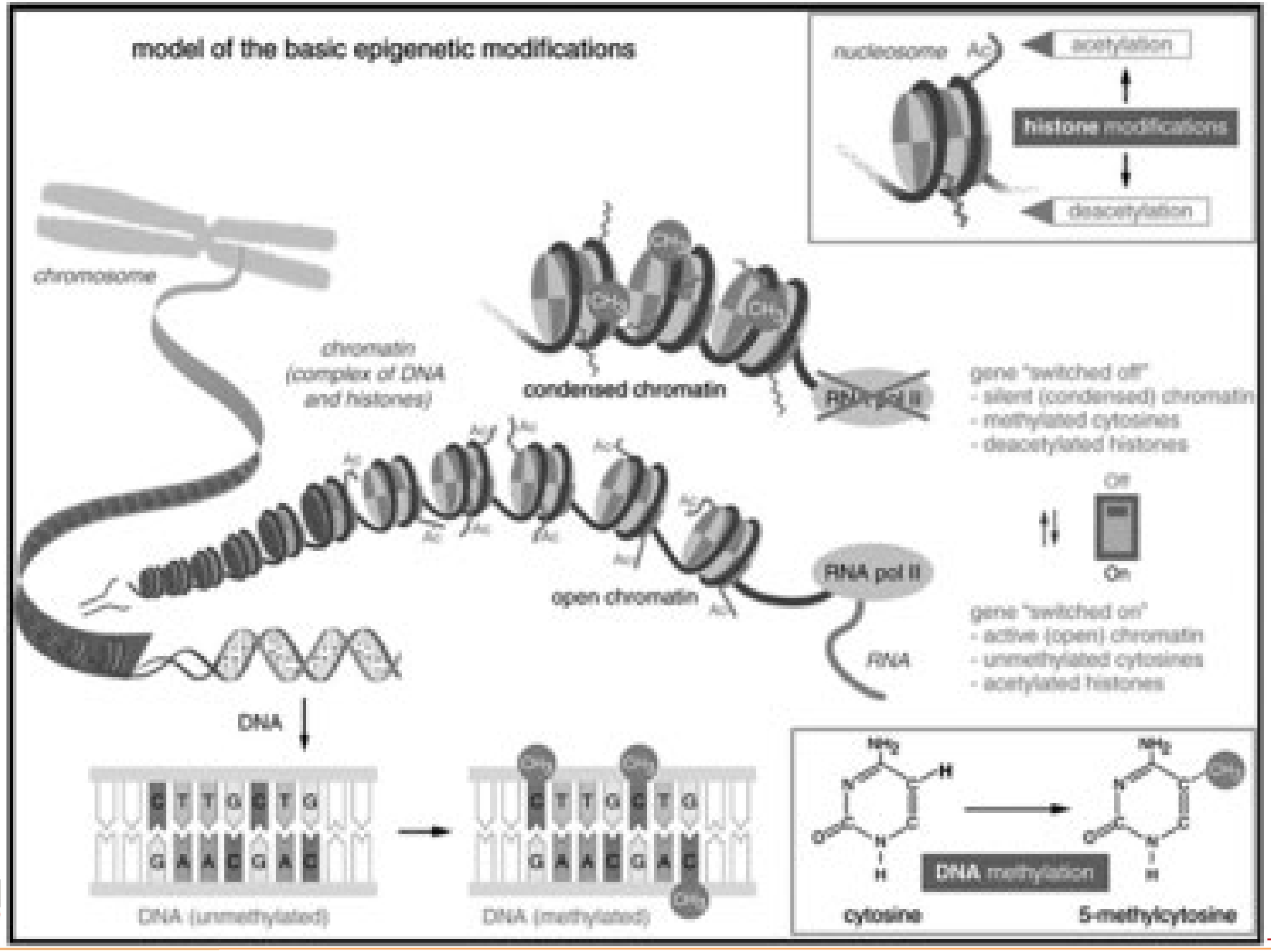
al'Absi et al. Neuropharmacology, 2021

Epigenetics

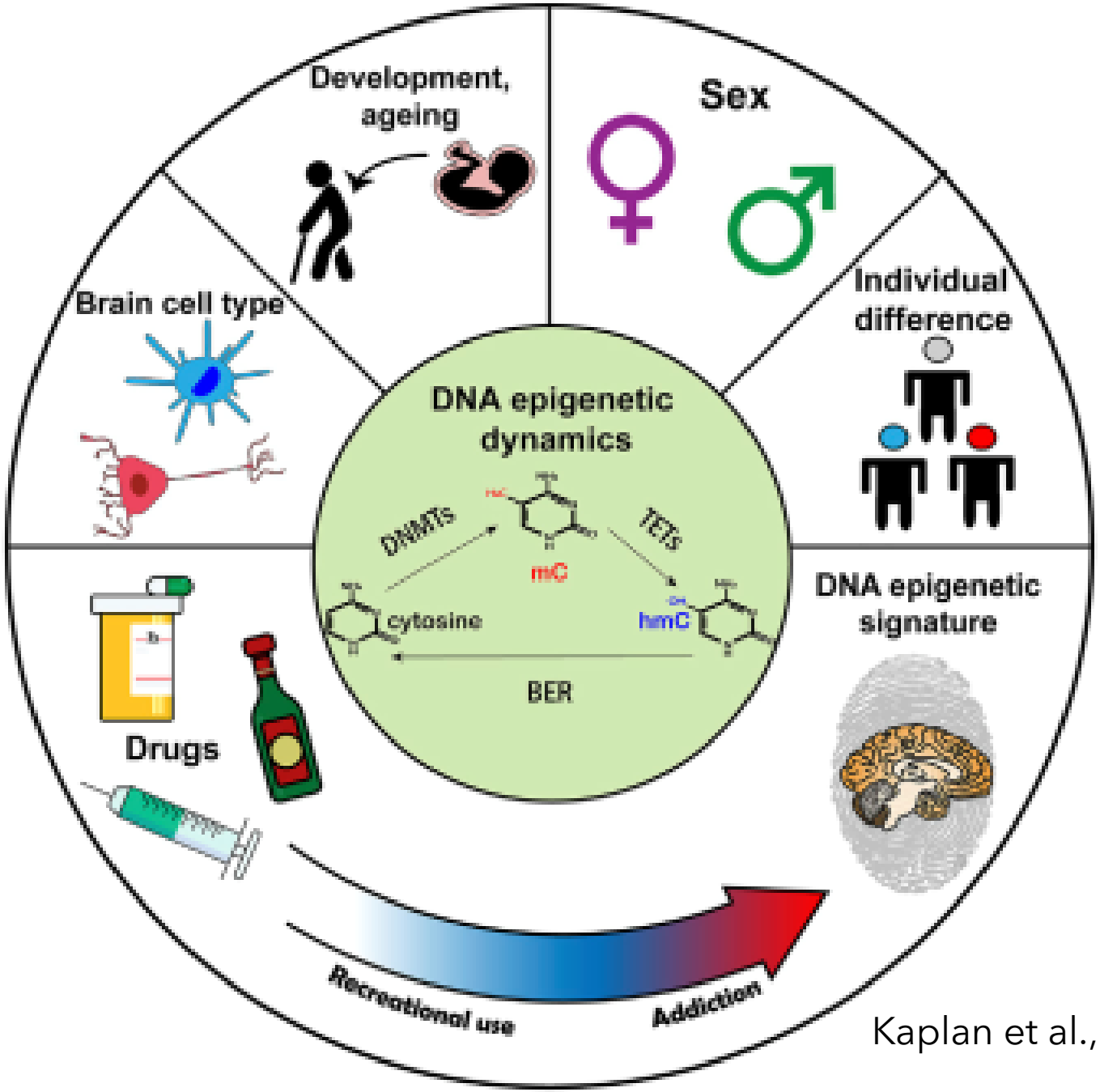
Epigenetics

The study of changes in gene function that are heritable through cell division, yet reversible, and that do not involve changes in DNA sequence.

John and Rougeulle. Front Cell Develop Biol, 2018



Nowak et al., 2022



Kaplan et al., Front Genetics, 2022

Epigenetics

- Brain
  - Nucleus accumbens
  - Prefrontal cortex
  - Hypothalamus
- Blood cells
- Placenta
- Glucocorticoid receptor gene

Attachment

Attachment Theory

The central theme of ***attachment theory*** is that primary caregivers who are available and responsive to an infant's needs allow the child to develop a sense of security. The infant knows that the caregiver is dependable, which creates a secure base for the child to then explore the world.

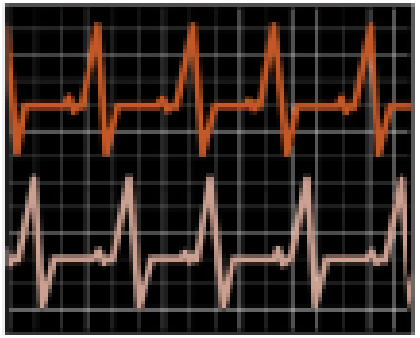
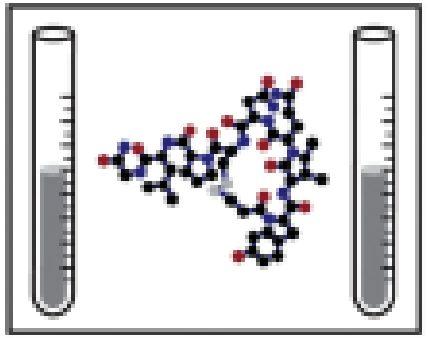
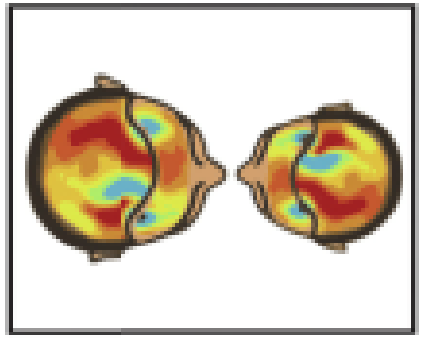
Biology

- Oxytocin
  - Produced in hypothalamus
  - Modulates emotional functions of the amygdala and brain stem
  - In context of safety, allows optimal expression of positive social behaviors
  - Regulation of emotion, autonomic nervous system, homeostasis, coping, and healing
- Vasopressin
  - Produced in hypothalamus
  - Activates more possessive and aggressive sides of attachment (protection)

Carter CS, 2017

Biobehavioral synchrony in human attachments

Parents

Behavioral synchrony	Heart rate coupling	Endocrine fit	Brain-to-brain synchrony
			
• Synchronized behavior in gaze, affect, vocal, and touch • Mother-specific father-specific	• Synchronized HR during synchronized interactions	• Coordinated OT response following contact • Coordinated cortisol response to stress	• Coordinated brain oscillations in alpha and gamma rythms

Feldman R, 2017

Disrupted Attachment

- Strong evidence for importance of oxytocin pathways
- Increasing evidence for genetic and epigenetic differences that may affect capacity to cope with early life adversity
- Consequences include personality disorders, vulnerability to substance abuse, and addictions

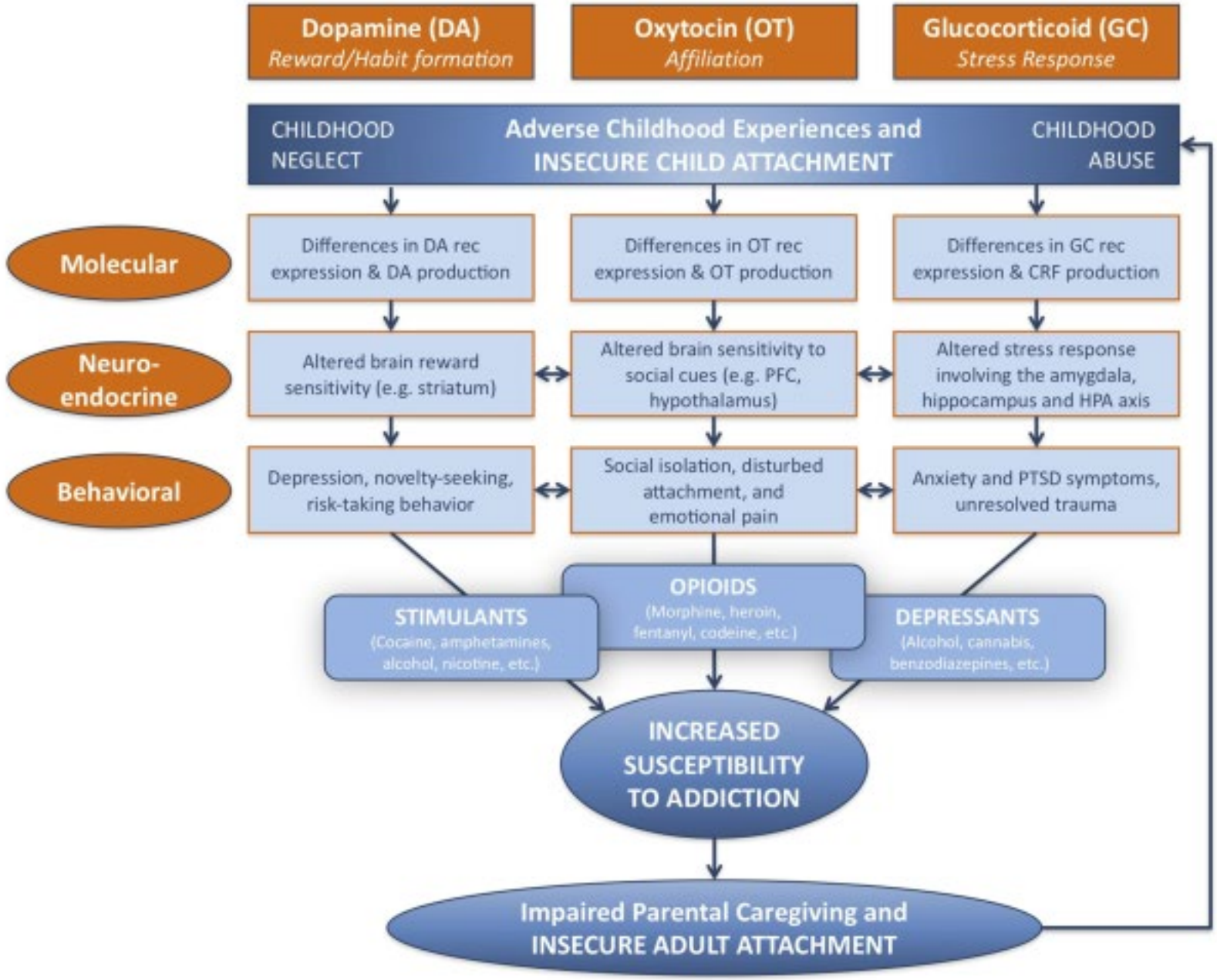
Carter CS, 2017

Mothering, Substance Use Disorders and Intergenerational Trauma Transmission: An Attachment-Based Perspective

Florien Meulewaeter, Sarah S. W. De Pauw and Wouter Vanderplasschen*

Discussion: Findings suggest disruptive attachment can increase the vulnerability for SUDs on the one hand, but can be an expression of underlying trauma on the other, hence serving as a covert mechanism by which trauma can be transmitted across generations. **Results indicate the need for preventive, attachment-based and trauma-sensitive interventions targeted at disruptive intergenerational patterns.**

Meulewaeter F et al., 2019



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Strathearn L et al., 2019

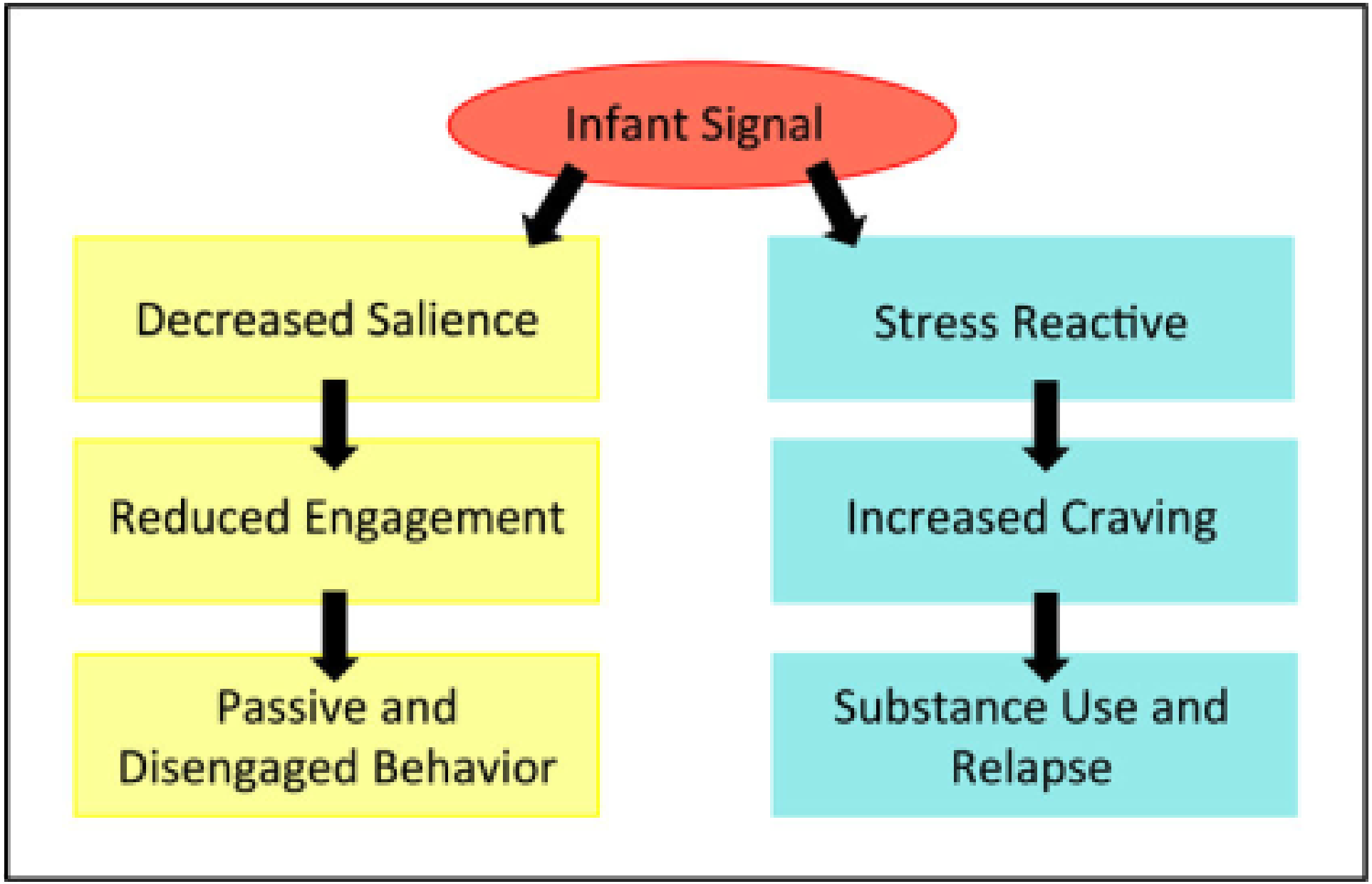
Parenting

Neurobiology of parenting and addiction

- Dysregulation of neural circuits implicated in stress and reward processing
- Decreased neural responses to infant affective cues
- Decreased response in reward-brain regions when viewing own infant's smiling face

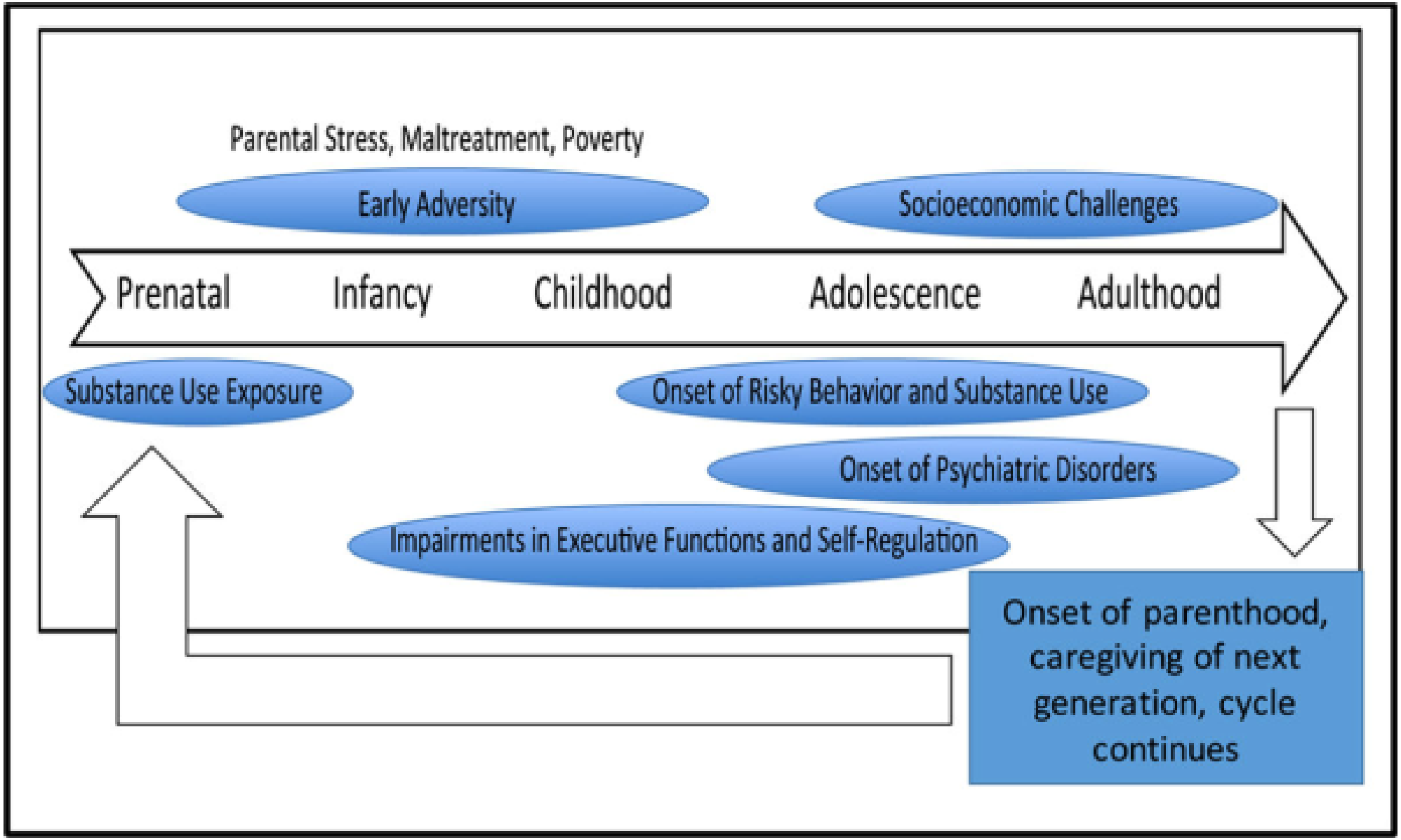
Infant cues may be less rewarding and pleasurable, underscoring passive and disengaged behaviors.

Rutherford H and Mayes LC, 2019



Rutherford H and Mayes LC, 2017

So what?



Rutherford H and Mayes L, 2017

Thank you.

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