The Neuroscience of Pain, Addiction and Trauma

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ASAM THE PAIN & ADDICTION Common Threads Course

The Neuroscience of Pain, Addiction and Trauma

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Disclosure Information

Corey Waller MD, MS, DFASAM, FACEP

Income – Salary from HMA and Shifts in the ED

Objectives

- Learners will be able to describe the role of trauma in brain function
- Learners will be able to describe the neuroscience of addiction
- Learners will be able to describe the neuroscience of pain
- Bonus! Learners will integrate this information into treating patients

Is All Addiction The Same?

Patient 1

- Early life trauma
  - Neglect
  - Sexual assault
- Isolation from friends
- Early use of marijuana
- Heavy episodic drinking in early high school
- Opioids at 19 y/o
- Heroin at 22 y/o

Patient 2

- Parents divorced and had shared custody
  - No neglect
  - No assault
- Lots of friends
- Tried MJ once in HS, used couple times per month in college
- Episodic binge drinking on college
- Finished college
- Went to medical school
- Given naloxone in the resident call room

The Neurotransmitters and Hormones of Trauma

Hypothalamus-pituitary-adrenal (HPA) axis

- Stress ⬆ corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) from the paraventricular nucleus of the hypothalamus.
- This in turn ⬆ Adreno-cortico-trophic hormone, which binds to the adrenal gland stimulating the release of glucocorticoids (i.e. cortisol)

- Increased Norepinephrine from the Locus Coeruleus
- Decreased Dopamine from NAc with chronic stress

The Structural Impact

Hippocampus – Past event memory with little or no emotional context

- Increases trauma/CRF equals decreases development of dendritic spines and branches
- This makes long term memory allocation and more difficult

Amygdala – The heart of the emotional brain. It has been call the brain within the brain.

- Interacts with 95% of other brain structures
- Central bed nuclei is responsible for emotional memory
- Lateral bed nuclei houses the fear response

The Structural Impact…

Orbitofrontal Cortex – assigns value to a reward

- Trauma decreases gonadotrophin (GR) and mineralocorticoid (MR), receptors making it more "sensitive" when stimulated

Anterio-medial Prefrontal Cortex (amPFC) – integrates input information and creates the response. Also responsible for "personality".

- When inputs are deranged, the response is disorganized and reactive
- Also, less overall input with low dopamine and impaired amygdala

The Structural Impact…

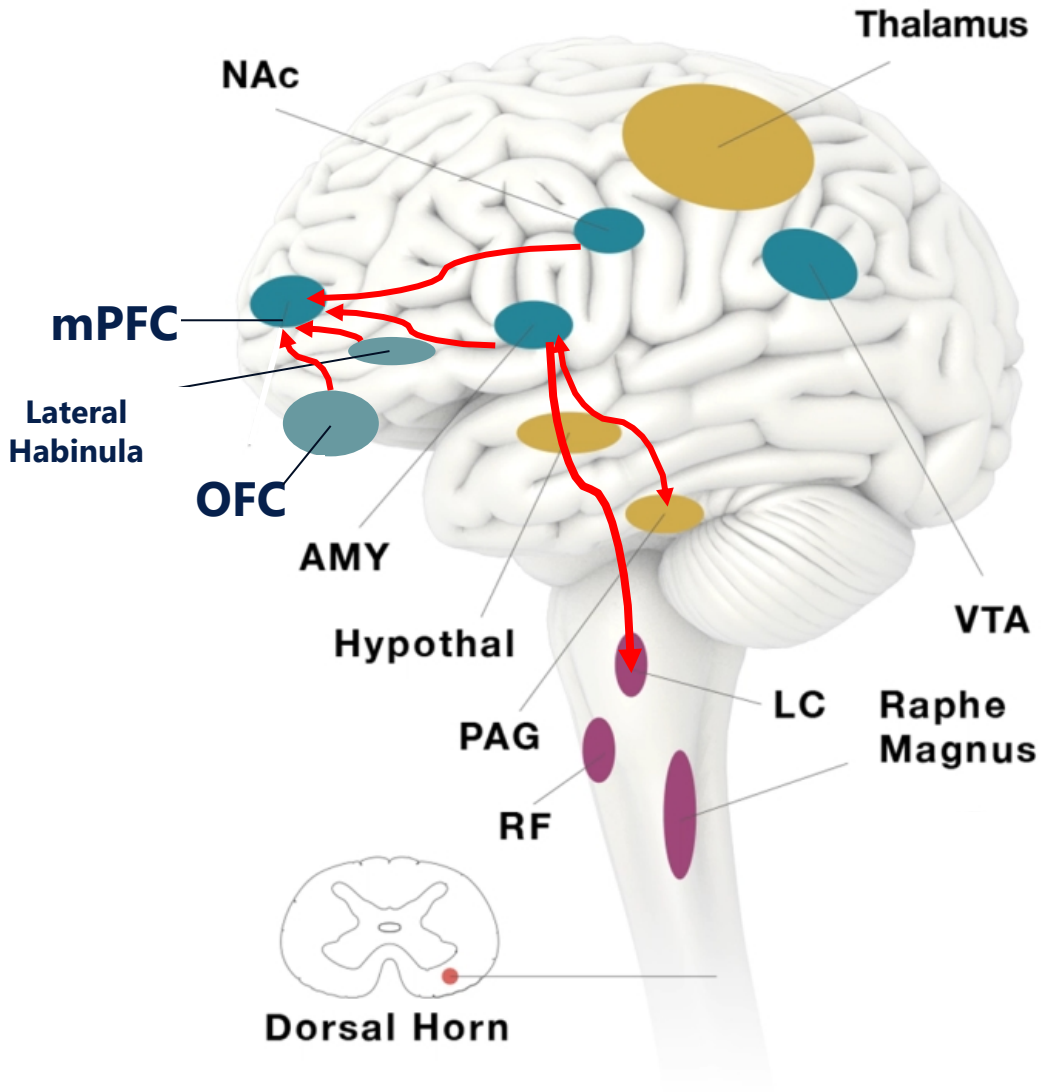
Lateral Habinula (LH)– holds learned responses to pain, stress, anxiety and reward

- Trauma creates maladaptive learned responses that are optimized for the traumatic environment

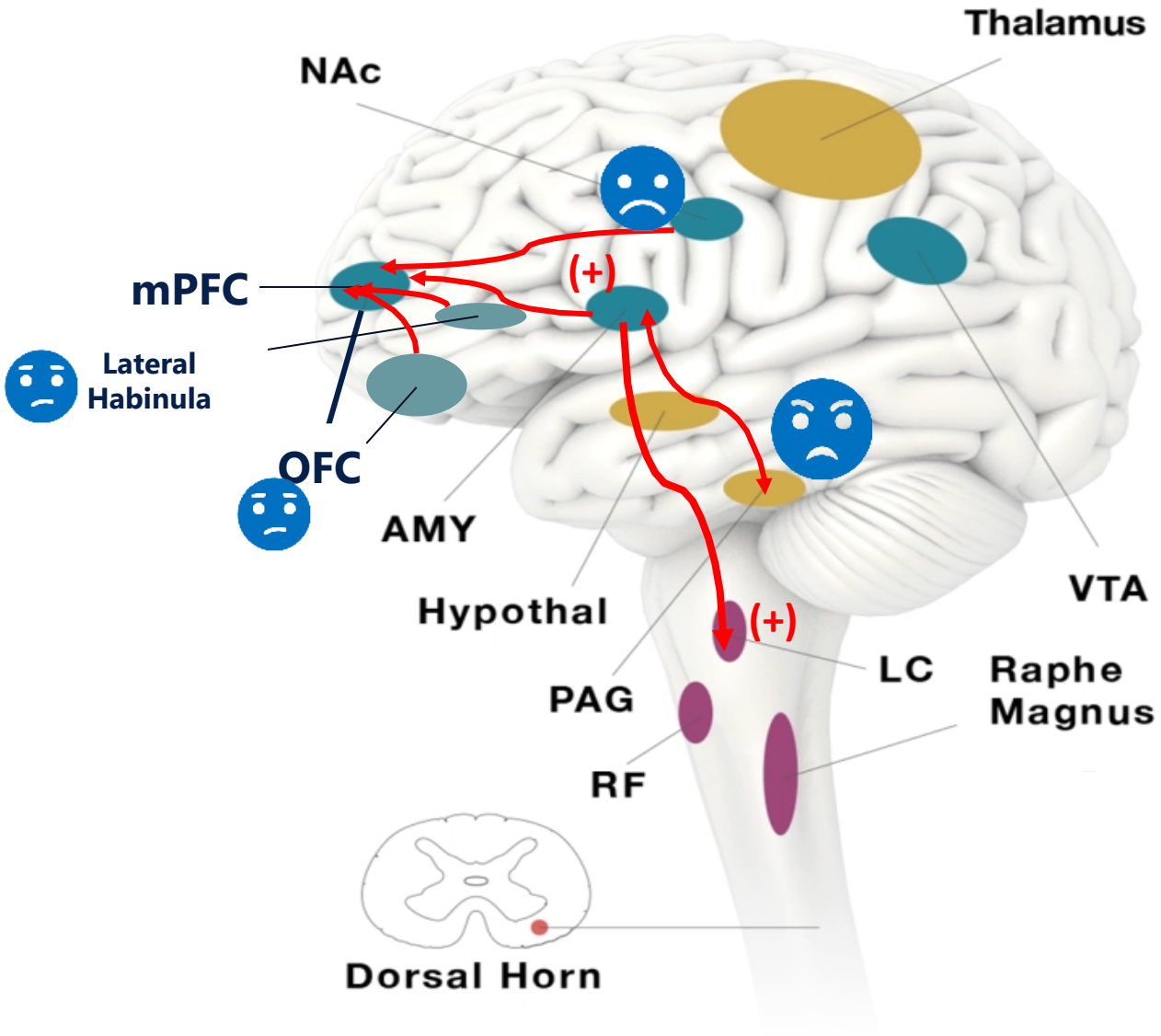
Periaqueductal grey (PAG)– production of endorphins for mood stabilization and pain control

- Also known as the location modulating aggression and defiant behavior
- Trauma decreases local endorphins through CRF mechanism
- This in turn creates less modulatory control over aggression and defiant behavior

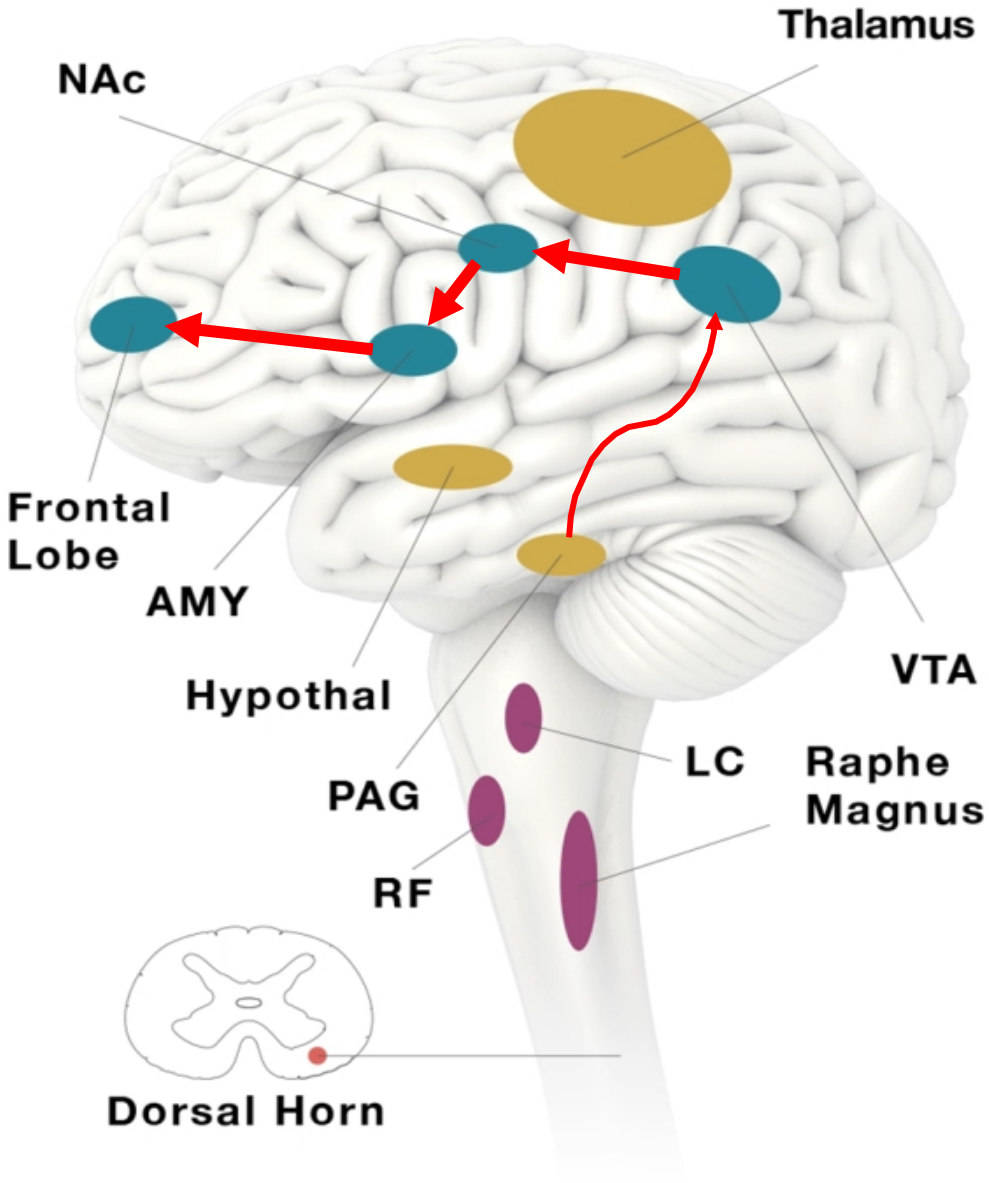
Normal Connections

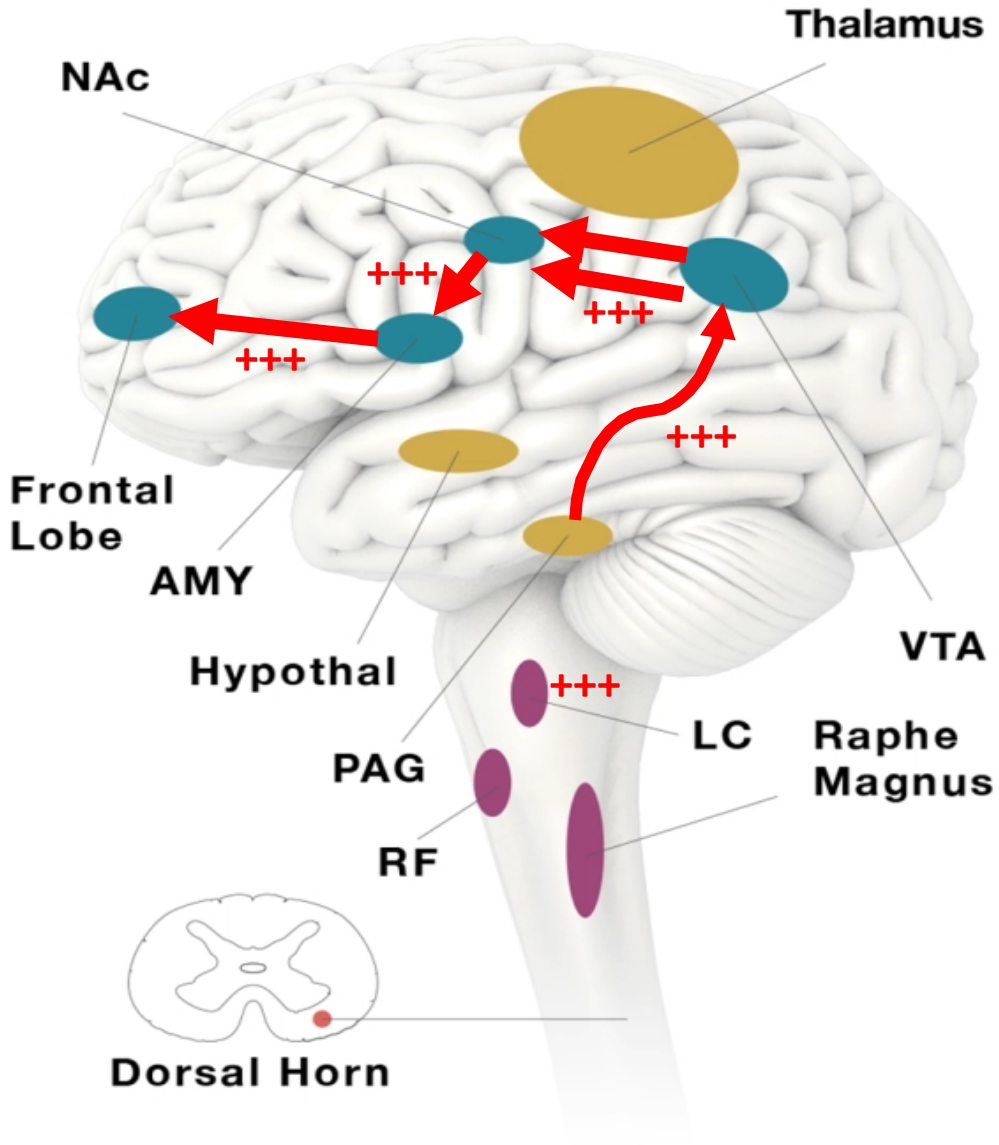


Post Trauma Connections



"A MAJOR REASON PEOPLE TAKE A DRUG IS THEY LIKE WHAT IT DOES TO THEIR BRAINS"


Thalamus
NAc
Frontal
Lobe
AMY
Hypothal
VTA
LC
Raphe
Magnus
PAG
RF
Dorsal Horn


Thalamus
NAc
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Frontal
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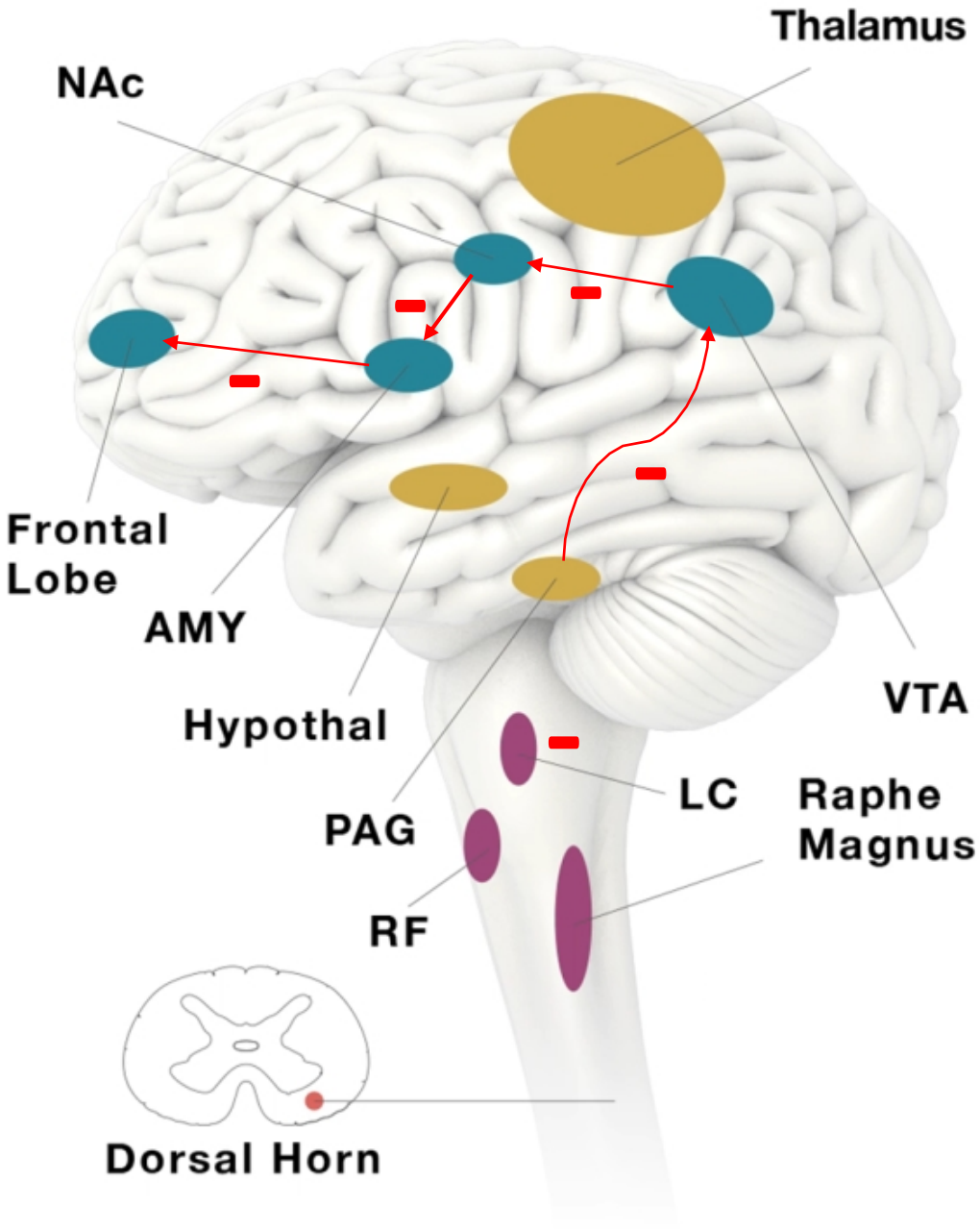
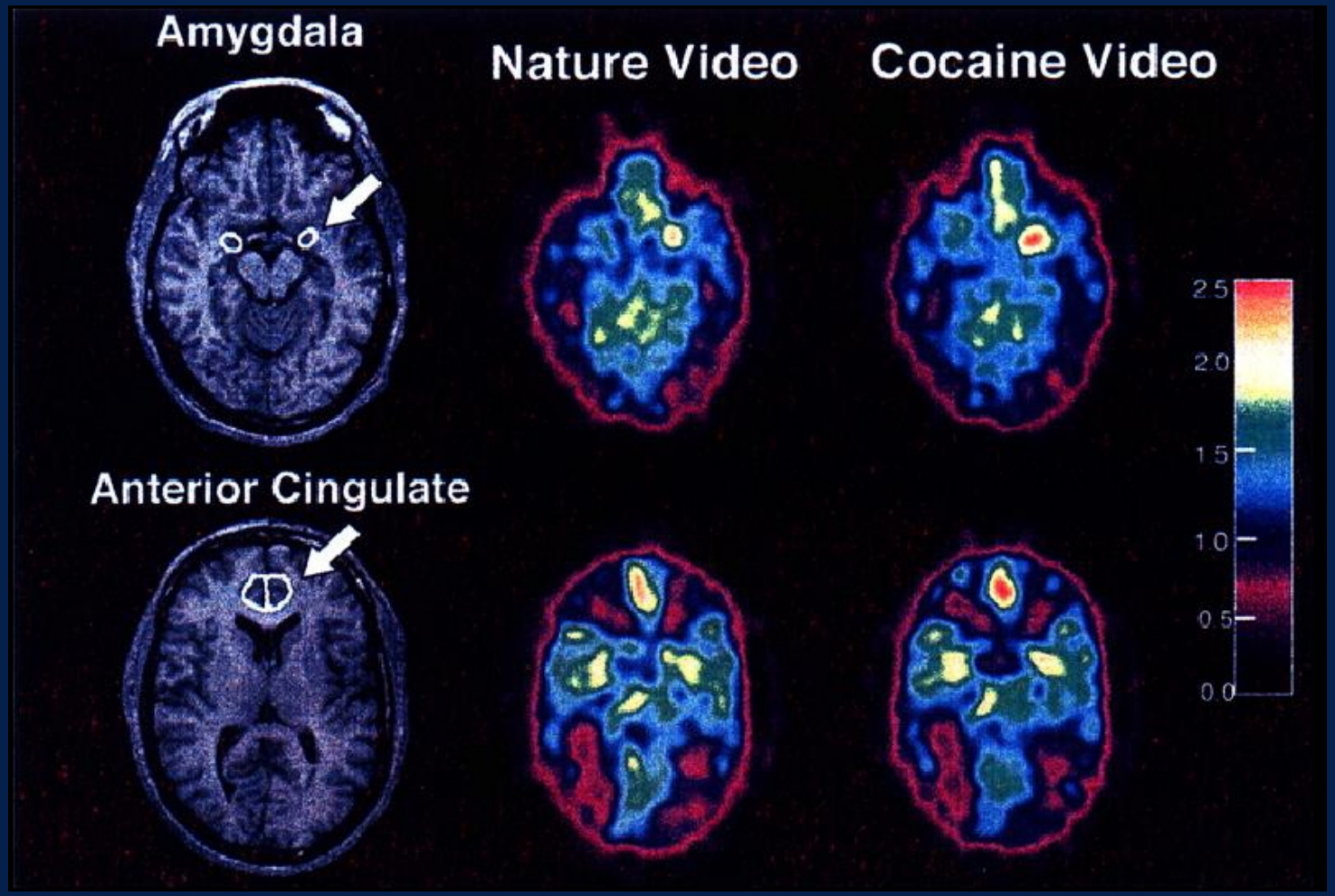
Dorsal Horn


Thalamus
NAc
Frontal
Lobe
AMY
Hypothal
VTA
LC
Raphe
Magnus
PAG
RF
Dorsal Horn

"Go!" System

POSITIVE REINFORCEMENT

PET/fMRI of Cocaine Craving



Childress et al., 1999; Am.J.Psychiat

Cocaine Cue Reactivity

- Drug Cues can trigger a strong, affect-positive state of drug desire (GO!)
- Cues can be used to study brain substrates of "GO!" in the imaging setting
- Brain substrates: Limbic Activation
  - Anterior cingulate
  - Amygdala
  - Insula
  - Ventral Striatum (NAc)
  - Orbitofrontal Cortex

Same Processes Present In…

- Opiates – heroin craving correlated with inferior frontal lobe, prefrontal cortex, insula
- Nicotine – smoking videos correlated with OFC, insula, anterior cingulate, DLPFC
- Sex – arousal correlated with anterior cingulate, mPFC, OFC, insular, amygdala, ventral striatum

But "GO!" isn't the whole story…

STOP System

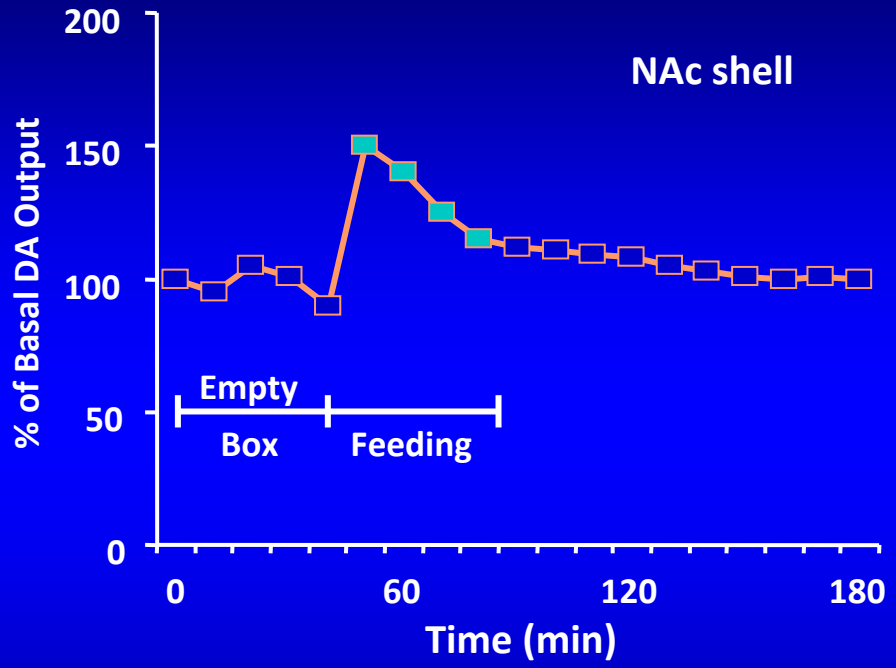
- Frontal Lobes
  - Critical for good decision making, disinhibition
  - Lower activity (blood flow and glucose metabolism) in cocaine users
  - Less concentrated gray matter (fewer nerve cells) in cocaine users and alcoholics
  - Unclear if cause or consequence, yet children w/ADHD and CD have poor frontal lobe functioning

Neurotransmitters - The Big Two:

- **Serotonin:** mood, emotion, sleep and appetite
- **Dopamine:** motivation, pleasure and elation

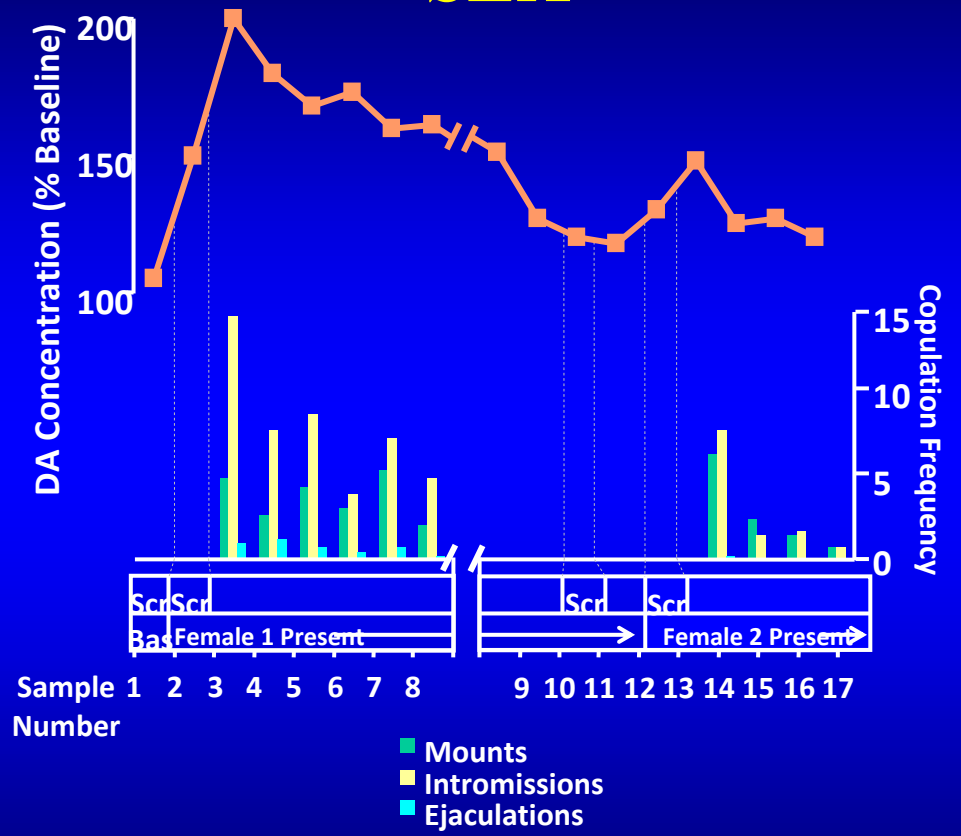
Natural Rewards Elevate Dopamine Levels

FOOD



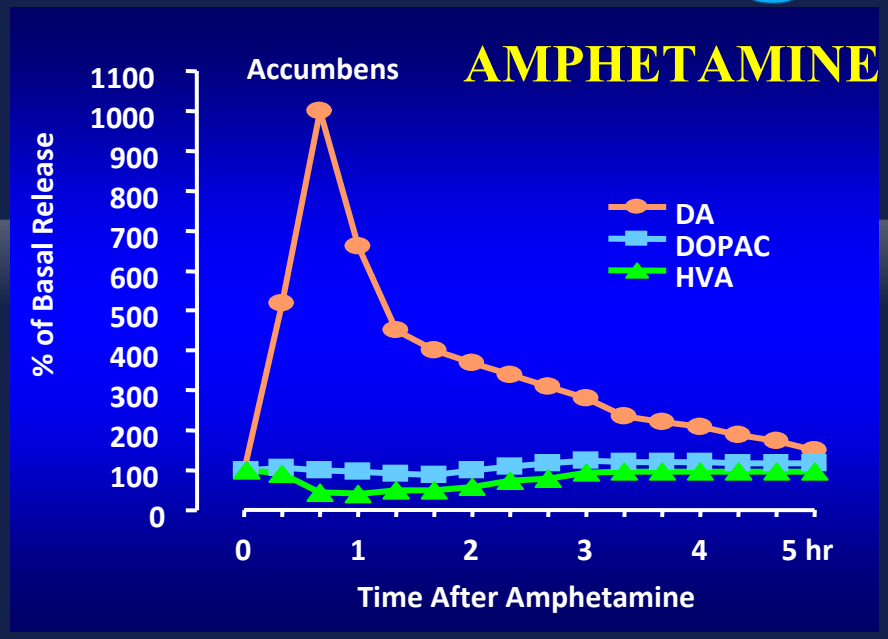
Source: Di Chiara et al.

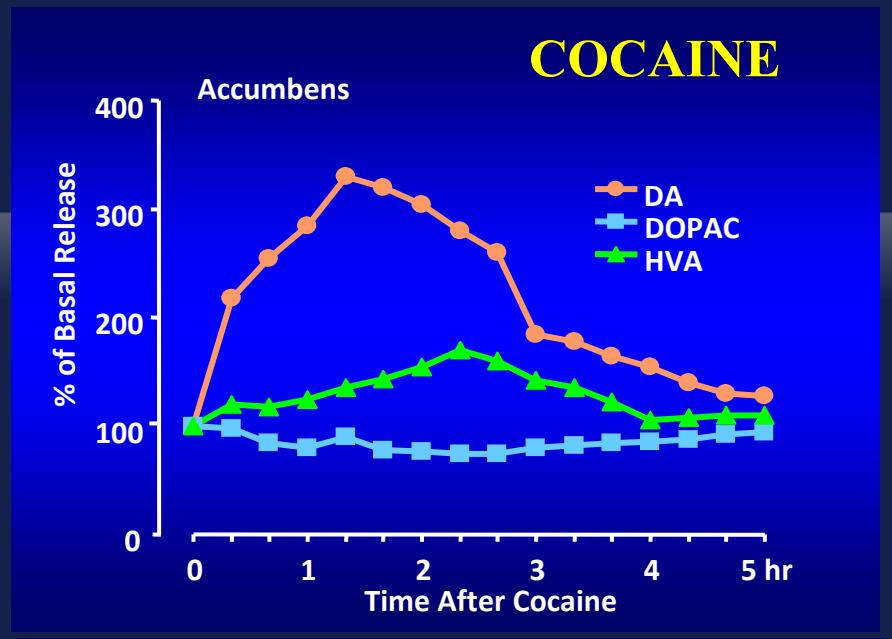
SEX

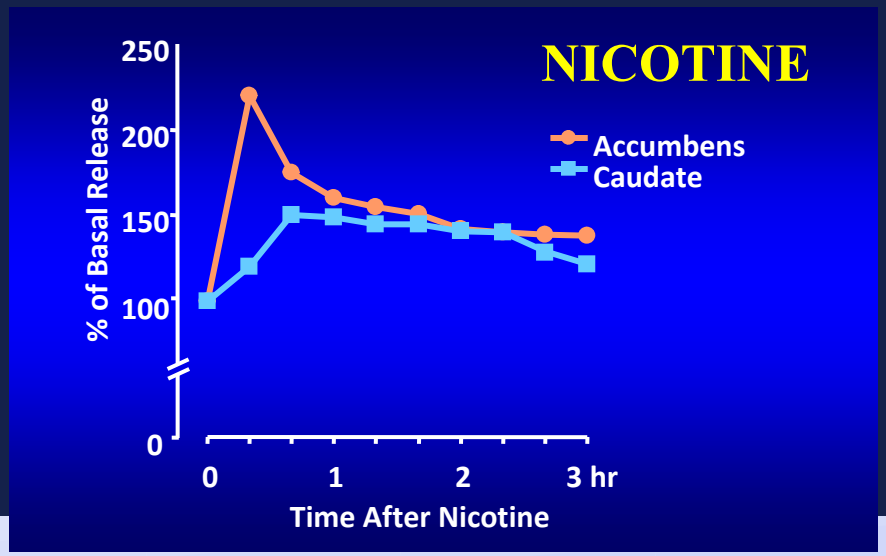


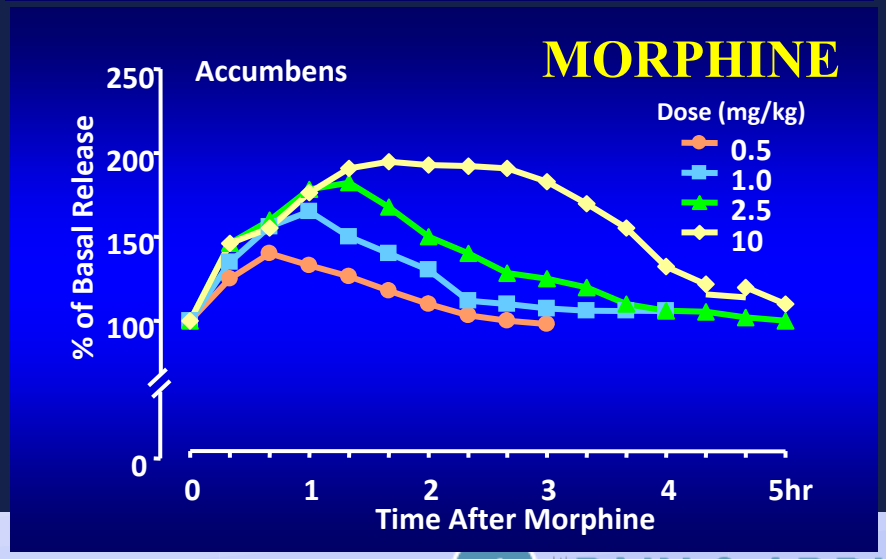
Source: Fiorino and Phillips

Effects of Drugs on Dopamine Levels









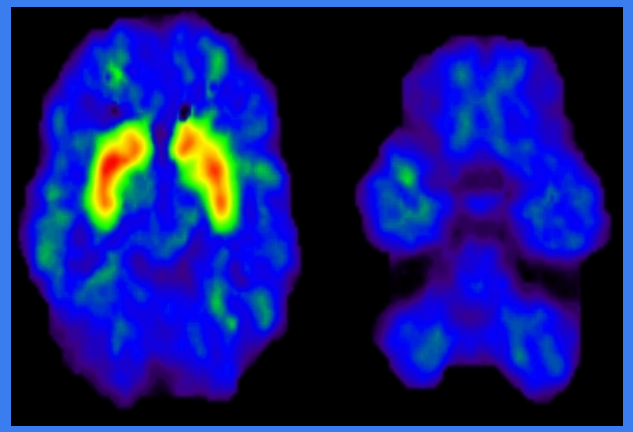
Source: Di Chiara and Imperato

Implications – Down Regulation

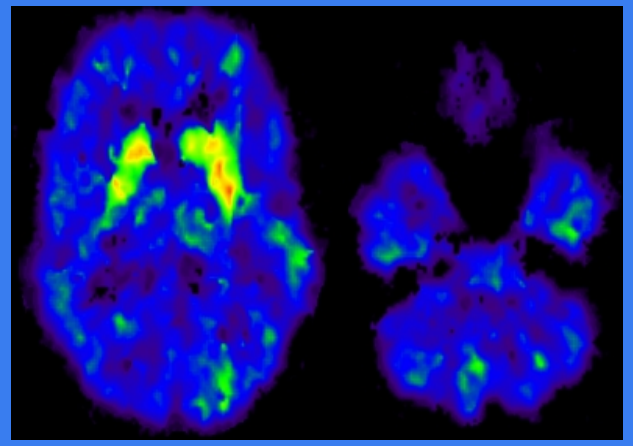
- Immediate effect of drug use is an increase in dopamine or NT's
- *Continued use of drugs reduces the brain's dopamine (or NT) production*
- Because dopamine is part of the reward system, the brain is "fooled" that the drug has survival value for the organism
- The reward system responds with "drug seeking behaviors"

Prolonged Drug Use Changes The Brain in Fundamental and Long-Lasting Ways

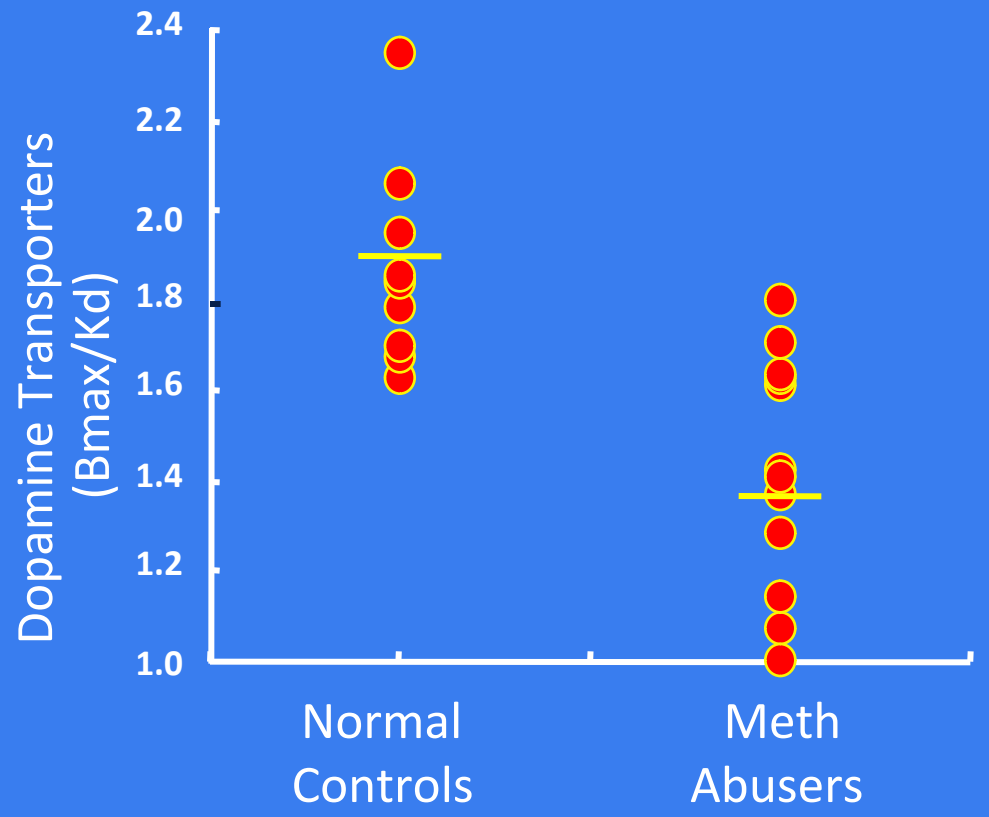
Dopamine Transporters in Methamphetamine Abusers



Normal Control



Methamphetamine Abuser

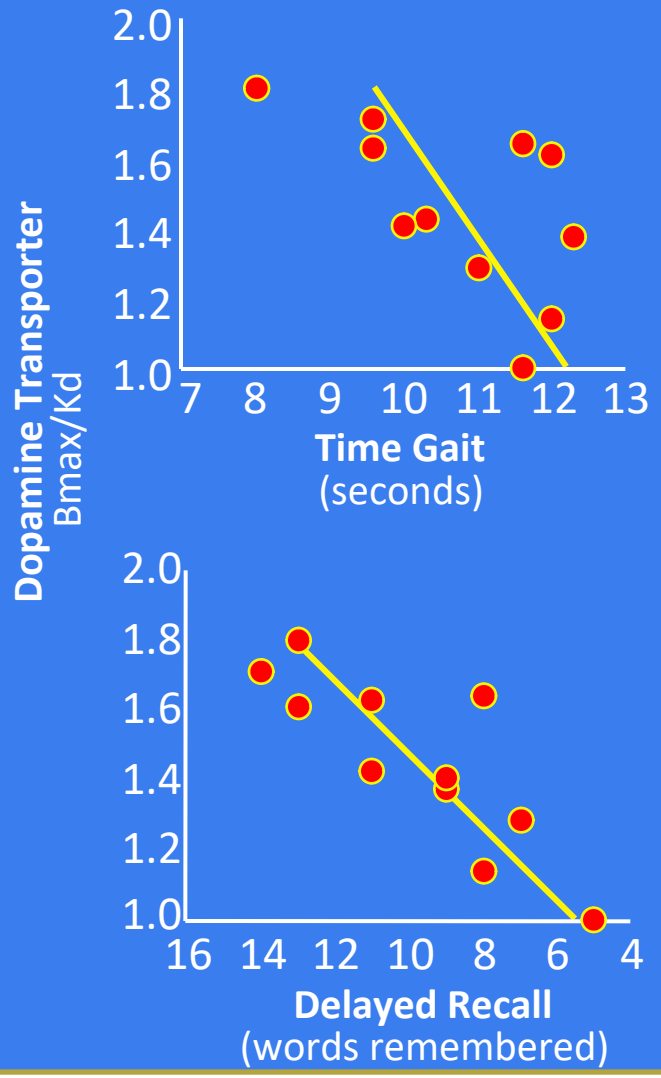


$p < 0.0002$

BNL - UCLA - SUNY
NIDA - ONDCP - DOE

- *Methamphetamine abusers have significant reductions in dopamine transporters.*

Dopamine Transporters in Methamphetamine Abusers



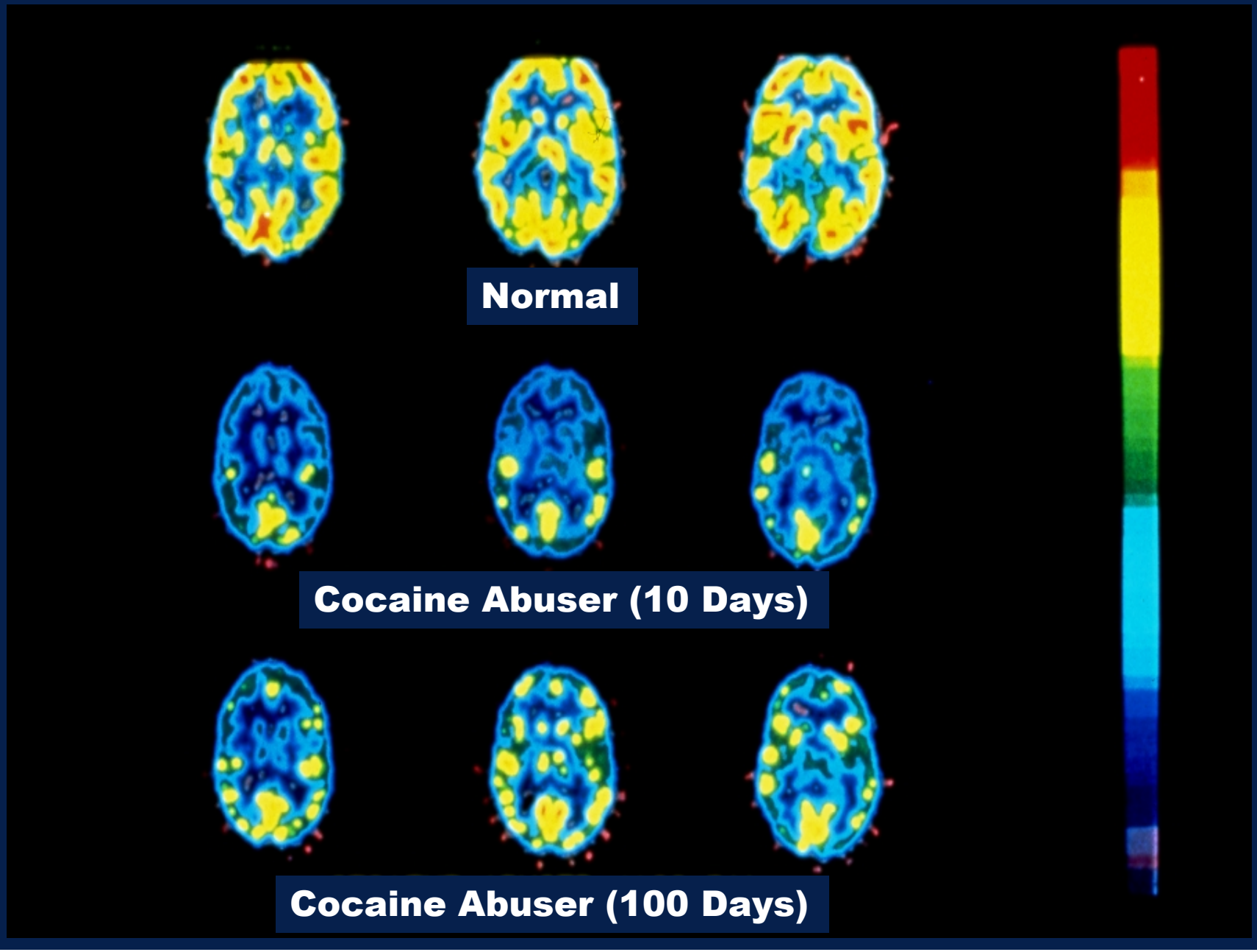
Motor Task

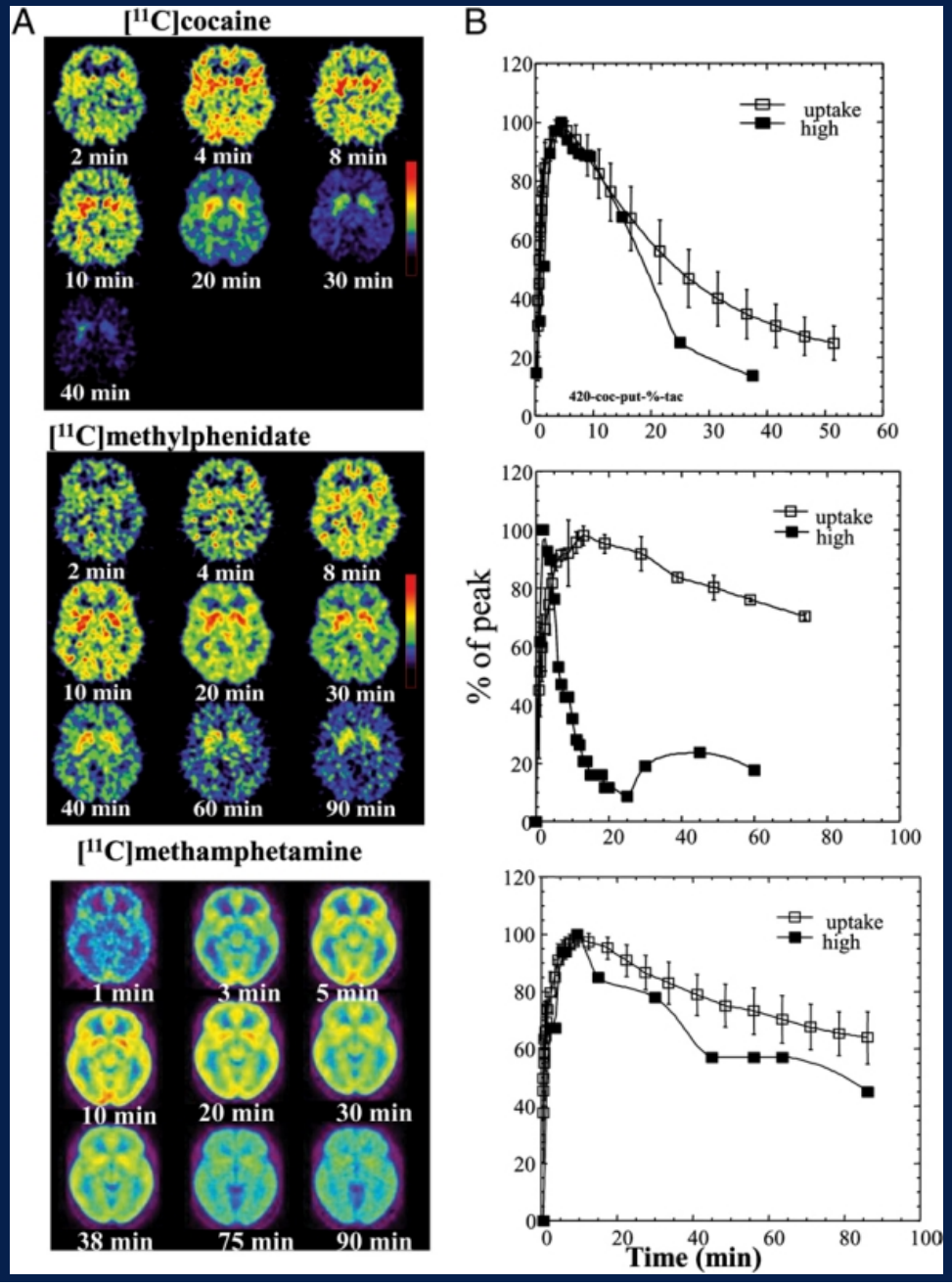
Loss of dopamine transporters in the meth abusers may result in slowing of motor reactions.

Memory Task

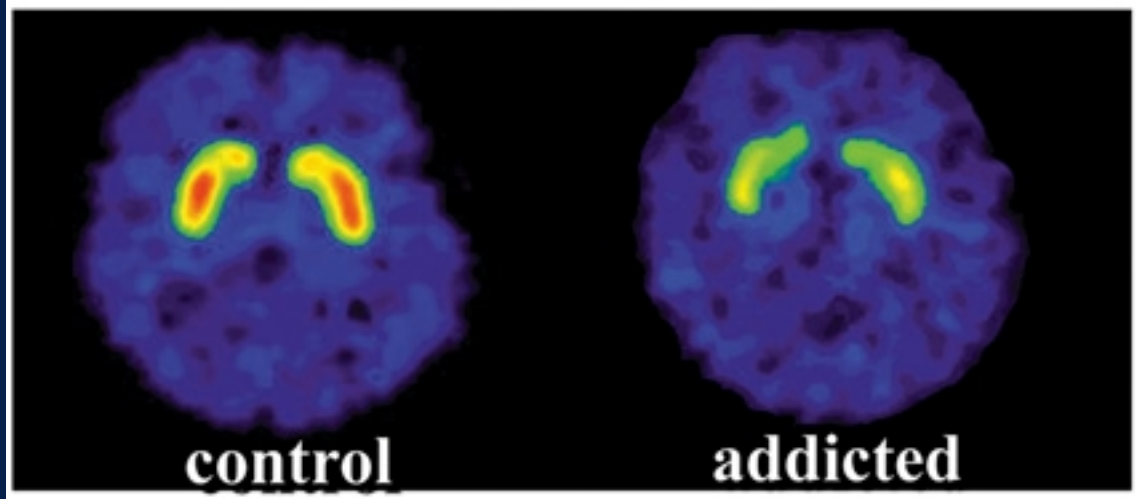
Loss of dopamine transporters in the meth abusers may result in memory impairment.

BNL/UCLA/SUNY
NIDA, ONDCP, DOE


Normal
Cocaine Abuser (10 Days)
Cocaine Abuser (100 Days)

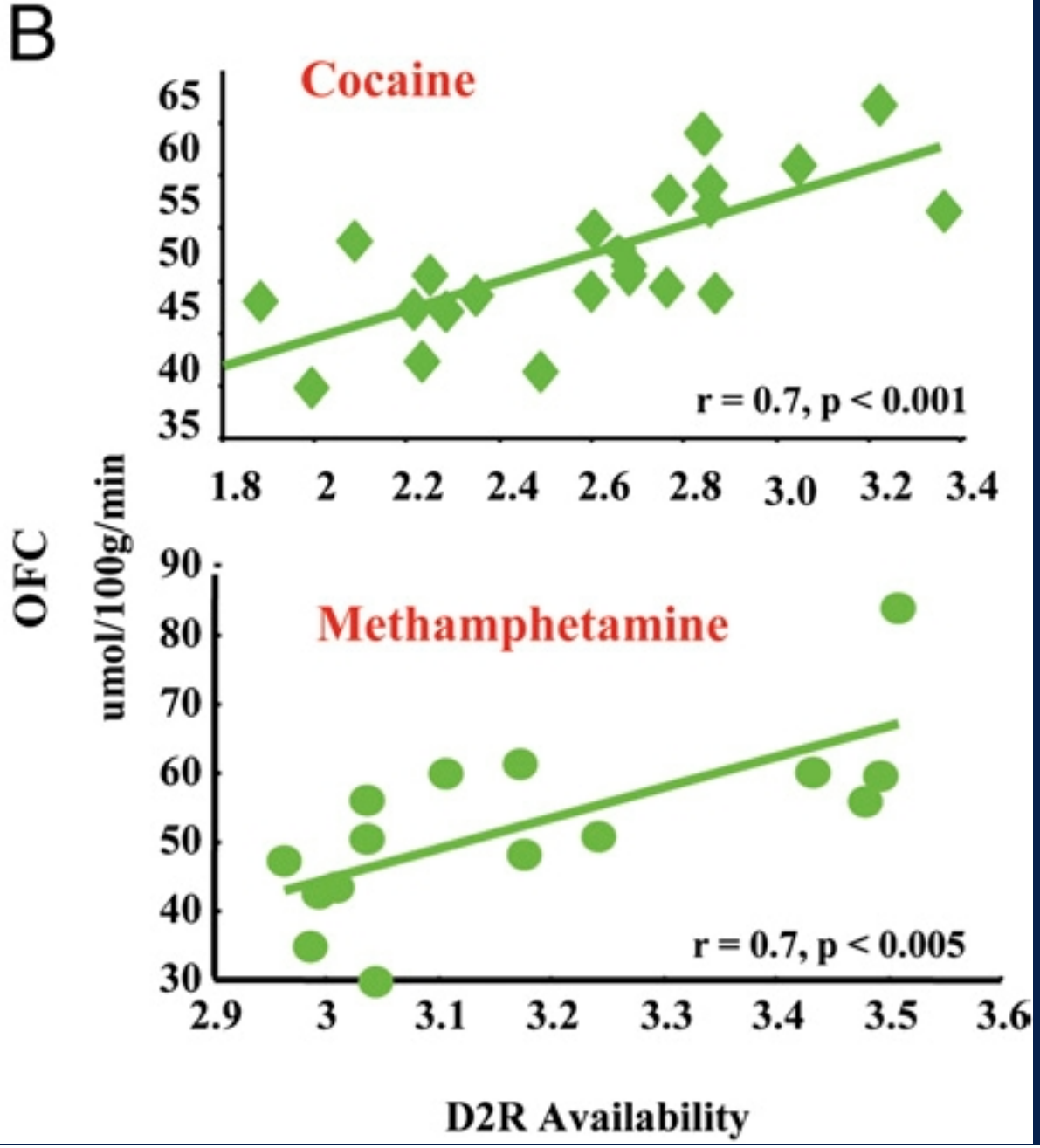

A
[11C]cocaine
2 min
4 min
8 min
10 min
20 min
30 min
40 min
[11C]methylphenidate
2 min
4 min
8 min
10 min
20 min
30 min
40 min
60 min
90 min
[11C]methamphetamine
1 min
3 min
5 min
10 min
20 min
30 min
38 min
75 min
90 min
B
uptake
high
420-coc-put-%-tac
% of peak
Time (min)

A

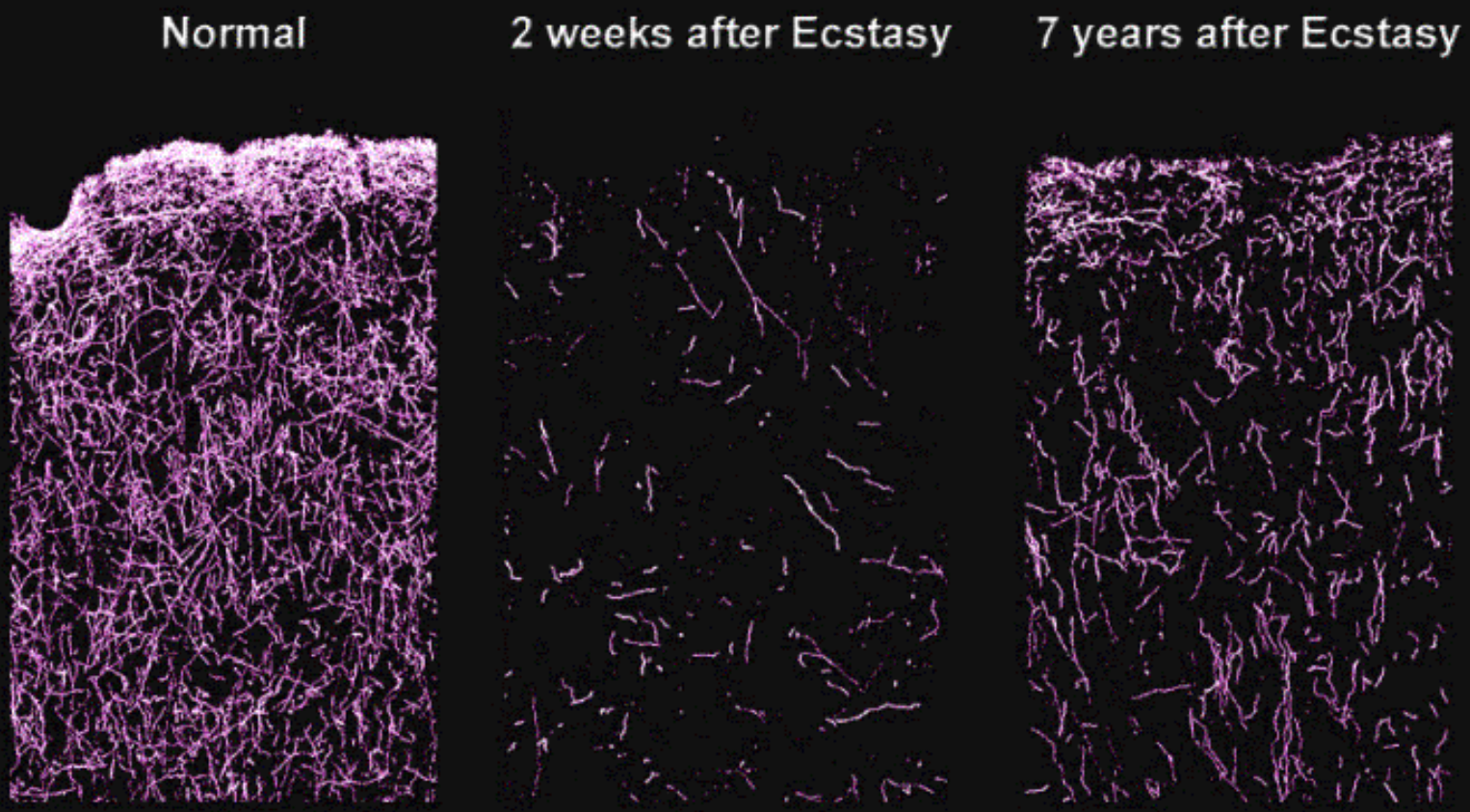

DA D2 receptors
control
addicted

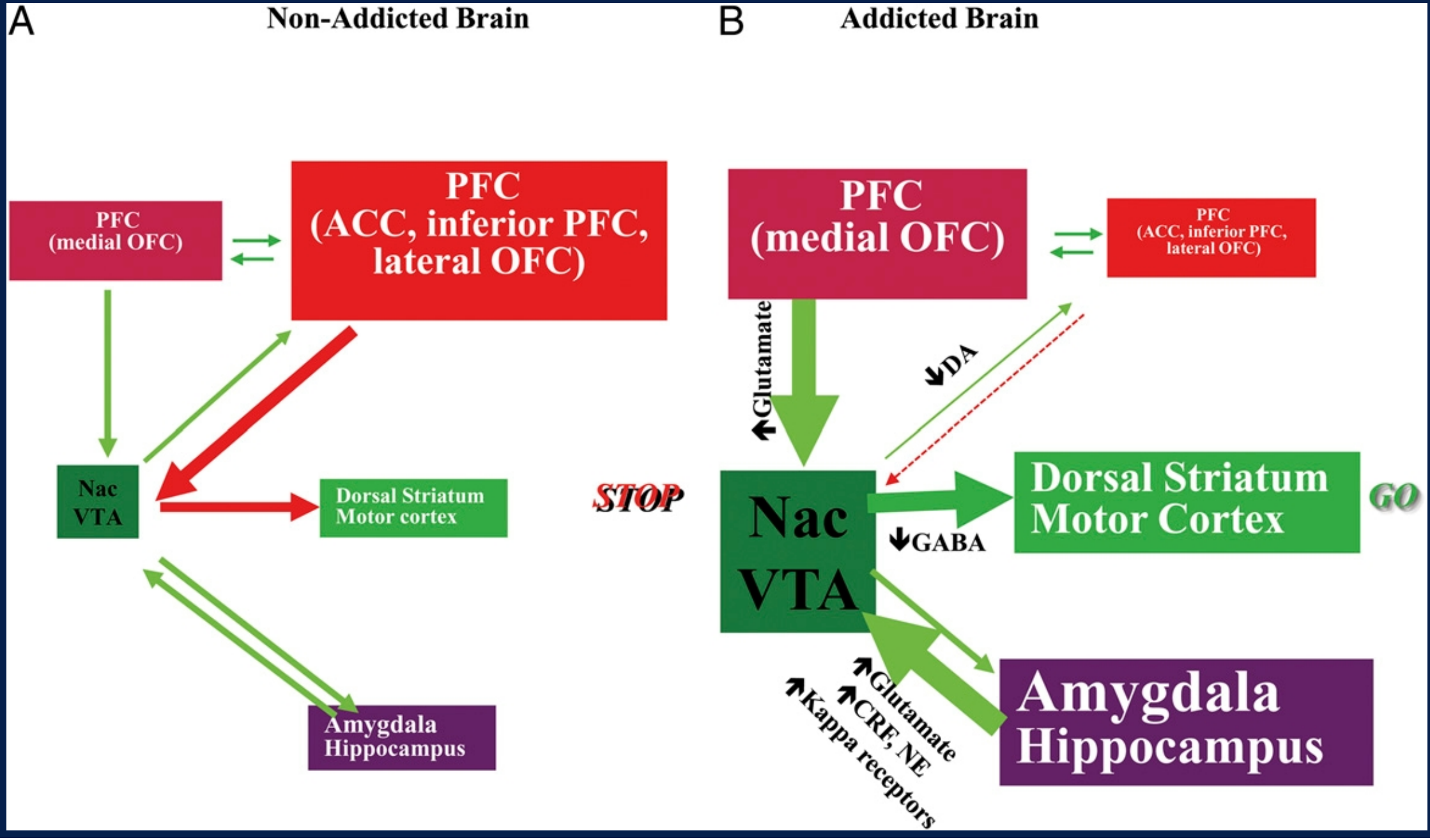

Brain glucose metabolism
OFC
control
addicted

B


Cocaine
r = 0.7, p < 0.001
Methamphetamine
r = 0.7, p < 0.005
OFC
umol/100g/min
D2R Availability

Serotonin Present in Cerebral Cortex Neurons




A
Non-Addicted Brain
PFC
(medial OFC)
PFC
(ACC, inferior PFC,
lateral OFC)
Nac
VTA
Dorsal Striatum
Motor cortex
Amygdala
Hippocampus
STOP
B
Addicted Brain
PFC
(medial OFC)
PFC
(ACC, inferior PFC,
lateral OFC)
Glutamate
DA
Nac
VTA
GABA
Dorsal Striatum
Motor Cortex
GO
Glutamate
CRF, NE
Kappa receptors
Amygdala
Hippocampus

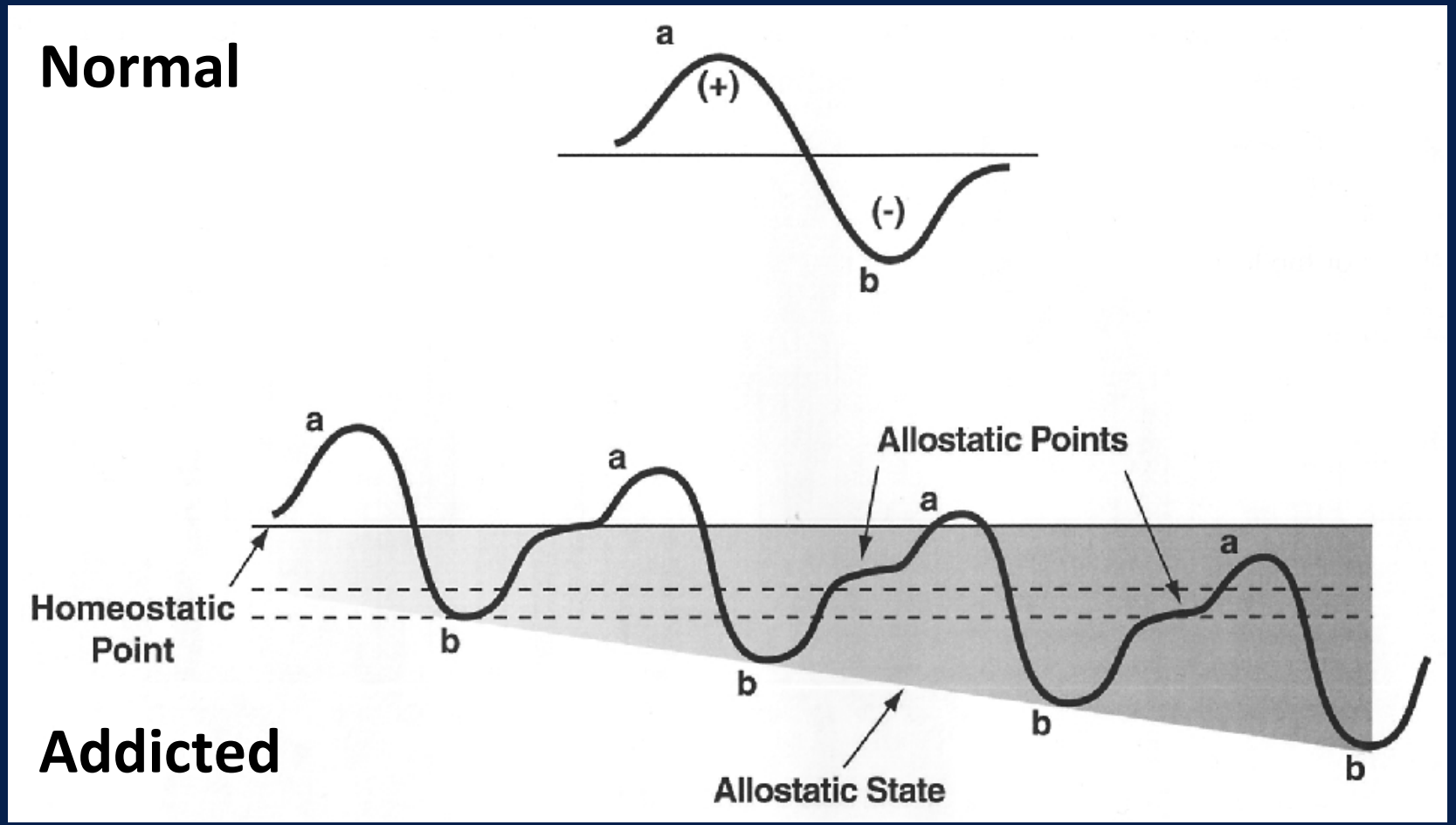
Transition to Addiction

Negative Reinforcement

Opponent-Process Model

- 'a' process – unconditional response – positive mood state
- 'b' process – unconditional, counter-adaptive negative opposite response – negative mood state

Brain Dysregulation in Addiction (CNS activity, mood, behavior)



Koob & LeMoal, *Neurobiology of Addiction*, 2006

Adaptive Changes

Allostasis: maintaining stability (or homeostasis) through change

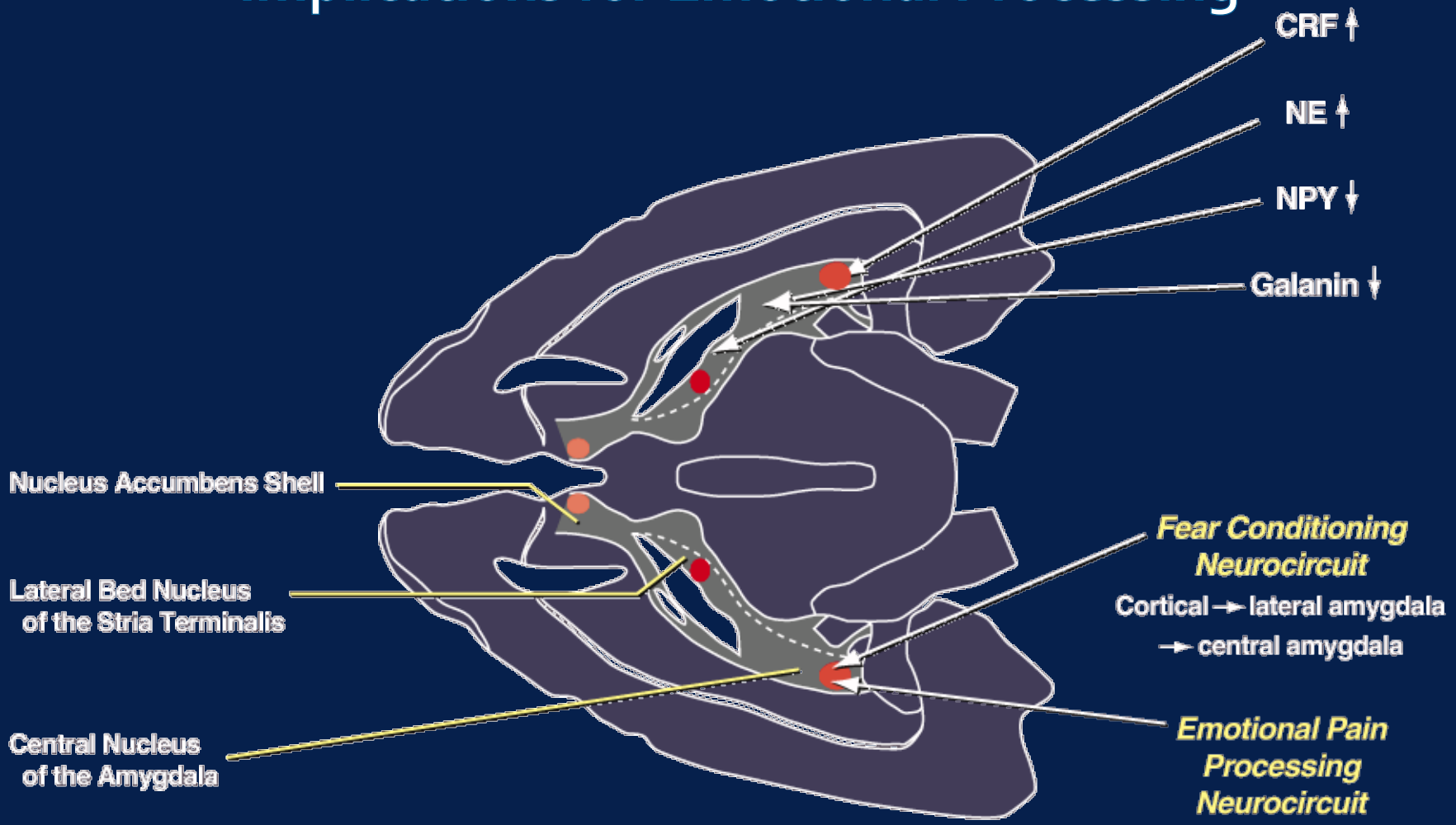
Allostatic Load: The wear and tear that the body experiences due to repeated cycles of allostasis as well as the inefficient turning-on or shutting off of these responses

Definitions

Extended Amygdala **—** Forebrain macrostructure composed of central medial amygdala, bed nucleus of the stria terminalis (BNST), and a transition zone in the medial part of the nucleus accumbens. A rich substrate for neurochemical and neurocircuitry interactions that produce the "dark side" of motivation.

Corticotropin-Releasing Factor — 41 amino acid polypeptide "brain stress" neurotransmitter that controls hormonal, sympathetic, and behavioral responses to stressors

Neurochemical Changes in the Extended Amygdala during the Development of Dependence: Implications for Emotional Processing



Major Neurocircuits Underlying Addiction

Acute reinforcing effects of drugs

- Activation of extended amygdala system, ventral tegmental area, arcuate nucleus, ventral striatal-ventral pallidal thalamic cortical loops

Acute withdrawal, negative affect, anxiety

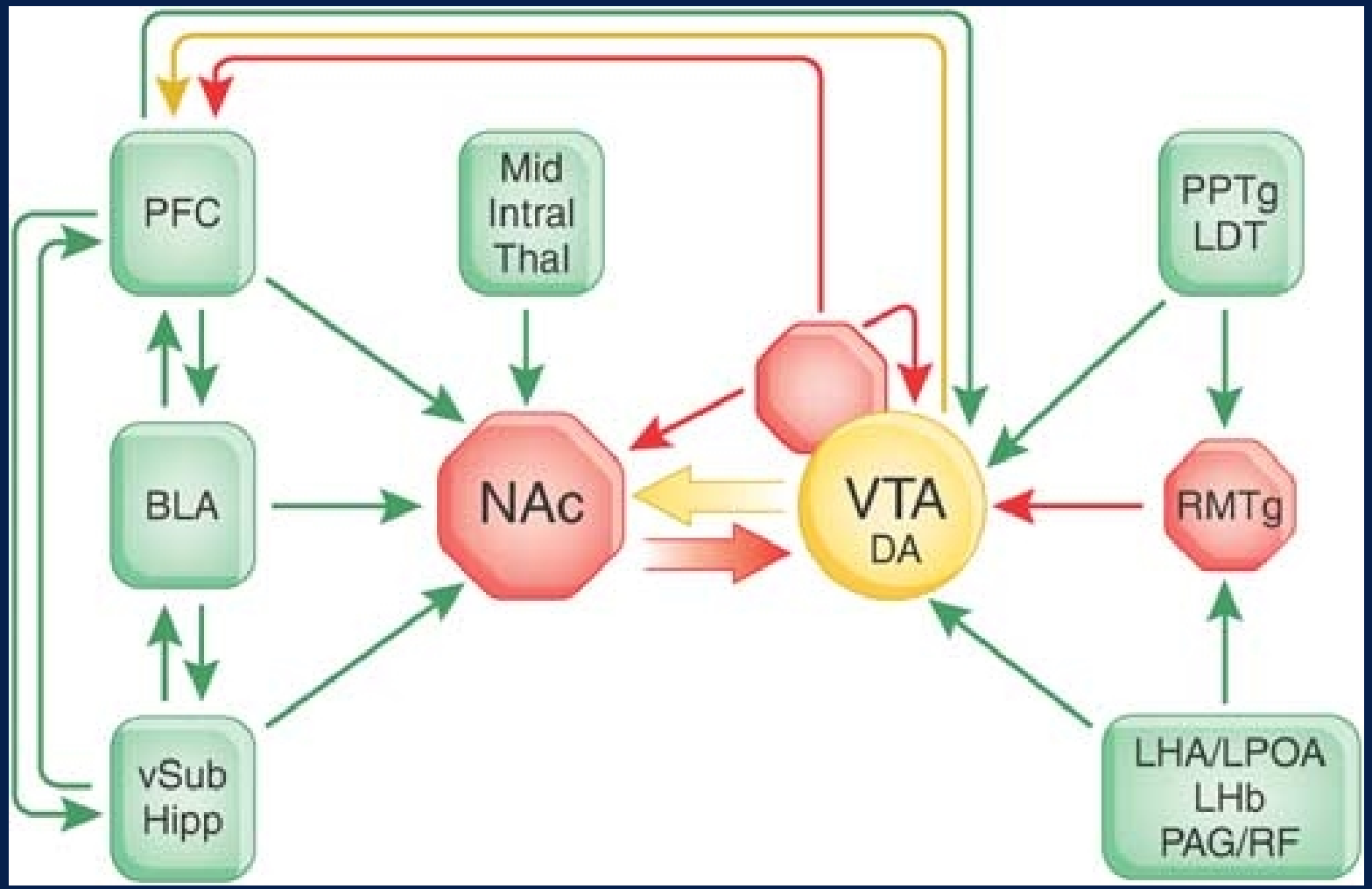
- Decrease function in extended amygdala reward system
- Increase in brain stress neurocircuitry

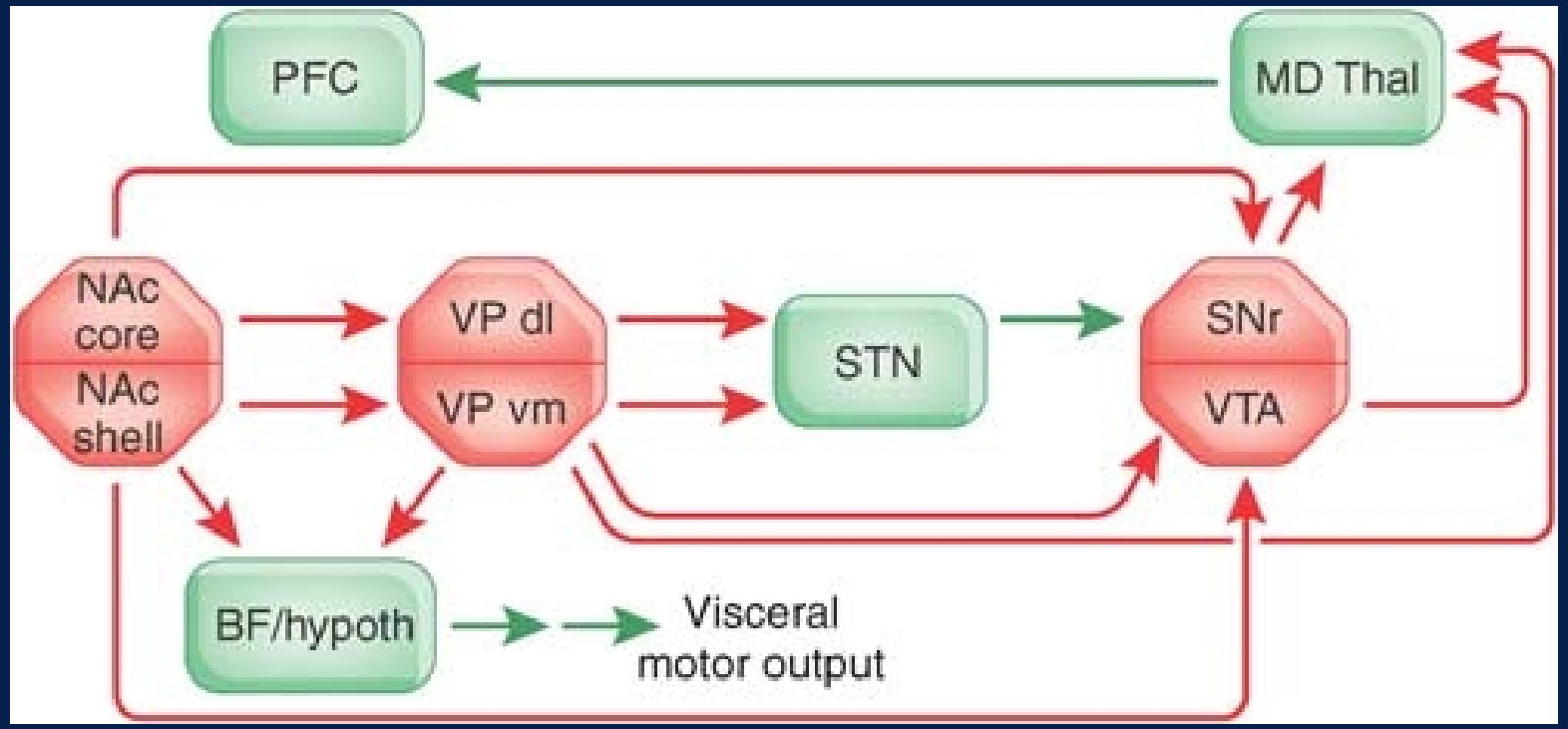
Preoccupation/anticipation/craving

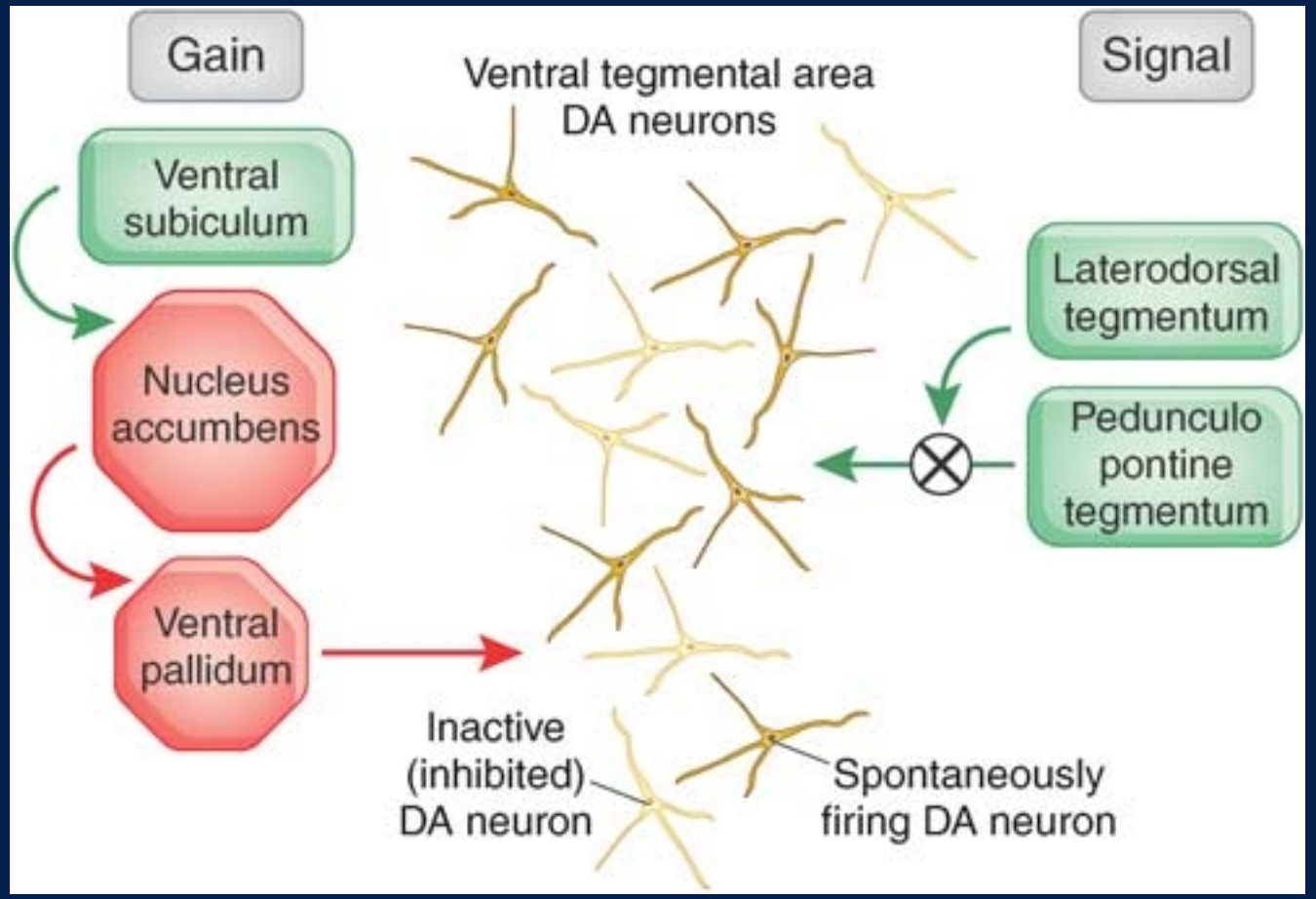
- Increase activity in extended amygdala (prefrontal cortex & basolateral amygdala)

Transition to addiction

- Positive reinforcement – ↑ extended amygdala
- Negative reinforcement - ↑ stress neurocircuits


PFC
Mid
Intral
Thal
PPTg
LDT
BLA
NAc
VTA
DA
RMTg
vSub
Hipp
LHA/LPOA
LHb
PAG/RF


PFC
MD Thal
NAc core
NAc shell
VP dl
VP vm
STN
SNr
VTA
BF/hypoth
Visceral motor output


Gain
Signal
Ventral tegmental area
DA neurons
Ventral
subiculum
Nucleus
accumbens
Ventral
pallidum
Laterodorsal
tegmentum
Pedunculo
pontine
tegmentum
Inactive
(inhibited)
DA neuron
Spontaneously
firing DA neuron

Conclusions

- Dopamine is still the main player
- However, both structural and homeostatic changes occur that reach far beyond the NAC
- The role of the Amygdala is most likely more prominent than we first thought

Pain vs Suffering

"If you are distressed by anything external, the pain is not due to the thing itself, but to your estimate of it; and this you have the power to revoke at any moment."

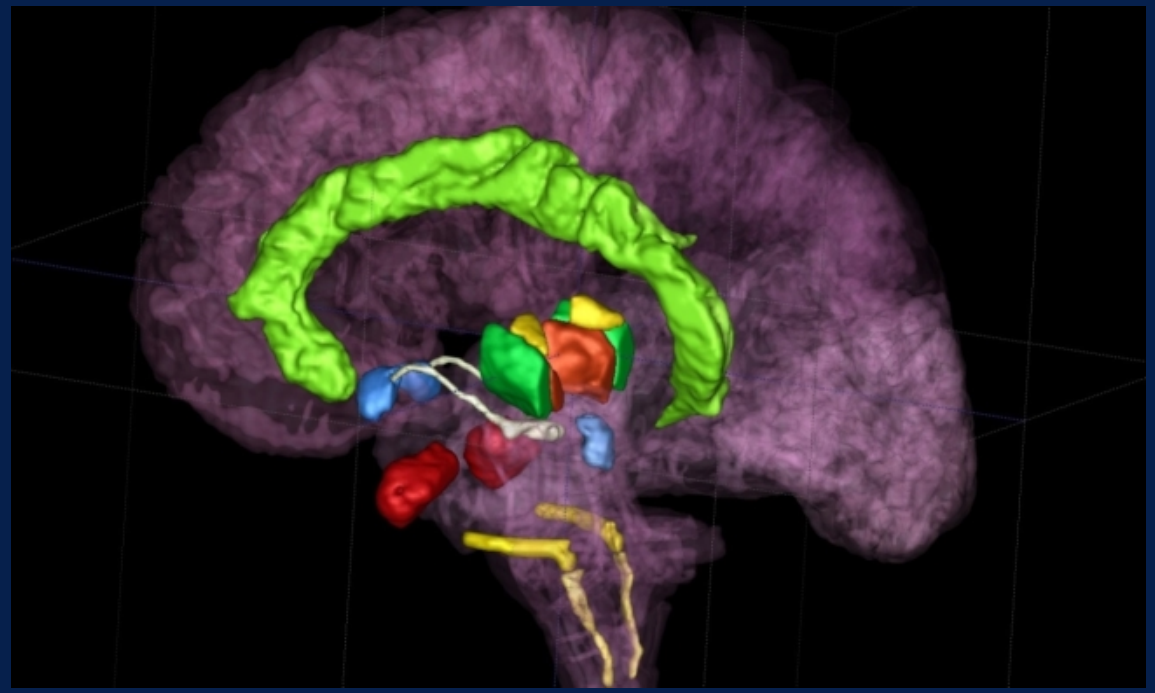
— Marcus Aurelius, Meditations

Confounding Issues

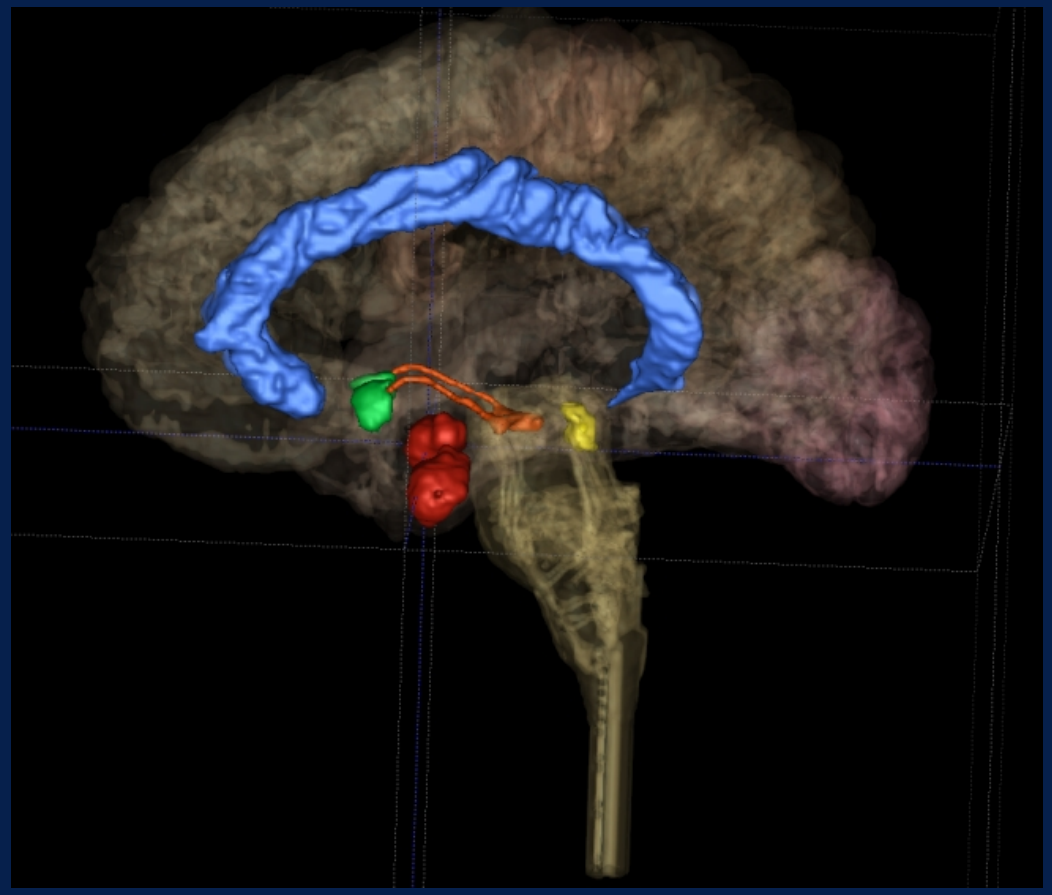
- Early Life Trauma
- Superimposed Mental Illness
- Social Instability
- Familial Predisposition
- The Current Health Care System

What is Our Goal?

- Get rid of all your pain?
- Make you forget you have pain?
- Decrease your pain and improve your function!



Pain

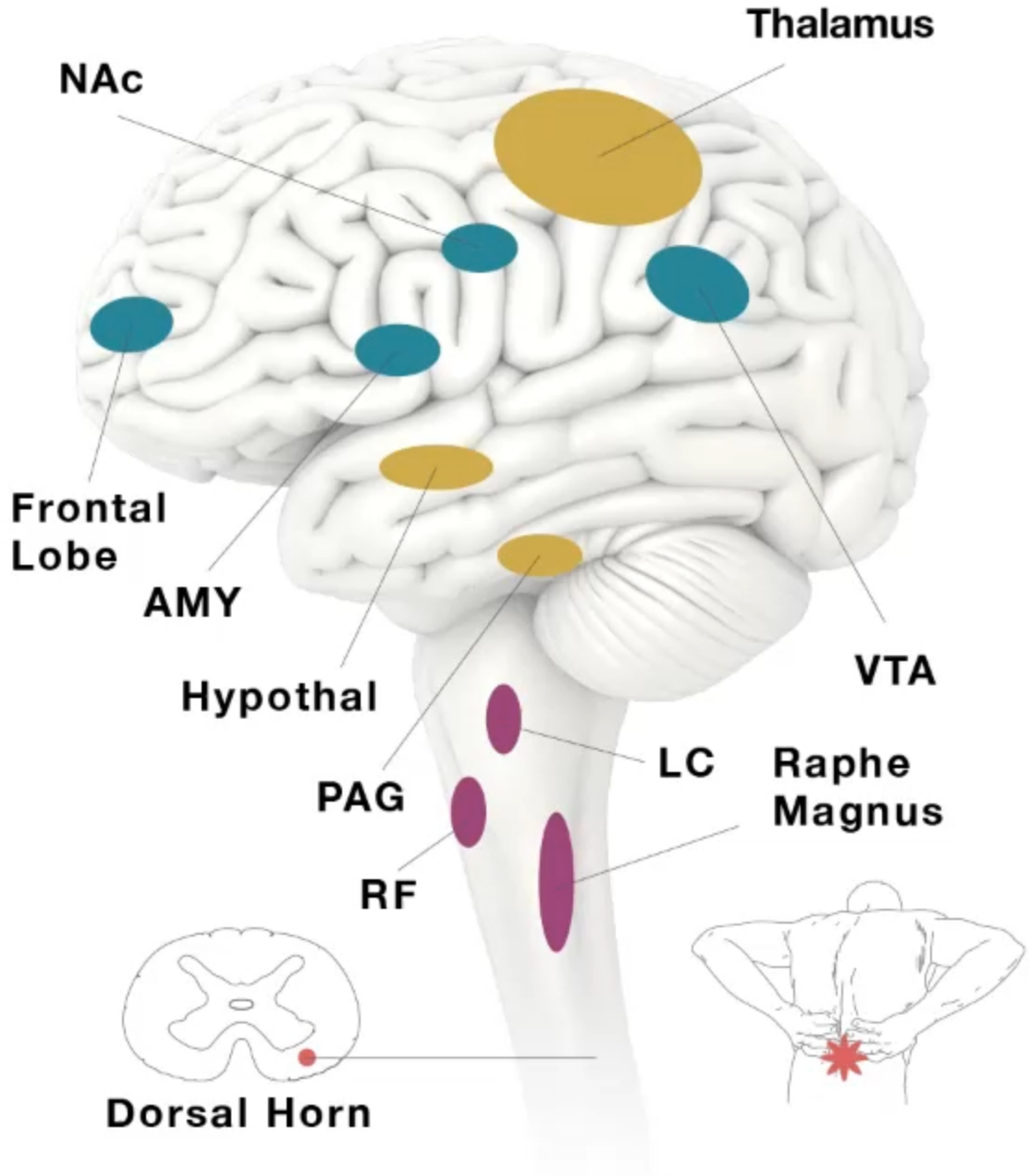


Addiction

Neuroscience of Pain

Ascending Tracts

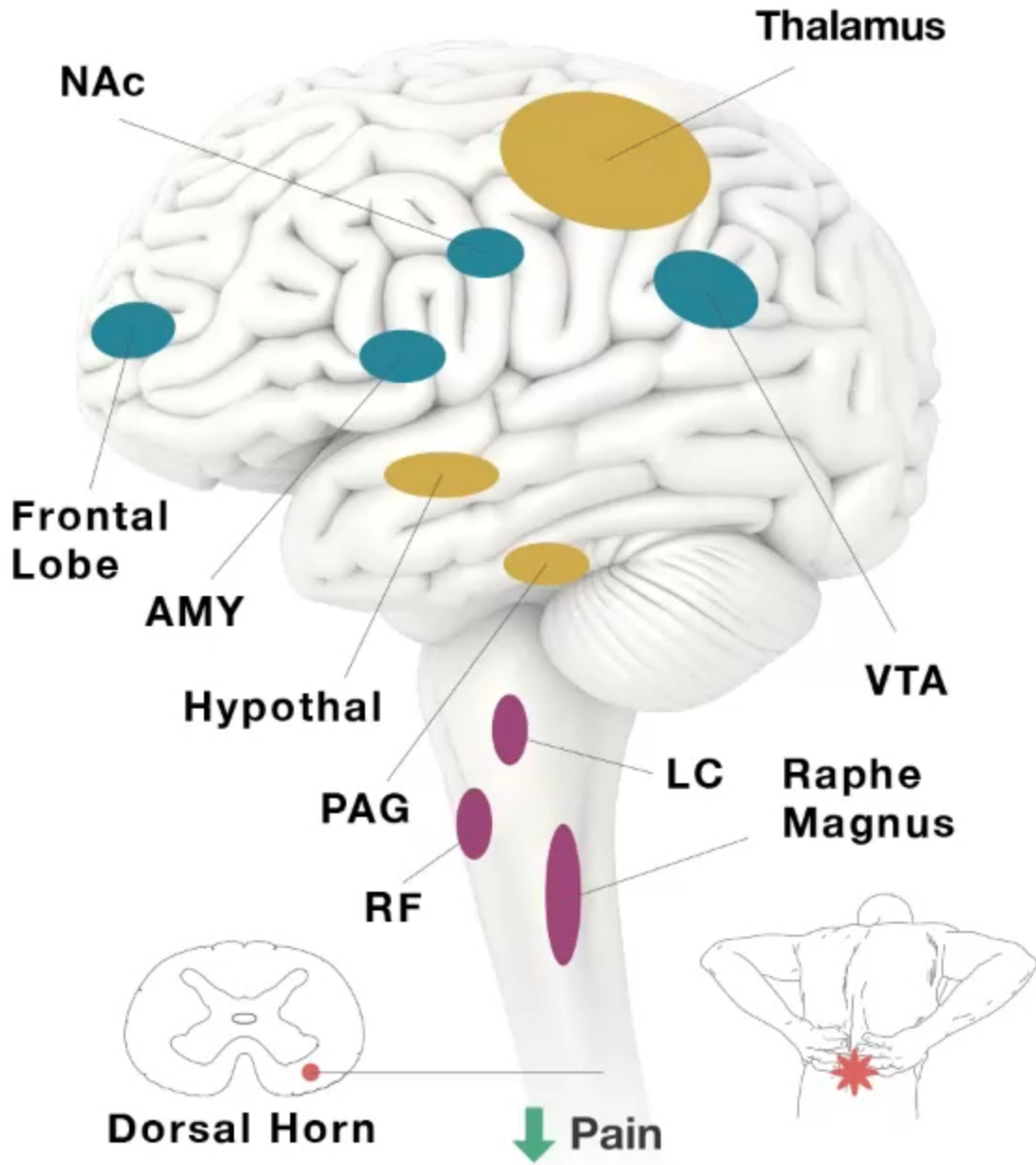
- Spinothalamic/Cervicothalamic (localization)
- Spinoreticular (arousal, sleep/wake cycles)
- Spinomesencephalic (PAG, emotional context of pain)
- Spinohypothalamic (endocrine response)

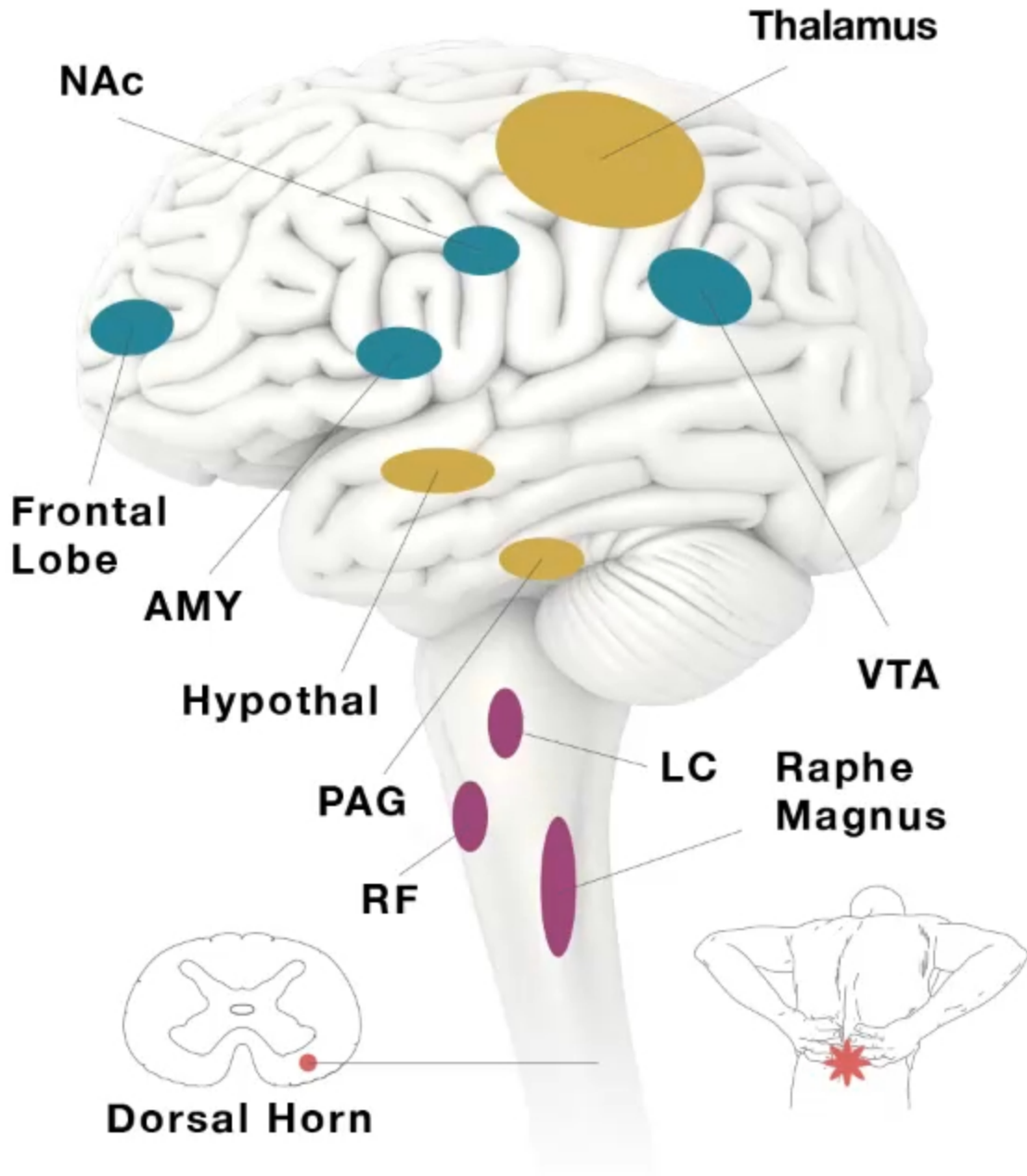

Thalamus
NAc
Frontal
Lobe
AMY
Hypothal
VTA
LC
Raphe
Magnus
PAG
RF
Dorsal Horn

Neuroscience of Pain

Descending tracts (GABA inhibits)

- PAG → Locus Coeruleus (NE)→ Dorsal horn (can increase pain)
- PAG → Raphe Magnus (5HT, Enk) → Dorsal horn (will decrease pain)


Thalamus
NAc
Frontal
Lobe
AMY
Hypothal
VTA
LC
Raphe
Magnus
PAG
RF
Dorsal Horn
Pain


Thalamus
NAc
Frontal
Lobe
AMY
Hypothal
VTA
LC
Raphe
Magnus
PAG
RF
Dorsal Horn

Who Cares and Why Does it Matter?

- Opioids (PAG, Ventral Medulla, Dorsal Horn)
- Serotonin (amygdala, Raphe Magnus)
- Norepinephrine (Locus Coeruleus)
- Why GABA matters
  - Enk inhibits GABA thus allowing release of the above
  - With benzos or EtOH descending pathways are inhibited

Normal Response with "High/Average Pain Tolerance"

- Acute on chronic pain (twisting a chronically painful back)
- Emotionally asses and if all good then,
- Increase descending inhibition
- Thus decreasing the ascending pain signal
- All happening while we produce our own endorphins from the dorsal horn and the periaqueductal grey (PAG)

- **This equals less pain and greater function**

Normal Response with "Low Pain Tolerance"

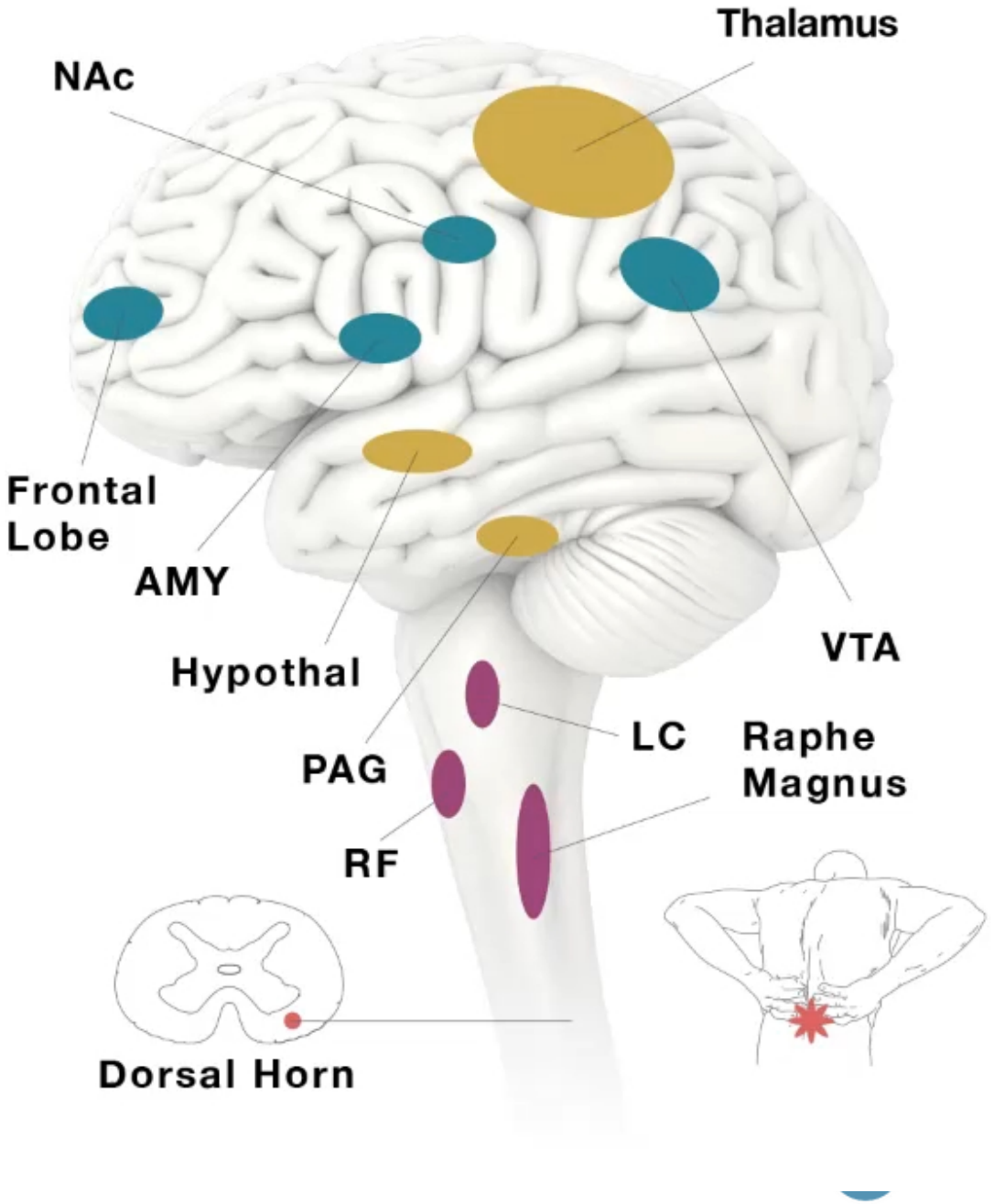
- Acute on chronic pain (twisting a chronically painful back)
- Emotionally assess and not all good
- Increase in descending excitatory pathway
- Decrease in inhibitory pathway
- Increase in perceived pain followed by hysteria and tachypnea
- This changes the pH in the serum and thus increases the amount of endorphin released in response from PAG and Zone II and III of the dorsal horn
- Then after the panic like state, pain normalizes

When Opioids are Added

- Decreased production of endogenous opioids
- Body "ramps up" pain signal frequency
- Thus greater signal from Ascending tracks (spinothalamic, Spinoreticular and Spinomesencephalic)
- More pain in widened area
- Decreased endorphin production from PAG and Dorsal Horn
- Worsened sleep patterns
- More emotional lability from opioid effects in limbic system

So…

- Emotionally assess and all good or not all good?
- Increase in descending excitatory pathway to overcome outside opioids
- Decrease in inhibitory pathway given presence of opioid
- Increase in perceived pain followed by hysteria (tachypnea blocked by opioids)
- So no change in the pH in the serum and thus no increase in the amount of endorphin released from PAG and Zone II and III of the dorsal horn
- Then after the panic like state, pain continues and in many cases widens in area and intensity from increased c-fiber signal


Thalamus
NAc
Frontal
Lobe
AMY
Hypothal
PAG
RF
LC
Raphe
Magnus
VTA
Dorsal Horn

Conclusions

- Trauma causes a maladaptive response in the reward (VTA and Nac) and value (OFC, mPFC) systems
- Substances make the brain feel "right", thus increasing addiction liability
- Trauma and opioids create maladaptive responses in the pain signaling pathways leading to more severe and chronic pain