Singer Amy Winehouse performs in Dingle

Wall Street Journal

"THEY TRIED TO MAKE ME GO TO REHAB"

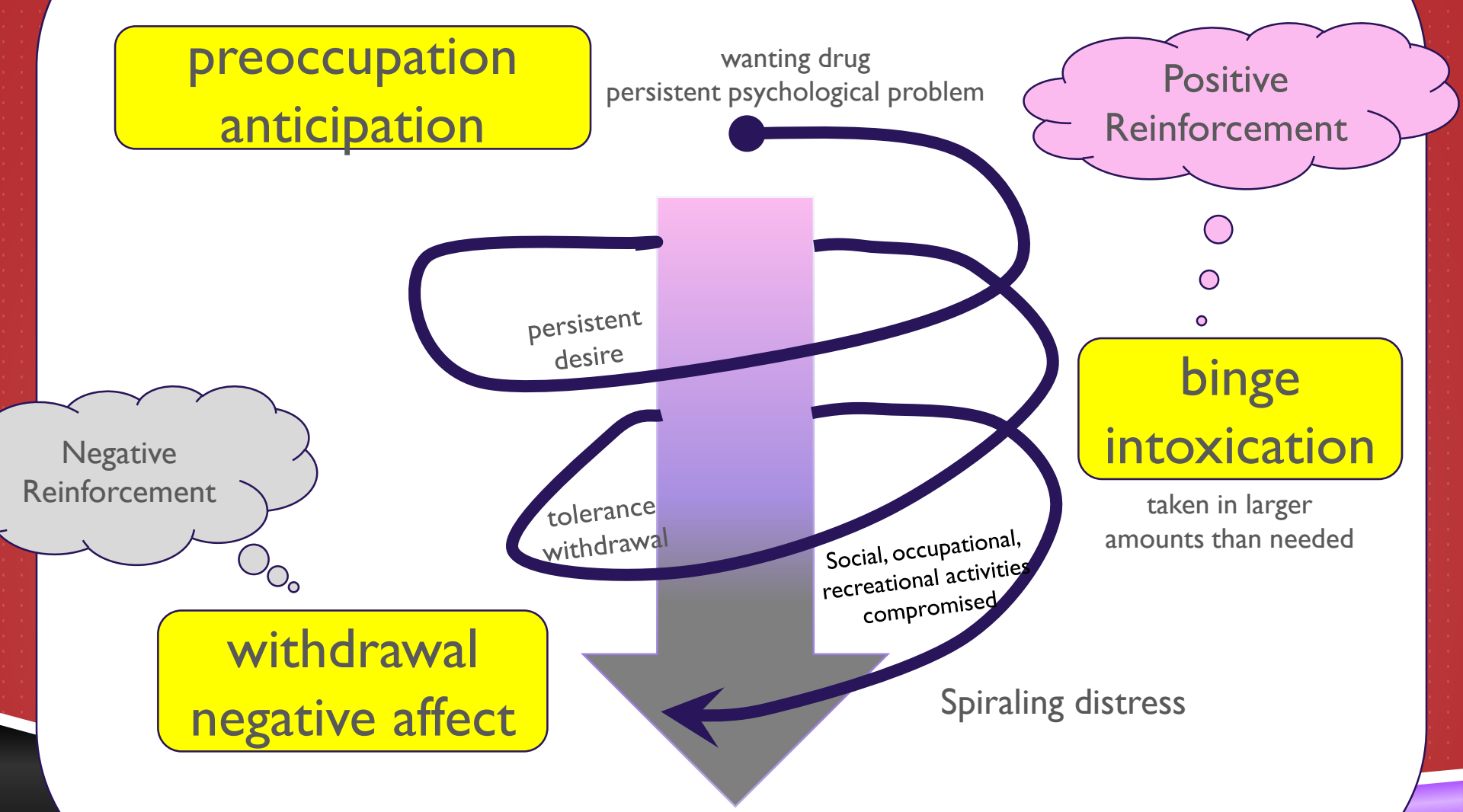
Mary ET Boyle, Ph. D.

Department of Cognitive Science

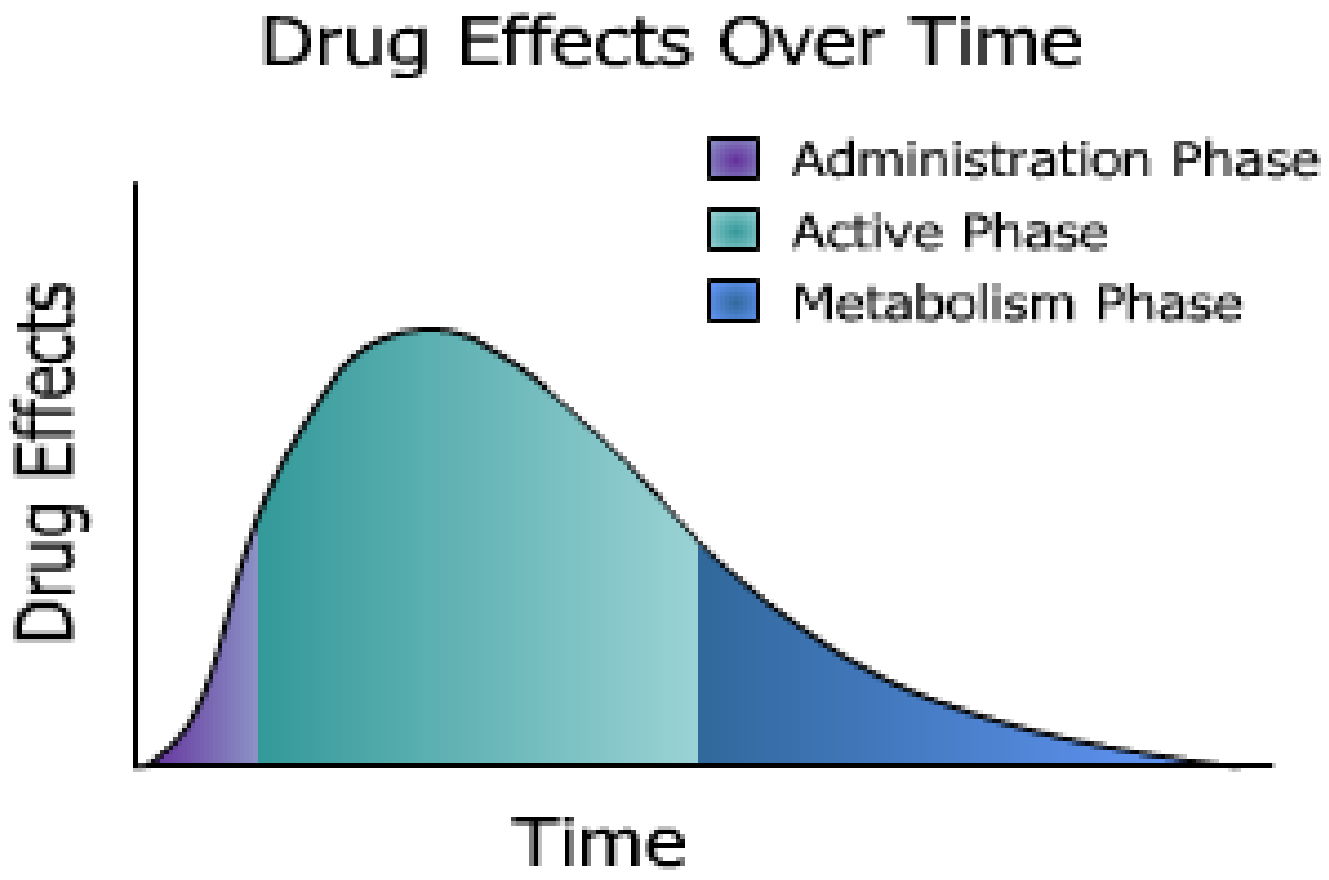
UCSD

Part 2

The spiraling distress/addiction cycle

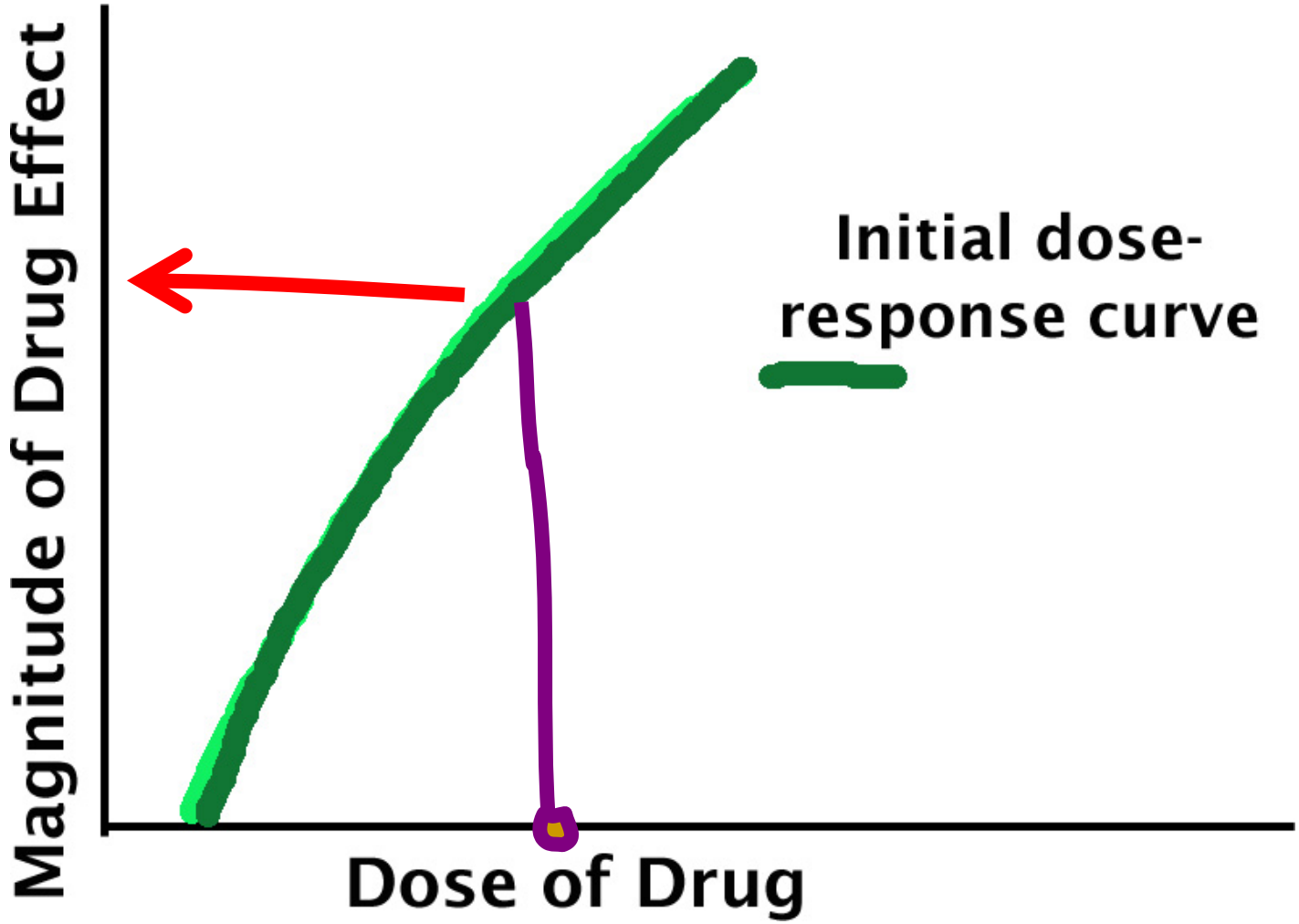


Adapted from Koob & Le Moal (2001) *Neuropsychopharmacology* **24,** 97–129

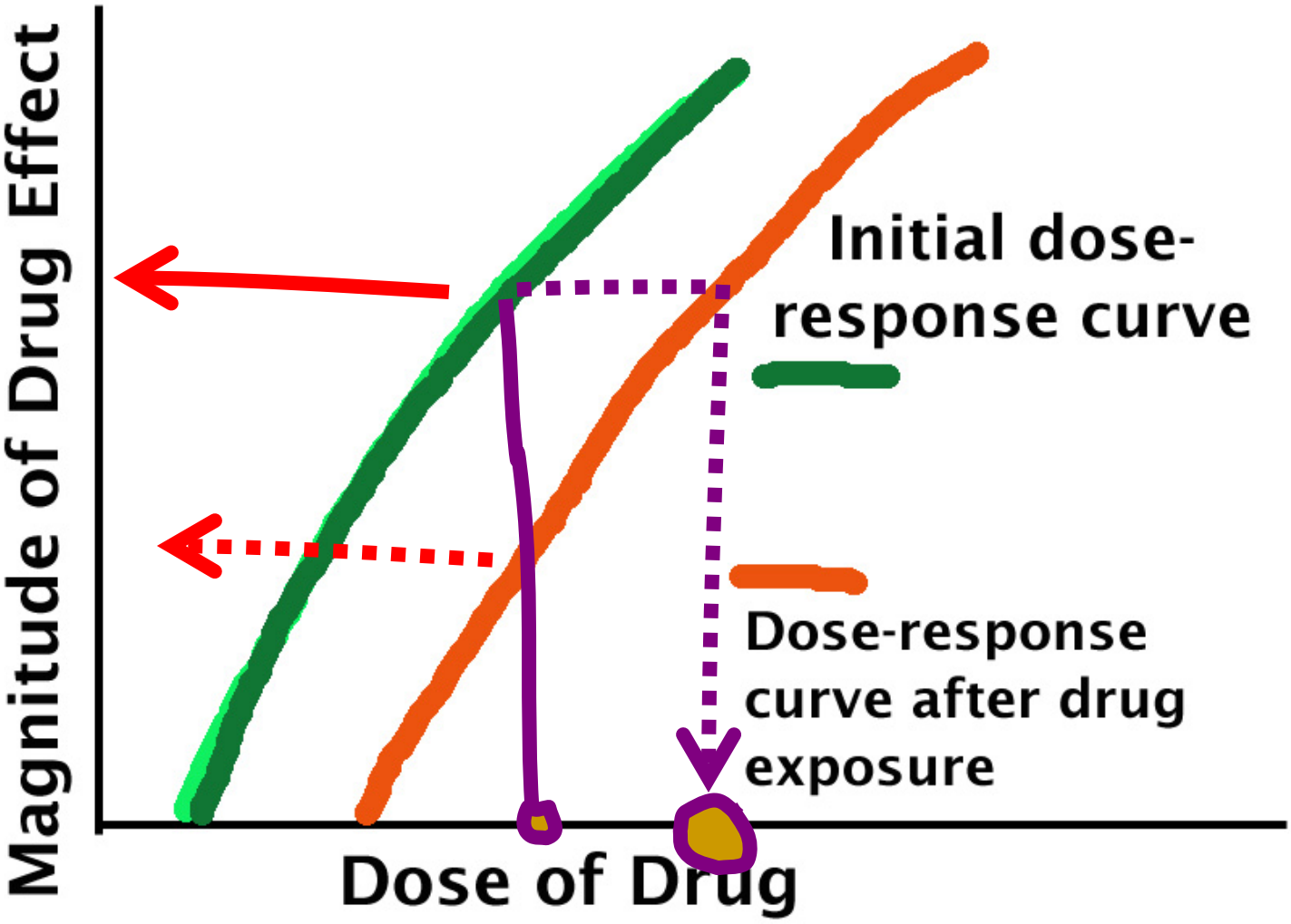


active drug → metabolism → inactive drug

DOSE RESPONSE CURVE...

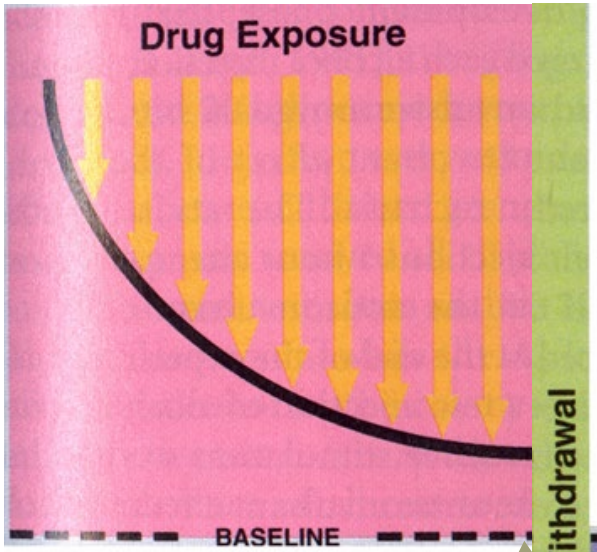


DOSE RESPONSE CURVE...



TOLERANCE &WITHDRAWAL
REWARD SYSTEM DYSREGULATION

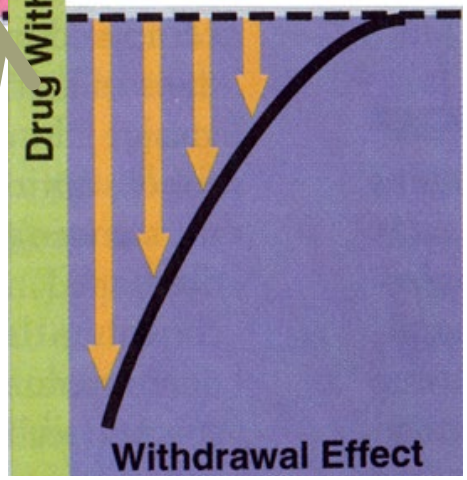
Drug **effect decreases** with increased exposure



Drug exposure leads to the development of **adaptive** neural changes that produce tolerance by counteracting the drug effect.

Withdraw from drug

With no drug to **counteract** them, the neural adaptations produce withdrawal effects **opposite** to the **effects** of the drug.

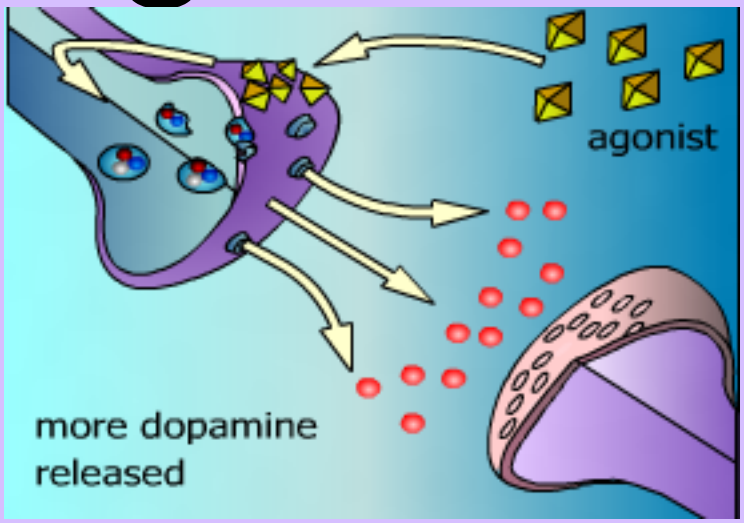


The magnitude of the withdrawal effect is **proportional** to the tolerance of the drug.

ALTERING THE FUNCTION OF NEUROTRANSMITTERS CAN CHANGE BEHAVIOR.

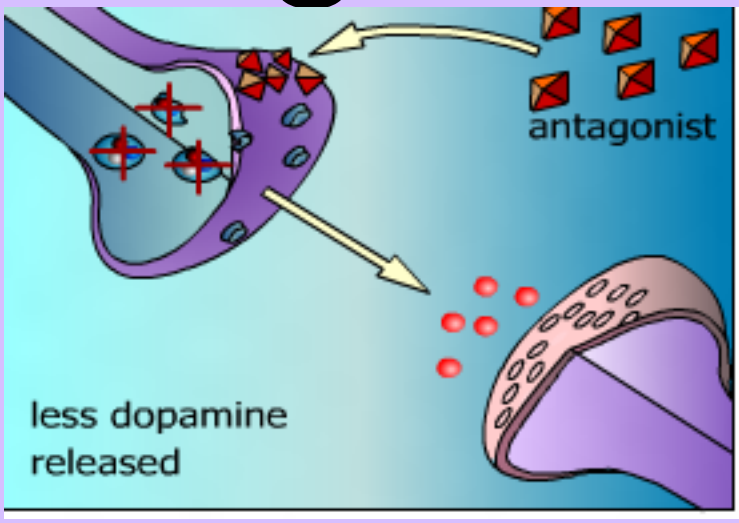
mimics or ***facilitates*** the release

agonist

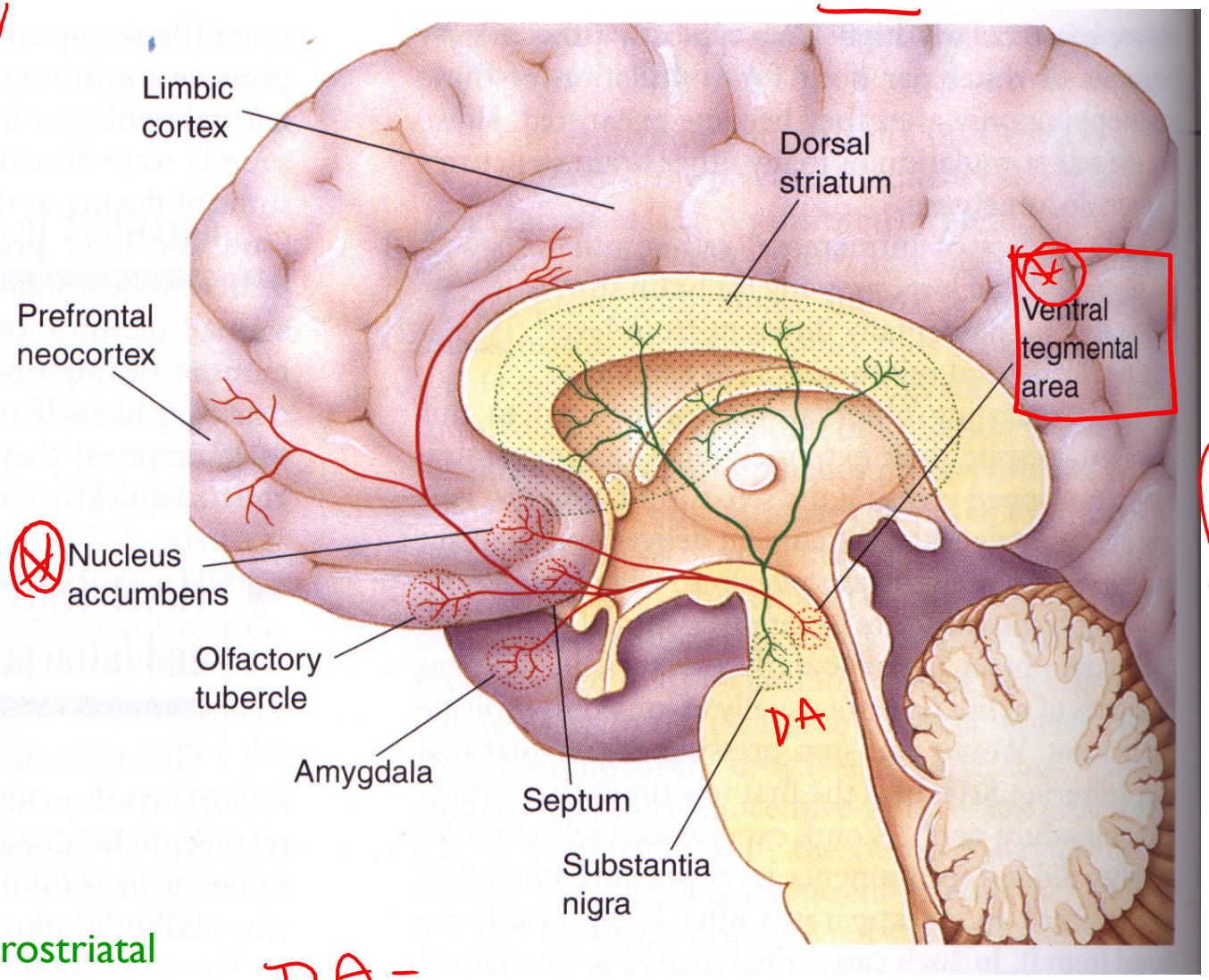


oppose or ***blocks*** the release

antagonist



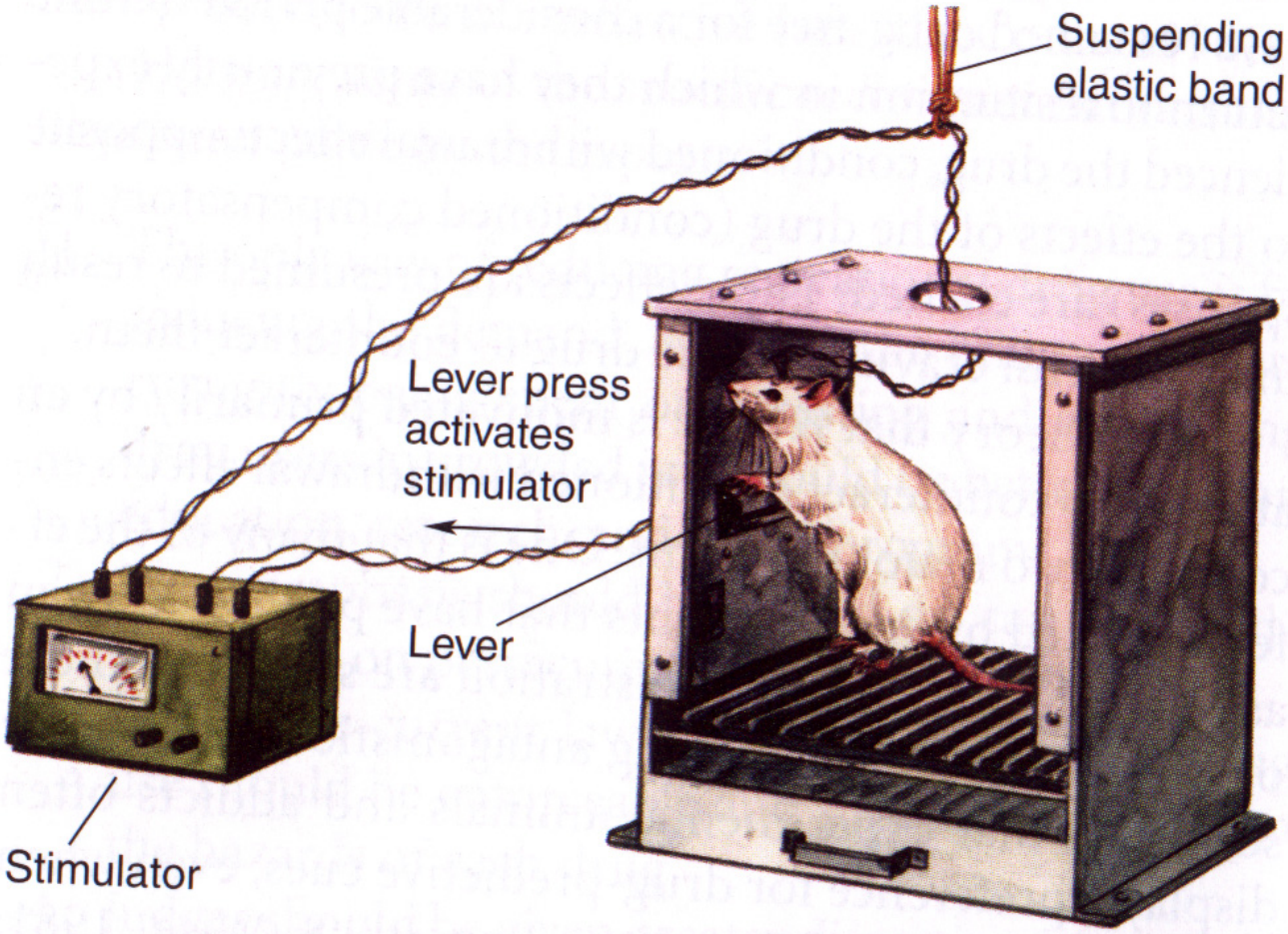
MESOTELECEPHALIC DA SYSTEM



Nigrostriatal pathway

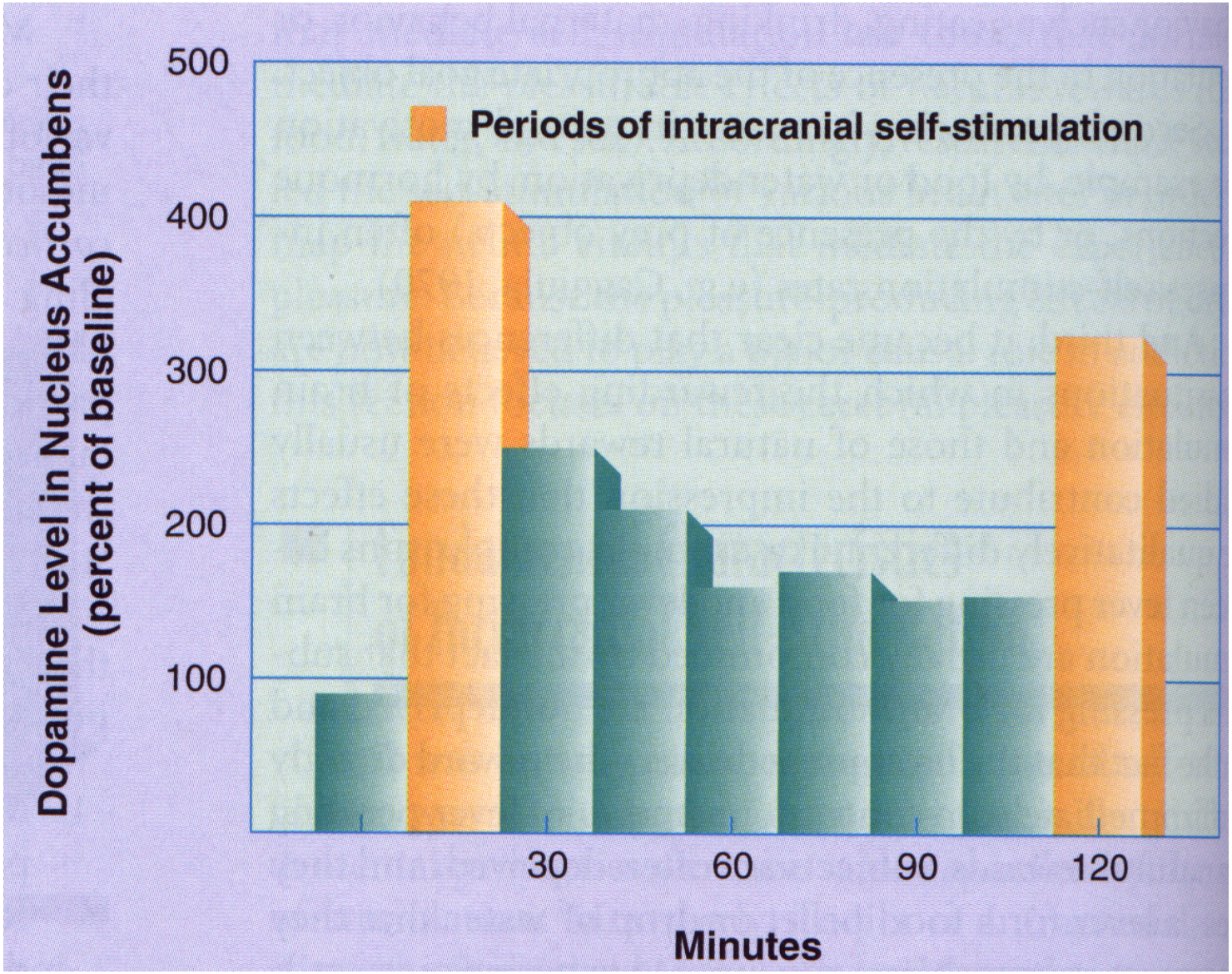
Mesocorticolimbic pathway

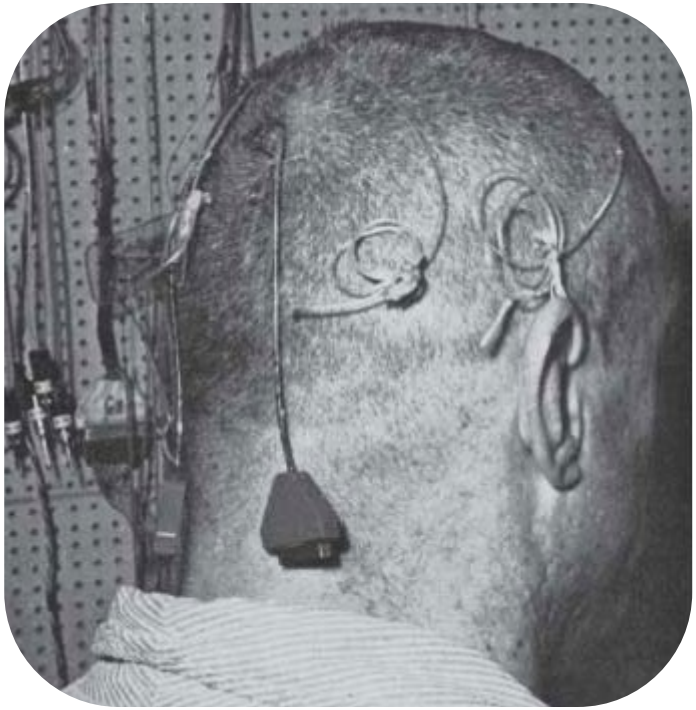
PLEASURE CENTERS OF THE BRAIN...



ICSS: intracranial self-stimulation

INCREASE IN DA RELEASE IN N. ACCUMBENS...





chronically implanted electrodes, one of which activated the medial forebrain bundle passing through the septum, a key part of the pleasure circuit. From Robert G. Heath, "Depth recording and stimulation studies in patients," in Arthur Winter, ed., *The Surgical Control of Behavior* (Springfield, Il.: Charles C. Thomas, 1971), 24. Reprinted with permission from Charles C. Thomas.

nature neuroscience

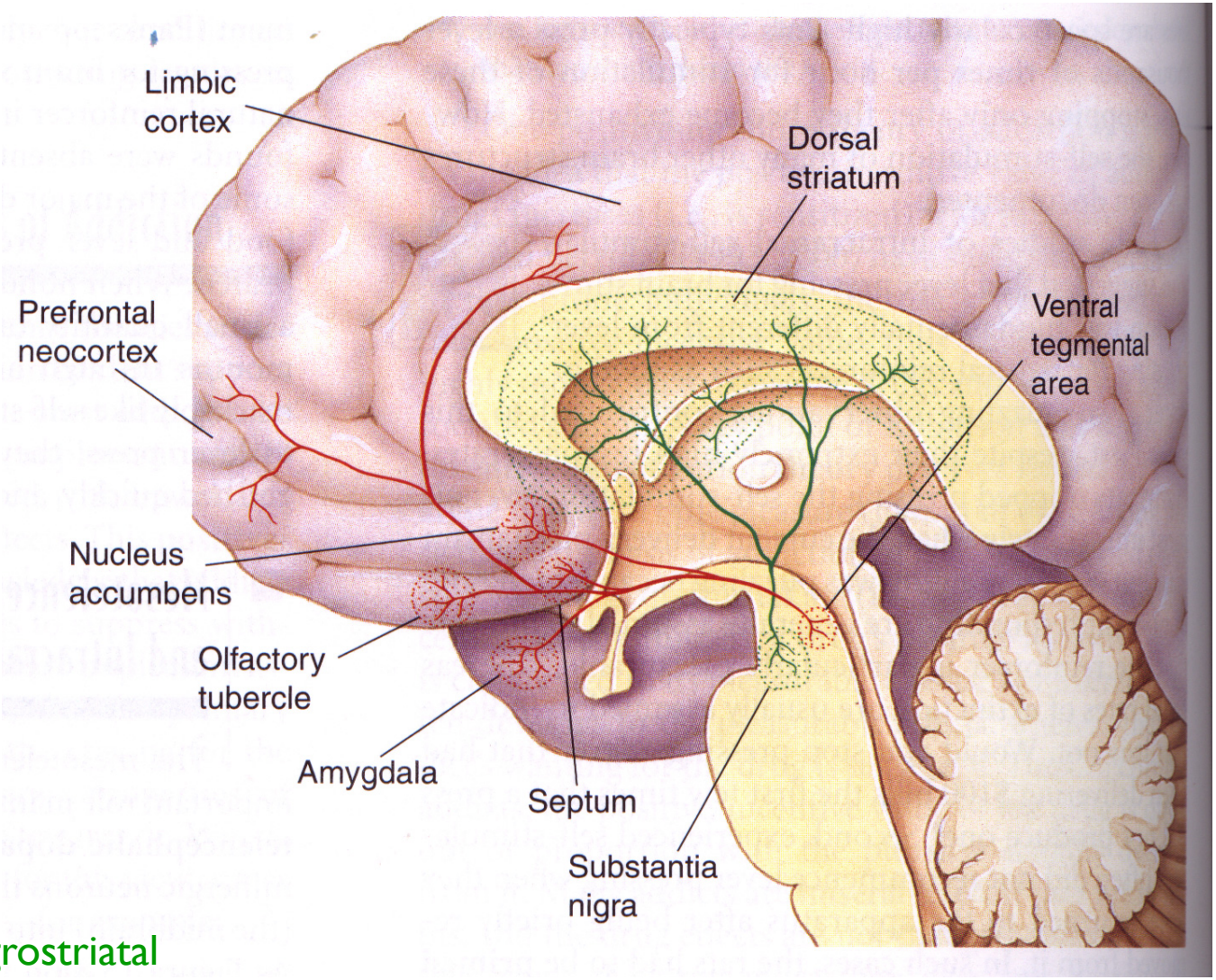
Is there a common molecular pathway for addiction?

Eric J Nestler

Eric Nestler (2005) *Nature Neuroscience* **8**, 1445 - 1449

Drugs of abuse	Cause common effects:	Characterized by:
Diverse chemicals	acute	immediate reward → repeated use → addiction
Distinct targets & effects	chronic	Loss of control over drug use. Negative emotional symptoms withdrawal.

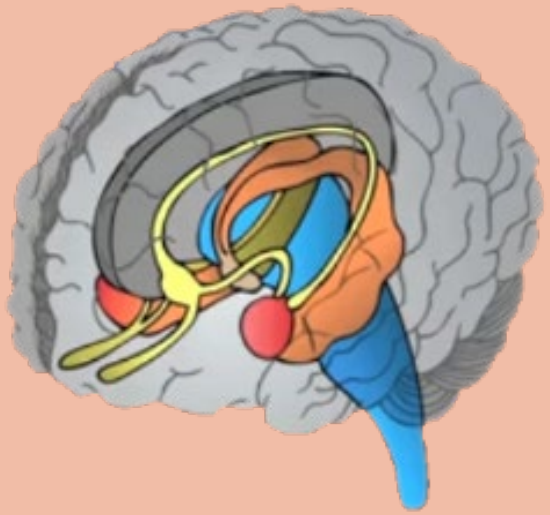
MESOTELECEPHALIC DA SYSTEM



Nigrostriatal pathway

Mesocorticolimbic pathway

Common actions on brain reward circuits

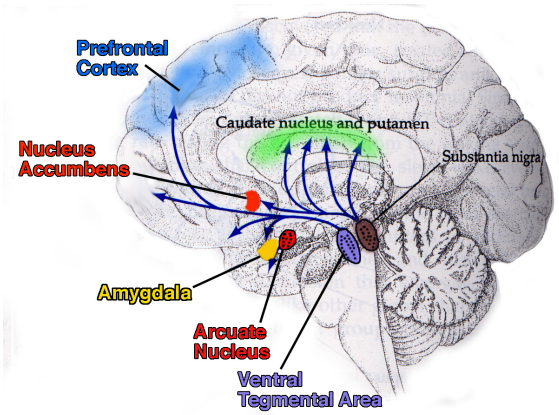


All drugs of abuse affect the limbic system.

Mesocorticolimbic system→ dopaminergic neurons in the ventral tegmental area → NAc.

Examples of common effects on the VTA-NAc.

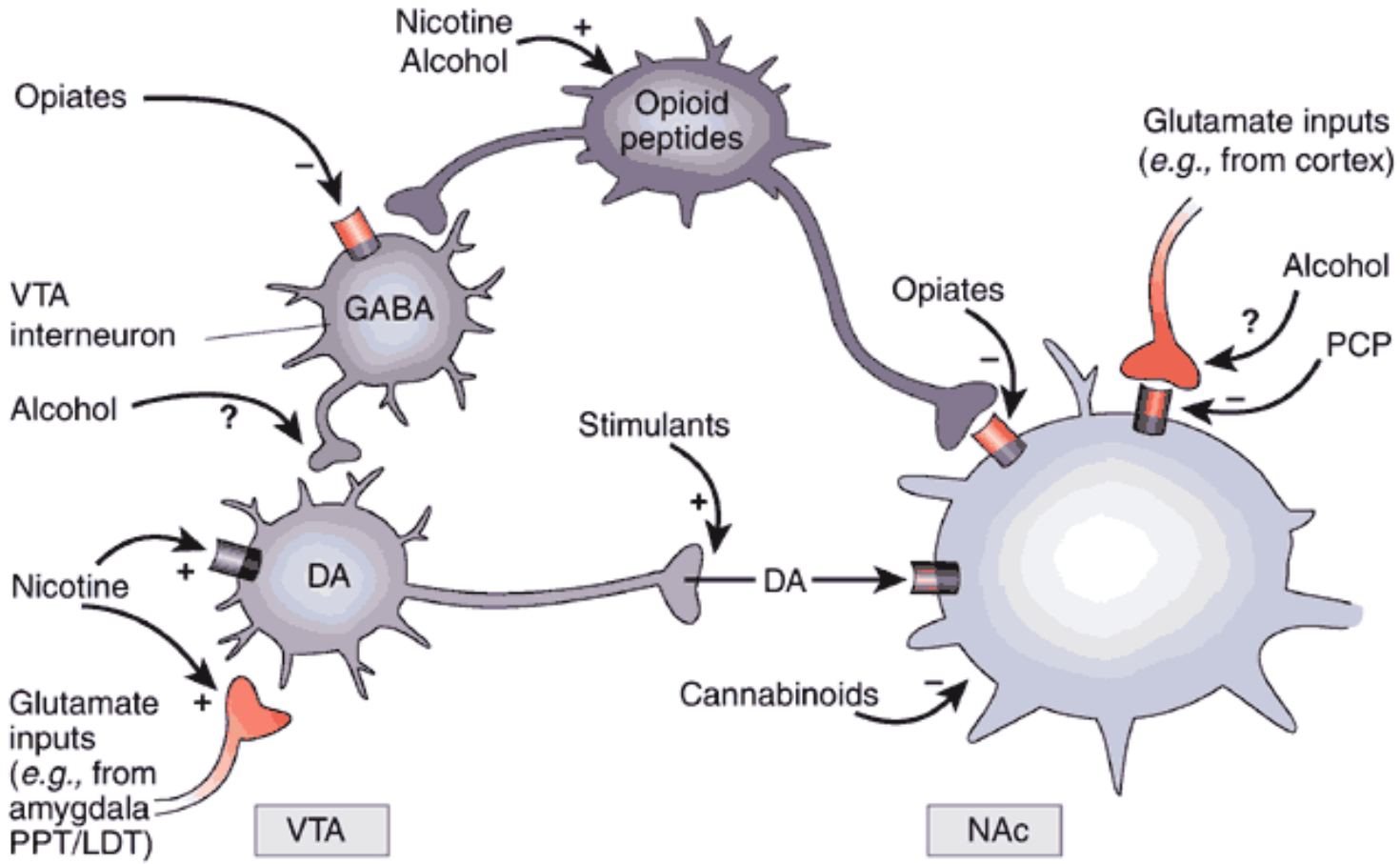
- Stimulants directly *increase* dopaminergic transmission in the NAc.



- Opiates do the same (indirectly) they inhibit GABAergic interneurons in the VTA, which *dis*inhibits VTA dopamine neurons.
- Opiates also *directly* act on opioid receptors on NAc neurons

Eric Nestler (2005) *Nature Neuroscience* **8**, 1445 - 1449

Highly simplified scheme of converging acute actions of drugs of abuse on the VTA-NAc.



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"On the basis of these common acute actions, one would expect that chronic exposure to drugs of abuse would also cause common chronic functional changes in the VTA-NAc pathway. Indeed, numerous common chronic adaptations have been described, examples of which are discussed in the next sections. Consistent with common mechanisms of addiction are the observations that certain drugs of abuse, under particular experimental conditions, can induce cross-tolerance and cross-sensitization to one another with respect to their locomotor activating and rewarding effects[9,10]."

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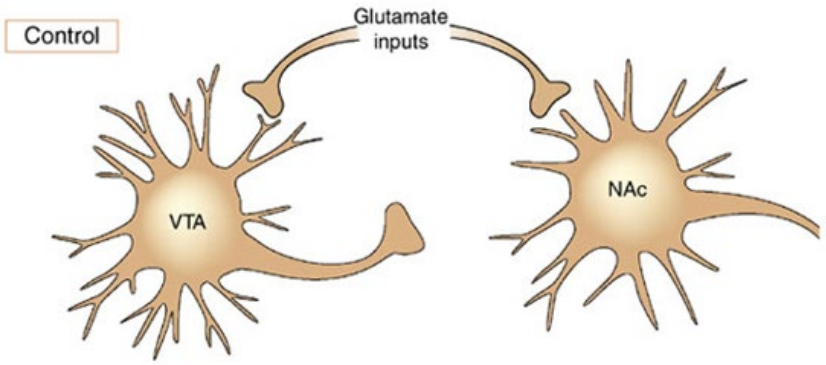
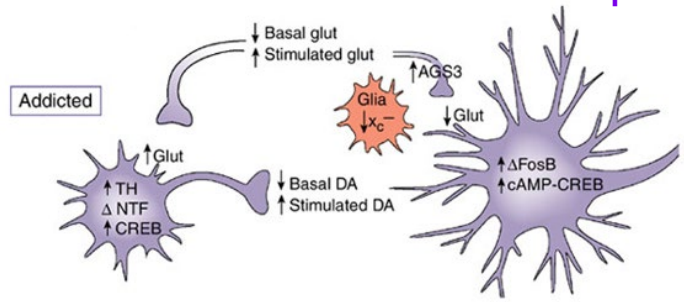
Highly simplified scheme of some common, chronic actions of drugs of abuse on the VTA-NAc



Under **normal** conditions – there are **glutamatergic inputs to both the VTA and NAc** neurons.

Tolerance: homeostatic response to repeated drug activation of the system



"**Chronic** exposure to any of several drugs of abuse causes an **impaired dopamine system**"

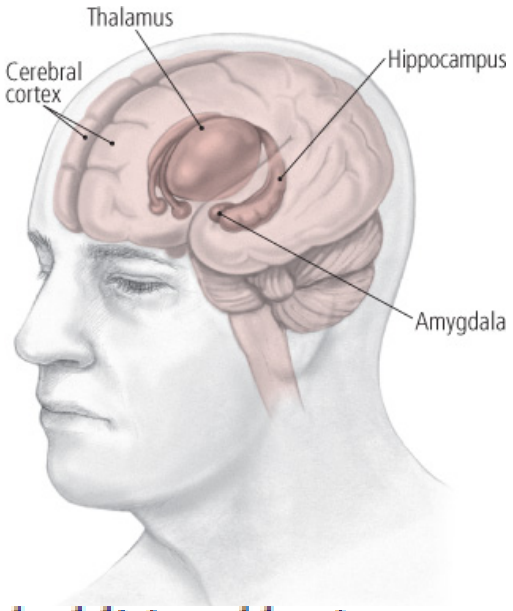
It also becomes sensitized
→more dopamine is released in response to the drug and its cues.

"Baseline levels of dopamine function are reduced, and normal rewarding stimuli may be less effective. "

Eric Nestler (2005) *Nature Neuroscience* **8**, 1445 - 1449

Addiction also involves *powerful* emotional memories.

→Amygdala



More recent work has established that several additional brain areas that interact with the VTA and NAc are also essential for acute drug reward and chronic changes in reward associated with addiction. These regions include the amygdala (and related structures of the so-called 'extended amygdala'), hippocampus, hypothalamus and several regions of frontal cortex, among others[1,2,4,10–13]. Some of these areas are part of the brain's traditional memory systems; this has led to the notion, now supported by increasing evidence, that important aspects of addiction involve powerful emotional memories[2,4,5,11–13].

Eric Nestler (2005) *Nature Neuroscience* **8**, 1445 - 1449