Neural Mechanisms Linking Behavioral Dysregulation in Substance Abuse, Psychopathology and Stress

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Stress, Anxiety, and its consequences

Stress is a part of our everyday lives. But the impact of stress can have very different effects:

-Stress can lead to anxiety, that provides motivation and helps us to avoid reckless or dangerous activities

-However, when stress is experienced in excess, either in terms of intensity or duration, it can have deleterious consequences

-Depending on the individual, stress can lead to major psychiatric disorders, including drug abuse, post-traumatic stress disorder, depression, or suicide

-Stress is also a precipitating factor in disorders such as schizophrenia

We have found that stress can have very different effects on the dopamine system that correlate with its effects on activation or depression of responses

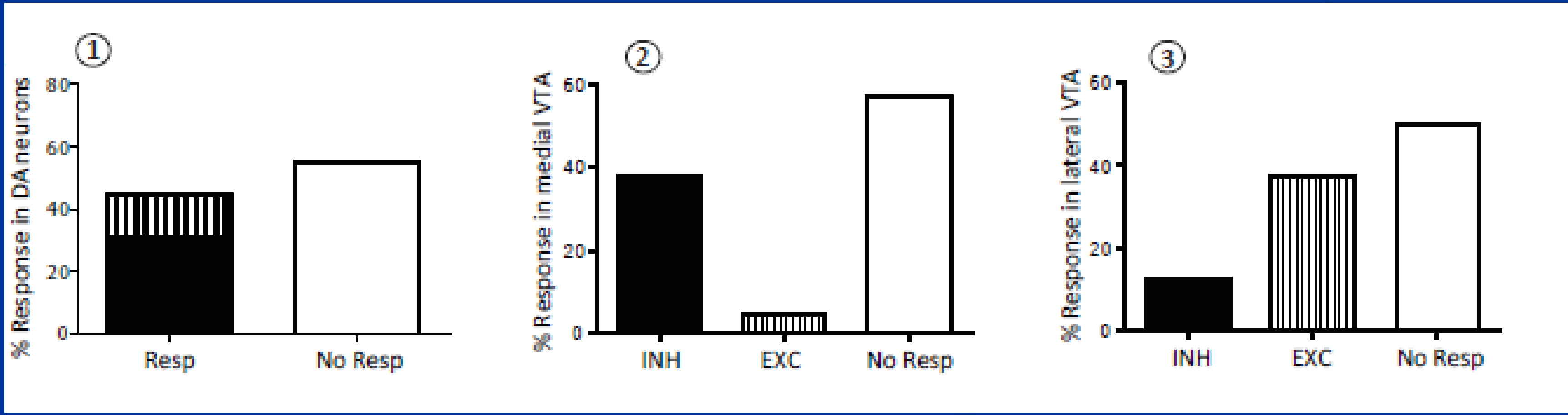
Stress can be defined in a number of ways depending on the experiment

A stressor can be noxious, it can be physiological, and it can be psychological, with each type of stressor affecting the system in common or unique ways.

How does a simple single noxious stimulus affect single dopamine neurons?

Single Footshock Stimuli Produce Excitation and Inhibition of DA Neuron Firing Depending on Location

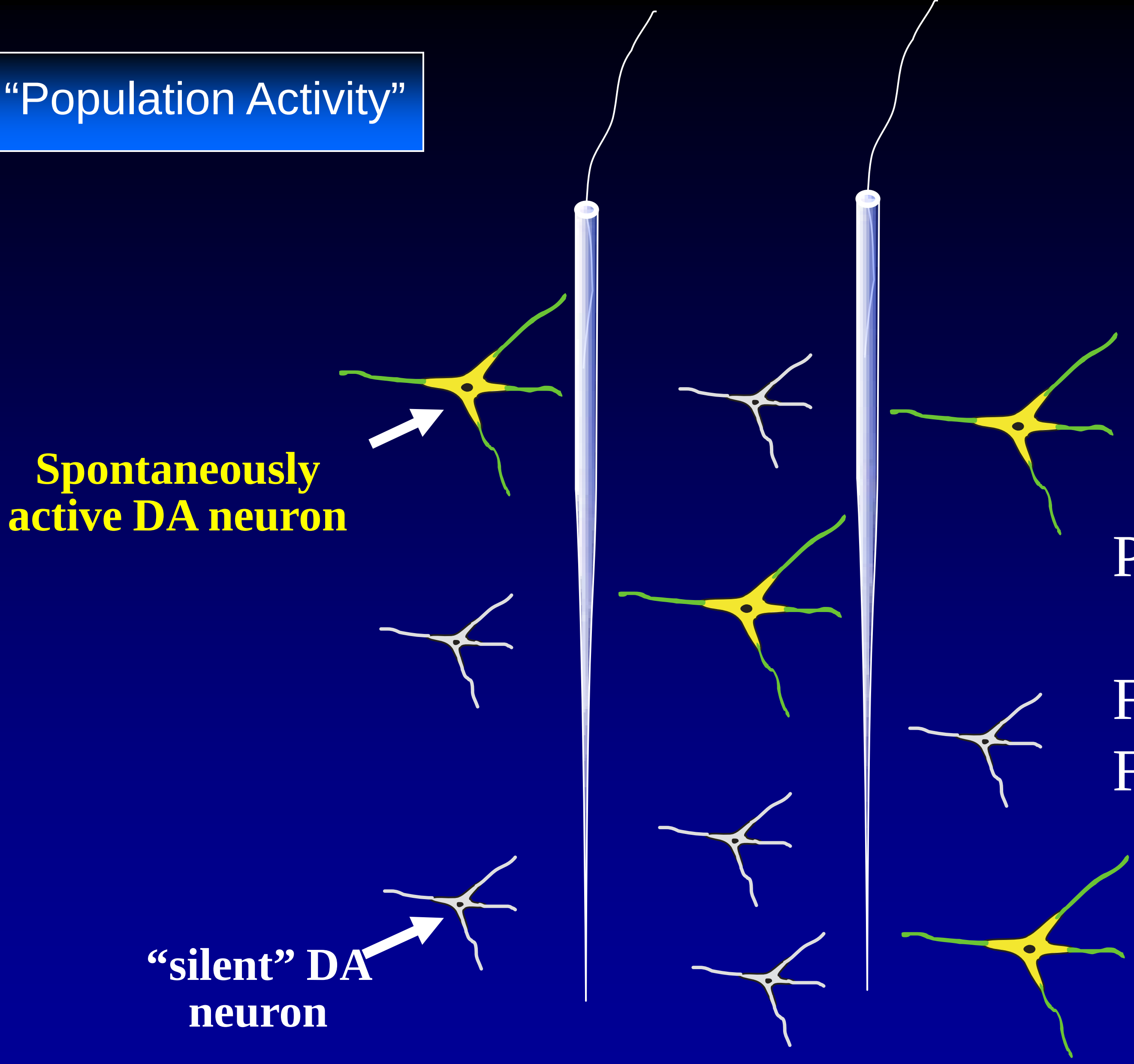
Medial VTA Lateral VTA



In contrast, neurochemical studies show that stressors *increase* DA release in postsynaptic targets

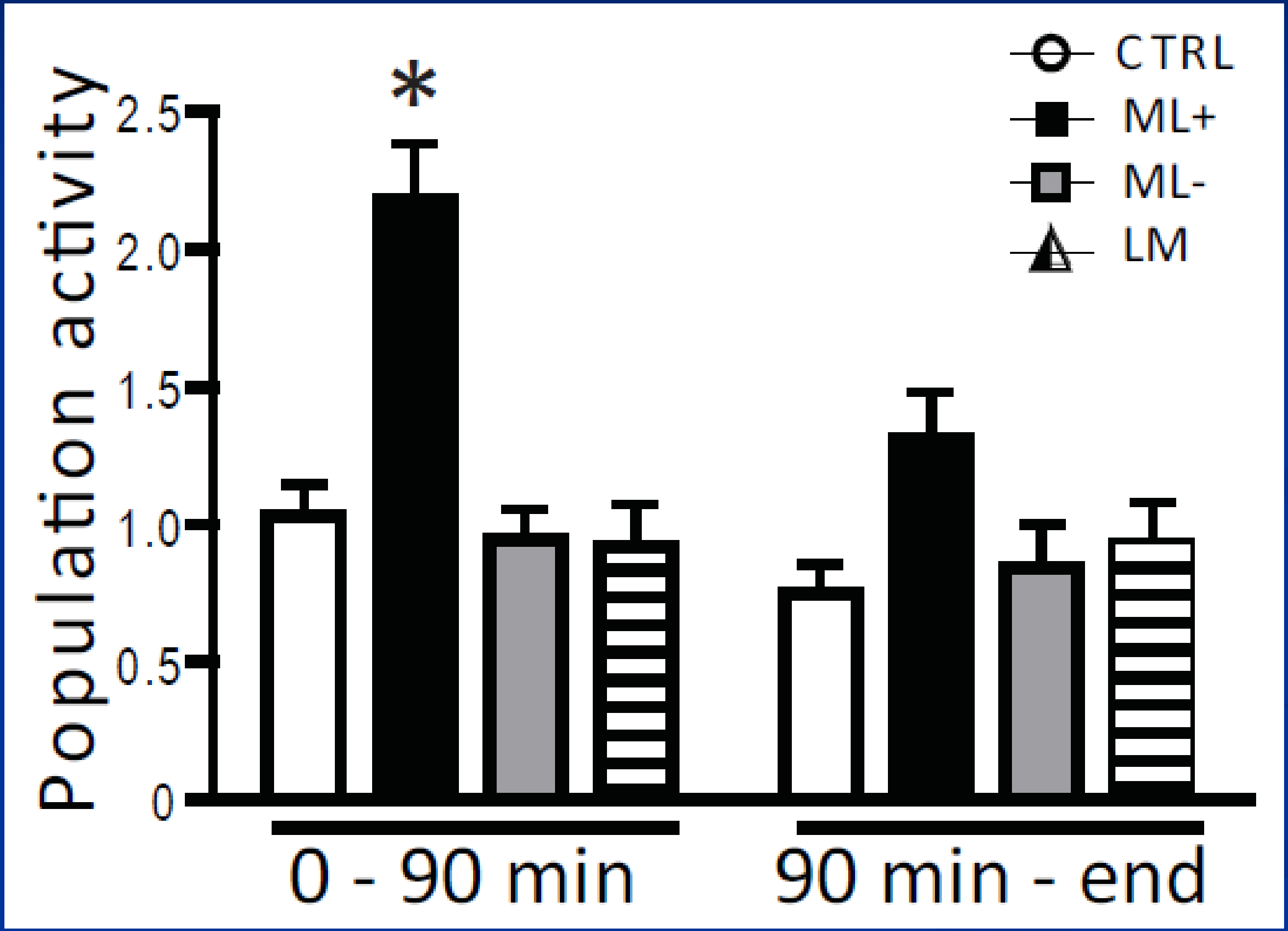
However, this may be related to the type of DA neuron recording performed

VTA "Population Activity"



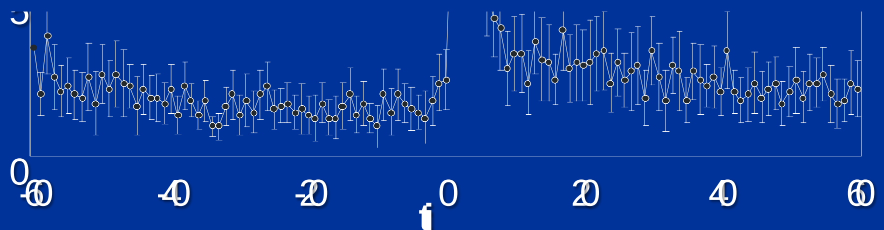
Population
Activity
Firing Rate
Firing Pattern

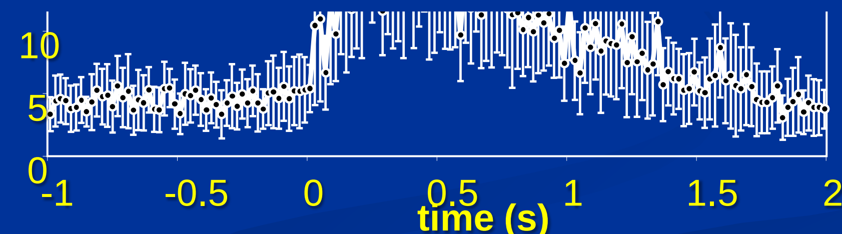
In Contrast to Single Stimuli, Repeated Footshock Induces a Transient Increase in DA Neuron Population Activity Selectively in the Medial VTA



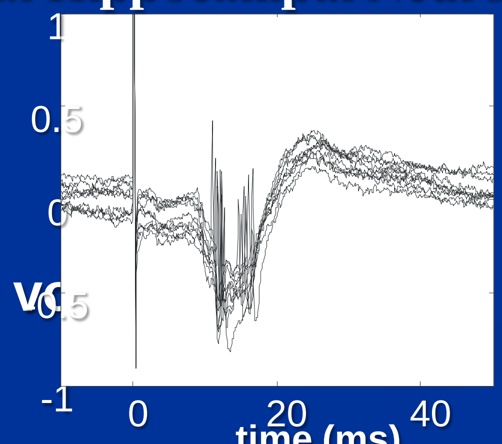
This is consistent with neurochemical studies of DA release in response to footshock

What other stress-related systems that affect DA neurons are affected by footshock?



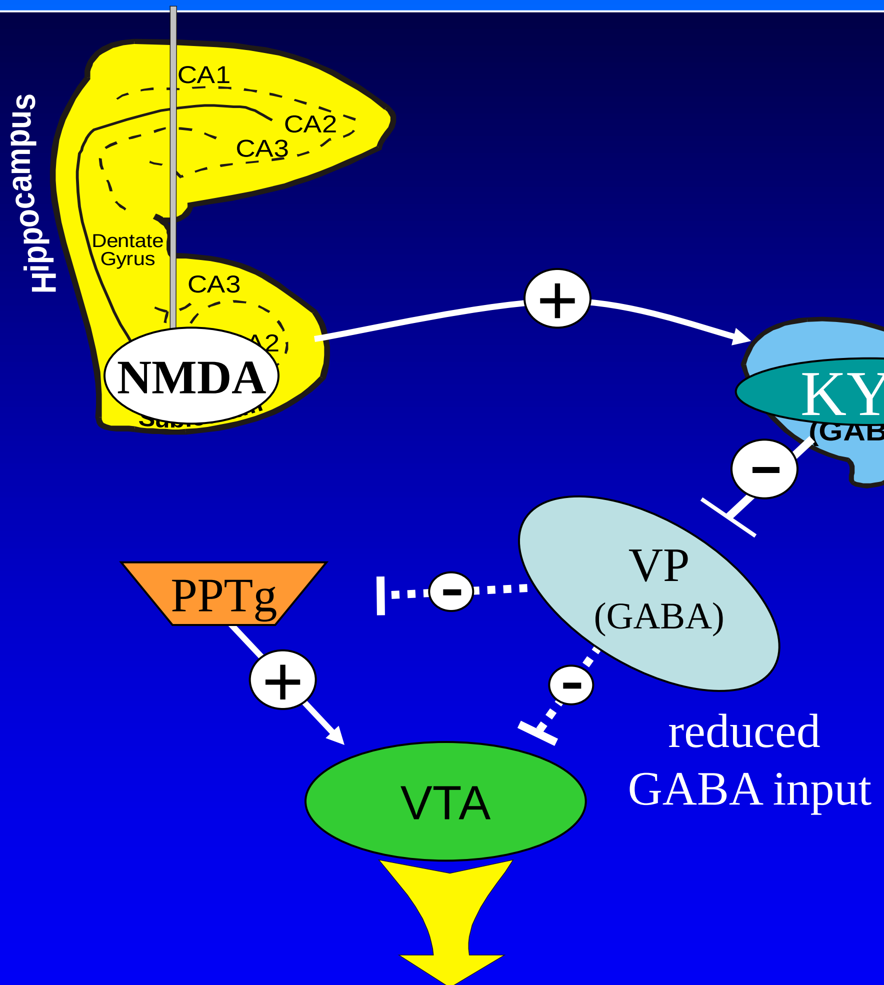


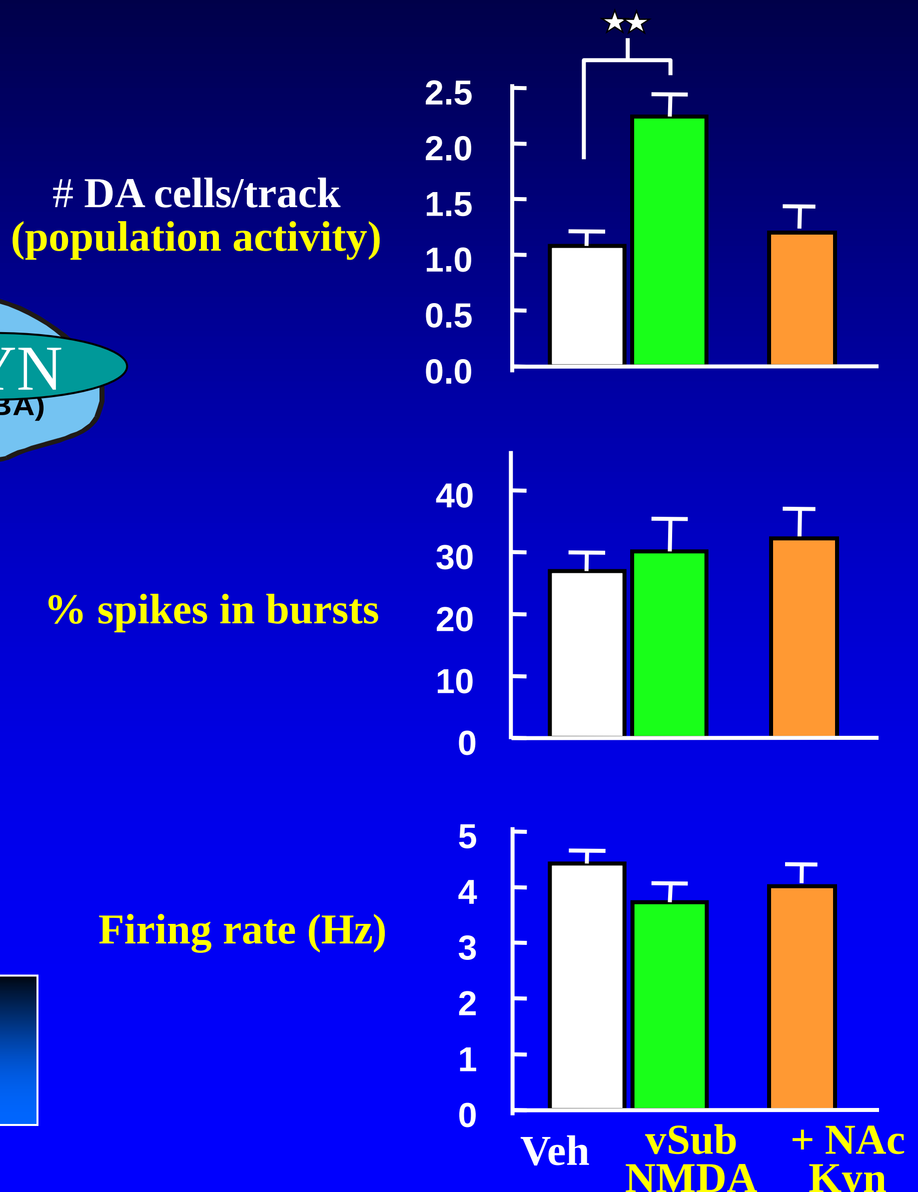
Stimulation of the Basolateral Amygdala Also Drives Ventral Hippocampal Neuron Firing



The Ventral Hippocampus exerts unique effects on DA neuron activity

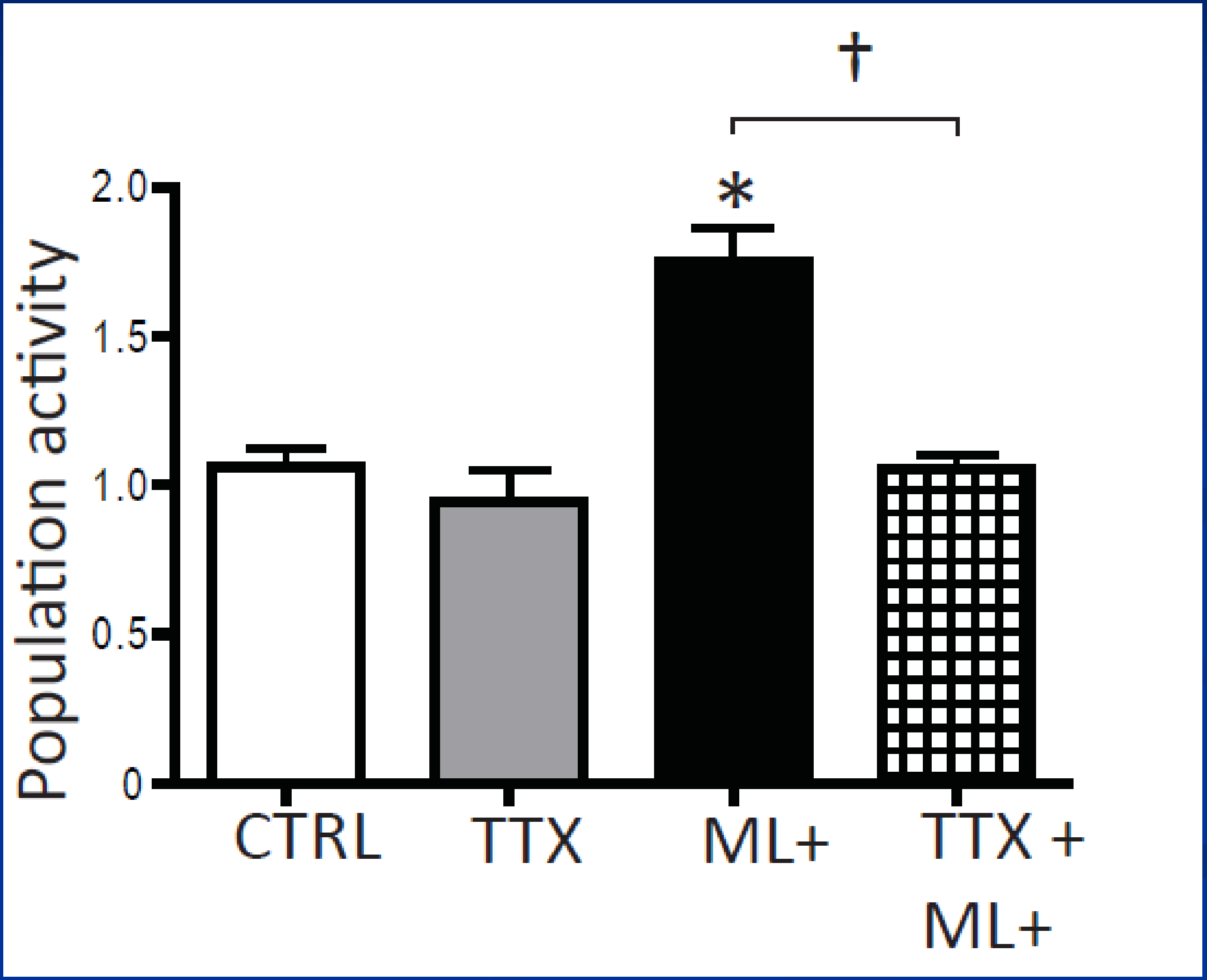
Activation of the ***hippocampal-NAc pathway*** increases DA neuron population activity, but does not affect burst firing

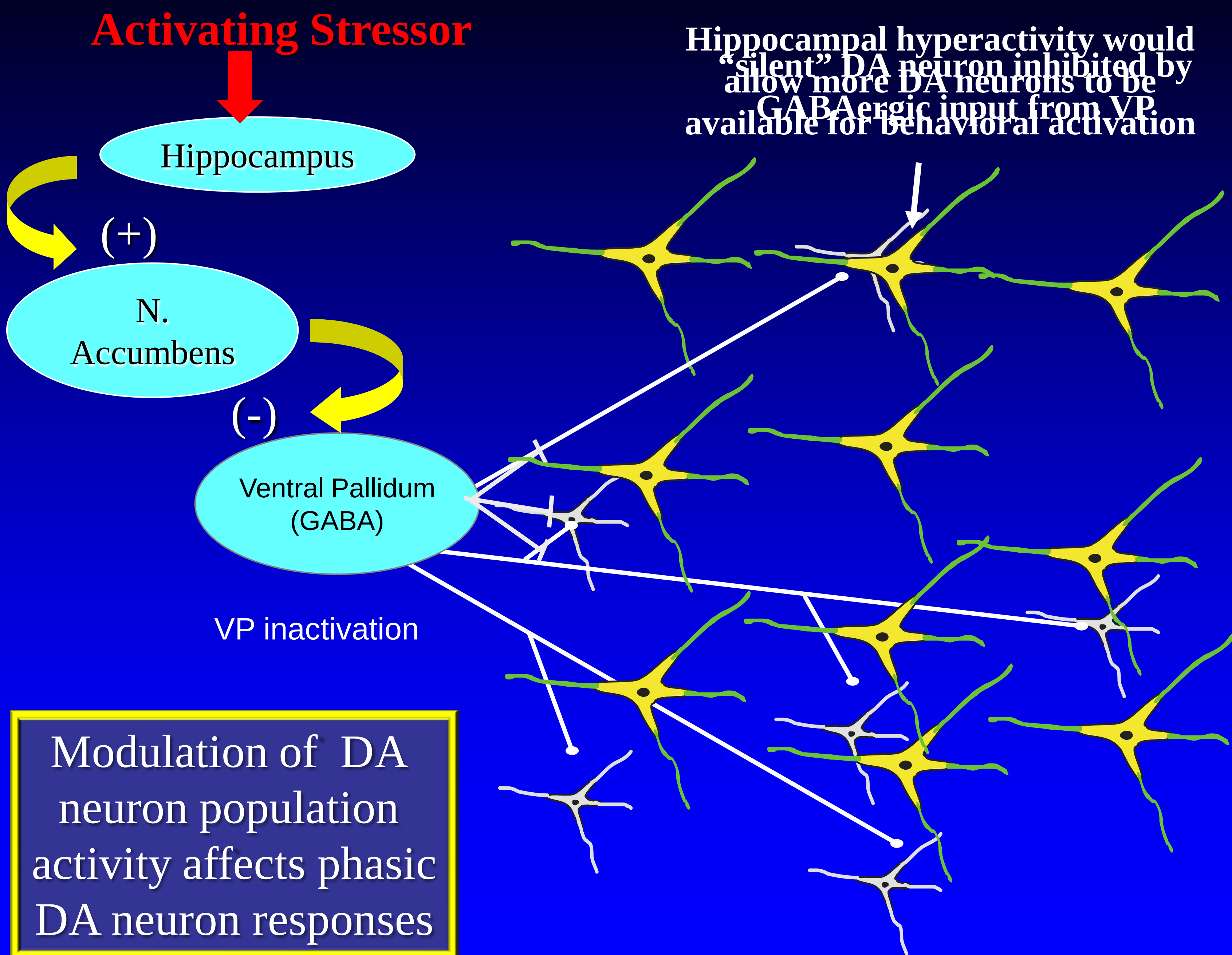




↑ DA neuron population activity
no effect bursting activity

Inactivation of the Ventral Subiculum Prevents Repeated Footshock-Induced Activation of VTA DA Neuron Firing

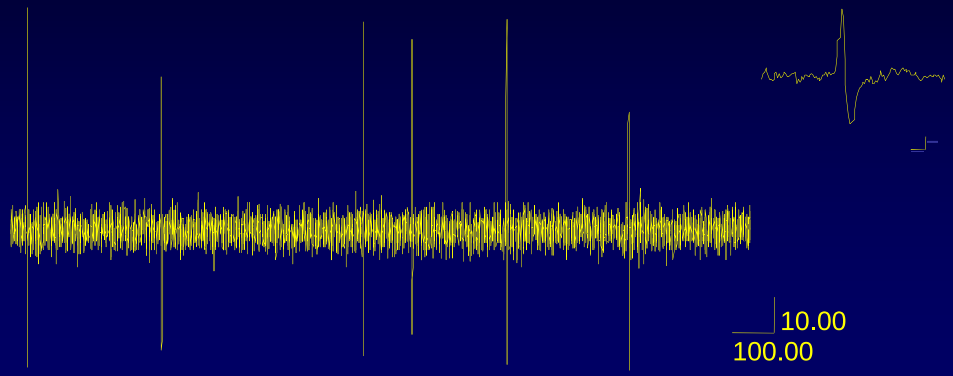




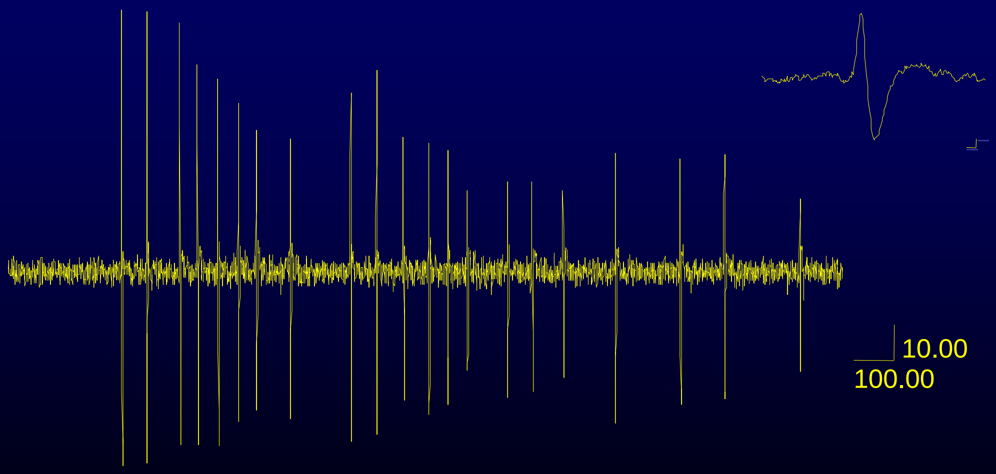
Activating Stressor
Hippocampus
(+)
N. Accumbens
(-)
Ventral Pallidum (GABA)
VP inactivation
Hippocampal hyperactivity would allow more DA neurons to be available for behavioral activation
“silent” DA neuron inhibited by GABAergic input from VP.
Modulation of DA neuron population activity affects phasic DA neuron responses

DA Neuron Firing Pattern

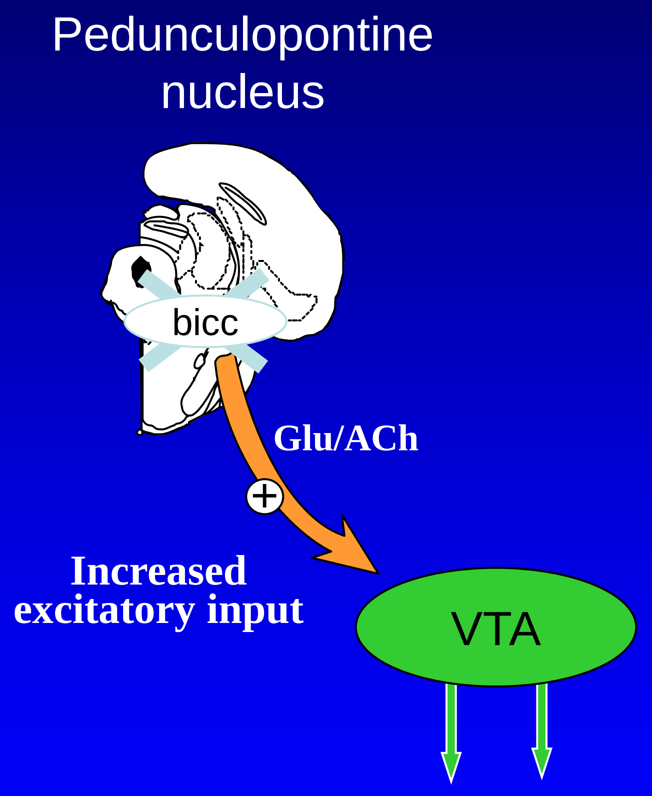
Irregular Firing

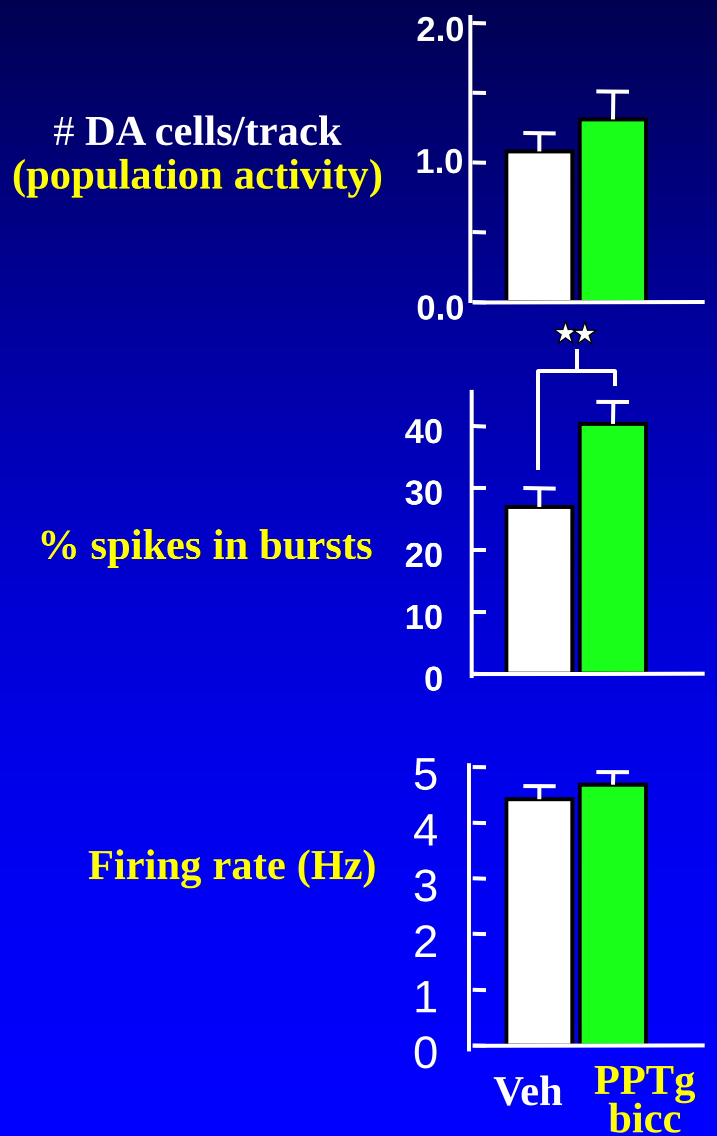


Burst Firing



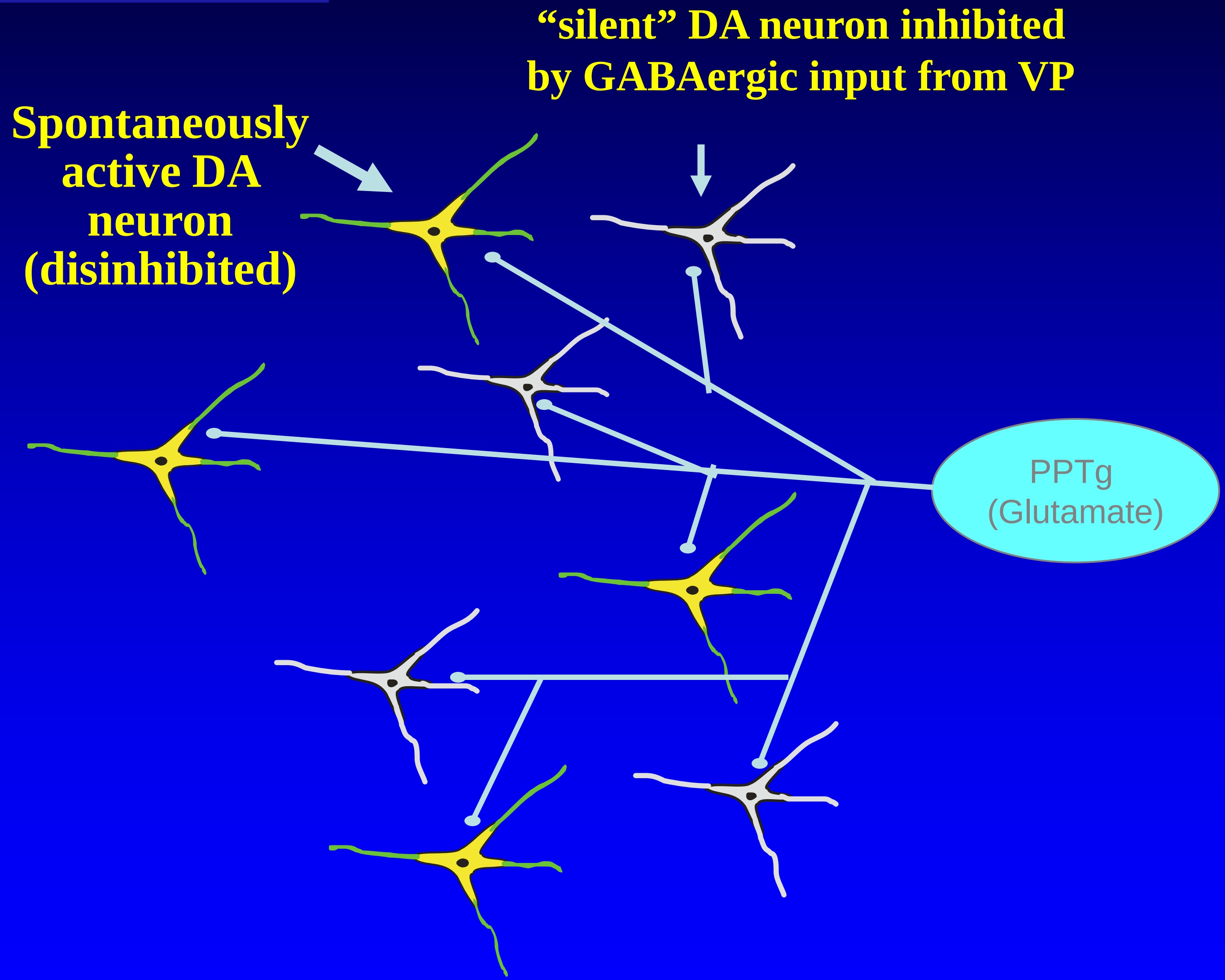
Activation of the *pedunculopontine nucleus* increases DA neuron burst firing, but does not affect population activity





Selective increase in DA neuron BURST FIRING

Regulation of Phasic DA Neuron Activity



NMDA only affects depolarized, spontaneously firing DA neurons

Model:

By setting the baseline tonic discharge of dopamine neurons, the hippocampal subiculum (via the accumbens-ventral pallidum) controls the number of dopamine neurons that can be phasically activated by the PPTg

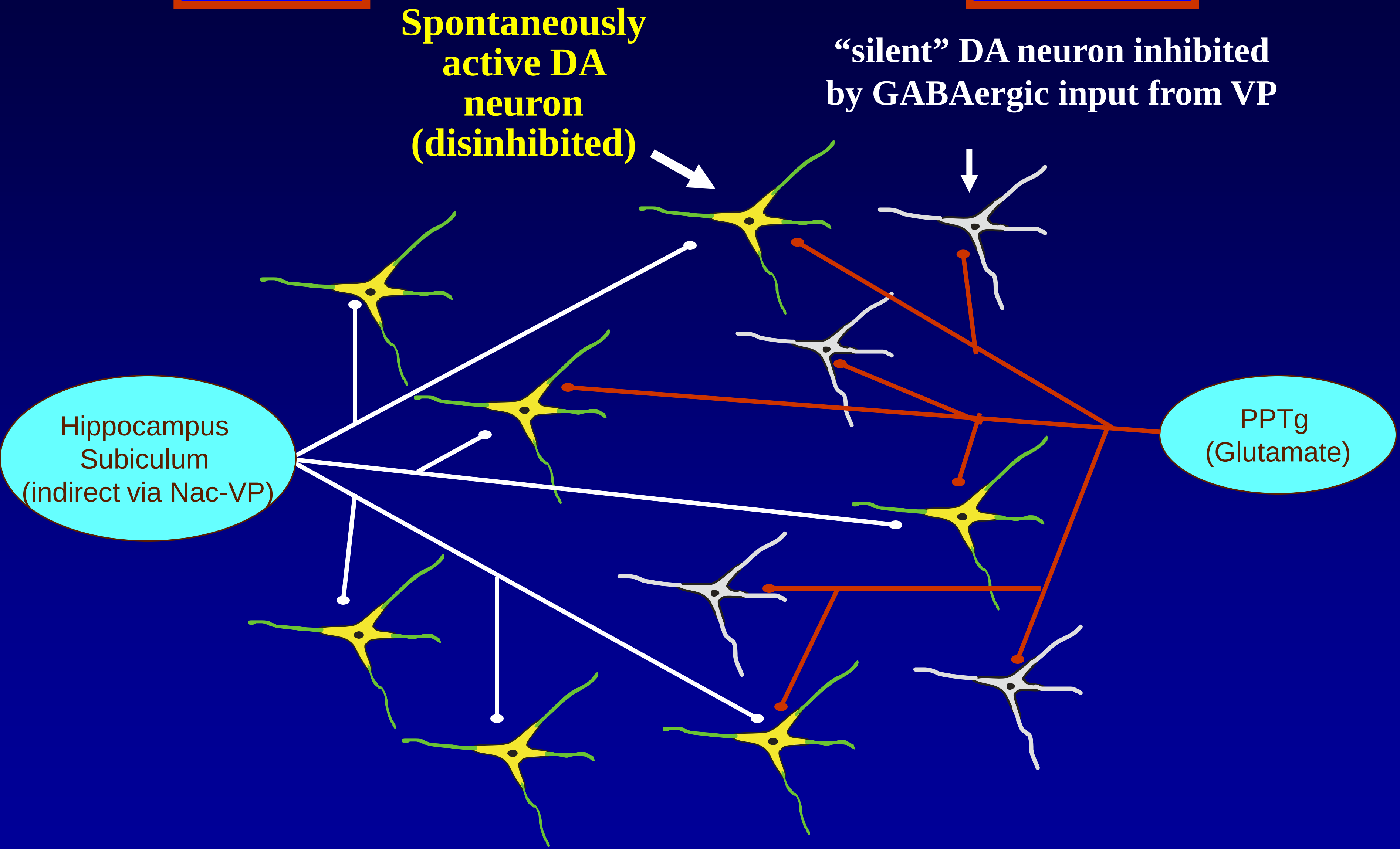
Therefore, the PPTg provides the “signal,” and the ventral subiculum is the “gain” or the level of amplification of this signal

The ventral subiculum of the hippocampus plays a role in context-dependent processing, which sets the type of response that is appropriate with the current context or setting

The “gain” is a property of the context, and can be varied depending on the characteristics of the environment

"Gain"

"Signal"

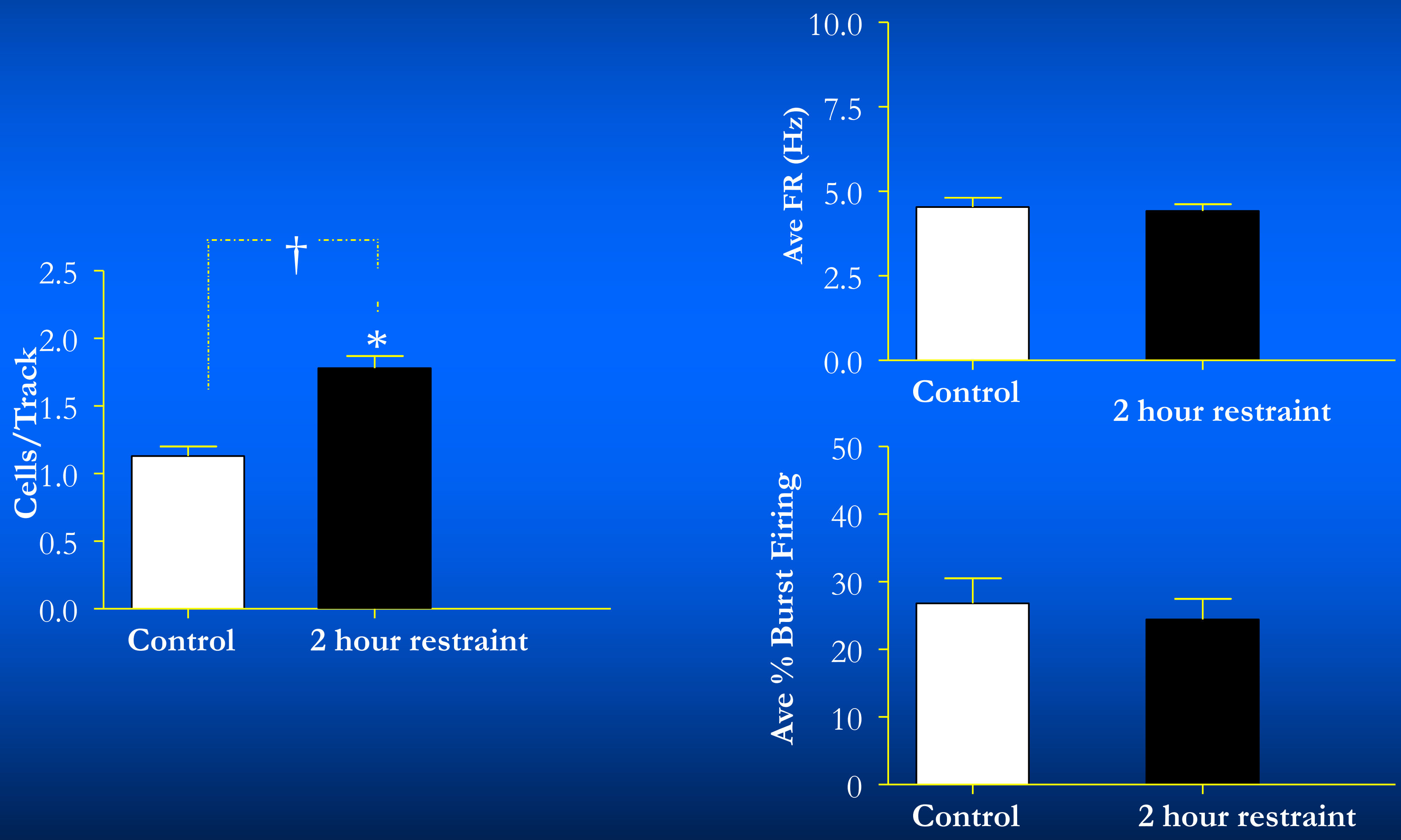

Spontaneously active DA neuron (disinhibited)
"silent" DA neuron inhibited by GABAergic input from VP
Hippocampus
Subiculum
(indirect via Nac-VP)
PPTg
(Glutamate)

Therefore repeated noxious stimuli increase the amplitude of phasic DA responses by increasing DA neuron population activity

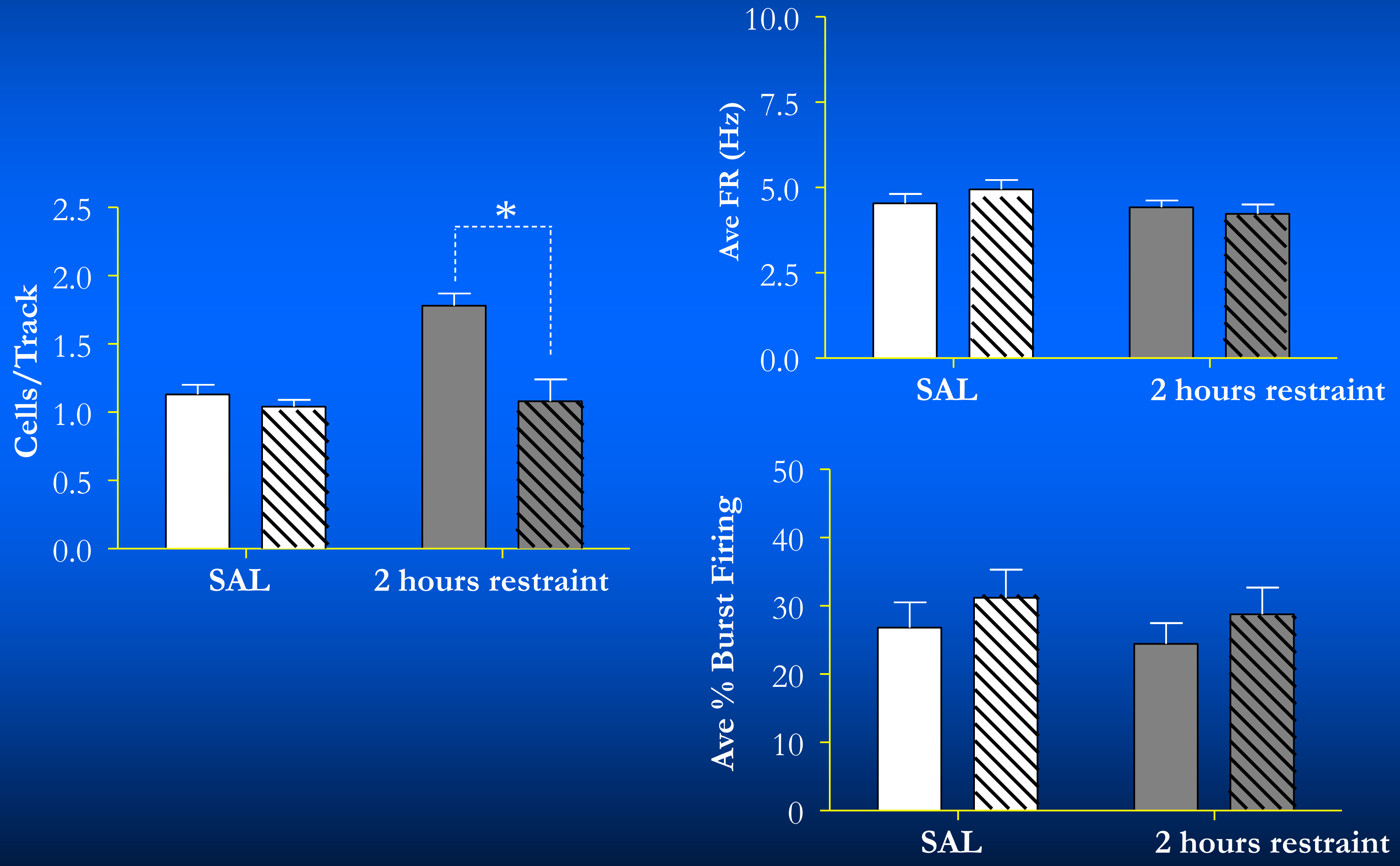
Psychological stressors, particularly when severe, can also increase DA system responsivity via sensitization

Such stressors play a prominent role in drug abuse and across psychiatric disorders

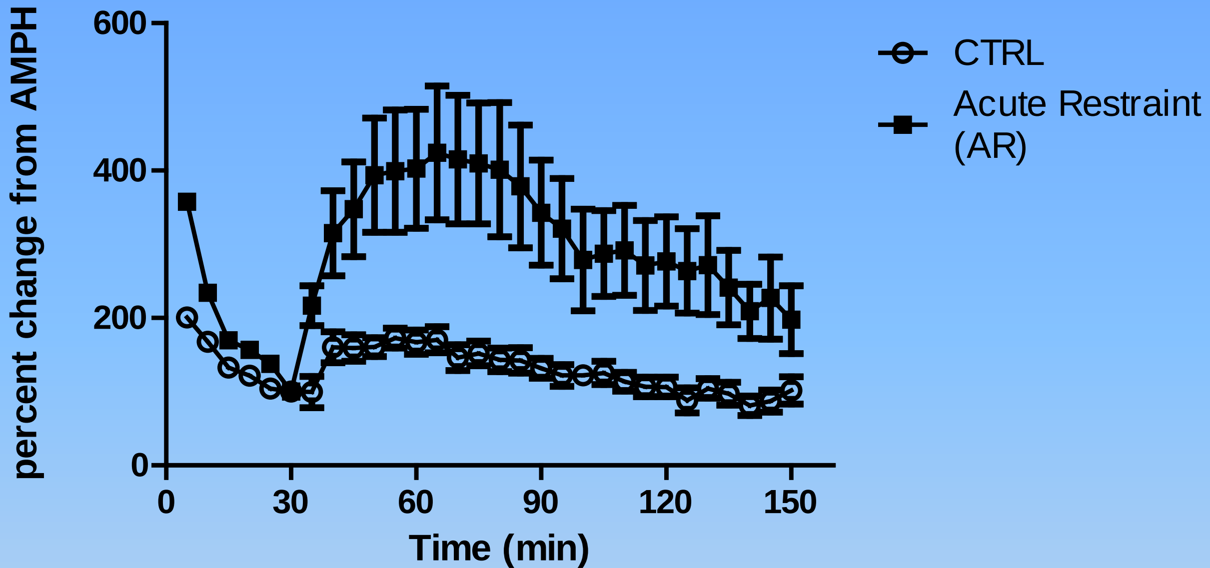
Two Hours of Restraint Stress Increases Tonic DA Neuron Firing to Baseline

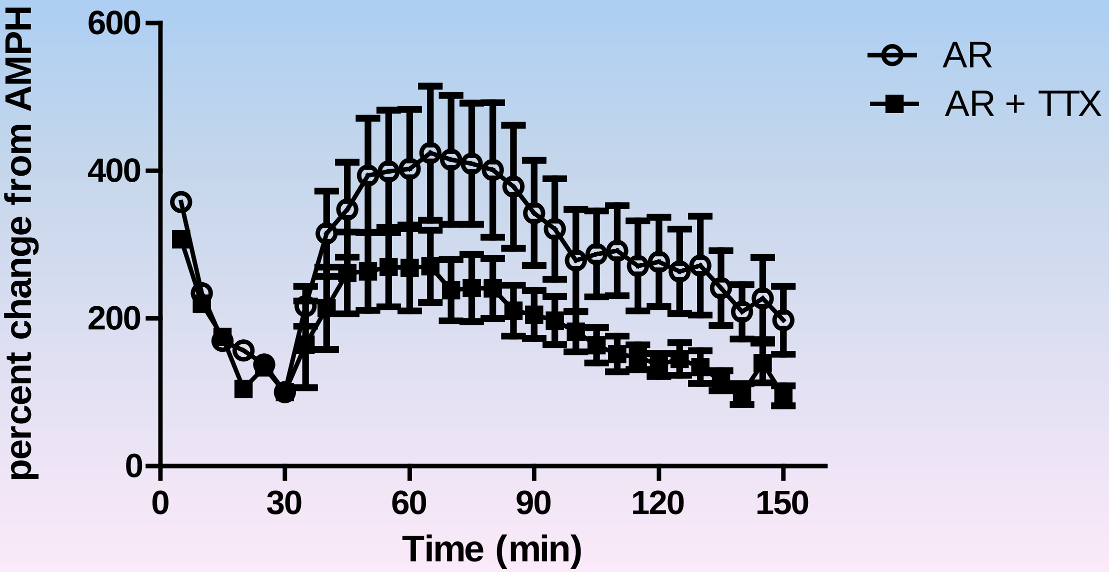


vSub Inactivation by TTX Restores Tonic DA Neuron Firing

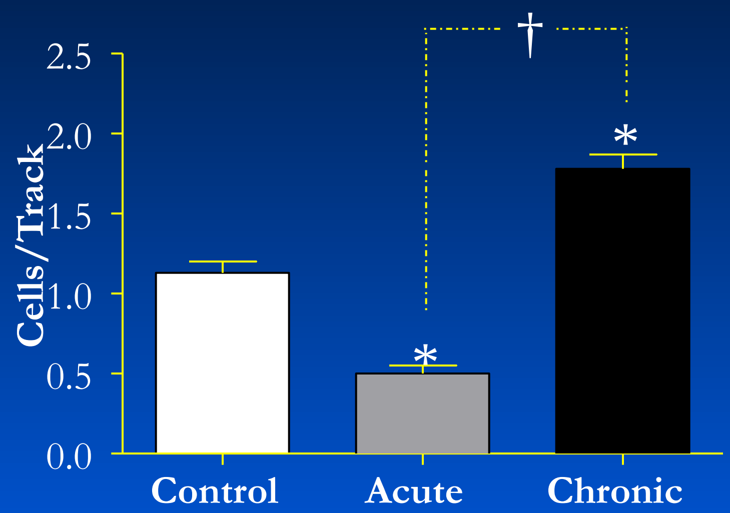


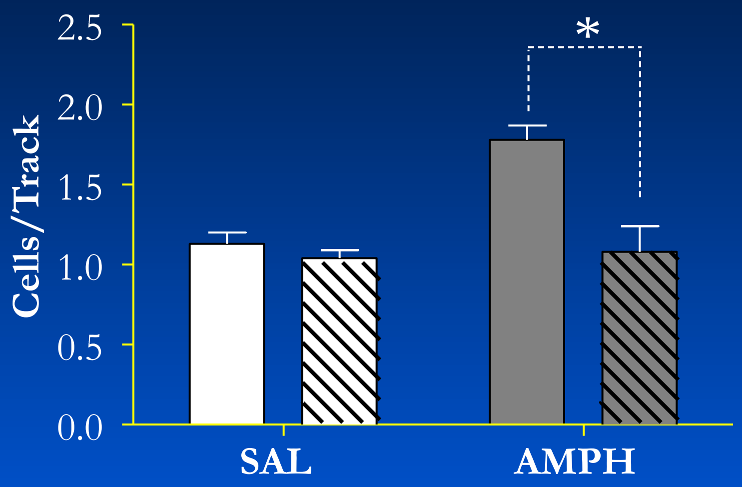
vSub Inactivation by TTX Reverses Stress-Induced Sensitization to Amphetamine

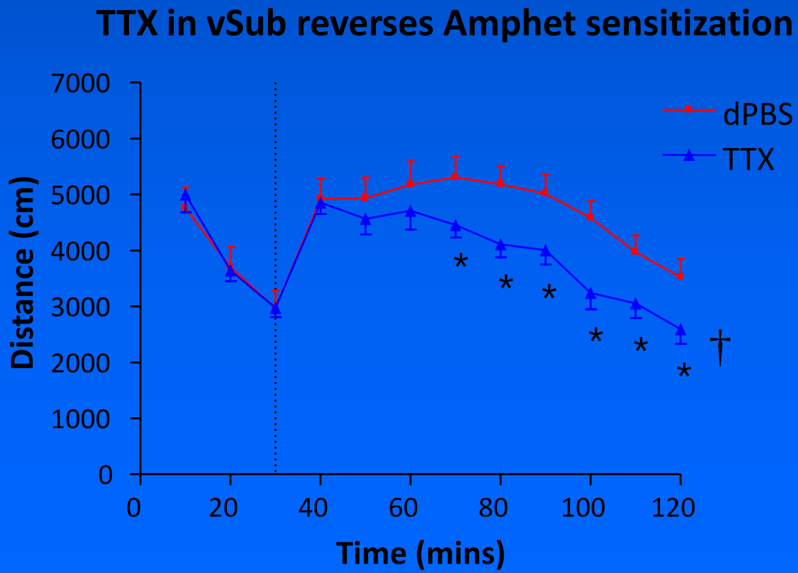




Repeated Amphetamine Treatment, like Restraint Stress, Increases Tonic DA Neuron Firing

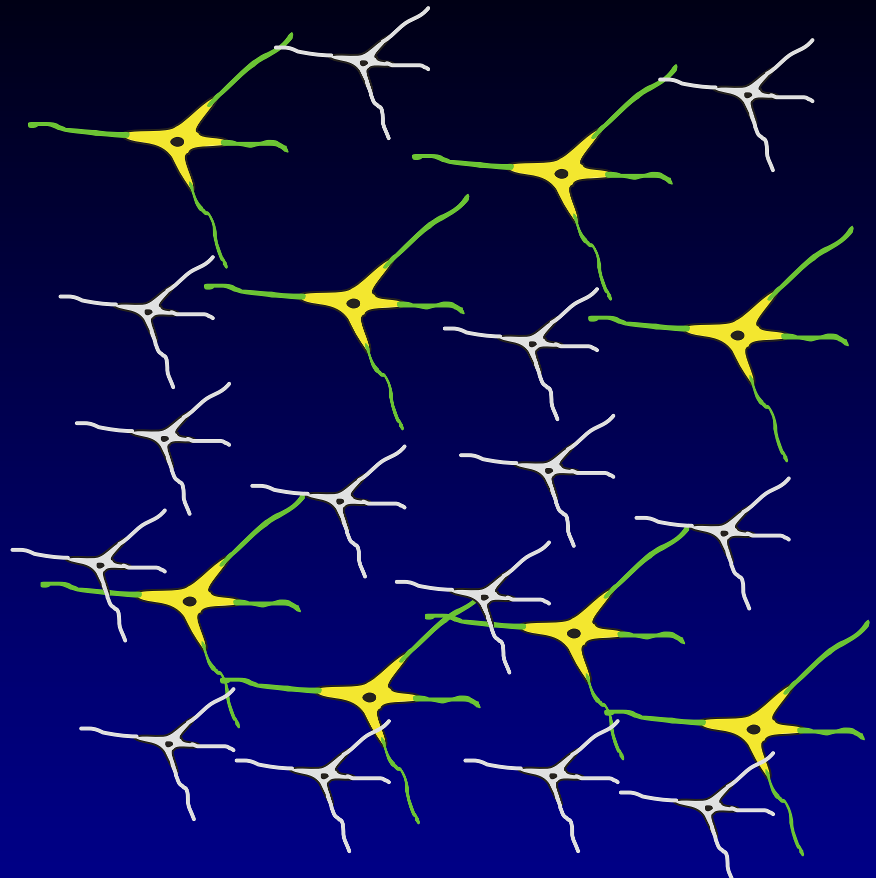


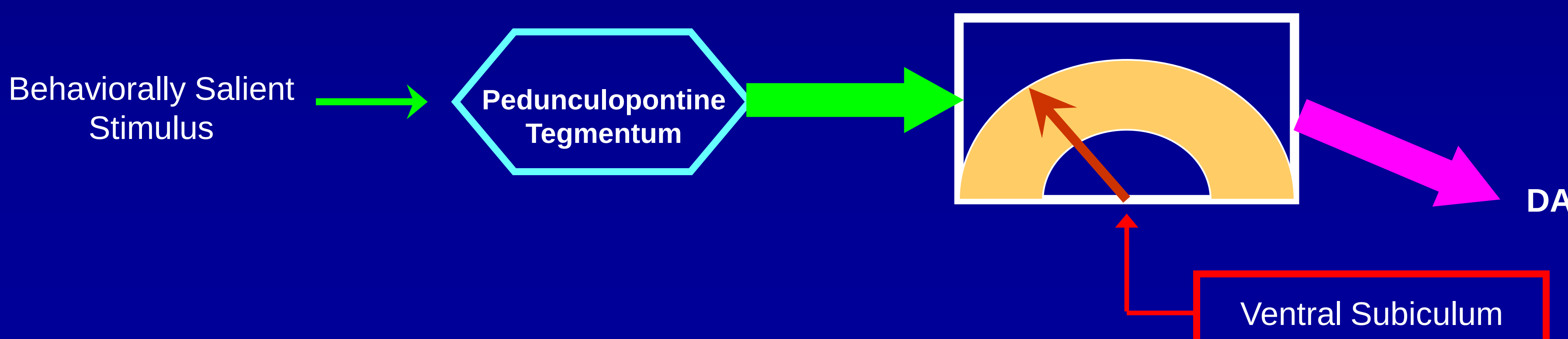




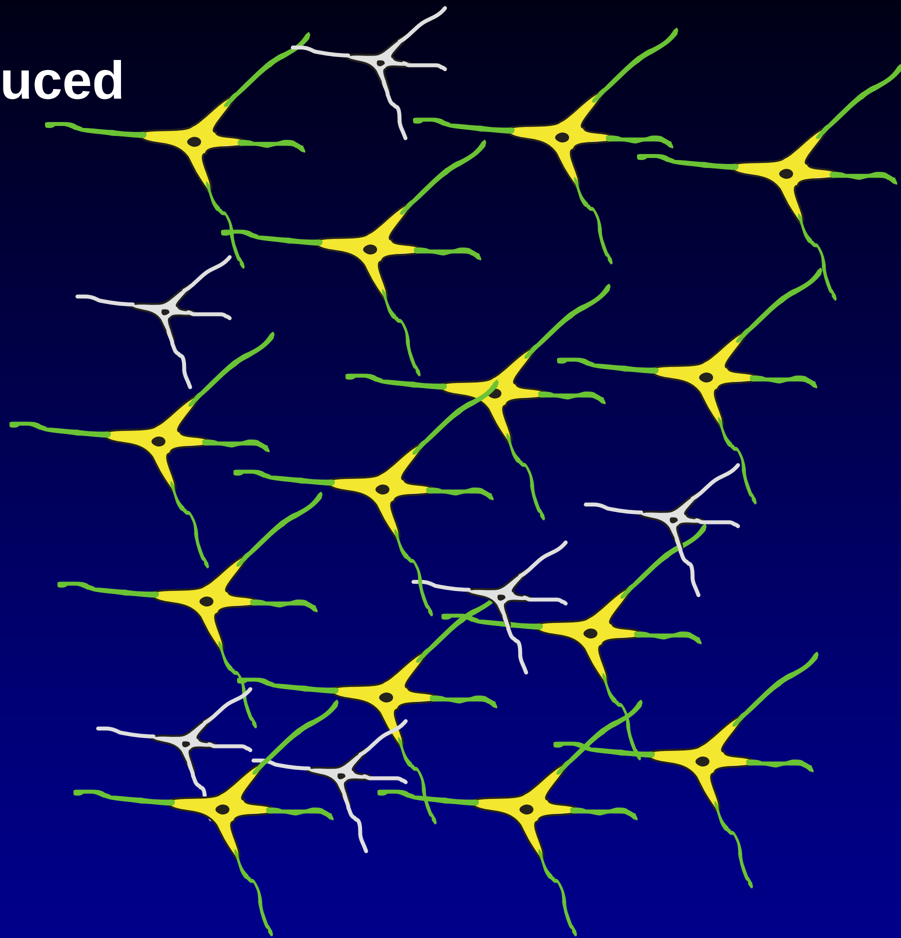
Amphetamine sensitization is also context-dependent, and cross-sensitizes with stress via the same neuronal substrates

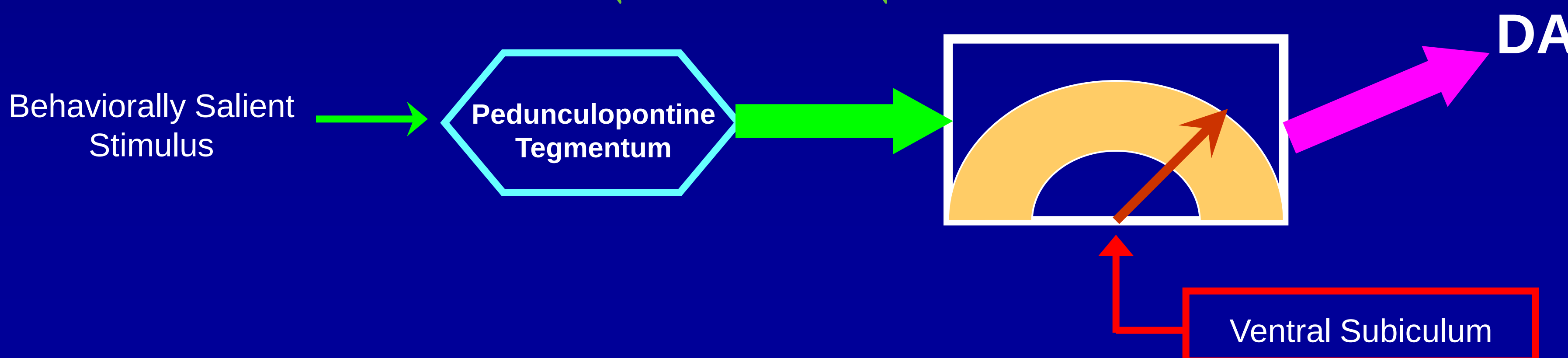
Benign Context:





Restraint- or Amphetamine-induced Activation:



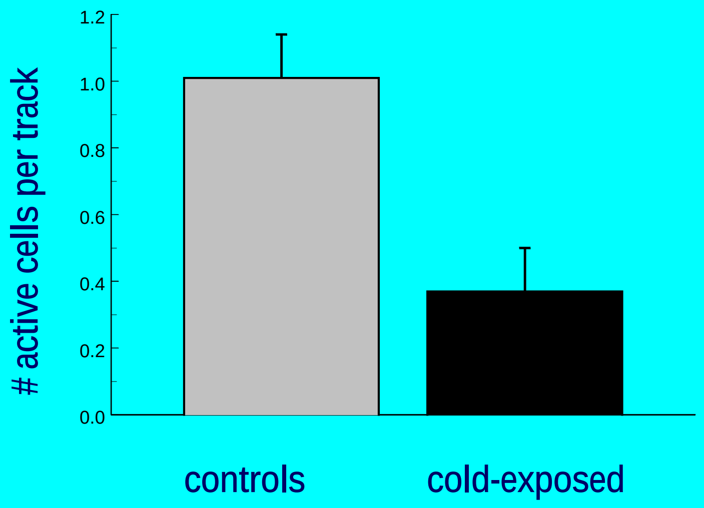


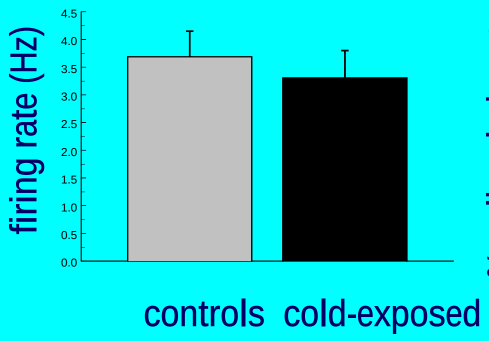
Acute or repeated restraint stress as well as amphetamine sensitization therefore increases DA neuron responsivity by causing a hippocampal-dependent activation of DA neuron firing.

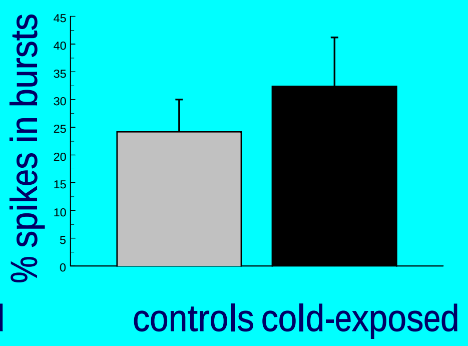
This activation could be related to stress disorders such as drug abuse and PTSD, in which the system is oriented towards increased response to stimuli

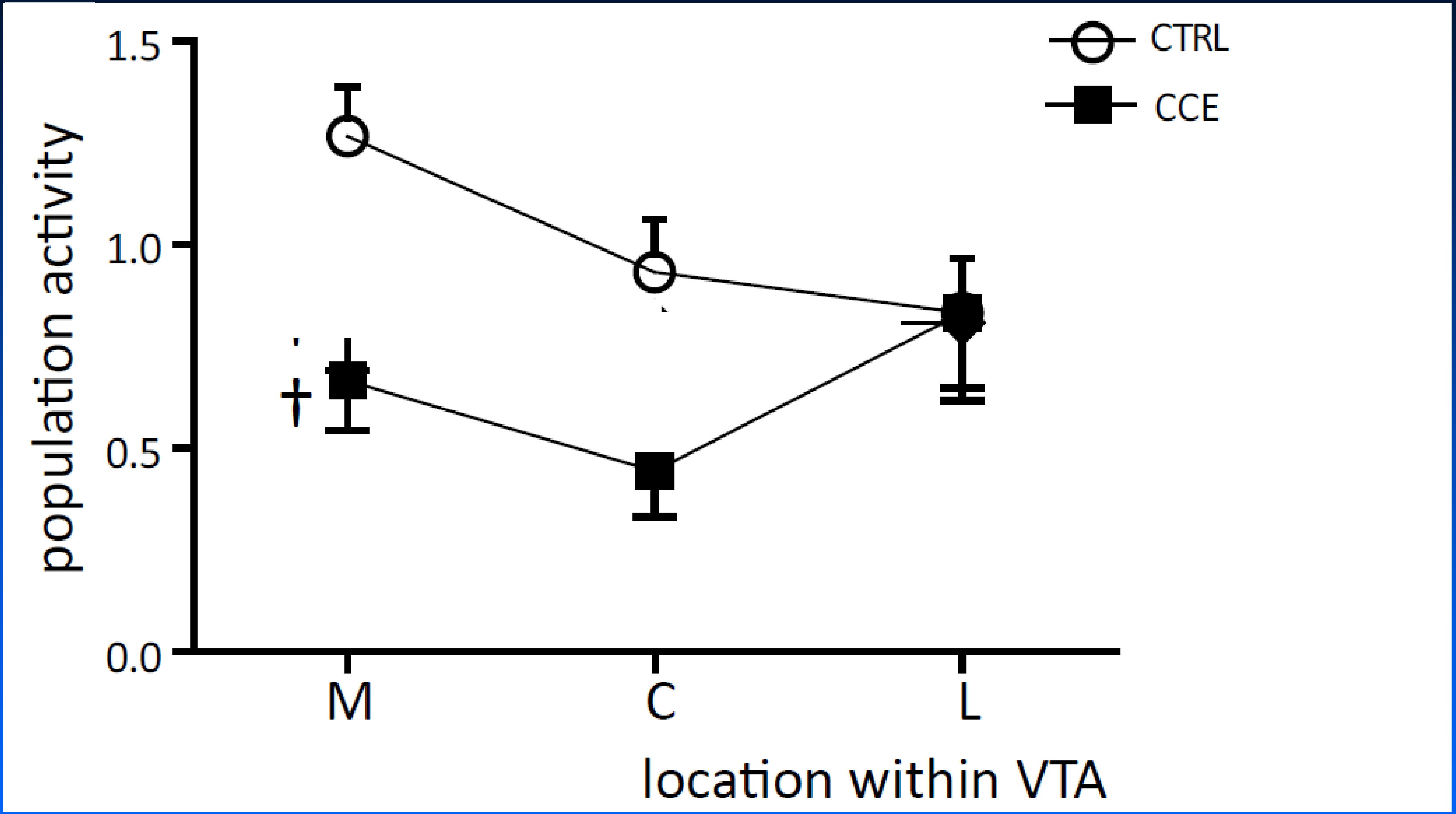
In contrast, following an acute stressor there is often an opposite effect induced; one of sustained attenuation of DA neuron activity

Effects of Chronic Cold Stress on VTA DA Neuron Activity



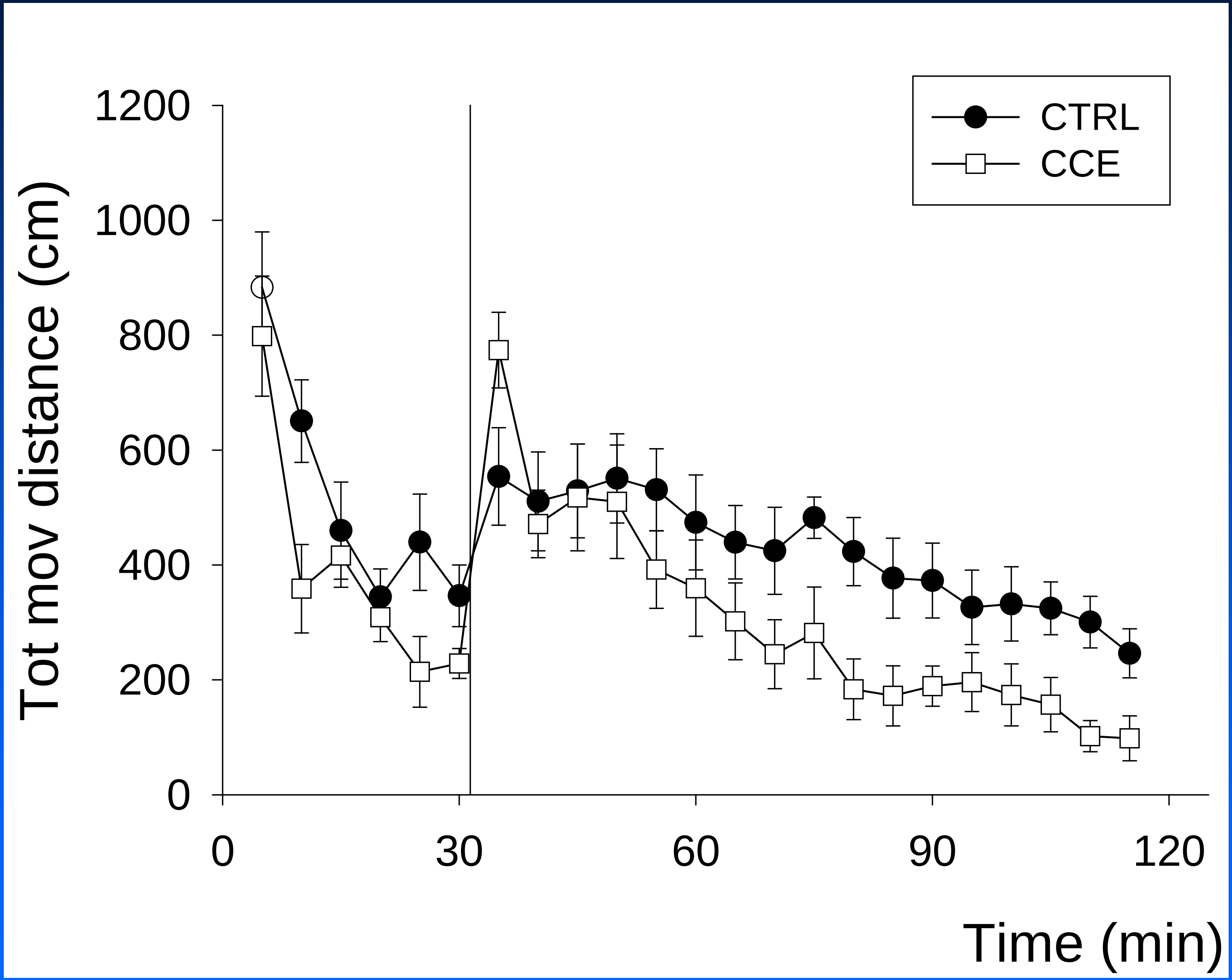




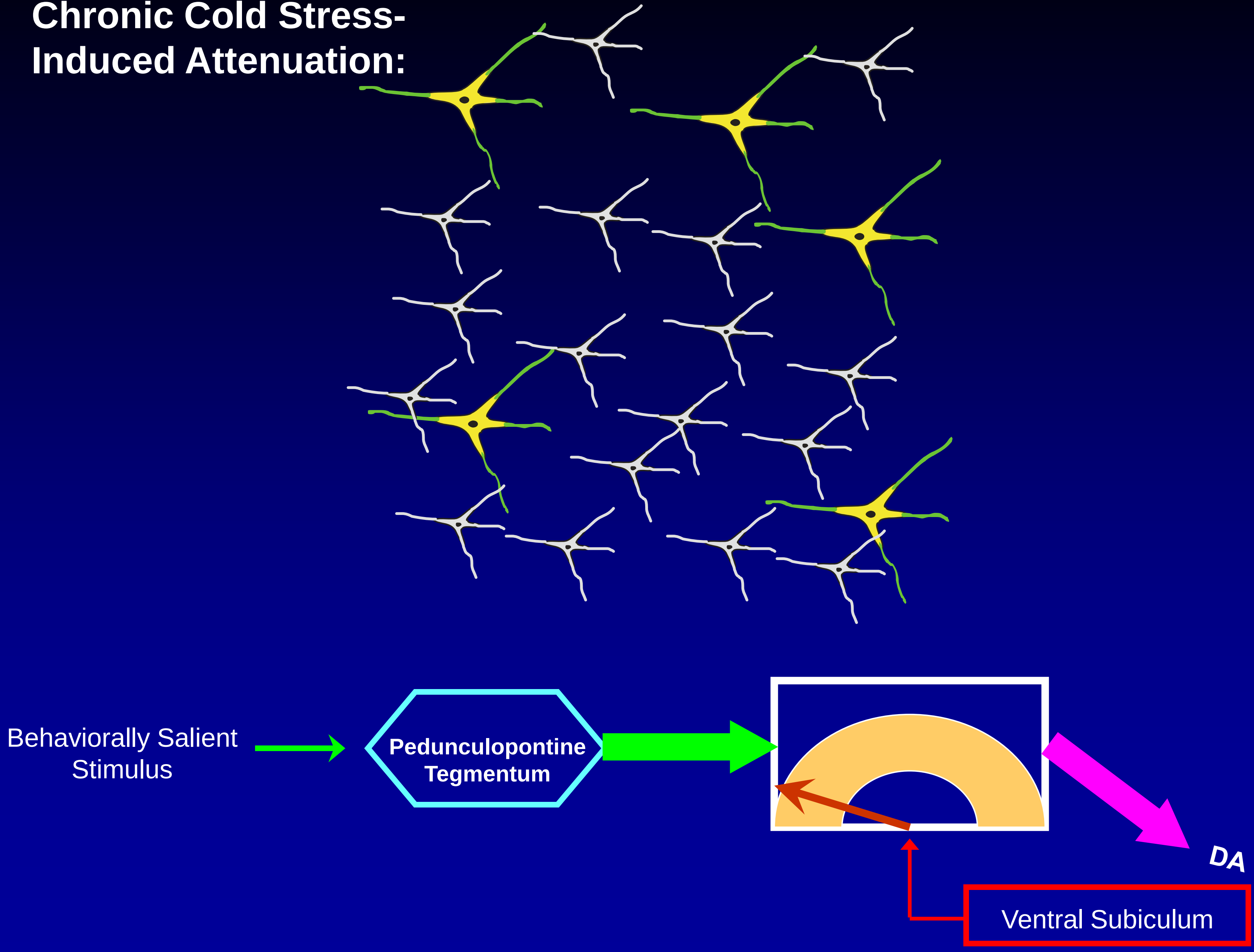


Chronic Cold Stress decreases DA neuron population activity primarily in reward-related medial VTA

Chronic Cold Stress Decreases Behavioral Response to Amphetamine



Chronic Cold Stress-Induced Attenuation:



Conclusions and Hypothesis:

These studies suggest that stress can affect DA transmission and behavior via distinct mechanisms:

Stressors that are behaviorally activating tend to increase DA neuron drive in a context-dependent manner, whereas those associated with depressed conditions attenuate DA neuron drive.

The population activity, or number of dopamine neurons firing, we propose reflects the responsivity of the DA system to external stimuli.

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