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

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”

Spontaneously active DA neuron

“silent” DA neuron

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?
Footshock Stimulation Activates Ventral Hippocampal Neurons

Locus Coeruleus Stimulation Activates Ventral Hippocampal Firing

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 activity.

- **Hippocampus**
  - CA1
  - CA2
  - CA3
  - Dentate Gyrus
  - Subiculum

- **Nucleus Accumbens**
  - GABA input

- **VTA**
  - Reduced GABA input

- **PPTg**
  - VP (GABA)

- **KYN**
  - NMDA + NAc
  - Kyn

- **Firing rate (Hz)**
  - Veh
  - vSub NMDA
  - + NAc Kyn

- **# DA cells/track (population activity)**

- **% spikes in bursts**
Inactivation of the Ventral Subiculum Prevents Repeated Footshock-Induced Activation of VTA DA Neuron Firing
Modulation of DA neuron population activity affects phasic DA neuron responses

Activating Stressor

Hippocampus

(+) N. Accumbens

(-) Ventral Pallidum (GABA)

Hippocampal hyperactivity would allow more DA neurons to be available for behavioral activation

“silent” DA neuron inhibited by GABAergic input from VP.
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

### Changes in Firing Parameters

- **# DA cells/track (population activity)**
- **% spikes in bursts**
- **Firing rate (Hz)**

**Pedunculopontine nucleus**

- Increased excitatory input

**VTA**

- Selective increase in DA neuron BURST FIRING

**Glu/ACh**

**bicc**
Regulation of Phasic DA Neuron Activity

“silent” DA neuron inhibited by GABAergic input from VP

Spontaneously active DA neuron (disinhibited)

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.
Spontaneously active DA neuron (disinhibited)

“silent” DA neuron inhibited by GABAergic input from VP

Hippocampus Subiculum (indirect via Nac-VP)

“Gain”

“Signal”

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

- **Cells/Track**
  - Control: ~1.5
  - 2 hour restraint: ~2.5

- **Ave FR (Hz)**
  - Control: ~5.0
  - 2 hour restraint: ~5.0

- **Ave % Burst Firing**
  - Control: ~30%
  - 2 hour restraint: ~30%
vSub Inactivation by TTX Restores Tonic DA Neuron Firing

**Graphs:**
- **Left Graph:**
  - Y-axis: Cells/Track
  - X-axis: Group (SAL, 2 hours restraint)

- **Right Graphs:**
  - Top Graph:
    - Y-axis: Ave FR (Hz)
    - X-axis: Group (SAL, 2 hours restraint)
  - Bottom Graph:
    - Y-axis: Ave % Burst Firing
    - X-axis: Group (SAL, 2 hours restraint)
vSub Inactivation by TTX Reverses Stress-Induced Sensitization to Amphetamine

The graph shows the percent change from AMPH over time for different conditions:

- CTRL
- Acute Restraint (AR)
- AR + TTX

The x-axis represents time in minutes, ranging from 0 to 150. The y-axis represents the percent change from AMPH, ranging from 0 to 600.
Repeated Amphetamine Treatment, like Restraint Stress, Increases Tonic DA Neuron Firing

TTX in vSub reverses Amphet sensitization

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

Behaviorally Salient Stimulus → Pedunculopontine Tegmentum → Ventral Subiculum

DA
Restraint- or Amphetamine-induced Activation:

Behaviorally Salient Stimulus → Pedunculopontine Tegmentum → DA

Ventral Subiculum
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

- **# active cells per track**
  - Controls: 1.0
  - Cold-exposed: 0.3

- **Firing rate (Hz)**
  - Controls: 3.0
  - Cold-exposed: 2.5

- **% spikes in bursts**
  - Controls: 20%
  - Cold-exposed: 15%

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**Graphs:**
- Comparison of controls vs. cold-exposed for each parameter.
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:

Behaviorally Salient Stimulus → Pedunculopontine Tegmentum → Ventral Subiculum

DA
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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