



Rapid dopamine signaling promotes drug-seeking behavior and relates to associative aspects of cocaine addiction

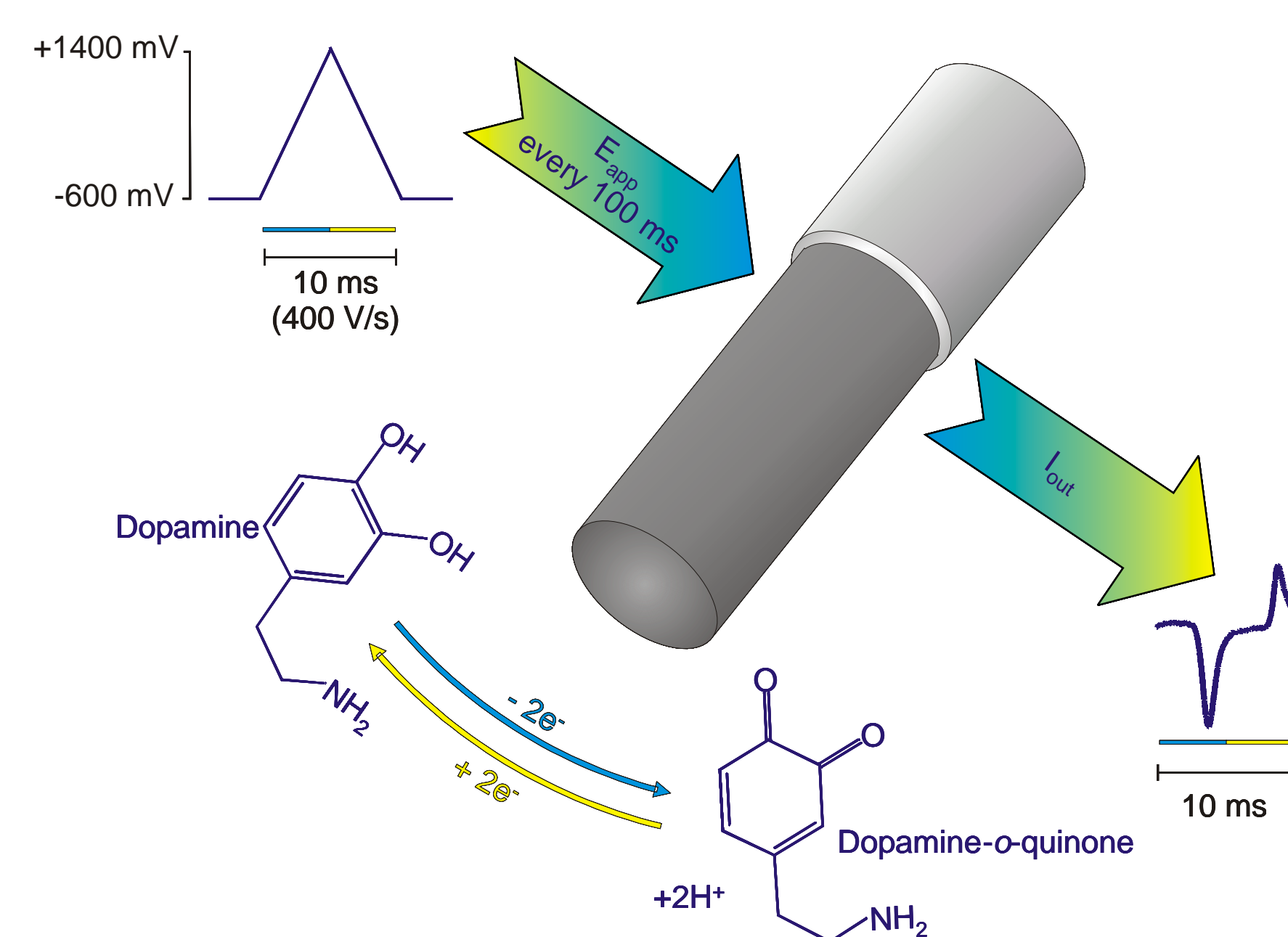
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Introduction

The dopaminergic projection from the ventral tegmental area to the nucleus accumbens is critically involved in mediating the reinforcing properties of cocaine^{1,2}. Although these neurons respond to rewards on a subsecond timescale^{3,4}, most neurochemical studies have only addressed dopamine's role in drug addiction by examining minute-to-minute changes in the tonic (basal) levels of extracellular dopamine⁵⁻¹⁰. To investigate the role of phasic (subsecond) dopamine signaling¹¹, we measured dopamine every 100 ms in the nucleus accumbens using fast-scan cyclic voltammetry¹².

Detection of dopamine



Using fast-scan cyclic voltammetry, dopamine is electro-oxidized by application of voltage. This liberates two electrons which are detected as current at a carbon-fiber microelectrode.



Selectivity

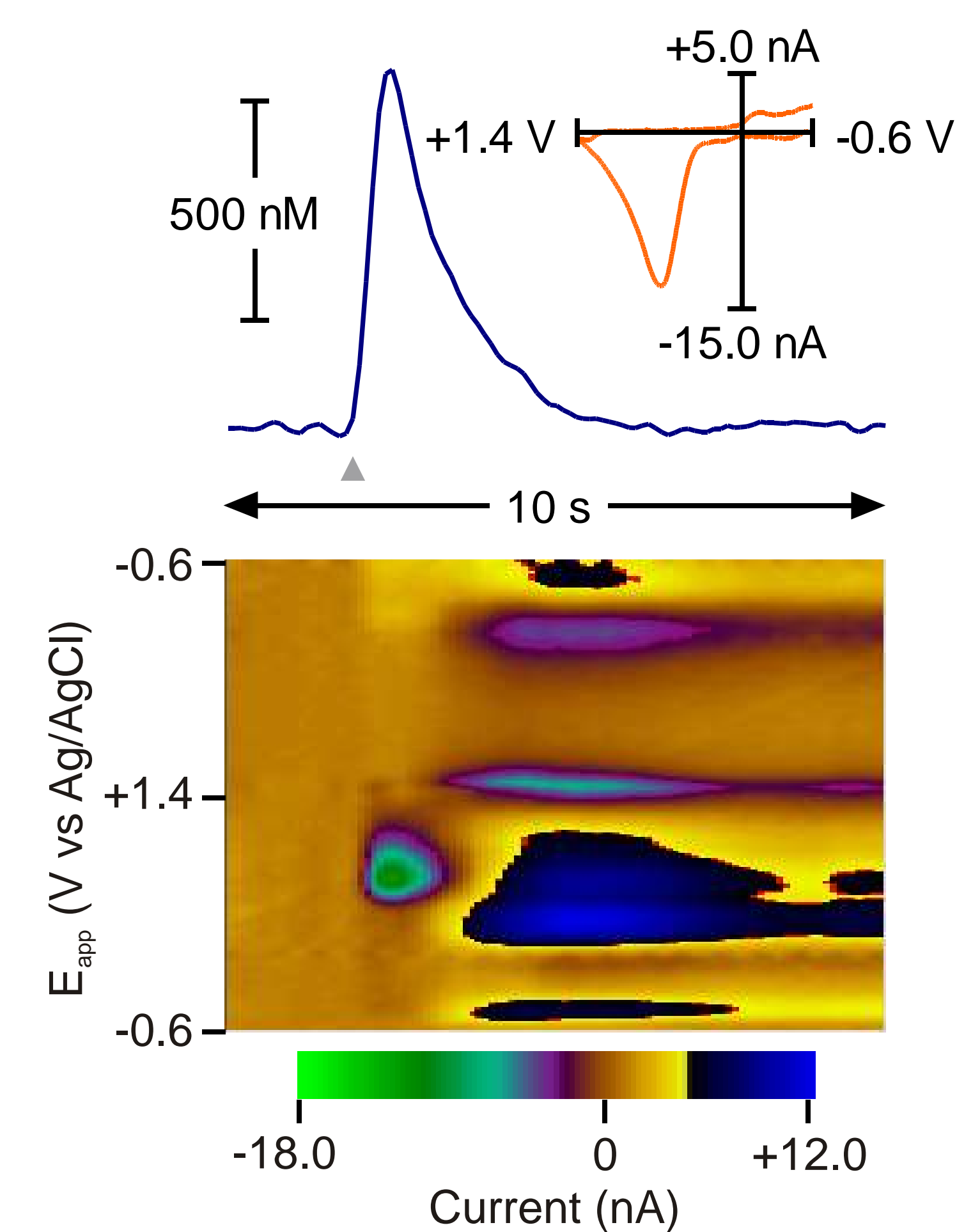
Anatomical: Postmortem histological verification confirmed that all the recording sites were in the core of the nucleus accumbens.

Physiological: Stimulating dopaminergic cell bodies before and after behavioral sessions and detecting dopamine demonstrated that recording sites could support rapid dopamine release.

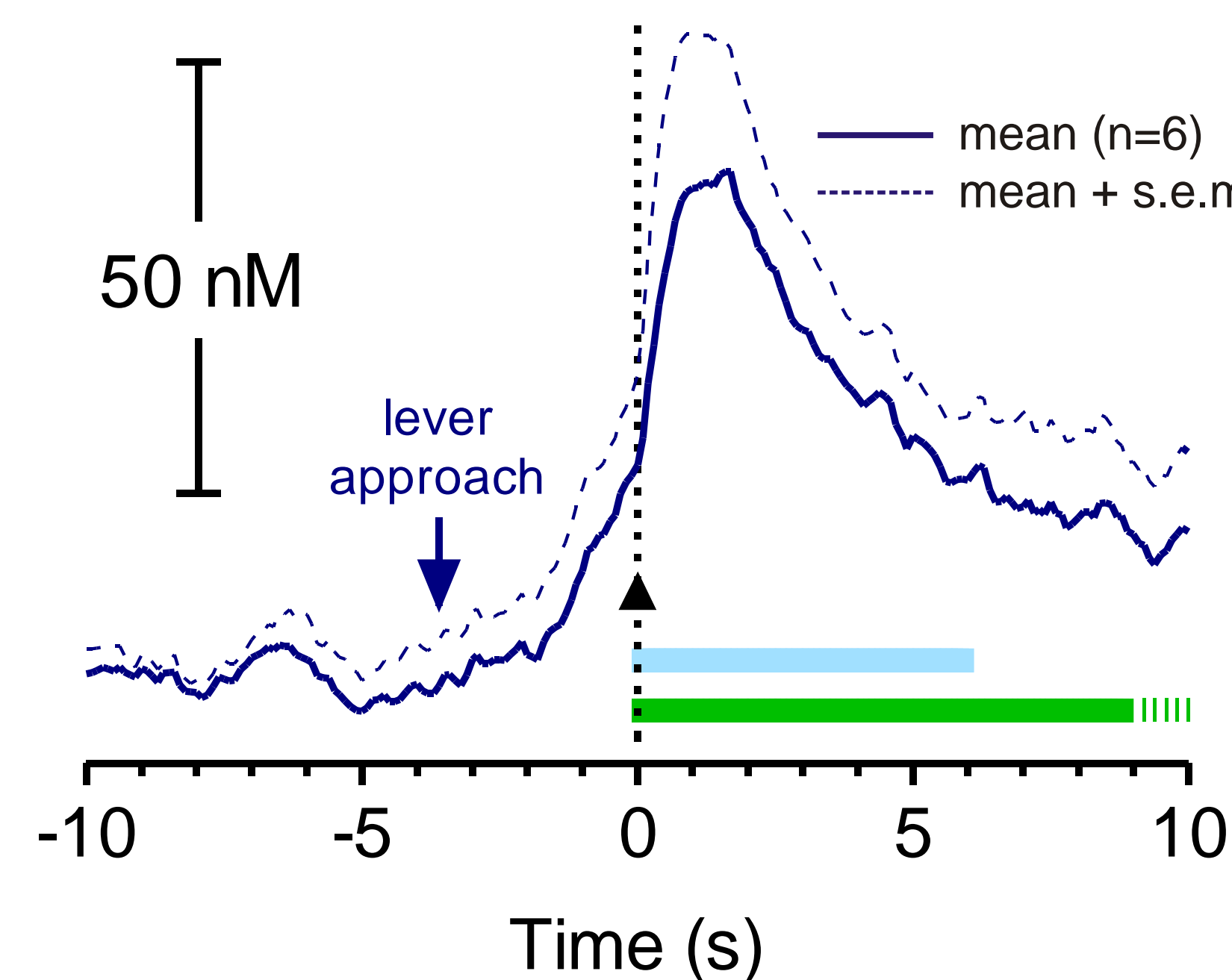
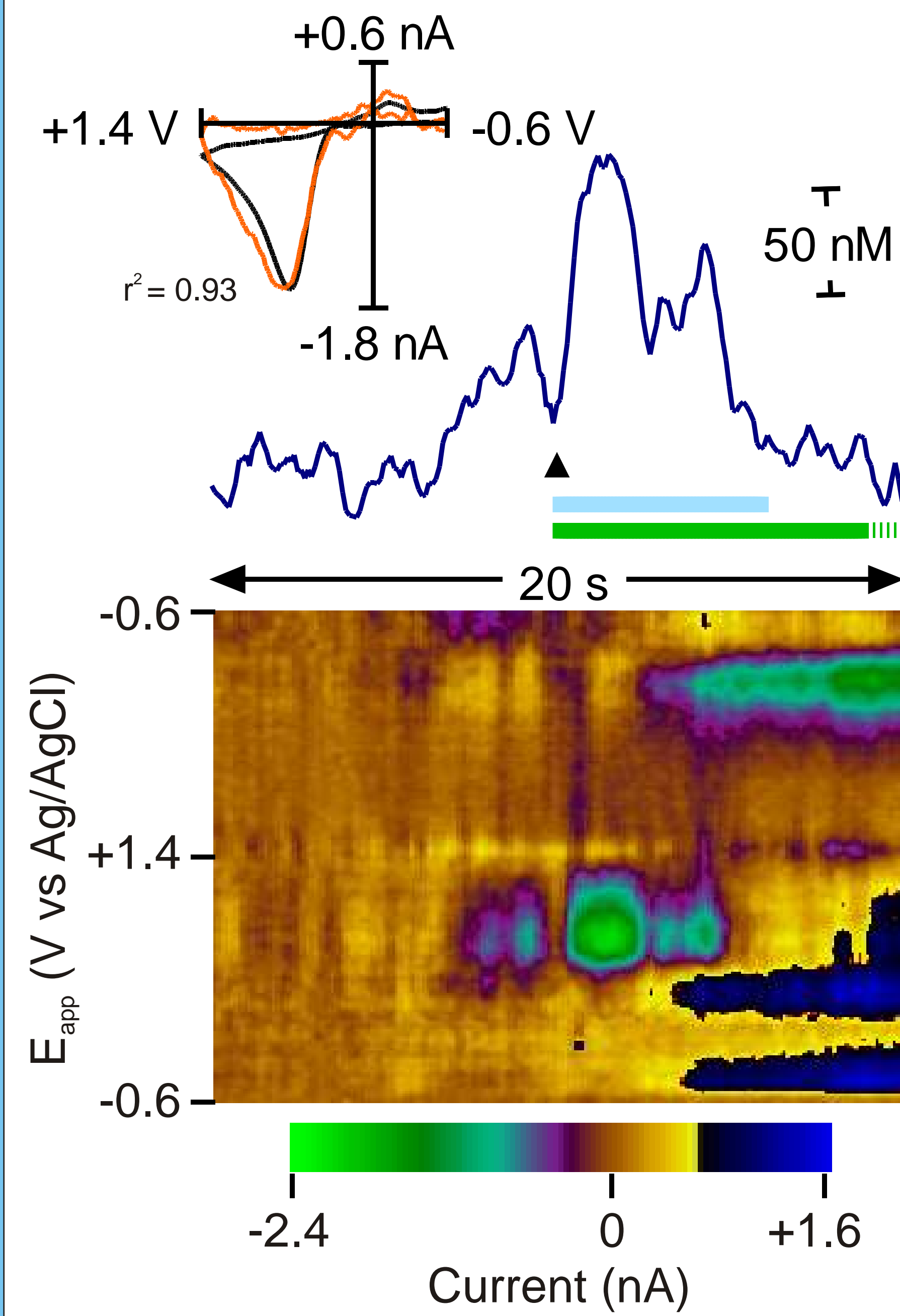
Pharmacological: In the presence of the monoamine oxidase inhibitor, pargyline (75 mg/kg, intraperitoneal), signals were not attenuated.

Chemical: Cyclic voltammograms of signals during behavioral session were compared to those from electrical stimulations at the same recording site and those from *in vitro* calibration of the electrode. In addition to oxidizable species, both movement artifacts and ionic changes in the extracellular space (especially pH) produce current at the electrode. These can be identified using the cyclic voltammogram and eliminated from dopamine signals with differential measurements.

Dopamine release can be evoked by electrical stimulation

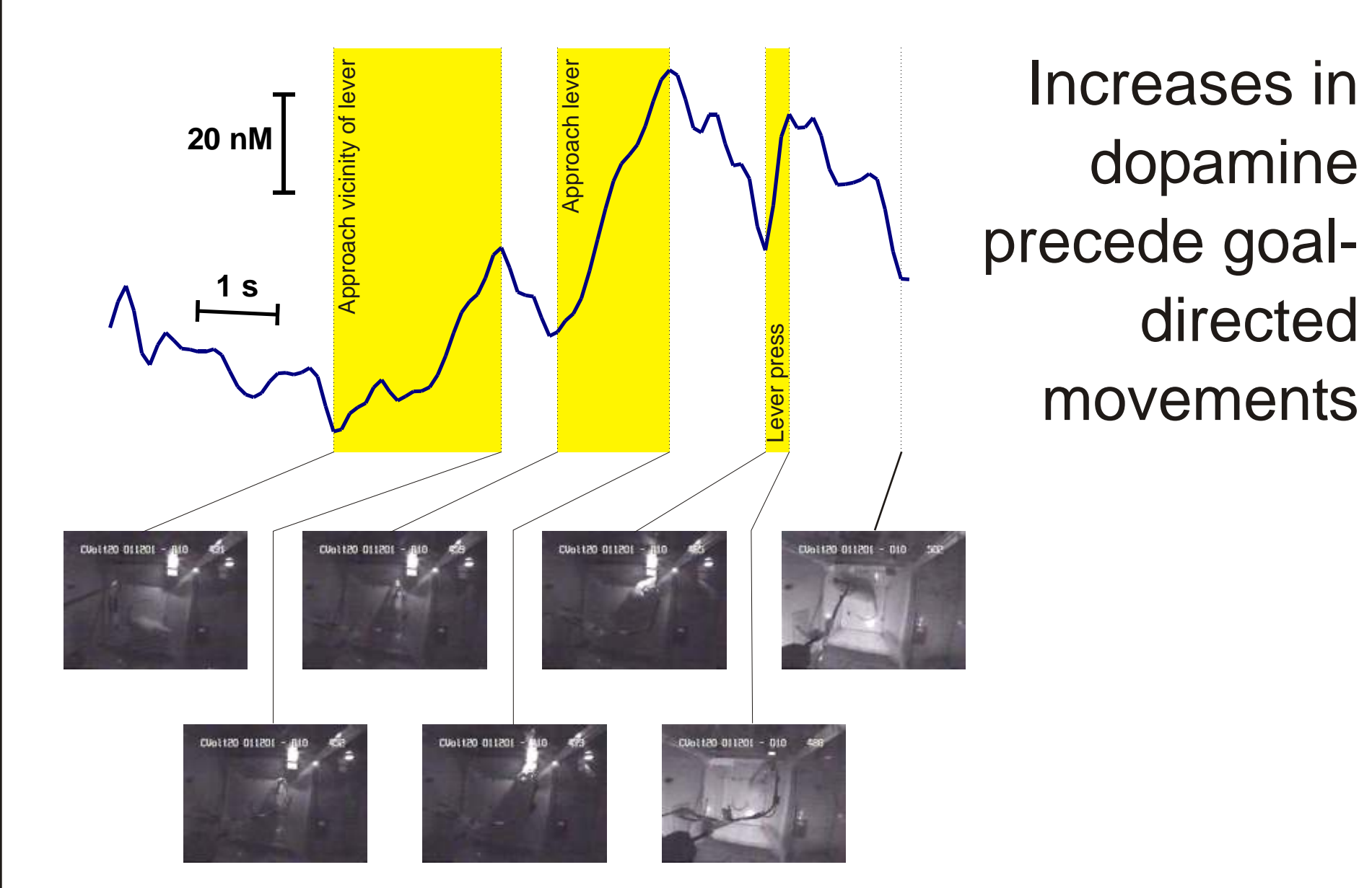


Dopamine increases during responding for cocaine

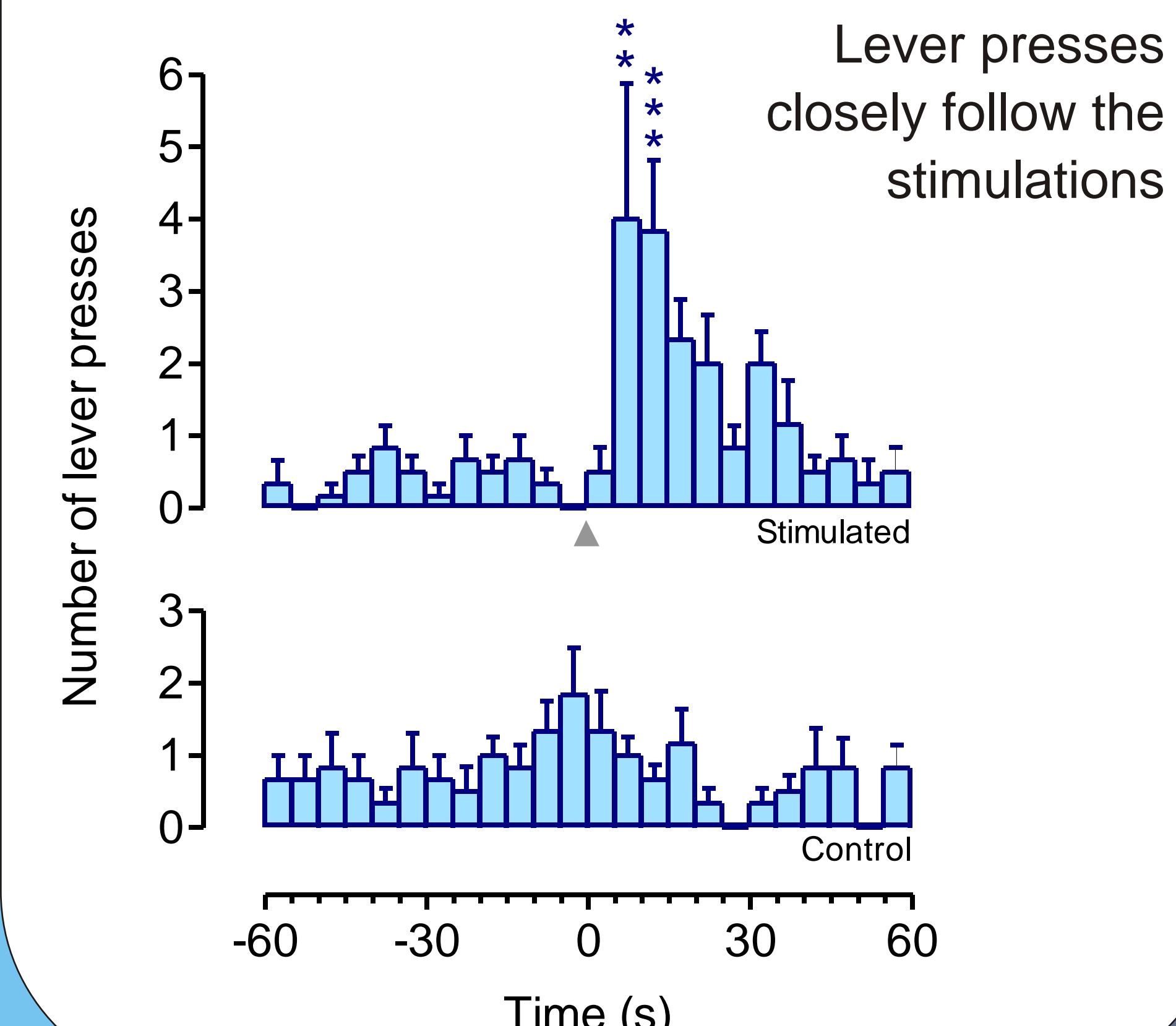
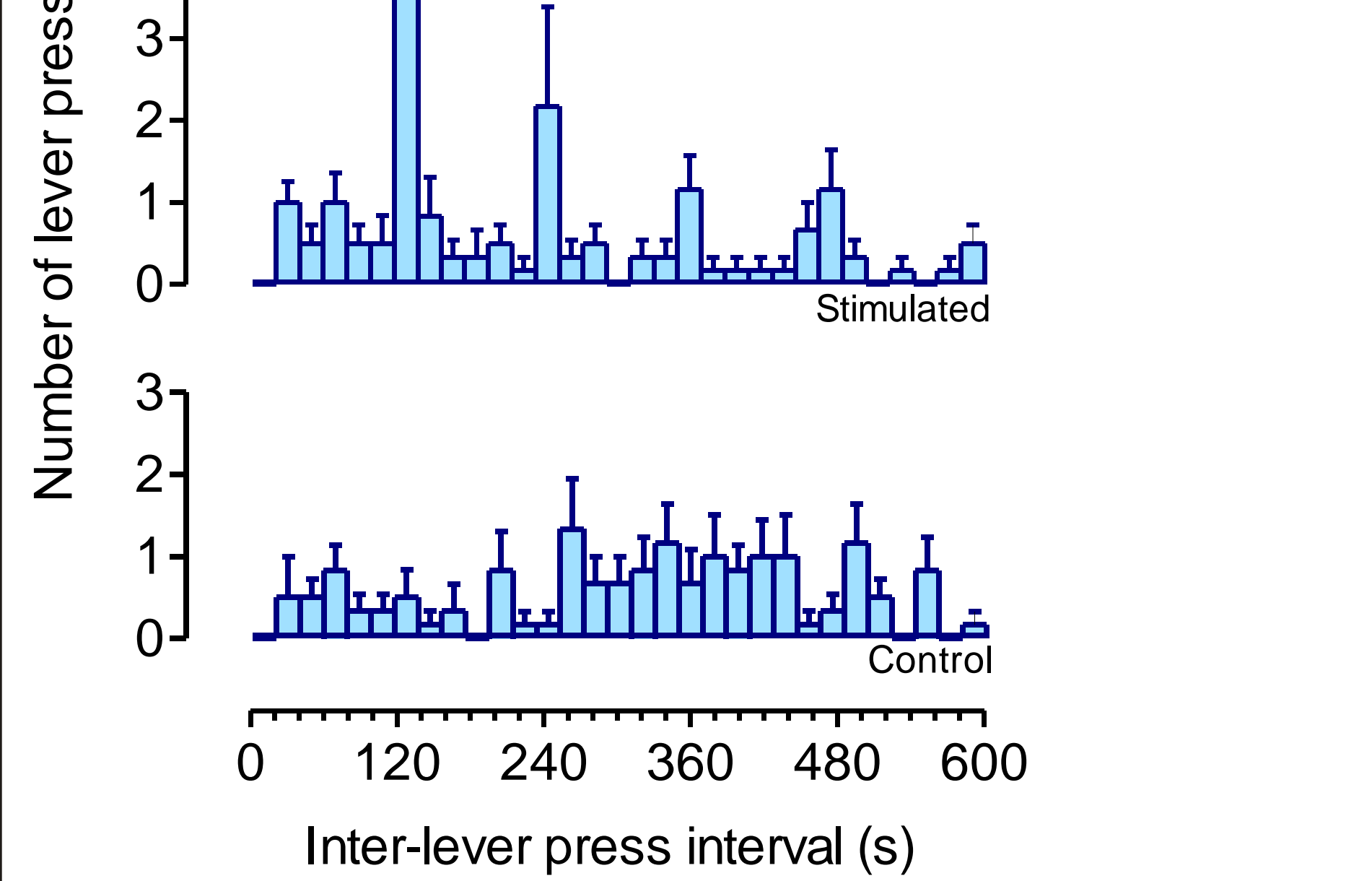


- Key**
- ▲ electrical stimulation (24 pulses, 60 Hz)
 - ▲ lever press
 - cocaine infusion (0.33 mg, 6 s)
 - paired cue (20 s)

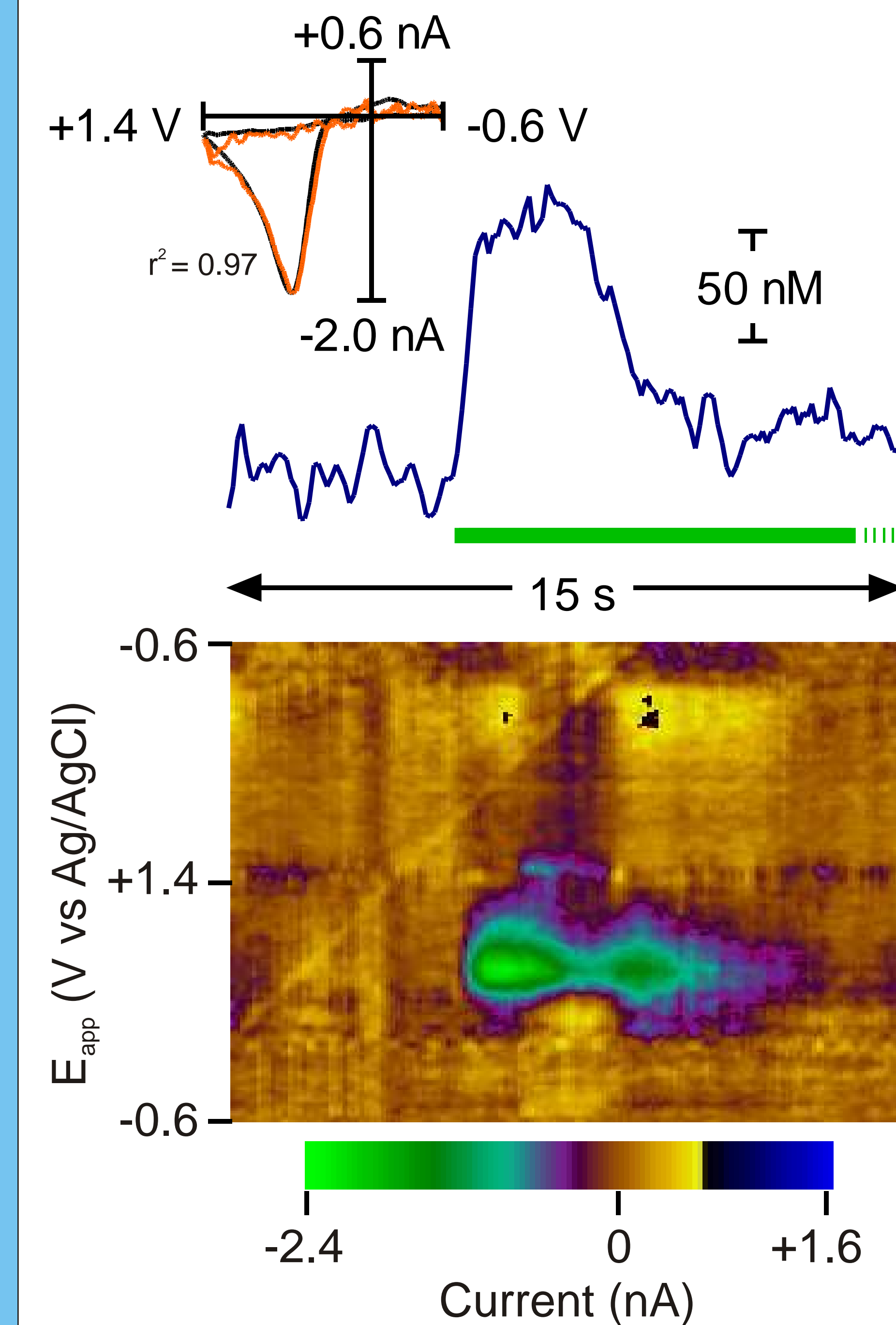
Rapid increases in dopamine promote drug-seeking behaviors



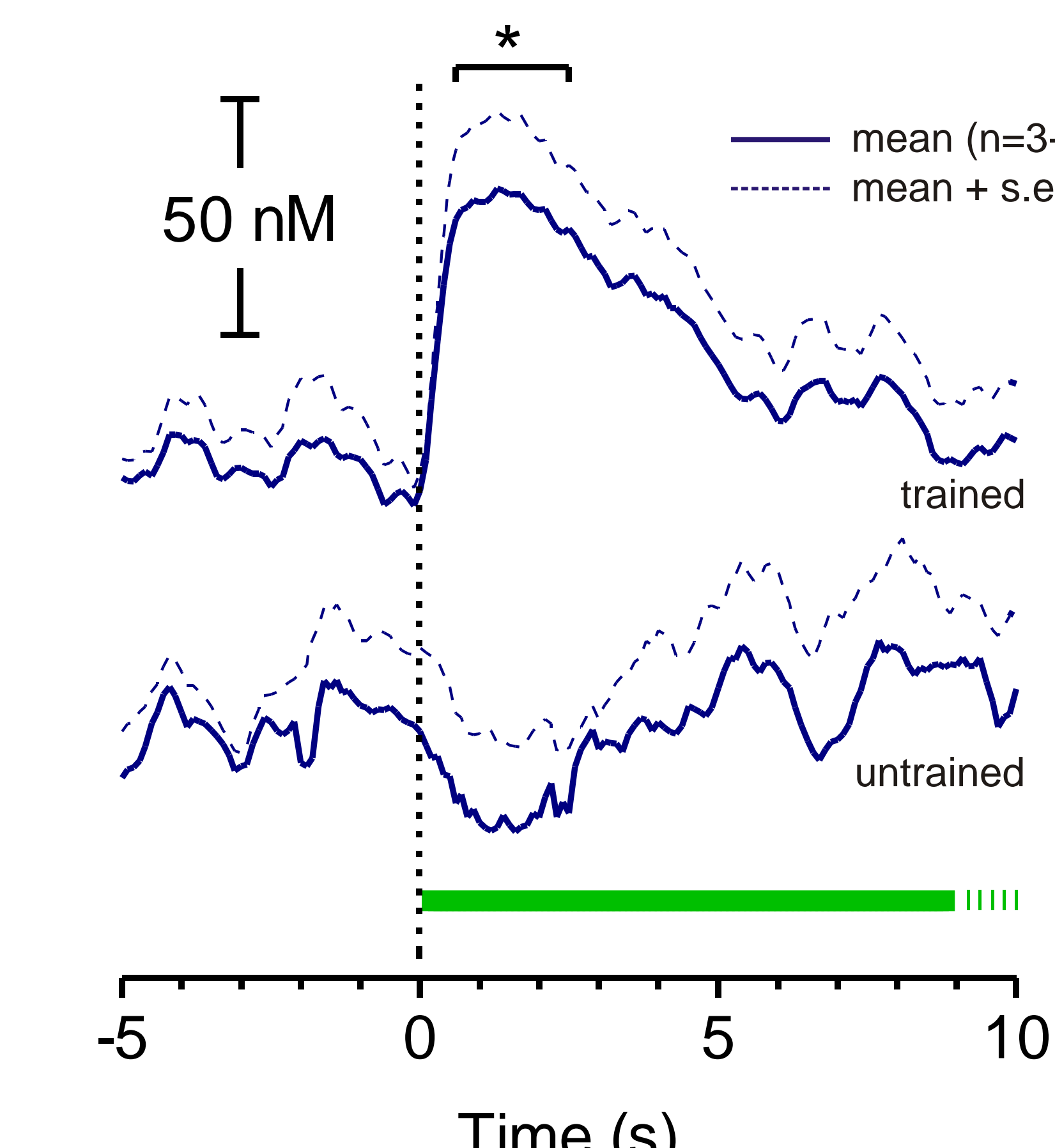
Increases in dopamine precede goal-directed movements



Dopamine release is evoked by cues with learned salience

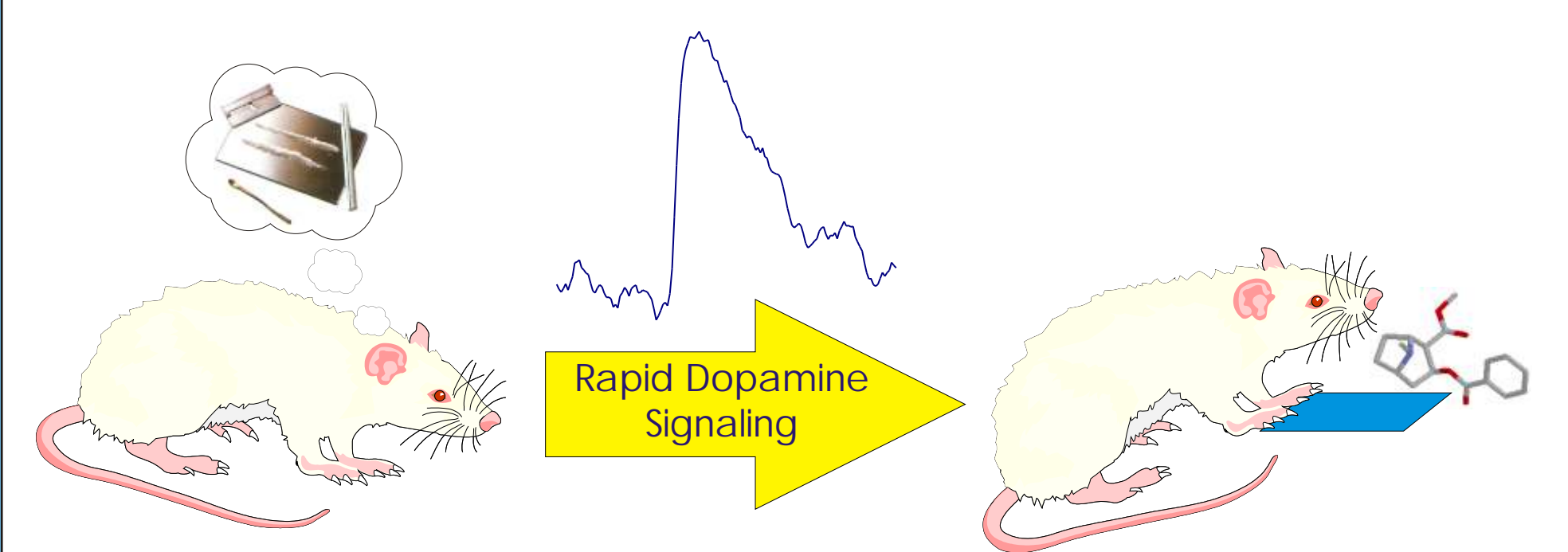


Dopamine increases following a cue which has been paired to cocaine self-administration



Conclusions

In cocaine addiction, the dopaminergic system samples sensory information on a millisecond timescale for salience with respect to this drug. These stimuli cause rapid dopamine signaling that promotes initiation of drug-seeking behaviors.



Such a functional role for subsecond dopamine signaling could generalize to other reinforcers and may have evolved to improve acquisition of natural reinforcement.

References

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Acknowledgments

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