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THE STATE UNIVERSITY OF NEW JERSEY

# Relapse to Cocaine Binge: a Behavioral Trap?

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**Research: Neural bases of**

- **cocaine addiction**
- **disorders involving binge eating**

A quick reflection on Rutgers' past 50 years-

How did we get to where we are?

- **1970** – NJ Governor declares that community health care must have priority over research. He *saw no reason why research should be conducted by faculties of medical schools*.

- He asks the state legislature to consolidate Rutgers University Medical School (RMS) and the New Jersey College of Medicine and Dentistry (NJCMD, formerly the failing Seton Hall Medical School) for the purpose of delivering general practitioners to city clinics throughout the state.

- **1 month later** The Medical and Dental Education Act of 1970 removes RMS from its University setting in Rutgers, merging RMS with NJCMD into the College of Medicine and Dentistry of New Jersey, and later to be renamed UMDNJ, signed into law by the Governor.

- **2 days later**
  - Dean Stetten resigns and later became Deputy Director of NIH.
  - Four department chairs, of Medicine, Surgery, Biochemistry and Psychiatry, and many faculty at RMS resign.

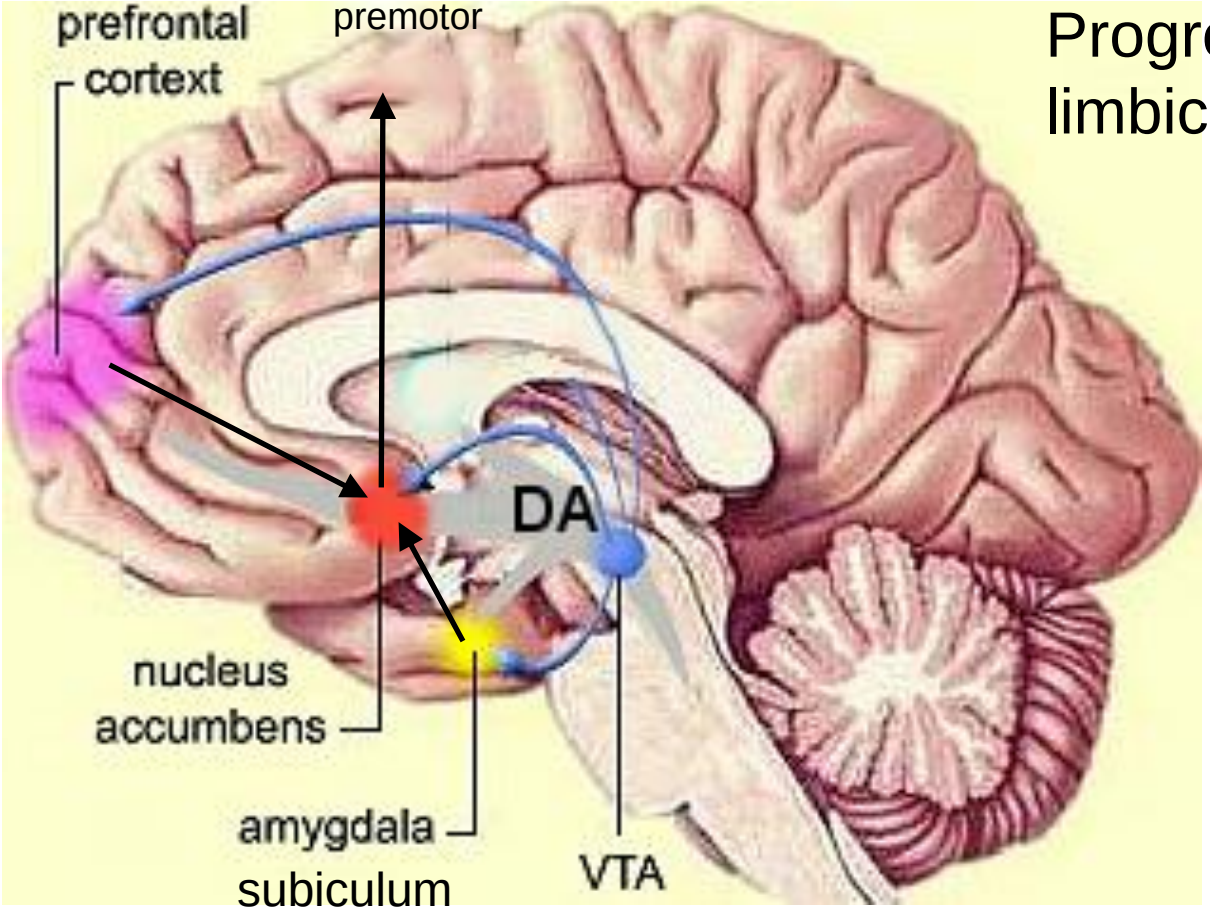
*Ron Morris, M.D.*

It was difficult to put back together, but here we are,
with world-class leadership in neuroscience,
and high hopes for our future.

My lab's interest: the mechanisms that drive cocaine self-administration, both during cocaine binge and relapse to cocaine taking.

We are guided by the many studies implicating the brain's mesolimbic dopamine system.

The mesolimbic DA system projects most heavily to the nucleus accumbens. Nauta (1978) hypothesized that the limbic system gains access to the motor system via the accumbens.

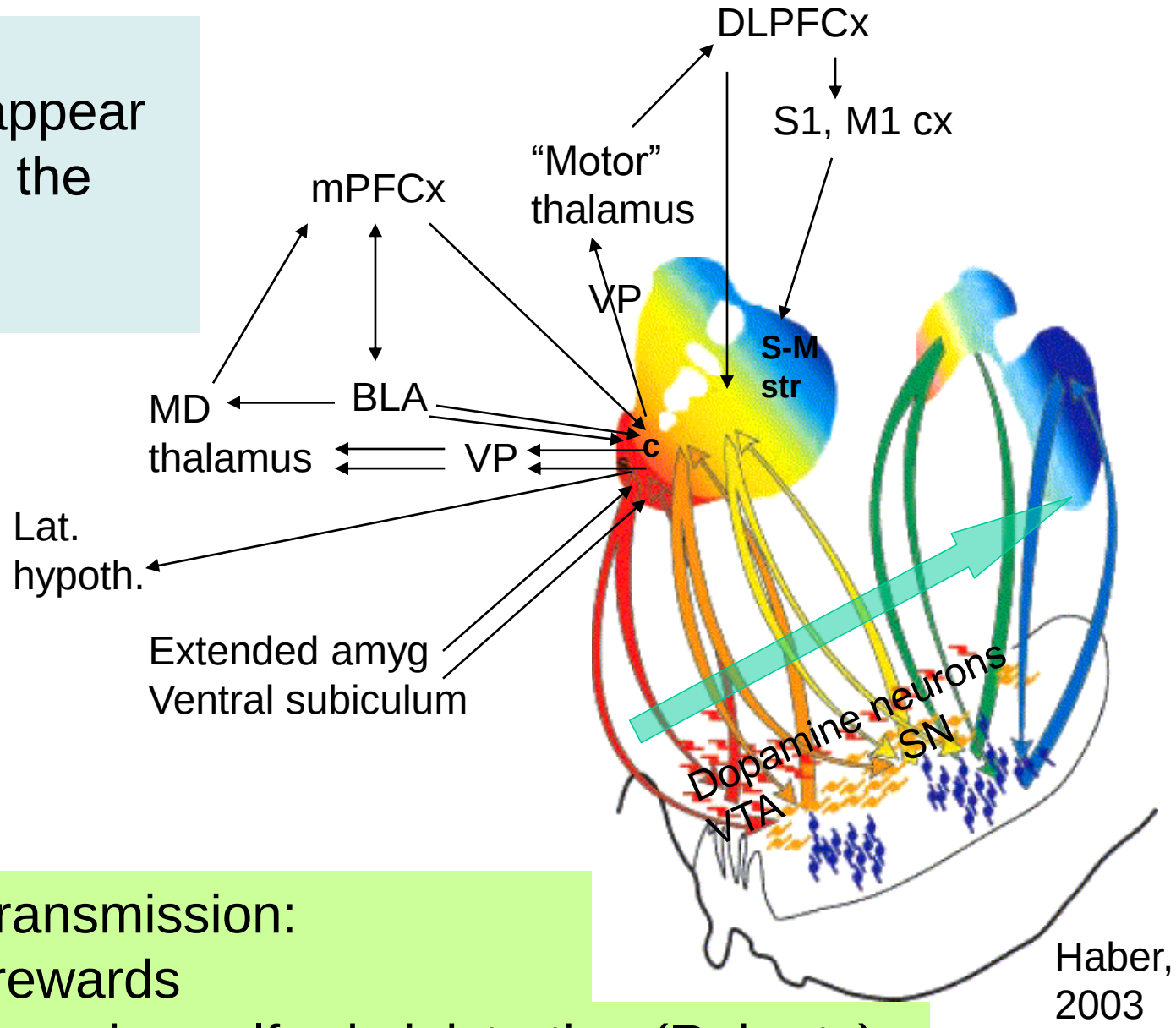



Progression of limbic signals + DA

→ motivational signals

→ motor signals

The anatomical connections do appear to "spiral" toward the motor system.




Haber, 2003

Accumbens DA transmission:

- stimulated by rewards
- necessary for cocaine self-administration (Roberts)

Therefore, we record activity of accumbens neurons during:

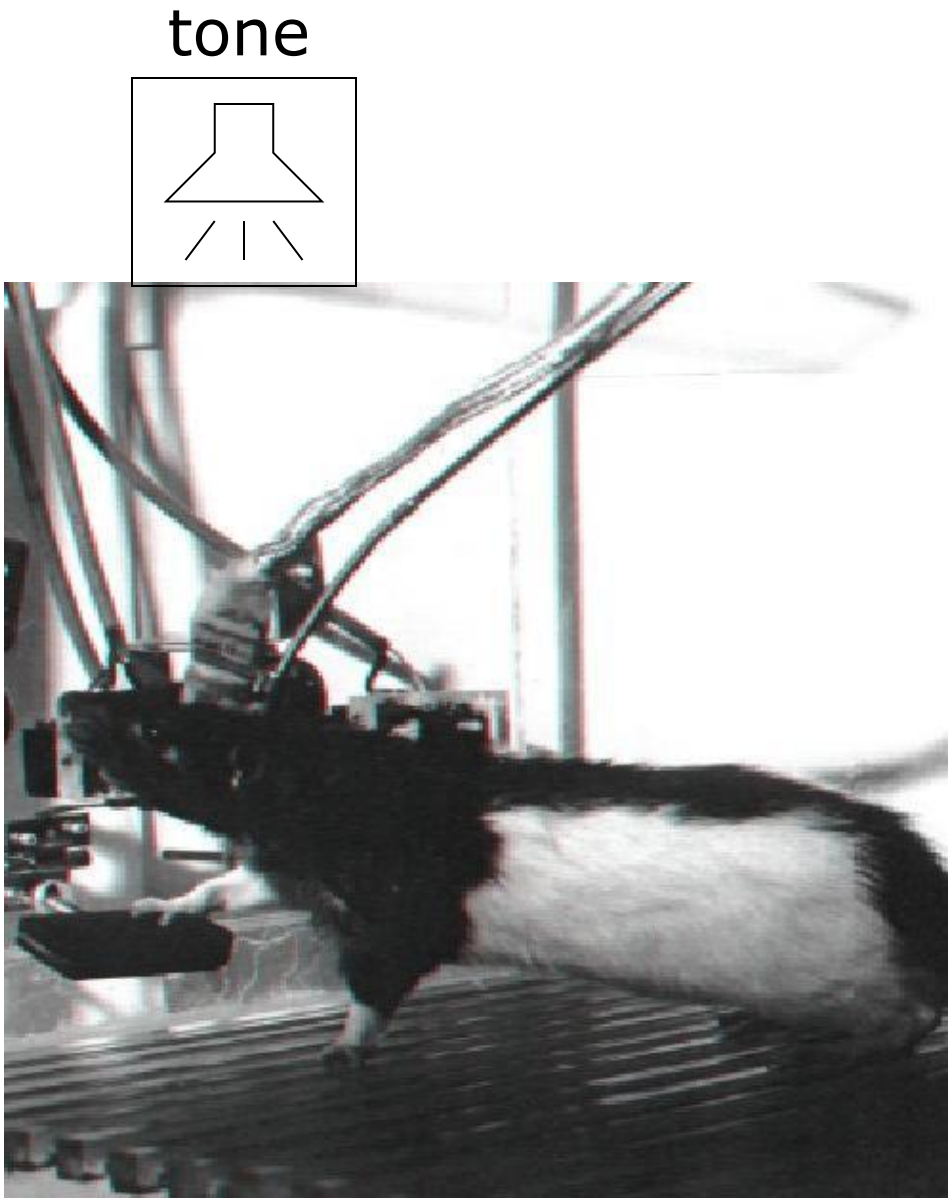
1. cue-induced relapse model (Part One of talk)
2. self-administration binge (Part Two of talk)

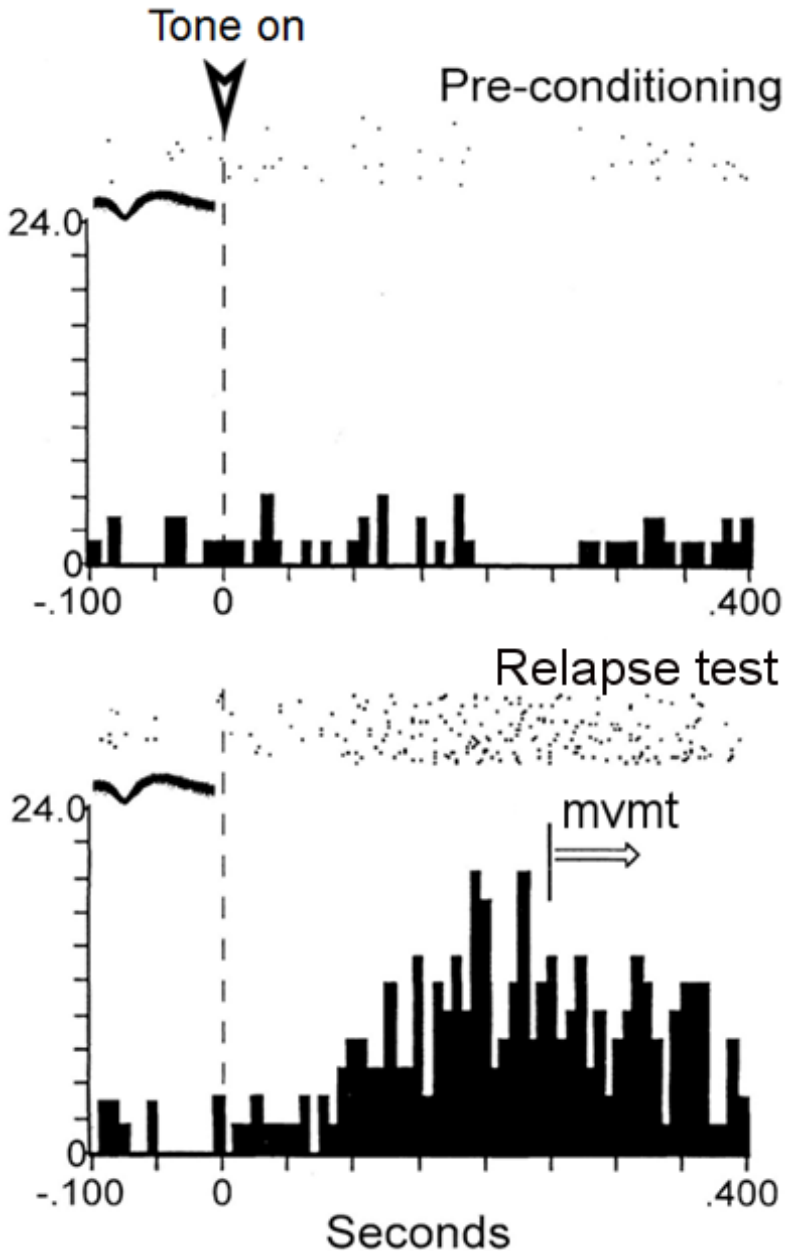
Part One: Relapse

<u>Tone discrimination</u>

Lever press produces cocaine infusion only if tone is on.

(6 hrs/day, 7 days/wk)

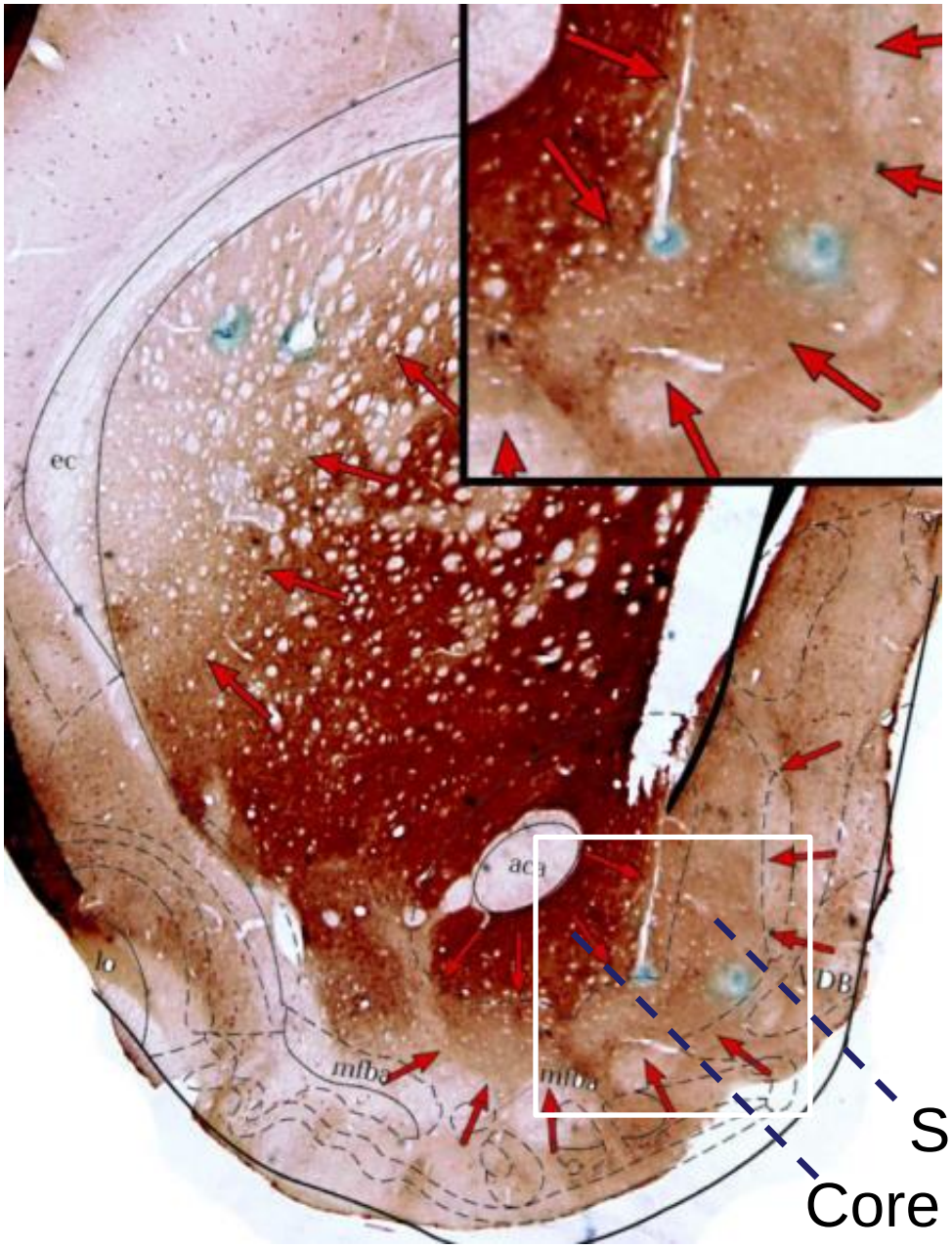





Self-administration (3 weeks)

Abstinence (lived in S-A chamber for 3 weeks)

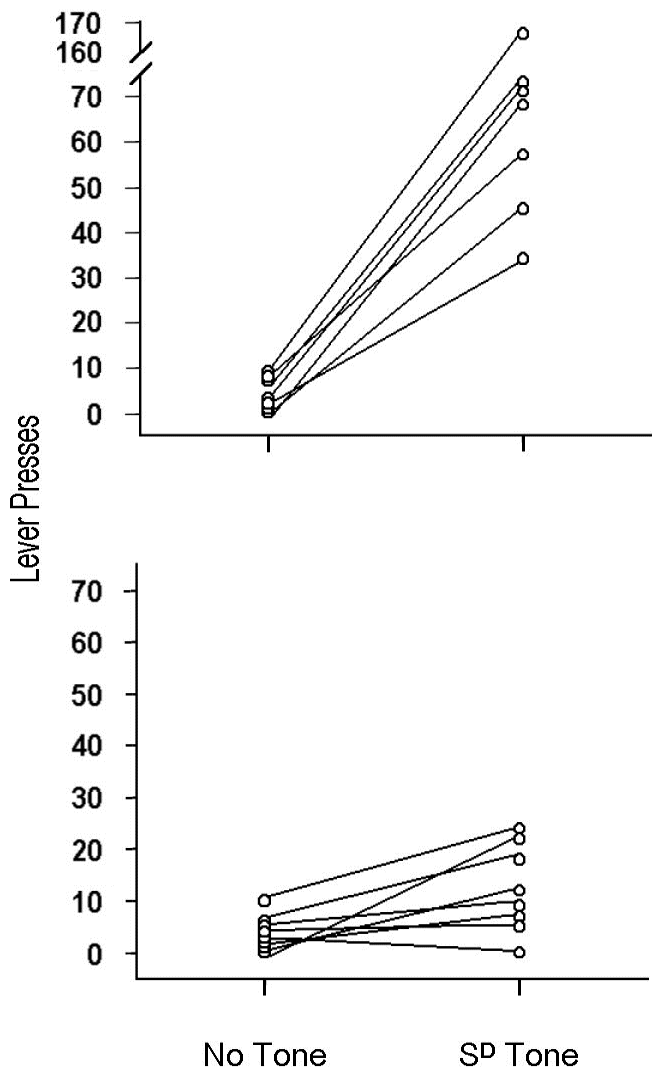
Accumbens neurons show short-latency responses to the cocaine cue.


ec
ac
lo
mfba
mfba
DB
Shell
Core

Cue-induced reinstatement

high responders to cue

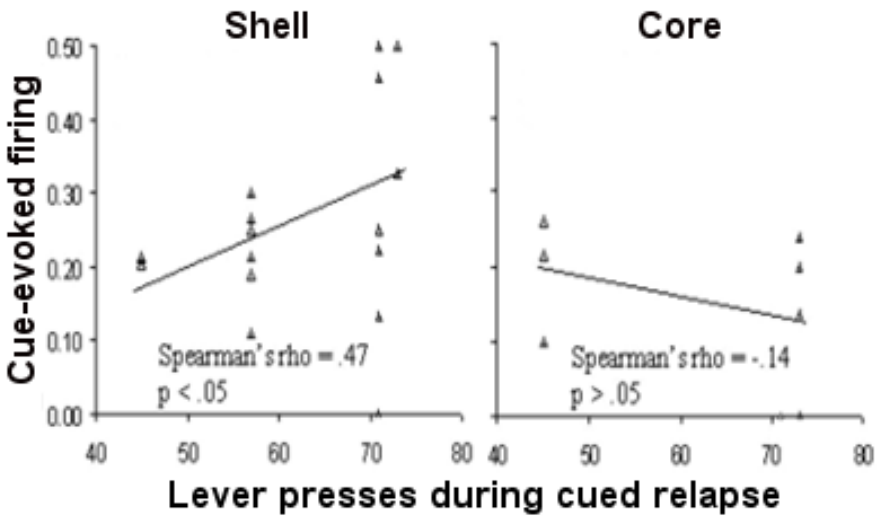
low responders to cue




*lever*

*lever*
*cocaine cue*

Cue-induced firing

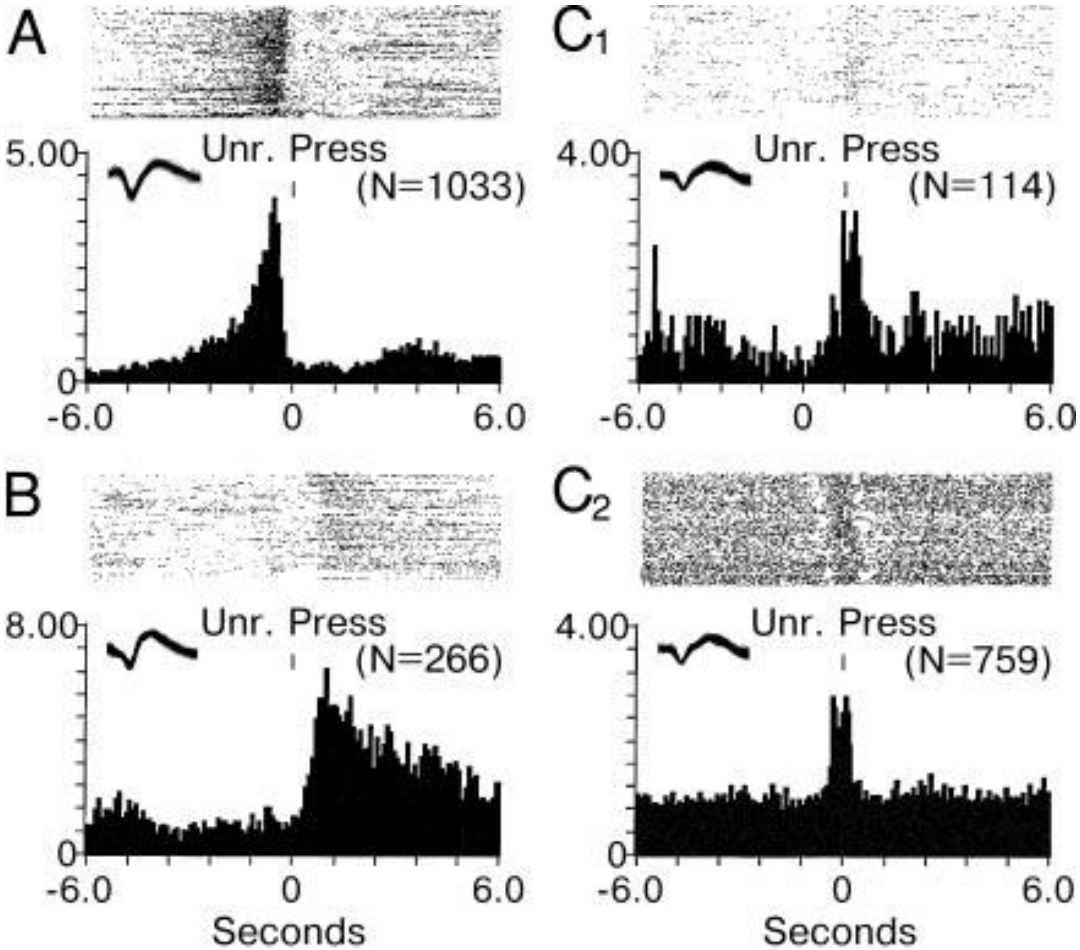



Relative to core neurons, shell firing:

- discriminated the cocaine cue from a neutral tone
- was correlated with degree of drug seeking

Four NAc core neurons

Core neurons showed much stronger phasic firing during the operant <u>response</u> than shell neurons.

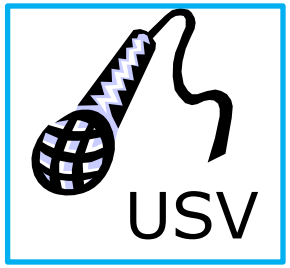


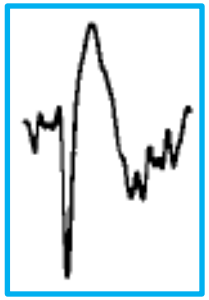

Together with shell's <u>cue</u> responsiveness, these data are consistent with a spiral flow of information from medial-to-lateral striatum, toward the motor system.

Part Two

During a cocaine self-administration binge, we have recorded a repeating pattern of neural activity in the basal forebrain.

Ultrasonic vocalizations (USVs) enlighten the interpretation of this pattern.



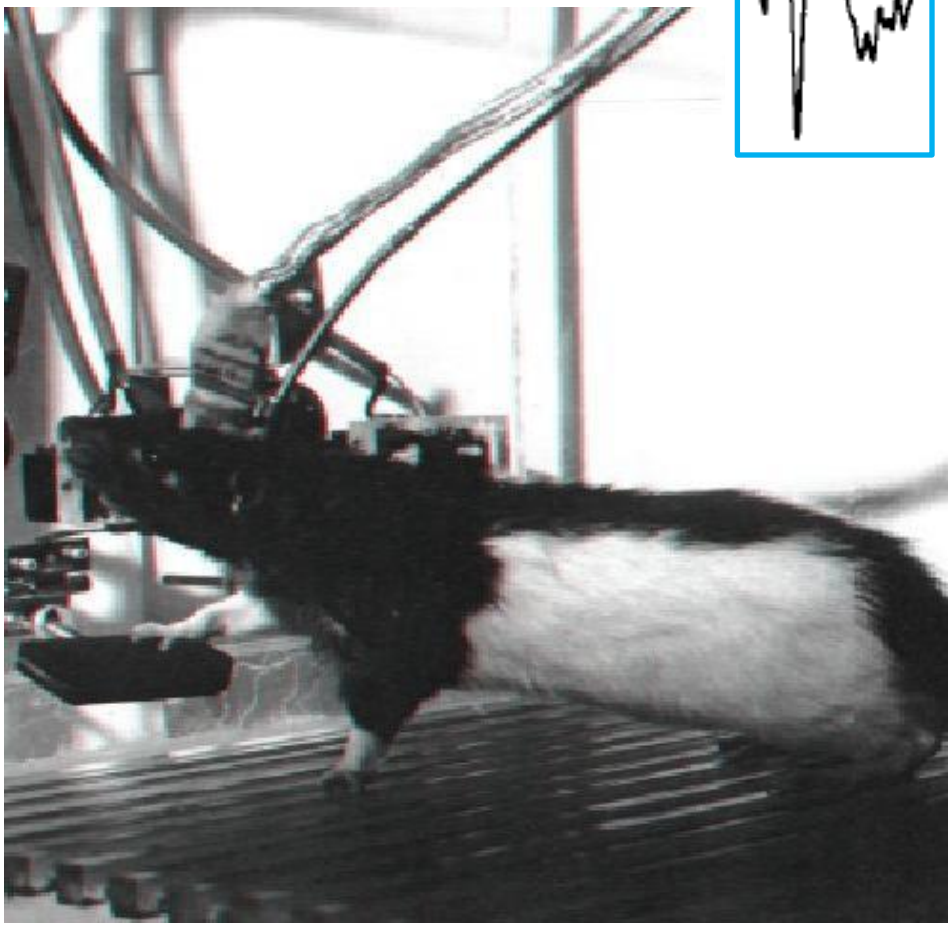



## Cocaine self-administration binge

FR1: each operant response produces a cocaine infusion.

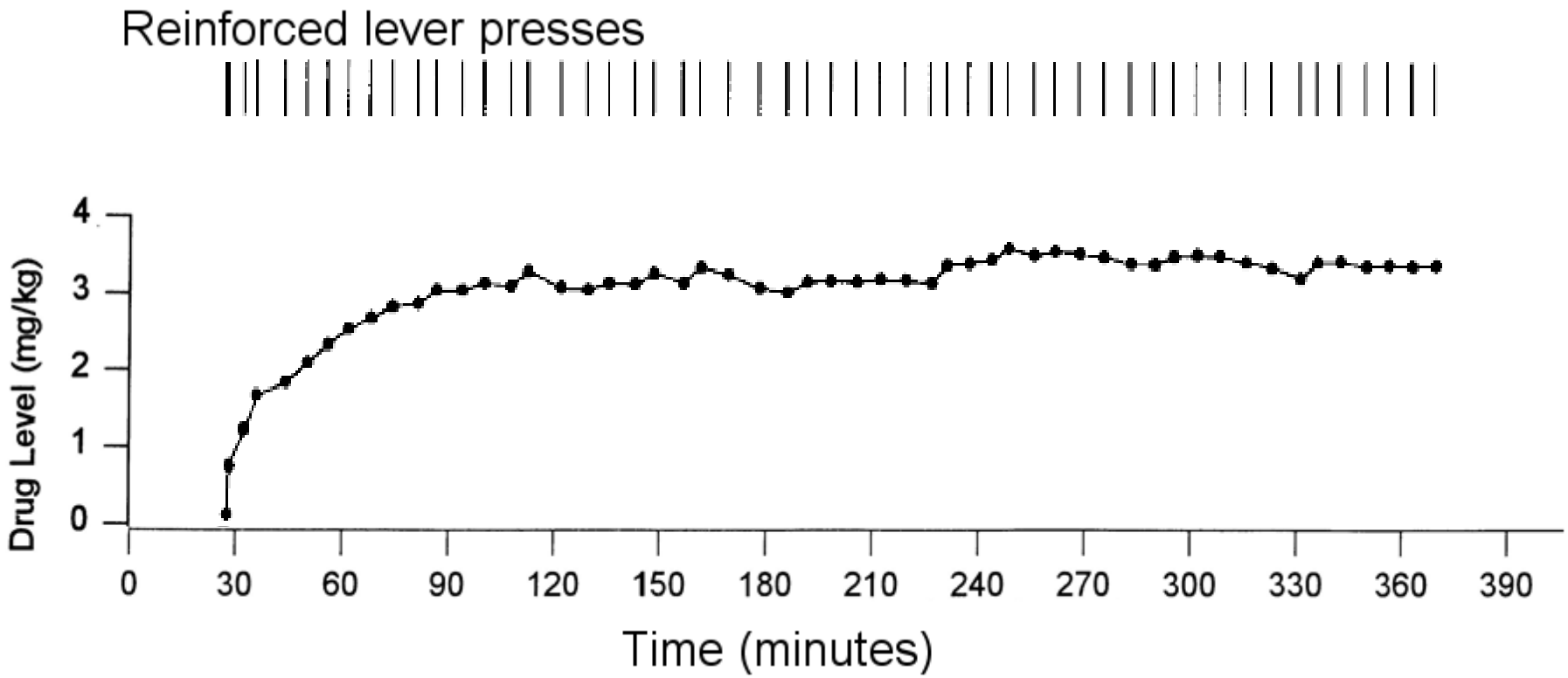
6 hours/day
7 days/week

Animals live 24/7 in the self-administration chamber.



Operant device

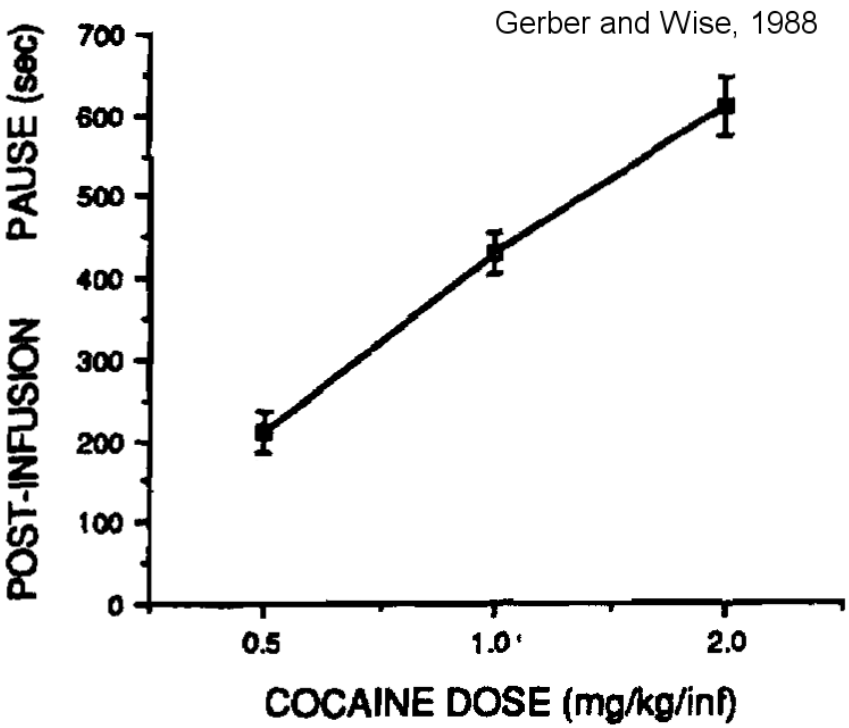
1. Sequence of lever presses
2. Calculated drug level
(one session)



Pickens and colleagues (1968): stimulant self-administration fits a "drug satiety" model (Wise et al. 1995).

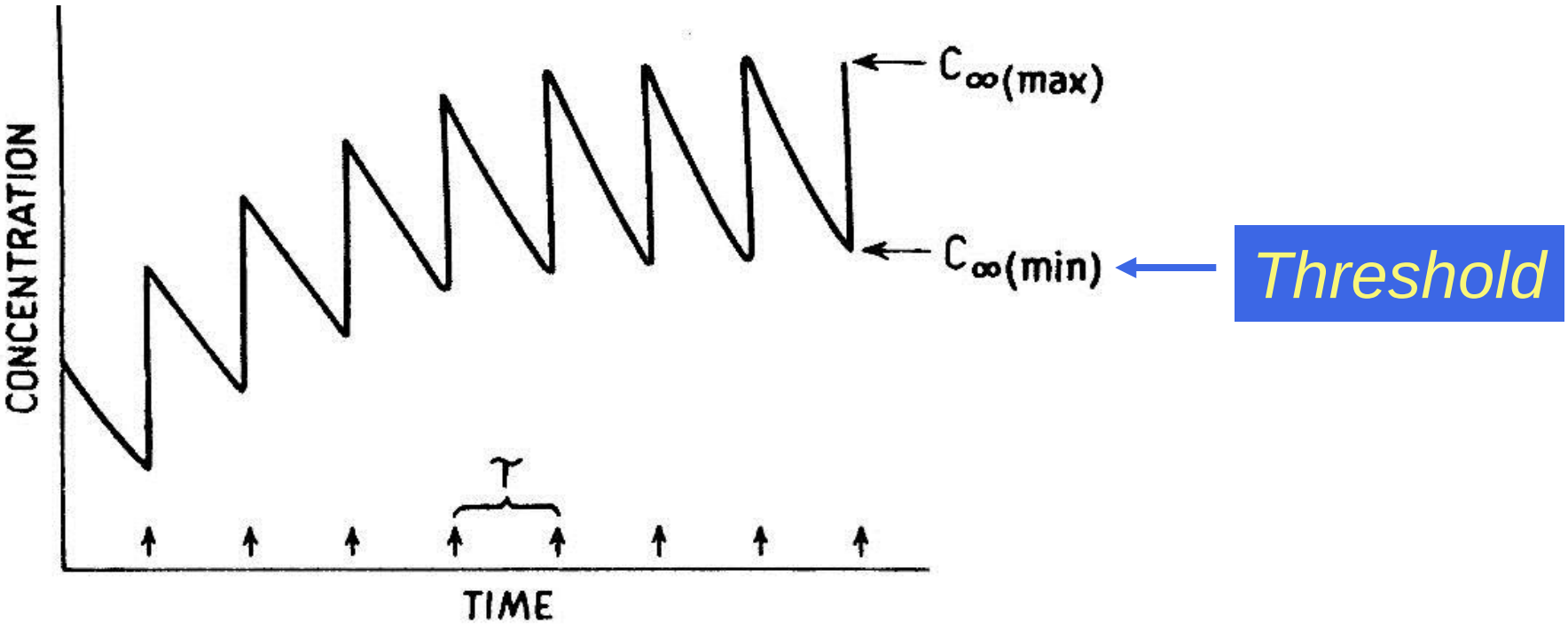
Animals "titrate" their cocaine level.

Binge behavior:
The animal's goal appears to be to maintain cocaine at its satiety level.

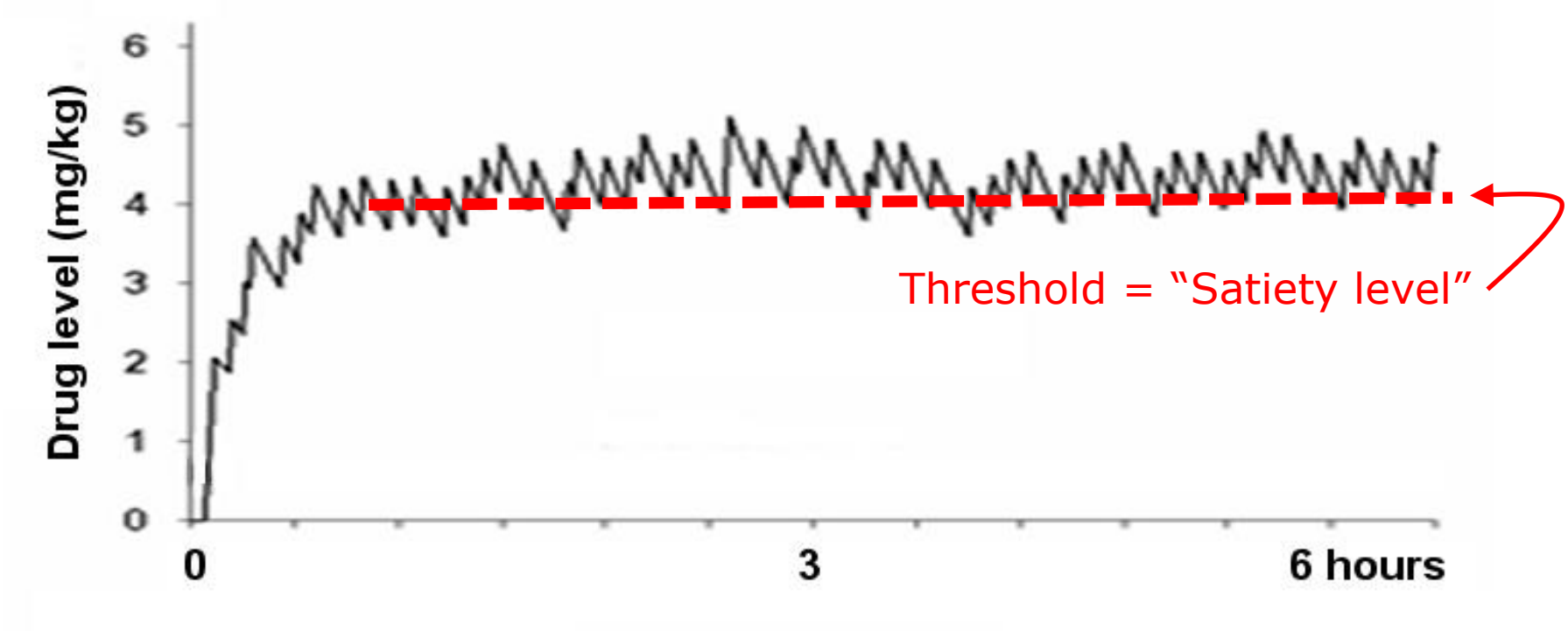


per infusion

Yokel and Pickens (1973) showed that each self-infusion occurs at the LOW ("threshold") level of drug.



Closer look at drug level during S-A




Self-infusion cycle is 6 - 7 minutes.

Animals are able to discriminate their cocaine level.

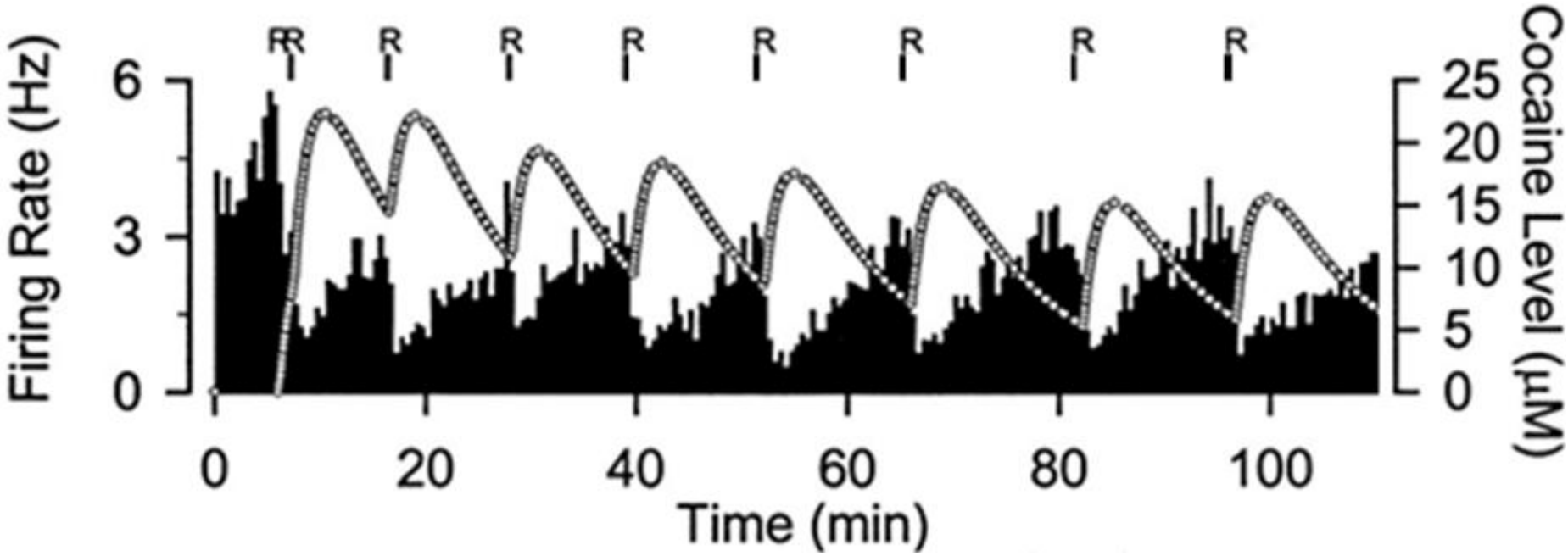
Therefore, there must be some neurons that enable rats to do this.

A prime candidate:

“Progressive reversal”

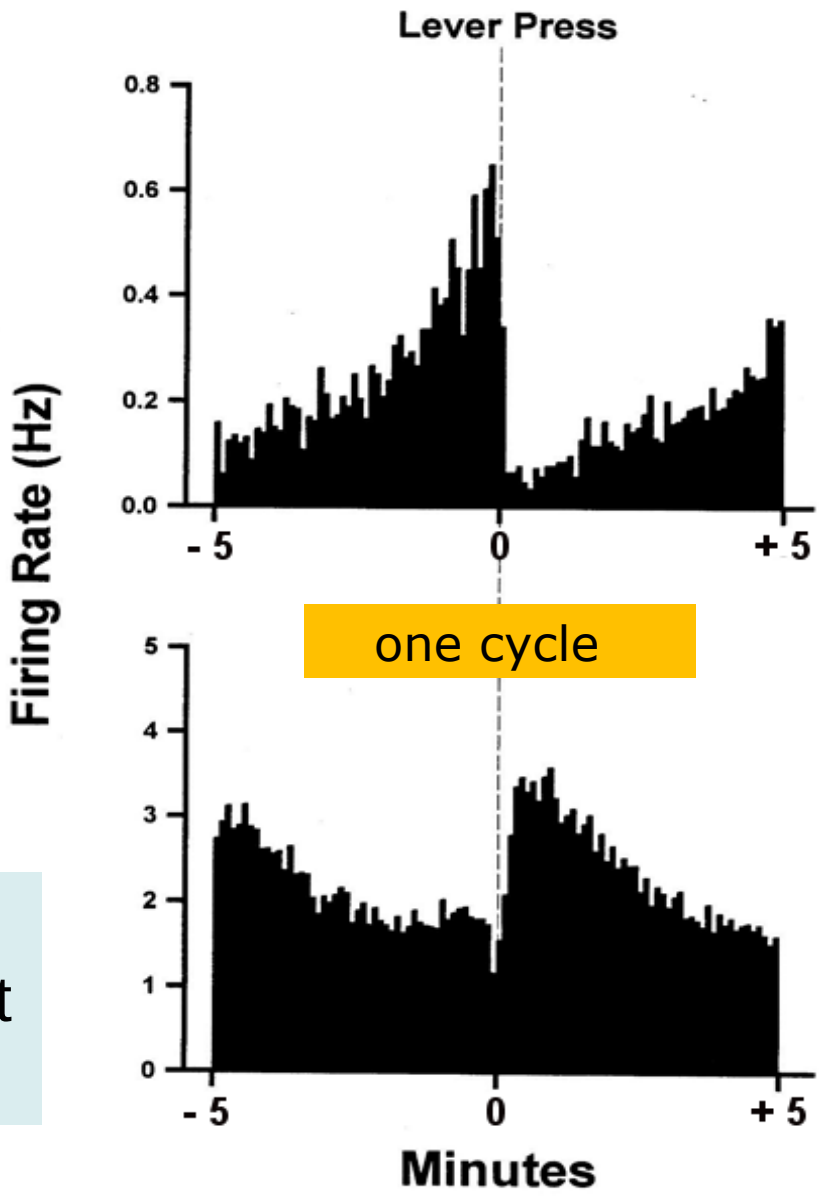
the most prominent firing pattern we have observed in accumbens

# Progressive reversal firing pattern



The ***progressive reversal*** firing pattern:

- duration of reversal is significantly correlated with inter-infusion interval
- <u>firing rate</u> is significantly correlated with calculated cocaine level
- may transduce low cocaine levels into neural signals that promote drug seeking




(Peoples and West, 1996)

# Can ultrasonic vocalizations enlighten our interpretation of firing patterns?

# Rat Ultrasonic Vocalizations (USVs)

Two Ranges:

Negative affect

22-kHz range

(18-32.99 kHz)

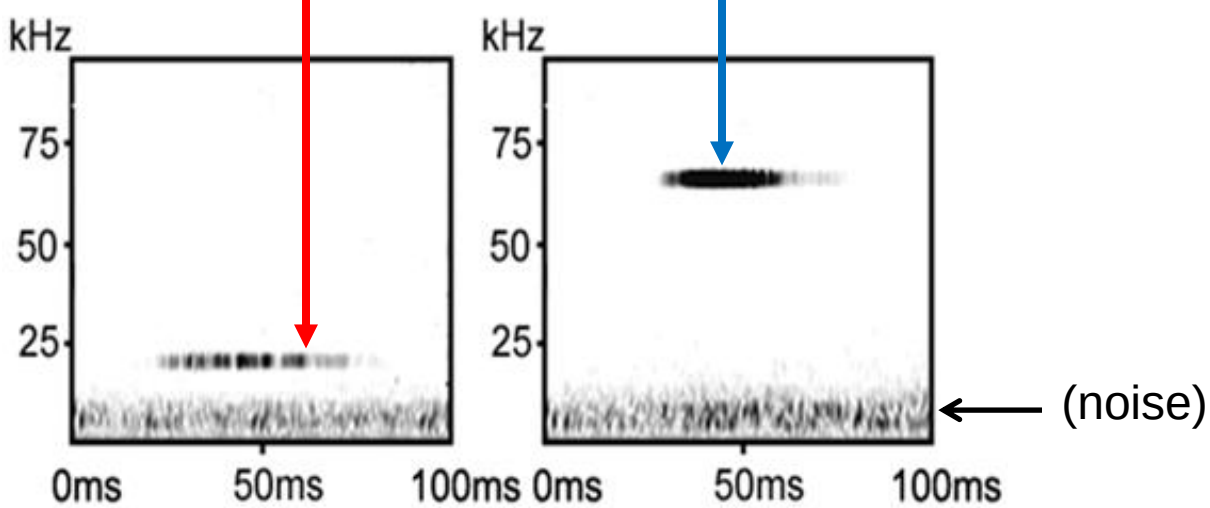
(predator; footshock)

Positive affect

50-kHz range

(38-80 kHz)

(social play; reward cues)

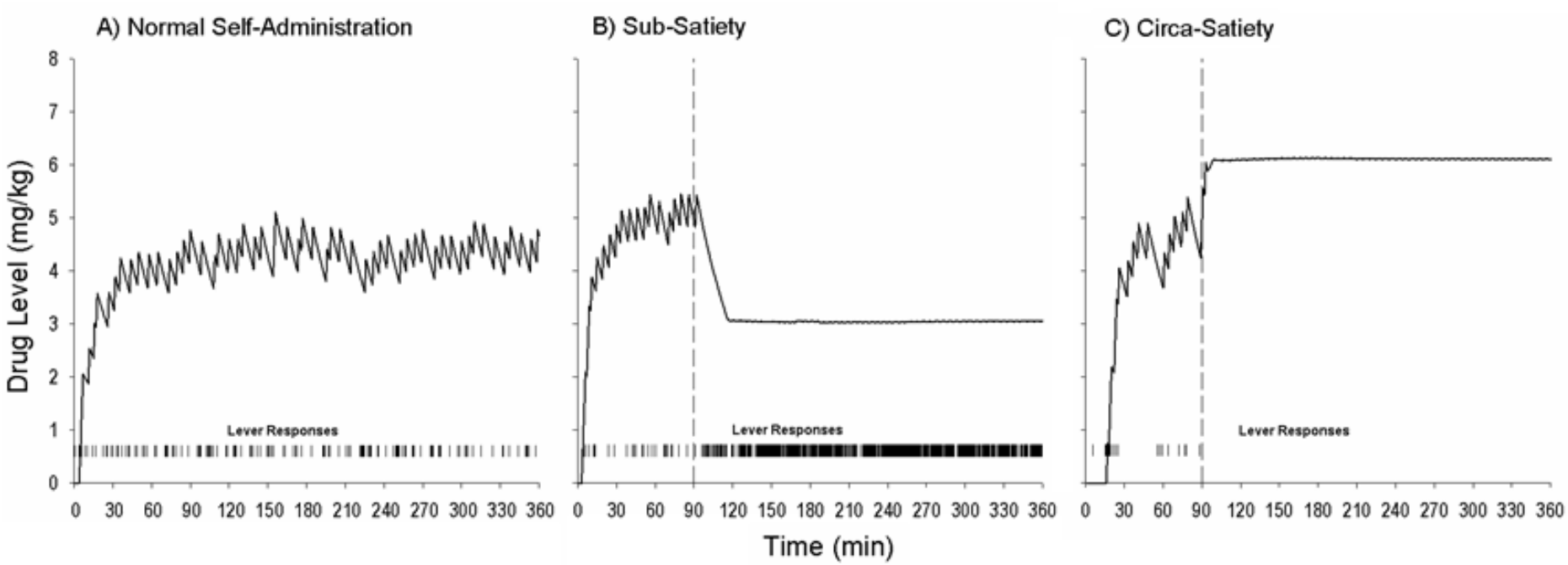


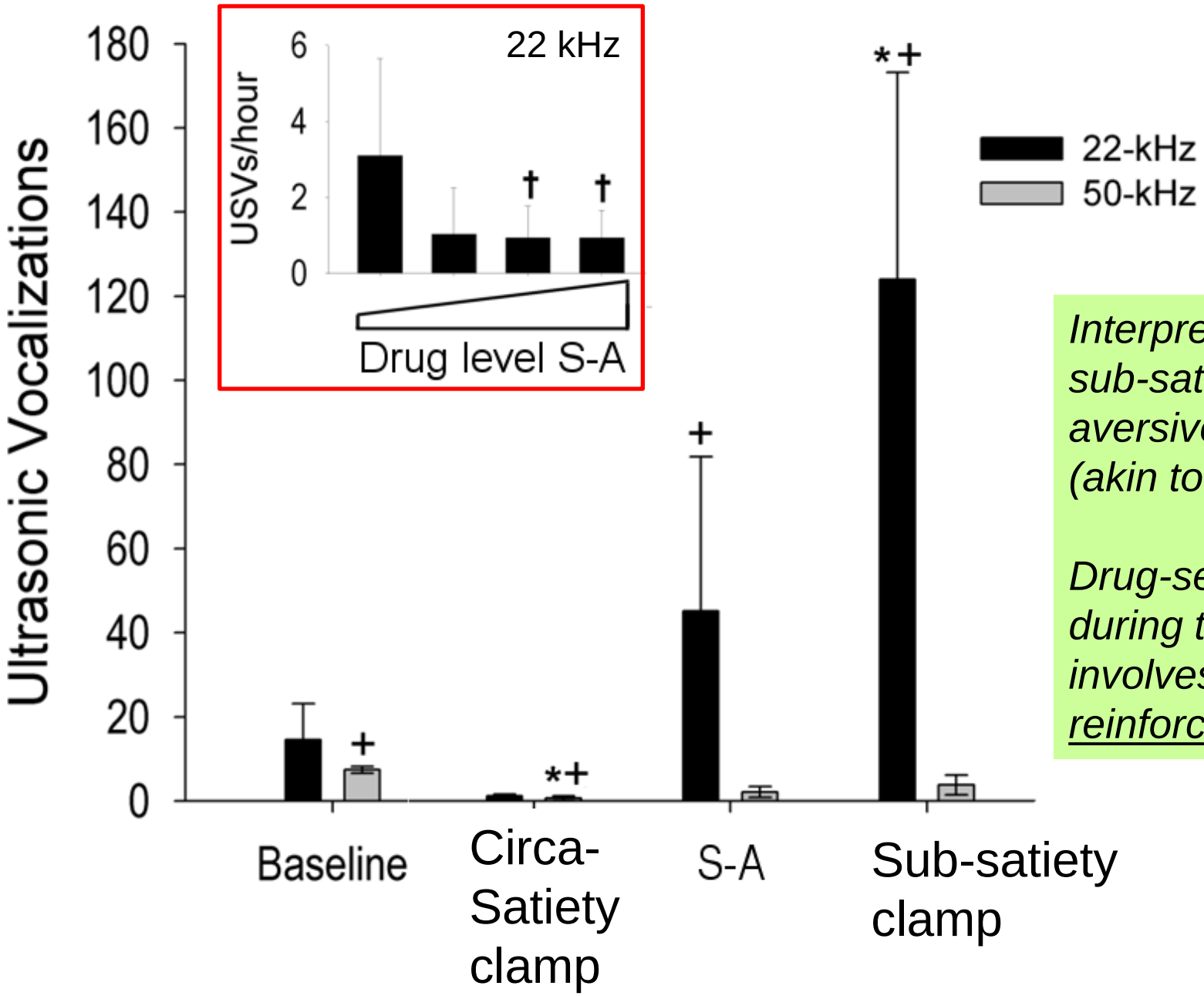
Hypothesis:

- 22 kHz calls are emitted during sub-satiety
- 50 kHz calls are emitted during satiety

To test this, we "clamped" cocaine levels above or below each animal's satiety level in the middle of an S-A session, by experimenter-administered “i.v. drip”.

# Typical cocaine accumulation curves of one animal



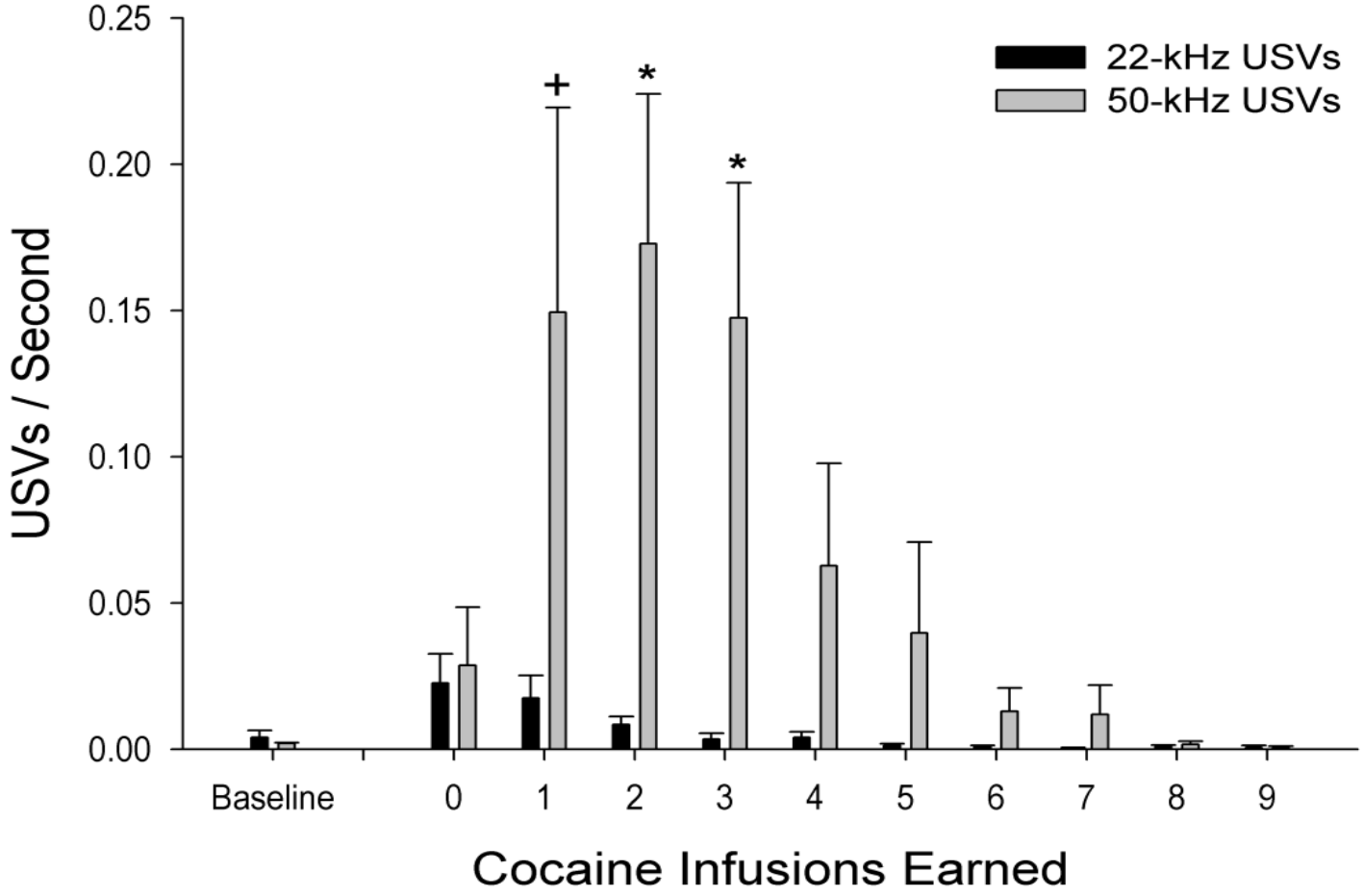



*Interpretation: sub-satiety is an aversive state (akin to hunger).*

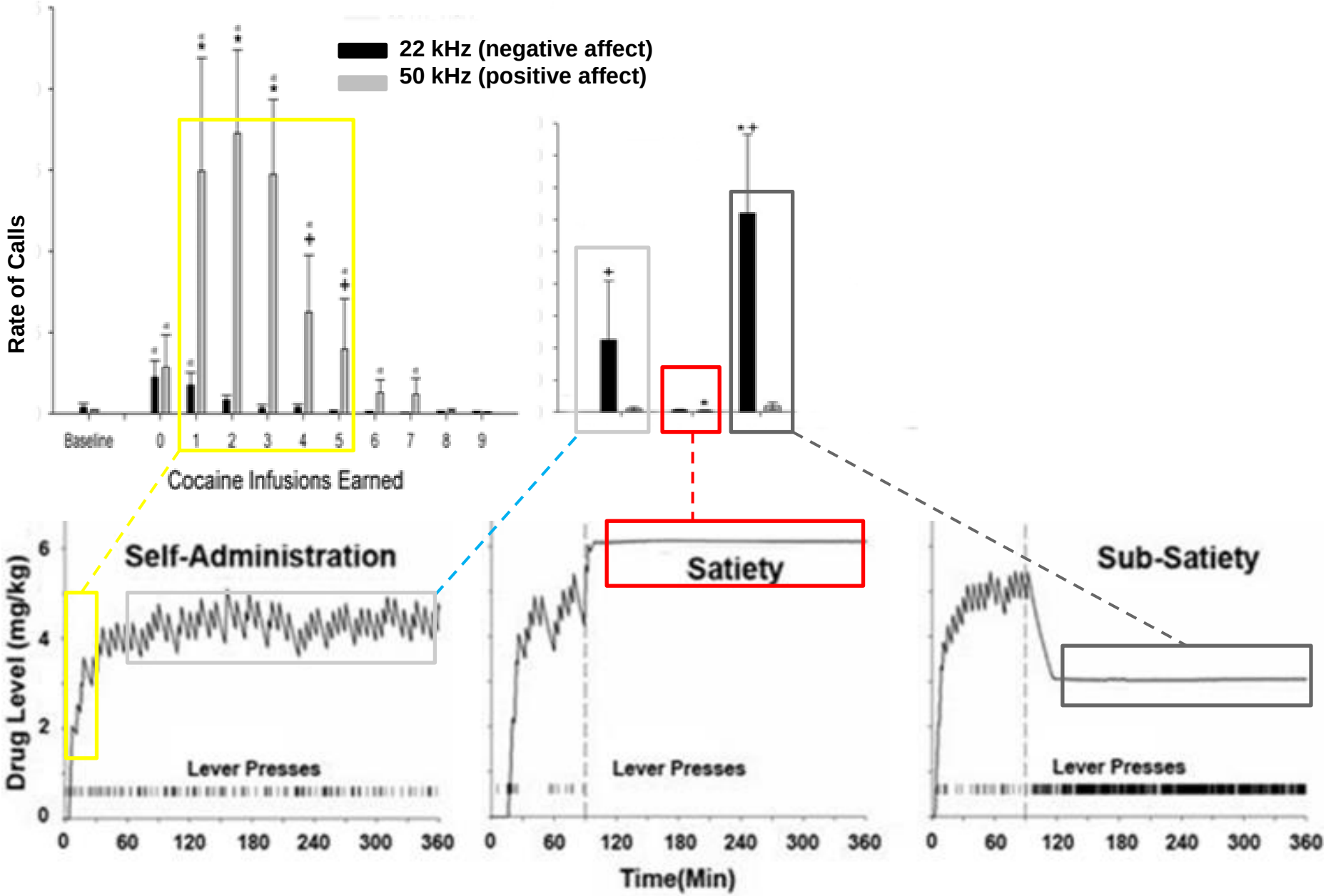
*Drug-seeking during the binge involves <u>negative reinforcement.</u>*

If the drug binge involves a negative emotional state, why does relapse occur?

Answer: Start of binge ("load-up") involves positive affect. Negative affect disappears (temporarily).




Barker et al, Psychopharmacology, 2013

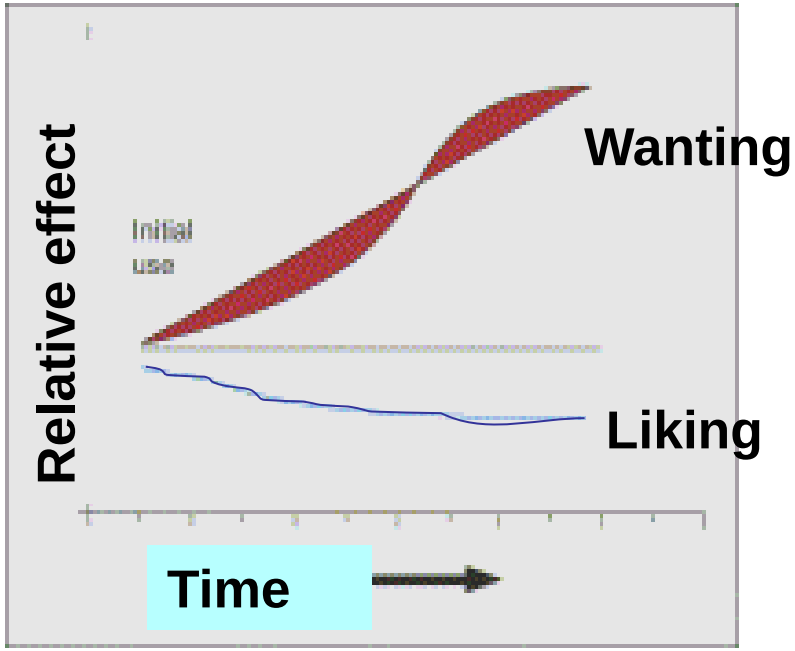

22 kHz (negative affect)
50 kHz (positive affect)
Rate of Calls
Baseline
0
1
2
3
4
5
6
7
8
9
Cocaine Infusions Earned
Self-Administration
Satiety
Sub-Satiety
Drug Level (mg/kg)
Lever Presses
Lever Presses
Lever Presses
0
60
120
180
240
300
360
Time(Min)

# Neurobiology of cocaine abuse: reinforcement?

Does cocaine self-administration (binge behavior) involve

- positive reinforcement?
  does the euphoria fade over long-term abuse? (Berridge)

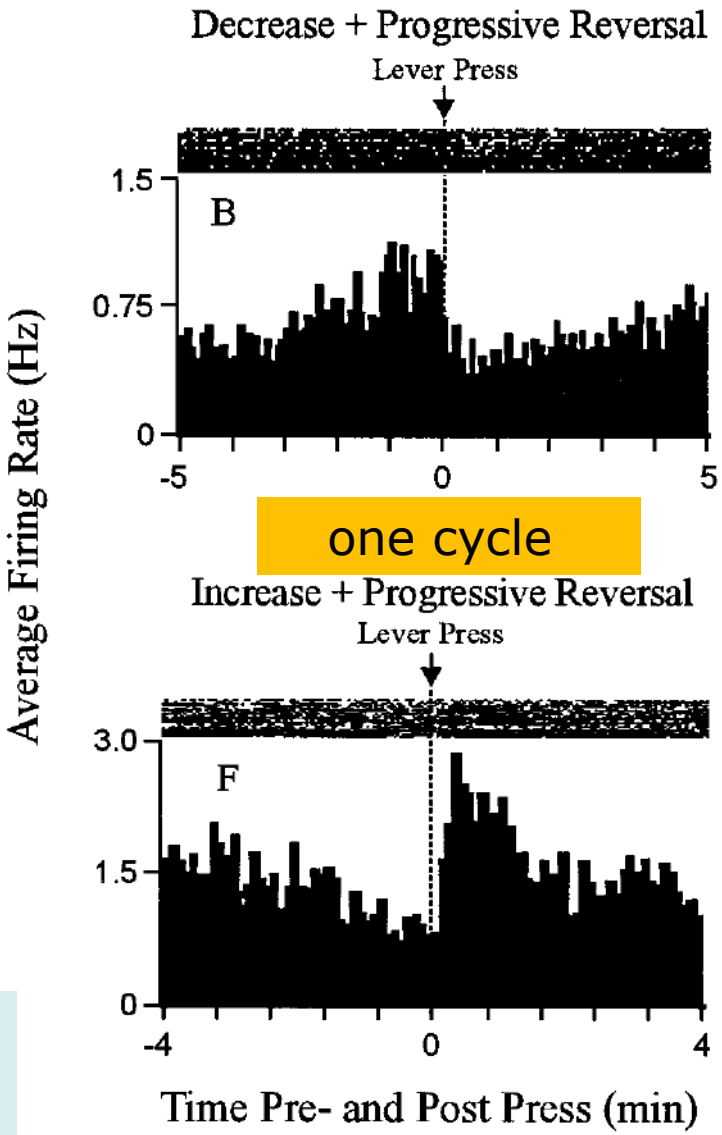
- negative reinforcement?
  take another dose to escape dysphoria? (Koob)



***Progressive reversal*** firing patterns occur in major dopamine target areas

- accumbens
- olfactory tubercle
- ventral pallidum
- lateral preoptic nucleus

These areas connect to the VTA, in turn connected to the lateral habenula, where excitation is associated with aversion.




Thus at low drug level: a crescendo of <u>aversive</u> signals may drive the next drug seeking response.

Interpretations:

- Load-up involves positive reinforcement, because 50kHz calls increase while 22kHz calls cease.
- Positive affect is experienced even after chronic drug use. This disagrees with the idea that “liking” has faded out.
- But the entire remainder of the binge lacks any evidence of positive affect. Instead, only negative calls occur each time drug level falls.
- Each fall in drug level appears to be experienced as beginning withdrawal, an aversive state.

## Interpretations

- Thus, relapse can involve craving the euphoric rush of load-up.
- But after the fleeting positive affect is gone, the subject is trapped because each fall in drug level is aversive and compels taking another infusion.
- This may resemble a drive state, or an irritant the subject tries to escape, via another infusion of cocaine, i.e., negative reinforcement.
- Relapse also can involve an attempt to escape negative affect, as in stress-induced relapse.

## Interpretations

- The results support the opponent-process hypothesis of addiction: relapse can be motivated by the lure of a positive “rush” during loading, which is quickly followed by being “trapped” by aversive feelings of withdrawal each time drug level starts to fall.

- Thus understanding mechanisms underlying negative affect may inform behavioral and pharmacological therapies.

# Jersey Roots, Global Reach