# Operant Animal Models of Drug-Seeking Behavior

**Pia Bäckström**

**National Public Health Institute**
**Department of Mental Health and Alcohol Research**
**Helsinki, Finland**

# Operant chamber a.k.a. Skinner box

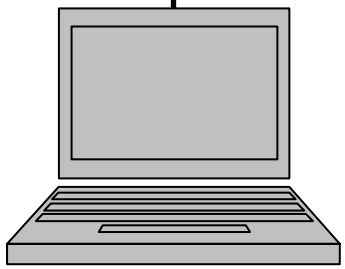
Infusion line
for drug delivery

Tone generator
& loudspeaker

Stimulus
lights

Levers

Floor bars can be
electrified



Computer (controls
schedule contingencies
and collects data)

# Why study drug-seeking behavior?

- One of the characteristics of drug addiction
  - Recurring relapses even after years of abstinence
- Chronic drug or alcohol exposure leads to adaptive changes in the central nervous system
  - The mechanisms underlying drug seeking and relapse differ from those mediating the acute effects of drugs

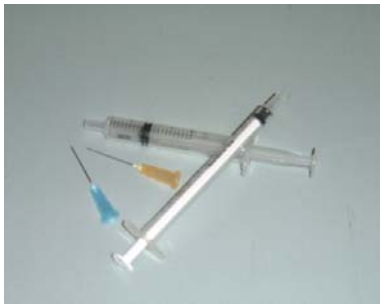
$\Rightarrow$ Effective pharmacological treatment of addiction requires knowledge of the neurobiology of drug-seeking behavior

# Drug seeking and relapse can be triggered by

- Stress

- Priming doses of the drug

- Drug-associated stimuli (cues)



# Major neurotransmitters

- Dopamine
- Glutamate

Also

- GABA
- Noradrenaline
- Serotonin
- Endocannabinoids
- The endogenous opioid system
- …

# Operant models of drug-seeking behavior

- Progressive ratio schedules of drug self-administration
- Fixed-interval second-order schedules of drug self-administration
- Extinction/Reinstatement model

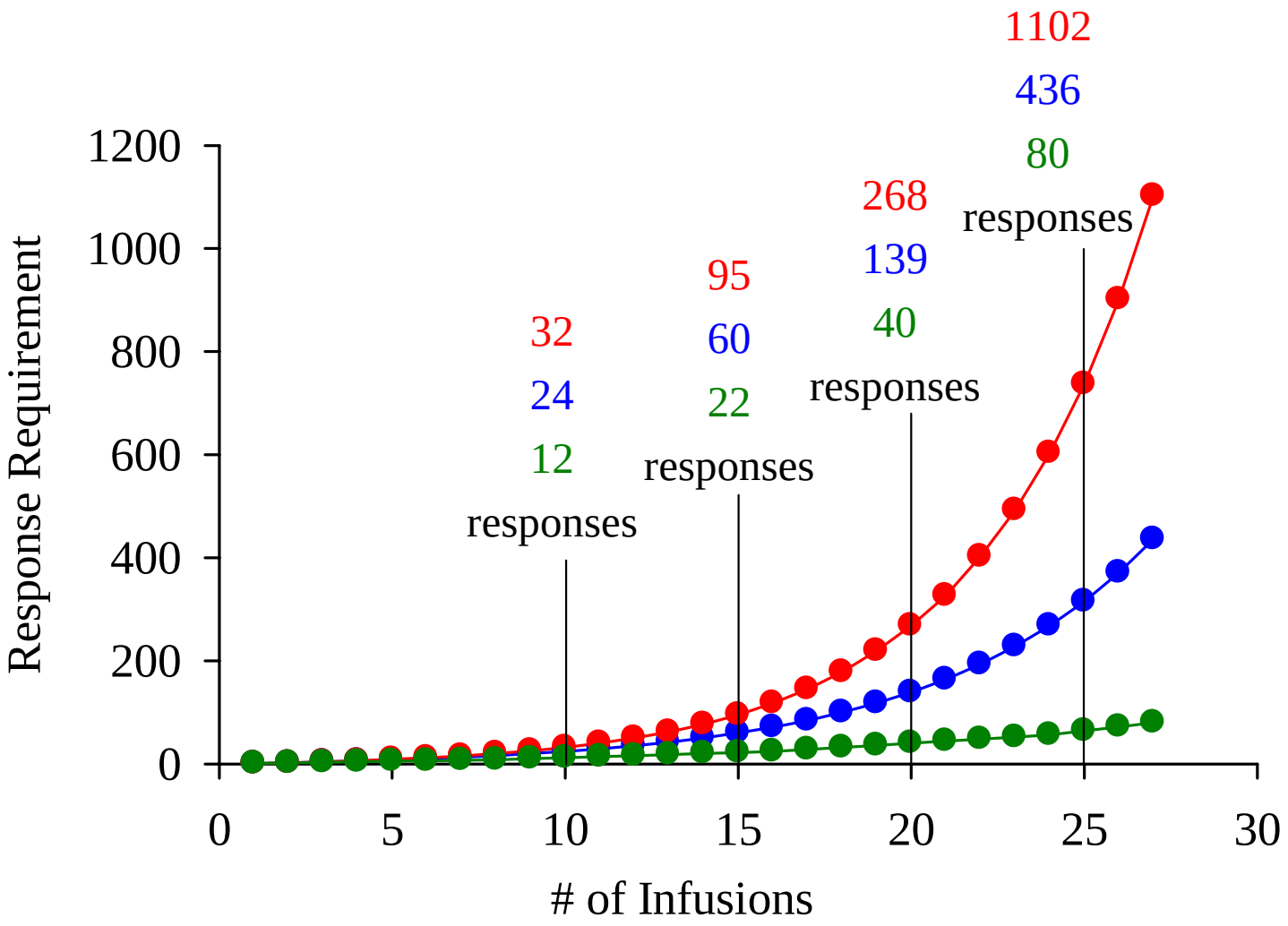
# Progressive ratio (PR) schedules of drug self-administration

- Number of responses required for each reinforcer increases progressively during the session

- Session ends when no responding for a pre-determined time period (e.g. 1 hour; final response ratio = ”break point”)

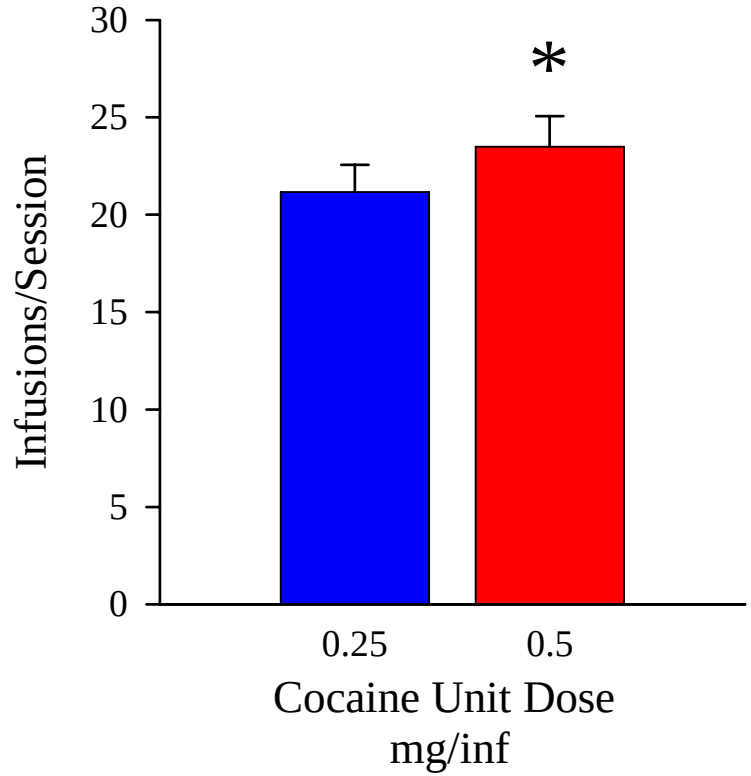
- Measure the maximal effort (motivation) to obtain the drug

# Progressive ratio schedules

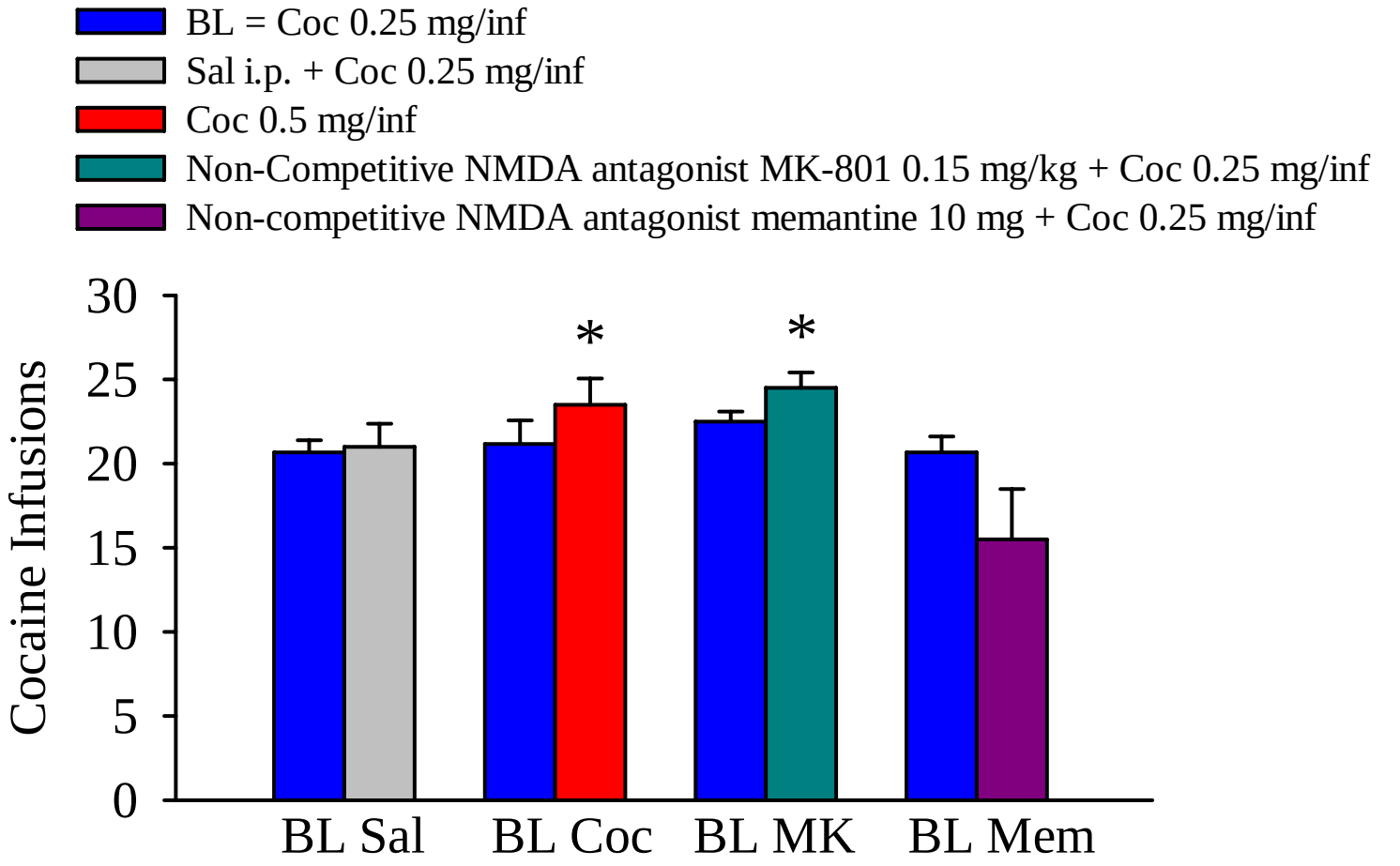


# Progressive ratio schedules

– Increasing the drug unit dose increases the break point (increased motivation to work for the drug)



# Effects of glutamate receptor antagonism on progressive ratio cocaine self-administration



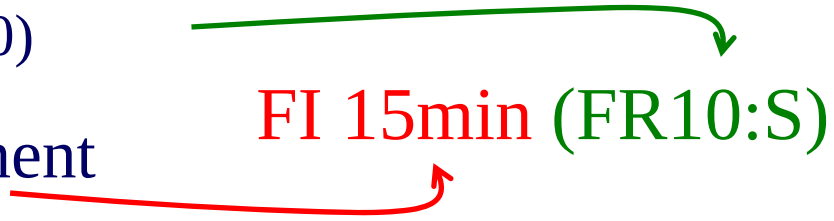

Hyytiä et al. Eur J Pharmacol 378 (1999)

# Progressive ratio (PR) schedules of drug self-administration

- Number of responses required for each reinforcer increases progressively within a session
  - Large changes in reinforcer magnitude may result in only small changes in breakpoint
- Session ends when no responding for a pre-determined time period (e.g. 1 hour; final response ratio = ”break point”)
  - Sessions end at unknown and varying times and may be long
- Measure the maximal effort (motivation) to obtain the drug
  - Measure drug seeking ***under the influence of the drug***
  - Motor suppressant effects of medications must be controlled for

# Fixed-interval second-order schedules of drug self-administration

- ”Schedules within schedules” or ”superimposed schedules”
- Fixed-ratio (FR) component
  - A stimulus (S; e.g. light or tone) is presented after a fixed number of responses (e.g. 10)
- Fixed-interval (FI) component
  - The first completed fixed-ratio component after a pre-determined interval delivers the reinforcer (e.g. FI 15 min)




- The stimuli become gradually conditioned to drug effects and support responding on their own

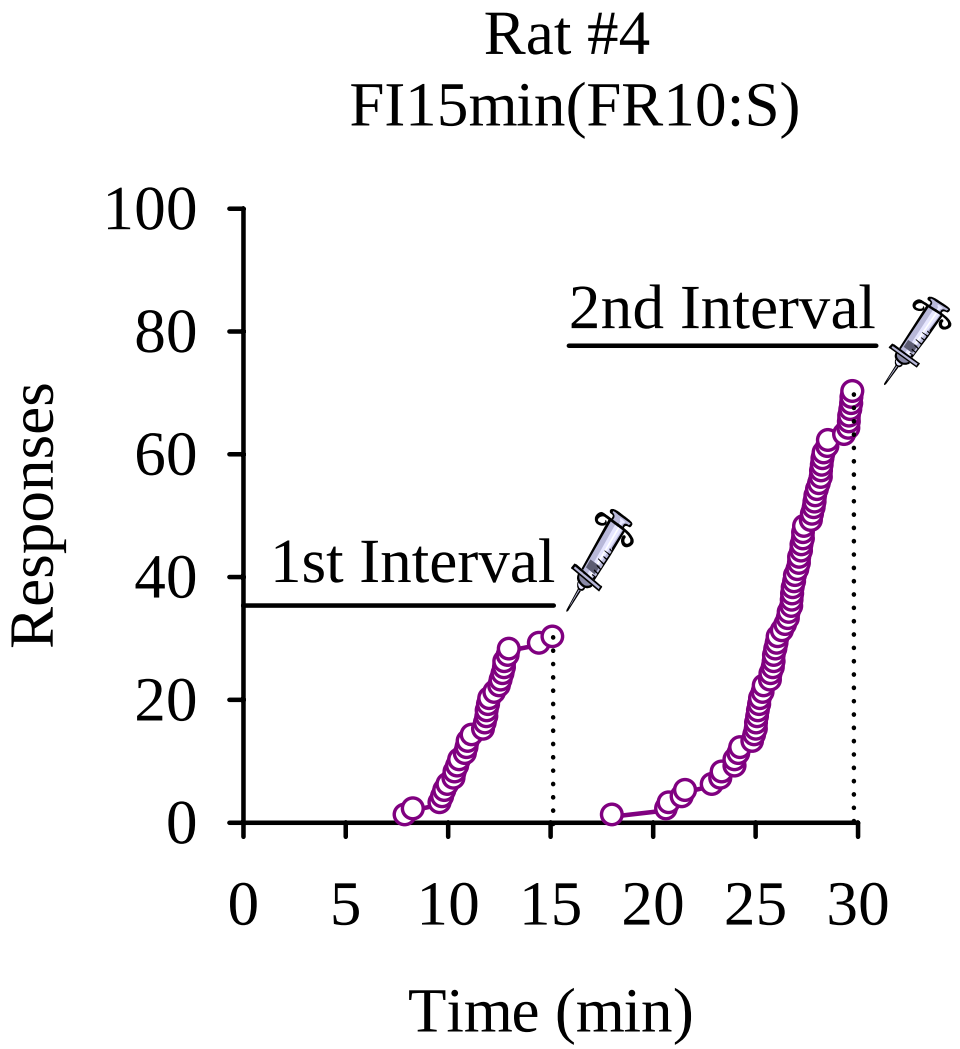
# Fixed-interval second-order schedules of drug self-administration

- Typically 4-5 intervals
- 1st interval measures drug seeking in the undrugged state
- 2nd interval measures drug seeking under the influence of (a small dose of) the drug

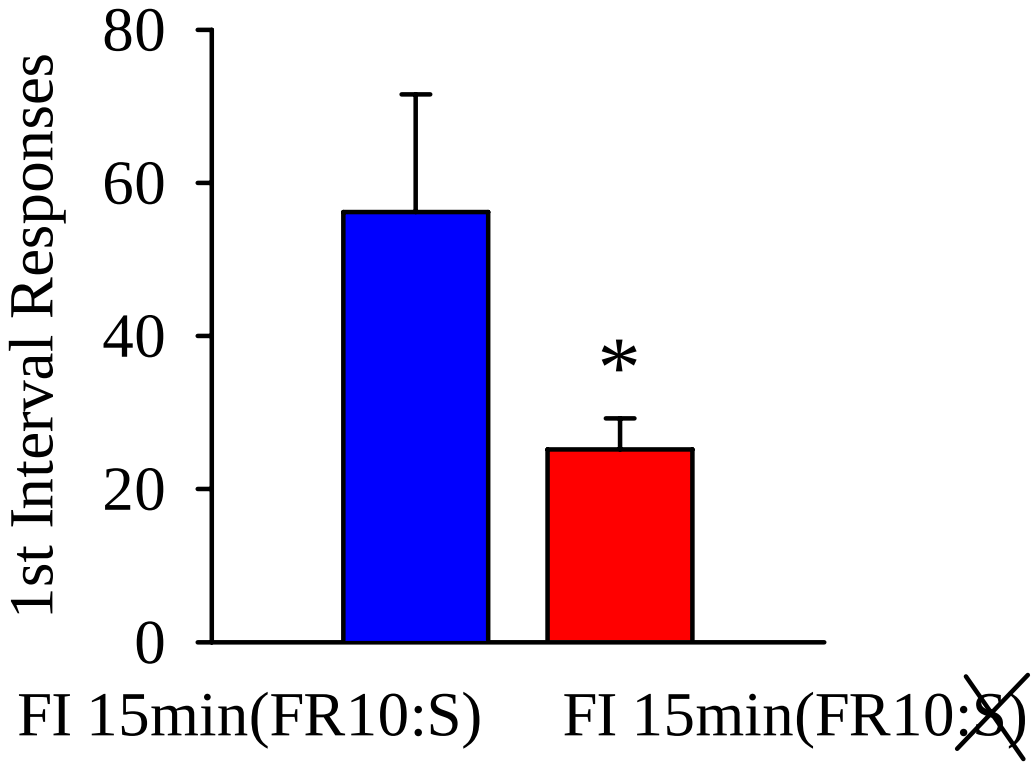
# Fixed-interval second-order schedules of drug self-administration

- Responding is influenced by
  - Conditioned reinforcing properties of the stimulus
  - Ability of the stimulus to guide behavior
  - Incentive value (strength) of the reinforcer
  - Motivation to respond for the reinforcer

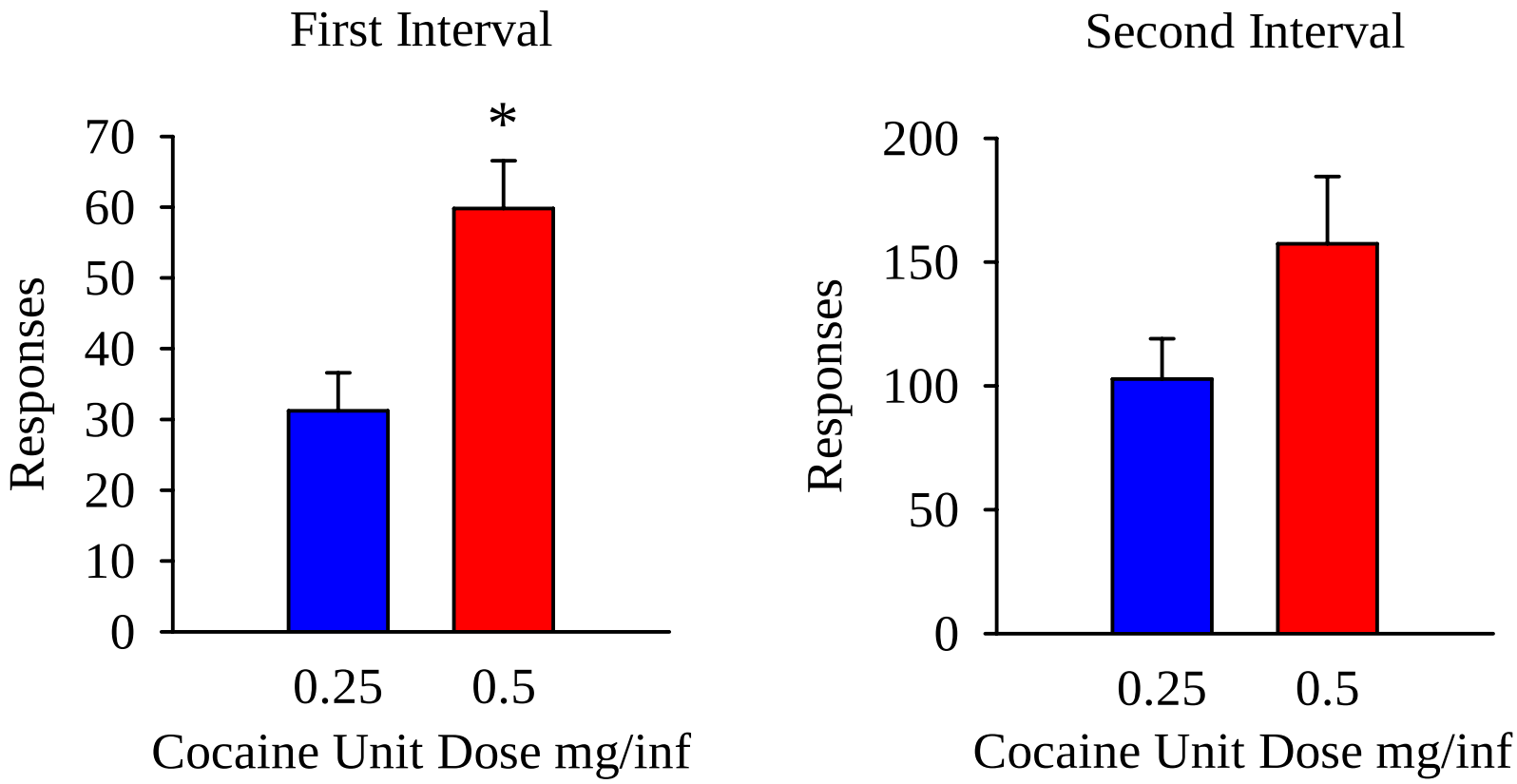
# A typical response pattern during a fixed interval second-order schedule



# Stimulus omission decreases 1st interval responding for cocaine



# Increasing the cocaine unit dose increases responding/drug seeking

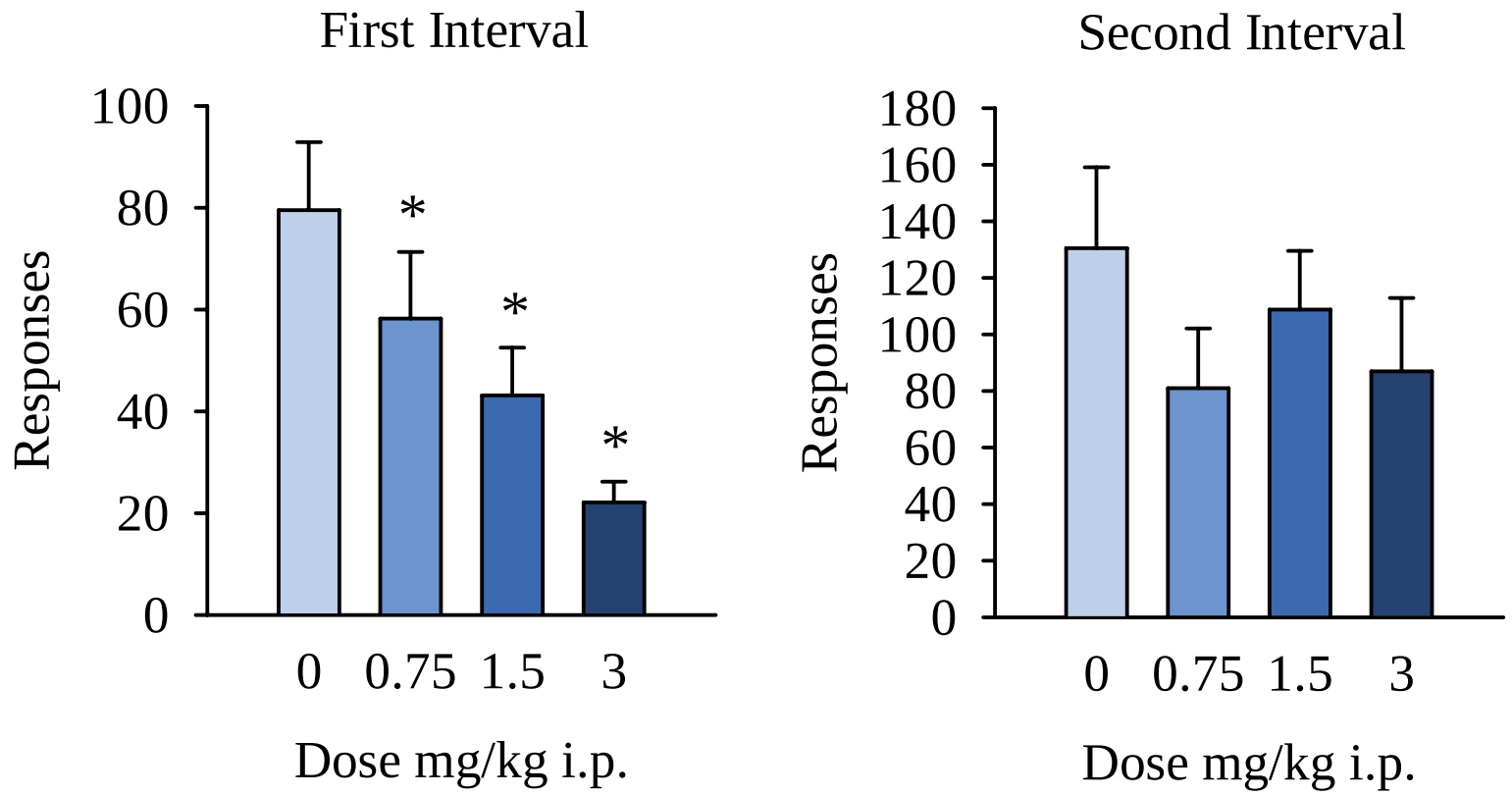



Bäckström and Hyytiä Psychopharmacology 166 (2003)

# Fixed-interval second-order schedules of drug self-administration

- Support high rates of responding
  - Response rates often variable from day to day
- No direct relationship between response rate and reinforcer delivery
  - Responding may be more habitual than goal-directed
- Responding is partly dependent on the conditioned reinforcing properties of drug-associated stimuli
- Effects of medications on stimulus perception, motor performance, perception of time etc.

# AMPA/Kainate glutamate antagonist CNQX decreases 1st but not 2nd interval cocaine seeking



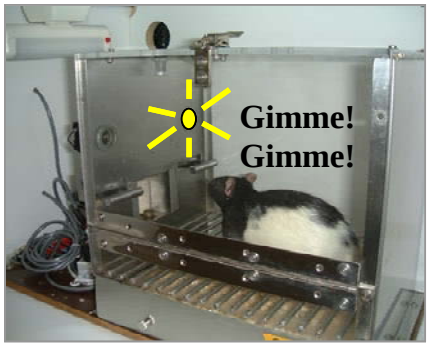

Bäckström and Hyytiä Psychopharmacology 166 (2003)

# The extinction/reinstatement model

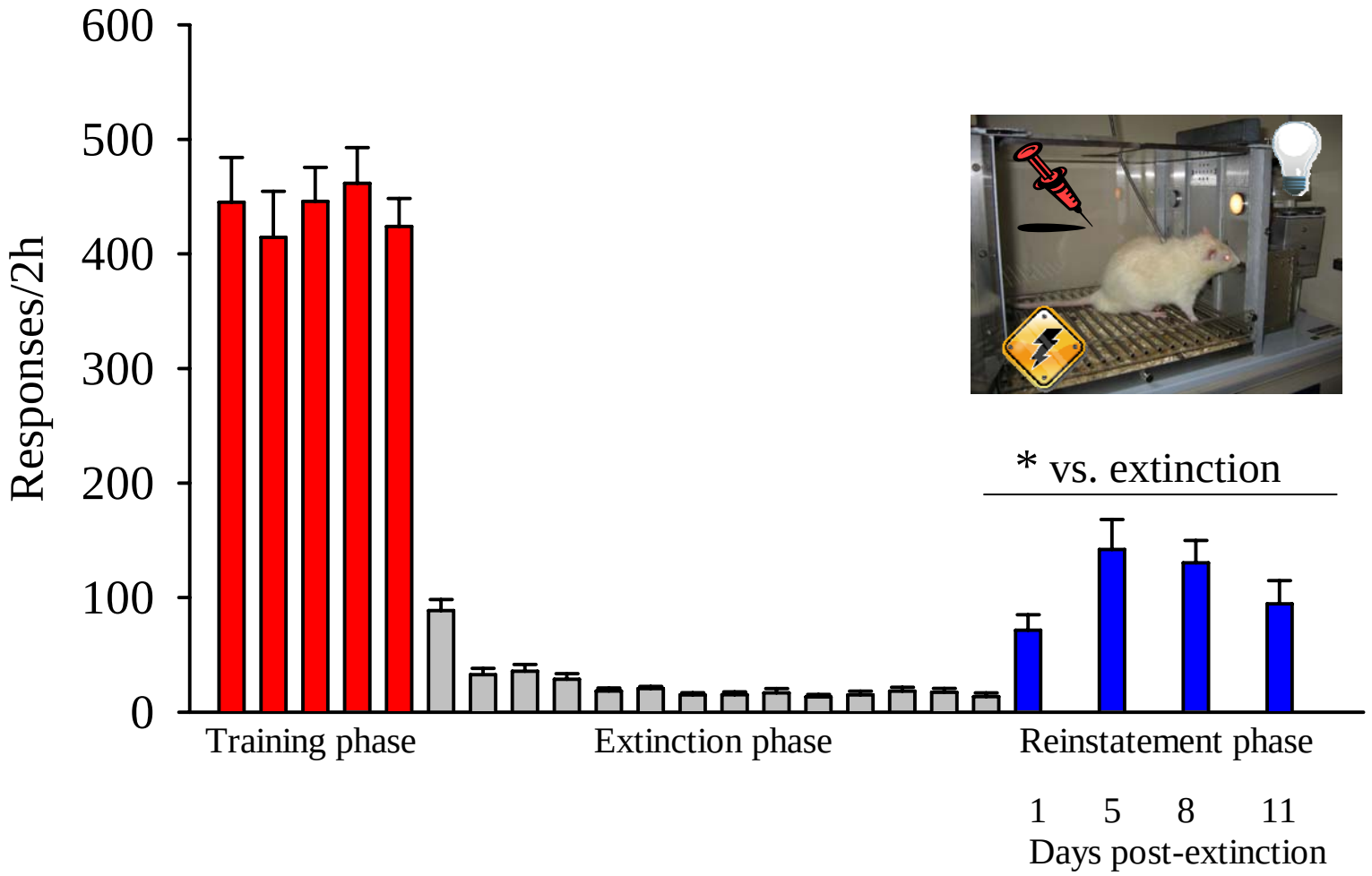
1. Training/conditioning (1-2 months):
   Drug (+ stimulus)

2. Extinction (2-3 weeks):
   ~~Drug~~ ~~(+ stimulus)~~

3. Relapse test(s):
   ~~Drug~~ + stimulus (light, tone…)
   ~~Drug~~ + stress (foot shock)
   ~~Drug~~ + priming dose of drug



# The extinction/reinstatement model



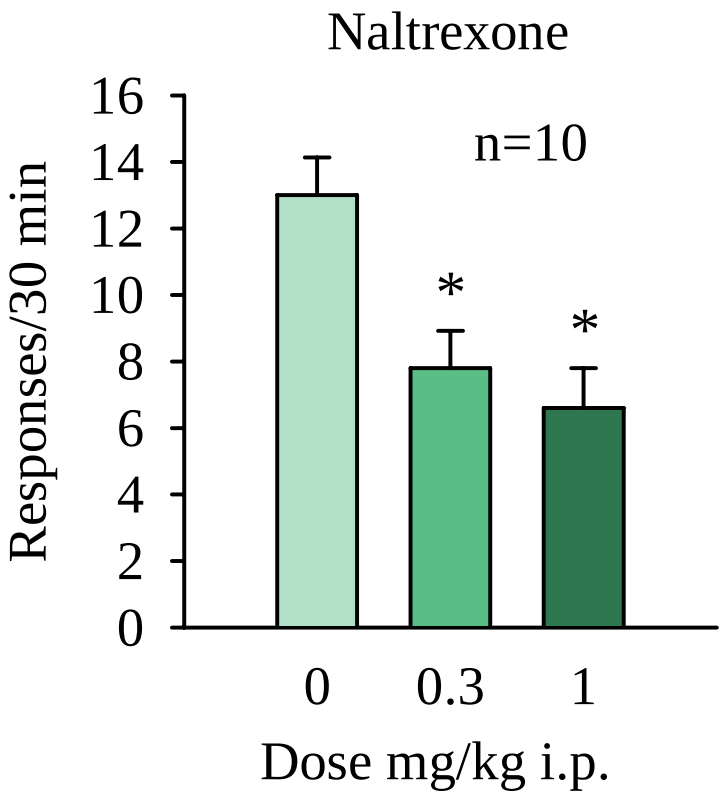
# The extinction/reinstatement model

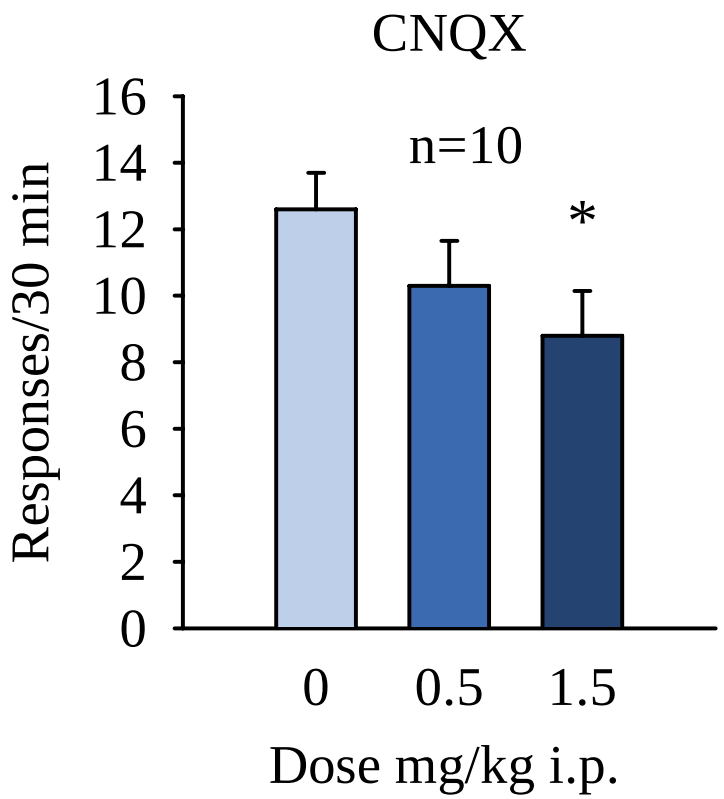
- Drug seeking induced by drug-conditioned stimuli, stress, and priming doses of the drug can be measured separately or in combinations
- Drug seeking is usually measured in the undrugged state and after withdrawal mimicking the human condition
- Laborious, weeks or months of training, extinction, and testing

# The extinction/reinstatement model

- Not all animals meet stability criteria for training, extinction, and relapse; some animals may not relapse at all
- Variability in relapse response rates
- Usually no ability to consume the drug
- Compared to human addicts, animals have no motivation to stay abstinent
  - recently punishment models have been developed
- Possible motor suppressant effects of medications

# The opiate antagonist naltrexone and the AMPA/Kainate glutamate antagonist CNQX attenuate cue-induced alcohol seeking




Bäckström and Hyytiä Alc Clin Exp Res 28 (2004)

# Acknowledgements

Petri Hyytiä
Kalervo Kiianmaa

Harri Nurmi
Heidi Kemppainen


Supported by

The Finnish Foundation for Alcohol Studies
The Ella and Georg Ehrnrooth Foundation
The Yrjö Jahnsson Foundation