



*Department of Experimental Psychology,
University of Cambridge, UK*

**Psychological and neurobiological mechanisms
of relapse and vulnerability to relapse:
implications for treatment**

Daina Economidou

Recreational drug use



Escalated drug taking



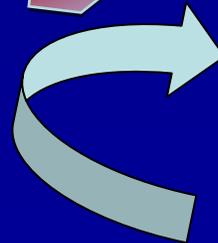
**Compulsive
drug seeking and taking**



**Cease Drug Taking
Drug Abstinence**



Impulsivity



**Maintenance of
drug abstinence**

5-Choice Serial Reaction Time Task (5-CSRTT)



Low impulsive (LI) rats

High impulsive (HI) rats



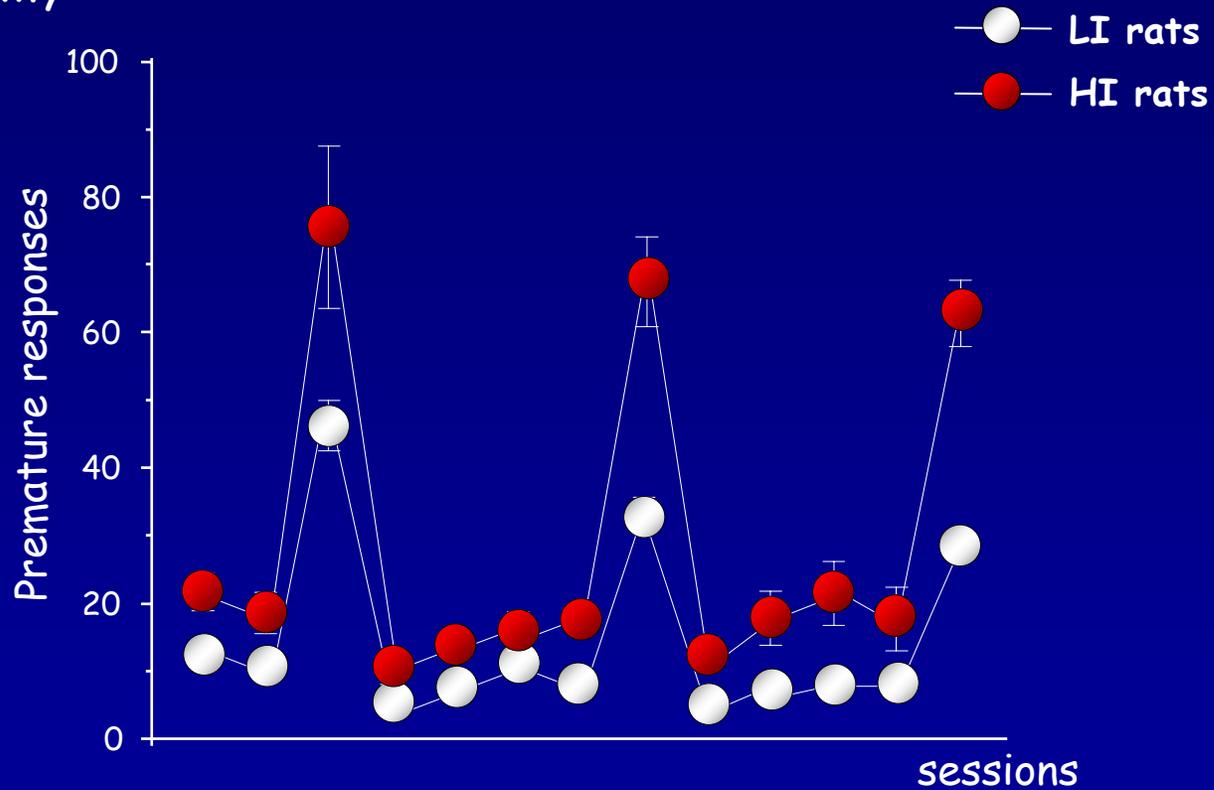
Relapse
to cocaine seeking
following punishment-induced abstinence



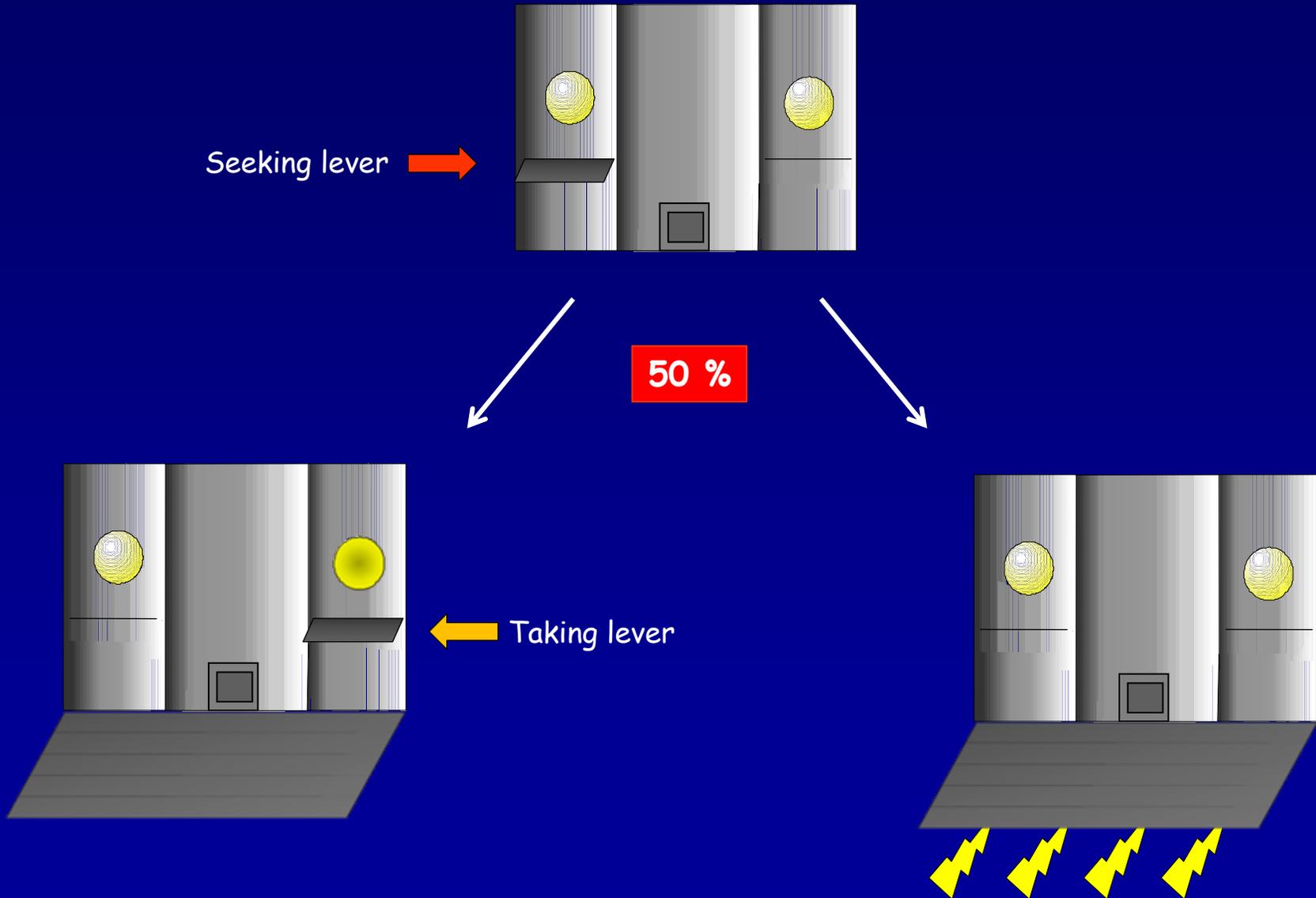
Bari et al., 2008 Nature Protocols

High (HI) and Low Impulsive (LI) rats in the 5-CSRTT

* "Waiting impulsivity"



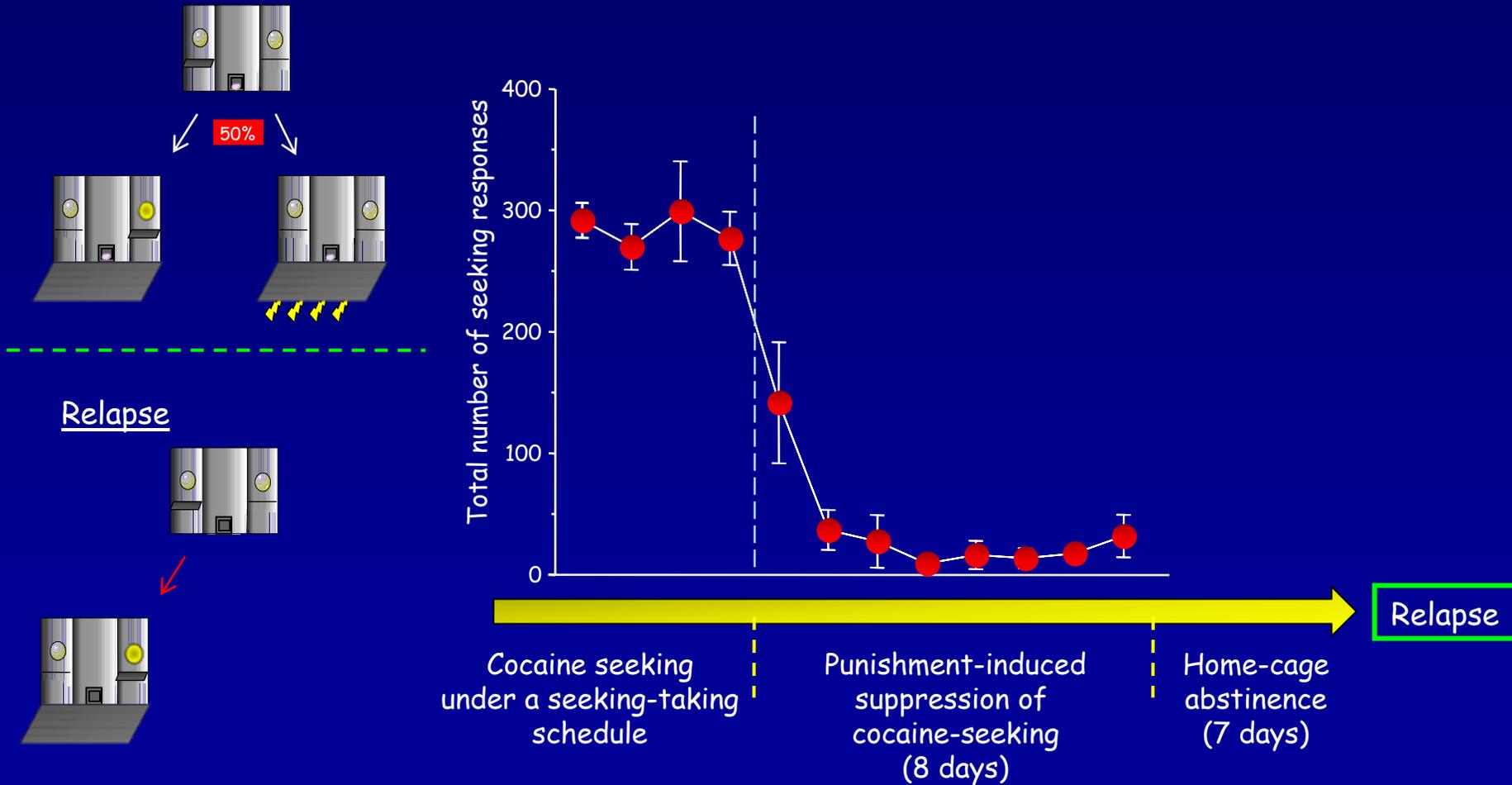
Punishment-induced suppression of cocaine seeking



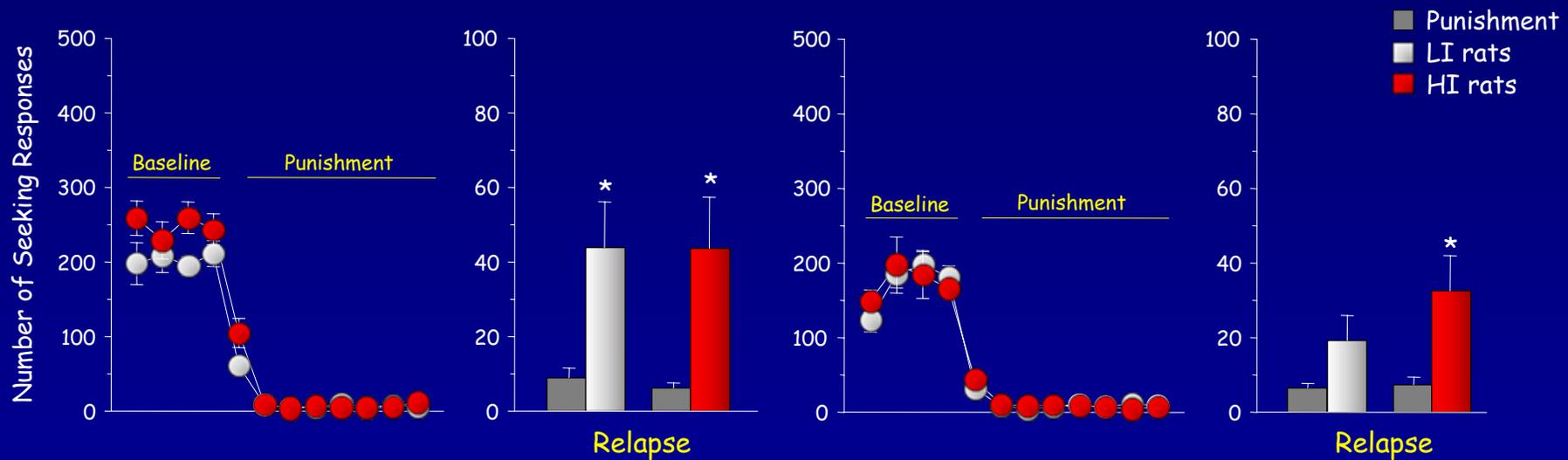


Compulsive drug seeking by rats under punishment: effects of drug taking history

Pelloux Y et al., *Psychopharmacology* 2007

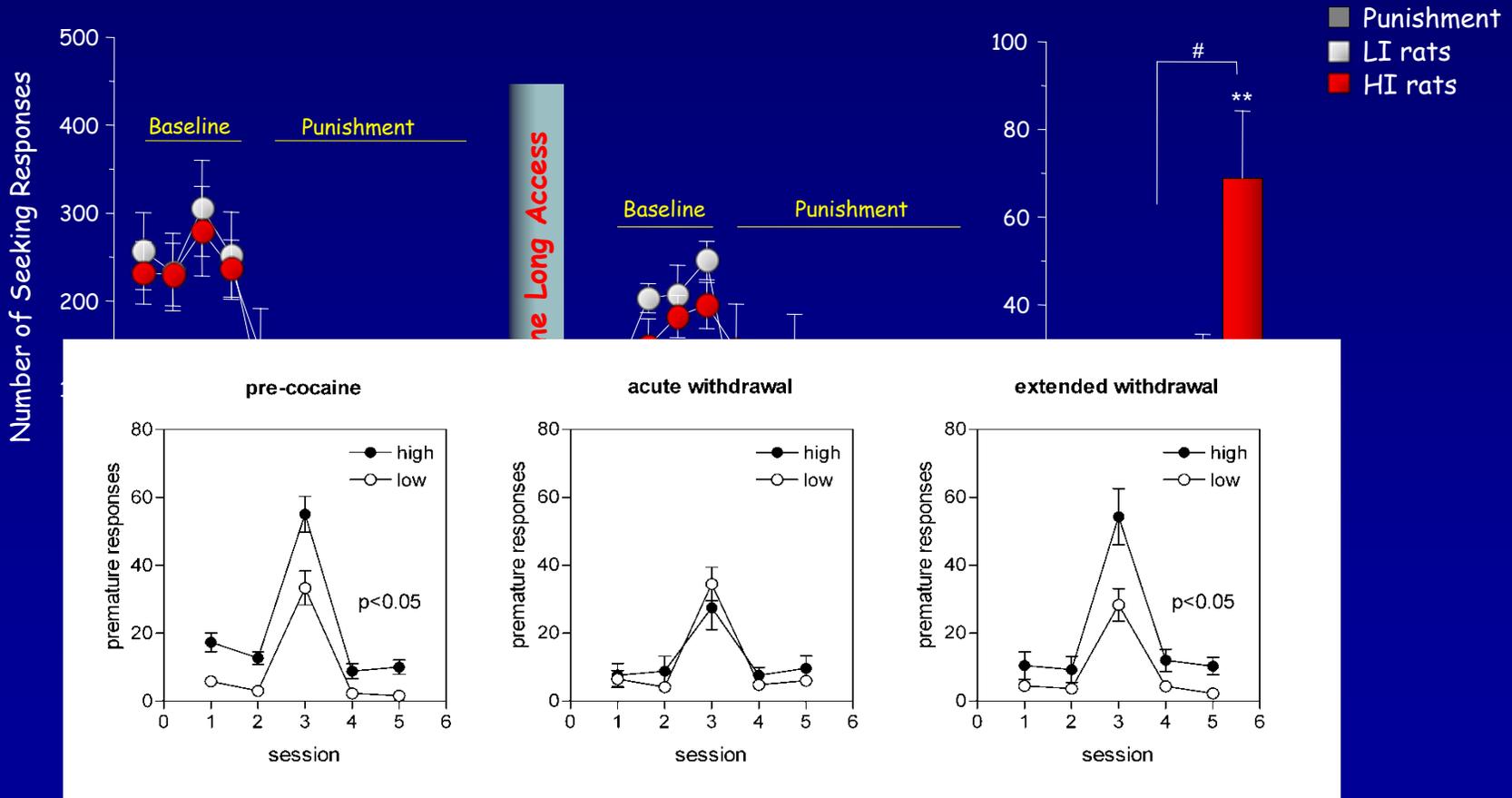


Relapse to cocaine-seeking in HI and LI rats following short cocaine taking history



* P < 0.05 versus punishment

Relapse to cocaine-seeking in HI and LI rats following cocaine long access (12 days, 6h/day)

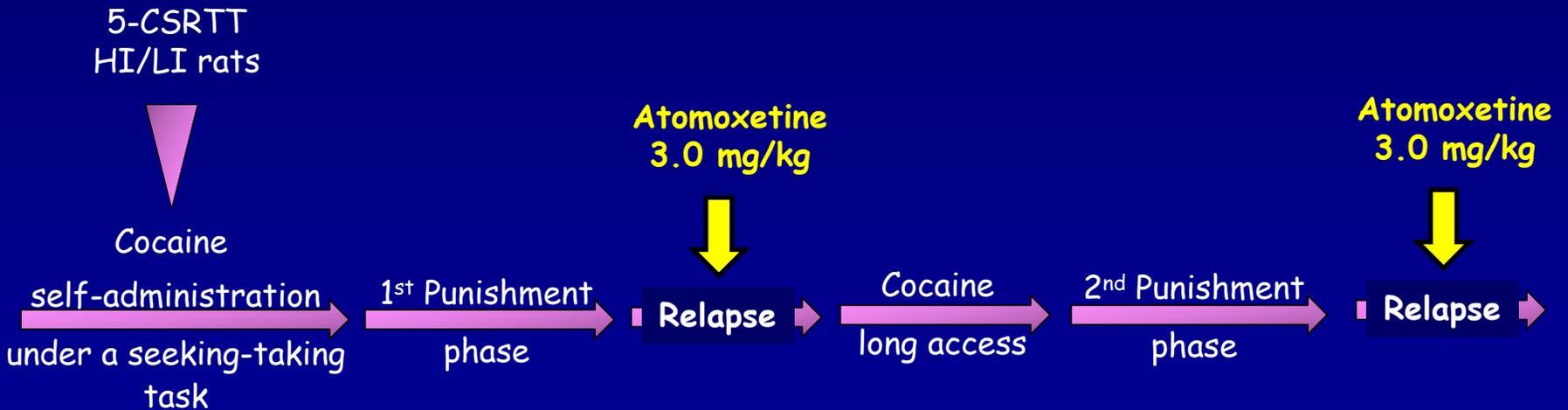


** P < 0.01 versus punishment

P < 0.05 HI versus LI rats

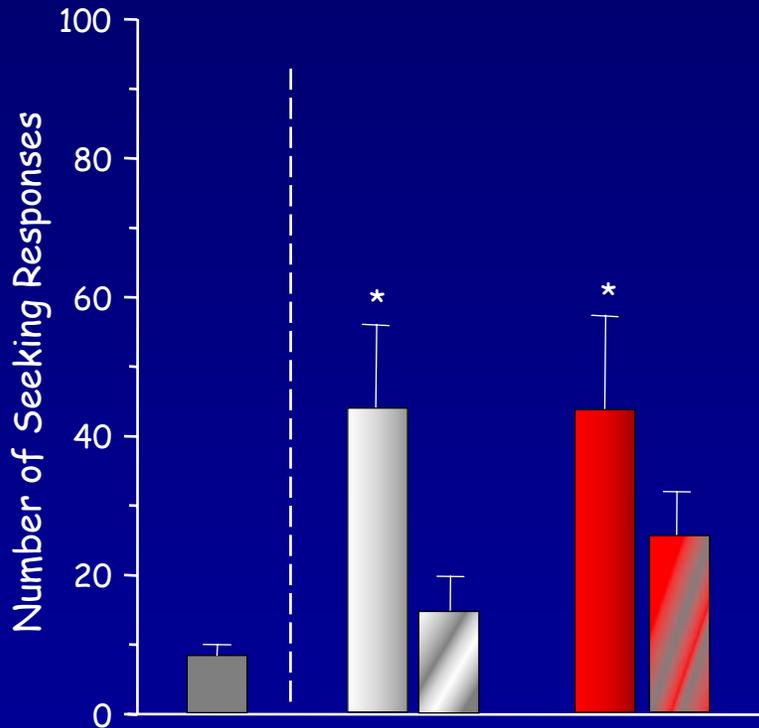
Atomoxetine

- ➔ Selective noradrenaline reuptake inhibitor
- ➔ Clinical efficacy in the treatment of ADHD
- ➔ Shown to reduce impulsive behaviour in both human and animal studies

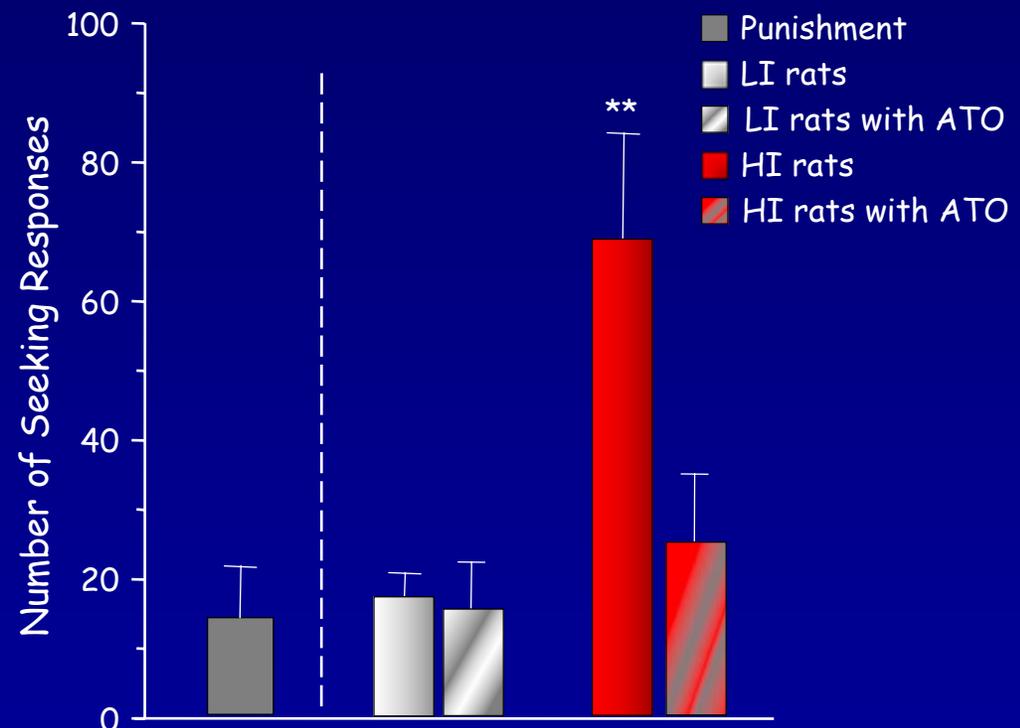


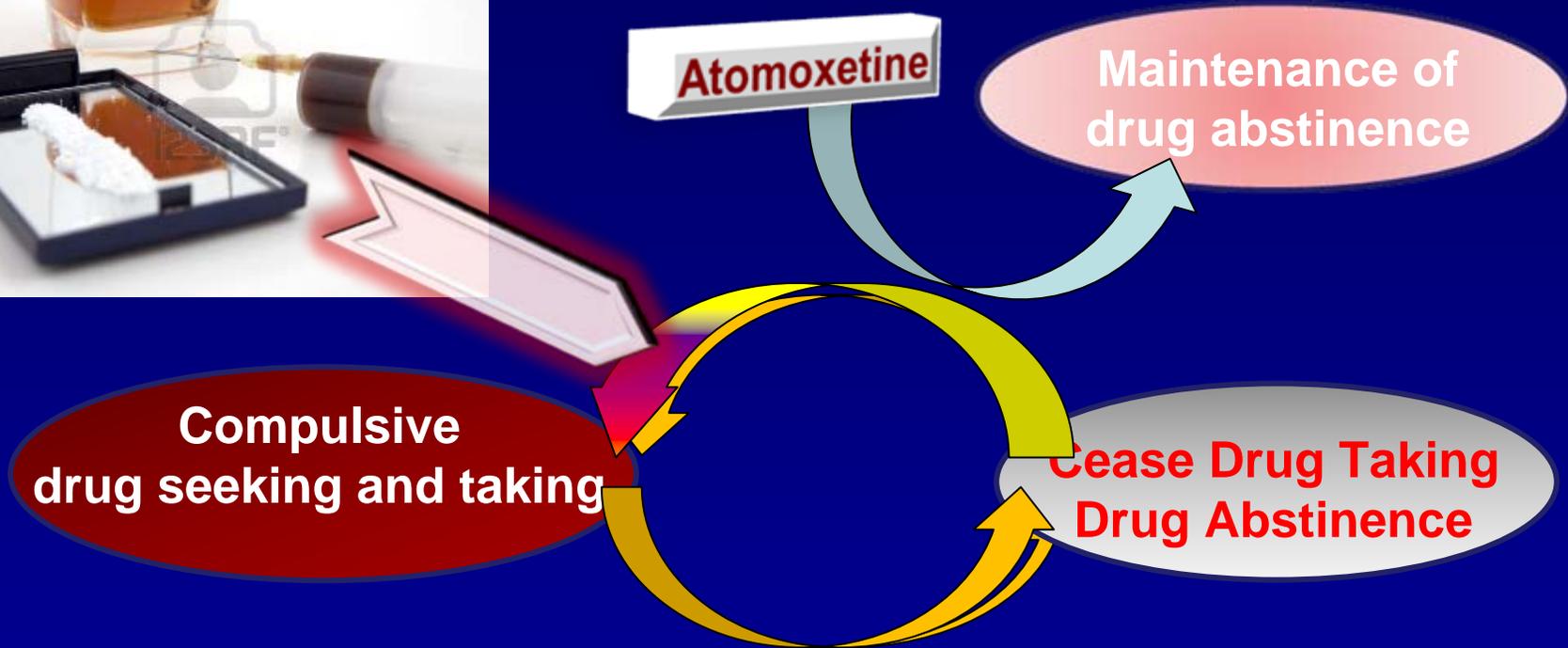
Effect of atomoxetine (3.0 mg/kg, IP) treatment on relapse to cocaine-seeking following punishment-induced abstinence in HI vs LI rats

Following cocaine short access



Following cocaine long access





- Second-order schedule of reinforcement → Cocaine seeking
→ Heroin seeking
- Cue-induced relapse to cocaine seeking following abstinence

*Non-selected animals

Animal models to study CS-controlled drug-seeking and relapse



- Second-order schedule of reinforcement
- Cue-induced relapse following abstinence



Atomoxetine (ATO) Vs Methylphenidate (MPH)

(NET < SERT < DAT)

(DAT < NET < SERT)

- ➔ Clinical efficacy in the treatment of ADHD
- ➔ Reduce impulsive behaviour in both human and animal studies
- ➔ **Distinct pharmacological properties**

| | ATO | MPH |
|------|------|--------|
| NET | 5 | 339 |
| DAT | 1451 | 34 |
| SERT | 77 | >10000 |
| | | Ki, nM |

Bymaster et al., Neuropsych. 2002

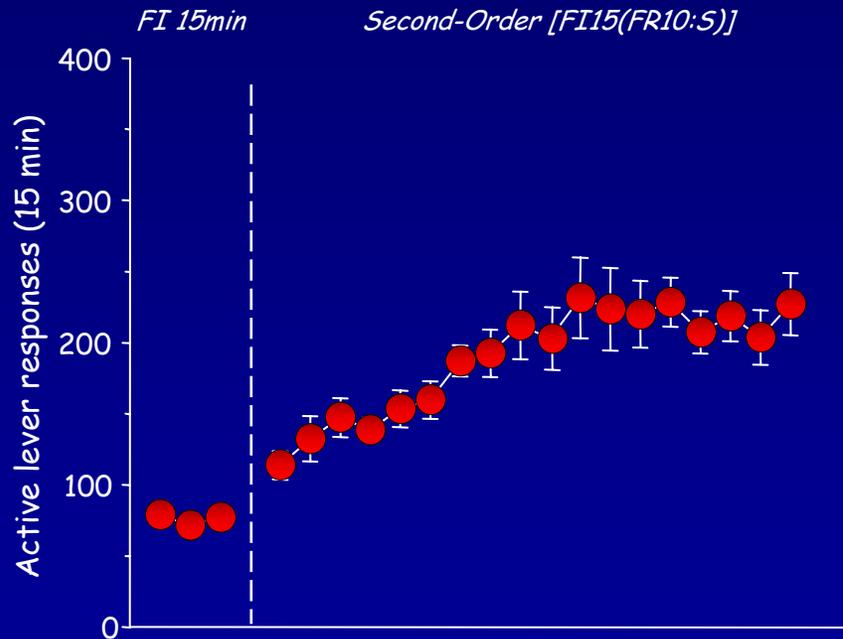
Cocaine seeking under the second-order schedule of reinforcement



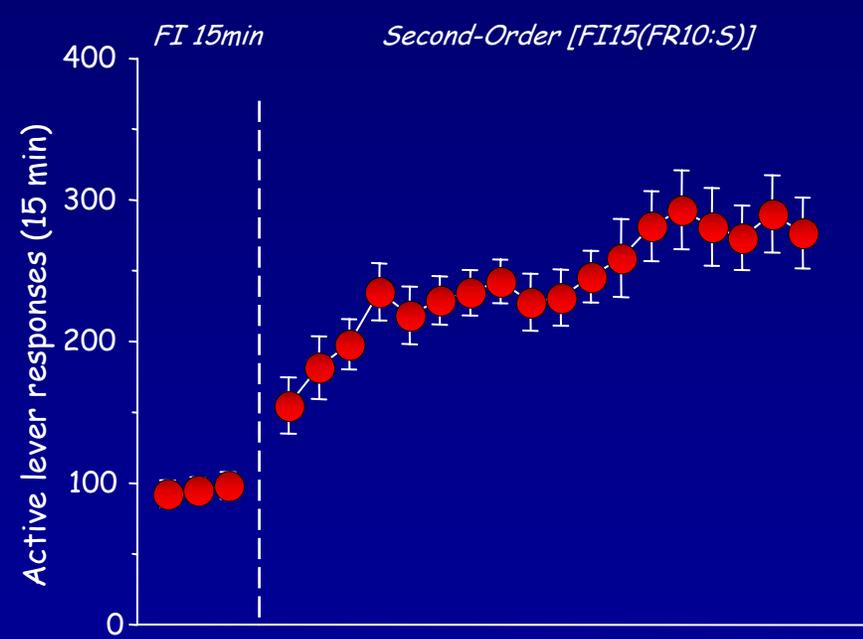
Typical pattern of responding under the second-order schedule of reinforcement

1st drug-free seeking interval

Cocaine

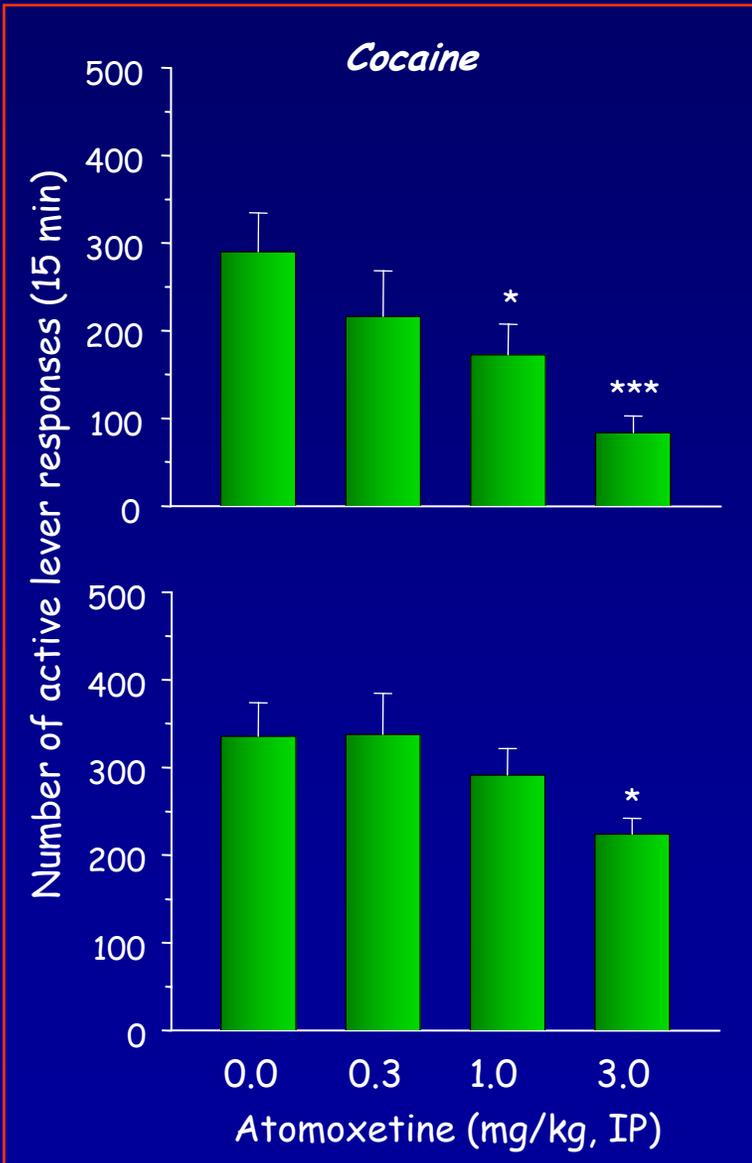


Heroin

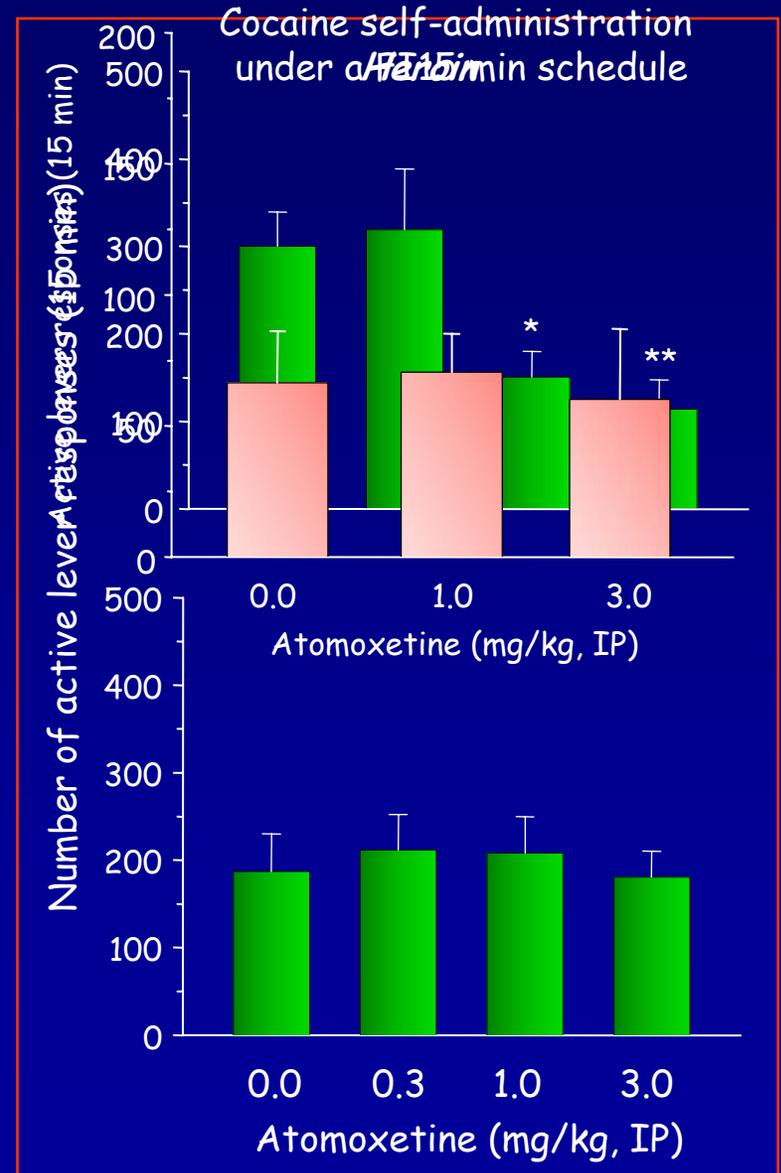


Effect of atomoxetine treatment on cocaine and heroin seeking under the second-order schedule of reinforcement

1st Interval

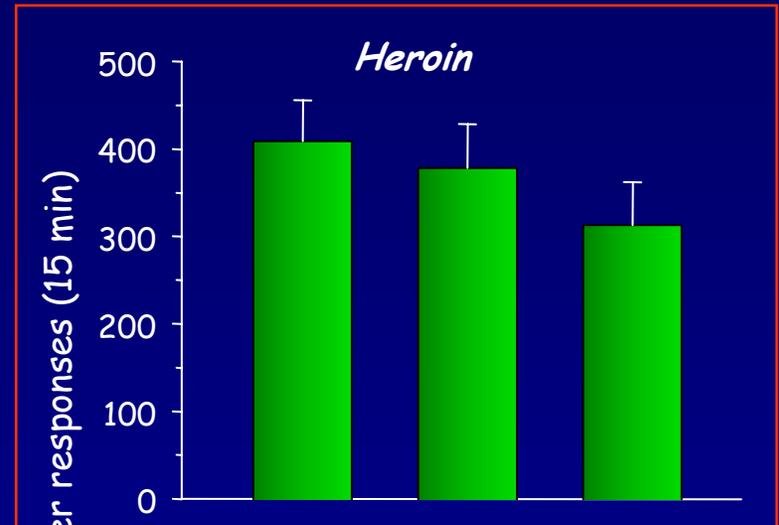
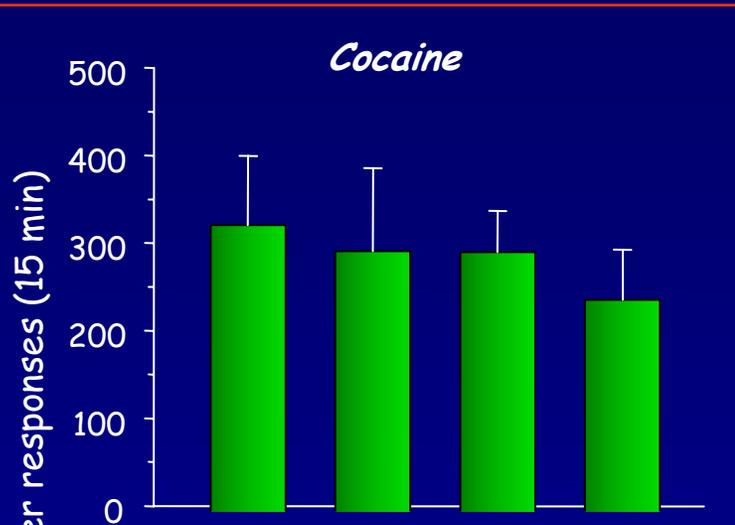


2nd Interval

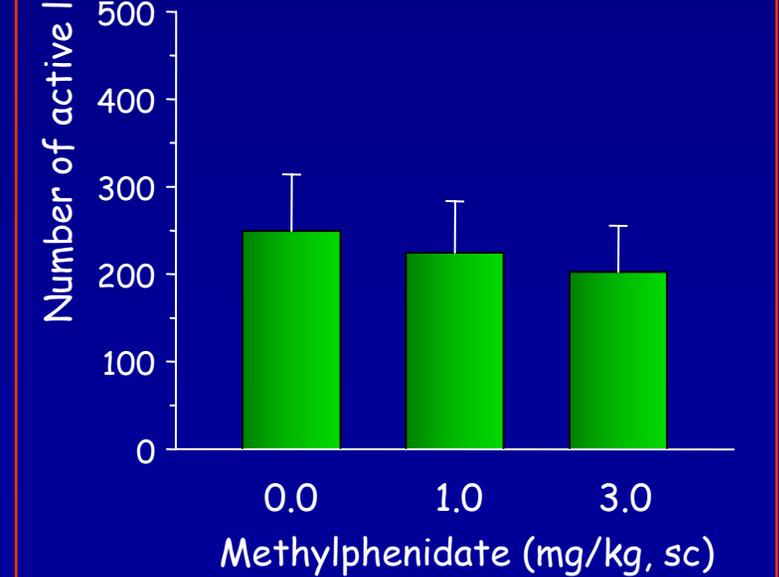
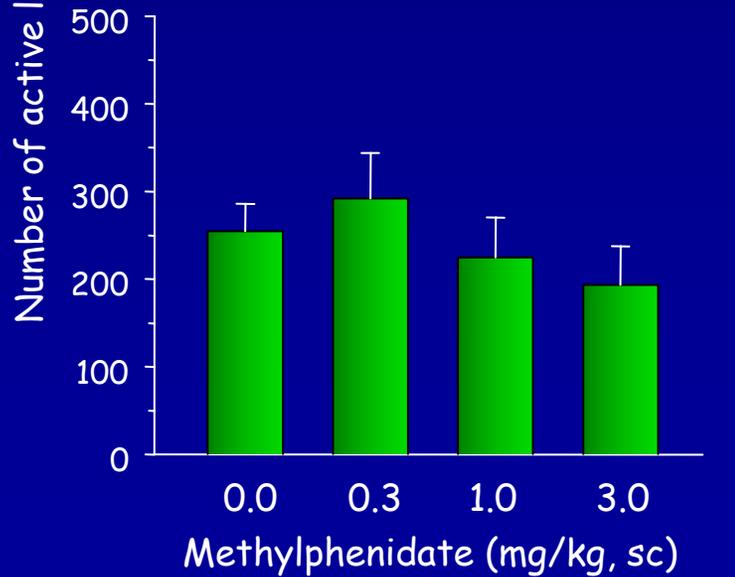


Effect of methylphenidate treatment on cocaine and heroin seeking under the second-order schedule of reinforcement

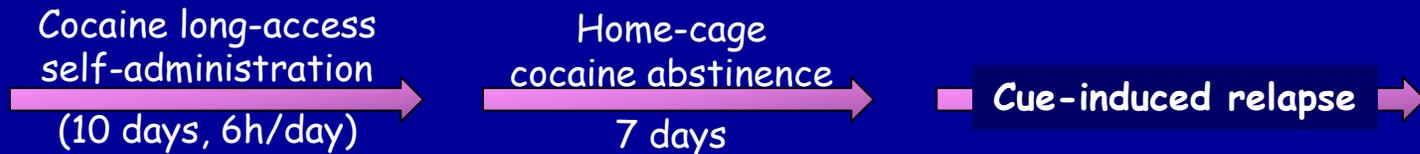
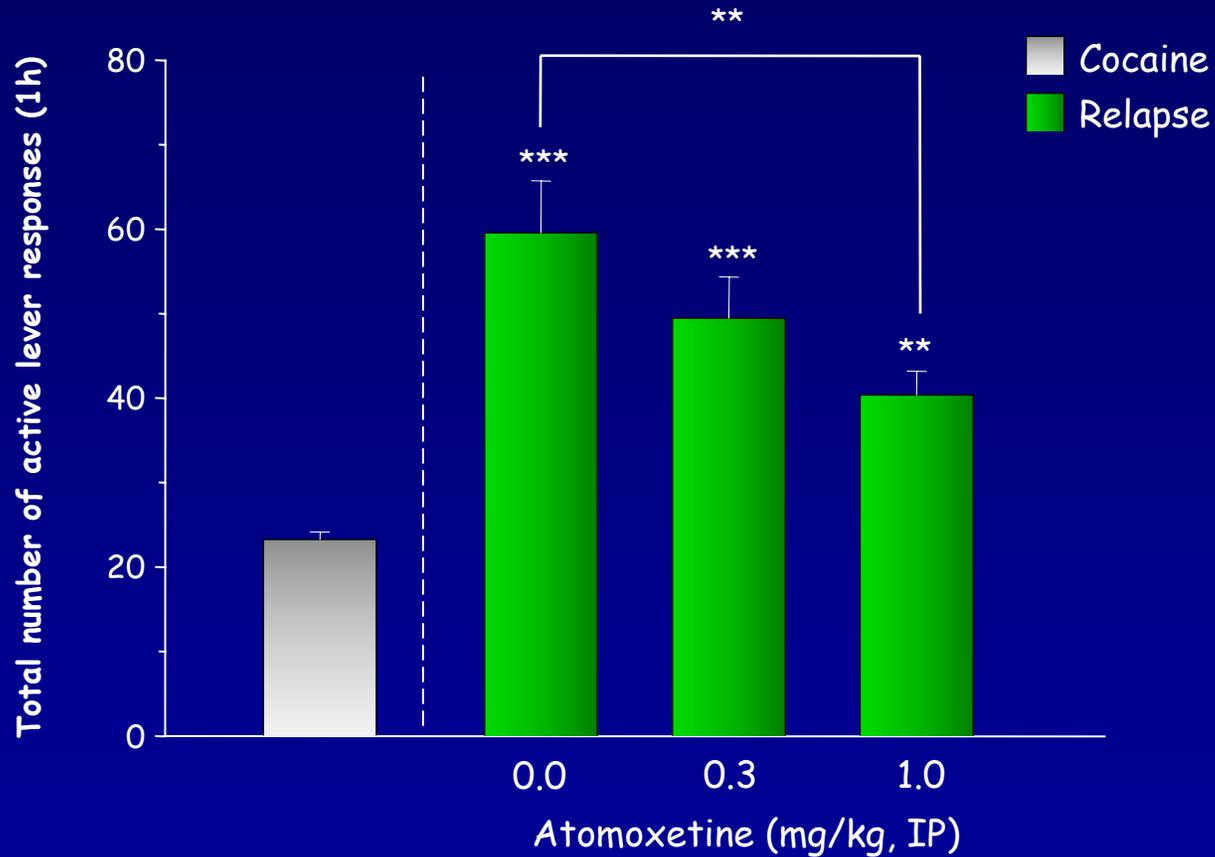
1st Interval



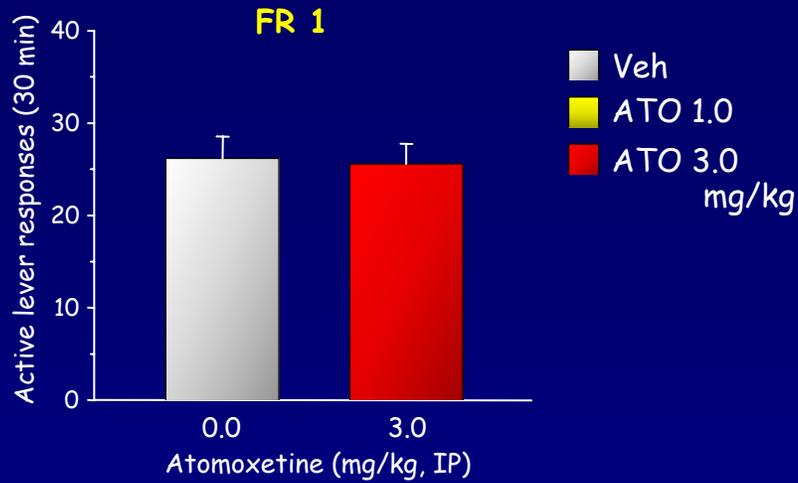
2nd Interval



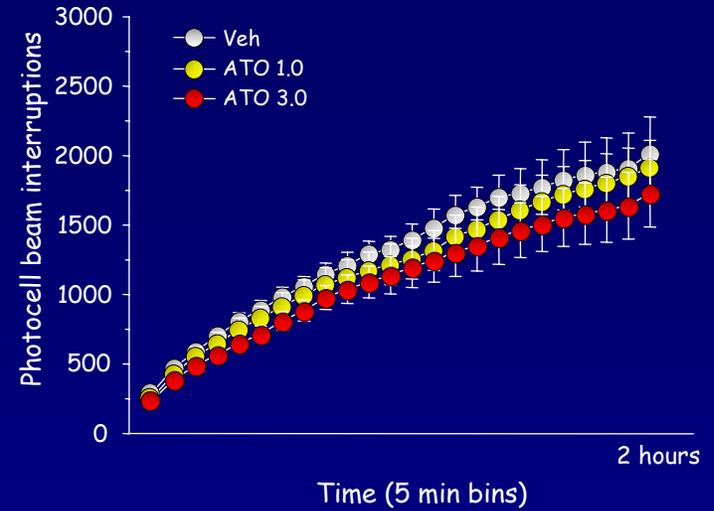
Effect of atomoxetine treatment on cue-induced relapse to cocaine seeking following abstinence



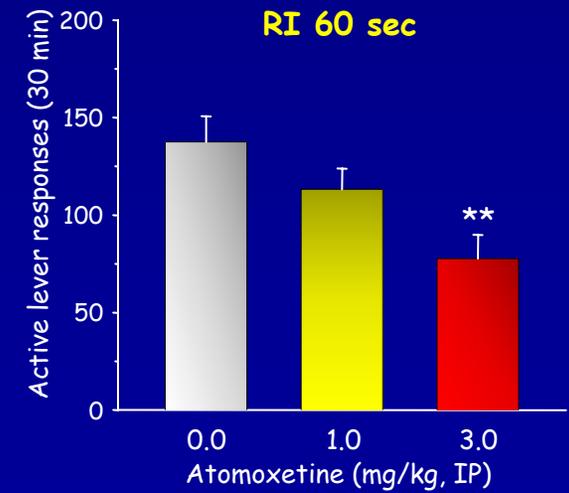
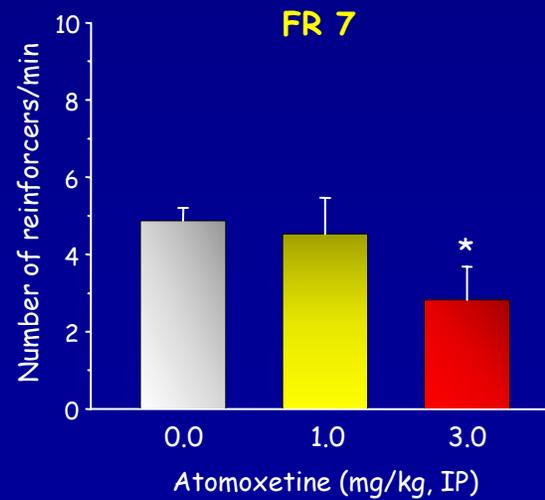
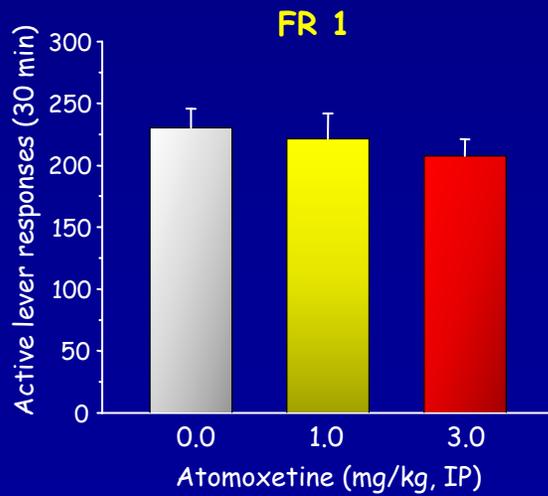
Cocaine self-administration



Spontaneous locomotor activity



Sucrose self-administration



CONCLUSIONS

- ★ **Atomoxetine** treatment selectively decreased both CS-maintained cocaine- and heroin-seeking.
- ★ **Atomoxetine** treatment significantly attenuated the reinstatement of cocaine-seeking following punishment-induced abstinence and conditioned cue re-exposure.
- ★ These effects were highly selective for cue-controlled drug-seeking and relapse.

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- ★ Selective NET inhibition by atomoxetine may provide a novel potential therapy for relapse prevention **to both stimulant and opiate drug-seeking**.
 - ★ An important consideration for the use of atomoxetine in drug addiction treatment is its well known increased tolerability and patient compliance.

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Lilly

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