The anatomical basis of desire and addiction

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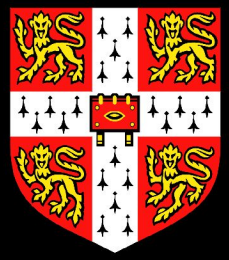
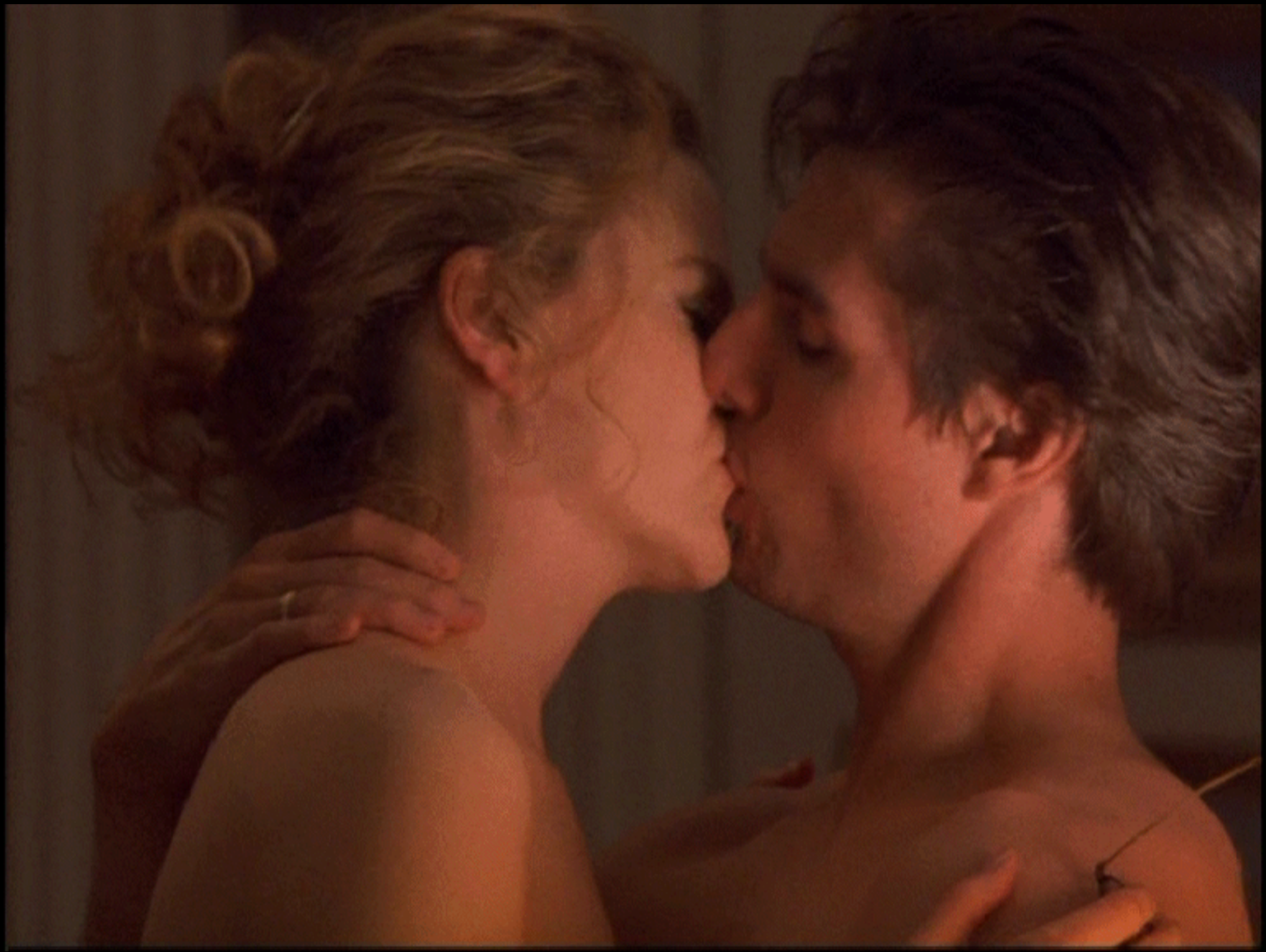


Friday 14 February 2003, 2–2.30pm
British Neuropsychiatry Association Annual Meeting
Institute of Child Health, London

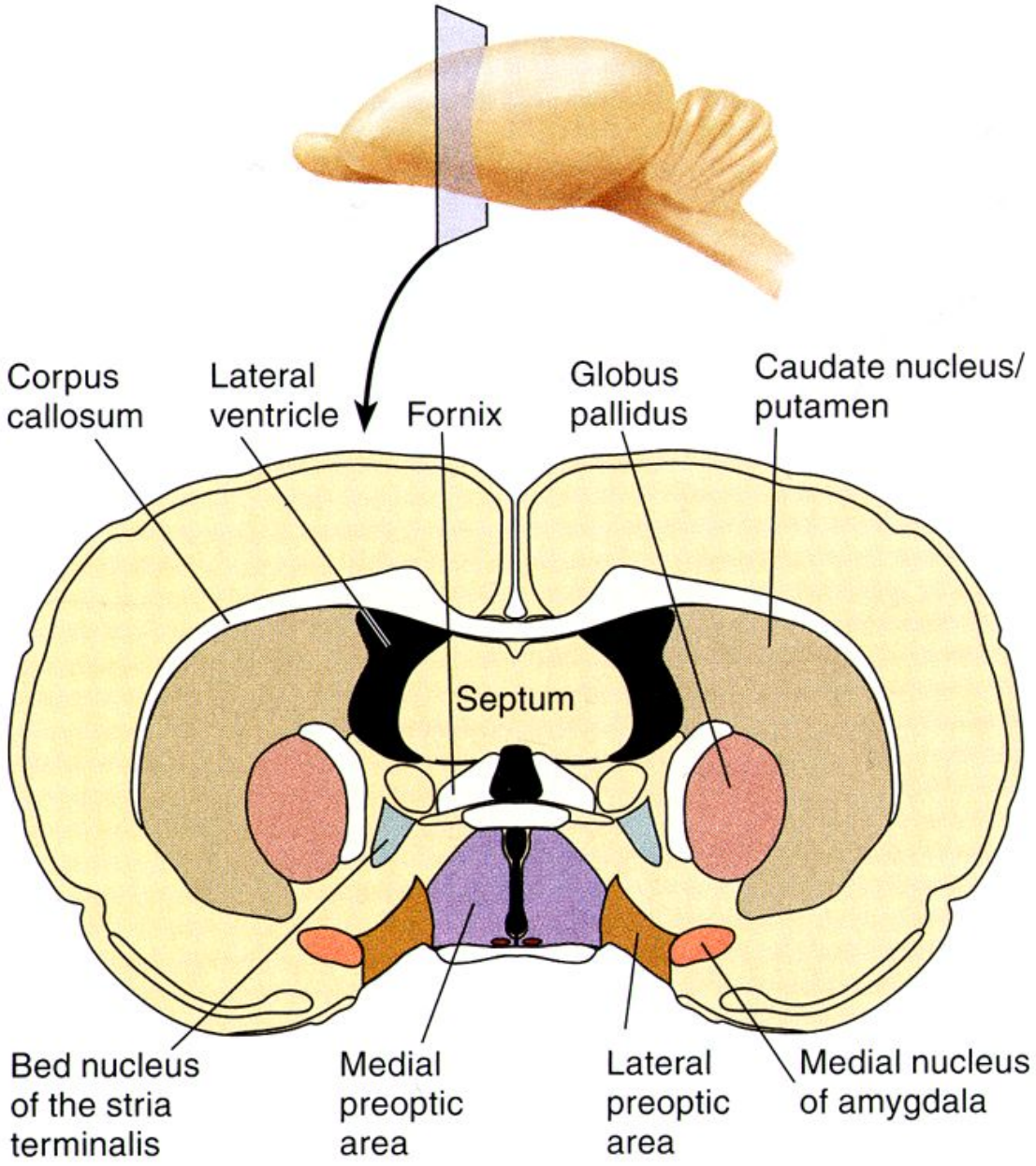


Kubrick (1999): ‘Eyes Wide Shut’

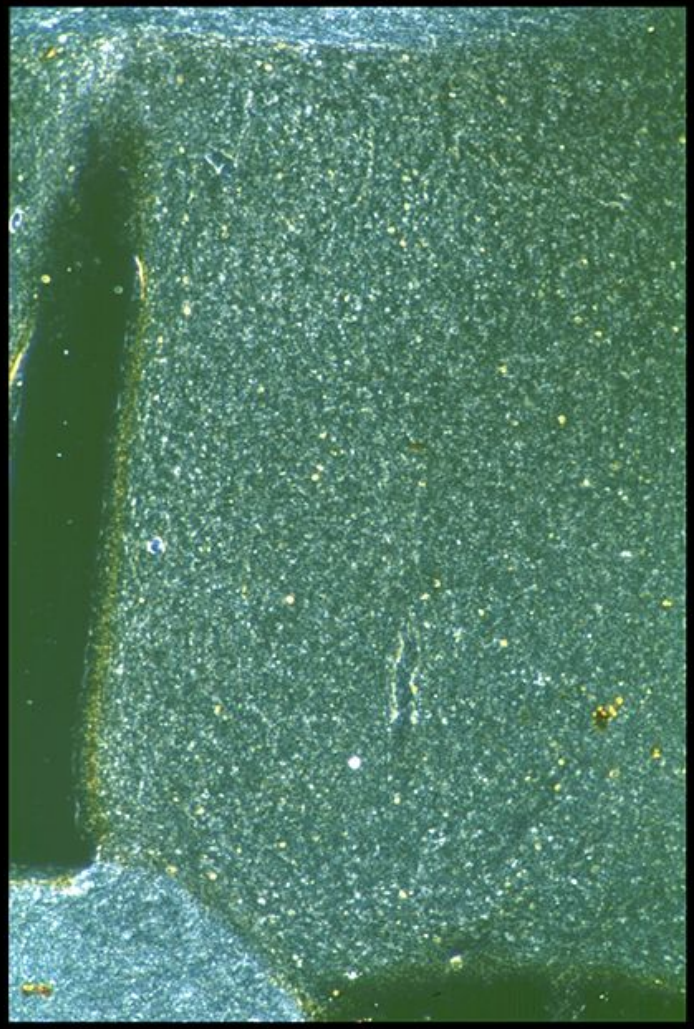
Demme (2001): 'Blow'

Hypothalamic preoptic area and (part of) the amygdala

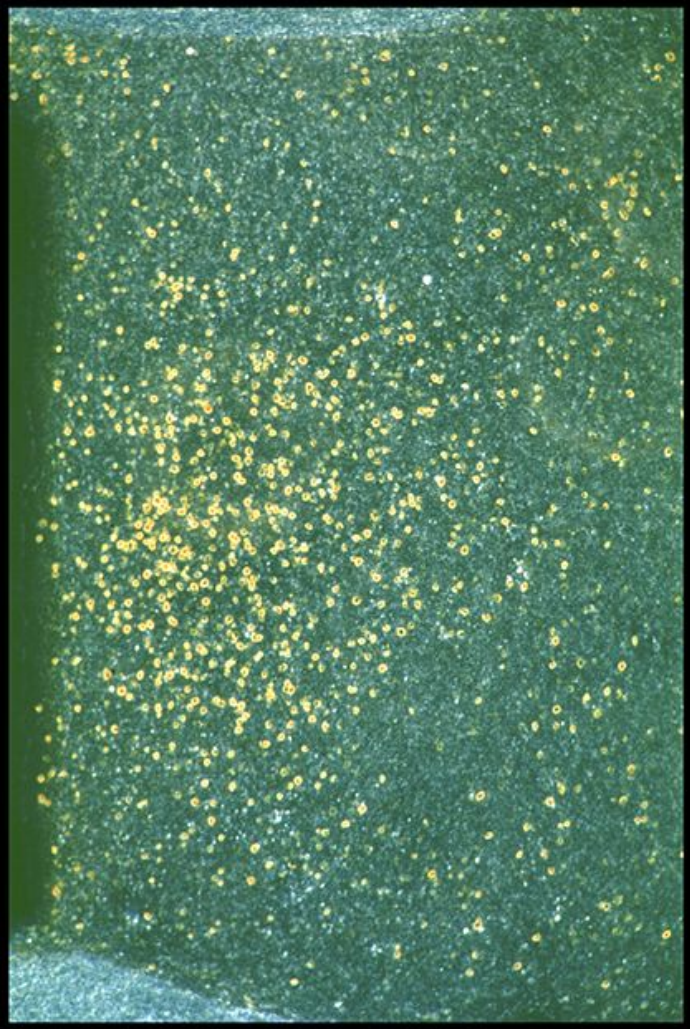
Coronal section of rat brain



Induction of *c*-fos expression in the medial preoptic area by sexual behaviour in male rats



control



sexual activity

Everitt & Baum; see also e.g. Robertson et al. (1991)

Second-order schedules (e.g. of sexual reinforcement)

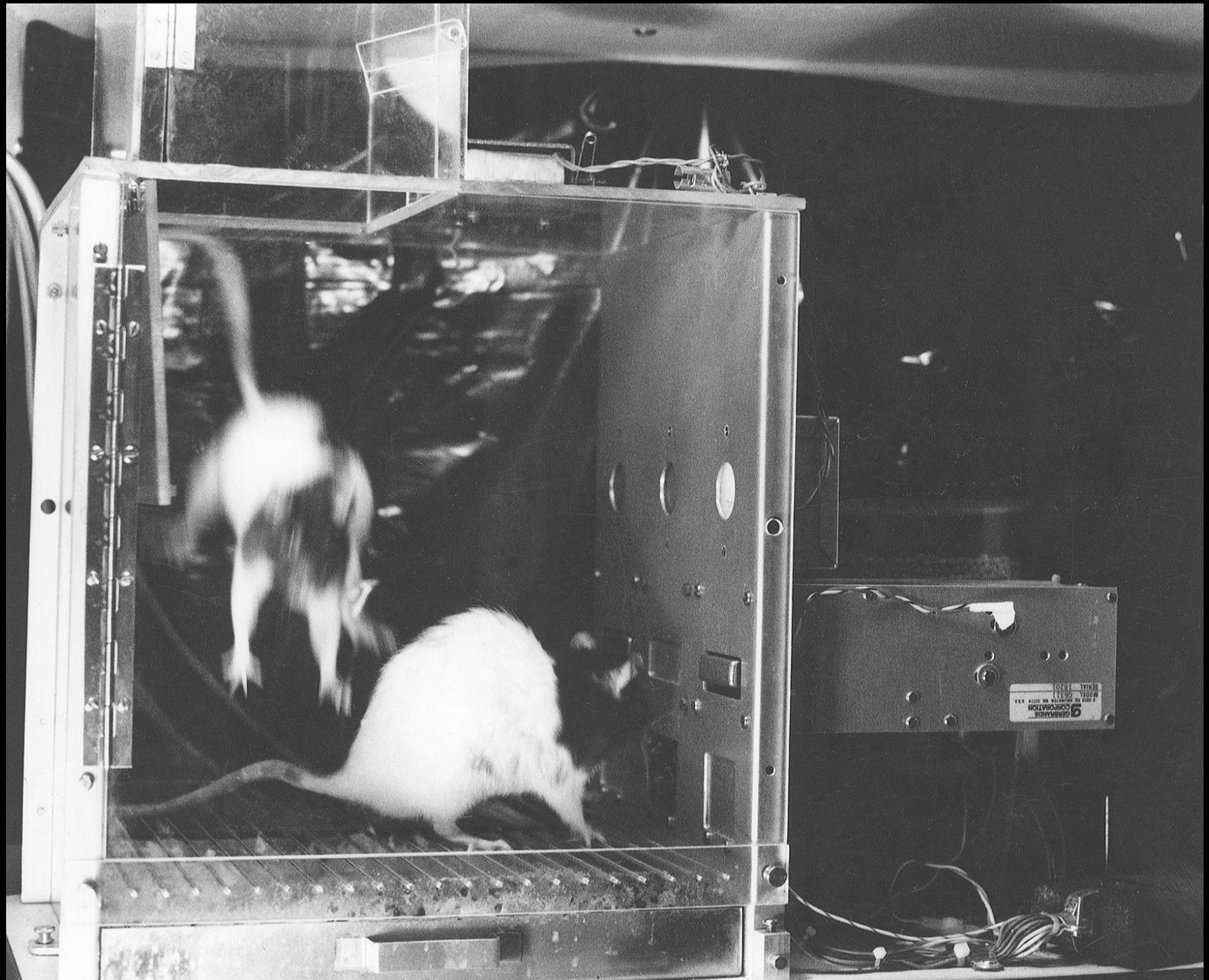
For example,

FI 15 min : (FR10:S)

(Fixed ratio 10)
Every 10 responses earns one ***stimulus***

(Fixed interval 15 minutes)
The first time the subject
earns a stimulus after 15 minutes
have elapsed, it also earns ***primary reinforcement***

Kelleher (1966)



Double dissociation of appetitive / consummatory behaviour

Effects of

- ***basolateral amygdala (AMY) lesions***
- ***medial preoptic area (POA) hypothalamic lesions***
- ***castration (CAS)***

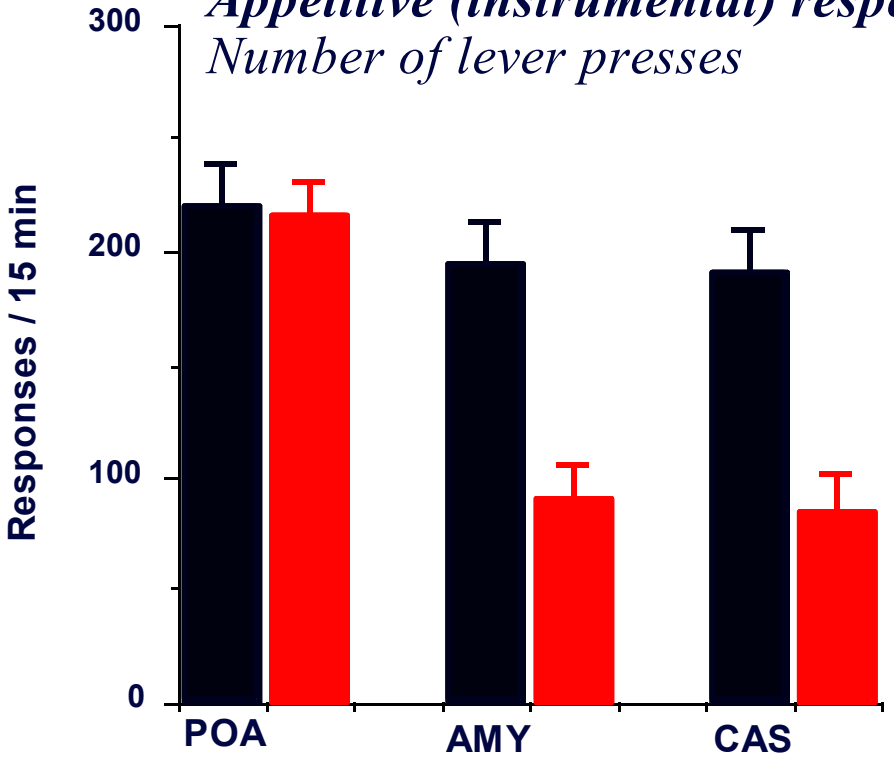
on appetitive and consummatory sexual responses *in male rats.*

Sham

Operated

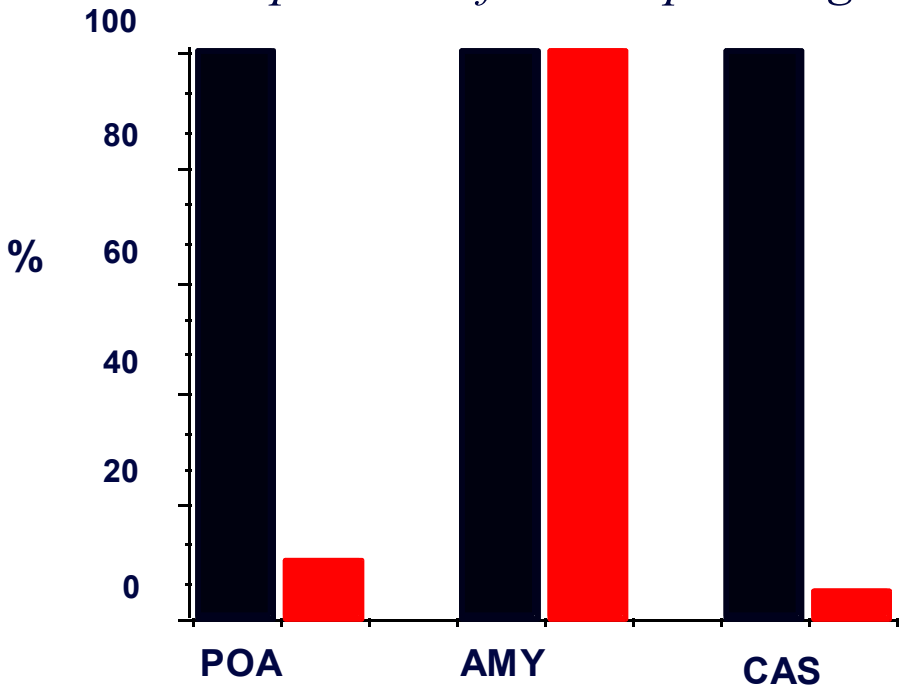
Appetitive (instrumental) responses

Number of lever presses



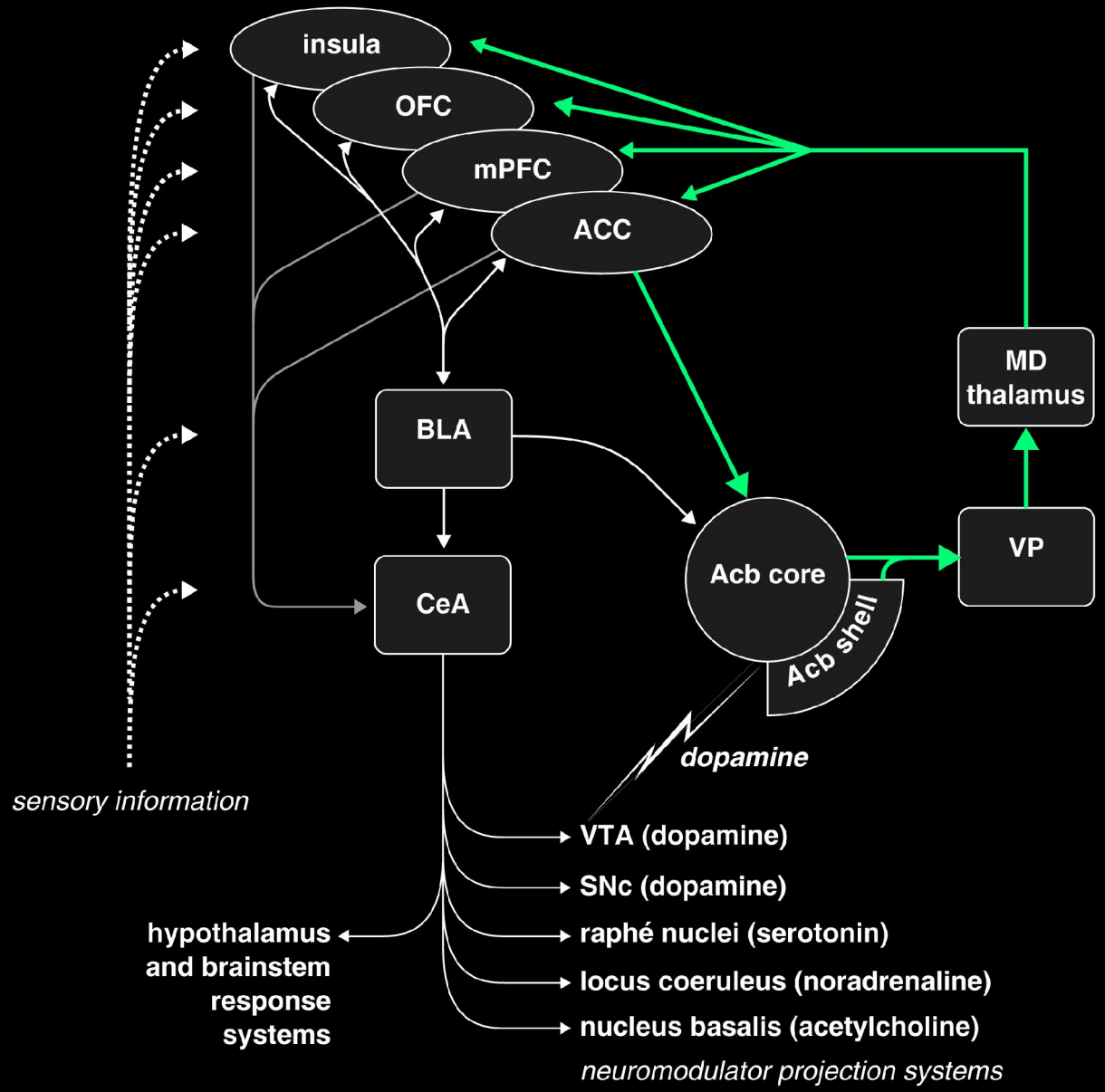
Consummatory responses

Proportion of rats copulating



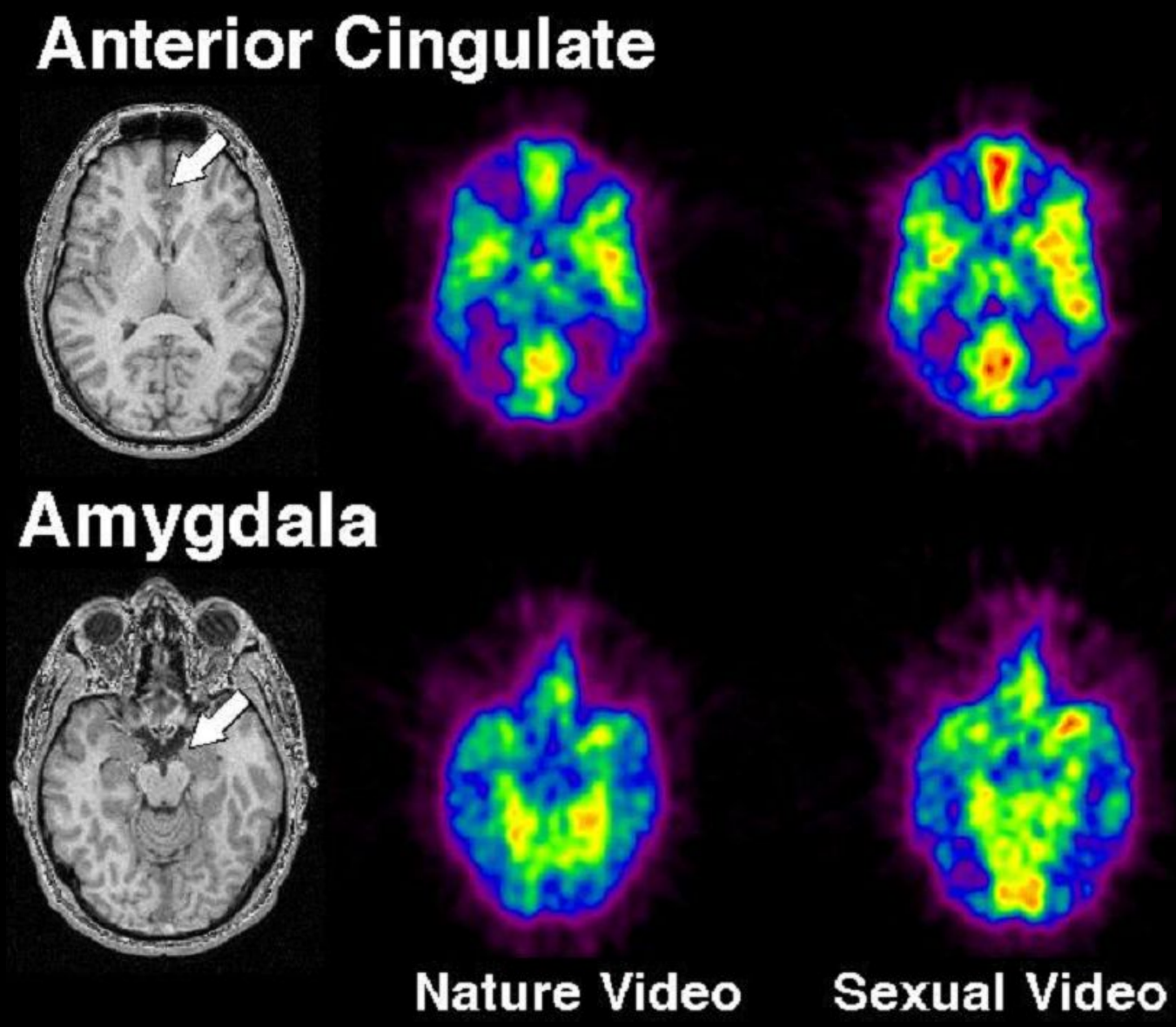
Everitt & Stacey (1987); Everitt, Cador & Robbins (1989)

The ‘limbic’ corticostriatal circuit



DeLong & Georgopoulous (1981); Cardinal et al. (2002)

Sexual stimuli activate nodes of this limbic circuit

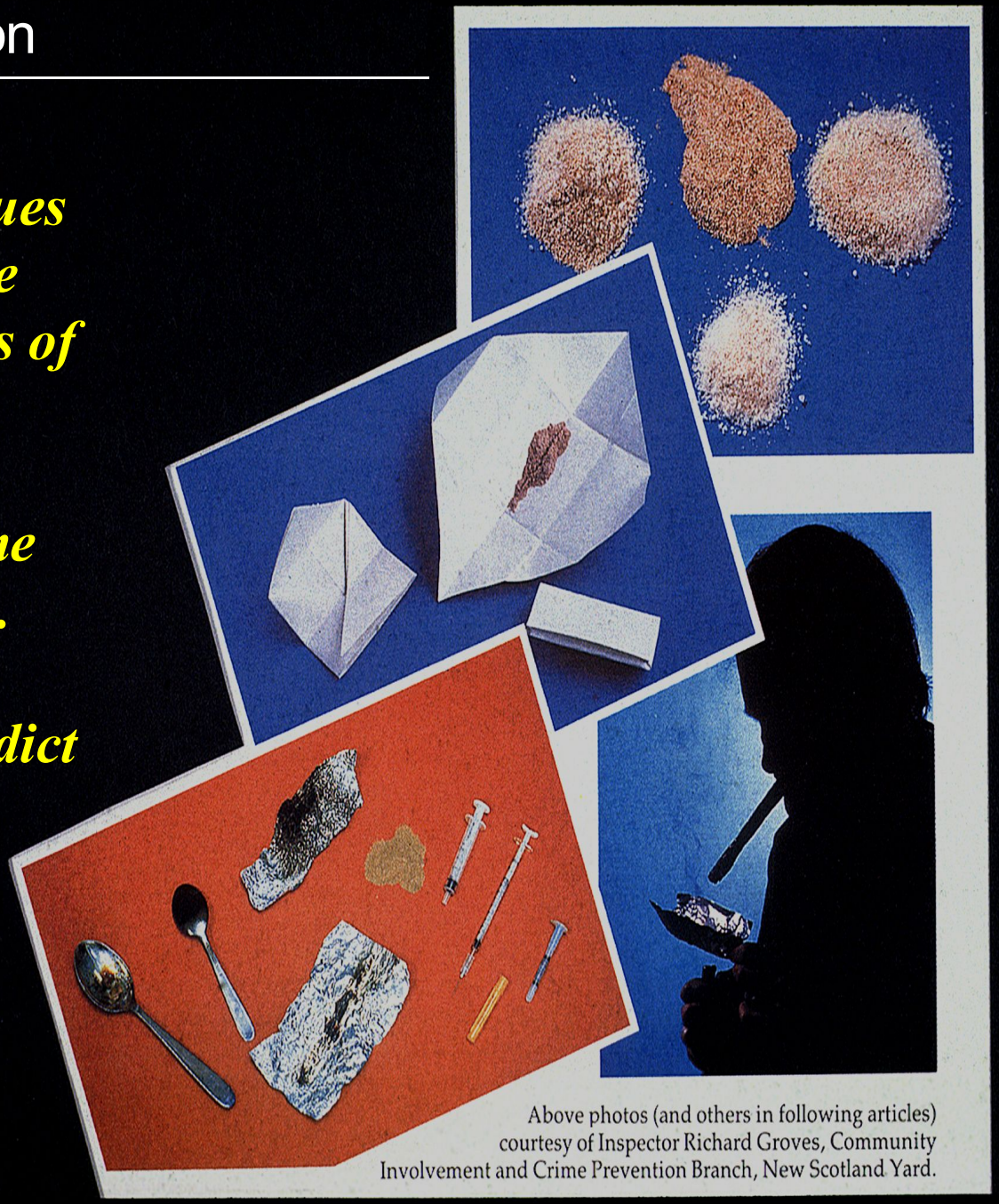


Childress et al. (1999→); see also Garavan et al. (2000)

Conditioning and addiction

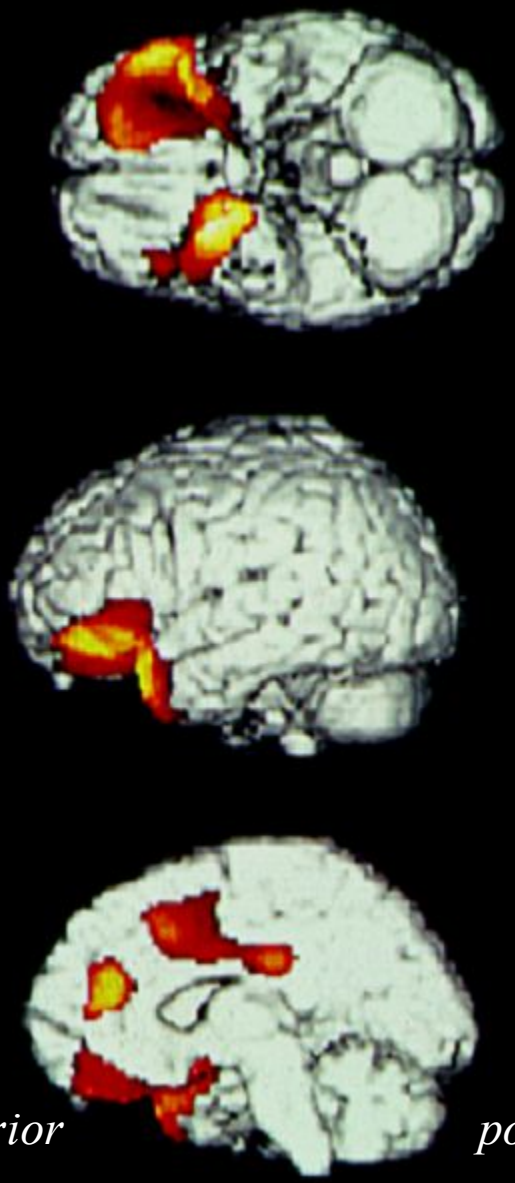
Environmental stimuli (cues and contexts) may become associated with the effects of drugs such as cocaine through Pavlovian conditioning. They become conditioned stimuli (CSs).

They may motivate an addict to seek out drugs — cue-induced (conditioned) craving.



Above photos (and others in following articles) courtesy of Inspector Richard Groves, Community Involvement and Crime Prevention Branch, New Scotland Yard.

Cue-induced cocaine craving activates limbic structures



medial temporal lobe — amygdala

Subjects watching a cocaine video; activations correlated with subjective reports of craving

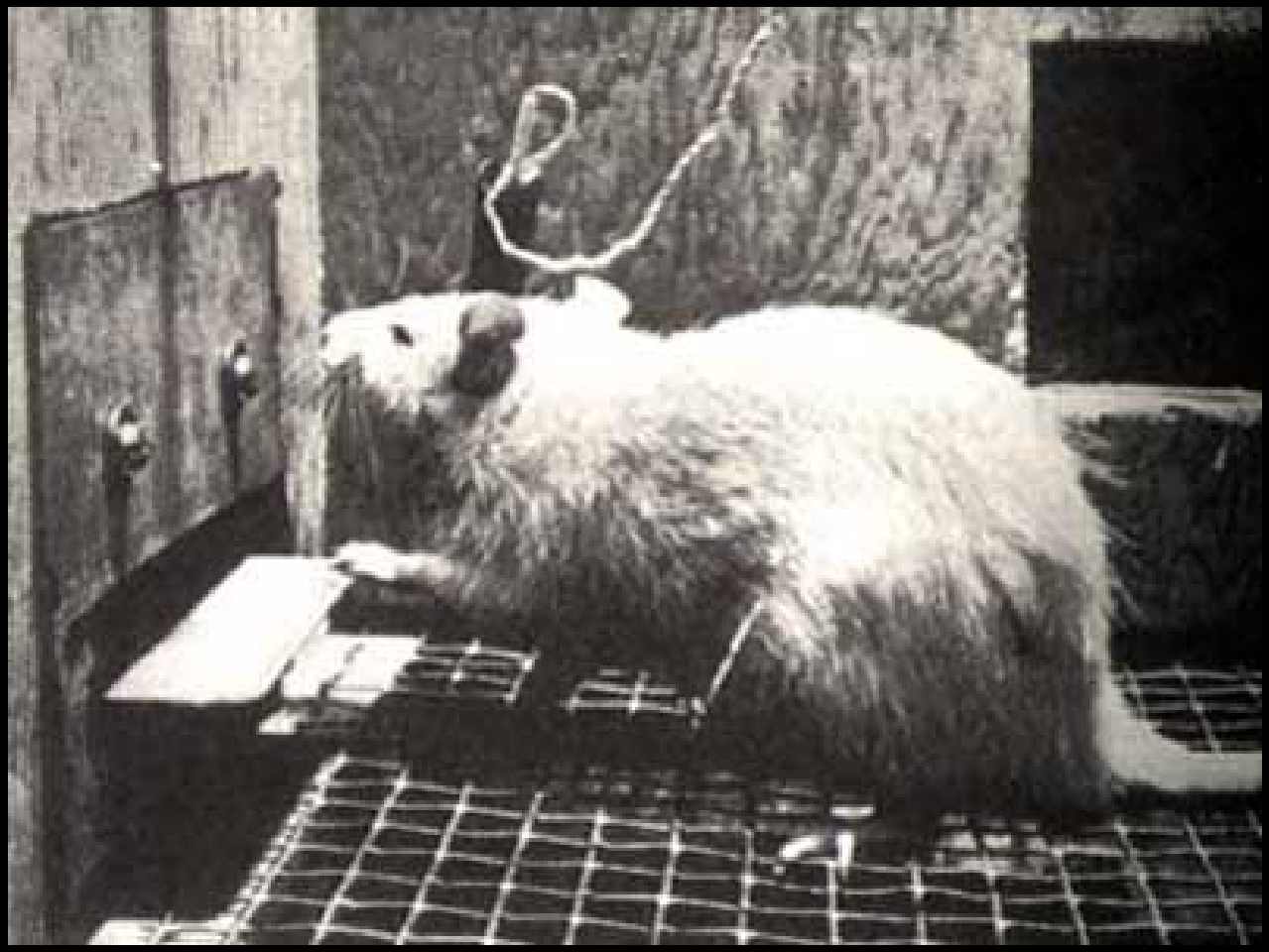
orbital prefrontal cortex

anterior cingulate cortex

anterior *posterior*

Childress et al. (2000)

Electrical intracranial self-stimulation (ICSS)

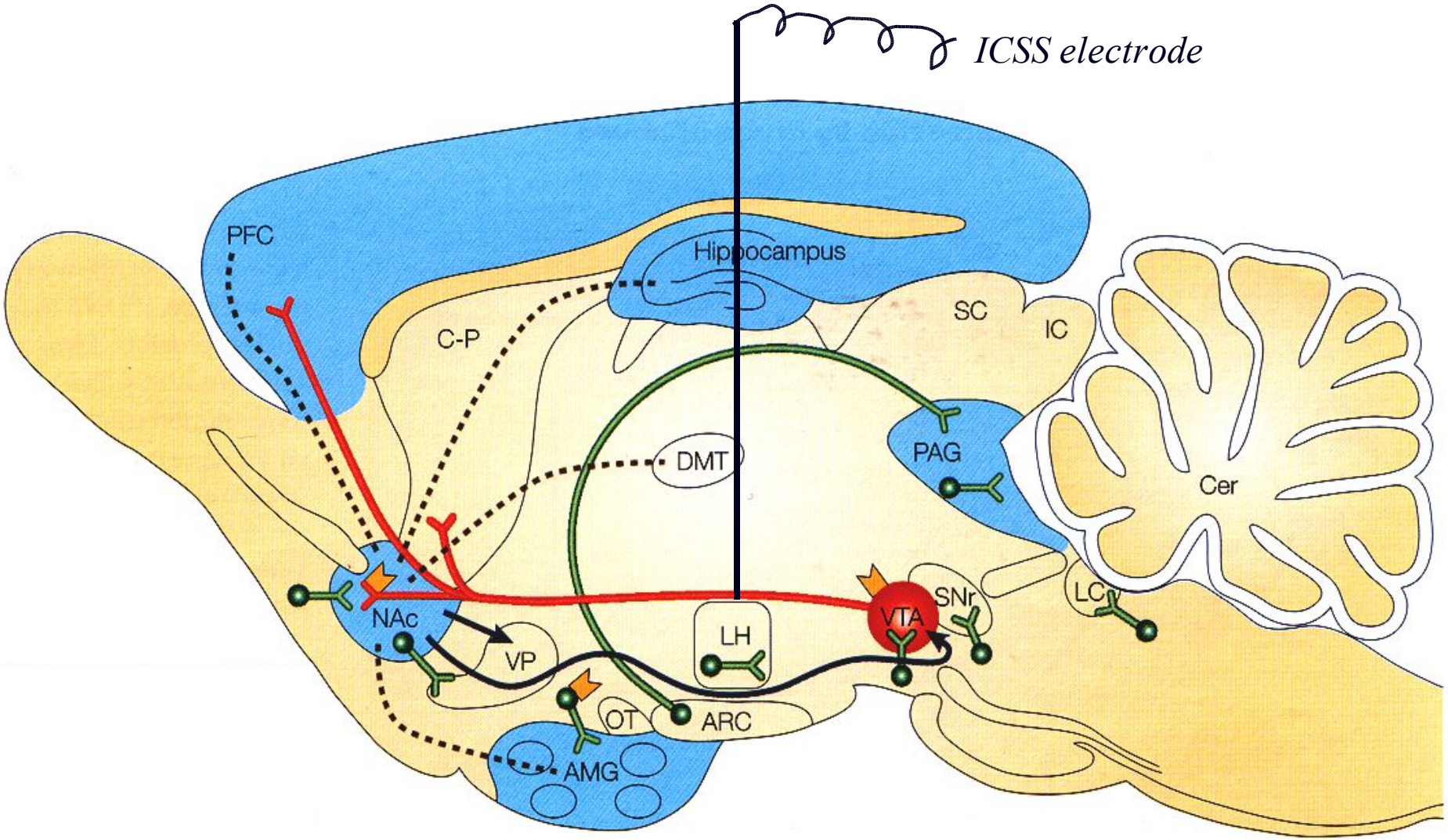


The mind is its own place, and in itself, can make heaven of Hell, and a hell of Heaven.

(Satan, in John Milton's *Paradise Lost*, book 1, ll. 254–5)

Olds & Milner (1954)

The mesolimbic dopamine system and ICSS — a ‘reinforcement pathway’ (though *not* necessarily a ‘pleasure system’)

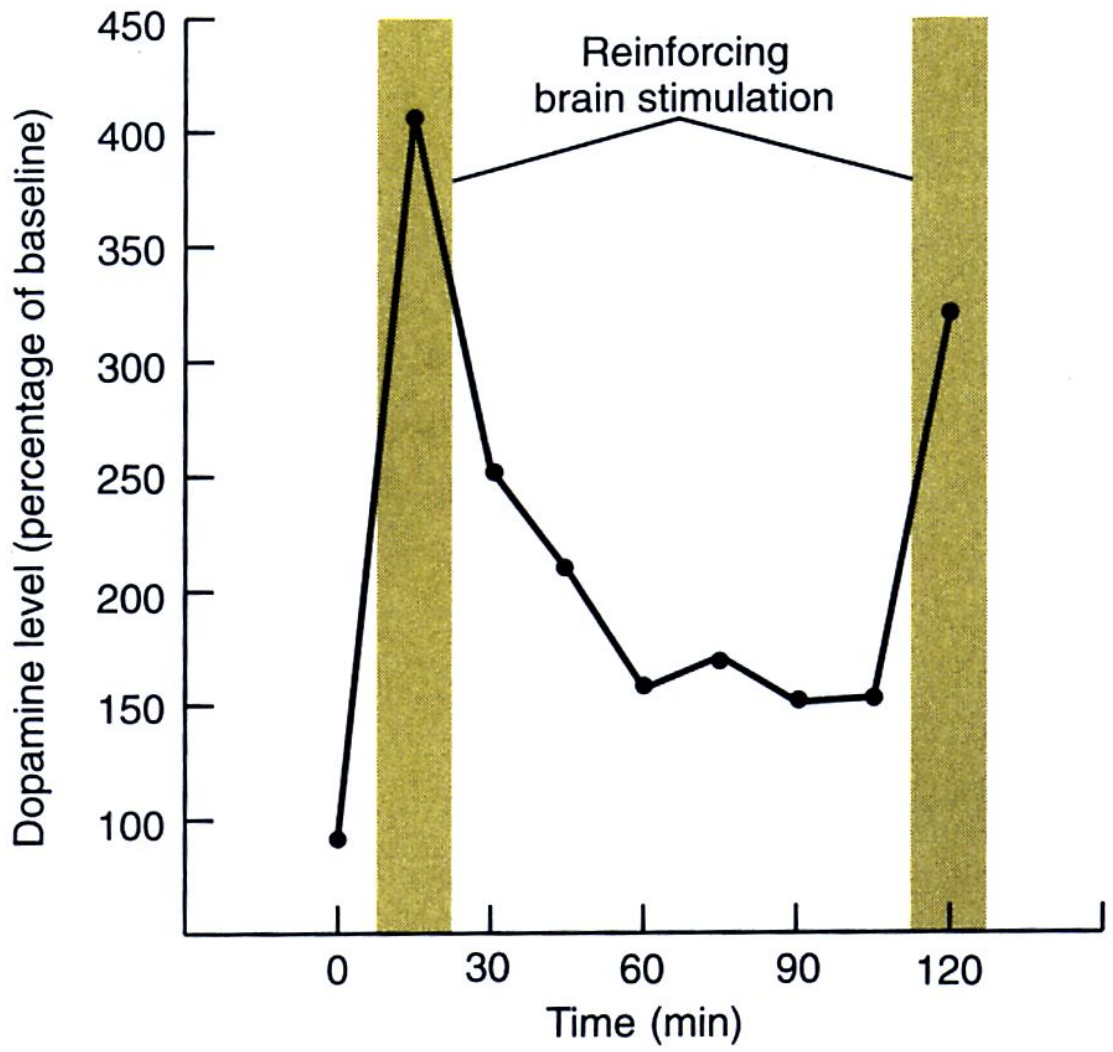


Remote-controlled rats and a cocaine sniffer rat

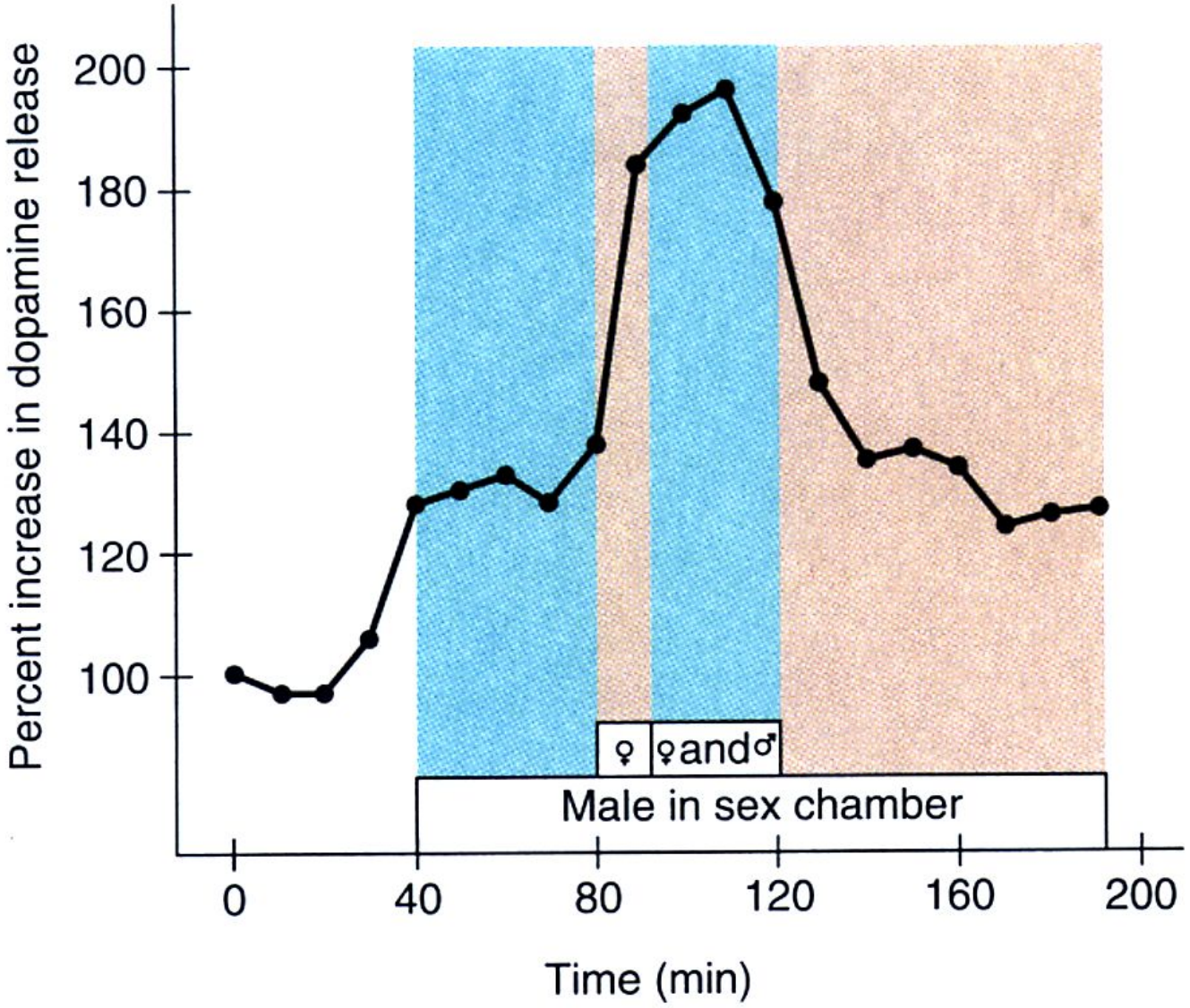
Otto *et al.* (2002). *Appl. Animal Behav. Sc.* 77: 217

Talwar *et al.* (2002). *Nature* 417: 37

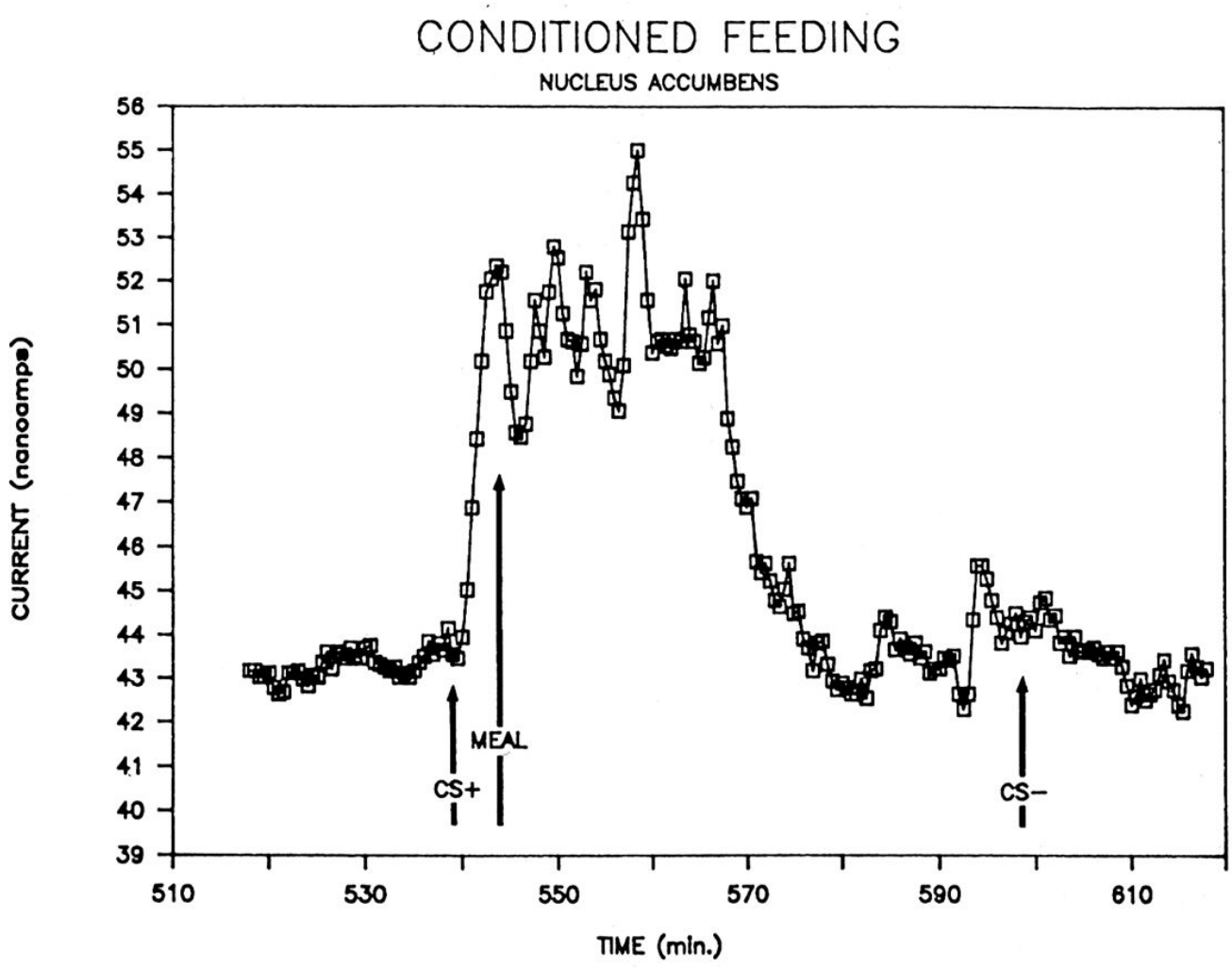
Dopamine release in the nucleus accumbens during ICSS



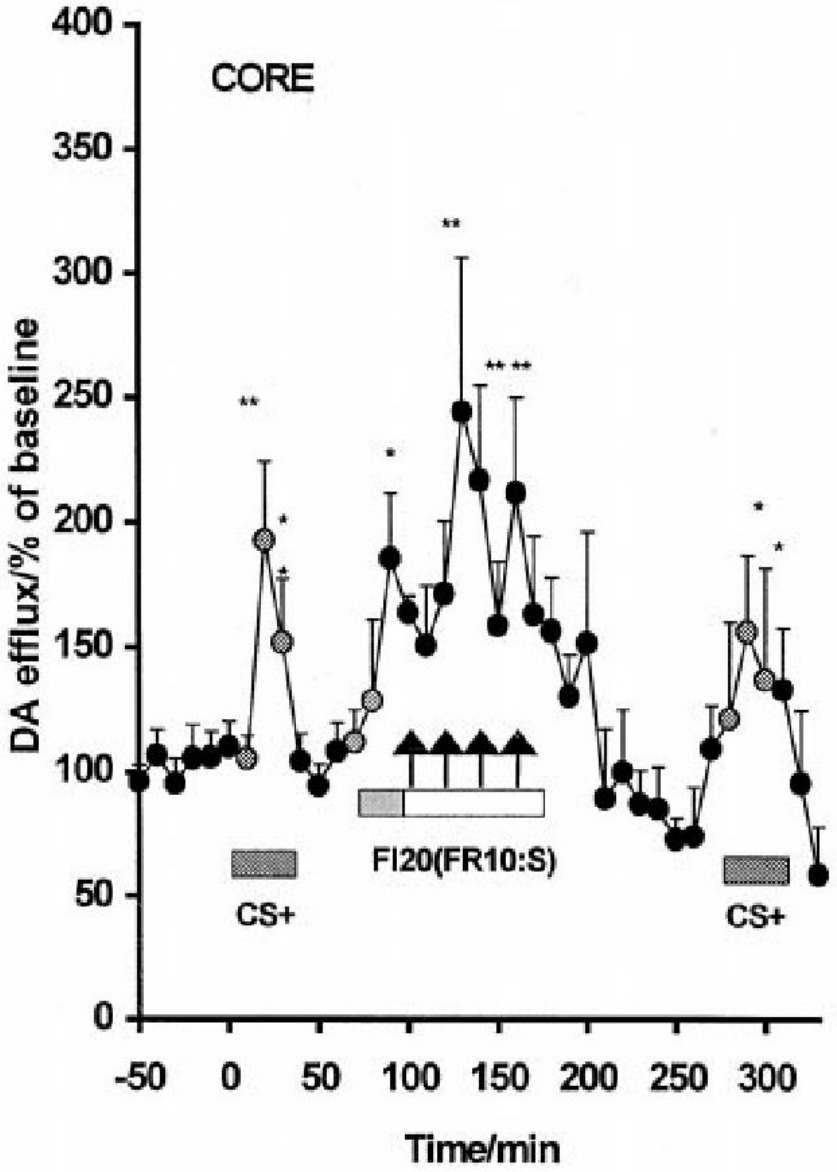
Dopamine release in the nucleus accumbens of a male rat during sexual behaviour — and in anticipation of sex



Dopamine release in the nucleus accumbens during ingestion of a preferred food — and in response to a CS for food



Dopamine release in the nucleus accumbens during IV cocaine self-administration — and to a CS for cocaine

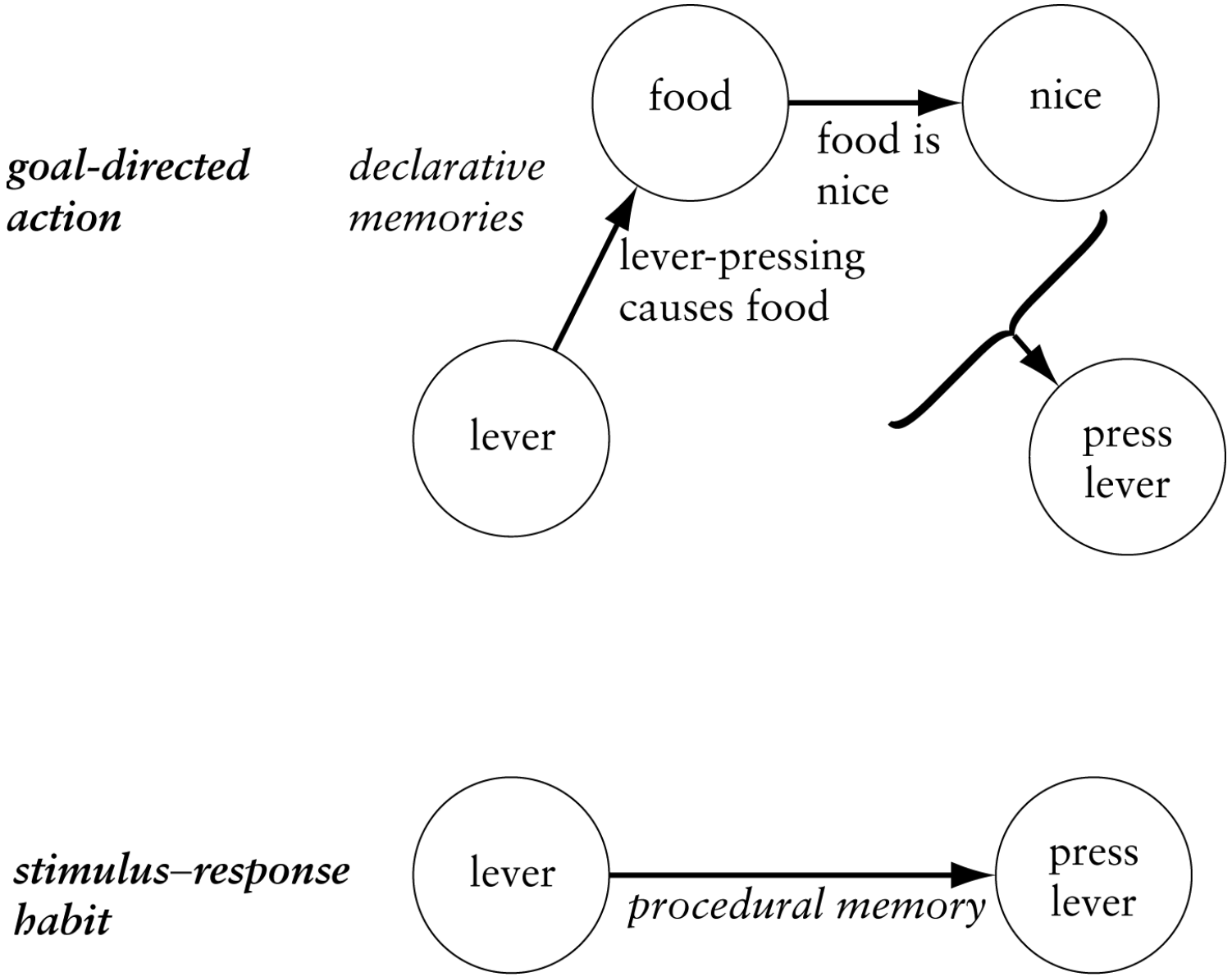


Ito et al. (2000)

Learning theory and neurobiology

- Animals form multiple psychological representations during Pavlovian and instrumental conditioning.
- For example, an animal learning to respond for a reward encodes
  - the instrumental (action–outcome) contingency;
  - the value of the outcome as an instrumental goal;
  - the (dissociable) 'affective' value of the outcome;
  - direct stimulus–response 'habits';
- … and is influenced by Pavlovian processes including **conditioned reinforcement** and **Pavlovian–instrumental transfer.**
- The neural basis of some of these processes is starting to be understood.

Animals work for reinforcement for several reasons, including...

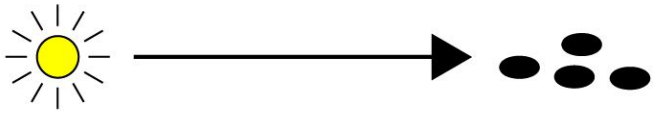


after Dickinson (1980)

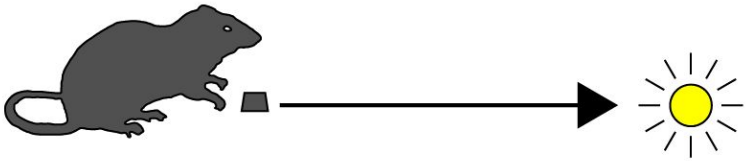
… but cues paired with reinforcement can also motivate

Conditioned reinforcement

Training

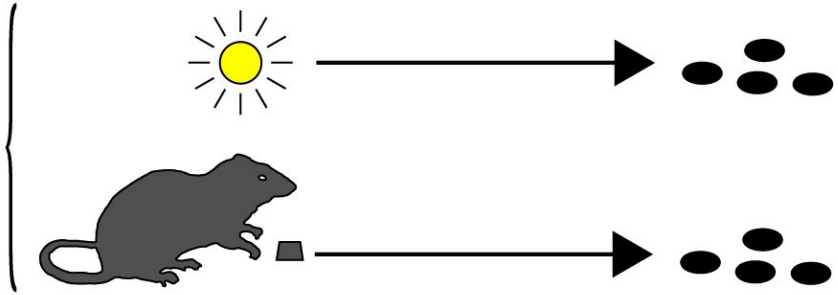


Test



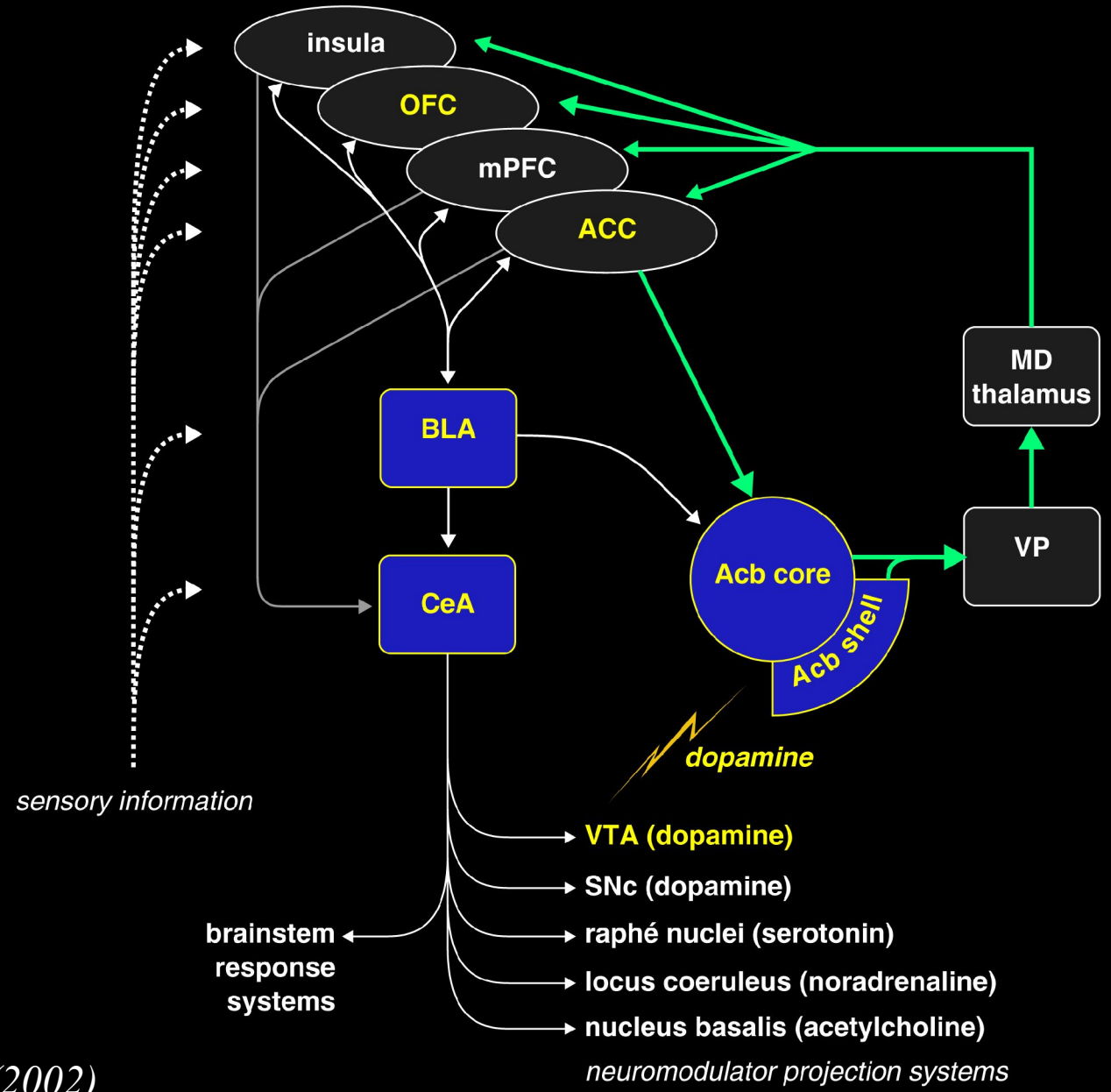
Pavlovian–instrumental transfer (PIT)

Training



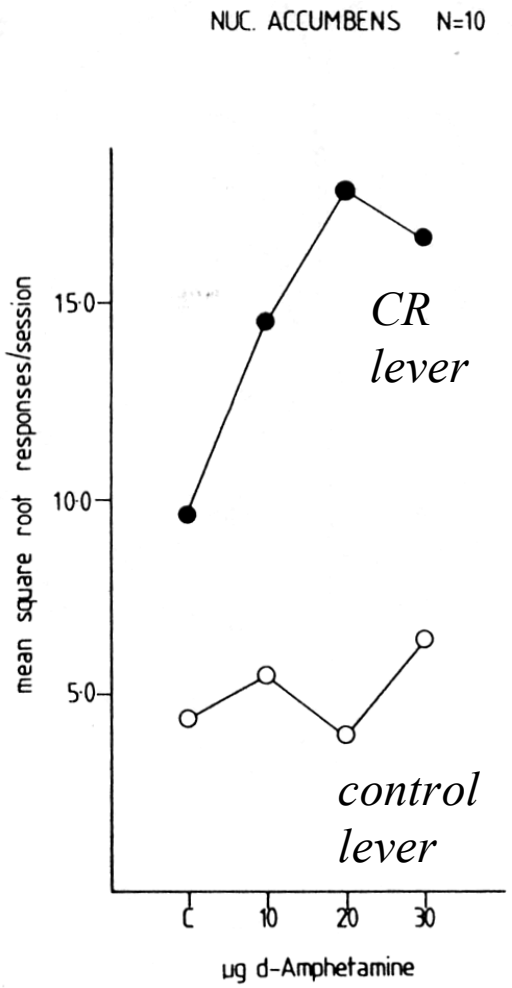
Test

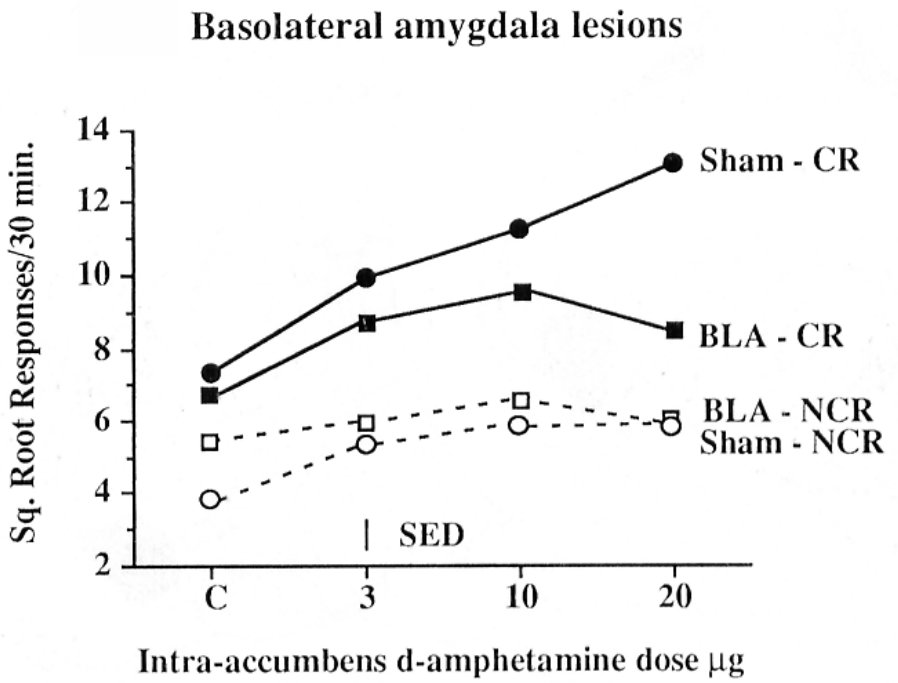
The limbic corticostriatal circuit: conditioned motivation



Cardinal et al. (2002)

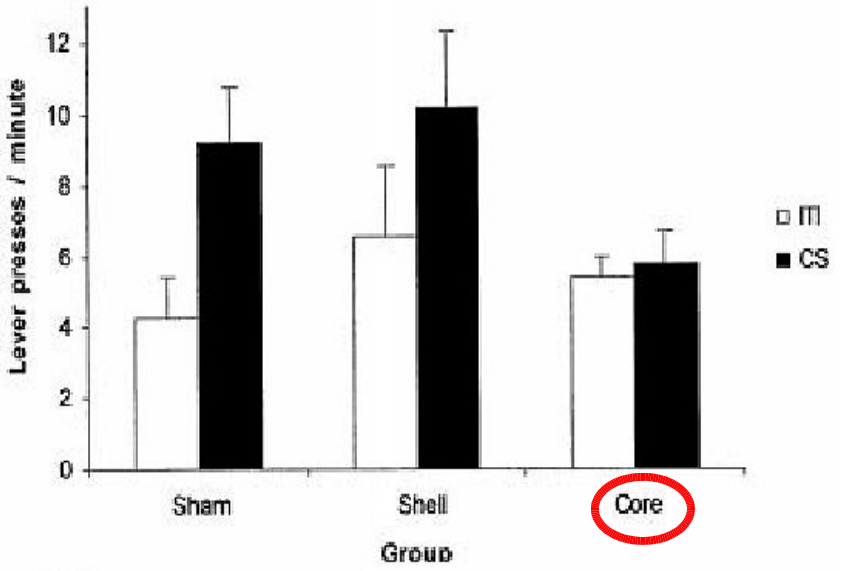
Conditioned reinforcement depends in part upon the basolateral amygdala, and can be enhanced by intra-accumbens amphetamine

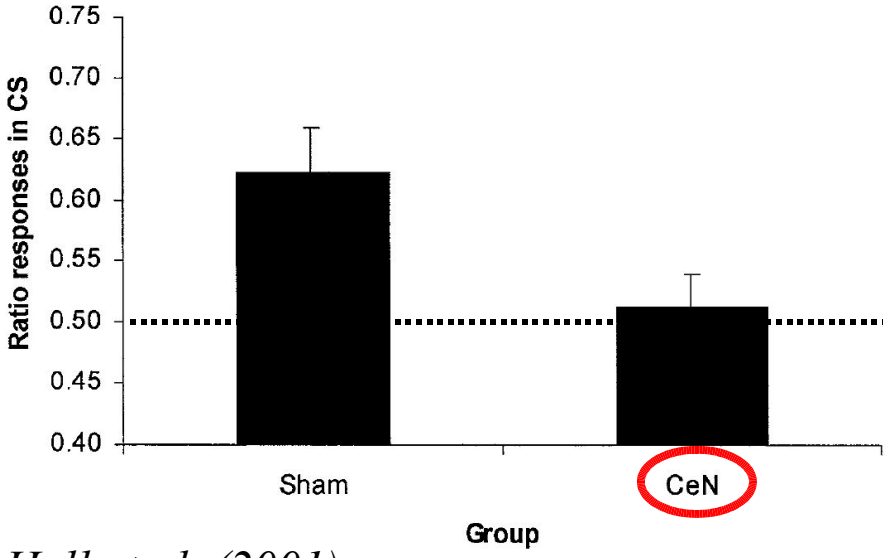


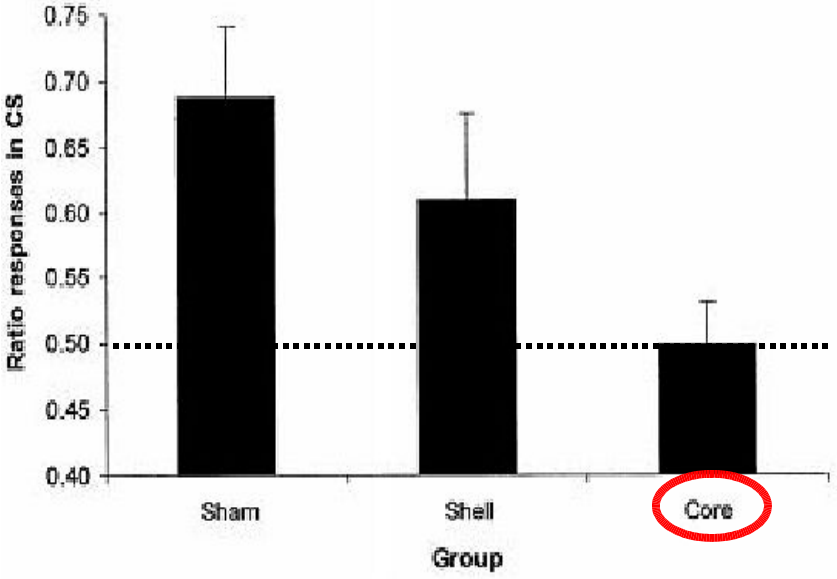


Taylor & Robbins (1984); Burns et al. (1993)

Lesions of the nucleus accumbens core (or central nucleus of the amygdala) abolish PIT



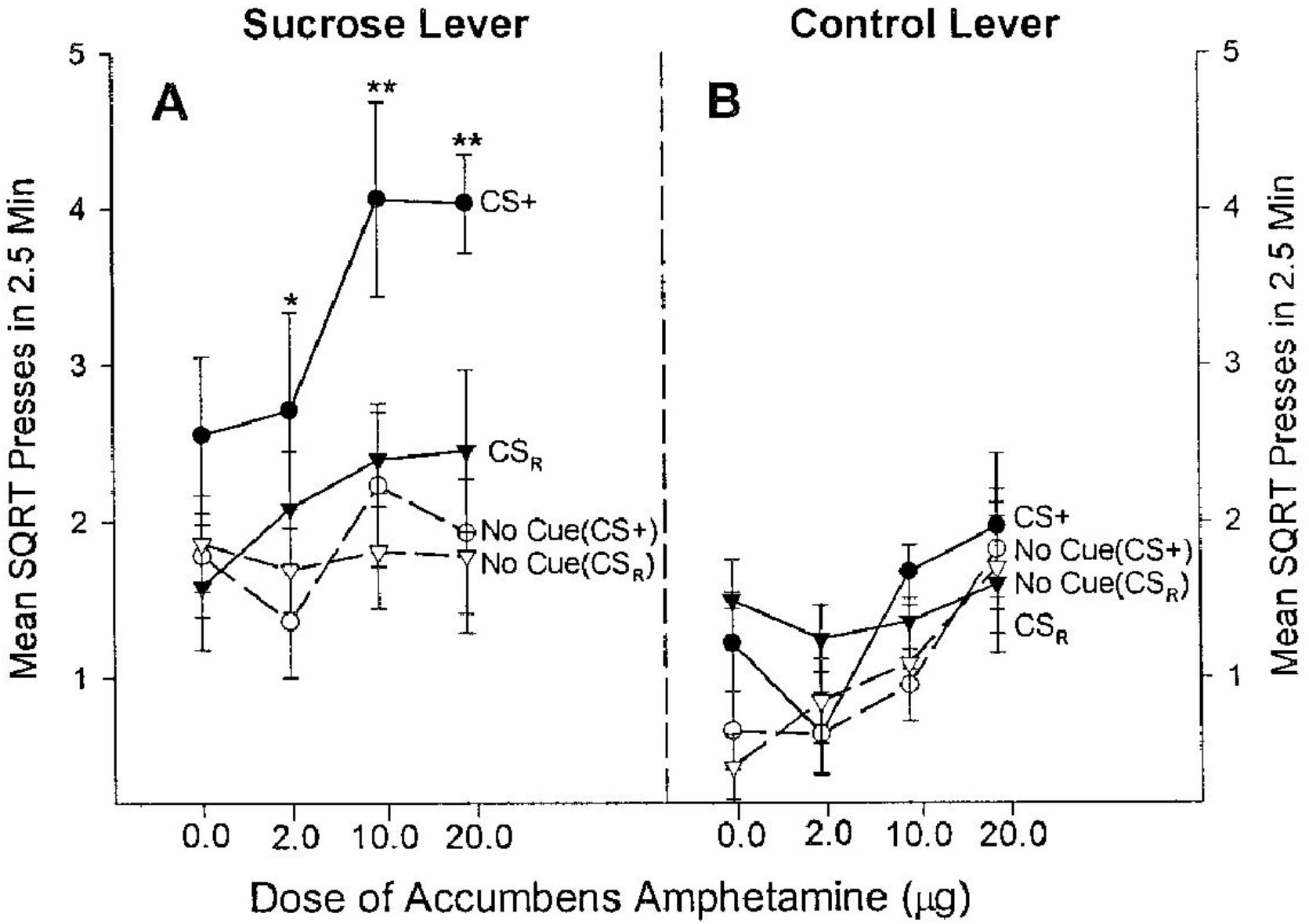




chance

Hall et al. (2001)

Intra-accumbens amphetamine enhances PIT



Wyvell & Berridge (2000)

The nucleus accumbens and dopamine in motivation

- The nucleus accumbens, its dopamine innervation, and associated amygdaloid structures appear critical for **conditioned stimuli** to motivate behaviour.

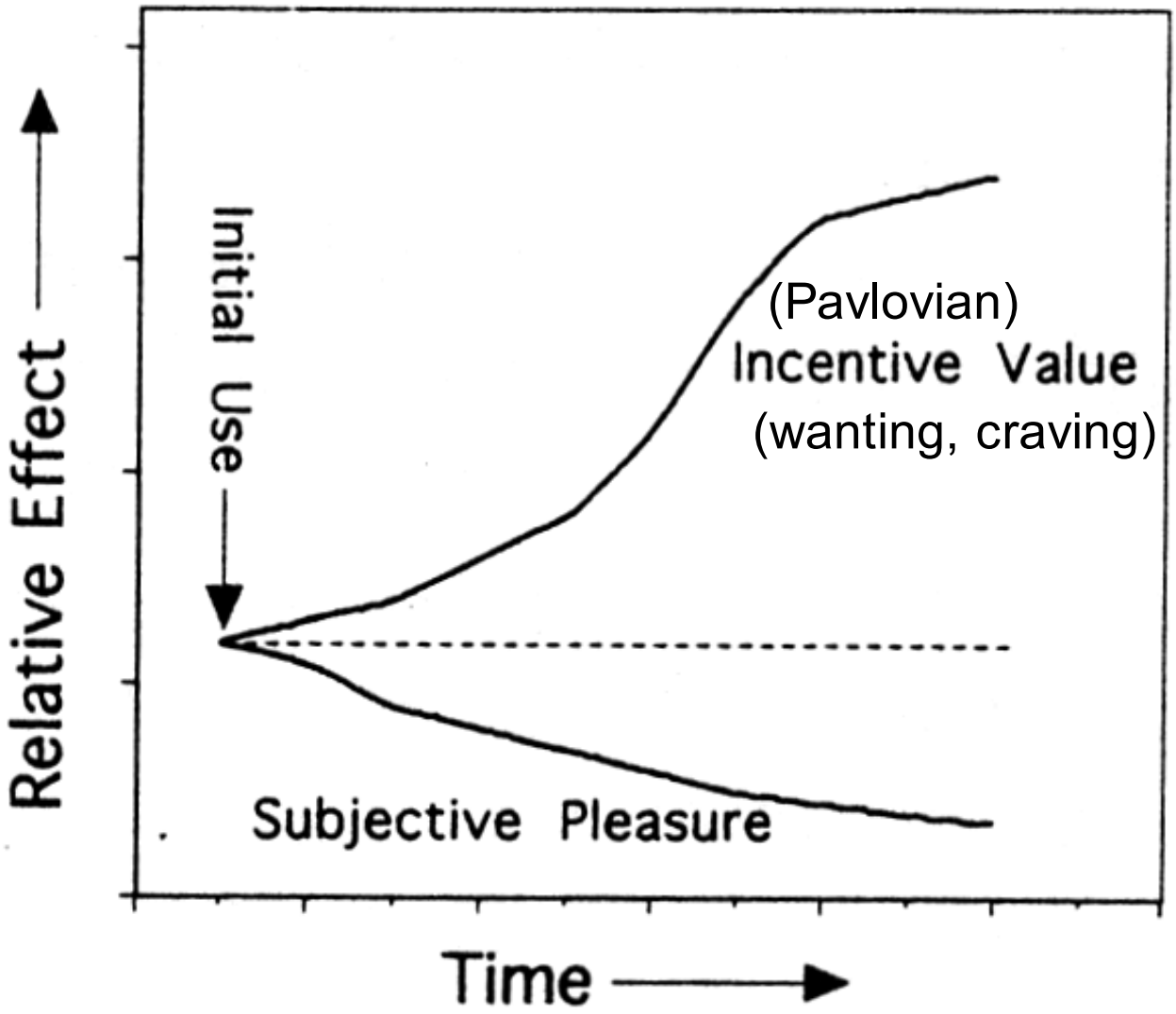
- **Pavlovian conditioned motivation** (sometimes referred to as 'wanting' or 'craving') can be distinguished from true goal-directed actions, and from hedonic value ('liking').

- This system may play an important role in pathologically heightened motivation. Furthermore, many addictive drugs enhance the responsiveness of the VTA $\rightarrow$ nucleus accumbens dopamine system (**sensitization**). This is associated with increased Pavlovian conditioned motivation.

- This system is a potential **therapeutic target.**

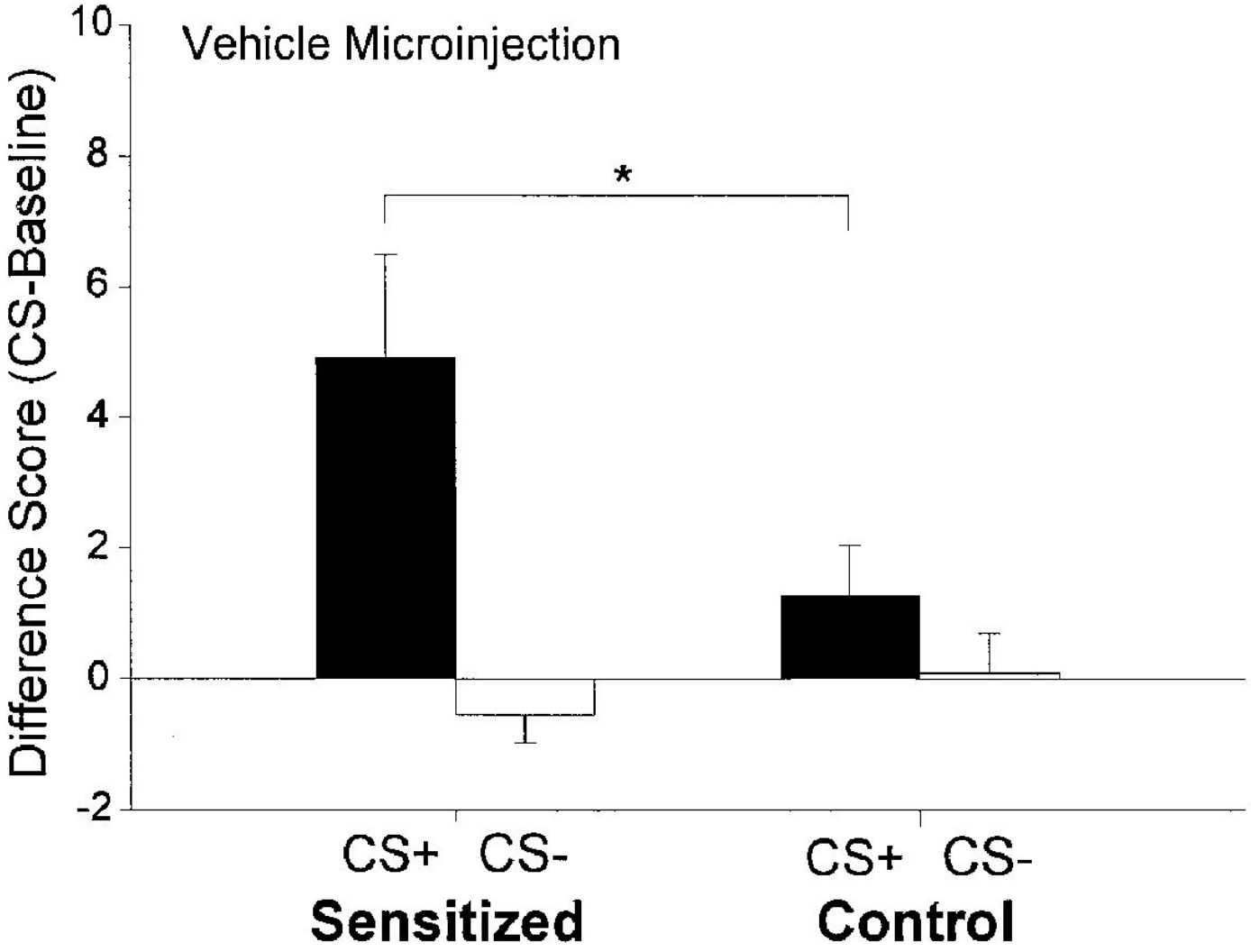
Robinson & Berridge (1993); Cador et al. (1995); Berridge & Robinson (1998); Pilla et al. (1999); Wyvell & Berridge (2001); Cardinal et al. (2002)

Incentive sensitization theory of drug addiction



Robinson & Berridge (1993); Berridge & Robinson (1998); Robinson & Berridge (2003)

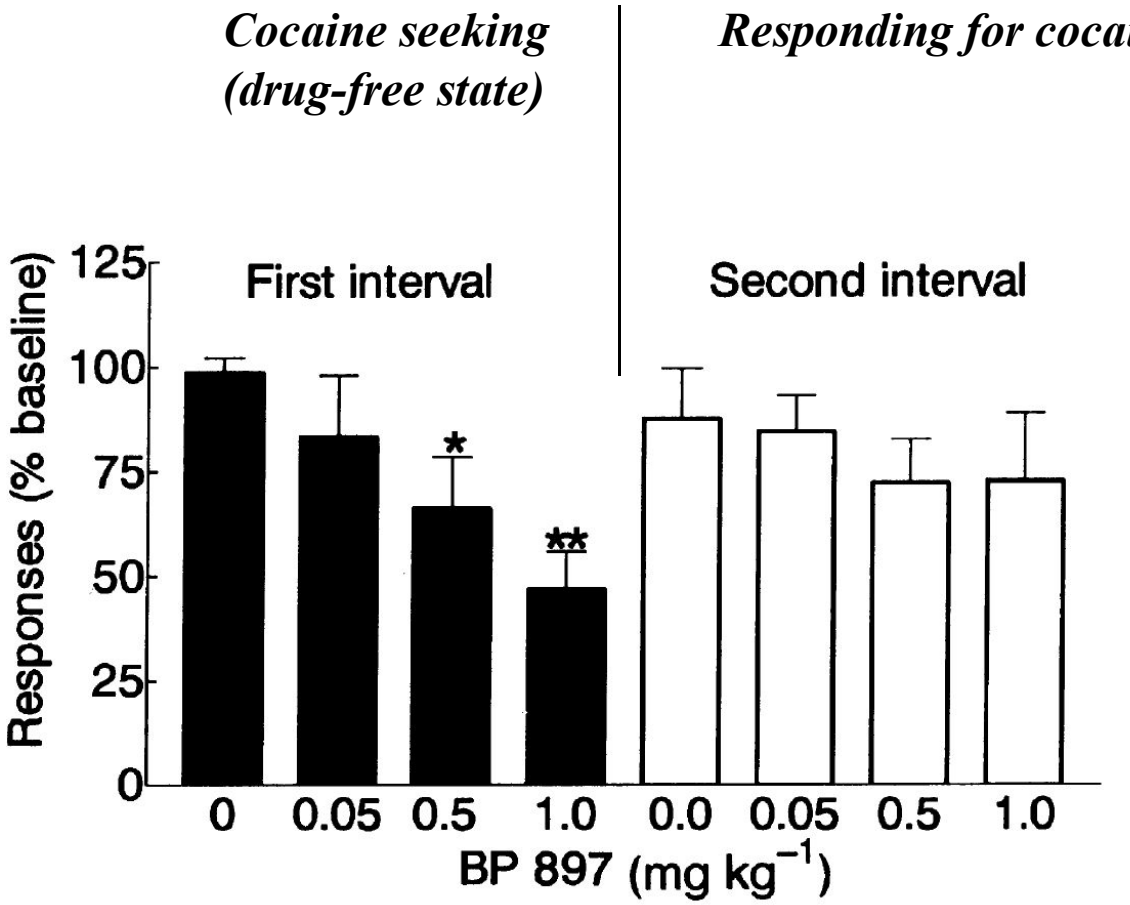
Amphetamine sensitization enhances subsequent PIT



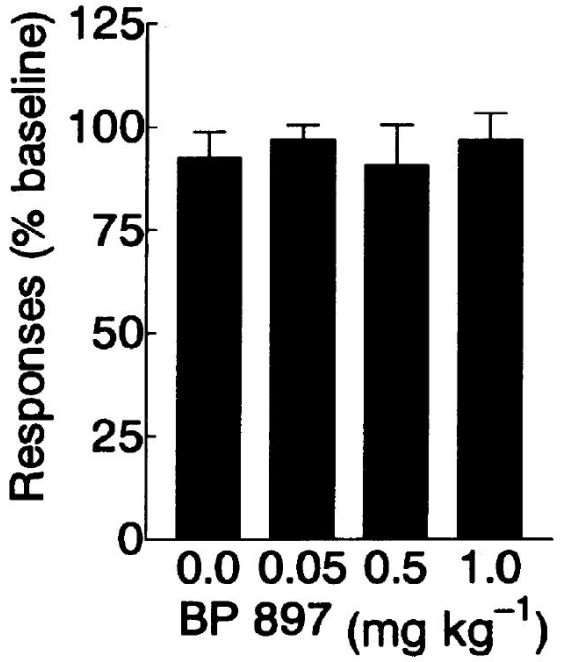
Wyvell & Berridge (2001)

Therapeutic potential: cocaine-seeking behaviour

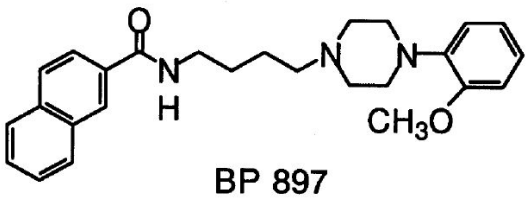
BP897 (dopamine D3 partial agonist) reduces cocaine seeking



FI 15 min (FR10:S) second-order schedule

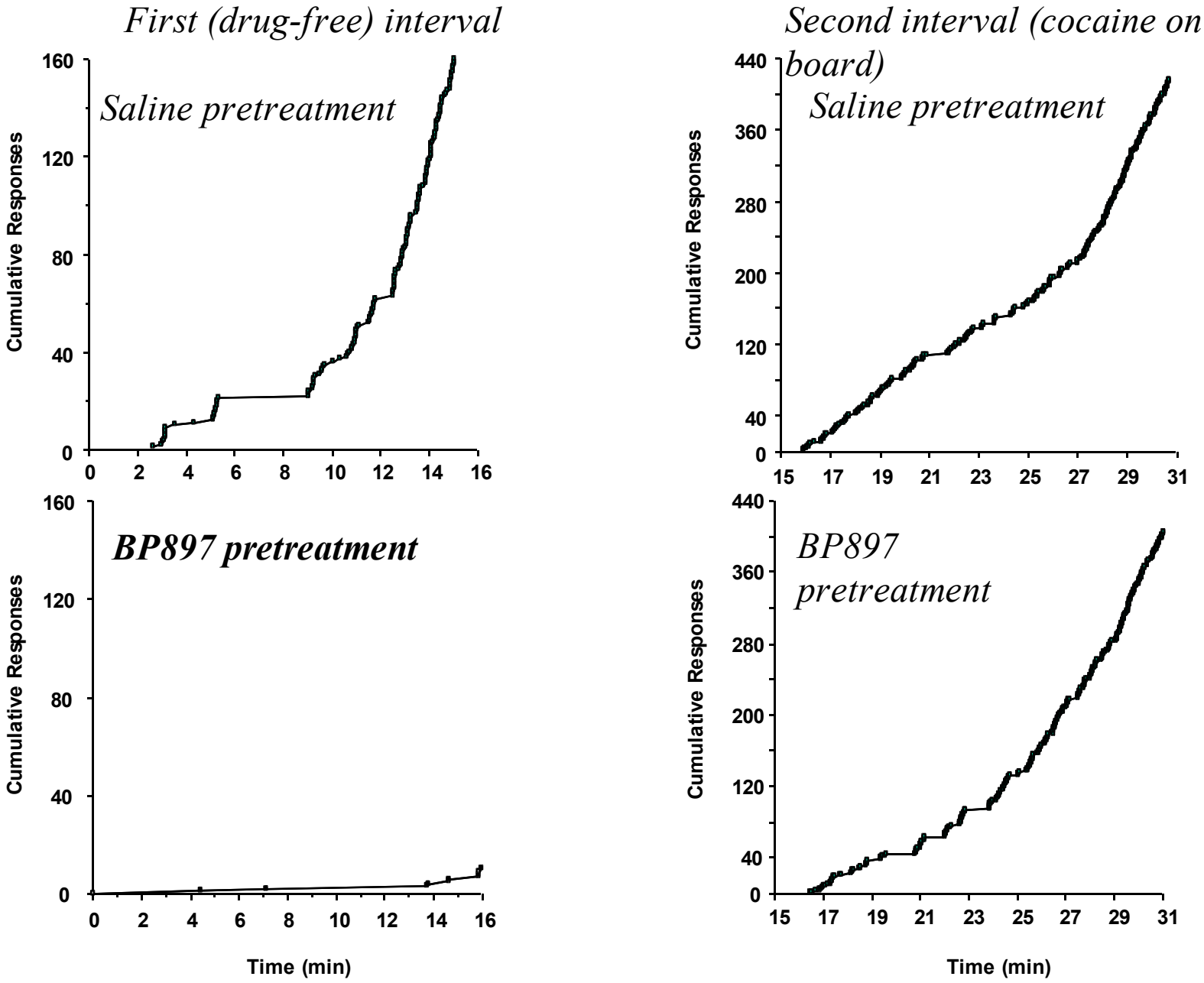


FR1 schedule for cocaine

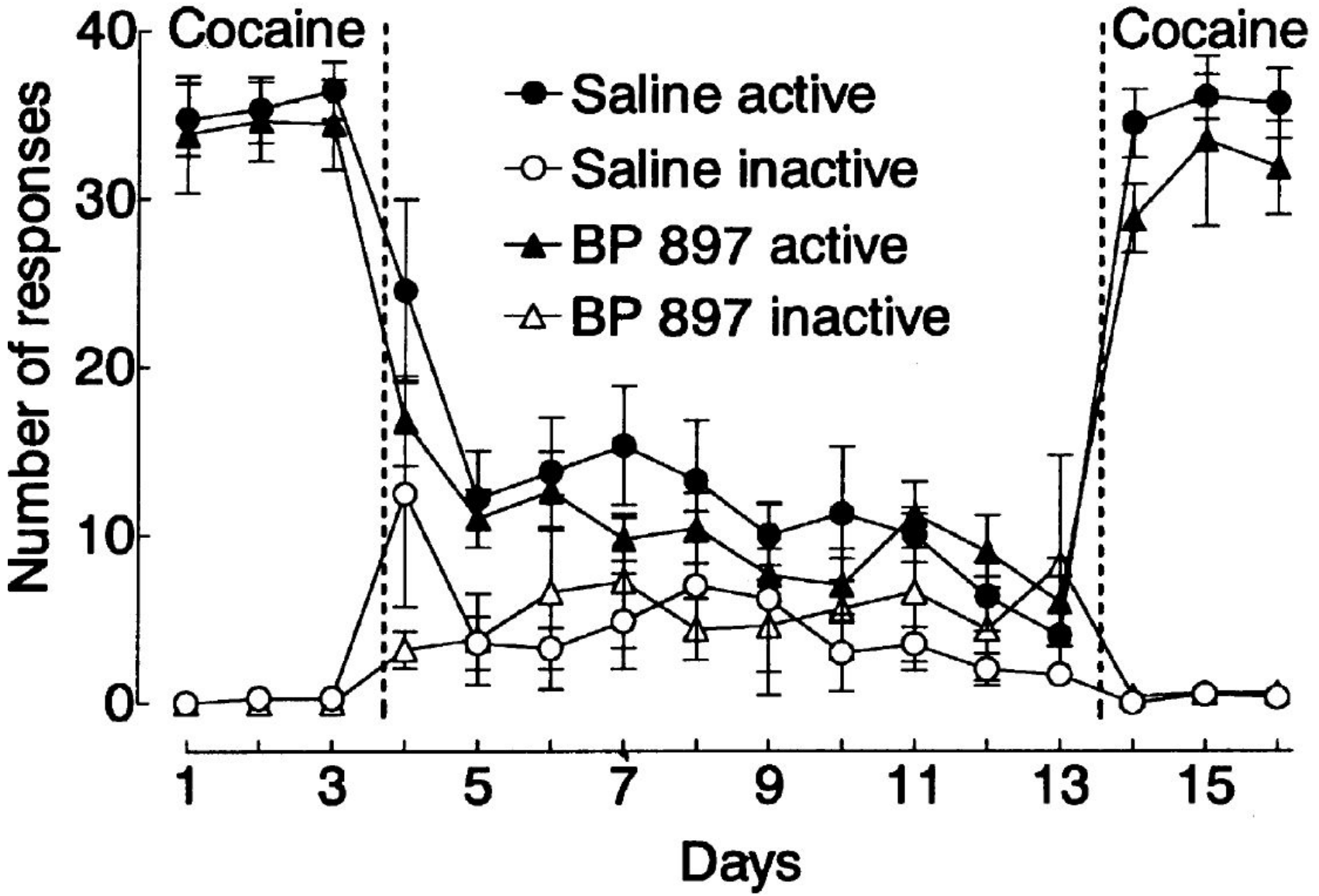


Pilla et al. (1999)

BP897 reduces cocaine seeking in second-order schedules



BP897 is not itself self-administered



Pilla et al. (1999)

Summary

• Natural reinforcers (sex, food) and artificial reinforcers (drugs of abuse, ICSS) activate **common neural sites** within the limbic system.

• Moving from correlative studies to causal experiments in animal models, it appears that that the nucleus accumbens, amygdaloid structures that project to it, and their dopamine innervation mediate the ability of **conditioned stimuli** paired with reinforcement to motivate behaviour directed towards obtaining that reinforcement.

• Pavlovian conditioned motivation is an important aspect of **desire and addiction.**

• This system is a potential **therapeutic target.** Dopamine D3 receptors are selectively expressed in limbic structures; drugs acting at these receptors suppress drug-seeking in animal models and are entering human clinical trials.