The anatomical basis of desire and addiction

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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,

\[
\text{FI 15 min : (FR10:S)}
\]

(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.

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

Cue-induced cocaine craving activates limbic structures

- medial temporal lobe — amygdala
- orbital prefrontal cortex
- anterior cingulate cortex

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


Talwar et al. (2002). Nature 417: 37
Dopamine release in the nucleus accumbens during ICSS

- If dopamine receptors are blocked, so is self-stimulation of the brain.

Graph showing dopamine release over time during ICSS.
Dopamine release in the nucleus accumbens of a male rat during sexual behaviour — and in anticipation of sex

![Graph showing dopamine release over time](image-url)
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

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

Cocaine seeking (drug-free state)

Responding for cocaine with cocaine on board

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

FR1 schedule for cocaine

Pilla et al. (1999)
BP897 reduces cocaine seeking in second-order schedules

First (drug-free) interval

Saline pretreatment

BP897 pretreatment

Second interval (cocaine on board)

Saline pretreatment

BP897 pretreatment
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 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.