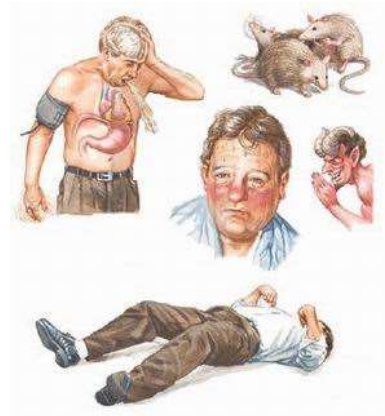# PSYC1022: The Psychology of Addiction
Topic 7: Withdrawal & Tolerance (II)
Dr. Helena Pacitti

Outline:
- Conditioned withdrawal
  - Wikler
  - Supporting empirical evidence
    - Instrumental & Pavlovian learning in addiction
- Conditioned tolerance
  - Siegel "compensatory response hypothesis"
  - Opponent process model & homeostasis
   - Pavlovian conditioning in addiction

1

Conditioned Withdrawal

Abraham Wikler: withdrawal represented a significant barrier to abstinence that promotes relapse to drug use
- cycle of abstinence-withdrawal-relapse.
- articulated this idea with reference to instrumental learning:
  - *Addicts* learn to perform a particular action (drug use) in order to pre-emptively avoid an expected withdrawal syndrome or terminate a current withdrawal syndrome (negative reinforcement).
  - *Recreational* drug use maintained by the rewarding properties of the drug (positive reinforcement)
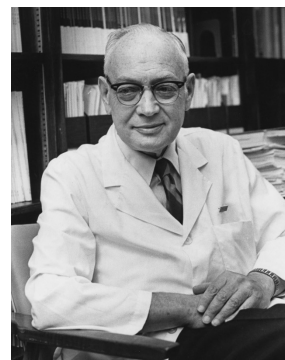
2

Conditioned Withdrawal

Why does relapse occur after withdrawal when the probability of another withdrawal is unlikely?
- Wikler argued that environmental cues that predicted withdrawal could come to elicit a conditioned withdrawal state, through the process of Pavlovian conditioning.
  - e.g. an addict has undergone withdrawal in a particular environment (e.g. bedroom). That environment (CS) may elicit a conditioned withdrawal state (CR) when encountered in the future, which would motivate a relapse to drug use (via negative reinforcement).
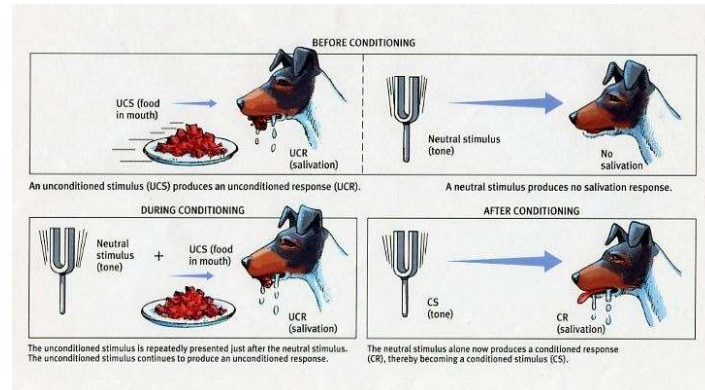

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Conditioned Withdrawal

O'Brien (1977): studied conditioned withdrawal in opiate addicts maintained on methadone.
- Baseline: skin temperature measured whilst subjects were placed in a room & injected with saline
- Conditioning: subjects were placed in the same room with a sound & a peppermint odour added. Injected with naloxone (opiate antagonist) to produce a withdrawal state (indexed by reduced skin temperature)
- Test: subjects were placed in the same room with the sound & peppermint odour, but injected with saline
  - conditioned decrease in skin temperature akin to that produced by naloxone precipitated withdrawal, but this was not seen with saline prior to conditioning
- Environmental cues can produce conditioned withdrawal, which may promote relapse.


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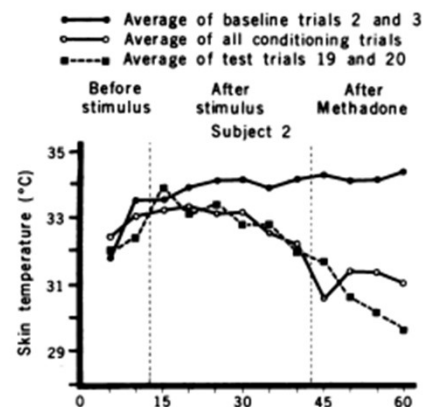
Conditioned Tolerance

One problem for Conditioned Withdrawal as a model of addictive behaviour were anecdotal reports from relapsed addicts which suggested that the cause of their relapse were cues/contexts that were most strongly associated with drug use in the past, not those associated with withdrawal

- in order for cues linked to drug use to become conditioned to the withdrawal state, these cues would have to be stored in memory for hours if not days until the withdrawal event occurred
  - long 'trace' conditioning is less effective than short 'delay' conditioning.
    - Thus, it seemed unlikely that cues associated with drug use should elicit conditioned withdrawal.
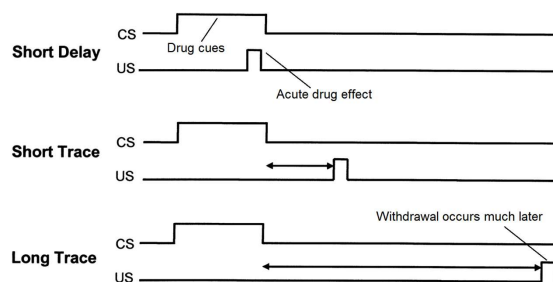

5

Conditioned Tolerance

Shepard Siegal addressed this criticism & defended the negative reinforcement account by way of the "compensatory response hypothesis" which is built on:

1. Solomon & Corbit (1974) Opponent Process Model,
2. Bernard & Cannon: homeostasis, whereby the body seeks to maintain an optimal internal state by possessing an array of detectors which detect whether the current internal state is greater or less than a 'set-point' or optimum.
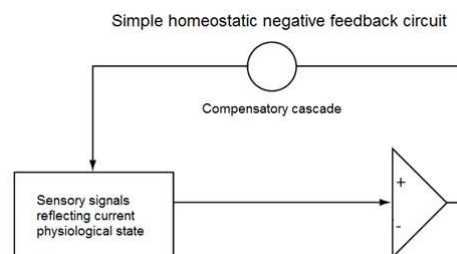

6

Conditioned Tolerance

Siegal argued that drugs of abuse shift ones biological state away from the optimum, provoking an array of compensatory responses to return to homeostasis.
- Top row: subjective (conscious) experience of the drug user upon taking the drug at initial exposure (left) or after many exposures once tolerance has taken place (right).
- After many exposures, the A state (pleasure/reward) decreases, and the B state (withdrawal) increases.


Berridge 2004; Redrawn from Solomon & Corbit 1974
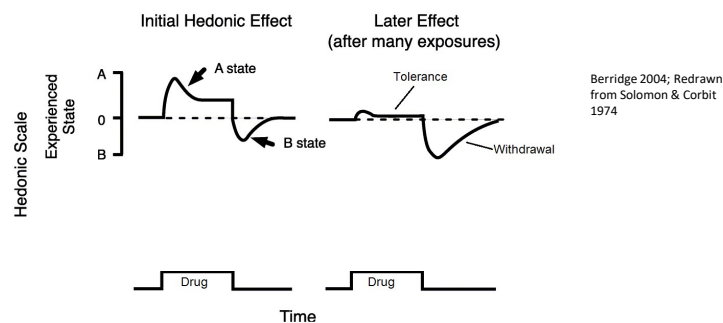
7

Conditioned Tolerance

Siegal's insight was that other compensatory responses are mobilized in response to the drug *immediately following ingestion* (bottom row).
- The "A" process is the direct drug effect on receptor binding and its downstream cascade, whereas the "B" process is the mobilized compensatory or opponent (homeostatic) processes to correct the imbalance.
    - The net product of the underlying "A" & "B" process gives rise to the experienced states "A" & "B" (top row).
   - Note, that the underlying "B" process gets larger after many exposures.

8

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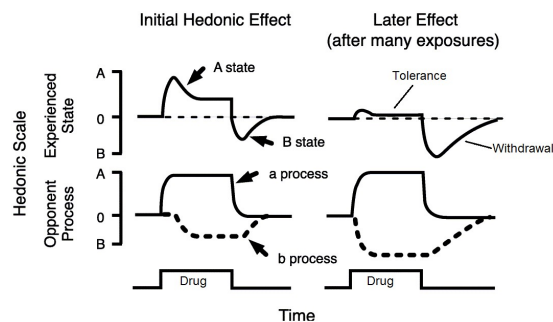
Conditioned Tolerance

Siegal's contribution suggested that the growth of the "B" process (underlying compensatory response) was due to Pavlovian conditioning of this "B" process to external cues associated with *drug use*.

- The implication is that cues associated with drug use, can elicit a drug-opposite "conditioned tolerance" effect, akin to withdrawal.
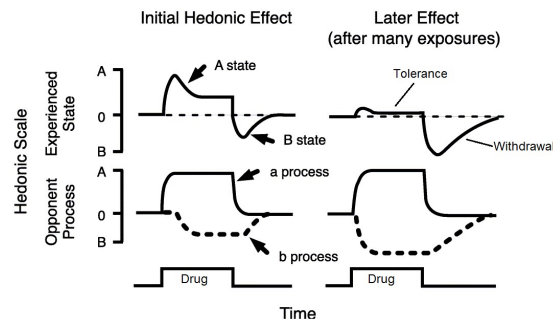
9

Conditioned Tolerance

Siegal argued that tolerance to high doses was mediated by conditioned compensatory responses elicited by drug associated cues (CS)

- administered rats with 15 doses of heroin & escalated the dose from 1 mg/kg to 8 mg/kg over this period. On the intervening day, rats were administered with saline.
  - Heroin & saline injections occurred in distinct environments (drug-context conditioning).
- Test: rats administered 15 mg/kg of heroin, in either the heroin context or the saline context
  - Rats in the heroin context were protected from overdose by a conditioned compensatory response, whereas rats in the saline context were not, resulting in a doubling of the mortality rate.
- These findings indicate that drug associated cues/contexts can elicit a drug-opposite response.

Test environment	% overdose death
Saline	64%
Heroin	32%

Siegel et al. (1982)

10

Conditioned Withdrawal & Tolerance

Theory of conditioned withdrawal was criticized because cues associated with drug use could not be easily associated with withdrawal events that occurred much later

- Siegal's demonstration that conditioned compensatory responses are mobilized immediately following drug ingestion, illustrated how cues associated with drug ingestion (CS) can elicit a drug-opposite, compensatory or withdrawal like state (CR).
  - e.g., when an addict encounters drug associated cues (CS), these cues elicit a withdrawal like (aversive) state (CR), which motivates the addict to take the drug in order to correct this state (negative reinforcement to achieve homeostasis).
- Thus, Siegal could explain drug-cue precipitated relapse within a negative reinforcement framework.

11

Summary

Knowledge & understanding of:

- diagnostic criteria used to classify substance use disorders.

- neurological mechanisms that underpin tolerance & the behavioural profile of tolerance.

- withdrawal syndromes that are caused by chronic exposure to various drugs of abuse.

- processes of & empirical evidence for conditioned withdrawal & conditioned tolerance

- how principles of associative learning contribute to the development & maintenance of drug addiction.

12