The study of the relationship between the physiological actions of drugs and their effects on behavior and psychological function

- Drugs do not create behaviors outside the normal species-typical repertoire
- They alter the probability of occurrence of behaviors
The behavioral effects of drugs are due to complex interactions amongst the pharmacological actions of drugs, the state of the organism ("set"), and the environmental circumstances surrounding drug administration ("setting").

Evaluating the behavioral effects of drugs

Primary Evaluation
Unconditioned effects on behavior

- Motor activity
  - locomotion, catalepsy, balance, strength
- Seizures
- Eating and drinking

Secondary evaluation

Tests of more specific functions
(either unconditioned or conditioned (learned))

- Analgesia
Secondary evaluation

- Learning and memory
  - several different forms

Spatial Radial Maze Task

“Win-Shift”

<table>
<thead>
<tr>
<th>Lots of spatial (room) cues</th>
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<tr>
<td>Rats/mice use these cues to avoid revisiting arms (ecologically valid)</td>
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All arms baited, must not revisit arms

- Different brain systems than non-spatial

Morris water maze test of hippocampal function

- Use spatial cues in room (posters, etc) to locate submerged platform (same place ea. time)
- Measure latency to mount platform & swim path (distance traveled to platform)
- Different brain systems than visible platform
Fear and Anxiety (Mon)

Method Used by Davis and His Colleagues to Investigate the Augmented Startle Response

Nonrecurring-Items Delayed Nonmatching-t0-Sample Test

1. The monkey receives the sample object to be held in front of the wall between the
2. A second object is presented to the monkey during the delay period.
3. The monkey is confronted with the sample object and an unfamiliar object.
4. The monkey must receive the sample object and then select the unfamiliar object to continue the trial beyond it.

Secondary Eval • Anxiety • Elevated Plus Maze

Secondary evaluation
- Learning and memory
- Anxiety
- Schedule-controlled behavior

Schedules of reinforcement
Positive reinforcement
  - Presentation increases the probability of the preceding behavior
Negative reinforcement
  - Removal increases the probability of the preceding behavior
Punishment
  - Decreases the probability of a behavior
**Ratio schedules**

Reinforcement is based in the number of responses made

- Fixed vs. variable (FR vs. VR)
  - Continuous reinforcement (FR1)

**Interval schedules**

Reinforcement is based on the amount of time that has elapsed since the last reinforcement

- Fixed vs. variable (FI vs. VI)

**DRL schedules**

(differential reinforcement of low rates)

- Version of a FI; get reinforcement after fixed time, but if respond before time is up causes "time out" and resets clock

**Schedules of reinforcement**

Operant procedures used for two primary reasons:

1) To ask questions about the stimulus properties of drugs ("what does it feel like")
2) To ask questions about the reinforcing and/or incentive properties of drugs ("will you work for it")
**Drugs as discriminative stimuli**

$S_D = \text{stimulus that signals availability of reinforcement (e.g., red vs. green light)}$

Animals learn to respond when appropriate $S_D$ is present

Drugs can serve as a $S_D$
- Animals learn to respond appropriately in presence of drug $S_D$
- $S_D$ is related to interoceptive cues of drug

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**Drugs as discriminative stimuli**

Method to ask animals about the interoceptive cues associated with different drugs

Press left lever if on morphine > get food
Right lever if given saline > get food

Give new drug - is it like morphine?
- Left lever - Yes
- Right lever - No

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**Drugs as discriminative stimuli**

Using drug discrimination techniques find that animals classify drugs just like humans

E.g., amphetamine and cocaine alike, but different than morphine, but morphine like heroin and other opiates
Measurement of drug reward

Goal is to determine abuse potential of different drugs and to study mechanisms by which drugs produce rewarding effects and dependence

- Measure effects on withdrawal symptoms
- Self-administration paradigms
- Conditional place preference

Effects on withdrawal

Steps:

- Produce physical dependence with prototypical drug (e.g., morphine)
- Withdraw and give unknown
- If block withdrawal symptoms will probably produce similar dependence syndrome
  (Not conclusive)

Self-administration paradigms

- Two Behavioral Paradigms

- Drug Self-Administration
  - The rat presses the lever to self-administer drug either into an area of the brain or into general circulation

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Self-administration paradigms

Procedures:

- Substitution procedures
- Choice procedures

Predictive validity: All drugs self-administered by animals are also self-administered by people

Drugs that maintain self-administration
amphetamines, barbiturates, cathinone, cocaine, codeine, ethanol, fentanyl, heroin, methadone, methamphetamine, MDMA, methylphenidate, morphine, nicotine, PCP, THC

Drugs that do not
aspirin, haloperidol, imipramine, lidocaine, mescaline, LSD

FR Schedules

- typical measure rate or number of responses (or infusions)
- inverted U curve

Sizemore et al. (1997)
Self-administration paradigms

FR Schedules

Descending limb?
- incapacity
- satiety
- loss of reward

Dose of Cocaine

Sizemore et al. (1997)

On ascending limb typically assume:
- increase in rate = increase in reward

On descending limb, typically assume:
- decrease in rate = increase in reward
  
  {increase in rate = decrease in reward
  (represents a compensatory response to loss of reward)}
**Self-administration paradigms**

Increase in rate = decrease in reward

Fits dopamine (DA) antagonist studies
- DA antagonists increase rate (as does decreasing dose)

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**Problem**

E.g., 6-OHDA lesion

(decreased rate interpreted as decreased reward)

Roberts et al. (1980)

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**Problem**

“How can both an increase and a decrease in rate of drug intake be used to draw the same conclusion? The dilemma is unmistakable: rate is an ambiguous measure of reinforcing efficacy” (Arnold & Roberts, 1997)
Self-administration paradigms

Problem of rate is old issue

Electrical self-stimulation

Faster rate with lower of two current intensities, but choose higher of two intensities (Hodos & Valenstein, 1962)

Self-administration paradigms

Progressive ratio schedules

Progressive increase in responses required
1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 603 ...

Self-administration paradigms

Progressive ratio schedules

Measure of motivation to take drug (how hard will will work for it), defined by “breakpoint”

Self-administration paradigms
Self-administration paradigms

“Breakpoint” (highest ratio achieved)

Comparing different drugs
DA antagonists vs. 6-OHDA

Problems: One data point, cumulative dosing, etc.
Conditioned place preference

Pavlovian context conditioning procedure
- Pair drug administration with place in environment
- Take advantage of a principle of reward
  - stimuli that are rewarding, “elicit approach responses and maintenance of contact with the stimulus”
- On test day: measure where spend time

Conditioned place preference

Two Behavioral Paradigms (continued)

Advantages
- Simple
- Limited training required
- Test in non-drug state

Disadvantages
- Not measure drug reward but rewarding properties of secondary reinforcer
Sample question

Which schedule of reinforcement is used to calculate “breakpoint”?

(a) FR10
(b) VI15
(c) DRL schedule
(d) Variable ratio
(e) Progressive ratio