Conditioned Place Preference:
Relation to Self-Administration and Predictor of Abuse Potential

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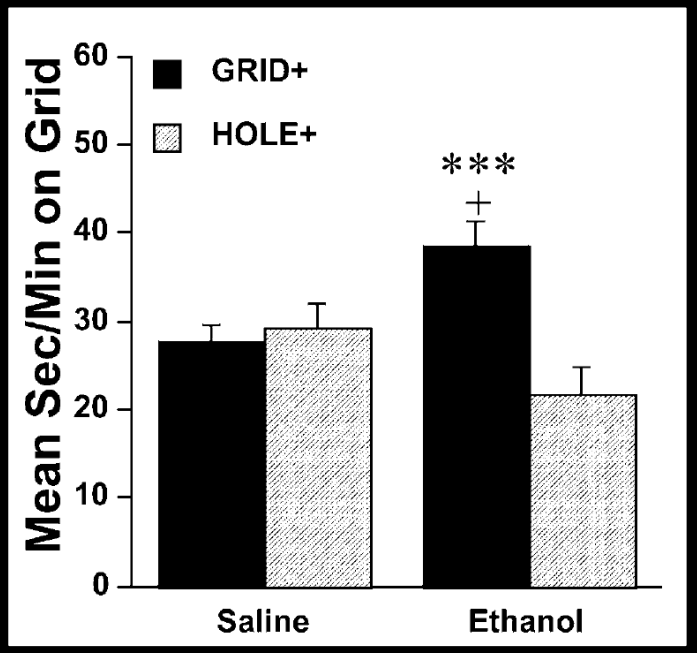
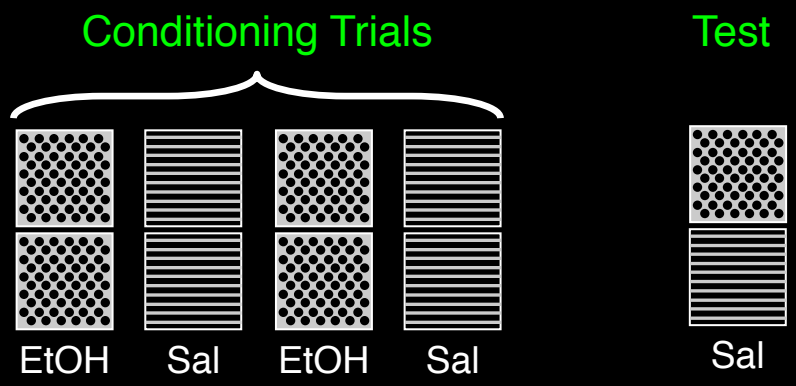
CPP: Background

- Associative learning procedure [Pavlovian]
- Research tool used to study:
  - Learning/memory/motivational processes
  - Rewarding/aversive drug effects
  - Conditioned approach/reward/reinforcement
  - Drug seeking behavior, relapse
  - Brain mechanisms, genetic influences, etc.
  - Putative relapse-reduction medications
- Shown across many species:
  - Planarians, drosophila, zebrafish, goldfish, crayfish, chickens, Japanese quail, musk shrews, hamsters, rats, mice, non-human primates, humans

Place Conditioning: Mouse





DBA/2J mice; 2 g/kg ethanol

Cunningham et al. (*Psychopharmacology*, 2003)

Self-Administration vs. CPP

Self-administration tests assess the rewarding properties of a drug. If animals actively work at a behavioral task to receive a dose of the drug, it is likely that the drug will be rewarding in humans.

Conditioned place preference is a method related to self-administration in which animals choose to spend time in one of two distinct environments, that is, the site where they previously received a drug or where they previously received placebo. Conditioned place preference is not as rigorous a behavioral test as self-administration in determining the rewarding properties of a drug.

HHS, FDA, CDER. "Guidance for Industry: Assessment of Abuse Potential of Drugs" (*DRAFT GUIDANCE, January 2010)*

Self-Administration vs. CPP

reinforcing

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These tests are only as rigorous as the scientists using them!

Self-Administration vs. CPP

Task	Training Conditions	Behavior
SA	Response → Drug	↑ Pr (Response)
CPP	Context → Drug	↑ Pr (approach & contact w/context)

Reinforcement: experimental contingency that increases the probability of a class of behaviors (Mackintosh, 1975)

Reward: appetitive reinforcer that has a "positive" effect on physiological or motivational processes or states

Do SA & CPP measure the same thing?

- Substantial overlap in drugs that produce SA and CPP
- Some discrepancies
- Some overlap in mechanisms
- Some discrepancies in mechanisms

Overlap in drugs that produce SA and CPP

Drug	CPP[a]	Self-administration[a]	Example references
Stimulants			
Amphetamine	+	+	Yokel and Wise 1976; Spyraki et al. 1982b
Methamphetamine	+	+	Pickens et al. 1967; Trazon et al. 1992
Cocaine	+	+	Nomikos and Spyraki 1988; Caine and Koob 1994
Nicotine	+	+	Corrigall and Coen 1989; Shoaib et al. 1994
Caffeine	+	+	Atkinson and Enslen 1976; Bedingfield et al. 1998
Methylphenidate	+	+	Martin-Iversen et al. 1985; Weeks and Collins 1987
Apomorphine	+	+	Baxter et al. 1974; Parker 1992
SKF 82958	+	+	Self et al. 1996; Abrahams et al. 1998
Bromocriptine	+	+	Hoffman et al. 1988; Wise et al. 1990
7-OH-DPAT	+	+	Mallet and Beninger 1994; Caine et al. 1999
Bupropion	+	+	Ortmann 1985;Tella et al. 1997
Opiates			
Morphine	+	+	Bardo et al. 1984; Glick et al. 1992
Heroin	+	+	Ettenberg et al. 1982; Hand et al. 1989
Fentanyl	+	+	Shearman et al. 1977; Mucha and Herz 1985
Methadone	+	+	Collins and Weeks 1965; Steinpreis et al. 1996
Other drugs			
Ethanol	+	+	Reid et al. 1985; Le et al. 2000
Diazepam	+	+	File 1986; Naruse and Asami 1990
Midazolam	+	+	Szostak et al. 1987; Pain et al. 1997
Δ^9-THC	+	+	Takahashi and Singer 1979; Lepore et al. 1995
Clonidine	+	+	Shearman et al. 1977; Tierney et al. 1988
Scopolamine	0	0	Glick and Cox 1975; Lynch 1991
Haloperidol	0	0	Weeks and Collins 1987; Di Scala and Sandler 1989
Fenfluramine	–	0	Baxter et al. 1973; Davies and Parker 1993
Imipramine	–	0	Weeks and Collins 1987; Papp 1989
Naloxone	–	0	Weeks and Collins 1987; Shippenberg and Bals-Kubik 1995

[a] The "+" symbol indicates a positive effect, the "0" symbol indicates no effect and the "–" symbol indicates an aversion

Bardo & Bevins (*Psychopharmacology*, 2000)

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- Substantial convergence in drugs that produce SA and CPP
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- Some overlap in mechanisms
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Drugs with different effects on SA & CPP

Drug	CPP[a]	Self-administration[a]	Example references
Pentobarbital	0	+	Collins et al. 1984; Lew and Parker 1998
Phencyclidine	0	+	Marquis et al. 1989; Aquas et al. 1990
LSD	+	0	Meehan and Schechter 1998
Buspirone	+	0	Balster 1990; Neisewander et al. 1990
Pentylenetetrazole	+	0	Gauvin et al. 1991

Bardo & Bevins (*Psychopharmacology*, 2000)

Pentobarbital	+/-	Bossert & Franklin, 2001
Phencyclidine	+/-	Kim et al., 2003; Shin et al., 2005

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Do SA & CPP measure the same thing?

- Different forms of associative learning
  - generally involve different types of behavior
- Both can be used to test the ability of novel drugs to strengthen behaviors that reflect rewarding effects
- Both have value as tools for assessing abuse liability using animals

CPP: tool for assessing abuse potential

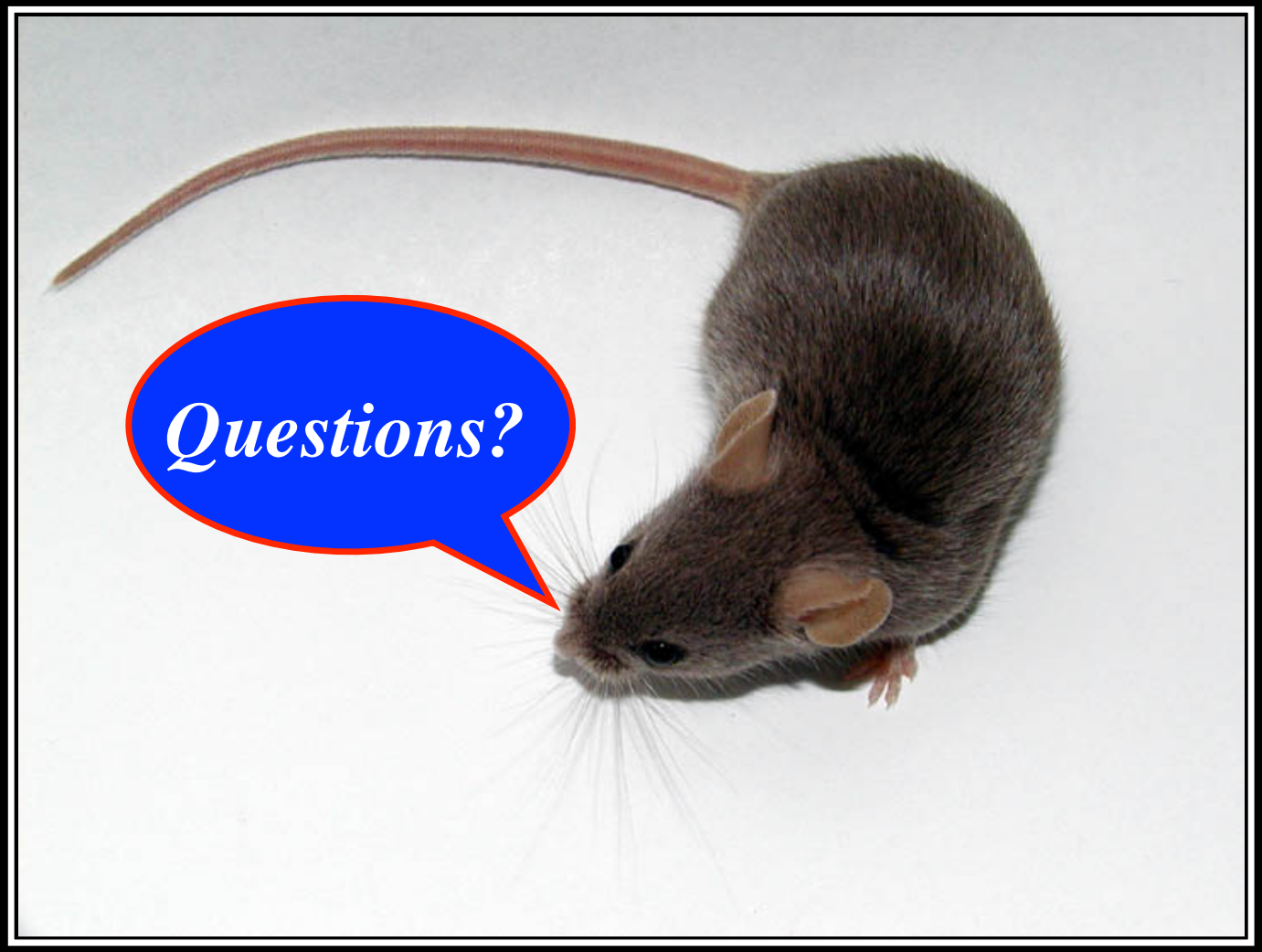
- Disadvantages:
  - Limitations on within-subject testing
    - Dose-effect testing is cumbersome
  - Might require larger n's
  - Optimal parameters can vary with drug
  - Drug is experimenter administered
    - Less face validity

CPP: tool for assessing abuse potential

- Advantages:
  - No surgery required
  - Multiple routes of administration
  - Drug is experimenter administered
    - Precise control over dose, timing
  - Detects either rewarding or aversive effects
  - Effects measured without drug present
  - Rapid acquisition (high throughput)
  - Concurrently determine locomotor effects
  - Reference Dose/Drug procedure

When might CPP be especially useful?

- Early assessment of abuse potential before investing resources in required GLP-compliant testing (SA, DD, PD)
- IV formulation is not yet available or possible
- Sensorimotor drug effects interfere with operant self-administration


Questions?