Learning mechanisms of drug dependence.

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In this talk...

- Development of drug habits.
- Impact of environmental cues.
- Cue exposure therapy.
- Extending the drug cue.
Stages in drug addiction

Use

goal-directed
drug seeking & taking

Abuse
drug seeking &
taking habits

vulnerability

abstinence/
relapse

Addiction
(dependence)

compulsive drug
seeking
Development of a drug-seeking habit?

Drug-associated stimuli come to drive drug seeking and ultimately drug use.
Caudate putamen dopamine evoked by cocaine cues

Volkow et al., 2006 Journal of Neuroscience
Stages in drug addiction

1st exposures

Use

Abuse

Addiction

Drug-associated Stimuli

Goal directed: A-O learning

Habits: S-R learning
Cocaine Self Administration in Rats

Drug-associated Stimuli

FR1
Cocaine Self Administration in Rats

Drug-associated Stimuli

FR1
Cocaine Self Administration in Rats

Drug-associated Stimuli

FR1

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Cocaine Self Administration in Rats

Drug-associated Stimuli

FR1

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Cocaine Self Administration in Rats

Drug-associated Stimuli

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Cocaine Self Administration in Rats

Drug-associated Stimuli

FR1

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FI15(FR10:S)
Assignment of Incentive Salience

Arroyo et al, 1998, *Psychopharmacology*
Assignment of Incentive Salience

Arroyo et al, 1998, *Psychopharmacology*
A Learning mechanisms involved in drug seeking and drug taking behaviour

- Pavlovian-instrumental interactions
- Pavlovian conditioning
- Instrumental learning (drug seeking & taking)

B Drug seeking under Action-Outcome control

1. [Diagram showing the process]
2. [Diagram showing the process]

C Drug seeking under habitual or Stimulus-Response control

1. [Diagram showing the process]
2. [Diagram showing the process]

Belin et al. 2009
A Learning mechanisms involved in drug seeking and drug taking behaviour

pavlovian-instrumental interactions → pavlovian conditioning

instrumental learning (drug seeking & taking)

B Drug seeking under Action-Outcome control

1. Thinking
2. Action

C Drug seeking under habitual or Stimulus-Response control

1. Action
2. Reward

Belin et al. 2009
The other dopamine pathway
Working neurological model

Belin et al. (2013) *Current Opinion in Neurobiology*
Circuitry recruitment...

- Begin on FR1

- Gradually move up to FI15(FR10:S)
Blocking DA receptors in the dorsal striatum during goal-directed and habitual cocaine *seeking*

**B** Drug seeking under Action-Outcome control

B: Drug seeking under Action-Outcome control

**C** Drug seeking under habitual or Stimulus-Response control

C: Drug seeking under habitual or Stimulus-Response control

FR1

FI15(FR10:S)
Blocking DA receptors in the dorsal striatum during goal-directed and habitual cocaine seeking

**B** Drug seeking under Action-Outcome control

**C** Drug seeking under habitual or Stimulus-Response control

FR1

<table>
<thead>
<tr>
<th>Active</th>
<th>Inactive</th>
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<tbody>
<tr>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
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<td>40</td>
<td>30</td>
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<td>30</td>
<td>40</td>
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<tr>
<td>20</td>
<td>50</td>
</tr>
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</table>

FI15(FR10:S)

<table>
<thead>
<tr>
<th>Active</th>
<th>Inactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>15</td>
</tr>
<tr>
<td>200</td>
<td>10</td>
</tr>
<tr>
<td>150</td>
<td>25</td>
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<tr>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td>0</td>
<td>40</td>
</tr>
</tbody>
</table>

Murray et al., 2012; *Neuropsychopharmacology*
Instrumental learning in addiction

differential effects of reinforcer devaluation

1. Action-Outcome: Goal-directed drug seeking and taking

Stimulus → Response → Reinforcer
deviation

2. Stimulus-Response: Habitual drug seeking and taking

Stimulus → Response → Reinforcer
deviation
Prolonged training and the development of a S-R habit: resistance to reinforcer devaluation

Adams & Dickinson 1981

N – not devalued
D - devalued
Cocaine seeking-taking chained schedule

1) seeking lever RI2s

Inside operant chamber

seek

Devaluation: Extinction of the taking link

Zapata, Minney & Shippenberg, J. Neurosci 2010
from: Olmstead, Lafond, Everitt & Dickinson 2001
Cocaine seeking is resistant to reinforcer devaluation – habitual – after a long, but not brief, cocaine taking history.

Inactivation of the dorsolateral striatum reinstates sensitivity to reinforcer devaluation – i.e. goal-directed.

Zapata, Minney & Shippenberg, J. Neurosci 2010
Conditioned Stimuli – Conditioned Reinforcers

Willuhn et al, 2012, PNAS
Conditioned Stimuli – Conditioned Reinforcers

Drug-associated stimuli come to drive drug seeking and ultimately drug use.
‘Needle Freaks’

“When you are new to injecting you start to sort of feel the hit as soon as the needle hits your skin even though it can not have possibly entered your blood stream or hit your brain, you do feel it and they call that needle buzzing. It is so strong; it is like the buzz itself before it actually hits you.”

-Male, 41 years old, amphetamine injector, 7 years injecting

Cue-exposure therapy

- Exploits association between interoceptive unconditioned/rewarding drug effects and exteroceptive stimuli that have been associated with those effects.
Cue-exposure therapy

- Exploits association between interoceptive unconditioned/rewarding drug effects and exteroceptive stimuli that have been associated with those effects.

Extinguish stimuli associated with the unconditioned/rewarding/reinforcing effects of drug
Urge to use
Extinction
Table 1. Urge changes during the treatment sessions for subjects in the cue exposure conditions

<table>
<thead>
<tr>
<th></th>
<th>Enter</th>
<th>Exit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Session 1</td>
<td>4.0 (3.0)</td>
<td>3.3 (2.3)*</td>
</tr>
<tr>
<td>Session 2</td>
<td>4.1 (3.3)</td>
<td>2.3 (2.1)**</td>
</tr>
<tr>
<td>Session 3</td>
<td>2.7 (2.5)</td>
<td>2.3 (1.7)</td>
</tr>
<tr>
<td>Session 4</td>
<td>2.3 (2.3)</td>
<td>1.7 (1.4)</td>
</tr>
<tr>
<td>Session 5</td>
<td>3.4 (3.1)</td>
<td>2.6 (1.9)</td>
</tr>
</tbody>
</table>

*p < 0.10; **p < 0.001.

Niaura et al., 1999, *Addiction*
# Extinction

Niaura et al., 1999, *Addiction*

<table>
<thead>
<tr>
<th>Treatment condition</th>
<th>Brief cognitive-behavioral</th>
<th>Cognitive-behavioral and nicotine gum</th>
<th>Cognitive-behavioral and cue exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>34.4% (11/32)</td>
<td>48.6% (17/35)</td>
<td>32.3% (10/31)</td>
</tr>
<tr>
<td>3 months</td>
<td>34.4% (11/32)</td>
<td>34.3% (12/35)</td>
<td>19.4% (6/31)</td>
</tr>
<tr>
<td>6 months</td>
<td>25.0% (8/32)</td>
<td>20.0% (7/35)</td>
<td>16.1% (5/31)</td>
</tr>
<tr>
<td>12 months</td>
<td>12.5% (4/32)</td>
<td>14.3% (5/35)</td>
<td>12.9% (4/31)</td>
</tr>
</tbody>
</table>
Cue-exposure therapy

Table 1
Treatment Effects of Controlled Trials of Cue Exposure Treatment for Alcohol, Tobacco, and Opiate Dependence as Reported by Conklin and Tiffany (2002)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Effect size</th>
<th>Magnitude</th>
<th>Treatment effect</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drummond and Glaudier (1994)</td>
<td>Alcohol</td>
<td>+0.17 to 0.30</td>
<td>Small</td>
<td>Favorable</td>
<td>Inpatient</td>
</tr>
<tr>
<td>Monti et al. (2001)</td>
<td>Alcohol</td>
<td>+0.5420</td>
<td>Medium</td>
<td>Favorable</td>
<td>Inpatient</td>
</tr>
<tr>
<td>Sitharthan et al. (1997)</td>
<td>Alcohol</td>
<td>+0.6070</td>
<td>Medium</td>
<td>Favorable</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Monti et al. (1993)</td>
<td>Alcohol</td>
<td>+0.7345</td>
<td>Large</td>
<td>Favorable</td>
<td>Inpatient</td>
</tr>
<tr>
<td>Raw and Russell (1980)</td>
<td>Tobacco</td>
<td>-0.0251</td>
<td>–</td>
<td>–</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Niaura et al. (1999)</td>
<td>Tobacco</td>
<td>-0.2029</td>
<td>Medium</td>
<td>Unfavorable</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Corty and McFall (1984)</td>
<td>Tobacco</td>
<td>-0.4500</td>
<td>Medium</td>
<td>Unfavorable</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Lowe et al. (1980)</td>
<td>Tobacco</td>
<td>-0.5180</td>
<td>Large</td>
<td>Unfavorable</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Dawe et al. (1993)</td>
<td>Heroin</td>
<td>+0.0805</td>
<td>–</td>
<td>–</td>
<td>Inpatient</td>
</tr>
</tbody>
</table>

Notes: Magnitude designations are based on Cohen (1988): small = ~0.20, medium = ~0.5, large = ~0.8. Favorable or unfavorable designations are based on the effect size valence: positive effect sizes reflect favorable CET outcomes and negative effect sizes reflect unfavorable CET outcomes. Effect sizes smaller than 0.10 were considered ambiguously close to zero and were not designated with a magnitude or as being favorable or unfavorable.
‘Threats to extinction’

- Renewal – context specific
- Reinstatement – cue/drug/stress
- Spontaneous recovery – time as context
Cue-exposure therapy

- Exploits association between interoceptive unconditioned/rewarding drug effects and exteroceptive stimuli that have been associated with those effects.
Cue-exposure therapy

- Exploits association between interoceptive unconditioned/rewarding drug effects and exteroceptive stimuli that have been associated with those effects.
Drug is more than reward or reinforcer
Drug states as stimuli
Drug states as stimuli
Drug states as stimuli
Drug states as stimuli
Drug can serve as an interoceptive CS
Pavlovian Drug Discrimination

Nicotine or Saline
Measure

36x 0x

20 min
Pavlovian Drug Discrimination

Murray & Bevins, 2007, Eur J Pharmacol
Nicotine Conditioned Stimulus
Drug can act like an exteroceptive CS

• Cue competition - Overshadowing

Train Together

Test Separately
Compound Acquisition

Murray et al., 2011, *Addict Biol*
Compound Acquisition

Murray et al., 2011, *Addict Biol*
Element Testing

Test Day 1

Test Day 2

Murray et al., 2011, Addict Biol
Cue-exposure therapy

- Exploits association between interoceptive unconditioned/rewarding drug effects and exteroceptive stimuli that have been associated with those effects.
Cue-exposure therapy

- Exploits association between interoceptive unconditioned/rewarding drug effects and exteroceptive stimuli that have been associated with those effects.
Alcohol exposure therapy


Alcohol exposure therapy

Table 2
Mean Changes (and Standard Deviations) in Outcome Measures at 6 Months Compared With Pretreatment

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>CE (n = 22)</th>
<th>CBT (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>6 Months</td>
</tr>
<tr>
<td>Drinking frequency (days per month)*</td>
<td>21.64 (7.99)</td>
<td>6.23 (8.24)</td>
</tr>
<tr>
<td>Consumption per occasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(standard drinks)*</td>
<td>8.80 (1.67)</td>
<td>3.75 (2.97)</td>
</tr>
<tr>
<td>SADQ-Cb</td>
<td>19.00 (1.38)</td>
<td>4.55 (4.33)</td>
</tr>
<tr>
<td>ICQb</td>
<td>13.00 (0.44)</td>
<td>4.14 (3.78)</td>
</tr>
<tr>
<td>CDSES</td>
<td>36.36 (10.49)</td>
<td>78.18 (15.63)</td>
</tr>
</tbody>
</table>

Note. Time effects were significant at $p < .001$ on all measures. CE = cue exposure; CBT = cognitive-behavioral therapy; SADQ-C = Severity of Alcohol Dependence Questionnaire—Form C; ICQ = Impaired Control Questionnaire; CDSES = Controlled Drinking Self-Efficacy Scale.

* For group × time interactions, $p < .05$.

Sitharthan et al., 1997, J Consult Clin Psychol
Pharmacokinetic contributions

Tonic

Pharmacokinetic contributions

Shiffman et al, 2003, *Psychopharmacology*
Extinction
In summary...

- Development of drug habits.
- Impact of environmental cues.
- Cue exposure therapy.
- Extending the drug cue.
Acknowledgements

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