Cognitive Enhancement And Drug Cue Extinction: Building Models, Building Bridges
From the animal bench

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Intravenous Drug Self-Administration

Each drug infusion is paired with a discrete visual cue

Model of drug-seeking and drug-taking behavior in humans
Phases of Addiction in Preclinical Drug Self-Administration Studies

- Acquisition Phase
- Maintenance Phase
- Extinction Phase
- Reinstatement Phase

* Emphasis of efforts directed toward medication development
Cues Associated with Drug Use Cause Relapse to Drug-Seeking Behavior

Cues retain saliency if their association with drug is not extinguished explicitly.

Kalivas et al 2006
## Response vs. Cue Extinction

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Drug-Cue Association</th>
<th>Clinical Analog</th>
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</thead>
<tbody>
<tr>
<td>Response Extinction</td>
<td>No drug, No cues</td>
<td>Intact</td>
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<tr>
<td>Cue Extinction</td>
<td>No drug, Cues present</td>
<td>Weakened</td>
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<tr>
<td>Study</td>
<td>Drug</td>
<td>Follow-up</td>
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<tr>
<td>Conklin &amp; Tiffany (2002)</td>
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<td><strong>Meta-Analysis of Cue-Exposure Treatment Studies</strong></td>
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<tr>
<td>Childress et al. (1987)</td>
<td>Opiates/Cocaine</td>
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<tr>
<td>Dawe et al. (1993)</td>
<td>Opiates</td>
<td>6 weeks, 6 months</td>
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<tr>
<td>Drummond &amp; Glaubier (1994)</td>
<td>Alcohol</td>
<td>1, 3, 6 months</td>
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<tr>
<td>Franken et al. (1999)</td>
<td>Opiates</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Götestam &amp; Melin (1983)</td>
<td>Nicotine</td>
<td>1 month</td>
</tr>
<tr>
<td>Kasvikis et al. (1991)</td>
<td>Opiates</td>
<td>1, 3, 6 months</td>
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<tr>
<td>Lowe et al. (1980)</td>
<td>Nicotine</td>
<td>48 h, 3, 6 months</td>
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<td>McLellan et al. (1986)</td>
<td>Opiates</td>
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<tr>
<td>Monti et al. (1993)</td>
<td>Alcohol</td>
<td>0–3, 3–6 months</td>
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<tr>
<td>Niaura et al. (1999)</td>
<td>Nicotine</td>
<td>1, 3, 6, 12 months</td>
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<tr>
<td>O'Brien et al. (1979)</td>
<td>Cocaine</td>
<td>—</td>
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<tr>
<td>Powell et al. (1993)</td>
<td>Opiates</td>
<td>6 months</td>
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<tr>
<td>Rankin et al. (1983)</td>
<td>Opiates</td>
<td>—</td>
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<tr>
<td>Raw &amp; Russell (1980)</td>
<td>Alcohol</td>
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<tr>
<td>Rohsenow et al. (2000)</td>
<td>Nicotine</td>
<td>3, 6, 12 months</td>
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<tr>
<td>O'Brien et al. (1990)</td>
<td>Alcohol</td>
<td>6, 12 months</td>
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<tr>
<td>Sitharphanth et al. (1997)</td>
<td>Alcohol</td>
<td>6 months</td>
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</tbody>
</table>
The overall effect size of exposure therapy targeting drug-related cues is not significant:

\[ d = 0.0868; \text{ 95\% confidence interval} = 0.11 \pm 0.28 \]

In cocaine addicts, this may be due in part to drug-induced dysfunction of memory systems critical for effective cue extinction learning and consolidation.
New approaches for increasing the efficacy of drug cue extinction learning are needed!
Part 1: Building a behavioral model in animals

cognitive-enhancing pharmacotherapy
+
cocaine-cue extinction training
Drug Targets

Glycine Site (A) and Glycine Transporter-1 (B)
DCS Facilitates Cocaine-Cue Extinction Learning

Number of Responses to Reach Extinction Criterion
< 10% of self-administration baseline responses for 30 min

Nic Dhonnchadha et al Neuropsychopharmacology 2010
DCS Attenuates Subsequent Reacquisition of Cocaine Self-Administration

Nic Dhonnchadha et al Neuropsychopharmacology 2010
DCS Has No Effect on Reacquisition if Administered without Extinction Training

Nic Dhonnchadha et al Neuropsychopharmacology 2010
Changes in the Model

to be more translational and to improve efficacy

• weekly 1hr extinction training sessions for 3wk

• use GlyT-1 inhibitor rather than partial agonist at Gly site
Org 24598 Deters Relapse for a Prolonged Period

Achat-Mendes et al, Submitted 2012
Org 24598 Has No Effect on Reacquisition if Administered without Extinction Training

Achat-Mendes et al Submitted 2012
Ro 4543338 Deters Relapse for a Prolonged Period

Nic Dhonnchadha et al Drug and Alcohol Dependence 2011
Ro 4543338 Has No Effect on Reacquisition if Administered without Extinction Training

Nic Dhonnchadha et al Drug and Alcohol Dependence 2011
Conclusions

Glycine-based cognitive enhancers:

Deter relapse by augmenting extinction consolidation

GlyT-1 inhibitors > glycine site partial agonist

Augmenting cocaine-cue extinction training with cognitive enhancers in both rats and monkeys is encouraging from a translational perspective
Other Potential Targets for Augmenting Drug Cue Extinction Learning

- mGluR5 Positive Allosteric Modulators (Gass and Olive, 2008)
- N-Acetylcysteine (Zhou and Kalivas, 2008)
- Orexin-1 Agonists (Aston-Jones et al, 2008)
- eCB Uptake Inhibitors (Bitencourt et al, 2008)
- CB1 Agonists (Pamplona et al, 2006)
- Neuropeptide Y (Gutman et al, 2008)
- α_{2A} Antagonists (Powers et al, 2009)
- Benzodiazepine Inverse Agonists (Morris and Bouton, 2007)
- α_{7} nAchR Agonists (Buccafusco and Terry, 2009)
- α_{4}β_{2} nAchR Agonists (Sarter et al, 2009)
Acknowledgements

Brid Nic Dhonnchadha, PhD – Boston University, Psychology
Brittany Lovascio – Boston University, Psychology
Neha Shrestha, MA – Boston University, Psychology

Jonathan Szalay – Boston University, Graduate Program for Neuroscience

Hengye Man, PhD – Boston University, Biology
Amy Lin – Boston University, Biology

Gary Kaplan, MD – BUSM Psychiatry and Pharmacology and VA Medical Center
Kimberly Leite-Morris, PhD - BUSM Psychiatry and Pharmacology and VA Medical Center

Roger Spealman, PhD – Harvard Medical School, Psychiatry
Cindy Achat-Mendes, PhD – Harvard Medical School, Psychiatry
Donna Platt, PhD – Harvard Medical School, Psychiatry

Support: DA024315, DA11716, DA11054, RR00168 and Boston University Center for Neuroscience
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Gary Kaplan, M.D.
Bench Research and its Clinical Translation

Michael Otto, Ph.D.
To the Human Laboratory and Beyond