AMPHETAMINE EFFECTS AND THE POSSIBLE ROLE OF SENSITIZATION IN PATHOLOGICAL GAMBLING

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Addiction is a brain disorder caused by chronic exposure to drugs (Leshner, 1997)

Pathological Gambling (PG) shares many features of drug addiction (Holden 2001; Petry, 2006; Potenza, 2006)

PG may be caused by chronic exposure to gambling

Neuroplasticity (Tamminga and Nestler, 2006) ➔ Sensitization (increased dopamine; DA) response to drug or environmental signals for reward (Robinson and Berridge, 2001)

Robust sensitization: Repeated low-dose amphetamine
Hypotheses

• Acute effects of gambling activity resemble those of a stimulant drug (amphetamine)

• Chronic effects of gambling (i.e., PG) resemble those of chronic amphetamine exposure

• Both of these effects are mediated by DA

• Correspondence closest for low doses (which do not induce supra-physiological levels of DA)
Study 1:
Slot Machine and Amphetamine (20 mg) Effects in PG and Controls: Pre-treatment with D1-D2 DA Receptor Blocker, Fluphenazine
### Mean Desire to Gamble (0-10)

<table>
<thead>
<tr>
<th>Group</th>
<th>Healthy Control</th>
<th>Pathological Gamblers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Desire to Gamble</td>
<td>0.25</td>
<td>4.41</td>
</tr>
<tr>
<td></td>
<td>0.92</td>
<td>7.68</td>
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</table>

**Diagram:**

- **Baseline**
- **Post-Slot Machine**

**Text:**

15-min Slot Machine Game Primes Desire to Gamble
Effects of DA D1-D2 Receptor Antagonist

Pre-Treatment:

Placebo

Drug
Fluphenazine (3-mg) Pre-treatment in Gamblers

Pre-Treatment: Placebo Drug
A Low Dose of Amphetamine Primes Desire to Gamble

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<tr>
<td>Mean Desire to Gamble (0-10)</td>
<td>Baseline</td>
<td>6.00</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Post-Amphetamine</td>
<td>3.90</td>
<td>0.18</td>
</tr>
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</table>

Amphetamine (20 mg)
Effects of DA D1-D2 Receptor Antagonist

Pre-Treatment: Placebo    Drug
Effects of DA D1-D2 Receptor Antagonist

Fluphenazine (3-mg) Pre-treatment in Gamblers

Pre-Treatment:

Placebo

Drug

Mean Desire to Gamble (0 - 10)

PRE

Amphetamine

POST

3.90

3.75

6.00

5.50
Primed Desire to Take Amphetamine Again

**Effects of Fluphenazine (3-mg) Pre-Treatment on Desire for Amphetamine**

- **Amphetamine (20 mg)**
  - Pathological Gamblers: 5.15
  - Healthy Control: 2.90

**Mean Desire to Take Capsule Again (0-10)**

- **Group**: Pathological Gamblers, Healthy Control
- **Pre-Treatment**: Placebo, Drug
Conclusions

• Slot machine and amphetamine both increase or “prime” desire to gamble in PGs but not controls

• Blockade of DA receptors reduces priming effects of slot machine and amphetamine on Desire to Gamble and to Take Amphetamine Again

• Effects are modest but reliable
Chronic Exposure to Gambling and Response to Amphetamine: PET Study of PGs and Controls
Baseline (Drug-Free) Striatal DA D2/D3 Receptor Binding

Striatal Dopamine D2/3 Receptor Levels at Baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline Tracer Binding to D2/D3 Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Control</td>
<td>2.515, 3.221, 2.612</td>
</tr>
<tr>
<td>Pathological Gamblers</td>
<td>2.450, 3.083, 2.663</td>
</tr>
</tbody>
</table>

Cluster Analysis
- **Associative**
- **Limbic**
- **Sensorimotor**
Post-Amphetamine Striatal DA D2/D3 Receptor Binding

Displacement of Tracer by Amphetamine (0.4 mg/kg): Dopamine Release

Mean % Change from Baseline in Tracer Binding

-0.119
-0.246
-0.181
-0.244
-0.191
-0.276

Healthy Control
Pathological Gamblers

Associative
Limbic
Sensorimotor
Post-Amphetamine Binding in Limbic Striatum (Nucleus Accumbens)

Correlation of Amphetamine-Induced Dopamine Release with PG Severity on SOGS

R Sq Linear = 0.241

South Oaks Gambling Screen Score
After Large Wins on a Slot Machine Game in Limbic Striatum (Nucleus Accumbens)

Conclusions

• No difference in baseline availability of D2/D3 DA receptors in PG vs. Controls

• Amphetamine causes significantly more DA release in associative and motor compartments of striatum in PG

• Amphetamine causes graded increase in DA release in limbic striatum as a function of PG severity

• A parallel relationship was reported for DA release in response to large rewards in a slot machine game
Study 3

Correlation or Cause?

Induction of hyper-reactivity to amphetamine in animals by chronic exposure to gambling-like schedule of reinforcement
DA neuron response to conditioned cue for reward (juice) in 3 monkeys: Effects of reward uncertainty

Discrete coding of reward probability and uncertainty by dopamine neurons Christopher D Fiorillo; Philippe N Tobler; Wolfram Schultz
Science; Mar 21, 2003; 299, 5614; pg. 1898
Probability of reward delivery (Payoff > 0 vs. Payoff = 0) over 1000s of spins on a commercial slot machine is 45.8% (Tremblay et al., 2011)

Fiorillo et al. model (50% = maximal uncertainty) has high ecological validity

Present Study (Chronic Version of Fiorillo et al):

Treatment: 15 sessions @ 45 min under different conditioned (light) schedules of sucrose delivery from 0-100% (n =8/group)

Test: Response (locomotor activation) to repeated weekly low doses of amphetamine
Post-treatment Locomotor Response - No Drug
Post-treatment Locomotor Response – 3RD Dose of Amphetamine
Study 3b: Include 75% conditioning group, placebo and low dose challenge
Test Response to Low Dose Challenge (0.5 mg) after 5 Weekly Doses (1 mg/kg)
Gambling and Amphetamine have parallel acute and chronic incentive motivational effects in PG subjects as reflected by ‘cross-priming’.

DA mediates these effects.

Effects not seen in Controls, consistent with Sensitization.

Similar effects can be induced by chronic exposure of naïve animals to gambling-like reinforcement schedules.

Chronic exposure to gambling may induce PG much like chronic exposure to amphetamine induces stimulant addiction.
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