AMPHETAMINE EFFECTS AND THE POSSIBLE ROLE OF SENSITIZATION IN PATHOLOGICAL GAMBLING

Martin Zack, PhD
Neuroscience Research Department
Centre for Addiction and Mental Health
Toronto, Ontario Canada M5S 2S1
E-mail: martin.zack@camh.ca
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
15-min Slot Machine Game Primes Desire to Gamble

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Pathological Gamblers</th>
<th>Healthy Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Desire to Gamble (0-10)</td>
<td>Baseline</td>
<td>0.25</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>Post-Slot Machine</td>
<td>7.68</td>
<td>4.41</td>
</tr>
</tbody>
</table>
Effects of DA D1-D2 Receptor Antagonist

Fluphenazine (3-mg) Pre-treatment in Controls

PRE            Slot Machine Game          POST

Placebo          Drug

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

Fluphenazine (3-mg) Pre-treatment in Gamblers

Pre-Treatment: Placebo Drug

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>Slot Machine Game</th>
<th>POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Desire to Gamble (0-10)</td>
<td>4.75</td>
<td>4.95</td>
<td>7.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.50</td>
</tr>
</tbody>
</table>

Graph showing the mean desire to gamble before (PRE) and after (POST) Fluphenazine (3-mg) pre-treatment in gamblers. The graph compares the mean desire to gamble under Placebo and Drug conditions during slot machine game.
A Low Dose of Amphetamine Primes Desire to Gamble

Amphetamine (20 mg)

Mean Desire to Gamble (0-10)

6.00
3.90
0.18
0.09

Group
Pathological Gamblers
Healthy Control

Baseline
Post-Amphetamine

Desire to Gamble
Fluphenazine (3-mg) Pre-treatment in Controls

Pre-Treatment: Placebo  Drug

Effects of DA D1-D2 Receptor Antagonist
Fluphenazine (3- mg) Pre-treatment in Gamblers

PRE                   Amphetamine                   POST

Mean Desire to Gamble (0 - 10)
7.00
6.00
5.00
4.00
3.00
5.50
3.75
3.90
6.00

Effects of DA D1-D2 Receptor Antagonist

Pre-Treatment:

Placebo  Drug
Primed Desire to Take Amphetamine Again

![Graph showing the effects of Fluphenazine (3-mg) pre-treatment on desire for amphetamine. The graph compares healthy controls and pathological gamblers after pre-treatment with placebo and drug. The y-axis represents the mean desire to take the capsule again (0-10), and the x-axis represents the groups (Healthy Control, Pathological Gamblers). The results show a higher desire for the placebo in healthy controls compared to pathological gamblers, and a lower desire in pathological gamblers after drug pre-treatment.]
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
Study 2

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

- **Healthy Control**
  - Baseline Tracer Binding to D2/D3 Receptors:
    - Baseline (Drug-Free) Striatal DA D2/D3 Receptor Binding

- **Pathological Gamblers**
  - Baseline Tracer Binding to D2/D3 Receptors:

*Note: The diagram illustrates the baseline tracer binding levels for both groups, with the Healthy Control group showing a higher average binding level compared to the Pathological Gamblers group.*
Displacement of Tracer by Amphetamine (0.4 mg/kg): Dopamine Release

Group
Pathological Gamblers
Healthy Control

Mean % Change from Baseline in Tracer Binding

Group
Healthy Control
Pathological Gamblers

Mean % Change from Baseline in Tracer Binding

0.000
0.100
0.200
0.300
0.400

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

* *

Associative Limbic Sensorimotor

Post-Amphetamine Striatal DA D2/D3 Receptor Binding
Post-Amphetamine Binding in Limbic Striatum (Nucleus Accumbens)
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
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
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

Drug-Free Baseline

Locomotor Response (Beam Breaks/90 min)

Group

0 25 50 100

1562 1021 1325 1169
Post-treatment Locomotor Response – 3\textsuperscript{rd} Dose of Amphetamine

![Graph showing Locomotor Response (Beam Breaks/90 min) post-amphetamine challenge dose #3 for different groups. The groups are labeled 0, 25, 50, and 100, with corresponding locomotor response values of 3745, 4089, 5460, and 4197, respectively.](image-url)
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
Aditi Kalia
Bindiya Chugani
Daniel Tatone
Kelly Smart
Sarah Mathewson

Dr. Isabelle Boileau
Dr. Paul J. Fletcher
Dr. Doris Payer
Dr. Robert Featherstone
Dr. Steve Kish
Dr. Daniela Lobo
Dr. Daniel Digiacomo