AMPHETAMINE EFFECTS AND THE POSSIBLE ROLE OF SENSITIZATION IN PATHOLOGICAL GAMBLING

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Background

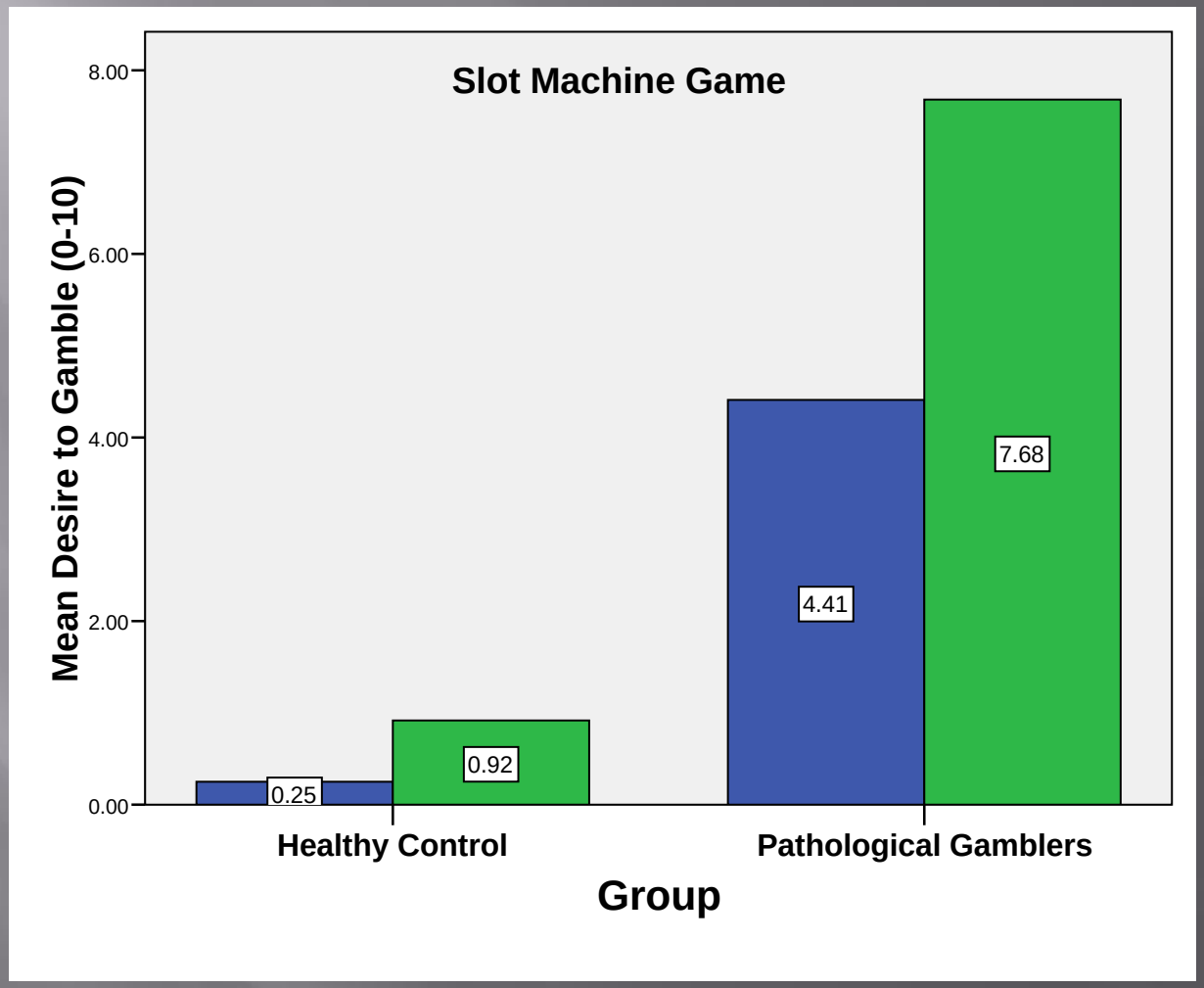
- Addiction is a brain disorder ***caused by*** chronic exposure to drugs (Leshner, 1997)
- Pathological Gambling (PG) shares many features of drug addiction (Holden 2001; Petry, 2006; Potenza, 2006)
- PG may be ***caused by*** chronic exposure to gambling
- Neuroplasticity (Tamminga and Nestler, 2006) ➔ 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

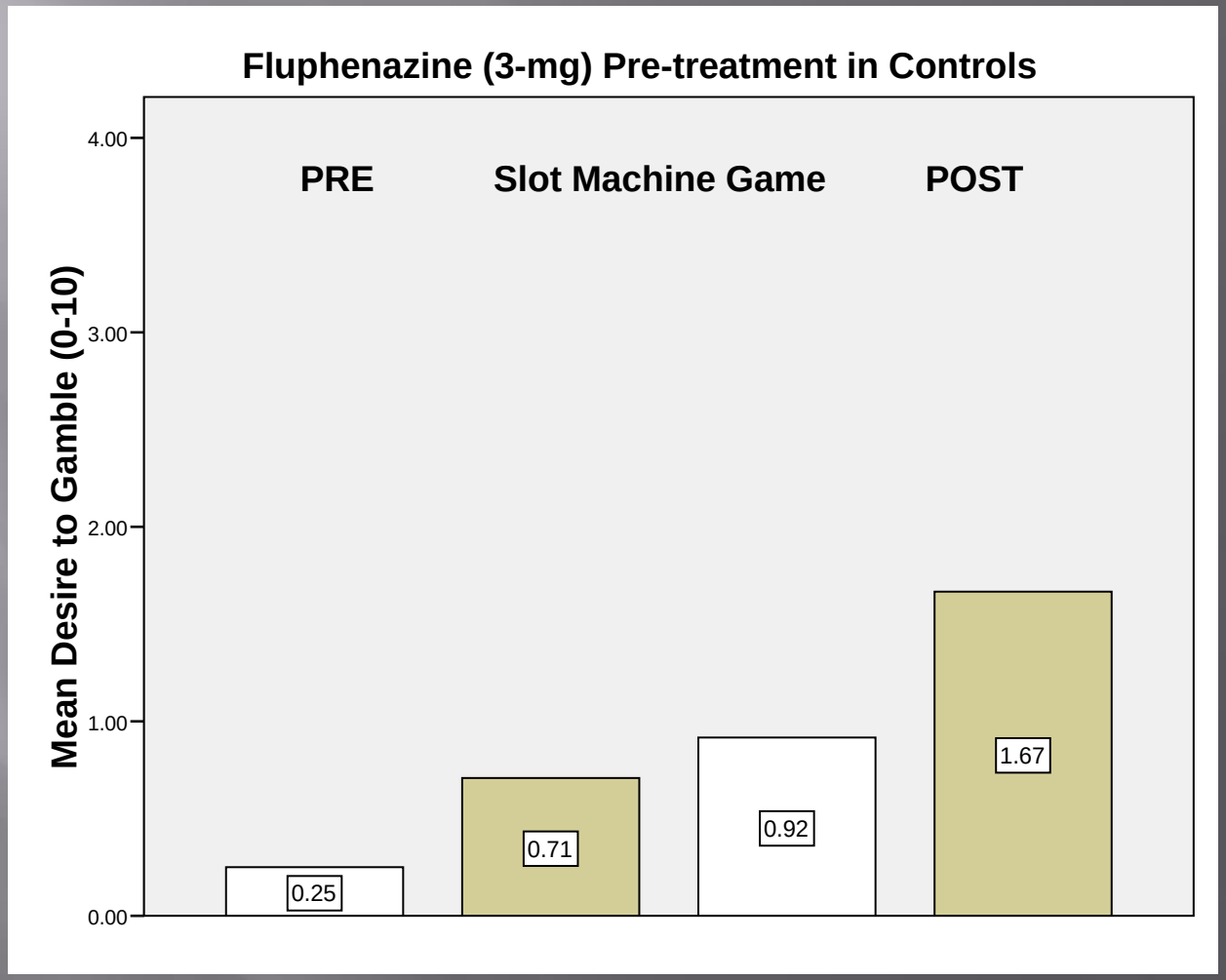
15-min Slot Machine Game Primes Desire to Gamble



Baseline

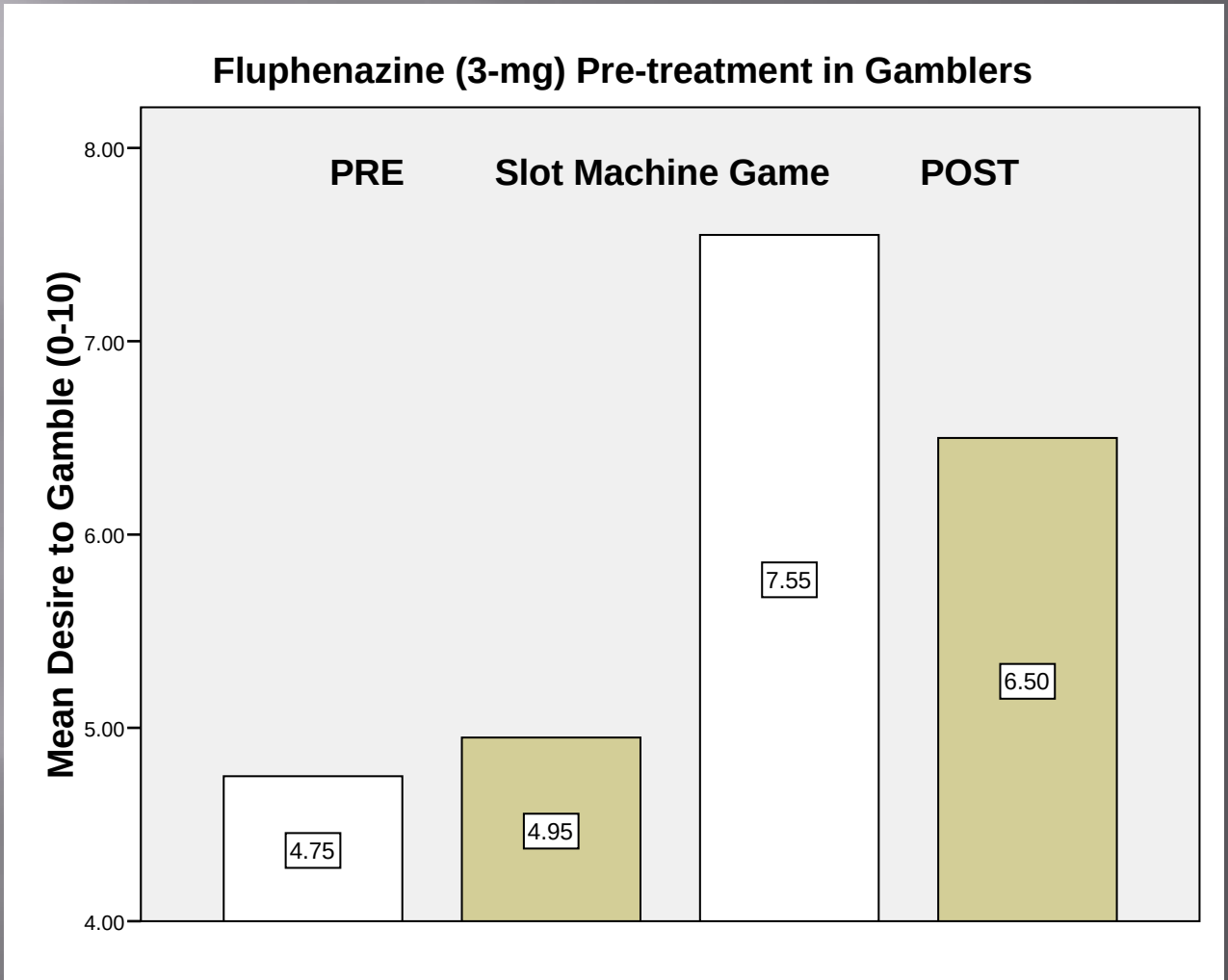
Post-Slot Machine

Effects of DA D1-D2 Receptor Antagonist



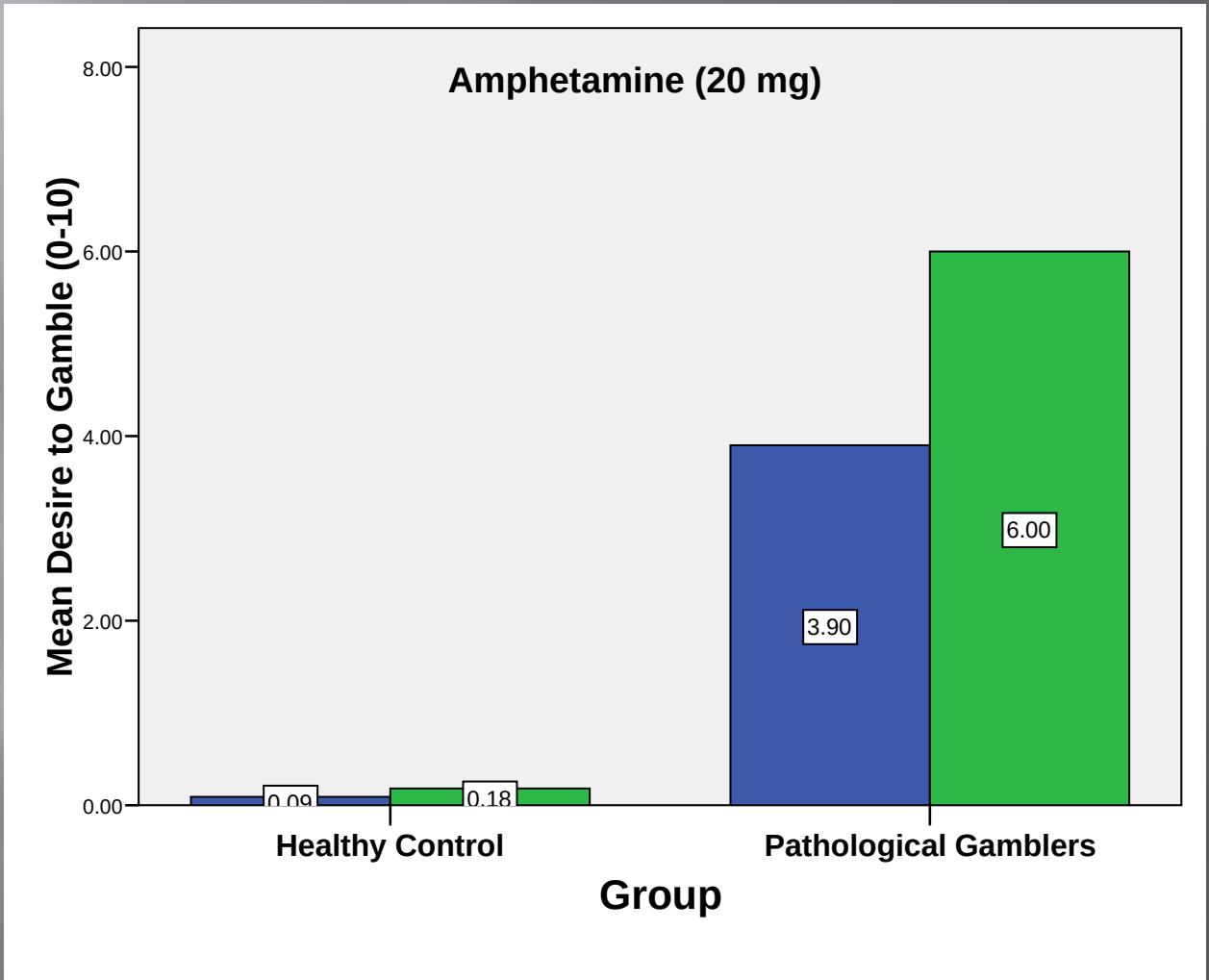
Pre-Treatment: Placebo Drug

Effects of DA D1-D2 Receptor Antagonist



Pre-Treatment: Placebo Drug

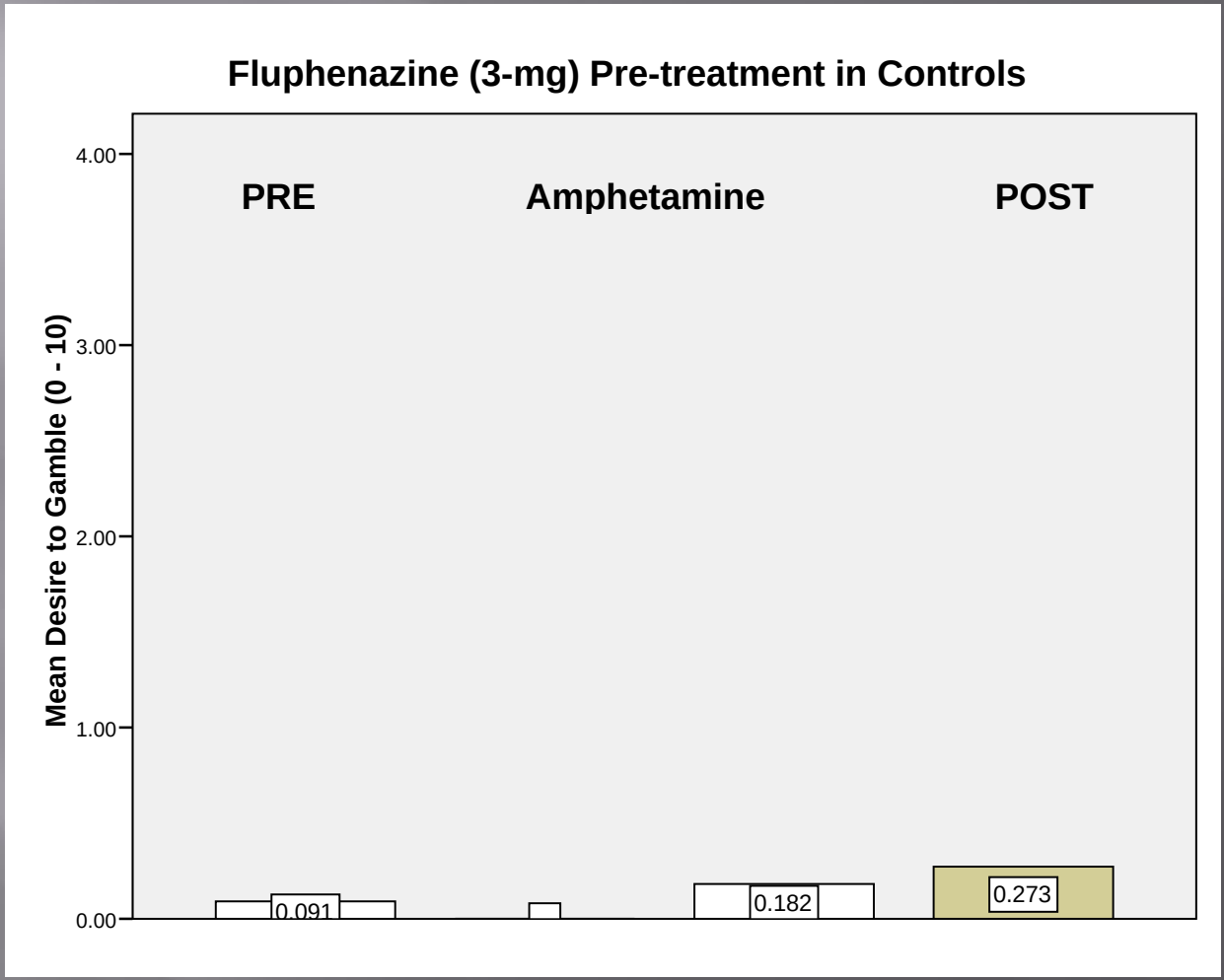
A Low Dose of Amphetamine Primes Desire to Gamble



Baseline

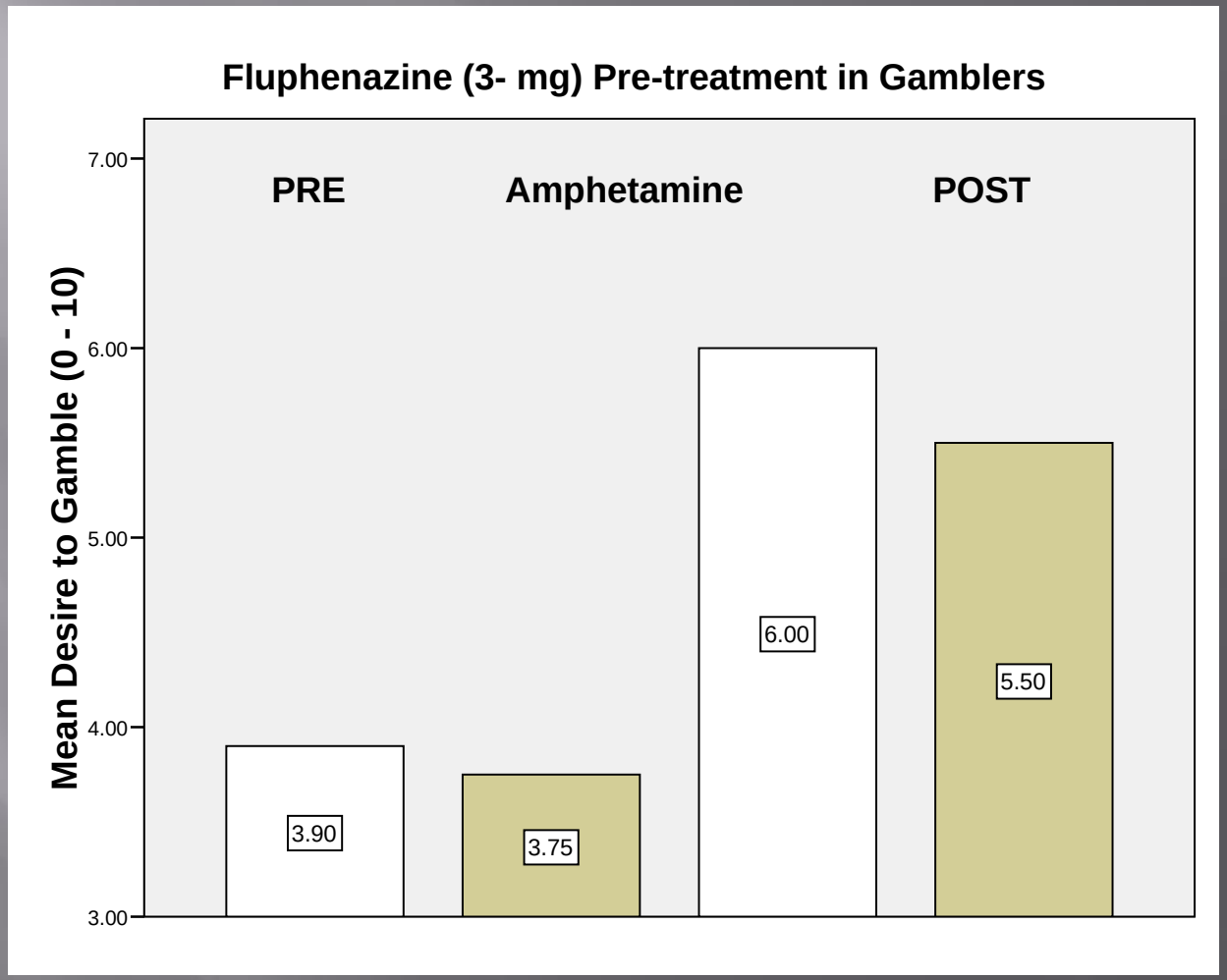
Post-Amphetamine

Effects of DA D1-D2 Receptor Antagonist



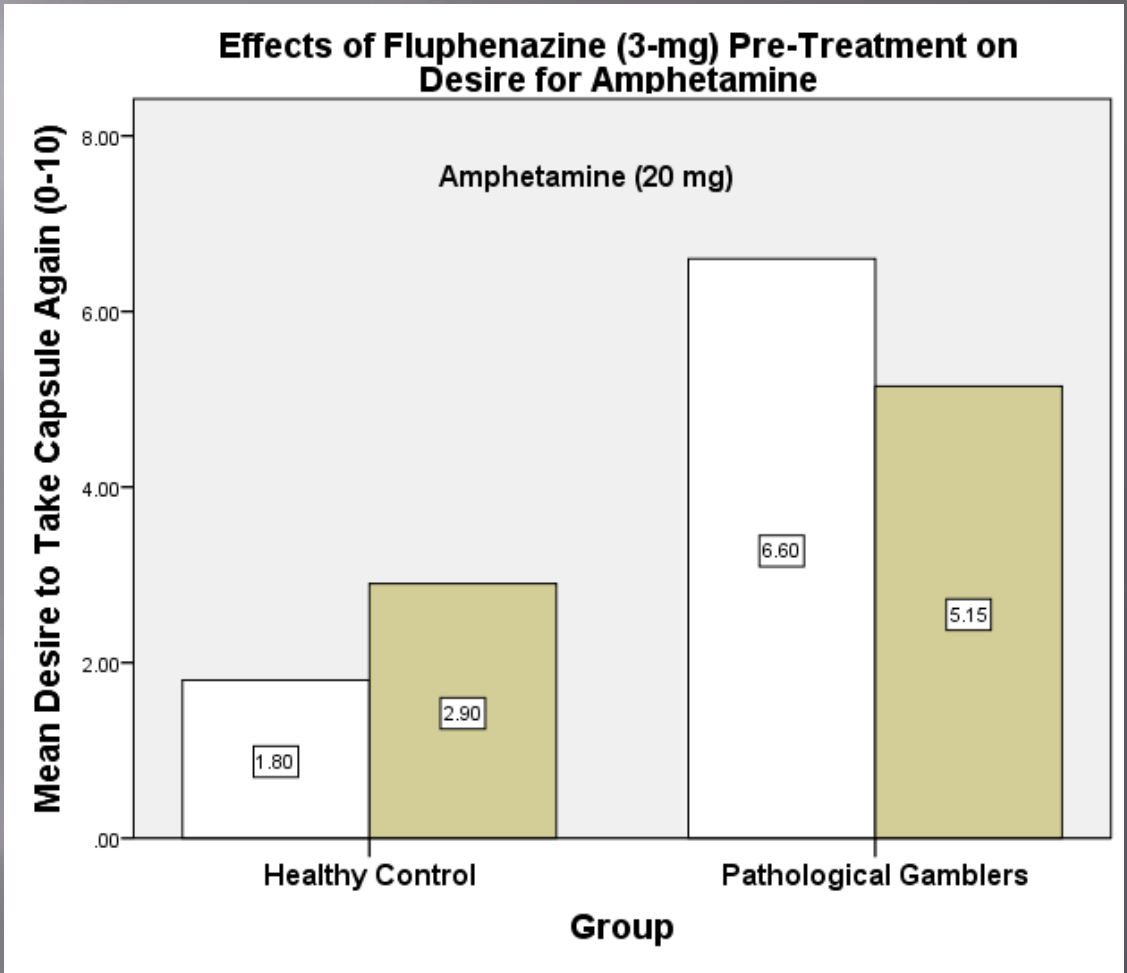
Pre-Treatment: Placebo Drug

Effects of DA D1-D2 Receptor Antagonist



Pre-Treatment: Placebo Drug

Primed Desire to Take Amphetamine Again



Pre-Treatment: Placebo Drug

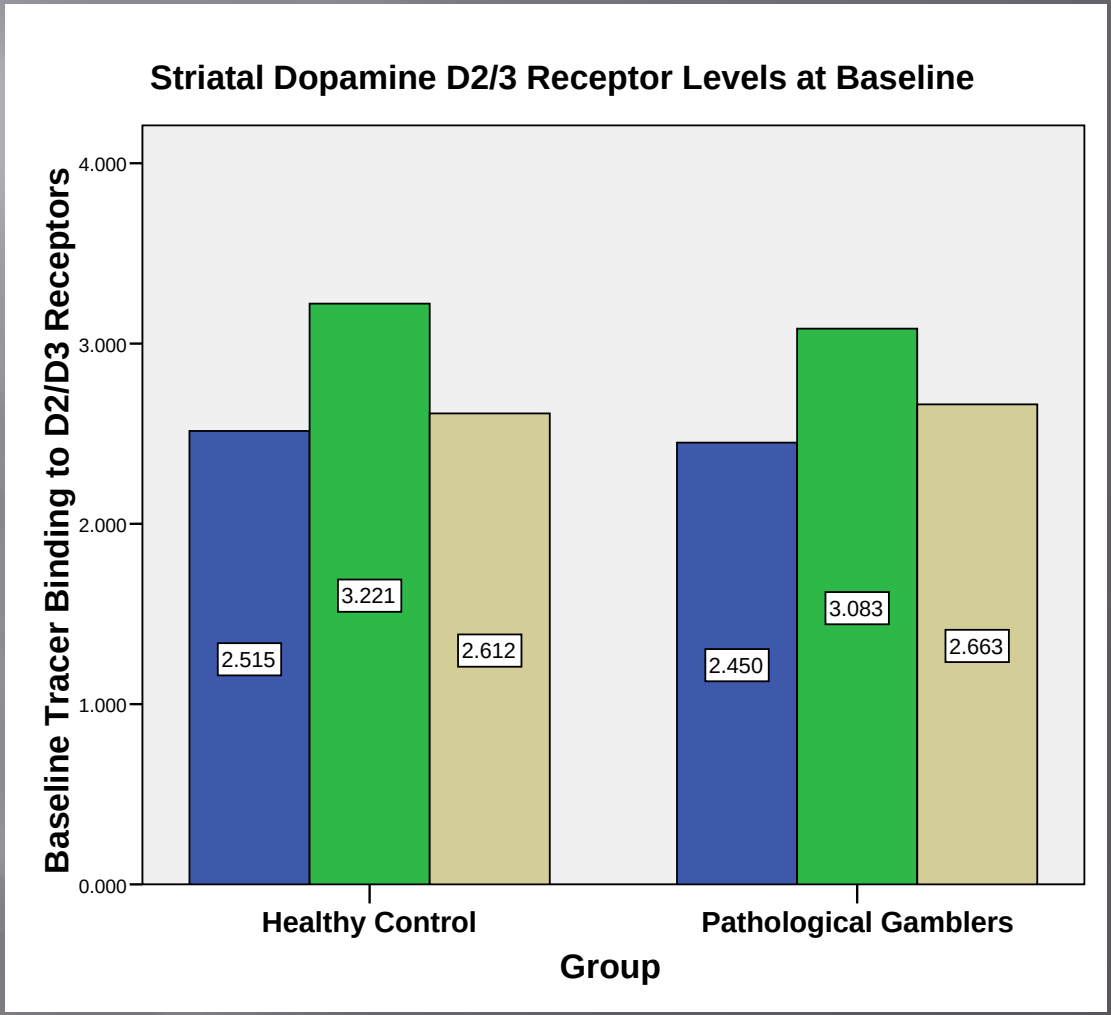
Conclusions

- 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

Study 2

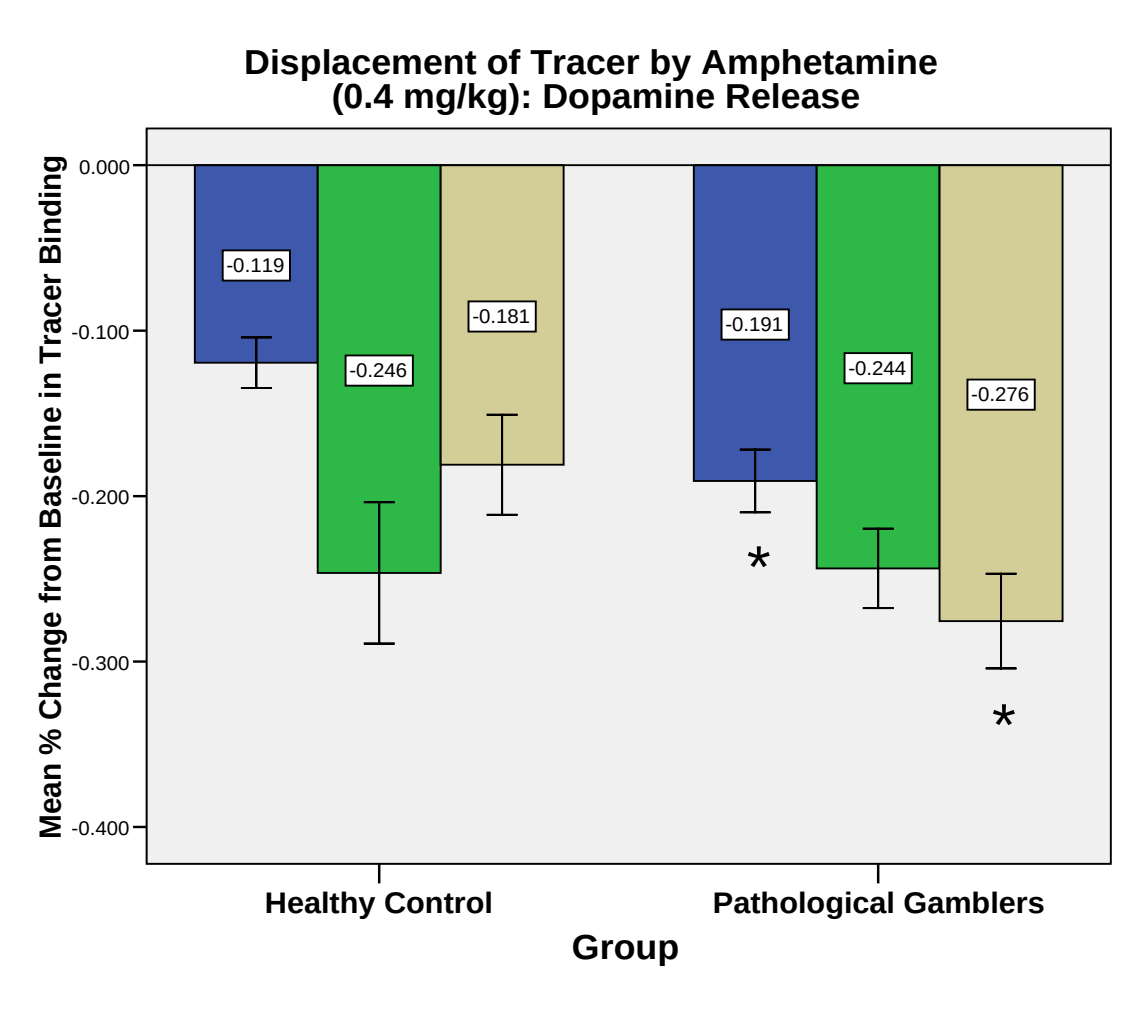
Chronic Exposure to Gambling and Response to Amphetamine:
PET Study of PGs and Controls

Baseline (Drug-Free) Striatal DA D2/D3 Receptor Binding



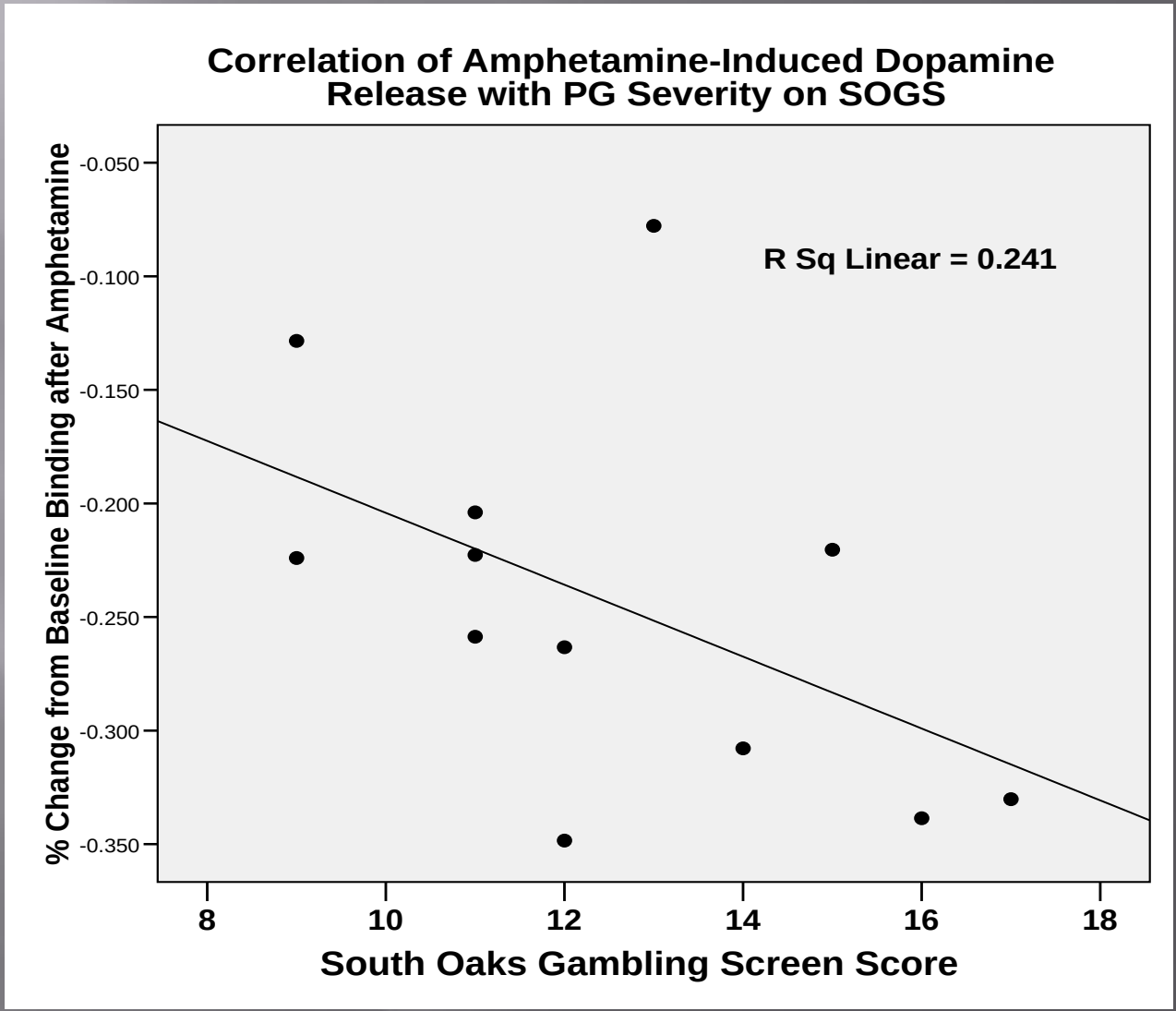
Associative Limbic Sensorimotor

Post-Amphetamine Striatal DA D2/D3 Receptor Binding

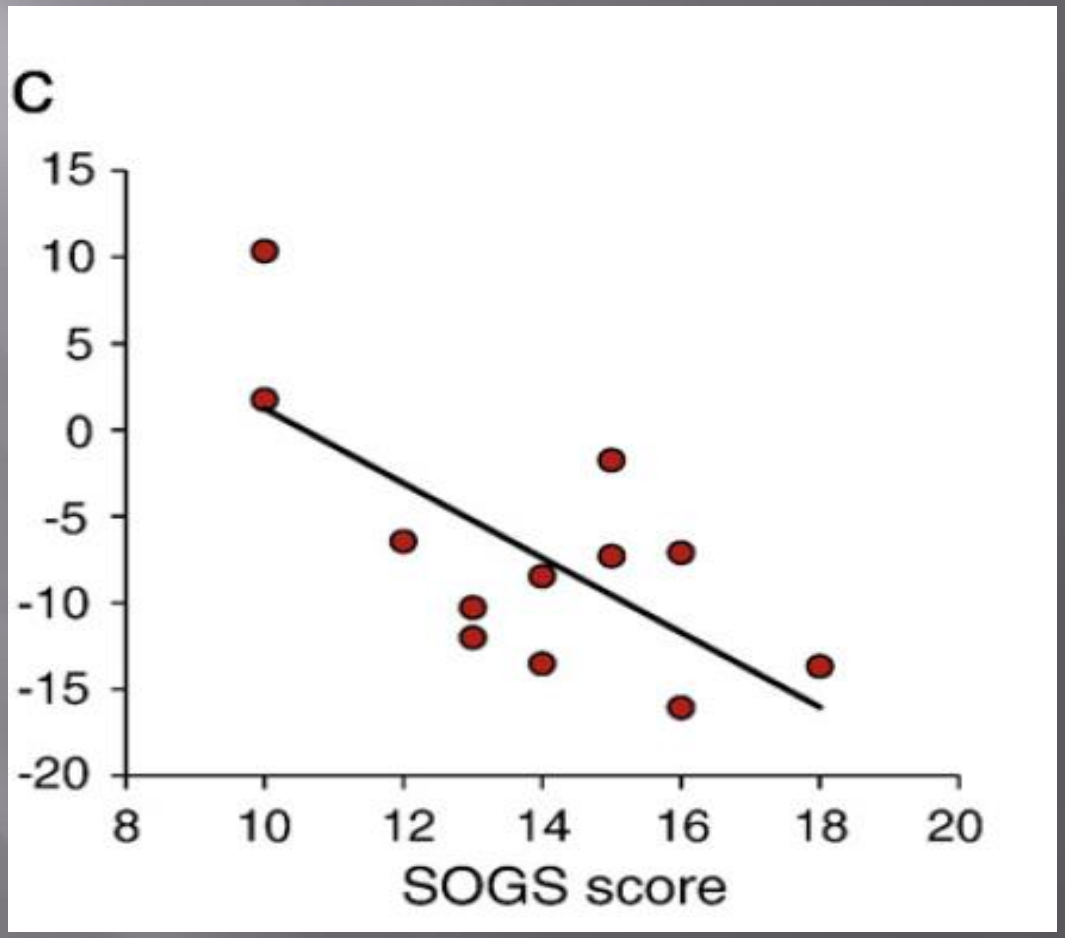


Associative Limbic Sensorimotor

Post-Amphetamine Binding in Limbic Striatum (Nucleus Accumbens)



After Large Wins on a Slot Machine Game in Limbic Striatum (Nucleus Accumbens)



Joutsa J, et al Mesolimbic dopamine release is linked to symptom severity in pathological **gambling**. ***Neuroimage.*** 2012 May 1;60(4):1992-9. doi: 10.1016/ j.neuroimage.2012.02.006.

Conclusions

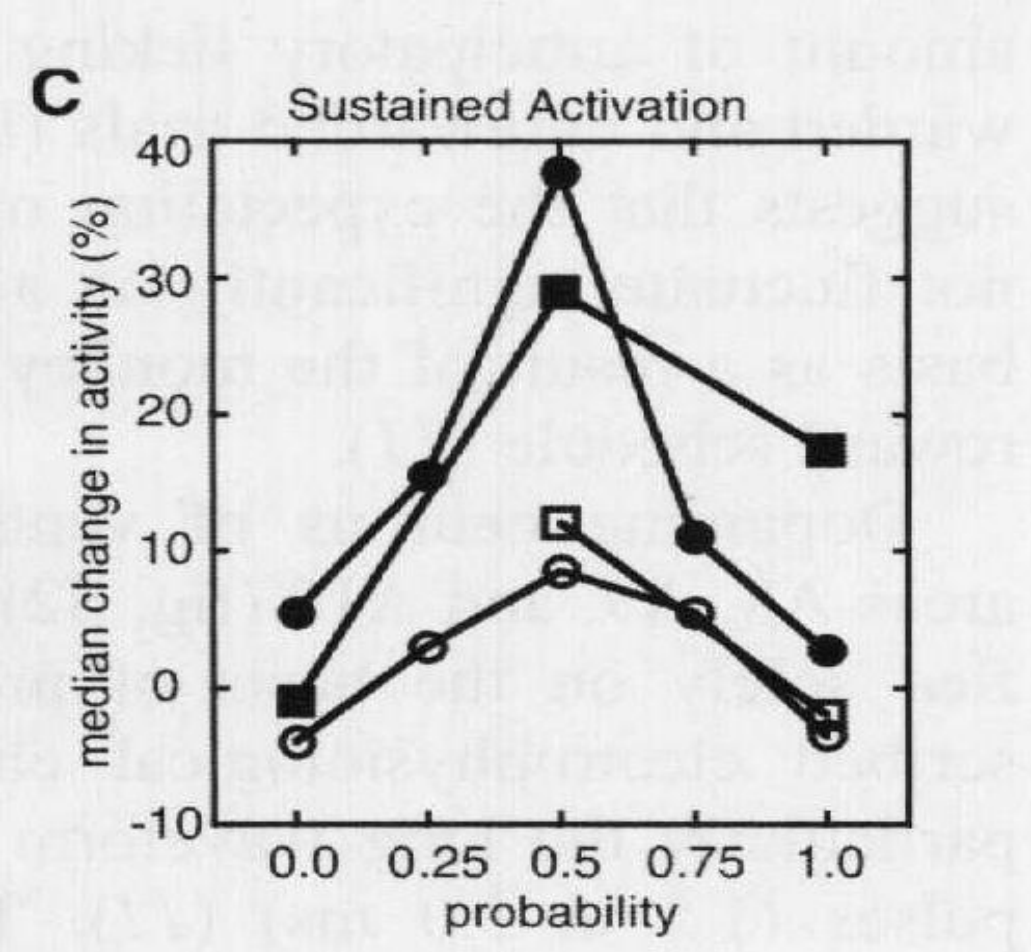
- No difference in baseline availability of D2/D3 DA receptors in PG vs. Controls
- Amphetamine causes significantly more DA release in associative and motor compartments of striatum in PG
- Amphetamine causes graded increase in DA release in limbic striatum as a function of PG severity
- A parallel 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)

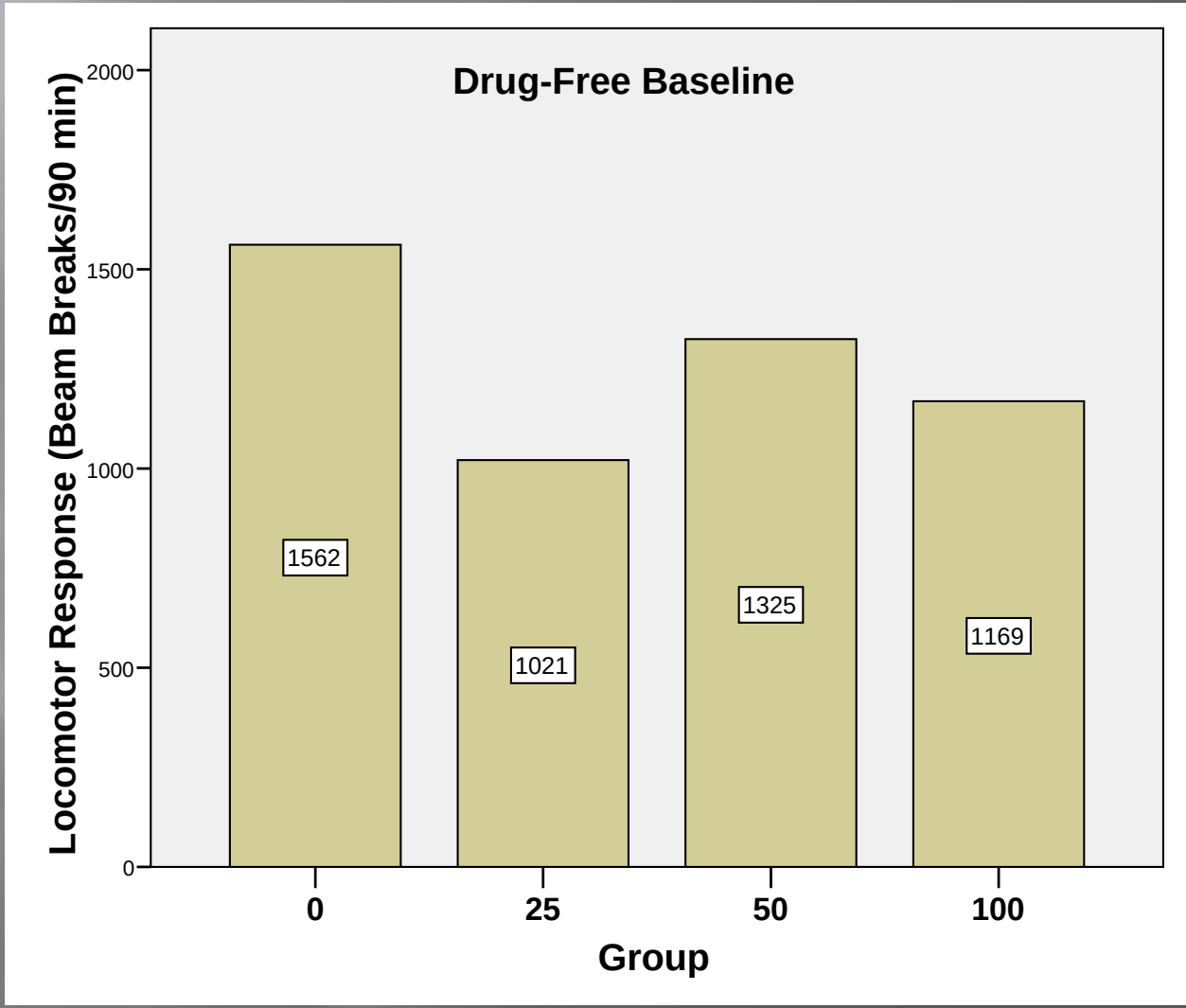
Fiorillo et al. model (50% = maximal uncertainty) has high ecological validity

Present Study (Chronic Version of Fiorillo et al):

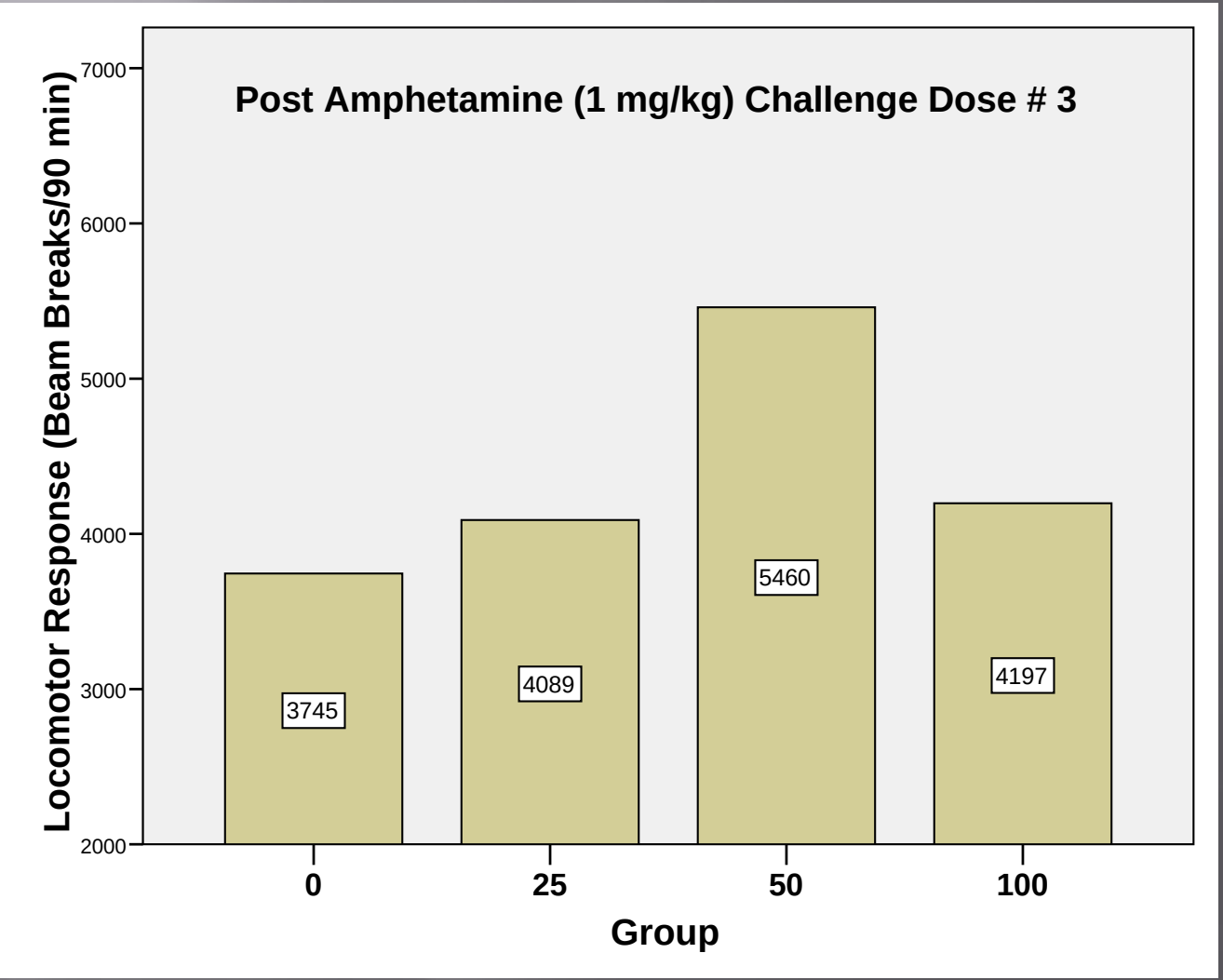
Treatment: 15 sessions @ 45 min under different conditioned (light) schedules of sucrose delivery from 0-100% (n =8/group)

Test: Response (locomotor activation) to repeated weekly low doses of amphetamine

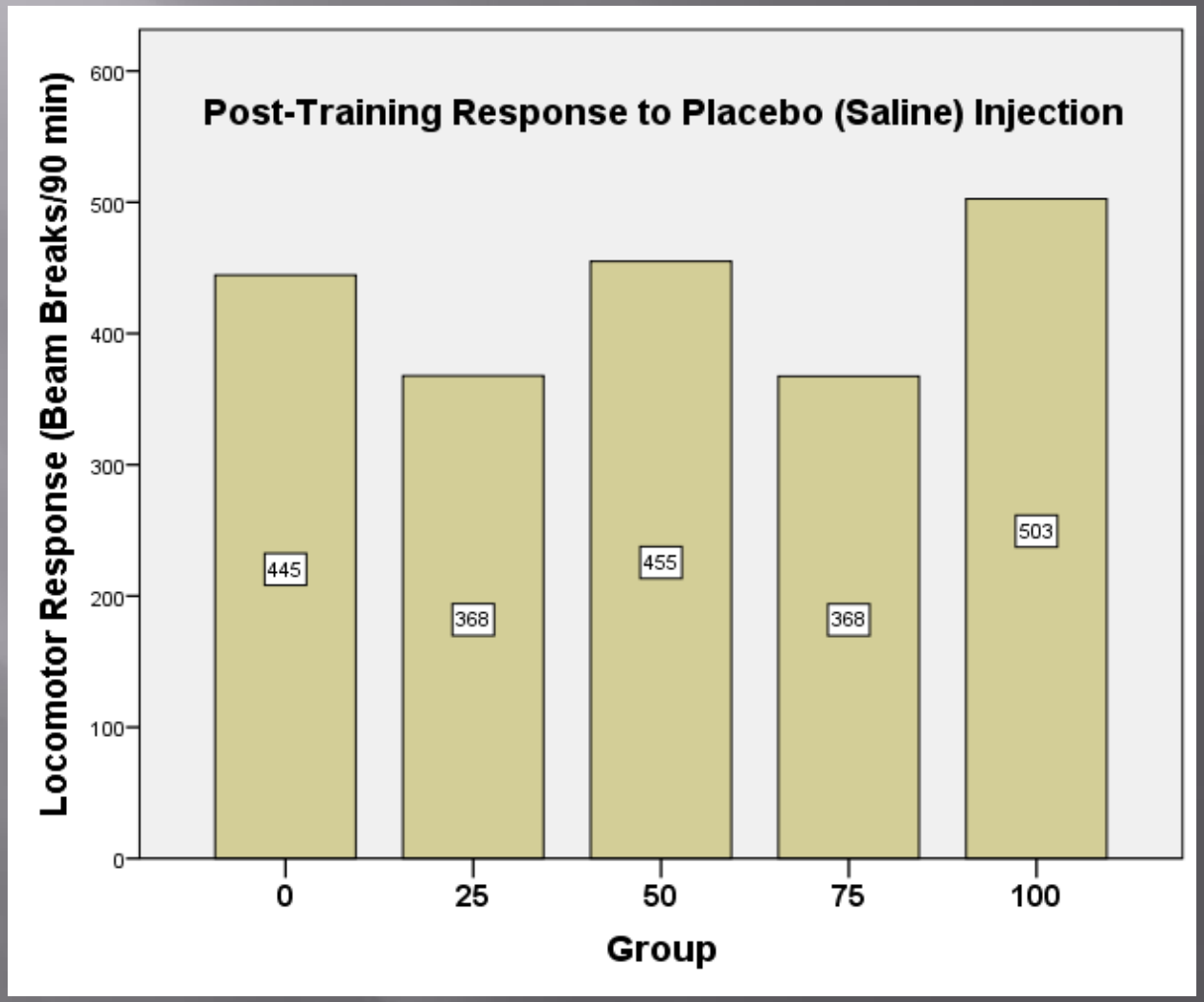
Post-treatment Locomotor Response – No Drug



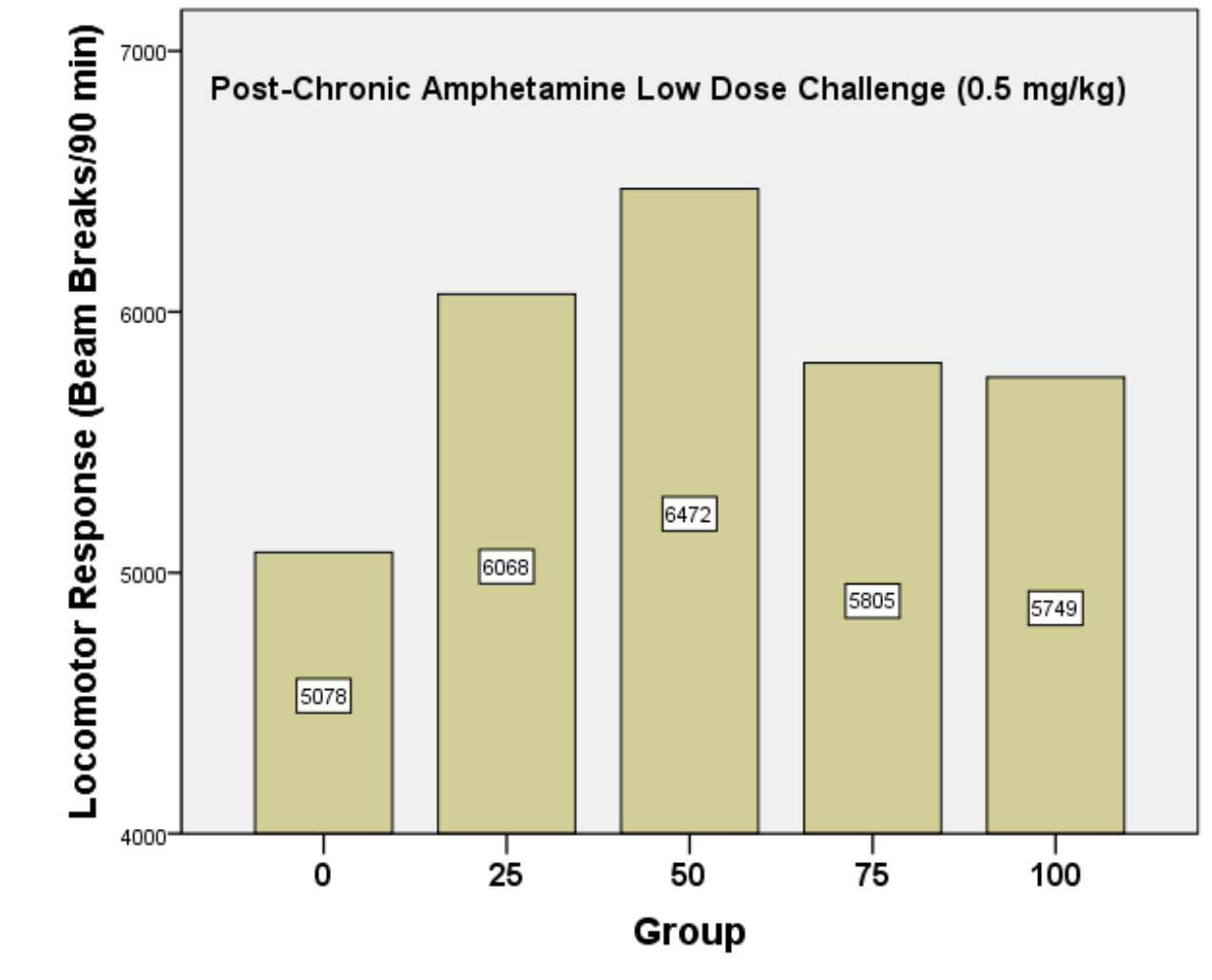
Post-treatment Locomotor Response – 3RD Dose of Amphetamine



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)



General Conclusions

- 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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