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A D2 Antagonist Enhances the Rewarding and Priming Effects of a Gambling Episode in Pathological Gamblers

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Previous research indicated shared neurochemical substrates for gambling and psychostimulant reward. This suggests that dopamine substrates may directly govern the reinforcement process in pathological gambling. To investigate this issue, the present study assessed the effects of the relatively selective dopamine D2 antagonist, haloperidol (3 mg, oral) on responses to actual gambling (15 min on a slot machine) in 20 non-comorbid pathological gamblers and 18 non-gambler controls in a placebo-controlled, double-blind, counterbalanced design. In gamblers, haloperidol significantly increased self-reported rewarding effects of gambling, post-game priming of desire to gamble, facilitation of reading speed to Gambling words, and gambling-induced elevation in blood pressure. In controls, haloperidol augmented gambling-induced elevation in blood pressure, but had no effect on other indices. The findings provide direct experimental evidence that the D2 substrate modulates gambling reinforcement in pathological gamblers.
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INTRODUCTION

Pathological gambling is a psychiatric disorder that often can incur devastating consequences (Morasco *et al*, 2006; Scherrer *et al*, 2005). Evidence on the neurochemical mediators of the rewarding or reinforcing effects of gambling activity itself has just begun to emerge. Recent fMRI research found that a gambling-like guessing game with monetary rewards activates the mesolimbic reward system in pathological gamblers and controls (Reuter *et al*, 2005). This study found that mesolimbic activation induced by the game was lower in gamblers than in controls, and the more severe the gambling pathology, the weaker the game-induced activation. The investigators interpreted their findings as consistent with a 'reward deficiency syndrome' in pathological gamblers.

Other work has found that engaging in actual casino gambling elevates activity of the hypothalamic–pituitary axis in problem and non-problem gamblers, as reflected by increased plasma levels of norepinephrine, cortisol, and a concomitant increase in heart rate (Meyer *et al*, 2004). In addition, casino gambling led to elevated dopamine levels in both groups, with higher levels emerging in the problem gamblers.

Another line of inquiry used a pharmacological cross-priming strategy to elucidate the general neurochemical mediators of gambling reinforcement (Zack and Poulos, 2004). This study found that the nonspecific dopamine agonist, *d*-amphetamine, selectively primed motivation to gamble in pathological gamblers. This finding indicates shared neurochemical substrates for gambling and psychostimulant reward. This suggests that, as in the case of psychostimulants, activation of specific dopamine substrates may directly govern the reinforcement process in pathological gambling. Evidence on this issue is critical for understanding gambling's addictive-like effects in vulnerable individuals.

A great deal of research has implicated the D2 receptor as a critical substrate modulating psychostimulant reward (Nader and Czoty, 2005; Self and Stein, 1992; Volkow *et al*, 1999, 2002). In addition, research on vulnerability to pathological gambling has emphasized the importance of the D2 receptor in genetic risk for this disorder (Comings *et al*, 1996). This is in line with other research indicating a strong link between anomalies in genes that code for the D2 receptor and risk for a variety of addictive–compulsive disorders (Blum *et al*, 1995, 1996).

Neuroimaging studies have consistently found deficits in D2 receptor binding (ie low availability) in individuals who manifest addictive–compulsive disorders, including cocaine and methamphetamine abuse (Volkow *et al*, 1990, 2001),

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heroin addiction (Wang *et al*, 1997), alcoholism (Volkow *et al*, 1996), and obesity (Wang *et al*, 2001). This pattern of results has fostered the hypothesis that compulsive seeking of addictive reinforcers may represent a compensatory response to genetically mediated or drug-induced deficits in D2 receptor function (eg Grace, 2000; Noble, 2000; Volkow *et al*, 2004).

In line with this, alcoholics with lower levels of striatal D2 receptors report greater craving and display greater cue-induced activation of the medial prefrontal cortex and anterior cingulate—brain regions involved in motivation and attention (Heinz *et al*, 2004). In cocaine addicts, PET research shows that exposure to cocaine cues increases endogenous dopamine activity at D2 receptors in the dorsal striatum and the magnitude of this effect predicts craving (Volkow *et al*, 2006). These findings suggest that individuals with low levels of striatal D2 receptors are more susceptible to cue-induced addictive motivation and that acute elevations in dopamine transmission at these receptors may directly mediate this process.

In light of this evidence on the importance of the D2 receptor in problem gambling and other addictive disorders, the present study examined the effects of the relatively selective D2 antagonist, haloperidol on responses to a brief episode of slot machine gambling in pathological gamblers and healthy controls.

MATERIALS AND METHODS

Subject Characteristics

Twenty (three female) nontreatment seeking pathological gamblers, with no comorbidity on screening tests, and 18 (four female) healthy controls, were recruited by newspaper advertisements and paid for participation. Gamblers were explicitly advised that the study was not intended to treat their gambling problems. All subjects underwent a physician's exam before testing. Sample age was 21–64 ($M = 38.9$, $SD = 11.7$) years. There were no group differences on any demographic variables. Neither group showed clinically relevant elevations in anxiety, depression; alcohol use or drug abuse. Mean (SD) drinks/week were 2.8 (2.4) for gamblers and 1.6 (1.9) for controls. Mean (SD) scores on the Beck Depression Inventory-short form (Beck and Beck, 1972) were 3.6 (3.1) for gamblers, and 1.1 (1.9) for controls.

All gamblers scored $\geqslant 5$ ($M = 11.0$, $SD = 4.4$) for DSM-IV Pathological Gambling (Beaudoin and Cox, 1999). Their gambling expenses were substantial. Mean (SD) weekly expenditure on gambling was $279 (266), corresponding to 20.3% (12.4) of their income, with an average maximum loss on a single occasion of $7563 (22 179). Controls all scored 0 on the DSM-IV, spent $1.0 (1.3) per week on gambling, and reported an average maximum loss on a single occasion of $7.1 (8.4). Thus, controls were essentially non-gamblers. Among gamblers, regular gambling activities were: casino games (15/20), slots (12/20), sports (8/20), horseracing (6/20), lottery (4/20), and bingo (1/20).

Scales and Apparatus

Visual analog scales (VAS; 0–10; Not At All—Extreme) measured perceived Good Effects and Bad Effects of the capsule. The Addiction Research Center Inventory (ARCI; Haertzen, 1965) provided a complementary standardized measure of drug effects, and the short form of the Profile of Mood States (POMS; Shacham, 1983) measured a range of subjective states.

VAS also measured the pleasurable effects (Enjoyment, Excitement, Involvement) of the slot machine game, as well as Desire to Gamble.

A rapid reading task (Lexical Salience Task) measured reading reaction time (in ms) to degraded Gambling words (eg w*a*g*e*r) *vs* Neutral words (eg w*i*n*d*o*w). The task and stimuli are identical to those detailed in a previous study (Zack and Poulos, 2004). Salience is operationally defined as the difference in reading latency to Gambling *vs* Neutral words.

A commercial slot machine currently used in Ontario casinos ('Cash Crop'; WMS Gaming Inc., Chicago, IL) served as the motivational prime. Subjects could wager 1–45 credits/spin, and were told that they would receive a monetary bonus proportional to their final credit tally from each session.

Blood pressure was assessed with an automated wrist cuff (HEM-601 Omron Inc, Vernon Hills, IL).

Selection of Haloperidol as Dopamine D2 Probe

Haloperidol (3 mg, oral) induces 60–70% D2 receptor occupancy and reaches peak blood levels at 2.75 h post-administration (Nordstrom *et al*, 1992). Of the dopamine antagonists available for human use in Canada, haloperidol (particularly at the subclinical dose employed in this study) is the most selective for the D2 receptor. *In vitro* data from rats and cloned human cells (Arndt and Skarsfeldt, 1998; Schotte *et al*, 1996) show that haloperidol's affinity for D2 is 15 times greater than for D3, the dopamine receptor for which it has the next greatest affinity; 9–13 times greater than for the α-1 adrenoreceptor; and 18–34 times greater than for the serotonin 2A receptor; with no appreciable affinity for other transmitter binding sites. Studies of post-mortem human brain (Richelson and Souder, 2000) indicate modest affinity for the α-1 adrenoreceptor ($\sim 15\%$ of affinity for D2). A notable exception to this preferential binding profile is the sigma receptor, to which haloperidol binds with roughly equal affinity as for the D2 receptor (Schotte *et al*, 1996). This may contribute to its ability to quell hallucinations (cf. Keats and Telford, 1964).

Procedure

The study was carried out in accord with the ethical standards of the Helsinki Declaration (1975). After providing informed consent, subjects attended two test sessions, 1 week apart (to ensure washout), where they received 3 mg oral haloperidol or placebo in a double-blind, counterbalanced design.

On each test session, 2.75 h after dosing, subjects played a slot machine with $200 in credits in a mock-bar laboratory. They gambled for 15 min or until their credits were exhausted.

ARCI and POMS were administered at pre-capsule, and again immediately before the slot machine game at expected peak blood drug levels. Desire to Gamble was rated at these

two times as well as right after the slot machine game. Pleasurable effects were measured after the slot machine game followed immediately by the Lexical Salience Task. Blood pressure was measured at 30-min intervals throughout the session.

To minimize possible residual priming effects of the slot machine, subjects remained at the laboratory for 4 h after testing was completed. They were assessed by a registered nurse before dismissal and sent home by prepaid taxi. Upon dismissal, subjects received a sealed 50-mg dose of diphenhydramine (Benadryl) to use in the event of a delayed dystonic reaction.

Data Analytic Approach

Mean effects were assessed with 2 (Treatment: Drug, Placebo) $\times 2$ (Group: gamblers, controls) analyses of variance (ANOVA). Where appropriate, within-subjects' variables were included in the ANOVA (eg word condition in the Lexical Salience Task). For variables where pre-capsule baseline scores were available (VAS ratings of Desire to Gamble), analyses of covariance (ANCOVA) were conducted, using the baseline score as the co-variate, to control extra-experimental variance and isolate Treatment effects (Wainer, 1991).

RESULTS

Effects of Capsule

To assess the effectiveness of the blind, at the end of the study subjects were asked to report which day they believed they received the drug. A 2 (Treatment Sequence: Drug on Session 1, Drug on Session 2) $\times 3$ (Response Option: Believe Day 1, Believe Day 2, Don't Know) χ^2 of responses in the full sample was nonsignificant, χ^2 $(df = 2,\ N = 20) = 2.61,\ p > 0.27$. Overall, 33/38 subjects answered 'Don't Know;' two correctly and one incorrectly reported Session 1; and two incorrectly reported Session 2. The pattern did not differ in gamblers *vs* controls, $\chi^2 < 2.3$, p's > 0.32, with one correct report in gamblers, and one in controls. Thus, subjects could not discriminate drug from placebo, so that any differences in response to the slot machine were not owing to the presumed effects of being under the influence of a drug on gambling reinforcement.

Table 1 shows the mean (SD) self-reported effects of the capsule on the ARCI, POMS, and VAS at 2.75 h after dosing (peak drug levels for haloperidol) along with pre-capsule scores for each treatment in gamblers and controls.

ARCI. A 2 (Group) $\times 2$ (Treatment) $\times 2$ (Time) $\times 7$ (Subscale) ANOVA of ARCI ratings yielded the following treatment-related effects: A significant Treatment $\times$ Time interaction, $F(1, 216) = 5.50,\ p = 0.025$, and a marginally significant Treatment $\times$ Time $\times$ Subscale interaction, $F(6, 216) = 2.06,\ p = 0.060$, with no other significant effects involving Treatment, p's > 0.50. The Treatment $\times$ Time interaction reflected a general decline in scores from pre-capsule to post-capsule under haloperidol as against a general increase in scores from pre- to post-capsule under placebo. As shown in Table 1, the marginally significant three-way interaction reflected a selective reversal in the pattern of scores on the MBG sub-scale, which tended to increase from pre- to post-capsule under placebo in gamblers only, but decreased in both groups from pre- to post-capsule under haloperidol. The direction of effects and absolute effect sizes for the various Subscales are highly consistent with previous research that tested an acute 3-mg dose of haloperidol in healthy volunteers (Enggasser and de Wit, 2001; Wachtel *et al*, 2002). A significant main effect of Group, $F(1, 36) = 5.46,\ p = 0.025$, reflected somewhat higher overall mean (SD) scores, aggregated across Subscales and Treatments, in gamblers, 3.8 (0.8), than controls, 3.2 (0.8).

POMS. A 2 (Group) $\times 2$ (Treatment) $\times 2$ (Time) $\times 6$ (Subscale) ANOVA of POMS ratings yielded no significant effects involving Treatment, p's > 0.10.

VAS. A 2 (Group) $\times 2$ (Treatment) $\times 2$ (Subscale) ANOVA of VAS scores yielded a marginally significant Treatment $\times$ Subscale interaction, $F(1, 36) = 3.44,\ p = 0.072$, with no other significant Treatment-related effects, p's > 0.56. Table 1 reveals that this result reflected a modest but consistent increase in reported Bad Effects in each group under haloperidol *vs* placebo, whereas Good Effects scores did not change appreciably owing to the drug treatment.

Effects of Slot Machine Game

Self-reported pleasurable effects of game. Figure 1 shows the mean (SEM) ratings of gambling-induced Enjoyment, Excitement, and Involvement and indicates that haloperidol increased scores on each sub-scale in gamblers, but did not appear to alter scores appreciably in controls. These observations were corroborated by the analyses. A 2 (Group) $\times 2$ (Treatment) $\times 3$ (Subscale) ANOVA yielded a significant main effect of Group, $F(1, 36) = 6.36,\ p = 0.016$, a Treatment $\times$ Group interaction, $F(1, 36) = 4.17,\ p = 0.048$, and no significant higher order effects, p's > 0.50. The Group effect reflects higher scores in gamblers than controls across Subscales and Treatments. The interaction reflects the significant increase in Subscale scores under haloperidol in gamblers but not in controls; and the lack of significant higher order effects indicates that haloperidol exerted a consistent augmenting effect across all three subscales. The mean shared variance for the three subscales was $r^2 = 0.66$, for gamblers, and $r^2 = 0.65$, for controls. Thus, a common pleasurable effect of the game accounted for about two-thirds of the variance in the sub-scale scores, whereas about one-third of the variance was unique to each sub-scale.

Self-reported motivation to gamble. Figure 2 shows mean (SEM) Desire to Gamble ratings before and after the slot machine game. The figure indicates that haloperidol on its own had no effects on pre-game Desire in either group. Desire scores rose from pre- to post-game under placebo in each group; and the degree of this game-induced increase appeared to be greater under haloperidol in gamblers but not in controls. Analyses corroborated these observations.

A preliminary 2 (Group) $\times 2$ (Treatment) ANOVA of pre-capsule Desire ratings (not shown) yielded a significant main effect of Group, $F(1, 36) = 38.39,\ p < 0.001$, and no other significant effects, p's > 0.26, reflecting a significantly

Table 1 Mean (SD) Subjective Effects of Capsule (3 mg Haloperidol; Placebo) at Peak Blood Levels (2.75 h Post-Administration) on Sub-scales of the ARCI, POMS (short-form), and Visual Analog Scales (Good/Bad Effects; 0–10) in Healthy Control Subjects ($n = 18$) and Pathological Gamblers ($n = 20$)

	Placebo		Haloperidol	
	Pre-capsule	**Post-capsule**	**Pre-capsule**	**Post-capsule**
Controls				
ARCI-AMP	3.6 (1.1)	2.8 (1.5)	3.6 (1.5)	3.0 (1.2)
ARCI-MBG	4.9 (3.0)	4.4 (2.9)	5.7 (3.2)	3.9 (3.1)
ARCI-LSD	1.8 (1.0)	2.3 (1.1)	2.1 (1.1)	2.3 (1.3)
ARCI-BG	6.2 (1.5)	5.8 (1.8)	6.7 (1.8)	5.8 (1.3)
ARCI-PCAG	3.5 (2.6)	3.8 (2.6)	3.1 (2.7)	4.0 (2.5)
ARCI-EUPH	1.2 (1.4)	1.0 (1.1)	1.7 (1.6)	0.6 (0.8)
ARCI-SED	1.1 (1.8)	1.4 (2.0)	1.0 (1.7)	1.4 (1.9)
POMS-DEP	0.3 (1.2)	0.3 (0.8)	0.2 (0.7)	0.2 (0.7)
POMS-VGR	9.3 (5.6)	8.3 (6.1)	10.7 (5.7)	9.3 (6.8)
POMS-CFS	0.8 (0.9)	0.6 (1.0)	0.4 (0.6)	0.7 (1.4)
POMS-TNS	0.9 (1.5)	0.7 (1.2)	0.9 (1.5)	0.8 (1.4)
POMS-ANG	0.3 (0.8)	0.0 (0.0)	0.2 (0.4)	0.1 (0.2)
POMS-FTG	2.7 (3.0)	2.0 (2.9)	2.2 (2.9)	1.4 (2.1)
Good effects	N/A	1.0 (2.4)	N/A	0.8 (1.4)
Bad effects	N/A	0.2 (0.5)	N/A	0.6 (1.4)
Gamblers				
ARCI-AMP	3.7 (2.5)	3.8 (2.0)	4.4 (2.0)	3.8 (1.8)
ARCI-MBG	5.1 (5.0)	6.0 (5.2)	5.5 (3.9)	4.8 (4.0)
ARCI-LSD	2.7 (1.3)	3.1 (2.2)	2.2 (1.3)	2.3 (1.8)
ARCI-BG	6.2 (2.5)	5.9 (2.4)	6.6 (1.6)	5.7 (1.9)
ARCI-PCAG	4.3 (2.8)	5.1 (3.0)	4.5 (2.5)	5.6 (2.1)
ARCI-EUPH	1.6 (2.2)	2.1 (2.4)	1.5 (1.6)	1.4 (1.7)
ARCI-SED	1.8 (1.8)	2.6 (2.4)	2.0 (1.6)	2.8 (1.6)
POMS-DEP	1.2 (2.4)	0.5 (1.3)	1.4 (3.5)	0.6 (1.4)
POMS-VGR	6.7 (4.0)	5.4 (4.7)	7.7 (3.4)	4.7 (3.4)
POMS-CFS	1.1 (1.2)	1.6 (2.7)	1.3 (1.3)	1.0 (1.7)
POMS-TNS	3.0 (3.2)	2.1 (3.1)	3.7 (3.3)	1.9 (2.6)
POMS-ANG	0.7 (1.3)	0.3 (0.9)	0.3 (0.7)	0.0 (0.0)
POMS-FTG	4.7 (4.1)	3.1 (4.1)	4.0 (4.1)	3.9 (3.2)
Good effects	N/A	1.5 (2.0)	N/A	1.4 (2.1)
Bad effects	N/A	0.2 (0.8)	N/A	0.8 (1.8)

ARCI, Addiction Research Center Inventory, Sub-scales; AMP, amphetamine; MBG, morphine-benzedrine group; LSD, hallucinogens; BG, benzedrine group; PCAG, pentobarbital-chlorpromazine group; EUPH, euphoria; SED, sedation; POMS, Profile of Mood States (short form), Sub-scales; DEP, depression; VGR, vigor; CFS, confusion; TNS, tension; ANG, anger; FTG, fatigue.

greater mean (SD) pre-capsule baseline Desire to Gamble in gamblers, 3.6 (1.8) than controls, 0.4 (1.8) on each test session. To isolate the Treatment effect (Wainer, 1991), a 2 (Group) $\times$ 2 (Treatment) $\times$ 2 (Pre-Post Game) ANCOVA of Desire to Gamble scores was conducted using pre-capsule Desire scores as the co-variate. The ANCOVA yielded a significant three-way interaction, $F(1, 35) = 4.21$, $p = 0.048$, and a marginal main effect of Group, $p = 0.056$, reflecting higher overall scores in gamblers than in controls.

Simple effects analyses found that there was no significant effect of Treatment on pre-game Desire for either gamblers or controls, p's > 0.50. Under placebo, the game increased Desire scores in gamblers, $t\ (35) = 6.31$, $p < 0.001$, and in controls, $t(35) = 3.90$, $p < 0.001$. Under haloperidol, the

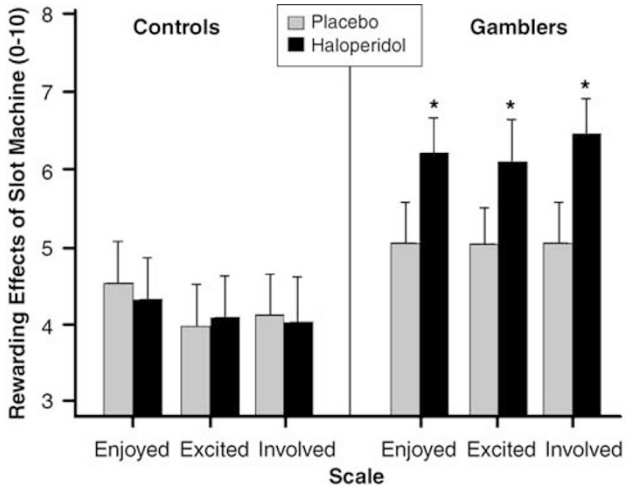

Figure 1 Mean (SEM) self-reported pleasurable effects of a 15-min slot machine game in healthy control subjects ($n=18$) and pathological gamblers ($n=20$) under haloperidol (3 mg, oral) and placebo. *Drug treatment effect, $p<0.001$.

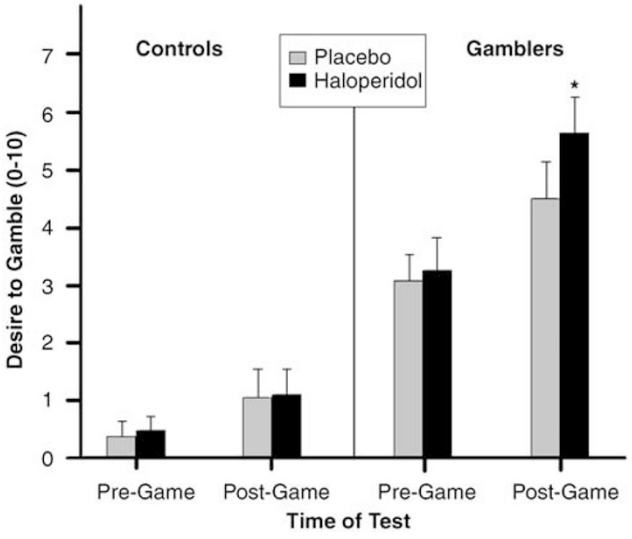

Figure 2 Mean (SEM) self-reported desire to gamble before and after a 15-min slot machine game in healthy control subjects ($n=18$) and pathological gamblers ($n=20$) under haloperidol (3 mg, oral) and placebo. *Drug treatment effect, $p<0.001$.

pre–post increase in Desire was significantly amplified in gamblers, $t(35)=4.13$, $p<0.001$, but not in controls, $p>0.50$. Thus, haloperidol selectively enhanced the priming effects of the slot machine game in pathological gamblers.

Activation of semantic networks: the lexical salience task. Table 2 reports the mean (SD) reading response time (RT; ms) scores for Gambling and Neutral control words and for the Ancillary word conditions on the Lexical Salience Task for controls and gamblers under each Treatment. The table shows that, in each group, RT was considerably slower to Neutral words than to all other types of words under placebo and haloperidol. As noted earlier, the difference in RT to a class of target words relative to motivationally irrelevant Neutral words measured salience; the greater the difference, (Neutral minus Target), the greater the salience.

A 2 (Group) $\times 2$ (Treatment) $\times 5$ (Word Condition) ANOVA yielded a significant three-way interaction, $F(4,144)=3.00$, $p=0.021$. Simple effects analyses for controls found that the RT difference from Neutral under drug *vs* placebo did not change significantly for Gambling words, $p>0.06$; increased for Alcohol words, $t\ (144)=7.50$, $p<0.001$; and decreased for both Positive, $t\ (144)=7.91$, $p<0.001$, and Negative Affect words, $t\ (144)=11.08$, $p<0.001$. Thus, in controls, Gambling words were no more salient under drug than placebo; Alcohol words were more salient under drug, and Affective words, regardless of valence, were less salient under drug. Inspection of the scores for controls in Table 2 shows that, under placebo, RT to Alcohol words was unusually slow relative to the other motivationally relevant words. Thus, the relatively greater difference in RT to Alcohol *vs* Neutral words under haloperidol in these subjects could well have reflected regression to the mean.

Inspection of the RT scores for gamblers in the various non-Neutral word conditions under placebo reveals that they were generally quite similar. Simple effects analyses for gamblers found that haloperidol significantly increased the RT difference from Neutral for Gambling words, $t\ (108)=2.91$, $p<0.01$; and for Positive Affect words, $t\ (108)=5.26$, $p<0.001$; but did not alter relative RT to the other types of words, p's >0.50. Thus, the results for gamblers indicate that Gambling words and Positive Affect words were relatively more salient under haloperidol than placebo.

Physiological effects: systolic blood pressure. Figure 3 shows the effects of the slot machine game on systolic blood pressure (mmHg) under haloperidol and placebo in controls. Figure 4 shows the corresponding scores for gamblers. The figures indicate that, under placebo, blood pressure increased from pre-game to post-game in both groups. In addition, in both groups, the game-induced increase in blood pressure was greater under haloperidol. These observations were corroborated by analyses.

A 2 (Group) $\times 2$ (Treatment) $\times 8$ (Time of Test) ANOVA of systolic blood pressure scores yielded a significant Treatment $\times$ Time interaction, $F\ (7,252)=2.64$, $p=0.012$, and a significant three-way interaction, $F\ (7,252)=2.89$, $p=0.006$. The two-way interaction reflected a consistent augmentation in the effects of Time (post-game minus pre-game minimum) under haloperidol *vs* placebo in controls, $t\ (252)=6.15$, $p<0.001$, and in gamblers, $t\ (252)=5.16$, $p<0.001$. The three-way interaction reflected a group difference in the time at which the pre-game minimum occurred under each treatment. In controls, minimum blood pressure occurred 30 min before onset of the slot machine under placebo and immediately before the game under haloperidol; in gamblers this pattern was reversed, with the pre-game minimum occurring just before game onset under placebo, but 30 min before game onset under haloperidol. Notably, haloperidol augmented the game-induced increase in blood pressure to a comparable degree in both groups.

Table 2 Mean (SD) Reading Response Time (ms) for Word Stimuli on Lexical Salience Task Under Placebo and Haloperidol (3 mg) in Healthy Control Subjects ($n = 18$) and Pathological Gamblers ($n = 20$)

	Word conditions				
	Test		Ancillary		
Treatment	**Gambling**	**Neutral**	**Alcohol**	**Positive affect**	**Negative affect**
Controls					
Placebo	1060 (239)	1221 (359)	1158 (317)	1018 (198)	1011 (247)
Haloperidol	998 (237)	1147 (319)	1036* (229)	995* (235)	1007* (216)
Gamblers					
Placebo	950 (366)	1064 (402)	933 (337)	945 (341)	931 (347)
Haloperidol	895* (261)	1036 (349)	906 (255)	869* (225)	905 (281)

*$p < 0.05$, simple effect of Treatment (Drug *vs* Placebo) for salience (RT difference from Neutral) for a given word condition.

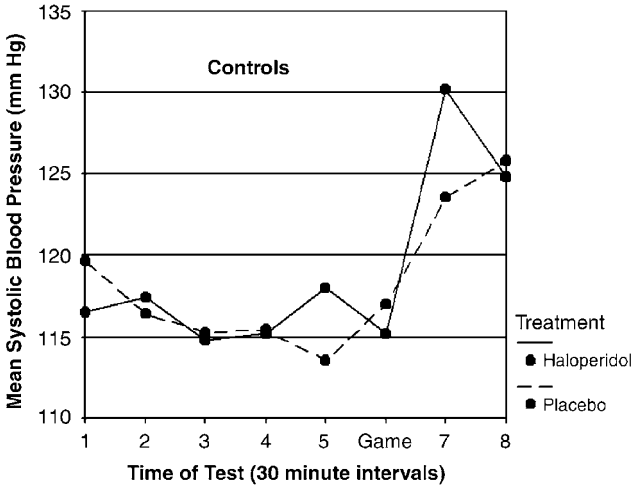

Figure 3 Mean (SEM) systolic blood pressure (mm Hg) at pre-capsule baseline and at 30 min intervals before and after a 15-min slot machine game in healthy control subjects ($n = 18$) under haloperidol (3 mg, oral) and placebo.

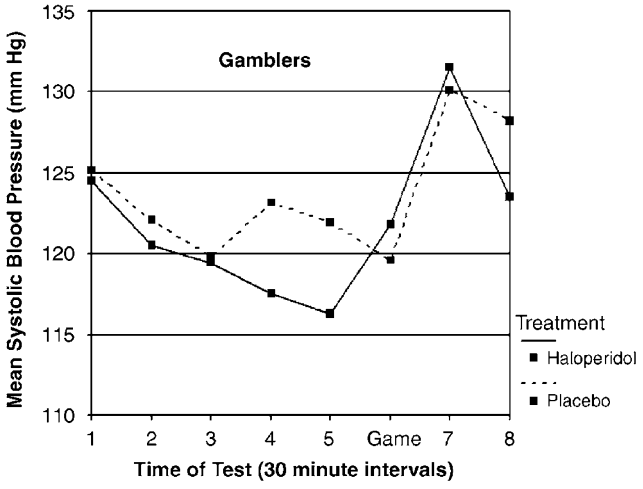

Figure 4 Mean (SEM) systolic blood pressure (mm Hg) at pre-capsule baseline and at 30 min intervals before and after a 15-min slot machine game in pathological gamblers ($n = 20$) under haloperidol (3 mg, oral) and placebo.

Betting behavior in slot machine game. A series of 2×2 ANOVA's of betting behavior in the slot machine game (mean credits bet per spin, maximum credits bet per spin, final credits earned) yielded no significant effects involving Treatment, p's > 0.25. The single significant result was a main effect of Group for mean (SD) total spins/game, which were more numerous in gamblers, 89.4 (39.4) than in controls, 60.6 (41.6), $F(1, 36) = 9.57$, $p = 0.004$.

DISCUSSION

Haloperidol, on its own, had no significant differential effects in pathological gamblers and healthy controls on subjective drug or mood effects as assessed by the ARCI, POMS, and VAS drug effect scales. In both groups, there were marginally significant effects on the ARCI MBG subscale (decreased well-being) and on the VAS Bad Effects scale that were consistent with the typical effects of a neuroleptic drug. Overall, the pattern and magnitude of scores and effect sizes were highly comparable with those reported in previous studies using the same dose in physically healthy volunteers (Enggasser and de Wit, 2001; Wachtel *et al*, 2002).

Considering first the findings for gamblers, haloperidol augmented the pleasurable effects of the slot machine game as reflected by the Enjoyment, Excitement, and Involvement scales. The mean squared intercorrelation for the three sub-scales was $r^2 = 0.66$, for gamblers, indicating that a common pleasurable effect of the game accounted for about two-thirds of the variance in the sub-scale scores, whereas about one-third of the variance was unique to each sub-scale.

Haloperidol on its own had no significant effect on pre-game Desire to Gamble in problem gamblers. Under

placebo, the slot machine game increased Desire to Gamble and haloperidol significantly amplified this priming effect in gamblers. Thus, haloperidol had consistent effects across rewarding and motivational aspects of the slot machine game, a pattern that cross-validates the two types of indices. Haloperidol also enhanced the salience of Gambling words relative to Neutral words, as evidenced by faster automatically executed reading responses on the Lexical Salience Task. With respect to physiological activation, the slot machine led to a significant increase in blood pressure under placebo and haloperidol significantly augmented this effect. Thus, haloperidol increased the rewarding, priming, and physiological activating effects of gambling in pathological gamblers. Effects were clear and convergent across self-report, automatic reading responses, and blood pressure indices.

A number of results for controls were consistent with those for gamblers. First, in controls, haloperidol on its own had no significant effect on pre-game Desire to Gamble. Second, under placebo, the slot machine game primed Desire to Gamble and increased systolic blood pressure in controls. This latter finding is consistent with the previously noted findings of elevated sympatho-adrenal responses in problem and non-problem gamblers during casino gambling (Meyer *et al*, 2004). Finally, haloperidol augmented the pressor effects of the game in controls and the magnitude of the drug effect was quite similar to that of gamblers.

In contrast to gamblers, in controls, haloperidol did not enhance the pleasurable rewarding effects of the game, primed desire to gamble or reactivity to Gambling words on the Lexical Salience Task. Thus, in control subjects who were essentially non-gamblers, haloperidol enhancement of physiological activation appears to be dissociated from its effects on rewarding-motivational responses to gambling activity. However, control subjects did appear to find playing the slot machine to be reinforcing, as indexed by self-reported pleasurable effects of the game and the game-induced priming of Desire to Gamble under placebo. It is unclear what accounts for the dissociation in the effects of haloperidol on the physiological and reward indices in the non-gambler controls. This raises the question of how haloperidol might affect social gamblers in this experimental paradigm. It is possible that a history of gambling and concomitant conditioned responses or tolerance may contribute to haloperidol's effects on gambling reinforcement. There is some evidence in research with animals that the dopamine system and the D2 receptor in particular play a different role in the reinforcing properties of addictive stimuli in addicted *vs* nonaddicted subjects (cf. Dockstader *et al*, 2001).

The finding that partial D2 blockade enhanced the rewarding-motivational effects of gambling in pathological gamblers may seem somewhat surprising. Given the apparent neurochemical similarities between gambling and psychostimulant reinforcement (Zack and Poulos, 2004), research on the effects of dopamine antagonists on psychostimulant reward is relevant. Extensive research with animals using a variety of paradigms has found that D2 blockade consistently decreases the reinforcing efficacy of psychostimulant drugs (Amit and Smith, 1992; Bari and Pierce, 2005; Britton *et al*, 1991; Caine *et al*, 2002; Fletcher, 1998). In studies with humans, the effects of D2 antagonists on psychostimulant reward have been inconsistent. Some studies have found no effect (eg Brauer and de Wit, 1997; Wachtel *et al*, 2002); others have found decreased psychostimulant reward (eg Gunne *et al*, 1972; Jonsson, 1972; Sherer *et al*, 1989); and one study has found increased psychostimulant reward (Brauer and de Wit, 1996). In their review of the psychostimulant literature, Brauer *et al* (1997) discuss the seeming lack of correspondence between the animal and human research in terms of functional dosing and a variety of methodological differences. In light of this, a dose–response assessment of haloperidol effects on gambling reinforcement would constitute a valuable extension to the present inquiry.

Evidence from neuroimaging studies, however, does appear to be congruent with the present findings for gamblers. In a series of studies, Volkow *et al* (1999, 2000) found that lower D2 receptor availability was consistently correlated with greater subjective rewarding effects of the psychostimulant, methylphenidate in healthy volunteers. In other words, the lower the availability of D2 receptors, the greater was the liking of the drug. Also, as alluded to previously, the present findings parallel an earlier 'paradoxical' finding that pre-treatment with either 1- or 2-mg of the D2 antagonist, pimozide increased discriminability and 'liking' of a 20-mg dose of d-amphetamine in volunteers (Brauer and de Wit, 1996).

Interestingly, in a separate study, Volkow *et al* (2003) found that methylphenidate-induced increases in blood pressure were highly correlated with plasma epinephrine and with increases in striatal dopamine. They suggested that methylphenidate's pressor effects were partly mediated by DA-induced increases in peripheral epinephrine. This account raises the possibility that the elevation in gambling-induced blood pressure under haloperidol in the present study may have reflected elevations in striatal dopamine with corresponding effects on epinephrine.

As noted in the Introduction, genetic studies have provided correlational evidence indicating that low D2 receptor function is a key risk factor for development of pathological gambling (Comings *et al*, 1996). Subsequent fMRI research with healthy volunteers found that those with the genetic variant (A1 allele) linked with low D2 receptor function displayed increased activation to anticipated rewards in reward-relevant brain regions during a simulated gambling task (Cohen *et al*, 2005). The present findings extend this line of inquiry using a pharmacological approach to demonstrate that low D2 receptor availability induced by a drug enhances the reinforcing effects of slot machine gambling in pathological gamblers. These results are consonant with the neuroimaging findings cited above, and provide experimental evidence for a neurochemical–behavioral relationship that may underlie the association between anomalies in D2 receptor genes and risk for pathological gambling.

Given the apparent neurochemical similarity between gambling and psychostimulant reinforcement (Zack and Poulos, 2004), the present findings suggest that other dopamine substrates that are modulated by D2 and influence psychostimulant reinforcement, for example, D1 and D3 receptors (Xu, 1998), could well be important for gambling reinforcement. Finally, the present findings

suggest that drugs that enhance dopamine transmission at the D2 substrate may be promising candidates for investigating medications for pathological gambling.

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