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Haloperidol modifies instrumental aspects of slot machine gambling in pathological gamblers and healthy controls

-Frank model: D1 (No-Go) vs D2 (Go Learning, positive reinforcement)

-Counter-intuitive D2 agonist/antagonist effects in low doses

Anne-Marie Tremblay, Renée C. Desmond, Constantine X. Poulos & Martin Zack

Clinical Neuroscience Section, Centre for Addiction and Mental Health, Toronto, Canada

ABSTRACT

Instrumental conditioning has been implicated in persistence at slot machine gambling, but its specific role remains unclear. Dopamine (DA) mediates aspects of instrumental responding, and D2 antagonists reliably alter this process. This study investigated the effects of the preferential D2 antagonist, haloperidol (3 mg) on reward-related betting behavior in 20 subjects with pathological gambling (PG) and 18 healthy Controls. Hierarchical regression assessed the prospective relationship between Payoff and Bet Size on consecutive trials, along with potential moderating effects of Cumulative Winnings and Phase of game (early/late) under drug and placebo. Payoff predicted Bet Size on the next trial regardless of other factors, consistent with an instrumental view of slot machine gambling. Under placebo, this correlation varied as a function of Winnings and Phase in PG subjects but was strong and invariant in Controls. Under haloperidol, the Payoff–Bet Size correlation in PG subjects resembled the invariant pattern of Controls under placebo. In contrast, the Payoff–Bet Size correlation rose then fell sharply over trials under haloperidol in controls. The correlation of Payoff with Bet Size is remarkable given that there is no actual contingency between winning and betting, and suggests that reward expectancies largely drive slot machine gambling. By blocking inhibitory D2 receptors, haloperidol may have reversed 'tolerance' to monetary reward mediated by increased tonic DA in PG subjects. Disturbance of the Payoff–Bet Size correlation in Controls may reflect indiscriminate reward signaling under haloperidol in subjects with normal DA function. Indirect enhancement of DA transmission may reduce undue reward-related responding in PG subjects.

Keywords D2, dopamine, expectancy, gambling, instrumental, slot machine.

Correspondence to: Martin Zack, Clinical Neuroscience Section, Centre for Addiction and Mental Health, 33 Russell Street, Toronto, ON M5S 2S1, Canada.
E-mail: martin_zack@camh.net

INTRODUCTION

Approximately 1–3% of the general population in developed countries meet diagnostic criteria for pathological gambling (PG). The form of gambling (e.g. cards, slots) most strongly linked with PG varies as a function of factors like gender and ethnicity (Potenza *et al.* 2001; Barry *et al.* 2008). Despite this variability, large-scale studies in several countries have found that access to, and participation in, slot machine gambling is consistently associated with higher rates of PG and poorer outcomes in those who manifest it (Petry 2003; Wheeler, Rigby & Huriwai 2006; Williams, West & Simpson 2007; Kessler *et al.* 2008; Saez-Abad & Bertolin-Guillen 2008; Bakken *et al.* 2009). A better understanding of the processes that mediate slot machine gambling could therefore have important benefits for individuals and communities.

Research into the structural motivating features of slot machines has found that 'big wins', especially early in the course of gambling, near-misses (outcomes that closely approximate winning patterns) (Kassinove & Schare 2001), sensory features like bells and lights, and speed of play all influence betting behavior in these games (Loba *et al.* 2001). Early theorists argued that the intermittent schedule of monetary reward, which would deter extinction, was central to persistence at slot machines (Skinner 1953). This assumes that slot machine gambling conforms to the basic principles of instrumental conditioning. However, the prospective relationship between winning and betting in slot

machines remains unclear. Evidence for such a relationship would support a role for instrumental conditioning in slot machine gambling and suggest that insights from the extensive literature on instrumental conditioning could be applied to reduce the harmful effects of this activity. The first goal of this study was to investigate the role of instrumental conditioning in slot machine gambling by directly assessing the relationship between payoff and bet size on consecutive trials over the course of the game.

Evidence that instrumental conditioning can explain slot machine betting patterns would also suggest which neurochemical processes mediate this behavior. In particular, it would suggest a key role for dopamine (DA), which, despite controversy over its specific roles in acquisition versus expression of instrumental responses, is widely accepted as a key determinant of positive reinforcement (Fields *et al.* 2007; Dalley & Everitt 2009). A better understanding of how DA affects the impact of winning on betting is also important given the critical role of DA in addiction (Robbins & Everitt 1999; Robinson & Berridge 2000; Volkow *et al.* 2007), to which PG has been likened (Grant, Brewer & Potenza 2006), as well as the apparent association between PG and Parkinson's disease (Voon, Potenza & Thomsen 2007a). To our knowledge no research has directly investigated the role of DA on instrumental aspects of slot machine gambling in PG subjects and non-PG controls. A second goal of this study was to address this important gap in the literature.

Imaging studies on neural responses to monetary reward can provide a context for this investigation. In a decision-making task for varied amounts of monetary reward, cocaine abusers exhibit overall reduced regional brain reactivity to variations in the different monetary value conditions (Goldstein *et al.* 2007). In a decision task with monetary reward and loss, alcohol abusers show reduced activation of ventral striatum during anticipation of monetary gain relative to controls (Wrase *et al.* 2007). In a decision task with risky and safe monetary rewards, a mixed sample of substance abusers display reduced posterior mesofrontal cortex activation in response to risky rewards in particular (Bjork *et al.* 2008). These findings echo previous functional magnetic resonance imaging (fMRI) results for PG subjects: using a gambling-like guessing game, Reuter *et al.* (2005) found that PG subjects displayed significantly less activation in the medial prefrontal cortex and ventral striatum during anticipation and receipt of monetary reward compared with healthy controls. In PG subjects, greater symptom severity was associated with greater deficits in activation in both brain regions. Reuter *et al.* proposed that deficits in striatal response could reflect decreased reward sensitivity (Volkow *et al.* 2002). If striatal activation accurately indexes the reinforcing value of monetary reward, Reuter *et al.*'s findings suggest that a given monetary payoff should have less ability to promote betting behavior on a slot machine in PG subjects than in controls.

The regional patterns of activation seen in fMRI studies strongly suggest that they are measuring the activity of DA neurons. Empirical support for this was provided by Schott *et al.* (2008), who measured neural activation in healthy subjects during a gambling task with probabilistic monetary rewards and losses while concurrently assessing DA release in terms of displacement of the DA D2/D3 receptor ligand raclopride. They reported that 'Across the cohort, a positive correlation emerged between neural activity of the substantia nigra/ventral tegmental area (SN/VTA), the main origin of dopaminergic neurotransmission, during reward anticipation and reward-related [(11)C] raclopride displacement as an index of DA release in the ventral striatum, major target of SN/VTA dopamine neurons' (p. 14 311). Thus, gambling-induced striatal activation does appear to index DA release in healthy subjects.

Recently, Steeves *et al.* (2009) conducted a similar investigation in Parkinson's patients with and without PG. They found that patients with PG demonstrated greater decreases in raclopride binding in the ventral striatum during gambling (13.9%) than controls did (8.1%), indicating greater gambling-induced DA release in the co-morbid group. Baseline striatal binding levels were also lower in the co-morbid group. Thus, in contrast to PG subjects without Parkinson's disease (Reuter *et al.* 2005), PG subjects with Parkinson's appear to exhibit more rather than less striatal response to gambling than matched controls without PG. Although there is no definitive explanation for this discrepancy research on the role of D2 receptors in reward-related learning in healthy subjects may provide a clue.

Parkinson's disease involves profound alterations in DA function. Studies with healthy subjects suggest that D2 antagonists can mimic some of the cognitive deficits seen in Parkinson's disease (Mehta *et al.* 1999). Research on reward-related approach and avoidance learning in healthy subjects treated with the preferential D2 agonist cabergoline (1.25 mg), the preferential D2 antagonist haloperidol (2 mg), or placebo (Frank & O'Reilly 2006) found 'that cabergoline impaired, while haloperidol enhanced, Go learning from positive reinforcement' (p. 497). The investigators also observed that 'the opposite effects of cabergoline and haloperidol on Go/No-Go learning directly replicate our prior results in Parkinson's patients' (p. 497). Together, these findings indicate that at modest doses, D2 receptor antagonists can approximate the cognitive and incentive-motivational profile of Parkinson's disease. Frank and O'Reilly noted that modest doses of D2 antagonists act predominantly at presynaptic receptors, reducing these receptors' inhibitory

effects. As a result, DA release from rewarding stimuli should be enhanced. To the extent that this 'disinhibitory' effect models the situation in Parkinson's disease it may explain the relatively greater DA response to gambling seen in the Parkinson's patients with PG (Steeves *et al.* 2009). The lower baseline D2 levels (i.e. decreased inhibitory signal) in the Parkinson's patients with PG versus those without PG are consistent with this possibility.

The pattern of effects described above suggests that a modest dose of haloperidol in non-Parkinsonian PG subjects may approximate the effects seen in PG subjects with Parkinson's. That is, haloperidol may increase gambling-induced DA release in otherwise healthy PG subjects. Frank and O'Reilly's results suggest that this effect may also be observed in non-PG controls. In motivational terms, they suggest that a modest dose of haloperidol should increase the ability of monetary reward to elicit a betting response. A test of the effects of haloperidol on reward-related betting behavior in a slot machine game would not only provide an opportunity to see if the pattern conforms to instrumental learning principles; it would also reveal whether the expected pattern of effects of D2 blockade seen in experimental models of reinforcement and gambling emerge on an actual gambling device.

Initial evidence provides indirect support for these possibilities. In a recent study, haloperidol (3 mg) was found to increase the subjective reinforcing effects of a 15-minute episode of gambling on a commercial slot machine in otherwise healthy PG subjects ($n = 20$), as evidenced by increased ratings of Enjoyment, Excitement and Involvement in the game and increased post-game Desire to Gamble compared with placebo (Zack & Poulos 2007). PG subjects also exhibited an enhanced cognitive priming effect under the drug, as measured by greater post-game verbal fluency to Gambling words (e.g. wager) versus Neutral words (e.g. window) on a rapid reading task. Addiction-related words have been found to activate the mesocortico-limbic DA system in cocaine addicts (Goldstein *et al.* 2009), supporting the possibility that increased DA release under haloperidol mediated the enhanced cognitive priming of Gambling words in PG subjects. In contrast to the findings for PG subjects, healthy non-PG controls ($n = 18$) exhibited no change in subjective reinforcing or priming effects of the slot machine game under haloperidol versus placebo (Zack & Poulos 2007). However, both PG subjects and Controls exhibited a significant and comparable post-game increase in systolic blood pressure relative to placebo, confirming that the drug was physiologically active in Controls. Increased systolic blood pressure has been found to selectively coincide with increases in striatal DA release in healthy subjects who received varying doses of the DA reuptake inhibitor methylphenidate (Volkow *et al.* 2003). These findings are consistent with the possibility that haloperidol increased gambling-induced DA release in PG subjects and Controls. However, group differences in subjective and cognitive effects of haloperidol suggest that increased DA release led to increased positive reinforcing effects of the slot machine in PG subjects but not in Controls.

Comparison of group mean betting scores on the slot machine revealed no group by drug interactions. Each group displayed equivalent mean bet size per trial and mean number of trials played under haloperidol versus placebo. A group difference emerged for trials played, with PG subjects playing more trials (i.e. faster rate of play) than Controls under both drug and placebo. There were no differences in mean winnings received as a function of drug condition or group. Thus, aggregate scores did not indicate a change in positive reinforcement under the drug as operationally defined by an increase in average bet size or number of trials played.

In the course of a slot machine game, as in all gambling activities, the occurrence and magnitude of monetary payoffs varies. On some trials, the player may receive a large payoff; on others no payoff at all. Overall, these variations should average out across multiple subjects and sessions. Positive reinforcement involves an increase in the probability of a response as a result of a rewarding outcome. In a slot machine game, positive reinforcement can be indexed by an increase in the ability of a given reward to elicit a betting response. The prospective correlation between the size of a payoff on a given trial (number of credits) and the size of the wager on the subsequent trial (number of credits) gauges this effect and provides a complementary index of reinforcing efficacy in terms of the graded effects of varying rewards on the strength of the criterion response (betting). The study cited above, in which cocaine abusers displayed a blunting in the differential neural response to varying amounts of monetary reward (Goldstein *et al.* 2007), suggests that a loss of reward-response calibration may be an important feature of the addicted state. If PG subjects resemble cocaine abusers cf. (Pallanti *et al.* 2006; Potenza 2008), they should exhibit a similar deficit in calibration (i.e. weaker payoff–bet size correlation) compared with Controls under placebo. If an increase in reward-related DA release rectifies this deficit, PG subjects should show a significant increase in the strength of the payoff–bet size correlation under haloperidol.

The effects of haloperidol on reward-related betting behavior in healthy Controls may be predicted from research on the effects of haloperidol on instrumental responding in healthy animals. Sanger & Perrault (1995) noted that 'Within-session decrements in instrumental responding are a characteristic effect of certain neuroleptic drugs including haloperidol and pimozide' (p. 708). In a comparison of typical and atypical neuroleptics on fixed

ratio lever pressing for food (1 reward/10 presses), these investigators found that 'The presence of within-session response decrements was confirmed for haloperidol and demonstrated with remoxipride, but similar effects were not observed with clozapine, thioridazine, risperidone, sertindole, setoperone, sulpiride and amisulpride' (p. 708). Within-session reductions in instrumental responding under haloperidol suggest a change in the reinforcing efficacy of reward as a result of experience under the drug. In other words, healthy animals may need to be exposed to, and respond for, rewarding stimuli during D2 receptor blockade to manifest a change in overt instrumental responding. On the slot machine, such an effect would be discernible as a change in the strength of the correlation between payoff and bet size as trials continued over the course of the game. Conversely, a within-session change of this kind could well be obscured by an overall estimate of bet size, which may account for the apparent lack of effect of haloperidol on betting when measured in terms of the mean credits wagered. At a more general level, mean credits wagered would not reveal the differential reinforcing effects of varying payoffs, making the payoff–bet size correlation a more sensitive index of positive reinforcement regardless of when in the session it is measured.

The evidence described above suggests that the payoff–bet size correlation on consecutive trials can reveal whether slot machine gambling conforms to the basic principles of instrumental reinforcement. If PG resembles substance addiction, PG subjects, like cocaine abusers, should exhibit insensitivity to variations in monetary reward, as reflected by a lower payoff–bet size correlation, compared with controls under placebo. By blocking inhibitory D2 receptors, haloperidol should increase reward-related DA release relative to placebo (Pehek 1999; Frank & O'Reilly 2006). This should enhance sensitivity (in terms of reward-related 'phasic' DA release) to variations in monetary reward in PG subjects, strengthening the payoff–bet size correlation in these subjects under the drug. In controls, haloperidol would be expected to promote a within-session decline in reward-related responding as it does in healthy animals (Sanger & Perrault 1995).

These hypotheses were tested using hierarchical linear regression. Sequential entry of predictors (drug, group, stage of game) enabled an assessment of their expected interactive effects on the relationship between payoff on a given trial and bet size on the next trial while controlling for variation introduced by each individual predictor alone. The marginal utility or value of a given reward (e.g. 10 credits) will vary depending on the rewards accumulated to that point in the game (e.g. 50 versus 500 credits). This parallels the differential value and reinforcing efficacy of a given reward depending on whether an animal is sated or deprived with respect to that reward (Ahn & Phillips 1999; Dranias, Grossberg & Bullock 2008; Johnson, Gallagher & Holland 2009). To determine if the extent of prior reward influenced the relationship between current payoff and bet size, cumulative winnings were also included as a predictor in the model.

MATERIALS AND METHODS

Subjects

The sample included 20 physically healthy, drug- and medication-free, non-treatment-seeking PG subjects (Gamblers) and 18 healthy volunteers (Controls). Table 1 reports the sample characteristics and confirms that the groups did not differ in age, gender ratio, ethnic composition or relative frequency of smokers, P's > 0.12. Gamblers exhibited significantly higher levels of depression and alcohol misuse than Controls, but the values on these scales were very low, in no case approaching clinical cut-off values, indicating lack of co-morbidity in the PG group.

In Gamblers, the mean (SD) score on the South Oaks Gambling Screen (Lesieur & Blume 1987) of 8.2 (2.9) indicated moderate PG severity. Mean expenditure on gambling as a percentage of income was 20.3%, or ~4 times the average percentage of income Canadians spend on all forms of leisure. Gamblers scored higher than Controls on the Hamilton Depression Scale (Hamilton 1960), but well below the cut-off score of 15 for clinical depression. Table 1 shows that Controls were essentially non-gamblers. Importantly, 17 of 18 Controls had never played a slot machine, and one had played a slot machine once before. Thus, the 'instrumental task' was new to Controls, whereas all Gamblers had extensive experience with slot-machines.

As noted elsewhere (Zack & Poulos 2007), there were no differences as a function of Group or Drug Condition in mean (SD) bet size 13.0 (8.3), payoff 13.5 (18.3), or final tally 403.8 (610.6) credits. A group difference (not modified by Drug Condition, $P > 0.23$) emerged for the number of trials, with Gamblers playing more trials (faster play; $P = 0.004$), than Controls under drug (85.6 versus 61.9) and placebo (93.3 versus 59.3). In addition, there was no evidence of adverse effects (no significant differences from placebo) on the Addiction Research Center Inventory of subjective drug effects (Haertzen 1965) or the Profile of Mood States-short form (Shacham 1983), nor could subjects reliably distinguish drug from placebo, based on retrospective self-report at the conclusion of test day 2 (Zack & Poulos 2007).

Apparatus

A commercial slot machine ('Cash Crop'; WMS Gambling Inc, Detroit, MI) was employed. The screen displayed a

Table 1 Mean (SD) background characteristics for pathological gamblers ($n = 20$) and controls ($n = 18$).

	Group	
Characteristic	*Pathological gamblers*	*Controls*
Gender (M : F)	17:3	14:4
Age	36.6 (11.4)	41.6 (11.7)
Ethnicity (*N*)		
Caucasian	15	11
East Asian	1	2
South Asian	2	2
African/Caribbean	1	2
Middle Eastern	1	0
American/First Nations	0	1
South Oaks Gambling Screen	8.2 (2.9)*	0
DSM-IV-pathological gambling	11.0 (4.4)*	0
Average $ spent/week gambling	279.8 (266.2)*	1.0 (1.3)
Percent income spent gambling	20.3 (12.4)*	0.4 (0.5)
Hamilton Depression Scale	3.6 (3.1)*	1.1 (1.8)
Alcohol Dependence Scale	2.4 (3.2)*	0.4 (0.7)
Drug Abuse Screening Test	0.5 (0.8)	0.1 (0.2)
Timeline followback: drinks/week	2.8 (2.4)	1.6 (1.9)
Smokers: non-smokers	6:14	1:17

*Group difference, $P < 0.05$.

3 × 3 array of icons. Subjects could bet on any combination (one to nine) of horizontal, vertical and diagonal 'lines' on any trial (spin). They could bet 1–5 credits/line, for a maximum bet of 45 credits per trial. Apart from this, there were no restrictions on betting or speed of play. To register a bet, subjects pressed on the desired icon(s) on the screen. They initiated the trial by pressing a button.

A winning combination involved any row, column or diagonal line of identical icons. In keeping with the theme (Cash Crop), the icons were familiar agriculture symbols represented by cartoon-style pictures: a farmer, a bunch of carrots, a tractor and a barn. The icons 'spun' in coordinated columns, which stopped sequentially from left to right. Credits were dispensed individually so subjects saw the tally rise on winning trials. Bells and flashing lights accompanied the delivery of credits, enhancing the sensory aspects of the game. Non-rewarded trials presented no signals apart from a '0' in the win box below the icon display. A separate box showed the total credits available (Cumulative Winnings), which were updated after every spin. The duration of the bells (one 'ding' per credit delivered) and lights on winning trials was yoked to the delivery of credits on that trial. Thus, each payoff provided a graded, multi-dimensional index of reward: numerical (climbing credit tally), visual and auditory. This kind of reward typifies commercial slot machines, enhancing the external validity of the task.

The number of credits wagered and won on every trial was recorded electronically by a cable feed from the slot machine to a computer in the next room. Subjects were not aware that their bets were being recorded but were advised of this during debriefing. The game was situated in a mock-bar laboratory, and each subject played individually without supervision. They received an initial stake of $200 (400 credits) on each test session and were advised that they would receive a monetary bonus, proportional to their final winnings, when the study was over. The game ended after 15 minutes or when credits were exhausted, whichever came first.

Procedure

The study was approved by the institutional research ethics board and conducted in accordance with the principles of the Helsinki Declaration (1975; 1989). Subjects were recruited by newspaper advertisements, provided written informed consent at the start of the study and were paid for participation upon completion. Prior to testing they underwent a screening interview and physician's exam with blood and urine analyses to verify drug-free status. The physician's exam was performed by a psychiatric resident who took a complete medical and psychiatric history. Subjects with a current or lifetime psychiatric disorder or history of treatment for a psychiatric disorder apart from PG were excluded. Lack of family history of schizophrenia and bipolar disorder, and lack of prior head trauma with loss of consciousness, were also verified.

Volunteers who passed the physician's exam attended two procedurally identical test sessions, with a 1-week inter-session interval to ensure drug washout. At the start of the test sessions, haloperidol (3 mg) or a visually

identical placebo capsule was administered in counterbalanced sequence across subjects. This dose of haloperidol would be expected to block 60–70% of D2 receptors in neurologically healthy individuals (Nordstrom, Farde & Halldin 1992). Subjects received their capsule along with a standard breakfast at 9 a.m. on test days. Smokers were permitted one cigarette before each session and none during testing.

Subjects played the slot machine 2.75 hours after dosing, at expected peak blood drug levels (Nordstrom *et al.* 1992). At game time, the experimenter escorted the subject to the mock bar and advised them that they could bet as many credits as they wished to a maximum of 45 per trial. The experimenter remained for the first 30 seconds to ensure the subject understood the game and then departed stating that she would be back shortly. The experimenter returned 15 minutes later. Subjects remained at the lab for 4 hours and received 50 mg of diphenhydramine upon departure to take in case of dystonia.

Data compilation and analysis

Regression

Hierarchical linear regression was employed. This analytic procedure is designed for hypothesis testing when individual rather than mean scores on the dependent variable are the critical consideration. In the present case, the dependent variable was Bet Size and the primary relationship under consideration was the correlation between Payoff on a given trial and Bet Size on the next trial. Hierarchical regression permitted assessment of systematic changes in the strength of the Payoff–Bet Size relationship as a function of PG status, drug status, stage of the game and cumulative winnings. Under the hypotheses, the moderating effects of PG status on the Payoff–Bet Size relationship were expected to vary as a function of drug status, as well as stage of the game. That is, these three variables were expected to interact with Payoff leading to a four-way interactive effect on Bet Size. To test this hypothesis, variability introduced by each individual factor must be partitioned from variability due to the interaction among them. By entering the individual factors and their respective interactions hierarchically, each stage of the analysis examined the unique variance in Bet Size explained by a given interaction term when variance in its constituent factors had been accounted for. In this way, if a main effect of an individual factor emerged along with a significant interaction involving that factor it was possible to conclude that the interaction was not attributable to the effect of the individual factor because each effect reflects a distinct portion of variance in the dependent variable (Evans 1991). Hierarchical regression also reduced the impact of non-independent observations (i.e. share variance among subjects with similar features) in the model (Bryk & Raudenbush 1992).

Statistical analyses were conducted with SPSS (v. 16, Chicago, IL). The analysis assessed the relationship between Payoff (primary predictor) on trial n (credits) and Bet Size (criterion) on trial n + 1 (credits), together with the key moderating factors, Drug Condition (Haloperidol, Placebo), Group, Cumulative Winnings (Payoff minus Bet Size for trial n, cumulated over preceding trials), and Phase of game (first half of trials, second half of trials). Product terms coded the interaction between predictors.

With five predictors, an omnibus analysis would entail 10 three-way interactions, 5 four-way interactions plus the overall 5-way interaction. To achieve intelligible effects while preserving parsimony, two analyses were conducted, one for each Drug Condition, with four predictors and their respective interactions in each analysis. This enabled a test of group differences in betting profiles under drug-free conditions, which could then be compared with those observed under the drug. Bonferroni correction was applied to control for the increase in family-wise alpha with two analyses.

Stem-leaf plots revealed a marked positive skew for Payoff, Cumulative Winnings and Bet Size. To restore the normality of these variables, a logarithmic transformation was applied. The log transformation reduces positive skew, preserves the rank order of individual scores (Smith 1993) and preserves the normality of multiplicative terms (Bland & Altman 1996), which were critical in the present design. The log-transformed scores thus permitted an unbiased assessment of the relationship between Payoff and Bet Size.

As expected, Cumulative Winnings were inversely correlated with Phase of game (on average, commercial slot machines pay out less than they take in), $r = -0.21$, $P < 0.001$. To reduce suppressor effects due to inversely correlated predictors, Cumulative Winnings were also coded dichotomously (less than/greater than median). Levels of all dichotomous variables were coded as –0.5 and +0.5 to equate their weightings in the analyses [1]. In each analysis, main effects were assessed in stage 1; and two-way, three-way and four-way interactions in stages 2–4, respectively.

[1] Parallel regression analyses including Cumulative Winnings and Trial number (rather than Phase) as continuous rather than dichotomous variables yielded the same pattern of significant effects as reported in the Results. However, in these analyses individual differences in total trials played could result in different weightings of the corresponding Payoffs and Bets. In addition, analyses of continuous trials and winnings do not permit a clear illustration of the primary Payoff × Bet Size correlation as a function of Winnings (low, high) or Phase of the game (early, late).

Analysis of means

The total number of trials played by all subjects was 5599. The total number of trials where Payoff = 0 was 3035, which corresponds to 54.2% of all trials. Thus, more than half of the scores were confined to the negative tail of the Payoff distribution. Statistically, this meant that variation in Bet Size when Payoff = 0 (constant) was essentially due to unexplained individual differences (error variance). To address this, trials where Payoff = 0 were excluded from the regression analyses. Effects of non-reinforcement on Bet Size, along with the other moderating factors, were analyzed categorically (Payoff = 0, Payoff > 0) with analysis of variance (ANOVA). Notably, the proportion of rewarded trials (45.8%) closely matches the reward rate (50%) that yields maximum DA release following the conditioned stimulus (CS) in a conditioned reward paradigm with monkeys (Fiorillo, Tobler & Schultz 2003).

A second issue concerned the impact of 'Big Wins' on Bet Size. The Payoff distribution (when Payoff = 0 removed) approximated the expected normal SD/range ratio of 6 when Payoff scores > 98th percentile were excluded. These statistically extreme scores were designated as Big Wins. The effect of Big Wins (Payoff ≤ 98th percentile, Payoff > 98th percentile) on Bet Size was analyzed with ANOVA. The timing (Trial number) of a Big Win in the game should vary randomly as a function of the other factors. This was also verified using ANOVA.

Cumulative Winnings (log transformed) were also assessed as a function of Group, Drug Condition and Phase with ANOVA. Box plots in each group confirmed the absence of outliers.

RESULTS

Regression

Placebo

Table 2 reports the results of the regression analysis for the Placebo condition and reveals a significant four-way interaction among all predictors. R^2 change was significant at stages 1, 2 and 4. Thus, the four-way interaction explained significant incremental variance in Bet Size over the lower-order effects (Bonferroni $P = 0.022$). Adjusted R^2 for the four-way interactive model was

Table 2 Hierarchical linear regression of relation between Payoff (log credits on trial n) and Bet Size (log credits on trial n + 1) and moderators of this relationship in pathological gamblers ($n = 20$) and healthy controls ($n = 18$) at each level of treatment (Placebo).

Model change	*R*	R^2	*Adj.* R^2	*Std. Err. Est.*	R^2 *change*	*F*	*d.f.1*	*d.f.2*	*Bonferroni P change*
1	0.422	0.178	0.175	0.3131	0.178	70.06	4	1297	<0.001
2	0.490	0.240	0.234	0.3017	0.062	17.64	6	1291	<0.001
3	0.493	0.243	0.235	0.3016	0.003	1.22	4	1287	0.604
4	0.497	0.247	0.238	0.3010	0.004	6.44	1	1286	0.022

Predictor/Effect	*Un-standardized b*	SE_b	*Beta*	t	*Bonferroni P value*
Group	0.159	0.159	0.218	1.00	0.636
Phase	–0.398	0.159	–0.577	–2.51	0.024[a]
Payoff	0.277	0.069	0.348	4.01	<0.001[a]
Winnings	–0.137	0.050	–0.195	–2.71	0.014[a]
Group × Phase	–0.674	0.318	–0.489	–2.12	0.068
Group × Payoff	0.098	0.138	0.154	0.71	0.956
Group × Winnings	–0.165	0.101	–0.343	–1.64	0.204
Phase × Payoff	–0.133	0.138	–0.216	–0.97	0.666
Phase × Winnings	0.207	0.101	0.446	2.05	0.080
Payoff × Winnings	0.009	0.044	0.022	0.20	>0.999
Group × Phase × Payoff	0.625	0.276	0.507	2.27	0.046[a]
Group × Phase × Winnings	0.414	0.202	0.447	2.05	0.082
Group × Payoff × Winnings	–0.001	0.087	–0.003	–0.01	>0.999
Phase × Payoff × Winnings	0.097	0.087	0.238	1.11	0.534
Group × Phase × Payoff × Winnings	–0.442	0.174	–0.546	–2.54	0.022[a]

Group: Gamblers, Controls (–0.5, +0.5); Phase: Median split—first/second half of trials (–0.5, +0.5); Winnings: Median split of cumulative winnings (difference in payoff minus bet size, cumulated over trials) up to trial n (–0.5, +0.5).
[a]Significant semi-partial correlation (unique variance shared) by predictor(s) and criterion (bet size).

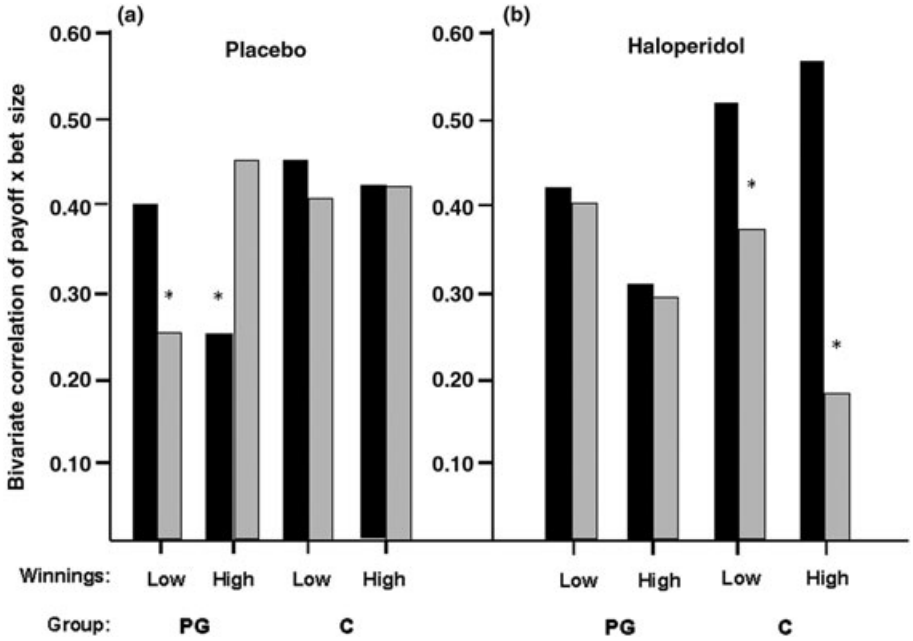

Figure 1 Bivariate correlation between Payoff (log credits paid on trial n) and Bet Size (log credits bet on trial n + 1) for the first and second half of trials (Phase 1, 2) in a slot machine game when Cumulative Winnings were high versus low (sub-median, supra-median) in subjects with pathological gambling (PG; $n = 20$) and healthy controls (C; $n = 18$). Panel (a) shows scores under Placebo. Panel (b) shows scores under Haloperidol (3 mg). *$P < 0.05$, simple effect of Phase

0.238. Thus, the factors and their interactions collectively explained about one-fourth of the variance in Bet Size under Placebo.

Figure 1a depicts the bivariate correlations between Payoff on trial n and Bet Size on trial n + 1 for each Group, Phase and level of Cumulative Winnings under Placebo. Panel a shows that in Gamblers, the strength of the Payoff–Bet Size correlation decreased over the course of the game when Winnings were low but increased over the course of the game when Winnings were high. In contrast, in Controls, the strength of the Payoff–Bet Size correlation declined slightly when Winnings were low but remained unchanged when Winnings were high. Thus under placebo, Gamblers decreased or increased their betting response to a win of given size depending on their available resources, whereas Controls did not modulate their betting response to wins as a function of available resources. The opposite direction of the Phase effect as a function of Winnings in Gamblers, coupled with the lack of significant Phase effect at either level of Winnings in Controls, appears to account for the four-way interaction.

Figure 2, panels a–h, show the scatter plots for the Placebo condition at each level of Group, Phase and Cumulative Winnings. In each panel, the slope of the regression line reflects the strength of the bivariate correlation between Payoff and Bet Size. Inspection of the panels confirms the absence of outliers, ensuring that the correlation coefficients accurately reflect the relationship between the two key variables. Panels 2a–d show the scores for Group PG and illustrate the decrease in Payoff–Bet Size correlation over the course of the game when Winnings were low, and corresponding increase in this correlation over the course of the game when Winnings were high. Panels e–h depict the scores for Group C and reveal that the slope of the regression line was highly consistent over the course of the game at each level of Winnings.

Haloperidol

Table 3 reports the results for the Haloperidol condition and shows that R^2 change was significant at stages 2 and 3. Thus, the four-way interaction did not explain significant variance in Bet Size under the drug (Bonferroni $P = 0.24$), and the three-way interactive model provided the best fit of the data. Adjusted R^2 for this model was 0.201. Thus, the factors and their interactions collectively explained about one-fifth of the variance in Bet Size under Haloperidol.

Inspection of the Beta coefficients reveals a significant Group × Phase × Payoff interaction, $\beta = -0.195$, Bonferroni $P = 0.014$. Thus, under Haloperidol, the relationship between Payoff and Bet Size, compared during early versus late trials, differed as a function of PG status. A significant Phase–Winnings interaction also emerged,

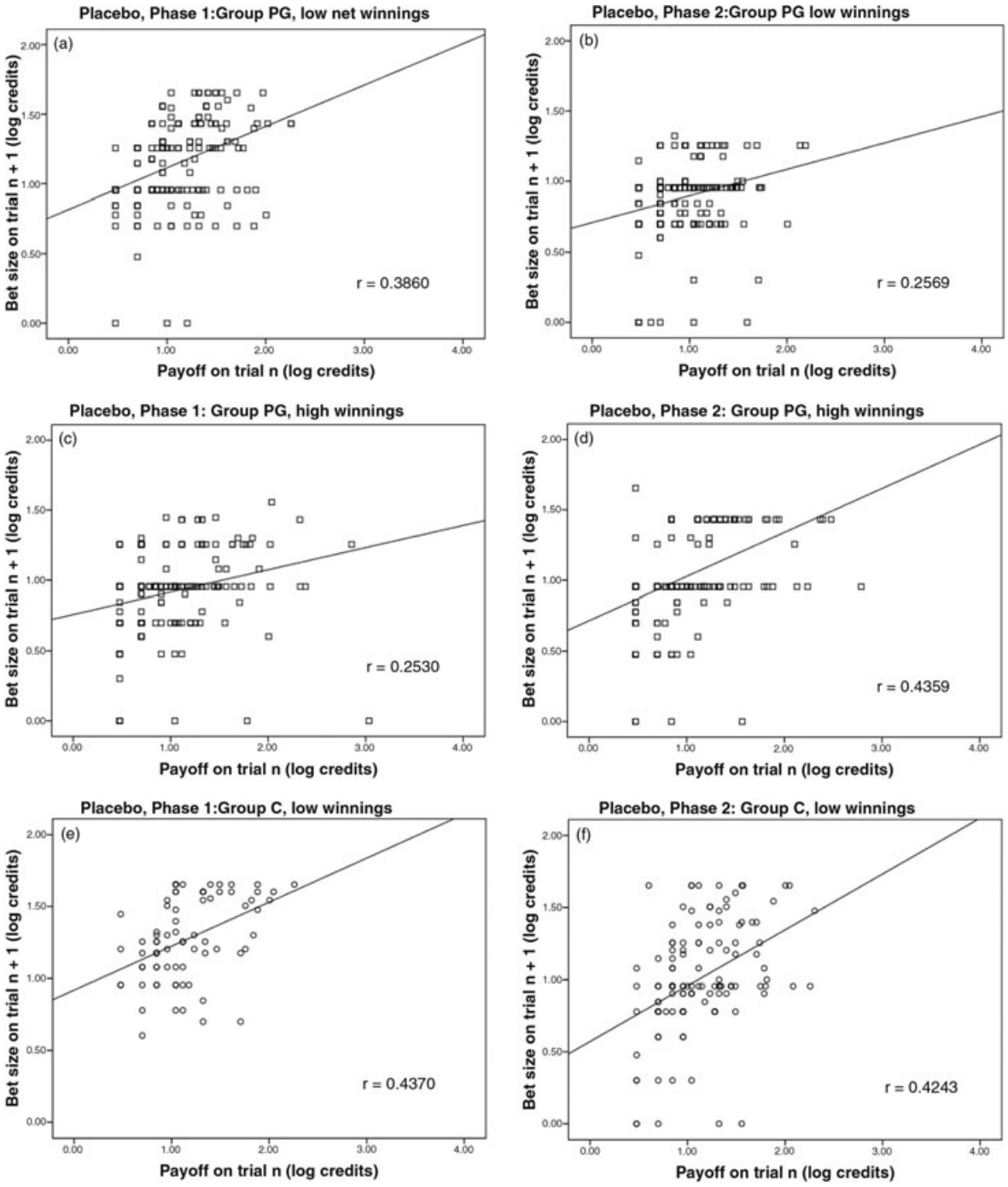

Figure 2 Scatter plots of the bivariate correlation between Payoff (log credits paid on trial n) and Bet Size (log credits bet on trial n + 1) for the first and second half of trials (Phase 1, 2) in a slot machine game when Cumulative Winnings were high versus low (sub-median, supra-median) in subjects with pathological gambling (Panels a–d) and healthy controls (Panels e–h) for the Placebo treatment session

$\beta = 0.572$, Bonferroni $P = 0.014$. Thus, the change in overall Bet Size from Phase 1 to Phase 2 varied depending on available resources. Regarding the latter result, bivariate correlations in the full sample revealed that when Winnings were low, average Bet Size, regardless of Payoff, declined over the course of the game, $r = -0.42$, $P < 0.001$. In contrast, when Winnings were high, average Bet Size increased marginally over the course of the game, $r = 0.14$, $P = 0.052$.

Figure 1b shows the bivariate correlations between Payoff and Bet Size for each level of Group, Phase and Winnings under Haloperidol and illustrates the three-

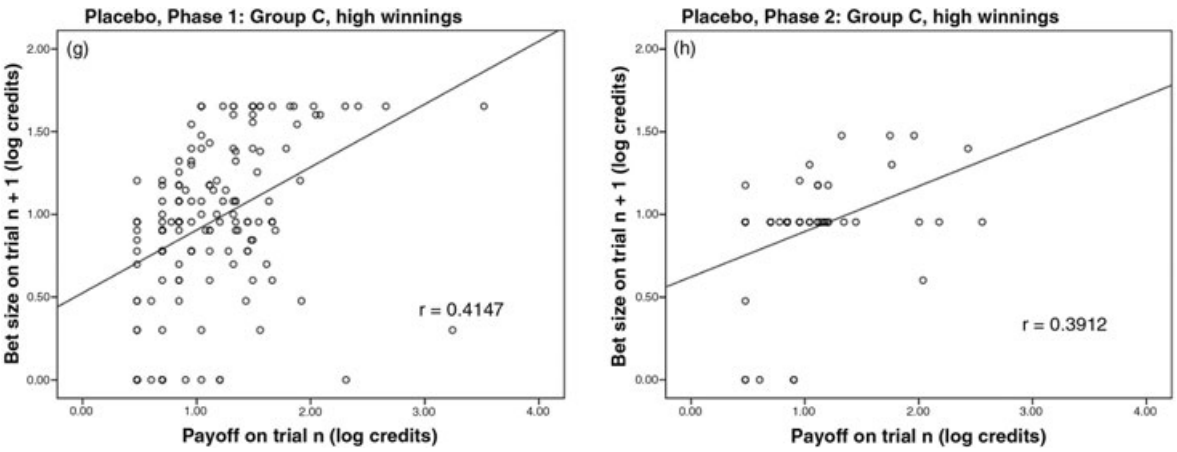

Figure 2 *Cont.*

Table 3 Hierarchical linear regression of relation between Payoff (log credits on trial n) and Bet Size (log credits on trial n + 1) and moderators of this relationship in pathological gamblers ($n = 20$) and healthy controls ($n = 18$) at each level of treatment (Haloperidol).

Model	*R*	R^2	*Adj.* R^2	*Std. Err. Est.*	R^2 *change*	*F change*	*d.f.1*	*d.f.2*	*Bonferroni P change*
1	0.409	0.167	0.165	0.3389	0.167	63.22	4	1257	<0.001
2	0.449	0.201	0.195	0.3327	0.034	8.89	6	1251	<0.001
3	0.458	0.210	0.201	0.3315	0.008	3.16	4	1247	0.026
4	0.459	0.211	0.202	0.3313	0.002	2.42	1	1246	0.240

Predictor/Effect	*Un-standardized b*	SE_b	*Beta*	t	*Bonferroni P value*
Group	−0.008	0.170	−0.011	−0.05	>0.999
Phase	−0.217	0.163	−0.293	−1.33	0.364
Payoff	0.457	0.075	0.549	6.07	<0.001[a]
Winnings	0.057	0.056	0.075	1.01	0.578
Group × Phase	0.171	0.148	0.115	1.16	0.496
Group × Payoff	−0.038	0.151	−0.056	−0.25	>0.999
Group × Winnings	−0.017	0.112	−0.032	−0.15	>0.999
Phase × Payoff	−0.139	0.145	−0.211	−0.96	0.678
Phase × Winnings	0.288	0.107	0.572	2.69	0.014[a]
Payoff × Winnings	−0.085	0.047	−0.213	−1.80	0.144
Group × Phase × Payoff	−0.257	0.095	−0.195	−2.72	0.014[a]
Group × Phase × Winnings	0.126	0.086	0.125	1.46	0.290
Group × Payoff × Winnings	0.089	0.094	0.203	0.94	0.696
Phase × Payoff × Winnings	−0.016	0.091	−0.038	−0.18	>0.999
Excluded from model:					
Group × Phase × Payoff × Winnings	−0.294	0.189	−0.344	−1.56	0.240

Group: Gamblers, Controls (−0.5, +0.5); Phase: Median split—first/second half of trials (−0.5, +0.5); Winnings: Median split of cumulative winnings (difference in payoff minus bet size, cumulated over trials) up to trial n (−0.5, +0.5).
[a]Significant semi-partial correlation (unique variance shared) by predictor(s) and criterion (bet size).

way interaction. The left half of Panel b shows that Gamblers exhibited a highly consistent relationship between Payoff and Bet Size over the course of the game (i.e. no Phase effect) when Winnings were low as well as high.

Figure 3, panels a–h, shows the scatter plots for the Haloperidol condition. Panels a–d depict the scores for PG subjects. Comparing panel a with b and panel c with d reveals the highly consistent Payoff–Bet Size correlation across Phases in PG subjects under

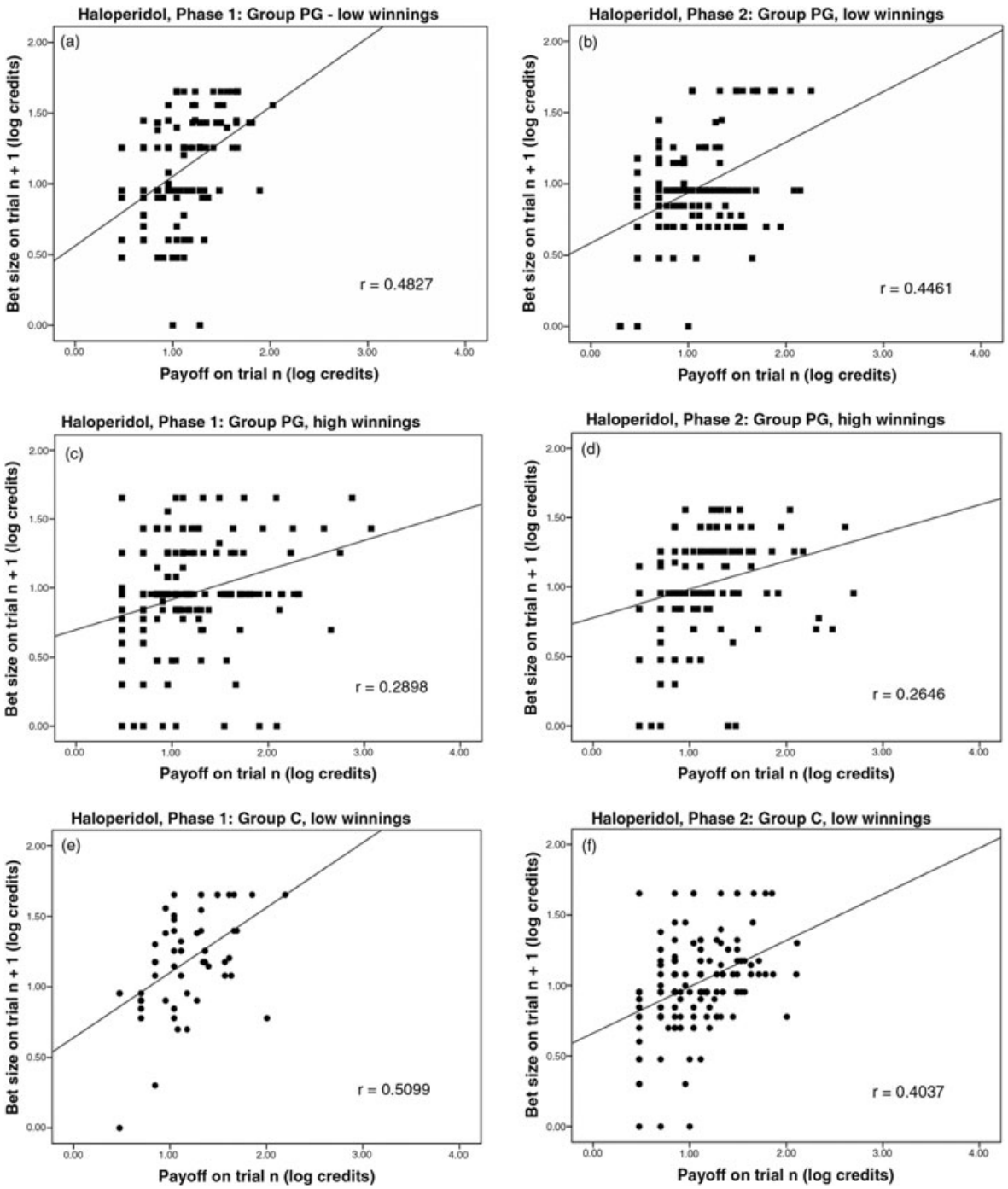

Figure 3 Scatters plot of the bivariate correlation between Payoff (log credits paid on trial n) and Bet Size (log credits bet on trial n + 1) for the first and second half of trials (Phase 1, 2) in a slot machine game when Cumulative Winnings were high versus low (sub-median, supra-median) in subjects with pathological gambling (Panels a–d) and healthy controls (Panels e–h) for the Haloperidol (3 mg) treatment session

the drug. Thus, in contrast to Group PG's pattern under placebo, under haloperidol, calibration of their Bet Size to Payoff remained stable throughout the game when Winnings were low and when they were high.

The right half of Fig. 1b shows the corresponding bivariate correlations for Controls and reveals a markedly different profile of effects. The strength of the correlation between Payoff and Bet Size was significantly greater during Phase 1 than Phase 2 at each level of Winnings.

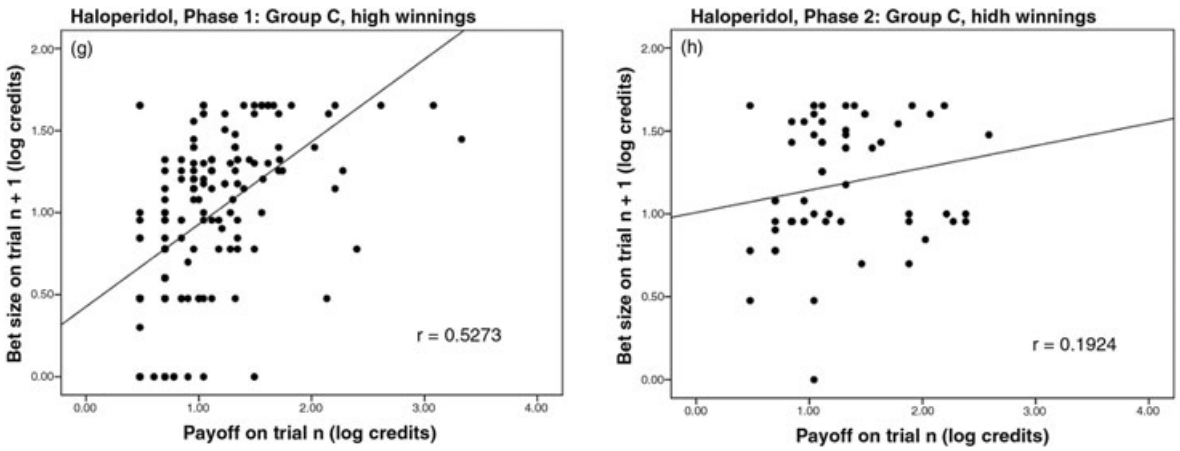

Figure 3 *Cont.*

Thus, under Haloperidol, Control subjects' betting response to the current payoff was very strong early in the game but became increasingly dissociated from current payoff as the game continued [2].

Panels e–h show the scatter plots for Controls under haloperidol. Comparing panel e with f and panel g with h reveals that the slope of the regression line declined significantly over the course of the game at each level of Winnings. Thus, in contrast to their pattern under placebo, under haloperidol, calibration of Bet Size to Payoff in Group C was highly unstable throughout the game—very strong in early trials and much weaker in later trials. That is, the extent to which Payoff guided Bet Size declined markedly under the drug in Controls.

[2] A preliminary analysis found that the decline in the Payoff-Bet Size correlation over phases under haloperidol was more pronounced in Control subjects who, due to counterbalancing, played the slot machine first under placebo on session 1 and then under drug on session 2. Although the Payoff-Bet Size correlation also declined significantly over phases under haloperidol in Controls who received drug on day 1, the relatively greater decline in those who received drug on day 2 suggests that haloperidol may have acted to disrupt Pavlovian-to-instrumental transfer of perceived associations between Bet Size and Payoff, established when subjects first encountered the game while drug-free. This is consistent with the literature showing that D2 antagonists have particularly strong disruptive effects on re-activation of recently acquired associations that serve to promote active seeking/approach of stimuli with learned incentive value.

Berridge KC (2007), The debate over DA's role in reward: the case for incentive salience. Psychopharmacology (Berl) 191:391–431. Lex A, Hauber W (2008) Dopamine D1 and D2 receptors in the nucleus accumbens core and shell mediate Pavlovian-instrumental transfer. Learn Mem 15:483–491. Phillips AG, Vacca G, Ahn S (2008) A top-down perspective on dopamine, motivation and memory. Pharmacol Biochem Behav 90:236–249.

Analysis of means

Non-reinforced trials

A 2 (Payoff: credits = 0, credits > 0) × 2 (Group) × 2 (Drug Condition) × 2 (Phase) × 2 (Cumulative Winnings: low, high) ANOVA of log-transformed Bet Size scores yielded a Payoff × Winnings interaction, F (1, 5568) = 32.44, $P < 0.001$, reflecting a greater difference in mean (SD) Bet Size (credits) following non-reinforced, 9.2 (9.7) versus reinforced trials, 13.0 (11.1), when Winnings were low, as against 11.2 (9.4) for non-reinforced versus 13.4 (10.6) for reinforced trials when Winnings were high. A Payoff × Group interaction, F (1, 5568) = 15.61, $P < 0.001$, reflected a greater difference in Bet Size for non-reinforced, 10.8 (10.7) versus reinforced trials 15.2 (12.7) in Controls compared with 10.1 (8.7) and 12.2 (9.4) credits for non-reinforced and reinforced trials, respectively, in Gamblers. There were no Drug Condition × Payoff interactions, P's > 0.16 (Effect size, $\eta 2 < 0.001$, $n = 5601$), and no higher-order effects involving Payoff, P's > 0.11 ($\eta 2 < 0.002$, $n = 5601$).

Big wins

The mean (SD; range) value of a Big Win (excluding trials where Payoff = 0) was 467 (547; 162–3300) credits. The mean (SD; range) value of a normative Win (excluding trials where Payoff = 0) was 15.0 (20; 1–160) credits.

A 2 (Big Win: payoff ≤ 98th percentile; payoff > 98th percentile) × 2 (Group) × 2 (Drug Condition) × 2 (Phase) × 2 (Cumulative Winnings) ANOVA of log-transformed Bet Size scores, excluding non-reinforced trials (Payoff = 0), yielded a Drug Condition × Phase × Big Win interaction, F (1, 2534) = 4.62, $P = 0.032$, a marginal Drug Condition × Group × Phase × Winnings interaction, F (1, 2534) = 2.80, $P = 0.095$, and no

higher-order interactions, $Ps > 0.81$ ($\eta 2 < 0.001$, $n = 2564$). The three-way interaction reflected a greater increase in mean (SD) Bet Size (credits) after a Big Win, 22.1 (13.7), than a normative Win, 14.0 (11.8), in Phase 1, as opposed to a Big Win, 15.0 (13.1), versus normative Win, 12.7 (10.4), in Phase 2 under Haloperidol. Under Placebo, the increase in Bet Size was comparable for a Big Win 24.7 (18.1) versus normative Win 14.5 (11.4) in Phase 1 as for a Big Win 19.1 (9.7) versus normative Win 11.3 (8.3) in Phase 2. Thus, Big Wins coincided with increased Bet Size, and this effect was consistent throughout the game under Placebo but declined in the second half of the game under Haloperidol.

A 2 (Big Win) × 2 (Group) × 2 (Drug Condition) × 2 (Cumulative Winnings) ANOVA of Trial number yielded no significant effects involving Big Win, $Ps > 0.12$ ($\eta 2 < 0.001$, $n = 2564$). Therefore, the timing of a Big Win did not differ as a function of Group, Drug Condition or Cumulative Winnings.

Cumulative winnings

A 2 (Group) × 2 (Drug Condition) × 2 (Phase) ANOVA of log-transformed Cumulative Winnings yielded main effects of Drug Condition, $F(1, 2556) = 8.79$, $P = 0.003$, and Phase, $F(1, 2556) = 143.96$, $P < 0.001$; a Group × Phase interaction, $F(1, 2556) = 32.40$, $P < 0.001$, a marginal Drug Condition × Phase interaction, $F(1, 2556) = 3.68$, $P = 0.055$, and no other significant effects, $Ps > 0.16$ ($\eta 2 < 0.001$, $n = 2564$).

The Drug Condition effect reflected greater mean (SD) log-transformed Cumulative Winnings under Haloperidol, 2.45 (0.42), than Placebo, 2.41 (0.45). However, the raw mean credits were virtually identical for Haloperidol, 392 (347), and Placebo, 391 (455). The Phase effect reflected greater log-Winnings in Phase 1, 2.51 (0.31), than Phase 2, 2.33 (0.52). Corresponding raw means were 421 (416) for Phase 1 versus 360 (392) for Phase 2. The Group × Phase effect reflected a larger decline in log-Winnings from Phase 1, 2.58 (0.30), to Phase 2, 2.28 (0.60), in Controls compared with a decline from 2.48 (0.32) to 2.38 (0.47) in Gamblers. The raw means for Phases 1 and 2 were 513 (597) and 392 (525) in Controls, as against 371 (254) and 346 (293) in Gamblers. The marginal Drug Condition–Phase interaction reflected a somewhat greater decline in log-Winnings from Phase 1, 2.50 (0.28), to Phase 2, 2.30 (0.57), under Placebo compared with a decline from 2.53 (0.35) to 2.37 (0.47) under Haloperidol. The lack of three-way interaction, $P = 0.163$ ($\eta 2 = 0.001$, $n = 2564$), ensured that group differences in the pattern of Winnings under drug and placebo did not account for the groups' different betting profiles under each level of Drug Condition.

DISCUSSION

This study investigated three main questions: Does slot machine gambling conform to the basic principles of instrumental reinforcement? Does DA mediate this process? Do PG subjects differ from Controls in their betting profile under placebo and their response to manipulation of DA? The correlation between Payoff on a given trial and Bet Size on the next trial operationally defined reinforcement: the stronger the correlation, the greater the reinforcement.

Evidence from animals suggested that a modest dose of haloperidol would induce a within-session decline in reinforced responding in healthy subjects (Sanger & Perrault 1995). Neuroimaging evidence from otherwise healthy subjects with PG showing hypo-responsiveness to monetary reward in the ventral striatum, the terminal region for mesolimbic DA neurons, suggested that a given Payoff would be less reinforcing for PG subjects than Controls under placebo (Reuter *et al.* 2005). Parallel profiles of reward-related responding in patients with Parkinson's disease and healthy subjects under a modest dose of haloperidol suggested that haloperidol would simulate patterns seen in Parkinson's patients in response to gambling (Frank & O'Reilly 2006; Steeves *et al.* 2009). Specifically, blockade of inhibitory D2 receptors under a modest dose of a D2 antagonist should increase reward-related DA release in PG subjects, with a corresponding increase in instrumental responding to rewarding stimuli under the drug.

In line with our first hypothesis, Payoff reliably predicted Bet Size on the subsequent trial regardless of other factors. The proportional increase in the criterion response (Betting) as a function of variations in the outcome of that response (Payoff) indicates that slot machine gambling conforms to the basic principles of instrumental conditioning. In Control subjects, who were essentially naive to slot machines, the Payoff–Bet Size correlation was highly consistent over the course of trials under placebo and seemingly unaffected by available resources in the form of Cumulative Winnings. In contrast, PG subjects' betting response to reward under placebo varied over the course of the game depending on Cumulative Winnings, becoming less responsive over trials when Winnings were low but more responsive over trials when Winnings were high. This pattern suggests that PG subjects were betting strategically to maximize their opportunity to extend play based on their available resources. Based on findings from cocaine abusers (Goldstein *et al.* 2007), PG subjects under placebo were expected to be relatively insensitive to variations in monetary reward throughout the game compared with healthy subjects. Accordingly, the Payoff–Bet Size correlation under placebo, averaged over

Phases and levels of Winnings, was weaker in PG subjects ($r = 0.33$) than in Controls ($r = 0.42$). However, this effect was moderated by Cumulative Winnings, indicating a heightened sensitivity to accumulated rewards in PG subjects rather than a general insensitivity to variations in current reward.

In line with our third hypothesis, healthy Controls exhibited a significant within-session decline in the Payoff–Bet Size correlation under haloperidol. Relative to placebo, this involved a heightened sensitivity to reward during the early stages of the game and a decreased sensitivity to reward during later trials. The pattern of effects indicates a preferential sensitivity to the marginal utility of a given Payoff (value added was more pronounced during early trials and less pronounced in later ones) and a corresponding decrease in sensitivity to the absolute value of a given Payoff.

The betting profile of PG subjects under haloperidol resembled the profile of Controls under placebo. The Payoff–Bet Size correlation was highly consistent regardless of Phase or Cumulative Winnings. Thus, PG subjects' betting behavior was more consistently guided by rewarding outcomes under the drug and more sensitive to variations in the magnitude of monetary reward.

Whereas haloperidol enhanced the calibration of Bet Size to Payoff in PG subjects, it disrupted this calibration in Controls. The differential effects of haloperidol may well reflect differences in the groups' behavior at drug-free baseline. Baseline-dependent effects are often observed with D2 manipulations. For example, the improvement in reward-related instrumental Go responding occasioned by haloperidol is significant in subjects with low working memory but not in subjects with high working memory (Frank & O'Reilly 2006). Low working memory has been observed in PG subjects (Leiserson & Pihl 2007), consistent with the apparent facilitative effect of haloperidol on PG subjects' reward-response calibration in the present study. The detrimental effect of haloperidol in Controls has also been observed in previous studies. For example, in healthy subjects who played a probabilistic decision-making task for money under haloperidol (1 mg) or L-dopa (100 mg), haloperidol was associated with a loss of differential striatal activation in response to reward-related versus non-reward-related stimuli and a corresponding decline in correct selection of the rewarding response option (Pessiglione *et al.* 2006). In other words, low-dose haloperidol rendered the instrumental response of healthy subjects indiscriminate. Taken together, these findings suggest that differences in baseline DA function contributed to the groups' differential response to haloperidol in the present study.

Grace (2000) proposed that chronic exposure to stimulants and alcohol increases baseline 'tonic' DA levels (i.e. sensitization), which preferentially stimulate high affinity inhibitory D2 receptors. This in turn reduces the intensity of DA release from a reward of given size. This would account for tolerance to the rewarding effects of a given dose of drug, which characterizes the addicted state. By blocking inhibitory D2 receptors, haloperidol would be expected to partially negate this effect. That is, a modest dose of haloperidol could act to reverse tolerance. To the extent that PG subjects resemble substance abusers, haloperidol might partially reverse the effects of chronic exposure to gambling, reinstating robust DA release in response to monetary reward. This would account for the close resemblance between the tightly calibrated betting profiles of PG subjects under haloperidol and that of gambling-naive Controls under placebo.

A recent theoretical account noted that 'tonic levels of striatal dopamine will be higher in a deprived state than in a sated state (as also suggested by Weiner & Joel 2002), given that the animal has reason to expect a higher overall reward rate in its motivated state' (Niv *et al.* 2007, p. 514). By partially blocking the tonic DA signal at D2 receptors, haloperidol may have reduced perceived deprivation (need for reward) such that PG subjects responded in a more discriminating manner to varying amounts of monetary reward. If PG resembles substance addiction, then, compared with PG subjects, Controls would be expected to have lower levels of tonic DA (Grace 2000). As such, Controls would be partially 'sated' with respect to monetary reward. In these subjects, a reduction in inhibitory feedback at D2 receptors could increase phasic DA release and enhance the reinforcing effects of initial rewards yet at the same time more rapidly induce satiation of reward seeking, such that only rewards with very high marginal utility could elicit a betting response. In short, differences in baseline tonic DA signaling at high affinity D2 receptors may account for the more measured reward-related responding of PG subjects and also explain the progressive decline in reward-related responding in Controls.

The ANOVAS revealed that Big Wins coincided with increased Bet Size relative to normative wins and that this difference was consistent throughout the game under Placebo. However, under Haloperidol, the enhancing effect of Big Wins on Bet Size declined significantly from the first to the second half of the game. This pattern of effects was not modified by Group. These results are consistent with the interpretation provided above, in that, other things being equal, the marginal utility of a Big Win would be greater early, when few rewards had been encountered, rather than late in the game.

Taken together, the regression analyses and ANOVAS yielded results that were largely consistent with previous studies that examined the effects of D2 probes on reward-related responding in experimental models e.g. (Frank & O'Reilly 2006; Pessiglione *et al.* 2006; Schott *et al.* 2008).

Given that the present findings emerged on an actual commercial slot machine, their congruity with the literature supports the external validity of the experimental models. At the same time, the congruity of the present findings with these prior models is remarkable given a fundamental difference between the slot machine game and those models. Specifically, in the present study there was no actual contingency between the criterion response and its outcome: in a slot machine, the payoffs on individual trials are all independent. Nevertheless, both PG subjects and Controls acted *as if* a contingency existed because Payoff correlated positively with Bet Size on the next trial in all conditions. This novel result raises the possibility that an illusory correlation between Payoff and Bet Size led to an actual correlation between these events, i.e. a self-fulfilling prophecy.

It is well established that, over the course of conditioning trials, cues for reward (CS) acquire a capacity to evoke DA release originally evoked by delivery of the reward itself (unconditioned stimulus; US) (Waelti, Dickinson & Schultz 2001). CS-induced DA release is greatest when the US is maximally uncertain (i.e. 50% variable ratio schedule) (Fiorillo *et al.* 2003). This closely matches the 46% frequency of reward delivery (i.e. Payoff ≠ 0) seen on the slot machine, suggesting that cues for monetary reward might well have elicited DA release in the present study.

In slot machine gambling, the act of betting is a close antecedent of reward. Because the outcome of the bet is unknown, the best predictor may be the outcome of prior bets. As such, the learned expectation of reward could guide behavior much as expectations guide a placebo response. In both cases, reinforcement derives as much or more from the subjective/anticipated effects of the US as from the objective reward imparted by it. This interpretation suggests that placebo effects may be an important matter to consider when devising interventions for PG cf. (Grant *et al.* 2008).

The reliable Payoff–Bet Size correlation seen in this study indicates that immediate rewards are especially salient in terms of their effects on reward expectancy in slot machine gambling. At the same time, the moderating effects of Phase on responses to normative wins in Controls and to Big Wins in both groups suggest an updating process so that betting is not exclusively stimulus bound or myopic. Thus, DA would appear to play a critical role in modulating discrete and ongoing betting behavior in these individuals. To the extent that persistent betting involves reactivation of a learned expectancy (Redish *et al.* 2007), efforts to reduce PG could involve establishing new expectancies—perhaps by playing the games under conditions that promote this. For example, medications that restore optimal DA transmission at D2 (and D1) receptors could render the DA-releasing effects of gambling less extraordinary or overvalued.

Although the enhanced Payoff–Bet Size calibration in PG subjects under haloperidol suggests a possible therapeutic effect of low-dose D2 antagonists, the subjective effects of the game suggest otherwise. As previously noted, haloperidol was associated with enhanced self-reported pleasurable effects of the game and increased priming of motivation to gamble in PG subjects (Zack & Poulos 2007). To our knowledge, 'typical' D2 antagonists, like haloperidol, have never been given chronically to otherwise healthy patients with PG. However, clinical trials with the 'atypical' D1-D2 receptor antagonist olanzapine have shown that the drug had very similar effects to placebo, making it difficult to isolate the role of D2 blockade (Fong *et al.* 2008; McElroy *et al.* 2008). In those studies, the placebo effects were substantial, and both drug and placebo groups improved relative to pre-treatment baseline. These findings further underscore the influence (both favorable and unfavorable) of expectancy effects in PG subjects.

The clinical significance of the D2 receptor in PG is illustrated by studies of direct D2 agonists. Findings from healthy controls, Parkinson's patients and patients with Restless Legs Syndrome suggest that these drugs reduce reward-related neural activation, promote risk-taking, and may aggravate or precipitate symptoms of PG (Quickfall & Suchowersky 2007; Voon *et al.* 2007b; Pizzagalli *et al.* 2008; Riba *et al.* 2008; Santesso *et al.* 2009; Bostwick *et al.* 2009). Direct, preferential stimulation of D2 receptors would approximate the state believed to promote tolerance to drug reward in substance abusers (Grace 2000). As such, D2 agonist effects may model the situation in drug-free PG subjects. If so, administration of a preferential D2 antagonist would be expected to restore homeostasis. The present findings support this possibility.

In contrast to the apparent adverse effects of direct D2 agonists, manipulations that increase D2 receptor availability have been shown to decrease rates of stimulant and alcohol self-administration in animals (Thanos *et al.* 2001, 2008). One way to enhance D2 signaling without preventing D2 receptors from exerting their modulating effects is to employ an indirect DA agonist. In a recent small-scale pre-clinical study, we found that the DA-norepinephrine reuptake inhibitor modafinil significantly reduced mean bet size in PG subjects, although the drug had bidirectional effects on subjective motivation to gamble in high versus low impulsive subjects (Zack & Poulos 2009). Animal studies suggest that D2 receptors may have mediated some of modafinil's inhibitory effects (Korotkova *et al.* 2007). These findings suggest that modafinil and other indirect DA-enhancing medications (Mutschler *et al.* 2010) may have therapeutic potential

for PG subjects, but also highlight the importance of considering individual differences when evaluating DA medications.

The present study had a number of limitations. First, DA transmission was not directly measured. Therefore, the proposed increase in reward-related DA release under haloperidol can only be inferred. Also, the use of a single dose of haloperidol limits the extent to which the findings may be extrapolated. More generally, the precise role of DA in the different elements of slot machine gambling (e.g. acquisition/learning, expression/performance) cannot be established from the present data. There is intense debate surrounding the role of DA in reward-related behaviors in general and addictive behavior in particular. An adequate consideration of these theories with respect to slot machine gambling is beyond the scope of this investigation. Like most commercial slot machines, reward delivery in this game was accompanied by bells and lights, which were indexed to the number of credits won (one ding/credit) and time-locked to the delivery of credits on the tally line. This provided a coordinated, multidimensional (numeric, visual, auditory), graded reward signal on winning trials. Because the multidimensional nature of rewards was consistent across Drug Condition, Group and Phase of the game, variations in the relationship between Payoff and Bet Size as a function of these variables cannot be attributed to the fact that the reward was 'coded' in a multidimensional manner. Nonetheless, it is possible that the effects observed here would have been less robust if the reward signal were less salient. Lastly, the present sample excluded PG subjects with major depression or alcohol use disorders. Although this permitted unambiguous attribution of group-related effects to PG status, the high rates of co-morbidity (>50%) of these disorders in PG suggest that the findings may not generalize to the broader population of individuals with PG. To the extent that this affects the treatment of PG, direct comparison of co-morbid and non-co-morbid PG subjects in this paradigm is an important avenue of future investigation.

Despite these limitations, the present study yielded several important results. First, the reliable prospective correlation between Payoff and Bet Size provides clear support for the role of instrumental conditioning in slot machine gambling. As such, strategies for curbing the adverse effects of these devices may be derived from the extensive literature on this topic. Second, the finding that haloperidol modified reward-related responding in both groups indicates that DA plays a critical role in initial responses to gambling as well as well-established ones. Third, the within-session changes and outcome-specific betting patterns found here highlight the importance of assessing variability in gambling-related responses along with aggregate or mean effects to fully characterize the processes involved. Fourth, the apparent ability of varying Payoffs to systematically influence Bet Size despite the lack of contingency between them suggests that in probabilistic models like gambling, reward-related expectancies can drive betting behavior even though the expectancy is not borne out (i.e. Bet Size does not causally affect Payoff). This in turn suggests that modifying such expectancies may enhance cognitively oriented PG interventions. Finally, the results point to possible alterations in the DA system of PG subjects similar to those seen in substance abusers. Research designed to directly compare DA function in PG subjects and substance abusers could help to specify the neurochemical commonalities between 'behavioral' and substance addictions.

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Authors Contribution

AMT analyzed and reported the findings. RCD executed the study, collected the data, summarized and reported result. CXP co-designed and co-supervised the study. MZ co-designed and co-supervised the study, developed analytic approach, and reported the results. All authors consulted on the text of the manuscript. CXP and MZ performed final revisions.

References

Ahn S, Phillips AG (1999) Dopaminergic correlates of sensory-specific satiety in the medial prefrontal cortex and nucleus accumbens of the rat. J Neurosci 19:RC29.

Bakken IJ, Gotestam KG, Grawe RW, Wenzel HG, Oren A (2009) Gambling behavior and gambling problems in Norway 2007. Scand J Psychol 50:333–339.

Barry DT, Steinberg MA, Wu R, Potenza MN (2008) Characteristics of black and white callers to a gambling helpline. Psychiatr Serv 59:1347–1350.

Berridge KC (2007) The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl) 191:391–431.

Bjork JM, Momenan R, Smith AR, Hommer DW (2008) Reduced posterior mesofrontal cortex activation by risky rewards in substance-dependent patients. Drug Alcohol Depend 95:115–128.

Bland JM, Altman DG (1996) Transforming data. BMJ 312:770.

Bostwick JM, Hecksel KA, Stevens SR, Bower JH, Ahlskog JE (2009) Frequency of new-onset pathologic compulsive gambling or hypersexuality after drug treatment of idiopathic Parkinson disease. Mayo Clin Proc 84:310–316.

Bryk AS, Raudenbush SW (1992) Hierarchical Linear Models: Applications and Data Analysis Methods. Newbury Park, CA: Sage.

Dalley JW, Everitt BJ (2009) Dopamine receptors in the learning, memory and drug reward circuitry. Semin Cell Dev Biol 20:403–410.

Dranias MR, Grossberg S, Bullock D (2008) Dopaminergic and non-dopaminergic value systems in conditioning and outcome-specific revaluation. Brain Res 1238:239–287.

Evans MG (1991) The problem of analyzing multiplicative composites: interactions revisited. Am Psychol 46:6–15.

Fields HL, Hjelmstad GO, Margolis EB, Nicola SM (2007) Ventral tegmental area neurons in learned appetitive behavior and positive reinforcement. Annu Rev Neurosci 30:289–316.

Fiorillo CD, Tobler PN, Schultz W (2003) Discrete coding of reward probability and uncertainty by dopamine neurons. Science 299:1898–1902.

Fong T, Kalechstein A, Bernhard B, Rosenthal R, Rugle L (2008) A double-blind, placebo-controlled trial of olanzapine for the treatment of video poker pathological gamblers. Pharmacol Biochem Behav 89:298–303.

Frank MJ, O'Reilly RC (2006) A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. Behav Neurosci 120:497–517.

Goldstein RZ, Alia-Klein N, Tomasi D, Zhang L, Cottone LA, Maloney T, Telang F, Caparelli EC, Chang L, Ernst T, Samaras D, Squires NK, Volkow ND (2007) Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? Am J Psychiatry 164:43–51.

Goldstein RZ, Tomasi D, Alia-Klein N, Honorio Carrillo J, Maloney T, Woicik PA, Wang R, Telang F, Volkow ND (2009) Dopaminergic response to drug words in cocaine addiction. J Neurosci 29:6001–6006.

Grace AA (2000) The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and psychostimulant craving. Addiction 95 (Suppl 2):S119–S128.

Grant JE, Brewer JA, Potenza MN (2006) The neurobiology of substance and behavioral addictions. CNS Spectr 11:924–930.

Grant JE, Kim SW, Hollander E, Potenza MN (2008) Predicting response to opiate antagonists and placebo in the treatment of pathological gambling. Psychopharmacology (Berl) 200:521–527.

Haertzen CA (1965) Addiction Research Center Inventory (ARCI): development of a general drug estimation scale. J Nerv Ment Dis 141:300–307.

Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62.

Johnson AW, Gallagher M, Holland PC (2009) The basolateral amygdala is critical to the expression of pavlovian and instrumental outcome-specific reinforcer devaluation effects. J Neurosci 29:696–704.

Kassinove JI, Schare ML (2001) Effects of the "near miss" and the "big win" on persistence at slot machine gambling. Psychol Addict Behav 15:155–158.

Kessler RC, Hwang I, LaBrie R, Petukhova M, Sampson NA, Winters KC, Shaffer HJ (2008) DSM-IV pathological gambling in the National Comorbidity Survey Replication. Psychol Med 38:1351–1360.

Korotkova TM, Klyuch BP, Ponomarenko AA, Lin JS, Haas HL, Sergeeva OA (2007) Modafinil inhibits rat midbrain dopaminergic neurons through D2-like receptors. Neuropharmacology 52:626–633.

Leiserson V, Pihl RO (2007) Reward-sensitivity, inhibition of reward-seeking, and dorsolateral prefrontal working memory function in problem gamblers not in treatment. J Gambl Stud 23:435–455.

Lesieur HR, Blume SB (1987) The South Oaks Gambling Screen (SOGS): a new instrument for the identification of pathological gamblers. Am J Psychiatry 144:1184–1188.

Lex A, Hauber W (2008) Dopamine D1 and D2 receptors in the nucleus accumbens core and shell mediate Pavlovian-instrumental transfer. Learn Mem 15:483–491.

Loba P, Stewart SH, Klein RM, Blackburn JR (2001) Manipulations of the features of standard video lottery terminal (VLT) games: effects in pathological and non-pathological gamblers. J Gambl Stud 17:297–320.

McElroy SL, Nelson EB, Welge JA, Kaehler L, Keck PE, Jr (2008) Olanzapine in the treatment of pathological gambling: a negative randomized placebo-controlled trial. J Clin Psychiatry 69:433–440.

Mehta MA, Sahakian BJ, McKenna PJ, Robbins TW (1999) Systemic sulpiride in young adult volunteers simulates the profile of cognitive deficits in Parkinson's disease. Psychopharmacology (Berl) 146:162–174.

Mutschler J, Bühler M, Diehl A, Mann K, Kiefer F (2010) Disulfiram, an old drug with new potential in the treatment of pathological gambling? Med Hypotheses 74:209–210.

Niv Y, Daw ND, Joel D, Dayan P (2007) Tonic dopamine: opportunity costs and the control of response vigor. Psychopharmacology (Berl) 191:507–520.

Nordstrom AL, Farde L, Halldin C (1992) Time course of D2-dopamine receptor occupancy examined by PET after single oral doses of haloperidol. Psychopharmacology (Berl) 106:433–438.

Pallanti S, Bernardi S, Quercioli L, DeCaria C, Hollander E (2006) Serotonin dysfunction in pathological gamblers: increased prolactin response to oral m-CPP versus placebo. CNS Spectr 11:956–964.

Pehek EA (1999) Comparison of effects of haloperidol administration on amphetamine-stimulated dopamine release in the rat medial prefrontal cortex and dorsal striatum. J Pharmacol Exp Ther 289:14–23.

Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD (2006) Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 442:1042–1045.

Petry NM (2003) A comparison of treatment-seeking pathological gamblers based on preferred gambling activity. Addiction 98:645–655.

Phillips AG, Vacca G, Ahn S (2008) A top-down perspective on dopamine, motivation and memory. Pharmacol Biochem Behav 90:236–249.

Pizzagalli DA, Evins AE, Schetter EC, Frank MJ, Pajtas PE, Santesso DL, Culhane M (2008) Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. Psychopharmacology (Berl) 196:221–232.

Potenza MN (2008) Review. The neurobiology of pathological gambling and drug addiction: an overview and new findings. Philos Trans R Soc Lond B Biol Sci 363:3181–3189.

Potenza MN, Steinberg MA, McLaughlin SD, Wu R, Rounsaville BJ, O'Malley SS (2001) Gender-related differences in the characteristics of problem gamblers using a gambling helpline. Am J Psychiatry 158:1500–1505.

Quickfall J, Suchowersky O (2007) Pathological gambling associated with dopamine agonist use in restless legs syndrome. Parkinsonism Relat Disord 13:535–536.

Redish AD, Jensen S, Johnson A, Kurth-Nelson Z (2007) Reconciling reinforcement learning models with behavioral

extinction and renewal: implications for addiction, relapse, and problem gambling. Psychol Rev 114:784–805.

Reuter J, Raedler T, Rose M, Hand I, Glascher J, Buchel C (2005) Pathological gambling is linked to reduced activation of the mesolimbic reward system. Nat Neurosci 8:147–148.

Riba J, Kramer UM, Heldmann M, Richter S, Munte TF (2008) Dopamine agonist increases risk taking but blunts reward-related brain activity. PLoS ONE 3:e2479.

Robbins TW, Everitt BJ (1999) Drug addiction: bad habits add up. Nature 398:567–570.

Robinson TE, Berridge KC (2000) The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction 95 (Suppl 2):S91–S117.

Saez-Abad C, Bertolin-Guillen JM (2008) Personality traits and disorders in pathological gamblers versus normal controls. J Addict Dis 27:33–40.

Sanger DJ, Perrault G (1995) Effects of typical and atypical antipsychotic drugs on response decrement patterns in rats. J Pharmacol Exp Ther 272:708–713.

Santesso DL, Evins AE, Frank MJ, Schetter EC, Bogdan R, Pizzagalli DA (2009) Single dose of a dopamine agonist impairs reinforcement learning in humans: evidence from event-related potentials and computational modeling of striatal-cortical function. Hum Brain Mapp 30:1963–1976.

Schott BH, Minuzzi L, Krebs RM, Elmenhorst D, Lang M, Winz OH, Seidenbecher CI, Coenen HH, Heinze HJ, Zilles K, Duzel E, Bauer A (2008) Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. J Neurosci 28:14311–14319.

Shacham S (1983) A shortened version of the Profile of Mood States. J Pers Assess 47:305–306.

Skinner BF, ed. (1953) Science and Human Behavior. New York: Free Press.

Smith RJ (1993) Logarithmic transformation bias in allometry. Am J Phys Anthropol 90:215–228.

Steeves TD, Miyasaki J, Zurowski M, Lang AE, Pellecchia G, Van Eimeren T, Rusjan P, Houle S, Strafella AP (2009) Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. Brain 132:1376–1385.

Thanos PK, Volkow ND, Freimuth P, Umegaki H, Ikari H, Roth G, Ingram DK, Hitzemann R (2001) Overexpression of dopamine D2 receptors reduces alcohol self-administration. J Neurochem 78:1094–1103.

Thanos PK, Michaelides M, Umegaki H, Volkow ND (2008) D2R DNA transfer into the nucleus accumbens attenuates cocaine self-administration in rats. Synapse 62:481–486.

Volkow ND, Fowler JS, Wang GJ, Goldstein RZ (2002) Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. Neurobiol Learn Mem 78:610–624.

Volkow ND, Wang GJ, Fowler JS, Molina PE, Logan J, Gatley SJ, Gifford A, Ding YS, Wong C, Pappas NR, Zhu W, Swanson JM (2003) Cardiovascular effects of methylphenidate in humans are associated with increases of dopamine in brain and of epinephrine in plasma. Psychopharmacology (Berl) 166:264–270.

Volkow ND, Fowler JS, Wang GJ, Swanson JM, Telang F (2007) Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. Arch Neurol 64:1575–1579.

Voon V, Potenza MN, Thomsen T (2007a) Medication-related impulse control and repetitive behaviors in Parkinson's disease. Curr Opin Neurol 20:484–492.

Voon V, Thomsen T, Miyasaki JM, de Souza M, Shafro A, Fox SH, Duff-Canning S, Lang AE, Zurowski M (2007b) Factors associated with dopaminergic drug-related pathological gambling in Parkinson disease. Arch Neurol 64:212–216.

Waelti P, Dickinson A, Schultz W (2001) Dopamine responses comply with basic assumptions of formal learning theory. Nature 412:43–48.

Weiner I, Joel D (2002) Dopamine in schizophrenia: dysfunctional information processing in basal gangliathalamocortical split circuits. In: Dopamine in the CNS II (Handbook of Experimental Pharmacology). Di Chiara G (ed). Springer-Verlag: Berlin. pp. 417–472.

Wheeler BW, Rigby JE, Huriwai T (2006) Pokies and poverty: problem gambling risk factor geography in New Zealand. Health Place 12:86–96.

Williams RJ, West BL, Simpson RI (2007) Prevention of Problem Gambling: A Comprehensive Review of the Evidence. Guelph: Ontario Problem Gambling Research Centre.

Wrase J, Schlagenhauf F, Kienast T, Wustenberg T, Bermpohl F, Kahnt T, Beck A, Strohle A, Juckel G, Knutson B, Heinz A (2007) Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. Neuroimage 35:787–794.

Zack M, Poulos CX (2007) A D2 antagonist enhances the rewarding and priming effects of a gambling episode in pathological gamblers. Neuropsychopharmacology 32:1678–1686.

Zack M, Poulos CX (2009) Effects of the atypical stimulant modafinil on a brief gambling episode in pathological gamblers with high vs. low impulsivity. J Psychopharmacol 23:660–671.

