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Serotonin and dopamine play complementary roles in gambling to recover losses

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ABSTRACT

Continued gambling to recover losses – 'loss-chasing' – is a prominent feature of social and pathological gambling. However, little is known about which neuromodulators influence this behaviour. In 3 separate experiments, we investigated the role of serotonin activity, D₂/D₃ receptor activity, and beta-adrenoceptor activity on the loss-chasing of age and IQ-matched healthy adults randomised to treatment or an appropriate control/placebo. In Experiment 1, participants consumed amino acid drinks that did or did not contain the serotonin precursor, tryptophan. In Experiment 2, participants received a single 176µg dose of the D₂/D₃ receptor agonist, pramipexole, or placebo. In Experiment 3, participants received a single 80mg dose of the beta-adrenoceptor blocker, propranolol, or placebo. Following treatment, participants completed a computerised loss-chasing game. Mood and heart rate was measured at baseline and following treatment. Tryptophan depletion significantly reduced the number of decisions made to chase losses, and the number of consecutive decisions to chase, in the absence of marked changes in mood. By contrast, pramipexole significantly increased the value of losses chased and diminished the value of losses surrendered. Propranolol markedly reduced heart rate but produced no significant changes in loss-chasing behaviour. Loss-chasing can be thought of as an aversively motivated escape behaviour controlled, in part, by the marginal value of continued gambling relative to the value of already accumulated losses. Serotonin and dopamine appear to play dissociable roles in the tendency of individuals to gamble to recover or to seek to 'escape' from previous losses. Serotonergic activity seems to promote the availability of loss-chasing as a behavioural option, while D₂/D₃ receptor activity produces complex changes in the value of losses judged worth chasing. Sympathetic arousal, at least as mediated by beta-adrenoceptors, does not play a major role in loss-chasing choices.

INTRODUCTION

Continued gambling to recover previous losses, or loss-chasing (Lesieur 1977), is a central feature of human decision-making (Kahneman and Tversky 2000). However, in a clinical context, excessive loss-chasing is also a prominent indicator of impaired control in a significant proportion of those individuals who report problems with their gambling behaviour (Corless and Dickerson 1989, McBride et al 2010, Sacco et al 2010). Left unchecked, loss-chasing can produce a dangerous spiral of gambling involvement, increasing financial liabilities but diminishing resources; and, potentially, the serious adverse family, social and occupational consequences of pathological gambling (Lesieur 1979).

At a psychological level, loss-chasing is complex and frequently involves conflicted motivational states, pitting the desire (or need) to keep playing against the dread of suffering even greater losses (Lesieur 1977); powerful emotional states that are mediated by activity within dissociable neural circuits (Campbell-Meiklejohn et al 2008). Gambling to recover losses is also associated with heightened states of arousal (see below) and a preoccupation with gambling activities that is a prominent feature of the clinical presentation of gambling problems (Dickerson et al 1987, McBride et al 2010). Consequently, loss-chasing may represent a salient target for the development of therapeutic interventions.

Despite its centrality to problem gambling, we know little about the way loss-chasing is influenced by the activity of neurochemical systems. A small amount of clinical evidence suggests that pathological gambling is associated with serotonergic dysfunction as exemplified by (inconsistent) reports of reduced concentrations of the serotonin metabolite, 5-hydroxyindoleacetic acid in cerebrospinal fluid (Bergh et al 1997, Roy et al 1988) and by reports of increased prolactin release (and reports of a 'high') following acute challenge with

the 5-HT_{2c} receptor agonist, meta-chlorophenylpiperazine (Pallanti et al 2006). Selective serotonin reuptake inhibitors have also shown promise as a treatment of pathological gambling via their anti-compulsive and anxiolytic effects (Grant and Potenza 2006, Pallesen et al 2007). Finally, serotonin exerts pronounced — albeit, complex — influences on impulsive behaviours (Winstanley et al 2004), which both promote loss-chasing (Breen and Zuckerman 1999) and are exaggerated in problem gamblers (Blaszczynski et al 1997).

The pathophysiology of problem-gambling is also highly likely to involve dysfunction of the dopaminergic midbrain, and its mesolimbic and prefrontal projections sites (Hewig et al 2010, Potenza 2008). Compared to matched healthy control subjects, pathological gamblers show reduced neuronal responses within mesostriatal nuclei while engaging in a simulated gambling behaviour for monetary reward (Reuter et al 2005). Administration of the psychostimulant, amphetamine, to pathological gamblers can prime cognitions about gambling (Zack and Poulos 2004) while the D₂ receptor antagonist, haloperidol, can enhance the rewarding properties of such behaviour (Zack and Poulos 2007). Finally, accumulating evidence indicates that dopaminergic treatments are associated with pathological gambling (and other impulse control problems) in a minority of patients with Parkinson's Disease (Voon et al 2007), presumably reflecting a disturbance of dopamine's wider role in reinforcement learning and the computation of action-value relationships (Dagher and Robbins 2009, Voon et al 2010). Thus, the extant evidence suggests that both serotonin and dopamine dysfunction mediate aspects of problematic gambling (Zeeb et al 2009). However, to date, their role in the central feature of loss-chasing behaviour has not yet been explored experimentally.

One way to start to understand the neurochemical substrates of the excessive loss-chasing sometimes observed in problem gamblers is to investigate the roles of different neuromodulators in the chasing behaviour of healthy adults with limited gambling

experiences. Information gained from such experiments will assist the formulation of hypotheses about how disturbances in the activity of neuromodulators mediate loss-chasing in the pathological state. Here, in 3 experiments, we used a behavioural model of loss-chasing developed in our laboratory and already validated with functional magnetic resonance imaging (Campbell-Meiklejohn et al 2008) to compare the loss-chasing behaviour of non-clinical healthy adults (who reported only very limited gambling involvement) following manipulations of serotonergic, dopaminergic (D_2/D_3) and beta-adrenoceptor activity.

In Experiment 1, we investigated the effects of tryptophan depletion on the tendency to continue gambling to recover losses and tested between 2 hypotheses with clearly divergent predictions. Serotonin is known to play a prominent role in the control of non-rewarded activity and the inhibition of behaviour following the occurrence of punishing or aversive events (Soubrie 1986). Furthermore, temporary reductions in central serotonin activity, achieved through tryptophan depletion, can diminish punishment-induced inhibition of ongoing behaviour in healthy adults (Crockett et al 2009). On this basis, we might expect that tryptophan depletion will increase the tendency to continue gambling in order to recover previous losses through a loss of serotonin-dependent behavioural inhibition.

On the other hand, serotonin also mediates important aspects of learning about negative events (Bari et al 2010, Daw et al 2002, Deakin and Graeff 1991, Evers et al 2005). Dayan et al (2008) has proposed that failures of behavioural control following reductions in serotonin activity (experimental or clinical) can produce pervasive increases in the size of negative prediction errors that, in turn, engender negative affective states in vulnerable individuals (Dayan and Huys 2008). Experimentally, tryptophan depletion can improve the accuracy of predictions of negative or punishing outcomes in healthy adults (Cools et al 2008). Moreover, Evers et al (2005) showed that tryptophan depletion enhances neural activity in response to

errors during reversal learning within the anterior cingulate region; an area that is activated while making decisions to stop chasing losses (Campbell-Meiklejohn et al 2008). Thus, we might also predict that tryptophan depletion will enhance the salience of bad outcomes during a run of losing gambles, and diminish subsequent loss-chasing behaviour.

In Experiment 2, we investigated the effects of a single dose of the non-ergoline D₂/D₃ receptor agonist, pramipexole. Alongside other dopaminergic treatments, treatment with pramipexole has been associated with gambling problems in a subset of Parkinson's Disease patients (Voon et al 2007). However, there has been no test of whether D₂/D₃ receptors agonists alter chasing behaviour during a run of losing gambles.

Pramipexole is significantly more selective for D₃ than D₂ receptors and binds to dopamine (autoreceptor and post-synaptic) receptors in mesolimbic reward pathways (Camacho-Ochoa et al 1995) (see Supplemental Information). Single low doses of pramipexole (e.g. 0.5mg) can impair reinforcement learning in healthy adults (Pizzagalli et al 2008), and increase risky choices in lottery-type games (Riba et al 2008), possibly through blunted reward signalling of mesolimbic pathways (Riba et al 2008, Santesso et al 2009). In the light of this, and evidence that low doses of pramipexole, and other agents acting upon D₂ receptors impair the signalling of bad outcomes ('negative prediction errors') (Frank and O'Reilly 2006, Santesso et al 2009, van Eimeren et al 2009), we tested the hypothesis that single doses of pramipexole increase loss-chasing behaviour and, perhaps, influence the value of losses that individuals are prepared to chase.

Although it is unlikely that the findings we report in Experiments 1 and 2 reflect gross changes in subjective states associated with either tryptophan depletion or treatment with

pramipexole, it is possible that our observations relate to changes in alerting or arousal, perhaps reflecting the relatively prolonged protocols of pharmacological experiments. For example, while tryptophan depletion typically does not modify state affect in adults who have been screened for affective disorders, it may attenuate physiological (cardiac) responses to negative performance feedback (van der Veen et al 2008). Moreover, field studies indicate that commercial gambling is associated increased in sympathetic arousal (Anderson and Brown 1984, Meyer et al 2000). However, it is unclear whether changes in arousal might increase or decrease the tendency to keep gambling to recover losses. Previously, we have found that single doses of the beta-adrenoceptor antagonist, propranolol, reduced decision-makers' attention towards punishment-related cues (Rogers et al 2004), potentially releasing loss-chasing behaviour. Therefore, in Experiment 3, we tested whether changes in arousal, as reflected in the kind of reduced heart rate produced in healthy adults by a single dose of the beta-adrenoceptor antagonist propranolol would influence loss-chasing behaviour.

Materials and Methods

Participants and Designs

All participants were given a clinical examination by an experienced psychiatrist, including a semi-structured SCID-I interview to ensure that none of the following exclusion criteria were met: (i) major physical illness, (ii) current or previous DSM-IV major mood or psychotic disorder (iii) current or previous DSM-IV substance abuse disorder. Participants were assessed with the South Oaks Gambling Screen (Lesieur and Blume 1987); all scores were either 0 or 1, indicating no evidence of gambling problems or pathological gambling.

Experiment 1. Thirty four healthy adults participated. None had any history of mood disorder; there was no restriction on the phase of menstrual cycle in female participants.

Seventeen participants (8 males) ingested an amino-acid drink that did not contain tryptophan (T-) and 17 participants (8 males) ingested an amino-acid drink that did contain tryptophan (T+). The T+ participants and T- participants were matched in terms of their gender (see Table S1), age ($F < 1.00$), and cognitive ability (Raven et al 1998) ($F(1, 30) < 2.08$).

Participants followed a low-protein diet ($< 2\text{g}$) the day before the study, and fasted overnight before attending the laboratory at 8.30 am on the day of the experiment. Measures of state positive and negative affect (Watson et al 1988) were taken at this time along with 15ml blood samples to obtain total plasma tryptophan concentrations. Participants then drank an amino-acid drink over a 60min period. None of the participants reported side effects beyond transitory nausea. Participants were given a low-protein ($< 2\text{g}$) lunch at midday. Repeat state positive and negative affect measurements, and a second blood sample, were collected +5h after consumption of the amino acid drink, before completing the loss-chasing game.

Experiment 2. Thirty healthy adults were randomly assigned to receive 176 μg of pramipexole (PPX) or placebo (Placebo-PPX). Each group contained 7 males. There were no significant differences between those participants who received placebo and those who received pramipexole in terms of their age or cognitive ability (Table S2) (both $F_s < 1.00$).

The 176 μg dose of pramipexole used in Experiment 2 is comparable to dosages shown to be clinically effective for restless leg syndrome (Manconi et al 2007). There are good reasons to suppose that the subjective (Hamidovic et al 2008) and behavioural (Pizzagalli et al 2008, Riba et al 2008, Santesso et al 2009) effects of low doses of dopaminergic agents reflect pre-synaptic actions at the auto-receptors that regulate the activity of mid-brain dopaminergic neurones (Frank and O'Reilly 2006, Grace 1995). As

described below, we replicate findings that single (1mg) low doses of pramipexole reduce psychometric measurements of state positive affect in healthy adults and that have been taken to suggest a pre-synaptic mode of action (Hamidovic et al 2008). However, our 176µg dose is also comparable to those shown to reduce serum prolactin over 2hr (Schilling et al 1992), at least raising the possibility that our results also involve some post-synaptic receptor activity (Ben-Jonathan 1985).

Participants attended the laboratory at 8.30am and completed baseline assessments of state positive and negative affect (Watson et al 1988). Baseline measures of systolic/diastolic blood pressure (BP) and heart rate (HR) were collected. Following this, participants received a single 176µg dose of pramipexole or a gelatine capsule containing lactose. Two hours later (+2h), further measurements of systolic/diastolic BP and HR were taken. State positive and negative affect were also collected at this time, before completion of the loss-chasing game.

Experiment 3. Fourteen (7 males) participants were randomly assigned to receive 80mg propranolol (Placebo-PPL) and 14 participants (8 males) were randomly assigned to receive a lactose placebo (PLA-PPL). The 2 groups of participants were well-matched in terms of their age (see Table S4), $F < 1$, and their cognitive ability ($F(1, 24) = 1.87$).

Participants attended the laboratory in the mornings having fasted for 2h and without caffeine intake. State positive and negative affect (PANAS) (Watson et al 1988), systolic BP, diastolic BP and HR was assessed at baseline and then every 30min thereafter. Participants completed the computerised loss-chasing game +75min following treatment.

Loss-chasing Game

A version of our loss-chasing game suitable for functional magnetic resonance imaging has been described in detail elsewhere (Campbell-Meiklejohn et al 2008). On each play, participants were required to choose between gambling to recover a loss (at the risk of doubling its size) or quitting (and sustaining a certain loss). Such dilemmas induce risky choices in a variety of social and economic contexts (Shafir and Tversky 1995). Descriptive theories of choice (under uncertainty) attribute this behaviour to the fact that losses fall on the convex part of a psychophysical function relating nominal value (e.g. monetary outcomes) to subjective value or utility, such that the decreases in utility associated with chasing and suffering larger losses are proportionately smaller than the decreases in utility associated with certain but smaller losses (Kahneman and Tversky 2000). Previously, we found that gambling to recover losses during our game is positively associated with psychometric measures of the tendency to chase losses in other gambling activities (Campbell-Meiklejohn et al 2008).

Figure 1 about here

At the start of the game, participants were told that they had a fictional £20,000 to play with, but that the participant with the most points at the end of the experiment would win a real prize of £70. On each 'round' of the game, an initial £10, £20, £40, £80 or £160 was subtracted from their game total. This amount appeared below the choices: 'Quit' and 'Play' (Figure 1). At this point, participants could choose to 'Quit', sustaining this loss and ending the round immediately ('quit-loss' outcome), or they could choose to 'Play', that is, chase the loss. Thus, they could gamble on recovering an amount equal to the loss but at the risk of increasing their losses by the same amount. If the outcome of a decision to gamble were positive ('chase-win' outcome), the loss was recovered and the round ended. If the outcome

were negative ('chase-loss' outcome), the loss was doubled and participants given another chance to quit or to chase in the next choice of the round. The options for each choice – 'Play' or 'Quit'– appeared equally often on the left and right sides of the displays.

Outcome displays (see Figure 1), indicated whether participants had won a gamble and that no money was lost ('chase-win'); whether they had lost a gamble and the amount lost ('chase-loss'); or the amount lost if participants chose to quit the round ('quit-loss'). At the end of each round, participants were also informed of their final losses in a 'round-loss' display. This display indicated the total cumulative losses for that round, in red text if the losses were greater than 0 but in green text if 0. Rounds of the loss-chasing game began with losses of £10, £20, £40, £80 or £160. If participants continued losing, losses kept doubling until they reached £640, at which point the round ended, having incurred the maximum loss.

All participants played 20 rounds of the loss-chasing game. Chase-win outcomes were positioned randomly within each round such that winning outcomes occurred equally often after any number of (between 0 and 5) consecutive losses. The outcomes of the loss-chasing game were distributed such that 14 rounds returned all losses if participants decided to play on every choice of the game. However, 6 rounds resulted in the maximum loss of £640.

Participants were not told anything about the probabilities of good versus bad outcomes so that their decisions were made under conditions of 'ambiguity' (Camerer and Weber 1992). In order to discourage participants from adopting conservative strategies by which they quit early to preserve as much of their play money as possible, no information was provided about their cumulative game total of play money during the game. Participants were also informed that they would not achieve the best possible score by exclusively playing or quitting.

To summarise, participants were confronted with a series of dilemmas involving a choice between gambling to recover a loss of at the risk of doubling its size, or sustaining the loss and ending the chase, while at the same time preserving as much as possible the resources that allowed play to continue (Campbell-Meiklejohn et al 2008). The value of these resources (experimenter-defined points) was provided by the context of an inter-participant competition requiring participants to retain as many points as possible. This mixture of nominal and actual rewards have been used in economics to demonstrate behaviour qualitatively and quantitatively similar to that observed outside the laboratory (Cubitt et al 1998).

Statistical Analysis

Dependent measures included the proportion of choices to gamble (or chase) out of all choices made during the game, and the mean number of losses chased per round. We analysed the magnitude (or value) of losses chased and the magnitude (or value) of losses surrendered during the game. These values were expressed as ratios to the mean values of all losses encountered during the game; see Supplementary Information for more details.

Demographic, subjective and loss-chasing measures for the 3 experiments were tested using one-way analysis of variance (ANOVA) with the between-subjects factors of treatment (T- vs T-, pramipexole vs placebo, or propranolol vs placebo) and gender.

RESULTS

Experiment 1: Tryptophan Depletion

Physiological and subjective effects. Consumption of the amino acid drink without tryptophan (in the T- treatment) produced a significant reduction in total plasma concentration

5 hours later compared to the control drink (in the T+ treatment) (see Table S1). However, the T- treatment did not produce any marked changes in either state positive or negative affect compared to the T+ treatment (Table S1) (all $F(1, 30)_{s} < 2.29$).

Figure 2 about here

Loss-chasing. Participants who received the T- treatment showed a marked and significant reduction in the proportion of decisions to chase losses compared to participants who received the T+ treatment (Figure 2a) ($F(1, 30) = 8.43, p < .01$). The number of consecutive decisions to chase in a run of losing gambles was also reliably reduced following tryptophan depletion (Figure 2b) ($F(1, 30) = 8.06, p < .01$).

In contrast to the effects on the proportion of gambles to recover losses, there was no significant change in the *value* of losses that the tryptophan-depleted participants decided to chase (expressed as ratios to the mean values of all losses encountered during the game; Supplementary Information) (Figure 3a) compared to the participants who received the control procedure ($F_s < 1$). Neither was there any significant change in the *value* of losses surrendered when deciding to quit (Figure 3b) ($F_s < 1$).

Experiment 2: Pramipexole

Physiological and subjective effects. Systolic BP, diastolic BP and heart rate were not significantly altered following treatment with pramipexole compared to treatment with placebo (see Supplementary Information and Table S3) (all $F(1, 25)_{s} < 1.86$).

Treatment with pramipexole significantly reduced state positive affect in comparison to placebo across the +2h following treatment, $F(1, 26) = 10.05$, $p < .005$ (Table S2). Specifically, while positive affect tended to increase following treatment with placebo ($F(1, 13) = 3.53$, $p = .08$), it was significantly decreased following treatment with pramipexole ($F(1, 13) = 6.84$, $p < .05$). At +2h, when completing the loss-chasing game, participants who received pramipexole reported lower positive affect than those who received placebo ($F(1, 26) = 8.34$, $p < .01$). Pramipexole did not alter state negative affect compared to placebo (all $F_s < 1$).

Figure 3 about here

Loss-chasing. Pramipexole slightly reduced the number of decisions to chase, and the number of consecutive decisions to chase, during a run of losing gambles compared to placebo (Figure 2); however, neither of these effects were statistically significant ($F_s < 1$). However, by contrast, pramipexole significantly *increased* the value of losses that participants decided to gamble to recover (Figure 3a) ($F(1, 26) = 4.94$, $p < .05$), and also significantly *reduced* the value of losses participants surrendered (Figure 3b) ($F(1, 26) = 5.87$, $p < .05$). These changes in the value of losses chased and surrendered remained significant when positive affect at +2hr was entered as a covariate, ($F(1, 25) = 4.48$, $p < .05$ and $F(1, 25) = 4.39$, $p < .05$, respectively). They were also broadly unaltered when the statistical analysis was performed on the unadjusted value of losses chased or values surrendered (see Supplementary Information).

Experiment 3: Propranolol

Physiological and subjective effects. Propranolol did not produce significantly different larger or smaller changes in systolic or diastolic BP compared to placebo, (all $F_s < 1$). HR diminished over the 75min following treatment (73.64 ± 10.82 bpm vs 62.04 ± 7.68 bpm), $F(1,$

24)= 60.30, $p < .0001$. However, this reduction was significantly greater following propranolol compared to placebo (Table S5) ($F(1, 24) = 4.98$, $p < .05$). Since baseline HR tended to be greater in participants treated with propranolol compared to participants treated with placebo ($F(1, 24) = 2.64$), we also examined the treatment effects on the proportionate change in participants' HR. This confirmed that propranolol produced a significantly larger reduction in heart rate compared to placebo ($18.64 \pm 8.45\%$ vs $11.08 \pm 11.38\%$) ($F(1, 24) = 4.64$, $p < .05$).

State positive and state negative affect were not substantially different following treatment with propranolol compared to treatment with placebo (see Supplementary Information and Table S4) ($F < 1.00$ and $F(1, 24) = 1.61$, respectively). There were no significant group differences in either measure at +75min when the loss-chasing game was completed.

Loss-chasing. There were no significant differences between propranolol and placebo in terms of the number of decisions to chase, number of consecutive decisions to chase (Figure 2), or the value of losses chased and the value of losses surrendered (Figure 3), all $F_s < 1$.

DISCUSSION

Our findings suggest that serotonin and dopamine play complementary roles in the tendency to keep gambling to recover losses. Serotonin activity appears to play a role in sustaining loss-chasing behaviour while dopamine activity, involving at least the D_2/D_3 receptor system, appears to regulate the magnitude of losses chased or surrendered at that point when players decide to quit gambling. By contrast, both these aspects of loss-chasing are broadly independent of changes in sympathetic arousal, at least as mediated by beta-adrenoceptor activity. Our data highlight novel hypotheses about the monoaminergic mechanisms that promote the expression of this central, but poorly understood, aspect of gambling behaviour.

In Experiment 1, we investigated the effects of tryptophan depletion to test whether central serotonin activity mediates loss-chasing behaviour. This might have been manifested in at least 2 ways. First, several lines of evidence suggest that serotonin mediates the inhibition of non-rewarded or punished behaviour (Crockett et al 2009, Dayan and Huys 2008, Soubrie 1986). So, tryptophan depletion, leading to a reduction in serotonin activity, might have been expected to increase gambling to recover losses in our healthy adult participants. By contrast, serotonin activity also plays a significant role in learning from, and coping with, aversive events (Bari et al 2010, Daw et al 2002, Deakin and Graeff 1991, Evers et al 2005). Given that tryptophan depletion can also improve the prediction of punishing outcomes (Cools et al 2008), and enhance neural responses to punishing outcomes within the anterior cingulate cortex (Evers et al 2005), we also anticipated that tryptophan depletion might increase the salience of bad outcomes and diminish loss-chasing behaviour. In fact, while producing no marked changes in healthy adults' state affect, tryptophan depletion significantly reduced the proportion of decisions participants made to chase losses, and also reduced the number of consecutive decisions to chase, during a run of losing gambles. This suggests that, in this instance at least, serotonin activity helps to sustain loss-chasing rather than inhibit it.

Descriptive theories of choice under uncertainty attribute loss-chasing behaviour to the idea that the prospective reductions in subjective value or utility associated with chasing and suffering larger losses still are proportionately smaller than the reductions in utility associated with the smaller losses already incurred (Kahneman and Tversky 2000). Under these conditions, it makes sense for gamblers to continue to play, so long as the necessary resources are available. From this perspective, loss-chasing can be viewed as an aversively-motivated escape behaviour but one controlled, at least in part, by the marginal utility of continued play relative to its cessation. Our finding that tryptophan depletion reduced our behavioural model of loss-chasing suggests that, in this instance at least, diminished central serotonin activity

reduced the marginal utility of continued play, perhaps by increasing the salience of future bad outcomes across their range of values (Cools et al 2008, Deakin and Graeff 1991).

Further experiments will be needed to establish the relationship between serotonin activity and gambling to recover losses. However, given serotonin's complex contribution to impulse control, we should not assume that this relationship will be linear (Winstanley et al 2004).

Our finding that tryptophan depletion reduced loss-chasing is in line with other observations, obtained using simple elicitation procedures to measure risk attitudes, that carriers of the 10-repeat allele of the STin2 gene (that results in *higher* serotonin tone) show increased risk-seeking choices for losses (Zhong et al 2009). By contrast, our present data are apparently inconsistent with findings that 2 weeks treatment with tryptophan, as a dietary substrate reduced shifts between risk-averse choices when making single decisions between certain gains and uncertain larger or smaller gains, and risk-seeking choices when making single decisions between certain losses and uncertain larger or smaller losses (Murphy et al 2009). Collectively, these data indicate that serotonin's influence upon gambling to recover losses may vary depending upon a number of psychological and pharmacological factors, including whether the experimental situation involves single or multiple consecutive choices and whether there is a context of other choices that involve positive expected values.

The effects of a single 176µg dose of pramipexole were quite different. This treatment did not increase the proportion of decisions to chase losses or the number of consecutive decisions to chase during a run of losing gambles; however, pramipexole did significantly increase the value of losses that participants were willing to chase and, at the same time, reduce the value of losses that participants were willing to surrender when quitting. Thus, a single dose of pramipexole induced a preference for chasing larger losses at the expense of smaller losses.

We acknowledge that the mode of action of the single 176µg dose of pramipexole used in Experiment 2 remains uncertain. While the behavioural effects of low doses of dopaminergic drugs may reflect pre-synaptic action at the auto-receptors of dopamine neurones within the mid-brain (Frank and O'Reilly 2006, Santesso et al 2009), single doses of 100µg and 200µg pramipexole may also reduce serum prolactin, suggesting a post-synaptic action of the drug at dopamine receptors in the anterior pituitary (Schilling et al 1992). Here, replicating previous findings, we note that our dose of 176µg pramipexole also significantly reduced participants' positive state affect (Hamidovic et al 2008). This suggests that, in this experiment at least, doses of pramipexole influenced the performance of our loss-chasing game via activity at D₂/D₃ dopamine auto-receptors

D₂ and D₃ receptors are predominantly expressed within reinforcement pathways in the nucleus accumbens and amygdala (Camacho-Ochoa et al 1995) where both appear to influence the reinforcement value of drugs of stimulants such a cocaine (Caine et al 1997, Thiel et al 2010). At the current time, we have no way of knowing which of these receptor subtypes makes the larger contribution to the loss-chasing behaviour observed. Previous experiments have suggested that activity at D₂ receptors can impair learning from the bad outcomes of risky decisions ('no-go learning') by impairing the expression of dips in mid-brain dopamine activity that signal negative prediction errors (Frank and O'Reilly 2006, Frank et al 2007a, Frank et al 2007b, Frank et al 2009). However, our data suggest that this insensitivity to losing outcomes associated with D₂/D₃ receptor activity produces more complex changes in risky choices than a simple failure to learn from negative events. Rather, we speculate that impairments in the detection of dips in dopamine activity following bad outcomes produced a straight failure to register small losses; thus increasing the number of pramipexole-treated participants' decisions to quit for small stakes. However, the reduced

sensitivity to losing outcomes associated with D_2/D_3 activity also further diminished the reduction in subjective value associated with chasing unsuccessfully and suffering larger losses still relative to the reduction in subjective value associated with already certain losses; thus promoting decisions to chase for larger value losses compared to placebo.

Changes in reinforcement learning following treatment with pramipexole (Pizzagalli et al 2008) are associated with altered signalling within the anterior cingulate region following bad outcomes (Santesso et al 2009) and blunted signalling within striatum following good outcomes (Riba et al 2008). Previously, we have observed that attenuated neural responses to bad gambling outcomes within the anterior cingulate sulcus is also associated with continued chasing behaviour during performance of our loss-chasing game (Campbell-Meiklejohn et al 2008). This is consistent with recent electrophysiological evidence that the reward-related functions of the anterior cingulate and mid-line structures may be disrupted in pathological gamblers (Hewig et al 2010). Therefore, the findings of Experiment 2 raise the possibility that single doses of pramipexole increase the value of losses judged worth chasing via altered reinforcement signalling within a distributed neural circuit encompassing the anterior cingulate region and its afferent ventral striatal targets (Nakano et al 2000).

Finally, the results of Experiment 3 indicate that while a single dose of 80mg propranolol significantly reduced heart rate compared to placebo, it did not significantly alter the number of decisions to chase losses, the value of losses chased, or the value of losses surrendered. These findings suggest that the cognitive and emotional aspects of loss-chasing modelled by our game — though obviously not the excitement associated with commercial gaming activities (Anderson and Brown 1984) — are not influenced by manipulations of beta-adrenoceptor activity. They also provide some reassurance that

the effects of tryptophan depletion and pramipexole we observed in Experiment 1 and 2 cannot be attributed to undetected changes in sympathetic and/or peripheral arousal. However, loss-chasing behaviour might well be influenced by other aspects of noradrenaline function including activity of α 2-adrenoceptors that influence activity of the ascending innervation of the locus coeruleus and modulate the processing of negative decision outcomes in the cingulate area (Riba et al 2005).

Several limitations to our findings need to be addressed in future investigations. First, while our loss-chasing game captures the essential feature of continued play that brings mounting losses, this feature limits our ability to isolate the *specific* psychological mechanisms that might be influenced by serotonin and D_2/D_3 activity to influence gambling to recover losses. Tryptophan depletion and single low doses of pramipexole produced distinct behavioural changes in gambling to recover losses, but additional experiments are needed to establish how these changes relate to what we already know about serotonin's role in avoidance or punishment-induced inhibition (Crockett et al 2009, Soubrie 1986) and what we know about the role of D_2 receptors in learning from negative outcomes (Frank 2006). Second, the clinical implications of these findings need to be explored by examining the effects of serotonergic and dopaminergic treatments on performance of our loss-chasing game in samples of pathological gamblers; as well as testing loss-chasing as a model of impaired control in other addictions (Rogers et al in press). We might also examine the role of other neurotransmitters, such as the opiate and glutamate systems, which may sustain gambling problems (Grant et al 2007, Grant et al 2008).

Pathological gambling is a source of enormous personal and family distress and represents a significant public health issue (Shaffer and Korn 2002). Yet, we know very

little about the biological factors that confer vulnerability for gambling problems, with no licensed pharmacological treatments currently available to clinicians. The experiments represented here represent one way to start to tackle these issues empirically; namely, by investigating the neural and pharmacological basis of the cognitive and behavioural biases evident in the individuals who present at the clinic. These findings suggest that the general persistence of gamblers in playing to recover losses is modulated by serotonin activity while the evaluation of losses that gamblers judge worth chasing is mediated by activity of the D₂/D₃ receptor system.

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DISCLOSURE

We report no biomedical financial interests or potential conflicts of interest.

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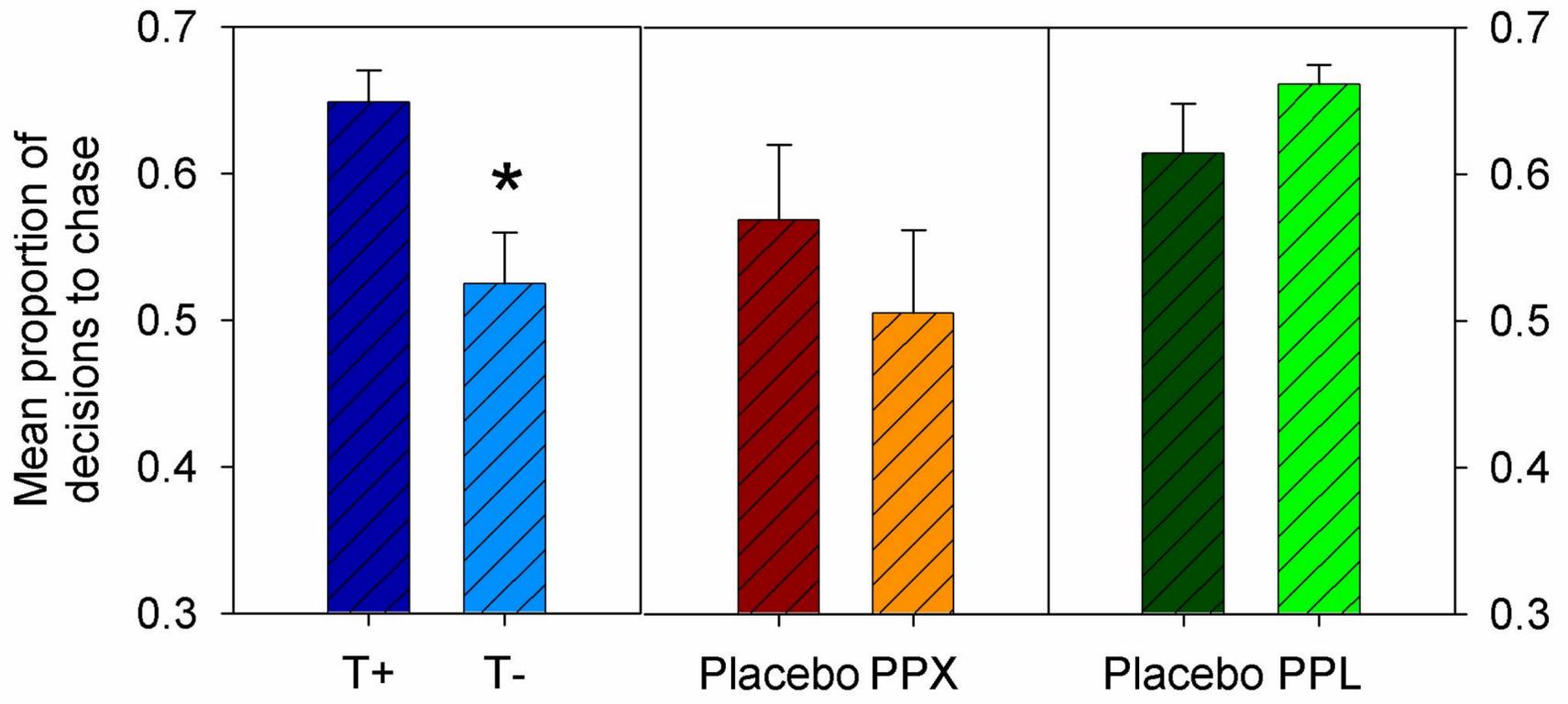
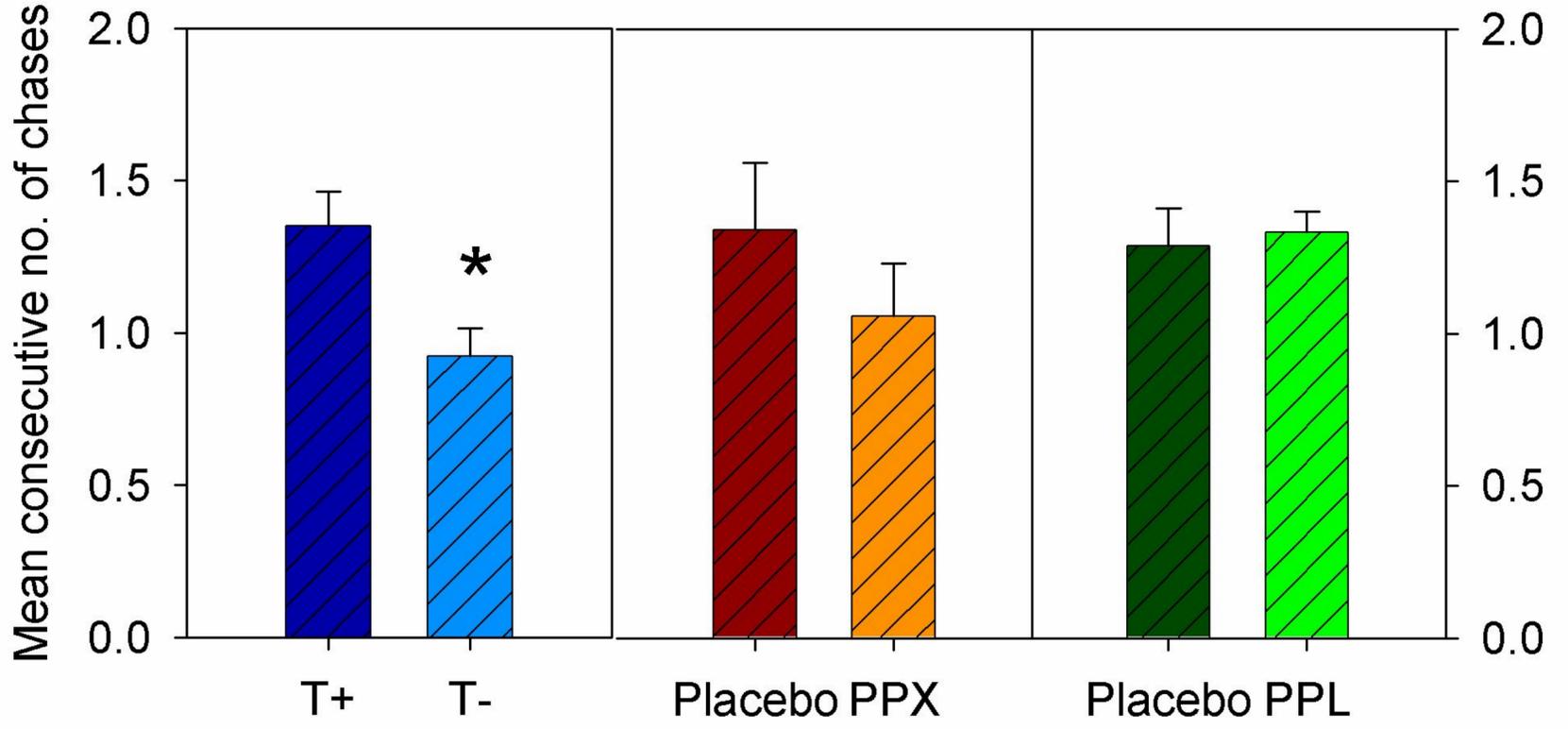
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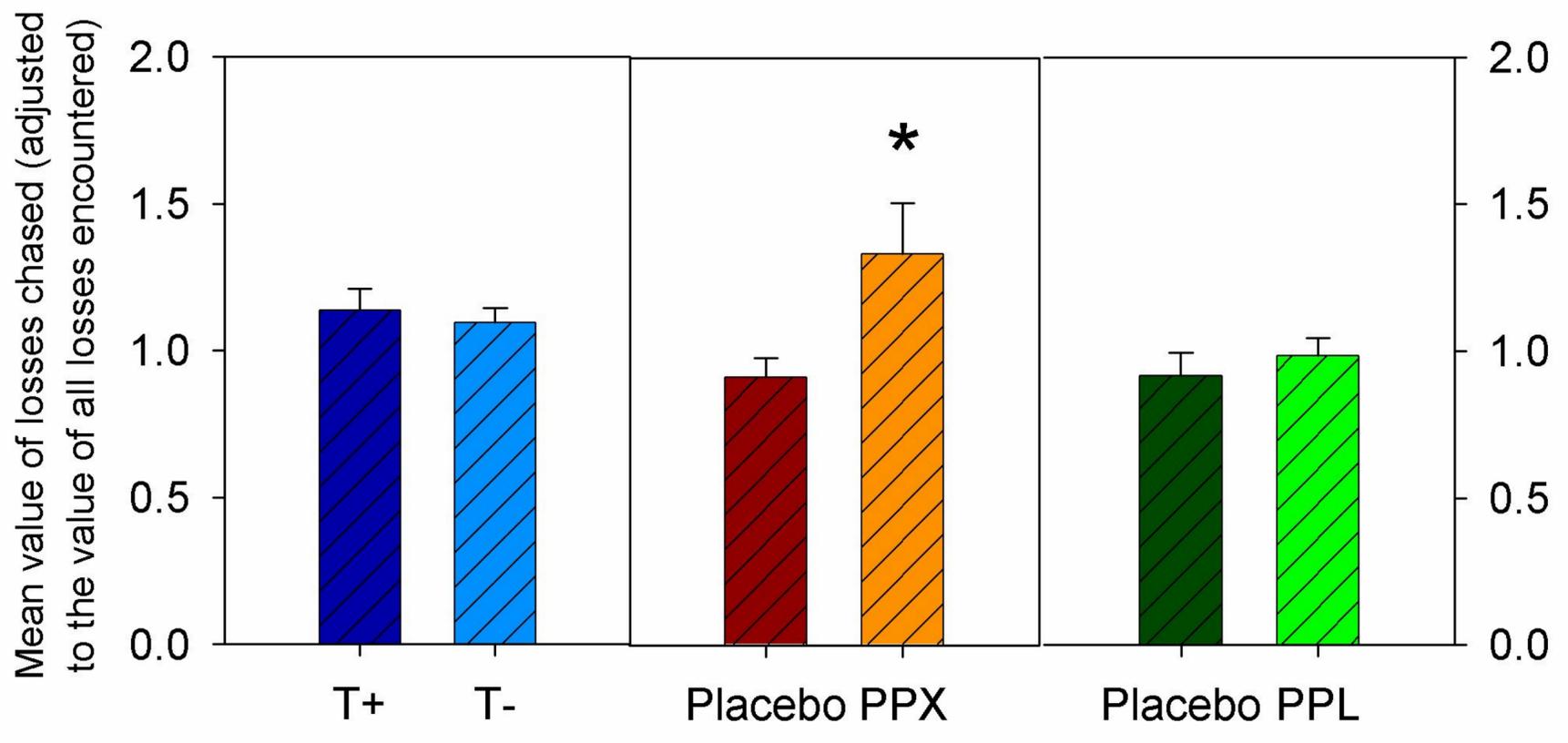
Figure 1 Display sequences for the loss-chasing game. At the beginning of each round of the game, a loss was imposed and a decision made either to play (gamble further) or quit (to accept the loss) and end the round. Consecutive losses and decisions occurred until a maximum round loss of £640 was incurred, participants won a gamble and cleared their losses or participants chose to quit, at which point the round ended.

Figure 2 Persistence of loss-chasing behaviour in 3 samples of healthy, non-clinical adult participants following tryptophan depletion (vs a control amino acid drink), a single 176µg of the D₂/D₃ receptor agonist, pramipexole (vs placebo) and a single 80mg dose of the beta-adrenoceptor antagonist, propranolol (vs placebo). (a) Mean proportion of decisions to chase losses during the loss-chasing game. (b) Mean consecutive number of decisions to chase losses per round of the loss-chasing game. * p < .05.

Figure 3 The use of value information in the loss-chasing behaviour in 3 samples of healthy, non-clinical participants following tryptophan depletion (vs a control amino acid drink), a single 176µg of the D₂/D₃ receptor agonist, pramipexole (vs placebo) and a single 80mg dose of the beta-adrenoceptor antagonist, propranolol (vs placebo). (a) Mean value of losses chased (adjusted to the value of all losses encountered). (b) Mean value of losses surrendered (adjusted to the value of all losses encountered). * p < .05.



a**b**

a**b**