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Dopamine release in ventral striatum during Iowa Gambling Task performance is associated with increased excitement levels in pathological gambling

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ABSTRACT

Aims Gambling excitement is believed to be associated with biological measures of pathological gambling. Here, we tested the hypothesis that dopamine release would be associated with increased excitement levels in Pathological Gamblers compared with Healthy Controls. **Design** Pathological Gamblers and Healthy Controls were experimentally compared in a non-gambling (baseline) and gambling condition. **Measurements** We used Positron Emission Tomography (PET) with the tracer raclopride to measure dopamine D 2/3 receptor availability in the ventral striatum during a non-gambling and gambling condition of the Iowa Gambling Task (IGT). After each condition participants rated their excitement level. **Setting** Laboratory experiment. **Participants** 18 Pathological Gamblers and 16 Healthy Controls. **Findings** Pathological Gamblers with dopamine release in the ventral striatum had significantly higher excitement levels than Healthy Controls despite lower IGT performance. No differences in excitement levels and IGT performance were found between Pathological Gamblers and Healthy Controls without dopamine release. Pathological Gamblers showed a significant correlation between dopamine release and excitement level, while no such interaction was found in Healthy Controls. **Conclusions** In pathological gamblers dopamine release in the ventral striatum appears to be associated with increased excitement levels despite lower IGT performance. The results might suggest a 'double deficit' function of dopamine in pathological gambling, where dopamine release reinforces maladaptive gambling through increasing excitement levels, reducing inhibition of risky decisions, or a combination of both. These findings may have implications for the understanding of dopamine in pathological gambling and other forms of addiction.

Keywords Decision-making, dopamine, excitement, Iowa Gambling Task, pathological gambling, Positron Emission Tomography, ventral striatum.

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INTRODUCTION

Pathological gambling is an impulse control disorder characterized by maladaptive gambling behaviour [1]. It is widely suggested that gambling excitement is central to the disorder [2–5], and that gambling excitement is associated with physiological measures of arousal [6–8]. Physiological arousal is generally increased during gambling [6,8–13], but problem or pathological gamblers do not necessarily differ in physiological arousal from non-problem gamblers [14–18]. Rather, differences in physiological arousal between pathological gamblers and non-problem gamblers appear to be associated with different types of decisions [19].

Other biological measures might also be associated with excitement levels in pathological gambling. Dopamine, for instance, is a neurotransmitter that has been associated with drug addiction [20–22] and pathological gambling [23–28]. Dopamine release is associated with change in subjective experience and reinforcement of behaviour, although the exact role of subjective experience in relation to the dopamine system remains debated (see e.g. [29–31]).

In a recent study [28] we found that dopamine release is associated with poorer performance on the Iowa Gambling Task (IGT) in pathological gamblers (PG) compared with healthy controls (HC). However, the study did not investigate excitement levels experienced from gambling, and to date no study has investigated the role of dopaminergic neurotransmission during gambling in relation to excitement levels of pathological gamblers. The present study focused upon the relation between dopaminergic neurotransmission and excitement levels in pathological gambling. We investigated dopaminergic neurotransmission in the ventral striatum of PG and HC playing the IGT, and compared the differences in excitement levels from gambling. We also extended our previous findings [28] to control for a possible interaction between excitement levels and IGT performance.

We hypothesized that dopamine release would be associated with increased excitement levels in PG compared with HC. We used positron emission tomography (PET) to measure the binding potential (BP_{ND}) of [^{11}C]raclopride to dopamine $D_{2/3}$ receptors in a baseline and a gambling condition. The change in binding potential (ΔBP_{ND}) between baseline and gambling conditions provided a measure of dopamine release during gambling. Decreased raclopride binding potentials indicate dopamine release, because dopamine occupies more receptors and leave fewer receptors available for binding by raclopride. Conversely, increased raclopride binding potentials indicate inhibition of dopamine release, because dopamine occupies fewer receptors and leave more receptors available for binding by raclopride.

METHODS AND MATERIALS

Participants

The cohort consisted of 18 PG and 16 HC; all were right-handed males between the ages of 22 and 55 years. PG were recruited through the Center for Ludomani (Center of Pathological Gambling) in Odense, Denmark. PG were referred only if they were still gambling actively. We recruited an age-matched non-gambling HC group through local newspaper advertisement; they were defined as individuals who might gamble occasionally, but not habitually, and who showed no symptoms of problem gambling or pathological gambling. Subjects gave written informed consent to a protocol approved by the official Midtjyllands Regional Science Ethics Committee, and were compensated for time participation and travel expenses. The average age of PG was 33.6 years [standard deviation (SD) = 9.3] and 31.7 for HC (SD = 8.0), $F_{(1, 32)} = 0.39$, not significant (NS).

All participants were screened using the Structured Clinical Interview for DSM-IV (SCID-I) [32,33] for Axis I psychopathology. This included a special module assessing pathological gambling. Participants were excluded if they met criteria for present psychopathology including affective disorders, anxiety disorders, psychotic disorders or substance abuse disorders. Subjects were also excluded if they suffered from neurological disorders or conditions that made them ineligible for PET and magnetic resonance imaging (MRI) scanning (e.g. pacemakers or prosthetic devices). None of the PG suffered from substance dependence comorbidity, and only few participants suffered from past alcohol or substance dependence (one HC and three PG). PG were included if they met full DSM-IV criteria for pathological gambling. HC were excluded if they met criteria for more than one symptom on the SCID-I pathological gambling module.

PROCEDURE

IGT

The IGT is a computerized card game which simulates real-life decision-making in the way that it factors reward and punishment. Individuals with lesions in the ventromedial pre-frontal cortex—or orbitofrontal cortex (OFC)—have impaired performance on the IGT [34,35]; individuals suffering from substance dependence and pathological gambling also show impaired decision-making [36–43]. The task consists of four card decks (for example, A, B, C and D). In decks A and B ('disadvantageous decks'), choosing a card is followed by an immediately high gain of money, but at unpredictable trials the selection is followed by a high penalty, leading to a net loss over time. In decks C and D ('advantageous decks') the immediate gain is smaller, but the future loss is also smaller, leading to a net gain over time. The IGT score is calculated as the number of cards selected from advantageous minus disadvantageous decks [(C + D) – (A + B)], usually measured across five blocks of 20 trials (1–20, 21–40 and so on) for a total of 100 cards.

The IGT takes about 20 minutes to administer. As scanning times were 60 minutes, three different versions of the IGT were used. We used the regular ABCD version and subsequent KLMN and QRST versions, where the differences between card decks become increasingly ambiguous. Participants therefore had to adapt continuously to a new learning situation throughout the scanning period. As we used three different versions of the IGT during the PET scans, we measured group differences as the average performance across the three different versions. We also used a measure of combined IGT performance (advantageous minus disadvantageous decisions across all three versions) to test for correlation with excitement levels and change in binding potentials.

Excitement levels

Subjects were asked to rate their excitement levels ('How exciting do you think the game is right now?') after each of the versions (ABCD, KLMN and QRST) on a visual analogue scale ranging from 1 to 10, where 1 is the lowest and 10 is the highest. Excitement levels were measured on individual games and as the average rating across all versions.

PET/MRI methods

Participants were scanned twice with the ECAT HR (CTI/Siemens) PET tomograph operating in three-dimensional acquisition mode during baseline and gambling condition on the IGT. During the baseline scan we used a non-decision approach similar to that of Bolla *et al.* [44,45], where the computer automatically instructed the participants which cards to chose; during the gambling scan participants chose freely among the decks. During both scans participants saw the accrued increase or decrease in earnings during the game consistent with previous studies (see e.g. [37]). Participants were scanned first in the baseline condition then in the gambling condition. Before each scan we obtained a brief attenuation scan, followed by an intravenous (i.v.) bolus injection of [^{11}C]raclopride (168–364 MBq). Baseline and gambling scans were conducted on the same day. The time between scans was a minimum of 120 minutes between injections. Participants were asked to abstain from cigarette and coffee use on the day of scanning. Dynamic emission recordings were obtained for 60 minutes following tracer administration for a total of 22 frames of increasing duration. Anatomical MRI studies were carried out on a GE 3T high-resolution MRI scanner using a T1-weighted sequence optimized for MRI/PET correlation. Emission recordings summed over the whole hour of scanning for both the baseline and activation conditions were co-registered individually to the native MR images using Montreal Neurological Institute (MNI) tools, and then transformed into the common stereotaxic coordinate space [46]. Using a cerebellar region of interest (ROI), cerebellar time–activity curves (TACs) were generated for each subject and each scan. Using the cerebellar TACs, voxel-wise maps of [^{11}C]raclopride BP_{ND} (binding potential) were obtained for the ventral striatum using the ERLiBiRD method [47] for the baseline and activation scans. The ventral striatum mask was determined using criteria similar to those of Mawlawi *et al.* [48]. We obtained measures of baseline binding potentials (BP_{ND}) and change in binding potential (ΔBP_{ND}) between baseline and gambling conditions. Baseline raclopride binding potentials provided an index of the number of available dopamine $D_{2/3}$ receptors, while change in binding potentials provided an index of the difference in number of available dopamine $D_{2/3}$ receptors between baseline and gambling normalized to baseline in percentage: $\Delta BP_{ND} = [(\text{baseline} - \text{gambling})/\text{baseline}] \times 100$.

Table 1 shows the binding potentials of PG and HC in baseline and gambling conditions. As reported previously [28], PG and HC with decreased raclopride binding potentials (indicating dopamine release) both differed significantly from baseline, as did PG and HC with increased binding potentials. PG and HC did not differ in magnitude of baseline binding potentials or magnitude of change in binding potential, but PG with decreased binding potentials had significantly poorer IGT performance than HC with decreased binding potentials on the ABCD version, $F_{(4,\ 10)} = 12.48$, $P < 0.001$, but not in all versions combined. The results remained significant after correction for three multiple comparisons ($P < 0.005$). No differences were found in IGT performance between PG and HC with increased binding potentials.

Statistical analysis

We used paired-sample *t*-tests to determine differences in binding potentials and excitement levels from baseline to gambling condition and differences between groups. We measured differences in IGT performance and excitement levels between PG and HC using two-way analysis of variance (ANOVA). Finally, we used Pearson's bivariate

Table 1 Binding potentials (BP_{ND}) in baseline and gambling condition of pathological gamblers and healthy controls.

	Pathological gamblers						*Healthy controls*					
	Baseline			*Gambling*			*Baseline*			*Gambling*		
	n	*Mean*	*SD*	*Mean*	*SD*	*t*	*n*	*Mean*	*SD*	*Mean*	*SD*	*t*
$\Delta BP_{ND} \geq 0$	8	2.07	0.25	1.89	0.30	5.70***	7	2.04	0.59	1.77	0.51	3.93**
$\Delta BP_{ND} < 0$	10	1.94	0.50	2.08	0.57	−2.81*	9	2.02	0.15	2.23	0.25	−3.50**

*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$. $\Delta BP_{ND} \geq 0$ represents individuals with decreased binding potentials (i.e. dopamine release). $\Delta BP_{ND} < 0$ represents individuals with increased binding potentials (i.e. dopamine inhibition). SD: standard deviation.

correlation analysis to determine correlations between changes in binding potential and excitement levels.

RESULTS

Both PG, $t_{(17)} = 7.85$, $P < 0.00001$, and HC, $t_{(15)} = 4.07$, $P < 0.01$, showed increased excitement levels from non-gambling to gambling condition. However, PG had a significantly higher increase in excitement levels than HC, $t_{(32)} = 2.77$, $P < 0.01$. These differences in excitement level increase were specific to individuals with dopamine release. Figure 1 and Table 2 show that PG with decreased binding potentials had a significantly larger increase in excitement levels from baseline to gambling condition than HC with decreased binding potentials, $t_{(13)} = 3.28$, $P < 0.01$. The differences remained significant after correcting for the multiple comparisons of increase and decrease in binding potential ($P = 0.012$). No differences in change of excitement levels were seen among PG and HC with increased binding potentials. PG with decreased binding potentials also had significantly higher excitement levels during gambling than HC with decreased binding potentials, $t_{(13)} = 2.14$, $P = 0.05$, while there were no differences in excitement levels between PG and HC with increased binding potentials.

A two-way analysis of variance (ANOVA) showed that PG had significantly higher excitement levels than HC throughout the three games, $F_{(2,\ 31)} = 6.45$, $P = 0.01$ (see Fig. 2). However, these differences were due entirely to increased excitement levels in PG with decreased binding potentials. PG with decreased binding potentials had significantly higher excitement levels throughout the games than HC with decreased binding potentials, $F_{(2,\ 12)} = 10.69$, $P < 0.005$, while no differences in excitement levels were found between PG and HC with increased binding potentials. PG with decreased binding potentials also had significantly higher excitement levels than PG with increased binding potentials, $F_{(2,\ 15)} = 6.94$, $P = 0.01$, while there were no differences between HC with decreased binding potentials and HC with increased binding potentials. The results are illustrated in Fig. 2.

Finally, Fig. 3 shows that PG had a significant positive correlation between change in binding potential and excitement levels, $t_{(18)} = 0.52$, $P < 0.05$; the correlation was insignificant among HC and in the combined cohort of PG and HC. Neither PG nor HC showed significant correlations between excitement levels and IGT performance or between IGT performance and change in binding potential. This suggests that higher dopamine release was associated with increased levels of excitement in PG, and that the excitement levels were not associated with better IGT performance. The correlation between excitement levels and baseline binding potentials was insignificant in PG, HC and the combined cohort of PG and HC.

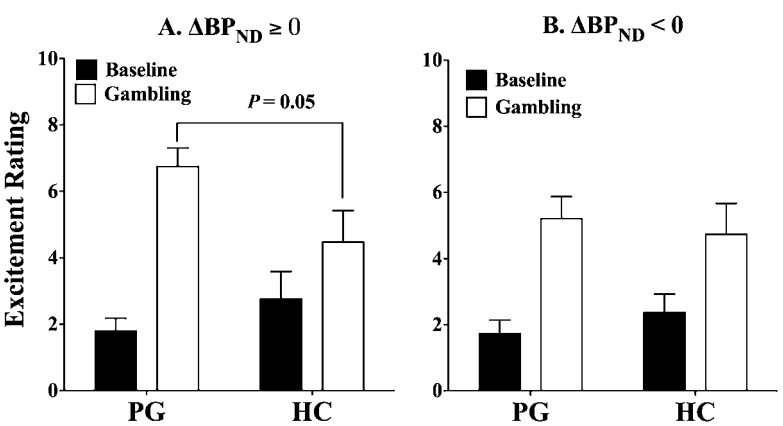

Figure 1 Excitement levels in pathological gamblers (PG) and healthy controls (HC). (a) PG with decreased binding potentials ($\Delta BP_{ND} \geq 0$) have significantly higher excitement levels during gambling than HC with decreased binding potentials. (b) PG and HC with increased binding potentials ($\Delta BP_{ND} < 0$) do not differ in excitement level

Table 2 Excitement levels in baseline and gambling condition of pathological gamblers and healthy controls.

	Pathological gamblers						*Healthy controls*					
	Baseline			*Gambling*			*Baseline*			*Gambling*		
	n	*Mean*	*SD*	*Mean*	*SD*	*t*	*n*	*Mean*	*SD*	*Mean*	*SD*	*t*
$\Delta BP_{ND} \geq 0$	8	1.79	1.10	6.75	1.57	8.67***	7	2.76	2.20	4.48	2.49	2.06
$\Delta BP_{ND} < 0$	10	1.73	1.30	5.20	2.12	4.38**	9	2.37	1.68	4.74	2.78	3.55*

*$P \leq 0.01$, **$P \leq 0.005$, ***$P \leq 0.0001$. $\Delta BP_{ND} \geq 0$ represents individuals with decreased binding potentials (i.e. dopamine release). $\Delta BP_{ND} < 0$ represents individuals with increased binding potentials (i.e. dopamine inhibition). SD: standard deviation.

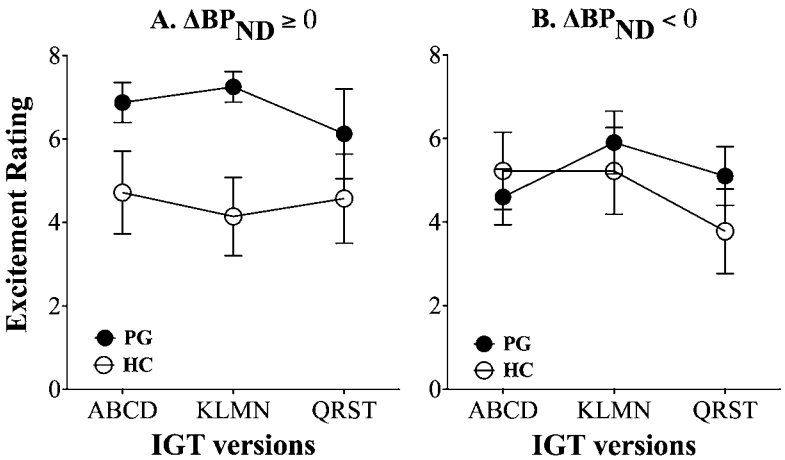

Figure 2 Two-way analyses of variance (ANOVAs) of excitement levels between pathological gamblers (PG) and healthy controls (HC). (a) PG (filled circles) with decreased binding potentials ($\Delta BP_{ND} \geq 0$) have significantly higher excitement across games than HC (open circles) with decreased binding potentials. (b) PG and HC with increased binding potentials ($\Delta BP_{ND} < 0$) do not differ in excitement levels across games

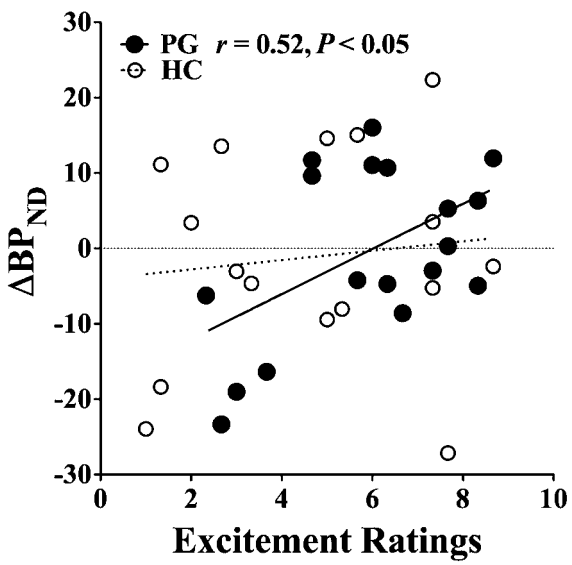

Figure 3 Correlation between binding potential changes and excitement levels and Iowa Gambling Task (IGT) performance. Pathological gamblers (PG, filled circles) show a significant correlation between excitement levels on the abscissa and change in binding potential (ΔBP_{ND}) on the ordinate, while the correlation failed to reach significance levels in healthy controls (HC, open circles). Values above zero indicate dopamine release, while values below zero indicate dopamine inhibition

DISCUSSION

Our data showed that PG with decreased binding potentials in the ventral striatum (indicating dopamine release) had significantly higher excitement levels than HC, despite lower IGT performance. Furthermore, we found a significant correlation between change in binding potential and excitement levels in PG, while no such interaction was found in HC.

PG with decreased binding potentials had significantly higher excitement levels than HC with decreased binding potentials, even though they did not differ in magnitude of dopamine release. We have argued previously [28] that PG do not suffer from a hyperdopaminergic condition, but rather have increased dopaminergic sensitivity towards gambling. We also note that the dopaminergic 'gain' may vary, such that the relative effect in dopaminergic changes depend upon baseline dopamine levels [49]. The present data suggest that PG have a relatively stronger sensitivity to experience excitement from dopamine release during gambling compared with HC. Furthermore, the excitement levels of PG seem to be proportional to the dopaminergic changes during gambling, consistent with the positive correlation between excitement levels and change in binding potential in PG. Finally, it is interesting to note that the majority of studies of physiological arousal in pathological gambling find no differences in physiological arousal between PG and non-problem gamblers [14–18]. Although dopaminergic neurotransmission and physiological arousal are distinct biological measures, these data might suggest a more complex interaction between biological and behavioural measures [22]. This is consistent with reports of increased dopamine response in relation to specific stimuli such as uncertain outcomes [24], reward prediction error [25] and gains [27].

PG and HC with increased raclopride binding potentials did not differ in excitement levels. Physiologically, the increase in binding potentials might reflect an inhibition of dopamine release, i.e. blocking of dopamine release at the pre-synaptic level, or a reduction in dopamine release, i.e. the release of dopamine was smaller than the re-uptake of dopamine in the synaptic cleft. In either case, the increase in raclopride binding (i.e. the decreased dopamine) was associated with reduced levels of excitement in pathological gambling. While the increase in excitement levels was specific to the group of PG with dopamine release, we note that some PG with increased raclopride binding potentials had high excitement levels. Therefore, dopamine is probably not the only factor contributing to gambling excitement among PG.

As previously reported [28] Pathological Gamblers with decreased binding potentials had significantly poorer IGT performance than Healthy Controls on the ABCD version, but not on all versions combined. These results might be due to increased complexity in the KLMN and QRST versions, or a fatigue factor for which there is no control in the present design. Despite lower IGT performance, Pathological Gamblers with decreased raclopride binding potentials had increased levels of excitement from gambling. The present data might therefore suggest a 'double deficit' function of dopamine in pathological gambling, where dopamine release reinforces maladaptive gambling through increasing excitement levels, reducing inhibition of risky decisions, or a combination of both. Such dopamine function might have implications for other forms of addiction, e.g., substance dependence, where craving and liking is associated with repeated drug taking behavior despite negative consequences.

However, there are also dopaminergic differences between pathological gambling and substance dependence. We found no overall differences in baseline binding potentials or change in binding potentials between PG and HC. This is in contrast with the literature on substance dependence, where substance-dependent individuals have significantly lower dopamine $D_{2/3}$ receptor availability than healthy controls [50], have a lower decrease in binding potential from drug taking [20] and show a reduced hedonic response to drug taking [31]. The differences might suggest that PG do not suffer from the same down-regulation or 'blunting' of the dopamine system as seen in substance dependence, but instead have increased dopaminergic sensitivity towards gambling compared with healthy controls. Our sample of PG was screened for substance use disorders, which may limit the generalizability of the findings, but might also provide an opportunity to discern the diversity of mechanisms at play among the various addictive behaviours. Our data might therefore have implications for understanding the role of dopamine in the so-called 'behavioural' addictions [23,51], and may indicate neurobiological distinctions between behavioural and substance-dependent addictions at the level of the ventral striatum.

While a double deficit condition might explain the increased vulnerability toward gambling among pathological gamblers, the relation between behavioral impairment and subjective experience is still debated. For instance, Schultz [29] notes that the dopaminergic relation between subjective feelings and behavior is unclear: 'To induce subjective feelings of pleasure and positive emotion is a key function of rewards, although it is unclear whether the pleasure itself has a reinforcing, causal effect for behavior (i.e., I feel good because of the outcome I got and therefore will do again what produced the pleasant outcome) or is simply an epiphenomenon (i.e., my behavior gets reinforced and, in addition, I feel good because of the outcome)' (p. 92). Regardless of the relation between excitement levels and impaired IGT performance our data suggest that both measures are associated with dopamine release in pathological gambling, and in this capacity they contribute to the understanding of dopaminergic dysfunctions in pathological gambling.

We specifically targeted the ventral striatum, because this region has been associated with monetary reward behaviour in gambling and pathological gambling [25–28]. Our data support the involvement of dopaminergic neurotransmission in the ventral striatum in relation to dysfunctions of pathological gambling. However, the conclusions from our study are limited to the anatomical region of the ventral striatum, and other regions such as the putamen, caudate nucleus and whole striatum as well as other receptors such as dopamine D_1 receptors should be included in further studies of dopaminergic neurotransmission in pathological gambling.

Finally, most participants had increased excitement levels from gambling compared with baseline, regardless of the direction of change in binding potential. This suggests that it was generally much less exciting to execute computer-instructed choices than to perform the gambling task. While the increase in excitement levels from baseline to gambling overall was independent of groups, we note that the change in excitement levels was significantly larger in PG with decreased binding potentials than in HC. We also note that our measure of excitement levels was specific to the gambling situation, and might not account for other aspects such as trait measures of excitement.

In conclusion, we find evidence that dopamine release in the ventral striatum is associated with increased excitement levels in pathological gambling despite lower IGT performance. The results might suggest a 'double deficit' function of dopamine in pathological gambling, where dopamine release reinforces maladaptive gambling through increasing excitement levels, reducing inhibition of risky decisions, or a combination of both. These findings may have implications for the understanding of dopamine in pathological gambling and other forms of addiction.

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Declarations of interest

The authors declare that they have no competing financial interests.

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