Acta Psychiatr Scand 2010: 122: 326–333

DOI: 10.1111/j.1600-0447.2010.01591.x

ACTA PSYCHIATRICA SCANDINAVICA

Dopamine release in ventral striatum of pathological gamblers losing money

Linnet J, Peterson E, Doudet DJ, Gjedde A, Møller A. Dopamine release in ventral striatum of pathological gamblers losing money.

Objective: To investigate dopaminergic neurotransmission in relation to monetary reward and punishment in pathological gambling. Pathological gamblers (PG) often continue gambling despite losses, known as 'chasing one's losses'. We therefore hypothesized that losing money would be associated with increased dopamine release in the ventral striatum of PG compared with healthy controls (HC).
Method: We used Positron Emission Tomography (PET) with [^{11}C]raclopride to measure dopamine release in the ventral striatum of 16 PG and 15 HC playing the Iowa Gambling Task (IGT).
Results: PG who lost money had significantly increased dopamine release in the left ventral striatum compared with HC. PG and HC who won money did not differ in dopamine release.
Conclusion: Our findings suggest a dopaminergic basis of monetary losses in pathological gambling, which might explain loss-chasing behavior. The findings may have implications for the understanding of dopamine dysfunctions and impaired decision-making in pathological gambling and substance-related addictions.

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Key words: pathological gambling; dopamine; neurotransmitters; cognitive impairment; behavior

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Accepted for publication June 23, 2010

Significant outcomes

- Pathological gamblers (PG) who lost money had significantly increased dopamine release in the left ventral striatum compared with healthy controls (HC).
- Gambling behavior was stable over time, suggesting a trait characteristic rather than state characteristic.

Limitations

- Using both reward and punishment in the gambling paradigm possibly reduced dopamine release among participants.
- Like other studies of dopaminergic neurotransmission, we found a lateralized effect of dopamine release.
- It was unclear how reward immediacy and outcome uncertainty was associated with IGT performance and dopamine release.

Introduction

Pathological gambling is an impulse control disorder characterized by maladaptive gambling behavior (1). PG prefer immediate rewards on delayed discounting tasks (2, 3) and on executive functions tasks such as the Iowa Gambling Task (IGT) (4–9). The preference for immediate rewards persists despite losses on the IGT, and is consistent with the notion of 'chasing one's losses' – a key symptom of pathological gambling (1). We have previously shown that loss-chasing persists in PG within single episodes of IGT performance (6) and that dopamine release in the ventral striatum is associated with impaired IGT performance in pathological gambling (9). Dopamine release might therefore be associated with monetary losses in pathological gambling. Several lines of research support the involvement of dopamine in monetary gains and losses, where the ventral

striatum appears particularly involved in the dopaminergic dysfunctions of PG.

The dopamine system is sensitive to non-pharmacological behavioral stimulation (10–12). For instance, Koepp et. al. (10) found that skilled video game players had significant dopamine release in the striatum while playing video games for money. Parkinson's disease sufferers treated with dopamine agonists have significantly higher prevalence of pathological gambling than individuals who receive other forms of treatment (13–15). While the dopaminergic mechanism behind the increased risk of pathological gambling is currently unknown, Steeves et. al. (16) found that Parkinson's disease patients suffering from pathological gambling had significantly higher dopamine release in the ventral striatum when gambling than Parkinson's disease patients without pathological gambling. The gambling task was rigged such that all participants ended up winning the same amount of money. These studies support the hypothesis that dopamine release is associated with winning money both in HC and in PG and suggest that dopamine is a biologic marker of intrinsic behavior with particular relevance for gambling.

Individuals suffering from substance abuse and dependence have cognitive and behavioral decision-making impairments similar to PG (17–20), which might be associated with dopaminergic dysregulations. Substance-dependent individuals have significantly lower dopamine $D_{2/3}$ receptor availability than HC (21). Lower receptor availability is associated with increased drug liking among HC (22, 23), whereas individuals with higher receptor availability show resilience toward drug liking and the risk of developing addiction (24). The ventral striatum is specifically involved in drug expectation and monitoring of reward (25–27), and these functions are found to be deficient in pathological gambling (28). The involvement of the ventral striatum in drug-seeking behavior and addiction is supported by findings in the animal literature (29–31).

Finally, the dopamine system might be associated with dysfunctional learning in pathological gambling. Dopaminergic reward learning, the so-called *reward prediction error*, is associated with increased activation of midbrain dopamine neurons, which stimulate synaptic dopamine release in the striatum and throughout the brain (32–34). PG show reduced activation in the ventral striatum in relation to reward prediction error (28), which may be associated with the temporal and probabilistic discounting of reward. Kobayashi and Schultz (32) reported that time delay between stimulus and reward reduces the dopamine response, and McClure *et al*. (35, 36) found two distinct pathways for immediate and delayed rewards: immediate reward was associated with increased activation in the limbic and midbrain dopamine system, particularly in the ventral striatum; delayed reward, in contrast, was associated with increased activation in the lateral prefrontal cortex. These findings are consistent with other reports of immediate and delayed rewards (37, 38). Dopamine activation is also associated with probabilistic discounting; the more uncertain the outcome, the higher the sustained dopamine activation. Fiorillo *et al*. (33) found increased sustained activation of midbrain dopamine neurons toward stimuli with uncertain reward probability. The sustained activation was distinct from the phasic activation in reward prediction error. The authors concluded that uncertainty in itself contributes to the dopaminergic reward properties of uncertainty, which may explain why PG continue gambling despite losses. The association between dopamine and temporal and probabilistic discounting is consistent with the findings that PG have a higher preference for immediate rewards despite long-term losses on the IGT.

Taken together, these lines of research suggest that the dopamine system, and the ventral striatum in particular, play a central role in pathological gambling as well as substance dependence. Whereas dopamine release in HC appears specifically associated with monetary gains, dopamine release in pathological gambling might also be associated with monetary losses; particularly in relation to immediate outcomes (temporal discounting) or outcome uncertainty (probabilistic discounting). Increased dopamine release during losses could explain loss-chasing behavior in pathological gambling. Furthermore, the role of dopamine in pathological gambling might hold important implications for understanding cognitive and behavioral dysfunctions associated with addiction, as confounds of drug use causing changes to the dopamine system can largely be excluded.

Based on our previous findings (6, 9), we therefore hypothesized that losing money on the IGT would be associated with increased dopamine release in the ventral striatum of PG compared with HC. We defined losses as IGT performance associated with overall losses and gains as IGT performance associated with overall gains or a neutral outcome ('0'). We used Positron Emission Tomography (PET) with [^{11}C]raclopride, a tracer of the dopamine $D_{2/3}$ receptors, to measure dopaminergic neurotransmission during a baseline and a gambling condition of the IGT. We

measured baseline binding potentials (BP_{ND}) and change in binding potential (ΔBP_{ND}) between baseline and gambling condition. Baseline raclopride binding potentials provide an index of the number of $D_{2/3}$ receptors available for dopamine binding. Decreased raclopride binding potentials from baseline to gambling condition indicate dopamine release, because dopamine occupies more receptors during gambling and leaves fewer receptors available for raclopride binding. Conversely, increased raclopride binding potentials indicate that dopamine occupies fewer receptors during gambling thereby leaving more receptors available for raclopride binding.

Aims of the study

To investigate the dopamine release in the ventral striatum of pathological gamblers (PG) without alcohol or substance dependence comorbidity and healthy controls (HC) during monetary gains and losses on the Iowa Gambling Task (IGT). We used PET with the radioligand [^{11}C]raclopride to measure dopaminergic neurotransmission during a baseline and a gambling condition of the IGT, with the hypothesis that PG would have increased dopamine release toward monetary losses compared with HC.

Material and methods

Participants

The cohort consisted of 16 PG and 15 HC, all right-handed men between the age of 22 and 55. PG were recruited through the Danish Center for Pathological Gambling [*Center for Ludomani*], and only referred if they were still actively gambling. A HC group, matched for gender, age, and education, was recruited through local newspaper advertisement, using the same intake criteria and procedures. HC were defined as individuals who might gamble occasionally, but not habitually, and showed no symptoms of problem gambling or pathological gambling (see below). 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 30.7 years (SD = 7.5), and 34.1 for HC (SD = 9.5), $F(1, 29) = 1.23$, *ns*.

All participants were screened for Axis I psychopathology using the Structured Clinical Interview for DSM-IV (SCID-I) (39, 40). 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 neurologic disorders or conditions that made them unfit for PET and MR scanning (e.g., pacemakers or prosthetic devices). None of the PG suffered from substance dependence comorbidity. PG were included, if they met full DSM-IV criteria for pathological gambling. HC were included if they had no more than one symptom on the SCID-I indicating a potential gambling tendency.

As a measure of external validity, we used the South Oaks Gambling Screen (SOGS) (41, 42) to assess symptom severity of gambling behavior. The SOGS is a self-administered questionnaire ranging from 0 to 20. A score of 5 or more indicates risk of pathological gambling, and subjects ranging from 3 to 4 are at risk for problem gambling. The SOGS shows good reliability and validity with the DSM-IV criteria for pathological gambling (43). HC were excluded if they had a SOGS score of or more. In our study, the average SOGS score among PG (13.12 ± 2.06) was significantly higher than in HC (0.13 ± 0.35), $F(1, 29) = 579.93$, $P < 0.000001$.

Procedure

Iowa Gambling Task (IGT). The IGT is a computerized card game, which simulates real-life decision-making in the way it factors reward and punishment. Individuals with lesions in the ventromedial prefrontal cortex or orbitofrontal cortex have impaired performance on the IGT (44, 45), as do individuals suffering from substance dependence and Pathological Gambling (4–6, 18, 20). 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 points, the selection of a card is followed by a higher penalty, so that in the long run, these decks produce a net loss. In decks C and D ('advantageous decks'), the immediate gain is smaller, but the delayed loss is also smaller, so that in the long run, these decks lead to a net gain. The total number of trials was set to 100 cards. The IGT provides two measures: A total amount of monetary outcome (gains or losses), and an IGT score, which is calculated as the number of cards selected from advantageous minus disadvantageous decks [(C + D) − (A + B)].

The IGT takes about 20 min to administer. As scanning times lasted 60 min, three different card sets of the IGT were used. We used the regular

ABCD version, and subsequent KLMN and QRST versions, where the contingencies between card decks become increasingly ambiguous. Normally, group differences on the IGT are measured as performance [(C + D) − (A + B)] across five blocks of 20 cards (1–20, 21–40 and so forth). As we used three different versions of the IGT, however, we measured group differences in performance across the three different versions (ABCD, KLMN, and QRST). Monetary outcome was measured as the total amounts won or lost.

PET/MRI methods

Participants were scanned twice with the ECAT HR (CTI/Siemens) PET tomograph operating in 3-D acquisition mode during baseline and gambling performance on the IGT. The first scan was a baseline scan, where the computer randomly instructed the participants which cards to chose. During the second scan, which was the gambling condition, participants were allowed to choose freely among decks. Before each scan, a brief attenuation scan was obtained, followed by a i.v. bolus injection of [11C]raclopride (168–364 MBq). Dynamic emission recordings were obtained for 60 min following tracer administration for a total of 22 frames of increasing duration. Anatomic MRI scans were carried out on a GE 3T high-resolution MRI scanner using a T1-weighted sequence optimized for MRI/PET coregistration. Emission recordings summed over the whole hour of scanning for both the baseline and the activation conditions were individually coregistered to the native MR images using MNI tools, and then transformed into the common stereotaxic coordinate space (46). Using a cerebellar ROI, cerebellar time activity curves (TACs) were generated for each subject and each scan. Using the cerebellar TACs, voxel-wise maps of [11C]raclopride, binding potentials (BP_{ND}) 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}) normalized to baseline in percentage [(Baseline − Gambling)/Baseline) × 100].

Statistical analysis

We used one-way analysis of variance (ANOVA) to investigate group differences between PG and HC of binding potentials (BP_{ND}) and change in binding potentials (ΔBP_{ND}). We used a two-way factorial design to determine the interaction between binding potential changes and group (PG vs. HC), with changes in binding potential as the dependent variable. Finally, we used a repeated-measures analysis to determine differences in gambling performance across the three IGT versions.

Results

PG and HC showed no overall differences in baseline binding potentials (BP_{ND}) or change in binding potentials (ΔBP_{ND}) (Table 1). However, PG and HC showed significant differences in binding potential changes (ΔBP_{ND}) in relation to monetary losses and gains (Table 1 and Fig. 1). PG who lost money had significantly higher dopamine release in the left ventral striatum than HC, $F(1, 29) = 5.52$, $P < 0.05$ ($P < 0.02$ one-tailed). In Fig. 1, dopamine release results in positive values because raclopride binding potentials decrease from baseline to gambling condition (baseline > gambling = positive value). Conversely, dopamine inhibition results in negative values because raclopride binding potentials increase from baseline to gambling condition (baseline < gambling = negative value).

PG and HC who won money did not differ in binding potential changes, but the two-way ANOVA showed a significant interaction effect, $F(2, 28) = 4.18$, $P = 0.05$, where dopamine release was associated with losses within PG and gains within HC. No group differences were found in the right ventral striatum.

A repeated-measures analysis showed that IGT performance was stable across the three games

Table 1. Binding potentials (BP_{ND}) and change in binding potential (ΔBP_{ND}) in pathological gamblers (PG) and healthy controls (HC)

	Healthy controls			Pathological gamblers		
	n	Mean	SD	*n*	Mean	SD
BP_{ND}						
Left ventral striatum	15	2.19	0.29	16	2.13	0.42
Right ventral striatum	15	2.00	0.28	16	1.96	0.35
ΔBP_{ND}						
Left ventral striatum	15	−2.89	15.15	16	0.08	13.88
Right ventral striatum	15	−2.25	15.71	16	−0.07	13.04

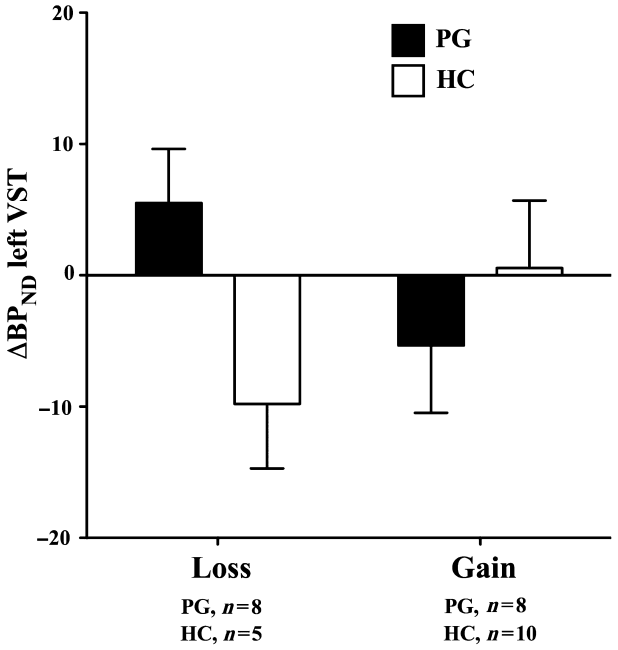

Fig. 1. Binding potential changes (ΔBP_{ND}) in left ventral striatum of pathological gamblers (PG) and healthy controls (HC). PG who lose money (PG, black bar, $n = 8$) have significantly higher dopamine release in the left ventral striatum than HC (white bar, $n = 5$). PG who win money (PG, black bar, $n = 8$) do not differ in dopamine release from HC (white bar, $n = 10$). Mean and standard errors are illustrated in the bars and error bars, respectively.

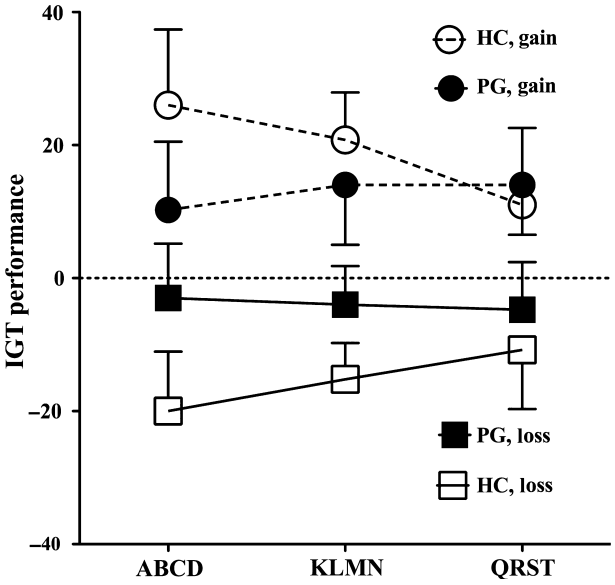

Fig. 2. Iowa Gambling Task performance in pathological gamblers (PG) and healthy controls (HC). Gambling performance remains stable across the three games among HC and PG. HC who win money (HC, white circles) perform significantly better than HC who lose money (HC, white squares), and PG who win money (PG, black circles) perform significantly better than PG who lose money (PG, black squares). The abscissa shows the three games, and the ordinate shows gambling performance.

(Fig. 2). HC with monetary gains performed significantly better than HC with losses, $F(4, 10) = 14.56$, $P = 0.0005$, and PG with monetary gains performed significantly better than PG with losses, $F(4, 11) = 6.34$, $P < 0.02$. There were no differences in IGT performance between HC and PG who lost money, or between HC and PG who won money.

Discussion

This study showed that PG who lost money on the IGT had significantly higher dopamine release in the left ventral striatum than HC who lost money. PG and HC who won money did not differ in dopamine release. The data suggest a dopaminergic dysfunction toward losses in pathological gambling, which might explain loss-chasing behavior in the disorder.

The increased dopamine release toward monetary losses in pathological gambling suggests a dopaminergic basis of susceptibility to immediate reward seeking in PG, which is not seen in HC. While punishment behavior usually reduces dopaminergic activation (34), our data suggest increased dopamine release in PG who prefer higher immediate rewards despite long-term losses. These results are consistent with the findings by McClure et al. (35, 36) and suggest that PG have increased dopamine activation in the mesolimbic pathway toward immediate rewards, but reduced mesolimbic dopamine release toward delayed rewards. In HC, this pattern is reversed. Our data might provide indirect evidence of weakened PFC functions toward losses in pathological gambling, which is consistent with the literature on IGT performance. However, our findings are limited to the striatal regions, and further studies involving frontal and prefrontal regions are needed to fully answer this question.

One-third of HC lost money, which is similar to other studies of IGT performance (20). It is currently unclear why some HC have impaired IGT performance, but the impairments in HC appear more homogenous and seems not to involve dopamine dysfunctions. Our data therefore suggest increased dopamine release in PG toward monetary losses, while other factors than dopamine release contributed to the losses in HC.

We found no differences in dopamine release between PG and HC who won money. This is consistent with studies of delayed reward suggesting that reward delay reduces dopamine activation (32). Inhibition of higher immediate rewards may have reduced the dopamine release in PG and HC

despite the long-term gains. Dopamine release might therefore have been higher if no monetary punishment was present in the task. Steeves et. al. (16) found significant dopamine release among Parkinson's patients with pathological gambling using a rigged reward task, which had a 3:1 reward vs. penalty ratio, and always produced an overall gain. In contrast, the IGT uses both monetary reward and punishment on each trial, and to win money higher immediate rewards must be inhibited. The inhibition of higher immediate rewards could explain the differences in dopamine release of winning between the present study and that of Steeves et. al. (16). However, other factors such as differences in dopamine $D_{2/3}$ regulation and synthesis between PG with and without Parkinson's disease might also account for the differences.

We found no differences in baseline binding potentials between PG and HC. Our findings contrast the literature on substance dependence, where substance-dependent individuals have significantly lower binding potentials than HC (21). Although Volkow et. al. (21) compared binding potentials throughout the striatum, and we specifically investigated the ventral striatum, these differences in results may suggest a down-regulation of receptor availability as a consequence of substance abuse, which is not present in pathological gambling. We note that comorbidity between pathological gambling and alcohol and substance dependence disorders is generally high (49–54), and that presence of substance dependence increases severity of pathological gambling (55) or risk thereof (56). However, our population of PG was screened for alcohol and substance dependence. It is therefore possible that lower levels of baseline dopamine binding potentials are found in individuals suffering from comorbidity of pathological gambling and alcohol or substance dependence.

Our results only reached significance level in the left ventral striatum. This lateralization is consistent with the findings by Steeves et. al. (16) and other studies of dopamine reward behavior (12, 57). While there may be an empirical basis for these lateralized results, they may also reflect methodological limitations of sample size and power in our study. Another limitation in our study was that we could not differentiate the influence of immediate reward (temporal discounting) and outcome uncertainty (probabilistic discounting) in monetary losses and gains. Further studies are needed to determine the relation between reward immediacy and outcome uncertainty on the IGT. Finally, we note that we did not find overall differences in binding potential changes between PG and HC. PG only differed with regard to monetary losses. This suggests that PG are not hyperdopaminergic per se, but have increased dopamine susceptibility toward certain types of decisions and behavior.

In conclusion, we find evidence that PG have increased dopamine release in the ventral striatum toward monetary losses compared with HC. These dopaminergic dysfunctions might be associated with loss-chasing behavior in pathological gambling. The results might have implications for the understanding of dopamine dysfunctions and impaired decision-making in pathological gambling and substance-related addictions.

Acknowledgements

This study was supported by funding from the Danish Agency for Science, Technology and Innovation grant number 2049-03-0002 and 2102-05-0009; and from the National Center for Responsible Gaming as provided by The Institute for Research on Pathological Gambling and Related Disorders in the Division on Addictions at Cambridge Health Alliance. Its contents are solely the responsibility of the author(s) and do not necessarily represent the official views of the Danish Agency for Science, Technology and Innovation or the National Center, the Institute, or Cambridge Health Alliance. The first author and Principal Investigator had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

None of the authors have any conflicts of interest to declare.

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