

Response Perseveration and Ventral Prefrontal Sensitivity to Reward and Punishment in Male Problem Gamblers and Smokers

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Pathological gambling (PG) is associated with maladaptive perseverative behavior, but the underlying mechanism and neural circuitry is not completely clear. Here, the hypothesis was tested that PG is characterized by response perseveration and abnormalities in reward and/or punishment sensitivity in the ventral frontostriatal circuit. Executive functioning was assessed to verify if these effects are independent of the dorsal frontostriatal circuit. A group of smokers was also included to examine whether impairments in PG generalize to substance use disorders. Response perseveration and reward/punishment sensitivity were measured with a probabilistic reversal-learning task, in which subjects could win and lose money. Executive functioning was measured with a planning task, the Tower of London. Performance and fMRI data were acquired in 19 problem gamblers, 19 smokers, and 19 healthy controls. Problem gamblers showed severe response perseveration, associated with reduced activation of right ventrolateral prefrontal cortex in response to both monetary gain and loss. Results did not fully generalize to smokers. Planning performance and related activation of the dorsal frontostriatal circuit were intact in both problem gamblers and smokers. PG is related to response perseveration and diminished reward and punishment sensitivity as indicated by hypoactivation of the ventrolateral prefrontal cortex when money is gained and lost. Moreover, intact planning abilities and normal dorsal frontostriatal responsiveness indicate that this deficit is not due to impaired executive functioning. Response perseveration and ventral prefrontal hypo-responsiveness to monetary loss may be markers for maladaptive behavior seen in chemical and nonchemical addictions.

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INTRODUCTION

Pathological gambling (PG) is a psychiatric disorder with an estimated lifetime prevalence of 0.4–1.6% in the United States and Canada (Petry *et al*, 2005; Slutske, 2006). It is associated with psychosocial problems (Lejoyeux *et al*, 2002), criminal offences (Rosenthal and Lorenz, 1992), and sometimes even suicide (Petry and Kiluk, 2002). Although classified as an impulse control disorder (American Psychiatric Association, 1994), PG is often considered a behavioral addiction (Petry, 2006; Potenza, 2006; Tammenga and Nestler, 2006) and shares many clinical characteristics

with substance dependence, such as psychiatric comorbidity (Petry *et al*, 2005), genetic vulnerability (Eisen *et al*, 2001; Ibanez *et al*, 2003), and responsiveness to specific pharmacological treatments (Eisen *et al*, 2001; Grant and Kim, 2006; Hollander *et al*, 2005b; Ibanez *et al*, 2003). An alternative view emphasizes the similarities between PG and obsessive-compulsive disorder (OCD; Hollander *et al*, 2007).

Neuroimaging studies in PG are sparse and have demonstrated increased cue reactivity in response to gambling cues similar to alcohol and drug craving (Crockford *et al*, 2005; Potenza *et al*, 2003b). In addition, decreased ventral frontostriatal activation relative to control subjects was reported in a Stroop task measuring attention and inhibition (Potenza *et al*, 2003a) and in a gambling task using monetary reward (Reuter *et al*, 2005). Finally, in an FDG-PET study, gambling for money led to a higher relative metabolic rate than gambling for points only in pathological gamblers, confirming the

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relevance of monetary reward in PG (Hollander *et al*, 2005a).

The ventral frontostriatal reward circuit has been implicated in the development and maintenance of drug addiction (Volkow *et al*, 2004). Reduced activation of this circuit in response to monetary reward has also been reported in PG (Reuter *et al*, 2005), suggesting that PG is characterized by a similar blunted response to rewarding stimuli as found in substance dependence. The Reuter *et al* study, however, employed a gambling paradigm in which the subject had no influence on receiving reward or punishment; moreover, no neutral stimuli were presented. Therefore, neither reward-based learning nor separate contributions of reward and punishment to the reported activations could be assessed. A paradigm that taps into reward and punishment evaluation, and activates ventral frontostriatal brain regions, is the probabilistic reversal-learning task (PRLT; Clark *et al*, 2004; Cools *et al*, 2002; Dias *et al*, 1996; O'Doherty *et al*, 2001, 2003; Remijnse *et al*, 2005; Remijnse *et al*, 2006). In this paradigm, subjects acquire stimulus-reward associations, after which reward and punishment contingencies are reversed and subjects have to adjust their strategy to the altered stimulus-reinforcement associations. This process is referred to as 'affective switching', and the inability to learn these altering associations results in response perseveration. Therefore, in the present study, not only evaluation of reward and punishment was assessed, but also its effect on behavior. Reversal learning has been largely overlooked in research on addictive behaviors (Clark *et al*, 2004), although a recent preliminary study reported impaired reversal learning in PG (Patterson *et al*, 2006).

In addition to deficits in punishment and reward evaluation, several studies have reported executive function (EF) deficits in substance use disorders (Lundqvist, 2005; Montgomery *et al*, 2005; Noel *et al*, 2001; Verdejo-Garcia and Perez-Garcia, 2007; Verdejo-Garcia *et al*, 2005) and, to a lesser extent, in PG (Goudriaan *et al*, 2006; Kertzman *et al*, 2006; Ruge and Melamed, 1993). EFs are supervisory cognitive functions that are mainly mediated by dorsal frontostriatal circuitry. Neuroimaging studies have found prefrontal dysfunctions during performance of EFs in substance users (Forman *et al*, 2004; Hester and Garavan, 2004; Kaufman *et al*, 2003). A key EF is planning, which is the ability to achieve a goal through a series of intermediate steps. Planning has been widely investigated with the Tower of London (ToL; Shallice, 1982). In this task, subjects rearrange colored balls on pegs from a start-state into a goal-state in as few moves as possible. Performance on the ToL has been shown to be impaired in alcohol dependence (Noel *et al*, 2001). Neuroimaging studies have confirmed involvement of the dorsal striatum and the dorsolateral prefrontal cortex (DLPFC) during performance of the ToL (Owen *et al*, 1996; van den Heuvel *et al*, 2003). Using a task sensitive to dorsal frontostriatal function (ie the ToL) and a task sensitive to ventral frontostriatal function (ie the PRLT) enabled us to investigate whether impairment in PRLT performance is associated with similar impairments when performing the ToL. To test whether any findings in PG generalize to another (chemical) addiction, we also included a group of substance-dependent subjects. Similar abnormalities in PG and nicotine dependence (ND) may

point to a common mechanism across several types of addictive behaviors, chemical and nonchemical.

In summary, we expected response perseveration and decreased ventral frontostriatal responsiveness to reward in problem gamblers and smokers relative to healthy controls. In addition, employing the ToL, we expected diminished planning abilities and dorsal frontostriatal hypoactivation in problem gamblers and smokers, compared to healthy controls.

MATERIALS AND METHODS

Subjects

A total of 19 problem gamblers (4 left-handed), 19 smokers (3 left-handed), and 19 healthy controls (1 left-handed) participated in this study. Gamblers were recruited from two Dutch addiction treatment centers where they received cognitive behavioral therapy. Smokers and healthy controls were recruited through advertisements in local newspapers. Because most treatment-seeking gamblers are men, only male participants were included. Smokers and healthy controls were matched to the problem gamblers for age and educational level. The ethical review board of the Academic Medical Center approved the study, and all participants provided written informed consent. The main inclusion criterion for problem gamblers was current treatment for gambling problems. In addition, problem gamblers were interviewed according to DSM-IV-TR criteria using the Dutch version of section T of the Diagnostic Interview Schedule (DIS; Robins *et al*, 1998), to assess whether they fulfilled criteria for a formal PG diagnosis. The South Oaks Gambling Screen (SOGS; Lesieur and Blume, 1987) was administered to obtain a sensitive measure of gambling severity (Strong *et al*, 2003). Smokers were included if they smoked at least 15 cigarettes per day. The Fagerström interview (Heatherton *et al*, 1991) served as an additional measure of ND severity on a scale of 0–10. Healthy controls were all nonsmokers and were not allowed to engage in a gambling activity more than twice a year. Smokers were instructed to abstain from smoking 10 h before entering the experimental session. Similarly, gamblers were instructed to abstain from gambling at least 10 h before the start of the experimental session.

Exclusion criteria for all groups were: lifetime diagnosis of schizophrenia and psychotic episodes, 12-month diagnosis of manic disorder (section F of the Dutch Composite International Diagnostic Interview (CIDI); World Health Organization, 1997), treatment for mental disorders other than those under study in the past 12 months, use of psychotropic medication, difficulty reading Dutch, age under 18 years, positive urine screen for alcohol, amphetamines, benzodiazepines, opioids or cocaine, consumption of more than 21 standard units (10 g) of alcohol per week, history of or current: treatment by a neurologist, systemic disease, brain trauma, exposure to neurotoxic factors. Groups were mutually exclusive with regard to the psychiatric disorder under study. For instance, problem gamblers and healthy controls did not smoke (with the exception of two problem gamblers who smoked less than five cigarettes a day). Additional exclusion criteria for healthy controls and smokers, but not for problem

gamblers, were: anxiety disorders (CIDI, section D), depression (CIDI, section E), OCD (CIDI, section K), post-traumatic stress disorder (CIDI, section K), and attention deficit hyperactivity disorder (ADHD), assessed with Conners' Adult ADHD Rating Scales (CAARS; Conners *et al*, 1999). Severity of depressive symptoms was assessed with the Beck Depression Inventory (BDI; Beck *et al*, 1961). Problematic alcohol use was screened with the Alcohol Use Disorders Identification Test—Consumption (AUDIT-C; Bush *et al*, 1998).

Paradigms

We used a self-paced, PRLT including an affectively neutral condition (Figure 1) and a pseudorandomized self-paced version of the ToL (Figure 2). Both tasks have been described in detail elsewhere (Remijne *et al*, 2005; van den Heuvel *et al*, 2003). The scanning session began with the reversal-learning task and ended with the ToL. In between, a structural MRI was acquired. After a break, a second scanning session was used that

consisted of two other tasks (a stop-signal task and a cue reactivity task). Data from these tasks will be reported elsewhere.

Imaging Acquisition and Preprocessing

Imaging data were obtained using a 3.0 T Inera full-body fMRI scanner (Philips Medical Systems, Best, the Netherlands) with a phased array SENSE RF six-channel receiver head coil. A total of 35 axial slices (voxel size $3 \times 3 \times 3$ mm, interslice gap 0.3 mm, matrix size 64×64 mm, PRLT: TR/TE = 2.50 s/30 ms, ToL: TR/TE = 2.28 s/35 ms, bandwidth 90 kHz) of T2*-weighted echo planar images (EPIs), sensitive to blood oxygenation level-dependent (BOLD) contrast, were obtained, covering the entire brain except for the inferior regions of the cerebellum. Also a structural scan of 170 sagittal T1-weighted slices of the entire brain was made to co-register it with the fMRI data (voxel size $1 \times 1 \times 1$ mm). Imaging analysis was done using SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK). Images were slice-

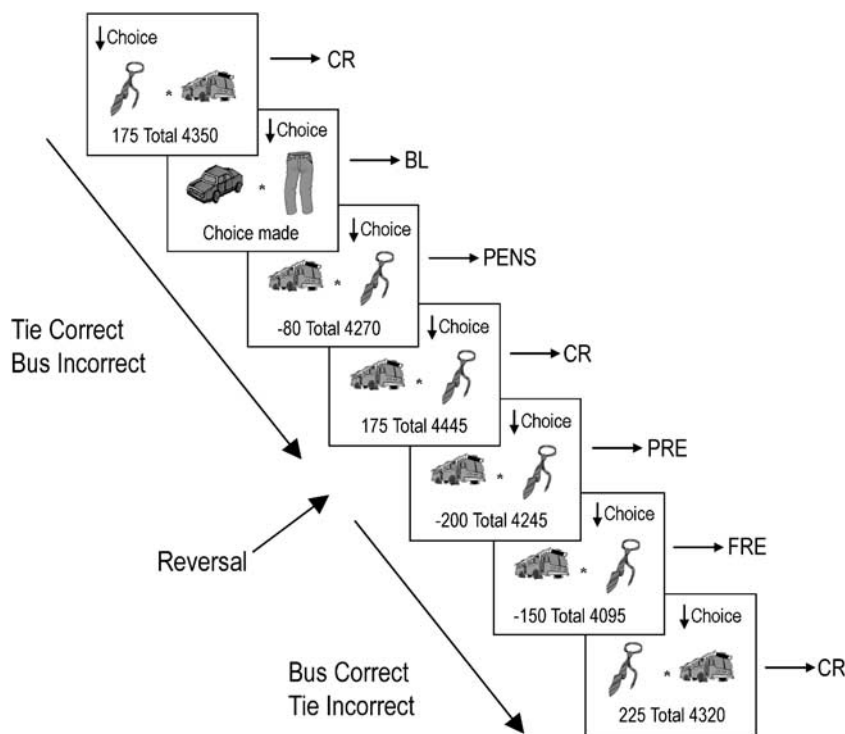


Figure 1 Probabilistic reversal-learning task (PRLT). During each trial two stimuli, ie a picture of a bus and a tie, were presented simultaneously at either side of a screen with randomized locations until the subject responded (3 s maximum). Subjects selected either stimulus by pressing the left or right button on a button box. Upon a correct response, either positive or negative feedback was given based on an 80 : 20 ratio, resulting in a gain or a loss of a random amount of 80–250 points. Each trial ended with a 2 s display of both the number of points won or lost in that trial and the amount of accumulated points in the task up to that trial, followed by a fixation cross for 1 s, which indicated the start of the next trial. An affectively neutral baseline task consisting of two different, equivalent stimuli in terms of visual complexity and semantic category (the picture of a car and a pair of trousers) was randomly intermixed with experimental trials, and responses in this task were given neutral feedback ('response made'). Subjects were instructed in advance which of the two baseline stimuli to select. The task ended after 400 trials (including the baseline task) and lasted approximately 25 min. The main task instruction was to strive to obtain a maximum number of points; subjects were not encouraged to respond as quickly as possible. Subjects were informed beforehand that they could earn real money with the task. The task started with a five Euro credit. After the scanning session, participants received the total amount of accumulated points during the task divided by 1000 in Euros. To familiarize participants with the concept of probabilistic errors, before scanning subjects performed a brief version of the PRLT that did not contain reversal stages. Subjects were not informed that the actual task contained reversal stages. CR, correct response; BL, baseline trial; PENS, probabilistic error, no shift; PRE, preceding reversal error; FRE, final reversal error.

timed, reoriented, and realigned to the first volume. Next, T1-co-registered volumes were normalized to an SPM T1 template and spatially smoothed using an 8 mm FWHM Gaussian kernel.

Statistical Analysis

Demographic and clinical data were analyzed using univariate analysis of variance (ANOVA) in SPSS 13.0

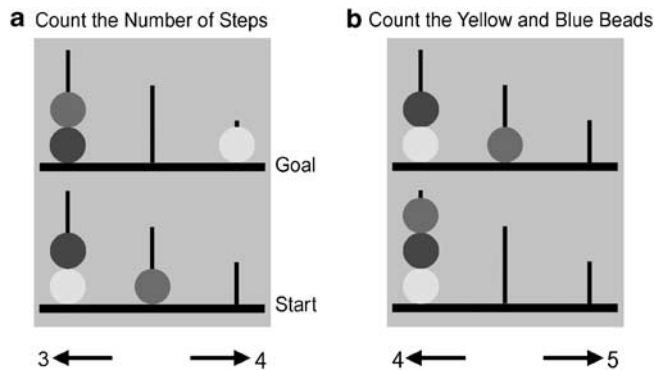


Figure 2 Tower of London (ToL). This version consisted of six conditions, including a baseline condition and five planning conditions of increasing difficulty, requiring planning of 1–5 moves. During the planning conditions, subjects saw a starting configuration together with a target configuration, with the instruction to ‘count the number of steps’ required to achieve the target configuration. In both configurations, three colored beads were placed on three vertical rods, which could accommodate one, two, and three beads each. One bead could be moved at a time and only when there was no other bead on top. Subjects were required to determine the minimum number of moves necessary to reach the target configuration. Two possible answers were shown. Subjects had to press the button corresponding to the side (left or right) of the screen where the correct answer was presented. In the baseline condition, subjects simply had to count the total number of yellow and blue beads. No feedback regarding the answers was provided during the task. The task was self-paced with a maximum response time for each trial of 30 s and lasted 15 min. To ensure that participants were familiar with the task, it was explained and practiced outside the scanner.

(SPSS Inc., Chicago, Illinois). fMRI data were analyzed in the context of the general linear model, using δ functions convolved with a canonical hemodynamic response function to model responses to each type of stimulus. Contrast images containing parameter estimates were entered into a second-level (random effects) analysis. Main effects across groups for each contrast were analyzed with one-way ANOVA implemented in SPM2 and are reported with a cluster size restriction of 10 voxels at a $p < 0.05$ corrected for multiple comparisons according to the false discovery rate (FDR) method (Genovese *et al*, 2002; Remijne *et al*, 2005). Group interactions are reported at $p < 0.001$, masked with the appropriate main effect at $p < 0.05$.

PRLT

fMRI data for one smoker were corrupt for the PRLT due to scanner failure. Therefore, 18 instead of 19 smokers were used for analysis of this task. To ensure adequate power, for each subject a minimum of 10 trials per condition were required for fMRI analyses. As a result, for calculation of the reward–baseline contrast, 5 problem gamblers had to be excluded, leaving 14 problem gamblers for analysis. For calculation of the reversal–baseline contrast, 2 smokers and 8 gamblers had to be excluded, leaving 16 smokers and 11 gamblers for analysis. ANOVA was used to analyze behavioral data (amount of money won and mean reaction time (MRT) with Group (problem gamblers, smokers, and healthy controls) as between-subject factor. For fMRI analyses, the following events were modeled to feedback onset: neutral feedback, monetary gain, monetary loss (not followed by reversal), monetary loss followed by reversal, and monetary gain followed by a reversal (regressor of no interest). The following contrasts were computed: monetary gain *vs* baseline, monetary loss *vs* baseline, and monetary loss followed by a reversal *vs* baseline.

Table 1 Demographic and Clinical Characteristics for Problem Gamblers, Smokers, and Healthy Controls

| | Problem gamblers (n = 19) | Smokers (n = 19) | Healthy controls (n = 19) | p-value (2-tailed) |
|--|------------------------------|---------------------|------------------------------|-----------------------|
| Mean age in years (SD) | 34.3 (9.4) | 34.8 (9.8) | 34.1 (9.3) | 0.97 |
| Mean education level (SD) | 4.1 (0.9) | 4.2 (1.1) | 4.4 (1.2) | 0.42 |
| DIS-T, pathological gambling LT diag number (%) | 15 (79%) | 0 | 0 | |
| DIS-T, pathological gambling 12M diag. number (%) | 12 (63%) | 0 | 0 | |
| Fagerström test for nicotine dependence, mean (SD) | 5.0 (0) ^a | 5.1 (1.5) | | |
| CIDI anxiety 12M diag. number (%) | 5 (26%) | 0 | 0 | |
| CIDI depression 12M diag. number (%) | 5 (26%) | 0 | 0 | |
| Total comorbidity, number (%) | 7 (37%) | 0 | 0 | |
| Conners' Adult ADHD rating scale, mean (SD) | 53.5 (13.8) | 46.1 (11.3) | 44.4 (6.1) | 0.029 |
| Beck depression inventory, mean (SD) | 12.1 (12.1) | 4.5 (4.0) | 3.7 (4.1) | 0.005 |
| South Oaks Gambling Screen 12 months, mean (SD) | 8.9 (2.4) | | | |
| Alcohol use disorders identification test, C | 4.1 (2.3) | 4.6 (2.3) | 3.6 (2.1) | 0.35 |

Abbreviations: DIS-T, Diagnostic Interview Schedule, section T; LT diag, lifetime diagnosis; 12M Diag, 12-month diagnosis; CIDI, Composite International Diagnostic Interview; ADHD, attention deficit hyperactivity disorder.

^aTwo gamblers smoked (less than 5 cigarettes a day).

ToL

For the ToL, one smoker failed to comply with task instructions and fMRI data from one smoker were corrupt due to scanner failure. Therefore, 17 smokers were used for analysis of this task. A mixed model ANOVA was used to investigate performance differences (number of correct responses and MRT) between the three groups, with Group as a between-subject factor (three levels) and Difficulty as a within-subject factor (five levels). For the fMRI analyses, the following six events were modeled to stimulus onset: baseline, one step, two steps, three steps, four and five steps, erroneous response (regressor of no interest). For each subject, two contrasts were computed: all steps vs baseline and a parametric contrast for increasing task difficulty, not taking into account the baseline trials.

RESULTS

Demographic and Clinical Results

Table 1 summarizes demographic and clinical characteristics for the problem gamblers, smokers, and healthy

controls. The three groups did not differ with regard to age and educational level. Of the 19, 15 (79%) problem gamblers were diagnosed with lifetime PG; 12 of them (63%) also met the criteria for this disorder in the past 12 months. Fagerström scores indicated medium ND for the smokers, as well as for the two problem gamblers who smoked. It should be noted, however, that all smokers smoked more than 15 cigarettes per day, whereas the two smoking problem gamblers smoked less than 5 cigarettes per day. Seven problem gamblers (37%) suffered from comorbid anxiety and depression disorders in the past 12 months. Problem gamblers obtained significantly higher scores on the CAARS and BDI compared to both smokers and healthy controls. Smokers and healthy controls did not differ on the CAARS and the BDI.

PRLT

In the PRLT, the three groups differed significantly with regard to the amount of money won ($F(2, 53) = 10.00$, $p < 0.0005$; Figure 3). *Post hoc* tests showed that problem gamblers won less money than smokers ($t(19.31) = 2.86$, $p = 0.01$), and smokers won less money than healthy controls ($t(33.60) = 2.42$, $p < 0.05$). No differences in MRT were found between the groups. Performance was significantly negatively correlated with the score on the CAARS G scale ($r = -0.31$, $p < 0.05$) and the BDI ($r = -0.39$, $p < 0.005$). Group differences in the amount of money earned, however, remained significant after adjusting for differences between groups in CAARS ($F(2, 52) = 7.22$, $p < 0.005$) and BDI scores ($F(2, 52) = 5.76$, $p < 0.005$). This effect also remained significant when only considering problem gamblers fulfilling a PG diagnosis for the last 12 months ($n = 12$; $F(2, 46) = 5.76$, $p < 0.005$) or when analyzing only problem gamblers without comorbid anxiety or depression ($n = 12$; $F(2, 46) = 4.38$, $p < 0.05$).

Monetary gain was associated with activation of right ventrolateral prefrontal cortex (VLPFC) and frontal oper-

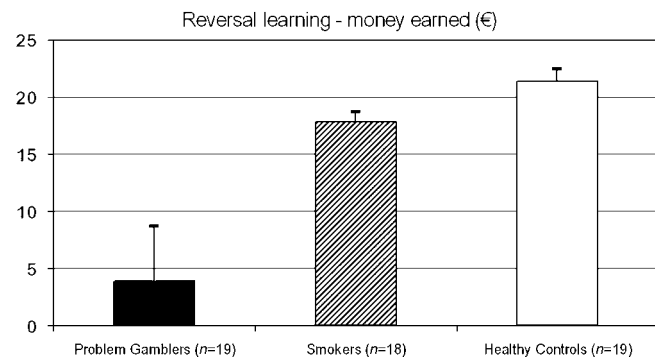


Figure 3 Amount of money earned in probabilistic reversal-learning task (PRLT). Error bars show SEM.

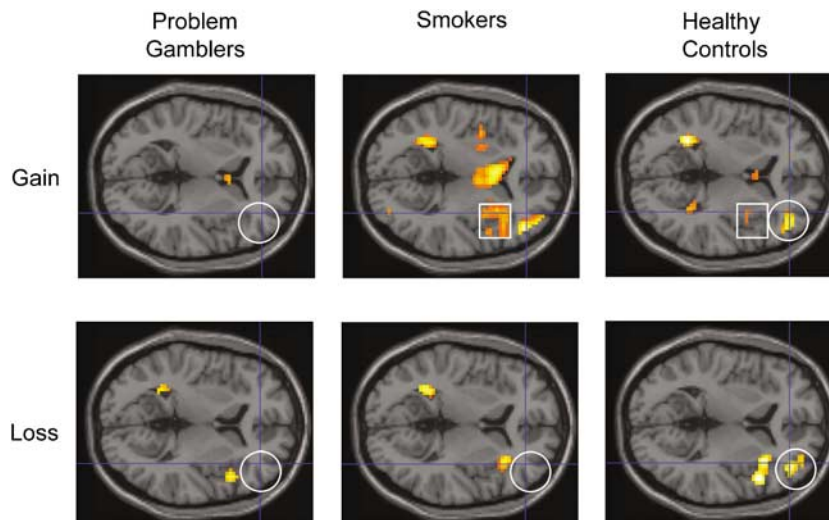


Figure 4 Probabilistic reversal-learning task. BOLD activations (main effects) for the contrasts monetary gain–baseline and monetary loss–baseline. Activations are shown at $p < 0.05$ uncorrected to show the extent of activity. Circle indicates hypoactive right ventrolateral prefrontal cortex (VLPFC) to monetary gain in problem gamblers compared to healthy controls, and hypoactivation of right VLPFC to monetary loss in both problem gamblers and smokers, compared to healthy controls. Square indicates hyperactivation of right anterior insula to monetary gain in smokers relative to healthy controls.

Table 2 PRLT: BOLD Activations for Main Effects and Group Interactions

| | L/R | Reward | | | | Punishment | | | | Reversal | | | |
|---------------------------------|-----|--------|-----|----|---------|------------|-----|----|-------------------|----------|-----|-----|---------|
| | | x | y | z | Z-value | x | y | z | Z-value | x | y | z | Z-value |
| Main effects ^a | | | | | | | | | | | | | |
| Ventrolateral PFC | R | 45 | 39 | 3 | 4.73 | | | | | 39 | 54 | 3 | 3.80 |
| Insula | R | | | | | 33 | 21 | 9 | 3.65 [#] | 36 | 18 | -3 | 5.67 |
| Frontal operculum | R | 51 | 9 | 18 | 4.33 | 48 | 15 | 6 | 3.76 ^c | 48 | 12 | 15 | 3.41 |
| Dorsolateral PFC | R | | | | | | | | | 39 | 36 | 30 | 4.92 |
| SMA | R | | | | | | | | | 21 | 9 | 66 | 4.72 |
| ACC | R | | | | | | | | | 9 | 36 | 33 | 3.15 |
| Posterior Parietal | L | | | | | | | | | -42 | -45 | 39 | 3.24 |
| | R | 51 | -36 | 54 | 4.58 | | | | | 48 | -42 | 45 | 5.77 |
| Occipital | R | 30 | -90 | -6 | 3.75 | | | | | | | | |
| Caudate | L | -3 | 12 | 6 | 3.78 | | | | | | | | |
| | R | 3 | 12 | 6 | 3.95 | | | | | | | | |
| Subthalamic region | L | -3 | -15 | -6 | 3.81 | -3 | -15 | -6 | 3.34 [#] | -3 | -18 | -6 | 4.11 |
| Group interactions ^b | | | | | | | | | | | | | |
| HC-Pr | | | | | | | | | | | | | |
| Ventrolateral PFC | R | 33 | 42 | 6 | 3.36 | 39 | 42 | 3 | 3.13 | | | | |
| Cerebellum | L | | | | | | | | | -30 | -66 | -30 | 3.15 |
| Pr-HC | | | | | | | | | | | | | |
| Occipital | R | 27 | -78 | 36 | 3.33 | | | | | | | | |
| HC-Sm | | | | | | | | | | | | | |
| Ventrolateral PFC | | | | | | 36 | 42 | 6 | 3.03 | 36 | 39 | 9 | 3.21 |
| premotor | | | | | | 48 | 3 | 21 | 3.46 | | | | |
| Sm-HC | | | | | | | | | | | | | |
| Insula | R | 33 | 24 | 6 | 3.93 | | | | | 33 | 30 | -3 | 3.38 |
| Frontal operculum | | | | | | | | | | 54 | 21 | 15 | 3.75 |
| Dorsolateral PFC | R | 54 | 21 | 39 | 4.45 | | | | | | | | |
| Premotor | R | 27 | 21 | 48 | 4.15 | | | | | | | | |
| Motor | R | 12 | -18 | 60 | 3.69 | | | | | | | | |
| Posterior Parietal | L | -30 | -33 | 51 | 3.37 | | | | | | | | |
| | R | 33 | -57 | 57 | 3.97 | | | | | | | | |

Abbreviations: ACC, anterior cingulate cortex; HC, healthy controls; PFC, prefrontal cortex; Sm, smokers; SMA, supplementary motor area; Pr, problem gamblers.

^aMain effects across groups are reported at $p < 0.05$, FDR corrected, minimum cluster size 10 voxels, unless reported otherwise.

^bGroup interactions are reported at $p < 0.001$ unless otherwise indicated.

^c $p = 0.089$, FDR corrected.

[#] $p < 0.001$, uncorrected.

culum, right parietal and occipital cortex, as well as bilateral caudate nucleus and subthalamic region (Figure 4; Table 2). Interaction analyses revealed significantly lower VLPFC activation in problem gamblers relative to healthy controls (Figures 4 and 5). In addition, in smokers we found significantly increased activation relative to healthy controls in right insula (Figure 4), right (pre)frontal areas, and bilateral parietal regions.

Monetary loss was associated with activation of right frontal operculum and insular cortex, as well as subthalamic region. Problem gamblers and smokers showed significantly less VLPFC activation than healthy controls (Figures 4 and 5). Monetary loss followed by a reversal was associated with activation of right frontal operculum and right insular

cortex, as well as in the subthalamic region. In addition, we observed activation of right DLPFC, right supplementary motor area (SMA), right dorsal anterior cingulate, and bilateral parietal cortex. Significant group differences were observed in controls relative to problem gamblers (cerebellum) and smokers (VLPFC), and in smokers relative to healthy controls (right frontal operculum and right insula).

ToL

A significant main effect of Difficulty ($F(4, 49) = 26.88$, $p < 0.0001$) showed that error rates increased with increasing planning demands. The three groups did not differ with regard to the proportion of correct responses

($F(2, 52) = 1.73$, NS). The Difficulty by Group interaction was not significant either ($F < 1$, NS). A significant main effect of Difficulty was found for MRT ($F(4, 49) = 82.17$, $p < 0.0001$), indicating longer reaction times with increasing task load. MRT was similar for the three groups ($F(2, 52) = 1.07$, NS) and the Difficulty by Group interaction was also not significant ($F < 1$, NS). After restricting problem gamblers to those meeting a formal PG diagnosis in the last 12 months ($n = 12$), no significant group effects were observed either.

Imaging results showed robust activations in bilateral dorsolateral prefrontal and parietal cortex, dorsal medial prefrontal cortex, and bilateral striatum, both when comparing task *vs* baseline and for task load (Figure 6; Table 3). However, group comparisons failed to reveal significant interaction effects between groups with the exception of small parietal and cerebellar foci in controls relative to problem gamblers and smokers, respectively.

Correlation Between PRLT and ToL

Amount of money won on the PRLT was not correlated with proportion of correct answers on the ToL ($r = 0.026$, NS).

DISCUSSION

The present study aimed at investigating abnormalities in behavioral performance and in the neural circuitry underlying reward and punishment sensitivity and planning in problem gamblers, compared to smokers and healthy controls. The main finding of the present study was a failure of the problem gamblers to adequately perform the reversal task, associated with response perseveration and lower responsiveness of the right VLPFC during winning and losing money. In contrast, planning in the problem gamblers was intact as indicated by normal performance on the ToL and normal responsiveness of the dorsal frontostriatal circuitry.

Decreased Reward Responsiveness in Problem Gamblers

The brain areas activated during the PRLT have also been reported in previous studies employing reversal-learning paradigms (Cools *et al*, 2002; O'Doherty *et al*, 2001, 2003; Remijnse *et al*, 2005, 2006). The most relevant areas activated by monetary gain were the right VLPFC, right frontal operculum, bilateral caudate nucleus, and subthalamic region. Compared to healthy controls, problem gamblers showed decreased responsiveness of VLPFC to monetary gain. Our findings are consistent with those of Reuter *et al* (2005), showing hypoactivation of the ventral prefrontal cortex in pathological gamblers in response to monetary gain. Moreover, in a recent study employing a decision-making task that was similarly developed to assess responses to monetary gain and loss (the Iowa Gambling Task), decreased responsiveness of the ventral prefrontal cortex in gambling and nongambling substance-dependent subjects during decision-making was found, compared to a task in which no decision-making was required (Tanabe *et al*, 2007). It should be noted, however, that in these studies group differences were observed in the medial instead of lateral ventral prefrontal cortex, a brain region

that was incompletely covered in our study due to signal dropout. Moreover, prefrontal hypo-responsiveness to monetary rewards has also been reported in two studies in cocaine abusers (Goldstein *et al*, 2007; Goldstein and Volkow, 2002).

It has been suggested that decreased dopamine function in the ventral striatum in addicted individuals results in a diminished sensitivity for drug-related as well as other rewarding stimuli. This ventrostriatal hypoactivity has been linked to increased reward-seeking behavior as a compensatory mechanism for existing reward deficiency (Blum *et al*, 2000). In PG this may relate to the high amounts of money spent in gambling episodes. Decreased ventrostriatal activity in turn has been found to be related to hypoactivity of the ventral prefrontal cortex (Volkow *et al*, 2004), which contains extensive ventrostriatal dopaminergic projections. Therefore, the current findings are consistent with the view of PG as a behavioral or nonchemical addiction. Interestingly, decreased responsiveness of the VLPFC has also been observed in patients with OCD in a study by our group, using an identical version of the PRLT (Remijnse *et al*, 2006). Hypo-responsiveness of the ventral prefrontal cortex to reward, therefore, seems to be a common phenomenon in both chemical and behavioral addictions on the one hand and OCD on the other hand, supporting the view that addictive behaviors and OCD may be part of an obsessive-compulsive spectrum (Hollander *et al*, 2007). This might be related to the maladaptive perseverative behavior that these disorders have in common.

Interestingly, the smokers were characterized by hyper-responsiveness rather than hypo-responsiveness of the insular cortex to monetary gain compared to both healthy controls and problem gamblers. In addition, in smokers we found increased activity in DLPFC, and posterior parietal cortex during rewarding feedback, indicating recruitment of higher-order cognitive functions similar to those activated during the ToL (Mitchell and Cusack, 2008; van den Heuvel *et al*, 2003). In this respect, smokers demonstrated an activation pattern that is atypical for addiction. A possible explanation may be that ND constitutes an atypical addiction: the percentage of individuals that develops addictive behaviors is quite low in gambling as well as in most drugs of abuse (around 15%), but the percentage of individuals that develop a dependence to nicotine is very high (Grant *et al*, 2004; Kessler *et al*, 1994). Finally, it should also be noted that the smokers had been abstinent for more than 10 h, which may also have influenced the results (Xu *et al*, 2006).

Decreased Punishment Sensitivity in Problem Gamblers

Punishment, ie monetary loss, was associated with activation of right insula, right frontal operculum, and subthalamic region, areas that have been reported before in studies examining the effects of abstract punishments (O'Doherty *et al*, 2001). In healthy controls, but not in smokers and problem gamblers, we additionally found right VLPFC activation, an area very close to the region that was hypoactive in response to reward reception in problem gamblers. The problem gamblers failed to activate right VLPFC to rewarding as well as punishing stimuli, which was coupled with a very poor performance. In contrast, smokers

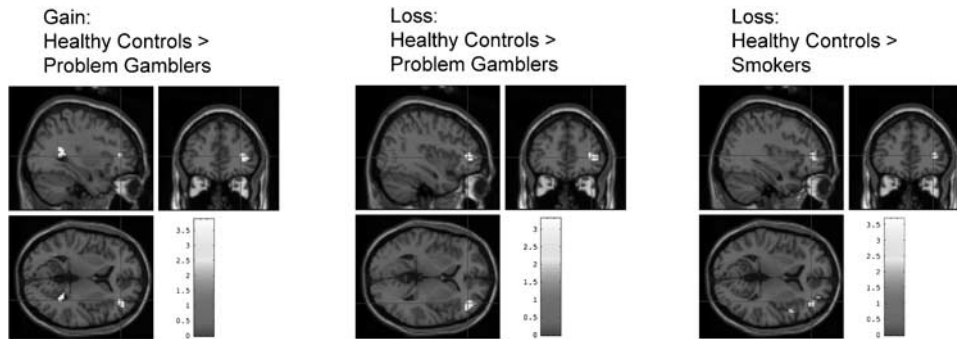


Figure 5 Probabilistic reversal-learning task. BOLD activations (group interactions) showing hypoactivation for problem gamblers compared to healthy controls in right ventrolateral prefrontal cortex (VLPFC) during monetary gain (left panel), and hypoactivation for both problem gamblers and smokers compared to healthy controls in right VLPFC during monetary loss (middle and right panels, respectively). Activations are shown at $p < 0.05$ uncorrected to show the extent of activity. Lighter color indicates higher t -score.

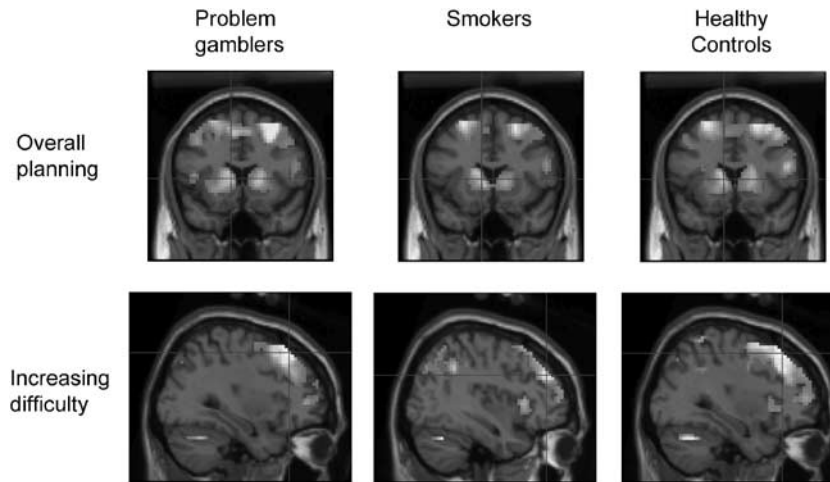


Figure 6 Tower of London BOLD activations (main effects) for the contrasts planning-baseline and parametric. Activations are shown at $p < 0.05$, FDR corrected. Upper panel shows activation of dorsal striatum for the planning-baseline contrast. Lower panel shows activation of dorsolateral prefrontal cortex for the parametric contrast, modeling increasing task difficulty.

Table 3 ToL: BOLD Activations for Main Effects and Group Interactions

| | L/R | Overall planning | | | | Increasing difficulty | | | |
|---------------------------------|-----|------------------|-----|-----|---------|-----------------------|-----|----|---------|
| | | x | y | z | Z-value | x | y | z | Z-value |
| Main effects ^a | | | | | | | | | |
| Dorsolateral PFC | L | -39 | 33 | 36 | 7.61 | -42 | 33 | 33 | > 7.83 |
| | R | 45 | 36 | 30 | 7.38 | 39 | 42 | 30 | 7.6 |
| MPFC/ACC | L | -6 | 21 | 48 | 7.49 | 0 | 30 | 42 | 7.83 |
| | R | -12 | -63 | 60 | > 7.8 | -9 | -63 | 57 | > 7.83 |
| Precuneus | L | 9 | -63 | 51 | > 7.8 | 9 | -54 | 54 | 7.76 |
| | R | -39 | -45 | 45 | 7.09 | -54 | -45 | 48 | 7.09 |
| Posterior parietal | L | 45 | -39 | 45 | 7.24 | 48 | -57 | 48 | 7.16 |
| | R | -9 | 15 | 6 | 7.46 | -18 | 3 | 15 | 5.77 |
| Dorsal striatum | L | 18 | 18 | 6 | 6.99 | 18 | 6 | 21 | 5.8 |
| | R | | | | | | | | |
| Group Interactions ^b | | | | | | | | | |
| HC-Sm posterior parietal | R | | | | | 30 | -48 | 39 | 3.37 |
| HC-Pr cerebellum | R | 3 | -42 | -15 | 3.88 | | | | |

Abbreviations: ACC, anterior cingulate cortex; HC, healthy controls; MPFC, medial posterior frontal cortex; PFC, prefrontal cortex; Sm, smokers; Pr, problem gamblers.

^aMain effects across groups are reported at $p < 0.05$, FDR corrected, minimum cluster size 10 voxels.

^bGroup interactions are reported at $p < 0.001$.

only failed to activate right VLPFC to punishing stimuli, associated with an intermediate performance.

Consistent with earlier reports (O'Doherty *et al*, 2003; Remijne *et al*, 2005, 2006), punishment trials that resulted in a reversal activated a large neural network, including dorsal prefrontal areas, compared to punishing trials not resulting in a behavioral shift. When comparing problem gamblers to healthy controls only decreased activation in the left cerebellum was observed. It should be noted, however, that the worst performing problem gamblers had to be excluded from this analysis as poor performance on this learning task inherently results in too few reversal trials to allow meaningful comparisons. Although our findings in this respect thus need to be interpreted with caution, it is interesting to note that cerebellar pathology has been associated with 'frontal-like' impairments, for example, impaired set-shifting and planning (Bellebaum and Daum, 2007; Gottwald *et al*, 2004). In line with our expectations, we observed VLPFC hyporesponsiveness in smokers relative to healthy controls during reversal trials. In addition, this group also showed hyperresponsiveness of right insula and frontal operculum during reversals, compared to healthy controls. This hyperresponsiveness was also observed in response to rewarding stimuli. In the present study, ND thus seems to be characterized by a hyperresponsive right insular cortex in response to motivational feedback. Interestingly, it was recently reported that smokers who acquired brain damage in the insula find it easy to quit smoking (Naqvi *et al*, 2007). The present findings indicate that the insula may not only be related to the rewarding effects of smoking, but also to a general hyperresponsiveness to reward in smokers.

Intact Planning

The three groups showed a similar performance on the planning task (ToL), and a dorsal frontostriatal and parietal network was activated with increasing task difficulty in all three groups. Apparently, in the present study, problem gamblers and smokers were characterized by normal EF as shown by normal performance and intact neural responsiveness of the dorsal frontostriatal network during a planning task. Problem gamblers showed less posterior parietal activation during increasing planning difficulty with intact performance. This may indicate that less attention-related processing was involved during planning for problem gamblers than for healthy controls, pointing to mild attention deficits that are too subtle to be detected by our present performance measures. *Post hoc* tests on the behavioral data (not shown), however, indicated that problem gamblers performed better during the more difficult conditions of the ToL than the other groups, which makes this a less probable explanation. Alternatively, these results may thus indicate that problem gamblers are actually better at planning and therefore need to recruit the posterior parietal cortex to a lesser extent.

Smokers showed less cerebellar activation than healthy controls during overall planning. Although executive dysfunction has been linked to cerebellar pathology, as noted earlier, in the present study such an interpretation remains speculative in the absence of impaired planning abilities in smokers.

Impaired EFs have been reported in a wide range of substance use disorders (Lundqvist, 2005; Montgomery *et al*, 2005; Noel *et al*, 2001; Verdejo-Garcia and Perez-Garcia, 2007; Verdejo-Garcia *et al*, 2005). This may indicate that in these substance use disorders, EF impairment is the result of neurotoxicity of the drugs of abuse. In the present study, the group with the 'behavioral addiction' of PG did not suffer from neurotoxic damage due to substance abuse, whereas the smokers were intentionally selected because of the negligible neurotoxicity of tobacco compared to most other substance use disorders drugs of abuse (including alcohol; Mudo *et al*, 2007). Moreover, nicotine apparently does not interfere with BOLD signal response (Jacobsen *et al*, 2002). However, several other studies have reported EF impairments in PG (Goudriaan *et al*, 2006; Kertzman *et al*, 2006; Ruge and Melamed, 1993). For example, Goudriaan *et al* employed a ToL task and reported performance impairments in their group of pathological gamblers. Three explanations can be put forward to account for this discrepancy. First, although all problem gamblers in our study were treated for PG in an outpatient clinic, not all of them met the criteria for a formal DSM-IV PG diagnosis, whereas all gamblers in the Goudriaan *et al* study did. This is also reflected in higher SOGS scores in the Goudriaan *et al* study. Exclusion of problem gamblers that did not fulfill a 12-month PG diagnosis, however, did not change our results. Second, in the present study, a computerized ToL was used, requiring the identification of the number of correct moves, which may be less affected by impulsivity. PG is associated with behavioral impulsivity and may predispose for impulsive responding in the original ToL during the first moves (Goudriaan *et al*, 2006). Third, smoking status was not an exclusion criterion for the PG group in the Goudriaan *et al* study. Smoking is also related with impulsivity (Mitchell, 1999; Reynolds *et al*, 2007). The combination of smoking and problem gambling may have led to decreased performance on the ToL on the Goudriaan *et al* study. Therefore, in future studies it would be highly informative to also include a group of smoking problem gamblers.

Strengths and Limitations

The main strengths of the study are the relatively large sample sizes of the group, the inclusion of a control and a comparison (smokers) group, and the inclusion of a ventral and a dorsal prefrontal task in one study.

However, also some limitations of the present study should be noted. The current sample consisted of problem gamblers who were in treatment at the time of data collection, whereas the smokers were not actively seeking treatment. This may partially explain the more severe impairments in reversal learning in problem gamblers compared to smokers. Moreover, it can be argued that the higher prevalence of comorbid anxiety and/or depression in problem gamblers may have biased our results. However, omitting problem gamblers with comorbidity from the analyses did not change the pattern of results with regard to impaired reversal learning. In addition, group differences remained significant after controlling for ADHD and depression scores in the analyses.

We did not assess lifetime smoking behavior of our participants. Therefore, smoking history of the currently nonsmoking healthy controls and problem gamblers may have influenced the results. The 10 h abstinence that was required for the smokers may potentially have negatively influenced performance of this group due to withdrawal effects. The intact planning performance of the smokers argues against this explanation, however.

Inherent to the task design, in participants that performed poorly on the reversal learning task not enough reversal trials were available for reliable assessment of reversal-related BOLD activity. Therefore, whereas the reversal learning task used in the present study may be a powerful tool to detect decision-making deficits in chemical and nonchemical addictions, inability to perform the task adequately may also hamper identification of the neural substrate underlying this deficiency.

CONCLUSIONS

In the present study problem gamblers were characterized by response perseveration and hyporesponsiveness of right VLPFC to both monetary loss and gain. This aberrant functioning could not be explained by impaired EFs and concomitant abnormal activation patterns in the dorsal frontostriatal circuit. Although prospective study designs are necessary to further explore this issue, it may be speculated that ventral prefrontal hyporesponsiveness to rewarding stimuli, as exemplified by problem gamblers in this study, may be a neurocognitive marker for the development of addictive behaviors. Ventral prefrontal hyporesponsiveness to punishment, as exemplified by both problem gamblers and smokers, may be crucial in the continuation of addictive behaviors despite serious adverse consequences.

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DISCLOSURE/CONFLICTS OF INTEREST

None of the authors report potential conflicts of interest.

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