

Distorted Expectancy Coding in Problem Gambling: Is the Addictive in the Anticipation?

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Background: Pathologic gamblers are known to have abnormal neural responses associated with experiencing monetary wins and losses. However, neural responsiveness during reward and loss expectations in pathologic gamblers has not yet been investigated.

Methods: We used a functional magnetic resonance imaging paradigm that allowed us to investigate the dissociable reward- and loss-related expectancies with various probabilities of winning or losing different amounts of money in 15 patients with problem gambling (PRGs) and 16 healthy control subjects (HCs).

Results: Compared with HCs, PRGs showed stronger activation in the bilateral ventral striatum to 5 euro than to 1 euro trials. PRGs also showed more activation of the bilateral ventral striatum and left orbitofrontal cortex associated with gain-related expected value than HCs. In addition, regression analyses indicated a highly significant negative correlation between gambling severity scores and right amygdala activation associated with gain-related expected value coding. There were no group differences in brain activation for loss-related expected value.

Conclusions: PRGs show higher activity in the reward system during reward expectation than HCs, whereas we observed no difference between PRGs and HC in the loss value system. Furthermore, the negative relation between gambling severity and amygdala activation in gain expected value coding suggests that more severe PRGs are less likely to be risk averse during gambling. Our study provides evidence that PRGs are characterized by abnormally increased reward expectancy coding, which may render them overoptimistic with regard to gambling outcomes.

Key Words: Expectancy, fMRI, loss, neuroimaging, pathological gambling, reward

Most pathologic gamblers (PGs) have erroneous beliefs about gambling (1). For example, they overestimate the probability of winning on a slot machine or in a poker game or have the idea that they can influence their chances, although these are fixed (2–7). These cognitive distortions are thought to underlie continued gambling by PGs despite incurring high losses.

To make advantageous decisions, people must estimate expected reward values related to certain behaviors and continually update these reward expectations according to the encountered consequences. The expected value of certain behaviors can be divided in gain- (EV+) and loss (EV-) related expectancy values, EV+ being reward magnitude times the probability of obtaining the reward, and EV- being loss magnitude times the probability of obtaining the loss. Using this gain and loss expectancy value model, EV+ and EV- have been found to be processed in different brain areas. In humans, activity of the ventral striatum (8–12), a region known to receive afferent input from midbrain dopaminergic neurons (12), has been shown to respond to conditioned stimuli predicting reward delivery (13,14) according to the EV+ model (9). In addition, the orbitofrontal cortex has been implicated in EV+ coding (9) and is known to represent subjective hedonic experience for

rewarding outcomes (for a review, see Peters and Büchel) (15). The amygdala, on the other hand, has a role in processing predictions of loss and/or aversive events (9,16–18) and was indeed shown to respond to EV- in a guessing task with varying loss magnitudes and probabilities (9).

Studying these dissociable value systems for gain and loss predictions could provide better insight into the systems that drive maladaptive choice behavior in PGs (19,20). For example, Frank *et al.* (21) found that Parkinson patients, who are characterized by a midbrain dopaminergic deficit, are better at learning to avoid choices that lead to negative outcomes than learning from positive outcomes. Interestingly, dopamine medication reversed this bias, rendering Parkinson patients more sensitive to positive than to negative predictions. Pathologic gamblers who experience higher excitement levels during gambling showed higher dopamine release, whereas this relationship was absent in healthy control subjects (HCs) (22), and PGs had higher dopamine release when losing money in a gambling game compared with HCs (23), thereby resembling medicated Parkinson patients (24). These higher dopamine levels during gambling could reflect increased sensitivity to gain-related (EV+) predictions in pathologic gambling. However, no neuroimaging data are currently available on how this expectancy of potential rewards manifests itself at a neurophysiologic level in PGs. However, it has been suggested that PGs are less loss averse than HCs (25,26). A neurocognitive study showed that PGs showed less heart rate changes compared to HCs during a card game when losing money (26). Furthermore, a functional magnetic resonance imaging (fMRI) study showed impaired performance on a reversal learning task coupled with an attenuated ventral medial prefrontal cortex response in problem gamblers (PRGs) compared with HCs when losing money (25). Thus, PGs could also be suffering from an insensitivity to losses, rendering them less loss averse than HCs.

In view of the cognitive distortions discussed here and findings of aberrant choice behavior in PRGs (25–27), we hypothesized that expectancy of potential gains (EV+) would result in a higher neural

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response in the ventral striatum, ventral medial prefrontal cortex, and orbitofrontal cortex in PRGs than in HCs. On the basis of studies indicating that PRGs could be less loss aversive and/or less sensitive for monetary losses (25, 26), we hypothesized that neural responses associated with loss expectancy would be decreased in PRGs compared with HCs. To test these hypotheses, we used an fMRI paradigm that allowed us to investigate gain and loss expected value coding during various probabilities of winning different amounts of money in PRGs compared with HCs.

Methods and Materials

Participants

Fifteen PRGs and 16 HCs participated in this study. The PRGs were recruited from Dutch addiction treatment centers, and the HCs were recruited through advertisements in local newspapers. Because most treatment-seeking PRGs are men, only male participants were included. The ethical review board of the Academic Medical Centre approved the study, and all participants provided written informed consent.

The PRGs were interviewed with section T of the Diagnostic Interview Schedule (28) to assess the diagnostic criteria for DSM-IV-TR Pathological Gambling. In addition, the South Oaks Gambling Screen (SOGS) (29) was administered as a general indication of gambling problems and to facilitate comparisons with other studies in PRGs and pathologic gamblers.

Exclusion criteria for all groups were as follows: lifetime diagnosis of schizophrenia or psychotic episodes; 12-month diagnosis of manic disorder (Composite International Diagnostic Interview [CIDI], section F), substance dependence or abuse (CIDI, section L), alcohol dependence or abuse (CIDI, section J), obsessive-compulsive disorder (CIDI, section E) or posttraumatic stress disorder (CIDI, section K); 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; history or current treatment for neurologic disorders; major physical disorders; brain trauma; exposure to neurotoxic factors.

For more details of the questionnaires used, see Supplement 1.

Paradigm

We used a modified version of a guessing task originally developed by Yacubian *et al.* (9). Each trial consisted of two phases: 1) the expectation (reward or loss) and anticipation phase and 2) the outcome phase. Specifically, each trial began with a 2-sec presentation of a circle with the backside of 10 playing cards and €1 or €5 depicted in the middle (see Supplement 1). Either 30% or 70% of the playing cards were highlighted, indicating the probability of winning the amount depicted in the middle of the circle. Participants were informed that one of the cards would always be a red ace, that all the other cards were black cards, and that a win would occur when a red ace appeared within the highlighted area and a loss when the red ace appeared outside the highlighted area. Subjects indicated whether they expected to win or lose by a left or right button press. Expectations were assessed to investigate whether differences in expectation of winning or losing were present between PRGs and HCs and to make sure that participants were paying attention to the task. After indicating their expectation, the display was kept constant during an additional 4-sec anticipation period. After this period, all cards were flipped, and feedback regarding the win or loss was displayed in the middle of the circle. In addition, the accumulated amount of money earned was displayed

in the top right-hand corner of the screen. Two seconds later, the 3- to 10-sec intertrial interval started.

Trial order was pseudo-randomized and predetermined (i.e., the volunteer had no influence on the probability and the magnitude of each individual trial and outcome). Altogether, subjects played 192 trials (96 low-probability and 96 high-probability trials). In 30% of the low-probability trials and in 70% of the high-probability trials, the participants won the displayed amount of money.

In summary, the task consisted of a $2 \times 2 \times 2$ factorial design with factors probability (70% or 30%), magnitude (1 or 5 euro) and outcome (gain or loss), resulting in eight anticipation conditions and eight outcome conditions.

Before entering the scanner, subjects received a standardized verbal description of the task and completed a practice session. It was clearly explained to the subjects that they could not influence the outcome of the trials by their performance and that wins and losses would be random, but that the highlighted area indicated their chance of winning. The participants started with 0 euros in the bank. In addition, participants were told that they would receive the amount of money in the bank at the end of the task as part of their participant reimbursement.

Imaging Acquisition and Preprocessing

Imaging data were obtained using a 3-Tesla Intera full-body MRI scanner (Philips Medical Systems, Best, The Netherlands) with a phased array SENSE RF eight-channel receiver head coil. Thirty-five axial slices (voxel size $2.29 \times 2.29 \times 3$ mm, matrix size 96×96 mm, repetition time/echo time = 2.3 sec/30 msec) of T2*-weighted echo planar images, sensitive to blood oxygenation level-dependent (BOLD) contrast were obtained, covering the entire brain except for the inferior regions of the cerebellum. A T1-weighted structural scan was made for coregistration with the fMRI data (voxel size $1 \times 1 \times 1$ mm; 170 slices). Imaging analysis was performed using SPM5 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, United Kingdom). Images were manually reoriented and slice-timed, realigned and unwrapped. Next, images were warped to Montreal Neurological Institute space using each subject's coregistered T1 image and spatially smoothed using an 8-mm full width at half maximum Gaussian kernel.

Statistical Analysis

Demographic and clinical data were analyzed using univariate analysis of variance (ANOVA) and Tukey's post hoc tests in SPSS 16.0 (SPSS, Chicago, Illinois). Non-normally distributed data (i.e., age, Beck Depression Inventory scores, SOGS scores) were analyzed using Mann-Whitney *U* Tests. Repeated-measures ANOVAs were used to analyze anticipation reaction times (RTs) and percentage of indications of expecting to win, with group as a between-subject factor (PRGs and HCs) and magnitude (5 or 1 euros) and probability (70% or 30%) as within-subject factors. All analyses were performed using two-tailed significance testing at $\alpha = .05$.

The fMRI data were analyzed in the context of the general linear model, in which both anticipation and outcome events were modeled according to a 2 (magnitude) \times 2 (probability) design. Anticipation related responses were modeled as a small box-car with a duration of 6 sec (beginning of a trial and 6000 msec after trial onset), and outcome-related responses were modeled using delta functions, convolved with a canonical hemodynamic response function. Thus, our analysis was tailored to investigate expectancy coding and the power to detect differences in the outcome phase was limited because of collinearity issues between the anticipation and outcome regressors.

Table 1. Expected Value for the Different Conditions

	Condition			
	1	2	3	4
Probability	.3	.7	.3	.7
Magnitude	1	1	5	5
Outcome	1	1	5	5
Total EV	−.4	.4	−2	2
EV+	.3	.7	1.5	3.5
EV−	−.7	−.3	−3.5	−1.5

Mean corrected versions of these vectors were used as linear contrasts in subsequent Statistical Parametric Mapping analyses.

EV+, gain-related expectancy value; EV−, loss-related expectancy value.

To test whether processing expected value associated with gains (EV+) and losses (EV−) is dependent on dissociable systems, we investigated BOLD responses for each of our 8 anticipation conditions modulated by EV+ or EV− (see Table 1), analogous to previous studies (8,29). Thus, based on expectancy value theories, a positive EV (EV+) for a given trial consistent of the probability of winning times the magnitude of winning. For example, in a 30% probability trial of gaining 5 euros, the EV+ is $.3 * 5 = 1.5$. The EV−, for the same trial is consequently 70% probability of losing 5 euros $.7 * -5 = -3.5$. See Table 1 for each trial and corresponding EV+, and EV−.

Next, contrast images containing parameter estimates were computed for each subject and entered into second-level between-group comparisons. Group interactions on reward magnitude and reward probability were tested using two separate two-way ANOVAs, group \times reward magnitude and group \times reward probability. In addition, to explore EV+ and EV− effects as a function of gambling severity, regression analyses were performed using the SOGS score as a predictor variable in the PRG group.

For all analyses, the threshold was set at the voxel level to family wise error, corrected $p < .05$. For reasons of brevity, we focus in this report on subcortical and frontal areas. Similar to the method used by Yacubian *et al.* (9) and based on previous studies, correction for hypothesized regions was based on volumes of interest. Specifically, correction for the ventral striatum was based on an 18-mm-diameter sphere centering on $x, y, z = 15, 9, -9$ mm (9,30). For magnitude-dependent activation during the anticipation phase, as expected in the orbitofrontal cortex (OFC) (10,15), we used a 60-mm-diameter sphere centering on $x, y, z = 21, 42, -9$ mm. Involvement of the amygdala during anticipation of aversive events (i.e., losses) has been reported previously (9,18) and correction for multiple comparison was based on the amygdala regions of interest

provided by the WFU PickAtlas Tool v2.4 (31), which incorporates the automatic anatomical labeling atlas (32). Finally, correction for the hypothesized ventromedial prefrontal cortex activation (33) was based on an anatomically defined 36-mm-diameter sphere centered between the genu of the corpus callosum and the anterior pole (center: $x, y, z = 0, 52, -3$).

Results

Demographic and Clinical Results

Table 2 summarizes demographic and clinical characteristics for PRGs and HCs. No significant differences between the groups were present regarding age, Wechsler Adult Intelligence Scale scores, Alcohol Use Disorder Identification Test (AUDIT), smoking behavior, and Beck Depression Inventory scores. As expected, PRGs had higher SOGS scores than HCs, and all PRGs fulfilled the criteria of “probable pathologic gambler” defined by a SOGS score of 5 or higher (29). Furthermore, all PRGs met at least three DSM-IV criteria, and, except for one PRG, all PRGs met criteria of a current DSM-IV-TR pathologic gambling diagnosis. Mean age of onset of gambling problems was 26.1 years (range: 16–52 years), and mean duration of gambling problems was 10.5 years (range: 1–37 years).

Behavioral Performance

For the expectations to win, there was no main effect of group [$F(1,29) = 2.27, p = .14$]. However, as expected, the main effect of probability [$F(1,29) = 184.60, p = .00$] was significant, showing higher expectation of winning in 70% than in 30% trials. Surprisingly, there was also a main effect of magnitude [$F(1,29) = 6.08, p = .020$], with 5 euro trials more often considered to lead to a win than 1 euro trials. In addition, there was a significant interaction effect between magnitude and probability [$F(1,29) = 53.91, p = .00$], indicating that expectations were higher for trials having 70% chance of winning 5 euros than for trials with 30% change of winning 1 euro.

There were no RT differences between the groups [$F(1,29) = 1.78, p = .193$]. There was a main effect of probability on RT, showing longer RTs during 30% compared with 70% win trials [$F(1,29) = 13.27, p = .001$]. A main effect of magnitude was also present, showing longer RTs during 1 euro trials compared with 5 euro trials [$F(1,29) = 4.39, p = .045$]. In addition, there was a significant interaction effect between RTs on magnitude and winning probability [$F(1,29) = 9.41, p = .011$]. Trials with higher probability and lower magnitude showed shorter RTs, whereas trials with lower probability and higher magnitude showed longer RTs. For details, see Table 3.

Table 2. Demographic and Clinical Characteristics for Problem Gamblers and Healthy Control Subjects

	Problem Gamblers ($n = 15$)	Healthy Control ($n = 16$)	t Test and Mann–Whitney U Significance (p Value, Two-Tailed)
Age, Mean (SD)	38.00 (13.42)	34.92 (11.98)	$U(28) = 73, Z = -1.13, p = .272$
WAIS Score, Mean (SD)	14.00 (2.95)	15.00 (4.00)	$t(26) = .58, p = .454$
BDI, Mean (SD)	8.87 (7.03)	6.00 (4.04)	$U(28) = 67.5, Z = 1.39, p = .17$
AUDIT	5.93 (6.03)	6.23 (5.03)	$t(26) = .11, p = .744$
No. of Smokers	10	7	$\chi^2 = 1.64, df = 1, p = .200$
SOGS 12 Months, Mean (SD) ^a	10.00 (4.03)	.08 (.28)	$U(28) = 7, Z = -4.40, p = .00$
First-Degree Family History of Addiction, No. of People	7	6	—

AUDIT, Alcohol Use Disorder Identification Test; BDI, Beck Depression Inventory; SOGS, South Oaks Gambling Screen; WAIS score, Wechsler Adult Intelligence Scale, total score of the subtests Digit Span and Letter-Number sequencing.

^aSignificant differences between groups, $p < .05$.

Table 3. Behavioral Data on Expectations of Winning or Losing and Reaction Times in Each Condition

	Condition	Problem Gamblers (n = 15)	Healthy Controls (n = 16)
Indication to Win, Percentages (SD)	70% 5 euro	92.53 (8.33)	89.10 (20.02)
	70% 1 euro	88.38 (21.49)	86.03 (19.27)
	30% 5 euro	29.81 (33.24)	20.15 (27.62)
	30% 1 euro	16.00 (21.14)	13.42 (15.90)
Reaction Times, Seconds (SD)	70% 5 euro	1.55 (4.72)	2.65 (3.15)
	70% 1 euro	1.54 (4.25)	2.69 (3.31)
	30% 5 euro	1.44 (4.42)	2.58 (3.17)
	30% 1 euro	1.65 (4.58)	2.76 (3.29)

Imaging Results

Reward Magnitude and Probability-Related Activation.

Compared to HCs, PRGs showed a stronger BOLD signal for trials with 5 euros versus 1 euro in bilateral dorsal striatum (peak: x, y, z : 18, 21, -6 mm, $Z = 3.43$, and peak: x, y, z : $-12, 12, 9$ mm, $Z = 3.29$; both $p < .05$, corrected, see Figure 1). There were no group differences for 70% as opposed to 30% trials.

Results of the analyses in which participants' subjective expectations (instead of the objective gain-related and loss-related expected values) were used as regressors are also included in Supplement 1. As expected, given the high overlap between subjective and objective expectations (Table 3), these results were similar to those obtained when using objective expectations.

Gain-Related Expected Value (EV+). Figure 2A shows that BOLD responses associated with the linear model of EV+ (Table 1) were stronger in PRGs compared with HCs in bilateral dorsal striatum (peak: x, y, z : 18, 24, 0 mm, $Z = 4.39$, and peak: x, y, z : $-9, 12, 9$ mm, $Z = 3.80$; both $ps < .05$, corrected) and in the left OFC (peak: x, y, z : $-30, 21, -18$ mm, $Z = 3.35$; $p < .05$, corrected).

Loss-Related Expected Value (EV-). There were no group differences in amygdala activity and loss-related expected value. Both groups activated the left amygdala (peak: x, y, z : $-21, 0, 21$ mm, $Z = 3.10$; $p < .05$, corrected) corresponding to the linear model of EV- (Table 1 and Figure 3).

Regression Between Gambling Severity and EV+ and EV-.

Within the group of PRGs, gambling problem severity (SOGS score) showed highly significant negative correlations with activation of right amygdala during EV+ (peak at x, y, z : 30, 0, -15 ; $r = -.76, Z =$

3.28; both $ps < .05$, corrected; see Figure 4). No regions displayed a positive correlation between SOGS score and EV+ in PRGs. In addition, no significant association was found between gambling severity and EV-.

Discussion

This study investigated the neurobiology of gain and loss expectancy processing using an fMRI task testing various combinations of reward magnitude and probability in PRGs and HCs. Importantly, we showed that gain expectancy coding is enhanced in PRGs compared with HCs as indicated by an increased BOLD response in bilateral dorsal striatum and left orbitofrontal cortex, whereas loss expectancy coding was similar in both groups.

Reward Expectancy

During the anticipation phase of the task, the relationship between reward magnitude and striatal activation was stronger in PRGs compared with HCs, suggesting heightened anticipatory reward sensitivity in PRGs, congruent with previous studies indicating the striatum as involved in reward and motivation processing (30,34). In addition, PRGs showed increased activation during gain-related expectations in the dorsal striatum and orbitofrontal cortex compared with HCs. Interestingly, the dorsal striatum has been linked to action–outcome associations (35,36), whereas the ventral striatum seems to be more directly involved in the processing of reward per se. The increased dorsal striatum activation found in PRGs in the EV+ contrast appeared to be due to their enhanced sensitivity for reward magnitude as opposed to HCs, whereas increased OFC activity in PRGs was driven by both reward magnitude and reward probability. Moreover, enhanced dorsal striatum responsiveness could indicate that PRGs are overly optimistic with regard to gambling outcomes, that is, PRGs may have a stronger action–outcome association with gambles. Our post hoc analyses modeling the subjective expectations of the participants (Supplement 1) indicated a similar result; PRGs compared with HCs showed an enhanced responsiveness in the dorsal striatum and ventromedial prefrontal cortex toward potential greater wins. These findings of enhanced reactivity to reward expectancy in areas (striatum, ventromedial prefrontal cortex, orbitofrontal cortex) mainly innervated by dopamine midbrain projections (12) suggest that dopaminergic dysfunction may contribute to pathologic gambling. This conclusion is consistent with findings of aberrant dopaminergic function in pathologic gamblers indicated by previous studies of peripheral markers (37,38) and the phenomenon of dopamine-agonist-induced pathologic gambling in Parkinson disease (24,39). Indeed, a dopamine challenge in problem gamblers showed increased motivation to gamble and facilitated the reading of gambling-relevant words in problem gamblers receiving amphetamine (40).

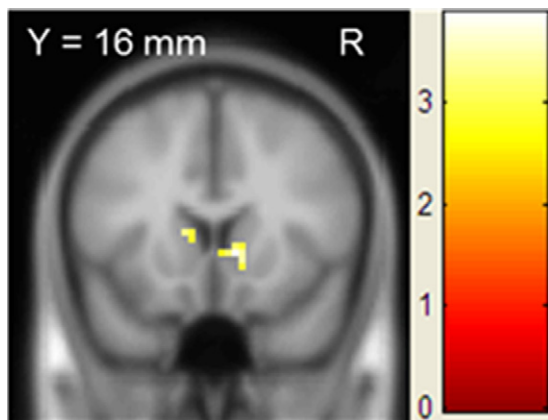


Figure 1. Activation during the anticipation of monetary reward overlaid on a template T1-weighted magnetic resonance image at $p < .001$ (uncorrected). Compared to healthy controls, problem gamblers showed stronger blood oxygenation level–dependent signal changes when expecting a win of 5 euros as opposed to a win of 1 euro in bilateral ventral striatum. R, right side of the brain.

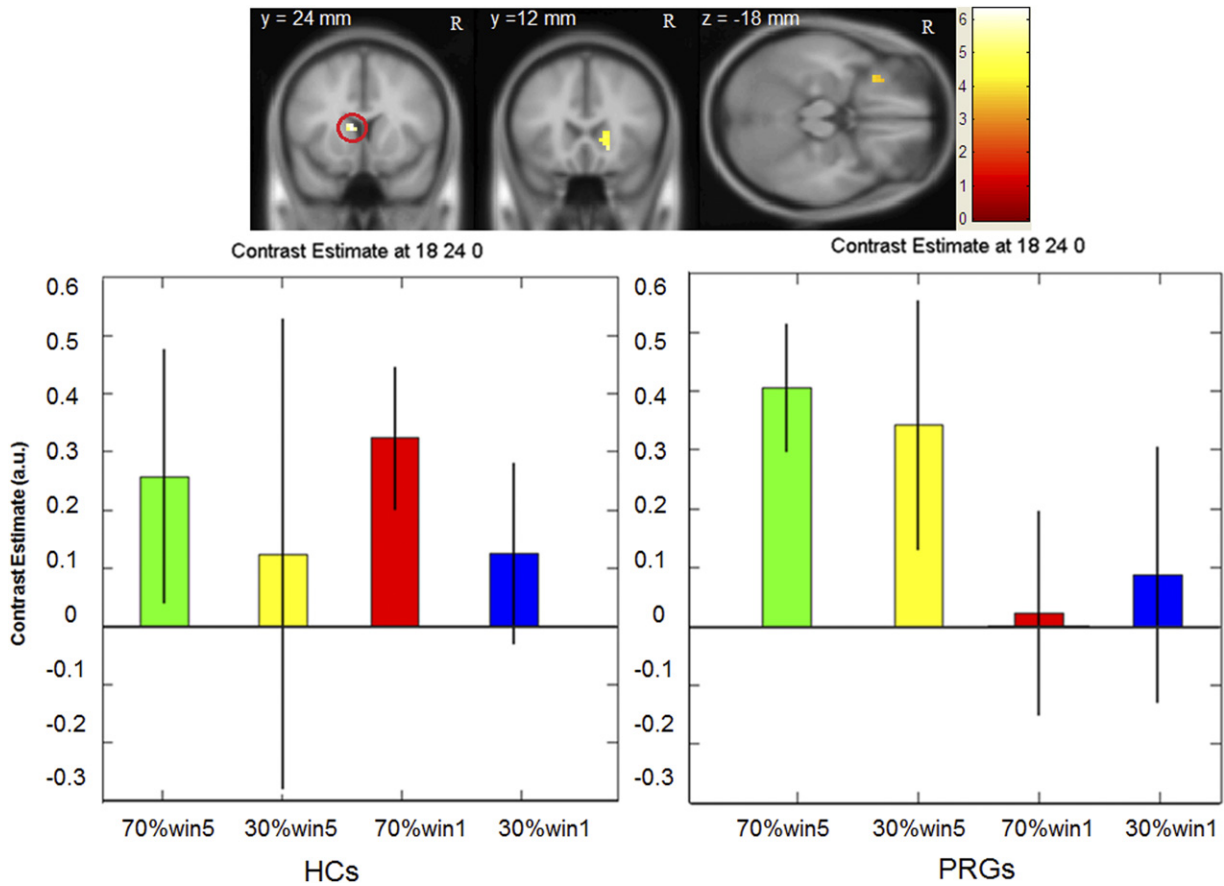


Figure 2. (A) Activation expressing gain-related expected value overlaid on a template T1-weighted magnetic resonance image at $p < .001$ (uncorrected). Blood oxygenation level dependent responses associated with the linear model of the gain-related expectancy values (Table 1) were stronger in problem gamblers (PRGs) compared with healthy control subjects (HCs) in bilateral ventral striatum and in left orbitofrontal cortex. R, right side of the brain; L, left side of the brain. **(B)** Contrast estimates in the right ventral striatum (peak coordinates x, y, z; 18, 24, 0) corresponding to each gain-related expectancy values condition in HCs and PRGs. a.u., arbitrary units.

We did not find behavioral evidence for distorted probability estimation in PRG relative to HCs, because HCs and PRGs did not differ in their estimation of winning in high- and low-probability trials. Furthermore, all participants indicated a higher win expectation during 5 euro trials compared with 1 euro trials. It is unclear why subject indicated that they expected to win during 5 euro trials more often than in the 1 euro trials. It could be that the prospect of winning 5 euros is more exciting than winning 1 euro (41) and that

increased excitement leads to an overestimation of positive outcomes (42). However, our design was not designed to test for these behavioral effects, and therefore the absence of behavioral group \times reward interactions should be interpreted with caution. Moreover, our task was not particularly sensitive to measure cognitive distortion. The binary questions regarding participants' guesses (i.e., whether they were going to win or lose) and the instructions to the participants that the task provided unambiguous, explicit visual

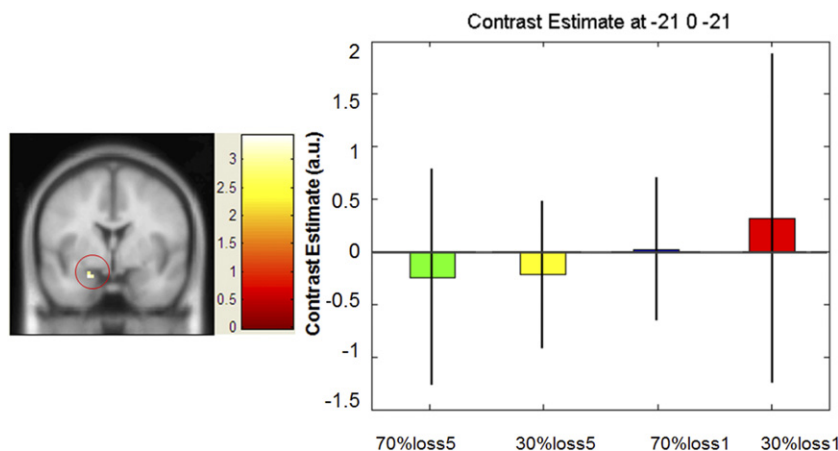


Figure 3. Activation expressing loss-related expected value overlaid on a template T1-weighted magnetic resonance image at $p < .001$ (uncorrected). Both groups activated the left amygdala corresponding to the linear model of loss-related expectancy values. Contrast estimates and standard errors of blood oxygenation level dependent response in the left amygdala for each condition corresponding to the loss-related expectancy values model are presented in the right panel of the figure. a.u., arbitrary units.

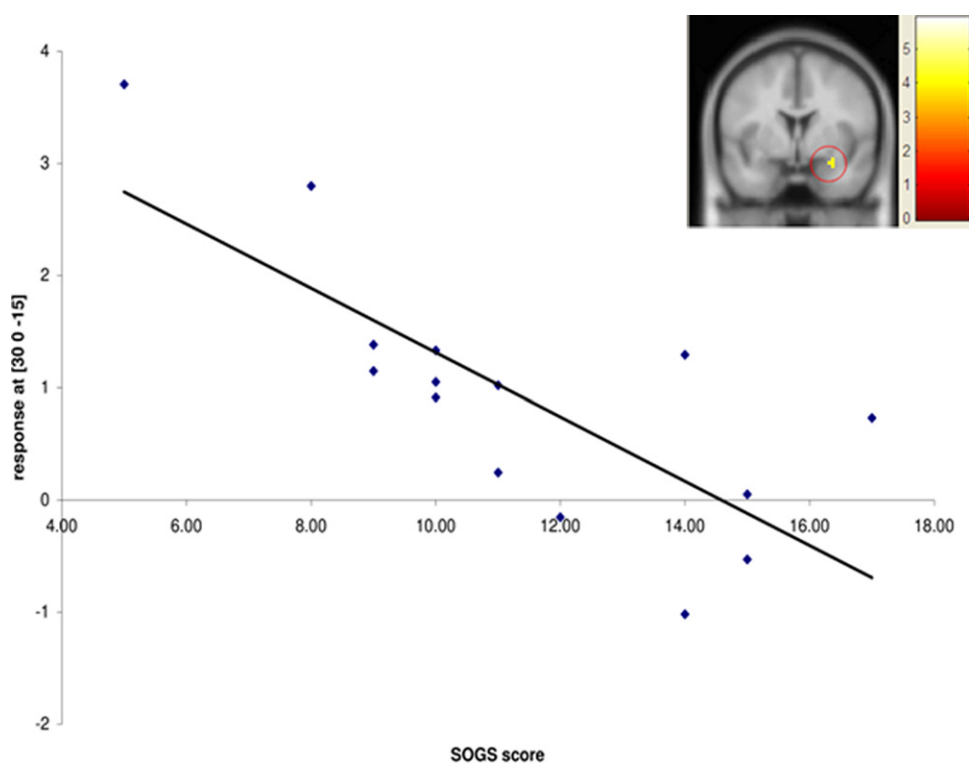


Figure 4. Activation during gain-related expected value and relation with gambling problem severity overlaid on a template T1-weighted magnetic resonance image at $p < .001$ (uncorrected). Gambling problem severity (South Oaks Gambling Screen [SOGS] score) was entered as a single regressor in the contrast of gain-related expectancy values, indicating a significant negative relation in problem gamblers between SOGS scores and brain activation during gain-related expectancy values in the right amygdala ($r = -.76$).

cues on two probabilities (instead of a whole range of possibilities) in each trial likely contributed to the absence of group differences.

Our findings of a negative relationship between gambling severity and amygdala activation in EV+ coding is interesting because diminished amygdala activity or lesions to the amygdala are associated with reduced harm avoidance (43–45). Also, recent theories regarding amygdala function have posited that the amygdala subserves the detection of uncertainty (17,46) or ambiguity (47) in the environment, triggering increased vigilance and arousal. Therefore, our findings of diminished amygdala activation may indicate that more severe PRGs are less likely to be risk averse, adding to their increased sensitivity for potential gains. However, these are exploratory and preliminary findings, and further research is needed. We found no correlation between SOGS scores and activation of striatum and OFC during expectancy, which is inconsistent with previous studies showing a relationship during reward outcome (48,49). It should be noted, however, that our PRG group was presumably more homogenous in their SOGS scores than the groups in previous studies and that our study is the first to examine striatum and OFC activity during reward expectancy instead of during reward outcome.

Loss Expectancy

Although we found that left amygdala activity showed a positive relationship with loss expectancy values, congruent with previous findings (9), we did not find evidence of aberrant loss expectancy coding in PRGs compared with HCs. Thus, from these findings we conclude that PRGs are hypersensitive to potential gains rather than insensitive to potential losses. Whereas a balanced, probably homeostatic, system of gain and loss processing is likely important for generating adequate expectations under uncertainty, predominance of either subsystem may result in unrealistic expectations, as in pathologic gambling. Alternatively, mood disorders such as major depression are likely to be characterized by increased sensitivity to loss expectation. Amygdala activity during processing loss antic-

ipation is possibly modulated primarily by serotonergic neurotransmission (50,51), and selective serotonin reuptake inhibitors (SSRIs) may be effective in disorders with dysfunctional amygdala activity (52,53), whereas reward processing in the ventral striatum is mainly under dopaminergic control (54,55).

Limitations, Strengths, and Future Directions

Because our analysis focused on expectations of wins and losses, the power to detect differences in the outcome phase was limited due to collinearity issues between the anticipation and outcome regressors. We therefore only reported on expectancy and anticipation of reward and loss, and not on reward and loss outcome. Furthermore, because of the absence of a neutral baseline in our design, the main effects of this task could not be assessed. Finally, it may be argued that more ecologically valid tasks are more likely to detect behavioral group differences because they could use a faster succession of trials, more variable win and loss changes, and more variable wins and losses in the outcome phase, resembling real gambling games.

Although the sample sizes of our groups were modest, our sample of 15 PRGs and 16 HCs is similar to other fMRI studies investigating problem gambling with samples ranging from 10 to 20 subjects per group (25,48,56,57). Furthermore, our cohort of PRGs was selected using stringent exclusion criteria, resulting in a rather homogeneous cohort with no psychiatric disorders other than pathologic gambling. Therefore, it is unlikely that our results can be explained by the simultaneous presence of other disorders (such as depression) common in addictions. However, our PRG group was heterogeneous in terms of gambling game preferences. Previous studies have indicated that subtypes of pathologic gambling may be associated with distinct (neuro)psychologic profiles (19,58). Therefore, larger-scale neurocognitive and neuroimaging studies are needed to test whether for example subtypes of problem gamblers preferring chance-based games (e.g., slot machines, roulette) or skill-

based games (e.g., poker) are associated with differential neural processing of reward and loss expectations.

Future studies investigating reward and loss expectancy as well as feedback processing in pathologic gambling may aid in further understanding whether increased reward or loss expectancy modulates the response to gain or loss outcomes (i.e., prediction errors), leading to disadvantageous choice behavior in pathologic gamblers. One would normally expect that overestimation of the probability to win would result in an augmented prediction error signal when losses occur, which then would induce learning behavior—that is, modify choice behavior. However, previous neuroimaging studies on reward processing in PRGs showed a blunted response of the ventral striatum and ventromedial prefrontal cortex after experiencing monetary gains and losses in PRGs compared with HCs (25,48). These findings therefore suggest that PRGs show a diminished prediction error signal when unexpected gains occur. Future imaging studies in PRGs comparing anticipation and outcome phases of expected and unexpected outcomes are needed to clarify these issues.

In conclusion, we found evidence of higher activity in the reward system during reward expectation in PRGs compared with HCs. In addition, we observed no difference between PRGs and HCs in the expectancy of loss. Together, these factors suggest an enhanced sensitivity to potential gains in pathologic gambling, probably dependent on dysfunctional dopamine neurotransmission.

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