Imaging studies in pathological gambling: similarities and differences with alcohol dependence
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Chapter 3

Distorted expectancy coding in problematic gambling: Is the addictive in the anticipation?

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In revision
Chapter 3

Abstract

**Background:** Most pathological gamblers overestimate their winning chances and this may (partly) explain why pathological gamblers continue to play despite high losses. However, the neurobiological basis for this dysfunction in reward expectancy is not yet known.

**Methods:** We employed an fMRI paradigm that allowed us to investigate the dissociable reward and loss related expectancies during different probabilities of winning or losing different amounts of money in 15 patients with problematic gambling (PRGs) and 16 healthy controls (HCs).

**Results:** Compared to 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.
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Introduction
Most pathological gamblers have erroneous beliefs about gambling (Raylu and Oei, 2004). They, for example, overestimate the probability to win on a slot machine, or have the idea that they can influence their chances although these are fixed (Joukhador et al., 2003; Toneatto et al., 1997). These cognitive distortions are thought to underlie continued gambling by pathological gamblers despite incurring high losses.

In order to make advantageous decisions, people must estimate expected reward values related to certain behaviours, and continually update these reward expectations according to the encountered consequences. The difference between the actual outcome of certain behaviours and the prediction of the outcome has been described as the prediction error. In reinforcement learning, this prediction error is used to update future predictions of reward. In fMRI studies of reinforcement learning, predictions and prediction errors have been used to model fMRI data (O’Doherty et al., 2003) and have shown that the mesolimbic dopaminergic system is involved in reward processing and reward-dependent learning (Schultz, 2007; Tobler et al., 2007). In a guessing task with fixed probabilities, we can express the prediction error as the actual reward or loss minus the predicted outcome (i.e. expected value). The expected value can be further 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 found to be processed in different brain areas. In humans, activation of the ventral striatum (Knutson et al., 2005; McClure et al., 2004; Pagnoni et al., 2002; Yacubian et al., 2006), a region known to receive afferent input from midbrain dopaminergic neurons (Haber et al., 1995b), has shown to respond to conditioned stimuli predicting reward delivery (McClure et al., 2003; O’Doherty et al., 2003) according to the above-described EV+ model (Yacubian et al., 2006). In addition, the orbitofrontal cortex has been implicated in EV+ coding (Yacubian et al., 2006) and is known to represent subjective hedonic experience for rewarding outcomes (for a review see; Peters and Buchel, 2010). The amygdala, on the other hand, has a role in processing predictions of loss and/or aversive events (Breiter et al., 2001; Glascher and Buchel, 2005; Kahn et al., 2002; Yacubian et al., 2006) and was indeed shown to respond to EV- in a guessing task with varying loss magnitudes and probabilities (Yacubian et al., 2006).

Studying these dissociable value systems for gain and loss predictions could provide a better insight in the systems that drive maladaptive choice behaviour in pathological gamblers (Brand et al., 2005; Goudriaan et al., 2005). For example, Frank et al (2004; Frank et al., 2004) 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. Pathological gamblers (PGs) showed higher dopamine release during gambling than healthy controls (Linnet et al., 2010), thereby resembling medicated Parkinson patients (Steeves et al., 2009). These higher dopamine levels during gambling could make PGs more sensitive to gain related (EV+) predictions. However, no neuroimaging data are currently available on how this increased expectancy of potential rewards manifests itself at a neurophysiological level.

Previous neuroimaging studies on reward processing in problem gamblers (PRGs) have investigated brain activation patterns associated with winning or losing money, showing a blunted response of the ventral striatum and ventromedial prefrontal cortex for monetary gains and losses in PRGs compared to healthy controls (HCs) (de Ruiter et al., 2009; Reuter et al., 2005). It remains unclear whether this blunted neural response to gains or losses in problem gamblers is also present during the preceding expectation of winning or losing
money. For example, cognitive distortions in pathological gamblers, such as overoptimistic thoughts about winning chances, may be associated with increased neural expectancy responses to potential wins. Such overactivation during the expectancy phase, together with a desensitised response of the brain reward circuitry to money (de Ruiter et al., 2009; Reuter et al., 2005), may lead to a less efficient coding of reward values. This may in turn result in maladaptive behaviour patterns and enhanced motivation to gamble despite real-life negative outcomes. Thus, dysfunctions in several neural sub-processes essential for reward learning may be involved in problem gamblers who display continued gambling despite serious negative consequences.

In view of the cognitive distortions discussed above (Joukhador et al., 2003; Toneatto et al., 1997) we hypothesized that expectancy of potential gains (EV+) would result in a higher neural response in the ventral striatum, ventral medial prefrontal cortex and orbitofrontal cortex in PRGs than in HCs. In addition, we hypothesized that neural responses associated with loss expectancy would not be affected in PRGs. To test these hypotheses we employed an fMRI paradigm which allowed us to investigate gain and loss expected value coding during different probabilities of winning different amounts of money in PRGs compared to HCs.

**Methods**

**Participants**

Fifteen problematic gamblers (PRGs) and 16 healthy controls (HCs) participated in this study. PRGs were recruited from Dutch addiction treatment centres where they received cognitive behavioural therapy. HCs were recruited through advertisements in local newspapers. Because most treatment-seeking problem gamblers 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.

PRGs were interviewed with section T of the Diagnostic Interview Schedule (Robins et al., 1998) to assess the diagnostic criteria for DSM-IV-TR Pathological Gambling. In addition, the South Oaks Gambling Screen (SOGS; Lesieur and Blume, 1987) was administered, as a general indication of gambling problems and to facilitate comparisons with other studies in PRGs and PGs.

Exclusion criteria for all groups were: lifetime diagnosis of schizophrenia or psychotic episodes; 12-month diagnosis of manic disorder (CIDI, section F), substance dependence or abuse (CIDI, section L), alcohol dependence or abuse (CIDI, section J), obsessive compulsive disorder (CIDI, section E) or post-traumatic 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 neurological disorders; major physical disorders; brain trauma; or exposure to neurotoxic factors.

To obtain a measure of subjects’ global capacity to effectively handle information, we assessed the total score on the subscales Digit span and Number-Letter sequencing from Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981). The Beck Depression Inventory (BDI; Beck et al., 1996) was administered to all groups to assess severity of depressive symptoms since depression may influence reward expectancy and reward experience. PRGs and HCs were excluded when they drank more than 21 standard units (10 g) of alcohol per week. A measure of alcohol problem severity was obtained by administering the Alcohol Use Disorders Identification Test (AUDIT; Bush et al., 1998), with
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a score higher than 8 indicating harmful use. Gambling game preferences and family addiction history were assessed by interview.

Paradigm
We used a modified version of a guessing task originally developed by Yacubian et al. (2006). Each trial consisted of two phases: (1) expectation (reward or loss) and anticipation phase, and (2) outcome phase. Specifically, each trial began with a 2-sec presentation of a circle with the backside of ten playing cards and €1 or €5 depicted in the middle (see Supplementary data 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 would occur when the red ace appeared outside the highlighted area. Subjects indicated whether they expected to win or to 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 3-10 sec inter-trial 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 a total of 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 2x2x2 factorial design with factors probability (70% or 30%), magnitude (one or five Euro) and outcome (gain or loss), resulting in 8 anticipation conditions and 8 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. In addition, participants were told that they would receive the amount of money won 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. A total of 35 axial slices (voxel size 2.29x2.29x3mm, matrix size 96x96 mm, TR/TE=2.3s/30ms) 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. A T1-weighed structural scan was made for co-registration with the fMRI data (voxel size 1x1x1 mm; 170 slices). Imaging analysis was performed using SPM5 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, London, UK). Images were manually reoriented and slice-timed, realigned and unwarped. Next, images were warped to MNI space using each subject’s co-registered T1 image, and spatially smoothed using an 8mm FWHM 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 Inc., Chicago, Illinois). Non-normally distributed data (i.e. age, BDI 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 euro) and probability (70 or 30%) as dependent measures. All analyses were performed using two-tailed significance testing at $\alpha=0.05$.

FMRI data were analyzed in the context of the general linear model, in which both anticipation and outcome events were modeled, resulting in 16 regressors (2x2x2 conditions times 2 phases). Anticipation related responses were modeled as a small box-car with a duration of 6 sec (beginning of a trial and 6000 ms 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. Furthermore, 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 (Knutson and Cooper, 2005; Yacubian et al., 2006).

<table>
<thead>
<tr>
<th>Condition</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability</td>
<td>0.3</td>
<td>0.7</td>
<td>0.3</td>
<td>0.7</td>
<td>0.3</td>
<td>0.7</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Magnitude</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Outcome</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>-1</td>
<td>-1</td>
<td>-5</td>
<td>-5</td>
</tr>
<tr>
<td>EV+</td>
<td>0.3</td>
<td>0.7</td>
<td>1.5</td>
<td>3.5</td>
<td>0.3</td>
<td>0.7</td>
<td>1.5</td>
<td>3.5</td>
</tr>
<tr>
<td>EV-</td>
<td>-0.7</td>
<td>-0.3</td>
<td>-3.5</td>
<td>-1.5</td>
<td>-0.7</td>
<td>-0.3</td>
<td>-3.5</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

Table 1: Expected value for all different conditions
Mean corrected versions of these vectors were used as linear contrasts in subsequent SPM analyses. EV+ = gain related expectancy value; EV-: loss related expectancy value.

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-way ANOVA. 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 to $p<0.05$ corrected for multiple comparison. For reasons of brevity, we focus in this report on sub-cortical and frontal areas. 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 centring on $x,y,z \pm 15, 9, -9$mm (ODoherty et al., 2004; Yacubian et al., 2006). Magnitude-dependent activation during the anticipation phase, as expected in the orbitofrontal cortex (OFC), (Knutson et al., 2005; Peters and Buchel, 2010), we employed a 60-mm diameter sphere centring on $x,y,z \pm 21, 42, -9$mm. Involvement of the amygdala during anticipation of aversive events (i.e. losses) has been reported previously (Glascher and Buchel, 2005; Yacubian et al., 2006), and correction for multiple comparison was based on the amygdala regions of interested provided by the WFU PickAtlas Tool v2.4 (Maldjian et al., 2003) that incorporates the automatic anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Finally, correction for the hypothesized ventromedial prefrontal cortex activation (Knutson et
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al., 2003) was based on an anatomically defined 36-mm-diameter sphere centred between the genu of the corpus callosum and the anterior pole (centre: 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, WAIS scores, AUDIT, smoking behavior and BDI scores. As expected, PRGs had higher SOGS scores than HCs and all PRGs fulfilled the criteria of ‘probable pathological gambler’ defined by a SOGS score of five or more (Lesieur and Blume, 1987). Furthermore, except for one PRG, all PRGs met criteria of a current DSM-IV-TR pathological gambling diagnosis (PG). 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: 0-37 years). All PRGs indicated that they played multiple games, but their game of preference varied (casino games 13.3%, internet gambling 26.7%, slot machines 40%, and lottery 20%).

<table>
<thead>
<tr>
<th></th>
<th>Problematic gamblers (n=15)</th>
<th>Healthy controls (n=16)</th>
<th>T-test and Kruskal-Wallis, significance (p value, 2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>38.00 (13.42)</td>
<td>34.92 (11.98)</td>
<td>U(28)=73, Z=-1.13, p=0.272</td>
</tr>
<tr>
<td>WAIS score, mean (SD)</td>
<td>14 (2.95)</td>
<td>15.00 (4.00)</td>
<td>T(26)= 0.58, p=0.454</td>
</tr>
<tr>
<td>Beck Depression Inventory, mean (SD)</td>
<td>8.87 (7.03)</td>
<td>6.00 (4.04)</td>
<td>U(28)=67.5, Z=1.39, p=0.17</td>
</tr>
<tr>
<td>AUDIT</td>
<td>5.93 (6.03)</td>
<td>6.23 (5.03)</td>
<td>T(26)= 0.11, p=0.744</td>
</tr>
<tr>
<td>Number of Smokers</td>
<td>10</td>
<td>7</td>
<td>X²=1.64, df=1 p=0.200</td>
</tr>
<tr>
<td>South Oaks Gambling Screen 12 months, mean (SD)*</td>
<td>10.00 (4.03)</td>
<td>0.08 (0.28)</td>
<td>U(28)=7, Z=4.40, p=0.00</td>
</tr>
<tr>
<td>First degree family history of addiction, number of people</td>
<td>7</td>
<td>6</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2: Demographic and clinical characteristics for PRGs and HCs
* = indicated significant differences between groups with p < 0.05. WAIS score: total score of the subtests Digit Span and Letter-Number sequencing.

Behavioral performance
For the expectations to win there was no main effect of group (F(1,29)=2.27, p=0.143). However, as expected, the main effect of probability (F(1,29)=184.60, p=0.00) 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=0.020) 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=0.00), indicating that expectations were higher for trials having 70% change of winning 5 euro than for trials with 30% change of winning 1 euro.

There were no RT differences between the groups (F(1,29)=1.78, p=0.193). There was a main effect of probability on RT, showing longer RTs during 30% compared to 70% win trials.
(F(1,29)=13.27, \(p=0.001\)). A main effect of magnitude was also present, showing longer RTs during 1 euro trials compared to 5 euro trials (F(1,29)=4.39, \(p=0.045\)). For details see Table 3.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Problematic gamblers (n=15)</th>
<th>Healthy controls (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication to win, percentages (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% 5 euro</td>
<td>92.53 (8.33)</td>
<td>89.10 (20.02)</td>
</tr>
<tr>
<td>70% 1 euro</td>
<td>88.38 (21.49)</td>
<td>86.03 (19.27)</td>
</tr>
<tr>
<td>30% 5 euro</td>
<td>29.81 (33.24)</td>
<td>20.15 (27.62)</td>
</tr>
<tr>
<td>30% 1 euro</td>
<td>16.00 (21.14)</td>
<td>13.42 (15.90)</td>
</tr>
<tr>
<td><strong>Reaction times, seconds (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% 5 euro</td>
<td>1.55 (4.72)</td>
<td>2.65 (3.15)</td>
</tr>
<tr>
<td>70% 1 euro</td>
<td>1.54 (4.25)</td>
<td>2.69 (3.31)</td>
</tr>
<tr>
<td>30% 5 euro</td>
<td>1.44 (4.42)</td>
<td>2.58 (3.17)</td>
</tr>
<tr>
<td>30% 1 euro</td>
<td>1.65 (4.58)</td>
<td>2.76 (3.29)</td>
</tr>
</tbody>
</table>

Table 3: Behavioural data on expectations of winning and reaction times on each condition

**Imaging results**

**Reward magnitude and probability related activation**

Compared to HCs, PRGs showed a stronger BOLD signal for trials with five versus one euro in bilateral ventral 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 \(p<0.05\), corrected) (see figure 1a). There were no group differences for 70% as opposed to 30% trials. For group main effects please see supplementary data Table 1.

![Figure 1: Activation during the anticipation of monetary reward overlaid on a template T1-weighted MR image at \(p < 0.001\) (uncorrected).](image)

**Gain related expected value (EV+)**

Figure 2 shows that BOLD responses associated with the linear model of EV+ (Table 1) were stronger in PRGs compared to HCs in bilateral ventral 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 \(p<0.05\), corrected) and in the left OFC (peak: x,y,z: -30, 21, -18 mm, Z=3.35; \(p<0.05\), corrected). For group main effects please see supplementary data Table 2.
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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<0.05, corrected) corresponding to the linear model of EV- (Table 1 and Figure 3).

Regression between gambling severity and gain and loss related expected value
Within the group of PRGs, gambling problem severity (SOGS score) showed high significant negative correlations with activation of right amygdala during EV+ (peak at x, y, z: 30, 0, -15; r=-0.76, Z=3.28; both p<0.05, 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-. 
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![Image of brain scan and regression line with r = -0.76]

**Figure 4 Activation during gain-related expected value and relation with gambling problem severity overlaid on a template T1-weighted MR image at p < 0.001 (uncorrected).** Gambling problem severity (SOGS score) was entered as a single regressor in the contrast of EV+, indicating a significant negative relation in PRGs between SOGS scores and brain activation during EV+ in the right amygdala ($r = -0.76$). R = right side of the brain.

**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 to HCs as indicated by an increased BOLD response in bilateral ventral 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 ventral striatal activation was stronger in PRGs compared to HCs, suggesting heightened reward sensitivity in PRGs, congruent with previous studies indicating the ventral striatum as being involved in reward and motivation processing (Haruno and Kawato, 2006; O’Doherty et al., 2004). In addition, PRGs showed increased activation during gain related expectations in the ventral striatum and orbitofrontal cortex compared to HCs. These findings of enhanced reactivity to reward expectancy in areas (striatum, orbitofrontal cortex) mainly innervated by dopamine midbrain projections (Haber et al., 1995a) suggest that dopaminergic dysfunction may contribute to pathological gambling. This conclusion is consistent with studies showing exaggerated dopamine release during gambling games in pathological gamblers compared to HCs (Linnet et al., 2010). In addition, aberrant dopaminergic function in pathological gamblers is indicated by previous studies of peripheral markers (Bergh et al., 1997; Meyer et al., 2004) and the phenomenon of dopamine-agonist induced pathological gambling in Parkinson’s disease (Steeves et al., 2009; Voon et al., 2009). It may seem inconsistent that we did not find behavioral evidence for distorted probability estimation in PRG, since HCs and PRGs did not differ in their estimation of winning in high and low probability trials.
However, participants were instructed that the task provided unambiguous, explicit visual cues on the probabilities in each trial, which may account for 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 (De Martino et al., 2010; Killcross et al., 1997; LeDoux, 1998). Also, recent theories regarding amygdala function argue that the amygdala subserves the detection of uncertainty (Kahn et al., 2002; Whalen, 2007) or ambiguity (Hsu et al., 2005) 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 gain. However, these are post-hoc explanations and hence further research is needed.

**Loss expectancy**

Although we found that the left amygdala showed a positive relationship with loss expectancy values, congruent with previous findings (de Ruiter et al., 2009; Reuter et al., 2005; Yacubian et al., 2006), and also with studies showing amygdala activation during anticipation of aversive events (Glascher and Buchel, 2005; Kahn et al., 2002), we did not find evidence of aberrant loss expectancy coding in PRGs compared to 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 likely is important for generating adequate expectations under uncertainty, predominance of either subsystem may result in unrealistic expectations, as in pathological gambling. Alternatively, mood disorders like major depression are likely to be characterized by increased sensitivity to loss expectation. However, amygdala activity during processing loss anticipation is possibly modulated primarily by serotonergic neurotransmission (Hariri et al., 2002; He et al., 2010), and selective serotonin reuptake inhibitors (SSRIs) may be effective in disorders with dysfunctional amygdala activity (Harmer et al., 2006; Paulus et al., 2005), whereas reward processing in the ventral striatum is mainly under dopaminergic control (Schultz, 2007; Tobler et al., 2007).

**Limitations, strengths and future directions**

The present study is not without limitations. Since our analysis focused on expectations of wins and losses, the power to detect differences in the outcome phase was limited due to collinearity issues. We, therefore, only reported on expectancy and anticipation of reward and loss, and not on reward and loss outcome. Furthermore, it may be argued that more ecologically valid tasks are more likely to detect behavioural group differences, because they could employ a faster succession of trials, 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 (de Ruiter et al., 2009; Goudriaan et al., 2005; Potenza et al., 2003a; Potenza et al., 2003b; Reuter et al., 2005). Furthermore, our cohort of problem gamblers was selected using stringent exclusion criteria, resulting in a rather homogeneous cohort with no psychiatric disorders other than pathological 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 pathological gambling may be associated with distinct (neuro)psychological profiles
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(Goudriaan et al., 2005; and for a review see van Holst et al., 2010), Therefore, larger-scale neurocognitive and neuroimaging studies are needed to test whether for example subtypes of problematic gamblers preferring chance-based or skill-based games are associated with differential neural processing of reward and loss expectations.

Future studies investigating reward and loss expectancy as well as feedback processing in pathological 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 behaviour in pathological gamblers. In healthy subjects, learning occurs when the actual outcome differs from the predicted outcome, resulting in a prediction error (Schultz and Dickinson, 2000). This prediction error can be used to adjust the value of certain options so that they better reflect the true reward value which will be used to guide future decisions. Thus, 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 behaviour, i.e. modify choice behaviour. However, from previous studies showing attenuated responses towards gain and losses in pathological gamblers (de Ruiter et al., 2009; Reuter et al., 2005), it appears that gamblers fail to show this enhanced prediction error signal when unexpected outcomes occur. Lacking this prediction error signal will become apparent as a learning deficit, which could explain disadvantageous decision making skills consistently found in PRGs (Brand et al., 2005; Goudriaan et al., 2005).

In conclusion, we found evidence of higher activity in the reward system during reward expectation in PRGs compared to 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 probably dependent on dysfunctional dopamine neurotransmission in pathological gambling.

Supplementary data

1: Guessing task

Each trial began with a 2-sec presentation of a circle with the backside of ten playing cards and €1.00 or €5.00 depicted in the middle. Either 30% or 70% of the playing cards were highlighted, indicating the probability of winning the amount depicted in the middle of the circle. Subjects indicated whether they expected to win or lose. After indicating their expectation (left or right button press), 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 (a win occurred when a red ace was within the highlighted area and a loss occurred when the red ace was outside the highlighted area). In addition, the total amount accumulated was displayed in the top right-hand corner of the screen. An additional two seconds later, the 3-10 sec interstimulus interval started.
2: Participants
15 problematic gamblers were recruited from Dutch addiction treatment centres where they received cognitive behavioural therapy. This therapy consisted of a maximum of 12 sessions (duration of 1.5 hours) of group therapy. In these 12 sessions, aberrant cognitive constructs were detected and targeted; coping strategies and new behaviour were trained, all with the goal of achieving long lasting abstinence of gambling behaviour. All problematic gamblers had attended at least 4 sessions, of which ten participants had attended all 12 sessions.

### Table 1a: Main effects of 5 euro > 1 euro

<table>
<thead>
<tr>
<th>MNI coordinates peak values</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>L/R x y z Z value</td>
<td></td>
</tr>
<tr>
<td>Ventral striatum</td>
<td>R 5 9 -6 3.89</td>
</tr>
</tbody>
</table>

### Table 1b: Main effects of 70% > 30%

<table>
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<th>MNI coordinates peak values</th>
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</tr>
</thead>
<tbody>
<tr>
<td>L/R x y z Z value</td>
<td></td>
</tr>
<tr>
<td>Ventral striatum</td>
<td>R</td>
</tr>
</tbody>
</table>

### Table 2a: Main effects of gain related expected value

<table>
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<th>MNI coordinates peak values</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>L/R x y z Z value</td>
<td></td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td>L -36 36 -6 3.35</td>
</tr>
<tr>
<td>Ventral striatum</td>
<td>R 12 6 -3 3.62</td>
</tr>
</tbody>
</table>

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