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Imbalance in the sensitivity to different types of rewards in pathological gambling

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Pathological gambling is an addictive disorder characterized by a persistent and compulsive desire to engage in gambling activities. This maladaptive behaviour has been suggested to result from a decreased sensitivity to experienced rewards, regardless of reward type. Alternatively, pathological gambling might reflect an imbalance in the sensitivity to monetary versus non-monetary incentives. To directly test these two hypotheses, we examined how the brain reward circuit of pathological gamblers responds to different types of rewards. Using functional magnetic resonance imaging, we compared the brain responses of 18 pathological gamblers and 20 healthy control subjects while they engaged in a simple incentive task manipulating both monetary and visual erotic rewards. During reward anticipation, the ventral striatum of pathological gamblers showed a differential response to monetary versus erotic cues, essentially driven by a blunted reactivity to cues predicting erotic stimuli. This differential response correlated with the severity of gambling symptoms and was paralleled by a reduced behavioural motivation for erotic rewards. During reward outcome, a posterior orbitofrontal cortex region, responding to erotic rewards in both groups, was further recruited by monetary gains in pathological gamblers but not in control subjects. Moreover, while ventral striatal activity correlated with subjective ratings assigned to monetary and erotic rewards in control subjects, it only correlated with erotic ratings in gamblers. Our results point to a differential sensitivity to monetary versus non-monetary rewards in pathological gambling, both at the motivational and hedonic levels. Such an imbalance might create a bias towards monetary rewards, potentially promoting addictive gambling behaviour.

Keywords: functional MRI; pathological gambling; addiction; reward; striatum
Abbreviations: ICD = impulse control disorder

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Introduction

Pathological gambling is a psychiatric disorder that is often associated with serious deleterious psychosocial consequences, and has a relatively high prevalence, estimated between 1% and 2% in Western countries (Welte *et al.*, 2008; Wardle *et al.*, 2010). It shares similarities with drug addiction, including risk-seeking behaviour (Ligneul *et al.*, 2013) and core features such as tolerance, withdrawal and craving symptoms (Petry, 2007; Potenza, 2008). Accordingly, pathological gambling has often been conceptualized as a behavioural addiction, offering a valuable framework for studying the neurophysiological mechanisms underlying addictive behaviours without the confounding effect of neurotoxic drugs (van Holst *et al.*, 2010*a*). In line with this perspective, a number of theories coined in the field of drug addiction have been tentatively applied to pathological gambling in past years, in particular in relation to reward sensitivity (Goudriaan *et al.*, 2004; van Holst *et al.*, 2010*b*).

A popular hypothesis, referred to as the reward deficiency syndrome, posits a blunted sensitivity to reward in addiction (Comings and Blum, 2000; Volkow *et al.*, 2002*a*). Addicts would be equipped with an underactive reward system, resulting from a chronic hypodopaminergic state in subcortical brain regions. As a consequence, they would be driven to seek out intense rewarding experiences (such as drug consumption or excessive gambling) as a way to compensate for this deficit. Although this view has received empirical support from functional MRI and PET studies in the context of drug addiction (Garavan *et al.*, 2000; Volkow *et al.*, 2001, 2002*b*; Asensio *et al.*, 2010; for a review see Hommer *et al.*, 2011), similar evidence remains scarce and heterogeneous in the field of pathological gambling (Clark, 2010; Joutsa *et al.*, 2012). Yet, some functional MRI studies have reported results consistent with such a decreased reward sensitivity, as evidenced by a blunted activation of the ventral striatum and ventral prefrontal cortex of pathological gamblers in response to monetary gains (Reuter *et al.*, 2005; de Ruiter *et al.*, 2009; Chase and Clark, 2010; Balodis *et al.*, 2012).

An alternative hypothesis suggests that addictive behaviours result from a motivational bias in which the urge to procure the object of addiction overrides the incentive value of alternative sources of reward (Goldstein and Volkow, 2002; Goldstein *et al.*, 2007). Such motivation, often triggered by environmental cues predictive of future rewards, is under the influence of a mesocorticolimbic brain system, which includes the ventral striatum and orbitofrontal cortex (Berridge, 2007). In addicts, this circuit may be hypersensitive to addiction-related cues in comparison with other reward cues, leading to a critical imbalance in incentive motivation (Robinson and Berridge, 2003). This hypothesis is supported by clinical observations indicating that exposure to drug or gambling-related cues induces specific attentional biases and feelings of craving in addicted populations (Grant and Kim, 2001; Fadardi and Cox, 2009; Brevers *et al.*, 2011). However, corroborating evidence from neuroimaging studies is more mixed; whereas a few functional MRI studies show enhanced responses to gambling cues in the reward system of pathological gamblers (Crockford *et al.*, 2005; Goudriaan *et al.*, 2010; van Holst *et al.*, 2012), others report decreased cue-induced responses in the same areas (Potenza *et al.*, 2003). Besides, it remains unclear whether such an imbalance would be primarily driven by an increased sensitivity to money or a decreased sensitivity to other rewards, and whether it primarily impacts motivational or hedonic processes.

In order to test these two hypotheses, a critical approach—which has not been used so far—is to compare the brain activations elicited by monetary versus non-monetary rewards in pathological gamblers. Here we used a validated functional MRI protocol allowing the comparison of monetary and visual erotic rewards during dissociable anticipation and outcome phases (Sescousse *et al.*, 2010). While the 'reward deficiency hypothesis' predicts a global decrease in reward sensitivity regardless of reward type, the 'imbalance hypothesis' suggests an asymmetrical response to the two rewards. Note, however, that these two hypotheses are not mutually exclusive, since the 'reward deficiency hypothesis' is traditionally associated with the processing of reward outcomes, whereas the 'imbalance hypothesis' focuses more specifically on reward anticipation. Importantly, monetary and erotic rewards were delivered in the same probabilistic fashion in the absence of decision-making, to avoid the confounding effect of gambling on reward-related brain responses.

This approach may have implications for our understanding of impulse control disorders (ICDs) observed in a subset of patients with Parkinson's disease. Those ICDs, including pathological gambling and hypersexuality, are often considered as side effects of dopaminergic therapy (Lim *et al.*, 2008; Weintraub *et al.*, 2010), further suggesting a link between dopamine and gambling addiction (Sescousse and den Ouden, 2013). A handful of recent neuroimaging studies have identified frontostriatal circuits associated with increased risk-seeking and reward sensitivity in patients with Parkinson's disease with such ICDs (Steeves *et al.*, 2009; Voon *et al.*, 2010, 2011*a*). However, those studies could not distinguish between different types of ICDs, and only employed monetary rewards to investigate underlying brain mechanisms. By contrast, our protocol investigates 'pure' pathological gambling using both monetary and erotic rewards, and is therefore complementary to these previous studies.

Materials and methods

Participants

A total of 20 pathological gamblers and 20 healthy control subjects, all males and right-handed, participated in this study. All were heterosexual males, because men are generally more responsive to visual sexual stimuli than women (Hamann *et al.*, 2004) and because pathological gambling has a higher prevalence in males compared to females (Kessler *et al.*, 2008). The data of two pathological gamblers were finally excluded, because of technical problems with the task presentation in one case, and because of a highly inconsistent behaviour (in terms of hedonic ratings, see below) throughout the task in the other case. Therefore, the data presented in this paper are based on 18 pathological gamblers and 20 healthy control subjects. Note that this study builds upon an earlier study using the same task in healthy volunteers (Sescousse *et al.*, 2010), but that an entirely new sample of

Table 1 Demographic and clinical characteristics of pathological gamblers and healthy control subjects

	Healthy control subjects ($n = 20$)	Pathological gamblers ($n = 18$)	Group comparison
Age	31 (7.3)	34.1 (11.6)	$t(36) = 1.02$, $P = 0.32$
Education level (number of years)	13.2 (1.7)	12.1 (2.6)	$t(36) = 1.53$, $P = 0.14$
Monthly income (€)	1537.5 (1010.7)	2139 (1385.8)	$t(36) = 1.54$, $P = 0.13$
Sexual Arousability Inventory	88.6 (12.6)	92.5 (14.3)	$t(36) = 0.90$, $P = 0.37$
Alcohol Use Disorders Identification Test	4.2 (3.5)	5.9 (3.9)	$t(36) = 1.49$, $P = 0.14$
Number of current smokers	5	10	$\chi^2 = 3.70$, df = 1, $P = 0.05$
Number of years of smoking (all subjects - lifetime)	4.6 (8.9)	11.1 (13.6)	$t(36) = 1.76$, $P = 0.09$
Fagerström Test for Nicotine Dependence	0.1 (0.3)	1.1 (1.8)	$t(36) = 2.30$, $P = 0.03$
Hospital Anxiety and Depression (depression subscale)	3.4 (2.3)	4.3 (3.1)	$t(36) = 1.01$, $P = 0.32$
Hospital Anxiety and Depression (anxiety subscale)	6.1 (2.7)	8.2 (3.0)	$t(36) = 2.28$, $P = 0.03$
South Oaks Gambling Screen	0.05 (0.2)	9.2 (2.6)	$t(36) = 15.8$, $P < 0.001$

All values are mean (SD). Groups were compared using independent sample *t*-tests, except for Chi-square test where indicated.

healthy control subjects was recruited to achieve the desired matching between groups (see below). All participants were recruited through advertisement and gave written informed consent to be part of the experiment, which was approved by the local ethics committee.

All participants underwent a semi-structured interview (Nurnberger *et al.*, 1994) performed by a psychiatrist. All pathological gamblers met the DSM-IV-TR [Diagnostic and Statistical Manual of Mental Disorders (fourth edition, text revision)] criteria for pathological gambling and had a minimum score of 5 on the South Oaks Gambling Screen questionnaire (SOGS; Lesieur and Blume, 1987) (range: 5–14). Importantly, all were active gamblers, and none followed a therapy or treatment. Healthy control subjects had a score of 0 on the South Oaks Gambling Screen questionnaire, except one participant who had a score of 1. In both groups, a history of major depressive disorder or substance abuse/dependence (except nicotine dependence) in the past year was considered a criterion for exclusion. All other DSM-IV-TR axis I disorders were excluded based on lifetime diagnosis. In the gambling group, one participant met past (>1 year) criteria for alcohol dependence, one for alcohol abuse and one for cannabis abuse. In the control group, one participant met past criteria for alcohol abuse.

We used a number of questionnaires to assess the participants: the Fagerström Test for Nicotine Dependence (FTND; Heatherton *et al.*, 1991) served as an indicator of nicotine dependence severity; the Alcohol Use Disorders Identification Test (AUDIT; Saunders *et al.*, 1993) was used to estimate alcohol consumption; the Hospital Anxiety and Depression scale (HAD; Zigmond and Snaith, 1983) was used to assess current depressive and anxiety symptoms; and finally the Sexual Arousability Inventory (SAI; Hoon and Chambless, 1998) was used to measure sexual arousability. Besides age and education, pathological gamblers and control subjects were matched on alcohol consumption and depressive symptoms (Table 1). Pathological gamblers scored slightly higher on anxiety and nicotine dependence scales, although only two scored above the cut-off value for nicotine addiction ($\geqslant 5$). This is in line with the clinical description of pathological gambling, characterized by a high comorbidity with substance addiction and mood disorders, and more generally by an addictive personality (Lorains *et al.*, 2011). Importantly, the two groups did not differ on income level and sexual arousability, thereby ensuring a comparable motivation across groups for monetary and erotic rewards. Note that the similar level of sexual arousability in both groups did not result from a voluntary matching by the experimenters, precluding a potential selection bias in the gambling group.

To further assess the participants' motivation for money, we asked them about the frequency with which they would pick up a 0.20 € coin from the street on a scale from 1 to 5 (Tobler *et al.*, 2007) and matched the two groups on this criterion (control subjects: 3.2 ± 1.6; gamblers: 3.8 ± 1.5; $P = 0.22$). Finally, to ensure that all participants would be in a similar state of motivation to see erotic stimuli, we asked them to avoid any sexual contact during a period of 24 h before the scanning session. We also sought to enhance the motivation for money by telling the participants that the financial compensation for their participation would amount to the winnings accumulated in one of the three runs of the study. For ethical reasons, however, and unbeknown to the participants, they all received 78€ cash at the end of the experiment.

All participants were medication-free and instructed not to use any substance of abuse other than cigarettes on the day of the scan.

Task

All participants completed 171 trials of the same incentive delay task previously used in young healthy subjects (Sescousse *et al.*, 2010) (Fig. 1). Briefly, each trial consisted of an anticipation phase, a discrimination task and an outcome phase. During anticipation, participants saw one of 12 cues announcing the type (monetary/erotic), probability (25/50/75%) and intensity (low/high) of an upcoming reward. An additional control cue was associated with a null reward probability. After a variable delay period (question mark representing a pseudo-random draw), subjects were asked to perform a visual discrimination task within a maximum time of 1 s. Success on this task allowed the participants to view the outcome of the pseudorandom draw, whereas erroneous or slow response led automatically to reward omission. In rewarded trials, the outcome was either an erotic image (with high or low erotic content) or the picture of a safe mentioning the amount of money won (high or low amount). Following each reward outcome, participants were asked to provide a hedonic rating on a 1–9 continuous scale (1 = very little pleased; 9 = very highly pleased). In non-rewarded and control trials, participants were presented with 'scrambled' pictures. A blank screen was finally used as an intertrial interval of variable length.

Task stimuli

Two categories (high and low intensity) of erotic pictures and monetary gains were used. Nudity being the main criteria driving the reward

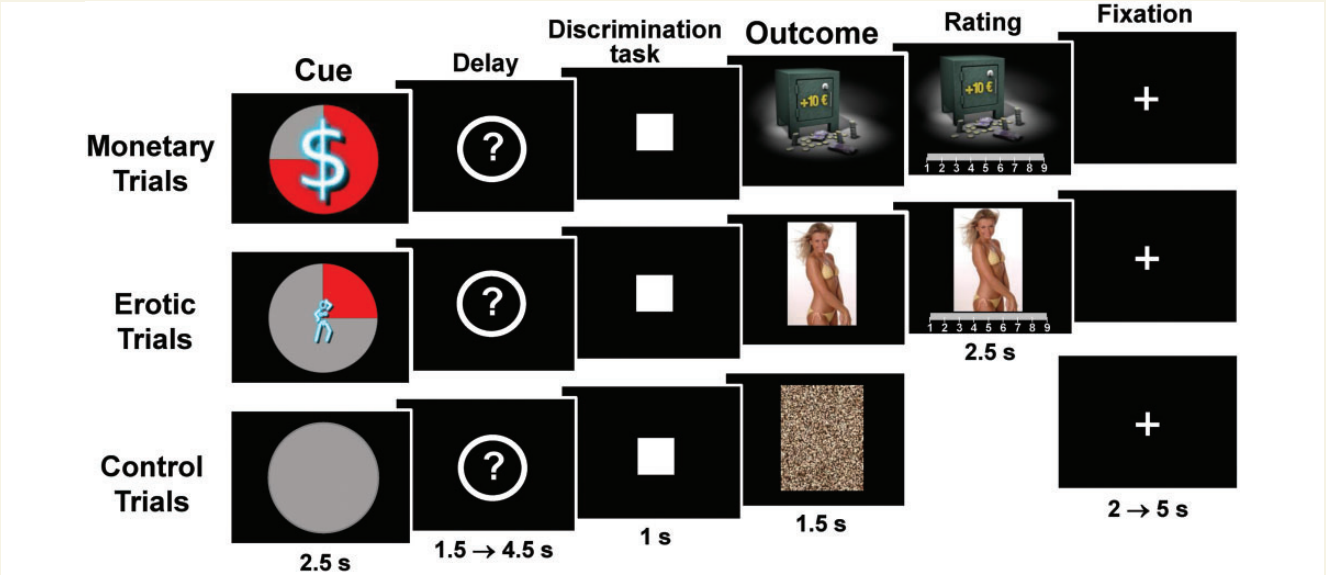

Figure 1 Incentive delay task. Subjects first saw a cue informing them about the type (pictogram), intensity (size of pictogram) and probability (pie chart) of an upcoming reward. Three cases are represented here: a 75% chance of receiving a large amount of money (*top*), a 25% chance of seeing a low erotic content picture (*middle*) and a sure chance of getting nothing (control trials, *bottom*). Then the cue was replaced by a question mark, symbolizing a delay period during which a pseudorandom draw was performed according to the announced probability. Following this anticipation phase, participants had to perform a target discrimination task within <1 s. The target was either a triangle (left button press required) or a square (right button press required). Both their performance and the result of the pseudorandom draw determined the nature of the outcome. In rewarded trials, subjects saw a monetary amount displayed on a safe (high or low amount, *top*) or an erotic picture (with high or low erotic content, *middle*), and had to provide a hedonic rating on a continuous scale. In non-rewarded and control trials, subjects saw a scrambled picture (*bottom*).

value of erotic stimuli, we separated them into a 'low intensity' group displaying females in underwear or bathing suits and a 'high intensity' group displaying naked females in an inviting posture. Each erotic picture was presented only once during the course of the task to avoid habituation. A similar element of surprise was introduced for the monetary rewards by randomly varying the amounts at stake: the low amounts were 1, 2 or 3 € and the high amounts were 10, 11 or 12 €. The pictures displayed in non-rewarded and control trials were scrambled versions of the pictures used in rewarded trials and hence contained the same information in terms of chromaticity and luminance.

Functional magnetic resonance imaging data acquisition

Imaging was conducted on a 1.5 T Siemens Sonata scanner, using an 8-channel head coil. The scanning session was divided into three runs. Each included four repetitions of each cue, with the exception of the control condition, repeated nine times. This yielded a total of 171 trials. Within each run the order of the different conditions was pseudorandomized and optimized for further signal deconvolution. The order of the runs was counter balanced between participants. All scanning sessions were scheduled at the same time of the morning, and preceded by a short training in which participants received oral instructions and were familiarized with the cognitive task.

Each of the four functional runs consisted of 296 volumes. Twenty-six interleaved slices parallel to the anterior commissure–posterior commissure line were acquired per volume (field of view = 220 mm, matrix 64×64, voxel size = $3.4 \times 3.4 \times 4$ mm, gap 0.4 mm), using a gradient-echo echoplanar (EPI) T_2*-weighted sequence (repetition time = 2500 ms, echo time = 60 ms, flip angle = 90°). To improve the local field homogeneity and hence minimize susceptibility artefacts in the orbitofrontal area, a manual shimming was performed within a rectangular region including the orbitofrontal cortex and the basal ganglia. A high-resolution T_1-weighted structural scan was subsequently acquired in each participant.

Functional magnetic resonance imaging data analysis

Preprocessing and statistical analyses of functional MRI data were conducted with SPM2 (Wellcome Department of Cognitive Neurology, University College London, www.fil.ion.ucl.ac.uk/spm/software/spm2). This version of SPM was used to ensure direct comparability of the current results with our previous study using the same protocol in healthy subjects (Sescousse *et al.*, 2010). The first four functional volumes of each run were removed, and the remaining images were corrected for slice-timing artefacts, and spatially realigned to the first image of each time series. We then searched for residual artefacts in the time series with the tsdiffana utility (http://imaging.mrc-cbu.cam.ac.uk/imaging/DataDiagnostics) and modelled them with dummy regressors in our general linear model. The functional images were then normalized to the MNI stereotaxic space using SPM2's EPI template, and spatially smoothed with a 10 mm full-width at half-maximum isotropic Gaussian kernel. Anatomical scans were normalized to the MNI space using the icbm152 template brain and averaged across all participants.

Each participant's data set was then subjected to an event-related analysis. Anticipation-related responses were modelled as 2.5 s box-car functions time-locked to the onset of the cue. Responses to monetary

and erotic cues were modelled separately, and modulated by two orthogonal parametric regressors accounting for the trial-to-trial variations in reward probability and intensity. The control condition was modelled in a separate regressor. Outcome-related responses were modelled as events time-locked to the appearance of the reward. The two rewards (monetary/erotic) × two possible outcomes (rewarded/non-rewarded) were modelled as four separate conditions. Two covariates linearly modelling the probability and the ratings were further added to each rewarded condition, while another covariate modelling the probability was added to each of the non-rewarded conditions. A last regressor modelled the appearance of a scrambled picture in the control condition. All regressors were subsequently convolved with the canonical haemodynamic response function and entered in a first level analysis. A high-pass filter with a cut-off of 128 s was applied to the time series. Contrast images were calculated based on the parameter estimates output by the general linear model, and were then passed in a second level group analysis.

Group differences were investigated for several contrasts of interest, using two-sample *t*-tests (those analyses are equivalent to group × condition interactions). First, during the anticipation phase, we examined the contrast 'monetary > erotic cue' in gamblers minus control subjects. Using the parametric regressors of our general linear model, we also searched for group × intensity and group × probability interactions for each reward cue separately. At the time of the outcome, differences between control subjects and gamblers were investigated for each reward separately, using the contrasts 'monetary reward > control' and 'erotic reward > control'. We then computed correlations between the blood oxygen level-dependent signal and the subjective ratings, and compared those correlations between the groups. All between-group comparisons were thresholded using a family-wise error (FWE) corrected $P < 0.05$. Based on our *a priori* hypotheses regarding the roles of the ventral striatum and orbitofrontal cortex during reward anticipation/rating and reward outcome, respectively, the FWE correction for multiple comparisons was restricted to small volumes of interest corresponding to these regions. These volumes were defined as 12-mm spheres centred around peak voxels derived from previous independent studies. More specifically, peak voxels for the ventral striatum were derived from a recent meta-analysis on reward processing (Liu *et al.*, 2011), whereas peak voxels for the orbitofrontal cortex were derived from our previous study using the same protocol (Sescousse *et al.*, 2010) (Figs 3, 4 and 5).

As the above group × condition interactions can reflect different types of scenarios (i.e. a between-condition difference in control subjects alone, in gamblers alone or in both groups), we further investigated the precise form of these interactions. To this aim, we performed two additional analyses. First, we examined the previous contrasts in each group individually, using one-sample *t*-tests. Unless otherwise mentioned, these within-group analyses were thresholded with a voxel-level uncorrected $P < 0.001$ and a cluster-level corrected $P < 0.05$ accounting for multiple comparisons across the whole brain. Furthermore, we performed illustrative region of interest analyses within brain regions defined functionally from the whole-brain group × condition interaction analyses. Each region of interest was created by taking the intersection of the functional cluster of interest and a 10-mm sphere centred on the cluster's highest peak voxel. The per cent signal change was calculated with the MarsBaR toolbox (http://marsbar.sourceforge.net). To represent the per cent signal change as a function of the hedonic ratings in Fig. 5, we built a second model in which rewarded trials were binned by rating into quartiles such that each bin had an equivalent number of trials. For simplicity the per cent signal change was averaged across hemispheres for bilateral regions of interest.

Results

Behaviour

Reaction times and hit rates during the discrimination task, as well as hedonic ratings, were analysed in separate four-way ANOVAs including reward type, probability and intensity as within-subject factors, and group (control subjects/gamblers) as a between-subject factor. Only 19 control subjects were included in the analysis of ratings, as data could not be fully collected for one participant due to technical problems.

We found a robust group × reward type interaction on reaction times [$F(1,36) = 8.1$, $P < 0.01$]. This interaction was driven by faster reaction times in gamblers for monetary compared to erotic rewards (Tukey's HSD test: $P < 0.01$) (Fig. 2A), suggesting that gamblers were more strongly motivated by monetary gains than erotic pictures. There was also a strong main effect of intensity on reaction times [$F(1,36) = 50.7$, $P < 0.001$], indicating that higher reward intensity increased motivation. However, there were no intensity × group or higher-order interactions ($P > 0.56$), suggesting a similar discrimination between high and low intensity rewards in both groups regardless of reward type (Supplementary Fig. 1). There was no main effect of probability on reaction times or any interaction with the group ($P > 0.41$). The analysis of hit rates did not reveal any significant differences between groups.

There was no main effect of reward or group, as well as no group × reward interaction, on the hedonic ratings ($P > 0.30$). This suggests that monetary and erotic rewards were similarly valued both within and between groups. There was a robust main effect of reward intensity on the ratings [$F(1,35) = 178.0$, $P < 0.001$], but no interaction with the group ($P > 0.55$), suggesting that the two intensity categories (high versus low) were equally perceived in both groups (Fig. 2B). Similarly, we observed a main effect of probability on the ratings [$F(2,70) = 10.6$, $P < 0.001$], but no interaction with the group ($P > 0.37$). Overall these results show that the rating patterns of gamblers and control subjects were qualitatively similar.

Functional magnetic resonance imaging results

Reward anticipation phase

Based on the group × reward interaction observed in the reaction time data, we searched for a similar interaction at the brain level. Specifically, we searched for the brain regions more strongly activated by monetary compared to erotic cues (see results for each group in Fig. 3A), and performed a contrast between gamblers and control subjects. This analysis revealed significant results in the ventral striatum bilaterally ($x, y, z = -9, 0, 3$, $T = 4.22$; $18, 0, 0$, $T = 4.12$) (Fig. 3B; other foci are reported in Supplementary Table 1). This interaction was driven, at least partly, by a differential sensitivity to monetary versus erotic cues in gamblers, as indicated by the overlap of activations observed between Fig. 3A and 3B (see also Supplementary Fig. 2 for a formal conjunction). The extraction of per cent signal change further demonstrated that this

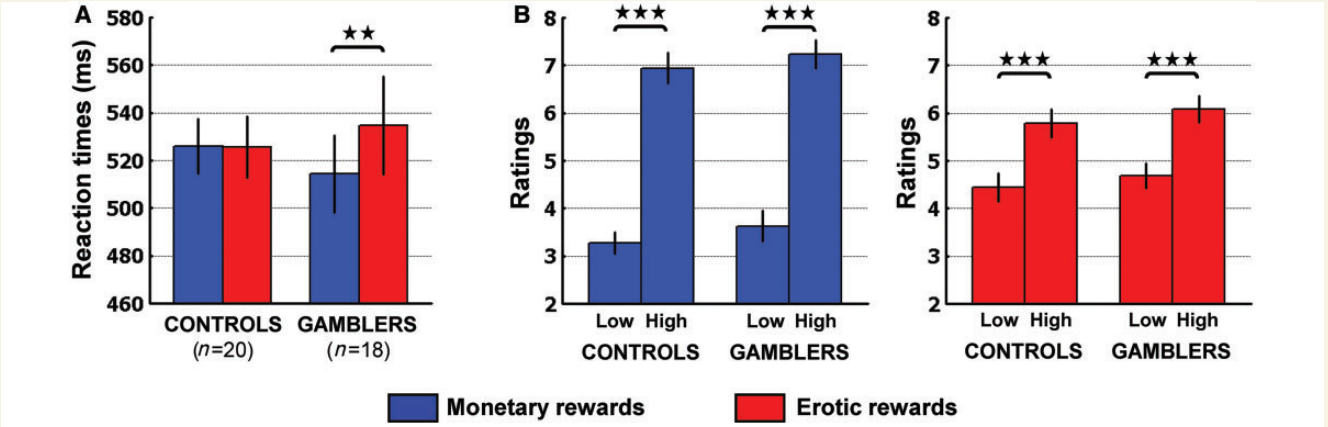

Figure 2 Behavioural results. (**A**) Plot of mean reaction times according to reward type (monetary/erotic) and group (control subjects/gamblers) in the discrimination task. There is a significant group × reward interaction, driven by shorter reaction times for monetary compared to erotic cues in gamblers. (**B**) Plot of mean hedonic ratings according to reward type, intensity and group. There is a robust main effect of intensity on the ratings, demonstrating that the high versus low categories were well perceived by the participants. Error bars indicate SEM. Asterisks denote significance of Tukey's HSD tests (***$P < 0.001$; **$P < 0.01$).

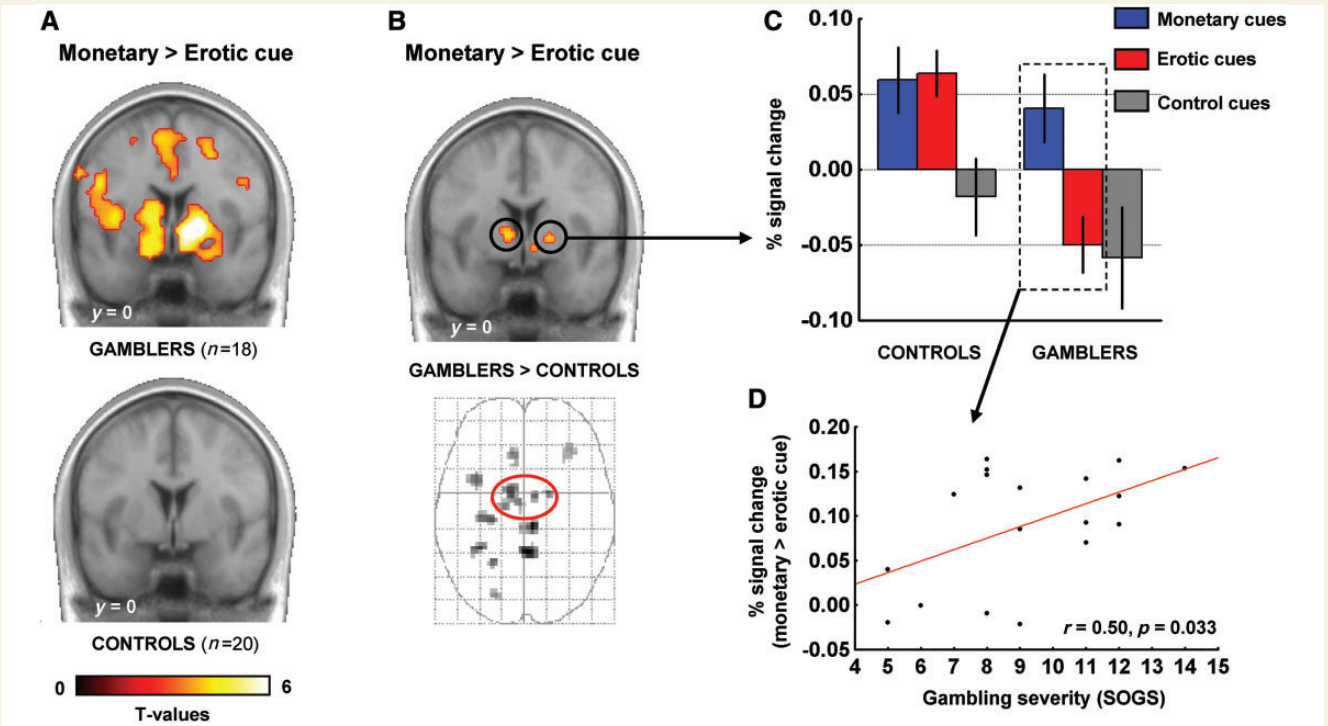

Figure 3 Blunted response to erotic cues in the ventral striatum of pathological gamblers. (**A**) T-maps showing the brain regions responding more strongly to monetary than erotic cues in gamblers and control subjects. Activations are overlaid on an average anatomical scan of all subjects (display threshold: $P < 0.001$ voxel-level uncorrected and $P < 0.05$ cluster-level corrected). (**B**) The direct comparison between the two groups reveals a significant interaction in the ventral striatum, shown on a coronal slice of an average brain and an axial projection plane (display threshold: $P < 0.001$ uncorrected and cluster size >10 voxels). Note that activations in the ventral striatum survive a family-wise error corrected threshold of $P < 0.05$ within 12-mm spheres whose centres were defined independently based on a recent meta-analysis (Liu *et al.*, 2011) (left: $x, y, z = -12, 10, -6$: right: $x, y, z = 12, 10, -4$). (**C**) Plot of mean per cent signal change according to the type of cue in the ventral striatum, showing a markedly decreased response to erotic cues in gamblers. Error bars indicate SEM. (**D**) The differential response to monetary versus erotic cues in gamblers shows a significant correlation with the severity of gambling symptoms as indexed by the South Oaks Gambling Screen (SOGS) scale.

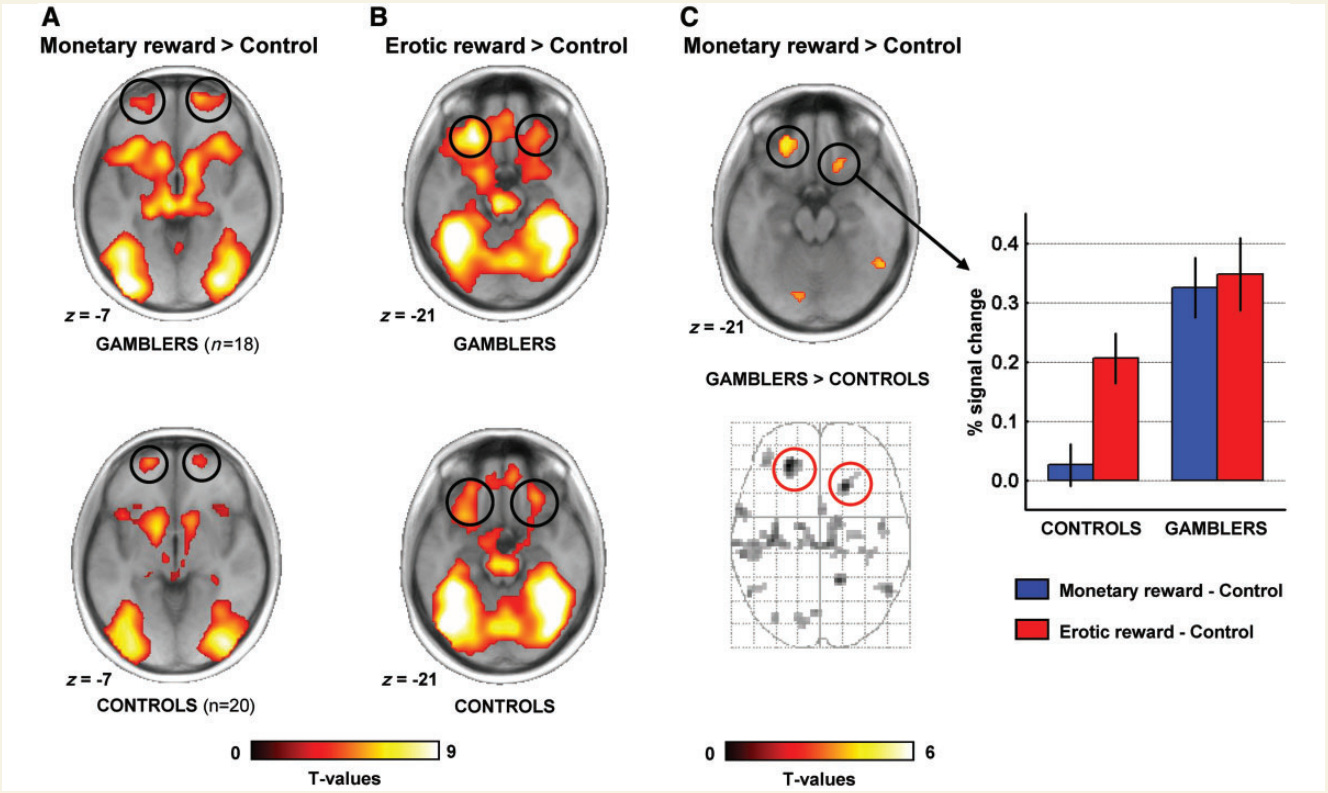

Figure 4 Brain activation pattern in the orbitofrontal cortex at the time of reward outcome. (**A**) Monetary rewards recruit the anterior lateral orbitofrontal cortex (OFC, circled) in both gamblers and control subjects. (**B**) Conversely, erotic rewards recruit the posterior lateral orbitofrontal cortex (circled) in both gamblers and control subjects. Activations are overlaid on an average anatomical scan of all subjects (display threshold: $P < 0.001$ voxel-level uncorrected and $P < 0.05$ cluster-level corrected, except for the right anterior orbitofrontal cortex in control subjects which only survives a cluster-level corrected $P < 0.11$). (**C**) The comparison of monetary responses between the two groups reveals enhanced activity in a posterior portion of the lateral orbitofrontal cortex of gamblers compared with control subjects. Activations are shown on an axial slice of an average anatomical scan and an axial projection plane (display threshold: $P < 0.001$ uncorrected and cluster size >10 voxels). Note that activations in the posterior orbitofrontal cortex survive a family-wise error corrected threshold of $P < 0.05$ within 12-mm spheres whose centres were defined independently based on our previous study (Sescousse *et al.*, 2010) (left: $x, y, z = -30, 33, -15$: right: $x, y, z = 30, 33, -15$). The region revealed by this interaction overlaps with the posterior lateral orbitofrontal cortex found to respond to erotic rewards in gamblers and control subjects. The plot of mean per cent signal change further illustrates that this region responds strongly to both monetary and erotic rewards in gamblers, but only to erotic rewards in control subjects. Error bars indicate SEM.

differential reactivity in the ventral striatum of gamblers was due to a decreased response to erotic cues, rather than an increased response to monetary cues, compared with control subjects (Fig. 3C). Furthermore, to investigate whether this response pattern was related to the severity of gambling symptoms, we plotted the difference in per cent signal change between monetary and erotic cues against the South Oaks Gambling Screen questionnaire scores. This analysis revealed a significant positive correlation in our striatal region of interest ($r = 0.50$; $P = 0.033$, Fig. 3D). Additional analyses examined each reward cue separately (contrasted against the control cue), but failed to reveal any significant differences between gamblers and control subjects (at $P < 0.001$).

We also searched for potential group differences in the coding of expected reward intensity and probability, but did not find any significant interactions either for monetary or erotic rewards (at $P < 0.001$). Finally, to ensure that the group × reward interaction reported in Fig. 3B was not driven by differences in smoking habits between control subjects and gamblers, we performed the same analysis again after including Fagerström Test for Nicotine Dependence scores as a covariate of no-interest. The group × reward interaction observed in the ventral striatum survived this more stringent procedure, demonstrating that this result cannot be attributed to differences in smoking habits.

Reward outcome phase

Based on our previous study showing reward-specific responses in the lateral orbitofrontal cortex of healthy subjects (Sescousse *et al.*, 2010), we first mapped these responses in each group independently. In line with our previous findings, monetary rewards elicited activity in the anterior lateral orbitofrontal cortex, in both control subjects ($x, y, z = -18, 60, -12$, $T = 4.22$; 21, 57, −12, $T = 4.81$) and gamblers ($x, y, z = -27, 57, -9$, $T = 4.73$; 18, 60, −9, $T = 6.52$) (Fig. 4A). Similarly, as expected from our previous results, erotic rewards elicited activity in the posterior lateral orbitofrontal cortex in both control subjects ($x, y, z = -27, 24, -15$, $T = 6.66$; 27, 33, −18, $T = 5.74$) and gamblers ($x, y, z = -24, 30,$

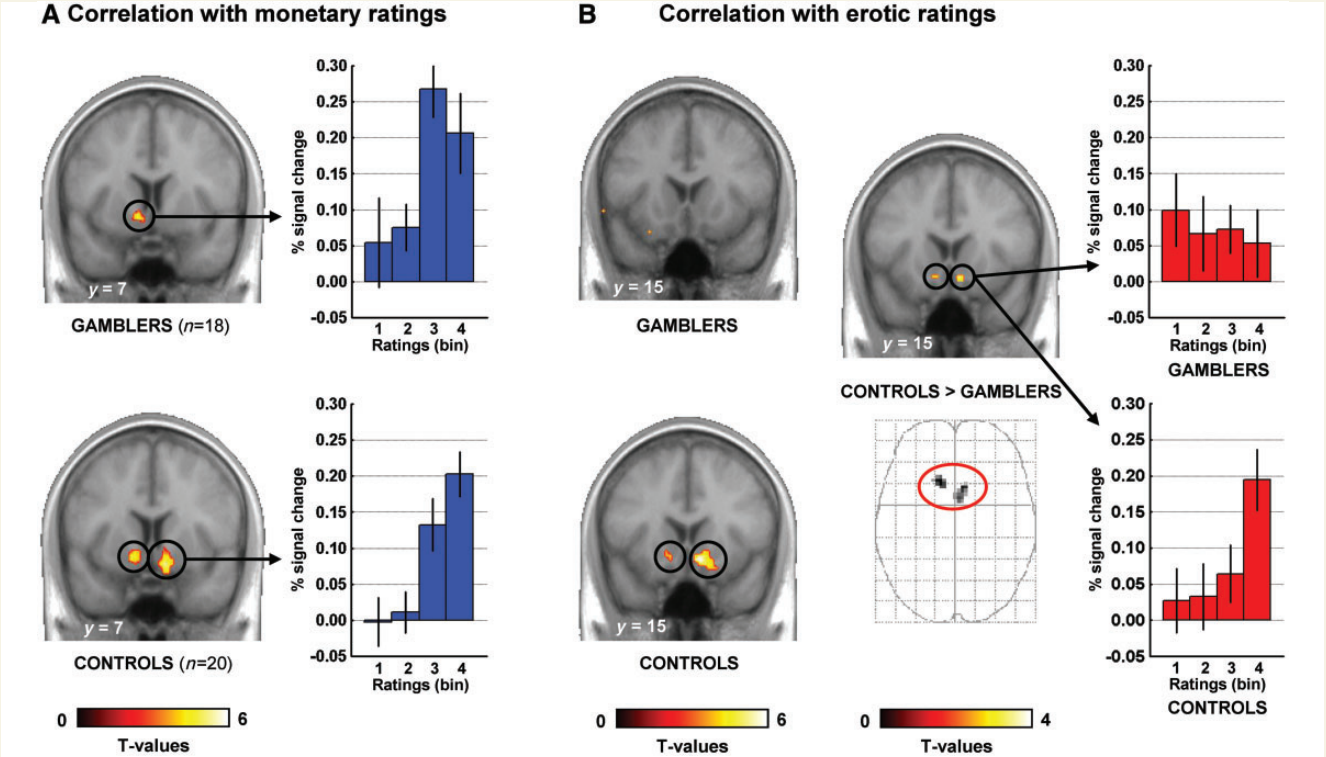

Figure 5 Representation of reward hedonic value in the ventral striatum. (**A**) The T-maps show the brain regions where activity correlates with monetary ratings in gamblers and control subjects, illustrating a similar response pattern for both groups in the ventral striatum. Activations are overlaid on an average anatomical scan of all subjects (display threshold: $P < 0.001$ voxel-level uncorrected and $P < 0.05$ cluster-level corrected, except for the left ventral striatum in control subjects, which only survives a cluster-level corrected $P < 0.12$). The plots show the mean per cent signal change extracted from the ventral striatum, after trials were binned by rating into quartiles such that each bin has an equivalent number of trials. (**B**) Activity in the ventral striatum correlates with erotic ratings in control subjects but not in gamblers (display threshold: $P < 0.001$ voxel-level uncorrected and $P < 0.05$ cluster-level corrected). The direct comparison between the two groups reveals a significant interaction in the ventral striatum, shown on a coronal slice of an average brain and an axial projection plane (display threshold: $P < 0.005$ uncorrected and cluster size >20 voxels). Activations in the ventral striatum survive a family-wise error corrected threshold of $P < 0.05$ within 12-mm spheres whose centres were defined independently based on a recent meta-analysis (Liu *et al.*, 2011) (left: $x, y, z = -10, 8, -4$: right: $x, y, z = 12, 10, -6$). The plots show the mean per cent signal change extracted from the striatal region where the interaction is significant. Error bars indicate SEM.

-18, $T = 9.50$; 27, 30, -18, $T = 5.69$) (Fig. 4B). Other foci, pertaining for the most part to a 'common reward network' including the ventral striatum, midbrain, thalamus, insula and anterior cingulate cortex, are reported in Supplementary Table 2.

Brain responses to monetary and erotic reward outcomes were further compared between the two groups. Whereas previous studies reported blunted responses to monetary rewards in gamblers compared to control subjects (Reuter *et al.*, 2005; de Ruiter *et al.*, 2009; Chase and Clark, 2010), such hypoactivations were not observed in our data (only one cluster lying at the edge of the right dorsolateral prefrontal cortex was observed at $P < 0.005$). In contrast, when compared to control subjects, gamblers showed enhanced responses with monetary gains in several brain regions, with the two most significant clusters located in a posterior portion of the lateral orbitofrontal cortex ($x, y, z = -24, 39, -24$, $T = 4.98$; 18, 24, -24, $T = 4.59$) (Fig. 4C). Importantly, conjunction analyses revealed that these clusters significantly overlapped with the regions responding to monetary gains in gamblers alone (Supplementary Fig. 3), and with those previously found to respond to erotic rewards in both groups (Supplementary Fig. 4; note that this overlap is also visible from the comparison of Fig. 4B and C). The extraction of per cent signal change further confirmed that this posterior orbitofrontal cortex region was activated by both monetary and erotic rewards in gamblers, but only by erotic rewards in control subjects (Fig. 4C). Following the same procedure used for the anticipation phase, we also plotted the difference in per cent signal change between monetary and erotic outcomes as a function of South Oaks Gambling Screen questionnaire scores in gamblers. This analysis revealed a similar positive correlation, although only marginally significant in this case ($r = 0.45$, $P = 0.062$).

Finally, we examined the brain regions encoding the hedonic value of rewards, i.e. responding parametrically with the subjective ratings. In monetary trials, we found that activity in the ventral striatum correlated with these ratings in both control subjects ($x, y, z = -15, 6, -9$, $T = 5.31$; 9, 3, -6, $T = 6.84$) and gamblers ($x, y, z = -15, 12, -9$, $T = 4.67$) (Fig. 5A; other foci are reported in Supplementary Table 3). No group × rating interaction was

observed (at $P < 0.001$). In erotic trials, we found a similar correlation between the hedonic value of erotic pictures and blood oxygen level-dependent activity in the ventral striatum of control subjects (x, y, $z = -15$, 24, -9, $T = 5.31$; 12, 12, -9, $T = 5.71$), but not in the ventral striatum of gamblers, even at a threshold of $P < 0.005$ (Fig. 5B; other foci are reported in Supplementary Table 3). To test for a significant difference between groups, we directly contrasted the parametric regressors modelling the erotic ratings. This analysis revealed a significant group × rating interaction specifically in the bilateral ventral striatum (x, y, $z = -12$, 21, -9, $T = 3.63$; 6, 15, -12, $T = 3.49$) (Fig. 5B).

Similarly as for the reward anticipation phase, we performed the above analyses again after including Fagerström Test for Nicotine Dependence scores as a covariate of no-interest. The results showed that the group × reward and group × rating interactions reported in Figs 4C and 5B, respectively, were not affected by this procedure, ruling out a potential interpretation of these findings as resulting from between-group differences in smoking habits.

Discussion

Our results reveal reward processing differences between pathological gamblers and control subjects, both at the time of reward anticipation and reward outcome.

Reward anticipation

A prime goal of this study was to compare the processing of monetary and non-monetary cues in pathological gamblers. Compared with control subjects, the ventral striatum of pathological gamblers showed a differential response to monetary versus erotic cues, which appeared largely driven by a reduced sensitivity to erotic cues. In line with the 'imbalance hypothesis' and the role of the ventral striatum in instrumental motivation (Berridge, 2007; Knutson and Greer, 2008), this asymmetrical response pattern could represent a neurophysiological mechanism by which monetary cues overpower other stimuli in terms of incentive salience. This finding parallels previous results showing that non-drug related cues (e.g. monetary cues) elicit blunted brain responses in drug addicts (Goldstein *et al.*, 2007; Wrase *et al.*, 2007; Buhler *et al.*, 2010) as well as in adolescents at risk for addiction (Peters *et al.*, 2011; Schneider *et al.*, 2012). Thus, the driving force of addiction might not be necessarily based on a hypersensitivity towards addiction-related cues, but more generally to an imbalance in the reactivity of the mesocorticolimbic circuit to addiction-related versus non-related stimuli (Buhler *et al.*, 2010).

Two additional findings support this view in our study. First, the amplitude of the differential response to monetary versus erotic cues in the ventral striatum was predicted by the severity of gambling symptoms, strengthening the idea that this differential cue reactivity is a characteristic trait of pathological gambling. Second, this differential response was mirrored in the behaviour of pathological gamblers, who showed faster reaction times following monetary than following erotic cues. As the two groups scored similarly on the Sexual Arousability Inventory scale and gave similar ratings to both rewards, the present results are unlikely to reflect a pre-existing lack of interest for sexual stimuli in pathological gamblers. Instead, we suggest that the concurrent availability of monetary and erotic rewards triggered a motivational hierarchy favouring monetary rewards in pathological gamblers. A similar effect has recently been reported in abstaining smokers, who attribute higher reward value to cigarette cues than to neutral cues that are equally predictive of reward (Freeman *et al.*, 2012).

Reward outcome

In contrast to the predictions of the 'reward deficiency hypothesis', our results did not reveal lower striatal activity in pathological gamblers relative to control subjects at the time of reward outcome. Although this negative finding might seem surprising in light of previously published studies (Reuter *et al.*, 2005; de Ruiter *et al.*, 2009; Chase and Clark, 2010), several differences might explain this discrepancy. First, in our study, reward outcomes were contrasted against a neutral condition instead of using losses or reward omission trials as a comparison baseline. This procedure ensured that the results were not confounded by a potentially different loss aversion in pathological gamblers. Furthermore, we used larger monetary rewards compared with previous studies, which delivered relatively small gains in comparison with the amounts typically wagered by pathological gamblers. Therefore, it cannot be excluded that the previously reported reduced striatal activations reflected an effect of low monetary reward saliency.

Interestingly, our results demonstrate that the ventral striatum of pathological gamblers was unable to properly encode the hedonic value of erotic rewards. This parallels previous observations showing that the ventral striatum of smokers fails to encode the magnitude of non-drug rewards (monetary gains), despite normal hedonic ratings (Martin-Soelch *et al.*, 2003). Given the role of this structure in computing a 'common neural currency' meant to allow the comparison of different rewards on a common scale (Montague and Berns, 2002; Izuma *et al.*, 2008; Sescousse *et al.*, 2010), one possibility is that pathological gamblers might experience problems in assessing the relative value of monetary versus non-monetary rewards. This might lead in turn to a biased preference for monetary incentives.

Finally, we examined how monetary and erotic reward outcomes mapped onto the orbitofrontal cortex of pathological gamblers. This analysis was motivated by accumulating evidence suggesting a postero-anterior functional organization in the lateral orbitofrontal cortex of healthy subjects; while the anterior orbitofrontal cortex would process secondary/abstract rewards such as money, the posterior orbitofrontal cortex would process more primary/concrete rewards such as food or erotic stimuli (Bechara and Damasio, 2005; Kringelbach, 2005; Sescousse *et al.*, 2010, 2013). The present results confirmed this dissociation in control subjects, but revealed a more complex pattern in pathological gamblers. Indeed, monetary rewards did not only recruit the anterior orbitofrontal cortex as observed in control subjects, but also recruited a more posterior portion of the orbitofrontal cortex. This finding, highlighting enhanced responsiveness to monetary gains in pathological gamblers, is difficult to reconcile with the 'reward

deficiency hypothesis'. However, it is consistent with the results of a recent functional MRI study showing that the same posterior orbitofrontal cortex area produces altered responses to monetary rewards in pathological gamblers (Miedl *et al.*, 2012). Moreover, this area was found to largely overlap with the region responding to erotic rewards in both groups in our own study. Although based on a reverse inference, one tempting interpretation of this finding is that pathological gamblers might experience monetary gains as a primary reward (Montague, 2006). This possibility concurs with the fact that pathological gamblers seem to pursue money not necessarily for what it can buy—i.e. as a secondary reward—but for its own sake, as if it were intrinsically reinforcing. This behaviour might in turn explain why these patients are less likely to set monetary limits before gambling, and often report being unaware of whether they are winning or losing during play (Nower and Blaszczynski, 2010).

Potential limitations

This study compared the processing of monetary and erotic rewards in pathological gamblers versus healthy control subjects. At first sight, one might be concerned by potential confounds arising from psychological differences existing between those rewards. For instance, money is only delivered at the end of the experiment, and can be accumulated and exchanged, whereas erotic stimuli have an immediate reward value directly tied to the visual stimulation. However, the use of between-group analyses militates against such confounding effects: indeed, any of these effects would be present in both groups and therefore cancelled out in a group comparison. Moreover, most of these psychological differences between monetary and erotic rewards are inherent to the underlying distinction between primary and secondary reinforcers, and are hence meaningful in the present context. Similarly, it could be argued that the use of independent rating scales for monetary and erotic rewards does not provide a direct assessment of the relative value and matching of those rewards. Although this is true, such matching in terms of hedonic value was not a requirement for the interpretation of our functional MRI results, which were not concerned with reward comparison *per se*, but with group comparisons.

Another difference between erotic and monetary rewards concerns novelty. Indeed, all erotic images were novel (to avoid habituation and gradual loss of appetitive value, Fiorino *et al.*, 1997) whereas monetary gains were drawn from a selection of three unpredictable amounts for each reward level. However, this slight difference is unlikely to explain our findings because, if anything, it would have biased our results in the opposite direction of what we observed. That is, we would have expected increased activations for more novel stimuli, whereas we observed altered brain responses to erotic stimuli in pathological gamblers.

Conclusion

This study supports the idea of an imbalance in the reward sensitivity of pathological gamblers, where both an increased sensitivity to monetary rewards and a decreased sensitivity to non-monetary rewards may contribute to the disease. It is unclear whether such an imbalance would be cause or a consequence of the addiction. However, the observed correlation with gambling severity, which has been linked to disease duration (Denis *et al.*, 2012), suggests that this imbalance is more likely to be a consequence of accumulated years of gambling. Interestingly, this 'imbalance hypothesis' may prove more powerful than the 'reward deficiency hypothesis' for explaining the specificity of gambling addiction, i.e. why gambling behaviour is favoured over other excessive reward-driven behaviours (such as drug intake) in pathological gamblers. Accordingly, our results suggest that enhancing the saliency of non-monetary rewards may be a fruitful strategy as part of a therapeutic approach for treating pathological gambling.

A range of ICDs, including pathological gambling and hypersexuality, have been observed in patients with Parkinson's disease as a consequence of their dopaminergic treatment. However, it remains unclear whether these diverse ICDs reflect distinct vulnerabilities and can be differentiated at the brain level (Voon *et al.*, 2011*b*). Our results, which demonstrated several dysfunctional mechanisms specifically in the context of pathological gambling, suggest that these ICDs may have distinct signatures in the ventral striatum. To further unravel the core pathophysiological mechanisms of specific 'behavioural addictions', future comparisons between pathological gamblers and patients with Parkinson's disease suffering from dopamine-induced ICDs should supplement current studies investigating these disorders separately (Steeves *et al.*, 2009; Voon *et al.*, 2010, 2011*a*).

Finally, our findings should have important clinical implications for understanding how addictive behaviours affect brain functions without the confounding effects of neurotoxic substances. A wealth of neuropsychological data has implicated the orbitofrontal cortex in impulsive and risky decision-making in pathological gamblers (Cavedini *et al.*, 2002; Lawrence *et al.*, 2009). The present observation that monetary rewards recruit the posterior portion of the orbitofrontal cortex specifically in pathological gamblers may help refine those theories as well as the functional divisions of the orbitofrontal cortex in gambling addiction. The latter finding may also shed light on a range of neurological disorders where, as is the case after orbitofrontal cortex lesions, there is no primary deficit in intellectual function but major deficits in motivation.

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Supplementary material

Supplementary material is available at *Brain* online.

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