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Aberrant neural signatures of decision-making: Pathological gamblers display cortico-striatal hypersensitivity to extreme gambles

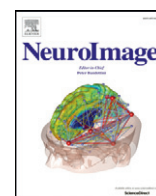Sofie V. Gelskov [a,b,*,*], Kristoffer H. Madsen [a,c], Thomas Z. Ramsøy [a,d,1], Hartwig R. Siebner [a,e,1]

[a] Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Kettegaard Alle 30, 2650 Hvidovre, Denmark
[b] Brain and Consciousness group (EHESS/CNRS/ENS), Ecole Normale Supérieure, PSL Research University, 29 rue d'Ulm, 75005 Paris, France
[c] Section for Cognitive Systems, DTU Compute, Technical University of Denmark, Asmussens Alle, Building 322, 2800 Kongens Lyngby, Denmark
[d] Center for Decision Neuroscience, Dept. of Marketing, Copenhagen Business School, Solbjerg Plads 3, 2000 Copenhagen, Denmark
[e] Department of Neurology, Copenhagen University Hospital Bispebjerg, Bispebjerg Bakke 23, 2400 Copenhagen, Denmark

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ABSTRACT

Pathological gambling is an addictive disorder characterized by an irresistible urge to gamble despite severe consequences. One of the hallmarks of pathological gambling is maladaptive and highly risky decision-making, which has been linked to dysregulation of reward-related brain regions such as the ventral striatum. However, previous studies have produced contradictory results regarding the implication of this network, revealing either hypo- or hypersensitivity to monetary gains and losses. One possible explanation is that the gambling brain might be misrepresenting the benefits and costs when weighting the potential outcomes, and not the gains and losses per se. To address this issue, we investigated whether pathological gambling is associated with abnormal brain activity during decisions that weight the utility of possible gains against possible losses. Pathological gamblers and healthy human subjects underwent functional magnetic resonance imaging while they accepted or rejected mixed gain/loss gambles with fifty–fifty chances of winning or losing. Contrary to healthy individuals, gamblers showed a U-shaped response profile reflecting hypersensitivity to the most appetitive and most aversive bets in an executive cortico-striatal network including the dorsolateral prefrontal cortex and caudate nucleus. This network is concerned with the evaluation of action–outcome contingencies, monitoring recent actions and anticipating their consequences. The dysregulation of this specific network, especially for extreme bets with large potentials consequences, offers a novel understanding of the neural basis of pathological gambling in terms of deficient associations between gambling actions and their financial impact.

Introduction

Pathological gambling is a mental disorder characterized by an irresistible urge to engage in monetary gambling despite harmful consequences. With a prevalence reaching 1–2% in many Western societies (Welte et al., 2008; Wardle et al., 2010), this disorder constitutes a severe public and personal health issue. Pathological gambling has recently been classified as a behavioral addiction and shares many core symptoms with drug addictions such as withdrawal, tolerance, and high preoccupation (Petry 2007; Leeman and Potenza 2012).

Risky decision-making is an important hallmark of pathological gambling. Indeed, gamblers have a high tolerance toward risk (Clark 2010; Brevers et al. 2013), and pathological gambling has been linked

to alterations of dopaminergic regions linked to reward, risk, and motivation, such as the ventral striatum and the ventromedial prefrontal cortex (vmPFC) (van Holst et al. 2010; Limbrick-Oldfield et al. 2013; Potenza 2014). However, while some studies have found hypoactivation of the mesolimbic reward pathway in response to the anticipation or outcome of rewards (Reuter et al. 2005; de Ruiter et al. 2009; Balodis et al. 2012), other studies have reported hyperactivation of the same pathway to anticipated reward (van Holst et al. 2012; Worhunsky et al. 2014), anticipated losses (Romanczuk-Seiferth et al. 2015), or gambling cues (Crockford et al. 2005; Goudriaan et al. 2010). Interestingly, positron emission tomography (PET) studies revealed no general differences between gamblers and healthy controls in the magnitude of striatal dopamine release (Joutsa et al. 2012; Linnet et al. 2011) but showed a positive correlation between striatal dopamine release and gambling severity (Joutsa et al. 2012), and dopamine release and gambling excitement (Linnet et al. 2011). These discrepant response patterns are reflected in two main accounts of pathological gambling. On the one hand, the reward deficiency theory predicts a hyposensitive

reward system due to a dysfunctional dopamine D2 receptor found in substance addicts (Blum et al. 1990; Noble et al. 1991) and gamblers (Comings et al. 1996; Comings et al. 2001). A lower dopaminergic tone in the brain would push gamblers to seek higher rewards, in order to reach the threshold at which a "reward cascade" is initiated in the brain. On the other hand, the sensitization theory predicts a strong motivational bias toward objects of addiction (Robinson and Berridge 1993, 2008) leading to hypersensitivity in dopaminergic regions. In gamblers, the motivation to gamble would be triggered by gambling cues in the environment, which would override the incentive value of alternative sources of reward (Goldstein and Volkow 2002; Goldstein et al. 2007).

These discrepancies underscore that the neural basis of pathological gambling remains unsettled. While studies contrasting monetary punishments and rewards can address how decision-values are computed in the brain, they do not address how gains and losses are integrated during gambling. Recently, we developed a gambling task that probes both the magnitudes of gain and loss values separately, as well as how gains and losses are balanced against each other in "mixed" (gain/loss) gambles (Gelskov et al. 2015). When balancing gains and losses, people tend to be more sensitive to potential losses than to equivalent gains, a decision-bias known as loss aversion (Kahneman and Tversky 1979). In practice, people typically reject 50/50 gambles unless they can win around twice as much as they can lose. Previous studies using mixed gambles with healthy participants found that the separate valuation of gains and losses involve reward-related dopaminergic target regions, specifically the ventral striatum and the vmPFC (Tom et al. 2007). However, when the entire gain/loss gamble is taken into account (i.e., potential gain, potential loss, and the consequences of winning or losing), other studies have found an important role for the amygdala in loss aversion (De Martino et al. 2010; Gelskov et al. 2015). In the present study, we used this task in a population suffering from gambling addiction as a means to gain insight into aberrant value-based decision-making.

Recently, a behavioral study found that problem gamblers are less loss averse than control subjects (Brevers et al. 2012, but see also Giorgetta et al. 2014). Here, we ask whether pathological gambling might reflect deficient balancing of possible gains against losses during decision-making. In a recent study, we found that activity of the amygdala and ventral striatum reflected the degree of loss aversion in healthy participants when they decided to accept or reject extreme gain–loss gambles (Gelskov et al. 2015). Here, we used individual gambling behavior to investigate how the decision-making process is tuned by inter-individual variation in loss aversion (i.e. being more or less loss averse), and whether loss aversion is also reflected in mesolimbic reward-related areas in gamblers. To address these issues, we used fMRI and a gambling task in which participants had to accept or reject mixed gambles on the basis of the ratio between the absolute gain and loss value. Our study design allowed us to address whether pathological gamblers balance positive and negative values differently from healthy controls and whether the integration of gain–loss ratios in gambling decisions is associated with abnormal activity in brain regions involved in value-based decision-making.

Material and methods

Participants

Fourteen male, un-medicated pathological gamblers (mean age in years: 29.43; SD: 6.05; range: 20–40) and 15 healthy control subjects (all male; mean age in years: 29.87; SD: 6.06; range: 21–38) were recruited specifically for this study. Two additional gamblers were initially scanned but excluded before inclusion in the analysis because they misunderstood the task: One participant only responded when accepting a bet, while another participant thought that all gambles would be paid out at the end of the session. Gamblers were recruited through a Danish

treatment center for pathological gambling. No participant had additional mental health issues apart from pathological gambling based on the structural clinical interview for DSM-IV, Axis I (SCID-I, Research version, patient and nonpatient versions; First et al. 2002), including disorders such as drug use or dependency. The presence of pathological gambling was confirmed by structural interview based on the SCID module for pathological gambling. All gamblers had a South Oaks Gambling Screen (SOGS) score above 5 (Table 1; Lesieur and Blume 1987; Danish versions of SOGS and SCID modules were translated by J. Linnet). Participants were screened for MR compatibility, history of neurological disorders, and signed informed consent forms. The study was approved under the ethical protocol KF 01–131/03, issued by the local ethics committee.

Participants were tested on two separate days 1–2 weeks apart. During the first test session, participants underwent neuropsychological testing, questionnaires, and interviews (see Table 1). Participants were also endowed with 200 Danish Kroner (i.e., the Danish monetary currency, DKK, 1 DKK ≈ 0.16 US dollar), which they were told to bring back the following week for the fMRI test session as a gambling stake.

Gambling task and stimuli

During the fMRI session, participants performed a gambling task, which required them to accept or reject mixed gain–loss gambles with equal probability of winning or losing (Fig. 1A). On each trial, subjects were presented with a pie chart with either a potential gain amount or a potential loss amount, according to main condition (i.e. "loss first"

Table 1
Demographic and neuropsychological characteristics of participants.

Variables, group means (SD of means)	Pathological gamblers (n = 14)	Control subjects (n = 15)	Test statistics (2-sample, 2-tailed t-tests and chi-square tests)
Demographic data			
Age (years)	29.43 (6.05)	29.87 (6.06)	$t(27) = 0.2, P = 0.85$
Educational level[a,b]	3.15 (1.68)	4.6 (1.12)	$t(26) = 2.72, P = 0.01$
Clinical data			
Gambling score (SOGS)	11.36 (3.97)	0.33 (0.9)	$t(27) = 10.48, P < 0.001$
Smokers[b]	4	0	$\chi^2 = 5.39, df = 1, P = 0.02$
Alcohol (AUDIT)[b]	9.23 (5.32)	8.67 (4.47)	$t(26) = 0.31, P = 0.76$
Handedness (left)	2	4	$\chi^2 = 0.14, df = 1, P = 0.71$
Neuropsychological data			
WAIS subtests:			
"Vocabulary"	10.36 (2.50)	13.47 (1.25)	$t(27) = 4.29, P < 0.001$
"Information"	10.00 (2.08)	12.80 (2.01)	$t(27) = 3.69, P < 0.001$
Depression (BDI)	17.00 (10.57)	3.47 (2.95)	$t(27) = 4.77, P < 0.001$
Impulsiveness (BIS-11)[b]	74.93 (7.25)	58.36 (8.63)	$t(26) = 5.50, P < 0.001$
"Attention"	2.25	2.14	$t(26) = 1.57, P = 0.13$
"Motor"	2.47	1.95	$t(26) = 4.35, P < 0.001$
"Non-planning"	2.8	2.71	$t(26) = 5.63, P < 0.001$
Anxiety (GAD-10)	12.57 (9.02)	8.27 (5.89)	$t(27) = 1.53, P = 0.14$
Risk-taking (DOSPERT)			$t(27) = 1.57, P = 0.13$
"Perceived risk"	-0.25 (0.25)	-0.51 (0.20)	$t(27) = 3.14, P = 0.004$
"Expected benefit of risk"	0.46 (0.41)	0.40 (0.31)	$t(27) = 0.49, P = 0.63$
Behavioral data			
Loss aversion, Lambda (λ)	1.45 (0.49)	1.83 (0.83)	$t(27) = 1.47, P = 0.077$[c]
Response time (ms)	927 (240)	959 (122)	$t(27) = 0.45, P = 0.66$

Abbreviations: SOGS, South Oaks Gambling Screen; AUDIT, Alcohol Use Disorders Identification Test; WAIS, Wechsler Adult Intelligence Scale; BDI, Beck Depression Inventory; BIS-11, Barratt Impulsiveness Scale, 11th ed., GAD-10, Generalized Anxiety Disorder test; DOSPERT, Domain-Specific Risk-Taking scale.

[a] Highest educational level (scoring): 1 = Lower/general secondary school, 2 = vocational education and training, 3 = upper secondary school, 4 = professional college degree, 5 = bachelors degree or similar, 6 = masters degree.

[b] One gambler did not complete the AUDIT screen, one did not complete the smoking and educational screen. One control subject did not complete the BIS-11 questionnaire.

[c] Non-parametric permutation test used due to non-normal distributions.

or "gain first" conditions). After a varying display time (2–5 s), the second amount of the mixed gamble was presented and subjects decided to accept or reject the current gamble by pressing one of two buttons in the scanner. Both, the first "magnitude presentation phase" and the ensuing "decision phase" were jittered in steps of 0.5 s (i.e., 2, 2.5, 3, 3.5, 4, 4.5, and 5 s) pseudo-randomly from trial to trial. Instructions were read aloud to the participants, where after they completed a short training session until they were familiar with the task. Participants

were told that no feedback would be given about the outcome of single bets during scanning, but that after the fMRI session, the computer would select two random bets: the ones that had been *accepted* during the gambling session, would be "played out" and participants would either lose money from their endowment or win additional money, while if they had rejected the bet, no 50/50 gamble was played out. Participants were told to follow their "gut feelings" and that there was no right or wrong answers.
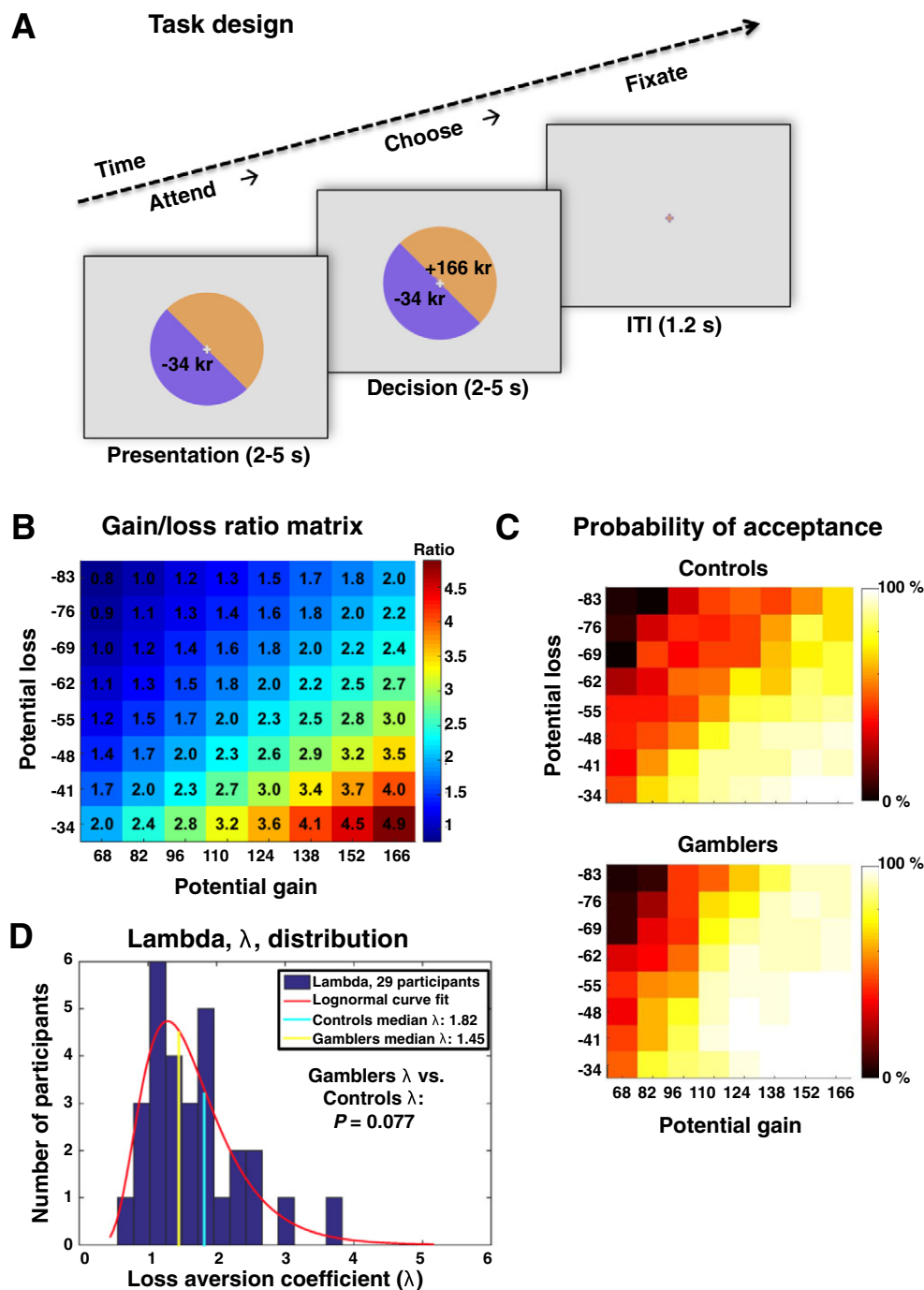
Fig. 1. Gambling task in the scanner, stimulus matrix, and choice behavior. A) Event-related fMRI paradigm; participants first received either a potential loss or a potential gain amount (i.e. the magnitude "Presentation" phase). Then, when both amounts were presented, participants chose whether to accept or reject the gamble (i.e., "Decision" phase). Inter-trial intervals (ITIs) separated trials. NB: "kr" = "DKK". B) Color-coded heat map representing gambling ratios (gain/loss). Stimuli consisted of 64 different gain–loss ratios, corresponding to 8 potential gain amounts (68–166 DKK; increments of 14) by 8 potential loss amounts (34–83 DKK; increments of 7). Color-coding reflects ratios from lowest (0.82) to highest (4.9). All gain/loss ratios were presented twice in randomized order, once in a "gain first" and once in a "loss first" condition. C) Color-coded heat maps representing choice patterns for gamblers (left) and controls (right). The color-coding from black to red to yellow to white reflects the increasing percentage of accepted gambles (black ➔ white: 0–100%). D) Loss aversion coefficient, lambda (λ), for all participants. Note the right skewed distribution. Non-parametric permutation test indicated a trend toward less loss aversion in pathological gamblers compared to healthy controls (*P* = 0.077).

Stimuli consisted of mixed gambles presented on yellow and purple pie charts with one monetary amount (i.e., potential gains and losses in Danish currency) presented in each half of the chart (Fig. 1A). The 64 stimuli combined the 8 potential gain amounts (68–166 DKK; in increments of 14 DKK), with the 8 potential loss amounts (34–83 DKK; in increments of 7 DKK; see gain/loss ratio matrix in Fig. 1B). The 64 mixed gambles were presented once in a "gain first" and once in a "loss first" condition, yielding a total of 128 trials. Each of the stimuli belonged to one of 8 classes, identified by the angle of the pie chart which was rotated with 45° (0°–360°) for each class. Thus, although each amount (e.g. +82 DKK) appeared 16 times, it was only presented once in the same physical position on the screen per main condition (gain or loss first), as to avoid any low-level repetition effects. To ensure that subjects were attentive to the task and to increase the amount of ratios below 1, we added 18 highly disadvantageous catch trials. These trials combined 3 low-gain amounts (i.e., 34, 41, 48 DKK) with 3 high-loss amounts (i.e., 138, 152, 166 DKK). All subjects rejected at least 89% of the catch trials, indicating that subjects paid attention to the task (gamblers rejected 98% of all catch trials; range: 95–100%; control subjects rejected 98.9% of catch trials; range 89–100%). There was no difference in proportion of rejected catch trials between groups ($P = 0.61$, $t(27) = 0.52$, SD = 2.99). Finally, we added 24 "baseline" trials: empty pie charts without any amounts (note that neither catch trials nor baseline trials were used in the behavioral analysis or included as regressors of interest). Stimuli were presented and button presses recorded using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

Based on the participant's choices on the 128 regular trials, we calculated the individual degree of loss aversion, lambda (λ), by fitting a logistic regression to each participant's binary response (accept/reject). In contrast to Tom et al. (2007), we used the full gain/loss ratio of the mixed gambles as independent variable to derive the individual "decision-boundary" lambda in each participant. This was due to our focus on the full gamble ratio in the fMRI analyses, rather than the single gain and loss values. Lambda was estimated as the gain/loss ratio for which the probability of accepting a trial was equal to the probability of not accepting a trial (i.e. 0.5).

Magnetic resonance imaging

Functional and structural brain scans were acquired using a Siemens Magnetom Trio 3 T MRI scanner with an 8-channel head coil. Blood oxygen level dependent (BOLD) functional MRI was collected using a T2*-weighted echo-planar imaging sequence (295 volumes; 41 slices; 3 mm isotropic resolution; repetition time: 2430 ms; echo time: 30 ms; flip angle: 90°; field of view: 192 mm, horizontal plane) optimized for detecting BOLD signal in the orbitofrontal cortex (Deichmann et al. 2003). Slices were oriented axially and the phase encoding direction was anterior–posterior. Note that the orientation of the field of view did not allow full coverage of the superior parietal cortex. A high-resolution three-dimensional structural scan of the whole brain was acquired using a T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence for the purpose of manual co-registration (1 mm isotropic voxels; FOV: 256 mm; acquisition matrix 256 × 256; TR: 1540; TE: 3.93 ms, inversion time: 800 ms, and a flip angle of 9°) and creating a group-specific normalized anatomical template for display of functional maps in the figures. The first two volumes were discarded as dummy scans to allow the field to reach steady state.

Analysis of fMRI data

The fMRI data were analyzed using SPM8 software (Wellcome Department of Cognitive Neurology). Pre-processing included slice time correction, spatial realignment to the mean image, manual co-registration of images, normalization to a standard EPI image (i.e., MNI template image; functional voxels of 2 × 2 × 2 mm), smoothing using

an isotropic 8 mm full-width at half maximum Gaussian kernel, and high-pass temporal filtering (cut-off frequency 1/128 Hz). The general linear model (GLM) estimated a 24-parameter Volterra expansion of the 6 estimated motion rigid body realignment parameters, which were included as regressors of no interest as described in Friston et al. (1996). We also included additional regressors for catch trials, error trials (i.e., 250 ms > reaction time > 2500 ms and trials with no answer) as well as two "button-press regressors" modeling out the motor activation related to finger button presses. In five subjects, brain volumes were excluded because of excessive head movement (i.e., global head movement above 8 mm, local head movement above 2 mm), and DVARS (i.e., the root mean squared (RMS) change in BOLD signal from volume to volume, where «D» refers to the temporal derivative of time courses and «VARS» to the RMS variance over voxels above 5% change in global BOLD signal as defined in Power et al., (2012)).

In each participant, we captured task-related BOLD signal changes using a GLM, which modeled the magnitude presentation phase and decision phase of each trial (see Fig. 1A). The BOLD signal changes during the magnitude presentation phase was divided into separate "gain events" and "loss events," each modeled with their individual amounts as parametric linear modulations. BOLD signal changes during decision-making were parametrically modulated with the absolute gain–loss ratio including a first (i.e. linear) and second (i.e. quadratic) order polynomial modulation (i.e $(gain/loss)^2$). All regressors of interest were convolved with the canonical hemodynamic response function.

The individual parameter estimates for first and second order polynomial modulation of increasing gain–loss ratios was then entered in two separate second-level group analyses. These second-level t-tests included the individual loss aversion score (i.e., lambda) as covariate to model the influence of individual differences in loss aversion. A separate second-level model included the individual SOGS scores as index of gambling severity. Differences in regional BOLD response between gamblers and controls were assessed using two-sample t-test. At the group level, clusters were considered significant if they exceed a threshold of $P < 0.05$ corrected for multiple comparisons with family-wise error correction across the whole brain (i.e. on a cluster level), using an entry threshold of $P_{Uncorrected} < 0.001$. In addition, various trend activations in relevant cortico-limbic structures are reported at $P_{Uncorrected} < 0.001$. Coordinates are displayed in MNI stereotactic space. For the purpose of highlighting the main BOLD activation clusters (i.e. caudate and DLPFC, Fig. 4) and performing scatter plots of parameter estimates based on individual behaviors (i.e. plotting loss aversion in amygdala and gambling severity in precuneus, Fig. 5), we created anatomical masks for these regions using the WFU PickAtlas (Maldjian et al. 2003). For the masks covering bilateral caudate, amygdala, and precuneus, we used predefined "AAL" atlas masks (Tzourio-Mazoyer et al. 2002), while for the DLPFC mask, we constructed a mask covering Brodmann areas 8–10, 46, and the middle frontal gyrus (MFG). Note that none of these masks were used to ameliorate any of the fMRI results reported in the main text or in the tables.

Results

Demographic and neuropsychological data

Demographic and neuropsychological data are listed in Table 1. Groups did not differ significantly with respect to age, handedness, general anxiety, or alcohol dependency. However, gamblers showed slightly higher smoking dependency, lower educational level, higher overall impulsiveness and differed in the way they perceived risks compared to non-gambling controls. Importantly, all gamblers had a SOGS of more than 5, indicating that they were all in the pathological range (median: 10; range: 6–19). In contrast, all but two control subjects scored 0 on the same test (median: 0; range: 0–3), indicating no problems with gambling.

Depression is a common co-morbidity in pathological gamblers, and consistently, we also found a substantial increase in depressive symptoms in the gambling group compared to the control group. However, there was no correlation between gambling behavior (i.e., λ) and BDI scores in the gamblers ($R = 0.2739$, $P = 0.3651$).

We also found a significant difference in performance on the WAIS subtests probing vocabulary and general knowledge ("information") levels. Again, we found no correlations between these measures and gambling behavior (i.e., correlation between WAIS information and λ: $R = 0.0124$, $P = 0.9679$; and between WAIS vocabulary and λ: $R = 0.2320$, $P = 0.4456$).

Behavioral data

Fig. 1C shows the distribution of accepted gambles for a given gain–loss ratio for gamblers and controls. Most participants consistently showed loss averse behavior: They accepted a given gamble only when the gain amount clearly exceeded the loss amount (i.e. lambda > 1). Gamblers tended to be less loss averse. The mean proportion of accepted vs. rejected trials in gamblers was 65% vs. 35%, and in controls, 55% vs. 45%, but inter-individual variability was substantial in both groups: median lambda in gamblers was 1.45 (SD = 0.49; mean = 1.45; range: 0.56–2.59), with a positively skewed distribution of λ's (skewness coefficient of 0.42), while median lambda in healthy controls was 1.82 (SD = 0.83; mean = 1.83; range: 1.01–3.83; positive skewness: 0.93). Therefore, the difference in lambda between groups only reached borderline significance ($P = 0.077$; t(27) = 1.47). Note that the lambda distribution was non-normal (Shapiro–Wilks test of normality: $P = 0.0353$, $W = 0.9218$). We therefore employed a random permutation test based on resampling (also known as a randomization test) to assess differences in lambda between pathological gamblers and healthy controls. The number of iterations used was 10.000.

The number of error trials was comparable between groups. Gamblers as a group had 30 error trials (15 non-response, 15 very fast or slow responses) with 0–8 error trials per subject. Control subjects made in total 27 errors (16 non-response, 11 very fast or slow responses) with 0–8 error trials per subject. Mean response times were also similar between groups ($P = 0.66$; t(27) = 0.45; gamblers: 927 ms; SD = 240; controls: 959 ms; SD = 122). Decisions to accept or reject a gamble were more difficult when the subjective utility of gains and losses were similar. This was reflected in response times, as both groups responded slower when the Euclidian distance between the individual gain/loss ratio and the group mean lambda decreased (gamblers: $R = 0.15$, $P < 0.001$; controls: $R = 0.15$, $P < 0.001$).

Linear increase in neural activity with increasing gain–loss ratios

In the decision-making phase, a large bilateral cluster in the anterior cingulate cortex (ACC) and the vmPFC ($P < 0.001$; x, y, z = −8, 40, 6; $Z = 4.75$; k = 759), bilateral mid-cingular cortex and adjacent precuneus, ($P < 0.001$; x, y, z = −10, −30, 52; $Z = 4.43$; k = 1933), and superior frontal gyrus (SFG; $P < 0.001$; x, y, z = 18, 38, 56; $Z = 4.34$; k = 633) showed a linear increase in BOLD response with increasingly appetitive gain–loss ratios across all 29 participants. Fig. 2 shows that this linear effect was mainly driven by the gamblers, who showed a gradual increase of the BOLD response with increasingly appetitive gamble ratios in the pregenual portion of ACC ($P < 0.001$; x, y, z = −8, 36, 8; $Z = 5.18$; k = 518; Fig. 2A) and the right vmPFC ($P = 0.003$; x, y, z = 8, 34, −10; $Z = 4.23$; k = 307) as well as in the mid cingulum/precuneus ($P = 0.031$; x, y, z = −10, −30, 52; $Z = 4.40$; k = 188), right inferior temporal gyrus/parahippocampus ($P = 0.002$; x, y, z = 34, 2, −30; $Z = 4.23$; k = 329), and postcentral gyrus ($P = 0.001$; x, y, z = 62; −20, 44; $Z = 4.11$; k = 356). Control subjects, on the other hand, showed dispersed activation clusters in a range of areas (left precuneus: $P < 0.001$; x, y, z = −6, −58, 32; $Z = 4.72$; k = 1010; right lingual gyrus: $P = 0.002$; x, y, z = 18; −86, −8; $Z =$
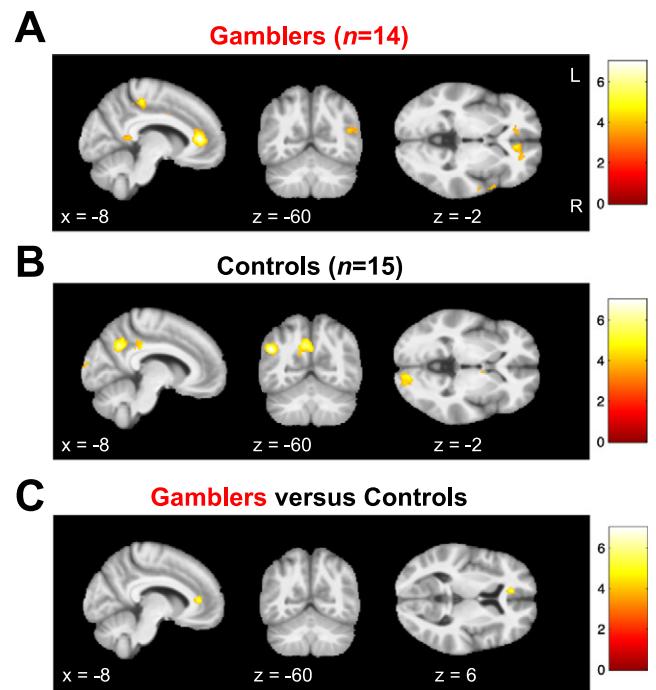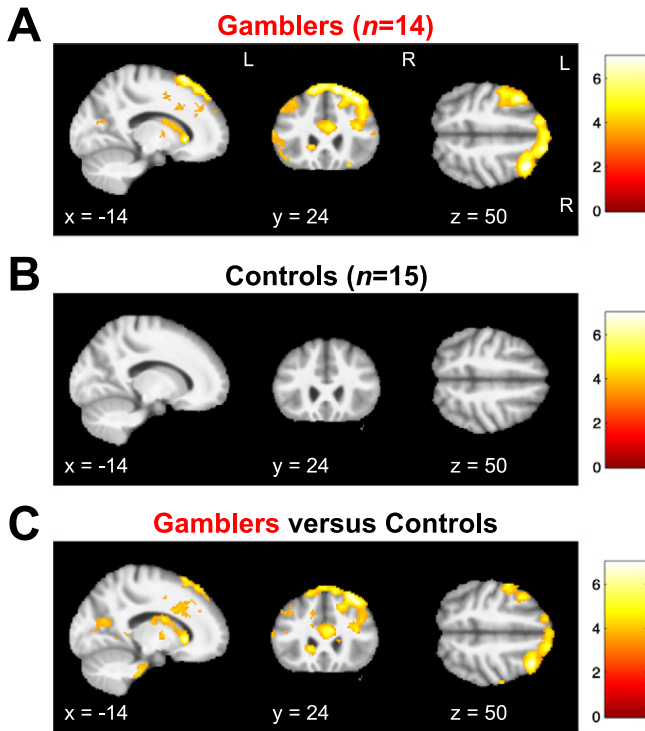

Fig. 2. Color-coded statistical t-score maps: Brain regions showing a positive linear relationship between the BOLD response and increasing gain–loss ratios of the gambles A) in gamblers, B) in controls, and C) contrasting the two groups. When contrasting groups, BOLD activation revealed a trend difference in pregenual ACC (gamblers > controls). Maps are thresholded at $P < 0.001$ (uncorrected) and displayed on a group-specific normalized anatomical template based on structural T1 images.

4.67; k = 332; left cuneus: $P = 0.028$; x, y, z = −14, −100, 10; $Z = 4.27$; k = 193; and right posterior lobe of the cerebellum: $P = 0.001$; x, y, z = 42, −70, −34; $Z = 4.09$; k = 351) with peak activation in the left angular gyrus ($P < 0.001$; x, y, z = −48, −60, 30; $Z = 5.06$; k = 433; Fig. 2B). Although we found no significant decreases in activation for increasingly appetitive bets, we did find trends in the anterior insula of the control group (L: $P < 0.001$, uncorrected; x, y, z = −32, 24, −2; $Z = 3.83$; k = 74; R: $P < 0.001$, uncorrected; x, y, z = 42, 24, 4; $Z = 3.64$; k = 14). When contrasting the groups, no significant differences were found. However, gamblers showed a trend toward a higher increase in activity with increasingly appetitive gambles in the left pregenual ACC ($P < 0.001$, uncorrected; x, y, z = −8, 36, 6; $Z = 4.33$; k = 98; Fig. 2C). Results showing the impact of individual degree of loss aversion on the linear increase in neural activity with increasing ratios can be found in Supplementary Fig. 1 and Supplementary Table 1.

Quadratic increase in neural activity with increasing gain–loss ratios

When combining BOLD signal from all participants, a large network of prefrontal areas in the dorsal and mesial frontal lobe showed a quadratic increase in neural activity with increasing gain–loss ratios peaking in right dorsal SFG ($P < 0.001$; x, y, z = 12, 24, 60; $Z = 5.38$; k = 1769). Further activations for this contrast included the left middle frontal gyrus ($P < 0.001$; x, y, z = −38, 10, 50; $Z = 4.81$; k = 605), bilateral angular gyri (L: $P = 0.022$; x, y, z = −42, −64, 40; $Z = 4.24$; k = 227; R: $P < 0.001$; x, y, z = 52, −56, 38; $Z = 4.68$; k = 488), left inferior frontal gyrus ($P = 0.004$; x, y, z = −42, 26, −16; $Z = 4.09$; k = 330), and right inferior temporal gyrus ($P = 0.001$; x, y, z = 66, −14, −22; $Z = 4.30$; k = 409). As shown in Fig. 3, separate analyses for each group reveal that this effect was only consistent in gamblers. In gamblers, several brain areas showed quadratic increases as a function of gamble ratios, including a large bilateral prefrontal cluster covering

Fig. 3. Color-coded statistical t-score maps: Brain regions showing a positive quadratic relationship between the BOLD response and increasing gain–loss ratios of the gambles in A) gamblers, B) controls, and C) contrasting the two groups. Maps are thresholded at $P < 0.001$ (uncorrected).

Table 2
Functional MRI results: quadratic increases in regional BOLD activity with increasing gamble ratios.

Cluster peak	Left/ Right	x	y	z	Z value	P-value	Cluster size (k)
Gamblers: Quadratic increase in regional activity with gamble ratios							
Dorsolateral prefrontal cortex	Right	34	24	50	5.45	<0.001	6941
Superior frontal gyrus*	Right	12	26	60	5.44		
Dorsolateral prefrontal cortex*	Left	−36	10	46	5.25		
Caudate	Left	−14	20	−2	5.01	< 0.001	776
Caudate*	Right	14	10	12	4.17		
Caudate*	Right	6	14	−2	4.13		
Parahippocampus	Right	22	−40	−4	4.90	< 0.001	448
Inferior temporal gyrus	Right	54	−6	−34	4.71	< 0.001	667
Middle temporal gyrus*	Right	60	−40	−8	4.41		
Middle temporal gyrus*	Right	66	−16	−20	4.28		
Angular gyrus	Right	50	−58	40	4.49	0.001	394
Inferior frontal gyrus/operculum	Left	−60	16	16	4.37	< 0.001	674
Superior temporal gyrus	Left	−40	−58	16	4.04	< 0.001	613
Angular gyrus*	Left	−42	−64	40	4.02		
Controls: Quadratic increase in regional activity with gamble ratios							
No significant activation							
Gamblers > controls: Larger quadratic increase in regional activity with gamble ratios in gamblers							
Caudate	Left	−14	20	−2	5.36	< 0.001	6781
Dorsolateral prefrontal cortex	Right	34	24	50	5.36		
Precentral gyrus/sub gyral*	Left	−32	−16	32	4.84		
Parahippocampus	Right	22	−40	−4	5.16	< 0.001	3463
Calcarine gyrus	Left	−26	−66	12	4.89		
Parahippocampus/sub gyral*	Left	−24	−50	0	4.78		
Cerebellum posterior lobe	Right	26	−68	−26	4.44	< 0.001	899
Cerebellum anterior lobe*	Right	12	−54	−32	4.18		
Inferior frontal gyrus/operculum	Left	−60	16	16	4.39	0.031	208
Insula	Left	−32	4	−14	4.03	0.002	370
Insula	Right	42	−2	−10	4.02	0.045	187
Controls > gamblers: Larger quadratic increase in regional activity with gamble ratios in controls							
No significant group differences							

$P < 0.05$, FWE corrected at cluster level.
* Local maxima within cluster with Z score > 4.

the dorso-lateral parts of middle and superior frontal gyri, and a focalized subcortical cluster covering head and body of both left and right caudate nuclei (Fig. 3A; full list of activations can be found in Table 2). In contrast, the activity profile in controls did not reflect any quadratic modulation of activity with increasing gain–loss ratio (Fig. 3B; Table 2).

When contrasting gamblers with controls, we found significantly stronger quadratic modulation of neural activity with gain–loss ratio in a large set of brain regions (Fig. 3C), including the large bilateral cortico-striatal cluster. Within this cluster, the left caudate nucleus showed the strongest group difference at the subcortical level and the right DLPFC displayed the strongest group effect at the cortical level. The full list of activation clusters is given in Table 2. Noteworthy, no clusters displayed stronger quadratic modulation of neural activity with gain–loss ratio in controls compared to gamblers.

It should also be noted that the quadratic BOLD increase to aversive and appetitive gambles survived in gamblers even when including BDI or the WAIS scores as covariates in the second-level t-tests (i.e. modeling out the effect of depression, vocabulary or general knowledge levels, which were differing between groups according to behavioral tests, see Table 1). Results, where the effect of depression has been modeled out of the quadratic increase in neural activity with increasing ratios, can be found in Supplementary Fig. 2.

To illustrate the underlying shape of the quadratic modulation of BOLD signal during decision-making, we assigned each of the 64 gain–loss ratios to one of 16 adjacent"bins" in a post hoc GLM. When plotting activation in each of these bins as a function of increasing gain–loss ratio, we found that the BOLD response profile in gamblers was U-shaped (Fig. 4B). In order to determine if a linear or a cubic model was more appropriate to describe the effect, we tested if the additional variance explained by including higher order polynomial terms (quadratic and cubic) were significant. In gamblers but not controls, a nested regression model verified that the quadratic fit was more appropriate to describe the nature of the curve, than a linear fit. Note that these

descriptive data should not be seen as separate results, but merely a complementary analysis to illustrate the underlying shape of the BOLD response profiles.

Impact of individual loss aversion

Across both groups, the individual degree of loss aversion, indexed by the individual decision-boundary lambda, enhanced the sensitivity to extreme gain–loss ratios of mixed gambles in a network of brain regions with peak activation in right amygdala ($P < 0.001$; x, y, z = 24, −4, −26; $Z = 5.01$; k = 1988). Apart from the main activation peak in the amygdala, regions included the DLPFC/SFG ($P < 0.001$; x, y, z = 32, 24, 56; $Z = 4.86$; k = 2372), left middle temporal/parahippocampal gyrus ($P < 0.001$; x, y, z = −44, −24, −24; $Z = 4.59$; k = 1435), precuneus ($P < 0.001$; x, y, z = −4, −62, 26; $Z = 4.40$; k = 1169), and vmPFC ($P = 0.009$; x, y, z = 8, 26, −18; $Z = 4.31$; k = 281).

In pathological gamblers, the individual degree of loss aversion was associated with an enhanced sensitivity to extreme gain–loss ratios in a dorsal frontal network with a regional peak in the DLPFC (Fig. 5A; see also Table 3 for full list of activations). This cortical network closely
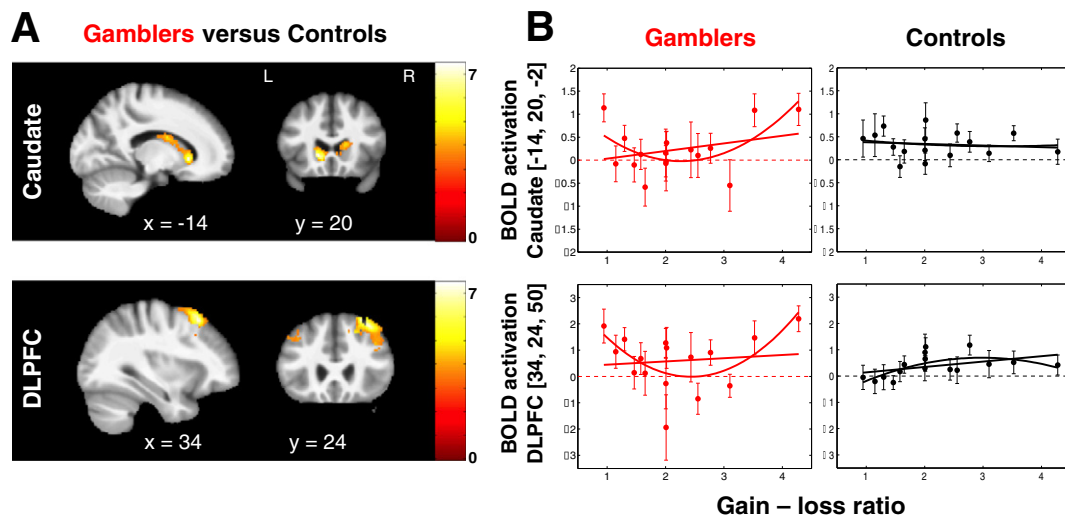
Fig. 4. U-shaped modulation of the BOLD response to increasing gain–loss ratios in pathological gamblers. A) Color-coded statistical parametric maps showing clusters with higher sensitivity to extreme positive and negative gain–loss ratios in gamblers compared with controls. Maps are thresholded at $P < 0.001$ uncorrected. To highlight the two principal regions differing between groups, anatomical masking of the caudate nuclei (top) and DLPFC (bottom) is used. B) These scatter plots are based on a "post hoc" GLM analysis created for illustrative purposes, where adjacent gain–loss ratios were clustered together into 16 ratio-"bins" (the range of ratios is displayed on the x-axis). The y-axis indicates regional neural activity (as estimated by the BOLD response in an 8-voxel sphere around peak activation) in the decision phase for gamblers (red) and controls (black). A nested regression model suggest that activation is better explained by a quadratic compared to a linear relationship with gain–loss ratio in the caudate nucleus ($P = 0.02$) and DLPFC ($P = 0.02$) in gamblers (left panel) but not in controls (right panel).

resembled the prefrontal areas showing a U-shaped activity increase with increasing gain–loss ratios in gamblers presented in Fig. 3.

In non-gambling controls, a more ventral and posterior network showed enhanced sensitivity to extreme gamble ratios as a function of loss aversion, with the right amygdala having the strongest effect size (Fig. 5A, middle right panel; Table 3). The direct comparison of the two groups yielded a significantly stronger effect of loss aversion on the activity profile in the DLPFC for gamblers compared to controls (Table 3), whereas the modulatory effect of loss aversion on amygdala activity was not significantly different between groups.

When plotting the relationship between BOLD parameter estimates and loss aversion, individual loss aversion in the healthy controls (but not gamblers) enhanced the U-shaped relationship between neural
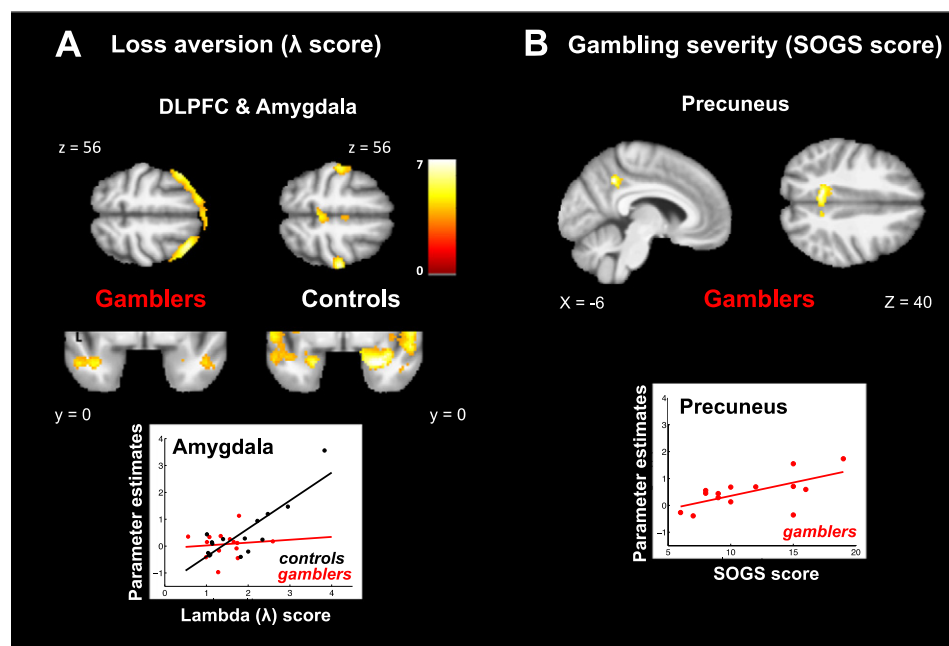
Fig. 5. Modulation of the U-shaped relationship between neural activity and gain–loss ratios by A) individual degree of loss aversion and B) severity of gambling. A) Color-coded statistical parametric maps illustrating how degree of individual loss aversion (reflected by high individual λ-values) enhanced the U-shaped relationship between neural activity and gamble ratios in pathological gamblers (left panels) or controls (right panels). The below graph illustrates the relation between the individual parameter estimate for the U-shaped relationship between neural activity and gain–loss ratios (y-axis) and individual loss aversion (x-axis) in the bilateral amygdala (controls: $P < 0.001$; $R^2 = 0.83$; gamblers: $P = 0.11$; $R^2 = 0.71$). B) Top: Color-coded statistical parametric map showing a bilateral cluster in precuneus, where the neural sensitivity to extreme gambles increased with gambling severity in pathological gamblers. Right: The scatter plot shows the linear relation ($P = 0.016$; $R^2 = 0.63$) between individual parameter estimates of the U-shaped relation between ratio and neural activity in the precuneus region (y-axis) and the individual gambling severity expressed by individual SOGS scores (x-axis). All BOLD activations are whole brain activations displayed at threshold $P < 0.001$ (uncorrected).

Table 3
Functional MRI results: effect of loss aversion on quadratic increase in regional BOLD activity with gamble ratios.

Cluster peak	Left/Right	x	y	z	Z value	P-value	Cluster size (k)
Gamblers: Enhanced quadratic increase in regional activity to gamble ratios with loss aversion							
Dorsolateral prefrontal cortex	Right	32	24	56	4.91	<0.001	2009
Dorsolateral prefrontal cortex*	Left	−42	16	54	4.81		
Dorsolateral prefrontal cortex*	Right	44	22	52	4.70		
Middle temporal gyrus	Right	66	−24	−16	4.51	<0.001	1007
Fusiform/parahippocampus*	Right	32	−8	−32	4.43		
Middle temporal gyrus*	Right	56	−44	−6	4.40		
Inferior temporal gyrus	Left	−44	−24	−24	4.43	<0.001	626
Temporal lobe/sub gyral*	Left	−36	0	−28	4.12		
Middle temporal gyrus*	Left	−60	−40	−14	4.06		
Precuneus	Left	−4	−62	26	4.06	0.007	293
Controls: Enhanced quadratic increase in regional activity to gamble ratios with loss aversion							
Amygdala	Right	28	0	−26	5.50	<0.001	4760
Middle temporal gyrus*	Right	60	−8	−12	5.14		
Parahippocampus*	Right	20	4	−26	4.98		
Postcentral gyrus	Right	54	−14	50	5.07	0.001	417
Precentral gyrus*	Right	40	−20	64	4.70		
Cuneus	Left	−2	−92	22	4.64	<0.001	1178
Middle occipital gyrus*	Left	−16	−94	14	4.42		
Cuneus*	Right	10	−80	30	4.21		
Lingual gyrus	Right	10	−70	−6	4.59	<0.001	551
Lingual gyrus*	Right	16	−64	−10	4.02		
Middle temporal gyrus	Left	−46	6	−24	4.59	<0.001	1967
Insula*	Left	−36	−14	−4	4.52		
Postcentral gyrus	Left	−46	−16	54	4.53	0.004	321
Precuneus/Mid Cingulum	Right	4	−32	52	4.17	<0.001	521
Precuneus/Mid Cingulum*	Left	−4	−42	50	4.11		
Gamblers > controls: Larger quadratic increase in activity to ratios with loss aversion in gamblers							
Dorsolateral prefrontal cortex	Left	−42	16	54	4.60	<0.001	761
Superior frontal gyrus*	Left	−14	20	66	4.21		
Superior frontal gyrus*	Left	−10	28	60	4.11		
Dorsolateral prefrontal cortex	Right	44	22	52	4.53	<0.001	457
Dorsolateral prefrontal cortex*	Right	34	22	56	4.49		
Middle temporal gyrus	Right	66	−24	−16	4.22	0.028	214
Controls > gamblers: Larger quadratic increase in activity to ratios with loss aversion in controls							
Cerebellum posterior lobe	Right	30	−58	−46	4.86	<0.001	629
Cerebellum posterior lobe*	Right	34	−44	−48	4.63		
Cerebellum posterior lobe*	Right	14	−66	−40	4.07		
Superior occipital gyrus	Right	34	−88	28	4.69	0.016	246
Middle occipital gyrus*	Right	36	−90	18	4.21		
Middle occipital gyrus*	Right	40	−92	4	4.03		
Anterior prefrontal	Left	−14	58	4	4.41	0.011	264
Precuneus	Left	−14	−52	−50	4.40	0.005	318
Cerebllum posterior lobe	Left	−14	−60	−48	4.15		
Inferior frontal gyrus/sub gyral	Left	−26	34	−4	4.36	0.038	196

$P < 0.05$, FWE corrected at cluster level.
* Local maxima within cluster with Z score > 4.

activity in the amygdala (Fig. 5A, bottom graph. Note that this effect was robust to the exclusion of the most loss averse control subject). With the exception of a few voxels in the right amygdala (see Fig. 5A, middle panel), loss aversion in pathological gamblers was not linked to altered amygdala response during decision-making.

Impact of severity of pathological gambling

We investigated whether gambling severity in gamblers as indexed by the individual SOGS scores modified the U-shaped response to extreme ratios during decision-making. A whole-brain search revealed a focal enhancement of the sensitivity to extreme ratios with gambling severity in bilateral precuneus ($P = 0.003$; x, y, z = −6, −48, 40; $Z = 4.59$; k = 335; Fig. 5B, top panel). Accordingly, the correlation between percent BOLD signal changes in a bilateral precuneus region (restricting activity to this region through anatomical masking) and gambling severity was highly significant (Fig. 5B, bottom graph).

Brain responses to single potential gains and losses

Since the win and loss amount of a mixed gamble was presented sequentially in each trial, we were able to capture regional changes in the BOLD signal corresponding to single potential gains and losses (but see also discussion of the jittering used in the Discussion section). During this passive evaluation phase, we searched for between-group differences in BOLD response to gains, losses, increasing gains, and increasing losses. There were no significant group differences for these contrasts, but we found a bilateral trend toward a higher BOLD response to potential gains in gamblers compared to controls in the amygdala (L: $P < 0.001$, uncorrected; x, y, z = −26, 2, −22; $Z = 3.19$, k = 6; R: $P < 0.001$, uncorrected; x, y, z = 24, −2, −10; $Z = 3.43$; k = 7).

Discussion

Contrasting healthy and pathological decision-making with a mixed gamble task, we measured task-related neural activity during gambling decisions, which required participants to trade off a possible gain

against a possible loss. In gamblers, a dorsal cortico-striatal network displayed a higher neural sensitivity to the most appetitive and aversive gain–loss ratios compared to healthy matched controls. The stronger tuning of dorsal cortico-striatal areas to extreme gain–loss ratios indicates that gamblers put more weight on the extremes of the decision frame offered by the gambling task. Importantly, this U-shaped neural response to gambling ratios was not observed in controls, suggesting that this specific hypersensitivity to extreme ratios constitutes a neural signature of pathological gambling.

Interestingly, the U-shaped tuning of neural activity to the most aversive and most appetitive gambles was not expressed in core regions of the reward network, such as ventral striatum or orbitofrontal cortex. Instead, it was expressed bilaterally in a dorsal cortico-striatal "associative" or "executive" network, including the caudate nucleus and the DLPFC. The recruited DLPFC included the dorsal and mesial superior and middle frontal gyri, corresponding to BA 6/8/9 and "9/46d" (Badre and D'Esposito 2009, Goldstein and Volkow 2011). This dorsal cortico-striatal network is known to be involved in monitoring recent actions and anticipating their outcomes (for review see Yin and Knowlton 2006). In particular, the human caudate nucleus has been implicated in the reinforcement of action–outcome contingencies (Knutson et al. 2001; O'Doherty et al. 2004; Tricomi et al. 2004; Delgado et al. 2005).

Our present results suggest that this dorsal cortico-striatal network plays an important role in gambling decisions made by gamblers. Extreme gain–loss ratios are characterized as being highly relevant in terms of possible action–outcomes: the more appetitive a bet is, the more important it is to accept it; conversely, the more aversive a bet is, the more important it is to reject it. In healthy subjects, the dorsal striatum has been found to track stimulus salience or arousal, rather than linearly increasing subjective value (Barta et al. 2013). We infer that in pathological gamblers, this dorsal cortico-striatal network is hypersensitive and weights these extreme gain–loss ratios more strongly than in healthy subjects, when making gambling decisions.

Current theories of the neurobiological bases of pathological gambling are compelling in their simplicity, by predicting either a hypo- or hypersensitivity of the ventral striatum and other ventral core regions of the reward system such as the vmPFC. Accordingly, previous neuro-imaging studies in gamblers showed either diminished (Balodis et al. 2012) or enhanced (van Holst et al. 2012; Worhunsky et al. 2014) activation of ventral striatum during the anticipation of monetary reward. In the present study, no differences in neural activity between patholog-ical gamblers and non-gambling controls emerged in the ventral reward system when they evaluated single loss or gain amounts during the magnitude presentation phase or when they balanced possible gains and losses of the mixed gambles in the decision phase. Only the right and left amygdala showed a trend toward a stronger neural response to possible gains during the former phase. In other words, the decision to accept or reject a gamble was not consistently associated with a hyper- or hyposensitivity of the reward system. This negative finding is in agreement with a recent study where gamblers showed a normal reactivity of the ventral striatum to monetary reward cues but a blunted sensitivity to cues predicting erotic stimuli (Sescousse et al. 2013). The lack of a consistent pattern within this literature, with basically either opposite results or no striatal effect at all, indicate that explaining path-ological gambling by striatal up- or down-regulation might not be ade-quate. It has been suggested that the decision-making deficits seen in pathological gambling could emerge from an imbalance between dopa-minergic systems involving limbic motivational structures and prefron-tal control regions, rather than a disruption in either component in isolation (Clark et al. 2013). One good candidate of such cortico-striatal networks is the dorsal cortico-striatal loop, which has been implicated in action selection and processing action outcome contin-gencies (Yin and Knowlton 2006; Seo et al. 2012). Note that in the pres-ent study decisions are made based on internal representations of the balance between gains and losses rather than on outcome-based adap-tive processes, or strictly anticipatory processes. This is perhaps the

reason why we find areas that are more related to the choice of the ac-tion (i.e. accepting or rejecting a bet), rather than areas traditionally coding for anticipating or receiving outcomes.

Here, in non-gambling controls, loss averse behavior during the gambling task was associated with a stronger sensitivity to extreme gain–loss ratios in the amygdala. These results correspond well with our recent findings in a separate group of healthy individuals (Gelskov et al. 2015), where more loss averse participants showed an increased neural sensitivity in the amygdala to extreme gain–loss ratios of mixed gambles. These results persisted despite subtle differences be-tween studies. The actual game participants played in the scanner remained the same (i.e. distribution of monetary amounts, duration, and jittering of visual stimuli, etc.). However, the endowment proce-dure differed slightly. In the current study, participants received actual money bills (200 DKK) that they kept for 1–2 weeks before entering them as a stake in the gamble, while in the previous study, participants were led to believe they could lose money from their initial endowment. This difference in endowment strategy could perhaps explain why the healthy control subjects in the present study were a bit less loss averse (median lambda of 1.82) compared to our previous study (median lambda of 2.08). Although the statistical difference between the two healthy groups was not significant ($P = 0.18$, permutation test), the dif-ference in lambda between the previous healthy group and the current group of gamblers was significant ($P = 0.004$, permutation test). Anoth-er obvious difference between the studies is the age difference, as the present control group was older in order to match the gamblers ($P = 0.0175$, $t(29) = 2.52$; 2-sample t-test). However, if anything, this differ-ence should predict the opposite effect on lambda, since older healthy subjects tend to be more loss averse than younger. Furthermore, the two studies differed slightly in the way gamble ratios were modeled. In our previous study, we found that the amygdala was sensitive to var-iations in gain–loss ratios in relation to a subject-specific "decision-boundary" (i.e. the individual lambda score, λ). This model can be con-ceptualized as "V"-shaped BOLD response to increasing ratio, where the "low point" of the V was the individual λ-score. Two linear parametric regressors then classified each trial ratio as being more or less appetitive or aversive, according to how they differed from the individual λ (i.e., aversive ratios < individual λ < appetitive ratios). However, in the present study, we could not base our model on λ-scores, since a few par-ticipants simply had a too high or too low acceptance rates. Thus, we used the non-adjusted gain–loss ratio to evaluate the neural response to the full continuous spectrum of ratios (i.e. a "U"-shaped BOLD re-sponse to ratio). Note that the use of this slightly different quadratic model could be the reason that we do not replicate the amygdala activ-ity for increasingly appetitive and aversive gambles in healthy subjects. It might be the case that the amygdala is specifically tuned to the decision-boundary, λ, and the amygdala activation in our previous study could be related to the inclusion of the λ-score in the main regres-sors. This interpretation is in accordance with the fact that both analyt-ical methods showed that loss averse gambling behavior is associated with a higher sensitivity of the amygdala to highly aversive and highly appetitive potential outcomes during decision-making. Taken together, these findings points to a crucial role of the amygdala in biasing loss aversive decisions in healthy individuals.

In gamblers, the relation between loss averse behavior and neural activity to gamble ratios revealed only a non-significant trend in the amygdala. Instead, decision-related activity in the DLPFC changed as a function of loss aversion. This effect was significantly stronger for gam-blers compared to controls. Interestingly, this effect peaked at the same location in DLPFC where we found the stronger hypersensitivity to ex-treme ratios relative to controls. This indicates that in gamblers, the in-dividual degree of loss aversion is not reflected by areas predicting the emotional saliency or value of a stimulus such as the amygdala and the ventral striatum, but instead by the activity profile in the DLPFC. In this population, it thus seems that a cortical area sub-serving executive control functions such as working memory, task switching, and

representing action–outcome contingencies (Elliott 2003; Monsell 2003; Seo et al. 2012) is supplementing the amygdala in biasing loss averse gambling behavior. However, this proposal needs to be further investigated in future gambling studies.

Interestingly, we found a tendency toward less loss aversion in gamblers. According to traditional economic theories, this behavioral trend toward less irrational decisions has the counter-intuitive implication that gamblers acted more rational than controls. However, a more evolutionary account of loss aversion would state that decision-biases served the purpose of guiding instinctive decisions for instance when foraging for food. Indeed, loss aversion has been reported in lower primates such as capuchin monkeys (Chen et al. 2006; but see also Silberberg et al. 2008) indicating that loss aversion is a deeply rooted decision-making guideline that might even be an innate bias toward conservatism. A recent study by Giorgetta et al. (2014) found that pathological gamblers who were in later stages of clinical treatment were more loss averse than gamblers who were in earlier stages of treatment. Interestingly, they found that gamblers as a group (across treatment status) were more loss averse than healthy controls. In contrast, a previous study investigating behavioral loss aversion in gamblers found that active gamblers (i.e. not in treatment) were less loss averse than healthy controls (Brevers et al. 2012). This raises the question whether effective treatment can render pathological gamblers loss averse. In the present study, gamblers were recruited from a treatment center, and most had participated in cognitive therapy. Perhaps, this is the reason why we did not find a significant behavioral difference between gamblers and healthy controls but only a trend in this direction.

Finally, we found that gamblers with more severe gambling symptoms, as measured by the SOGS score, had an increased engagement of the precuneus when evaluating high and low gamble ratios. Precuneus and posterior cingulate cortex are often found in response to self-referencing tasks (see review by Cavanna and Trimble 2006), and a recent study investigating self-control in gamblers showed aberrant electrophysiological signals over the posterior cingulate cortex using MEG (Thomsen et al. 2013). These aberrant signals have been linked to the well-established fact that pathological gamblers suffer from increased impulsivity and lower self-control. In our study, the modulation of precuneus activity as a function of gambling severity might reflect similar, aberrant mechanisms of self-control. Yet, these speculations regarding the functional involvement of precuneus in pathological gambling need to be formally addressed in future studies.

Our results revealed an altered, U-shaped pattern of activity for both caudate nucleus and DLPFC when pathological gamblers evaluated monetary bets. Although this activation pattern might stem from co-occurring, but unrelated, dysfunctions of these brain regions, it might also originate from alterations in their functional connections. Previous studies in healthy subjects have provided ample evidence for the connectivity between caudate and PFC, by relying both on functional (e.g. Robinson et al. 2012) and structural (e.g. Verstynen et al. 2012) cortico-striatal connectivity. It is thus possible that the pathology of gambling reflects altered neural connectivity patterns in this specific cortico-striatal decision-making circuit.

Like in many previous gambling studies, we included only male subjects (e.g. van Holst et al. 2012; de Ruiter et al. 2009; Linnet et al. 2011; Sescousse et al. 2013). However, although epidemiological studies suggest that men represent the large majority of pathological gamblers (Kessler et al. 2008), pathological gambling also affects women. Because studies have shown differences between women and men in terms of gambling preferences (e.g., more solitary gambling forms such as slot machine vs. more socially engaging forms such as poker) and motivational backgrounds (e.g., escaping negative emotions vs. sensation-seeking behaviors; see review by Raylu and Oei 2002), the present results cannot be generalized to the female population. Therefore, it remains to be clarified whether female gamblers would show the same aberrant neural signatures of decision-making as the male gamblers in this study.

A point of improvement for future studies is the amount of gambling subjects included in this study (n = 14). Although the group size was comparable to previous fMRI studies (Crockford et al. 2005; Reuter et al. 2005; Thomsen et al. 2013; Balodis et al. 2012) and patients were well characterized, it would have been desirable to study a larger group. Further limitations include the method of jittering between events of interest. Since a fast and seamless gamble was prioritized, we chose to jitter the events themselves, and not introduce a jittered inter-trial interval (ITI) between them, although there was an ITI of 1.2 s between each decision-making phase and the magnitude presentation the lack of jittering here could in principle contribute to the fact that we did not find differences between groups in the magnitude presentation phase.

In sum, we show that a dorsal cortico-striatal network involved in action–outcome contingencies expresses a hypersensitivity to extreme gain–loss ratios in gamblers. The U-shaped response profile in DLPFC and precuneus was related to the individual degree of loss aversion during gambling task and severity of pathological gambling, respectively. These results stimulate future research to extend the focus of neuroimaging from the core reward system to dorsal cortico-striatal networks in pathological gambling.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2016.01.002.

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