Decreased Neuronal Activity in Reward Circuitry of Pathological Gamblers During Processing of Personal Relevant Stimuli

Moritz de Greck,[1]* **Björn Enzi,**[1] **Ulrike Prösch,**[2] **Ana Gantman,**[1]
Claus Tempelmann,[3] **and Georg Northoff**[1]

[1]*Department of Psychiatry at Otto-von-Guericke University Magdeburg, Leipziger Straße 44, 39120 Magdeburg, Germany*
[2]*AHG Clinic for Psychosomatic Medicine and Addictive Disorders, Schweriner See/Lübstorf, Am See 4, 19069 Lübstorf, Germany*
[3]*Department of Neurology at Otto-von-Guericke University Magdeburg, Leipziger Straße 44, 39120 Magdeburg, Germany*

◆ ━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━ ◆

Abstract: Pathological gamblers impress by an increasing preoccupation with gambling, which leads to the neglect of stimuli, interests, and behaviors that were once of high personal relevance. Neurobiologically dysfunctions in reward circuitry underlay pathological gambling. To explore the association of both findings, we investigated 16 unmedicated pathological gamblers using an fMRI paradigm that included two different tasks: the evaluation of personal relevance and a reward task that served as a functional localizer. Pathological gamblers revealed diminished deactivation during monetary loss events in some of our core reward regions, the left nucleus accumbens and the left putamen. Moreover, while pathological gamblers viewed stimuli of high personal relevance, we found decreased neuronal activity in all of our core reward regions, including the bilateral nucleus accumbens and the left ventral putamen cortex as compared to healthy controls. We demonstrated for the first time altered neuronal activity in reward circuitry during personal relevance in pathological gamblers. Our findings may provide new insights into the neurobiological basis of pathological gamblers' preoccupation by gambling. *Hum Brain Mapp 31:1802–1812, 2010.*   © 2010 Wiley-Liss, Inc.

Key words: pathological gambling; reward system; personal relevance; brain imaging; fMRI

◆ ━━━━━━━━━━━━━━━━━━━━━━━━━━━━━━ ◆

INTRODUCTION

"You've become insensible," he remarked. "You have not only renounced life, your own interests and those of your society, your duty as a man and a citizen, your friends (and you did have them all the same)—you've not only renounced every aim whatever in life, except winning at roulette—you have even renounced your memories."

Dostoyevsky, The Gambler, 1867

The Russian novelist Dostoyevsky describes two of the core symptoms of pathological gambling, which present-day psychiatrists would characterize as craving for gambling and increasing neglect of formerly self-relevant interests. Current diagnostic manuals [DSM-IV, American Psychiatric Association, 1994; ICD-10, World Health Organization, 1992] classify pathological gambling as an impulse-control disorder. However, resemblances to addictive disorders, such as alcoholism and cocaine addiction, allow a new perspective to be taken. Pathological gambling may be viewed as a nonsubstance related addictive disorder [Reuter et al., 2005].

The classification of pathological gambling as a nonsubstance-related addictive disorder suggests abnormalities in reward circuitry such as those in substance addiction. Such abnormalities have been found in the nucleus accumbens (NACC)/ventral striatum (VS), putamen, ventromedial prefrontal cortex (VMPFC), orbitofrontal cortex (OFC), ventral tegmental area (VTA) [for an overview see Knutson and Gibbs, 2007; McClure et al., 2004; O'Doherty, 2004; for the association of addictive disorders and reward circuitry see Martin-Soelch et al., 2001; Volkow et al., 2004, 2007a]. Reuter et al. [2005] investigated the neuronal activity of pathological gamblers using a card-guessing task and fMRI. During the receipt of monetary reward, they found altered neuronal activity in the reward circuitry of pathological gamblers including the right VS and VMPF when compared to healthy control subjects. Moreover, the authors found a diminished difference in neuronal activity between monetary gains and losses in these subjects. Potenza et al. [2003], who investigated pathological gamblers performing a Stroop task, also found reduced VMPFC activity. However in a different study, the same region showed increased activity in pathological gamblers during a black jack task with monetary reward when compared to the same task without it [Hollander et al., 2005]. During the presentation of gambling scenes, decreased activity of other regions such as the OFC, the thalamus, and the basal ganglia, was also observed [Potenza et al., 2003].

These results may be supplemented with findings from substance-related addictive diseases such as alcoholism and cocaine addiction. Much like pathological gamblers, alcoholic patients showed decreased neuronal activity in VS during monetary gains [Wrase et al. 2007] and reduced striatal dopamine activity during the intake of methylphenidate as measured with PET using [11C]-raclopride [Volkow et al., 2007b]. Cocaine addicted patients showed decreased neuronal activity during monetary rewards in OFC, lateral prefrontal cortex, and mesencephalon among others [Goldstein et al., 2007]. Finally, Tanabe et al. [2007] demonstrated altered neuronal activity during decision-making in the ventromedial prefrontal cortex and other regions, showing the similarity of pathological gambling to other addictive disorders.

Taken together, these findings demonstrate the crucial importance of reward circuitry in pathological gambling as well as its resemblance to other addictive disorders. According to Reuter et al. [2005], such reduced responsiveness to reward may symptomatically lead to the chronic impression of discontentment. This in turn may increase the risk to seek satisfaction by stronger reinforcers such as gambling, cocaine, or other drugs of abuse to obtain sufficient activation level in reward regions.

Another striking symptom of pathological gambling is a pronounced shift in personal relevance. Patients are increasingly preoccupied by gambling and so begin to neglect other formerly self-relevant stimuli and behaviors. Psychologically, the evaluation of personal relevance or self-relatedness, as previous studies have called it [de Greck et al., 2008, 2009; Kelley et al., 2002; Northoff and Bermpohl, 2004; Northoff et al., 2006; Phan et al., 2004], describes how important and how close to themselves subjects experience specific stimuli. Neurobiologically, tasks that engage the notion of self-relatedness, and hence personal relevance have implicated regions from reward circuitry such as the NACC, VTA, and the VMPFC [de Greck et al., 2008; Northoff et al., 2006; Northoff et al., 2007; Phan et al., 2004].

The recruitment of reward circuitry by stimuli of high personal relevance raises the question of the exact relationship between processing of reward and processing of personal relevance stimuli. In a preliminary study by our group, tasks of high personal relevance induced neuronal activity in exactly the regions implicated in reward function in healthy subjects [de Greck et al., 2008]. Recently, our group also found that alcoholic patients showed decreased neuronal activity in reward circuitry (i.e., left and right NACC/VS, VTA, VMPFC) during the evaluation of stimuli with a high personal relevance as compared to healthy controls [de Greck et al., 2009] showing that the apparent changes in behavior stem from a lack of activation in reward circuitry during the evaluation of stimuli of high personal relevance.

The general aim of our study was to explore the neural basis of the abnormal shift of perceived personal relevance in reward circuitry in unmedicated pathological gamblers. Specifically, we employed a paradigm to investigate the neuronal activity in reward circuitry of pathological gamblers during both a reward task consisting of monetary wins and losses, and during a task requiring the evaluation of self-relatedness, in which subjects rated different pictures containing gambling scenes, food or alcohol, as of high or low personal relevance.

Our hypothesis were twofold. First, we expected to replicate the findings of Reuter et al. [2005] by demonstrating

that pathological gamblers exhibit decreased neuronal activity in reward regions during the reward task. Moreover, we expected to extend these findings by differentiating between gains and losses. We predict less activation during monetary gains and less deactivation during monetary losses. Second, based on the clinical symptoms and our own findings in alcoholism [de Greck et al., 2009], we hypothesized disturbed activity in reward circuitry during the evaluation specifically of high personal relevance in pathological gamblers when compared to healthy controls.

MATERIALS AND METHODS

Subjects

We studied 16 pathological gamblers and 12 closely matched healthy controls using functional magnetic resonance imaging (fMRI). The study was approved by the local ethics committee and all participants gave written informed consent before participating in this study. All patients (excluding $n = 4$; see Supporting Information 1 for details concerning the subjects and for clinical characteristics) were scanned in an acute state, before starting a standardized inpatient behavioral psychotherapy.

Paradigm

We applied a paradigm [de Greck et al., 2008, 2009] that included three well-established tasks: each task included the presentation of three different types of stimuli (gambling, alcohol, and food stimuli; see Fig. 1 and Supporting Information 2 for details of the paradigm). The reward task a slightly modified adaptation of Reuter et al.s' [2005], contained a decision phase, where subjects attempted to win money by indicating either the left or the right site of the screen with either a left or right button, and were subsequently informed whether they had won or lost. In the personal relevance task, subjects evaluated presented stimuli with regard to their personal relevance as either high or low, indicated with a button press. The control task included the cognitive evaluation of the presented stimuli, asking whether they were horizontally or vertically aligned. Each task included the presentation of different types of stimuli, namely gambling, alcohol, and food stimuli (see Fig. 1 and Supporting Information 2 for details of the paradigm).

The stimuli were chosen to maximize our ability to investigate the specific relationship between reward and personal relevance. On the basis of previous imaging experiments we selected stimuli that show a strong reward value such as a natural reinforcers i.e., food [Killgore et al., 2003; Wang et al., 2004]. Clinical experience with gambling patients led us to implement pictures containing gambling stimuli that have been shown to illicit reports of strong personal relevance. These included photographs of common gambling situations such as roulette and slot machines [Crockford et al., 2005; Potenza et al., 2003]. We included alcohol-related stimuli to investigate why these patients developed pathological gambling, a nonsubstance-related addictive disorder, and not a substance-related disorder such as alcohol addiction.

Behavioral Tests

To control for differences in intelligence, affective state and personality traits between our two sample groups, we applied a number of behavioral tests, including the Beck-Depression-Inventory [BDI, Beck et al., 1961], the Schwerin Gambling Questionnaire [SGQ, Premper et al., 2007] and the Temperament and Character-Inventory [TCI, Cloninger et al., 1994] (see Supporting Information 1 for further details).

fMRI Data Acquisition and Analysis

Functional measurements were performed on a 3-Tesla whole body MRI system (Siemens Trio, Erlangen, Germany) with echo planar imaging (EPI) using an eight channel head coil. 32 T2*-weighted echo planar images per volume with blood oxygenation level-dependent (BOLD) contrast were obtained (matrix: 64×64; 32 slices per volume; FoV: 224×224 mm^2; spatial resolution: $3.5 \times 3.5 \times 4$ mm^3; TE = 30 ms; TR = 2,000 ms; flip angle = 80°). The slices were acquired parallel to AC-PC plane in an odd–even interleaved acquisition order. Functional data were recorded in eight scanning sessions containing 210 volumes per session for each subject. The first four volumes were discarded. The fMRI data were preprocessed and statistically analyzed by the general linear model approach [Friston et al., 1995] using the SPM2 software package (SPM2, http://www.fil.ion.ucl.ac.uk) and MATLAB 6.5 (The Mathworks, Natick, MA). All functional images were slice time corrected with reference to the first slice acquired, corrected for motion artifacts by realignment to the last volume, and spatially normalized to a standard T1-weighted SPM template [Ashburner and Friston, 1999]. The normalization was generated by warping the subject's last functional image to the SPM template and applying these parameters to the other functional images. The images were resampled to $2 \times 2 \times 2$ mm^3 and smoothed with an isotropic 6-mm full-width half-maximum Gaussian kernel.

The time-series fMRI data were filtered using a high pass filter and cut-off of 128 s. A statistical model for each subject was computed by applying a canonical response function [Friston et al., 1998]. All relevant periods (i.e., the decision phase, the feedback phase, and the baseline phase) were included in the SPM model. Regionally specific condition effects were tested by employing linear contrasts for each subject and different conditions. The resulting contrast images were submitted to a second level random-effects analysis. Here, one-sample t-tests were

Study design

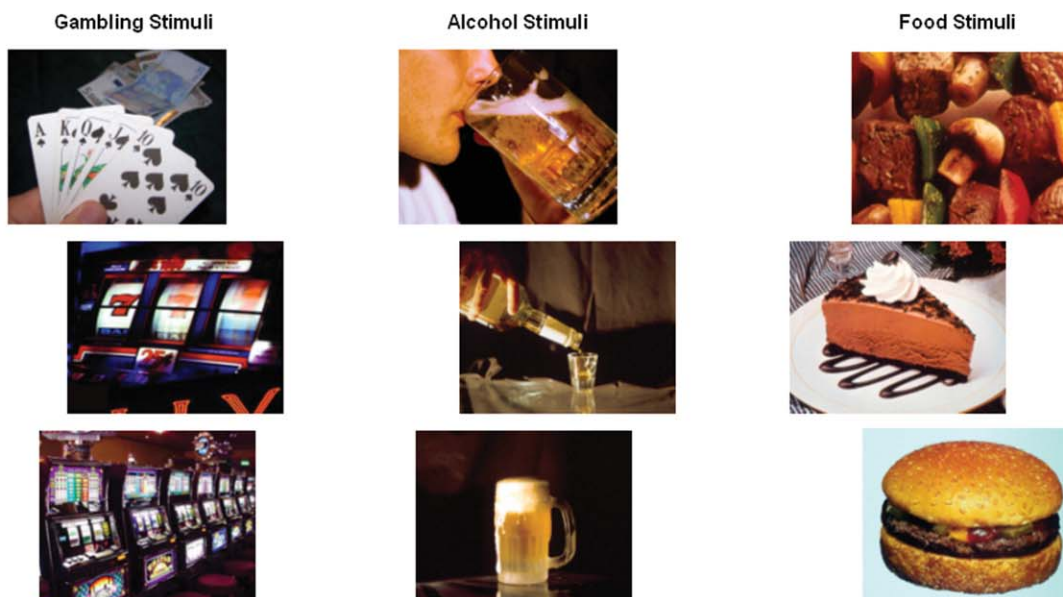### a. Trial design
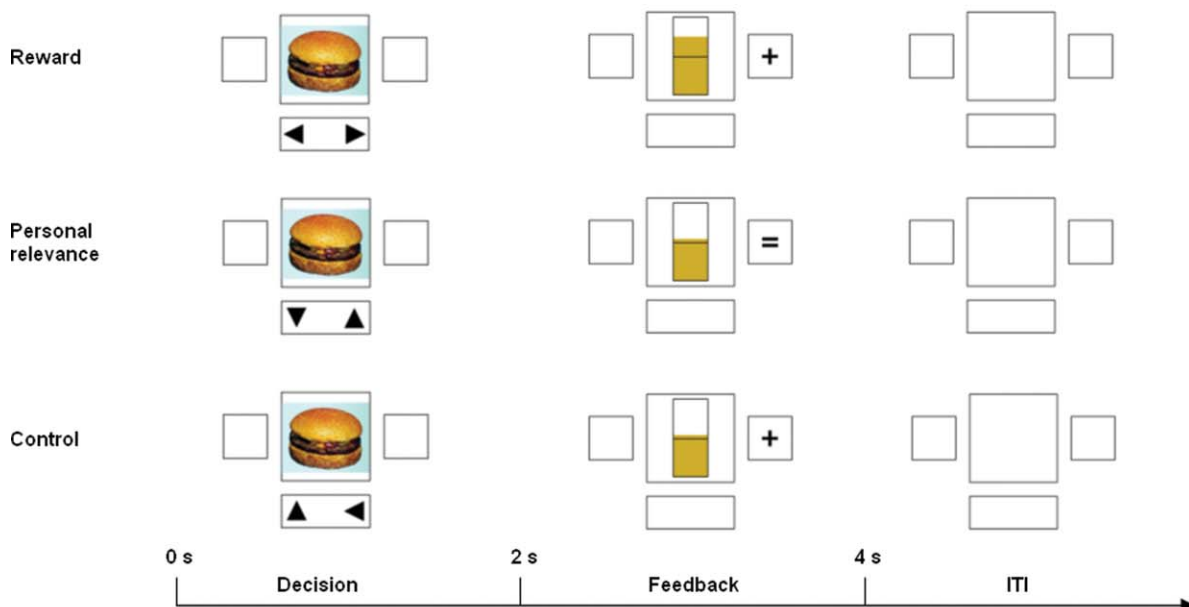
b. Stimulus types

Figure 1.

(**a**) The paradigm included three tasks. The reward task was a slightly modified adaptation of the task introduced by Reuter et al. [2005], which contained a decision phase, where subjects attempted to win money by indicating either the left or the right site of the screen with either a left or right button. In the following feedback period they were informed whether they had won or lost. The personal relevance task consisted of the evaluation of presented stimuli with regard to their personal relevance as one of two options: high or low, which could be indicated with a button press. The control task included the cognitive evaluation of the presented stimuli, asking whether they were horizontally or vertically aligned. (**b**) Each task included the presentation of three different types of stimuli (gambling, alcohol, and food stimuli). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
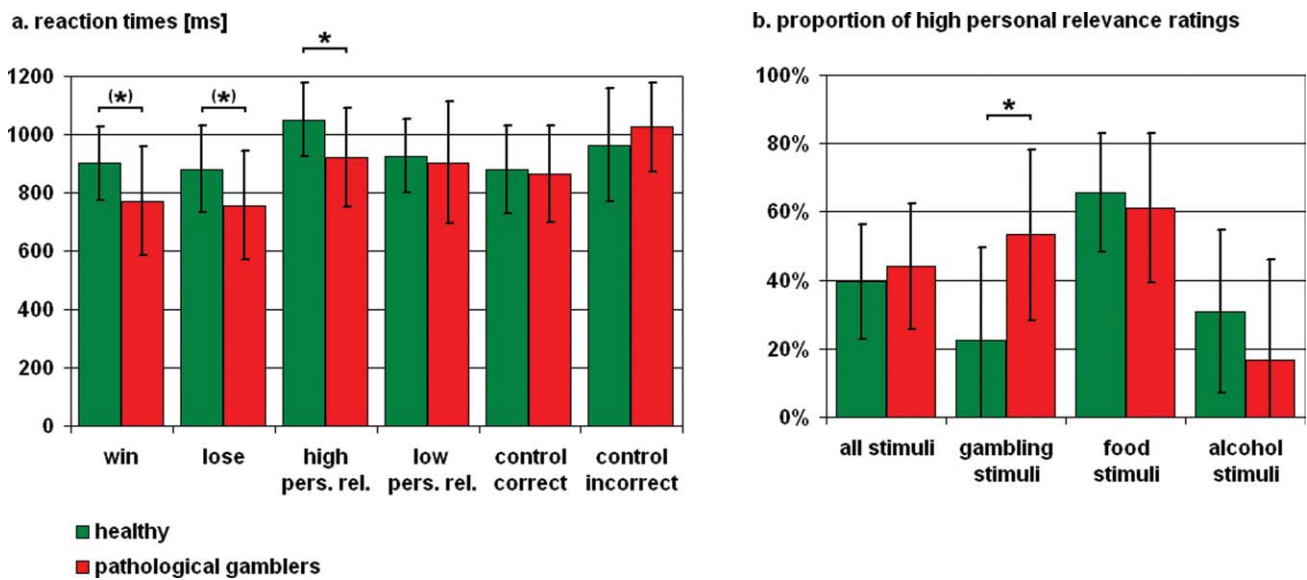
Figure 2.

Behavioral results. (**a**) Reaction times in ms. Pathological gamblers responded faster in five of our six conditions, reaching statistical significance for trials with high personal relevance (difference: 130,2 ms; $t(22) = 2.136$; $p = 0.044$) and a statistical trend for win and lose trials (win: difference: 128,8 ms; $t(22) = 1.971$; $p = 0.061$; lose: difference 124,9 ms; $t(22) = 1.808$;

$p = 0.084$). (**b**) Proportion of high personal relevance ratings. Pathological gamblers rated more gambling stimuli as high personally relvant compared to healthy (difference: −30.66%; $t(22) = -2.882$; $p = 0.009$). All other comparisons failed statistical significance. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

used on images obtained for each subject's volume set and different conditions. To control for the multiple testing problem we performed a false discovery rate correction [Nichols and Hayasaka, 2003]. The anatomical localization of significant activations was assessed with reference to the standard stereotactic atlas by superimposition of the SPM maps on a standard brain template provided by SPM2.

In a second step we analyzed the fMRI raw data using the Marseille Region of Interest Toolbox software package [Brett et al., 2002; MarsBaR 1.86, http://www.sourceforge.net/projects/marsbar]. Using a sphere-shaped "region of interest" (ROI, radius 5 mm) we extracted the raw data from activations found in the second level analysis. Mean normalized fMRI signal values from two following time steps (6 and 8 s after feedback onset) of the BOLD were included in the statistical analysis using repeated measurements analysis of variance (ANOVA) and paired-samples t-tests as well as independent-samples t-tests for group comparisons [Dreher et al., 2006; Yarkoni et al., 2005]. Since the ratio of high and low personal relevance trials could not be predefined as the ratio of win and loss trials we performed Levene's tests to check for possible inhomogeneity of variances.

Following the functional localizer approach [Lamm and Decety, 2008; Saxe et al., 2006] we first determined reward circuitry using the SPM contrast [win] > [lose]. In accordance with Goldstein et al. [2007] we calculated this contrast for a combined group of healthy subjects and

pathological gamblers, we did this to ensure that neither the group of healthy subjects nor the group of pathological gamblers should be favored and therefore have a dominant influence on the determination of the ROIs. Next we investigated signal changes in the same regions during win and loss as well as during high and low self-relatedness, comparing signal intensities between pathological gamblers and healthy subjects.

To further confirm our results we also calculated the SPM contrasts [win] > [lose] for both groups separately. Using the same regions of interest, but slightly different coordinates for both groups, we analogously performed an analysis of fMRI signal changes for win and lose and high and low personal relevance.

RESULTS

Behavioral Results

Behaviorally, pathological gamblers showed faster reaction times during the evaluation of high (but not low) personal relevance when compared to healthy subjects. The pathological gamblers were also faster during both win and lose events, but these comparisons failed statistical significance and reached only a statistical trend (see Fig. 2a and Supporting Information 3.1 for details of the statistics).

The analysis of personal relevance ratings among the three categories of stimuli (gambling, food, and alcohol) revealed that pathological gamblers evaluated significantly

more gambling stimuli as of high personal relevance when compared to healthy subjects. Food- and alcohol-related stimuli showed no such effect (see Fig. 2b and Supporting Information 3.2.2 for details).

While still lying in the scanner, our subjects were also instructed to rate their experience of craving for gambling, craving for alcohol, general contentment, and hungriness at the end of each run using a visual analogue scale. Pathological gamblers showed significantly greater scores in subjective craving for gambling when compared to healthy subjects. No other significant differences were observed (see Supporting Information 3.3 for details).

Pathological gamblers, when compared to healthy subjects using the Temperament and Character Inventory by Cloninger [TCI, Cloninger et al., 1994] showed significantly decreased scores for reward dependence and increased scores for novelty seeking as well as decreased scores for self-directedness (the latter two being only marginally significant). Using the Beck-Depression-Inventory [BDI, Beck et al., 1961], our group of pathological gamblers showed significantly higher depression scores when compared to healthy subjects.

fMRI Results

Determination of functional localizers for reward circuitry

We identified reward regions of our whole sample group at one time. Following the approach of Goldstein et al. [2007], we performed a one sample t-test on the SPM contrast [win] > [lose]. In accordance with the results of previous reward studies [de Greck et al., 2008, 2009; Knutson and Gibbs, 2007; Knutson et al., 2001a,b, 2003; McClure et al., 2004; O'Doherty, 2004; Potenza et al., 2003; Reuter et al., 2005], we observed neuronal activity in the left and right NACC, and the left putamen (coordinates with reference to the MNI stereotactic space: left NACC: −12, 10, 4; right NACC: 14, 12, 2; left putamen: −18, 6, −4; see images on the left in Fig. 3) as well as in other regions including the nucleus caudatus (see Table I). Further analysis focused exclusively on the left and right NACC and the left putamen, as these regions have proven to be crucially involved in the reward system in both healthy subjects and gambling patients (see Introduction and Discussion for details).

Alterations in reward circuitry during monetary gains and losses in pathological gamblers

Concentrating on the reward task, we found statistically significant alterations in regions primarily concerning deactivation during lose trials. In the left NACC and in the left putamen, we found less deactivation during lose in pathological gamblers as compared to healthy controls (see Supporting Information 4.1 for statistical details).

Alterations in reward circuitry during evaluation of high and low personal relevance in pathological gamblers

Relying on the functional localizer approach [Saxe et al., 2006], we investigated signal intensities during trials of

Figure 3.

Activations and fMRI signal changes in reward regions during reward and personal relevance. The second level group statistic for the contrast [win] > [lose] revealed activations in the left and right nucleus accumbens (NACC) and the left ventral putamen. The images on the far left show the t-contrast calculated with SPM2. The three diagrams in each line show the mean normalized fMRI signal changes (y-axis) for the conditions win and lose as well as high and low personal relevance (error bar: standard deviation) with $t = 0$ for the start of the feedback phase in healthy and pathological gamblers. The box diagrams on the right display the mean normalized fMRI values (y-axis) for the time points 6–8 s. The mean normalized fMRI signals between our groups have been statistically analyzed using independent-samples t-tests. (a) Left NACC (−12, 10, 4; $Z = 4.74$; P(FDR) = 0.001). We found a higher mean fMRI signal for win events compared to lose events in healthy subjects and pathological gamblers. In addition, we observed a significant stronger deactivation in healthy compared to pathological gamblers during lose events (difference: −0.06%; $t(22) = −2.278$; $P = 0.017*$). A neuronal differentiation between high and low personal relevance events was only observed in healthy subjects (difference: 0.12%; $t(11) = 2.627$; $P = 0.028*$), but not in pathological gamblers (difference: 0.02%; $t(11) = 0.774$; $P = 0.278$). Additionally pathological gamblers showed decreased signal intensities during events of high personal relevance (difference: 0.06%; $t(22) = 2.286$; $P = 0.016*$). (b) Right NACC (14, 12, 2; $Z = 5.64$; P(FDR) < 0.001). We found a higher mean fMRI signal for win events compared to lose events in healthy and pathological gamblers. A neuronal differentiation between high and low personal relevance events was observed only in healthy subjects (difference: 0.16%; $t(11) = 3.200$; $P = 0.004**$) and not in pathological gamblers (difference: 0.01%; $t(11) = 0.369$; $P = 0.360$). In addition, pathological gamblers showed decreased neuronal activity during events of high personal relevance (difference: 0.13%; $t(22) = 3.991$; $P < 0.001**$). (c) Left ventral putamen (−18, 6, −4; $Z = 4.57$; P(FDR) = 0.001). We found a higher mean fMRI signal for win events compared to lose events in both, healthy and gambling patients. In addition, we observed a significant stronger deactivation in healthy compared to pathological gamblers during lose events (difference: −0.07%; $t(22) = −2.725$; $P = 0.006**$). A neuronal differentiation between events of high and low personal relevance was only observed in healthy subjects (difference: 0.10%; $t(11) = 2.022$; $P = 0.034*$) but not in the patient group (difference: 0.01%; $t(11) = 0.173$; $P = 0.433$). The mean fMRI signal for high personal relevance was significantly decreased for pathological gamblers when compared to healthy (difference: 0.08%; $t(22) = 2.478$; $P = 0.011*$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
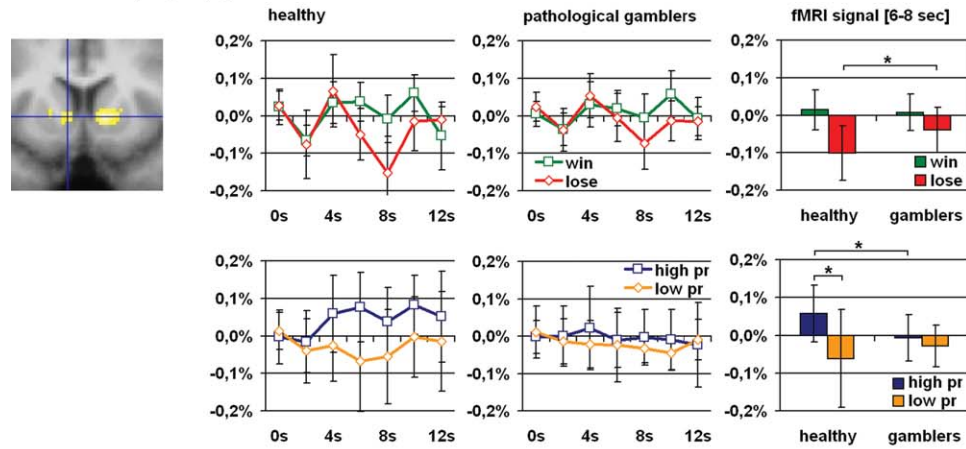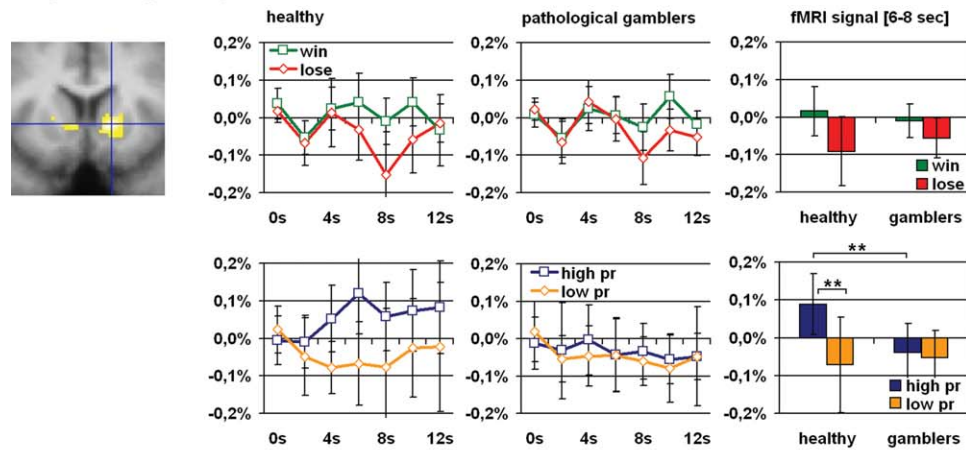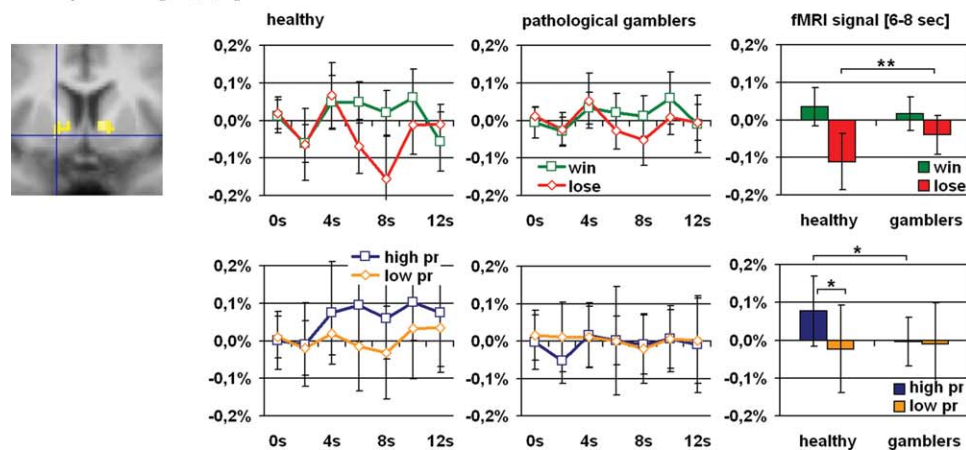
Figure 3. (legend on page 1807).

TABLE I. Activations of all subjects

ROI name	Coordinates (MNI)	P (FDR)	t-value	z-value
left nucleus accumbens	−12, 10, 4	0.001	6.29	4.74
right nucleus accumbens	14, 12, 2	<0.001	8.45	5.64
left ventral putamen	−18, 6, −4	0.001	6.13	4.57
left nucleus caudatus	−10, 16, 2	<0.001	6.79	4.98
right nucleus caudatus	18, 16, 10	<0.001	7.25	5.18
left supplemental motor area (BA6)	−4, −10, 64	0.001	6.12	4.67
right motor cortex (BA4)	48, −12, 58	0.003	5.25	4.21
left motor cortex (BA4)	−48, −10, 54	<0.001	6.92	5.04

Healthy subjects and pathological gamblers, $n = 24$, $P < 0.03$ (FDR), cluster size > 50; for the contrast [win] > [lose].

high and low personal relevance in reward circuitry ascertained by the SPM contrast and their neuronal activity during the reward task. In addition, we focused on the differences in signal changes between stimuli with high and low personal relevance and found that the evaluation of stimuli with high self-relatedness induced significantly less activity in pathological gamblers when compared to healthy subjects in all of the three ROIs (for details see Fig. 3 and Supporting Information 4.2 for statistical details). To control for cognitive-evaluative confounds implicated in our personal relevance task, we also analyzed the results of our control task (which also included cognitive-evaluative components but without reference to personal relevance). Here we found stronger fMRI signal changes during personal relevance trials with the evaluation of highly self-related stimuli, when compared to control events. These results were significant for the bilateral NACC and the left putamen (see Supporting Information 5 for details). Activation induced by the evaluation of highly personally relevant stimuli can in fact be associated with personal relevance itself rather than with the cognitive-evaluative component it recruits.

To further check for an effect of gambling and alcoholic stimuli on fMRI signals we performed another raw data analysis in our three main reward regions of the pathological gamblers. We hoped to find a difference between both categories of stimuli (gambling stimuli and alcoholic stimuli), which might have explained why the patients became addicted to pathological gambling. The statistical analysis of the mean fMRI signals however indexed no significant difference for [gambling stimuli] > [alcohol stimuli] in all of our three main reward regions (left NACC: $d = −0.02\%$, $t(11) = −0.868$, $P = 0.404$; right NACC: $d = 0.01\%$, $t(11) = 0.737$, $P = 0.477$; left Putamen: $d = 0.05\%$, $t(11) = 1.125$; $P = 0.285$.)

Control for depressive comorbidity

Depressive mood is a well known comorbidity in pathological gambling [Petry et al., 2005]. To prove that our results are indeed due to their pathological gambling and not to their depressive comorbidity, we correlated our imaging results for the condition "high personal relevance" with a psychological measurement of gambling severity (SFG scale) controlling for depression as indicated by the BDI score (partial correlation controlled for BDI).

In the left putamen as well as in the right nucleus accumbens, we observed a negative correlation between gambling severity as measured by the SFG and high personal relevance (putamen: $r = −0.56$, $P = 0.076$, statistical trend; right nucleus accumbens: $r = −0.52$, $P = 0.098$, statistical trend, both partial correlations controlled for BDI).

Whereas in the left nucleus accumbens we observed a significant negative correlation between gambling severity and high personal relevance ($r = −0.62$, $P = 0.044$, partial correlation controlled for BDI), i.e., gambling patients with the lowest degree of gambling severity show the strongest activation in the left nucleus accumbens during high personal relevance. Furthermore, we were not able to observe any significant correlation between high personal relevance and the SFG scale controlled for BDI in healthy subjects.

Confirmatory analyses

One might claim, that our selection of ROIs using both the healthy subjects and the patients as one sample group still favored the group of healthy subjects. Since the healthy subjects showed greater neural differentiation in this region compared to our pathological gamblers, their influence on the determination of the coordinates might have been bigger. We hence performed an additional raw data analysis: we compared the fMRI signals of our three main regions (left and right NACC, left putamen) taking optimal regions of interest for both groups. Please see

TABLE II. Activations of healthy subjects

ROI name	Coordinates (MNI)	P (FDR)	t-value	z-value
left nucleus accumbens	−12, 10, 4	0.014	7.21	4.88
right nucleus accumbens	10, 6, 4	0.014	6.12	4.45
left ventral putamen	−22, 10, −4	0.022	4.57	3.67
right precentral gyrus/BA 4	48, −12, 56	0.014	6.56	4.63
left precentral gyrus/BA 4	−48, −10, 56	0.014	6.25	4.50
left Cuneus/BA 19	−4, −84, 32	0.014	6.17	4.47
right anterior cingulate cortex	8, −34, 2	0.014	6.12	4.44
left superior frontal gyrus/BA 6	−4, −10, 72	0.014	6.02	4.40
left fusiform gyrus	−40, −70, −18	0.015	5.64	4.23

$n = 12$, P (FDR) < 0.03, cluster size > 30; for the contrast [win] > [lose].

TABLE III. Activations of pathological gamblers

ROI name	Coordinates (MNI)	P (FDR)	t-value	z-value
left nucleus accumbens	−8, 10, 0	0.011	7.13	4.56
right nucleus accumbens	10, 10, 0	0.010	8.79	5.05
left ventral putamen	−18, 12, 2	0.016	5.70	4.03
left medial frontal gyrus	−8, −8, 64	0.010	9.23	5.16
right superior frontal gyrus/BA 6	10, −20, 70	0.012	6.71	4.42
right medial frontal gyrus	10, −12, 52	0.011	7.29	4.61
right precentral gyrus	36, −14, 58	0.012	6.83	4.46
left superior frontal gyrus/BA 6	−10, −20, 76	0.012	6.77	4.44
left precentral gyrus/BA 4	32, −32, 52	0.014	6.06	4.18

$n = 12$, $P(FDR) < 0.03$, cluster size > 30; for the contrast [win] > [lose].

Table II for a description of the ROIs of the healthy subjects and Table III for the pathological gamblers' ROIs.

Alterations during monetary gains and losses in pathological gamblers: The additional analysis confirmed our previous results. Comparing the fMRI signal stemming from optimal regions for both groups of subjects, we again found less deactivation during lose in pathological gamblers as compared to healthy controls in all of our three core regions (see Supporting Information 4.3 for statistical details).

Alterations in reward circuitry during evaluation of high and low personal relevance in pathological gamblers: Again we were able to confirm our results. Pathological gamblers showed high significantly decreased fMRI signals in all of our three core regions (see Supporting Information 4.4 for statistical details).

In addition, it may be criticized that activity in reward regions during the evaluation of stimuli with high personal relevance is rather due to unspecific rewarding effects of the food and alcohol stimuli, than their high personal relevance [Gilman et al., 2008; Goldstone et al., 2009; Porubska et al., 2006]. To address this claim, we compared the mean fMRI signals of our healthy subjects induced by food and alcohol stimuli that were classified as high personal relevant with the mean fMRI signals induced by low personal relevant food and alcohol stimuli. We found significant higher mean fMRI signal changes during events with food and alcohol stimuli of high personal relevance compared to events with food and alcohol stimuli that were classified as low personal relevant. In addition we found small but significant negative BOLD responses during trials with low personal relevant food and alcohol stimuli (see Supporting Information 4.5 for details of the statistic analysis). Taken together, these findings demonstrate that it is rather unlikely, that our reward regions were activated by the nonspecific rewarding effects of the food and alcohol stimuli.

DISCUSSION

We investigated reward circuitry during the evaluation of personal relevance in pathological gamblers. Replicating the findings of Reuter et al. [2005], pathological gamblers showed reduced neuronal activity in bilateral NACC and left ventral putamen during a reward task. Extending these findings, we demonstrated that pathological gamblers showed reduced signal changes in the same reward regions during the evaluation of personal relevance when compared to healthy subjects. Taken together, we, for the first time, demonstrate neuronal abnormalities in reward circuitry of pathological gamblers during evaluation of personal relevance.

Alterations of Reward Circuitry in Pathological Gamblers During Monetary Wins and Losses

Our data are in accordance with the findings of Reuter et al. [2005] who found a decreased difference in neuronal activity during monetary wins and losses. In addition to this we were able to extend their results in two ways. First, we demonstrated that the diminished difference of neuronal activity between wins and losses stems from weaker deactivation in the left NACC and the left ventral putamen during lose-events rather than from smaller activation during win-events.

Alterations in Reward Circuitry of Pathological Gamblers During the Evaluation of Personal Relevance

The striking findings of our study concerns the alteration of brain activity during the evaluation of personal relevance in pathological gamblers. As expected we found a significant lack of neuronal activity in our three reward regions (left and right NACC, left putamen) during the evaluation of stimuli with high personal relevance. These findings are in line with our hypothesis and implicate diminished neuronal reactivity in reward circuitry of gambling-addicted patients during tasks of specifically high personal relevance. Our present findings complement previous ones from our group in which alcoholic patients also exhibited reduced neuronal activity in reward circuitry while viewing stimuli of high personal relevance [de Greck et al., 2009]. Also as in alcoholic patients, this reduced neuronal activity during self-relatedness in pathological gamblers is well in accordance with the clinical observation of a severe shift of personal relevance from formerly personally important habits to gambling as the only personally relevant activity. This assumption is supported by our behavioral finding that pathological gamblers classified gambling stimuli significantly more often as highly self-related when compared to healthy subjects.

Most importantly, our findings demonstrate for the first time that these clinical and behavioral alterations in the

perception of personal relevance may correspond to disturbed neuronal activity in reward circuitry on a neurobiological level. Moreover, stimuli classified as highly personally relevant eventually fail to induce neuronal activity in reward circuitry. Therefore, in line with previous postulations [Reuter et al., 2005], one might hypothesize that due to the apparent inability to stimulate their reward circuitry by even highly self-related stimuli, these patients might be forced to seek situations that provide stronger reinforcement such as gambling or drugs to create sufficient baseline activity in their reward circuitry.

Methodological Limitations

Finally, we must consider the methodological limitations of our study. First and foremost, the concept of personal relevance or self-relatedness may seem problematically vague empirically and/or conceptually. We used the concept from previous studies on personal relevance and self-relatedness [de Greck et al., 2008, 2009; Northoff and Bermpohl, 2004; Northoff et al., 2006, 2007] that allowed subjects to explicitly indicate whether a presented stimulus was of high or low personal relevance. Although this concept of personal relevance is a rather broad approach, we nevertheless decided to implement it in our paradigm. Our aim was to map the pathological gamblers' striking clinical phenomenon of a loss of personal relevant stimuli and habits as closely as possible. It did not however, allow us to control whether every subject had the same concept in mind as they evaluated the stimuli. Additionally, Berridge and Robinson [2003] have proposed that the concept of reward ought to be parsed into distinct facets such as the preconsummatory ("wanting") aspect and the hedonic consummatory ("liking") aspect. The hedonic consummatory aspect of reward however, has already showed robust effects in two previous studies by our group [de Greck et al., 2008, 2009] and this limitation allowed us to focus on the affects of self-relatedness on just one element of reward circuitry. It may be seen as problematic that our paradigm did not test for possible interactions between reward and personal relevance as we kept them entirely separate. We first attempted to create a task that engaged reward-associated regions without any active self-relatedness component to utilize the results as a functional localizer. We also aimed to introduce a personal relevance task without any traces of a reward component to elucidate whether self-relatedness recruits reward circuitry using Saxe's functional localizer approach [Saxe et al., 2006]. Finally our study was limited to a fairly low number of subjects because we chose to include only those patients receiving no medication. We hoped to ensure that we were investigating our pathological gamblers without any pharmacological confounds. As a result, our results may be considered preliminary until further confirmation can be attained by future studies with larger samples.

CONCLUSION

In this study, we have demonstrated the important underlying role of reward circuitry in pathological gambling. Pathological gamblers not only show diminished neuronal activity in reward circuitry (left and right NACC, left ventral putamen) during monetary wins and losses, but also—and more considerably—during the evaluation of stimuli with high personal relevance. While healthy subjects show high activity in reward circuitry during the evaluation of highly personally relevant stimuli, pathological gamblers lack this increase in neuronal activity. These findings may, in time, be found to correspond to the clinical observation of an increasing neglect of other (formerly relevant) activities and the total preoccupation with gambling.

ACKNOWLEDGMENTS

REFERENCES

American Psychiatric Association (1994): Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, 4th ed. Washington, DC: American Psychiatric Press.

Ashburner J, Friston KJ (1999): Nonlinear spatial normalization using basis functions. Hum Brain Mapp 7:254–266.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961): An inventory for measuring depression. Arch Gen Psychiatry 4:561–571.

Berridge KC, Robinson TE (2003): Parsing reward. Trends Neurosci 26:507–513.

Brett M, Anton JL, Valabregue R, Poline JB (2002): Region of interest analysis using an spm toolbox [abstract]. Presented at the 8th International Conferance on functional Mapping of the Human Brain, June 2–6, 2002, Sendai, Japan. Available on CD-ROM in NeuroImage, Vol 16, No 2, abstract 497.

Cloninger C, Przybeck T, Svrakic D, Wetzel R (1994): The Temperament and Character Inventory (TCI): A Guide to Its Development and Use. St. Louis, Missouri: Center for Psychobiology of Personality, Washington University.

Crockford DN, Goodyear B, Edwards J, Quickfall J, el-Guebaly N (2005): Cue-induced brain activity in pathological gamblers. Biol Psychiatry 58:787–795.

de Greck M, Rotte M, Paus R, Moritz D, Thiemann R, Proesch U, Bruer U, Moerth S, Tempelmann C, Bogerts B, et al. (2008): Is our self based on reward? Self-relatedness recruits neural activity in the reward system. Neuroimage 39:2066–2075.

de Greck M, Supady A, Thiemann R, Tempelmann C, Bogerts B, Forschner L, Ploetz KV, Northoff G (2009): Decreased neural activity in reward circuitry during personal reference in abstinent alcoholics—A fMRI study. Hum Brain Mapp 30:1691–1704.

Dreher JC, Kohn P, Berman KF (2006): Neural coding of distinct statistical properties of reward information in humans. Cereb Cortex 16:561–573.

Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith C, Frackowiak RSJ (1995): Statistical parametric maps in functional imaging: A general linear approach. Hum Brain Mapp 2:189–210.

Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R (1998): Event-related fMRI: Characterizing differential responses. Neuroimage 7:30–40.

Gilman JM, Ramchandani VA, Davis MB, Bjork JM, Hommer DW (2008): Why we like to drink: A functional magnetic resonance imaging study of the rewarding and anxiolytic effects of alcohol. J Neurosci 28:4583–4591.

Goldstein RZ, Alia-Klein N, Tomasi D, Zhang L, Cottone LA, Maloney T, Telang F, Caparelli EC, Chang L, Ernst T, Samaras D, Squires NK, Volkow ND (2007): Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? Am J Psychiatry 164:43–51.

Goldstone AP, de Hernandez CG, Beaver JD, Muhammed K, Croese C, Bell G, Durighel G, Hughes E, Waldman AD, Frost G, Samaras D, Squires NK, Volkow ND (2009): Fasting biases brain reward systems towards high-calorie foods. Eur J Neurosci 30:1625–1635.

Hollander E, Pallanti S, Baldini Rossi N, Sood E, Baker BR, Buchsbaum MS (2005): Imaging monetary reward in pathological gamblers. World J Biol Psychiatry 6:113–120.

Kelley WM, Macrae CN, Wyland CL, Caglar S, Inati S, Heatherton TF (2002): Finding the self? An event-related fMRI study. J Cogn Neurosci 14:785–794.

Killgore WD, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA (2003): Cortical and limbic activation during viewing of high- versus low-calorie foods. Neuroimage 19:1381–1394.

Knutson B, Gibbs SE (2007): Linking nucleus accumbens dopamine and blood oxygenation. Psychopharmacology (Berl) 191:813–822.

Knutson B, Adams CM, Fong GW, Hommer D (2001a): Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci 21:RC159.

Knutson B, Fong GW, Adams CM, Varner JL, Hommer D (2001b): Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport 12:3683–3687.

Knutson B, Fong GW, Bennett SM, Adams CM, Hommer D (2003): A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: Characterization with rapid event-related fMRI. Neuroimage 18:263–272.

Lamm C, Decety J (2008): Is the extrastriate body area (EBA) sensitive to the perception of pain in others? Cereb Cortex 18:2369–2373.

Martin-Soelch C, Leenders KL, Chevalley AF, Missimer J, Kunig G, Magyar S, Mino A, Schultz W (2001): Reward mechanisms in the brain and their role in dependence: Evidence from neurophysiological and neuroimaging studies. Brain Res Brain Res Rev 36:139–149.

McClure SM, York MK, Montague PR (2004): The neural substrates of reward processing in humans: The modern role of FMRI. Neuroscientist 10:260–268.

Nichols T, Hayasaka S (2003): Controlling the familywise error rate in functional neuroimaging: A comparative review. Stat Methods Med Res 12:419–446.

Northoff G, Bermpohl F (2004): Cortical midline structures and the self. Trends Cogn Sci 8:102–107.

Northoff G, Heinzel A, de Greck M, Bermpohl F, Dobrowolny H, Panksepp J (2006): Self-referential processing in our brain—A meta-analysis of imaging studies on the self. Neuroimage 31:440–457.

Northoff G, Schneider F, Rotte M, Matthiae C, Tempelmann C, Wiebking C, Bermpohl F, Heinzel A, Danos P, Heinze HJ, Bogerts B, Walter M, Panksepp J (2009): Differential parametric modulation of self-relatedness and emotions in different brain regions. Hum Brain Mapp 30:369–382.

O'Doherty JP (2004): Reward representations and reward-related learning in the human brain: Insights from neuroimaging. Curr Opin Neurobiol 14:769–776.

Petry NM, Stinson FS, Grant BF (2005): Comorbidity of DSM-IV pathological gambling and other psychiatric disorders: Results from the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry 66:564–574.

Phan KL, Taylor SF, Welsh RC, Ho SH, Britton JC, Liberzon I (2004): Neural correlates of individual ratings of emotional salience: A trial-related fMRI study. Neuroimage 21:768–780.

Porubska K, Veit R, Preissl H, Fritsche A, Birbaumer N (2006): Subjective feeling of appetite modulates brain activity: An fMRI study. Neuroimage 32:1273–1280.

Potenza MN, Steinberg MA, Skudlarski P, Fulbright RK, Lacadie CM, Wilber MK, Rounsaville BJ, Gore JC, Wexler BE (2003): Gambling urges in pathological gambling: A functional magnetic resonance imaging study. Arch Gen Psychiatry 60:828–836.

Premper V, Sobottka B, Fischer T (2007): Der Schweriner Fragebogen zum Gluecksspielen. Praxis Klin Verhaltensmedizin Rehabil 78:244–249.

Reuter J, Raedler T, Rose M, Hand I, Glascher J, Buchel C (2005): Pathological gambling is linked to reduced activation of the mesolimbic reward system. Nat Neurosci 8:147–148.

Saxe R, Brett M, Kanwisher N (2006): Divide and conquer: A defense of functional localizers. Neuroimage 30:1088–1096; discussion 1097–1099.

Tanabe J, Thompson L, Claus E, Dalwani M, Hutchison K, Banich MT (2007): Prefrontal cortex activity is reduced in gambling and nongambling substance users during decision-making. Hum Brain Mapp 28:1276–1286.

Volkow ND, Fowler JS, Wang GJ (2004): The addicted human brain viewed in the light of imaging studies: Brain circuits and treatment strategies. Neuropharmacology 47 (Suppl 1):3–13.

Volkow ND, Fowler JS, Wang GJ, Swanson JM, Telang F (2007a) Dopamine in drug abuse and addiction: Results of imaging studies and treatment implications. Arch Neurol 64:1575–1579.

Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Jayne M, Ma Y, Pradhan K, Wong C (2007b): Profound decreases in dopamine release in striatum in detoxified alcoholics: Possible orbitofrontal involvement. J Neurosci 27:12700–12706.

Wang GJ, Volkow ND, Telang F, Jayne M, Ma J, Rao M, Zhu W, Wong CT, Pappas NR, Geliebter A, et al. (2004): Exposure to appetitive food stimuli markedly activates the human brain. Neuroimage 21:1790–1797.

World Health Organization (1992): International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). World Health Organization, Geneva.

Wrase J, Schlagenhauf F, Kienast T, Wustenberg T, Bermpohl F, Kahnt T, Beck A, Strohle A, Juckel G, Knutson B, et al. (2007): Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. Neuroimage 35:787–794.

Yarkoni T, Gray JR, Chrastil ER, Barch DM, Green L, Braver TS (2005): Sustained neural activity associated with cognitive control during temporally extended decision making. Brain Res Cogn Brain Res 23:71–84.