Psychiatry Research: Neuroimaging 181 (2010) 165–173

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Neurobiological correlates of problem gambling in a quasi-realistic blackjack scenario as revealed by fMRI

Stephan F. Miedl [a,c,*], Thorsten Fehr [a,b], Gerhard Meyer [c], Manfred Herrmann [a,b]

[a] Department of Neuropsychology and Behavioral Neurobiology, Center for Cognitive Sciences (ZKW), University of Bremen, Germany
[b] Center for Advanced Imaging – CAI Bremen, University of Bremen, Germany
[c] Institute of Psychology and Cognition Research, University of Bremen, Germany

ARTICLE INFO

Article history:
Received 2 October 2009
Received in revised form 18 November 2009
Accepted 19 November 2009

Keywords:
fMRI
Thalamus
Addiction
Gambling

ABSTRACT

In the present study we obtained functional magnetic resonance imaging (fMRI) data in occasional gamblers (OG) and problem gamblers (PG) during a quasi-realistic blackjack game. We focused on neuronal correlates of risk assessment and reward processing. Participants had to decide whether to draw or not to draw a card in a high-risk or low-risk blackjack situation. We assumed PG would show differences in prefrontal and ventral striatal brain regions in comparison to OG during risk assessment and due to the winning or losing of money. Although both groups did not differ in behavioral data, blood oxygen level dependent (BOLD) signals in PG and OG significantly differed in thalamic, inferior frontal, and superior temporal regions. Whereas PG demonstrated a consistent signal increase during high-risk situations and a decrease in low-risk situations, OG presented the opposite pattern. During reward processing as derived from contrasting winning vs. losing situations, both PG and OG groups showed an enhancement of ventral striatal and posterior cingulate activity. Furthermore, PG demonstrated a distinct fronto-parietal activation pattern which has been discussed to reflect a cue-induced addiction memory network which was triggered by gambling-related cues.

1. Introduction

Pathological gambling is characterized by a craving for gambling, loss of control, and continuing gambling despite associated adverse consequences. It is classified as an impulse control disorder in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) with a lifetime prevalence of 0.5–1% (Petry et al., 2005). From a clinical point of view, pathological gambling is related to addictive behavior (Potenza, 2006), and there is emerging evidence that the underlying pathology on a neuronal level compares to cue-related behavior in drug addiction (Franklin et al., 2007). Gambling takes place in a complex social and context-specific environment, which cannot easily be transferred into an experimental setting. Furthermore, the gambling situation consists of a variety of cognitive (problem solving, risk assessment) and emotional (reward processing) behaviors, which may be prevalent in problem gamblers. In the present study we introduced an experimental design with a quasi-realistic blackjack game scenario to enhance ecological validity, and to allow for the analysis of different episodes of the game. We were particularly interested in separating the risk assessment and reward processing periods of the game because both have been shown to be impaired in pathological gambling (Reuter et al., 2005; Goudriaan et al., 2006).

Growing evidence suggests that risk assessment/decision making might be affected in pathological gambling, especially when gamblers have to choose between risky and safe options (Bechara, 2005). So far, most experimental data have been derived from the Iowa Gambling Task (IGT), as developed by Bechara et al. (1994), and introduced as a tool to measure "risk-anticipation". Patients with ventromedial frontal lobe (VMF) damage (Cavedini et al., 2002), patients with disinhibition behavior (substance dependencies, psychopathy and attention deficit/hyperactivity disorder; Blair, 2001), and pathological gamblers (Goudriaan et al., 2005) showed impaired performance on the IGT (Bechara et al., 1997). Tanabe et al. (2007) showed a reduced activation in the right prefrontal cortex during decision making in substance-dependent gamblers, as compared with substance-dependent controls on the IGT. These authors related gambling-associated problems to impaired working memory, stimulus reward evaluation, or cue reactivity. Furthermore, Brand et al. (2005, 2006) suggested dorsolateral prefrontal and orbitofrontal dysfunctions in pathological gamblers — both regions are discussed to be involved in decision making. In particular, the orbitofrontal cortex was reported to be sensitive to the amount of conflict inherent to decisions (Rogers et al., 1999).

In addition to impaired risk evaluation and risk taking, it has been shown that reward processing and the activity of the mesolimbic

* Corresponding author. Department of Neuropsychology and Behavioral Neurobiology, Center for Cognitive Sciences (ZKW), University of Bremen – Cognium Building, Hochschulring 18, D-28359 Bremen, Germany. Tel.: +49 421 218 68744; fax: +49 421 218 68759.
E-mail address: miedl@uni-bremen.de (S.F. Miedl).

0925-4927/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2009.11.008

dopaminergic reward system (Self and Nestler, 1998; Volkow et al., 2002) may be affected in pathological gambling. Additionally, there is evidence for a reduction in the sensitivity of the reward system. Reuter et al. (2005) compared pathological gamblers with healthy controls in a simple card-guessing game and demonstrated a ventral striatal and ventromedial prefrontal hypoactivation in pathological gamblers, which was positively correlated with gambling severity. D-Amphetamine, a non-specific dopamine agonist, was shown to prime gambling motivation in problem gamblers (Zack and Poulos, 2004). This points to a dysregulation of specific dopamine-related neuronal reward processes in problem gamblers. More recently, the same group (Zack and Poulos, 2007) demonstrated an enhancement of reward and priming effects of a gambling episode (playing slot machines) in pathological gamblers as compared with non-gamblers after D2 antagonist intake.

The majority of studies investigating neuronal correlates in pathological gambling are based on experimental settings which simplify the complex gambling environment. There are only a few studies which have introduced a more ecologically valid experimental gambling design to examine neuronal or neuroendocrinological responses while playing. Hewig et al. (2009) measured blood oxygen level dependent (BOLD) signal while playing blackjack in healthy participants. During the evaluative phase of decision making under risk conditions, the authors demonstrated that excessively risky and cautious decisions were associated with increased dorsal anterior cingulate cortex activity, similar to observed correlations of the error-related negativity (ERN) amplitude with both risk-taking and decision-making behavior (Gehring and Fencsik, 2001; Gehring and Willoughby, 2002) in a previous electroencephalography (EEG) study using the same design (Hewig et al., 2007). Evidence for the influence of gambling for real money (Ladouceur et al., 2003; Wulfert et al., 2005) was provided by Meyer et al. (2004), who compared the neuroendocrine responses of problem gamblers and healthy controls in two different situations: a real blackjack casino situation, where gamblers invested their own money, and an experimental control condition, where participants were playing for points in a laboratory environment. The results showed higher levels of norepinephrine and dopamine in problem gamblers compared with healthy participants in a "real money" casino environment, which became not significant in the control condition. Additional support for the crucial role of the applied stimulus material in relation to a specific addiction or disorder came from Volkow et al. (2003). The authors reported an orbitofrontal hypoactivation in addicted persons when confronted with natural reinforcers in contrast to an activation of the same area to substance-related cues. A similar finding was reported by Crockford et al. (2005), who showed cue-induced dorsolateral prefrontal activity in pathological gamblers during viewing of gambling-related cues. Thus, we decided to design the present experimental blackjack game scenario to be as realistic as possible, while considering necessary experimental efforts for methodologically correct parameterization.

The present functional magnetic resonance imaging (fMRI) study aimed at analyzing two major parts of the blackjack game, the periods of risk assessment and reward processing, using an ecologically valid quasi-realistic gambling scenario with comparatively high wagers in both problem gamblers and occasional gamblers. Based on the above-mentioned studies, we hypothesized that in problem gamblers both risk assessment and reward processing might be modulated by the gambling-related nature of the applied task: 1) For the period of risk assessment, we expect a signal increase in inferior frontal/orbitofrontal and thalamic brain regions, and particularly in problem gamblers during high-risk situations. 2) During reward processing, we expect a signal increase in the nucleus accumbens in both groups after win conditions. The quasi-realistic task, including gambling for real money, is supposed to counteract or override a generally observed hypoactivation in pathological gamblers associated with risk assessment and reward processing which is reported in experimental setups with a lower gambling-authenticity (Reuter et al., 2005; Tanabe et al., 2007).

2. Methods

2.1. Study participants

The study group consisted of 12 healthy male OG (range 25–49 years) and 12 male PG (range 29–57 years). All participants were right-handed according to a modified version of the Edinburgh Handedness Questionnaire (Oldfield, 1971). Both groups did not differ in age ($F[1,22]=2.97$, $P=0.1$), smoking behavior ($z=-1.7$, $P=0.1$), and frequency of blackjack gambling ($z=-0.6$, $P=0.6$; see also Table 1). We decided to investigate only male participants, as the prevalence of pathological gambling in men is reported to be two times higher than in women (Grant and Potenza, 2004). Participants were recruited through advertisements and were familiarized with the gambling environment in the laboratory. Frequency of overall gambling behavior ($z=-2.7$, $P<0.01$), as well as the percentage of income spent on gambling activities, was significantly higher in PG than in OG ($F[1,22]=22.14$, $P<0.01$; see Table 1). The preferred forms of gambling of PG were slot machines, roulette or internet-poker. Prior to enrollment in the study, all participants underwent a structured psychiatric interview.

OG and PG did not report a history of psychiatric or neurological illness or regular drug use and were not under current medication. In the PG group, five participants were presented with a diagnosis of problem gambling (3 or 4 criteria, Toce-Gerstein et al., 2003) and seven participants had a diagnosis of pathological gambling (≥ 5 criteria) according to DSM IV. Furthermore, all individuals were assessed with the German gambling questionnaire "Kurzfragebogen zum Glücksspielverhalten" (KFG; Petry, 1996; derived from 20 items as developed by "Gamblers Anonymous"). Instrumental (Cronbach's alpha $=0.79$) and retest ($r=0.80$) reliability of the scale are reported to highly fulfill the psychometric properties of a screening instrument (Petry, 1996). This questionnaire contains 20 items (4-point Likert-scale: 0 to 3 points) addressing lifetime gambling behavior. The threshold for pathological gambling is set at 16 points. All PG scored between 18 and 45 points, whereas OG scored between 0 and 12 points. In addition, all participants were evaluated with a German version of the South Oaks Gambling Screen (SOGS; Lesieur and Blume, 1987). Participants who scored ≥ 5 points were classified as "probable pathological gamblers". All PG scored ≥ 6 on the SOGS, and OG obtained ≤ 2. Both groups significantly differed with respect to DSM IV ($F[1,22]=48.58$, $P<0.01$), SOGS ($F[1,22]=78.88$, $P<0.01$), and KFG scores ($F[1,22]=82.68$, $P<0.01$); see also Table 1. The study protocol was designed according to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1984) and was approved by the local ethics committee. All participants were informed about the procedure and gave written informed consent to participate.

Table 1
Demographic and clinical data of PG and OG (mean ± standard deviation).

	PG ($n=12$)	OG ($n=12$)	
Age	39.5 ± 9.3	33.4 ± 8.0	$F[1,22]=2.97$, $P=0.10$
Number of smokers per group	10	6	$z=-1.7$, $P=0.09$
DSM IV	4.9 ± 1.9	0.7 ± 0.9	$F[1,22]=48.58$, $P<0.01$
SOGS	10.7 ± 3.8	0.7 ± 0.7	$F[1,22]=78.88$, $P<0.01$
KFG	28.2 ± 7.9	5.3 ± 3.7	$F[1,22]=82.68$, $P<0.01$
Percent of income spent on gambling	57.1 ± 34.7	7.3 ± 11.7	$F[1,22]=22.14$, $P<0.01$
Blackjack frequency	<1 time/month	<1 time/month	$z=-0.6$, $P=0.57$
Frequency of overall gambling behavior	>3 times/week	≤3 times/month	$z=-2.7$, $P<0.01$

2.2. Experimental design

The experimental blackjack task consisted of 206 trials (50 low-risk, 50 high-risk, 50 fill-, and 56 validity-trials). The low-risk trials reflect situations in which the player started with 12 or 13 points against the dealer's 7, 8, 9, or 10 points. Participants were informed that they played against the computer. High-risk trials consisted of the player with 15 or 16 points and the dealer with 7, 8, 9, or 10 points. The probability of losing while drawing a card [P(lose|hit)] over all low-risk trials was 0.34, and 0.56 over all high-risk trials. The trials were designed in a way that — according to the blackjack basis strategy (Baldwin et al., 1956) — in all high-risk and low-risk situations a hit was more advantageous for the player than a stand [P(lose|stand] = 0.77]. Fill-trials were composed of cards with pictures and numbers with no relation to the blackjack game, which served as low-level baseline condition in further analyses not reported here. Furthermore, we included 56 validity-trials, consisting of aces (1 or 11 points), and starting-situations with 14, 17, 18, 19, 20 or 21 points for the player. These validity-trials should guarantee a quasi-realistic blackjack scenario. Both fill- and validity-trials were modeled separately and excluded from further analysis. The bet was fixed at €5 in low-risk and high-risk trials, and at €1 in validity-trials.

All trial elements were presented against a black background. A trial started with a jeton representing a fixed bet (€1 or €5; frame 1, see Fig. 1a) for 500 ms, followed by a white fixation point for 1500 ms (frame 2). Thereafter, three cards were presented for a maximum of 6000 ms; on the upper part of the screen, there was one card for the dealer, and on the lower part of the screen, there were two. Within this period the player had to decide whether he wanted to take another card ("hit"; right mouse: left button click; index finger) or to stand ("no further card required"; right mouse: right button click; middle finger, frame 4). Thereafter, the dealer took cards according to the official blackjack rules (the dealer must hit until his total was 17 or higher). Dependent on the player's response (hit or stand), the dealer started to take another card 300 ms after the player decided to stand (stand response), and 2000 ms after the player's hit (hit response). The end of the round was presented for 3000 ms (frame 5), followed by a 2000-ms information screen displaying the running total of the player (frame 6) and a 2000-ms inter-trial fixation point (frame 7).

Before the fMRI scanning session all participants had to perform 10 min of practice trials outside the scanner. At the beginning of the game, each player started with a balance of €30. All study participants were informed that they might lose their starting balance and that they would receive the entire balance in cash at the end of the experiment. Wins and losses followed a pre-determined course independent from the player's decisions (see Fig. 1b). Trials were presented in a pseudo-randomized non-stationary probabilistic sequence (Friston, 2000). Participants lost 50% of the high-risk trials and 50 percent of the low-risk trials, and always finished the game with a total amount of €52. In contrast to official blackjack rules the player was allowed to hit or to stand only one time per round.

2.3. fMRI data acquisition

While participants performed the tasks, functional MRI data were collected on a 3 T Siemens Allegra scanner (Siemens, Erlangen, Germany) using a gradient echoplanar imaging (EPI) sequence covering 44 axial (AC–PC), interleaved slices (3 mm thick) encompassing the entire cerebrum and cerebellum (TR/TE = 2500/30 ms; FOV 192 mm). About 1000 volumes were obtained during each run. A T1-weighted structural 3D image of the brain was obtained using the MPRAGE sequence: 160 contiguous slices, TR = 2.3 s, TE = 4.38 ms, TI = 900 ms, FA = 8°, FOV 296 × 296 mm, in-plane resolution 1 × 1 mm, slice thickness 1 mm.

2.4. fMRI data analysis

Image analysis was performed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). For each session and participant, images were realigned to the first image in the time series to correct for head motion. These realigned images were spatially normalized into a standard stereotactic space

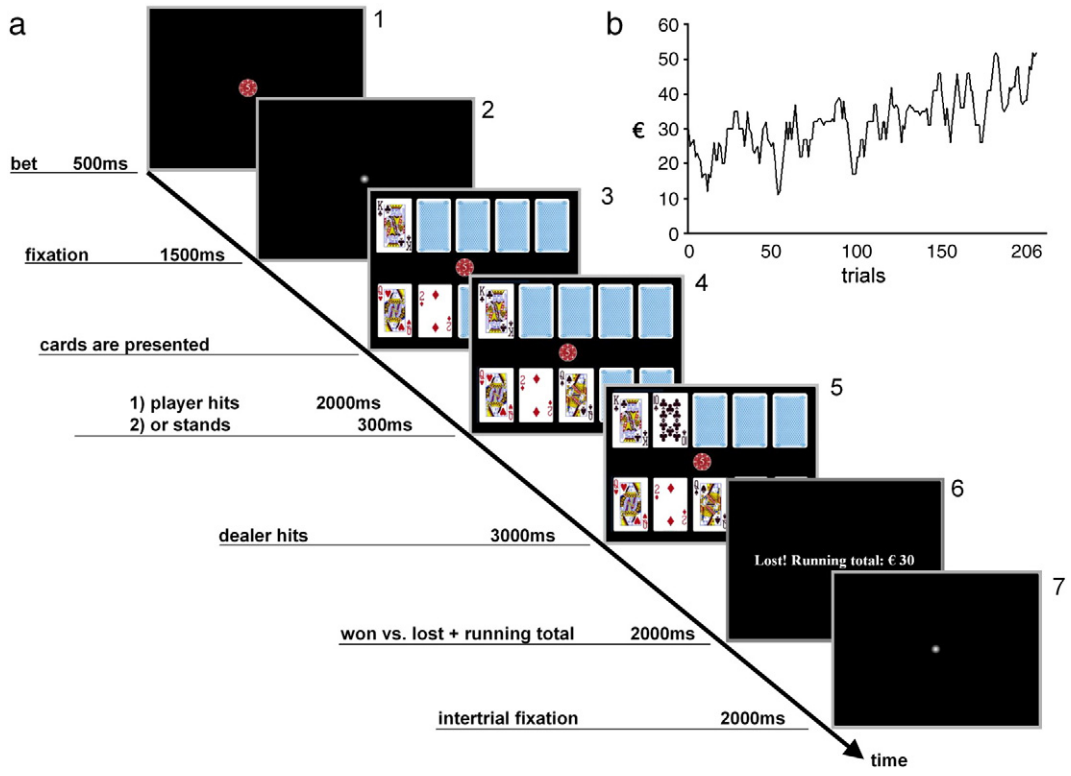

Fig. 1. (a) Trial description of and task elements in a quasi-realistic blackjack scenario, (b) pre-determined course of the game.

(Montreal Neurological Institute template) using a 12-parameter affine model. These spatially normalized images were smoothed to minimize noise and residual differences in gyral anatomy with a Gaussian filter set at 8 mm. Prior to statistical analysis a high pass filter (500 s) was applied to remove global effects. Pre-processed data sets were analyzed using a second-level random effect model that accounts for both scan-to-scan and participant-to-participant variability (Holmes, 1998).

The analysis of imaging data was restricted to low-risk and high-risk trials. Furthermore, we focused on two different time periods in the trials: 1) risk assessment, and 2) win or lose situations. The first time period covered the presentation of cards until the player's decision (Fig. 1a, frames 3 to 4), the second period comprised the time between the dealer's hit and the presentation of the information of winning or losing and the running total (Fig. 1a, frame 5 to 6). If the player's decision to hit resulted in a higher total than 21 (i.e., he lost the game), the second period covering win or lose perception was restricted to frames 4 to 5. Therefore, several trial elements and periods were modeled exclusively by the standard hemodynamic response function, and included as separate predictors (high-risk, low-risk, fill, validity, response, win, lose, equal, running total) in the design matrix. Risk assessment and reward processing were modeled as epochs; risk assessment with a duration from presentation of the cards until the response was given (see Fig. 1, frame 3 to 4); reward processing in a bust was modeled with a duration of 2 s (see Fig. 1, frames 4 to 5), and in all other cases with a duration of 3 s (see Fig. 1, frames 5 to 6). To compare PG and OG, second-level analyses were performed by calculating *t*-statistics including first level contrast images for pre-determined condition effects at each voxel for each participant and session for the following contrasts: high-risk vs. low-risk, low-risk vs. high-risk, high-risk-hit vs. high-risk-stand, high-risk-stand vs. high-risk-hit, win vs. lose, and lose vs. win. In a first analysis, we determined voxels showing a main effect of high-risk vs. low-risk, low-risk vs. high-risk, high-risk-hit vs. high-risk-stand, and high-risk-stand vs. high-risk-hit ($P<0.001$ uncorrected, cluster threshold (k) = 5). We further calculated an interaction analysis to test for voxels showing larger contrasts in PG than in OG and vice versa. To restrict the search volume to active regions showing a significant main effect of high-risk vs. low-risk, low-risk vs. high-risk, high-risk-hit vs. high-risk-stand, or high-risk-stand vs. high-risk-hit, respectively, the interaction analyses were masked inclusively by the corresponding contrast of the first group entered in the analysis ($P<0.001$ uncorrected; $k=5$). Thus, for an interaction analysis, PG vs. OG, the main effect of PG was entered as an inclusive mask. We calculated the same analyses as described above for the win vs. lose and lose vs. win conditions (FWE, $P<0.05$; $k=20$), and we compared groups (PG vs. OG; OG vs. PG) applying interaction analyses ($P<0.001$, $k=20$). Furthermore, conjunction analysis [conjunction null (Nichols et al., 2005)] was calculated including win vs. lose conditions for PG and OG ($P<0.05$, FWE-corrected, $k=20$). Estimates of percentage signal change in the high-risk, low-risk, win, and lose conditions were extracted from the significant clusters of brain regions for each participant using MarsBaR (Brett et al., 2002).

For the identification of activated anatomical structures, we transformed MNI (Montreal Neurological Institute) template based coordinates into Talairach coordinates (Talairach and Tournoux, 1988) using a matlab tool (mni2tal.m, http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach) and determined the anatomical regions using the Talairach Daemon Client software (http://ric.uthscsa.edu/projects/talairachdaemon.html).

3. Results

3.1. Behavioral data

Response times (RT) and risk assessment (hit vs. stand) in PG and OG did not differ significantly. A repeated measures ANOVA for RTs with the factors group (PG vs. OG) × risk (high-risk vs. low-risk) showed no significant main effect of group ($F[1,22]=0.9$; $P=0.3$), and group × risk interaction ($F[1,22]=0.02$; $P=0.9$). Both groups showed significantly longer RTs in high-risk compared with low-risk conditions (main effect of the factor risk; 1882 ± 629 ms vs. 1461 ± 452 ms; $F[1,22]=42.9$, $P<0.001$).

A repeated measures ANOVA for RTs with the factors group (PG vs. OG) × high-risk decision (high-risk-hit vs. high-risk-stand) revealed neither a significant main effect of group ($F[1,22]=0.76$; $P=0.5$) nor a group × high-risk decision interaction ($F[1,22]=1.01$; $P=0.33$). Both groups showed significantly faster RTs in high-risk-hit compared with high-risk-stand conditions (main effect of the factor high-risk decision; 1868 ± 600 ms vs. 2109 ± 747 ms; $F[1,22]=42.9$, $P<0.001$). In the low-risk condition only 10 out of 24 participants showed stand trials, and we therefore did not compare the respective RTs.

In addition, PG and OG did not differ in risk assessment. A repeated measures ANOVA for risk assessment with the factors group (PG vs. OG) × decision behavior (percent high-risk-hit vs. percent low-risk-hit) revealed no significant main effect of group ($F[1,22]=0.43$; $P=0.5$) and no group × decision behavior interaction ($F[1,22]=0.02$; $P=0.9$). Both groups showed a significantly lower percentage of high-risk compared with low-risk-hit trials (main effect of the factor decision behavior; $63.4\pm23.8\%$ vs. $96.5\pm8.8\%$; $F[1,22]=52.8$, $P<0.001$; see also Table 2).

Furthermore, PG and OG did not differ in the number of bust trials (in case participants draw another card and get over 21 points; see also Table 2) in low-risk ($F[1,22]=3.4$; $P=0.1$ and high-risk situations ($F[1,22]=1.2$; $P=0.2$).

A repeated measures ANOVA for the number of bust trials with the factors group (PG vs. OG) × bust (high-risk bust vs. low-risk bust) revealed neither a significant main effect of group ($F[1,22]=2.04$; $P=0.2$) nor a group × bust interaction ($F[1,22]=0.51$; $P=0.5$). Both groups showed a significantly lower number of bust trials in high-risk compared with low-risk trials (main effect of the factor bust; 8.1 ± 3.4 vs. 12.5 ± 0.9; $F[1,22]=46.2$, $P<0.001$; see also Table 2).

3.2. Functional imaging data

Neural correlates of risk assessment, as revealed by contrasting high-risk vs. low-risk conditions, resulted in significant activation patterns in PG ($P<0.001$, uncorrected) including bilateral frontal, temporal, right parietal, and bilateral parahippocampal and right thalamic regions (see Supplementary material Table 1S). The reverse contrast revealed activation patterns in OG ($P<0.001$ uncorrected; see Supplementary material Table 1S) in bilateral frontal, right superior temporal, and bilateral thalamic, insular, and parahippocampal regions. This dissociation was confirmed by an interaction analysis showing larger contrasts in OG compared with PG for low-risk vs. high-risk conditions (right superior temporal gyrus, and left thalamus), and a significant percent signal increase in PG compared with OG in right superior temporal gyrus, right inferior frontal gyrus, and right thalamus (see Table 3 and Fig. 2). Analyses contrasting high-risk-hit vs. high-risk-stand and high-risk-stand vs. high-risk-hit trials within PG and OG revealed no significant activation patterns.

Table 2
Behavioral data of PG and OG (mean ± standard deviation).

		PG ($n=12$)	OG ($n=12$)
Response time	High-risk	1992 ± 576	1772 ± 684
	Low-risk	1560 ± 417	1361 ± 481
Response time per decision in high-risk trials	High-risk-hit	2010 ± 526	1726 ± 657
	High-risk-stand	2168 ± 720	2050 ± 801
Percentage of hit trials	High-risk	61.2 ± 25.7	65.7 ± 22.7
	Low-risk	93.8 ± 11.1	97.2 ± 5.8
Number of bust trials	High-risk	7.3 ± 3.6	8.9 ± 3.2
	Low-risk	12.2 ± 1.1	12.8 ± 0.6

Table 3
Interaction analysis of brain regions activated during risk assessment — Talairach coordinates, anatomical regions and *t*-scores of the between group comparisons in the high-risk vs. low-risk task contrasts for PG vs. OG (A) and in the low-risk vs. high-risk task contrasts for OG vs. PG (B) (all $P<0.001$, uncorrected, $k=5$).

Regions	H	A					B				
		$(\text{high-risk}_{PG}>\text{low-risk}_{PG})>(\text{high-risk}_{OG}>\text{low-risk}_{OG})$					$(\text{low-risk}_{OG}>\text{high-risk}_{OG})>(\text{low-risk}_{PG}>\text{high-risk}_{PG})$				
		t	cl-size	*x*	*y*	*z*	*t*	cl-size	*x*	*y*	*z*
Inferior frontal gyrus	R	3.92	18	46	42	−5					
Superior temporal gyrus	R	4.28	50	67	−25	1	5.25	80	67	−21	8
	R						4.34	50	53	−13	6
	R						4.75	80	59	−31	7
	R						3.97	8	44	−27	7
Thalamus	L						3.75	11	−2	−25	9
	R	3.93	8	10	−33	3					

H, hemisphere; R, right; L, left.

Contrasting win vs. lose conditions ($P<0.05$; FWE-corrected) produced widespread bilateral parietal, occipital, frontal, and subcortical activation patterns in both PG and OG (see Supplementary material, Table 2S). Conjunction analysis ($P<0.05$, FWE-corrected; see Nichols and Hayasaka, 2003) demonstrated that both groups showed common activation patterns in brain regions related to reward processing (Ncl. accumbens, bilateral frontal regions, left parietal regions [precuneus], left occipital regions, bilateral cerebellum, left thalamus, and right posterior cingulate gyrus; see Fig. 3 upper part and Table 4).

Comparing activation patterns in win vs. lose situations between groups [(win>lose) PG vs. OG; threshold $P<0.001$, uncorrected, Fig. 4 and Table 4] resulted in right superior frontal, left inferior parietal, and left superior parietal signal increases; whereas the opposite contrast (OG>PG) for the win vs. lose condition became insignificant. Furthermore, lose situations compared with win situations did not show suprathreshold activations.

4. Discussion

Using fMRI, we investigated neuronal correlates in PG and OG during a quasi-realistic blackjack scenario with respect to both risk assessment and reward processing. The present data suggest that risk assessment was associated with comparable arousal-related neuronal networks in PG and OG. During high-risk situations, fronto-thalamic brain activity was enhanced in PG, whereas OG showed a significant signal increase in low-risk conditions. Winning contrasted with losing

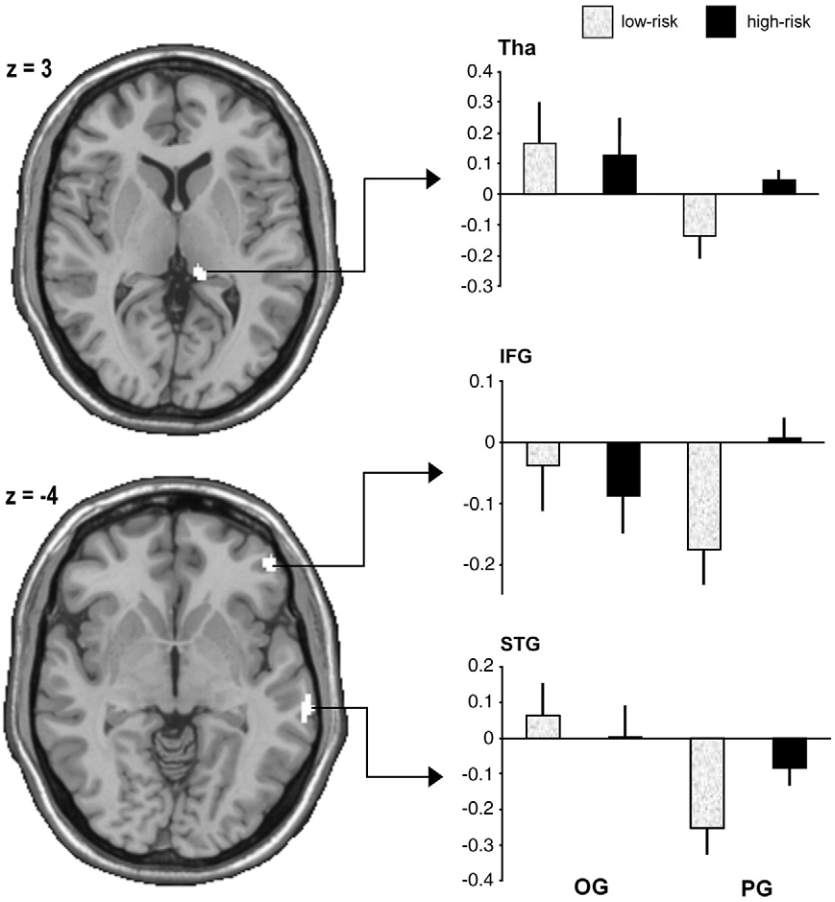

Fig. 2. Activation pattern and percent signal change (±1 SEM) derived from the high-risk vs. low-risk contrast in PG vs. OG ($P<0.001$ uncorrected) in the pulvinar nucleus of the thalamus (Tha), inferior frontal gyrus (IFG), and superior temporal gyrus (STG). MNI-to-Talairach-transformed coordinates are given in Table 3.

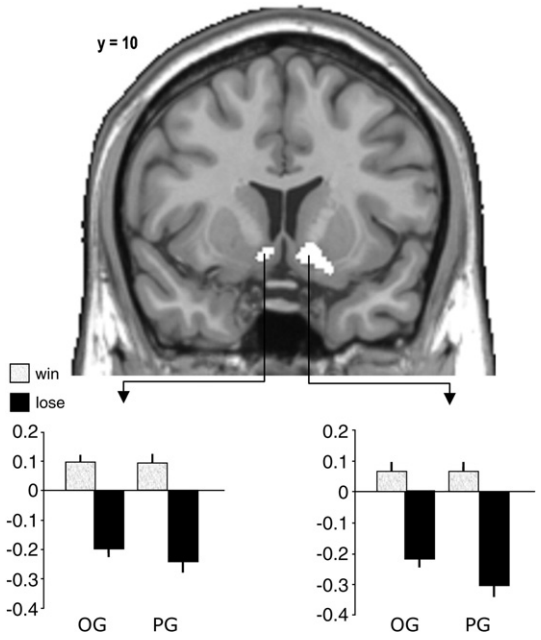

Fig. 3. Activation pattern and percent signal change (±1 SEM) derived from the win vs. lose contrast in the conjunction {null} analysis for OG and PG ($P<0.05$ FWE-corrected) in the nucleus accumbens. MNI-to-Talairach-transformed coordinates are given in Table 4.

Table 4
Brain regions activated during reward processing — Talairach coordinates, anatomical regions and *t*-scores of (A) a conjunction {null} analysis including win vs. lose contrasts of PG and OG ($P<.05$, FWE-corrected; $k = 20$), and (B) between group comparison (PG vs. OG) in the win>lose contrast ($P<0.001$, uncorrected, $k = 20$).

Regions	H	A					B				
		Conjunction {null} ($win_{PG}>lose_{PG}$) and ($win_{OG}>lose_{OG}$)					($win_{PG}>lose_{PG}$)> ($win_{OG}>lose_{OG}$)				
		t	cl-size	*x*	*y*	*z*	*t*	cl-size	*x*	*y*	*z*
Subcallosal gyrus	L	6.41	52	−14	5	−14					
	R	8.91	187	16	5	−14					
Superior frontal gyrus	L	7.12	23	−28	−1	63					
	R						4.67	23	24	15	56
Inferior parietal lobule	L						4.68	86	−32	−55	44
Superior parietal lobule	L						4.03	86	−28	−50	55
Precuneus	L	7.24	42	−18	−59	56					
Lingual gyrus	L	7.48	66	−22	−95	−5					
	L	7.13	87	−10	−80	−3					
Cuneus	L	7.58	87	−8	−79	8					
	L	7.94	66	−18	−99	0					
	L	7.13	31	−12	−60	9					
Nucleus accumbens	L	7.61	52	−8	9	−7					
	R	8.58	187	10	9	−9					
Cingulate gyrus	R	7.80	72	2	−24	29					
Thalamus	L	7.20	65	−10	−15	10					
	L	6.73	65	−16	−17	16					
Cerebellum	L	6.59	76	−4	−73	−20					
	R	7.51	76	2	−77	−23					
	R	7.29	76	10	−77	−18					
	R	6.85	31	2	−74	−8					

H, hemisphere; R, right; L, left.

money activated brain regions associated with reward processing in both PG and OG, whereas an interaction analysis between groups resulted in significantly larger contrasts in fronto-parietal regions in PG as compared to OG.

4.1. Risk assessment

Behavioral data derived from the risk assessment period of the game did not show any differences in the percentage of hit trials between groups, but significantly slower RT for high-risk situations in both groups. These data indicate that PG and OG did not differ on a behavioral level and that PG did not run a higher risk during the present blackjack game. The surplus in RT in high-risk situations might be associated with a higher amount of response conflict (Yang et al., 2007). Although behavioral data were comparable in both experimental groups, imaging data analysis during risk assessment showed group-related differences. Analogously, Fehr et al. (2006) showed a consistent color–word Stroop effect reflected in both behavioral and ERP data in a group of smokers and non-smokers. However, smoking-cue-related interference processing in smokers was only reflected in ERP topographies, but not in the respective behavioral data. This was explained by potential sequential (time-consuming) and parallel (time-saving) mental processing steps in the different mental domains.

To test the first hypothesis, a region of interest analysis based on percent signal change values was performed and indicated a dissociation between OG and PG in superior temporal gyrus, right inferior frontal/orbitofrontal gyrus, and right medial pulvinar brain regions in PG. OG presented increased activity during low-risk situations, whereas PG showed a signal increase in high-risk trials. These results confirmed the hypothesis of a signal increase in inferior frontal/orbitofrontal and thalamic brain regions, especially in problem gamblers during high-risk assessment. We suppose that this finding might be related to the highly authentic gambling task of the present study.

The thalamus had been shown to be involved in addictive behavior as reported by a variety of studies (Breiter et al., 1997; George et al., 2001; Due et al., 2002; Potenza et al., 2003; Franklin et al., 2007; Wang et al., 2007). The medial pulvinar nucleus of the thalamus is reciprocally interconnected with the cingulate gyrus and other limbic structures (Morgane et al., 2005) and is considered to play a crucial role in learning and memory (Mitchell et al., 2008), emotional experience and expression, drive (Sewards and Sewards, 2003; Nummenmaa et al., 2008), and motivation (Schmahmann, 2003). In addition, Leh et al. (2008) showed that human pulvinar was interconnected with subcortical structures (superior colliculus, thalamus, and caudate nucleus) as well as with cortical regions (primary and secondary visual areas, inferior temporal brain regions, posterior parietal association areas [area 7], frontal eye field, and prefrontal areas). These data demonstrate the important role of the pulvinar in human visual information processing and visuospatial attention. However, the direction of the neuronal response is still the subject of ongoing discussion. Tomasi et al. (2007) reported a hypoactivation of the medio-dorsal thalamus and the lateral geniculate body of the thalamus in cocaine abusers during a visuospatial attention task, whereas George et al. (2001) showed alcohol cue-induced dorsolateral prefrontal and anterior thalamus signal enhancement in alcoholics compared with healthy controls. Wang et al. (2007) demonstrated that right thalamus, orbitofrontal, and dorsolateral prefrontal cortex activation was related to abstinence-induced craving in smokers. These findings might reflect a dissociation within thalamic activity with respect to an addiction-related nature of the task. In common decision making paradigms (not referring to addiction-related stimulus material) there is evidence for a thalamic down-regulation in PG quite similar to the effects reported in cocaine users (Goldstein et al., 2007; Tomasi et al., 2007), whereas the

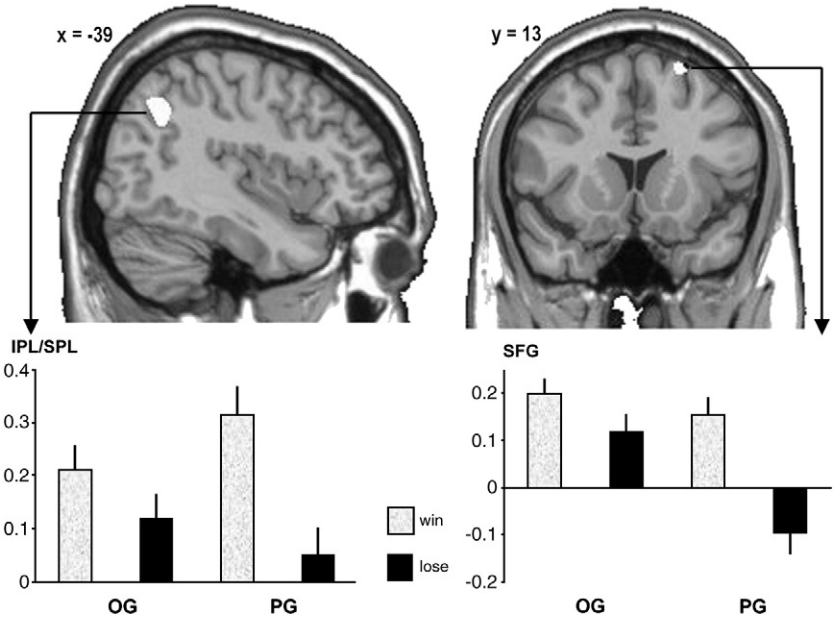

Fig. 4. Activation patterns and percent signal change (±1 SEM) resulting from the win vs. lose contrast in PG vs. OG ($P<0.001$ uncorrected) in the inferior parietal lobe/superior parietal lobe (IPL/SPL), and superior frontal gyrus (SFG). MNI-to-Talairach-transformed coordinates are given in Table 4.

processing of addiction-related stimuli enhances thalamic activity in PG, indicating cue-induced craving engagement.

Furthermore, the inferior frontal cortex (IFG) was found to be differentially activated in PG and OG in the high-risk vs. low-risk contrast. Potenza et al. (2003) related decreased activation in the right orbitofrontal cortex, basal ganglia, and thalamus in pathological gamblers compared with controls, while viewing videotaped scenarios with gambling content, to impulse regulation. Crockford et al. (2005), however, showed increased right dorsolateral prefrontal and right parahippocampal activity in pathological gamblers when compared with controls during gambling-related video material without an involvement of any actual gambling. The conflicting data were discussed with respect to differences in stimulus material and cue-induced craving (Wilson et al., 2004). These data might indicate that both IFG as well as the medial pulvinar activation in high-risk situations might reflect a cue-induced signal increase in PG. High-risk situations, characterized by physiological arousal, euphoria, distraction, and perceived control (Legg England and Gotestam, 1991), might serve as an addiction-cue in PG, while the low-risk situation signifies a "safe" hit in OG.

The higher right superior temporal gyrus (STG) activation in high-risk vs. low-risk task conditions in PG might be related to feature based serial exploratory search (Ellison et al., 2004) or intuitive judgments (Ilg et al., 2007). Similar to brain activity of the IGT reported in the anticipation phase (Lin et al., 2008), in the present task environment, the right STG might have been involved in updating the card constellation, especially in PG during high-risk assessment.

To conclude, neuronal correlates of problem gambling in the present quasi-realistic blackjack scenario might be characterized by an "expectancy shift" from looking for secure low-risk conditions in OG to seeking for thrilling high-risk situations in PG.

4.2. Win or lose situations and reward processing

With regard to our second hypothesis the nucleus accumbens showed a signal increase in win situations and a signal decrease in lose situations in both PG and OG corroborating the sensitivity of the dopaminergic reward system for reward processing in gambling (Blum et al., 1996). The present findings, showing a consistent ventral striatal signal increase across groups, corroborate the crucial role of the nucleus accumbens in human reward processing (Knutson et al., 2001). In contrast to Reuter et al. (2005), we did not find a differential activation of the accumbens in PG and controls, which might support our hypothesis that applying a quasi-realistic experimental paradigm will adjust striatal signal decrease in PG during reward processing. Additionally, this finding might also be related to differences in the experimental task design. In the study of Reuter et al. (2005), participants of a simple card-guessing game realized the moment of winning/losing the game immediately, whereas in the present quasi-realistic blackjack scenario, participants had first to calculate the sum of the card values before perceiving the win or loss information. Therefore, the relative high stimulus-complexity in the present experiment might have modulated reward processing (Fehr et al., 2007b).

Comparing PG with OG in the win vs. lose condition resulted in left inferior parietal, left superior parietal, and right premotor activations. The inferior parietal sulcus (IPS) has been reported to be activated during number tasks (Dehaene et al., 2003; Fehr et al., 2007a, 2008), while experiencing gains and losses (Lin et al., 2008), and is expected to play a crucial role in the amodal representation of quantity (Dehaene et al., 2004). Smolka et al. (2006) described left inferior parietal and right premotor cortex activation in a smoking-cue paradigm and demonstrated that brain activity in these regions correlated positively with the degree of nicotine dependence. Therefore, left parietal and right premotor activation, frequently associated with visuospatial attention (McCarthy et al., 1997; Kirino et al., 2000), motor preparation (Toni et al., 2002), and imagery (Rizzolatti and Craighero, 2004), might reflect neuronal correlates to the preparation of further gambling activity. Corroborating this line of argumentation, Fehr and colleagues (2006, 2007b) discussed early and late fronto-parietal ERP-differences between smokers and non-smokers during different nicotine-cue interference tasks as being related to addiction memory-related cue driven activation of neurally established perception–action cycle networks.

4.3. Limitations of the present study

There are several limitations of the present study. First, the OG group did not represent "normal control participants" naïve to the experimental condition as described in other studies related to the field of investigation. However, in order to focus on the differences between

normal and problematic gambling, we tried to test individuals who were equally familiar with blackjack gambling without demonstrating pathological gambling behavior. Consequently, PG and OG were rather similar with respect to blackjack gambling experience but significantly different with respect to overall gambling frequency. Second, ecological validity in the present experiment was limited as participants knew that they were playing against the computer in comparison to a casino situation playing against a person, a fact that also might have influenced neuronal activation patterns. In addition, only seven out of 12 PG fulfilled all DSM IV criteria for pathological gambling. Hence, it could be that the PG group in the present study suffered from a milder form of pathological gambling, although all participants in the PG group fulfilled the SOGS and KFG criteria for pathological gambling. Another shortcoming of the present study is that we only discriminated between smokers and non-smokers. It would have been more appropriate to assess the amount of cigarettes per day to test for differences regarding smoking behavior between groups more precisely. Furthermore, the group–related age difference was close to significant ($P = 0.10$) with a trend to higher age in the PG group, where compensatory activity due to declining neuronal structures (Park and Reuter-Lorenz, 2008) may have slightly biased our fMRI results. Another limitation of the study is that we could not clearly discriminate between risk assessment and preparatory stages of decision making. Different levels of risk implicated different decision behavior in both groups: Whereas hits and stands did not differ in high-risk situations, low-risk situations were almost exclusively characterized by hits. Nevertheless, as PG and OG did not differ in hit rate and response times (difference of high-risk-hit vs. high-risk-stand), and fMRI analyses did not demonstrate significant effects in both PG and OG in high-risk-hit vs. high-risk-stand and high-risk-stand vs. high-risk-hit contrasts, we assume that the reported results reflect group-specific differences in assessing different levels of perceived risk and not differences in decision making.

4.4. Conclusion

The present data suggest that problem gambling within a quasi-realistic and ecologically valid experimental setting is reflected in differential brain activation patterns during risk assessment and during reward processing. High-risk situations enhanced arousal-related brain networks in PG, whereas low-risk situations activated similar brain areas in OG. High-risk situations as well as winning money might serve as central addiction-cues for PG, which in turn activate addictive gambling behavior. In contrast to recent findings, the present data did not point to an alteration of reward-related activity in the accumbens in PG.

Acknowledgements

The present study was supported by a research grant (11/174/05) of the Bremen University Research Commission to Gerhard Meyer and Manfred Herrmann and by the BMBF Neuroimaging Program (01GO0202) from the Center for Advanced Imaging (CAI) to Manfred Herrmann). We would like to thank Dorit Kliemann and Juliana Wiechert for assistance during data acquisition.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2009.11.008.

References

Baldwin, R.R., Cantey, W.E., Maisel, H., McDermott, J.P., 1956. The optimum strategy in blackjack. Journal of the American Statistical Association 51 (275), 429–439.
Bechara, A., 2005. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nature Neuroscience 8 (11), 1458–1463.
Bechara, A., Damasio, A.R., Damasio, H., Anderson, S.W., 1994. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50 (1–3), 7–15.
Bechara, A., Damasio, H., Tranel, D., Damasio, A.R., 1997. Deciding advantageously before knowing the advantageous strategy. Science 275 (5304), 1293–1295.
Blair, R.J., 2001. Neurocognitive models of aggression, the antisocial personality disorders, and psychopathy. Journal of Neurology, Neurosurgery and Psychiatry 71 (6), 727–731.
Blum, K., Sheridan, P.J., Wood, R.C., Braverman, E.R., Chen, T.J., Cull, J.G., Comings, D.E., 1996. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. Journal of the Royal Society of Medicine 89 (7), 396–400.
Brand, M., Kalbe, E., Labudda, K., Fujiwara, E., Kessler, J., Markowitsch, H.J., 2005. Decision-making impairments in patients with pathological gambling. Psychiatry Research 133 (1), 91–99.
Brand, M., Labudda, K., Markowitsch, H.J., 2006. Neuropsychological correlates of decision-making in ambiguous and risky situations. Neural Networks 19 (8), 1266–1276.
Breiter, H.C., Gollub, R.L., Weisskoff, R.M., Kennedy, D.N., Makris, N., Berke, J.D., Goodman, J.M., Kantor, H.L., Gastfriend, D.R., Riorden, J.P., Mathew, R.T., Rosen, B.R., Hyman, S.E., 1997. Acute effects of cocaine on human brain activity and emotion. Neuron 19 (3), 591–611.
Brett, M., Johnsrude, I.S., Owen, A.M., 2002. The problem of functional localization in the human brain. Nature Reviews. Neuroscience 3 (3), 243–249.
Cavedini, P., Riboldi, G., Keller, R., D'Annucci, A., Bellodi, L., 2002. Frontal lobe dysfunction in pathological gambling patients. Biological Psychiatry 51 (4), 334–341.
Crockford, D.N., Goodyear, B., Edwards, J., Quickfall, J., el-Guebaly, N., 2005. Cue-induced brain activity in pathological gamblers. Biological Psychiatry 58 (10), 787–795.
Dehaene, S., Piazza, M., Pinel, P., Cohen, L., 2003. Three parietal circuits for number processing. Cognitive Neuropsychology 20, 487–506.
Dehaene, S., Molko, N., Cohen, L., Wilson, A.J., 2004. Arithmetic and the brain. Current Opinion in Neurobiology 14 (2), 218–224.
Due, D.L., Huettel, S.A., Hall, W.G., Rubin, D.C., 2002. Activation in mesolimbic and visuospatial neural circuits elicited by smoking cues: evidence from functional magnetic resonance imaging. American Journal of Psychiatry 159 (6), 954–960.
Ellison, A., Schindler, I., Pattison, L.L., Milner, A.D., 2004. An exploration of the role of the superior temporal gyrus in visual search and spatial perception using TMS. Brain 127 (10), 2307–2315.
Fehr, T., Wiedenmann, P., Herrmann, M., 2006. Nicotine Stroop and addiction memory — an ERP study. International Journal of Psychophysiology 62 (2), 224–232.
Fehr, T., Code, C., Herrmann, M., 2007a. Common brain regions underlying different arithmetic operations as revealed by conjunct fMRI-BOLD activation. Brain Research 1172, 93–102.
Fehr, T., Wiedenmann, P., Herrmann, M., 2007b. Differences in ERP topographies during color matching of smoking-related and neutral pictures in smokers and non-smokers. International Journal of Psychophysiology 65 (3), 284–293.
Fehr, T., Code, C., Herrmann, M., 2008. Auditory task presentation reveals predominantly right hemispheric fMRI activation patterns during mental calculation. Neuroscience Letters 431 (1), 39–44.
Franklin, T.R., Wang, Z., Wang, J., Sciortino, N., Harper, D., Li, Y., Ehrman, R., Kampman, K., O'Brien, C.P., Detre, J.A., Childress, A.R., 2007. Limbic activation to cigarette smoking cues independent of nicotine withdrawal: a perfusion fMRI study. Neuropsychopharmacology 32 (11), 2301–2309.
Friston, K.J., 2000. Experimental design and statistical issues. In: Mazziotta, J.C., Toga, A.W. (Eds.), Brain Mapping: The Disorders. Academic Press, San Diego, CA, pp. 33–58.
Gehring, W.J., Fencsik, D.E., 2001. Functions of the medial frontal cortex in the processing of conflict and errors. Journal of Neuroscience 21 (23), 9430–9437.
Gehring, W.J., Willoughby, A.R., 2002. The medial frontal cortex and the rapid processing of monetary gains and losses. Science 295 (5563), 2279–2282.
George, M.S., Anton, R.F., Bloomer, C., Teneback, C., Drobes, D.J., Lorberbaum, J.P., Nahas, Z., Vincent, D.J., 2001. Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. Archives of General Psychiatry 58 (4), 345–352.
Goldstein, R.Z., Alia-Klein, N., Tomasi, D., Zhang, L., Cottone, L.A., Maloney, T., Telang, F., Caparelli, E.C., Chang, L., Ernst, T., Samaras, D., Squires, N.K., Volkow, N.D., 2007. Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? American Journal of Psychiatry 164 (1), 43–51.
Goudriaan, A.E., Oosterlaan, J., de Beurs, E., van den Brink, W., 2005. Decision making in pathological gambling: a comparison between pathological gamblers, alcohol dependents, persons with Tourette syndrome, and normal controls. Brain Research. Cognitive Brain Research 23 (1), 137–151.
Goudriaan, A.E., Oosterlaan, J., de Beurs, E., van den Brink, W., 2006. Psychophysiological determinants and concomitants of deficient decision making in pathological gamblers. Drug and Alcohol Dependence 84 (3), 231–239.
Grant, J.E., Potenza, M.N., 2004. Pathological Gambling: A Clinical Guide To Treatment. Amer Psychiatric Pub Inc., Washington, DC.
Hewig, J., Trippe, R., Hecht, H., Coles, M.G., Holroyd, C.B., Miltner, W.H., 2007. Decision-making in blackjack: an electrophysiological analysis. Cerebral Cortex 17 (4), 865–877.
Hewig, J., Straube, T., Trippe, R.H., Kretschmer, N., Hecht, H., Coles, M.G.H., Miltner, W.H.R., 2009. Decision-making under risk: an fMRI study. Journal of Cognitive Neuroscience 21 (8), 1642–1652.
Holmes, A.P., Friston K.J., 1998. Generalisability, random effects, and population inference. Neuroimage 7, 754.
Ilg, R., Vogeley, K., Goschke, T., Bolte, A., Shah, J.N., Poppel, E., Fink, G.R., 2007. Neural processes underlying intuitive coherence judgments as revealed by fMRI on a semantic judgment task. NeuroImage 38 (1), 228–238.
Kirino, E., Belger, A., Goldman-Rakic, P., McCarthy, G., 2000. Prefrontal activation evoked by infrequent target and novel stimuli in a visual target detection task: an

event-related functional magnetic resonance imaging study. Journal of Neuroscience 20 (17), 6612–6618.
Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. Journal of Neuroscience 21 (16), RC159.
Ladouceur, R., Sévigny, S., Blaszczynski, A., O'Connor, K., Lavoie, M.E., 2003. Video lottery: winning expectancies and arousal. Addiction 98 (6), 733–738.
Legg England, S., Gotestam, K.G., 1991. The nature and treatment of excessive gambling. Acta Psychiatrica Scandinavica 84 (2), 113–120.
Leh, S.E., Chakravarty, M.M., Ptito, A., 2008. The connectivity of the human pulvinar: a diffusion tensor imaging tractography study. International Journal of Biomedical Imaging 2008, 789539.
Lesieur, H.R., Blume, S.B., 1987. The South Oaks Gambling Screen (SOGS): a new instrument for the identification of pathological gamblers. American Journal of Psychiatry 144 (9), 1184–1188.
Lin, C.H., Chiu, Y.C., Cheng, C.M., Hsieh, J.C., 2008. Brain maps of Iowa gambling task. BMC Neuroscience 9, 72.
McCarthy, G., Luby, M., Gore, J., Goldman-Rakic, P., 1997. Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. Journal of Neurophysiology 77 (3), 1630–1634.
Meyer, G., Schwertfeger, J., Exton, M.S., Janssen, O.E., Knapp, W., Stadler, M.A., Schedlowski, M., Kruger, T.H., 2004. Neuroendocrine response to casino gambling in problem gamblers. Psychoneuroendocrinology 29 (10), 1272–1280.
Mitchell, A.S., Browning, P.G., Wilson, C.R., Baxter, M.G., Gaffan, D., 2008. Dissociable roles for cortical and subcortical structures in memory retrieval and acquisition. Journal of Neuroscience 28 (34), 8387–8396.
Morgane, P.J., Galler, J.R., Mokler, D.J., 2005. A review of systems and networks of the limbic forebrain/limbic midbrain. Progress in Neurobiology 75 (2), 143–160.
Nichols, T., Hayasaka, S., 2003. Controlling the familywise error rate in functional neuroimaging: a comparative review. Statistical Methods in Medical Research 12 (5), 419–446.
Nichols, T., Brett, M., Andersson, J., Wager, T., Poline, J.B., 2005. Valid conjunction inference with the minimum statistic. NeuroImage 25 (3), 653–660.
Nummenmaa, L., Hirvonen, J., Parkkola, R., Hietanen, J.K., 2008. Is emotional contagion special? An fMRI study on neural systems for affective and cognitive empathy. NeuroImage 43 (3), 571–580.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1), 97–113.
Park, D.C., Reuter-Lorenz, P., 2008. The adaptive brain: aging and neurocognitive scaffolding. Annual Review of Psychology 60 (1), 173–196.
Petry, J., 1996. Psychotherapie der Glücksspielsucht. Beltz/Psychologie Verlags Union, Weinheim.
Petry, N.M., Stinson, F.S., Grant, B.F., 2005. Comorbidity of DSM-IV pathological gambling and other psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Journal of Clinical Psychiatry 66 (5), 564–574.
Potenza, M.N., 2006. Should addictive disorders include non-substance-related conditions? Addiction 101 (Suppl 1), 142–151.
Potenza, M.N., Steinberg, M.A., Skudlarski, P., Fulbright, R.K., Lacadie, C.M., Wilber, M.K., Rounsaville, B.J., Gore, J.C., Wexler, B.E., 2003. Gambling urges in pathological gambling: a functional magnetic resonance imaging study. Archives of General Psychiatry 60 (8), 828–836.
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. Nature Neuroscience 8 (2), 147–148.
Rizzolatti, G., Craighero, L., 2004. The mirror-neuron system. Annual Review of Neuroscience 27, 169–192.
Rogers, R.D., Owen, A.M., Middleton, H.C., Williams, E.J., Pickard, J.D., Sahakian, B.J., Robbins, T.W., 1999. Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. Journal of Neuroscience 19 (20), 9029–9038.
Schmahmann, J.D., 2003. Vascular syndromes of the thalamus. Stroke 34 (9), 2264–2278.
Self, D.W., Nestler, E.J., 1998. Relapse to drug-seeking: neural and molecular mechanisms. Drug and Alcohol Dependence 51 (1–2), 49–60.
Sewards, T.V., Sewards, M.A., 2003. Representations of motivational drives in mesial cortex, medial thalamus, hypothalamus and midbrain. Brain Research Bulletin 61 (1), 25–49.
Smolka, M.N., Buhler, M., Klein, S., Zimmermann, U., Mann, K., Heinz, A., Braus, D.F., 2006. Severity of nicotine dependence modulates cue-induced brain activity in regions involved in motor preparation and imagery. Psychopharmacology 184 (3–4), 577–588.
Talairach, J., Tournoux, P., 1988. Co-planar stereotaxic atlas of the human brain. Thieme, New York.
Tanabe, J., Thompson, L., Claus, E., Dalwani, M., Hutchison, K., Banich, M.T., 2007. Prefrontal cortex activity is reduced in gambling and nongambling substance users during decision-making. Human Brain Mapping 28 (12), 1276–1286.
Toce-Gerstein, M., Gerstein, D.R., Volberg, R.A., 2003. A hierarchy of gambling disorders in the community. Addiction 98 (12), 1661–1672.
Tomasi, D., Goldstein, R.Z., Telang, F., Maloney, T., Alia-Klein, N., Caparelli, E.C., Volkow, N.D., 2007. Thalamo-cortical dysfunction in cocaine abusers: implications in attention and perception. Psychiatry Research 155 (3), 189–201.
Toni, I., Thoenissen, D., Zilles, K., Niedeggen, M., 2002. Movement preparation and working memory: a behavioural dissociation. Experimental Brain Research 142 (1), 158–162.
Volkow, N.D., Fowler, J.S., Wang, G.J., Goldstein, R.Z., 2002. Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. Neurobiology of Learning and Memory 78 (3), 610–624.
Volkow, N.D., Fowler, J.S., Wang, G.J., 2003. The addicted human brain: insights from imaging studies. Journal of Clinical Investigation 111 (10), 1444–1451.
Wang, Z., Faith, M., Patterson, F., Tang, K., Kerrin, K., Wileyto, E.P., Detre, J.A., Lerman, C., 2007. Neural substrates of abstinence-induced cigarette cravings in chronic smokers. Journal of Neuroscience 27 (51), 14035–14040.
Wilson, S.J., Sayette, M.A., Fiez, J.A., 2004. Prefrontal responses to drug cues: a neurocognitive analysis. Nature Neuroscience 7 (3), 211–214.
Wulfert, E., Roland, B.D., Hartley, J., Franco, C., Wang, N., 2005. Heart rate arousal and excitement in gambling: winners versus losers. Psychology of Addictive Behaviors 19 (3), 311–316.
Yang, J., Li, H., Zhang, Y., Qiu, J., Zhang, Q., 2007. The neural basis of risky decision-making in a blackjack task. NeuroReport 18 (14), 1507–1510.
Zack, M., Poulos, C.X., 2004. Amphetamine primes motivation to gamble and gambling-related semantic networks in problem gamblers. Neuropsychopharmacology 29 (1), 195–207.
Zack, M., Poulos, C.X., 2007. A D2 antagonist enhances the rewarding and priming effects of a gambling episode in pathological gamblers. Neuropsychopharmacology 32 (8), 1678–1686.