ORIGINAL RESEARCH

The neural basis of impulsive discounting in pathological gamblers

Stephan F. Miedl · Daniel Wiswede · Josep Marco-Pallarés · Zheng Ye · Thorsten Fehr · Manfred Herrmann · Thomas F. Münte

Abstract Pathological gambling is thought to result from a shift of balance between two competing neurobiological mechanisms: on the one hand the reward system involved in the regulation of the urge to get rewards and on the other hand the top-down control system. Fifteen pathological gamblers (PG) and fifteen healthy controls (HC) were studied in an event-related functional magnetic resonance imaging experiment where participants had to choose either a smaller, but immediately available monetary reward (SIR) or a larger delayed reward (LDR). We examined contrasts between LDR and SIR decisions. Additionally, we contrasted choices near the individual indifference point (indifferent decisions) and clear SIR or LDR choices (sure decisions). Behavioral data confirmed former results of steeper discount rates in PG. Contrasting choices of LDR vs. SIR showed widespread bilateral activations in PG, including postcentral gyrus, thalamus, superior/medial frontal gyrus and cingulate gyrus, whereas HC demonstrated only focal left-sided pre/postcentral activity. Forgoing an immediate reward thus recruits a widespread brain network including typical control areas. Indifferent vs. sure decisions were associated with widespread activation in PG, including the bilateral fronto-parietal cortex, insula, anterior cingulate gyrus, and striatum, whereas in HC, only bilateral frontal cortex and insula were activated. The reverse contrast demonstrated more activity for sure decisions in the cingulate gyrus, insula, and medial frontal gyrus in HC, whereas PG showed inferior parietal and superior temporal activity. The present study demonstrates that pathological gambling is associated with a shift in the interplay between a prefrontal-parietal control network and a brain network involved in immediate reward consumption.

Keywords Delay discounting · Intertemporal choice · Pathological gambling · fMRI · Reward

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Introduction

Pathological gambling has been increasingly recognized as a health problem and is classified in the DSM IV as an impulse control disorder. Patients present with persistent and recurrent maladaptive patterns of gambling leading to impaired social functioning, severe financial problems, and consequent psychosocial problems (Petry et al. 2005; Grant et al. 2010b). Prevalence rates for pathological gambling have been estimated to be as high as 1 % (Cunningham-Williams et al. 1998; Shaffer et al. 1999).

The impulsive gambling behavior of PG can be conceptualized as the result of a shift of balance between two competing cognitive and—by extension—neurobiological mechanisms: on the one hand there is the reward system mediating the urge to retrieve rewards, which is opposed on the other hand by top-down (frontal) control systems (Grant et al. 2010a; McClure et al. 2004). The interplay of these two systems can be studied in intertemporal choice paradigms. These paradigms create a situation, in which either an early smaller reward or a larger later reward can be chosen. Delay discounting in intertemporal choice refers to the reduction of the present value of the later reward as the delay to that reward increases (Kirby et al. 1999). Indeed, PG discount delayed rewards at higher rates than controls (Petry 2001b) and gambling severity has been found to be the best single predictor of impulsive behavior in a delay discounting task in PG (Alessi and Petry 2003). Empirical evidence in humans and animals suggests that future gains are discounted in a hyperbolic (Frederick et al. 2003; Mazur 1984) or quasi-hyperbolic fashion (McClure et al. 2004; Laibson 1997). Hyperbolic discounting can be captured by the following function:

$$V = \frac{A}{1 + kD}$$

where V is the present value of the delayed reward A after a delay D, and k is the *delay discount rate*. A higher delay discount rate indicates a steeper discount function, i.e., a more pronounced devaluation of future rewards. Quasi-hyperbolic discounting has been proposed as an alternative (e.g., Laibson 1997; McClure et al. 2004). Here, two different discounting functions are spliced together, i.e., one that makes a principal distinction between the immediate present and the future and one that discounts exponentially and more shallowly. While there is empirical support for quasi-hyperbolic models, a good approximation of discounting behavior can often be reached with the simpler hyperbolic model (McKerchar et al. 2009). For example, steeper discounting functions have not only been found in PG (Alessi and Petry 2003; Petry 2001b) but also in substance addiction to heroine and cocaine (Kirby and Petry 2004; Kirby et al. 1999), tobacco (Reynolds 2004; Reynolds et al. 2004) and alcohol (Mitchell et al. 2005; Petry 2001a). A growing number of studies have used functional imaging to investigate the neural systems involved in delay discounting (e.g., Bickel et al. 2009; Boettiger et al. 2007; Engelmann and Brooks 2009; Hariri et al. 2006; Kable and Glimcher 2007; Luhmann et al. 2008; McClure et al. 2004, 2007; Peters and Büchel 2009; Pine et al. 2009; Weber and Huettel 2008; Xu et al. 2009; Marco-Pallares et al. 2010; Cooper et al. 2013; Costa Dias et al. 2013; Hare et al. 2014). We have previously focused on inter-individual differences in delay discounting and compared choices at or near the individual

indifference point, i.e., choices for which the immediately available reward and the delayed reward had roughly the same value for the individual, with choices clearly favoring either the immediate or the delayed reward (Marco-Pallares et al. 2010). Clear preference decisions were associated with activation in the ventral striatum and ventromedial prefrontal cortex; decisions at the indifference point gave rise to activation in medial prefrontal cortex, which was interpreted as a reflection of response conflict. A number of other neuroimaging studies have also examined individual differences in intertemporal choice (Kable and Glimcher 2007; Peters and Büchel 2009; Hariri et al. 2006) and will be examined in detail in the discussion section.

In the present investigation, we adopted the paradigm of Marco-Pallares et al. (2010) (Fig. 1) to investigate a group of 15 PG, diagnosed according to DSM IV criteria, and 15 matched healthy control participants (HC). We expected larger k-values in the PG group than in the HC group, as steeper discounting has been described as a consistent feature of PG. With regard to neuroimaging, we contrasted choices for large delayed rewards (LDR) with choices for small immediate rewards (SIR). Here, we expected differences between PG and HC in two systems. First we expected a more extensive recruitment of brain areas involved in executive control in PG whenever these subjects chose the LDR. Second, with regard to the core structures of the reward system (i.e., ventral striatum, nucleus accumbens) we expected greater activation in the PG for SIR decisions.

Moreover, we also examined the contrast between choices near the indifference point and clear choices for either LDR or SIR similar to our previous study (Marco-Pallares et al. 2010). Following our earlier results, we expected a recruitment of executive control areas for choices at the individual indifference point. We had no specific hypothesis with regard to differences between PG and HC for this comparison, as this contrast controlled for individual differences in k.

Methods

Participants

The study group comprised 15 male PG (range 27–47 years) and 15 male HC (range 28–44 years). All participants were right handed according to a modified version of the Edinburgh Handedness Questionnaire (Oldfield 1971). Groups did not differ in age (t(14)=.18, p=.86), number of smokers per group (both groups 11 smokers), quantitative smoking behavior (t(14)=−.43, p=.67), income per month (t(14)=−.32, p=.75), or years of education (t(14)=1.07, p=.30, see Table 1). Participants were recruited through advertisements, self-help groups, and other sources. The percentage of income spent on gambling activities was significantly higher in PG

Fig. 1 Experimental Paradigm: First, a fixation "+" sign appeared in the screen. After 8 s, the two options were presented (preparation phase). After an additional 4 s the fixation "+" turned to an "x" and subjects had to indicate their choice (response phase)
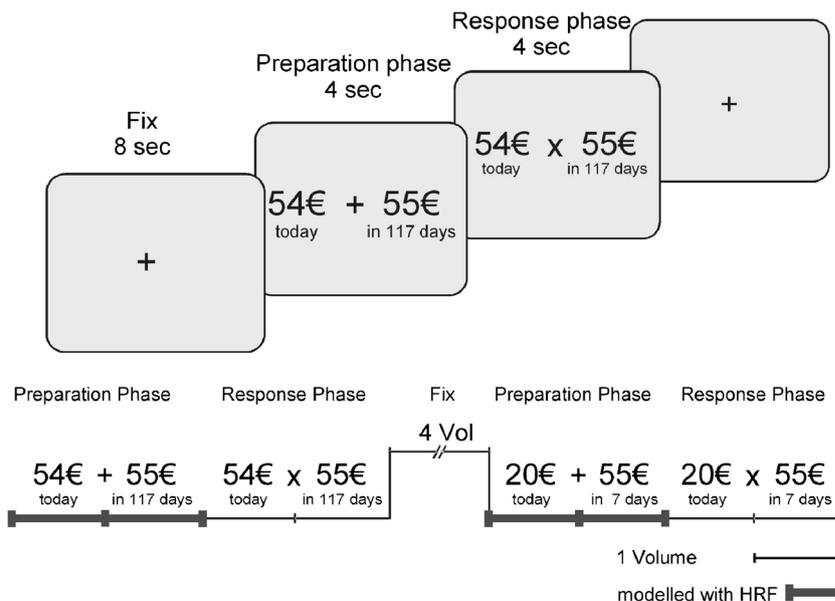
compared to HC (t(14)=−2.65, p=.02; see Table 1). PG predominantly engaged in slot machines, roulette, or internet-poker.

HC and PG neither reported a history of psychiatric or neurological illness (other than pathological gambling) nor regular drug use (except smoking and moderate amounts of alcohol) and were not under current medication. In the PG group, all participants had a diagnosis of pathological gambling according to DSM IV (≥5 criteria). Furthermore, all individuals were assessed with the German gambling questionnaire "Kurzfragebogen zum Glücksspielverhalten" (KFG; 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 high (Petry 1996). This questionnaire contains 20 items (4-point Likert-scale: 0 to 3

Table 1 Demographic data of participants

	PG (n=15)	Control (n=15)	
Age (years)	36.7±5.8	36.8±5.6	t(14)=.18, p=.86
cigarettes per day	14±11.2	12.4±7.7	t(14)=−.43, p=.67
DSM IV	6.8±1.8	0.3±0.6	t(14)=−12.55, p<.001
SOGS	10.9±2.8	0.8±1.3	t(14)=−11.14, p<.001
KFG	34.1±7.6	2.7±4.5	t(14)=−12.08, p<.001
Income spent on gambling (%)	82.1±116	2.4±3	t(14)=−2.65, p=.02
Income in € per month	1533±823	1450±642	t(14)=−.32, p=.75
Years of education	15.5±2.7	16.1±3.1	t(14)=1.07, p=.30

DSM IV – number of criteria fulfilled; SOGS and KFG – raw points

Abbreviations: *DSM IV* Diagnostic and Statistical Manual, 4th edition, *SOGS* South Oaks Gambling Screen, *KFG* Kurzfragebogen zum Glücksspielverhalten (German for Short Questionnaire on Gambling Behavior)

points) addressing lifetime gambling behavior. The threshold for pathological gambling is set at 16 points. All PG scored between 21 and 43 points, whereas HC scored between 0 and 16 points, implying that the latter group contained subjects engaging in recreational gambling. In addition, all participants were evaluated with a German version of the South Oaks Gambling Screen (SOGS) (Lesieur and Blume 1987). All PG scored≥6 points on the SOGS, and HC obtained≤4 points. Both groups significantly differed with respect to DSM IV (t(14)=−12.55, p<.001), SOGS (t(14)=−11.14, p<.001), and KFG scores (t(14)=−12.08, p<.001; Table 1). The study protocol complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1984) and was approved by the local ethics committee at the University of Bremen. All participants were informed about the procedure and gave written informed consent to participate.

Paradigm

A version of the monetary-choice task devised by Kirby (Kirby et al. 1999) and adapted to an fMRI environment by Marco-Pallares et al. (2010) was used. Participants took part in 4 runs, each with a fixed set of 27 choices between SIR and LDR (Table 2). The order of trials within each run was arranged such that the trial order correlated with neither the SIR or LDR amounts, nor with the temporal difference, delay, or the discounting rate. Each trial began with a fixation cross (+) that lasted 8 s followed by the two choices which were displayed while the cross was continuously present (e.g., "55 € today+57 € after 117 days", see Fig. 1).

After 3 s, the "+" (fixation cross) changed to an "x", and the participant was required to select the preferred option. Responses were given with the index finger of the right hand on an MR-compatible response-pad, pressing the left button

Table 2 Choices presented in run 1 and 3

	Order 1st run	Order 3rd run	SIR	LDR	Delay (days)	K indiff	K rank	LDR size
1	13	22	€ 34	€ 35	186	0.00016	1	S
2	1	7	€ 54	€ 55	117	0.00016	1	M
3	9	26	€ 78	€ 80	162	0.00016	1	L
4	20	15	€ 28	€ 30	179	0.0004	2	S
5	6	2	€ 47	€ 50	160	0.0004	2	M
6	17	18	€ 80	€ 85	157	0.0004	2	L
7	26	9	€ 22	€ 25	136	0.001	3	S
8	24	11	€ 54	€ 60	111	0.001	3	M
9	12	23	€ 67	€ 75	119	0.001	3	L
10	22	13	€ 25	€ 30	80	0.0025	4	S
11	16	19	€ 49	€ 60	89	0.0025	4	M
12	15	20	€ 69	€ 85	91	0.0025	4	L
13	3	5	€ 19	€ 25	53	0.006	5	S
14	10	25	€ 40	€ 55	62	0.006	5	M
15	2	6	€ 55	€ 75	61	0.006	5	L
16	18	17	€ 24	€ 35	29	0.016	6	S
17	21	14	€ 34	€ 50	30	0.016	6	M
18	25	10	€ 54	€ 80	30	0.016	6	L
19	5	3	€ 14	€ 25	19	0.041	7	S
20	14	21	€ 27	€ 50	21	0.041	7	M
21	23	12	€ 41	€ 75	20	0.041	7	L
22	7	1	€ 15	€ 35	13	0.1	8	S
23	8	27	€ 25	€ 60	14	0.1	8	M
24	19	16	€ 33	€ 80	14	0.1	8	L
25	11	24	€ 11	€ 30	7	0.25	9	S
26	27	8	€ 20	€ 55	7	0.25	9	M
27	4	4	€ 31	€ 85	7	0.25	9	L

Note that in runs 2 and 4 trials were presented representing the same K values but with slightly different absolute amounts

SIR small immediate reward, *LDR* large delayed reward, *K indiff* delay discounting value at which the two decisions are of equal subjective value, *K rank* trials were ranked according to K indiff into 9 classes, *LDR size* the size of the delayed reward was classified as small (S, between 25 and 35 €), medium (M, between 50 and 60 €) and large (L, between 75 and 85 €)

for left choice (in this case SIR) and with the middle finger pressing the right button for the right choice (in this case LDR). Each participant received € 16 for participation. In addition, to provide an incentive to perform the decisions as if they were real, participants were informed prior to the experiment that after the experiment they would receive the outcome of one of their 108 decisions. Participants were allowed to draw a trial number after the experiment was finished and their decision on that particular trial was derived from the log-files of the experiment. If the participant had chosen the immediate reward, he received the sum in cash, in case of a choice for the delayed reward the sum was transferred to the participant's bank account after the appropriate delay period.

Based on the results of earlier studies (e.g., Kirby 1997; Green et al. 1994; Raineri and Rachlin 1993) which had shown that discount rates decrease as the amounts of the rewards increase, the current paradigm grouped delayed rewards into three reward sizes, small (€25 to €35), medium (€50 to €60), and large (€75 to €85) as suggested by Kirby et al. (1999).

Image acquisition

MRI data were recorded using a 3-T Siemens Magnetom Allegra head scanner (Siemens, Erlangen, Germany) equipped with a standard quadrature head coil. Subjects were positioned on a scanner couch in a slightly dimmed fMRI chamber, and they wore foam earplugs to reduce scanner noise. A T1-weighted structural 3D image of the brain was obtained using the MPRAGE sequence: 176 contiguous slices, TR=2.3 s, TE=4.38 ms, TI=900 ms, FA=8°, FOV 256×256 mm, in-plane resolution 1×1 mm, slice thickness 1 mm.

Functional scans were performed using a single shot echo planar imaging sequence (EPI). T2*-weighted whole brain volumes were acquired in four runs with 193 volumes each (EPI-sequence; TR=2000 ms, TE=30 ms, flip angle =80°, FOV 192 mm, matrix 64×64, 34 slices, slice thickness 3 mm, interleaved acquisition order, standard AC-PC- Orientation, 2 dummy scans prior to data acquisition, four runs).

fMRI analysis

Data were analyzed and visualized using Brain Voyager QX 1.10 and 2.0 (Brain Innovation, Maastricht, Netherlands) and SPSS 13.0. Preprocessing was carried out as recommended in the Brain Voyager user guide (http://support.brainvoyager. com/functional-analysis-preparation/27-pre-processing/320- users-guide-preprocessing-of-functional-data.html). Functional data were slice-time corrected, motion parameters were estimated, and motion was corrected relative to the first volume of the run (trilinear/sinc interpolation). To remove low frequency drifts, data were high-pass filtered (3 cycles, three sine waves fall within the extent of the data). Structural and functional data were transformed into the standard space of Talairach and Tournoux (1988). Talairach data points were labelled using Talairach Daemon (Lancaster et al. 2000). The design matrix was modeled using the two gamma hemo-dynamic response functions for the preparation phase of the task (see thick lines in Fig. 1). To accommodate residual ana-tomical differences across subjects and to improve signal-to-noise ratio, functional data were smoothed using an 8 mm full-width-half-maximum isotropic Gaussian kernel.

Group data were analyzed using random effects analysis in the GLM framework based on z-transformed functional data. The analysis was highly comparable to that presented by Marco-Pallares et al. (2010). The first analysis included the within subject factor "decision" (SIR vs. LDR) and the be-tween subject factor group (HC vs. PG). In addition, we per-formed a GLM comparing indifferent vs. sure decisions (fac-tor "conflict"), which also contained a group factor. To make this comparison, we selected for each subject and each run, the six choices that presented a k-value closest to the individual k-rate and compared these choices against the other pairs. For example, if a participant presented an individual k-value of 0.0098 for the first run, the 13th to 18th choices in Table 2 were compared against the other choices. We make the as-sumption that the participant is indifferent to the two choices in these pairs, while he is sure about his decisions in the others.

Separate brain maps were generated for the main effects and interactions. The main effects are displayed as a T-statis-tic, which yields the same results as the F statistics, but allows to color-code the direction of changes. Maps are shown with a threshold of $p < 0.001$ uncorrected with a cluster size threshold of 10 voxels. All voxels activated at this threshold are displayed in the figures in native resolution without interpola-tion and plotted on the Talairach-transformed "Colin27-brain" (Holmes et al. 1998). For an activated cluster, the center of gravity was determined (Kim et al. 1997), which is defined as the average position of ROI voxels weighted by their T values. To correct for multiple comparisons, we determined a spatial extent threshold by 1,000 Monte Carlo simulations conducted using the AlphaSim program in AFNI. The criteria input to AlphaSim included uncorrected p-value (.001), voxel

size ($3 \times 3 \times 3$), spatial smoothing kernel (8 mm), and the num-ber of voxels of the whole brain mask (63900). Based on these parameters, a cluster extent of 22 voxels was necessary in order to achieve a corrected threshold of $p < .05$. In the tables, all clusters significant at this corrected level (corresponding to a size of 594 mm^3) are marked with an asterisk.

To pinpoint interaction effects, beta-values were extracted from the maxima of the activated clusters and subjected to analyses of variance (ROI analysis).

Results

Behavioral data

PG presented higher delay discount (k) values (0.06 ± 0.08) compared to HC (0.02 ± 0.03) (see Fig. 2). To allow parametric statistical testing, k-values were log-transformed and an ANOVA was performed with group (PG vs. HC) as between and size of LDR (small, medium, large) as within factors. There was a main effect of group (F1,28)=6.94, $p < 0.02$) but no significant interaction of the two factors (F(1,28)=2.43, p= 0.13). The consistency (percentage of participant's choices that were consistent with their assigned discount rate) was 96 ± 4 % (PG: 95 ± 4 %; HC: 96 ± 4 %) over all 4 runs. There were no significant differences between groups in consistency across the different runs (HC: 1st run: 95 ± 6 %; 2nd run: 96 ± 3 %, 3rd run: 94 ± 5 %, 4th run: 95 ± 5 %; PG: run: 98 ± 4 %; 2nd run: 97 ± 4 %, 3rd run: 95 ± 6 %, 4th run: 95 ± 5 %; F (3, 84)=3.4, $p > 0.7$).

For response times (HC: LDR 1193 ± 342 ms, SIR 962 ± 345 ms; PG: LDR 1064 ± 322 ms, SIR 893 ± 272 ms) neither a significant main effect of group (F(1,28)=0.8; $p = 0.4$) nor a group × decision interaction (F(1,28)=0.8; $p = 0.4$) emerged. The longer RTs in LDR compared with SIR decisions led to a main effect of the factor decision (F(1,28)=33.9, $p < 0.001$).
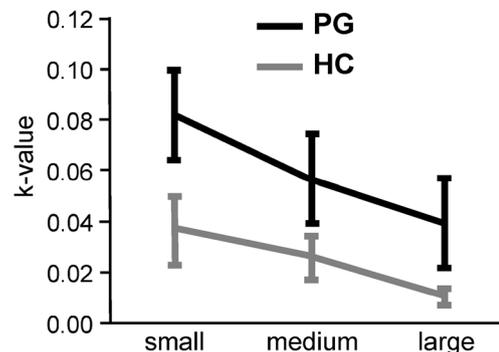

Fig. 2 K-values for small, medium, and large LDR for the two groups. Rewards are discounted more steeply by PG than HC. Moreover, smaller rewards are discounted more steeply than larger rewards in both groups. *Error bars* indicate standard error of the mean

fMRI results

Effects of decisions

A decision × group interaction was found in bilateral inferior parietal lobule, posterior cingulate, and left superior frontal regions (Fig. 3b, Table 3). This interaction was driven by higher beta value differences between LDR and SIR in PG relative to HC. This is also apparent in the ROI analysis (Fig. 4).

The comparison of LDR vs. SIR demonstrates widespread activations in PG, including bilateral inferior parietal lobule extending to the postcentral gyrus, thalamus, superior/medial
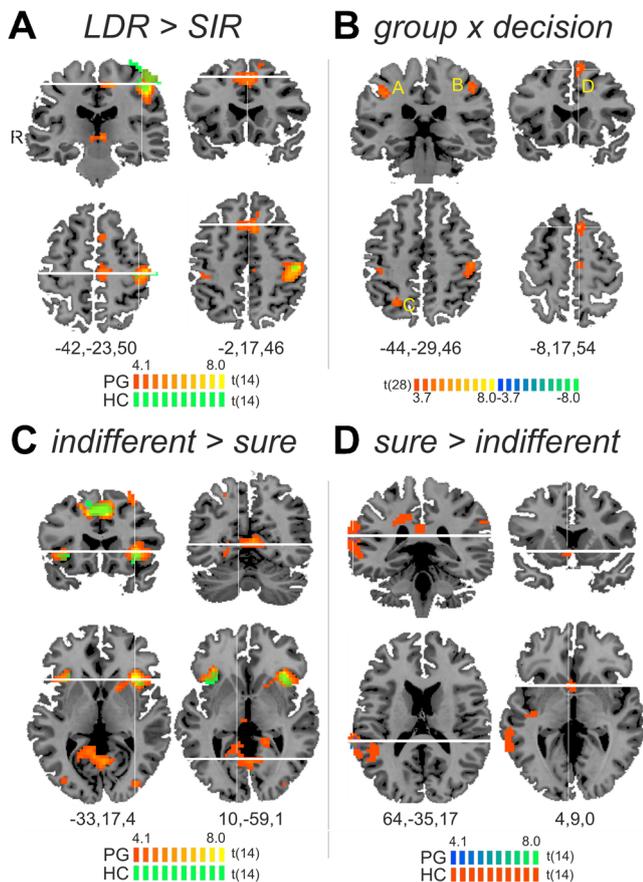

Fig. 3 **a** Activation differences between decisions for LDR and decisions for SIR separately for PG and HC. Whereas only a circumscribed activation in sensorimotor cortex was observed in HC, a number of brain areas were seen for this contrast in PG (see text). **b** Significant effects for the decision × group interaction were obtained in the Inferior Parietal Lobule (IPL), superior frontal gyrus (SFG), cuneus, precuneus, and cingulate gyrus (PCC). The interaction effect is shown in more detail in Fig. 4 for the identified regions. **c** Activation pattern for the contrast indifferent vs. sure for PG and HC. Both groups show activation of cingulate gyrus, supplementary motor area, and the bilateral insula. These areas have been associated with the processing of response conflict. **d** Only HC participants showed activation for the sure > indifferent contrast in the caudate nucleus and parietal and cingulate cortex

frontal gyrus, and cingulate gyrus, whereas HC only show focal activity in pre/postcentral regions (Fig. 3a and Table 4). The reverse contrast (SIR vs. LDR) revealed no significant effects at the specified statistical threshold.

Effects of conflict

The conflict × group interaction reveals significant effects in bilateral superior and middle frontal gyrus, insula, brainstem, precuneus, and cingulate gyrus (Table 5). These results are due to higher beta value differences between indifferent and sure decisions in PG relative to controls (see Fig. 3c and 3d).

In PG, indifferent decisions compared to sure decisions were associated with widespread activity including the bilateral fronto-parietal cortex, insula, anterior cingulate gyrus, and striatum, whereas HC showed activity in bilateral frontal cortex and insula only (Fig. 3c, Table 6). By contrast, HC showed more activity for sure compared to indifferent decisions in the cingulate gyrus, insula, and medial frontal gyrus, whereas PG showed inferior parietal and superior temporal activity for the same contrast (Fig. 3d, Table 7).

Discussion

In the present paper, we analyzed the neural basis of intertemporal choice in PG. Expectedly, PG discounted future rewards more steeply than control participants. Applying the formula of Mazur (1984, see Introduction) to the mean discount rate k of PG and HC (0.06 and 0.02, respectively) this means that a sum of 100 Euros is worth only 25 Euros after a delay of 50 days for PG, whereas it is worth 50 Euro for the control participants. By comparison, the mean discount rate

Table 3 Significant clusters for the group × decision interaction ((LDR_PG > SIR_PG) > (LDR_control > SIR_control)); $p < .001$, cluster-threshold 10 Voxel

Regions	Side	BA	Cluster size mm3	X	Y	Z	t
Inferior Parietal Lobule, Postcentral G	L	40,2	918	−44	−27	46	4.7
Superior Frontal G	L	6,8	756	−8	17	54	4.4
Inferior Parietal Lobule, Postcentral G	R	40,2	648	38	−29	41	5.1
Precuneus, Superior Parietal Lobule	R	7	432	25	−59	46	4.5
Cingulate G, Cuneus, Precuneus	R	31,7	405	6	−61	31	4.4

X,Y, Z values indicate center of gravity of the cluster in Talairach-space. Regions were labelled according to Lancaster et al. (2000). Column "t" represents maximal *t*-value for the given cluster

G Gyrus, *L* left, *R* right, *BA* Brodmann area

Fig. 4 Region of interest analysis for the interaction between group and decision for the regions indicated in Fig. 3b. For all four regions, PG showed an increase of activity for LDR relative to SIR decisions, whereas for HC, activity levels were similar for LDR and SIR decisions
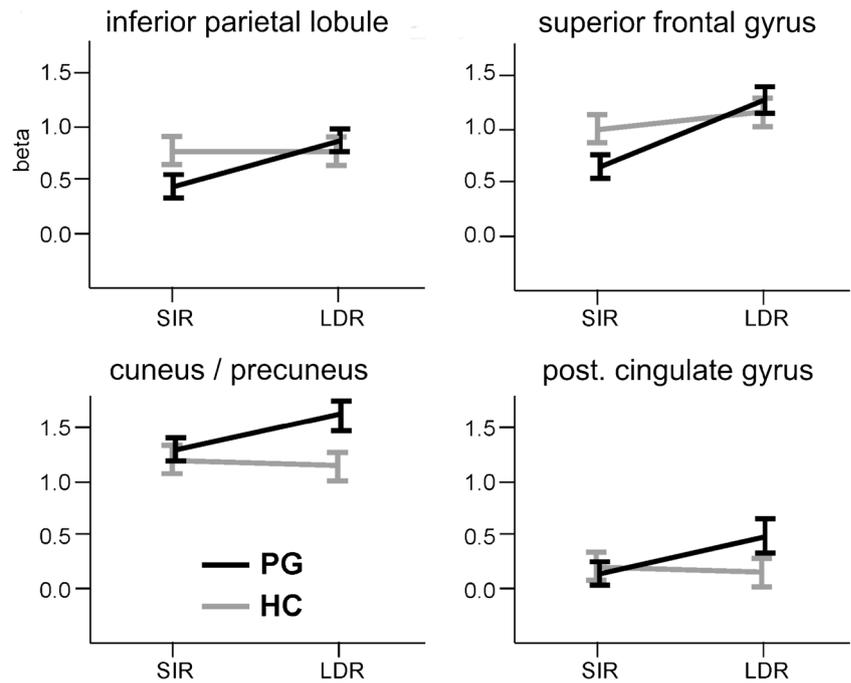
was 0.0074 in our earlier study of healthy students (Marco-Pallares et al. 2010) resulting in a devaluation of 100 Euros to 73 Euros after 50 days. A study on more than 500 students in

Table 4 Significant clusters of the main effect of decision (LDR > SIR); *p*<.001, cluster-threshold 10 Voxel

Regions	Side	BA	Cluster size mm3	X	Y	Z	t
PG							
Postcentral/ precentral G, Inferior Parietal Lobe	L	3,2,6,4, 40,1	6453*	−42	−23	50	8.7
Cingulate G, Medial / Superior Frontal G	R/L	6,8,32	3159*	−2	17	46	5.7
Inferior Parietal Lobule / Postcentral G	R	40,2	1134	38	−30	41	7.1
Medial Frontal G	L	6	972	−8	−22	51	6.5
Thalamus/Brainstem	R/L	*	945	2	−19	1	5.7
Precentral G	R	6,4	540	36	−10	59	5.2
Superior Frontal G	R	6	351	23	8	66	5.1
Claustrum, Inferior Frontal G, Insula	L	47,13	351	−30	24	1	5.5
HC							
Postcentral G	L	3,1,2	2979*	−38	−26	64	5.8
Postcentral/Precentral G	L	3,4	297	−40	−23	50	4.4

X,Y,Z values indicate center of gravity of the cluster in Talairach-space. Regions were labelled according to Lancaster et al. (2000). Column "t" represents maximal t-value for the given cluster

G Gyrus, *L* left, *R* right, *BA* Brodmann area

*Cluster surviving correction based on simulations conducted using AlphaSim included in AFNI

the USA revealed a similar discount rate (0.007) using the same paradigm (Kirby and Marakovic 1996). This underscores the exceedingly steep discounting function in our PG sample. The relatively high discount rate in our control participants can probably be attributed to our careful matching procedure, which resulted in a very high rate of smokers in the control group. For smokers, higher discount rates have been reported (Reynolds 2004; Reynolds et al. 2004).

The pronounced behavioral differences in delay discounting were accompanied by marked differences in brain activations. Whereas in controls, the contrast between LDR and SIR decisions revealed only small activation zones in

Table 5 Significant clusters for the group × conflict interaction; *p*<.001, cluster-threshold 10 Voxel

Regions	Side	BA	Cluster size mm3	X	Y	Z	t
Superior Frontal G, Middle Frontal G	R	8,6	1080*	28	24	59	6.5
Middle Occipital G	L	19	783*	−38	−80	10	7.4
Middle Temporal G							
Middle Frontal G	R	6	540	28	7	65	5.1
Superior Frontal G							
Insula	L	13	324	−33	25	10	4.7
Cingulate G	R	31	297	8	−33	33	5.3
Precuneus	L	19	270	−8	−82	39	4.8
Middle occipital G	R	19	135	32	−80	8	4.9

X,Y, Z values indicate center of gravity of the cluster in Talairach-space. Regions were labelled according to Lancaster et al. (2000). Column "t" represents maximal t-value for the given cluster

G Gyrus, *L* left, *R* right, *BA* Brodmann area

Table 6 Significant regions for the contrast indifferent > sure

Regions	Side	BA	Cluster size mm3	X	Y	Z	t
PG							
Anterior Cingulate, Cingulate G, Medial Frontal G, Superior Frontal G	R/L	24,32,6,8,9	15525*	4	22	41	11.7
Fusiform G, Cerebellum, Lingual G, Parahippocampal G, Posterior Cingulate	R/L	19,30,18,29	5265*	10	−59	1	6.1
Caudate, Claustrum, Inferior Frontal G, Insula, Putamen	L	47,13,45	4023*	−33	17	4	9.4
Inferior Frontal G, Insula	R	47,45,13	1377*	35	21	2	6.3
Middle Frontal G, Superior Frontal G	L	6,8	1053*	−30	13	52	6.7
Cuneus, Precuneus	R	18,19,31	1026*	27	−79	25	5.8
Brain Stem			945*	1	−18	−5	6.9
Middle Occipital G	L	19	810*	−33	−79	8	5.5
Precuneus	L	19,7	567	−27	−68	33	6.1
Superior Frontal G	L	6	486	−15	22	64	5.4
Middle Occipital G	R	19	459	32	−79	8	5.4
Precuneus	R	7	459	25	−65	37	6.0
Middle Frontal G	L	10	432	−33	45	13	6.5
Precuneus, Superior Parietal Lobule	R	7	351	22	−62	48	5.2
Middle Frontal G	L	6	324	−32	1	65	5.4
Lingual G, Parahippocampal G	L	19,30	270	−16	−42	0	4.8
Controls							
Cingulate G, Medial Frontal G, Superior Frontal G	R	32,8,6,9	4914*	2	22	41	9.4
Insula, Inferior Frontal G	L	13,47	675*	−34	16	0	6.0
Insula, Inferior Frontal G, Claustrum	R	13,47	567	33	18	0	5.2
Middle Frontal G	L	46	270	−47	34	23	4.8

Column "t" represents maximal t-value for the given cluster. Regions were labelled according to Lancaster et al. (2000)

G Gyrus, *L* left, *R* right, *BA* Brodmann area

*Cluster surviving correction based on simulations conducted using AlphaSim included in AFNI

Table 7 Significant regions for the contrast sure > indifferent, Column "t" represents maximal t-value for the given cluster

Regions	Side	BA	Cluster size mm3	X	Y	Z	t
PG							
Inferior Parietal Lobule, Superior Temporal G	R	40,42,22	864*	64	−35	17	−6.7
HC							
Inferior Parietal Lobule, Superior Temporal G, Middle Temporal G, Postcentral G	R	40,22,21, 2,42,3	7326*	61	−34	18	−8.7
Cingulate G, Precuneus	R	31	1485*	20	−35	33	−7.5
Insula, Superior Temporal G	R	13	1431*	45	−44	20	−8.6
Cingulate G, Posterior Cingulate	R\L	31, 23	783*	3	−37	27	−6.5
Postcentral G, Precentral G	L	3, 4	729*	−33	−21	48	−6.4
Cingulate G	L	24,6,31	513	−4	−7	48	−5.2
Supramarginal G, Inferior Parietal Lobule	L	40	486	−56	−38	30	−5.5
Caudate	R		459	4	9	0	−8.3
Postcentral G, Precuneus	L	7	324	−8	−51	62	−5.7
Insula, Claustrum, Superior Temporal G	R	13,22	324	39	−18	0	−5.6
Parahippocampal G	L		270	−25	−3	−15	−5.7
Postcentral G	L	2, 1	270	−57	−19	47	−5.0

Regions were labelled according to Lancaster et al. (2000)

G Gyrus, *L* left, *R* right, *BA* Brodmann area

*Cluster surviving correction based on simulations conducted using AlphaSim included in AFNI

the sensorimotor cortex, extensive activations were observed in PG, including the sensorimotor cortex, cingulate cortex, inferior, medial, and superior frontal gyri, inferior parietal lobule, insula, and thalamus. The finding of largely missing activation differences between LDR and SIR in controls is similar to our earlier study in students (Marco-Pallares et al. 2010). A likely interpretation of this pattern of results is that PG, in order to choose the LDR, have to recruit prefrontal areas that have often been associated with executive control processes (Doya 2008; Krämer et al. 2007; Marco-Pallares et al. 2008; Miller and Cohen 2001). More specifically, McClure et al. (2004) following economic theories (Laibson 1997) have proposed the existence of two different neural systems to explain the data pattern observed in an intertemporal choice paradigm: a "β-system" mainly comprising the ventral striatum and orbitofrontal cortex is presumably engaged by choices involving immediate rewards, and a δ-system encompassing prefrontal and parietal regions which is thought to be active in all decisions but in particular for difficult choices. As all choices in the present experiment involved immediate rewards, it is conceivable that our comparisons did not reveal the brain areas deemed typical for the β-system. The activations observed in the LDR > SIR contrast in PG show certain similarities to the δ-system, however. The combination of greater mean discount rate k with more activation in an executive function network in LDR > SIR in PG might suggest that PGs are geared towards immediate rewards (see the discussion of previous neuroimaging studies on pathological gambling below), and occasional decisions for LDR require a more pronounced recruitment of executive control areas than LDR decisions made by control participants. In fact, while McClure et al. (2004) found the δ-system active in all choices, its activity level varied as a function of difficulty.

We also assessed the effects of conflict that we assumed would exist for decisions representing k-values (see Table 2) at or near the individual indifference point at which SIR and LDR roughly yield the same subjective value for the participant. Decisions at this indifference point relative to "sure" decisions were mainly associated with activity in the medial prefrontal regions, including the cingulate gyrus and the supplementary motor area (Brodmann areas (24,32,8,6) as well as in left and right insula and adjacent structures (Brodmann areas 13 and 47). We have identified this network also in our previous study of intertemporal choice in healthy young students (Marco-Pallares et al. 2010), where it was most active for decisions near the indifference point. This network has been studied extensively with regard to performance monitoring (e.g., Marco-Pallares et al. 2008) and conflict detection (e.g., Botvinick et al. 2004) and has been highlighted in a review by Ridderinkhof et al. (2004). The activation pattern was very similar for PG and HC for the indifferent > sure contrast, albeit slightly more extended in the former group. Obviously, the individual indifference points were quite

different in PG and HC. Sure decisions relative to decisions near the indifference point were associated with striatal, cingulate, insula, and medial frontal activity exclusively in HC. This might demonstrate reward-related neuronal processing during sure decisions in HC. The observed activation pattern for the sure > indifferent contrast in HC was quite similar to the results of the same contrast in our previous study (Marco-Pallares et al. 2010), indicating that sure decisions did trigger the reward system in HC but not in PG.

How do these findings relate to previous neuroimaging observations in PG? In a previous study from our group (Miedl et al. 2010), we compared occasional and problem gamblers during a quasi-realistic blackjack game focusing on risk assessment and reward processing. Problem gamblers demonstrated a consistent signal increase in thalamic, inferior frontal, and superior temporal regions during high-risk situations and a decrease in low-risk situations, whereas the opposite pattern was seen in occasional gamblers. During reward processing as derived from contrasting winning vs. losing situations, both PG and occasional gambers showed an enhancement of ventral striatal and posterior cingulate activity. Moreover, only problem gamblers showed fronto-parietal activations to gambling-related cues, which were discussed as representing the activity of a cue-induced addiction memory network. This might be relevant also in the present intertemporal choice paradigm, as Dixon et al. (Dixon et al. 2006) have demonstrated that the discount rate of PG, while already enhanced in standard paper and pencil task of the kind used by many authors (Alessi and Petry 2003; Kirby and Petry 2004; Petry 2001b) and in the present study, is highly dependent on context. One of us (Miedl et al. 2012) recently compared delay and probability discounting in PG and matched controls. In line with the present study and a number of behavioral studies, the former showed increased discounting of delayed rewards, but a non-significant decrease in the discounting of probabilistic rewards. In the fMRI analysis, it was found that reward representations in the gamblers, but not in the normal subjects, were modulated as a function of condition, i.e., there were increased neural value correlations in the reward system in the delay discounting condition, whereas neural value correlations were decreased in the probabilistic discounting condition. This was taken as support for a hypoactive reward system in PG. Moreover, as the neural value signals for delayed rewards were negatively correlated with gambling severity, it appears as if mesolimbic reward representations for delayed rewards worsen over the course of pathological gambling. Wiehler and Peters (2014) recently reviewed the evidence for a relationship between delay and probability discounting in PG and found that the three available studies (Andrade and Petry 2012; Holt et al. 2003; Madden et al. 2009) did not report a correlation, while PG affected both delay and probability discounting, but mostly the former.

Reuter et al. (2005) compared PG to controls in a typical guessing reward task (not involving intertemporal choice) and observed a reduction of ventral striatal and ventromedial prefrontal activation in PG, which was negatively correlated with gambling severity. Interestingly, in a study of the effects of pramipexole, a dopaminergic D2/D3 receptor agonist often prescribed for Parkinson's disease and linked to the occurrence of pathological gambling in about 8 % of treated patients, our group observed a hyporesponsivity of the ventral striatum to rewards under pramipexole compared to placebo (Riba et al. 2008). In particular, the response to unexpectedly high "joker" rewards was blunted in this study. A further study of pramipexole (Ye et al. 2011) showed that activity related to the anticipation of rewards was increased under pramipexole, whereas the activity linked to the consummation of rewards was decreased (as in Riba et al. 2008). The striatal hyporesponsivity to the delivery of rewards on the one hand, and increased anticipation-related activity on the other hand, might lead to the PG's urge to obtain more rewards as soon as possible and might thus contribute to their steeper discounting function observed in the present investigation and by others (Alessi and Petry 2003; Petry 2001b; Dixon et al. 2006). As we demonstrated in the present study, this leads to a shift in the interaction between prefrontal and parietal areas related to control of impulsive actions and brain areas calling for the immediate consumption of a reward.

Limitations

As does every experimental study trying to examine a real-world behavior, the present study has a number of limitations. The present control group was selected to match the PG group closely with regard to smoking behavior, age, and education. Both groups thus comprised more smokers than an average healthy control sample would have contained. As smoking has been shown to be associated with steeper discounting of delayed rewards (Reynolds 2004; Reynolds et al. 2004), this might have led to smaller differences between PG and CG than would have been obtained with a non-smoking control group. Moreover, nicotine might have had a direct influence on activation patterns, as it has been shown that smokers show attenuated activation of the ventral striatum in reward tasks (Peters et al. 2011; Martin-Soelch et al. 2009; Luo et al. 2011). Thus, future studies should either use smoking as a covariate or optimally should investigate non-smoking PG, which would, however, be hard to find.

Another feature of the current experiment is that we varied the size of SIR and LDR on a trial by trial basis as suggested by Kirby et al. (1999), whereas most other fMRI studies on delay discounting have kept the immediate rewards constant and only varied the LDR (e.g., Miedl et al. 2012). Both variants of the paradigm have advantages and disadvantages. In a previous study using the current paradigm, we have therefore

centered the analysis around the individual k (Marco-Pallares et al. 2010).

Both behavioral and substance-dependent addictions show cue-induced craving and behaviors (Sharpe 2002; Kim et al. 2014). Therefore, the study of pathological gambling outside of its real-world context and without the specific gambling related cues is likely to underestimate the neural processes underpinning this behavioral addiction. The use of more realistic gambling scenarios (e.g., an imaging-compatible version of blackjack, Miedl et al. 2010) should be considered, even though such scenarios should be valid only for gamblers addicted to that particular game.

Conclusions

The present study revealed pronounced differences in the steepness of delay discounting between PG and HC, adding to the growing evidence that intertemporal choice paradigm capture at least one important aspect of the psychopathology of PG. In decisions for LDR, PG recruited an executive control network to a much larger extent than the HC, suggesting that these participants had to overcome a tendency to go for the immediate reward. Comparisons of sure decision (both for LDR and SIR) and indifferent decisions, i.e., decisions at or near the individual indifference point, revealed the activation of a performance or conflict monitoring network involving medial prefrontal structures and the insula. This network was recruited in both groups, but it has to be pointed out that the individual indifference points were different in PG and HC.

The functional differences between PG and HC in the current study could at least in part be driven by differences in brain structures between the two groups. Indeed, it has been shown that differences in delay of gratification can be explained by differences in brain structure (Drobetz et al. 2014) in a normal elderly population. With regard to PG and online gaming addiction, a number of studies have revealed changes in brain white and gray matter (Koehler et al. 2015; Weng et al. 2013; van Holst et al. 2012; Joutsa et al. 2011). To reveal a relationship between functional and structural changes in PG should be the topic of a larger study.

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