ORIGINAL ARTICLE

Altered Neural Reward Representations in Pathological Gamblers Revealed by Delay and Probability Discounting

Stephan F. Miedl, PhD; Jan Peters, PhD; Christian Büchel, MD

Context: The neural basis of excessive delay discounting and reduced risk sensitivity of pathological gamblers with a particular focus on subjective neural reward representations has not been previously examined.

Objective: To examine how pathological gamblers represent subjective reward value at a neural level and how this is affected by gambling severity.

Design: Model-based functional magnetic resonance imaging study with patients and control subjects.

Setting: Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf.

Participants: Participants were recruited from the local community by advertisement and through self-help groups. A sample of 16 pathological gamblers (according to the *DSM-IV* definition) was matched by age, sex, smoking status, income, educational level, and handedness to 16 healthy controls.

Results: Pathological gamblers showed increased discounting of delayed rewards and a trend toward decreased discounting of probabilistic rewards compared with matched controls. At the neural level, a significant group × condition interaction indicated that reward representations in the gamblers were modulated in a condition-specific manner, such that they exhibited increased (delay discounting) and decreased (probability discounting) neural value correlations in the reward system. In addition, throughout the reward system, neuronal value signals for delayed rewards were negatively correlated with gambling severity.

Conclusions: The results extend previous reports of a generally hypoactive reward system in pathological gamblers by showing that, even when subjective reward valuation is accounted for, gamblers still show altered reward representations. Furthermore, results point toward a gradual degradation of mesolimbic reward representations for delayed rewards during the course of pathological gambling.

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Author Affiliations: Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

PATHOLOGICAL GAMBLING IS classified as an impulse control disorder in the *DSM-IV*, with core features such as diminished self-control, compulsive gambling behavior, craving before gambling, and continuing gambling despite negative consequences similar to the features of addiction.[1] In general, pathological gamblers show impairments of planning and decision making,[2] elevated levels of impulsivity,[3] and impaired risk assessment.[4] In the context of monetary decision making, a hallmark of pathological gambling is increased discounting of delayed rewards,[5,6] which has also been reported for substance-based addiction in opioid-dependent patients,[7] alcoholics,[8] cocaine abusers,[9] and smokers.[10,11] Evidence exists of increasingly steep discounting of future rewards with increasing gambling severity.[12] In contrast, probabilistic rewards tend to be less steeply discounted in pathological gamblers compared with control subjects,[13] suggesting a reduction in risk aversion. Gambling severity may also show a negative correlation with the degree of probability discounting (PD).[14]

Recent neuroimaging studies have revealed the neural basis underlying delay discounting (DD)[15-23] and PD.[24-26] Steep discounting may be associated with elevated responsiveness of the ventral striatum (VS).[17] It is still debated whether 1 system[18,27] or 2 systems[20,28] are involved in valuation of delayed rewards. However, a number of studies have now shown that the VS, posterior cingulate cortex, and medial prefrontal cortex represent the subjectively discounted value of delayed rewards.[18,27] Parts of this network (VS and orbitofrontal cortex [OFC]) may code for subjective value in a domain-general man-

Table. Demographic Data

	Mean (SE) Data			
	Pathological Gamblers (n = 16)	Controls (n = 16)	*F* Value[a]	*P* Value
Age, y	35 (2)	38 (2)	0.75	.39
Fagerström score	3.87 (0.74)	3.37 (0.94)	0.17	.68
Years of education	12.75 (0.47)	13.12 (0.63)	0.22	.63
DSM-IV score	7 (0.42)	0.12 (0.08)	247.95	<.001
KFG score	33.43 (2.95)	0.93 (0.56)	116.77	<.001
SOGS score	10.06 (1.02)	0.18 (0.13)	90.93	<.001
Income per month, €	1436.25 (150.76)	1593.75 (229.21)	0.32	.57
Ratio of lost money to income	0.71 (0.24)	0 (0)	8.36	.007
BDI score	12.25 (2.68)	4.37 (0.76)	7.93	.008

Abbreviation: BDI, Beck Depression Inventory; KFG, Kurzfragebogen zum Glücksspielverhalten; SOGS, South Oaks Gambling Screen.
[a] For the *F* values, *df* = 1, 30.

ner,[26] that is, for delayed and probabilistic rewards. These regions have also been implicated in subjective reward valuation in a range of other domains.[29,30] In general, neuroimaging evidence suggests that neural responses in the reward system tend to be better accounted for by subjective estimates of value (eg, based on discounting models) than by objective properties of the rewards.[18,26]

A diminished response to nondrug rewards is observed in many forms of addiction,[31] but only a few neuroimaging studies examined reward processing in pathological gamblers.[32-36] Pathological gambling has been linked to reduced responses in the VS and ventromedial prefrontal cortex (vmPFC) during reward processing, an effect that was additionally correlated with gambling severity.[33] However, an analysis of subjective valuation processes was not possible in that study. Pathological gamblers demonstrated diminished reward and punishment sensitivity accompanied by ventrolateral prefrontal hypoactivity in an affective switching paradigm.[36] Miedl et al[34] reported enhanced frontoparietal activity in problem gamblers compared with occasional gamblers during reward processing in a quasi-realistic blackjack task. In addition, high levels of risk-taking behavior by problem gamblers during a blackjack game were accompanied by enhanced activity in the reward system in cases of infrequent success.[35] Finally, it has been shown that dopaminergic midbrain activity after near misses was positively correlated with gambling severity that was interpreted as abnormal reward system activity in states of cognitive distortions in problem gamblers.[32]

Herein we examined the neural basis of excessive DD and reduced risk sensitivity typically observed in pathological gambling. Previous studies[33,34,37] have primarily focused on objective reward properties (ie, magnitude and probability). However, altered reward-related neural responses in pathological gamblers may simply be a result of excessive discounting. To address this issue, we examined subjective neural reward representations in pathological gamblers using a computational model of intertemporal (DD) and risky (PD) decision making. At the behavioral level, we expected to observe steeper discounting of delayed rewards and reduced discounting of risky rewards in pathological gamblers compared with controls.[12-14] At the neural level, we expected to observe alterations in reward representations in the reward system, including the VS, OFC, and substantia nigra/ventral tegmental area (SN/VTA) in pathological gamblers compared with controls. Finally, in the gamblers we expected a modulation of reward representations by gambling severity.[33]

METHODS

PARTICIPANTS

The study group consisted of 16 controls (15 men and 1 woman; age range, 22-50 years) and 16 pathological gamblers (15 men and 1 woman; age range, 21-48 years). All participants were right-handed according to a modified version of the Edinburgh Handedness Inventory.[38] The groups did not differ in age ($F_{1,30}$=0.75 [P=.39]), smoking behavior (for 10 smokers in the control group and 12 smokers in the pathological gambling group, based on the Fagerström score,[39] $F_{1,30}$=0.17 [P=.68]), income ($F_{1,30}$=0.32 [P=.57]), and educational level ($F_{1,30}$=0.22 [P=.63]) (**Table**). Neural reward responses are affected by acute nicotine withdrawal[40]; thus, smokers were allowed to smoke freely before the experiment (satiation during functional magnetic resonance imaging [fMRI]). Participants were recruited through advertisements and self-help groups. Before enrollment in the study, all participants underwent a structured psychiatric interview and were familiarized with the experimental environment. No participant reported a history of regular drug use, and none were currently using medication. No active Axis I disorders were present apart from depression in 4 pathological gamblers. Depression was further assessed using the Beck Depression Inventory.[41] The mean (SE) Beck Depression Inventory score was 4.37 (0.76) for the controls and 12.25 (2.68) for the pathological gamblers group. The percentage of income spent on gambling activities was significantly higher in pathological gamblers compared with controls ($F_{1,30}$=8.36 [P=.007]) (Table).

Some previous studies[32,34-36,42] examined samples of problem gamblers, who have a milder form of gambling disorder. In contrast, gamblers in the present study fulfilled the *DSM-IV* criteria of pathological gambling (ie, ≥5 yes answers). Similar to other previous reports,[33,37,43,44] the present group of pathological gamblers thus exhibited relatively severe gambling behavior. Eleven of 16 gamblers played slot machines more than 3 times per week (15 of 16 reported ≥1 time per week).

All subjects completed the German gambling questionnaire Kurzfragebogen zum Glücksspielverhalten (KFG[45]; based

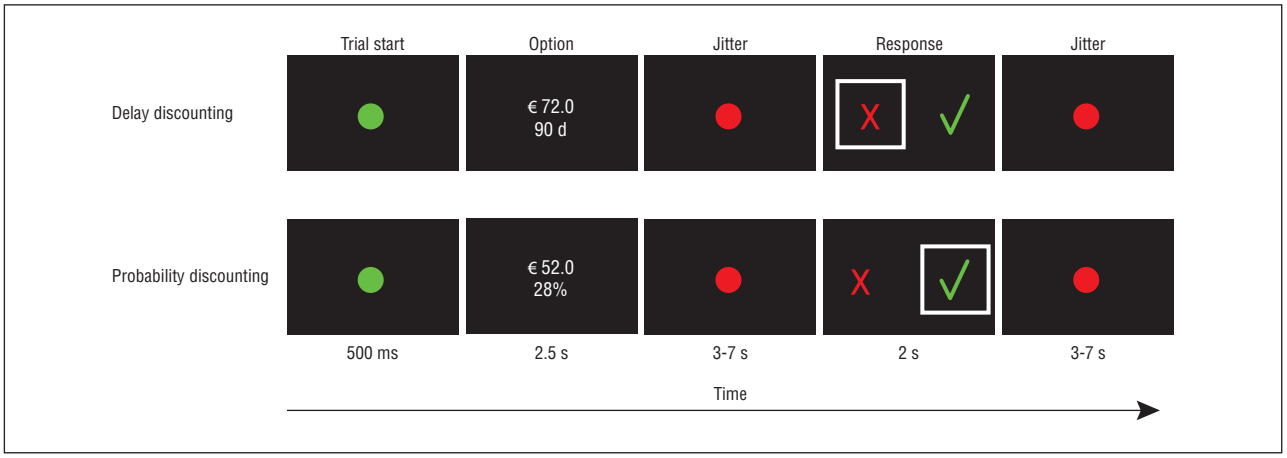

Figure 1. Illustration of the experimental paradigm during functional magnetic resonance imaging. Participants had to choose between immediate (€20.0; reference option) vs delayed rewards and between sure (€20.0) vs risky rewards. Adapted from Peters and Büchel.[26]

on 20 items developed by Gamblers Anonymous). Instrumental (Cronbach $\alpha = 0.79$) and retest ($r = 0.80$) reliability of the KFG are reported to highly fulfill the psychometric properties of a screening instrument.[45] The KFG contains 20 items (scored on a 4-point Likert scale, 0-3 points each) addressing lifetime gambling behavior. The threshold for pathological gambling is set at 16 points. Participants also completed a German version of the South Oaks Gambling Screen.[46] Participants who scored at least 5 points are classified as probable pathological gamblers. Both groups differed significantly with respect to *DSM-IV* score ($F_{1,30} = 247.95$ [$P < .001$]; pathological gambling group score, 5-10; control score, ≤1), South Oaks Gambling Screen score ($F_{1,30} = 90.93$ [$P < .001$]; pathological gambling group score, 5-18; control score, 0-2), and KFG score ($F_{1,30} = 116.77$ [$P < .001$]; pathological gambling group score, 18-54; control score, 0-8) (Table). The study protocol was designed according to the 1984 Declaration of Helsinki and was approved by the local ethics committee. All participants were informed about the procedure and gave written informed consent to participate.

BEHAVIORAL PRETEST

All participants completed 1 behavioral testing session before fMRI (average time between behavioral sessions, 1 day). This testing session consisted of short adaptive DD and PD tasks[26] to estimate the rate of DD and PD. Based on these estimated discount rates, subject-specific trials for the fMRI experiment were conducted as in previous studies.[22,26] All experiments were programmed using a computer-based paradigm (Presentation software; Neurobehavioral Systems, Inc).

fMRI TASK

We applied a previously described paradigm.[26] Participants made choices between a fixed immediate reward of €20.0 and larger delayed (DD) or risky (PD) rewards. Based on the behavioral pretest results, individual offers were calculated for each participant to ensure that participants chose the delayed/probabilistic offer in roughly 50% of the trials. The maximum amount of the delayed/probabilistic option was set to €80.0, and the minimum amount was set to €20.5. From this range of magnitudes, trials were created by selecting an equal, uniformly distributed number of offers (7 offers) with an estimated subjective value less than and greater than each indifference point (range, ±€4; based on the estimated discount rate from the pretest). Also, for each delay, 9 options were presented in which the amounts were selected (uniformly spaced) from the total range in amounts available (€20.5-€80.0), yielding 16 trials in total per delay/probability option. When the indifference point was larger than €50, an equal number of trials with a subjective value less than and greater than €50 were created. The delays ranged from none (immediate reward) to 1, 2, 7, 30, 90, and 180 days. The probabilities included 100%, 99%, 96%, 84%, 54%, 28%, and 17%.[47]

Participants were instructed that the fixed, immediately accessible reward would not be displayed, and they would only be shown the alternative (ie, delayed or probabilistic) offer. A green dot (500 milliseconds) (**Figure 1**) signaled the start of the trial. Next, the delayed or probabilistic offer was shown for 2500 milliseconds, followed by a red dot (jitter) that was shown for a random duration of 3 to 7 seconds, uniformly distributed. Thereafter, a red *x* and a green check mark were shown (assigned at random to either side of the screen). Participants pressed the red *x* to choose the fixed reward of €20.0 or the check mark to choose the delayed/probabilistic offer. After response feedback, another 3- to 7-second jittered interval preceded the start of the next trial. Trials of PD and DD were randomly intermixed. Participants completed 2 sessions, each lasting approximately 22 minutes and constituting 48 DD and 48 PD trials, yielding a total of 96 trials per condition. Before fMRI, participants were told that one of their choices would randomly be selected after scanning and that they would receive the reward amount via a fast bank transfer with the stated delay/probability. The average amount participants received was €27.0 for controls (range, €20.0-€56.4) and €24.4 for pathological gamblers (range, €20.0-€66.5).

COMPUTATIONAL MODELING

Behavioral data from the fMRI sessions were analyzed using maximum-likelihood estimation with an optimization procedure implemented using math computation software (fminsearch in MATLAB; MathWorks) similar to previous studies.[31,48] Specifically, we used the following Softmax sigmoid choice function

$$(1)\ P(o_i) = [exp(sv_{oi}/temp)]/[exp(sv_{o1}/temp) + exp(sv_{o2}/temp)]$$

to estimate the probability of choosing the actually selected option (o_i) given the subjective values of the available options sv_{o1} and sv_{o2}, corresponding to the subjective values of the smaller immediate reward and the larger later reward according to equations 2 and 3. *Temp* is a free parameter modeling the steepness of the sigmoid, that is, the stochasticity in the subjects' choices. For DD, we applied the hyperbolic model[49]:

$$(2) SV = A/(1 + kD),$$

where A is the objective reward amount, D is the delay, and k is a subject-specific discount rate. A similar model accurately describes PD:

$$(3) SV = A/(1 + k\varphi),$$

where φ is reward probability P following the odds-against-winning transformation (ie, $\varphi = [1 - P]/P$). Using equations 1 through 3, we minimized the log-likelihood (LL in equations 4 and 5) of the choice probabilities, summing across trials, given a particular set of model parameters θ:

$$(4) LL = \Sigma_t \log(P_{ot}|\theta).$$

We obtained the best-fitting parameter estimates for each subject and condition (k and *temp*) and calculated the subjective discounted value for each trial for each subject and condition. Model fit was quantified (and compared between controls and gamblers) using the Bayesian Information Criterion (BIC)[50]:

$$(5) BIC = -2LL + n\log(t),$$

where n is the number of free-model parameters and t is the number of trials included in the fitting procedure. Smaller BIC scores indicate a better model fit.

ANALYSIS OF REACTION TIMES

Reaction times (RTs) from the fMRI session were additionally analyzed as a function of subjective value. Trials were classified as trials in which the delayed/risky option had a higher subjective value than the reference amount of €20.0 and trials in which the subjective value was lower than the reference amount. The two-thirds of low-value trials with the lowest subjective values were then classified as lower trials, whereas the two-thirds of high-value trials with the highest subjective values were classified as higher trials. The remaining trials (in which subjective values were closest to the reference amount) were classified as similar trials. Typically, RTs reflect the degree of decision conflict on each trial and should follow an inverse U-shaped pattern.[48,51] To examine this, we fitted a second-order polynomial to the mean RTs from the 3 bins for each subject using MATLAB. We then used t tests to examine whether the quadratic term was on average lower than 0, which would indicate an inverse U-shaped RT distribution.

fMRI DATA ACQUISITION

We used a standard whole-brain acquisition sequence for fMRI. Details can be found in the eMethods (http://www.archgenpsychiatry.com).

fMRI DATA ANALYSIS

Data preprocessing and analysis were performed using SPM8 (Wellcome Department of Cognitive Neurology, University College London). Functional images were corrected for section time to the onset of imaging of the middle section and spatially realigned using a 6-parameter affine transformation. The functional images were coregistered to the high-resolution T1-weighted image, then realigned and resectioned to the first volume. A first-level model was constructed on the unsmoothed single-subject data using the following regressor. The presentation of delayed and probabilistic options was modeled by convolving the event train of stimulus onsets with the canonical hemodynamic response function separately for each session. For each event, a primary parametric regressor of interest was included in the model, coding for the subjective value of the decision option in each trial as calculated using equations 2 and 3. Additional parametric regressors for reward probability (PD condition) or inverse delay to reward (ie, 1/delay, DD condition), a measure of decision conflict calculated based on equation 1, and reward amount (A; see also equations 2 and 3) were included in the model and orthogonalized with respect to the subjective value regressor. Because variance is initially assigned to the first parametric regressor (in our case, subjective value), these additional parametric regressors do not affect the value effects that are the focus of the present report and are not of interest here. Error trials and button presses were modeled separately. To deal with residual variance caused by subject movement, the realignment parameters were included as additional regressors at the first level. For each participant, the following contrast images were computed: (1) delayed reward onset parametrically modulated by the subjective value and (2) probabilistic reward onset parametrically modulated by the subjective value. We created a custom template from the T1-weighted images of all participants (N = 32) using the DARTEL toolbox 6 as implemented in SPM8. Single-subject contrast images were normalized to Montreal Neurological Institute space using the individual participant DARTEL flow fields and then smoothed with an 8-mm gaussian isotropic kernel. We then entered the normalized and smoothed single-subject contrast images into a second-level random effects model using full factorial design SPM8. We included regressors modeling depression (Beck Depression Inventory score), smoking behavior (Fagerström score), and gambling severity (KFG score) into this analysis. All covariates were fitted in a group-specific manner to allow for a covariate × group interaction. Thus, group differences are not affected by the inclusion of these covariates.[52] For all analyses, the threshold was set to $P < .05$ corrected for multiple comparisons (based on the familywise error rate) using reduced search volumes (small volume correction [SVC]). We performed the correction for multiple comparisons using spherical search volumes centered at peak coordinates from previous studies (ie, independent data) with 12-mm spheres for the VS,[53] OFC,[54] ventral anterior cingulate cortex,[55] lateral parietal cortex,[26] medial prefrontal cortex,[26] posterior cingulate cortex,[26] intraparietal sulcus,[26] vmPFC,[56] and midbrain/SN.[57] All activations are displayed projected on the mean structural scan of all participants.

RESULTS

BEHAVIORAL DATA DURING fMRI

Pathological gamblers showed higher discount rates during DD than controls ($\log[k]$; $t_{30} = -2.82$ [$P = .004$, 1-tailed]) (**Figure 2**D; see also the median discount function in Figure 2E), whereas PD rates showed a trend to significance ($t_{30} = 1.49$ [$P = .07$, 1-tailed]) to be lower in pathological gamblers compared with controls (Figure 2I). Furthermore, discount rates of pathological gamblers showed no significant correlation to gambling severity (KFG score) during DD, whereas there was a trend to negative correlation during PD ($r = -0.44$ [$P = .09$]).

The fit of the behavioral model in terms of the BIC[50] was not significantly different between groups for DD (BIC controls, 58.03 [5.02]; gamblers, 54.78 [5.86]; $t_{30} = 0.42$ [$P = .68$]) or PD (BIC controls, 51.59 [3.98]; gamblers, 47.90 [3.98]; $t_{30} = 0.66$ [$P = .52$]), with data expressed as mean (SE). This finding indicates that group differences in neural responses are not confounded by differences in model fit between groups. There was also no sig-

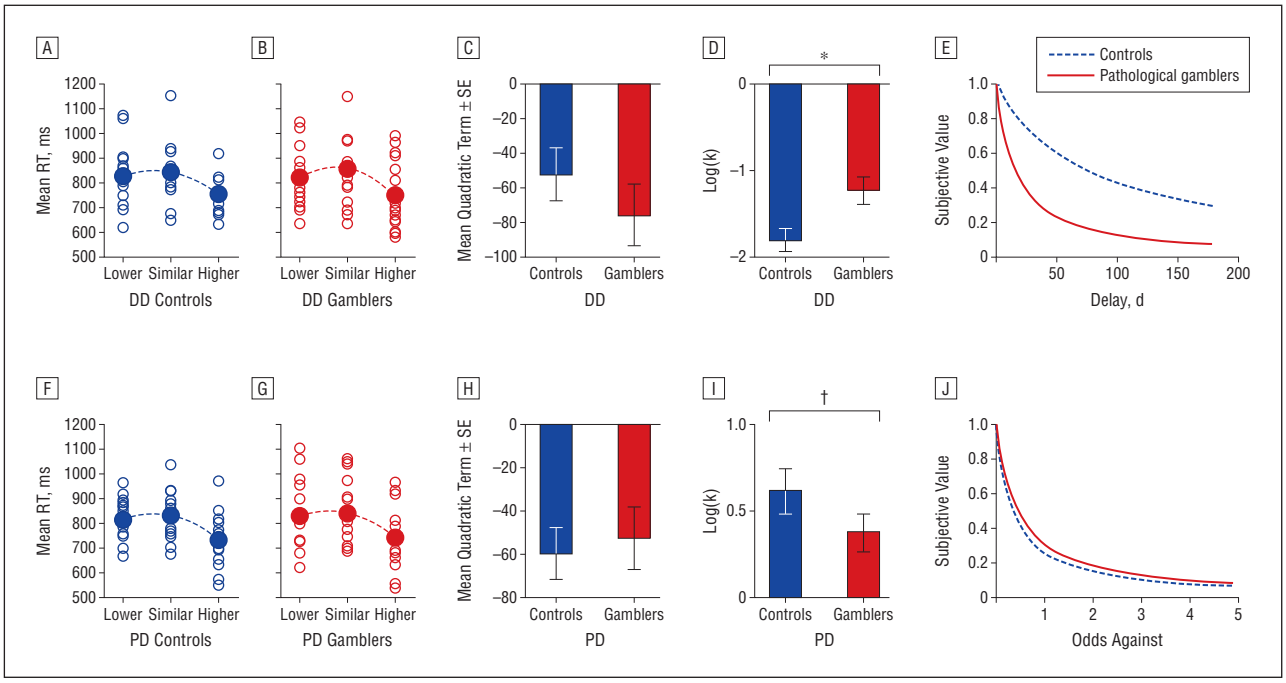

Figure 2. Reaction times (RTs) and quadratic terms in pathological gamblers and control subjects during delayed discounting (DD) and probabilistic discounting (PD). The RTs were slowest in pathological gamblers and controls when the fixed and the alternative offers during DD (A and B) and PD (F and G) had a similar subjective value with respect to the reference amount of €20. Quadratic terms did not differ between pathological gamblers and controls during DD (C) and PD (H). Pathological gamblers discounted delayed rewards more steeply than controls (D [*P=.004] and E), and controls showed a trend to higher discounting of risky options compared with pathological gamblers (I [†P=.07] and J). Error bars indicate standard error of the mean.

nificant condition × group interaction for the BIC ($F_{1,30}$=0.004 [P=.95]).

Reaction times were analyzed as a function of the subjective value of the delayed/risky option (lower than, similar to, or higher than the reference amount) (Figure 2A, B, F, and G) by fitting second-order polynomials to each participant's data. Quadratic terms for DD and PD were significantly lower than 0 in controls and gamblers (DD controls, t_{15}=−3.43 [P=.004]; DD gamblers, t_{15}=−4.99 [P<.001]; PD controls, t_{15}=−4.29 [P<.001]; PD gamblers, t_{15}=−3.65 [P=.002]). Both groups thus showed an inverse U-shaped RT distribution (Figure 2C and H) that was not significantly different between groups (DD, t_{15}=1.01 [P=.32]; PD, t_{15}=−0.38 [P=.71]).

fMRI RESULTS

Neural Reward Representations During DD and PD

We first examined brain regions in which the blood oxygenation level–dependent (BOLD) response exhibited a positive correlation with model-based subjective value across all subjects. During DD (**Figure 3**A), this analysis replicated previous findings in a sample of healthy controls.[26] Valuation-related activity was most prominent in the left lateral parietal cortex (x, y, z coordinates, −64, −46, 36; z value=4.28 [P_{svc}=.002]), right posterior cingulate cortex (15, −48, 33; z value=3.76 [P_{svc}=.01]), left medial prefrontal cortex (−15, 54, 12; z value=3.32 [P_{svc}=.04]), and VS (left: −10, 11, −3; z value=3.89 [P_{svc}=.007]; right: 10, 11, −2; z value=4.37 [P_{svc}=.001]). A complete list of activations is provided in eTable 1.

For PD (Figure 3B), we observed valuation-related activity that was highly similar to activity previously described in healthy young subjects,[26] encompassing the left intraparietal sulcus (x, y, z coordinates, −46, −57, 45; z value=3.35 [P_{svc}=.03]) and VS (left: −12, 8, −3; z value=4.23 [P_{svc}=.003]; right: 9, 8, −2; z value=4.10 [P_{svc}=.002]). eTable 2 shows a complete list of activations.

Modulation of Reward Representations in the Gamblers in a Condition-Specific Manner

We first examined overall differences in reward value representations (ie, across DD and PD). Gamblers showed higher value correlations than controls in the left dorsal caudate (peak x, y, z in millimeters, −18, 9, 19; z value=3.56), whereas controls showed higher activity in the right precuneus (22, −78, 49; z value=3.28). No other clusters emerged at P<.001 uncorrected. We next examined the condition-specificity of group differences in subjective reward representations and conducted group × condition interaction analyses. We first tested for brain areas showing more pronounced correlations with subjective value in gamblers compared with controls for DD and the reverse pattern for PD. This pattern of activity was observed throughout the reward system in the right OFC (x, y, z coordinates, 15, 36, −18; z value=3.93 [P_{svc}=.005]), VS (left: −14, 12, −2; z value=3.43 [P_{svc}=.02]; right: 14, 14, −2; z value=3.21 [P_{svc}=.04]), and rostral anterior cingulate cortex (3, 28, −6; z value=3.41 [P_{svc}=.02]) (**Figure 4**; for a complete list of activations, see eTable 3). The reverse interaction contrast yielded no significant clusters. Exclusion of the 2 female participants did not alter the overall pattern of

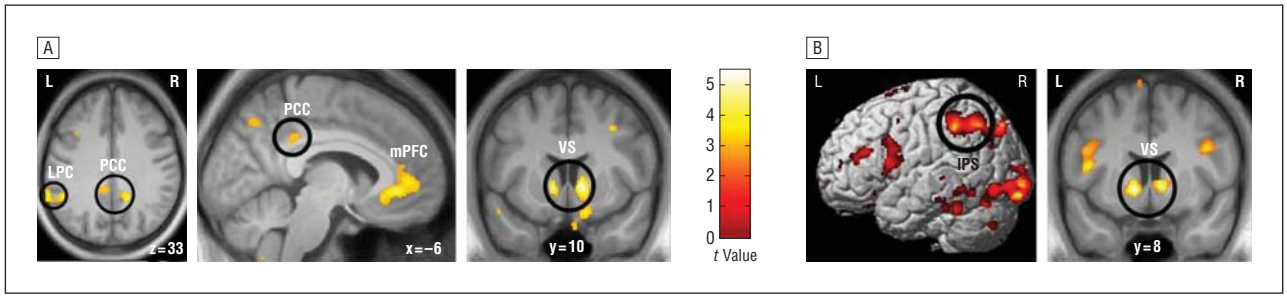

Figure 3. Subjective value correlation of functional magnetic resonance imaging findings in pathological gamblers and control subjects. Regions in which neuronal activity demonstrated a positive correlation with the subjective value are shown. A, Average effect of delayed discounting (DD). B, Average effect of probabilistic discounting (PD) (display threshold, $P<.005$, uncorrected). IPS indicates intraparietal sulcus; L, left; LPC, left parietal cortex; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; R, right; VS, ventral striatum.

results (right OFC, $P_{svc}=.003$; left VS, $P_{svc}=.04$; right VS, $P_{svc}=.03$; rostral anterior cingulate cortex, $P_{svc}=.02$).

Modulation of Reward Representations for DD and PD by Gambling Severity

We next examined correlations between gambling severity and the neural subjective value correlation in the gamblers. For DD, **Figure 5** shows a network of regions, including the right vmPFC (x, y, z coordinates, 16, 60, −2; z value = 3.77 [$P_{svc}=.01$), left SN/VTA (−6, −16, −8; z value = 3.27 [$P_{svc}=.045$]), and left VS (−12, 12, −2; z value = 3.59 [$P_{svc}=.02$]), in which gambling severity (KFG score) within the pathological gambling group negatively correlated with the subjective value signal during DD (for a complete list, see eTable 4). In contrast, the identical analysis for PD revealed no significant clusters at $P<.001$ uncorrected. As for the interaction analysis, exclusion of the 2 female participants did not change the overall pattern of results (right vmPFC, $P_{svc}=.02$; left SN/VTA, $P_{svc}=.055$; left VS, $P_{svc}=.03$).

COMMENT

We examined differences in the neuronal representation of subjective reward value in gamblers and healthy controls. In particular, we applied DD and PD tasks in which trial × trial estimates of subjective reward value could be obtained through computational modeling. Behavioral results replicated previous findings,[5,6,12-14] such that gamblers showed increased discounting of delayed rewards and a trend toward decreased discounting of probabilistic rewards. Neuroimaging results across all participants replicated valuation-related effects observed in healthy young adults.[26] More important, however, reward representations in the gamblers were modulated in a condition-specific manner. Throughout the reward system, neural value correlations in the gamblers were enhanced in DD, whereas they were attenuated in PD. Furthermore, within the pathological gambling group, valuation signals in the VS, vmPFC, and SN/VTA for delayed rewards were negatively correlated with gambling severity, whereas no such effect was observed for probabilistic rewards.

Discount rates during DD were higher in gamblers compared with controls, likely reflecting enhanced levels of impulsivity in gamblers in accordance with earlier studies[5,6] but unlike previous findings[12] in which gambling severity was not correlated with DD rates. These rates could be due to design-specific differences. Compared with the present paradigm, Alessi and Petry[12] used higher amounts (≤$1000) and longer delays (≤25 years); however, decisions had no monetary consequences for participants. Furthermore, in the present study, PD rates showed a trend to be lower in gamblers compared with controls. Also, the trend toward a negative correlation of PD rates with gambling severity during PD points to a certain degree of diminished risk sensitivity with increasing gambling severity.[14]

Neural subjective value signals across all subjects replicated previous findings for DD and PD.[26] The observation of a striatal representation of a subjective value during DD and PD confirms that this region plays a crucial role in subjective reward processing,[18,58] which is largely independent of the modality of the decision option.[26,29] In addition, however, neural subjective value representations in the gamblers were modulated in a condition-specific manner. For probabilistic rewards, the correlation between BOLD signals in the reward circuit (in particular the VS and OFC) and subjective value was less pronounced in the gamblers than in the controls. Conversely, this correlation was more pronounced for delayed rewards. This effect was not due to group differences in the fit of the behavioral model (ie, the difference in BIC scores between groups was not significant). Thus, even when subjective value was accounted for in the analysis of the neuroimaging data, gamblers still showed altered neural reward representations.

Previous studies have suggested a general hypoactivity of the reward system in gamblers.[33,37,59] Using a parametric analysis, our data extend these observations by showing that the neural representation of subjective value in gamblers is modulated differentially for risky and delayed rewards. It should be pointed out that the nature of the parametric analyses conducted in the present study cannot be directly compared with previous investigations of reward processing in addiction. We examined correlations of neural activity with subjective value, based on computational models. Thus, the observed neural group differences indicate that activity in specific neural circuits is related (ie, regression) to subjective value. These results therefore address the issue of how well

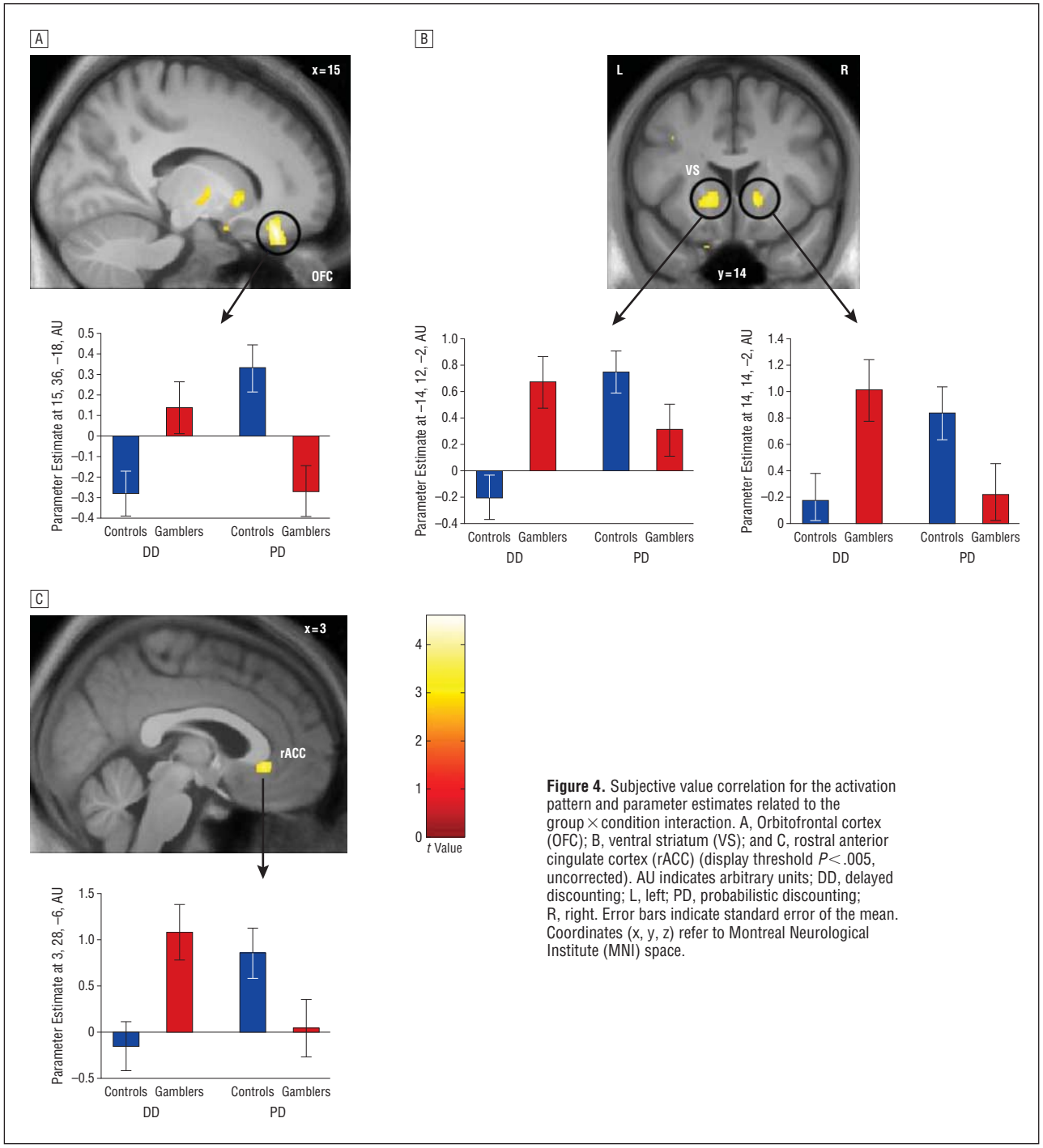

Figure 4. Subjective value correlation for the activation pattern and parameter estimates related to the group × condition interaction. A, Orbitofrontal cortex (OFC); B, ventral striatum (VS); and C, rostral anterior cingulate cortex (rACC) (display threshold $P < .005$, uncorrected). AU indicates arbitrary units; DD, delayed discounting; L, left; PD, probabilistic discounting; R, right. Error bars indicate standard error of the mean. Coordinates (x, y, z) refer to Montreal Neurological Institute (MNI) space.

model-based subjective value accounts for neural activity (eg, in the reward system) but deliberately ignores the absolute level of activity (which has been the focus of many previous neuroimaging studies on addiction).[10,33] The important point is that categorical comparisons between addicts and controls can be confounded by differences in subjective valuation. Herein we demonstrate that, even when subjective valuation is accounted for, neural reward representations still show considerable alterations in pathological gamblers.

The degree to which value was correlated with reward-circuit activity (ie, in the VS, OFC, and SN/VTA) in DD was negatively correlated with gambling severity. Therefore, our results expand previous findings of a general reduction in reward-related responses in the VS and vmPFC with increasing gambling severity[32,33] to subjective value representations in these regions, specifically in DD.[18,60]

The generally increased correlation of VS and OFC activity in gamblers with subjective value for the DD task is also of interest. The reward signal in the VS is greater in subjects who practice steep DD compared with subjects who discount less[17] (see Peters and Büchel[31] for further discussion of this issue). The increased value correlation for DD in the gamblers (in combination with a negative correla-

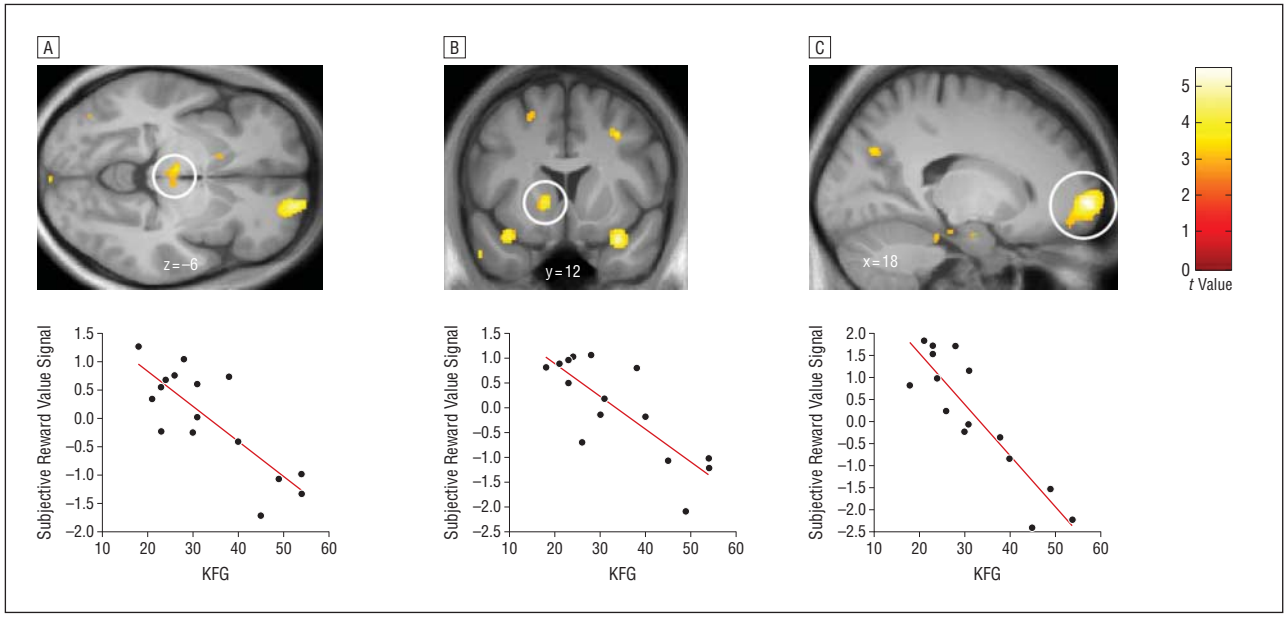

Figure 5. Subjective value correlation for signal in brain regions during delayed discounting (DD) in pathological gamblers. A, Substantia nigra. B, Ventral striatum. C, Ventromedial prefrontal cortex. The value signal showed a negative correlation with gambling severity (measured by the Kurzfragebogen zum Glücksspielverhalten [KFG] score) in pathological gamblers (display threshold, $P<.005$, uncorrected).

tion of this signal with gambling severity) might therefore point to a gradually decreasing striatal reward encoding from milder to more severe pathological gambling. In line with this idea, Voon et al[42] observed increased VS valuation signals to gain cues after dopamine agonist medication in problem gamblers and compulsive shoppers. The authors interpreted the overestimation of reward values as a possible mechanism underlying the development of behavioral addictions,[61] such as initiation of problematic gambling behavior after a win. Because part of this sample consisted of problem gamblers, a subclinical stage of pathological gambling, enhancement of the VS reward value signal in the present sample might have been driven by gamblers with less severe gambling. This would be in line with previous reports of a reward hypersensitivity in problem gamblers.[35]

Furthermore, the control group of the present study was matched for smoking behavior, age, and education to the pathological gambling group and therefore included heavy smokers. Consequently, this control group differs considerably from samples of healthy volunteers in previous studies.[22,26] Attenuated representations of subjective value in the VS and OFC for DD in the control group might therefore be related to smoking habits. For example, smokers typically demonstrate less VS activation during reward processing.[10,62-64] In addition, in conjunction with previous results,[26] the attenuated subjective value encoding in the VS and OFC of the present controls during DD (but not PD) may point toward a task-specific influence of smoking habits, similar to previous behavioral findings.[65] However, this possibility would need to be addressed in a direct comparison of smokers and nonsmokers.

An additional point is that the immediate and certain rewards were kept constant throughout the experiment. Therefore, we analyzed subjective value signals for delayed and probabilistic rewards but not directly for immediate and certain rewards. One possibility of addressing this point in future studies would be to keep the delayed or probabilistic reward fixed and to modulate the subjective value of the immediate or certain reward.

One could argue that diminished representations of probabilistic subjective values in gamblers may result from their high familiarity with risky decision-making scenarios. Excessive exposure to risky gambling situations and stereotypical behavior during slot-machine gambling might have led to this general decrease in reward valuation, which may be a consequence of habit-based automatic responding.[66] During DD (a task that may be considered somewhat less related to gambling than PD), the gradual decrease of the neural value correlation with increasing gambling severity may reflect an overestimation of subjective values of gamblers scoring low in gambling severity. Taken together, the reward system of less severe gamblers might be sensitive to the representation of rewards in a context unrelated to gambling. This task dependency of reward system alterations in gamblers fits well with the observation that gamblers are also more impulsive in a gambling-related context.[67] Concepts of therapy should therefore put a particular emphasis on contextual factors, which appear to play a central role in this disorder.

CONCLUSIONS

Using computational models of DD and PD, we examined alterations in subjective neural reward representations in pathological gamblers and matched controls. Using model-based functional neuroimaging, we observed an important dissociation in neural subjective value representations between gamblers and controls. Correlations between neural activity in the VS and OFC and subjective values were attenuated in gamblers for risky rewards. In contrast, for delayed rewards, correlations in

these same regions were significantly enhanced in the gamblers but at the same time negatively correlated with gambling severity. Our findings therefore suggest that task-dependent effects with respect to alterations in reward representations in gamblers need to be incorporated into new neural models of this disease.

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Correspondence: Stephan F. Miedl, PhD, Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany (s.miedl@uke.de).
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