Mesolimbic dopamine release is linked to symptom severity in pathological gambling


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Background: Brain dopamine neurons code rewarding environmental stimuli by releasing endogenous dopamine, a transmission signal that is important for reinforcement learning. Human reward-seeking gambling behavior, and especially pathological gambling, has been presumed to be modulated by brain dopamine.

Methods: Striatal dopamine release was studied with \(^{11}\)C-raclopride positron emission tomography (PET) during gambling with an ecologically valid slot machine gambling task. Twenty-four males with and without pathological gambling (DSM-IV) were scanned three times, and the effects of different gambling outcomes (high-reward and low-reward vs. control task) on dopamine release were evaluated.

Results: Striatal dopamine was released in both groups during high-reward but also low-reward tasks. The dopamine release during the low-reward task was located in the associative part of the caudate nucleus. During the high-reward task, the effect was also seen in the ventral striatum and the magnitude of dopamine release was associated with parallel gambling “high”. Furthermore, there was a positive correlation between dopamine release during the low-reward and the high-reward task. There was no general difference in the magnitude of dopamine release between pathological gamblers and controls. However, in pathological gamblers, dopamine release correlated positively with gambling symptom severity.

Conclusions: Striatal dopamine is released during gambling irrespective of gambling outcome suggesting that the mere expectation/prediction of reward is sufficient to induce dopaminergic changes. Although dopamine release during slot machine gambling is comparable between healthy controls and pathological gamblers, greater gambling symptom severity is associated with greater dopaminergic responses. Thus, as the dopamine reward deficiency theory predicts blunted mesolimbic dopamine responses to gambling in addicted individuals, our results question the validity of the reward deficiency hypothesis in pathological gambling.

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Introduction

Rewards drive goal-directed behavior in humans, a multifaceted psychobiological sequence which, on a neural level, seems to be regulated by mesolimbic dopaminergic neurotransmission. Partly overlapping and competing hypotheses point to the role of dopamine in the hedonic impact of rewards, in the learning and future prediction of rewards, or in the incentive salience of reward-predicting stimuli (Berridge, 2007). In drug addiction, reduced brain dopaminergic responsiveness has been considered to be of importance in individual addiction vulnerability. The dopamine reward deficiency hypothesis states that a person with certain functional genetic polymorphisms may develop a syndrome, which is characterized by a constant dopaminergic reward deficient state and diminished responses to natural rewards (Blum et al., 2000). To compensate the underlying unresponsiveness, the person compulsively searches for unnatural rewards, such as substances of abuse. The dopamine D2 receptor gene (DRD2) has been considered to be of particular importance in the genetics of the reward deficiency syndrome (Blum et al., 2000; Comings and Blum, 2000). This hypothesis is not without controversy and
there are also a number of studies contradicting the reward deficiency hypothesis (for a review, see Hommer et al., 2011). Recently, a refined model of addiction has been proposed. According to this model, although the dopamine release induced by the drug of abuse becomes attenuated, the enhanced conditioned stimulus to drug cues drives the compulsive behavior (Volkow et al., 2010). There are a number of neuroimaging studies which support this model in drug addictions (Vollko et al., 2004).

Pathological gambling (PG), a disorder affecting approximately 1.6% of the adult population (Schaffer et al., 1999), is defined as persistent or maladaptive gambling behavior characterized by excessive time consumed to gambling or thinking about gambling, needing to gamble with increasing amounts of money, chasing one’s losses, unsuccessful efforts to stop gambling and financial/social problems due to gambling. Hence, PG can also be considered as a behavioral addiction since the characteristics and diagnostic criteria share many common features with substance addictions (Potenza, 2008). Several neurotransmitters, and especially dopamine, have been implicated in the neurobiology of PG (Potenza, 2008). The role of dopamine in PG is further supported by reports of associations between dopaminergic medications and impulse control disorders in patients with Parkinson’s disease (Voon et al., 2009).

There are only a few reported functional imaging studies in pathological gamblers with contradicting support for the concept of reward deficiency. Diminished ventral striatal hemodynamic response (fMRI BOLD signal) has been seen in pathological gamblers during winning in a simplified simulation of gambling as compared to controls (indirectly supporting deficient dopamine system without a directly dopaminergic biomarker) (Reuter et al., 2005). On the other hand, the only dopaminergic positron emission tomography (PET) study did not report differences in baseline striatal dopamine receptor availability, or in dopamine release, between pathological gamblers and healthy controls while they were performing the Iowa Gambling Task, which simulates decision-making (Linnet et al., 2011).

Firing of dopamine neurons in the brain reward circuitry is evoked not just by a reward, but also the prediction of a reward (Fiorelli et al., 2003; Schultz et al., 1997), that could be one of the driving forces in the obsessive need to gamble. The present study was designed to investigate dopaminergic mechanisms in human gambling, and the concept of reward deficiency in PG. We chose to study the dopamine function during slot machine gambling, the most commonly preferred gambling method of pathological gamblers (Dowling et al., 2005). Gambling with a slot machine involves rapid and alternating combinations of rewards, reward predictions, prediction errors, uncertainty and behavioral conditioning together with near-miss effects (Habib and Dixon, 2010) and losses disguised as wins (Dixon et al., 2010). The dopaminergic sum effect could explain why slot machines are the preferred method of gamblers. Hence, instead of using a task that abstractly models gambling, the task in the present study involved real money gambling with a commercial electronic slot machine during PET scanning, thus highlighting the ecological validity of the task. By altering the payout of the slot machine, we isolate effects of hedonic reward and conditioned expectation of reward.

**Materials and methods**

**Subjects**

Twenty four Caucasian male subjects participated in the study. Each subject was scanned three times with $^{[11C]}$raclopride PET, and the data set thus consisted of 72 PET scans. Twelve of the subjects were pathological gamblers (DSM-IV) and twelve were healthy male controls without gambling problems matched for age and BMI. All subjects were right handed, except for one control subject who was ambidextrous with right hand dominance. Exclusion criteria were substance dependence (including alcohol), major axis-I disorder, clinically relevant medical conditions, medication known to affect central dopamine function, intoxicated or recent substance use (within 36 h prior to the PET study), and consumption of coffee/tea within the last 12 h prior to PET study. In the psychiatric interviews, none of the subjects reported history of psychostimulant use. The study protocol was approved by the local ethical committee. After complete description of the study to the subjects, written informed consent was obtained.

Prior to PET scans, each subject underwent medical interviews by a physician (JJ) and by a consultant psychiatrist (SN), together with a basic MRI scan, basic blood laboratory tests and urine drug screen. The subjects were screened by South Oaks Gambling Screen (SOGS) (Lesieur and Blume, 1987) and Beck Depression Inventory (BDI) (Beck et al., 1988). PET diagnoses were confirmed by a consultant psychiatrist according to DSM-IV criteria of symptom presence within the past six months. A structured psychiatric interview (SCID-I) (First et al., 1996) was used to exclude current major axis-I disorders and substance dependence.

**PET imaging**

$^{[11C]}$Raclopride was synthesized by a previously described method (Langer et al., 1999). PET imaging was performed using GE Advance PET scanner (General Electric Medical Systems, Milwaukee, WI, USA) in the 3D-mode (Lewellen et al., 1996). A rapid bolus injection of $^{[11C]}$raclopride [mean (SD) dose = 207 (9.6) MBq, injected mass ranging from 0.2 to 2.3 μg] was given at the beginning of the scanning. The total scanning time was 54 min consisting of 15×1 min, 7×2 min, and 5×5 min frames. A Velcro strap was used to minimize the head movement, and head motion tracking (Polaris, Northern Digital Inc., Canada) was applied during the scans. Infrared light reflectors for Polaris tracking tool were attached on the top of head using a plastic cap fixed with rubber bands. The motion tracking data was used to determine the optimal reference frames for frame-by-frame motion correction, image quality control, and exclusion of differences in motion between groups or scans.

Heart rate and blood pressure were measured before the tracer injection (0 min) and twice during the gambling (15 and 30 min). Behavioral analog scale mood ratings (scale from 0 to 10) of “urge to gamble”, “high”, “alertness”, “positive mood” and “excitement” were recorded at the same time points during gambling tasks.

**Stimulus**

Each subject underwent three $^{[11C]}$raclopride PET scans on the same day under three different conditions: high-reward, low-reward and control task. The order of the conditions was fully counter-balanced, and the interval between injections was 3 h to allow sufficient decay of the previous bolus of $^{[11C]}$raclopride. Subjects were blinded to the study purpose and to the prearranged pseudorandom outcomes of the gambling sessions. The subjects performed the tasks during the whole 54 min scanning time while lying supine in the scanner controlling the task functions with a computer mouse.
The sensorimotor control task was to select button A or B when lit on the screen together with sound signals, providing visual, auditory, and motor activation without gambling (Fig. 1b). For high-reward and low-reward tasks, software from a commercial slot machine was used including original sound effects (“Double pot”, Finnish Slot Machine Association, Fig. 1a). Each participant was given 20 € as their starting bankroll (loaded in the program as the task started), and they were instructed that, if they should lose the initial amount, it would be automatically reloaded by the slot machine, and that they could keep the possible winnings without having to pay for the possible losses.

The normal payback rate of the commercial slot machine version is approximately 93%. For the present study, the software was programmed differently for the two gambling tasks: 1) High-reward — impossible to lose, certain winning, corresponding to a mean payback rate of 371%, and 2) Low-reward — no marked net win or loss, the net win curve remained around the initial amount during the whole task (Fig. 1c). For the high-reward task, the aim of the programming was to maximize the gambling “high” and dopamine release, and the program gave big wins especially during the first 25 min of gambling/scanning.

The gambling tasks were executed with an Adobe Flash (Adobe Systems Inc, San Jose, CA, USA) version of the game. Instead of using real randomness, specific C programs were generated for high-reward and low-reward, which were interpreted by Adobe Flash. Gambling with the “Double pot” slot machine requires very little skill; the machine has three spinning wheels with symbols with five win lines and the possibility to attempt doubling the wins with a “coin flip” button. Wins are indicated in text on the display on top of the slot machine, and are associated with the sound of coins dropping into a container and a particular tune. The time interval between the start of the spin and the outcome is approximately 4 s.

The high-reward task produced a mean (SD) net monetary win of 54.20 (11.90) euros [the highest net monetary win at single time-point was 93.70 (4.50) euros around 30 min of scanning]. The low-reward task produced a mean result of −3.20 (8.10) euros (Fig. 1c). Ranges of individual spin payouts were 0–20 euros in the high-reward task and 0–16 euros in the low-reward task. To reduce variability in the results, the possibility to double the largest wins was removed from the software (doubling option limited to 2 €). Since gambling speed and doubling varied from subject-to-subject, the gambling sequence was not identical between the subjects. However, the groups did not differ in magnitude of the winnings in the high-reward task, and all subjects had essentially similar net win slopes in both high-reward (mean (SD) net wins at the end of the scan 55.70 (13.60) euros in the control group and 52.60 (10.40) euros in pathological gamblers, P = 0.53) and low-reward (−5.80 (8.90) in controls and −0.40 (6.40) in pathological gamblers, P = 0.11) tasks (Fig. 1c). On average (SD) 460 (44) individual games (spins) were played by the subjects during one scanning session. Although pathological gamblers played more spins (played faster) than controls [mean (SD) 483 (39) in pathological gamblers and 437 (39) in controls, P < 0.001], their winnings did not markedly differ from controls because of the programming of the software.

Image preprocessing

External motion tracking was used to control group and stimulus related differences in subject motion that might affect the outcome of the PET measurement. There were no statistically significant differences between the groups or stimulus conditions in the subject motion and >97% of the frames had within frame motion less than the resolution of the scanner indicating good image quality (Supplementary material). Misalignments between PET sessions and between frames in each session were compensated for by using a mutual information algorithm in Statistical Parametric Mapping (SPM, Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/).

Kinetic analysis

The simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996) with cortex of the cerebellum as reference tissue was applied in the quantification of [11C]raclopride binding (BPND). SRTM yields binding potential (BP) of [11C]raclopride through the ratio at equilibrium of specifically bound radioligand to that of non-displaceable radioligand in tissue, hence denoted as BPND (Innis et al., 2007). Voxel-by-voxel maps of BPND were generated using the basis functions method of Gunn et al. (1997).

For the voxel-wise SPM analysis, spatial normalization of the movement corrected images to MNI space was carried out using a [11C]raclopride template created from data set of healthy volunteers (Haltia et al., 2007). Individual voxel-wise BPND images were smoothed with a 10-mm Gaussian kernel (voxel size 2 x 2 x 2 mm3). An average smoothed BPND image of the whole sample was calculated, and a binary mask with a threshold of BPND > 0.75 was created to confine the analyses to the basal ganglia area.

Regions of interest (ROIs) for extracting the time-activity course (TAC) data were delineated with Imadeus (version 1.20, Forima Inc., Turku, Finland) individually for each subject using coregistered brain MR images as a structural reference. ROIs were drawn

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**Fig. 1.** Gambling tasks. Screen view of the gambling task (Double pot-slot machine), which was used for the high-reward and the low-reward tasks. b. Screen view of the sensorimotor control task. c. Mean net win curves of the high-reward task (upper two curves) and the low-reward task (lower two curves). Error bars indicate 95% confidence intervals at corresponding time-points. Blue = controls. Red = pathological gamblers. Note: the groups did not differ in net wins (rmANOVA group x time interaction F1,3 = 1.69, P = 0.21, and F1,3 = 1.77, P = 0.16, for the high-reward and the low-reward tasks, respectively).
bilateral to the ventral striatum on two planes, the caudate on 3–6 planes, and the putamen on 3–5 planes on transaxial sections according to the gray-white matter border of the basal ganglia. Cerebellar ROIs were drawn to cerebellar cortical gray matter on 4–7 planes in the middle of the rostro-caudal axis.

Statistical analyses

One control subject was excluded from the SPM analysis because of partially missing cortical binding data due to a scanner malfunction. In addition, one low-reward scan of a pathological gambler was not available for analysis (failed radiochemical synthesis). Therefore, the final data set for SPM analysis consisted of 68 scans, and the final data set for ROI analysis consisted of 71 scans.

In the comparison of pathological gamblers and controls, a 2 × 3 repeated-measures ANOVA model was used in SPM and for the ROI-analysis (two groups, three conditions). Dopamine release (condition effects) and differences in dopamine release between the groups (group × condition interactions) were tested with a one-tailed height threshold of F(1, 70) = 2.30, with a cluster-level FWE-corrected P < 0.05 considered significant. The study was designed to test specifically dopamine release during gambling, and therefore, one-tailed t-tests were used in the SPM analyses. The highest peak of statistical significance of the dopamine release during the high-reward scan was defined with a conservative two-sided F-contrast with a height threshold of F = 8.80, df = 1,41, FWE-corrected P = 0.05 at voxel level. The analyses were performed with SPM5 running in Matlab R2008b for Windows (Math Works, Natick, MA, USA). After identifying the region where dopamine release occurred in rmANOVA, BPFNDs from the cluster of the highest peak of dopamine release [52 voxels, peak at (−10 4 2)] were extracted with MarsBar toolbox (Brett et al., 2002) implemented in SPM5, and used for subsequent analyses. For correlations with behavioral ratings, dopamine release was estimated by calculating relative (% delta values with the formula: (BPND(high-reward/low-reward) − BPND(control))/BPND(control)).

Changes in behavioral ratings (BR) were calculated as delta values with the formula: (BR30min + BR15min)/2 − BR0min, and analyzed with repeated measures ANOVA. Correlation analyses were performed with Spearman’s rank order test and group-differences were studied with Kruskal–Wallis one-way ANOVA or Mann–Whitney U-test, when appropriate. The normality of the distributions was evaluated using Shapiro–Wilk test and by a visual inspection of the histograms.

Dopamine release during gambling

Gambling induced dopamine release [as indicated by negative [11C]raclopride delta BPND] in the right striatal region in all subjects during both high-reward and low-reward tasks (Fig. 2). The dopamine release during the low-reward scan was located in the associative striatal part of the caudate nucleus (Fig. 2b). During the high-reward scan, the effect was also seen in the ventral striatum (Fig. 2a). There were no significant group or interaction effects, nor areas with increased BPND. High-reward dopamine release correlated significantly with low-reward dopamine release (Fig. 3a). The positive correlation between high-reward and low-reward dopamine release in the whole sample was confirmed also by ROI-analysis in the right ventral striatum (r = 0.66, P = 0.001) and the right caudate (r = 0.78, P < 0.001). Unlike the more functional voxel-based analysis, the repeated-measures ANOVA with the conventional ROI data did not show statistically significant findings. The order of high-reward and low-reward tasks (high-reward scan performed first, or high-reward scan performed last) or the number of spins played during the tasks did not have effect on dopamine release in the whole sample or in pathological gamblers/controls separately.

Mood ratings and physiological measures

The changes in mood ratings during the tasks are presented in Table 2. The high-reward task induced gambling “high” in both pathological gamblers and controls, whereas the low-reward task did not (Table 2). Right striatal BPND change during high-reward

Table 1

Demographic data.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 12)</th>
<th>Pathological gamblers (n = 12)</th>
<th>Mann–Whitney U P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.0 (19–55)</td>
<td>30.0 (22–49)</td>
<td>0.62</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comprehensive school</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vocational or high school</td>
<td>10</td>
<td>8</td>
<td>0.64*</td>
</tr>
<tr>
<td>University or university of applied sciences</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 (23–35)</td>
<td>27.5 (21–36)</td>
<td>0.75</td>
</tr>
<tr>
<td>Gross income per month (€)</td>
<td>1 000 (400–3500)</td>
<td>2 425 (250–3600)</td>
<td>0.30</td>
</tr>
<tr>
<td>BDI score</td>
<td>0.0 (0–2)</td>
<td>6.0 (1–19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daily nicotine use (n)</td>
<td>3</td>
<td>6</td>
<td>0.40*</td>
</tr>
<tr>
<td>Age of onset of PG (years)</td>
<td>na</td>
<td>17 (10–39)</td>
<td>na</td>
</tr>
<tr>
<td>PG duration (years)</td>
<td>na</td>
<td>12 (1–20)</td>
<td>na</td>
</tr>
<tr>
<td>SOGS score</td>
<td>0.5 (0–1)</td>
<td>14.0 (10–18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Debt due to gambling (euro)</td>
<td>0</td>
<td>20,000 (0–75,000)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Demographic characteristics of the subjects presented as number of subjects or median values (range). Education = highest completed degree. BDI = Beck Depression Inventory. SOGS = South Oaks Gambling Screen (scores 3 or 4 indicate possible pathological gambling, and scores > 4 indicate probable pathological gambling) (Lesieur and Blume, 1987). n = number of subjects. h = hours. € = euro. na = not applicable.

* Fischer’s Exact test.
gambling correlated with “high” ($r = -0.47$, $P = 0.02$) (Fig. 3b), “positive mood” ($r = -0.52$, $P = 0.01$) and “alertness” ($r = -0.43$, $P = 0.04$) indicating higher positive mood and alertness with higher dopamine release (cluster BPND, controls and gamblers combined). In the low-reward scan, dopamine release was not associated with any of the behavioral ratings ($r = -0.25$ to $0.09$, $P > 0.28$). Of the physiological measures (heart rate, RR syst–diastrum), heart rate task×time interaction was significant ($F = 10.78$, $df = 2,42$, $P < 0.001$) indicating accelerating heart rate during the high-reward, and decelerating heart rate during the low-reward scan, but no differences between the groups.

Addiction severity

In pathological gamblers, SOGS scores correlated positively with dopamine release during high-reward (SOGS vs delta BPND $r = -0.59$, $P = 0.04$) (Fig. 3c), but not during low-reward (trend toward the same direction, SOGS vs delta BPND $r = -0.56$, $P = 0.08$). The positive correlation between high-reward dopamine release (negative delta BPND) and SOGS score was confirmed using the ROI data in the right ventral striatum (SOGS vs delta BPND $r = -0.78$, $P = 0.003$).

Control task dopamine receptor availability

There were no differences between the groups in the control task BPNDs (rmANOVA group effect). No significant correlations were seen between control task dopamine receptor availability and SOGS score, DSM-IV PG item score, duration of gambling problems, age at the beginning of gambling problems or BDI score in pathological gamblers (effect of age partialled out in the correlations).

Discussion

Our results indicate that basal ganglia dopamine is released during gambling with wins correlating with hedonic measure, and a similar effect is seen in gambling without net wins, which does not correlate with hedonic measure. Here we use the term hedonia to indicate pleasure, as captured by the terms ‘positive mood’ and ‘high’. Unexpectedly, there is no general difference in dopamine release between...
Mood rating delta values \[ \frac{(BR_{15\text{min}} + BR_{30\text{min}})}{2} \] change from the level of prior to the task, presented as mean (SD) values.

Gambling releases dopamine

Activation of the mesolimbic dopaminergic reward circuitry, as evidenced by striatal dopamine release, has been shown to be triggered by various pharmacological (Volkow et al., 2004) and non-pharmacological (Egerton et al., 2009) rewarding stimuli. The dopamine release from pharmacological agents is associated with self-reported “high”, depending on the pharmacokinetics of the drug – the faster the entry to the brain, the greater the experienced “high” and dopamine release (Volkow et al., 2004). Of the non-pharmacological rewards studied with \[^{11}C\]Craclopride PET displacement method, monetary reward during a video game (without a sensorimotor control task or movement correction) (Koepp et al., 1998), a gambling task (patients with Parkinson’s disease) (Steeves et al., 2009), a delayed monetary incentive task (Schott et al., 2008), or an active card selection task (Zald et al., 2004); food (after fasting) (Small et al., 2003); and music (individuals who respond exceptionally strongly to music) (Salimpoor et al., 2011) have been shown to produce measurable and statistically significant striatal dopamine release. However, several non-pharmacological studies only show trends toward dopamine release, or significant effects only in subpopulations, indicating existing effects, but smaller effect sizes or more individual variability in non-pharmacological stimuli as compared to pharmacological agents (Egerton et al., 2009).

A previous study reported no differences between pathological gamblers and healthy volunteers in the magnitude of dopamine release during Iowa Gambling task (Linnet et al., 2011). However, their subanalysis of subjects losing money during the task revealed higher dopamine release in pathological gamblers compared to healthy volunteers (Linnet et al., 2010). The present results with an ecologically valid non-pharmacological stimulus, show that gambling with both winning and no net winning releases dopamine in the right striatal region in both pathological gamblers and healthy controls. An even greater dopamine release during the high-reward scan might have been possible with progressively increasing net wins until the end of the task. However, we chose to maximize the unexpected rewards (wins) during the task and to make gambling more realistic using a non-linear net win curve. Since incentive motivation appears to be associated with striatal dopamine asymmetry (Tomer et al., 2008), the asymmetric finding in the present study could reflect hemispheric differences in dopaminergic reward processing. It is also possible that, with the present statistical power, the captured effect is a peak of broader dopamine release, but this doesn’t seem likely since the results did not show even near-significant dopamine release in left striatal area. Moreover, a recent \[^{11}C\]Craclopride PET study with healthy volunteers has indicated that reward processing during gambling may be lateralized to the right ventral striatum (Martin-Soelch et al., 2011).

Dopamine release during high-reward correlates with low-reward

The results of the present study show that the changes in dopamine during high-reward gambling are parallel with the changes during low-reward gambling. This is true in both healthy controls and pathological gamblers even though both groups only experienced gambling “high” during the rewarding task. The effect in high-reward scan was localized both to the ventral striatum and associative regions of the striatum (Kegeles et al., 2010), whereas in low-reward, dopamine release was detected mainly in the associative striatum (in the border of the caudate and the ventral striatum) (Fig. 2). The dopaminergic responses during low-reward were not associated with any of the mood ratings and the overall mood effect of low-reward gambling was negative (decrease in positive mood). The dopamine reaction in low-reward situation is thus apparently not associated with hedonia. Although there were small occasional rewards also during the low-reward scan, possible hedonia was overshadowed by negative/neutral mood due to monotonous low-reward gambling (Table 2). Therefore, as the time resolution of \[^{11}C\]Craclopride PET is limited, we have interpreted the net-effect of low-reward signal as not hedonic.

Midbrain dopamine neurons have been shown to encode both the reward risk and the reward value in monkeys (Fiorillo et al., 2003), and the human brain has been reported to respond hemodynamically to risk and reward value in a card task (Preuschoff et al., 2006). In the present study, the activation of the dopaminergic system in low-reward gambling may be linked to conditioning, and the reward-predicting response of the dopaminergic system may mostly be due to a powerful conditioned stimulus of the slot machine gambling task. Indeed, it has been shown in rats that dopamine acts selectively in a form of stimulus-reward learning in which incentive salience is assigned to reward cues (Flagel et al., 2011). However, dopamine release capacity also seems to show high inter-individual variability, irrespective of the challenge (Buckholtz et al., 2010b; Scott et al., 2007) and the individuality of dopamine release could be associated with the tight correlation between high and low reward scans. There is some evidence for this in the literature as the ventral striatal fMRI response to reward cues does not only correlate with dopamine release in the corresponding task (Schott et al., 2008), but also with pharmacologically or placebo-induced dopamine release (Buckholtz et al., 2010a; Scott et al., 2007). Since we chose to isolate the effects of gambling-induced positive/neutral mood instead of positive/negative mood, the tasks involved winning and no net winning, not winning and losing as in normal gambling. Gambling with major losses would have introduced more negative mood, possible aversive effects and anxiety, thus complicating the interpretation of pure reward value effect of dopamine.

Dopamine release correlates with addiction severity

Correlation analyses showed that the most severely addicted gamblers (highest scores in SOGS) released more dopamine during high-reward gambling than less addicted gamblers. This bears importance with respect to the dopamine reward deficiency theory. If there were reward deficiency in PG, one would expect a blunted dopamine
response in the most addicted individuals, a response which would need enhancement by higher bets or more frequent gambling. The present results are opposite to that expectation; when the winnings were fixed and moderate, endogenous dopamine was released, but the most addicted individuals released the most dopamine while obtaining the most pleasure from the task. There are several lines of evidence that also contradict the dopamine reward deficiency theory. A PET study investigating Parkinson’s disease patients with and without PG, showed increased dopamine release during gambling in patients with PG (Steeves et al., 2009). Personality traits commonly associated with pathological gambling, such as impulsivity and antisociality, are also associated with increased, and not decreased, mesolimbic dopamine responses (Buckholtz et al., 2010a; Forbes et al., 2009; Steel and Blaszczynski, 1998), although the data is not completely uniform (Beck et al., 2009). Furthermore, increased midbrain reactivity to near-misses during gambling has been observed in pathological gamblers (Chase and Clark, 2010). These findings together with the present data indicate enhanced mesolimbic reactivity to gambling related stimuli in pathological gambling, contradicting the reward deficiency syndrome in pathological gambling. However, there are also results favoring the reward deficiency hypothesis in pathological gambling as Reuter et al. reported blunted hemodynamic responses in the ventral striatum in pathological gamblers during simulated gambling (Reuter et al., 2005).

Limitations

There are limitations in the present study, which should be considered in the interpretation of the results. First, the repeated-measures ANOVA with the ROI-data did not show statistically significant findings. It should be noted, however, that the voxel-wise analysis identified the peak effect in a region (border of the caudate nucleus and the ventral striatum), which was not totally covered by any single ROI of the conventional basal ganglia ROI-analysis. Furthermore, the slice thickness and different orientation of slices of the non-normalized images used in the ROI analysis are likely to cause excess variation in measures from very small structures like the ventral striatum (particularly with transaxial slices with 4.25 mm slice thickness), which is controlled in SPM analysis with similarly sliced, normalized images. Second, it is possible that the reduction in raclopride binding was caused by motor activation during the scans (Badgaiyan et al., 2003). However, the control tasks included similar motor activation as the gambling tasks, and there were no differences in subject motion between the groups or scans as measured with an external motion detector. Moreover, the reduction in BPND was seen on the side ipsilateral to the hand controlling the task (except in one subject). Finally, since single-scan SRTM approach was used to derive BPNDs instead of kinetic analysis, changes in non-specific binding during high-reward and low-reward tasks cannot be conclusively ruled out in the present study.

Conclusions

The gambling sessions in the present study involved over 400 rapid repetitions (one per every seven seconds) of unrelated events, which had the same elements of risk, prediction of reward and reward delivery (win) or no reward (loss). The reported dopaminergic responses are net effects of these events compared between different reward values (high-reward vs. low-reward). The dopaminergic response to reward–predicting stimulus and the linkage between addiction severity and dopamine release in pathological gamblers may play roles in the development and the symptomatology of the maladaptive gambling behavior. Studies of secondary networks apart from dopamine circuitry, such as the functional connections from the dopamine system on the opioid system (Fattore et al., 2010), are needed to identify other mechanisms in reward processing which could be targeted for pharmacotherapy of gambling addiction.

Disclosure statement

The authors have no competing financial interests. Dr. Joutsu, Mr. Johansson, Dr. Piepponen, Ms. Arponen, and Dr. Alho report no relationships with commercial interests. Dr. Niemela has received lecturer honoraria or travel grants from Astra Zenea, Bristol–Myers, Janssen, Lilly, Lundbeck, Pfizer, Reckitt Benckiser and Swedish Orphan Biovitrum; provided expert testimony to Pfizer; and is a member of the advisory board for Pfizer and Lundbeck. Mr Ollikainen works as a software developer for Finland’s Slot Machine Association, whose main purpose is to raise funds for charity. Dr. Hirvonen has received a research grant from the Orion-Farms Research Foundation. Dr Voon has received speaker honoraria from Boehringer Ingelheim, Lundbeck, and Motac. Dr Rinne serves as an associate editor of the Journal of Alzheimer’s Disease, serves as a consultant to GE Healthcare Finland and is involved in contract research with GE Healthcare Finland, Bristol–Myers Squibb, Pfizer, OrionPharma, and AC Immune SA. Dr Hietala has received speaker’s bureau honoraria and/or travel funds from Janssen, Bristol–Myers, Lilly, Astra–Zenea, Pfizer and Lundbeck; serves as a member of the advisory board of Servier and as a consultant for Orion-Pharma. Dr Kaasinen has received speaker honoraria and/or travel grants from Boehringer-Ingelheim, GSK, Orion-Pharma, Abbott, UCB and Lundbeck; and serves as a member of the advisory board of UCB and as a consultant for Orion-Pharma and Lundbeck.

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Appendix A. Supplementary data

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References
