At-risk for pathological gambling: imaging neural reward processing under chronic dopamine agonists

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Treatment with dopamine receptor agonists has been associated with impulse control disorders and pathological gambling (PG) secondary to medication in previously unaffected patients with Parkinson’s disease or restless legs syndrome (RLS). In a within-subjects design, we investigated the underlying neurobiology in RLS patients using functional magnetic resonance imaging. We scanned 12 female RLS patients without a history of PG. All patients were scanned twice: once whilst taking their regular medication with low dose dopamine receptor agonists and once after a washout phase interval. They performed an established gambling game task involving expectation and receipt or omission of monetary rewards at different levels of probabilities. Upon expectation of rewards, reliable ventral striatal activation was detected only when patients were on, but not when patients were off medication. Upon receipt or omission of rewards, the observed ventral striatal signal under medication differed markedly from its predicted pattern which by contrast was apparent when patients were off medication. Orbitofrontal activation was not affected by medication. Chronic dopamine receptor agonist medication changed the neural signalling of reward expectation predisposing the dopaminergic reward system to mediate an increased appetitive drive. Even without manifest PG, chronic medication with dopamine receptor agonists led to markedly changed neural processing of negative consequences probably mediating dysfunctional learning of contingencies. Intact orbitofrontal functioning, potentially moderating impulse control, may explain why none of the patients actually developed PG. Our results support the notion of a general medication effect in patients under dopamine receptor agonists in terms of a sensitization towards impulse control disorders.

Keywords: reward; fMRI; restless legs syndrome; dopamine agonists; pathological gambling
Abbreviations: DA = dopamine agonists; PG = pathological gambling; RLS = restless legs syndrome

Introduction

Pathological gambling (PG) has been reported as an expensive side-effect of treatment with dopamine agonists (DA). Accounts of previously unaffected patients with neurological illnesses that lost tens of thousands of dollars because of newly adopted gambling behaviour were issued and even received public recognition in the past years. While the first reports were on patients suffering from Parkinson’s disease under high doses of DA medication (Dodd et al., 2005; Gallagher et al., 2007; Voon et al., 2007),...
recently patients with restless legs syndrome (RLS) attracted
attention because they acquired dysfunctional habits of gambling
even under low doses of DA (Driver-Dunkley et al., 2007; Tippmann-Peckert et al., 2007) within several weeks after a new
treatment regimen was initiated or doses were increased. According
to the reports, PG resolved in all patients after discontinuation of the
treatment. DA are therefore assumed to cause a reversible increase
of the predisposition towards PG (Voon et al., 2007).

PG, according to the Diagnostic and Statistical Manual of
Mental Disorders (DSM)-IV, is classified as a compulsive disorder
with failure to resist gambling impulses despite negative personal,
family or vocational consequences. While the prevalence for PG in
the general population is estimated ~0.5% in the USA (Petry
et al., 2005) and 0.2% in Germany (Meyer, 2007), ~4–8% of
patients with Parkinson’s disease taking DA are reported to show
PG behaviour (Gallagher et al., 2007). As various DA have been
implicated in precipitating compulsive disorders like PG (Dodd
et al., 2005; Gallagher et al., 2007; Voon et al., 2007), a class
effect can be assumed, but the underlying neurobiology is still
unclear. A breakdown of reward-hierarchies due to alteration of
incentive processing has been suggested as a potential basis
(Gallagher et al., 2007; Riba et al., 2008). Indeed, agonists
preferring the D2/D3 receptor like pramipexole, ropinirole or
cabergoline, frequently used in the treatment of Parkinson’s
disease or RLS, act predominantly on the mesolimbic dopaminergic
system (Sokoloff et al., 2006) that mediates reward functions.
Conclusively, studies of low single doses of DA in healthy subjects
reported impairment of reward-related learning (Pizzagalli et al.,
2008) and altered functional magnetic resonance imaging (fMRI)
activation of the dopaminergic reward system (Riba et al., 2008).
Stimulation of presynaptic D3 autoreceptors reducing phasic firing
of dopamine neurons via inhibitory feedback (Pizzagalli et al.,
2008) has been suggested as the underlying mechanism.
However, while short-term administration of DA has been demon-
strated to decrease firing of dopamine neurons, animal research
has shown that chronic treatment is associated with recovery of
the firing rates to normal levels, desensitization of D2/D3 autore-
ceptors (Chernoloz et al., 2008) and downregulation of the dopa-
mine transporter (Joyce et al., 2004). Furthermore, while the acute
administration of DA in healthy subjects commonly relates to
nausea, lowered alertness, reaction time and motor speed slowing
and negative affect (Pizzagalli et al., 2008), chronic treatment in
patients not only leads to higher motor function but is com-
monly associated with better well-being and positive affect
(Sokoloff et al., 2006). Therefore, effects from single dose studies
in healthy subjects are far from being capable to fully explain the
predisposition towards pathologic gambling in patients on a reg-
ular DA medication.

Hence, we studied the effects of long-term DA medication on
fMRI brain activation during a gambling task in a sample of RLS
patients using a within-subject design with patients on and off
medication. The clinical presentation of RLS commonly involves
a wide spectrum of sensory discomfort during rest, accompanied
by motor restlessness and an irresistible urge to move. As inactivity
increases symptoms, sleep is often disturbed. Moving alters the
sensations, providing temporary alleviation, but DA greatly relieves
the symptoms (Allen et al., 2003; Trenkwalder et al., 2005).
Severe impairment of motor coordination, cognitive deficits or
neuropsychiatric problems, including impulse control disorders as
described for Parkinson’s disease irrespective of medication are not
typically observed in untreated RLS, thus providing a basis to study
side-effects of DA medication in combination with a markedly
reduced risk of biasing co-morbidities.

Among the specific reward mechanisms potentially involved in
the development of PG under DA, altered coding of errors in the
prediction of rewards during gambles has been suggested
(Pizzagalli et al., 2008; Riba et al., 2008). Prediction errors are
coded in the mesolimbic dopaminergic system as demonstrated
in studies of dopaminergic firing rates in monkeys (Fiorillo et al.,
2003; Schultz, 2007) and of fMRI activation of dopaminergic brain
regions, especially the ventral striatum in humans (Knutson
et al., 2001; Aber et al., 2005, 2006). Receipt of unpredicted rewards
(positive prediction error) is related to increases in signal and
learning of the behaviour associated with the occurrence of
rewards (Schultz, 2007). In contrast, the omission of predicted
rewards (negative prediction error) relates to decreases in signal
(Fiorillo et al., 2003; Aber et al., 2006) and extinction of the beha-
vour associated with losing the incentive. Altered fMRI activation
of the ventral striatum upon winning and losing money, potentially
representing dysfunctional prediction error processing, was accord-
ingly observed in a sample of pathological gamblers (Reuter
et al., 2005). Together with hypoactivation of the orbitofrontal cortex
(Potenza et al., 2003a, b; Reuter et al., 2005), ventral striatal dys-
function seems to characterize pathological gamblers.

Besides changes in prediction error processing, alterations of
appetitive motivation in the presence of prospective rewards and
elevated novelty seeking have been identified as potential risk
factors for the development of PG, at least in Parkinson’s disease
(Voon et al., 2007).

Using an established paradigm (Aber et al., 2006), well suited to
investigate variations of reward expectation and prediction error as
a discrete function of reward probabilities, we studied patients with
RLS syndrome ‘on’ and ‘off’ their regular long-term DA medication
in a within-subjects design. We assumed that DA medication is
related to an increased predisposition towards PG in patients treated
with DA, although only some develop manifest clinical symptoms.
We therefore expected to find congruent neurobiological correlates.
We hypothesized that there would be an alteration in mesolimbic fMRI brain activation upon expectation of rewards
when comparing patients on and off medication, and dysfunctional
prediction error signalling upon receipt and omission of
rewards when patients are under chronic DA medication. Thus,
we expected changes related to medication in ventral striatal or
orbitofrontal regions, in particular decreased activation upon
receipt of rewards, as demonstrated for manifest PG (Potenza
et al., 2003a, b; Reuter et al., 2005).

Methods

Patients

Twelve female outpatients of the Department of Neurology at the
University Clinic of Ulm (one left-handed, aged 43–66 years, all
non-smokers) with RLS treated with DA were included in and com-
pleted the study. The diagnosis was based on a detailed history and a
standardized general and neurological examination. All patients ful-
filled the revised essential criteria for the diagnosis of idiopathic RLS
defined by the International RLS Study Group (IRLSG) (Allen et al.,
2003). On average, patients had been diagnosed with RLS 4 years
before the study (Table 1) and had been suffering from RLS symptoms
for several years more. Stable treatment with DA was initiated at least
1 month and usually >1 year before scanning. Psychiatric, especially
substance-related problems were excluded in a psychiatric interview on
the basis of the Structured Clinical Interview for DSM-IV (SCID) (APA,
1994). None of the patients ever engaged in regular gambling or had
any evidence pointing to PG in the past. Severe acute or chronic cur-
cent medical conditions were excluded.

Each patient was tested on two occasions, once whilst taking their
regular DA and once after a washout phase without medication in
a balanced, randomized design. Scans were conducted 2 weeks
apart. Patients were treated either with pramipexole (five patients),
cabergoline (four patients) or ropinirole (three patients) (Table 1)
and were allowed an additional medication of l-dopa. For the scans
without medication, patients were asked to discontinue cabergoline for
at least 5 days, pramipexole and ropinirole for 48 h, and to refrain
from taking l-dopa for 24 h before scanning, according to the half-
lives of the drugs. The study was approved by the local ethics
committee of the University of Ulm. Written informed consent was
obtained after complete description of the study to the subjects and
prior to inclusion.

Task
We used a well-established monetary incentive task described
elsewhere in detail (Abler et al., 2006) with a parametric variation of
probabilities (0, 25, 50, 75 and 100%) to win a fixed amount of
money (1€). Each of the two sessions consisted of 60 trials (12 trials
per each probability; 120 trials in total). The trials started with a cue
(a coloured symbol) indicating the probability to win the money later
on. After an expectation period, subjects had to correctly react with
a button press to two different symbols. In reacting correctly, they
retained the previously announced chance to win 1€. Feedback (out-
come) followed the target’s disappearance and notified subjects of
the amount of money (1€ or 0€) they won in the trial. Reaction times
and errors were registered. Depending upon the reward probabilities,
subjects were not rewarded despite pressing the correct button in a
number of trials, i.e. a reward announced at a probability of 75% was
actually distributed in 75% (receipt of reward) and held back in 25%
(omission of reward) of the correct trials. Incorrect button presses
resulted in a feedback of zero euros at any probability. Receipt and
omission trials as well as the five trial types (0, 25, 50, 75 and 100%
chance to win) appeared in a random order. Right before scanning, all
subjects completed two sessions (60 trials/10 min each) of a practice
version of the task.

fMRI acquisition
A 3.0 T Siemens ALLEGRA Scanner (Siemens, Erlangen, Germany)
equipped with a head coil was used to acquire T2*-anatomical
volume images (1 × 1 × 1 mm voxels) and functional magnetic
resonance images. Twenty-three sagittal slices were acquired with an
image size of 64 × 64 pixels and a field of view of 192 mm. Slice
thickness was 3 mm with 0.75 mm gap resulting in a voxel size of
3 × 3 × 3.75 mm. Images were centred on basal structures of the
brain including subcortical regions of interest (basal ganglia and
prefrontal regions). Functional images were recorded using a
T2*-sensitive gradient echo sequence measuring changes in BOLD-
contrast. 401 volumes were obtained during each session at a TR of
1500 ms (TE 35 ms, flip angle 90°).

fMRI analysis
Image processing and statistical analysis were carried out using
Statistical Parametric Mapping (SPM5, Wellcome Trust Centre
for Neuroimaging, London, UK) with a random effects model for group
analyses. Pre-processing of the individual functional scans included
realignment to correct for motion artefacts, slice timing, spatial nor-
malization to a standard template (Montreal Neurological Institute,
MNI) and smoothing with an 8 mm full width at half maximum
(FWHM) Gaussian kernel. Intrinsic autocorrelations were accounted for
by AR (1) and low-frequency drifts were removed via high pass filtering.

After pre-processing, first level analysis was performed on each
subject estimating the variance of voxels for each trial according to
a general linear model. As in our previous study on healthy subjects,
we defined regressors to analyse each of the five types of expectation
phases sorted by reward probabilities of 0, 25, 50, 75 and 100%. Regressors modelled reward expectation including presentation of
the cue, the button press and the eight different types of outcome
(Table 2). Depending on the preceding reward expectation (0–100%)
and actual outcome (receipt of reward: R, omission of reward: O)
the eight outcome events were: (i) 0%; (ii) 25% R; (iii) 25% O;
(iv) 50% R; (v) 50% O; (vi) 75% R; (vii) 75% O; and (viii) 100%.
According to their actual durations, trials were modelled as timely
extended events and convolved with the hemodynamic response
function. The six re-alignment parameters modelling residual motion
were also included in the individual models.

The contrast images of parameter estimates for each level of
expectation and for each combination of probabilities and outcome
were then included in a second level group analysis. Replicating our
previous experiment (Abler et al., 2006), we computed analyses sep-
ately for expectation and outcome trials: one on the five different
expectations (Analysis 1a) and one on the eight outcome events
(Analysis 2). Conditions were weighted with a linear contrast to model
neural activations related to increasing reward expectation with increas-
ing probabilities (Analysis 1a) and a linear contrast to model activation
following prediction error theory (Analysis 2), formally modelling the size
of the prediction error (Fig. 2B). A third analysis was calculated including
only the two extremes of expectation regressors (Analysis 1b:
100–0%). Treatment effects (on, off medication) were tested by inter-
action analyses of medication with either expectation or outcome.
Statistical maps were thresholded at P < 0.05 with false discovery rate
(FDR) corrections for multiple comparisons. If effects failed significance
at that threshold, statistical maps were thresholded at P < 0.001.
paring trials with 0 and 25% against trials with 100% probability yielded significant acceleration of mean reaction times when comparing trials with 0 and 25% against trials with 100% probability ($P = 0.003$; 25% versus 100%: $P = 0.018$) for runs without dopaminergic medication and a significant acceleration comparing trials with 25% against trials with 100% probability ($P = 0.03$) when patients were on medication.

Mean reaction times in the neuropsychological tests after scanning were significantly faster in three of four tests when subjects took their regular medication than without DA (see Supplementary material). Patients rated their symptoms significantly worse when being off medication [average 6.0 on a visual analog scale from 1 to 10; $t(11) = 5.9$, $P = 0.0001$] against being on medication (average 2.0 on scale from 1 to 10). Without medication, they commonly reported re-occurrence or deterioration of their common symptoms like pricking, fidgeting, urge to move their legs and troubles with sleeping.

**Results**

**Behavioural responding**

Subjects pressed the correct button within the required time interval in 98% of the trials, irrespective of dopaminergic medication. An analysis of variance for repeated measures on mean reaction times revealed a significant main effect for levels of probability [$F(4,44) = 4.66$, $P = 0.003$], but not medication [$F(1,11) = 1.11$, $P = 0.315$], although patients appeared to respond slightly faster when taking DA (Fig. 1). The interaction of both factors was not significant [$F(4,44) = 0.52$, $P = 0.724$]. Post hoc tests (Bonferroni) yielded significant acceleration of mean reaction times when comparing trials with 0 and 25% against trials with 100% probability ($P < 0.05$). The linear contrast predicting increasing neural activations with increasing probabilities (analysis 1a) revealed a significant effect ($P < 0.001$) in right lateral orbitofrontal cortex (Table 2), when patients were on DA medication, but not when patients were off medication. Significant linear trends were additionally observed in occipital and parietal regions and in the cerebellum, predominantly when patients were ‘off DA’, but also ‘on DA’ (for details, see online Supplementary material). Comparing linear trends between on and off medication, no significant differences were to observe in the reward system even at lowered thresholds of $P < 0.05$.

Contrasting effects of expectation probabilities at their extremes (100% minus 0%, analysis 1b) revealed a statistically reliable effect in the left parahippocampus, the left ventral striatum and lateral orbitofrontal cortex bilaterally only when patients were on medication (Table 2). An interaction of this contrast with medication marginally failed pre-defined significance ($P = 0.006$) in the left ventral striatum ($-18/10/-4$) demonstrating higher differential activation when patients were ‘on DA’. Irrespective of medication status, additional locations bearing a significant contrast (100–0%) were found in occipital regions, and the cerebellum (for details, see online Supplementary material).

**fMRI results**

We directed our analyses to the question whether medication with DA alters fMRI activation in the dopaminergic reward system and particularly in those regions where altered activation was found in patients with manifest PG, i.e. the ventral striatum and orbitofrontal cortex. fMRI activation of these areas can be described as a function of reward probability and prediction error as shown for firing rates of dopamine neurons in animal experiments (Fiorillo et al., 2003; Schultz, 2007) and for fMRI signals in human subjects (Abler et al., 2006).

**Reward expectation**

The linear contrast predicting increasing neural activations with increasing probabilities (analysis 1a) revealed a significant effect ($P < 0.001$) in right lateral orbitofrontal cortex (Table 2), when patients were on DA medication, but not when patients were off medication. Significant linear trends were additionally observed in occipital and parietal regions and in the cerebellum, predominantly when patients were ‘off DA’, but also ‘on DA’ (for details, see online Supplementary material). Comparing linear trends between on and off medication, no significant differences were to observe in the reward system even at lowered thresholds of $P < 0.05$.

Contrasting effects of expectation probabilities at their extremes (100% minus 0%, analysis 1b) revealed a statistically reliable effect in the left parahippocampus, the left ventral striatum and lateral orbitofrontal cortex bilaterally only when patients were on medication (Table 2). An interaction of this contrast with medication marginally failed pre-defined significance ($P = 0.006$) in the left ventral striatum ($-18/10/-4$) demonstrating higher differential activation when patients were ‘on DA’. Irrespective of medication status, additional locations bearing a significant contrast (100–0%) were found in occipital regions, and the cerebellum (for details, see online Supplementary material).

**Receipt or omission of reward**

To contrast differential effects of outcomes depending on preceding reward expectations we tested linear effects of a positive prediction error versus linear effects of a negative prediction error (brain regions beyond the reward system are detailed in the
Supplementary material. Briefly, the contrast revealed a significant effect in bilateral occipital regions, both when on and off DA, in the posterior cingulate, and the right insula only when patients were on DA, and in medial prefrontal cortex when patients were off medication). With patients off DA, this analysis revealed significant effects ($P<0.05$, FDR corrected) in the left ventral striatum and medial orbitofrontal cortex. On DA, effects were significant only in the medial orbitofrontal cortex ($P<0.05$ FDR corrected). Accordingly, a significant ($P<0.05$ FDR corrected) interaction of this contrast with medication was observed in left ventral striatum (Table 2). As illustrated in Fig. 2B, these differential effects were mainly due to a decrease of differential activation when patients ‘on DA’ medication received rewards expected at a rather low probability of 25% (25% R), and due to an increased differential activation when they did not receive a reward announced at the high probability of 75% (75% O).

### Discussion

With the present study in DA-treated RLS patients on and off medication, we undertook the first experimental step to investigate the neural substrate of a pre-disposition that may mediate PG under chronic administration of DA. Neural signalling of reward expectation was increased by trend, thus potentially pre-disposing the dopaminergic reward system to mediate an increased appetitive drive under medication. We could further demonstrate a striking pattern of dysfunctional prediction error processing when patients received DA medication. Medial orbitofrontal activation, however, was not changed by medication.

Upon reward expectation, we found statistically reliable reward system activation only when the patients were taking their regular DA medication. The acceleration of overall reaction times under DA medication further supports this interpretation. Enhanced dopamine transmission caused by the medication has been related to this effect (Servan-Schreiber et al., 1998), which has been observed in our own previous study using the same task (Abler et al., 2006) and which is different from the motor speed slowing observed in single dose studies of DA (Pizzagalli et al., 2008).

Off the medication, patients displayed subthreshold activation. Therefore, the findings allow speculation about increased reward expectations and appetitive drive in the patients when ‘on DA’.

Upon receipt of omission of rewards, patients off DA medication displayed the expected signal distribution according to prediction error theory in the ventral striatum. The highest signal was observed when patients received a very unlikely but still possible reward expected at a probability of only 25%, i.e. upon a highly positive prediction error. The lowest signal occurred when patients did not receive a rather likely reward expected at a probability of 75%, i.e. upon a highly negative prediction error. Outcome events associated with lower prediction errors were accordingly lower in activation and followed the linear distribution along probabilities as expected from prior investigations (Abler et al., 2006). Strikingly, when patients were on steady state medication, the cardinal fMRI signals followed an opposite pattern, especially at high prediction errors: a highly positive signal was observed upon omission of an

### Table 2 Maximum z-values and MNI-coordinates of contrasts of interest derived by whole-brain second-level group analyses

<table>
<thead>
<tr>
<th>Contrast/Region</th>
<th>Off DA</th>
<th></th>
<th>On DA</th>
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<th>Off versus on DA</th>
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<tr>
<td></td>
<td>Z</td>
<td>NV Peak coordinates</td>
<td>Z</td>
<td>NV Peak coordinates</td>
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<td>x/y/z</td>
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<td>x/y/z</td>
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<td>Expectation: analysis 1a</td>
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<td>—increasing reward probability</td>
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<tr>
<td>Lateral orbitofrontal cortex</td>
<td>R</td>
<td>NS</td>
<td>4.71</td>
<td>29</td>
<td>44/26/–12</td>
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<tr>
<td>Expectation: analysis 1b</td>
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<td>—100% &gt; 0% reward probability</td>
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<tr>
<td>Ventral striatum</td>
<td>L</td>
<td>NS</td>
<td>3.52</td>
<td>20</td>
<td>–18/20/–8</td>
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<tr>
<td>Lateral orbitofrontal cortex</td>
<td>R</td>
<td>NS</td>
<td>3.87</td>
<td>50</td>
<td>–40/20/–2</td>
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<tr>
<td>Outcome: analysis 2</td>
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<td>—reward prediction error</td>
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<tr>
<td>Ventral striatum</td>
<td>L</td>
<td>3.6* 9</td>
<td>–10/14/–10</td>
<td>NS</td>
<td>3.7* 19</td>
</tr>
<tr>
<td>Medial orbitofrontal cortex</td>
<td>4.3* 61</td>
<td>0/44/–20</td>
<td>5.5* 296</td>
<td>–2/44/–18</td>
<td>NS</td>
</tr>
</tbody>
</table>

Only effects within the reward system are listed (for a full table, please see online Supplementary material). Reward expectation Analyses (1a and 1b) modelling effects of increasing reward probability (five levels) and comparing neural activations upon reward expectation at 100% versus 0% probability. Reward outcome Analyses of outcome regressors (eight levels) linearly related to prediction error. Results for whole-brain second-level comparisons were significant at $P<0.001$ uncorrected for multiple comparisons at the voxel level, resulting in cluster extents significant at a level of $P<0.05$. Effects surviving a FDR correction for multiple comparisons at the voxel level ($P<0.05$ FDR corrected) are indicated by an asterisk. For the interaction with medication (direction of contrast: ‘off > on DA’), ‘off DA’ results at $P<0.005$ at the voxel level and $P<0.05$ at the cluster level were used as inclusive mask. For the inverted contrast (direction: ‘on > off DA’), ‘on DA’ results were used as an inclusive mask (same levels of significance as above). Only activations in brain regions of interest (ventral tegmental area, ventral striatum, orbitofrontal cortex) are listed. Coordinates are SPM/MNI-coordinates. L/R/M = left/right/midline; Z = Z-level at peak coordinate; NV = Number of voxels in cluster; NS = no significant effect.
almost certain reward, the lowest signal was associated with the surprising receipt of the most unexpected reward. Given that highly positive prediction error signals relate to boost learning about the preceding behaviour and negative signals relate to its extinction, a pre-disposition to dysfunctional reward-related behaviour seems obvious. This observation contributes to an understanding of why pathological gamblers often do not learn from the negative consequences of losing even large amounts of money, and helps the understanding of their irrational beliefs in gambling strategies without comprehensible bases.

Given these marked changes in reward processing, an explanation is needed as to why none of the patients in our study actually reported problems with gambling or impulse control. That is, the dysfunction ventral striatal prediction error signalling obviously did not come with notable behavioural consequences. Studying actual pathological gamblers with reward tasks during fMRI, both mesolimbic and mesocortical dopaminergic pathways were involved. Besides changes of activation in the ventral striatum, decreases of activation were observed in the medial orbitofrontal cortex as part of the mesocortical system (Reuter et al., 2005). Also, pathological gamblers displayed decreased fMRI activation specifically in the medial orbital prefrontal cortex when tested with a stroop task (Potenza et al., 2003a) or during gambling cue presentation (Potenza et al., 2003b). This region has also been associated with impulse control disorders (Rogers et al., 1999). Thus, the preserved or even pronounced activation in the medial orbitofrontal cortex with patients on DA is presumably involved in an adaptive modulation of impulse control mediating the lack of behavioural consequences of altered ventral–striatal signalling under medication.

We conclude that the observed ventral striatal changes in fMRI activation on DA may lead to an increased predisposition towards PG under this medication. DA medication may stimulate an appetitive drive under which the subjective experience of possible rewards is stronger than without medication. This mesolimbic dopaminergic hyperactivation is paired with a dysfunctional processing of prediction errors leading to ignorance of negative consequences. Intact mesocortical functioning, however, may prevent symptom manifestation. Discontinuation of medication obviously leads to a rapid reversal of this effect as already observed in patients with manifest PG (1).

It is of note that the modest number of participants may limit generalization. In contrast, the on–off medication within-subject design in a naturalistic sample with standard clinical medication of different classes appears clinically relevant and suggests a general medication effect in patients under DA in terms of sensitization towards impulse control disorders.

**Supplementary material**

Supplementary material is available at *Brain* online.
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