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Levodopa administration modulates striatal processing of punishment-associated items in healthy participants

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Abstract

Rationale—Appetitive and aversive processes share a number of features such as their relevance for action and learning. On a neural level, reward and its predictors are associated with increased firing of dopaminergic neurons, whereas punishment processing has been linked to the serotonergic system and to decreases in dopamine transmission. Recent data indicate, however, that the dopaminergic system also responds to aversive stimuli and associated actions.

Objectives—In this pharmacological functional magnetic resonance imaging (fMRI) study, we investigated the contribution of the dopaminergic system to reward and punishment processing in humans.

Methods—Two groups of participants received either placebo or the dopamine precursor levodopa and were scanned during alternating reward and punishment anticipation blocks.

Results—Levodopa administration increased striatal activations for cues presented in punishment blocks. In an interaction with individual personality scores, levodopa also enhanced striatal activation for punishment-predictive compared to neutral cues in participants scoring higher on the novelty-seeking dimension.

Conclusions—These data support recent indications that dopamine contributes to punishment processing and suggest that the novelty-seeking trait is a measure of susceptibility to drug effects on motivation. These findings are also consistent with the possibility of an inverted U-shaped response function of dopamine in the striatum, suggesting an optimal level of dopamine release for motivational processing.

Keywords

Reward; punishment; striatum; levodopa; novelty-seeking

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Introduction

Dopaminergic neurons are best known for their response to rewards and anticipation of rewards (Glimcher 2011; Schultz et al. 1997). More recently, these neurons have been reported to also respond to punishment and its anticipation in rats and monkeys (Bromberg-Martin et al. 2010). In functional magnetic resonance imaging (fMRI) studies in humans, striatal activations have been shown during processing of both appetitive and aversive predictions (Carter et al. 2009; Delgado et al. 2008; Metereau and Dreher 2013; Seymour et al. 2007; Seymour et al. 2004). The hypothesis that striatal activations are related to activity of the dopaminergic system has been investigated in genetic, positron emission tomography (PET) and pharmacological imaging studies. Reward processing was shown to be influenced by genotypes affecting expression of dopamine receptors, dopamine transporters, and dopamine metabolism (Nikolova et al. 2011; Stice et al. 2012). Reward-related striatal activation in fMRI correlates with dopamine release as measured by raclopride PET (Schott et al. 2008), and reward-related behaviour and neural processing can be influenced by the administration of levodopa (Pessiglione et al. 2006) and dopamine agonists (Riba et al. 2008; Ye et al. 2011).

In contrast to the well-known involvement of dopamine in reward processing, less is known about the role of dopamine in punishment. In rats, a distinct subpopulation of dopamine neurons responds to the onset of aversive stimulation (Brischoux et al. 2009). Dopaminergic neurons responding to aversive stimuli in mice can be differentiated by their anatomical projections (Lammel et al. 2011), and a subpopulation of dopamine neurons in monkeys has been shown to respond to aversive cues and stimulation (Matsumoto and Hikosaka 2009). Recently, it has been suggested that the dopaminergic system controls action requirements in reward and punishment behaviour in humans (Guitart-Masip et al. 2011). However, a subsequent study showed that levodopa administration selectively enhanced representation of rewarding but not punishment-related actions (Guitart-Masip et al. 2012). In a genetic fMRI study, we found that dopamine transporter genotype influenced striatal activity related to the anticipation of punishment and recognition memory for items associated with reward and punishment (Wittmann et al. 2013). Further fMRI data suggest that punishment and loss anticipation activate the ventral striatum (Carter et al. 2009; Jensen et al. 2003) and that the striatum is part of a network responding to salience prediction errors (Delgado et al. 2008; Jensen et al. 2007; Metereau and Dreher 2013; Seymour et al. 2004), possibly with an anteroposterior gradient dissociating reward and punishment-based activations (Seymour et al. 2007). In a classical aversive conditioning study, levodopa enhanced aversive prediction error signals in SN/VTA (Menon et al. 2007), suggesting that dopamine could also play a role in instrumental aversive conditioning.

Drug responses are known to be influenced by the personality dimension of novelty seeking. High novelty-seekers report feeling more stimulated after amphetamine administration (Hutchison et al. 1999; Sax and Strakowski 1998), and the trait 'exploratory excitability' is correlated with amphetamine-induced changes in [11C]raclopride binding potential in the ventral striatum (Leyton et al. 2002). Higher novelty seeking has also been shown to be correlated with proneness to amphetamine sensitization over the course of three single doses given within one year (Boileau et al. 2006). These behavioural findings likely result from

differences in drug action on dopamine-mediated motivational processing in low and high novelty-seekers.

The current study investigated the effect of levodopa treatment in healthy participants on reward and punishment anticipation. Participants were randomly allocated to the levodopa or placebo group and scanned during a motivational anticipation task, followed one day later by a memory test for the motivational cues outside the scanner. The motivational anticipation task comprised alternating blocks of reward and punishment. In each block, trials consisted of a cue picture that predicted the motivational or neutral outcome of the trial, a subsequent reaction-time task and a feedback period. In line with previous studies (Adcock et al. 2006; Wittmann et al. 2008; Wittmann et al. 2005), we expected reward-predicting stimuli to activate the dopaminergic system and enhance episodic memory. Based on previous findings (Pessiglione et al. 2006), we expected higher reward-related activations in the levodopa group compared to the placebo group. We additionally expected levodopa administration to influence punishment processing, as suggested by animal studies reporting dopaminergic punishment signals (for a review see Bromberg-Martin et al. 2010). We also hypothesized that levodopa would modulate episodic memory for reward and punishment associated items based on recent results regarding dopaminergic genotype (Wittmann et al. 2013). To assess the interaction of drug treatment with individual differences in novelty seeking, participants completed Cloninger's Tridimensional Personality Questionnaire (TPQ; Cloninger et al. 1991). Based on previous studies (Hutchison et al. 1999; Jupp and Dalley 2014; Sax and Strakowski 1998), we expected that levodopa effects would be enhanced in participants with higher novelty-seeking scores.

Experimental procedures

Participants

28 healthy adults without history of neurological or psychiatric disorder (all right-handed, mean age [± SD] 24.4 ± 3.2 years; range 20-30 years; 11 men) participated in the study. All participants gave written informed consent, and the study was approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley. Participants were reimbursed for their participation with the sum won across three monetary reward tasks, the first of which was carried out in the scanner and is reported here.

Participants were randomly allocated to the levodopa (100 mg levodopa, 10 mg carbidopa) or placebo group according to a double-blind procedure. This dose is identical to previous pharmacological imaging studies (e.g. Kelly et al. 2009; Pessiglione et al. 2006). The groups did not differ in age, gender distribution or years of education (group mean [± SD] 16.6 ± 2 years). Drug was administered on the first day of testing. On the second day, participants received a memory test on stimuli from the first day fMRI session as described below.

Control measurements

Participants were tested for baseline alertness as measured by reaction time to a single centrally presented target at three time points during the testing day: before drug administration, between the first and second task and between the second and third task.

Blood pressure was measured at the same time points. At the end of the first testing day, participants were asked whether they thought they had received drug or placebo to test whether they were aware of drug status from possible side effects of the drug.

Behavioural task

After drug administration, participants were given written instructions and completed a practice version of the task. The fMRI session started one hour after drug administration which corresponds to the time to reach peak plasma concentration after oral administration (1-2 h, Crevoisier et al. 1987). Participants completed alternating blocks of a reward and punishment task (Wittmann et al. 2013).

Participants engaged in three sessions of 8-9 min length. Each session started with a reward block, which was followed by a punishment block (Figure 1). Each block contained 38 trials (reward blocks) or 32 trials (punishment blocks) of 4.3-11.1 s duration, half of which were potentially rewarded / punished and the other half neutral (neither reward nor punishment). The reward block contained six more trials than the punishment block to ensure overall monetary gain for all participants. Picture category (indoor or outdoor) indicated the motivational status of each trial. One category predicted neutral trials, the other category predicted reward in reward blocks and punishment in punishment blocks. Data from the first six trials of each block (three motivational and three neutral trials) were discarded to allow for reversal effects. Additionally, the last six trials in reward blocks were discarded to eliminate a potential confound of different block lengths. During each trial, participants saw a greyscale landscape photograph for 1500 ms, responded to it with a button press (right index or middle finger) indicating whether they were expecting a reward/punishment or not, waited a variable interval (delay, 200 - 3000 ms duration), and then responded to a number (target, 100 ms) by button press. Visual feedback (1000 ms duration) was given 1000 ms after presentation of the target. A variable fixation phase (500 - 4500 ms) followed. The speeded number comparison task (Wittmann et al. 2005) required participants to decide whether the target number (1, 4, 6 or 9) was lower or higher than 5. They responded as quickly as possible by button press with their right index or middle finger. A response time limit was used to determine trial outcome.

In reward trials, participants received no-win feedback ($0, yellow downward arrow) if their response to the target number was incorrect or exceeded the response time limit. After correct decisions within the time limit, they received win feedback ($1.50, green upward arrow). In punishment trials, participants received loss feedback (-$1.50, red downward arrow) if their response to the target number was incorrect or exceeded the response time limit. After correct decisions within the time limit, they received no-loss feedback ($0, yellow upward arrow). The time limit was adjusted individually in a staircase procedure to ensure reward and punishment rates of ~66%. In neutral trials, uninformative feedback was given. Participants were informed of the speed-accuracy requirements and cue categories. Frequency of target buttons and numbers was counterbalanced for each session. Participants were asked to pay attention to the cues to ensure awareness of the reward / punishment status of each trial, but not told that a memory test would follow.

In the memory test given one day after the study session, participants were shown all images from the study phase randomly mixed with newly presented distracter images. Participants received written instructions and the task was self-paced. First, participants indicated whether they recognized the image ('Old/New'). If they did, they then judged their memory according to the remember/know procedure ('Remember/Know/Guess') (Duzel et al. 1997; Tulving 1985). For images classified as new, participants indicated whether their decision was confident ('Sure/Guess'). Response time limits were set at 3 s for each decision. A fixation phase of 1.5 s followed. Every 96 trials, the task paused until participants were ready to continue.

After the memory test, participants completed the TPQ (Cloninger et al. 1991), which tests for personality differences in three dimensions defined as novelty seeking, reward dependence, and harm avoidance.

Behavioural analysis

Participants' reaction times and hit rates during the study task were analysed in repeated-measures ANOVAs. For analysis of the memory test, corrected hit rates were calculated by adding the remember and know rates for old stimuli (percentage of studied items classified as remembered or known) and subtracting the corresponding false alarm rate for distractors (percentage of unstudied items classified as remembered or known). We also calculated a corrected remember rate and a corrected know rate separately by subtracting the corresponding false alarm rates. Note that these response rates excluded trials in which participants guessed.

fMRI acquisition

Magnetic resonance images were acquired on a 3 T whole body scanner (Magnetom Trio, Siemens Medical Systems, Erlangen, Germany) with a head coil for RF transmission and signal reception. A field map was acquired with a double echo gradient echo field map sequence (TE, 4.92 and 7.38 ms; TR, 677 ms; matrix size, 64 × 64), using 56 slices covering the whole head, to improve distortion correction of the functional images. For functional images, we used BOLD signal sensitive T2*-weighted echo-planar imaging (EPI). Each volume contained 45 slices of 2 mm thickness and 3 mm in-plane resolution (TR, 2 s; matrix size, 74 × 74; GRAPPA factor 2). In each of three scanning sessions, approx. 255 functional whole brain volumes were collected. A T1-weighted whole-brain image ($1\times1\times1$ mm^3 resolution, matrix size 230×256, GRAPPA factor 2) was acquired for each participant. Scanner noise was reduced with ear plugs, and participants' head movements were minimized with foam pads.

fMRI analysis

Functional data quality was assessed using the *tsdiffana* utility (http://imaging.mri-cbu.cam.ac.uk/imaging/DataDiagnostics). Volumes affected by artefacts were removed and replaced with a neighboring volume.

Preprocessing and data analysis were performed using Statistical Parametric Mapping software implemented in Matlab (SPM8; Wellcome Trust Center for Neuroimaging,

London, UK). Using the FieldMap toolbox (Hutton et al. 2002; Hutton et al. 2004), field maps were estimated from the phase difference between the images acquired at the short and long TE. The EPI images were corrected for distortions based on the field map (Hutton et al. 2002) and the interaction of motion and distortion using the Unwarp toolbox (Andersson et al. 2001; Hutton et al. 2004). EPI images were then spatially normalized to the Montreal Neurological Institute (MNI) template by segmenting and warping the acquired anatomical image to the SPM template and applying these parameters to the functional images (voxel size $2 \times 2 \times 2$ mm^3), and smoothed using an 8 mm Gaussian kernel. A high-pass filter with a cutoff of 128 s was applied to the data.

For statistical analysis, trial-related activity for each participant was assessed by applying a canonical hemodynamic response function (Friston et al. 1998) to the following regressors: Reward-predictive cues, neutral cues from reward blocks, punishment-predictive cues, neutral cues from punishment blocks, gain outcomes, no-gain outcomes, loss outcomes, no-loss outcomes, neutral outcomes in reward blocks, and neutral outcomes in punishment blocks. To account for significant reaction time differences in response to the cues, the duration of the cue regressors corresponded to trial-by-trial reaction times. Outcome regressors were modelled as stick functions (duration = 0). A general linear model (GLM) was specified for each participant to model the effects of interest and six covariates capturing residual motion-related artefacts. In order to avoid potentially biased Type I errors in pooled error analyses, a partitioned-error ANOVA was specified by modelling main effects of block valence (reward and punishment) and motivation (motivational and neutral cues) and their interactions for each participant, followed by a random effects second-level analysis to assess the between-subjects effects of drug (Penny and Henson 2007). To assess individual differences, an additional analysis included regressors for the novelty-seeking subscale of the TPQ. To clarify the contribution of individual conditions to the main effects, follow-up analyses were carried out using simple contrasts (reward vs. neutral cues, punishment vs. neutral cues, and neutral cues from reward vs. punishment blocks).

The statistical threshold for the imaging results was set to $p < 0.05$, family-wise error rate (FWE) corrected within our a priori ROIs. The areas of interest were chosen based on experimental results from the reward-based memory paradigm: The striatum and substantia nigra/ventral tegmental area (SN/VTA) were chosen based on Wittmann et al. (2005, 2008, 2013). The striatum was anatomically defined using the Harvard-Oxford atlas distributed with FSL (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford University, Oxford, U.K.). Because the SN/VTA is not included in the database, a spherical small volume correction (SVC) was carried out. SVC was centered on the peak voxel reported in a previous study with the same task design (MNI coordinates 6, -21, -17; Wittmann et al., 2013). The SVC radius of 4.5 mm was chosen based on the anatomical volume of the SN/VTA as reported in (Geng et al. 2006). Activations are displayed at a threshold of $p < 0.005$ (uncorrected) with a cluster extent threshold of 5 voxels. All stereotaxic coordinates are given in MNI space. All brain images are shown in neurological orientation. All behavioural averages are given as mean values ± SE.

To better localize SN/VTA activity, relevant activation maps were superimposed on a mean image of the spatially normalized MT maps of 33 participants acquired earlier (Bunzeck and

Duzel 2006). MT imaging is based on the transfer of energy between protons in free water and highly bound protons within macromolecules (Wolff and Balaban 1989). Thus MT saturation is thought to be a more direct measure to image myelin and improves contrast between SN and surrounding white matter tracts (Helms et al. 2009) without the geometric distortion present in iron-based imaging such as susceptibility and R2* mapping. It has been shown to allow distinguishing the SN from surrounding structures as a bright area, which has been confirmed to be coextensive with the SN as delineated histologically by tyrosine hydroxylase immunohistochemistry (Bolding et al. 2013). It has also been shown to provide a measure of nigral degeneration in clinical populations such as Parkinson's disease (Eckert et al. 2004; Tambasco et al. 2011). However, we will refer to BOLD activity from the entire SN/VTA complex throughout this paper because dopamine neurons are dispersed throughout the SN/VTA complex and form a functional continuum in primates (Duzel et al. 2009). This is underlined by recordings showing that dopamine neurons in the SN and VTA respond to reward (Ljungberg et al. 1992; Tobler et al. 2003). Including both the SN and VTA is particularly relevant to a comparison of reward and punishment processing because animal data suggest that reward-signaling DA neurons are located more medially than DA neurons responding to motivational salience, which were found in the lateral SN (Matsumoto and Hikosaka 2009).

Result

Control measurements

Neither alertness nor blood pressure differed between the groups at any time point (mean reaction time [± SD], 315 ± 85 ms, $F_{2,2652.7} = 1.9$, $p = 0.18$; mean blood pressure, 121/72 mmHg, $F_{2,40.6} = 1.6$, $p = 0.21$). The number of participants who thought they had received levodopa did not differ between the groups (drug group: 7 participants, placebo group: 6 participants; X^2 (1) = .14, $p > 0.7$).

Behavioural data

Participants successfully categorized the motivational and neutral cues (mean hit rate [± SEM] neutral: 97 ± 0.6%, hit rate reward-predicting: 96 ± 2.9%, hit rate punishment-predicting: 96 ± 2.7%). As predicted, a one-way repeated-measures ANOVA (three motivational levels and drug status as between-subjects factor) on reaction times (RT) in the picture task revealed a main effect of motivation ($F_{1.5,39.8} = 33.9$, $p < 0.001$). There was no main effect of drug ($F_{1,26} = 1.3$, $p > 0.1$) and no interaction ($F_{1.5,39.8} = .09$, $p > 0.1$). Post-hoc one-tailed t-tests confirmed shorter RTs for reward cues ($t_{25} = 6.0$, $p < 0.001$) and punishment cues ($t_{27} = 6.6$, $p < 0.001$) compared to neutral cues (mean RT ± SEM: reward 643 ± 88 ms, punishment 631 ± 80 ms, neutral 741 ± 108 ms). In the reaction time task, the outcome rates approximated the targeted rate of 66% success in reward and neutral trials and 66% losses in punishment trials (reward rate ± SEM: .73 ± .007; punishment rate: .59 ± .007; hit rate in neutral trials: .69 ± .008), although a one-way repeated-measures ANOVA revealed a significant effect of motivational status ($F_{2,52} = 97.4$, $p < 0.001$) and no effect of drug ($F_{1,26} = 0.9$, $p > 0.1$) or interaction ($F_{2,52} = 1.0$, $p > 0.1$). A one-way repeated-measures ANOVA revealed a significant main effect of motivation on RTs to the number targets ($F_{1.4,35.9} = 90.0$, $p < 0.001$) but no main effect of drug ($F_{20.9,7906.5} = .003$, $p > 0.1$) or

interaction ($F_{1.4,35.9} = 2.1$, $p > 0.1$). Post-hoc one-tailed t-tests confirmed shorter RTs for reward ($t_{27} = 9.0$, $p < 0.001$) and punishment trials ($t_{27} = 10.4$, $p < 0.001$) compared to neutral trials (mean RT ± SEM: reward 388 ± 9 ms, punishment 372 ± 8 ms, neutral 467 ± 14 ms).

Memory performance in the delayed memory test was overall lower than in a previous study using this task (Wittmann et al., 2013). There was no motivational or drug effect on memory processing, possibly because the corrected hit rate was rather low (9.4 ± 2.2 %).

fMRI data

To confirm the success of our motivational manipulation, we first assessed the main effect of motivation (reward and punishment cues compared to neutral cues) across both the drug and placebo groups. Motivational cues elicited activations in the striatum, SN/VTA, dorsolateral prefrontal cortex, thalamus and anterior cingulate cortex compared to neutral cues (Figure 2). There was no difference in activity related to reward and punishment cues. A main effect analysis across all subjects during the feedback period of the trial revealed no significant activations for motivational vs. neutral outcomes.

Levodopa administration significantly affected activation of the striatum. During the cue period, striatal activity for both types of cues (motivational, neutral) was enhanced in the levodopa group during punishment blocks compared to reward blocks (Figure 3).

Participants' personality scores on the novelty-seeking scale of the TPQ (mean score ± SD: 20.5 ± 6.3; range 9-34) interacted with drug effects on brain activation. After levodopa administration compared to placebo, the novelty-seeking covariate correlated with striatal activation in response to punishment compared to neutral cues (Figure 4). Participants were then grouped into relatively high (mean score ± SD: 24.8 ± 1.2) and low (mean score ± SD: 15.4 ± 1.0) novelty-seekers by median split to display the groups' parameter estimates. Because harm avoidance and novelty seeking were negatively correlated in our sample, we performed a separate analysis using harm avoidance scores as a covariate. No significant correlations between harm avoidance and striatal activity were found, indicating that the striatal effects were mediated by the novelty-seeking trait.

Discussion

These results show that levodopa can modulate processing of monetary punishments dependent on baseline differences in self-reported novelty-seeking trait. Across all participants, levodopa enhanced striatal activity for all cue types shown in punishment blocks compared to reward blocks. In high novelty-seekers, striatal activation selectively increased after levodopa administration in response to punishment cues compared to neutral cues. These data suggest that dopamine is involved in aversive motivation and that novelty-seeking personality scores may serve as a measure of susceptibility to the motivational effects of dopaminergic drugs.

Independently of drug treatment, both reward and punishment anticipation activated the striatum and SN/VTA, and there were no significant differences between reward and

punishment anticipation. Responses of the reward system to punishment-related stimuli have recently been found in animal and human studies. In monkeys, aversive air puffs and their predictors can elicit increased dopaminergic firing (Joshua et al. 2008; Matsumoto and Hikosaka 2009). These punishment-coding dopaminergic neurons have been shown to be spatially separate from reward-coding neuronal populations (for a review, see Bromberg-Martin et al. 2010). Studies in rats and mice also found that distinct populations of dopamine neurons are excited or inhibited by the onset of aversive stimulation (Brischoux et al. 2009; Lammel et al. 2011). An analysis of neuronal subpopulations in the SN/VTA is not possible at the spatial resolution of fMRI, but previous neuroimaging studies reported larger-scale activations in the reward system during punishment anticipation (Carter et al. 2009; Delgado et al. 2008; Jensen et al. 2003; Jensen et al. 2007; Krawczyk and D'Esposito 2013; Metereau and Dreher 2013; Seymour et al. 2007; Seymour et al. 2004), leading to the suggestion that these structures respond to motivational salience independent of its valence. An involvement of the dopaminergic system in aversive processes in humans has previously been suggested on the basis of genetic (Wittmann et al. 2013) and pharmacological (Menon et al. 2007) studies.

In addition to the possible subregional differences outlined above, motivational processes can be influenced by the action requirements of the task. A recent study separating action from valence processing found that activation of the reward system by reward and punishment depends on action requirements (Guitart-Masip et al. 2011). In a subsequent pharmacological study with the same task design, levodopa was shown to specifically enhance actions leading to reward, but not actions leading to punishment (Guitart-Masip et al. 2012). This contrasts with the current results in our analysis across all participants, which showed that levodopa affected cue responses for both types of cues in punishment compared to reward blocks. The different findings in the two studies could have resulted from differences in task design. In our task, all cues were associated with speeded actions. The staircase procedure was designed to ensure that cue-related activations captured the anticipation of punishment and not its avoidance, while the Guitart-Masip et al. (2011, 2012) task specifically investigated responses to anticipated avoidance actions, with participants successfully avoiding >80% of potential punishments. It is possible that in the current study, the relatively high frequency of punishments (60% of trials) created an aversive context in punishment blocks, in which salience was enhanced for both types of cues. The interpretation that levodopa enhanced cue salience is supported by a recent study showing that oscillatory beta activity associated with motor preparation was higher when patients with Parkinson's disease were tested on vs. off levodopa medication in the absence of motivational outcomes (Oswal et al. 2012).

In the current study, levodopa administration enhanced striatal activity for both types of cues in punishment compared to reward blocks, while there was no effect on reward processing. This only partially confirms our hypothesis of a drug-related increase in reward and punishment processing. Previous studies found an increase in both reward-related (Pessiglione et al. 2006) and punishment-related (Menon et al. 2007) striatal activity under levodopa. The difference to our findings could have been caused by the block design of the current study, which possibly enhanced overall cue salience in punishment blocks compared to reward blocks. An involvement of the dopaminergic system in salience processing has

been suggested by previous studies in animals and humans (for review, see Bromberg-Martin et al. 2010; Winton-Brown et al. 2014). In the current study, there was no difference in RT between drug and placebo, which is consistent with previous studies that administered similar doses to healthy young participants (Knecht et al. 2004; Pessiglione et al. 2006).

Novelty-seeking scores correlated with striatal activation to punishment cues after dopaminergic drug administration. This effect is consistent with previous studies showing that the novelty-seeking personality dimension influences behavioral and neural drug responses (Jupp and Dalley 2014). Novelty-seeking scores are associated with polymorphisms in the D2 and D4 receptors that are also associated with higher risk of addiction (Gorwood et al. 2012; Noble et al. 1998) and inversely correlated with levels of midbrain dopamine D2 receptors (Zald et al. 2008), which could underlie the enhanced responsivity of higher-scoring participants to drugs acting on the dopamine system, such as amphetamine (Boileau et al. 2006; Hutchison et al. 1999; Leyton et al. 2002; Sax and Strakowski 1998). It has also been found that participants with high novelty-seeking scores show higher hormonal reactivity to dopaminergic drug challenges (Netter 2006). In rats, animals that exhibit high reactivity to novelty display more sensitivity to drug reinforcement (Piazza et al. 1989) and to cocaine self-administration (Belin et al. 2008).

In low novelty-seekers, the direction of the drug effect on striatal processing was opposite to the effect in high novelty-seekers. This is compatible with findings that striatal dopamine effects show an inverted U-shaped response function (Clatworthy et al. 2009; Cools et al. 2007) similar to that demonstrated for prefrontal dopamine in working memory experiments (Cools and D'Esposito 2011; Dang et al. 2012), for which working memory performance can serve as a behavioral indicator (Kimberg et al. 1997). For the striatum, a comparable behavioural indicator of baseline dopamine function could be the personality trait of novelty seeking, based on its association with D2 and D4 receptor function (Noble et al., 1998; Gorwood et al., 2012; Zald et al., 2008). The hypothesis of inverted U-shaped striatal effects is further supported by a recent study showing an inverted U-shaped relationship between sensation-seeking and striatal D2 receptor availability (Gjedde et al. 2010). The difference between these results and the linear effects in the midbrain found by Zald et al. (2008) could have resulted from the smaller range of novelty-seeking scores in the latter study, which tested mostly participants with relatively high novelty-seeking scores. In our study, scores also ranged from medium to high, suggesting that D2 receptor availability in midbrain and striatum linearly decreased with increasing novelty-seeking scores in our sample. A further link between personality and structural changes in the reward system was provided by a human tractography study that found a correlation of participants' novelty-seeking scores with connectivity in a limbic motivational network comprising ventral striatum, amygdala and hippocampus (Cohen et al. 2009). Novelty-seeking could thus be used as an indicator of baseline function of the motivational system. A caveat in the current study is the relatively high average novelty-seeking score in our sample. After the median split, the mean score of the 'low' novelty-seeking group was 15.4, which is above the mean of 13.0 in the original sample of Cloninger et al. (1991). Future studies could be designed to include the effect of the low end of the scale (score < 8) on drug susceptibility and motivational processing to investigate whether the reported inverted U-shaped properties of the motivational system on a receptor level (Gjedde et al. 2010) are also reflected in fMRI activations.

We recently investigated the influence of dopamine transporter genotype (DAT VNTR) on the same task that was also used in the current study (Wittmann et al. 2013). Striatal activation for both types of motivational cues was higher in 10-repeat homozygotes compared to heterozygotes, consistent with the current results for relatively high novelty-seeking participants. The previous study also indicated that episodic memory for both types of motivational cues was higher in 10-repeat homozygotes. In contrast, the current experiment found no differences in memory for different motivational categories and no effect of levodopa treatment. This difference could be the result of the overall design of the current study, in which participants performed three tasks on the day of drug administration, the first of which is presented here. The third task, which was carried out approximately 90 min after the end of the first task, presented picture stimuli from the same category (landscapes) that were used in the memory task. It is possible that this resulted in memory interference, leading to the low overall memory performance (corrected hit rate <10%) in the current study compared to previous studies (Wittmann et al. 2011; Wittmann et al. 2005; Wittmann et al. 2013) and masking possible effects of treatment or personality. The possibility that memory was low because of insufficient salience of the motivational cues seems unlikely, as significantly shorter RTs to the motivational cues indicate that they were behaviorally relevant to participants. The lack of behavioral drug effects is a possible limitation of the study. The absence of effects on RT is consistent with previous studies (Knecht et al. 2004; Pessiglione et al. 2006), while motivational memory effects were reported when overall memory performance was higher. Although we expected behavioral effects in the current study, the absence of behavioral effects eliminates a possible confound of differences in neural activity, thus allowing the conclusion that drug-related increases in striatal activation were not due to differences in behavior.

In conclusion, the present study showed that levodopa administration can modulate striatal processing of punishment cues. The interaction of drug with novelty-seeking personality scores is consistent with prior suggestions that novelty-seeking personality can indicate dopaminergic drug susceptibility and supports the hypothesis of an inverted U-shaped dopamine response function in the striatum. Future studies could be designed to capture a greater range of novelty-seeking scores and more closely investigate the interaction of drug and personality with the motivational modulation of memory and other cognitive functions.

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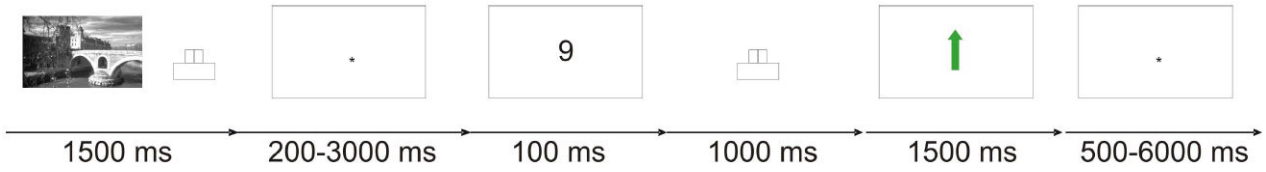

Fig. 1. Experimental design

Trial sequence for the study phase, shown exemplarily for a rewarded trial from a reward block. A cue picture was presented indicating whether participants could win money on that trial. Participants made a category decision on the picture, waited for the following number task, and then indicated quickly whether the number was higher or lower than five. In rewarded trials, they received win feedback (green upward arrow) after correct decisions made within a time limit and no-win feedback (yellow downward arrow) in incorrect trials. In neutral trials, they received uninformative feedback (black horizontal arrow). In punishment blocks, the cue category predicted punishment (red downward arrow) or neutral (yellow upward arrow) outcomes.

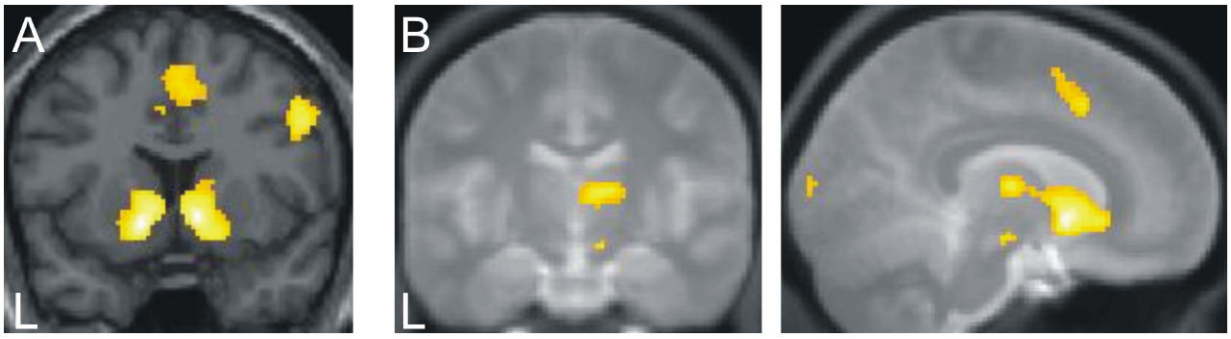

Fig. 2. Anticipation of reward and punishment across both groups

Higher activations ($p < 0.05$, FWE whole-brain corrected) to anticipation of rewards and punishments compared to neutral cues in (A) bilateral ventral striatum (MNI peak coordinates: left VS -12,10,-6; right VS 10,10,-4) and anterior cingulate (MNI peak coordinates 8,16,44), and (B) right SN/VTA (MNI peak coordinates 10,-14,-12). Colour bars indicate t values. To better localize SN/VTA activations, the two corresponding panels display an overlay onto an MT image (cf. methods section).

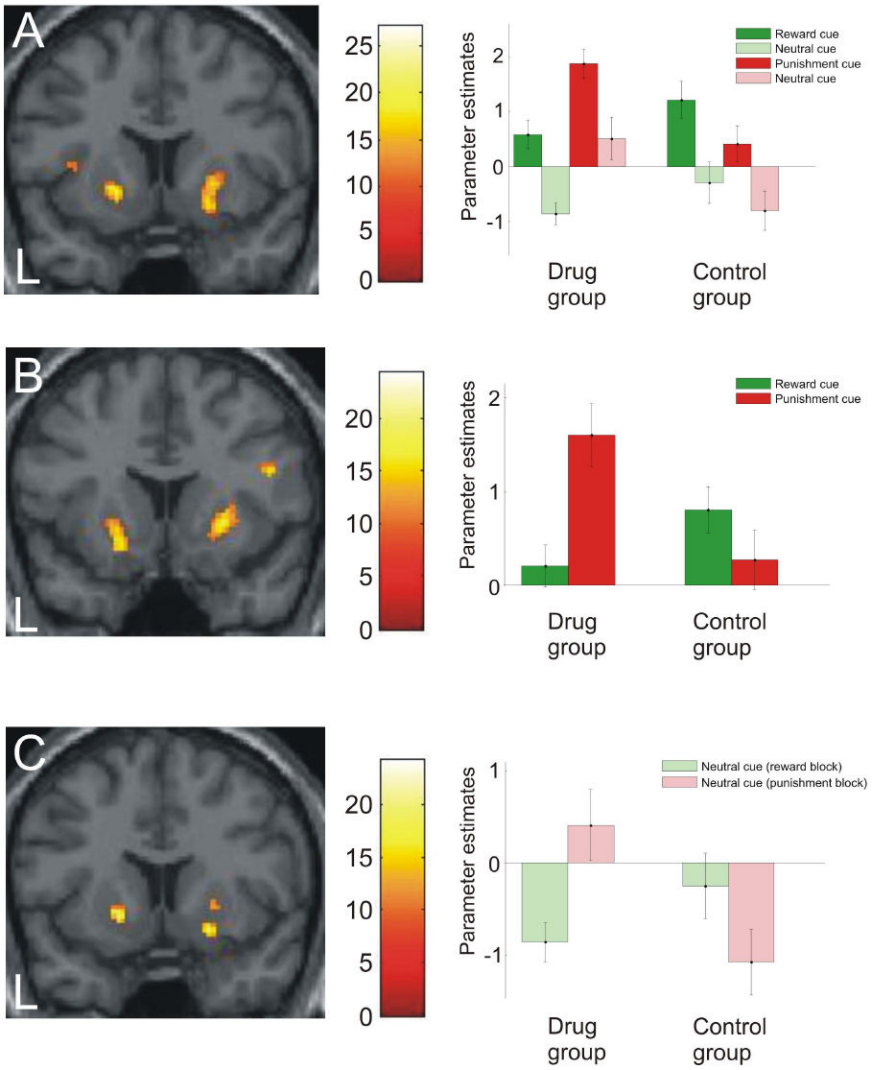

Fig. 3. Drug effects across all participants

Cue processing. In the levodopa group compared to placebo, A) both types of cues elicited higher striatal activation ($p < 0.05$, SVC) in punishment compared to reward blocks (MNI peak coordinates 22,10,-8). This effect is composed of B) higher striatal activation to anticipation of punishment compared to reward (MNI peak coordinates 26, 14, 0) and C) higher striatal activation to neutral cues in punishment compared to reward blocks (MNI peak coordinates 22, 10, -10). Clusters are shown at $p<0.005$, uncorrected, $k>5$ voxels. Colour bars indicate t values. Panels on the right of each activation map illustrate group differences in mean parameter estimates for peak voxels from the corresponding regions on the left.

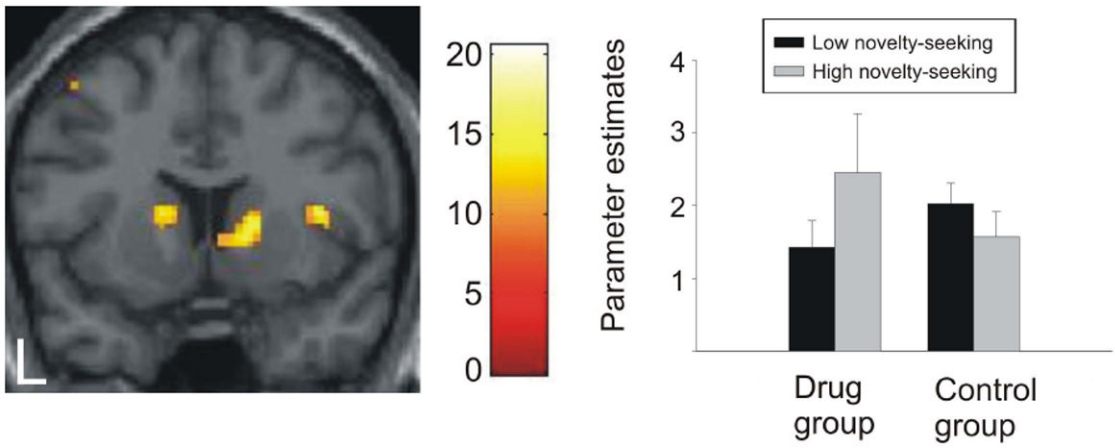

Fig. 4. Drug interaction with personality

After levodopa administration compared to placebo, striatal activation ($p < 0.05$, SVC) correlated with the novelty-seeking score for punishment compared to neutral cues (MNI peak coordinates 14,14,2). Clusters are shown at $p<0.005$, uncorrected, $k>5$ voxels. Colour bar indicates t values. Panel on the right presents mean (+SEM) parameter estimates separately for participants with low (black) and high (grey) novelty-seeking scores grouped by median split.