The role of dopamine in positive and negative prediction error utilization during incidental learning – insights from Positron Emission Tomography, Parkinson’s disease and Huntington’s disease

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Abstract

Incidental learning of appropriate stimulus-response associations is crucial for optimal functioning within our complex environment. Positive and negative prediction errors

(PEs) serve as neural teaching signals within distinct ('direct'/'indirect') dopaminergic pathways to update associations and optimize subsequent behavior. Using a computational reinforcement-learning model, we assessed learning from positive and negative PEs on a probabilistic task (Weather Prediction Task, [WPT]) in three populations that allow different inferences on the role of dopamine (DA) signals: (1) Healthy volunteers that repeatedly underwent [11C]raclopride Positron Emission Tomography, allowing for assessment of striatal DA release during learning, (2) Parkinson's disease (PD) patients tested both on and off L-DOPA medication, (3) early Huntington's disease (HD) patients, a disease that is associated with hyper-activation of the 'direct' pathway. Our results show that learning from positive and negative feedback on the WPT is intimately linked to different aspects of dopaminergic transmission. In healthy individuals, the difference in [11C]raclopride binding potential (BP) as a measure for striatal DA release was linearly associated with the positive learning rate. Further, asymmetry between baseline DA tone in the left and right ventral striatum was negatively associated with learning from positive PEs. Female patients with early HD exhibited exaggerated learning rates from positive feedback. In contrast, dopaminergic tone predicted learning from negative feedback, as indicated by an inverted-u-shaped association observed with baseline [11C]raclopride BP in healthy controls and the difference between PD patients' learning rate on and off dopaminergic medication. Thus, the ability to learn from positive and negative feedback is a sensitive marker for the integrity of dopaminergic signal transmission in the 'direct' and 'indirect' dopaminergic pathways. The present data are interesting beyond clinical context in that imbalances of dopaminergic signaling have not only been observed for neurological and psychiatric conditions but also been proposed for obesity and adolescence.

1. Introduction

Incidental stimulus-response learning heavily relies on striatal functioning (Poldrack et al., 2001; Jahanshahi et al., 2010). Within the striatum, dopamine (DA) transmission is known to play a key role in fostering learning via encoding the difference between expectations and outcomes of our actions (Montague et al., 1996; Schultz et al., 1997; Schultz, 2002). These prediction error signals (PEs) are utilized to update current beliefs and, importantly, to adapt subsequent behavior. Positive PEs are signaled via a transient increase in firing rate ('burst') and negative PEs are associated with a pause in tonic firing ('dip'). It has been proposed that DA mediates learning from positive as well as negative outcomes (Van Der Schaaf et al., 2014), but via two segregated ('direct' / 'indirect') pathways (Frank, 2005; Frank and O'Reilly, 2006; Frank et al., 2007b; Kravitz et al., 2010). Recently, direct experimental evidence has been provided for this model in healthy volunteers (Cox et al., 2015).

In the 'direct pathway', striatal D1 receptor expressing neurons predominantly send inhibitory projections directly to the output nucleus of the basal ganglia, the globus pallidus interna/substantia nigra pars reticulata (GPi/SNr). Postsynaptic D1 receptors are sensitive to bursts in DAergic transmission. Thus, correct stimulus-response associations are strengthened via D1-receptor related modulation of synaptic plasticity within the direct pathway subsequent to positive PEs. In the 'indirect pathway' (Gerfen et al., 1990; Surmeier et al., 2007), striatal neurons expressing D2-receptors predominantly send inhibitory projections first to the external segment of the globus pallidus. From there inhibitory projections reach the subthalamic nucleus (STN). The STN then sends excitatory projections back to the GPi/SNr. Postsynaptic D2 receptors are sensitive to detecting transient dips within the tonic DA signal (Goto and Grace, 2005; Day et al., 2006). Hence, wrong stimulus-response associations are weakened through D2 receptor activity in the indirect pathway subsequent to negative PEs (Klein et al., 2007; Jocham et al., 2009, 2014). Importantly, too low tonic DA may impair D2 receptor-related signaling, as the magnitude of extracellular tonic DA determines the background stimulation of DA receptors (Grace, 1991). In addition, too high tonic DA release may impede D2 receptor-related signaling, as high tonic DA levels can inhibit the phasic DA response via action on presynaptic D2 auto-receptors (Goto et al., 2007) or via hyperpolarization of DAergic neurons (Dyakonova et al., 2009). Thus, either too low or too high tonic DA levels may specifically impede the capability of detecting dips and, consequently, may alter learning from negative PEs in particular. Further, recent data indicate that the hemispheric asymmetry of DA signals is related to the propensity to learn from positive vs. negative PEs (Maril et al., 2013; Tomer et al., 2014; Aberg et al., 2015). A mechanistic explanation for this phenomenon is missing to date.

Consequently, it is important to differentiate between learning from positive and negative feedback to identify the specific involvement of different DA pathways or aspects of DA transmission. Further, an investigation of different aspects of DA transmission based on behavior on the same behavioral task will be beneficial for interpretation of the results.

Here, we assessed learning in response to positive and negative PEs in three populations that allow different inferences on the role of DA in incidental stimulus-response learning. Importantly, all participants completed the same probabilistic learning task, the Weather Prediction Task (WPT, Knowlton et al., 1994). To differentiate between learning from positive and negative PEs, we employed a computational reinforcement-learning model.

First, we explored the influence of DAergic signaling in a sample of healthy volunteers who repeatedly underwent [^{11}C]raclopride Positron Emission Tomography while completing the WPT with and without corrective feedback. Specifically, we investigated the impact of DA release, tonic DA level, and the asymmetry of phasic responses between left and right striatum on learning from positive and negative feedback. We hypothesized that the strength of phasic striatal DA transmission during procedural learning is linearly related to the participants' capability of learning from positive PEs. Further, we predicted that tonic DA levels within the striatum are associated with the ability to learn from negative PEs in an inverted u-shaped manner. Finally, we expected that asymmetry between left and right striatal signaling is related to learning from positive PEs.

Second, we investigated the effect of L-Dopa medication on learning from negative PEs in a sample of patients with Parkinson's disease (PD) who were tested both *on* or *off* medication when completing the WPT. Evidence (e.g. Agid et al., 1993; Kish, Shannak, & Hornykiewicz, 1988) suggests that in early PD dopamine depletion is mainly limited to dorsal striatum and the ventral striatum is relatively less affected. We expected patients *on* levodopa medication to be selectively impaired in learning from negative PEs compared to *off* medication due to an nonspecific increase in DAergic tone in the ventral striatum in the *on* state (Cools et al., 2006; Frank et al., 2007a).

Third, we investigated learning in a sample of early Huntington's disease (HD) patients, a disease that is associated with a hyper-activation of the 'direct' pathway. Thus, we hypothesized that these patients will be selectively impaired in successful learning from positive PEs.

2. Methods

2.1. General methods

2.1.1. WPT

All three studies (PET, PD & HD) involved the same stimulus-response learning task, a standard version of the Weather Prediction Task ([WPT], Knowlton et al., 1994; see Figure 1 in Wilkinson et al., 2014), with corrective feedback to ensure learning based on striatal DA transmission. In the PET study, participants also completed a control version of the WPT without corrective feedback. Further, the card patterns in the control task were not related to the outcome.

On each trial, participants were presented with a particular arrangement of cards comprising one, two or three of the four possible tarot cards. Participants were asked to decide whether the presented set of cards predicted sunshine or rain. There were 14 possible arrangements of cards, as the four card and no card patterns were not used. The four cards were assigned with a probability for predicting sunshine of 80%, 60%, 40% and 20%, respectively, and predicting rain otherwise. Prediction probabilities for the presented arrangements of cards were derived from the joint probability distribution of the individual cards they contained. (see Table 2 in Wilkinson et al., 2014).

After presentation of the stimuli during each trial, participants were asked to predict the weather on that trial, which required them to classify the card arrangement into one of the two possible outcomes (e.g. rainy / fine). Responses were made either via two response buttons (PET / PD study) or verbally to the experimenter (HD study). Following their response, feedback appeared on the screen depending on whether the response was correct (thumbs up) or incorrect (thumbs down). The feedback and the card arrangement both remained on the screen for a short period. After they disappeared a blank screen preceded the presentation of the next combination of cards. If participants failed to make a response, the card arrangement appeared on the screen for the same duration but no feedback was provided. For more details on the particular task designs used in the respective studies please see the original publications (Jahanshahi et al., 2010 [PD study]; Holl et al., 2012 [HD study]; Wilkinson et al., 2014 [PET study]).

2.1.2. Computational model

Performance on the WPT relies on updating of outcome predictions and related adaptation of subsequent response behavior. Thus, the task was previously used to assess PE-related learning (Rodriguez et al., 2006). As the aim of our study was to assess differential learning from positive and negative feedback, from a conceptual point of view, our computational model needs to fulfill two criteria: (1) The model incorporates two learning rates, separating learning from positive and negative feedback, and (2) the two learning rates need to be interpretable independently from other model parameters. Consequently, we used a slightly modified version of the classical Q-learning model (Frank et al., 2007b) with two separate learning rates that are fitted independently of the choice consistency parameter β (see equation (1)). The latter ensures that the learning rates are statistically independent of the choice consistency parameter, which is not the case when fitting is performed simultaneously. In more detail, our reinforcement learning model consists of four input nodes $I_{i=1,\dots,4}$ with weighted connections to two output nodes (Q-values) $Q_{j=1,2}$ that represent the presence or absence of the four different cues and the two possible outcomes in the WPT, respectively. On each trial, activity of the output nodes is computed as $Q_j = \sum_i q_{ij} I_i$, where q_{ij} is the weight connecting input node I_i and output node Q_j. Weights are initialized to 0 and updated in each trial by means of $q_{ij}(k+1) = q_{ij}(k) + \alpha^{+/-} S_j(R_j - Q_j) I_i$ where R_j encodes the correct output in this trial and S_j represents the subject's response. The latter is included for allowing the model to simulate the behavior of the individual participant rather than optimal learning. To assess learning from positive and negative PEs separately, we fitted two independent learning rates $\alpha^{+/-}$ for $R_j - Q_j \geq 0$ and $R_j - Q_j < 0$, respectively. For each participant the individual learning rates $\alpha^{+/-}$ were determined that minimized the sum of squared differences between the model's output and the participant's response: $\sum_{jk}\left(S_{jk} - Q_{jk}\right)^2 \rightarrow min$, with $j = 1, 2$ and k being the number of trials. In a subsequent step, we modeled each participant's choices of a particular outcome to follow a softmax distribution:

$$P\left(choice = S_j \mid Q_1, Q_2\right) = \frac{exp(\beta Q_j)}{exp(\beta Q_1) + exp(\beta Q_2)} \text{with } j = 1, 2 \qquad (1)$$

The choice consistency parameter β was fitted to participants' choices by minimizing the negative log likelihood of the choice probabilities P

$$LL = -\,ln\left(\prod_k P_k(Q_j)\right), \qquad (2)$$

while the two learning rates were held constant at the values optimized in the first step. Model fitting and estimation of all parameters was accomplished by nonlinear optimization.

In order to ensure that the modifications to a standard Q-learning model did not compromise adequate model fit, we compared the model described above with (1) a similar model with only one learning rate instead of two and (2) a Q-learning model with simultaneous fitting of all three free parameters. For quantitative model comparison, we performed random-effects Bayesian model comparison (Daunizeau et al., 2014) to estimate exceedance probabilities and expected model frequencies (Stephan et al., 2009). Additionally, we utilized the Bayesian information criterion $BIC = -2 * LL + k * ln(n)$ (Schwartz, 1978), where LL is the log likelihood of the model's choice probabilities, k is the number of free parameters of the respective model and $n=200$ represents the number of trials. Based on *BIC* we computed *ΔBIC* values that represent mean differences (per subject) between the respective model and the model with the lowest BIC value. We also computed pseudo-r^2 values as defined in Daw et al. (2006) to test if our model fitted subjects' learning performance above chance level.

In addition to a quantitative model fit comparison, we assessed if the respective models resembled participants' learning performance in a meaningful way. Therefore, we computed linear regression models with participants' mean percent correct responses as dependent variable and fitted model parameters as independent regressors.

Details of the model comparison are presented in Table 1. Across all subjects, model frequencies and exceedance probabilities favor standard QL which was identified as the best fitting model in 46% of participants. However, BIC values are almost identical for the three models and ΔBIC values of 1.76 and 0.32 do not provide any strong evidence against the two competing models. In addition, pseudo-r^2 values show that all three models fit similarly above chance level. Within all different study populations, the stepwise 2LR model provides the best or second best model fit, again with pseudo-r^2 values showing that the model fitted subjects' performance above chance level. Importantly, the stepwise 2LR model explained significant variance in participants WPT performance in all three studies according to regression analyses. Thus, modifications in our new model yield meaningful and independently interpretable parameter estimates without compromising adequate model fit.

2.1.3. *Statistical analyses*

All behavioral results were computed with PASW-SPSS-Statistics 19.0 (IBM Corporation, Somers, NY, USA). A significance criterion of $\alpha = .05$ was used, unless otherwise specified. All significance levels reported are two-tailed.

2.2. Methods PET study *(Wilkinson et al., 2014)*

2.2.1. Participants

Seven (3 female) healthy volunteers in the age of 45-70 ($M = 56.86$, $SD = 8.7$) were recruited. None of the participants had any neurological disorder or history of psychiatric illness, drug or alcohol abuse or were on any drug treatments that might influence performance. Participants were asked not to smoke or drink caffeinated drink for at least 12 h prior to the scan, although we did not control for their average daily consumption of caffeine or nicotine. Participants completed the Beck Depression Inventory (BDI-II) (Beck et al., 1961, 1996) to preclude signs of depression. The study was approved by the Research Ethics Committee of Hammersmith, Queen Charlotte's and Chelsea and Acton Hospitals Trust. Permission to administer radioactive substances was granted by the Administration of Radioactive Substances Advisory Committee of the UK. All participants gave written informed consent to take part in this study in accordance with the Declaration of Helsinki. For more details on selected participants, please see Wilkinson et al. (2014).

2.2.2. WPT

All participants completed 400 trials of the WPT in eight blocks of 50 trials each while having a [^{11}C]raclopride PET scan. For more details, see Wilkinson et al. (2014). Notably, here we analyzed participants’ task performance across the first four blocks of 200 trials to assess learning, as afterwards participants’ performance reached a plateau.

2.2.3. Control task

As for the WPT, the control task comprised 400 trials (of which we analyzed the first 200) that were completed while participants had a [^{11}C]raclopride PET scan. On each trial participants were presented with an arrangement of between one and three of four possible cards, these were in the same positions on the screen as the card arrangements that were used in the experimental conditions. However, here the patterns on the four cards were identical and were not related to any outcomes or followed by corrective feedback. The card arrangements remained on the screen for a fixed period of 7 s after which they disappeared and the next card arrangement appeared after 2s. Participants were required to press a response button with their right index finger to indicate they had seen the card arrangements.

2.2.4. Scanning procedure

All participants underwent [^{11}C]raclopride PET twice within four weeks. On each scanning session the respective task started 5 min before injection of tracer and ended 5 min before completion of [^{11}C]raclopride PET (total duration 60 min). Half of the participants completed the WPT during the first [^{11}C]raclopride PET session and the remainder did the control task first.

2.2.5. PET scanning

As stated in Wilkinson et al. (2014) PET was performed using an ECAT EXACT HR+ (CTI/Siemens 962, Knoxville, TN) tomograph with a total axial field of 15.5 cm. 63 transaxial image planes were displayed as 2.46 mm slices with a reconstructed axial resolution of 5.4 mm and a transaxial resolution of 5.6 mm. A 10-min transmission scan was performed prior to injection of the tracer to correct for tissue attenuation of 511 keV gamma radiation. Dynamic emission scans were acquired in three-dimensional mode. The mean injected doses of [^{11}C]raclopride for each group is listed in Table Table 1 of Wilkinson et al. (2014). Scanning began at the start of tracer infusion generating 20 periods over 60 min. A laptop was used to present the WPT or control task to the participants, and the tasks commenced 5 min before the injection of RAC. RAC was supplied by Hammersmith Imanet.

2.2.6. Image analysis

As stated in Wilkinson et al. (2014) parametric images of [^{11}C]raclopride binding potential (BP_{ND}) were generated using a basis function implementation of the simplified reference tissue model using cerebellar cortex to estimate non-specific tracer uptake (Gunn et al., 1997). An image of integrated [^{11}C]raclopride signal from 0 to 60 min (an “ADD” or summed image) was also created for each participant. The ADD images were then spatially normalized to an in-house [^{11}C]raclopride template in standard stereotaxic (MNI) space using statistical parametric mapping (SPM2) software (Wellcome Functional Imaging Laboratory, London). The transformation matrices were then applied to the corresponding [^{11}C]raclopride parametric image. A standard region-of-interest (ROI) object map that outlined putamen, heads of caudate nucleus and ventral striatum was defined on the [^{11}C]raclopride template with magnetic resonance imaging guidance. The ROI object map was then applied to the individual [^{11}C]raclopride parametric images to sample [^{11}C]raclopride BP_{ND}. The investigator analyzing the scans was blinded to the task associated with each scan.

2.3. Methods PD study *(Jahanshahi et al., 2010)*

2.3.1. Participants

Eleven individuals with a diagnosis of idiopathic PD (8 male) aged between 53 and 73 (*M=63.5, SD=6.2*) were included. Patients were recruited from the Movement Disorders Clinics at the National Hospital for Neurology and Neurosurgery. They met Parkinson's Disease Society Brain Bank diagnostic criteria for PD (Hughes et al., 1992). Disease duration ranged from 3 to 37 years (M=13.2, SD=10.7). Despite the wide range of disease duration, the majority of patients was in the early stage of PD, with disease durations of less than 14 years. Two patients, however, had relatively long disease duration of 30 and 37 years. Without those two patients the average disease duration was 8.76 years. Importantly, the results reported below did not change when the two subjects were excluded from the analyses (or disease duration was included as a covariate). All patients were non-demented as demonstrated by scores > 26 on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and non-depressed according to scores < 18 on the Beck Depression Inventory (BDI) (Beck et al., 1961). The MMSE has been recommended as a screening tool for identifying cognitively impaired patients and, specifically, for characterizing PD associated dementia (e.g. Dubois et al., 2007). All patients were treated with levodopa (Sinemet, Madopar) and were responding well and stable on their medication doses. PD patients were matched with the controls for age, education, sex, verbal IQ and dementia based on MMSE scores. For further details regarding the patient sample please see Jahanshahi et al. (2010).

Further, thirteen healthy volunteers (5 male) aged between 44 and 69 (*M=60.0, SD=9.7*) took part in the study. None of the controls had any neurological disorder, psychiatric illness, head injury, history of alcohol or drug abuse, or depression (BDI). For more details see Jahanshahi et al. (2010).

2.3.2. Task procedure

All participants performed 200 trials of the WPT separated into four blocks of 50 trials each (for more details see e.g. Jahanshahi et al., 2010) twice with different but parallel stimuli and outcomes (rainy/fine or cold/hot) presented on each occasion. Six of the PD patients were tested *off* medication first and the remainder was tested *on* medication first. PD patients completed the off and on medication conditions on 2 separate days, with a mean delay of 11.9 days (*SD=6.9*) in between. Controls completed the two assessments on the same day, separated by a long lunch break.

2.4. Methods HD study *(Holl et al., 2012)*

2.4.1. Participants

Eighteen individuals (9 male) with genetically proven HD (for genetic details, see Table 1 in Holl et al. (2012)) aged between 32 and 68 (*M=50.28, SD=10.2*) took part. Patients were recruited from the HD clinic at the National Hospital for Neurology and Neurosurgery and from the HD clinic at the Department of Psychiatry at Graz Medical University. Patients were in the early stages of the disease, with an average score on the Unified Huntington's Disease Rating Scale Total Functional Capacity (UHDRS TFC, Shoulson and Fahn, 1979) of 11.61 (*SD=.3*). The UHDRS motor score (Hungtington Study Group, 1996) was used for assessment of motor symptoms, patients presented with an average score of 20.39 (*SD=10.4*). All patients were non-demented, as demonstrated by scores >24 on the MMSE. The MMSE has been recommended as a screening tool for identifying cognitively impaired patients (e.g. Dubois et al., 2007). In addition, the patients were screened for clinical depression on the BDI. One patient had a BDI score of 18 and one had a score of 24 (moderate depression), but neither met the criteria for clinical depression in a psychiatric interview.

Eighteen healthy volunteers (9 male) aged between 30 and 74 (*M=50.00, SD=13.3*) took part in the study. Controls were recruited via an advertisement at a local adult education center in London and a participant recruitment website. Prior to participation in the study, controls were interviewed and screened for suitability. None of the controls had any neurological disorder, psychiatric illness, head injury, or history of alcohol or drug abuse. Further screening of the controls was achieved through completion of the MMSE and BDI, on which the controls had mean scores in the normal range.

For further information on the patients and controls sample, please see Holl et al. (2012).

Unfortunately, we had to exclude one healthy participant and one HD patient from modeling analyses, due to partial data loss.

2.4.2. Task procedure

All participants performed 150 feedback-based trials of the WPT separated in three blocks of 50 trials each (for more details see Holl et al., 2012).

3. Results

3.1. Results PET in healthy volunteers

3.1.1. *Striatal ^{11}C-Raclopride binding*

Here, we only report on post-hoc comparisons of RAC BP_{ND} between the WPT and baseline task across ROIs utilizing independent samples t-tests. For more details on analyses regarding RAC BP_{ND} data, we refer the reader to Wilkinson et al. (2014).

There was a trend for a reduction in RAC BP_{ND} in the right and left ventral striatum when performing the WPT compared to the control task (13.4% reduction in the right, $t(6)=-2.01$, $p=.09$, 6.0% reduction in the left, $t(6)=-2.18$, $p=.07$), indicating release of synaptic DA during feedback-based stimulus-response learning. This comparison did not trend towards significance for any other region, left putamen ($t(6)=-1.15$, $p=.29$), right putamen and right and left caudate (all ts < 1). For subsequent analyses we use the mean baseline and % change in RAC BP_{ND} of left and right ventral striatum (9.7%).

3.1.2. *Behavioral data*

As mentioned previously, in the original paper (Wilkinson et al., 2014) WPT mean proportion of correct responses across 8 blocks of 50 trials was analyzed. Here, we only analyzed participants' WPT performance across the first four blocks, as we were interested in the initial learning phase of the task. For this purpose, we utilize a repeated-measures ANOVA model with within-subjects factor block (4 levels). In addition, to assess the time of emergence and progression of learning across blocks in this condition, mean proportion of correct responses per block was compared to chance (50%) for all four blocks using one sample t-tests. Following Bonferroni corrections we adopted a significance threshold of $\alpha=0.0125$.

Although the repeated-measures ANOVA reported no significant differences between task-blocks ($F(3,6)=1.6$, $p=.23$) on learning performance, there was a trend for a linear association ($F(1,6)=4.47$, $p=.08$), indicating that participants' WPT performance increased across the initial four task-blocks. In line, participants' proportion of correct responses was significantly better than chance from block three onwards: (b1: $t(6)=3.31$; b2: $t(6)=3.08$; b3: $t(6)=3.72$, $p<.01$; b4: $t(6)=3.77$, $p<.01$).

3.1.3. *Modeling*

As learning the WPT was related to DA transmission within the ventral striatum only, we focus on ventral striatal RAC BP_{ND} in subsequent analyses. We utilized two separate regression models to test our hypotheses regarding the associations of learning from positive and negative PEs with averaged ventral striatal RAC BP_{ND} measures.

The first regression model included positive learning rate as dependent variable and baseline RAC BP_{ND} and % change in RAC BP_{ND} as regressors to test for a positive linear association between positive learning rates and phasic DA transmission. The second model included negative learning rate as dependent variable and baseline RAC BP_{ND} as well as RAC BP_{ND}^2 as regressors to test for a quadratic (inverted u-shaped) association between height of negative learning rate and tonic DA levels in the ventral striatum. In addition, we computed a regression model with positive learning rate as the dependent variable and ventral striatal DAergic asymmetry as a regressor. Asymmetry was assessed by percent difference between left and right baseline RAC BP_{ND}. Finally, we tested a possible quadratic (inverted u-shaped) association between modeled choice consistency and tonic DA release with a model similar to the second one. All regression models included age as a covariate to control for age related effects in DA transmission.

In line with our first hypothesis, learning from positive PEs showed a significant negative linear association with the % change in RAC BP_{ND} within ventral striatum for WPT compared to control task assessment ($R^2=.89$, $\beta=-.94$, $p=.001$, Figure 1A), indicating a positive linear association of phasic DA release and learning from positive PEs. Further, modeled negative learning rates showed a significant negative quadratic relationship with the baseline RAC BP_{ND} ($R^2=.89$, $\beta=-.74$, $p=.005$, Figure 1B) in ventral striatum. In addition, we observed a significant negative linear relationship between positive learning rate and asymmetry between left and right ventral striatal baseline RAC BP_{ND} ($R^2=.81$, $\beta=-.9$, $p=.006$, Figure 1C). Choice consistency was negatively associated with baseline RAC BP_{ND} ($R^2=.87$, $\beta=-.91$, $p=.006$) in a quadratic model.

3.2. Results PD

3.2.1. Behavioral data

As reported (Jahanshahi et al., 2010) WPT performance (averaged over 200 trials) of healthy controls did not differ significantly across sessions (session 1 (2): .68 (.72), $t(12)=-.99$, $p=.34$). Therefore, their data were collapsed across assessments to compare PD patients' overall learning performance *on* and *off* medication with the performance of healthy controls. When *off* medication, patients' performance was comparable to the controls' combined performance ($t(35)=-.92$, $p=.36$) indicating that dopamine levels within ventral striatum were still in an optimal range for learning the WPT. In contrast, when PD patients were tested *on* medication, their overall performance was significantly worse than the controls' combined performance ($t(35)=-2.26$, $p=.03$).

To assess the impact of levodopa on PD patients' performance an repeated-measures ANOVA was performed on mean proportion of correct responses with medication (*on* vs. *off*) as a within subjects variable and order of testing (*on* first vs. *off* first) as a between groups variable. This analysis revealed a significant main effect of medication (*F(1,9)=11.45, p=.01*). A post-hoc paired sample T-test revealed that PD patients showed better WPT performance *off* (.67) than *on* (.63) medication (*t(10)=2.72, p=.02*, Figure 2A). There was no significant main effect of order (*F(1,9)=1.64, p=.23*) or order x medication interaction (*F(1,9)=4.89, p=.06*).

3.2.2. Modeling

To test our hypothesis that PD patients *on* medication are specifically impaired in learning from negative PEs we set up a repeated-measures ANOVA with within-subjects variable medication (*off* / *on*). As gender is known to modulate PD onset and phenotype (Haaxma et al., 2007) Van den Eden et al., 2003) we included it as a covariate. As there was no effect of order in the behavioral data we did not include this variable. We observed a significant main effect of medication on participants' negative learning rates (*F(1,9)=7.57, p=.02***,** Figure 2B). A similar model yielded no significant effect of medication on positive learning rates (*F(1,9)=.07, p=.79*). There was no significant effect of medication on modeled response consistencies (*F(1,9)=.16, p=.23*).

3.3. Results HD

3.3.1. Behavioral data

We utilized a repeated measures ANOVA with within-subjects variable block (1-3) and between-subjects variable group (patients / controls). As the sample size (18) was reasonably large and there is recent evidence of gender-related differences in HD phenotype (Zielonka et al., 2013), we also included gender into our model. The analysis revealed a significant effect of block (*F(2,64)=17.1, p<.001*) indicating that, on average, participants learned the task. Learning performance in general was different for healthy controls compared with HD patients as revealed by a significant main effect of group (*F(1,32)=5.64, p=0.02*). The between-subject interaction of group x gender was significant (F(1,32)=4.9, p=.03, Figure 3A), showing that learning performance in general was different between gender-specific subgroups. In line, the three-way interaction of block x group x gender exhibited a trend for significance (*F(2,64)=2.87, p=.06*), indicating that learning was different between gender specific control and HD groups. All other interactions were non-significant.

In view of the significant gender x group interaction, post-hoc independent samples t-tests revealed that female HD patients showed lower over-all learning performance than female control participants (HD =.72, control =.61, *t(16)=3.5, p=.003*), whereas there was no difference for men (HD=.7, control=.7, *t(16)=.11, p=.92*).

3.3.2. Modeling

We computed two separate ANOVAs for positive and negative learning rates as dependent variables with group and gender as between-subject factors. There was no significant main effect in either model, but the group x gender interaction had a significant impact on participants' positive learning rates (*F(1, 30)=5.15, p=.03*, Figure 3B), whereas there was no such effect on learning rates from negative PEs (*F(1,30)=.15, p=.7*). Post-hoc independent samples t-tests revealed that female HD patients showed elevated learning from positive PEs compared to controls (*t(15)=2.13, p=.05*). There was no difference between male patients and control participants (*t(15)=.98, p=.34*). In addition, positive learning rates showed a positive linear association with assessed motor symptom severity across all HD patients ($R^2=.3$, $\beta=.55$, *p=.02*, Figure 3C). Motor symptom severity did not differ significantly between male and female HD patients (*t(15)=0.24, p=.81*).

There was no significant main effect of group (HD / controls, *F(1,30)=2.14, p=.15*) or a group x gender interaction (*F(1,30)=2.78, p=.11*) on participants' response consistencies between HD patients and healthy controls.

4. Discussion

4.1. Summary

For optimal functioning within our complex environment procedural learning of appropriate stimulus-response associations is crucial. Positive and negative PEs serve as neural teaching signals within distinct pathways to update these associations and optimize our subsequent behavior. Positive PEs are reflected in an increase in the phasic firing rate of dopaminergic neurons, whereas negative prediction errors are reflected in transient dips of the tonic dopamine signal (Schultz et al., 1997; Tobler et al., 2003). Here, we assessed stimulus-response learning from positive and negative PEs on the probabilistic WPT using computational modeling. We included data from healthy volunteers and from two samples of patients exhibiting specific alterations in predominantly one of the two segregated pathways. Consequently, the different patient populations should reveal disturbances mainly in either learning from positive or learning from negative PEs.

Taken together, our computational modeling results indicate that learning from positive and negative feedback on the WPT is intimately linked to different aspects of dopaminergic transmission. Phasic dopaminergic responses are predictive of learning from positive feedback on the WPT. In healthy individuals, we observed a linear association between difference in [^{11}C]raclopride binding potential as a measure for striatal DA release and positive learning rate on the WPT. Further, asymmetry between baseline DA tone in left and right ventral striatum is negatively associated with learning from positive PEs. Female patients with early progression of Huntington's disease, which is characterized by a hyper-activation of the direct pathway, exhibited exaggerated learning rates from positive feedback. In contrast, dopaminergic tone predicts learning from negative feedback on the WPT, as indicated by an inverted-u-shaped association observed with baseline [^{11}C]raclopride binding potential in healthy controls and the difference between PD patients *on* and *off* medication.

4.2. Learning from negative prediction errors on the Weather Prediction Task

Dopaminergic tone predicts learning from negative feedback on the WPT, as indicated by an inverted-u-shaped association observed with baseline RAC BP in healthy controls. This is in line with previous research showing that avoidance learning was associated in an inverted-u-shaped manner with D2 receptor availability (Cox et al., 2015). Importantly, because [^{11}C]-raclopride is competing with endogenous dopamine, D2 receptor availability as estimated by [^{11}C]-raclopride binding potential may depend on both, the occupancy of receptors by endogenous dopamine and D2 receptor density. Thus, baseline BP may in part be interpreted as reflecting dopaminergic tone. It has been shown that either too low or too high tonic dopamine levels impair behavior in different cognitive domains (Cools and D'Esposito, 2011; Floresco, 2013). Non-optimal dopamine levels seem to affect particularly the capability of detecting dips in tonic DAergic signaling and, consequently, may thus alter learning from negative PEs in particular. In healthy volunteers, depletion of dopamine precursors specifically improves avoidance learning, presumably via a better signal-to-noise ratio due to a reduction of DA tone in the indirect pathway, but leaves approach learning unaffected (Cox et al., 2015). Our results indicate that in PD patients, however, a drastic increase in the level of ventral striatal dopamine impairs learning from negative PEs. L-DOPA has previously been shown to specifically impair reversal learning (Cools et al., 2001) and disrupt activity in the nucleus accumbens in PD patients (Cools et al., 2007). Since dopaminergic tone is associated with the ability to learn from negative PEs in an inverted u-shaped manner, our results suggest that ventral striatal dopaminergic tone in PD patients *off* medication is still preserved at an optimal level. This is corroborated by comparable performance of PD patients *off* medication and healthy controls. Additional administration of L-DOPA then causes a suboptimal increase in DA levels in the ventral striatum, resulting in an impaired ability to detect dips in tonic DA. PD patients in our subject sample also received DA agonists besides L-DOPA (see Jahanshahi et al., 2010). Thus, withdrawal from both or even withdrawal from DA agonists alone might have caused the observed differences in PD patients *off* vs. *on* medication (Moustafa et al., 2012). However, our results on differences in PD patients' learning from negative PEs between *on* and *off* medication are consistent with earlier reports on the effects of dopaminergic medication on reinforcement learning in PD patients using different tasks (Frank et al., 2004, 2007a; Bodi et al., 2009). In line, Cools et al. (2006) demonstrated a medication-induced deficit that was restricted to conditions with unexpected punishment and Moustafa et al. (2013) reported reduced learning from negative feedback in PD patients under dopaminergic medication compared to unmedicated patients. Additionally, Moustafa et al. observed enhanced learning from positive feedback under dopaminergic medication. Notably, they used a simpler probabilistic stimulus-response learning task with only single cue stimuli. Together, these results suggest that dopaminergic tone predicts the ability to learn from negative PEs on the WPT, both in healthy individuals and in PD patients on dopaminergic medication. Importantly, the specific effect depends on the initial level of DA: Because of the basic non-linear relationship between DA levels and performance, additional heightening or lowering levels of DA might cause suboptimal performance on the WPT.

4.3. Learning from positive prediction errors on the Weather Prediction Task

Learning from positive PEs depends linearly on the magnitude of phasic dopamine release in healthy volunteers. Importantly, dopaminergic tone seems to be a powerful modulator of phasic DA transmission, as learning from positive PEs was best explained when we took into account both, % change in RAC BP as a measure of phasic dopamine release during learning and baseline RAC BP as an indicator of density and background stimulation of DA receptors. These results are in line with a previous report demonstrating the direct association between learning from positive feedback and signaling in the direct pathway in healthy volunteers (Cox et al., 2015). In their study, learning to approach options associated with a positive outcome in a probabilistic selection task was linearly associated with D1 receptor density in the striatum.

Further, we found the ability to learn from positive PEs to be negatively associated with the asymmetry between baseline DA tone in left and right ventral striatum in healthy volunteers. Our results are in line with previous findings. Gray (1981) postulated that individual differences in motivational behaviour are related to either a bias towards behavioural activation to approach incentives or behavioural inhibition to avoid punishment. Stronger approach motivation has been linked to greater left than right prefrontal activation according to EEG power (e.g. Sutton and Davidson, 1997), as well as PET and fMRI-related activation (Wager et al., 2003; Murphy et al., 2003). Presumably, this asymmetric activation is related to hemispheric asymmetry in dopaminergic transmission. Hemispheric asymmetry in DA has repeatedly been shown to be associated with approach and avoidance motivation and learning. In healthy volunteers, self-reported motivational bias between approach and avoidance was predicted by the asymmetry of frontal D2 binding (Tomer et al., 2014). Further, striatal and frontal asymmetries in D2 dopamine receptor binding predicted individual differences in learning from reward versus punishment (Tomer et al., 2014). PD patients with predominantly left hemispheric deficits were less willing to invest effort to maximize gain, indicating a selective impairment in approach motivation. In contrast, PD patients with a right hemispheric deficit exhibited impairments in avoidance motivation (Porat et al., 2014). Further, these patients were impaired in learning from positive vs. negative feedback, respectively (Maril et al., 2013). In contrast to Aberg et al. (Aberg et al., 2015), who reported a positive association between better learning from positive PEs and functional asymmetry in left and right ventral striatum, our data indicate a negative relationship. This seeming discrepancy can be explained by the indirect modulation of phasic responses by DA tone via inhibitory actions on the presynaptic cell (Goto et al., 2007; Dyakonova et al., 2009).

So what happens if the balance between the integrity of direct and indirect pathways is compromised? Female patients with early progression of Huntington's disease, which is characterized by a hyper-activation of the direct pathway, exhibited exaggerated learning rates from positive feedback in our study. In Huntington's disease (HD), a neurodegenerative, autosomal-dominant transmitted neurodegenerative disorder, cell death of striatal neurons already occurs in early and even pre-symptomatic stages of the disease. The progression of neuronal death in the striatum is gradual and proceeds from dorsal to ventral and from medial to lateral (Vonsattel et al., 1985; Aylward et al., 2004). In early stages of HD, cell death primarily affects GABAergic medium-sized spiny neurons within the indirect pathway. Furthermore, HD has been associated with a loss of pre-synaptic D2 auto-receptors, thus impairing the ability of tonic DA to regulate phasic responses (Cepeda et al., 2014). Reduced striatal D2 receptor availability has been reported even in asymptomatic HD patients and mutation carriers, suggesting that dopaminergic signaling is compromised early in HD (Weeks et al., 1996; van Oostrom et al., 2009). Taken together, this leads to a hyper-activation of the direct pathway already in very early stages of the disease. In line, HD patients in early stages of the disease have been shown to be generally impaired in procedural stimulus-response learning (Holl et al., 2012). Adding to this, our results indicate that in early HD, DA pathways are affected differentially in women and men and that impairments are selective for learning from positive PEs. While we predicted specificity for learning from positive PEs, the finding of a gender-specific effect in patients with early HD is novel. It has been proposed that a general gender difference in endogenous dopamine levels or other aspects of dopaminergic transmission (Pohjalainen et al., 1998; Kaasinen et al., 2001; Laakso et al., 2002) may account for gender differences in the vulnerability to neuropsychiatric disorders such as depression, schizophrenia or Parkinson's disease (Gillies et al., 2014). For Huntington's disease, however, penetrance and prevalence seems to be equal for both sexes. Interestingly, a large European study showed recently that women with HD exhibited more severe symptoms and a faster progression of the disease (Zielonka et al., 2013), and a large US study found that women have a longer duration of the disease (Foroud et al., 1999). Thus, there might be gender differences in the progression of the disease. Our results indicate a more severe impairment in learning from positive PEs in women with HD compared to men. This might be explained by an interaction of disease-specific effects with sex differences in dopaminergic transmission. Women have a higher presynaptic dopaminergic synthesis capacity (Laakso et al., 2002) and show a lower binding potential for [^{11}C]raclopride, suggestive of a higher striatal dopamine concentration (Pohjalainen et al., 1998). Further, women have been shown to have higher D2-like receptor binding potentials than men in frontal cortex, temporal cortex, and thalamus (Kaasinen et al., 2001). Together, these might produce an additive effect on the hyper-activation of the direct pathway, and, in consequence, exaggerated learning from positive PEs especially in women with early HD. However, as positive learning rate was associated with motor symptom severity across all patients, the gender specific effect might alleviate during further progression of the disease. In line with our results, Palminteri and colleagues observed an asymmetry in favor of reward-based relative to punishment-based learning in patients with early compared to late HD and to controls (Palminteri et al., 2012). Specifically, the authors found a higher reward bias and a higher reinforcement magnitude for gains compared to losses. However, learning rates for gain and loss conditions were not different between HD groups or compared to controls in their study. Importantly, the task they used differed from the WPT in that participants had to learn to approach, i.e. select, rewarding options and to avoid, i.e. to not choose, punishing options in different conditions. Taken together, our results indicate that future work should pay special attention to sex differences in HD.

An imbalance between tonic and phasic DA signaling may lie at the heart of alterations in dopamine-based learning, as has been observed in attention deficit hyperactivity disorder (Badgaiyan et al., 2015), depression (Dunlop BW and Nemeroff CB, 2007; Mörkl et al., 2016), schizophrenia (Juckel et al., 2006; Brunelin et al., 2013), obesity (Frank et al., 2012; Horstmann et al., 2015) or Parkinson's disease (PD) patients on dopaminergic medication (Jahanshahi et al., 2010). Further, within healthy volunteers, the layout of the dopaminergic system seems to be intimately linked to the individual level of personality traits such as approach/avoidance bias and impulsivity (Buckholtz et al., 2010; Tomer et al., 2014).

Taken together, our results demonstrate that solving the WPT relies on the integrity of different pathways within the dopaminergic system. In line with our hypotheses, data from healthy individuals, patients with PD *on* dopaminergic medication as well as from patients with HD show that variance within each pathway is linked to specific performance differences when solving the WPT.

5. Conclusions

The present data reveal that the WPT is suitable to disentangle learning from negative and positive feedback with the help of computational modeling. The ability to learn from positive and negative feedback might prove to be a sensitive marker for the integrity of dopaminergic signal transmission. In particular, it might differentiate between the involvement of the 'direct' and 'indirect' dopaminergic pathways. The present data are interesting beyond clinical context in that imbalances of dopaminergic signaling have not only been observed for psychiatric conditions but also for obesity (Kessler et al., 2014; Horstmann et al., 2015) and adolescence (Luciana et al., 2012). Thus, future work should differentiate between learning from positive and negative feedback since these processes rely on segregate neural mechanisms. In the case of medical conditions, specific learning impairments would point to associated specific neural changes that call for different treatment options.

Author contributions & Funding

DM and Annette Horstmann designed research, MJ, LW and Anna Holl contributed data, DM and JN implemented computational model, DM analyzed data, LD contributed to model comparisons, DM and Annette Horstmann wrote paper. All authors revised and edited the manuscript.

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Table 1: Model comparison between the stepwise modeling approach with two learning rates (stepwise, 2 LR) and two alternatives: a model with only one learning rate and stepwise fitting (stepwise, 1 LR) and a model with two learning rates and simultaneous fitting (standard QL).

		stepwise, 2 LR	**stepwise, 1 LR**	**standard QL**
All subjects (n=63)	pseudo-r^2	0.37	0.37	0.38
	BIC	11352	11261	11241
	ΔBIC	1.76	0.32	-
	model frequencies	0.27	0.26	0.46
	exceedance probabilities	0.03	0.02	0.95
	regression-model	***R^2=0.65 p<0.001***	***R^2=0.14 p=0.01***	*R^2=0.05 p=0.4*
PET (n=7)	pseudo-r^2	0.25	0.25	0.23
	BIC	1484	1485	1535
	ΔBIC	-	0.14	7.29
	model frequencies	0.45	0.44	0.11
	exceedance probabilities (%)	0.5	0.48	0.02
	regression-model	***R^2=.96 p=.01***	***R^2=.97 p=.001***	***R^2=.96 p=.02***
PD (n=22)	pseudo-r^2	0.23	0.29	0.21
	BIC	4677	4460	4953
	ΔBIC	9.86	-	22.41
	model frequencies	0.24	0.51	0.25
	exceedance probabilities (%)	0.05	0.9	0.05
	regression-model	***R^2=.91 p=1.17*10^{-9}***	*R^2=.05 p=.63*	*R^2=.11 p=.53*
HD (n=34)	pseudo-r^2	0.47	0.46	0.51
	BIC	5192	5315	4752
	ΔBIC	7.02	13.62	-
	model frequencies	0.29	0.03	0.68
	exceedance probabilities (%)	0.01	0	0.99
	regression-model	***R^2=.29 p=.02***	*R^2=.07 p=.33*	*R^2=.04 p=.76*

N.B. BIC = Bayesian Information Criterion. Values in bold indicate significant variance explanation. All three tested models showed comparable model fit according to pseudo-r^2 and BIC values. While standard QL shows the best fit according to estimated probabilities and model frequencies across all subjects, *ΔBIC* indicate no strong evidence against the other two models. Importantly, despite comparable model fit, only the stepwise model with two learning rates was able to explain significant variance in participants' WPT performance in all three studies according to regression analyses. LR = Learning rate.

Figure 1

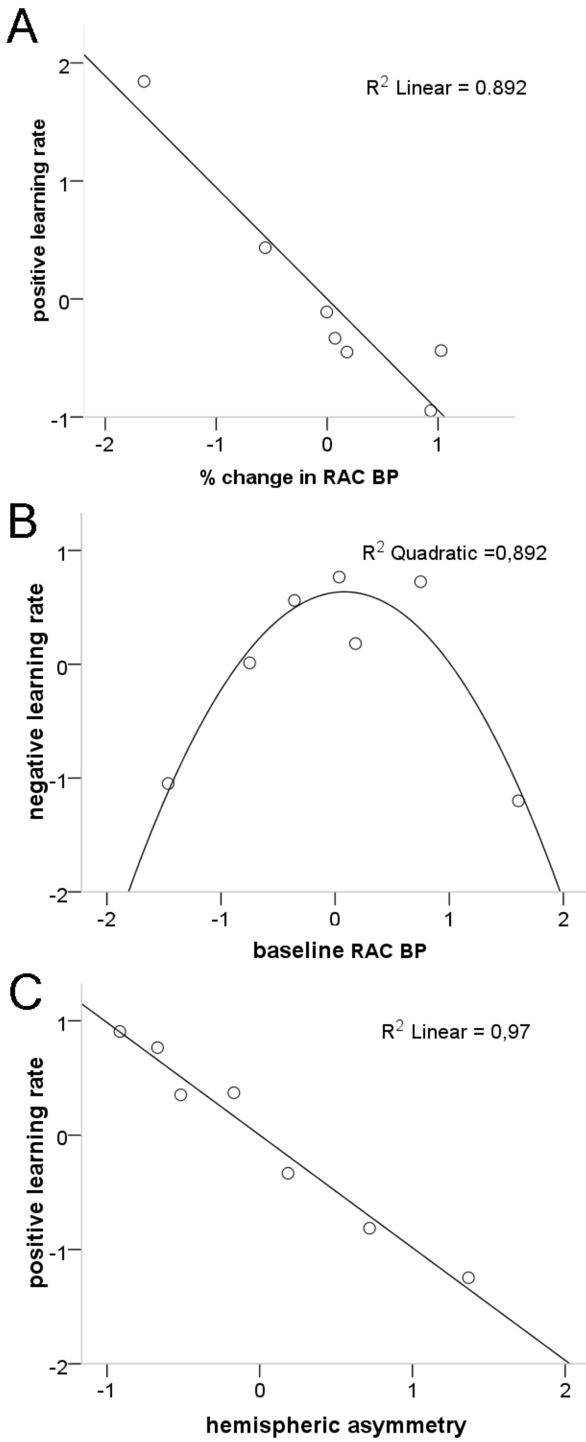

Figure 1 Association between phasic and tonic dopaminergic signaling and learning on the Weather Prediction Task. (A) Dopamine release, as measured by the change in [11C]raclopride binding potential between WPT control and feedback sessions, is positively associated with the ability to learn from positive prediction errors (PEs) in healthy subjects. (B) Dopaminergic tone, as estimated by baseline [11C]raclopride binding potential, is associated with learning from negative PEs in an inverted u-shaped

manner. (C) Hemispheric asymmetry between left and right ventral striatum in dopaminergic tone is negatively associated with learning from positive PEs.

Figure 2

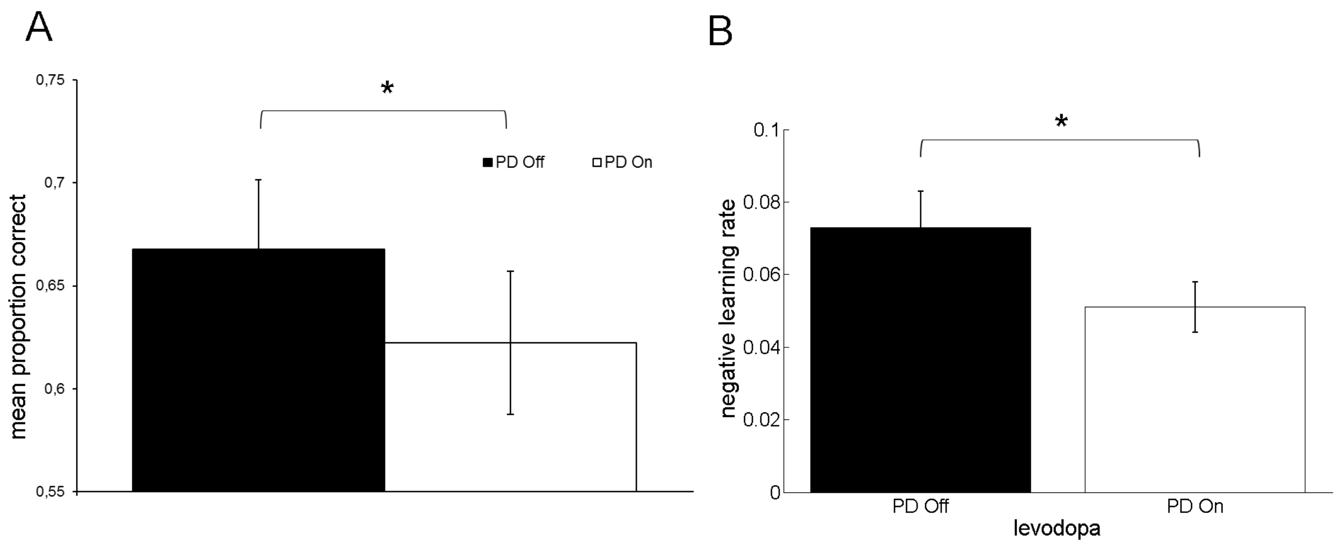

Figure 2 Behavioural differences between *off* and *on* dopaminergic medication in patients with Parkinson's disease on the Weather Prediction Task. (A) Mean proportion correct responses on the Weather Prediction Task for Parkinson patients *off* and *on* dopaminergic medication. (B) Parkinson patients *on* dopaminergic medication are impaired in learning from negative prediction errors on the Weather Prediction Task compared to *off* medication. Asterisk indicates p<.05.

Figure 3

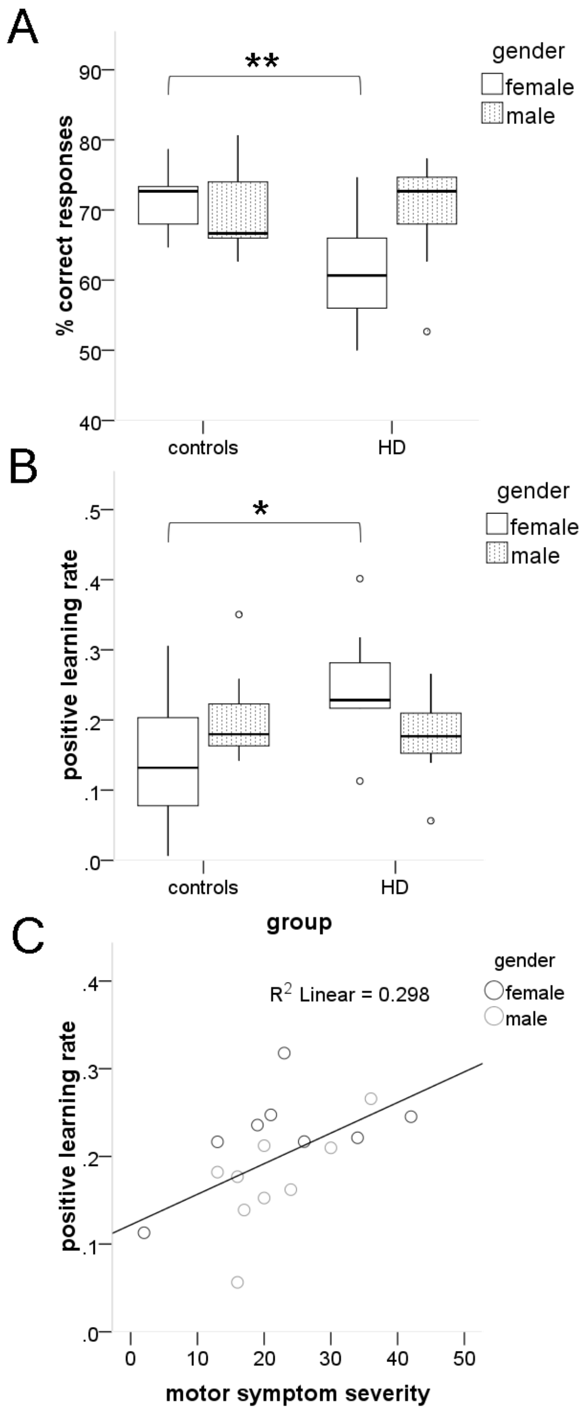

Figure 3 Gender-specific behavioral impairment in patients with Huntington's disease on the Weather Prediction Task. (A) Mean proportion correct responses on the Weather Prediction Task for healthy control subjects and early Huntington Disease (HD) patients split by gender. (B) Interaction between group (control/HD) and gender on the propensity to learn from positive prediction errors on the Weather prediction task. (C) Positive learning rate is positively associated with motor symptom severity across both genders in patients with early Huntington's disease.