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DOI:
10.1162/jocn_a_00706

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Acknowledgements: This work was supported by the European Union framework 7 initiative REPLACES (JMG, JCR), Birmingham Fellows scheme (JMG), Tourette Syndrome Association (DR, JCR), The Dorothy Feiss Scientific Research Grant (DR), Biotechnology and Biological Sciences Research Council (SB), European Research Council (ActSelectContext, 260424, SB). We thank Louise Marshall for helpful comments.

Abstract

Humans carry out many daily tasks in a seemingly automatic fashion. However, when unexpected changes in the environment occur, we have the capacity to inhibit prepotent behaviour and replace it with an alternative one. Such behavioural flexibility is a hallmark of executive functions. The neurotransmitter dopamine is known to be crucial for fast, efficient and accurate cognitive flexibility. Despite the perceived similarities between cognitive and motor flexibility, less is known regarding the role of dopamine within the motor domain. Therefore, the aim of this study was to determine the role of dopamine in motor flexibility. In a double-blind, 5-session, within-subject pharmacological experiment, human participants performed a reaction time task within a probabilistic context that was either predictable or unpredictable. The probabilistic nature of the predictable context resulted in prediction errors. This required participants to replace the prepotent or prepared action with an unprepared action (motor flexibility). The task was overlearnt and changes in context explicitly instructed, thus controlling for contributions from other dopamine-related processes such as probabilistic or reversal learning, and interactions with other types of uncertainty. We found that dopamine receptor blockade by high-dose haloperidol (D1/D2 dopamine receptors) impaired participant's ability to react to unexpected events occurring in a predictable context, which elicit large prediction errors and necessitate motor flexibility. This effect was not observed with selective D2-receptor blockade (sulpiride), with a general increase in tonic dopamine levels (levodopa), or during an unpredictable context which evoked minimal prediction error. We propose that dopamine is vital in responding to low-level prediction errors about stimulus outcome that requires motor flexibility.

Introduction

Much human behaviour is executed in a seemingly automatic fashion. These behaviours can be viewed as prepotent in that they take precedence over any other potential alternatives (Hikosaka and Isoda, 2010; Isoda and Hikosaka, 2011). When this behaviour becomes inappropriate through an unexpected change in the environment, humans are capable of engaging resources which inhibit these prepotent responses and replace them with alternative ones. Such behavioural flexibility in a short period of time is a hallmark of executive functions (Hikosaka and Isoda, 2010; Isoda and Hikosaka, 2011).

There is considerable evidence that the neuromodulator dopamine plays a crucial role in behavioural flexibility (Stelzel et al., 2010; van der Schaaf et al., 2012; Stelzel et al., 2013). Previous human work has highlighted the importance of dopamine in cognition-based switching tasks (Cools et al., 2001a; Cools et al., 2009; van Holstein et al., 2011), with continuing interest in the specific function of dopamine D1 and D2-receptors. Animal (Floresco et al., 2006; Haluk and Floresco, 2009), theoretical (Durstewitz and Seamans, 2008) and human (van Holstein et al., 2011; Stelzel et al., 2013) work has suggested that D2-receptor signalling is an essential component for efficient cognitive flexibility. However, there is also considerable evidence that D1-receptor signalling plays a significant role (Ragozzino, 2002), with recent proposals that cognitive flexibility relies on a cooperative interaction of both D1 and D2 receptors (Floresco, 2013).

A distinction can be made between cognitive and motor flexibility (Stelzel et al., 2013). Whereas the former will generally involve a complex rule change (set-shift: naming digits following naming letters) (Cools et al., 2001a), the latter requires the replacement of a prepared action with an unprepared one (Neubert et al., 2010; Galea et al., 2012). Motor flexibility has also been termed behavioural adaptation (Stelzel et al., 2013), motor-based behavioural switching (Hikosaka and Isoda, 2010) or action reprogramming (Mars et al., 2009; Neubert et al., 2010; Galea et al., 2012). We regard this terminology to reflect a similar process and therefore will use motor flexibility as a term which encompasses them all. Parkinson's disease patients, who suffer from a dopamine deficit, show specific impairments in motor (Cools et al., 1984; Galea et al., 2012) and cognitive flexibility tasks (Beatty and Monson, 1990; Cools et al., 2001a), with performance restored by dopaminergic medication (Cools et al., 2001b; Galea et al., 2012). Despite this work, the dissociable influence of D1 and D2-receptor signalling in motor flexibility is relatively unknown (Stelzel et al., 2013).

We addressed this issue by testing for the effects of a range of dopaminergic drugs on motor flexibility. Individuals use past experience to prepare movements in advance of upcoming events, and the degree of preparation is closely related to the predictability of a future event (Bestmann et al., 2008). Such preparation is advantageous when an event is predicted correctly, but occurs at the expense of a prolonged reaction time (RT) when an unexpected event results in a prediction error. In this case, a prepared action has to be replaced by an unprepared alternative movement. Importantly, the greater the prediction error is, the greater the cost in terms of a prolonged RT (Bestmann et al., 2008; Galea et al., 2012).

The brain's sensitivity to prediction error has been explained by models which implement optimal Bayesian inference (Kording and Wolpert, 2006; Friston et al., 2012; Iglesias et al., 2013). Interestingly, indirect evidence from human neuroimaging studies suggest that brain areas associated with dopamine release are sensitive to low-level prediction errors about stimulus outcome (Iglesias et al., 2013). In contrast, prediction errors at high or abstract levels of uncertainty are thought to be encoded by other neuromodulatory systems (Yu and Dayan, 2002, 2005). Such hierarchical models therefore predict that dopamine may have an important role for responding to prediction errors, even in the absence of other learning-related types of uncertainty (volatility; Behrens et al., 2007).

This study sought to isolate the contribution of dopamine for enabling motor flexibility in response to low-level prediction errors. To this end, we controlled for any role dopamine might have in the learning of probabilistic task contexts or reversal learning (Frank et al., 2007; Cools et al., 2009; Seo et al., 2010), by explicitly highlighting the current context to participants, and providing them with extended practise on each context prior to the main experiment. This also ensured that participants did not experience volatility/unexpected uncertainty, i.e. changes in the probability of the upcoming stimuli (Yu and Dayan, 2002, 2005; Behrens et al., 2007). Instead, participants experienced different degrees of expected uncertainty wherein they had advanced and stable knowledge about the overall predictability of the context (overall predictable context, *PC*, and overall unpredictable context, *UC*), but because of the probabilistic nature of each context a degree of irreducible uncertainty persisted. Therefore, participants knew about the context they were currently experiencing and consequently the (expected) uncertainty associated with each context, but had to quickly respond to violations of these expectations in the form of rare and surprising events. Consequently, the prediction errors experienced in the *PC* would specifically examine the role of dopamine in responding to low-level stimulus prediction errors whose behavioural outcome is termed motor flexibility.

In a double-blind, 5-session, within-subject design, participants performed a simple cued RT task (Galea et al., 2012). In the absence of learning, we found that combined D1/D2 receptor blockade (haloperidol) impaired participant's ability to react to unexpected events that elicit large prediction errors and thus require motor flexibility. This effect is neither observed with specific D2-receptor blockade (sulpiride), nor with a general increase in tonic dopamine levels (levodopa) or during an unpredictable context which evoked minimal prediction error.

Methods

Participants

15 self-assessed right-handed individuals with no current health problems or history of neurological/psychiatric illness (9 males, mean age = 27 ± 6 years old) participated in the study, with written informed consent. The study was approved by the research ethics committee of the Institute of Neurology, UCL.

General Procedure

In a double-blind, placebo-controlled design, each participant took part in 4 experimental drug sessions, each separated by at least 1 week, in which they performed a probabilistic sequence RT task. 8 participants were involved in an additional 5th session. Session order was pseudo-randomised so that placebo was evenly distributed across the 5 sessions. Participants sat in front of a computer screen positioned 30cm away and placed each of the fingers of their right hand on 1 of 4 response buttons. At the start of each block, a screen was displayed to inform the participant whether the upcoming block consisted of either an *UC* or *PC*. Subjects were therefore explicitly instructed about changes in the context. To focus participant's attention, an un-informative warning cue (white box) was then presented. This was followed by the presentation of 1 of 4 imperative stimuli (IS). Participants responded to the IS as quickly as possible, but not at the expense of accuracy. A fixation-cross followed (Figure 1a). Each imperative stimulus was associated with pressing a specific button (Figure 1a). These stimulus-response associations were learnt by the participants during a familiarisation period (100 trials) at the beginning of the *training* session (see below) in which feedback was provided to signal whether their response was correct. Learnt stimulus-response associations were characterized by an error rate of less than 7%.

During the main experimental sessions, participants were exposed to 72 blocks of 12 trials (864 trials), which was equivalent to 40 minutes of testing. Blocks alternated between *UC* and *PC*. During *UC*, there was a 0.25 probability of each imperative stimulus being presented on trial *t*. In contrast, during the *PC* the current stimulus on trial *t* was conditionally dependent on the stimulus of the previous trial, *t-1*. This generated sequences in which the imperative stimulus order 1-2-3-4 occurred with high probability (Figure 1a,b). Because of the probabilistic nature of the sequence, however, occasional violations of this predominant sequence order occurred.

Dopamine is known to be play a pivotal role in multiple learning processes such as reinforcement (Schultz et al., 1997; Niv et al., 2007) and probabilistic learning (Cools et al., 2009; Wilkinson et al., 2009; den Ouden et al., 2013). Here, we wanted to test for the specific role of dopamine in behavioural flexibility and therefore sought to eliminate learning-related contributions of dopamine. Thus, prior to the main experimental sessions, all participants underwent a *training* session in which the task was overlearnt. During *training*, participants were exposed to 72 blocks of 12 trials (864 trials), which was equivalent to 40 minutes of testing. To reiterate, at the start of each block, a screen was displayed to inform the participant whether the upcoming block consisted of either an *UC* or *PC*. At the end of training, the experimenters plotted the RT for the *UC* and *PC*. RT was averaged over every 12 trials (1 block) across training. Plateau performance was defined as participants showing no improvements in RT which were greater than 10msecs from the previous *UC* or *PC* block. A plateau in RT performance was assumed to reflect overlearning (Figure 1c). For both the *UC* and *PC,* all participants exhibited plateau performance during the last 10 blocks. Training ensured participants had strong priors about the nature of each context and were able to switch between them on the basis of the explicit feedback. This was crucial in ensuring the results were specific to the role of dopamine

in behavioural flexibility and not probabilistic or reversal learning (Cools et al., 2009; den Ouden et al., 2013).

Pharmacology

For each experimental session, participants arrived 2 hours prior to completing the task, and received either 100mg of the dopamine precursor levodopa (*levo*), 400mg of the D2 antagonist sulpiride (*sulp*), 2.5mg of the D1/D2-antagonist haloperidol ($halo_{2.5}$) or placebo (*plac*). Participants who underwent an additional 5th session were administered 1mg of haloperidol ($halo_{1}$). Haloperidol was administered 2 hours prior to the onset of the experiment, whereas levodopa and sulpiride were administered 1 hour prior. Placebo was administered randomly at either 1 or 2 hours before. The doses and administration times are similar to previous studies which have shown clear behavioural and neurophysiological effects for levodopa (Adam et al., 2012), sulpiride (Nitsche et al., 2006) and haloperidol (Frank and O'Reilly, 2006).

This combination of drugs was used in an attempt to partially dissociate the roles of dopamine D1 and D2-receptors during motor flexibility. Because selective D1-anatagonists available for human use have severe reported side effects (Hou and Schumacher, 2001), we exploited the hypothesized relative D1- and D2-receptor affinity differences between $halo_{2.5}$, $halo_{1}$ and *sulp*. Our approach was based on these drugs predicted effects in the basal ganglia, however it is important to emphasize that the role of the basal ganglia during this task must be taken with caution, simply due to the widespread changes the drugs have both in terms of receptor affinity and on different brain regions. First, sulpiride specifically blocks D2-receptors (O'Connor and Brown, 1982). Second, although haloperidol blocks D1- and D2-receptors, its affinity for D1-receptors is 25 times lower than for D2 (Bymaster et al., 1999). A dose of 1mg should be sufficient to detect a behavioural impairment on tasks which are D2-receptor dependent (Fitzgerald et al., 2000). By contrast, a dose of 2.5mg haloperidol ought to partially block both D1- and D2-receptors, whilst minimising the extra-pyramidal and sedative side effects that occur at higher doses. However, we are acutely aware that these differences between high and low dose haloperidol are not categorical. For instance, Fitzgerald et al., (2000) showed approximately 50% D2 occupancy at 1mg and 75% at 2.5mg. In addition, only a 14% increase in D1 occupancy has been found at 8.5mg of haloperidol (Reimold et al., 2007), but in support of our hypothesis in-vivo binding of D1-receptors was found to be 100% times greater than D2-receptors with haloperidol (Zhang and Bymaster, 1999). Finally, as haloperidol blocks the phasic uptake of dopamine it can lead to increased levels of tonic dopamine in the basal ganglia (Kuroki et al., 1999). To dissociate these effects we compared $halo_{2.5}$ with *levo* (which increases tonic dopamine). Although we assume this task is mediated by the basal ganglia, one cannot exclude that any observed effects are mediated via the frontal cortex. As such, we note that while sulpiride led to increased tonic dopamine in the prefrontal cortex, haloperidol did not (Kuroki et al., 1999; Li et al., 2005). Although it is not possible to directly test the isolated role of D1-receptors, this combination of drugs provided an insight into the possible independent roles of D1 and D2 receptors during motor flexibility.

At the end of each session, participants reported their attention and fatigue using a self-scored visual analog scale (1: poorest attention/maximal fatigue; 7: maximal attention/least fatigue), and reported whether they thought they had received an active or placebo drug.

Behavioural analysis

For all correct responses, RT was calculated as the time between imperative stimulus onset and the subsequent button press. A Kolmogorov-Smirnov test was performed on the standardized data (subtracted by mean and divided by SD) across all trial types and participants. This test rejected the null hypothesis that the data were normally distributed at $p<0.05$. Therefore, the data was log transformed (Galea et al., 2007). A Kolmogorov-Smirnov test now revealed the data now no longer significantly deviated from a normal distribution ($p>0.05$). Using this log-transformed data, average RTs were calculated for each trial type (unpredictable, *UC);* predictable-expected, *PC);* predictable-unexpected, *PC)*. The average RT from the *UC* was subtracted from both expected (predictable-expected) and unexpected (predictable-unexpected) trial types during the *PC* (ΔRT). This analysis mirrors the analyses in our previous work in PD patients (Galea et al., 2012), and allowed a simple comparison with minimal assumptions between sessions for the expected (> 0.75) and unexpected (< 0.12) trial types during the *PC*, and enabled us to quantify the cost of violation of expectations within the *PC* (Galea et al., 2012).

To assess whether the task was overlearnt during *training*, the last 10 blocks of the *training* session were compared with the *plac* session. A within-subject repeated-measures ANOVA (rmANOVA) compared session (*training*, *plac*) with context (*PC*, *UC*).

For the main experimental sessions, we compared the percentage of incorrect button responses (error), average RT across trial types and average ΔRT for expected and unexpected trial types during the *PC*. Within-subject rmANOVA compared these parameters across the 4 main drug sessions (*plac*, *levo*, *sulp*, $halo_{2.5}$). Due to multiple comparisons, a Bonferroni adjustment was made in which we accepted statistical significance at $p<0.025$. Post hoc paired t-tests explored significant effects (two-tailed). Due to only a subpopulation of participants being tested with 1mg of haloperidol, $halo_1$ was compared with $halo_{2.5}$ using a paired t-test. Estimates of effect size are given as partial eta squared (n_p^2). All data presented represent mean ± standard error.

Event-related surprise

In the current task, participants were required to respond as fast as possible but would always have some degree of uncertainty about the upcoming IS. Because of the probabilistic nature of the over-learnt sequences, occasional violations would occur in the form of unexpected IS. For these surprising IS, participants had to respond against their prior expectation. Increases in RT to such surprising IS should then relate to the magnitude of the prediction error during the *PC* (Galea et al., 2012). In contrast, during the *UC*, when prior expectations would be overall small, occasionally more surprising IS occur against an overall

UC, with little prediction error. We quantified the surprise enacted by a particular IS on a trial-by-trial basis. We estimated the conditional probability of each IS using a Bayesian update scheme (Harrison *et al.*, 2006, Strange *et al.*, 2005) in which we assumed that at the beginning of each session, participants started with the prior expectation of all IS being equally likely. Note that in each context, the overall probability of occurrence of all four stimuli was equal, and because these contexts had been over-learnt and were explicitly signalled at every change, a uniform prior reflects the expectations participants should have.

For each trial (*t*) there were 4 possible IS. Therefore, the conditional probability of IS *E* at trial *t*, $p(E_t)$, was estimated from the number of occurrences of IS *i* up to trial *t* (written as n_i^t , where *i* indexes the current IS type and *t* the trial number relating to the start of each session). Thus, the estimate at trial *t* is given by,

$$p_t(E_t = i) = \frac{n_i^t + 1}{\sum_i (n_i^t + 1)} \quad , \quad (p_0\,(E_0 = i) = \frac{1}{4}) \tag{1}$$

As a result of the 1st order Markov sequence, the IS occurring on the previous trial, *E(t-1)* could be used to form predictions for the IS on trial *t*. An approximation of the joint probability distribution can be estimated from a count of IS pairs up to trial *t* (written as n_{ij}^t , where *i* and *j* index the current and previous IS type) and is given by,

$$p_t(E_t = i, E_{t-1} = j) = \frac{n_{ij}^t + 1}{\sum_{ij} (n_{ij}^t + 1)} \tag{2}$$

The degree of surprise conveyed by a particular IS pair is then quantified as,

$$S(E_t = i, E_{t-1} = j) = -log2\,(p(E_t = i, E_{t-1} = j)) \tag{3}$$

The surprise (*S*) of observing IS type *i* on trial *t* after experiencing IS type *j* on trial *t-1* is given by the negative log of its predicted joint probability. Therefore, surprise is a stimulus-specific measure which reflects the unexpectedness of the current IS, given the previous IS, i.e. prediction error. The amount of surprise conveyed by the occurrence of an IS is high when an IS pair is infrequent. Accordingly during the *PC* surprise will be overall low, but occasional violations occur in the form of highly surprising infrequent IS pairs. Surprising trials also occur in the *UC*, but in this case, such IS appear in the context of an overall absence of predictability.

For training, we estimated surprise and mutual information (MI) independently for the *PC* and *UC* by separately combining these block types across a session. MI is a measure of learning which quantifies the predictability of the current trial, *t*, based on the IS presented on the previous trial, *t-1* (Harrison et al., 2006). During the *PC*, MI steadily increases as the uncertainty of an IS type on trial *t*, which is afforded by an IS

type on trial *t-1*, decreases. In contrast, MI remains low during the *UC* (Galea et al., 2012). To assess how RT was associated with MI and surprise on a trial-by-trial basis, a robust multiple regression (iteratively reweighted least squares) was performed with RT as the dependent variable and MI and surprise as independent variables. This produced β values for surprise and MI in the *PC* and *UC*. A MANOVA compared β values for surprise and MI between the *PC* and *UC*. Due to multiple comparisons, a Bonferroni adjustment was made in which we accepted statistical significance at $p<0.025$.

As participants over-learnt each context during training, only surprise was estimated for the main experimental data for the *PC* and *UC* by separately combining these block types across a session. Although participants did not receive any direct feedback regarding errors, we presumed they were still likely to be noticed. Despite trials in which an error occurred being removed, we hypothesized that post-error trials would still be influenced and exhibit the phenomenon of post-error slowing (Dutilh et al., 2012). To assess how RTs were associated with surprise and post-error trials on a trial-by-trial basis, independent robust multiple regressions (iteratively reweighted least squares) were performed for the *PC* and *UC*, with RT as the dependent variable and surprise and post-error trials as independent variables. A repeated-measures MANOVA compared the β values for surprise and post-error trials across the 4 main drug sessions (*plac*, *levo*, *sulp*, $halo_{2.5}$) and context (predictable, unpredictable). Due to multiple comparisons (surprise and post error trials), a Bonferroni adjustment was made in which we accepted statistical significance at $p<0.025$. Post hoc paired t-tests explored significant effects with two-tailed scores being presented. Due to only a subpopulation of participants being tested with 1mg of haloperidol, $halo_{1}$ was compared with $halo_{2.5}$ using a paired t-test. Estimates of effect size are given as partial Eta squared (n_p^2).

We assumed that surprise should be estimated for the *PC* and *UC* separately, given the contexts were fully known and prior expectations about the IS sequence differed between the two contexts. However this assumption was tested by estimating surprise across all blocks irrespective of its explicit context. For each main drug session (*plac*, *levo*, *sulp*, $halo_{2.5}$), we performed a formal model comparison between these scenarios using Bayesian model selection to detect which model explained a greater amount of the RT variance (Stephan et al., 2009). Initially, for each participant and model, a parametric empirical Bayes estimate of the log evidence was calculated (Dempster et al., 1981). Given these log evidences from all subjects, we treated each model as a random variable and computed the exceedance probability of one model being more likely than any other model (Stephan et al., 2009). All analysis and statistics were performed using Matlab (Mathworks, USA).

[Figure 1]

Results

Training

There was no significant difference between the *training* and *plac* session for RT suggesting the task was overlearnt by the end of training. RT for the *PC* was significantly faster than for the *UC* ($F_{(1,14)}=17$, $p=0.001$,

n_p^2=0.54). However there was no main effect of session (*training* vs. *plac*; $F_{(1,14)}$=1, p=0.3, n_p^2=0.07) or interaction ($F_{(1,14)}$=0.9, p=0.35, n_p^2=0.06; Figure 1c). We obtained β-values by regressing surprise and MI against RT throughout *training*. During the *PC*, increasing surprise was related to slower RTs, whereas increasing MI was associated with faster RTs. In contrast, surprise and MI had no influence on RT during the *UC* (Figure 1d). There was a statistically significant difference in β-values between the *UC* and *PC* (MANOVA: $F_{(2,29)}$=22, p=0.0005, wilk's ^=0.39, n_p^2=0.61). Context had a significant effect on the β-values obtained for both surprise ($F_{(1,30)}$=45, p=0.0005, n_p^2=0.60) and MI ($F_{(1,30)}$=9.8, p=0.004, n_p^2=0.25). This signifies that the task was overlearnt and so enables the dissociation between the role of dopamine in probabilistic learning, evident during training, and motor flexibility.

Psychological parameters

Participant's reporting of attention and fatigue was similar across sessions. This is represented by the non-significant difference between ratings of attention (*plac*=4.6±0.4, *levo*=4.4±0.2, *sulp*=4.3±0.4, $halo_{2.5}$=4.8±0.3; $F_{(3,42)}$=0.2, p=0.7, n_p^2=0.04) and fatigue (*plac*=3.7±0.5, *levo*=3.3±0.3, *sulp*=2.9±0.4, $halo_{2.5}$=3.5±0.5; $F_{(3,42)}$=0.6, p=0.6, n_p^2=0.04) across sessions. However, 33% of the participants believed they had taken an active drug during the placebo session, which was substantially less than during the 3 main drug sessions (*levo*=80%, *sulp*=73%, $halo_{2.5}$=80%).

Error rates

All participants were able to perform the task without difficulty, with low error rates observed for the entire experiment. Across all trial types, the percentage of errors did not significantly differ between sessions (*plac*=6.3±1.5%, *levo*=5.1±0.7, *sulp*=6.7±1.3, $halo_{2.5}$=6.1±1; $F_{(3,42)}$=0.06, p=0.8, n_p^2=0.03). In addition, post-error RTs were generally slower for all trial types, irrespective of session. However, predictable-expected trials were still faster than predictable-unexpected or unpredictable trials. This suggests that a similar pattern (see below) is observed, albeit the *PC* is less influential. An ANOVArm compared RTs for trials after an error across trial type (predictable-expected, predictable -unexpected, unpredictable) and session (*plac*, *levo*, *sulp*, $halo_{2.5}$). There was a significant main effect of trial type ($F_{(2,28)}$=12.1, p=0.0005, n_p^2=0.46), however the main effect of session ($F_{(3,42)}$=.1, p=0.35, n_p^2=0.07) and interaction were not significant ($F_{(6,84)}$=0.06, p=0.99, n_p^2=0.004). Paired t-tests revealed that predictable-expected trials (6.47 ±0.03 LOG ms) were associated with faster RTs relative to either predictable-unexpected (6.53 ±0.03) or unpredictable trials (6.52 ±0.03), irrespective of session ($t_{(14)}$>3.8, p<0.002).

Reaction time

Participant's RTs were compared across trial type (predictable-expected, predictable-unexpected, unpredictable) and session (*plac*, *levo*, *sulp*, $halo_{2.5}$). There was a significant main effect of trial type (ANOVArm: $F_{(2,28)}$=92, p=0.0005, n_p^2=0.87), session ($F_{(3,42)}$=4.6, p=0.007, n_p^2=0.25) and interaction between trial type and session ($F_{(6,84)}$=3.9, p=0.002, n_p^2=0.22; Figure 2a). Paired t-tests revealed significant differences between each trial type ($t_{(14)}$>6.3, p=0.0005); predictable-expected trials were associated with the

fastest RTs, whereas predictable-unexpected trials led to the slowest RTs (Figure 2a). In addition, there were global differences in RT between sessions. Paired t-tests revealed that *plac* and *levo* were significantly slower than *sulp* and $halo_{2.5}$ ($t_{(14)}$>2.1, p<0.04), irrespective of trial type. However, there were no significant differences between *plac* and *levo* ($t_{(14)}$=1.1, p<0.30) or *sulp* and $halo_{2.5}$ ($t_{(14)}$=0.94, p=0.36).

To account for these global differences and investigate the dynamic changes in RT during the *PC*, we subtracted the average RT for the *UC* from all RTs during the *PC* (ΔRT) (Galea et al., 2012). Participants displayed a selective slowing in RT to unexpected trials during $halo_{2.5}$ (Figure 2b). Participant's ΔRTs were compared across trial type (predictable-expected, predictable-unexpected) and session (*plac*, *levo*, *sulp*, $halo_{2.5}$). There was a significant main effect of trial type (ANOVArm: $F_{(1,14)}$=99, p=0.0005, n_p^2=0.87), session ($F_{(3,42)}$=3.8, p=0.016, n_p^2=0.22) and interaction between trial type and session ($F_{(3,42)}$=3.9, p=0.015, n_p^2=0.22; Figure 2b). There was no significant difference between sessions for expected trials (*plac*=-0.11±0.01 LOG ΔRT), *levo*=-0.11±0.02, *sulp*=-0.12±0.01, $halo_{2.5}$=0.10±0.02; $F_{(3,42)}$=0.05, p 0.98, n_p^2=0.003). In contrast, there was a significant difference for unexpected trials ($F_{(3,42)}$=20.4, p=0.0005, n_p^2=0.59). ΔRT was significantly slower during $halo_{2.5}$ relative to the 3 other sessions ($t_{(14)}$>5.8, p<0.0005).

[Figure 2]

Event-related surprise

To investigate the $halo_{2.5}$ effect on unexpected trials in greater detail, trial-by-trial surprise was used as a proxy for the level of prediction error. We obtained β-values by regressing surprise and post-error trials against RT separately for the *PC* and *UC* within each session. Across all sessions, surprise was associated with slower RTs during the *PC*, as reflected by a larger β-value. Crucially, during the *PC*, this RT deficit to surprise was exacerbated during the $halo_{2.5}$ session (Figure 2c). In contrast, RT was unaffected by post-error trials for the *PC* (*plac*=0.02±0.02 β-value, *levo*=0.02±0.01, *sulp*=-0.02±0.02, $halo_{2.5}$=0.02±0.01) or *UC* (*plac*=-0.02±0.01, *levo*=-0.001±0.03, *sulp*=-0.01±0.01, $halo_{2.5}$=-0.0042±0.02).We tested how RTs were influenced by surprise and post-error by obtaining β-values from trial-by-trial regression analysis. There was a statistically significant difference in β-values between context (*PC,UC*) (MANOVA: $F_{(2,13)}$=87.7, p=0.0005, wilk's ^=0.07, n_p^2=0.1) but not session ($F_{(6,84)}$=2.0, p=0.07, wilk's ^=2.0, n_p^2=0.70). However, the interaction between context and session was significant ($F_{(6,84)}$=2.3, p=0.02, wilk's ^=2.3, n_p^2=0.78). There were no significant differences for the β-values pertaining to post-error trials for session ($F_{(3,42)}$=0.15, p=0.93,n_p^2=0.075), context ($F_{(1,14)}$=3.9, p=0.066, n_p^2=0.46) or interaction between session and context ($F_{(3,42)}$=0.45, p=0.98, n_p^2=0.06). In contrast, there was a significant difference for the β-values relating to surprise between session ($F_{(3,42)}$=4.2, p=0.01,n_p^2=0.83), context ($F_{(1,14)}$=182, p=0.0005, n_p^2=1) and interaction between session and context ($F_{(3,42)}$=4.8, p=0.006, n_p^2=0.88). This was driven by surprise having a significantly larger influence on RT in $halo_{2.5}$ relative to the 3 other sessions specifically during the *PC* ($t_{(14)}$>3.34, p<0.004; Figure 2c).

Model comparison

We assumed that surprise should be estimated for the *PC* and *UC* by separately combining these block types across a session ($model_1$). However this assumption was tested by estimating surprise across all blocks irrespective of its explicit context ($model_2$). For each main drug session (*plac*, *levo*, *sulp*, $halo_{2.5}$), we performed a formal model comparison between these scenarios using Bayesian model selection to detect which model explained a greater amount of the RT variance (Stephan et al., 2009). For all sessions, the exceedance probabilities show that $model_1$ provides the most parsimonious explanation of the data ($model_1$: *plac* =0.71±0.2, *levo=0.73*±0.007, *sulp* =0.73±0.008 $halo_{2.5}$=0.72±0.02). Importantly, this analysis provides credence to our model assumption that participants were able to effectively switch between contexts using the explicit cues provided.

2.5mg vs. 1mg haloperidol

Within a subset of participants, we compared $halo_{2.5}$ and $halo_1$ and found that only the higher dose of haloperidol caused an increased RT impairment to unexpected events during the *PC*. A similar proportion of participants believed that they had taken an active drug during $halo_{2.5}$ (80%) and $halo_1$ (75%), whilst participant's ratings of attention and fatigue were not significantly different ($t_{(7)}<1.5$, $p>0.17$). Participant's RT deficit to unexpected events and surprise during the *PC* was significantly greater in $halo_{2.5}$ relative to $halo_1$ ($t_{(7)}>3.4$, $p<0.01$; Figure 3).

[Figure 3]

Discussion

The present results provide novel evidence of the importance of dopamine for motor flexibility. We show that during a task which used overlearnt probabilistic contexts and signalled changes in these explicitly to remove any potential role of dopamine in probabilistic learning, the dopamine antagonist haloperidol reduced motor flexibility. Specifically, participants were selectively impaired in reacting to unexpected events that elicited large prediction errors and thus required a prepared action to be replaced with an unprepared one. This effect was not observed with specific D2-receptor blockade, a general increase in tonic dopamine levels, or during an overall unpredictable context.

Several lines of evidence have pointed to the importance of dopamine in both motor and cognitive flexibility. For example, dopamine-depleted Parkinson's disease patients display deficits in tasks which examine motor (Cools et al., 1984; Galea et al., 2012) and cognitive flexibility (Cools et al., 2001a), with performance being restored by dopaminergic medication (Cools et al., 2001b; Galea et al., 2012). Previous animal and human work identified a specific role for dopamine D2-receptor signalling in cognitive flexibility (Cools et al., 2007; Haluk and Floresco, 2009). For instance, the D2-agonist bromocriptine reduces the error-cost associated with set-shifting (van Holstein et al., 2011). These results have been explained using the dual-state theory (Durstewitz and Seamans, 2008) in which D2-receptor stimulation favours fast flexible

behavioural switching. However, animal work also shows the importance of D1-receptor signalling (Ragozzino, 2002; Floresco et al., 2006), with suggestions that cognitive flexibility relies on a cooperative interaction of both D1 and D2 receptors (Floresco, 2013). Yet in humans there is a paucity of attempts to isolate the relative importance of D1- and D2-receptors for behavioural switching. We propose that the current results could be explained by a specific D1- or a D1/D2-receptor combination account. Neither sulpiride nor low-dose haloperidol had an effect on motor flexibility, which suggests that D2-receptor inhibition alone is not sufficient to impair motor flexibility. By contrast, high-dose haloperidol which blocks both D1- and D2-receptors did impair this ability, which suggests that either D1-receptor function or a combination of both D1/D2 receptor signalling is required for efficient motor flexibility. It is important to emphasize that the forthcoming discussion of the dissociable roles of D1- and D2-receptors during motor flexibility must be taken with caution, simply due to the widespread effects these drugs can have both in terms of receptor affinity and their complex effects within different brain regions.

While it is the case that systematic pharmacological manipulations do not allow for direct testing of the involvement of a specific brain area, we believe that a discussion of possible circuit-level mechanisms is warranted. Our previous work (Galea et al., 2012) showed Parkinson's disease patients off dopaminergic medication exhibited a similar impairment in motor flexibility (patients were selectively impaired in reacting to unexpected events that elicited large prediction errors and thus required a prepared action to be replaced with an unprepared one) as observed in the present study with haloperidol. Both results could be explained by the role dopamine plays in facilitating a "focusing function" of the basal ganglia (Mink, 1996; Redgrave et al., 1999b; Cools et al., 2001a; Frank, 2005). Specifically, during behavioural switching, dopamine acting on D1-receptors is thought to exert a "premotor-bias" that promotes the selection of the unprepared action, via the basal ganglia's direct pathway (Gerfen, 1992; Hikosaka and Isoda, 2010). As the basal ganglia appear to be more concerned with switching from an automatic to a more difficult task than vice versa (Cameron et al., 2009), D1-receptor activation could be particularly important in boosting weaker response signals to overcome dominant response signals. This suggests that the relative weighting of these signals would be important in terms of the switching cost associated with D1-receptor blockade. In fact, our results support this view because the deficit observed with haloperidol was highly specific to the unexpectedness (surprise) of the upcoming action.

On a more theoretical level, our results point at a role for dopamine to convey contextual confidence in situations when unexpected sensory information requires fast corrections of the prepotent but incorrect action. Put differently, when participants have strong prior expectations about a given context and the sequence of events therein, dopamine depletion leads to over-reliance on top-down predictions and an inability to react to bottom-up sensory information. First, when a violation occurs in such a situation of strong prior expectation, a low-level sensory prediction error occurs. To respond to this prediction error, one has to reprogram the selected action based on the correct sensory information. It appears as if D1-depletion diminishes the value of this information, which in turn delays motor flexibility because there is a need for a

greater accumulation of sensory information before bottom-up information overcomes the over-reliance on top-down predictions (Friston et al., 2012; Galea et al., 2012). As the sensory prediction error increases with the surprise of the upcoming action, so would the motor flexibility deficit associated with it. Physiologically, this scheme is compatible with the current notion that dopamine bursts in the basal ganglia are not related solely to unexpected rewards but also occur at short latency after any salient event, whether rewarding or not (Redgrave et al., 1999a; Redgrave and Gurney, 2006). For the present results, we propose that such bursts would occur in response to unexpected cues and that the size of the burst would be proportional to the prediction error. Animal experiments show that high levels of dopamine shift striatal neurons into an "up state" in which they respond more readily to corticostriatal inputs (Plotkin et al., 2011). We suggest that this is a way in which the system can highlight the relevance of the cortical inputs that occur during surprising events (Galea et al., 2012).

The brain's sensitivity to prediction errors has been conceptualised through models which implement optimal Bayesian inference (Kording and Wolpert, 2006; Friston et al., 2012; Iglesias et al., 2013). These models assume that the brain continuously updates a hierarchical generative model of its sensory inputs to predict future events and infer on the causal structure of the world. This updating process involves multiple, hierarchically related prediction errors that are weighted by their precision (perceived reliability). The prediction errors concern low-level sensory events as well as their probabilistic associations and how these change in time (Behrens et al., 2007). Interestingly, it has been suggested that brain areas associated with dopamine release are sensitive to low-level prediction errors about stimulus outcome, albeit on indirect grounds (Iglesias et al., 2013). In contrast, brain regions tied to acetylcholine (Ach) release are thought to be sensitive to prediction errors at a high or abstract level regarding stimulus probabilities (Iglesias et al., 2013). More generally, these neuromodulators are proposed to play a role in encoding the precision of these hierarchical prediction errors (Friston et al., 2012). The present study provided participants with two levels of expected uncertainty, in the form of an overall predictable and unpredictable context (Galea et al., 2012). Through the overlearning of stimulus probabilities and providing explicit context feedback, we were able to control for prediction errors associated with estimation and unexpected uncertainty which are linked to high-level volatility and the neuromodulator Ach (Yu and Dayan, 2002, 2005; Behrens et al., 2007; Iglesias et al., 2013). Therefore, participants knew the uncertainty associated with each context (controlling for estimation uncertainty) and which context they were currently experiencing (controlling for unexpected uncertainty). Even under these conditions, there is irreducible low-level stimulus uncertainty because of the probabilistic nature of each context. Consequently, the prediction errors experienced in the predictable context specifically examined the role of dopamine in responding to low-level stimulus prediction errors whose behavioural outcome is termed motor flexibility.

The current results indicate that the blockade of D2-receptor activation is not sufficient in altering motor flexibility. However, why has the apparent importance of D1-receptor activation during behavioural switching not been suggested by previous human work? One explanation is that preceding human work has

focused on D2-receptors (van Holstein et al., 2011; Stelzel et al., 2013). Although it has been shown that bromocriptine alters the neural activity associated with motor flexibility (Stelzel et al., 2013), it had a non-significant effect on behaviour. Therefore, this previous work is in support of our conclusion that inhibition of D2-receptor activity alone does not impair motor flexibility.

A surprising result was the global reduction in reaction times observed in both the haloperidol and sulpiride sessions. Generally, tonic dopamine is thought to enhance behavioural vigour (Niv et al., 2007), so one would expect a relative decrease in reaction time under levodopa, yet an increase in reaction time for dopamine antagonists. We have no definitive theoretical explanation to these findings. It is important to highlight reaction times during the haloperidol and sulpiride sessions were only identical for trials without a prediction error, i.e. all trials except the unexpected trials in a predictable context. In addition, since this effect was observed with sulpiride it can be assumed that it was dependent on D2-receptor signalling. As D2-receptor function is crucial for behavioural exploration (Galea et al., 2013), it is probable that D2-receptor activation would lead to greater competition between alternative actions. For trials without a prediction error, this would provide greater competition from alternative actions during the predictable context and a general increase in competition during the unpredictable context. If the basal ganglia were required to bias selection towards the correct action and away from other response alternatives then such increased competition could slow response times. D2 blockade would hypothetically decrease competition and allow the prepotent and correct response to be expressed at a faster rate.

We observed no behavioural effect with levodopa. This inability to show opponent behavioural results with levodopa and haloperidol are a common experimental finding (Pessiglione et al., 2006; Pine et al., 2010). This may appear at odds with our previous results where levodopa restored motor flexibility in Parkinson's disease patients (Galea et al., 2012). Although levodopa causes an increase in tonic dopamine, we previously suggested that it could restore phasic dopamine function in mild Parkinson's disease patients (Grace, 1991; Galea et al., 2012). Yet, this effect may only occur in clinical populations who have initial low-levels of phasic dopamine function (Grace, 1991). Therefore, in healthy individuals, levodopa might not lead to increased phasic dopamine activity, the mechanism proposed to be crucial for behavioural flexibility (Redgrave et al., 2010). Alternatively the task employed was very simple. Thus, following training, it is likely that participants were at a performance ceiling in terms of their ability to switch behaviours. If this was true then it would not have been possible for levodopa to improve motor flexibility.

Haloperidol not only blocks D1/D2-receptors but also acts as a serotonin and adrenergic receptor antagonist (Kroeze et al., 2003). Our previous results showed that Parkinson's disease patients display an identical motor flexibility deficit as haloperidol (Galea et al., 2012). This result lends additional support for a critical role of dopamine during motor flexibility. Nonetheless, it is possible that the behavioural consequences of haloperidol are a result of its inhibitory effect on any of these neuromodulators. For instance, serotonin plays an important role in cognitive flexibility (Clarke et al., 2004; Clarke et al., 2007) and levels of serotonin are

affected in Parkinson's disease patients (Politis et al., 2012). Therefore, it is feasible that these effects on serotonin contributed to both the haloperidol results reported here and previous patient results (Galea et al., 2012). However, to counter this, the Parkinson's patient's action reprogramming ability improved with levodopa. Whilst levodopa is known to cause dopamine to be released from serotonin terminals, it does not produce serotonin (Carta et al., 2010), thus suggesting that dopamine provided the dominant contribution to our results. Future research could examine the influence of other serotonin and adrenergic antagonists. However, a general caveat of human pharmacology studies is the unspecific nature of many available neuroactive drugs. Thus, we can only speculate that motor flexibility in humans is particularly sensitive to D1-receptor activity.

In conclusion, high-dose haloperidol impairs the ability to react to unexpected events that elicit large prediction errors and thus requires motor flexibility. This effect is not observed with either specific D2-receptor blockade or a general increase in tonic dopamine levels. To reiterate, as this task was overlearnt such effects were independent of the general role of dopamine in learning. We propose that dopamine D1-receptor function or a combination of D1/D2 receptor function could play an important role in responding to low-level prediction errors about stimulus outcome.

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Figure captions

Figure 1: *a. Task. b. Event probability matrices*: Numbers represent transition probabilities. *c. Training: reaction time:* The predictable (red) and unpredictable (blue) contexts were overlearnt during training, with no significant differences between the end of training and placebo. d. *Training: surprise & mutual information:* RT was positively correlated with surprise during the predictable context, whereas RT was negatively correlated with mutual information. In contrast, surprise and mutual information had no effect on RT during the unpredictable context. Error bars indicate standard error.

Figure 2: *a. Reaction time across trial types:* RT (Log msecs) across the predictable: expected, predictable: unexpected and unpredictable trial types for the placebo (black), levodopa (blue), sulpiride (green) and haloperidol$_{2.5}$ (red) sessions. *b. Delta reaction time:* ΔRT (subtracted by RT of unpredictable context) for unexpected events during the predictable context across the 4 main experimental sessions. Halo$_{2.5}$ showed a significant prolongation of RT relative to the 3 other sessions. Black lines indicate significant difference: all $p<0.003$. *c. Surprise:* Halo$_{2.5}$ showed a significantly greater sensitivity to surprising events during the predictable context. Surprise did not influence RT during the unpredictable context. Black lines indicate significant difference: all $p<0.008$. Error bars indicate standard error.

Figure 3: *Predictable context: unexpected event and surprise:* RT deficit to unexpected events during the predictable context was significantly greater during halo$_{2.5}$ (red) relative to halo$_1$ (grey). Similarly, halo$_{2.5}$ showed a significantly greater sensitivity to surprising events during the predictable context. Black lines indicate significant difference: all $p<0.01$. Error bars indicate standard error.

Fig.1

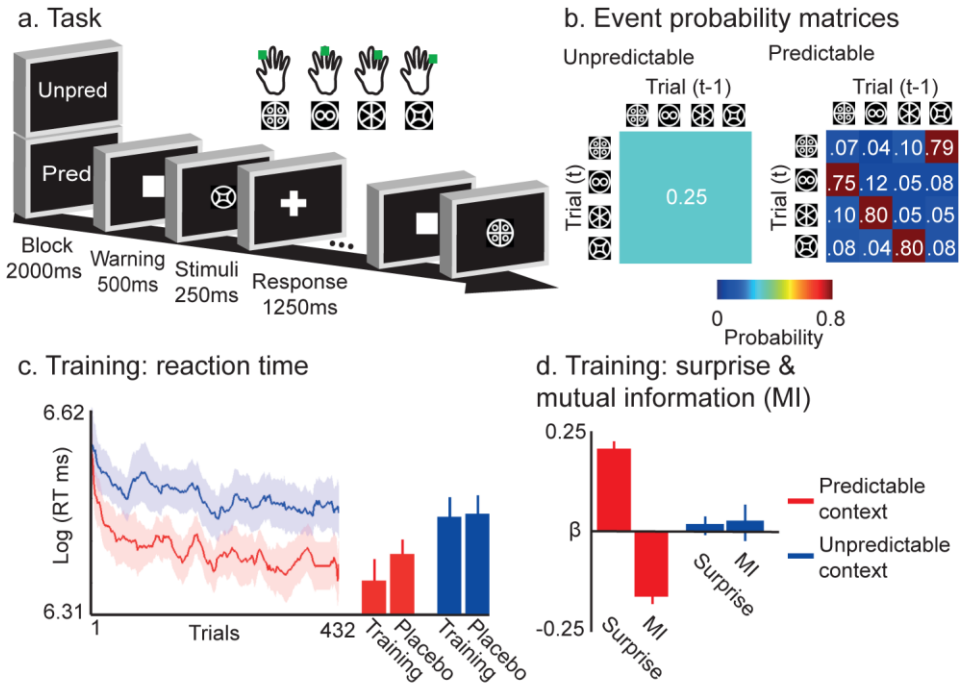
a. Task
Unpred
Pred
Block
2000ms
Warning
500ms
Stimuli
250ms
Response
1250ms
b. Event probability matrices
Unpredictable
Predictable
Trial (t-1)
Trial (t)
0.25
.07 .04 .10 .79
.75 .12 .05 .08
.10 .80 .05 .05
.08 .04 .80 .08
0
0.8
Probability
c. Training: reaction time
6.62
Log (RT ms)
6.31
1
Trials
432
Training
Placebo
Training
Placebo
d. Training: surprise & mutual information (MI)
0.25
β
-0.25
MI
Surprise
MI
Surprise
Predictable context
Unpredictable context

Fig.2

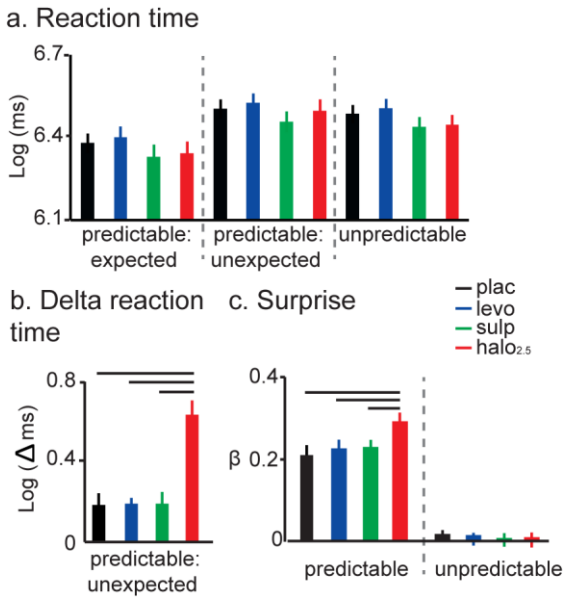
a. Reaction time
6.7
Log (ms)
6.4
6.1
predictable: expected
predictable: unexpected
unpredictable
b. Delta reaction time
c. Surprise
plac
levo
sulp
halo2.5
0.8
Log (Δms)
0.4
0
predictable: unexpected
0.4
β 0.2
0
predictable
unpredictable

Fig.3