The effects of dopaminergic medication on dynamic decision making in Parkinson’s disease

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A R T I C L E   I N F O

Article history:
Received 7 May 2013
Received in revised form 11 October 2013
Accepted 29 October 2013
Available online 19 November 2013

Keywords:
Prediction
Intervention
dynamic decision making
Dopamine overdosing hypothesis
Learning

A B S T R A C T

In the present study we address the following questions: (1) How is performance affected when patients with Parkinson’s Disease (PD) perform a dynamic decision making task? (2) Does dopaminergic medication differentially affect dynamic decision making? To address these questions participants were trained with different goals during learning: either they made intervention-based decisions or prediction-based decisions during learning. The findings show that overall there is an advantage for those trained to intervene over those trained to predict. In addition, the results are the first demonstration that PD patients ‘ON’ (N=20) compared to ‘OFF’ L-Dopa (N=15) medication and also relative to healthy age matched controls (N=16) showed lower levels of relative improvement in the accuracy of their decisions in a dynamic decision making task, and tended to use sub-optimal strategies. These findings provide support for the ‘Dopamine Overdose’ hypothesis using a novel decision making task, and suggest that executive functions such as decision making can be adversely affected by dopaminergic medication in PD.

1. Introduction

Everyday decision making is rarely ever restricted to one-shot situations. In fact, usually, people are required to make multiple decisions, repeatedly over time, and in the face of changing circumstances (e.g., deciding to invest money during unstable financial conditions). One empirical approach that has been used to investigate this kind of probabilistic sequential decision making, referred to as dynamic decision making (Brehmer, 1992; Osman, 2008, 2012; Witt et al., 2006). This is based on the common findings that knowledge acquisition is implicit since verbal reports are dissociated from decision-making performance, and because knowledge transfer from learning to test is restricted to trained goals only (Berry & Broadbent, 1984, 1988). Accuracy in maintaining the dynamic outcome to trained and untrained goals indicates the flexibility of knowledge gained, and indicates the success of making multiple repeated decisions in a task in which the outcome can change as a direct result of an action taken, as well as independently of actions taken (i.e., autonomously).

Many have speculated that procedural learning is necessary for this kind of decision making (Brehmer, 1992; Berry & Broadbent, 1984, 1988; Witt et al., 2006). This is based on the common findings that knowledge acquisition is implicit since verbal reports are dissociated from decision-making performance, and because knowledge transfer from learning to test is restricted to trained goals only (Berry & Broadbent, 1984, 1988). However, the view that dynamic decision making tasks are performed by implicit procedural learning processes has been challenged in recent studies

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showing that performance at test is unaffected by training procedures that are declarative (Prediction-based decision making) or procedural (Intervention-based decision making) (Osman, 2008, 2012; Osman & Speekenbrink, 2012).

Patient studies present important insights into the underlying mechanisms implicated in dynamic decision making, in particular studies involving patients with Parkinson’s disease (hereafter PD) who have motor and cognitive deficits associated with dopamine depletion in the basal ganglia. Empirical work has reliably shown that patients with PD are impaired at implicit procedural learning tasks (for a review see Siegert, Taylor, Weatherall, & Abernethy, 2006). However, in the few studies examining dynamic decision making using the procedures described, patients with PD show no impairments in performance when compared with healthy age matched controls (Osman et al., 2008; Witt et al., 2006). This is noteworthy given that the patients in these studies were receiving dopaminergic medication when performing the decision making task. There are paradoxical findings concerning the effect of dopaminergic medication such as Levodopa (L-dopa) in patients with PD. One might predict that increasing dopamine levels in depleted areas of the brain would lead to improved performance in procedural-learning tasks. However, findings suggest that increasing dopamine levels through medication adversely affects a range of decision making and learning behaviors which is explained by the ‘dopamine overdose’ hypothesis (Cools, Barker, Sahakian, & Robbins, 2001; Jahanshahi, Wilkinson, Gahir, Dharmandir, & Lagnado, 2010; Torta, Castelli, Zibetti, Lopiano, & Geminiani, 2009). While, in the early stages of PD, L-dopa improves impaired motor and cognitive functions associated with brain areas which have depleted levels of dopamine (e.g., putamen and dorsal caudate), it also increases dopamine levels in brain areas that are relatively unaffected in the early stages of PD (e.g., ventral striatum and prefrontal cortex, the latter areas considered to be involved in processing probabilistic cue Van Veen, Krug, & Carter, 2008). The resulting dopamine overdose impairs learning in PD patients tested ON medication (e.g., Cools et al., 2001; G Jahanshahi et al., 2010).

There is some indication that dopaminergic medication affects dynamic decision making. Rutledge et al. (2009) found that in a simple dynamic decision making task PD patients ON medication were impaired relative to those OFF medication. However, these findings were largely driven by differences in responses to different types of feedback introduced in the task design (explicit positive and negative feedback). In addition the dynamic task used by Rutledge et al. (2009) is not directly comparable to those of Osman et al. (2008) and Witt et al. (2006) in which patients were required to control an outcome to a specific goal on each trial. Thus, given the differences in the type of tasks and form of feedback used it is hard to draw any general conclusions about the kinds of dynamic decision-making impairments expected in PD while ON or OFF medication.

1.1. Present study

In the present study we aim to address the following questions: (1) How does PD affect performance in a dynamic decision making task? (2) Does dopaminergic medication differentially affect dynamic decision making? To address both questions, we presented patients with PD (both ON and OFF dopaminergic medication and healthy controls (HC) with two different training versions of the same dynamic decision-making task. In one version, participants were required to learn the probabilistic cue-outcome associations from trial to trial by using the cue values to predict the outcome value (prediction-based learners). The other version used the same cue-outcome task structure but instead, participants were required to reach and maintain a target outcome value through intervention by setting the cue values (intervention-based learners). To examine the effects of the different modes of learning on the flexibility and accuracy of knowledge of the underlying relationship between actions (cues) and outcomes, all participants were subsequently presented with tests of both intervention-based and prediction-based decision making.

2. Materials and methods

2.1. Participants

54 volunteers were recruited in total: 35 patients with the diagnosis of idiopathic Parkinson’s disease (20 ON medication, 15 OFF medication) and 19 age-matched healthy controls (HC). Demographic information for patients and HC, along with clinical characteristics of the patients, is summarized in Table 1. Patients were recruited from the National Hospital for Neurology and Neurosurgery. All were diagnosed as having idiopathic PD according to the UK Parkinson’s Disease Brain Bank criteria. The mean age of patients was M=67.90, SD=6.57, and mean disease duration was M=12.88 (SD=7.24, range 2–28 years). Stage of illness and disability were respectively assessed using two standardized scales: Hoehn and Yahr scale and Schwab and England Activities of Daily Living scale. All patients were in the mild to moderate stages of the disease, and reported moderate disability. Mean scores for the Hoehn and Yahr and Schwab and England scales for PD patients ON and OFF groups are provided in Table 1. Patients were non-demented, as demonstrated by the scores <26 on the Mini-Mental State Examination (MMSE). We used the Beck Depression Inventory-II (BDI-II), which has been validated as a screening tool for depression in PD (Visser, Leentjens, Marinus, Stiggelbout, & Van Hulven, 2006; Schrag et al., 2007). One patient reported moderate depression (scores >18), but was not on anti-depressants and their hospital records did not indicate a clinical diagnosis of depression. Therefore, on this basis they were included in the final analyses.

Twenty PD patients were tested while ON dopaminergic medication, 10 of whom were semi-randomly allocated to the Intervention-based decision-making condition (Interveners), and 10 were allocated to the Prediction-based learning condition (Predictors). 15 PD patients were examined while OFF dopaminergic medication, 7 were randomly allocated to be Predictors, and 8 were allocated to be Interveners. PD patients OFF medication had overnight withdrawal of medication.

Table 1

<table>
<thead>
<tr>
<th>PD patients ON medication (n=20, female=7)</th>
<th>PD patients OFF Medication (n=15, female=6)</th>
<th>Healthy controls (n=19, female=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
<td>68.07</td>
<td>7.06</td>
<td>69.85</td>
</tr>
<tr>
<td>Education</td>
<td>12.92</td>
<td>3.14</td>
<td>13.55</td>
</tr>
<tr>
<td>NART estimate of premorbid IQ</td>
<td>115.11</td>
<td>6.55</td>
<td>121.50</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.77</td>
<td>1.59</td>
<td>26.93</td>
</tr>
<tr>
<td>BDI-II</td>
<td>12.84</td>
<td>5.99</td>
<td>11.10</td>
</tr>
<tr>
<td>Disease duration</td>
<td>11.61</td>
<td>7.87</td>
<td>10.57</td>
</tr>
<tr>
<td>LEDD in milligrams (mg)</td>
<td>699.35</td>
<td>263.42</td>
<td>584.62</td>
</tr>
</tbody>
</table>

NART: National Adult Reading Test, MMSE: Mini Mental state Examination, BDI-II: Beck Depression Inventory, LEDD: Levodopa Equivalent Daily Dose.
analyses reported in the main text. All analyses were also conducted with these.

are not considered healthy within the typical bounds of studies in which patient

cut off, we considered it best to exclude them from the

two of the HCs scored below the cut-off on MMSE, and one scored above the BDI

were randomly allocated to be Interveners, and 8 were allocated to be Predictors.

were recruited for the study. None of the HCs had a history of neurological or physical or psychiatric illness, head injury or drug or alcohol abuse. All participants completed the BDI-II and the MMSE. Two of the age matched

controls scored below the cutoff on the MMSE. One participant scored above the

cutoff of 18 on the BDI-II, suggesting moderate self-reported depression. Eight HCs

were randomly allocated to be Interveners, and 8 were allocated to be Predictors.

In total 3 HC participants did not meet the criteria for MMSE or BDI. Because

two of the HCs scored below the cut-off on MMSE, and one scored above the BDI

were excluded from the analyses reported in the main text. All analyses were also conducted with these participants included, and none of the findings we report significantly altered as a result of exclusion of these participants.

2.2. Procedure

The study involved a yoking design. A participant in the Predictor group was

yoked to the immediately preceding participant in the Intervener group. The procedure involved allocating the first participant in the study to the Intervener group, and the next participant to the Predictor group. This allocation was repeated throughout the experiment in order to maintain the yoking design.

The experiment had ethical approval from the Joint Ethics Committee of the Institute of Neurology and The National Hospital for Neurology and Neurosurgery. Informed consent was obtained from all participants. Participants received 30 British pounds ($15.40 approx) for each hour of the study.

2.3. Behavioral tasks

The visual layout of the screen, cover story, and the main instructions were identical for Predictors and Interveners (see Fig. 1). Participants were presented with a story about a newly developed incubator designed especially for babies with an irregular state of health (a global measure based on heart rate, temperature, blood pressure). Interveners were informed that as a trainee maternity nurse they

would be operating a simulator in which they would try to regulate the conditions of the incubator to maintain a healthy stable state of a new born baby. The simulator was operated by varying three cue values (air pressure, oxygen, and humidity) which would affect the baby’s state of health (outcome). Predictors received essentially the same information, but were told that they would see the nurse regulating the incubator parameters and that their role would be to predict the subsequent change in a global measure of health.

for a mean of 16.17 h (SD = 3.37). The majority of PD patients were on levodopa or other dopaminergic medication, and/or anticholinergics. The levodopa equivalent daily dose (LEDĐ; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007) is presented in Table 1. When comparing PD patients ON medication with PD patients OFF medication, there were differences based on LEDĐ (see Table 1) suggesting that PD patients ON medication were receiving a higher dosage of dopamine than those OFF medication.

19 twenty healthy volunteers (HCs, 10 female) aged between 61 and 75 (M = 68.22, SD = 6.01) were recruited for the study. None of the HCs had a history of neurological or physical or psychiatric illness, head injury or drug or alcohol abuse. All participants completed the BDI-II and the MMSE. Two of the age matched

controls scored below the cutoff on the MMSE. One participant scored above the

cutoff of 18 on the BDI-II, suggesting moderate self-reported depression. Eight HCs

were randomly allocated to be Interveners, and 8 were allocated to be Predictors.

In total 3 HC participants did not meet the criteria for MMSE or BDI. Because

two of the HCs scored below the cut-off on MMSE, and one scored above the BDI

cut off, we considered it best to exclude them from the final analyses because they are not considered healthy within the typical bounds of studies in which patient comparisons are conducted. Therefore, these participants were excluded from the analyses reported in the main text. All analyses were also conducted with these participants included, and none of the findings we report significantly altered as a result of exclusion of these participants.

The cues varied in their relation to the outcome in the following ways: one was positively associated, the other negatively associated, and a third (null cue) was unrelated to the outcome. More formally, the structure of the system can be expressed in the following equation:

\[ y(t) = y(t-1) + 0.65x_1(t) - 0.65x_2(t) + e(t) \]

where \( y(t) \) is the outcome value on the current trial, \( e(t) \) the outcome value on the previous trial, \( x_1(t) \) the current value of the positive cue, \( x_2(t) \) the current value of the negative cue, and \( e(t) \) a random perturbation term which is normally distributed with a mean of 0 and a standard deviation of 8. The placement of the three cues on the screen was randomized for each participant.

The screen included three labeled cues and the outcome which was presented in two ways, as a value in the middle right of the screen, and also on a progress screen in which a short trial history (5 trials long) was displayed (See Fig. 1). Both Predictor and Intervener groups were shown the current state of health, new value of the state of health after manipulation and the target value of the healthy state. Predictors were also shown their prediction of the result in the form of a dashed line on the progress screen. The task was self-paced and patients instructed the experimenter to select the values of either outcome (prediction tasks) or cues (intervention task) they wanted changed for each learning and test trial. The entire task included a total of 112 trials, divided into a learning phase (40 trials) and a test phase consisting of two tests of intervention (20 trials each) interleaved with two tests of prediction (16 trials each).

2.3.1. Learning phase

Interveners: during each trial participants had to interact with the system by changing the value of the cues using a slider corresponding to each of them. Each slider had a scale that ranged from 0 to 100. On the start trial, the cue values were set to ’0’, the outcome value was set to 178, the target value was 62 throughout, and a safe range (± 10 of the target value) was given. When participants made their decision they clicked a button labeled ‘Submit’ which deactivated the cues and revealed on the progress screen the effects of their decisions on the outcome. The effects on the outcome value were cumulative from one trial to the next, and so while the cue values were returned to ‘0’ on
the next trial, the outcome value was retained from the previous trial. After completing the learning phase, participants then proceeded to the test phase. Predictors: the procedure was identical to Interveners, with the following exceptions. Once presented with the cue values, they predicted the outcome value by adjusting a slider that was placed alongside the outcome progress screen; this would move a line on the progress screen to indicate the outcome value. Once they made their decision, they clicked a button labeled ‘Submit’, which deactivated the outcome value slider and revealed the actual outcome value as well as their predicted outcome value. The button ‘Continue’ was then pressed to proceed to the next trial. The start of the next trial triggered the outcome value slider to become activated and the presentation of new cue values. The predicted value of the previous trial was omitted from the progress screen, but the trial history of the last five actual outcome values remained.

2.3.2. Test phase

After the learning phase, all participants were examined on a system in which the outcome was designed to achieve and maintain a specific criterion (outcome value \( \pm 62 \), and safe range \( \pm 10 \) of the target value). Intervention Test 1 involved the same procedure that the Interveners were following during the learning phase, but consisted of only 20 trials. For the Predictors this was the first occasion on which they could manipulate the cues. To examine the ability to control the system to a different goal, all participants were then presented with Intervention Test 2 in which they followed the same procedure as Intervention Test 1, with the following exceptions. In the Intervention Test 2 participants were informed that they needed to be even more careful in reaching and maintaining the outcome value (outcome value \( \pm 74 \)), and that staying within the safe range (\( \pm 5 \) of the target value) was of particular importance. The starting value was set to 156 in Intervention Test 2. In Intervention Test 2 Interveners and Predictors had no experience of the new criterion value, and so they would have to base their decisions on acquired knowledge of the system in order to control the new outcome value.

Predictive tests were designed to examine cue-outcome knowledge. No feedback was presented in either set of predictive tests. Each test included 16 trials, which were divided up in the following way. Participants were required to predict the value of a cue (positive, negative, null) based on the given values of the outcome and the other cues (e.g., predicting the positive cue value, based on the values of the negative, null and outcome values), or they were required to predict the outcome value given the value of the other three cues. Participants were not told that the test involved a mixture of 8 old trials and 8 new trials. Old trials were divided accordingly: 2 \times positive cue value, 2 \times negative cue value, 2 \times null cue value, 2 \times outcome value. These trials were randomly selected from the initial learning phase (for Interveners these were trials that they had generated themselves, for Predictors these were the same yoked learning trials in which they predicted the outcome value). The 8 new trials were divided in the same way as the old trials, but these trials were predetermined prior to the experiment and neither group had prior experience of them.

2.3.3. Dependent measures

Prediction performance was measured by an error score \( S_p(t) \) calculated as the absolute difference between predicted and expected outcome values:

\[
S_p(t) = |P(t) - y(t)| = |0.65 \times p(t) - 0.65 \times y(t)|,
\]

in which \( P(t) \) is a participant’s prediction on trial \( t \). We chose to compare predictions to expected rather than actual outcomes as the latter are subject to random noise.

Intervention performance was measured as the absolute difference between the expected achieved and best possible outcome:

\[
S_e(t) = |G(t) - y(t)| = |0.65 \times p(t) - 0.65 \times y(t)|,
\]

in which \( G(t) \) is the goal on trial \( t \): either the target outcome if achievable on that trial, or the closest achievable outcome.

Cue manipulation behavior was based on calculating the proportion of occasions across all training trials that each of the three cues was manipulated. The strategies that were identified during tests of intervention were based on calculating for participant the proportion of trials across blocks of each test in which a cue was changed (No-Cue Manipulation), one cue was changed (Manipulating-One-Cue), two cues were changed (Manipulating-Two-Cues), and all three cues were changed (Manipulating-All-Cues).

3. Results

3.1. Group differences in MMSE and BDI

To begin with, we conducted analyses to examine sub-group differences in IQ, Sex, MMSE, BDI, Hoehn and Yahr, and education. We found no significant results in any of the demographics or cognitive/behavioral measures. However, given that there were group differences based on IQ (See Table 1) we carried out ANOVAs on participants matched on IQ, and compared performance on three main task measures (performance during the learning phase averaged across all trials, and two measure of performance during the test phase, again averaged over all trials for each test of intervention, and averaged over all cues for predictive tests). The number of participants entered into the analyses makes it difficult to draw strong inferences, but does enable some insights into the pattern of results if IQ is matched (PD patients ON = Interveners = 4, Predictors = 5, PD patients OFF = Interveners = 5, Predictors = 2, HC = Interveners = 4, Predictors = 5). There were no significant group differences in learning performance for either Interveners or Predictors. There were also no differences based on condition or group in measures of performance for tests of intervention or tests of prediction (\( p > 0.3 \)).

Thereafter, we conducted additional ANCOVAs examining differences between the groups (IV) using MMSE and BDI as covariates (see Table 1), again we found no significant differences (\( p > 0.3 \)) against our three main task measures (Learning performance, Test of Intervention, Tests of Prediction).

3.2. Test phase

Direct comparisons between learning conditions could not be conducted as the error scores were incomparable (one based on the difference between achieved and best possible outcome value, and the other between predicted and expected outcome value). We therefore focus our analyses on the test phase, which was the first occasion in which both conditions were directly assessed for their ability to reach and maintain the outcome to a specific criterion (Tests of Intervention), and their ability to predict cue values from the state of the outcome, or predict the outcome from the pattern of cue values (Tests of Prediction).
3.2.1. Performance on tests of intervention

Intervention optimality scores were averaged across participants in each group for each of the two Tests of Intervention the Outcome and are presented in Fig. 2. An ANOVA with Condition (Interveners, Predictors), Group (PD patients ON, PD patients OFF, HC), and Test (Intervention Test 1, Intervention Test 2) as factors was conducted. Generally, all participants improved in their ability to control the outcome in Intervention Test 2 compared to Intervention Test 1, suggesting the presence of practice effects, as revealed in a main effect of Test, \(F_{(1,39)}=13.58; p=0.001, \eta=0.25\). There was no Test \(
\times\) Condition interaction \(F_{(5,39)}=2.41; p=0.12, \eta=0.05\). There was a significant Group effect \(F_{(5,39)}=3.69; p=0.01, \eta=0.32\). Planned comparisons indicated that PD patients ON medication showed poorer performance compared with PD patients OFF medication \(t(33)=2.83, p<0.005\), and when compared with HCs \(t(34)=2.59, p<0.05\). There was no difference in performance between PDs OFF medication and HCs \(t(29)=0.36, p>0.05\). There was also a significant Group \(
\times\) Test interaction \(F_{(6,117)}=5.64; p=0.01, \eta=0.19\). Planned comparisons showed that the improvement in performance from Test 1 to Test 2 was significantly smaller for PD patients ON compared to PD patients OFF and HCs \(F_{(1,50)}=2.74; p=0.03, \eta=0.26\). This performance improvement did not differ between PD patients OFF and Healthy Controls \(F_{(1,50)}=1.88; p=0.20, \eta=0.03\).

Cue manipulation behavior in Intervention Test 1 and Test 2 (see Fig. 3) was examined in of all three groups. There was a main effect of Cue-manipulation \(F_{(3,117)}=30.92; p<0.0005, \eta=0.42\), and a Group \(
\times\) Cue-manipulation interaction \(F_{(6,117)}=11.05; p<0.0005, \eta=0.58\). There was a group difference based on the proportion of test trials in which all cues were varied, \(F_{(1,50)}=21.39; p<0.0005, \eta=0.48\). Post-hoc tests revealed that PD patients ON medication opted to change all cues on more trials during test than HCs \(p=0.001\) and PD patients OFF medication \(p=0.002\). There was also a group difference based on the proportion of test trials in which only a single cue was varied, \(F_{(2,50)}=14.29; p<0.0005, \eta=0.34\). PD patients OFF medication tended to manipulate one cue more often than PD patients ON medication \(p=0.001\), and HCs \(p=0.005\). No other analyses approached significance.

The same set of analyses was conducted for Test 2, and revealed a similar pattern to Test 1 behavior. There was a main effect of Cue-manipulation \(F_{(1,317)}=40.07; p<0.0005, \eta=0.50\), and a Group \(
\times\) Cue-manipulation interaction \(F_{(6,317)}=9.47; p<0.0005, \eta=0.54\). There was a group difference based on the proportion of test trials in which all cues were varied, \(F_{(2,50)}=18.02; p<0.0005, \eta=0.41\). Post-Hoc Tests revealed that PD patients ON medication opted to change all cues on more trials during test than HCs \(p=0.005\) and PD patients OFF medication \(p=0.005\). There was also a group difference based on the proportion of test trials in which only a single cue was varied, \(F_{(2,50)}=11.37; p<0.005, \eta=0.30\). PD patients OFF medication tended to manipulate one cue more often than PD patients ON medication \(p=0.01\), and HCs \(p=0.005\). No other analyses approached significance.

3.2.2. Performance on tests of prediction

In Prediction tests all participants were required to predict values of the different variables. Thus, tests of prediction of the variables of interest (Positive, Negative, Outcome) provided the first opportunity to examine the accuracy of cue-outcome knowledge of the Interveners.
and Predictors. Prediction optimality scores for Test 1 and Test 2 are presented in Fig. 4. We collapsed across scores for the Tests, since an ANOVA with Test (Predictive Test 1, Predictive Test 2) Condition (Interveners, Predictors) Group (PD patients ON, PD patients OFF, HC) failed to show any differences in patterns of predictive accuracy. Therefore, we focus on overall performance in predictive accuracy using Type of Cue (Positive, Negative, Outcome), Familiarity of Trial (Old trials New trials), Condition (Interveners vs Predictors) and Group (PD patients ON, PD patients OFF, HC) as factors in an ANOVA. A main effect of Type of Cue $F(2,90) = 30.77; p = 0.001, \eta = 0.36$ was significant. Further analysis showed that predictions of the outcome were more accurate than predictions of the positive cue $t(48) = 10.97, p < 0.0001$ and the negative cue $t(48) = 9.80, p < 0.0005$. There were no differences in predictive accuracy between the positive and negative cues. There was a main effect of Familiarity of Trial suggesting that accuracy was greater for old trials compared to new trials $F(1,47) = 132.32; p = 0.0001, \eta = 0.78$. There was also a significant Type of Cue x Familiarity of Trial interaction, $F(2,90) = 33.94; p = 0.005, \eta = 0.41$, which was further examined. Analyses revealed that predictions were more accurate for old compared to new trials for the positive cue $t(100) = 10.38, p < 0.0001$, the negative cue $t(100) = 12.08, p < 0.0001$, and the outcome $t(100) = 2.91, p < 0.01$.

4. General discussion

To date, there has been no empirical study that has examined the effects of dopaminergic medication on dynamic decision making in patients with dopamine deficiency. In the present study, consistent with previous findings (Osman, 2008, 2012; Osman & Speekenbrink, 2012), there was no effect of training type (intervention- or prediction-based) on performance in test of Prediction and Intervention. This suggests that training in a dynamic decision making task via declarative or procedural-based methods does not differentially impact later performance on tests of intervention and prediction. This also suggests that procedural learning processes are not a necessary, but a sufficient basis for acquiring relevant knowledge that can successfully be transferred to a variety of different tests.

This study is the first of its kind to investigate the impact PD and dopaminergic medication on decision making by comparing patients with PD ON vs. OFF dopaminergic medication and HCs. We conducted several analyses to examine group differences in performance on various measures based on Age, Sex, Education, MMSE, depression and staging of disease, dosage, and found no differences between the groups. However, while we did not find group differences based on MMSE, which is a coarser measure of IQ, there were group differences based on the NART measure of premorbid IQ (see Table 1) which should be taken into consideration. As a result we conducted analyses to rule out the possibility that IQ contributed to the pattern of results, given the number of participants in the sub-set entered into the analyses, it is still unclear whether or not IQ impacted performance in the experiment. There were also differences between the two groups based on LEDD (see Table 1), indicating that PD patients ON medication normally received a higher dosage of dopamine than those OFF.
medicated PD patients (Dagher & Robbins, 2009), could explain that risk taking behavior, which is commonly associated with Osman & Speekenbrink, 2011). Though speculative, it is possible the outcome value, leading them to perceive the environment as salient feature of the task used here, it may be the case that PD patients ON medication tend to show hypersensitivity to novel outcomes (Bodi et al., 2009). However, when novelty is experienced in highly predictable environments, PD patients OFF medication show greater surprise PD patients ON medication (Galea, Bestmann, Beigi, Jahanshahi, & Rothwell, 2012).

In more noisy dynamic decision making environments, increased sensitivity to surprise may result in an enlarged error signal, which may impair learning stable cue-outcome relations, which can explain poorer performance while on medication. In fact, PD patients ON medication show more random guessing early in the cue-outcome learning tasks (Speekenbrink, Lagnado, Wilkinson, Jahanshahi, & Shanks, 2010), and take considerably longer to switch to strategies that enable them to better track cue-outcome associations over trials (Jahanshahi et al., 2010; Speekenbrink et al., 2010). To fully test this, future studies could examine dynamic decision making tasks in which training in the first part of the task would follow a discrete trial structure. What this means is that the effects on the outcome generated on each trial would not carry over from trial to trial, as they do in the DDM task used presently. More specifically randomizing the learning trials could involve randomizing the starting value ($\beta(\tau - 1)$) on each trial. If cumulative experiences of receiving feedback on one’s decision making benefits incremental cue-outcome learning processes, then preventing this through a randomization process as described, should impair the accuracy of intervention-based decisions and prediction-based decisions.

While departing from the pattern of findings reported in previous studies in terms of intervention performance, the present study produced findings consistent with prior studies suggesting that PD patients tested ON medication are unimpaired in tests of prediction (Osman et al., 2008). Moreover, the procedures used to measure predictive performance were similar in the present study to Osman et al. (2008) study. However, this pattern of results contrasts with many reported studies (see Table 2). For instance, Shohamy, Myers, Geggman, Sage, and Gluck (2006) reported that PD patients ON medication showed later success in transferring their cue-outcome knowledge to a novel version of a discrimination task, but were initially impaired during the early acquisition of cue-outcome knowledge. The critical difference between learning and transfer were the actual stimulus sets used. They proposed that PD patients ON medication show impaired cue-outcome knowledge because this is associated with concurrent-feedback based processing during learning, which does not necessarily impede the implementation of knowledge in later transfer tests. To explain this, they distinguished between the cortico–striatal system associated with incremental, stimulus–response learning, and the hippocampal system associated with the formation of rule-like flexible, stimulus–stimulus representations (e.g., Poldrack et al., 2001; Shohamy et al., 2004). Thus, the different stages

<table>
<thead>
<tr>
<th>Type of cue-outcome learning task</th>
<th>Findings</th>
<th>Type of feedback</th>
<th>Type of task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jahanshahi et al. (2010) Weather prediction</td>
<td>PD ON L-Dopa are impaired relative to HC</td>
<td>Discrete feedback</td>
<td>Static</td>
</tr>
<tr>
<td>Rutledge et al. (2009) Dynamic foraging</td>
<td>PD ON L-Dopa are impaired relative to HC</td>
<td>Discrete feedback</td>
<td>Cumulative change</td>
</tr>
<tr>
<td>Mimura, Oeda, and Kawamura (2006) Iowa gambling</td>
<td>PD ON L-Dopa are impaired relative to HC</td>
<td>Discrete feedback</td>
<td>Static</td>
</tr>
<tr>
<td>Coul, Altamirano, and D’Esposito (2006) Probabilistic Reversal</td>
<td>PD ON L-Dopa are impaired relevant to HC and PDs OFF L-Dopa</td>
<td>Discrete feedback</td>
<td>Static</td>
</tr>
<tr>
<td>Witt et al. (2006) Visual Discrimination Task</td>
<td>PD ON L-Dopa are unimpaired relative to HC</td>
<td>Cumulative outcome feedback</td>
<td>Cumulative change</td>
</tr>
<tr>
<td>Osman et al. (2008) Dynamic decision making – Control task</td>
<td>Dynamic decision making – Control task</td>
<td>Cumulative outcome feedback</td>
<td>Cumulative change</td>
</tr>
<tr>
<td></td>
<td>PD ON L-Dopa are unimpaired relative to HC</td>
<td>Cumulative outcome feedback</td>
<td>Cumulative change</td>
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</tbody>
</table>

One potential reason for this difference is that in the present study in the dynamic decision making tasks outcome feedback was presented in the form of a progress bar which revealed the fluctuations of the outcome value against the target value (see Fig. 1), and in the previous studies (Osman et al., 2008; Witt et al., 2006) this type of visualization of the outcome value was not used. Given that the visualization of the fluctuating outcome was a salient feature of the task used here, it may be the case that PD patients ON medication became hypersensitive to fluctuations in the outcome value, leading them to perceive the environment as more unstable than it actually was. The more unstable the dynamic environment, the more people tend to intervene on all the cues, which makes cue-outcome relations harder to detect (Osman & Speekenbrink, 2011). Though speculative, it is possible that risk taking behavior, which is commonly associated with medicated PD patients (Dagher & Robbins, 2009), could explain the hyper-sensitivity to the probabilistic task structure and the type of cue manipulation strategy favoured by PD patients ON medication in our study. In addition, PD patients ON medication tend to show hypersensitivity to novel outcomes (Bodi et al., 2009), which is not evident when tested OFF medication.

6 One aspect of these findings that we should draw attention to is that, given our yoking design, PD prediction-learners ON medication were estimating outcome values based on the trial history of PD choice-learners ON medication (same with the conditions OFF medication). When both groups were controlling the outcome, their pattern of cue manipulations were the same, suggesting that observers learned not only about cue-outcome relations, but also ways in which to control the outcome through observed cue manipulations.

Table 2 Main features of cue-outcome learning/decision making tasks that have reported evidence of impaired and unimpaired performance in patients with Parkinson’s Disease (PD) on dopaminergic medication.
(i.e. learning versus transfer) of their discrimination task were proposed to recruit these different brain systems, which were in turn differentially affected by L-dopa. In contrast to Shohamy et al.'s (2006) task, not only did training and transfer in the present study according to the stimuli used, but also participants' experiences of transfer tests were markedly different from their learning experiences; in particular, the predictive tests involved making predictions for trials taken out of their natural sequential order, in which no feedback was presented. Nevertheless, there was reliable evidence of transfer of knowledge regardless of the medication manipulation, and regardless of the specific type of experience during learning.

Rather than appealing to distinct brain systems that support different representations at different stages of learning and test, we propose that both interveners and predictors are required to different representations at different stages of learning and test, building on the work of Berry and Broadbent (1984) and the relationship between task structure and error-corrective processes. However, as we have outlined, the task structure may be flexible rule-based knowledge (Osman, 2010a, b). This knowledge can be used to control an outcome to an untrained criterion (Test Phase – Intervention Test 2) and to predict cue values from an outcome value, and an outcome value from cue values (Test Phase – Predictive Tests 1 and 2). Midbrain regions may still be needed in order to perform these tasks, because cue-outcome learning in the task is incremental, and also involves error-corrective processing. However, as we have outlined, the task structure may facilitate incremental cue-outcome learning because the effects of cue manipulation on the outcome, and the accuracy when predicting the outcome were experienced cumulatively. This type of task structure may facilitate incremental learning via the continuous updating of the representation of the effect of actions on the outcome.

5. Conclusion

The present study was the first to examine dynamic decision making in PD patients both ON and OFF dopaminergic medication. There were greater relative improvements in performance on tests of intervention in PD patients OFF medication compared to PD patients ON medication. In addition cue manipulation strategies were more successful for PD patients OFF than PD patients ON medication. To this end, we add to the growing literature suggesting that there are cognitive deficits as a result of dopaminergic medication, which lends further support to the Dopamine Overdose Hypothesis. We propose that learning in dynamic decision-making tasks relies on error correction processes which are encoded by phasic changes in dopamine levels. It may be the case that this encoding mechanism is disrupted by medication in patients with PD.

References