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

Magda Osman [a,b,e,*], Agata Ryterska [a,b,1], Kash Karimi [b], LingLing Tu [c,2], Ignacio Obeso [d,3], Maarten Speekenbrink [e,4], Marjan Jahanshahi [b]

[a] Biological and Experimental Psychology, School of Biological and Chemical Sciences, Queen Mary University of London, Mile End Road, London E1 4NS, United Kingdom
[b] Sobell Department of Motor Neuroscience and Movement Disorders, The National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, 33 Queen Square, London WC1N 3 BG, United Kingdom
[c] Department of Psychiatry, Sir Run Run Shaw Hospital, 3 East Qingchun Road, 310016 Hangzhou, Zhejiang, China
[d] Psychology Department at the St. George Campus, University of Toronto, 100 St. George Street, 4th Floor, Sidney Smith Hall, Toronto, Ontario, Canada M5S 3G3
[e] Cognitive, Perceptual and Brain Sciences, University College London, 26 Bedford Way, London WC1H 0AP, United Kingdom

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ABSTRACT

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, 2010a, b), first involves people deciding on which actions to take in order to control a dynamic outcome to a specific goal (e.g., controlling the production of sugar in a sugar factory) (Berry & Broadbent, 1984, 1988). Decision making performance in this type of paradigm is then examined in later tests of ability to control the fluctuating outcome to different goals (Osman, 2008, 2012; Osman, Wilkinson, Beigi, Parvez, & Jahanshahi, 2008; Osman & Speekenbrink, 2012). 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

* Corresponding author at: Biological and Experimental Psychology Centre, School of Biological and Chemical Sciences, Queen Mary University of London, Mile End Road, London E1 4NS, United Kingdom. Tel.: +44 207 882 5903.
E-mail addresses: M.Osman@qmul.ac.uk, m.osman@ucl.ac.uk (M. Osman).
[1] Tel.: +44 020 3108 0033; fax: +44 207 278 9836.
[2] Tel.: +86 571 8600 6613.
[3] Tel.: +1 416 978 5201.
[4] Tel.: +44 206 769 8548.

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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, Dharmindra, & 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 Hilten, 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
Demographic information of participants and clinical characteristics of patients with Parkinson's disease. NART: National Adult Reading Test, MMSE: Mini Mental state Examination, BDI-II: Beck Depression Inventory, LEDD: Levdopa Equivalent Daily Dose.

	PD patients ON medication ($n=20$, female=7)		PD patients OFF Medication ($n=15$, female=6)		Healthy controls ($n=19$, female=10)		P
	Mean	SD	Mean	SD	Mean	SD	
Age	68.07	7.06	69.85	5.56	67.38	4.78	0.53
Education	12.92	3.14	13.55	2.66	14.14	2.07	0.24
NART estimate of premorbid IQ	115.11	6.55	121.50	5.89	119.94	2.53	0.003
MMSE	28.77	1.59	26.93	3.52	29.92	1.27	0.99
BDI-II	12.84	5.99	11.10	5.30	6.28	5.91	0.40
Disease duration	11.61	7.87	10.57	8.13			0.74
LEDD in milligrams (mg)	699.35	263.42	584.62	199.31			0.01