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Effects of feedback delay on learning from positive and negative feedback in patients with Parkinson's disease off medication

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ABSTRACT

Phasic dopamine (DA) signals conveyed from the substantia nigra to the striatum and the prefrontal cortex crucially affect learning from feedback, with DA bursts facilitating learning from positive feedback and DA dips facilitating learning from negative feedback. Consequently, diminished nigro-striatal dopamine levels as in unmedicated patients suffering from Parkinson's Disease (PD) have been shown to lead to a negative learning bias. Recent studies suggested a diminished striatal contribution to feedback processing when the outcome of an action is temporally delayed. This study investigated whether the bias towards negative feedback learning induced by a lack of DA in PD patients OFF medication is modulated by feedback delay. To this end, PD patients OFF medication and healthy controls completed a probabilistic selection task, in which feedback was given immediately (after 800 ms) or delayed (after 6800 ms). PD patients were impaired in immediate but not delayed feedback learning. However, differences in the preference for positive/negative learning between patients and controls were seen for both learning from immediate and delayed feedback, with evidence of stronger negative learning in patients than controls. A Bayesian analysis of the data supports the conclusion that feedback timing did not affect the learning bias in the patients. These results hint at reduced, but still relevant nigro-striatal contribution to feedback learning, when feedback is delayed.

1. Introduction

Most living beings learn from the outcomes of their actions and adapt their behaviour accordingly, which defines reinforcement learning. In everyday-life, outcomes can vary not only in their valence, but also in their delay following an action. Often they occur immediately, as for example when making an error in driving your car and causing an accident. They can, however, also follow after a couple of seconds like when pushing a button on a coffee dispenser, or after a very long delay, for example in financial investments.

Reinforcement learning means gaining the knowledge of both which action previously resulted in a profitable outcome and which action previously resulted in a negative outcome. Animal studies associated outcomes that are better or worse than predicted with phasic increases and decreases in midbrain dopamine (DA) neuron activity, respectively (Schultz, 1997, 2000; Schultz and Dayan, 1997). Neural network models consider projections of this DA prediction error signal to the basal ganglia and prefrontal cortex (PFC, including the anterior cingulate cortex, ACC; Bédard and Larochelle, 1969; Haber and Fudge, 1997; Lavoie and Smith, 1989; Lehéricy et al., 2004; Lynd-Balta and Haber, 1994) as the neuronal underpinnings of reinforcement learning (Frank, 2005; Frank et al., 2004), underlying the adaptation of behaviour (Sheth et al., 2012). Based on DA effects on two separate so called Go and NoGo pathways within the basal ganglia (Aubert and Ghorayeb, 2000; Frank, 2005; Frank et al., 2004; Gerfen, 1992; Hernandez-Lopez et al., 1997, 2000), chronically increased and decreased DA levels have been linked to better learning from positive and negative feedback, respectively, which has indeed been shown in Parkinson's disease (PD) patients ON and OFF DA replacement medication (Frank et al., 2004; Frank and Samanta, 2007). Generally diminished DA baseline levels reduce the chance of DA bursts and increase the chance of DA dips reaching a certain threshold level, resulting in a more dominant NoGo-pathway during learning, whereas DA replacement medication seems to lead to a DA overdose in the ventral striatum (Cools and Barker, 2001, 2003; Frank, 2005) so that the Go pathway is selectively strengthened (see Frank et al., 2007).

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Kobza et al. (2012) showed, however, that a lack of DA does not always lead to a negative learning bias. They found learning to be unaffected in PD patients OFF medication when they learned from the choices of another person and the accompanying outcomes, suggesting that the mechanisms in observational learning differ. Another condition, in which feedback processing seems to be altered, relates to learning from delayed feedback. When comparing the feedback-based acquisition of stimulus-outcome associations, PD patients were significantly impaired in learning from immediate, but not from delayed feedback appearing seven seconds after a choice response (Foerde and Shohamy, 2011). While activity in the dorsal striatum appeared to underlie immediate feedback processing, the hippocampus was more strongly involved during learning from delayed feedback, as was shown via functional magnetic resonance imaging (fMRI) in healthy subjects (Foerde and Shohamy, 2011). The importance of the hippocampus for delayed feedback processing was further corroborated by deficits in amnestic patients with suspected hippocampal damage (Foerde et al., 2013). Recent studies using electroencephalography (EEG) added to the impression of different neural mechanisms for immediate and delayed feedback processing. They reported that the feedback-related negativity (FRN) was diminished for delayed compared to immediate feedback (Arbel et al., 2017; Peterburs et al., 2016; Weinberg et al., 2012; Weismüller and Bellebaum, 2016). The FRN is a feedback-locked event-related potential (ERP) component that has been linked to DA effects on the ACC (Holroyd, 2004; Holroyd and Coles, 2002, 2008). Reduced FRN amplitudes thus appear to suggest reduced DA system involvement with increasing temporal delay between action and outcome, so that overall a pattern of findings emerges that suggests a weaker or even absent role of DA in delayed feedback processing. As the bias for better learning from negative than positive action outcomes found for immediate feedback has directly been linked to the lack of DA in unmedicated PD patients, one might hypothesize that learning from delayed feedback should not be affected. The negative learning bias in this patient group should thus appear exclusively for immediate feedback.

On the other hand, the mentioned ERP studies also suggest similarities in the processing of immediate and delayed feedback. Irrespective of feedback delay, negative feedback elicited a larger FRN amplitude than positive feedback (Peterburs et al., 2016; Weismüller and Bellebaum, 2016). Moreover, even for delayed feedback the FRN reflected feedback expectations and was thus influenced by the reward prediction error (Weismüller and Bellebaum, 2016), suggesting that the DA system did indeed contribute to delayed feedback processing, at least to some extent. Striatum and hippocampus might work together in associating responses to outcomes (Dickerson and Delgado, 2015; Dickerson et al., 2011). Based on these considerations, it might thus also be possible that a lack of DA as in unmedicated PD patients has comparable effects on learning from delayed and learning from immediate feedback, leading to similar negative learning biases.

In this study, we applied variants of the probabilistic selection task first described by Frank et al. (2004) to explore whether the effect of reduced DA levels on the preference for learning to avoid a non-beneficial stimulus (learning from negative feedback) over learning to choose a beneficial stimulus (learning from positive feedback) is modulated by feedback delay. For this purpose, we compared the performance of two groups of PD patients OFF medication completing an immediate (see Kobza et al., 2012) or delayed feedback version of the probabilistic selection task with each other and with the performance of corresponding groups of healthy control subjects.

2. Material and methods

2.1. Participants

Four groups of subjects participated in the present study, two groups of PD patients OFF medication and two groups of healthy control subjects. With 12 participants in each patient group and 24 participants in each control group the sample sizes were slightly larger than in a previous study of our group applying variants of the same experimental paradigm and addressing a related research question (Kobza et al., 2012). One patient and one control group each completed an immediate and delayed feedback version of the probabilistic selection task, respectively. The patient group for the immediate feedback condition had a mean age of 56.8 years (SD = 9.8; 7 men). For ten of these patients we reused data from a sample of PD patients who had already been tested for a previous study by our group (see Kobza et al., 2012; the group of subjects learning actively from their own choices). To match the delayed feedback group (see below) two additional PD patients were recruited. Similarly, data for 20 control subjects were taken from our old data set for the immediate feedback group (Kobza et al., 2012) and four more control subjects were tested. The control group learning from immediate feedback had a mean age of 55.5 years (SD = 10.0; 14 men). The patient (9 men) and control groups (16 men) in the delayed feedback condition were on average 57.9 (SD = 8.5) and 59.1 years (SD = 6.6) old. All PD patients were listed for regular attendance at the Centre for Movement Disorders and Neuromodulation of the University Hospital Düsseldorf and were diagnosed by medical staff according to the UK Brain Bank criteria (Hughes and Daniel, 1992). Symptom severity in all PD patients was between stages I and III according to the Hoehn and Yahr classification (Hoehn and Yahr, 1967) and all patients had normal or corrected-to-normal vision. To compare symptom severity between ON and OFF medication states, the Unified Parkinson's Disease Rating Scale (UPDRS; Goetz et al., 2008; Movement Disorder Society Task Force on Rating Scales for Parkinson's, 2003) was administered twice for each patient, once in the OFF state and a second time 20 min after the intake of the regular medication after testing in the ON state. The average scores amounted to 21.8 (SD = 5.8) in the OFF state and 15.5 (SD = 6.0) in the ON state for patients in the immediate feedback condition. For patients in the delayed feedback condition the average scores were 30.2 (SD = 9.3) and 18.0 (SD = 10.2) for OFF and ON state, respectively. For both groups, the scores with and without medication differed significantly ($t(11) = 5.637$; $p < .001$; $d = 1.627$ for immediate feedback and $t(11) = 8.512$; $p < .001$; $d = 2.457$ for delayed feedback). The scores were obtained with different versions of the scale. For the 10 participants that entered analysis and were tested for our previous study (Kobza et al., 2012) the version from 2003 was used (Movement Disorder Society Task Force on Rating Scales for Parkinson's, 2003), whereas for the patients tested for the present study a newer version was used (Goetz et al., 2008), which yields higher symptom scores on average for lower stages of PD (Goetz et al., 2008). A direct comparison of the UPDRS scores between the two patient groups may thus be confounded and was therefore not conducted.

Exclusion criteria for patients were psychiatric or neurological diseases (other than PD), atypical PD, traumatic brain injury with sustained unconsciousness, suspected or documented drug or alcohol abuse, and regular psychotropic medication other than DA agonists. Finally, all PD patients were screened for comorbid depression and dementia after the experimental learning task was applied but still in the OFF medication state using the Beck Depression Inventory (BDI; Hautzinger et al., 2006) and the Mini Mental Status test (MMS; Folstein and Folstein, 1975), respectively. BDI scores were assessed in the patients in order to exclude that a negative affective bias could influence performance in the probabilistic selection task. None of the patients scored above 18, which would indicate clinically relevant depressive symptoms. More specifically, patients learning from immediate feedback had a mean BDI score of 7.3 (SD = 4.4), while those in the delayed feedback group had a mean score of 7.6 (SD = 4.2). The scores did not differ significantly between the two patient groups ($p = .870$). In the MMS all the patients scored above 27 (patients immediate feedback: mean = 28.0, SD = 1.5; patients delayed feedback: mean = 28.9, SD = .8), indicating that none of the patients showed signs of dementia or clinically relevant cognitive impairment. Scores for the MMS did not differ between patient groups ($p = .080$). BDI and MMS scores were