

Research article

The interactive effect of valence and context on reversal learning in individuals with Parkinson's disease

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ABSTRACT

Cognitive deficits in Parkinson's disease (PD) have increasingly been recognized over the last decade and reversal learning in particular has received a great deal of attention. In a classical reversal-learning paradigm, participants learn to associate various stimuli with specific responses (i.e. A → Positive; B → Negative), and subsequently learn to associate the same stimuli with opposite outcomes (i.e., A → Negative; B → Positive). Prior studies have revealed that medicated PD patients have a selective impairment with learning from negative, but not positive, outcomes, even when both reward- and punishment-related stimuli were equally relevant. The aim of the present study was to further understand this impairment by applying a novel reversal-learning paradigm, which enables the differentiation between positive/negative and cue/context reversal impairments. Twenty-seven medicated PD patients and twenty-nine healthy individuals matched for age, gender and education completed the cue-context reversal learning paradigm. The results revealed no significant differences in context reversal learning between individuals with PD and healthy controls. However, in cue reversal learning, healthy controls were significantly better at performing positive-to-negative reversal trials compared to individuals with PD, while individuals with PD were significantly better in negative-to-positive reversal trials compared to healthy controls. As such, the present study distinguishes between different types of reversal learning and suggests that different neural circuits are responsible for context and cue learning. These results improve our understanding of the possible effects of dopaminergic medications and may have important clinical implications.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterised by a myriad of complex motor and cognitive sequelae. The primary neuropathological insult in PD is the degeneration of dopamine (DA)-producing neurons located in the substantia nigra pars compacta, which subsequently leads to dopamine depletion in the striatum, which is a critical node in the parallel frontostriatal loops [1–4]. Suboptimal dopamine availability in this region impairs the function of distributed neural systems governing complex and higher order

processes across multiple cognitive domains such as executive dysfunction, memory and visuospatial deficits [5–7].

Whilst dopaminergic therapies greatly ameliorate the motor symptoms of PD (e.g., [8,9]), they have variable effects on cognitive function. Specifically, whereas dopaminergic treatment is beneficial for some aspects of cognition including verbal fluency and working memory, it can worsen other domains such as reversal learning ([10–16]; for review see [17]). Indeed, a series of studies have demonstrated that PD patients ON dopaminergic medication (e.g. levodopa) perform poorly on reversal learning tasks, whilst PD patients OFF medication perform similarly to healthy individuals [10,12,18,19]. This may sug-

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gest that, after learning stimulus-outcome associations, medicated PD patients may fail to update them.

It has been proposed that such reversal-learning impairment arises from a differential degeneration of dopaminergic neurones across the nigrostriatal projection, which results in a 'dopamine gradient' across the ventral and dorsal striatum [10,19,20]. In early PD, the dorsal striatum is severely depleted, while the ventral striatum remains relatively intact [21,22]. As problems with motor function begin to clinically manifest, dopaminergic therapy is typically prescribed. This alleviates motor dysfunction by increasing depleted dopaminergic stimulation in the dorsal striatum towards an optimal level. However, dopaminergic projections to the ventral striatum that have yet to be depleted end up being relatively "over-dosed" [10,11,16]. As a result, processes mediated by the depleted dorsal striatum (e.g. attentional set-shifting) are likely to become optimal with medication, whereas those processes mediated by the non-depleted ventral striatal-limbic circuitry, such as reversal learning, may become more impaired following medication.

Studies on reversal learning in medicated PD patients have focused on reversing the outcome of cue-related information. Specifically, they have tested what happens when participants need to reverse the outcome of a central and salient stimulus. These studies have found that medication-related impairments are restricted to trials where there is a positive to negative switch (i.e. a cue that was formerly associated with a positive outcome is now associated with a negative one) but not to those trials where there is negative to positive reversal in learning [12]. However, to the best of our knowledge no study has tested whether these impairments also exist when reversing the outcome of context-related information.

According to the item-in-context model, contextual information is processed in the hippocampus. Specifically, the perirhinal cortex is responsible for the processing of objects, the parahippocampal cortex represents the context, while the hippocampus integrates the information from these sources [23,24]. Therefore, it seems as if the hippocampus is responsible for placing objects into their proper context [25–27] and detecting novel changes in the relationship between objects and their surrounding context [28]. Studies have shown that individuals with small or dysfunctional hippocampi show a selective deficit in context-based reversal learning [29–31]. PD patients have intact hippocampal function and structure. Moreover, few studies that tested the effect of the incidental retention of contextual information have found no significant differences between PD patients and controls [32,33], suggesting intact ability to process contextual information. However, it is not yet clear whether PD patients would be able to reverse context related information despite their cue reversal learning being impaired.

The aim of the present study was to investigate the specific nature of negative and positive cues alongside context reversal learning in medicated PD patients and matched healthy controls using a novel cue-context partial reversal paradigm [31,34]. In a common reversal paradigm, participants acquire a stimulus-outcome association (S→Positive) and subsequently need to reverse the outcome of the same stimulus (S→Negative). This common paradigm does not take into account that every stimulus occurs in a specific context, which in itself may impact on reversal learning [35]. To address this limitation, our novel paradigm asked participants to learn cue and context-outcome associations (e.g. a **hat** on an **orange** background →Positive) and later view new associations, which required reversing the outcome of *either* the *cue* (e.g. a **phone** on an **orange** background →Negative) or the *context* (A **hat** on a **grey** background →Negative) of the acquired stimuli. This unique innovative manipulation enabled us to detect selective impairments in reversing positive and negative outcomes of cue and context related information.

We refer to context as the information that is processed in the periphery of our attention [35,36]. Similar to other context-related para-

digms, the nature of the stimuli establishes the cue-context relationship through bottom-up processing [37–39]. Specifically, presenting an object against a background color results in directed focal attention towards the object (For studies using similar context manipulation see [40–46]). Importantly, context effects in these cases are similar to the effects observed in conditions of 'environmental context' (for review see [47]).

Based on the literature cited above, we predicted no significant differences between medicated PD patients and healthy controls in context reversal learning. However, we predicted significant differences in cue reversal learning between the groups. Specifically, healthy controls will perform better in positive-to-negative reversal trials compared to medicated PD patients.

2. Method

2.1. Participants

Fifty-six individuals volunteered to participate in this study: twenty-seven individuals with PD and twenty-nine healthy individuals, matched for age, gender and education. The PD patients were recruited from the Parkinson's Disease Research Clinic at the Brain and Mind Centre (BMC), University of Sydney. The majority of patients were taking a cocktail of medications. Specifically, out of 27 patients 16 were taking different types of cocktails (at least 10 unique types of cocktails, all containing L-DOPA), 6 consumed only L-DOPA, 4 consumed Rasagiline (MAO-B inhibitor) and 1 consumed Benserazide (DOPA decarboxylase inhibitor). All patients satisfied the United Kingdom Parkinson's Disease Society Brain Bank criteria [48]. The study was approved by the Human Ethics Research Committee of the University of Sydney (in accordance with the Declaration of Helsinki) and written informed consent was obtained from all patients. Participants in the control group were recruited from the community. Specifically, we posted advertisements on bulletin boards in residential areas. Those who were interested in participating in the study contacted us and were invited to our lab for several tests. We excluded controls who had any neurological disorder. A clinical psychologist tested all participants using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). Three participants with a score < 26 on the MoCA were excluded from this study to rule out any confound of general cognitive impairments. Additional exclusion criteria included color blindness, a history of psychiatric or neurological disorders, use of illicit drugs or alcohol abuse or dependence. A detailed description of the demographics is listed in Table 1.

Table 1

A detailed description of the participants: Means and Standard deviations/ Frequencies.

	PD Patients (N = 27)	Healthy Controls (N = 29)
Age (years)	65.45 (9.36)	63.32 (4.04)
Male/female	15/12	13/16
Education (years)	13.9 (3.14)	13.11 (2.9)
Depression*	10.29 (9.95)	9.04 (5.95)
MoCA	27.79 (2.15)	28.21 (1.12)
LED**	711.62 (486.10)	
Hoehn & Yahr***	2.1 (0.2)	–
UPDRS****	45.1(0.8)	–

* Depression was measured by the Beck Depression Inventory (BDI-II). There were no significant differences between the groups ($p = .58$).

** Levodopa equivalent dose.

*** The distribution of PD patients across the Hoehn & Yahr stages is as follows: S1- 2; S2-19; S2.5-2; S3-2; S4-1.

**** UPDRS scale refers to part III only.

2.2. The cue and context reversal paradigm

In this task participants viewed a series of boxes on a computer screen (Fig. 1) [30,31]. On each box a picture of a target cue (one of various objects, e.g., a hat) was presented against a background context (different colours, e.g., blue). The participants were asked to either open the box or leave it closed. Each box was associated with a specific outcome (positive, i.e. gold coins or negative, i.e. a bomb), which was revealed by opening the box. Participants earned points for correct responses: conditions in which participants opened positive boxes whilst leaving negative boxes closed. Similarly, incorrect responses refer to conditions in which participants opened negative boxes or left positive boxes closed (Fig. 2). Each box had a unique cue and context (e.g., a box with a hat on a blue background had gold coins inside it, whereas a box with a car on a yellow background might had a bomb inside it).

The positive and negative boxes were counterbalanced across participants. The task had two phases: an *acquisition phase* followed by a *retention and reversal phase*. In the acquisition phase, participants learned by trial and error to predict the outcome of four different boxes (i.e. four initial cue-context pairings). The acquisition phase contained a minimum of 40 trials. To complete the acquisition phase and move on to the retention and reversal phase, participants needed to learn the box-outcome associations to a criterion of six consecutive correct responses. Participants' last six consecutive responses necessarily refer to the four original boxes (one box of each type) plus two new boxes. A subsequent retention and reversal phase started immediately after the acquisition phase without any signalled switch or delay. In this phase, participants received retention trials with the original boxes that kept the same learned outcome (e.g., a box featuring a hat on a blue background has gold coins inside) in addition to two new types of boxes that shared either the cue (e.g., a hat on a grey background) or the

Acquisition Phase



Retention and Reversal Phase

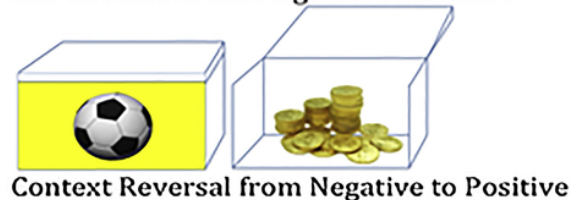
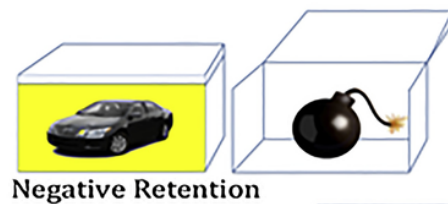
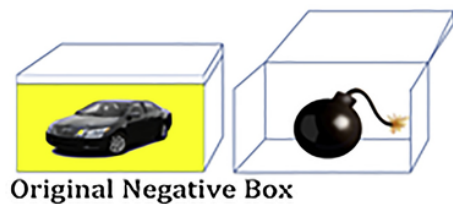
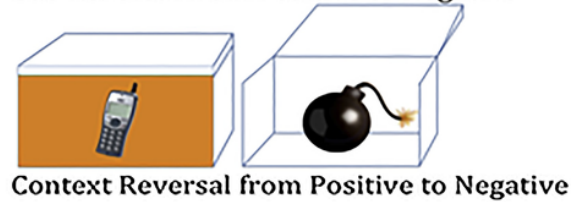
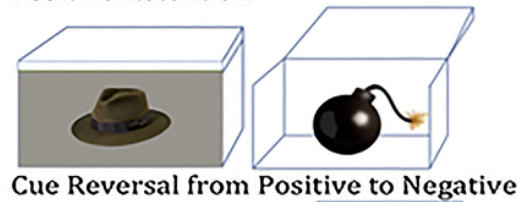
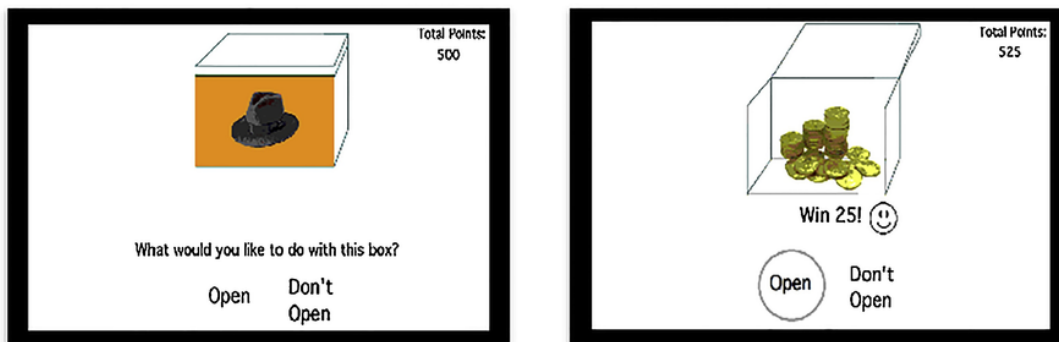


Fig. 1. Illustration of the different experimental conditions.

(a) Example of experimental trial with positive outcome box



(b) Example of experimental trial with negative outcome box

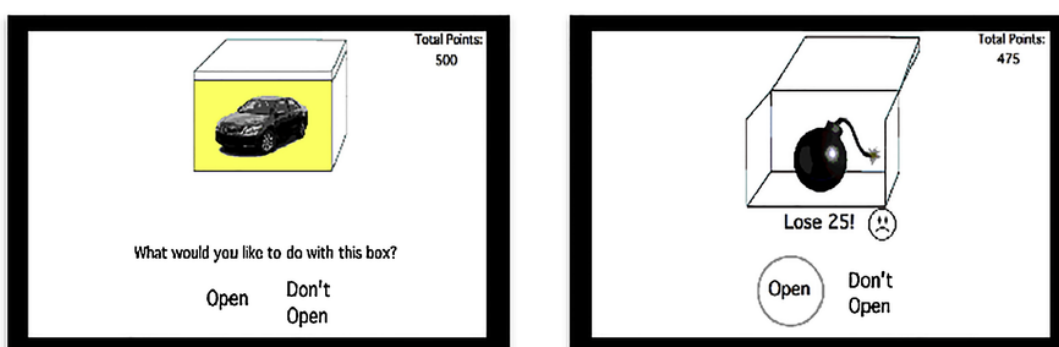


Fig. 2. Examples of experimental trials with positive and negative outcomes.

context (e.g., a phone on a blue background) with an original box (Fig. 1). Specifically, participants were first shown the exact same boxes they saw in the acquisition phase and the outcome of those boxes did not change (i.e. if an orange box with a hat on it had positive valence in the acquisition phase, its valence remained the same throughout the entire task and it was presented both as part of the acquisition and the retention trials). These are retention trials. In the reversal trials, we generated two new boxes from each original acquisition box, one that shared the same context with the original box (but had a new cue on it) and one that shared the same cue with the original box (but had new context). The new boxes were associated with the opposite outcome relative to the original boxes (i.e., if the box with the hat on the blue background had gold inside, then the boxes with the hat on a grey background and a phone on the blue background will have a bomb inside). Therefore, in order to successfully learn these new associations, participants needed to reverse the association rule of either the original cue or the original context. Reversal trials from positive to negative refer to boxes that shared either the same cue or the same context with the original positive box but now had a negative outcome. For example, if an original box had a hat on an orange background, in the reversal phase from positive to negative, participants viewed either a box with a hat on a *gray* background or a box with a *phone* on an orange background. While the first box refers to a cue reversal from positive to negative, the second box refers to context reversal from positive to negative (Fig. 1). Boxes in this phase were presented in 10 blocks of 12 boxes each (two boxes from each of the following conditions: positive/negative retention, positive/negative cue reversal, positive/negative context reversal). Boxes in each block were intermixed and presented in a random order to ensure that there would be no more than two identical consecutive boxes. This sums up to a total of 120 trials; 20 tri-

als per condition. At the end of the task participants saw their total earned points.

2.3. Data analysis

All analyses were performed using the Statistical Package of the Social Sciences version 22 (SPSS Inc., IL, USA). The data were checked for normality of distribution using Kolmogorov–Smirnov tests. Mixed model ANOVAs and Bonferroni post-hoc tests were used to investigate group (PD vs. controls), task (acquisition vs. retention) and outcome (positive vs. negative cue) differences. Additionally, group differences were assessed on reversal valence (positive-to-negative vs. negative-to-positive) and context (cue vs. context) using a mixed model ANOVA and Bonferroni post-hoc analyses. Alpha was set at 0.05 and all analyses were performed two-tailed.

3. Results

3.1. Acquisition and retention of stimulus–outcome associations

We conducted a group (PD vs. control) by phase (acquisition vs. retention) by outcome (positive vs. negative) mixed model ANOVA on the difference for the percentage of correct responses. The results revealed a significant main effect of group ($F(1,54) = 10.04, p = .003, \eta^2_p = .16$), indicating that in general, individuals with PD performed worse ($M = 65.76, SE = 2.58$) than healthy controls ($M = 77.11, SE = 2.58$). In addition, there was a significant main effect of phase ($F(1,54) = 4.89, p = .03, \eta^2_p = .08$), suggesting that in general participants performed better at acquiring stimulus–outcome associations ($M = 73.85, SE = 1.96$) than retaining them ($M = 69.02, SE = 2.23$). However, the outcome (positive vs. negative stimulus–outcome pairs)

had no effect on the ability to acquire or retain associations ($F(1,54) = .01, p > .05$), indicating no baseline differences in sensitivity to reward and punishment. Moreover and most importantly, there were no significant interactions of phase by group ($F(1,54) = 1.36, p > .05$), outcome by group ($F(1,54) = 1.15, p > .05$) or phase by outcome by group ($F(1,59) = .55, p > .05$) (Fig. 3). Finally, all of the participants (PD patients and healthy controls) successfully acquired the stimulus-outcome association to reach a criterion of 6 consecutive correct responses within the minimum of 40 trials. These results indicate that while healthy controls performed better than individuals with PD, both groups showed similar performance patterns across conditions, i.e. all participants were able to acquire stimulus-outcome associations within the minimum 40 trials.

3.2. Cue and context reversal

To test possible differences in reversing positive and negative outcomes of cue-and context-related information, we conducted a group (PD vs. control) by reversal type (cue vs. context) by reversal valence (positive-to-negative vs. negative-to-positive) mixed model ANOVA on the percentage of correct responses. Group served as a between-subjects factor while reversal type and reversal valence served as within-subject factors. The results revealed no main effects of group, reversal type or reversal valence ($F_s < 1$). However we found a significant interaction of group by reversal valence ($F(1,54) = 5.79, p = .02, \eta_p^2 = .10$) and a significant interaction of group by reversal type by reversal valence ($F(1,54) = 9.19, p = .004, \eta_p^2 = .15$). In order to understand the nature of this interaction we conducted mixed model ANOVA in conditions of cue and context reversals. The results revealed a significant interaction of group by reversal valence in cue reversal conditions ($F(1,54) = 18.49, p = .000, \eta_p^2 = .26$).

Follow up analyses with Bonferroni correction ($\alpha = .01$) revealed that healthy controls ($M = 72.61, SE = 2.89$) were significantly better at performing positive-to-negative reversal trials compared to individuals with PD ($M = 49.5, SE = 4.85$) ($t(54) = -4.22, p = .000$). However, individuals with PD ($M = 69.41, SE = 4.01$) were significantly better in negative-to-positive reversal trials compared to healthy controls ($M = 50.20, SE = 4.95$) ($t(54) = 2.55, p = .01$) (Fig. 4). However, there was no significant interaction between group and reversal valence in the context reversal conditions ($F(1,54) = .10, p > .05$), indicating that both groups were equally able to reverse context-related information (Fig. 5). As will be discussed below, these findings confirm and ex-

tend previous findings, suggesting that while medicated PD patients are impaired in positive-to-negative reversal learning, they outperform controls in negative-to-positive reversal learning.

While Pearson correlations between performance on the cue context reversal trials and disease progression and severity (as measured by time since onset, UPDRS, Hoehn & Yahr stages and Levodopa Equivalent Dose) revealed no significant results (all $p_s > .5$), the distribution of the participants across the different conditions provided further support to our conclusions. Specifically, we used the median number of correct responses in cue reversal learning from positive to negative and from negative to positive to divide the participants into two groups according to their performance. In reversal learning from positive to negative Chi square test revealed that the number of PD patients in the first group (number of correct responses above median) was significantly lower than the number of healthy controls. In contrast, the number of PD patients in the second group (number of correct responses below median) was significantly higher compared to healthy controls ($X^2(27) = 43.99, p = .02$). (Fig. 6). In cue reversal from negative to positive on the other hand Chi square test revealed that the number of PD patients in the first group (number of correct responses above median) was significantly higher than the number of healthy controls. In contrast, the number of PD patients in the second group (number of correct responses below median) was significantly lower compared to healthy controls ($X^2(20) = 32.12, p = .03$). (Fig. 7).

4. Discussion

The aim of the present study was to investigate reversal learning mechanisms in dopaminergic medicated PD patients, focusing on the effects of positive and negative reversals of both cue-and-context-related information. The results revealed a selective impairment in PD patients in positive-to-negative cue reversal learning compared to healthy controls; matched for age, gender and education. Specifically, after learning that a specific cue had a positive outcome, PD patients more often failed to subsequently associate the same cue with an unexpected negative outcome. These results are aligned with the previously proposed overdose hypothesis, in which it is postulated that dopaminergic treatment optimises processes mediated by the depleted dorsal striatum (e.g. attentional set-shifting), whilst processes mediated by the non-depleted ventral striatum and orbitofrontal loop, such as reversal learning, become aberrant following medication [12].

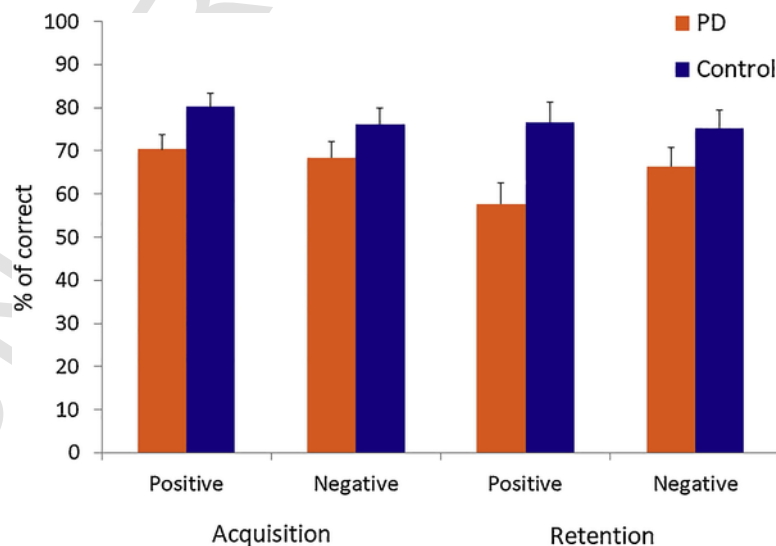


Fig. 3. Percentage of correct responses in the acquisition and retention trials. The results show no significant differences between the groups ($N = 56$; Error bars represent standard error).

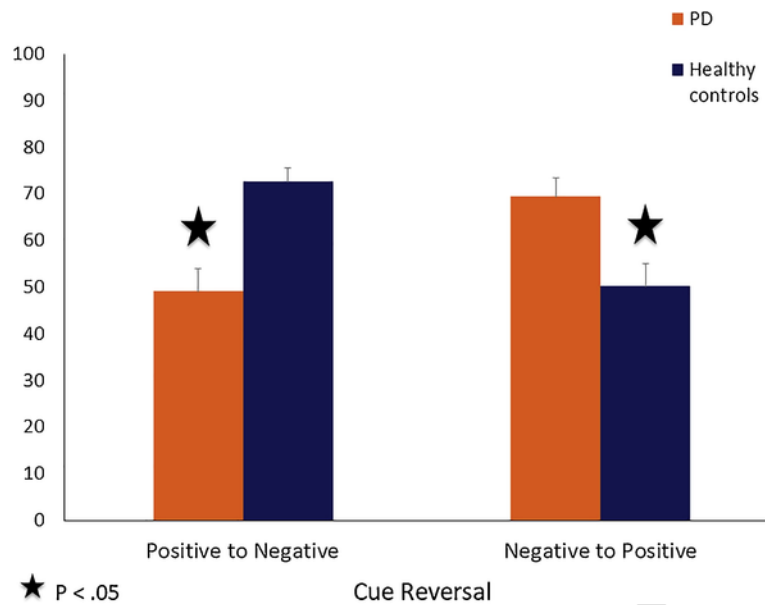


Fig. 4. Percentage of correct responses in cue reversal trials as a function of group (N = 56; Error bars represent standard error).

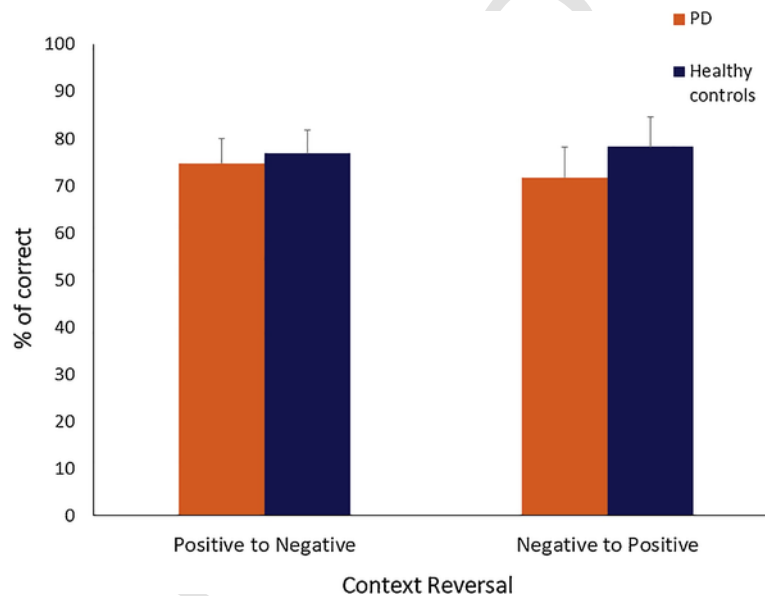


Fig. 5. Percentage of correct responses in context reversal trials as a function of group (N = 56; Error bars represent standard error).

Interestingly, in negative-to-positive reversal learning, PD patients performed better than healthy controls: after learning that a certain cue predicted a negative outcome, PD patients were able to more easily reverse it and learn that it predicted an unexpected positive outcome, a result that outperformed controls. Assuming reward learning is mediated by the dorsal striatum, this finding suggests that dopaminergic medication not only helps remediate reward learning but also enhances it relative to healthy individuals (Fibiger & Phillips, 1986; Wise & Rompre, 1989; Robbins & Everitt, 1996; Wise, 1996).

A possible support for these results may be found in computational modelling and brain imaging research. Specifically, it has been found that there may be different and potentially opposing representations of reward- and punishment-associated learning signals (e.g. [49,50]). Advances in computational modelling have put forward that phasic dopamine responses act as a reinforcement signal, acting to “stamp in” successful operant responses [51,52]. It has been proposed that dopaminergic medication might cause an overall increase in tonic DA

that obscures phasic DA dips that are evoked by error-correcting feedback necessary for reversal learning [14,53,54]. Indeed, Frank [55] has argued that while the direct (i.e. GO) pathway of the basal ganglia (composed of DA D1 receptors) is left relatively intact by initial depletion, the indirect (i.e. NO-GO pathway, comprised of DA-D2 receptors) is impaired. Accordingly, it is proposed that increase in tonic DA shifts the balance toward the GO pathway, thereby improving reward-learning relative to punishment-learning. On the other hand, decrease in dopamine shifts the balance in favour of the NO-GO pathway, which impairs reward-learning relative to punishment-learning. Therefore, when compared to healthy controls, medicated PD patients are impaired in positive-to-negative reversal learning, which involves punishment-learning, but perform significantly better in negative-to-positive-reversal conditions, which involve reward-learning.

Importantly, not only that PD patients out-perform healthy individuals in negative to positive reversal learning, the performance of the latter is close to chance. This selective cue- but not context impairment

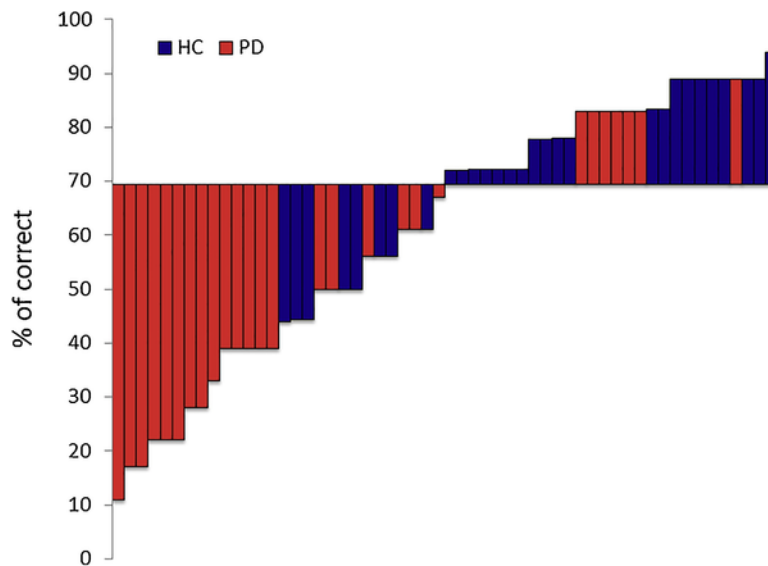


Fig. 6. Individual differences in percentage of correct responses (below and above median) in cue reversal learning from positive to negative as a function of experimental group (PD patients vs. healthy controls, N = 56).

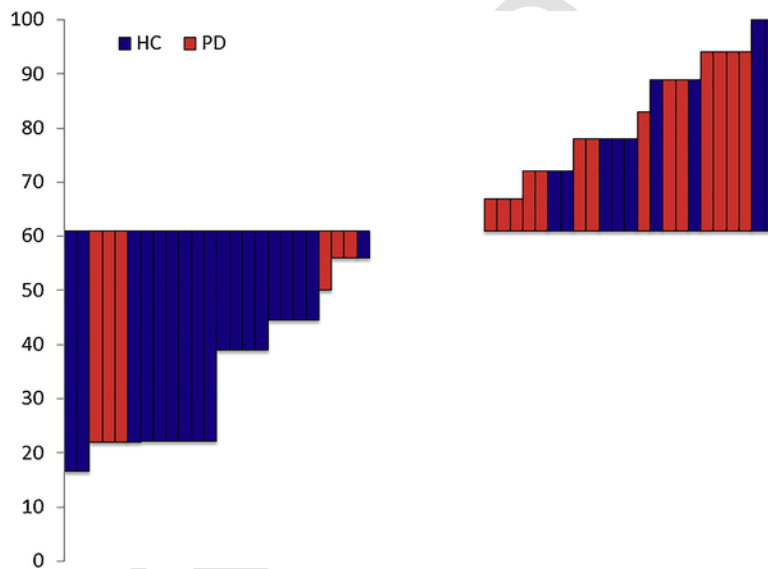


Fig. 7. Individual differences in percentage of correct responses (below and above median) in cue reversal learning from negative to positive as a function of experimental group (PD patients vs. healthy controls, N = 56).

in negative to positive reversal learning is in line with previous results [56,57]. It adds to the accumulative evidence suggesting that cue reversal learning tends to decline with age and more likely pronounced in reversal of negative information (e.g. [56,58–60]). Accordingly, the results may propose that the increased tonic DA in medicated PD patients not only improves their performance but also compensates for age related deficits.

Finally, the current study shows that medicated PD patients showed intact context reversal learning. Specifically, PD patients and healthy individuals learned equally well that a specific context associated with one outcome could subsequently be associated with a different outcome. A possible explanation for these findings may be found in the different underlying mechanisms of these various information-processing tasks. While cue-related-information is processed by the basal ganglia [61,62], contextual processing is regulated by the hippocampus [26,27], which is relatively intact in non-demented PD patients [63]. Additionally, context could be perceived as less relevant than cues, and

learned irrelevance has been shown to be neither influenced by dopamine, nor dependent on the frontal lobe [64].

Whilst the current study has both confirmed previous findings and provided new insights into reversal learning mechanisms in PD patients in their ON state, it may suffer a number of limitations. Firstly, there was no comparison between PD patients ON and OFF their medication, thus not allowing for a direct investigation of the role of dopamine on reversal learning. However, previous work has shown that PD patients off their medication perform similar to healthy controls in reversal learning paradigms using changing outcomes for different cues. Moreover, the current study identified a behavioural deficit while referring to brain mechanisms that were identified in previous studies. However, in order to reach more conclusive results regarding positive and negative cue and context reversal learning, future studies may wish to apply functional MRI methods to compare performance and brain activation in the different experimental conditions. In addition, participants were not told whether leaving a box unopened was a 'correct' or 'incorrect' response. As such, participants may confound risk aversion with learn-

ing, and risk aversion could itself differ between patients and controls. Yet, according to the results (Fig. 3), there were no significant differences between the patients and the control groups in the percentage of correct responses in the acquisition and retention trials. Most importantly, if participants confound risk aversion with learning, we should expect that patients would leave a box that shares the same cue with an original negative box closed as well (e.g., a car on a purple background) and struggle to learn it has a positive outcome. As can be seen in the results (Fig. 5), there were no significant differences between individuals with PD and healthy controls in this instance. However, future studies may wish to provide participants with feedback even if they do not open a box. In addition, there were no significant correlations between performance on the cue-context reversal paradigm and disease progression and severity. Hence, while the PD sample is relatively large, future studies may aim to test a larger sample in order to reach conclusive results regarding these relationships. Finally, a potential limitation of the current study may relate to the nature of the cue-context reversal paradigm. The basic assumption in this and other similar paradigms (e.g., [65–67]) is that participants are rational learners. However, it may be claimed that factors such as risk aversion would affect performance in the cue-context reversal paradigm. If this were the case, we would expect to see a strong effect of a negative or positive outcome. For example, participants who avoided risk would struggle to learn negative boxes. However, these participants would not be able to reach the learning criterion (six consecutive correct responses) and would automatically opt out of the experiment. Moreover, even if one claims that risk aversion is more likely to affect behaviour in conditions of reversal learning, it seems that the results of the current study do not support it. Specifically, because these tendencies represent inner values, they would be expected in both PD patients and healthy controls. Finally, even if such a tendency is specific to PD patients, and affects only conditions of reversal learning, the results of the present study show an exclusive deficit in conditions of positive cue (but not context) reversal learning. Therefore, the results of the current study suggest that medicated PD patients suffer a much more specific impairment which does not necessarily relate to general tendencies and behaviours. However, future studies may aim to test possible interactions between tendencies such as risk aversion, reversal learning, and PD patients in order to further clarify these points (see [44] for a similar approach).

To summarize, the present study distinguishes between different types of reversal learning and helps specify the selective impairment of medicated PD patients in conditions of cue reversal learning from positive to negative, while demonstrating their advantage relative to matched controls in negative-to-positive cue reversal learning. Moreover, it suggests that context reversal learning is intact in this population. These results improve our understanding of the possible effects of dopaminergic medications and may have important clinical implications. For example, developing focused treatment methods consisting of training sessions in a reversal learning task. Such treatment may improve medicated PD patients' ability to reverse positive cue associations and provide them with better skills to alter and adapt their behaviour according to changes in the circumstances. Hence, it may help learning that different activities such as strenuous physical exercise or loaded schedule are no longer rewarding due to their disease, and make their decision to reduce pressure easier.

Author contributions

ELG and AAM developed the study concept and study design. JMN and SJGL designed and supervised the clinical trials, JC and RWS supervised data collection, ELG and SHN analysed the data. All authors interpreted the data and drafted the manuscript. All authors have approved the final article.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Uncited references

[68–100].

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