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Maladaptive avoidance patterns in Parkinson's disease are exacerbated by symptoms of depressionhreatened plant translocation in Australia: A review

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Abstract

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder, characterized by a loss of dopaminergic neurons in the substantia nigra pars compacta. Given that dopamine is critically involved in learning and other cognitive processes, such as working memory, dopamine loss in PD has been linked both to learning abnormalities and to cognitive dysfunction more generally in the disease. It is unclear, however, whether avoidance behavior is impacted in PD. This is significant, as this type of instrumental behavior plays an important role in both decision-making and emotional (dys)function. Consequently, the aim of the present study was to examine avoidance learning and operant extinction in PD using a computer-based task. On this task, participants control a spaceship and attempt to shoot an enemy spaceship to gain points. They also learn to hide in safe areas to protect from (i.e., avoid) aversive events (on-screen explosions and point loss). The results showed that patients with PD (N = 25) acquired an avoidance response during aversive periods to the same extent as healthy age- and education-matched controls (N = 19); however, patients demonstrated greater hiding during safe periods not associated with aversive events, which could represent maladaptive generalization of the avoidance response. Furthermore, this impairment was more pronounced during the extinction phase, and in patients who reported higher levels of depression. These results demonstrate for the first time that PD is associated with maladaptive avoidance patterns, which could possibly contribute to the emergence of depression in the disease.

Keywords	Parkinson's disease; avoidance; extinction; generalization; depression; computer-based task.

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Highlights

- Dopamine loss in PD is linked to learning abnormalities and cognitive dysfunction.
- PD patients acquired an avoidance response to the same extent as healthy controls.
- Patients showed greater hiding during safe periods, mainly during extinction phase.
- Results could represent maladaptive generalization of the avoidance response.
- Findings demonstrate maladaptive avoidance patterns in PD and comorbid depression.

Maladaptive Avoidance Patterns in Parkinson's Disease are Exacerbated by Symptoms of Depression

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Abstract

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder, characterized by a loss of dopaminergic neurons in the substantia nigra pars compacta. Given that dopamine is critically involved in learning and other cognitive processes, such as working memory, dopamine loss in PD has been linked both to learning abnormalities and to cognitive dysfunction more generally in the disease. It is unclear, however, whether avoidance behavior is impacted in PD. This is significant, as this type of instrumental behavior plays an important role in both decision-making and emotional (dys)function. Consequently, the aim of the present study was to examine avoidance learning and operant extinction in PD using a computer-based task. On this task, participants control a spaceship and attempt to shoot an enemy spaceship to gain points. They also learn to hide in safe areas to protect from (i.e., avoid) aversive events (on-screen explosions and point loss). The results showed that patients with PD ($N = 25$) acquired an avoidance response during aversive periods to the same extent as healthy age- and education-matched controls ($N = 19$); however, patients demonstrated greater hiding during safe periods not associated with aversive events, which could represent maladaptive generalization of the avoidance response. Furthermore, this impairment was more pronounced during the extinction phase, and in patients who reported higher levels of depression. These results demonstrate for the first time that PD is associated with maladaptive avoidance patterns, which could possibly contribute to the emergence of depression in the disease.

Keywords: Parkinson's disease; avoidance; extinction; generalization; depression; computer-based task.

1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease, and a significant global problem. Its burden steadily increases over time [1], with a prevalence that is expected to double by 2030 [2]. It is characterized by a loss of dopaminergic neurons in the substantia nigra pars compacta, with 30-50% neuronal loss already apparent at time of diagnosis [3]. This loss of dopaminergic neurons significantly impacts the normal functioning of the basal ganglia, a brain circuit important for learning and decision-making [4].

While classically defined as a movement disorder, PD is also associated with a variety of non-motor symptoms. Prominent among these are subtle cognitive abnormalities, often occurring in the early stages of the disease, and progressing though to more severe cognitive impairment and dementia, with over 80% of individuals meeting criteria for dementia within 20 years of PD diagnosis [5, 6]. In addition, PD is characterized by a high rate of depression [7], which has been independently associated with cognitive dysfunction [8]. These non-motor symptoms significantly impact the quality of life of patients [9, 10]. Furthermore, even mild degrees of cognitive impairment are associated with increased disability [11], as well as shorter survival time in PD [12]. This has led the UK National Institute for Clinical Excellence to recognize that the management and treatment of non-motor symptoms is an important unmet need in people with PD [13]. A clearer understanding of cognitive processes in PD is therefore needed, as it may inform earlier detection of both cognitive and emotional dysfunction and lead to novel treatment avenues.

While cognitive impairment in PD can be heterogenous, one of the most common findings across multiple studies is that patients with PD are impaired on traditional executive functioning tasks. A recent meta-analysis assessed 33 studies of executive function in unmedicated patients in the early stages of PD, with results revealing impairment in executive tasks such as Word Fluency, Digit Span Backwards, the Trail Making Test, the Stroop Test

and the Wisconsin Card Sorting Task [14]. Executive function relies on the prefrontal cortex and impaired performance in PD patients is most commonly attributed to dopaminergic disruption impacting frontostriatal networks involved in these cognitive processes [15].

Building upon these findings, recent research has employed tasks designed to test more specific learning and memory processes. Findings from this line of work indicate that some types of learning processes are impacted, while others are spared in PD, suggesting that lower levels of striatal dopamine may impair particular learning processes. Specifically, an emerging pattern is that patients show impairment on tasks that involve incremental, feedback-based associative learning. These include tasks that assess probabilistic learning [16, 17], reversal learning [18-21], category learning and complex cue-outcome associative learning [22]. In contrast, PD patients tend to perform similarly to controls in tasks that involve declarative, non-feedback based learning [23] and transfer generalization [24, 25].

Most studies on associative feedback-based learning in PD have investigated learning that falls into a classical conditioning paradigm or, in other words, cue-outcome associative learning. Recent findings suggest that patients with PD are able to learn simple cue-outcome associations as well as healthy controls, regardless of medication state [22, 26], but show impaired performance in more complex, multiple-cue, associative learning tasks [22] and sequential, or 'chain' learning, tasks [26]. Other studies investigated learning in instrumental, or operant, conditioning paradigms, in which participants are required to discriminate between stimuli that require different responses. O'Callaghan and colleagues [27] found that learning rates on an instrumental discrimination task were reduced in patients with PD in comparison to healthy controls [see also 24, 28]. Further, O'Callaghan et al. reported a relationship between reduced stimulus-response learning and grey matter loss in frontostriatal regions of patients, suggesting that learning impairment may not solely be accounted for by dopaminergic disruption, but also by other pathological changes found in PD.

Moreover, patients with PD have been found to have difficulty learning stimulus-response contingency reversals and to be more likely to commit perseveration errors in a medicated state [e.g., 18, 19, 29, 30], as well as in a non-medicated state if probabilistic contingencies, which are more difficult to learn than deterministic contingencies, are used [20]. That is, consistent with findings of executive function impairment in PD, once patients have learnt to make a particular response in the presence of a given cue stimulus, they seem to have difficulty adapting to a change in contingencies when the cue stimulus now requires a different response to be made. It is possible that this lack of flexibility is caused by an inability to extinguish a previously acquired stimulus-response association and/or an inability to acquire a new stimulus-response association.

The aim of this study was to investigate acquisition and extinction of instrumental responses, in patients with PD. Research from animal studies suggests that dopamine plays a role in extinction processes [31], which suggests that extinction of previously learnt responses may be impaired in PD. For instance, genetically modified dopamine transporter knock-out mice seem resistant to extinction after being trained in an appetitive operant paradigm [32]. These findings support the idea that dopamine is involved in both learning and extinction of operant responses. Given these findings and the fact that patients with PD have difficulty with reversal learning, we hypothesized that patients with PD would have difficulty extinguishing instrumental responses. To date, no study has directly examined the performance of patients with PD on a task designed to test this hypothesis.

We further explored the potential association between depression and extinction performance, given that depression is prevalent in PD and may be associated with individual differences in extinction learning. To date, however, very few studies have investigated extinction learning in depressed patients. In a recent study, Tani et al. [33] found slower extinction of a fear response following social aversive conditioning in patients with

depression. In contrast, Kuhn et al. [34] found enhanced extinction of fear responses in depressed patients, but this study used an instructed extinction manipulation, so it is difficult to evaluate learning from feedback during extinction. Depression is, however, highly comorbid with anxiety [35, 36], and a considerable number of studies have found deficits in fear extinction in patients with anxiety [see meta-analyses reported by 37, 38]. These findings raise the possibility that depression might similarly be associated with reduced extinction learning and that this impairment in extinction learning may, at least in part, contribute to the mechanisms of depression in PD. We therefore predicted that depression levels might be associated with deficits in operant extinction in this study.

We used a computer-based avoidance task to investigate acquisition and extinction of instrumental avoidance responses [modified from 39, 40]. Avoidance behavior refers to a response made to prevent a particular negative outcome. The simple task used captures key components of common human and animal avoidance paradigms. This includes an acquisition phase, where behavior determines whether an aversive consequence occurs, and an extinction phase, where the avoidance behavior is no longer required because aversive consequences no longer occur. Thus, during the extinction phase, the previously acquired avoidance behavior is no longer adaptive, and performance of this behavior should decrease in frequency. Importantly, this task also includes an appetitive (approach) component that is disassociated from the aversive component of the task, where participants are able to gain points without risk of aversive consequences. This allows us to test whether any observed differences in acquisition and extinction are due to confounding factors, such as a lack of motivation, rather than impaired learning.

2. Methods

2.1. Participants

Participants included 25 patients with a diagnosis of idiopathic PD (19 males) and 19 healthy age-matched controls (nine males). All participants were recruited from the University of Sydney's Parkinson's Disease Research Clinic, at the Brain and Mind Centre. The stage of PD severity was assessed using the modified Hoehn-Yahr scale of motor function [41], with scores ranging from 1-4, indicating mild to severe stages of the disease. All patients scored within the normal range (scores greater than 24) on the Mini-Mental State Exam [MMSE; 42]. A measure of affective disturbance was obtained using the 21-item Beck Depression Inventory [BDI; 43], on which scores may range from 0 to 63, with higher scores indicating more severe depression. The control participants were excluded if reported neurological disorders or history of psychiatric illness. All participants provided written informed consent prior to testing and the research conducted was approved by the Research Integrity, Human Research Ethics Committee, Western Sydney University.

Due to time constraints or technical errors, some data were not collected from a few participants: MMSE and BDI were not administered to one control participant, MMSE and years of education were not recorded for one patient, and years of education was not recorded from another patient. Most patients were verified to be on dopaminergic medication at the time of testing, with the exception of one patient who was undergoing deep brain stimulation treatment for PD. Another patient's medication could not be verified at the time of writing.

Demographic information for patients and controls is presented in Table 1. Control participants did not significantly differ from patients with PD in terms of age or MMSE scores (see Table 1), however, patients did have fewer years of education ($t(31.3) = 3.06$, $p = .005$, CI95 [-.94 -4.72]). Given this difference, we also report analyses controlling for the number of years of education in the Results section. Patients with PD also reported more depressive symptoms, as their BDI scores were higher ($t(33.8) = 2.35$, $p = .025$, CI95 [.76 10.51]). Scoring on the BDI indicated that one patient fell in the severe range (score of 29 or

greater), three patients fell in the moderate range (score of 20-28), two patients and one control fell in the mild range (score of 14-19) and the remaining participants fell in the minimal range (score of 0-13).

Group	Age (years)	Education (years)	MMSE	BDI	Hoehn-Yahr	Disease duration (years)
PD	67.24 ± 9.64	11.96 ± 2.38	29.00 ± 1.14	10.80 ± 10.81	2.14 ± 0.59	7.05 ± 4.65
Controls	69.37 ± 9.49	14.79 ± 3.41	29.06 ± 1.06	5.17 ± 4.40		
p [CI95]	.469 [-8.01 3.75]	.005 [-.94 -4.72]	.871 [-.75 .63]	.025 [.76 10.51]		

Table 1. Demographics of patients with PD and controls. All results are expressed as mean ± standard deviation. Age, education and disease duration are shown in years. Hoehn-Yahr is a rating of motor function. MMSE = Mini-Mental State Examination. BDI = Beck Depression Inventory. The last row indicates the *p* values and 95% confidence intervals for Welch two-sample *t*-tests comparing the two groups.

2.2. Avoidance task

Avoidance behavior was tested using a computer-based task, programmed in the SuperCard language (Solutions Etcetera, Pollock Pines, CA), and run on a Macintosh computer. The keyboard was masked with the exception of the two keys required to perform the task, which were labeled “Right” and “Left” and were used to control a spaceship. The task consisted of two phases: an acquisition phase and an extinction phase (Figure 1). Participants were able to move the spaceship left or right to one of five horizontal locations

across the bottom of the screen (Figure 2A). Moving the spaceship to the farthest right or left location of the screen allowed entry into a 'safe area' (hiding response; Figure 2E). While hiding, participants were not able to attack small target enemy spaceship or be attacked by a larger sized mothership (Figure 2F). Hiding did not affect the visual appearance of the different on-screen stimuli.

During the 10-sec 'warning' period, the mothership appeared stationary in the center of the screen and points could neither be lost nor gained at this time (Figure 2C). During the acquisition phase, the warning period was followed by a 10-sec 'punishment' period (Figure 2D). During the punishment period, the mothership fired blue lasers every second, which resulted in a 5-point loss if the participant's spaceship was hit by the lasers; with a maximum of 50 points lost during this period. Participants could escape or avoid having their spaceship hit by moving it into one of the two safe areas. During the following inter-trial interval (ITI), a smaller target spaceship appeared randomly in one of six possible locations on the screen, approximately every second (Figure 2A). During this time, the participant's spaceship fired automatically and repeatedly (when outside the safe areas), allowing the participant to gain points by positioning the spaceship underneath the target ship (Figure 2B). Every successful hit resulted in the target being destroyed and the participant earning one point. During ITI, no attacks by the mothership occurred, allowing the participant to gain points without the risk of aversive events.

Figure 1 here

Following the 12 acquisition trials, there was a 12-trial extinction phase. The extinction phase excluded the punishment period, such that every 'warning' period was immediately followed by an ITI (and the mothership never fired lasers). Accordingly, the ITI

in the extinction phase was set to 30 sec, in order to keep the total trial duration consistent in the two phases (Figure 1). Since visual appearance of the different stimuli was not contingent on participant's behavior, the lack of a punishment period during extinction was always apparent. As during the acquisition phase, the participant's spaceship continued to fire automatically and repeatedly during the extinction ITI (when outside the safe areas), allowing to gain additional points. Lastly, it should be noted that the durations of the various periods within the task were doubled in the current study in comparison to previous studies with this task [e.g., 39, 40], to accommodate the motor and cognitive difficulties of the recruited older participants. The participants' firing response was made continuous and automatic to address the same need.

Figure 2 here

2.3. Procedure

The participant was seated at a comfortable viewing distance from the computer screen. The participant received the following instructions displayed on the computer screen: "You are about to play a game in which you will be piloting a spaceship. You may use LEFT and RIGHT keys to move your spaceship (see picture below). Your goal is to maximize your total score. The total score will be displayed at the bottom of the screen. (We'll start you off with a few points now.) Good Luck!", and a picture of the participant's spaceship shown at the bottom of the screen. Importantly, participants were not given explicit instructions on how to gain or lose points, nor were they informed about the safe areas or the hiding response. Participants were given one minute of practice time, during which they could shoot the target but neither the mothership nor lasers appeared (similar to ITI). The start of each new trial and the transition to the extinction phase was not explicitly signaled to the participant. A running

tally of points was displayed at the bottom of the screen, and was initialized to 325 at the start of the experiment. Points never fell below zero in order to minimize frustration.

2.4. Data analysis

The program recorded whether the participant's spaceship was in a safe area or not every 100 ms, allowing for a computation of the percentage of time spent hiding during the 10-sec warning period, the 10-sec period following the warning period and the 20-sec ITI. Hiding in the safe area during the punishment period was considered an escape response, as it allowed the participant to terminate ongoing point loss. Hiding during the warning period was considered an avoidance response, as it could prevent potentially upcoming point loss. But whereas hiding during the warning and punishment periods could be considered adaptive, at least during the acquisition phase, hiding during the ITI demonstrates response error. It precludes the opportunity to shoot at targets and gain points, and could result from the maladaptive generalization of avoidance behavior to a safe context.

Overall performance on the task was measured by total score, points gained (due to successful firing on targets), locomotion (presses on the left and right keys) during the entire task, as well as exploration hiding, i.e., % hiding during the first practice minute of the task.

2.5. Statistical analysis

We analyzed the hiding scores during each period in each phase via a series of 2 (group) x 12 (trial) multivariate analyses of variance (MANOVAs). The Pillai test statistic is reported as a measure of effect size. Additional multiple regression models that control for potentially confounding demographic variables (age, gender, years of education and MMSE scores) are also reported, especially since the two groups significantly differed in terms of years of education.

3. Results

Figure 3 illustrates the trial-by-trial hiding behavior for the warning, punishment and ITI periods within each trial.

Figure 3 here

3.1. Acquisition

Analyses of the warning and punishment periods during the acquisition phase revealed that acquisition of the hiding response was similar in the two groups. The analysis of the warning period revealed only a significant main effect of trial ($F(11, 32) = 12.26$, $p < .001$, Pillai's trace = .808), but no main effect of group nor an interaction ($F(1, 42) = .009$, $p = .926$, Pillai's trace < .001, and $F(11, 32) = .737$, $p = .696$, Pillai's trace = .202, respectively). Similarly, the analysis of the punishment period revealed only a significant main effect of trial ($F(11, 32) = 5.06$, $p < .001$, Pillai's trace = .635), and no main effect of group nor an interaction ($F(1, 42) = .046$, $p = .830$, Pillai's trace = .001, and $F(11, 32) = 1.43$, $p = .210$, Pillai's trace = .329, respectively).

The analysis of the ITI period during the acquisition phase revealed that patients with PD demonstrated higher numerical hiding rates than controls (mean (M) = 34.40, standard deviation (SD) = 13.82, in patients with PD vs. M = 27.54, SD = 8.72, in controls), although the effect was not statistically significant ($F(1, 42) = 3.59$, $p = .065$, Pillai's trace = .079). Neither the main effect of trial nor the interaction were significant ($F(11, 32) = 1.38$, $p = .229$, Pillai's trace = .322 and $F(11, 32) = .882$, $p = .567$, Pillai's trace = .233, respectively). Exploratory analysis revealed that there was a difference between the groups in ITI hiding during the last four trials of the acquisition phase ($t(34.56) = 3.11$, $p = .004$, CI95 [3.54 16.89]).

To control for potentially confounding demographic variables, the average hiding responding during the warning, punishment and ITI periods were each regressed on group, age, gender, years of education and MMSE scores (all predictors were entered simultaneously in the regression models). Group did not predict the hiding scores during the warning and punishment periods (coefficient = -1.80, *SE* = 5.07, *p* = .725 and coefficient = -1.57, *SE* = 6.47, *p* = .810, respectively), but it did predict the ITI hiding scores (coefficient = 10.19, *SE* = 4.86, *p* = .043).

3.2. Extinction

Although patients with PD had greater numerical hiding values during the warning period in the extinction phase, there were no significant main effects nor was there an interaction (main effect of trial: $F(11, 32) = 1.56$, $p = .160$, Pillai's trace = .349; main effect of group: $F(1, 42) = .745$, $p = .393$, Pillai's trace = .017; interaction: $F(11, 32) = .969$, $p = .493$, Pillai's trace = .250). Thus, our hypothesis regarding impaired extinction (as reflected in higher hiding scores during the extinction warning period) was not supported. Note, however, that both groups exhibited very high levels of hiding even in the last extinction trial (76% of patients and 63% of controls hid more than 80% of the time during the warning period), and this ceiling effect may have obscured any differences between groups.

Patients did, however, have higher hiding scores during the punishment and ITI periods. Note that during extinction the lasers were not presented; the punishment period, i.e., the 10 sec that followed the warning signal, was identical to the ITI, but these were analyzed separately to mirror the analyses on the acquisition data. The analysis of the punishment period revealed a main effect of group ($F(1, 42) = 4.83$, $p = .034$, Pillai's trace = .103), but no main effect of trial nor an interaction ($F(11, 32) = 1.18$, $p = .336$, Pillai's trace = .289, and $F(11, 32) = .766$, $p = .670$, Pillai's trace = .208, respectively). Similarly, the analysis of the

ITI revealed a main effect of group ($F(1, 42) = 6.66$, $p = .013$, Pillai's trace = .137), but no main effect of trial nor an interaction ($F(11, 32) = .607$, $p = .809$, Pillai's trace = .173, and $F(11, 32) = .771$, $p = .666$, Pillai's trace = .209, respectively).

To control for the effect of potentially confounding demographic variables, the average hiding scores during the warning, punishment and ITI periods during extinction were also regressed on group, age, gender, years of education and MMSE scores. Consistent with the MANOVAs reported above, group did not predict the hiding scores during the warning period (coefficient = 6.35, $SE = 7.85$, $p = .424$), but it did predict the punishment and ITI hiding scores (coefficient = 15.37, $SE = 5.52$, $p = .009$ and coefficient = 19.26, $SE = 6.55$, $p = .006$, respectively).

3.3. Association with depression symptoms

These differences in responding during the ITI suggest that avoidance patterns are impaired in PD, particularly during extinction. We further investigated whether the depression (BDI) scores might be related to this difference in hiding behavior between groups. Given that during extinction there was no discernable difference between the punishment and ITI periods and to simplify the following analyses, we computed overall hiding scores for the 30-sec period that comprised the punishment and ITI periods. To investigate the potential relationship between extinction learning and depression, we ran three regression models on the 30-sec extinction ITI hiding rates: one including group as a factor, another including both group and the BDI scores, and a third including an interaction term for the group and the BDI scores. The latter was included given that there was a reliable difference in BDI scores between groups, and thus the depression scores may be more strongly related to learning in the PD group than in the control group.

Correlational analyses demonstrated a significant correlation between BDI scores and extinction ITI hiding rates in patients (Pearson $r = .53$, $p = .006$; Spearman $r_s = .57$, $p = .003$), but not in controls (Pearson $r = -.04$, $p = .874$; Spearman $r_s = -.002$, $p = .993$). We then tested a linear regression model, where we regressed the extinction 30-sec ITI hiding scores on age, gender and group. Given that there was a trend-level difference in the acquisition of ITI hiding, we also included this factor in the regression model to control for its potential confounding effect (that is, to control for any individual differences in the acquisition ITI hiding scores that may have carried over in the extinction phase). All factors were entered in the model simultaneously. The model was significant ($R^2 = .75$, $F(4, 38) = 28.71$, $p < .001$). Including the BDI scores as an additional predictor significantly improved the fit of the model ($\Delta R^2 = .03$, $F(1, 37) = 5.05$, $p = .031$). The addition of the group x BDI interaction further improved the model fit ($\Delta R^2 = .03$, $F(1, 37) = 5.30$, $p = .027$). Therefore, the addition of the BDI scores and the group x BDI interaction afforded an increase of 6% in the amount of explained variance. Separate regression models for each group revealed an effect of BDI on the hiding scores in the PD group (coefficient = .395, $SE = .167$, $p = .028$), but not in the control group (coefficient = -.471, $SE = .402$, $p = .262$; note that both regression models controlled for age, gender, and the acquisition ITI hiding scores). Indeed, higher BDI scores were associated with a greater tendency to hide during the extinction ITI in the PD group but not in the control group (Figure 4). Finally, it is worth noting that these results were not confounded by years of education or MMSE scores; BDI scores still predicted the extinction ITI hiding scores in patients ($p = .026$), but not in controls ($p = .774$), when these factors were additionally included in the regression models.

Figure 4 here

These findings are well summarized by the results of a relative importance regression model [44] that estimated the contribution of each factor to the amount of explained variance (R^2) in the extinction ITI hiding scores. As expected, the acquisition ITI hiding scores accounted for a large proportion (63%) of the explained variance. More importantly, after controlling for this confounding factor, as well as age and gender, the BDI scores and the group x BDI interaction accounted for 12% and 16% of the explained variance, respectively, whereas group only accounted for 5% (Figure 5).

Figure 5 here

3.4. Overall performance

The number of gained points and the total scores were numerically lower in the patient group, though these comparisons did not reach significance (M = 407, SD = 197, in patients with PD vs. M = 502, SD = 119, in controls; $t(40.3) = 1.99$, $p = .054$, CI95 [-1.70 192.02], and M = 631, SD = 246, in patients with PD vs. M = 735, SD = 144, in controls; $t(39.8) = 1.76$, $p = .087$, CI95 [-15.72 223.95], respectively). Similarly, there was no significant difference in exploration hiding time (% hiding during the first practice minute) between groups (M = 32.72%, SD = 15.55, in patients with PD vs. M = 33.22%, SD = 14.56, in controls; $t(40.1) = .109$, $p = .914$, CI95 [8.73 -9.72]). However, the patients' average locomotion scores during the task (the number of presses on the left and right arrow keys) were significantly higher (M = 1600, SD = 884, in patients with PD vs. M = 1068, SD = 367, in controls; $t(33.8) = 2.72$, $p = .010$, CI95 [134 930]).

4. Discussion

Cognitive impairment is a non-motor symptom commonly found in PD that has been shown to impact quality of life even in its most subtle form [10]. Emerging evidence suggests

that the nature of cognitive impairment in PD is not global; instead, specific learning processes are impaired, while others remain spared [25]. The purpose of this study was to extend previous research on learning in PD by examining the specific processes of avoidance learning and operant extinction in this population using a computer-based task designed to capture key components of traditional avoidance paradigms. Although rates of avoidance behavior were similar in patients and controls, we found greater hiding during the safe ITI period in patients. Furthermore, we report an association between deficits in operant extinction and depression symptoms in patients.

4.1. Acquisition

Patients acquired the avoidance response as well as healthy controls, suggesting that the acquisition of this instrumental response is intact in PD. This result seems inconsistent with previous studies that reported impaired instrumental discrimination learning in PD [24, 27, 28]. However, patients in our study also exhibited marginally higher hiding rates during the ITI during acquisition, suggesting that there may have been some impairment in learning to discriminate between the appetitive approach response (shooting alien ships) that was most adaptive during the ITI and the avoidance hiding response that was more adaptive during the warning and punishment periods. Patients in our study therefore may have had some difficulty discriminating between danger and safety signals, particularly performing the appropriate response during safety periods.

A number of factors may account for the fact that our study failed to demonstrate a significant deficit in acquisition of instrumental behavior in patients, in contrast to previous studies. One reason for this difference may be due to the complexity of the tasks employed. In the previous studies mentioned [24, 27, 28], participants were required to discriminate between multiple response-outcome associations, whereas the task employed in the current study required participants to discriminate between only two potential responses (shooting

targets versus hiding). In classical conditioning paradigms, research suggests that PD patients are impaired in more complex tasks that require participants to learn multiple cue-outcome associations; however, simple cue-outcome learning generally remains intact [22]. This pattern of learning may also be true in the case of operant learning and could partially account for the current findings, as our relatively simpler task may have masked groups differences due to ceiling effects in performance during acquisition.

A further contributing factor that may account for the current findings is related to the valence of the outcomes employed. In previous studies, operant responses resulted in either positive consequences (points gained), or relatively neutral consequences (no points gained). In contrast, in the current study, shooting during the ITI resulted in positive consequences (points gained), but failing to perform the avoidance hiding response during a punishment period resulted in aversive consequences (points lost). It could be argued that differences in learning could be due to the salience of the outcome, such that aversive consequences are more salient to PD patients than positive outcomes. Indeed, research on reinforcement learning suggests that PD patients learn better from aversive than appetitive consequences, although dopaminergic medication can reverse this pattern [45, 46]. This explanation is consistent with the observation that many patients exhibit the '*Parkinsonian Personality'* - characterized by caution, risk aversion and anhedonia [47, 48]. While there is evidence to suggest that in some cases dopaminergic medication can cause increased impulsivity and risk taking in patients [49], this is not the case for the majority of PD patients, who tend to score more highly on risk aversive traits than the general population both premorbidly [50] and through the course of the disease [51]. If simple operant learning remains intact and PD patients tend to be more risk averse, it would follow that they may demonstrate a preference for learning and performing an avoidance response such as hiding rather than an appetitive (but sometimes risky) response, such as shooting in our task. This may explain why patients

in our study acquired the avoidance response as well as healthy controls and only may have had some difficulty acquiring the appetitive (shooting) response during safety periods. In contrast, acquisition of the correct stimulus-response contingencies would have relied more on learning from positive consequences in previous studies, potentially explaining why they found a more profound deficit in instrumental learning in patients than we did [24, 27, 28].

4.2. Extinction

The second aim of the study was to examine extinction of the avoidance response. We did not find a significant difference between groups in the amount of time spent hiding during the warning period in the extinction phase. In fact, hiding during this period did not seem to extinguish at all, with both groups maintaining a high rate of hiding. This ceiling effect in performance may have contributed to the lack of a significant group difference.

Nevertheless, patients exhibited a higher hiding rate during the ITI in the extinction phase. That is, patients maintained a relatively high rate of hiding during the ITI during extinction, despite the fact that no punishment periods occurred at all during this phase, whereas healthy controls reduced their rate of hiding. This reluctance to abandon the hiding response during extinction may reflect a deficit in learning about safety cues, which was perhaps most evident in performance during the most unambiguously safe period during the experiment, i.e., during the extinction ITI, where both the immediate ITI context and the overall extinction phase signaled safety. Similarly, it could reflect the maladaptive generalization of avoidance behavior to a safe context. Further, exploratory analyses showed group difference on the last four acquisition trials, suggesting that learning capabilities during acquisition could contribute to different extinction patterns (Figure 2).

An alternative explanation for these findings is that PD patients had perhaps a reduced ability to ‘shift’ a behavioral response, rather than an impairment in extinction learning itself. Set shifting refers to the ability to shift from one response to another. In the case of this task,

that would mean an ability to shift from a 'hiding' response to an 'active' shooting response. Such impaired attentional flexibility is one of the core cognitive deficits seen in PD, and has been shown to be related to perseveration (i.e., an inability to shift attention away from previously relevant information) and learned irrelevance (i.e., an inability to shift attention towards previously irrelevant information) [29]. In other words, patients with PD struggle to overcome learned attentional biases. While such set shifting impairment could account for performance in the extinction phase, where patients maintained the acquired hiding response throughout the extinction phase, this explanation fails to account for performance during the acquisition phase. That is, during acquisition patients were able to shift their behavioral response from an 'active' response during the ITI to a 'hiding' response during the warning and punishment periods. As such, the pattern of performance across both phases of the task appears to be better accounted for by the idea that dopamine dysregulation specifically impairs safety learning, particularly when both the immediate within-trial context (the ITI) and the general context (the extinction phase) signal safety.

4.3. Association with depression symptoms

We further found that the patients' depression scores accounted for their greater hiding rates during the extinction ITI. This suggests that depression might be linked to reduced learning about the appropriate alternative response to be performed during a safe period. In our task, the safety period consisted of the general ITI context, which is a diffuse set of cues that are present throughout the task, as opposed to the discrete threat cue (the appearance of the mothership). The finding that, in patients, depression was associated with reduced learning about this diffuse safety context is consistent not only with the literature on safety learning, but also with a literature linking depression to a more general impairment in learning about contextual cues. This latter body of research has shown that both patients diagnosed with depression and individuals with subclinical depression exhibit reduced learning about the

likelihood of an outcome occurring in the presence of contextual cues [52-55]. Evidence suggests that this is potentially due to a reduced ability to process and maintain contextual representations in an active memory state [53, 56]. Therefore, a lack of learning about the contextual cues present during the ITI may have contributed to the maladaptive avoidance patterns observed in patients, particularly in those who reported a high level of depression.

4.4. Clinical implications

The findings in this study have potential clinical relevance for the treatment of psychological disorders in PD patients. Affective disorders such as anxiety and depression are more prevalent in patients with PD than the general population [57-60], and exposure-based therapies are frequently employed in the psychological treatment of these disorders, amongst others. Exposure-based therapies partially rely on extinction to reduce fear responses, or to facilitate the processing of emotions [61]. However, our findings suggest that extinction is impaired in PD. This might suggest that exposure-based therapies may be less effective in a PD population due to an impairment in extinction processes, particularly in those who suffer from depression. As such, the impact of impaired extinction processes on the efficacy of exposure-based therapies warrants future empirical attention.

Our study also found intact avoidance learning in a PD population. Avoidance is a common maintaining factor of psychological disorders such as anxiety and depression. It is therefore possible that a potential contributing factor underlying the development of some psychological disorders in PD is intact avoidance learning coupled with impaired learning about safety. A similar pattern has been reported in previous studies investigating the relationship between learning and anxiety [37, 38, 62]. This suggests that dopaminergic deficits may not only affect cognitive function in PD but may also be associated with emotion dysregulation via its effects on avoidance behavior. Further research is needed to explore the

contribution of learning processes to both cognitive and emotional dysfunction in PD, and the extent to which they are driven by dopaminergic deficits.

A possible limitation that should be acknowledged in the current work is the ecological validity of using computer-based tasks with an aging population. There are age-related changes in cognition (e.g., decreased memory capacity and attentional control) and motor systems (e.g., difficulty with fine motor control and coordination), which might affect performance on these tasks [63]. Indeed, while the avoidance task used in the current study was adapted for this population (by doubling the duration of the various periods and eliminating the need to press a "fire" key), it is still possible that age affected the overall performance. For instance, limited performance could have masked potential group differences during the extinction phase of the avoidance response. Overall, the current study provides support to the potential of technology-based products in older adults [63, 64], and PD patients in particular [65], but also highlights the need to pay close attention to improving their ecological validity.

5. Conclusions

In summary, cognitive impairment is increasingly recognized as a non-motor symptom of PD; however, the specific nature of the impairment is not yet fully characterized. This study is the first to provide preliminary evidence that avoidance patterns are impacted in PD, thus increasing our understanding of not only the nature of the cognitive impairment observed in PD, but also its potential contribution to comorbid symptoms such as depression.

The results of this research open up several more lines of enquiry. One question raised is whether the altered performance observed in the patient group, and which was particularly pronounced in more depressed patients, is restricted to contextual cues, or whether this deficit generalizes to discrete cues as well. That is, it is unclear whether a deficit in learning about diffuse contextual cues may have contributed to the observed reluctance to abandon the

acquired hiding response in the presence of these safety cues. A second question raised is whether exposure-based psychological therapies will be as effective in this population if extinction is impaired. These are valid questions that future research could address in the hope to improve the treatment and management on non-motor symptoms in PD.

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Conflict of interest

All authors have no conflict of interest to declare. Opinions stated herein are solely those of the authors and do not necessarily represent the official views of the Department of Veterans Affairs or the U. S. Government.

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Figure captions

Figure 1. Schematic of within-trial timeline of the escape-avoidance task. (A) In the acquisition phase, 12 trials consisted of a 10-sec warning period, a 10-sec punishment period and a 20-sec inter-trial interval (ITI). (B) In the extinction phase, 12 trials consisted of a 10-sec warning period and a 30-sec ITI.

Figure 2. Schematic of the computer-based avoidance task. (A) A target enemy spaceship appears in one of six locations in the upper half of the screen approximately every second. (B) To earn points, the participants must position themselves below the target, allowing them to shoot the target. (C) A large mothership appears on the screen every 40 sec, signaling the 10-sec warning period. (D) During the acquisition phase, the warning period is followed by the appearance of 'blue lasers', which fire on screen for 10 sec (punishment period). Every time the participant's spaceship is hit, it results in a 5-point loss, with a maximum of 50 points lost. (E) 'Safe areas' are located at the bottom right and left of the screen. Moving into one of these areas is defined as 'hiding'. (F) When the participant's spaceship is located in a 'safe area', points cannot be lost, nor can they be gained.

Figure 3. Average trial-by-trial hiding scores during the warning, punishment, and ITI periods of each trial in controls and patients. Note that the lasers were not presented during extinction; the "punishment period" during extinction phase in the figure above corresponds to the 10 sec that followed the warning period and is identical to the 20-sec ITI period. Data are expressed as mean ± standard error of the mean.

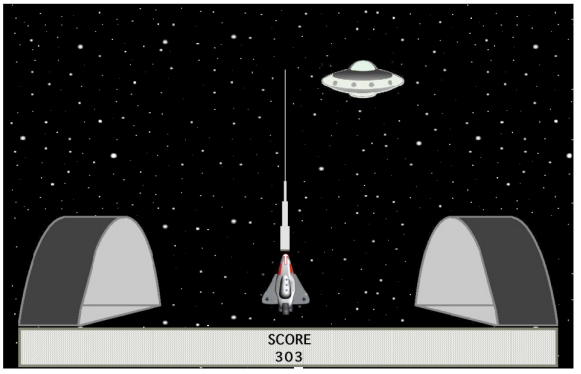
Figure 4. Average hiding scores during the extended 30-sec ITI period during extinction (comprising the 10-sec punishment period and the 20-sec ITI period) plotted as a function of BDI scores and group.

Figure 5. Relative importance metrics for each predictor obtained from a relative importance regression model on the 30-sec extinction ITI hiding scores.

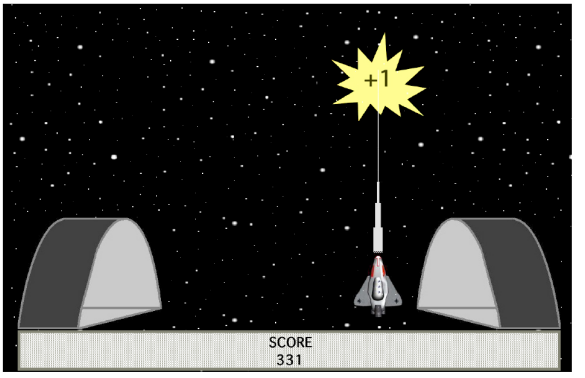
A Acquisition trial

B Extinction trial

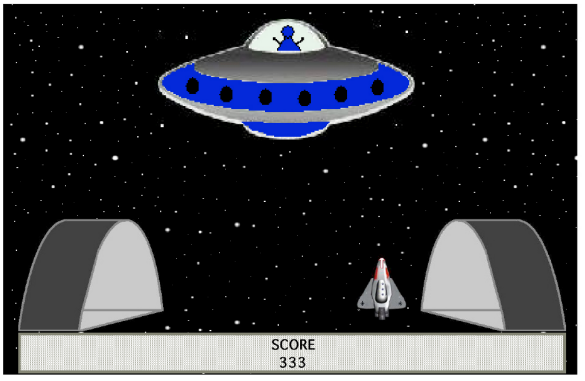
A


SCORE
303

B


+1
SCORE
331

C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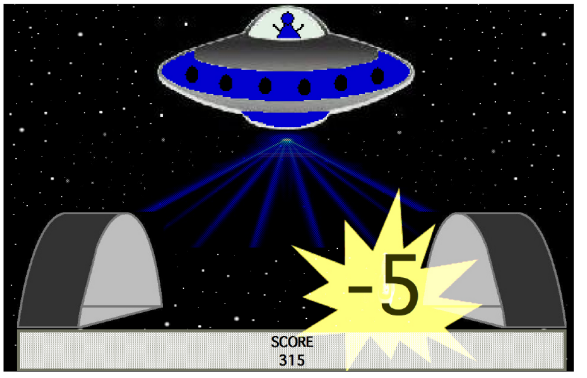
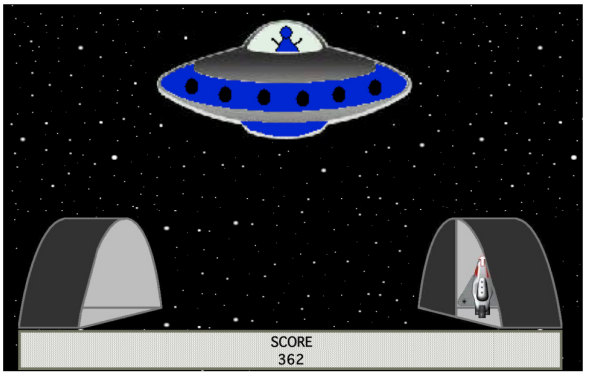
333

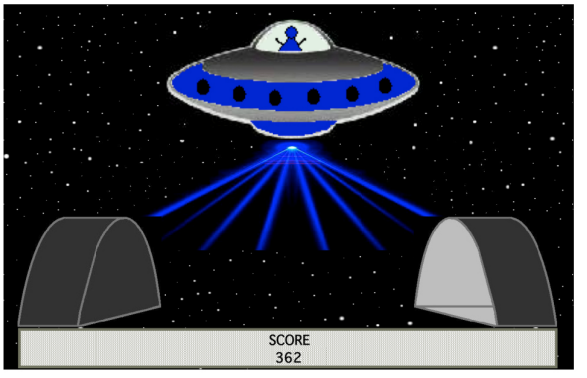
D

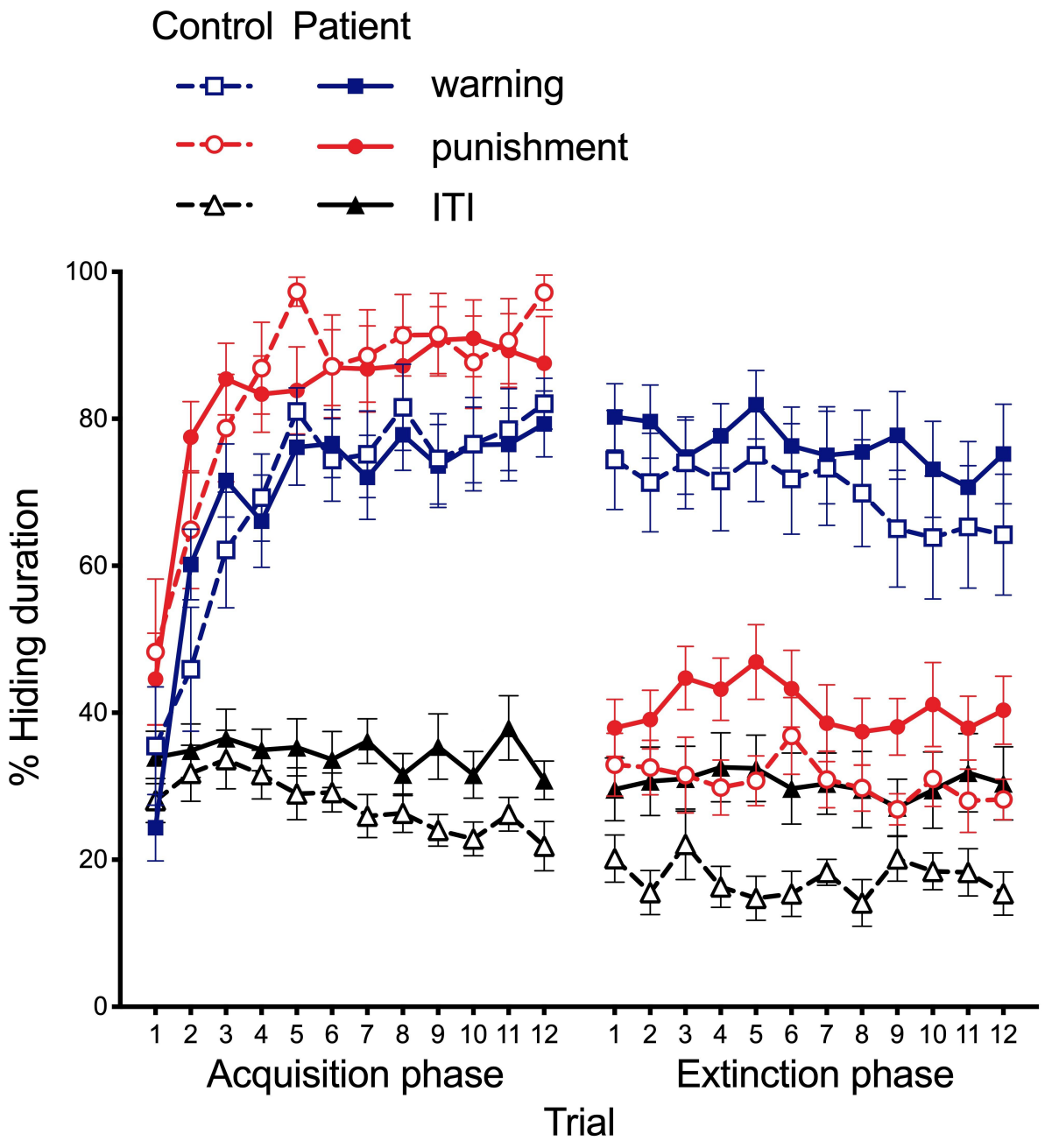

-5
SCORE
315

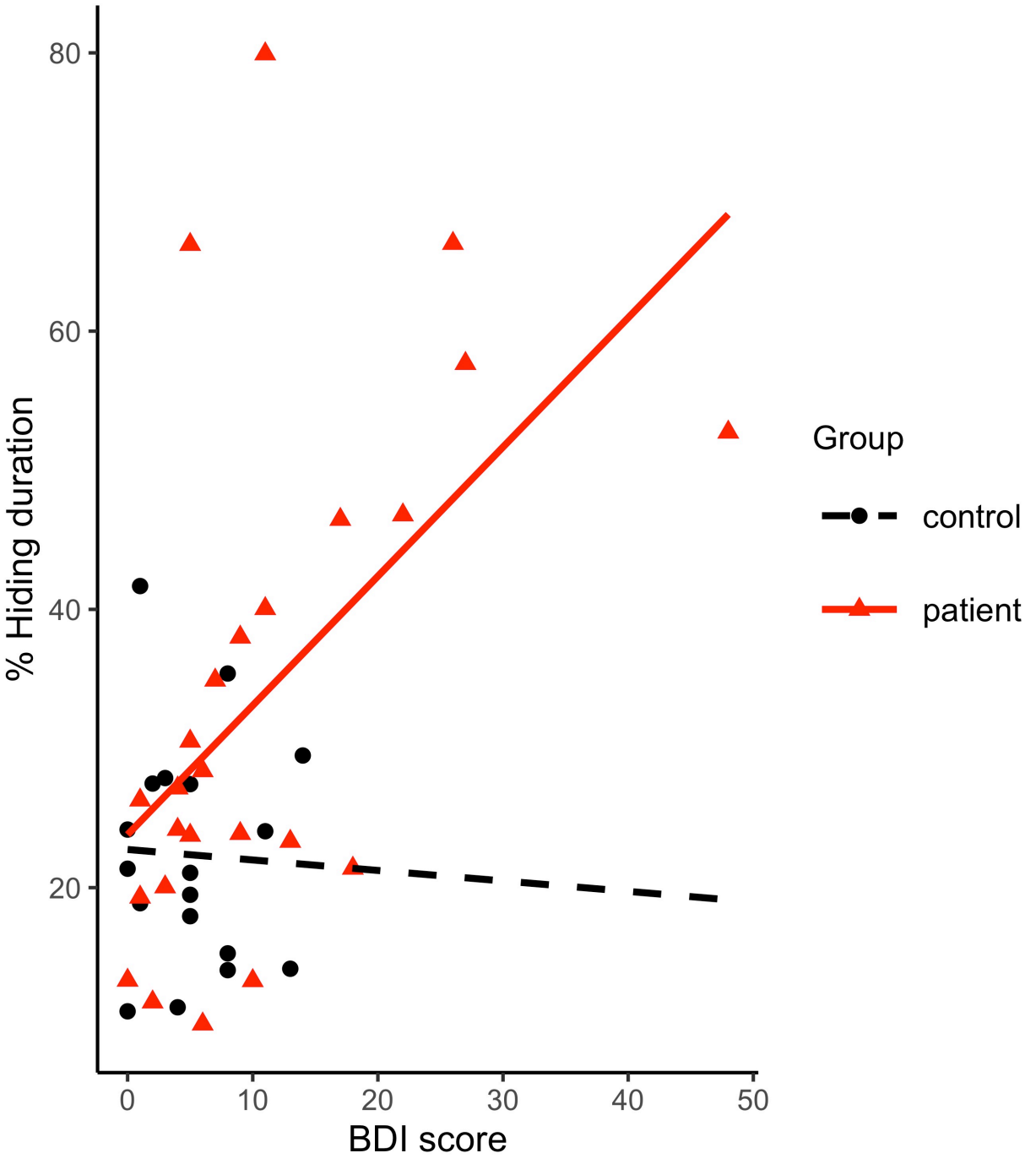
E

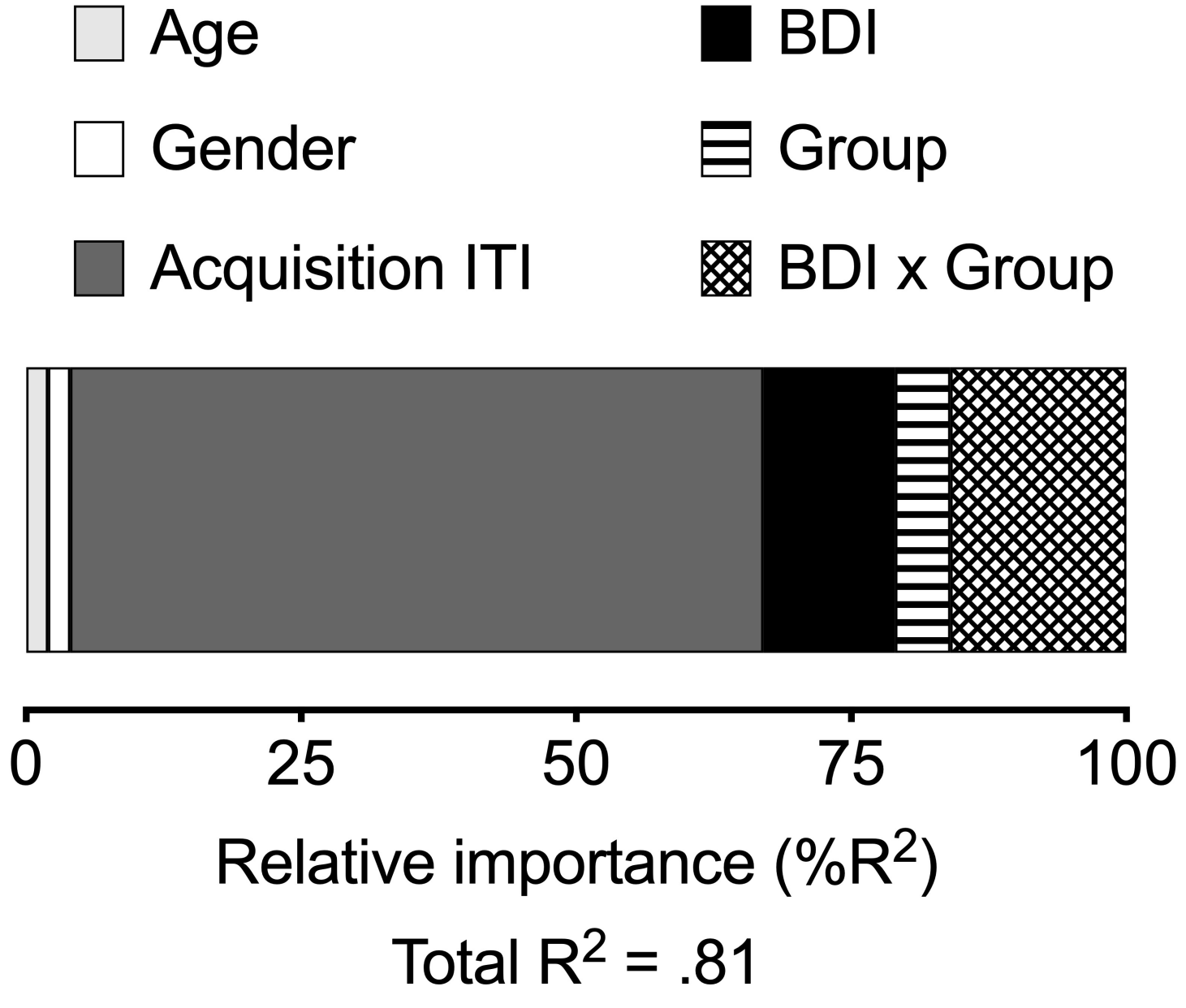

SCORE
362

F


SCORE
362


Control Patient
warning
punishment
ITI
% Hiding duration
100
80
60
40
20
0
1 2 3 4 5 6 7 8 9 10 11 12
1 2 3 4 5 6 7 8 9 10 11 12
Acquisition phase
Extinction phase
Trial


80
60
40
20
% Hiding duration
0
10
20
30
40
50
BDI score
Group
control
patient


Age
Gender
Acquisition ITI
BDI
Group
BDI x Group
0
25
50
75
100
Relative importance (%R2)
Total R2 = .81

Credit Author Statement:

Jony Sheynin: Formal analysis, Conceptualization, Methodology, Software, Writing - Original Draft;

Irina Baetu: Formal analysis, Writing - Original Draft;

Lyndsey E. Collins-Praino: Formal analysis, Writing - Review & Editing;

Catherine E. Myers: Conceptualization, Methodology, Writing - Review & Editing;

Robyn Winwood-Smith: Investigation, Writing - Review & Editing;

Ahmed A. Moustafa: Conceptualization, Resources, Supervision, Writing - Review & Editing;