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Research report

An EEG marker of reward processing is diminished in Parkinson's disease

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HIGHLIGHTS

- Dopamine neuron cell death leads to a host of deficits in Parkinson's disease.
- The reward positivity is theorized to be dependent on dopaminergic function.
- The reward positivity was blunted in people with Parkinson's disease.

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ABSTRACT

The electroencephalographic signal known as the Reward Positivity (RewP) scales with the reward prediction error following reward receipt. This signal is computationally identical to the dopamine-driven learning process relating to the discrepancy between reward expectation and reward acquisition. The current study aimed to investigate if the RewP is diminished in Parkinson's disease (PD). In this study, 28 people with PD and 28 age- and sex-matched healthy controls completed a reinforcement-learning task. In line with expectations, the RewP was smaller in persons with PD than in controls. Yet contrary to expectations, RewP amplitude did not differ in on vs. off medication conditions, and it was positively correlated with the number of years diagnosed with PD. We propose that this symptom-specific alteration in RewP may be a consequence of a common methodological procedure in PD research (e.g. restricted recruitment) or it might truly be a marker of early-stage disease (e.g. prior to network re-adaptation). These surprising findings motivate separate testable hypotheses for assessing aspects of PD with this novel neural marker of reward.

1. Introduction

The electroencephalogram (EEG) feature known as the reward positivity (RewP) has garnered a great deal of attention for its sensitivity to reward processing and reward learning (Walsh and Anderson, 2012). The RewP is a positive deflection in the event related potential (ERP) that is most commonly quantified over fronto-central sites and is usually maximal around 200–400 ms following reward presentation (Heydari and Holroyd, 2016; Holroyd et al., 2011; Proudfit, 2015). The amplitude of the RewP scales with the degree of positive reward prediction error, whereby "better than expected" outcomes evoke increasingly larger RewP amplitudes (Baker and Holroyd, 2011; Cavanagh, 2015; Holroyd and Umemoto, 2016). Importantly, this component has been theorized to be dependent on midbrain dopaminergic functions which underlie reward prediction error coding (Holroyd and Umemoto, 2016), a construct derived from reinforcement learning theories (Holroyd and Coles, 2002; Schultz et al., 1997). Due to its sensitivity to dopaminergic projections, as well as the simplicity of assessment, the RewP may be a very promising signal for the study of disorders relating to aberrant dopaminergic signaling such as Parkinson's disease (PD).

To date, very few reports have investigated feedback-related ERPs in PD populations. A recent report (Martinez-Horta et al., 2014) examined ERPs for win and lose feedback in apathetic and non-apathetic PD patients while on their medication. In that study, the use of difference waves (losses minus wins) revealed reduced ERPs to loss feedback in apathetic PD groups than non-apathetic PD and healthy controls. The current report aimed to extend these findings in two ways. First, we focused on the generation of the RewP, since unlike the loss condition, it conforms to a signed reward prediction error. Second, in the current report we investigated if dopaminergic medication had a modulatory effect on the RewP. Another report investigated feedback related EEG

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signals in PD populations (Mensen et al., 2015), however, the spatio-temporal windows used to quantify the feedback evoked signals were different from the RewP and other feedback related potentials. A recent review examined a variety of other scalp-recorded EEG signals in persons with PD and highlighted numerous electrophysiological markers of cognitive control that are diminished compared to controls (Seer et al., 2016). Importantly, the authors of this review suggest that differences in these EEG activities appear to map onto different stages of disease progression. It remains unknown how the RewP relates to disease progression in PD.

The steady reduction in phasic dopamine projections directly relate to the progressive motor deficits seen in PD, and this can affect different areas of the brain throughout disease progression. For example, the ventral striatum is less affected than the dorsal striatum during early stage PD (Cools et al., 2001; Seer et al., 2017). While dopamine replacement treatments such as levodopa (L-dopa) can restore motor function, their influence on executive impairments has mixed effects (Moustafa, 2011; Schott et al., 2007). There is a lack of understanding of the role of disease progression on reward-related neurological signals, as well as any modulation by dopaminergic therapy.

The current study aimed to investigate how the RewP is affected in PD, and if the duration of the disease or medication status alters this relationship. For our first aim, we sought to investigate if the RewP was smaller in people with PD compared to matched healthy controls (CTL). In both groups, we assessed known modulators of RewP amplitudes including condition differences in reward surprise ("better than expected" outcomes) and volition (Walsh and Anderson, 2012). The outcomes from volitional actions are valued higher than a-volitional (instructed) choices (Cockburn et al., 2014). This assignment of higher value for volitional outcomes has been credited to dopamine-driven processes in the basal ganglia that are compromised in PD (Cavanagh et al., 2017; Frank, 2005).

For our second aim, we investigated potential disease and medication-specific modulators of RewP amplitudes. Prior reports from this same cohort have all indicated that years since diagnosis was the major explanatory variable for aberrant learning and diminished neural signals (Cavanagh et al., 2017, 2018; Singh et al., 2018). We also examined the influence of depressive symptomatology, which has been shown to affect RewP amplitude (Proudfit et al., 2015; Weinberg and Shankman, 2017; Whitton et al., 2016), as well as moderation by L-Dopa equivalence dose (LED) or motor ratings from the United Parkinson's Disease Rating Scale (UPDRS).

2. Results

People with PD visited the lab twice, seven days apart: once on medication and once after a 15-h overnight withdrawal from their individual prescriptions of dopaminergic medication used to treat PD. Hereafter these conditions are referred to as ON or OFF. People with Parkinson's completed neuropsychological and questionnaire assessments in their ON state. The CTL group only visited the lab once. Table 1 describes the participant demographics, neuropsychological tests, and symptom scores. Persons with PD did not differ from controls in any demographic or neuropsychological measure except they had higher scores on the Beck Depression Inventory ($t(54) = -2.05$, $p = .046$, d = 0.546), which was expected as depression is common in PD.

Fig. 1 illustrates the experimental task. Participants were presented with one of four stimulus pairs, where each stimulus was a colored shape associated with a different probabilistic chance of winning (a green +1) or losing (a red 0) feedback. The conditions consisted of orthogonalized manipulations of difficulty (reward difference between stimuli) and volition (free vs. forced choice). Comparisons of task performance (reaction time and accuracy) used 2 (MEDICATION: CTL vs. ON or OFF) * 2 (VOLITION: choose vs. match) * 2 (DIFFICULTY: easy vs. hard) ANOVAs. There were no main or interactive effects with MEDICATION between CTL and ON or between CTL and OFF, nor were there differences between ON and OFF states. All task performance statistical outputs (Table S1) and line plots (Fig. S1) can be viewed in the supplement.

Table 1
Persons with PD and control participant demographics. All controls were age and sex matched to a person with PD. Only BDI differed between groups (PD > HC). BDI = Beck Depression Inventory, MMSE = Mini Mental State Exam, NAART = North American Adult Reading Test, UPDRS = United Parkinson's Disease Rating Scale (motor), LED = L-Dopa equivalence dose, Dx = Parkinson's diagnosis.

	PD	HC	Statistic
Sex	17 M, 11F	17 M, 11F	
Age	69.75 (8.59)	69.21 (9.23)	$t(54) = -0.23$, $p = .82$
Yrs Ed	17.25 (3.24)	16.63 (3.13)	$t(54) = -0.72$, $p = .47$
Yrs Ed Parents	12.49 (3.82)	12.37 (3.41)	$t(54) = -0.23$, $p = .82$
MMSE	28.64 (1.06)	28.82 (1.02)	$t(54) = 0.64$, $p = .52$
NAART	45.04 (10.20)	47.00 (7.36)	$t(54) = 0.83$, $p = .41$
BDI	7.64 (5.23)	4.93 (4.69)	$t(54) = -2.05$, $p = .046$
UPDRS ON	22.14 (10.15)		
UPDRS OFF	23.79 (8.71)		
LED	703 (440)		
Years since Dx	5.54 (4.18)		

2.1. Group differences

Fig. 2 shows the grand average waveforms for reward-locked ERPs collapsed across DIFFICULTY and VOLITION conditions, separated by each MEDICATION group. We first contrasted the RewP between groups in separate ANOVAs (ON or OFF vs. CTL). For the ON condition, the between-subjects ANOVA revealed a significant MEDICATION (CTL > ON) main effect on RewP amplitude ($F(1,54) = 6.270$, $p = .015$, $\eta^2 = 0.104$). There were no significant two-way or three-way interactions with either DIFFICULTY or VOLITION. All statistical outputs (Table S2) and line plots (Fig. S2) can be viewed in the supplement. Additionally, we investigated the ERPs for lose trials, however, there were no significant effects between MEDICATION groups. Figures and statistical analyses can be found in the Supplementary materials section (Fig. S3) as well as statistical test for win minus lose ERP difference waves (Fig. S4).

For the OFF condition, a similar ANOVA failed to reveal a significant MEDICATION difference ($F = 2.627$, $p = .111$, $\eta^2 = 0.046$); there were no significant interactions with group. Taken together, these results partially confirm our initial hypothesis in that the RewP is diminished in PD populations, but this was only statistically significant while they were on their medication.

2.2. Disease moderators of RewP within the PD group

Next, we examined any interactions between task and subject-specific moderators of the RewP within the PD group, including medication status (binary) and years since diagnosis (continuous) using a within-subject ANCOVA. There was no difference between ON and OFF conditions (No MEDICATION main effect ($F = 0.559$, $p = .454$, $\eta^2 = 0.011$), nor any interaction between MEDICATION with task conditions. There was a significant main effect for YrsDx ($F(1,53) = 10.921$, $p = .002$, $\eta^2 = 0.171$); this did not interact with any of the task-conditions. Given the absence of an influence of task conditions, these were averaged together for subsequent analyses for RewP amplitude. A stepwise multiple regression was conducted to examine the influence of MEDICATION, LED, BDI, AGE, YrsDx and UPDRS ratings on RewP amplitude. This analysis revealed that YrsDx was the only significant predictor of RewP amplitude ($\beta = 0.079$, $t = 3.318$, $p = .002$), with longer YrsDx correlating with larger RewP amplitudes. Notably, this was the opposite of our *a priori* hypothesis. No other

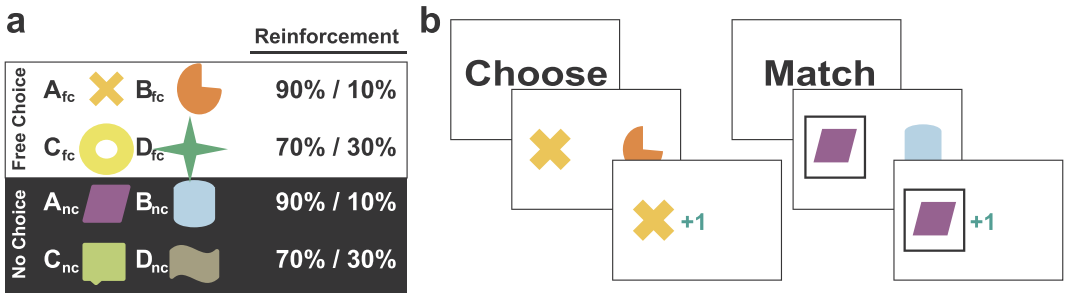

Fig. 1. Task description. a) The task used four different pairs of stimuli with easy (90%/10%) or hard (70%/30%) reinforcement rates and a free choice versus no choice dimension. b) Participants were informed whether they would 'choose', (make a free choice to sample the reinforcement probabilities), or 'match', (select the stimulus with the box around it). No-choice trials were yoked to free-choice trials to ensure equal reward values. The RewP was elicited by the presentation of probabilistic rewards (+1) following action selection.

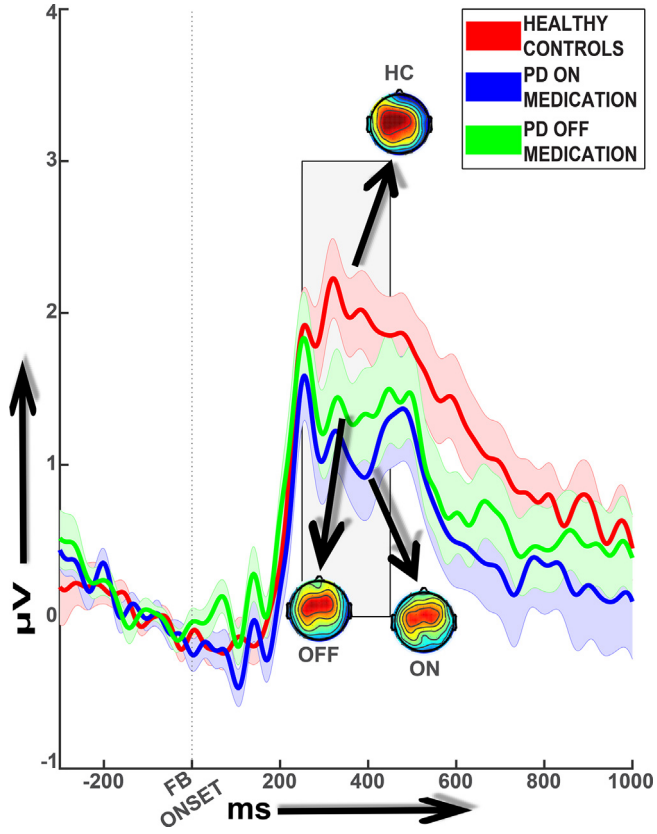

Fig. 2. ERPs time-locked to feedback for healthy controls and people with Parkinson's on medication collapsed across experimental conditions. The grey window represents the RewP time window (250–450 ms) used for ERP analyses. Topographic maps for rewards (scaled: ± 2 μV) reveal averaged activation related to rewarding feedback stimuli.

variable had a meaningful bivariate relationship with RewP (r's < .365, p's > .056; see Figs. S5 and S6 for correlation tables). Although depression is prevalent in PD and it is known to affect RewP amplitudes, BDI scores were not significantly correlated with YrsDx (r = 0.297, p = .125) verifying that YrsDx was the best predictor of RewP amplitude in this sample.

Fig. 3 shows how the RewP was correlated with YrsDx (ON: r(27) = 0.377, p = .048; OFF: r(27) = 0.408, p = .031). This relationship was not seen between YrsDx and ERP amplitudes during lose trials (ON: r(27) = 0.235, p = .228; OFF: r(27) = 0.237, p = .225), demonstrating further specificity. To assist in the interpretation of this outcome, which was the exact opposite of the *a priori* hypothesis, we split the data into two groups as in our prior report (Cavanagh et al., 2017) for earlier stage (N = 16, mean years since diagnosis = 2.875) and later stage PD (N = 12, mean years since diagnosis = 9.083). When compared to the CTL group, the earlier stage group had a significantly smaller RewP amplitude (ON: $t(42) = 3.238$, p = .002, d = 1.015; OFF $t(42) = 3.054$, p = .004, d = 0.956) but the later stage group did not (ON: $t(38) = 0.552$, $p = .584$, d = 0.186; OFF $t(38) = 0.612$, $p = .544$, d = 0.209). This finding suggests that our *a priori* hypothesis was correct, but that this was limited to the early-stage group.

3. Discussion

In the current study we found that the RewP amplitude is smaller in people with PD than matched controls, and that this diminishment is sensitive to the duration of PD. The cortically-generated RewP has been theorized to be modulated by phasic midbrain dopamine (Holroyd et al., 2008), since both these processes are sensitive and specific to the neural coding of events that are "better than expected". However, it is not known if one of these systems influences the other in a causal manner, if they are both influenced by a third variable, or if they reflect parallel processes. Despite these uncertainties, the best current understanding of the RewP suggests that it should be affected by variation in the dopaminergic system and thus by PD and L-dopa treatment. Our findings reported here provide an initial test of this intuitive hypothesis.

The influence of PD on the RewP was not moderated by any task-relevant variables (difficulty or volition), suggesting a generalizable phenomenon. Although the PD and control groups were significantly different when PD participants were ON medication, the OFF medication comparison did not significantly differ from the control group (although the findings were in the expected direction). This finding, as well as the lack of a difference between ON and OFF conditions ($\eta^2 = 0.010$) stand in stark contrast to the dominant hypothesis of a dopaminergic basis of the RewP (Holroyd et al., 2008). In addition, it was surprising that the variance associated with years since diagnosis was also specific to larger RewPs, even over-and-above mood, motor, demographic, and symptom-related variables. These specificities all point to a compelling, but under-explained consequence of PD-related dysfunction.

3.1. Why was the reduced RewP specific to early-stage PD?

The major interpretative hurdle in the current study is the unexpected finding that only early stage people with PD had a reduced RewP. We have two hypotheses for this unexpected occurrence. First, this unexpected increase in RewP amplitudes may pertain to specific disease-related characteristics of our sample, particularly that the duration of disease in our sample is not necessarily indicative of disease severity. There was no significant relationship between disease duration and our measure of motor dysfunction (UPDRS; r = −0.195, $p = .319$) suggesting the severity of disease was similar between those in the earlier stage and those in the later stages of the disease. Thus, biased sampling from the population may be a cause: participants had to be

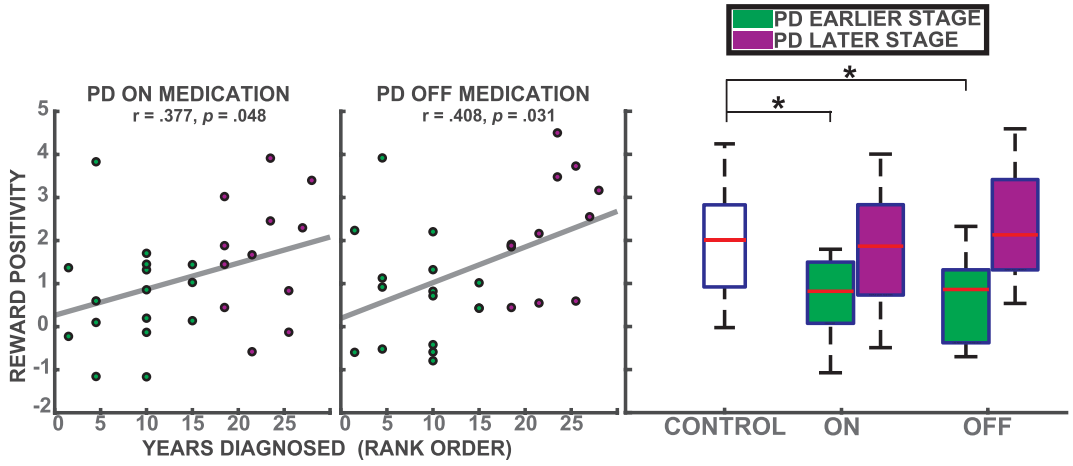

Fig. 3. RewP amplitude is sensitive to disease duration in PD. Scatterplots demonstrate the reliability of this relationship, and that it is insensitive to medication status. Boxplots of the median split of disease duration reveal that early stage PD is characterized by diminished amplitudes compared to matched controls, and that later stage disease is associated with a normalization of this initial effect. *$p < .005$.

able to tolerate a 15-h medication withdrawal to participate, similar to other studies (Cools et al., 2001, 2006). It is possible that this criterion restricted the sample of late-stage participants to those with mild symptom progression who are a unique subtype of PD patient. The second possibility is that the RewP truly reflects early-stage disease characteristics prior to network re-organization and adaptation to increasing medication load, which causes a re-balancing of RewP amplitudes. In either case, the RewP may potentially be able to parse distinct aspects of Parkinson's disease progression, suggesting an urgent need for replication and extension of these findings.

3.2. RewP in PD was not affected by depression

We found significant differences in BDI scores between our healthy controls and people with PD ($p = .022$). This significant increase of depression scores is not surprising given the documented high rates of depression and PD comorbidity (Dissanayaka et al., 2011; Menza et al., 1993). Although the RewP is similarly diminished in line with depressive symptoms (Bress et al., 2012, 2013; Foti and Hajcak, 2009), variance within the PD group was specific to the number of years diagnosed with the disease and not mood. Taken together, it is possible that mood may contribute to a diminished RewP in PD. However, this did not appear to be the case in the present sample. First, in many studies RewP modulation was not related to depression rates per se, but specific to anhedonia (Bress et al., 2012). Although those with PD in our study had significantly higher BDI scores than the CTL group, the mean BDI score for the PD group was modest (M = 7.64) suggesting these individuals were not severely depressed. Furthermore, BDI and years since diagnosis were not significantly correlated, and although correlations between BDI and the RewP were negatively correlated, these correlations were not significant (ON: $r = -0.007$, $p = .971$; OFF: $r = -0.159$, $p = .420$). Finally, our stepwise multiple regression revealed that BDI scores did not significantly predict the RewP and this predictor was subsequently removed from the model. Taken together, PD-specific variance appeared to be the major explanatory factor for diminished RewP in this current cohort. Given the intact behavioral performance, it remains unknown how a diminished RewP affects cognitive performance in PD, if at all. Future studies could examine more specific constructs such as anhedonia, apathy, and hierarchical reinforcement learning in order to understand the nature between PD and cortical reward signals involved in RewP generation.

4. Conclusions

The finding of a diminished RewP in PD verifies an intuitive and clinically important hypothesis. The symptom-specific diminishment in RewP may be a consequence of a common methodological procedure in PD research (e.g. restricted recruitment) or it might truly be a marker of early-stage disease (e.g. prior to network adaptation). These are testable alternative hypotheses, and each will further bolster the search for biomarkers of PD progression. A longitudinal study would be ideal for simultaneously addressing these promising clinical questions.

5. Experimental procedure

5.1. Participants

Participants included 28 people with PD recruited from the Albuquerque, New Mexico community and an equal number of sex- and age-matched healthy controls. The University of New Mexico Office of the Institutional Review Board approved the study and all participants provided informed consent. All persons with PD and control sessions were run at 9 AM. Persons with PD were counterbalanced across sessions based on a pre-defined randomized template. United Parkinson's Disease Rating Scale (UPDRS) motor scores were videotaped in each session and were scored by a neurologist. All participants had Mini Mental State Exam (MMSE) scores above 26. Parkinson's and control participants did not differ on any measurements of education or premorbid intelligence. All participants also completed the North American Adult Reading Test (NAART) and the Beck Depression Inventory (BDI; (Beck et al., 1996)) LED was calculated by converting the amount (mg) of levodopa present across all individual medication prescription taken by the person (See Table S3). Participants were paid $20/h for participation. Points earned or lost during the task did not affect the money earned. Participants were excluded from the experiment if they had a history of epilepsy or a head injury in the last 10 years that resulted in loss of consciousness for more than five minutes, not able to understand English, older than 85, or did not have normal or corrected to normal vision. PD participants were also excluded from the study if they had undergone deep brain stimulation. Healthy Controls were excluded from the study if they had any parkinsonian related diagnoses or if they took dopamine modulatory medications.

5.2. Data acquisition and preprocessing

Electrophysiological data were collected with a 64Ag–AgCl electrodes embedded in a stretch-lycra cap with a sampling rate of 500 Hz with low and high cutoffs at 0.01–100 Hz. CPz served as the reference electrode and FPz as the ground electrode. Data was recorded with a

Brain Vision system (Brain Products GmbH, Munich, Germany). Vertical electrooculogram (VEOG) activity generated by blinks was recorded by two auxiliary electrodes placed superior and inferior to the left pupil. All EEG processing was conducted in EEGlab (Delorme and Makeig, 2004). First, CPz was re-created via computation of the average reference (EEGlab function pop_reref.m). Very ventral electrodes (FT9, FT10, TP9, and TP10) were then removed, as they tended to be unreliable. The average reference was then recomputed for the remaining 60 electrodes. EEG data was filtered between 0.01 and 20 Hz. In order to capture all trial events, data was epoched around reward feedback screen onset (−6000 to 2000 ms). Using statistical deviations from the mean for each EEG channel, FASTER (Nolan et al., 2010) identified artifacts in each epoch for later rejection. Eye blink activities were removed following ICA (runica: Makeig et al., 1996). Epochs were then baseline corrected (−200 to 0 ms before feedback onset) and averaged to calculate event related potentials (ERP). The RewP was quantified at electrode sites Cz and was measured between conditions within a 250 to 450 ms window post feedback onset.

5.3. Task procedure

The task was programmed in Matlab using Psychtoolbox (Brainard, 1997). Participants used left and right index finger trigger buttons on a Logitech F310 Table gamepad for two alternative forced choice selections. For the difficulty condition, one stimulus pair had a clear better choice (90% vs. 10% rewarding) and the more difficult pair had a harder discrimination to learn (70% vs. 30% rewarding). Rewards on the more difficult pair should thus be "better than expected" and elicit a larger RewP. For the orthogonal volition condition, participants were instructed to "choose" a free choice ($_{fc}$) to select the better stimulus, or they were instructed to "match" which stimulus to select on a no-choice ($_{nc}$) trial. These stimulus pairs (and their probabilities of reward) were termed A_{fc}/B_{fc} (90% vs. 10% chance of winning) or C_{fc}/D_{fc} (70% vs. 30% chance of winning) for the free choice trials and A_{nc}/B_{nc} or C_{nc}/D_{nc} for the identically reinforced no-choice trials. No-choice trials were yoked to free choice selections to ensure identical reinforcement and behavioral selection. This forced the stimuli to be experientially equivalent even in the context of idiosyncratic behavior.

All trials began with an inter-trial-interval of 1000 ms. First, an instruction screen informed the participants if they would "Choose" or "Match" (500 ms duration) then a crosshair appeared for 800–1000 ms (jittered). Then, the stimulus pairs were presented for a maximum of 4000 ms and disappeared immediately after the choice was made. If the participant failed to make a choice within the 4000 ms, "No Response Detected" was presented. During free choice "Choose" trials, participants were able to select either of the presented stimuli. The no-choice "Match" trials had a square outline around the stimulus that participants were required to select; selection of the other option failed to register. Following a valid button press, the unselected stimulus disappeared from the screen while feedback was presented centrally for 1250 ms. Each block had 20 presentations of each stimulus pair and took an average of 24 min (SD = 3.57) to complete. Participants completed between three and five training blocks depending on accuracy (if free choice pairs were accurately selected > 60% of the time).

5.4. Analytic strategy

To address our first aim, we compared the amplitude of the RewP between PD and CTL groups. We only investigated reward signals for both theoretical (our hypothesis was specific to RewP) and methodological reasons (there were not enough loss trials in each of these conditions). However, to bolster the specificity of these findings we have included plots and statistical tests for loss ERPs and difference contrasts (win minus loss) in the supplement (Figs. S3 and S4), highlighting the specificity of these effects to the reward condition. In our study, people with PD participated twice (once ON their medication and once OFF). Since there was a within-subjects manipulation of medication status in the PD group yet no within-subjects manipulation in the CTL group, an analysis comparing these three groups together would create an imbalance in correlated (ON vs. OFF) vs. uncorrelated (PD vs. CTL) effects if included in a simple model. To address this, we performed two separate ANOVAs with between-subjects factors MEDICATION (ON versus CTL or OFF versus CTL) and within-subject factors VOLITION (choose, match), and DIFFICULTY (easy, hard). To test our second aim of symptomatic moderators of this effect within the PD group alone, we used an ANCOVA to examine if years diagnosed (YrsDx) interacted with MEDICATION (ON vs. OFF) or task conditions (VOLITION and DIFFICULTY). Due to a large positive skew, YrsDx was converted to rank order, as in prior studies (Cavanagh et al., 2017, 2018). To examine if symptomatic variance in RewP was specific to YrsDx, a stepwise regression included MEDICATION (ON vs. OFF), LED, BDI, AGE, YrsDx and UPDRS ratings. Only main or interaction effects with MEDICATION are reported here. Reports of effect size for ANOVA are partial-η^2, planned comparison effect sizes are reported as Cohen's d.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brainres.2019.146541.

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