Investigating the effects of dopaminergic medication and Parkinson's disease state on neural activation in the left ventral striatum

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Outcome processing is a crucial way in which we learn from our choices and navigate our environments. Neural signals of outcome processing are typically understood to depend on dopamine transmission involving the basal ganglia. However, causal relationships between the observed hemodynamic signal in human neuroimaging studies of outcome processing and the presence of dopamine-mediated outcome signals can only be examined via neuropsychological methods. Parkinson's disease, which results in depleted dopamine and thus diminished dopamine signaling in the basal ganglia, provides an excellent neuropsychological opportunity to understand the causal relationships between dopamine signaling and hemodynamic changes related to outcome processing in the striatum. This study investigates how Parkinson's disease and dopaminergic medication affect hemodynamic responses associated with a guessing task involving monetary gain and loss outcomes. The estimated hemodynamic responses in the left ventral striatum of 16 participants with Parkinson's disease, on and off levodopa/carbidopa medication, and 10 controls are compared for reward and punishment outcomes, using an ANOVA-based analysis approach. No medication or group effects were observed in any contrast (all $p > .05$). These null results are reckoned with in the context of existing literature surrounding dopamine and hemodynamic signals in the basal ganglia.

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1.0 Introduction

Feedback processing is an essential function of learning. We learn to make more optimal decisions based on the outcomes of past choices. For instance, a foray into gambling may be cut short by a losing bet, a negative outcome that dissuades further participation in the casino and future monetary loss. Outcomes are widely believed to be processed within the basal ganglia (Packard & Knowlton, 2002), a group of subcortical nuclei that includes the striatum and groups of dopaminergic neurons in the brainstem. Single neuron recordings in non-human primates have showcased the activity of dopamine neurons during tasks involving outcome processing and feedback learning (Apicella et al., 1991). In humans, functional magnetic resonance imaging (fMRI) studies have found differences in functional activation within the striatum, which comprises the basal ganglia nuclei that receive dopaminergic input from the brainstem (Delgado et al., 2000; Moses-Kolko et al., 2011). Dopamine signaling in the striatum is often assumed to be responsible for these differences in the hemodynamic response observed in fMRI studies of outcome processing (Chase et al., 2015; Daniel & Pollmann, 2014). Because fMRI has an inherent focus on blood oxygenation levels in the brain, it cannot be used to directly examine the dopaminergic process behind outcome processing in the striatum using this modality. However, it is possible to use fMRI to study the impact of known variations in dopamine signaling on hemodynamic responses in the striatum to test assumptions about dopamine-based learning from fMRI. The current study takes such an approach, by using fMRI to study outcome processing in individuals with PD in two different medication states, and in comparison to healthy controls (CTL).

Striatal neurons receiving dopaminergic input from the brainstem are believed to process outcomes in part by receiving a calculated reward prediction error (RPE; Daw & Doya, 2006). RPEs are characterized by a signal that is based on the difference between observed reward and expected reward (RPE = expected outcome – actual outcome). This neural response to outcomes, as found in single cell recordings, is asymmetrical about baseline firing. A large burst of dopamine firing is typical after an unexpected reward occurs. On the flipside, if an unexpected punishment or lack of reward is experienced, there is a comparatively small dip in dopamine firing (Schultz et al., 1993). The shape of positive and negative RPEs, and the associated dopamine signaling, can only directly be studied by high temporal resolution single cell recordings. This is problematic because single cell recordings are too invasive to be used in studying human neurocognition in healthy participants.

fMRI is a common non-invasive modality used to understand outcome processing and feedback learning in the human basal ganglia. Patterns of RPE response in fMRI have been indirectly measured by studying basal ganglia regions of interest (Delgado et al., 2000; Taswell, 2018). Importantly, because the MRI machine records blood oxidation level dependent (BOLD) signal, it cannot directly observe dopamine signaling. However, prior studies have observed BOLD signal changes consistent with what might be expected based on the single unit recording data. For instance, the BOLD response to an outcome processing task in the ventral striatum found a symmetry about baseline for positive and negative outcomes (Delgado et al., 2000; Delgado et al., 2003). Given the reality that many cognitive neuroscientists rely on fMRI as a modality to study the basal ganglia, and the ubiquity of dopamine-based learning theories of the neural signal, it is important to develop further approaches for studying the relationship between dopamine firing in the basal ganglia and local BOLD signals.

In order to study the relationship between dopamine, the neurotransmitter that signals outcome processing in the basal ganglia, and BOLD responses during outcome processing tasks, it is necessary to directly modulate levels of dopamine in the brain being observed. A neuropsychological approach is used in the present study to accomplish this. Parkinson's disease (PD) is characterized by a depletion of dopamine-containing neurons in the brain (Lotharius & Brundin, 2002). PD has been found in the feedback learning literature to negatively affect patients' ability to learn and process outcomes (for a review, see Foerde & Shohamy, 2011). Medication is typically provided to PD patients to alleviate symptoms of the disease (see Jankovic, 1999 for a review). Levodopa/carbidopa is one such medication regimen, which combines a dopamine precursor and metabolic inhibitor to encourage the production of dopamine as well as allow this precursor to cross the blood-brain barrier. Parkinsonian medication is known to affect behavioral measures of outcome learning, particularly in reward outcomes (Frank et al., 2004).

The present study involves PD patients who complete two fMRI sessions: one on and one off their typical Parkinsonian medication, and a group of neurotypical who complete a single fMRI session. Participants perform a guessing task within the scanner, in which on each trial they guess the value of a hidden number and then receive outcome information indicating a monetary gain or loss. Studying the BOLD response to these outcomes in the basal ganglia and comparing it between on- and off-medication states can allow us to draw conclusions about the relationship between the underlying dopaminergic processing and the observed BOLD signal in the striatal ROI while taking advantage of a within-subjects analysis. We expect to find a difference in overall magnitude of BOLD outcome responses between on- and off-medication states within participants with PD, as well between off-medication PD participants and CTLs.

2.0 Methods

2.1 Participants

Thirteen participants with PD were recruited from local PD support group meetings of the Parkinson's Disease Foundation of Western Pennsylvania and from a patient registry of the Movement Disorders Clinic at the University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania. Inclusion criteria required participants to be at least one year post-Parkinson's diagnosis, taking levodopa/ carbidopa monotherapy only for a minimum of 6 months, at least 45 years of age, and have a medically diagnosed Hoehn and Yahr stage of 4 or lower (Hoehn & Yahr, 1967) as assessed by a neurologist at the Movement Disorders Clinic. Participants were excluded for a history of brain trauma or neurological illness (such as traumatic brain injury, epilepsy, multiple sclerosis, stroke, aneurism, severe heart attack, severe diabetes, etc.), uncontrolled major medical problems (such as cancer), intracranial surgery including deep brain stimulation, native language other than English, left-handed or ambidextrous, major loss of vision or hearing, history of learning or cognitive disability, history of speech language or reading disorders, history of psychiatric or mental illness, history of illicit drug or alcohol abuse, weight in excess of 250 pounds, MRI contraindications (such as claustrophobia, metal in or on body), and inability to participate due to PD related motor disability (such as being unable to lie relatively still in MRI scanner). Common medications for other conditions (e.g. aspirin, blood pressure, cholesterol) and medications for mild depression and anxiety were permitted. After eligibility was assessed by a researcher, a final review was completed by a Movement Disorders Clinic neurologist for safety

and instructions for medication withdrawal and washout. All participants completed a University of Pittsburgh IRB approved consent form before participation.

One PD participant was excluded based on poor performance on the Mini Mental State Exam (indicating cognitive disability or decline). Another participant was unable to complete on on-medication session due to back pain. Finally, a third participant's fMRI data files were corrupted. This leaves a total sample of 10 participants with PD (see Table 1 for demographic information).

Seventeen CTL participants were also recruited. CTL participants were recruited with similar age and education to our PD cohort. CTL participants were subject to similar inclusion criteria to our PD participants, with the exception of accounting for Parkinsonian medication. One CTL participant was excluded from final analysis due to data loss, leaving a total sample of 16 controls. Average demographic information for both groups were compared via a t-test and there were no observed significant differences for mean years of education or age.

Table 1 Demographic information for participants included in the final analysis. No statistically significant differences between PD and CTL for age or education observed via t-test (all p > .1).

Summary Demographics Information

Group	Age		Education		Females in sample (Total N for group)
	M	SD	M	SD	Count
PD	70.30	9.14	16.6	2.7	6 (N = 10)
CTL	67.31	9.33	15.7	2.7	7 (N = 16)

2.2 Sessions: Medication State

Participants in the PD group completed two imaging sessions in different medication states: OFF and ON. In the OFF session, participants did a washout of their PD medication as is common for clinical neurological evaluations. A minimum withdrawal of 10 hours is necessary for sufficient washout (Nyholm, 2006). This washout was directed by a neurologist from the Movement Disorders Clinic (mean withdrawal period of 15.2 h, SD = 5.6 h, range: 10-26 h). Participants continued to take all of their other prescribed medications, such as blood pressure,

cholesterol and antidepressants. Participants resumed their dopaminergic medicine immediately after the OFF session was complete. In the ON session participants took their medication for PD as prescribed. The OFF and ON sessions were scheduled as closely together as possible, with some variation due to participant's schedules (M = 6 days, SD = 2.49 days, range: 1-9 days). The order of the sessions (OFF and ON) was counterbalanced across participants. CTL completed only one session, because they did not have a medication state manipulation. All participants were encouraged to bring a support person.

2.3 Functional Task: Guessing Task

Participants completed a simple guessing task during each imaging session (see Figure 1). This was the same guessing task used by Moses-Kolko et al. (2011), who modified a prior implementation of the task (Delgado et al., 2000) to create a fast event-related variant for more efficient data collection. In the guessing task, participants are tasked with guessing the value of a hidden number ranging from 1 to 9 (exclusive of 5), which is occluded by a question mark that remains on the screen for 2 s. Participants are instructed to guess if the hidden number is greater or less than 5 (participants are informed that 5 itself is not a possible hidden number). Participants guess by pressing a button on a hand control to indicate "above 5" or "below 5." To balance outcome valence for observation, outcomes of the trials are pre-determined and are in the same order across all participants (e.g., the first trial for every single participant is predetermined to be a loss trial). Once the participant makes their choice, they are shown a number for 750 ms that is generated to either confirm their choice if the given trial is a gain trial or contradict their choice if the given trial is a loss trial. The only thing that is affected by a participant's choice is the number

that is revealed after they make the choice, because the outcomes are predetermined. The displayed number is then replaced with information denoting whether the outcome is a reward or a punishment (a monetary gain or loss, respectively, to be paid at the end of the study). There are also two levels of magnitude: large ($1.20) and small ($0.60). Gain trials can therefore result in a perceived gain of $1.20 or $0.60 (printed in green text), and loss trials can result in a perceived loss of $1.20 or $0.60 (printed in red text). There are 50 trials for each magnitude and valence combination. The outcomes are presented to participants for 750 ms. If participants do not make a choice within 2 s after the initial guessing prompt, the displayed outcome is a pound-sign ('#') indicating the absence of a monetary gain or loss. Each trial ends with a 1 s fixation cross interval, to give a total duration of 4.5 s per trial, with one complete brain volume acquired every 1.5 s.

Because this is a fast-event related study, one of six different levels of jitter was applied between trials (1.5 s, 3.0 s, 4.5 s, 6.0 s, 7.5 s, 9 s). Due to data loss in some of our experimental files, keypress choices were unavailable for some participants and so all trials were included and coded as their intended reward/punishment value.

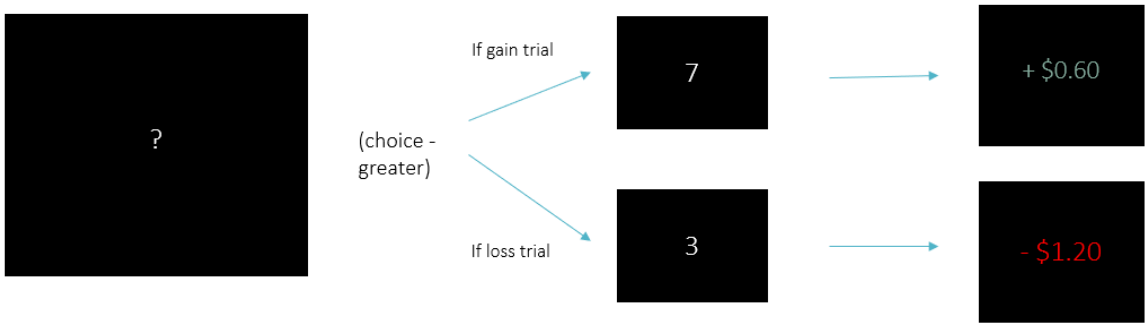

Figure 1 The above diagram shows the flow of events in which the participant guesses that the hidden number is greater than 5. If the trial in question is a gain trial, a number larger than 5 will flash on the screen to confirm the participant's guess was correct and a reward is administered (either $0.60 or $1.20 added to the payout at

the end of the study). If the trial in question is a loss trial, a number smaller than 5 will flash on the screen to contradict the participant's guess, and they will lose money from their final payout. Because the number of gain and loss trials is determined in advance and the same across all participants, there is no actual difference in the study payout for any given participant.

2.4 Neuroimaging Data Analysis

All scanning was performed on a Siemens 3 Tesla Trio (Erlangen, Germany) at Presbyterian Hospital at the University of Pittsburgh Medical Center. First, high-resolution structural images were obtained with a T1 MPRAGE sequence (TR=2200 ms; TE= 3.58 ms; FA= 9; FOV= 256x208; voxels= 0.5x0.5x1 mm; 176 sagittal slices). Functional blood oxygenation level-dependent (BOLD) images were also taken parallel to the anterior- posterior commissure (ACPC) (TR = 1500 ms, TE = 29 ms, FA = 80, FOV = 224x224; matrix = 64x64; voxels = 3.5 x 3.5 x 3 mm; 28 sagittal slices optimizing coverage of the basal ganglia. There were 5 functional runs, where each run was comprised of 160 TRs (total=800). Structural T2 images and susceptibility-weighted images were also obtained but are outside of the scope of this paper.

Data from the scans were reconstructed from DICOM format using Analysis of Functional NeuroImages software (AFNI; Cox, 1996) to AFNI's imaging format. Then, high-resolution structural T1-weighted MPRAGE data were skull-stripped within AFNI and remaining skull matter in the scans was removed manually (as needed). After reconstruction and quality checks including dimensional motion graphs and maximum motion displacement, the data were corrected for motion by including it as a covariate in the regression estimates (afni_proc.py). Groups did not significantly differ in average maximum motion displacement (ON M = 3.71 mm, OFF M = 3.95 mm, CTL M = 4.36 mm). Displacement greater than 5 degrees or 5 mm was considered

unacceptable. Motion chart outputs from ss_review_driver.py were examined by the research team and runs with spikes in movement above 5 mm or 5 degrees were flagged and removed. No valence condition was differentially affected by this correction because each run was designed to contain an equal number of trials for each condition. No subjects were removed from the final analysis as a result of these movement quality checks. Three CTLs had an average of two runs excluded (two participants with runs 1 and 2 excluded, and another with run 5 excluded), and no PD participants required run exclusion. Data were warped into the space of the Montreal Neurological Institute (MNI) atlas space (MNI 152 SSW in AFNI) using a non-linear registration and warp process. Data were smoothed using a full-width half-max function (3dBlurToFWHM). Then, the individual fMRI data were analyzed using a general linear model through 3dDeconvolve using a tent function to estimate 12 timepoints from 0 to 16.5 seconds after the start of each trial with the valence (positive, negative) and magnitude (small, large) modeled. Runs were modeled separately and then concatenated for final analysis.

To understand the relationship between dopamine levels and BOLD activity in the striatum, a spherical region of interest (ROI) centered within the left ventral striatum (LVS) was created with a radius of 4 mm within AFNI; this radius was chosen to avoid overlap with neighboring ventricles. The decision to focus on the left LVS was based on prior results that showed activation in this region in response to outcomes in the guessing task, with the center coordinate derived by averaging coordinates for reported LVS activation clusters (Delgado et al., 2000; Delgado et al., 2003; Moses-Kolko et al., 2011; Cox et al., 2008) [Montreal Neurological Instittue (MNI) coordinates: x = -14, y = 6, z = 2]. Then, the procedures of Moses-Kolko et al. (2011) were used to extract an estimated BOLD response within the LVS for each of the four trial types (large and small gain and loss). In brief, a series of TENT functions in AFNI was fitted to the BOLD response

during trials in each of the four conditions (large and small reward and punishment). This estimated 12 regression parameters for each of the four conditions, with each modelling 1.5 s of BOLD activity within a 16 s trial. Data from these 12 parameters were then down-sampled into 6 bins, in which the first and last TENT parameter estimate were averaged into the first bin, and then each subsequent pairs of parameter estimates were divided into 5 bins. This transformation allowed the analysis to conserve statistical power given a modest sample. Data were then averaged across magnitude in the on-medication, off-medication, and CTL groups.

2.5 Neuropsychological Battery

Several neuropsychological tests were administered to collect data pertaining to symptoms of PD and side effects of related medication, and to assess participants for possible exclusion due to cognitive impairment and depression. The testing battery consisted of the Mini Mental State Exam (MMSE; Folstein et al., 1975), Beck's Depression Inventory (BDI; Beck et al., 1996), the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn, 1987), and the Grooved Pegboard task. Participants with PD completed all of these tasks, while CTL participants completed all but the UPDRS.

The MMSE is a mental status exam. It consists of 11 items that probe basic awareness of time and place, along with working memory and ability to follow instructions. The test was administered during both patient sessions (on- and off-medication). One purpose of the MMSE was to screen for cognitive impairment in our CTL and PD samples, with those individuals scoring below the suggested cut-off of 24 out of 30 points (Folstein et al., 1975) excluded from the study (one PD participant was excluded as a result). For the remaining participants, MMSE scores were

compared via a t-test between PD and CTL to test for any confounding mental status difference between our groups, as well as between on- and off-medication sessions, to test for the same between medication states.

The BDI is a 21-item questionnaire in which participants rate their agreement with several statements indicative of depression (Beck et al., 1996). It was used to measure depressive symptoms in our participants and potentially exclude any participant with severe depression. Scores above 29 (out of a possible 63) are associated with severe depression. No participant was excluded as a result of BDI scores.

The UPDRS (Fahn, 1987) was used to measure severity of PD symptoms within our PD group only. There were no exclusion criteria associated with UPDRS scores.

The grooved pegboard task measures the ability to make precise and coordinated movements with the hands. This task was a measure of motor speed. It requires participants to place small grooved cylinders ("pegs") into a hole that is just large enough for one peg. Participants often must rotate the peg after picking it up so that the groove in the peg matches up with the groove in the hole. There are nine holes and participants must fill all of them as fast as possible. The amount of time it takes to do this is recorded with respect to both the dominant hand and non-dominant hand. A finger tapping task was also included to measure participants' motor ability. In this task, participants use a tap-counter apparatus for 10 s for three rounds and the administrator records the number of taps the participant is capable of doing in each of the three rounds.

Finally, a post-task questionnaire was given to both CTLs and PD participants to solicit qualitative judgements of individual performance and perceptions of the hidden rules of the guessing task. Questions included probes on the strategy used to complete the task and biographical information. For PD participants, additional questions probed the effect of

medication-state on their performance on the guessing task. The results from these tests are not analyzed in the present study.

3.0 Results

3.1 Neuropsychological Battery Analysis

For the neuropsychological tasks that were administered to patients during both the on- and off-medication sessions, a t-test was conducted to compare the scores across sessions. The t-test did not find significant differences between the on- and off-medication test results ($p > .1$) (Table 2)

Table 2 Scores between on and off medication sessions were not statistically significant for any neuropsychological test. (t-test, all $p > .1$)

Neuropsychological Test Results PD Participants

Test	On-Medication Session		Off-Medication Session	
	M	SD	M	SD
Mini Mental-State Exam	29.60	.70	29.60	.84
Beck Depression Inventory	9	5.01	8.3	2.54
Unified Parkinson's Disease Rating Scale	2	.67	1.89	.93

3.2 Functional Data Analysis

Two repeated-measures ANOVAs (2 x 6) examined the deconvolved signal in each of the two valence conditions between the two imaging sessions (on-medication and off-medication) across the 6 down-sampled bins estimated by the TENT function. Because our sample size and expected effect size were both small, it would be difficult to meaningfully interpret a three-way interaction including valence as a factor. Therefore, there are no direct statistical comparisons between the reward and punishment conditions. In addition, another two mixed-effects ANOVAs (2 x 6) were created to compare across CTL data and data from the off-medication session (with group as a between subjects factor). We expect to find a main effect of both time and session within each ANOVA. A main effect of time suggests that over time the hemodynamic response is changing. A main effect of session suggests that a manipulation of dopamine levels in the striatum (either via a medication-state manipulation or CTL versus off-medication PD) affects the overall magnitude of the response. These analyses were conducted within IBM SPSS Statistics (Version 27).

3.2.1 Medication State x Time Analysis

Within the punishment condition, a 2 x 6 ANOVA examining the estimated beta parameters in the LVS found a significant main effect of time [$F(5,45) = 3.15$, $p < .05$]. No main effect of medication-state was found [$F(1,9) = .38$, $p > .1$]. The interaction term between time and medication-state was marginally significant [$F(5,45) = 2.37$, $p = .054$]. This marginally significant interaction suggests that the overall shape and evolution of the BOLD response in the LVS may be affected by medication-state, although area-under-the-curve is approximately the same. Within

the reward condition, a significant main effect of time was also observed [$F(5,45)= 3.34$, $p < .05$]. However, no main effect of medication-state was found [$F(1,9) = .47$, $p > .1$], and no significant interaction between time and medication-state was observed [$F(5,45) = 1.89$, $p > .1$].

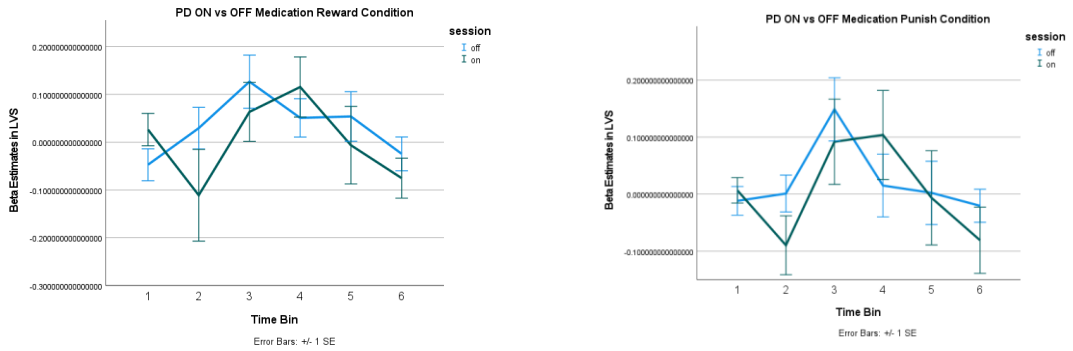

Figure 2 The two graphs above detail the hemodynamic response for the reward (left) and punishment (right) conditions. The y-axis measures estimated beta values from the TENT function in the LVS. The x-axis represents the six time bins created. The blue line represents the OFF medication session data, and the green line represents the ON medication.

3.2.2 CTL and PD (Off Medication) x Time Analysis

In addition to the analysis examining medication-state, two more 2 x 6 ANOVAs (with time entered as a repeated-measures variable) analyzed the differences in the hemodynamic response for the PD group in the off-medication state versus the CTL group. Within the punishment condition, a significant main effect of time was observed [$F(5,120) = 9.67$, $p < .001$]. However, no main effect of group was observed [$F(1,24) = 2.25$, $p > .1$], nor was there a significant interaction effect between group and time [$F(5,120) = 1.99$, $p > .1$]. Within the reward condition, a significant main effect of time was observed [$F(5,120) = 5.77$, $p < .001$]. No main effect of group was observed [$F(1,24) = 2.61$, $p > .1$], and no significant interaction effect was observed [$F(5,120) = 1.24$, $p > .1$].

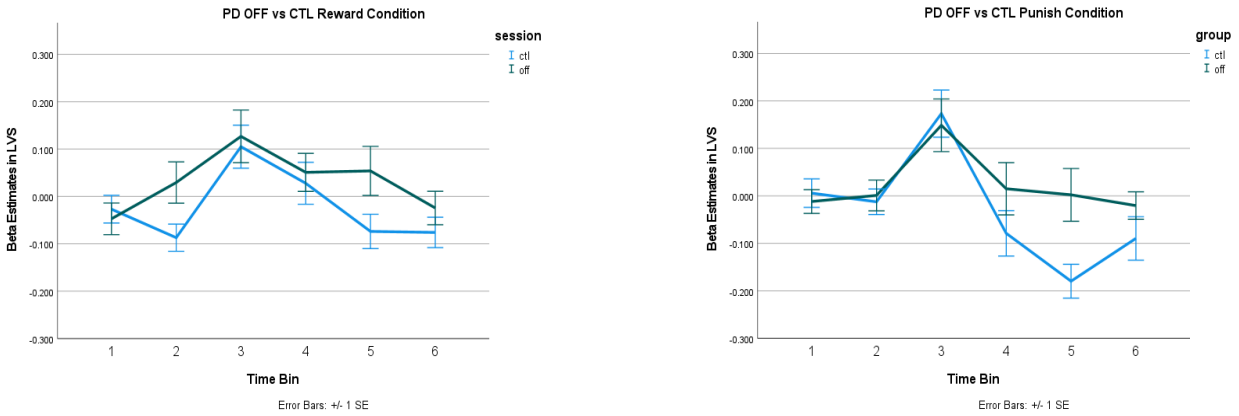

Figure 3 The two graphs above detail the hemodynamic response amongst the CTL group and off-medication PD participants for reward (left) and punishment (right) conditions. The y-axis measures estimated beta values from the TENT function in the LVS. The x-axis represents the six time bins created. The blue line represents CTL participants, and the green line represents PD participants in the OFF session.

4.0 Discussion

The present study was designed to better understand the relationship between dopaminergic signaling in the striatum during outcome processing and BOLD signal observed in fMRI. It was originally predicted that modulation of dopamine, including medication state (ON and OFF) and participant group (CTL or PD), would lead to significant differences in BOLD activation observed within the LVS during reward outcome processing.

Contrary to these predictions, no main effect of session or group was observed in any of the four analyses. Session and group also did not interact with time in any way to produce a significant interaction effect. This is surprising given that our experiment closely follows that of Moses-Kolko et al. (2011), in our task paradigm as well as our analysis and statistical methods. In studying mothers with postpartum depression and neurotypical control mothers, they found a significant interaction effect of group and time during high magnitude reward trials on the overall size of the BOLD response. This study also featured a sample relatively close in size to the present study, with 24 total participants. In contrast, the present study used an even more statistically powerful within-subjects medication state manipulation along with a between-subjects group manipulation.

It could be the case that our dopamine modulation manipulations were less powerful than we originally thought. One piece of evidence that points to the medication state factor being insufficient in modulating dopamine levels is our on- and off-medication neuropsychological test results. None of the neuropsychological tests chosen to measure behavioral and motor deficits as a result of PD yielded significant differences in the ON or OFF condition (see Table 2). Particularly concerning is the lack of difference in UPDRS scores between medication states, as this test is a

real-time measure of PD symptoms. Prior work in the PD literature consistently notes differences in UPDRS scores in different medication states (Argyelan et al., 2018; Bodi, et al., 2009). Not observing a difference in UPDRS scores as a function of medication is worrying, as one would expect downstream behavioral effects resulting from modulating dopamine levels. In addition, prior work in the lab, such as Moses-Kolko et al. (2011), studied younger participants. Our population, because of the nature of PD and our desire to match our control population in age, features older adults. Prior work has shown that striatal responses to outcomes in the guessing task are different between healthy older and younger controls (Cox et al., 2008), including a lower magnitude and less sustained profile of activation in older adults. Aging has also been shown to affect levels of monoamine oxidase-B (MAO-B), thus reducing overall levels of dopamine over time (Kumar & Andersen, 2004). This complication could have affected our statistical power by making the effect size smaller, making the analysis less sensitive to differences. In addition, because PD is characteristically a movement disorder, movement artifacts could have resulted in a distortion of the analyzed signal.

It is also important to consider that the present task allowed participants to passively observe outcome events, and that no learning strategy could successfully take place, since outcomes were predetermined and independent of participant behavior. Some studies of ventral striatal activation across multiple modalities have shown a decrease in activation and dopaminergic firing, especially during reward, when feedback is not used as a learning guide (Hakyemez et al., 2008; Calabro et al., 2023). It could be the case that tasks that do not allow for learning strategies to optimize behavior, like the guessing task, could result in a blunted striatal response.

Finally, our null results could indicate that striatal responses to outcome events are dependent on more than simply dopamine signaling. More recent literature studying the basal ganglia and its relationship to outcome processing has described a number of neurotransmitters and neuroanatomical regions integral to basal ganglia functioning (see Garcia-Garcia et al., 2017, for a review). GABA and glutamate are both important for communication between different brain regions during outcome processing, such as the prefrontal cortex and thalamus, in both positive and negative outcomes. GABA in particular is important for communication within the basal ganglia during outcome processing. Although dopamine can still be regarded as a primary vessel through which RPEs are calculated and outcomes are processed (Daw & Doya, 2006), the complexity of this feedback learning system can make single-factor manipulations (i.e. dopamine modulation) less powerful in terms of the observed effect on the hemodynamic response.

Future work in this area could address the above limitations by alterations in the participant sample. Greater levels of Parkinsonian symptomology in the dopamine-depleted group, and/or an increase in time since diagnosis, could lead to greater confidence that the dopamine manipulation is effective. Younger Parkinson's disease patients and younger controls could be compared to limit the effect of aging on the fidelity of the data.

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