RESEARCH ARTICLE

Motivational Vigor in Parkinson's Disease Requires the Short and Long Duration Response to Levodopa

James A. Brissenden, PhD,[1] Teresa Scerbak, BS,[2] Roger L. Albin, MD,[2,3] and Taraz G. Lee, PhD[1*]

[1]*Department of Psychology, University of Michigan, Ann Arbor, Michigan, USA*
[2]*Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA*
[3]*Neurology Service and Geriatric Research Education and Clinical Center, Veteran Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan, USA*

ABSTRACT: Background: Impaired movement vigor (bradykinesia) is a cardinal feature of Parkinson's disease (PD) and hypothesized to result from abnormal motivational processes—impaired motivation-vigor coupling. Dopamine replacement therapy (DRT) improves bradykinesia, but the response to DRT is multifaceted, comprising a short-duration response (SDR) and a long-duration response (LDR) only manifesting with chronic treatment. Prior experiments assessing motivation-vigor coupling in PD used chronically treated subjects, obscuring the roles of the SDR and LDR.

Methods: To disambiguate the SDR and LDR, 11 de novo PD subjects (6 male [M]:5 female [F]; mean age, 67) were studied before treatment, after an acute levodopa (L-dopa) dose, and in both the practical "*off*" (LDR) and "*on*" (LDR + SDR) states after chronic stable treatment. At each visit, subjects were characterized with a standard battery including the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and an incentivized joystick task to assess motor performance in response to varying rewards.

Results: L-Dopa induced a robust SDR and LDR, with further improvement in the combined SDR + LDR state. At baseline, after acute treatment (SDR), and after LDR induction, subjects did not exhibit the normal increase in movement speed with increasing reward. Only in the combined SDR + LDR state was there restoration of motivation-vigor coupling.

Conclusions: Although consistent with prior results in chronically treated PD subjects, the significant improvement in motor performance observed with the SDR and LDR suggests that bradykinesia is not solely secondary to deficient modulation of motivational processes. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; motivation; vigor; L-dopa; bradykinesia; dopamine

Introduction

A defining feature of Parkinson's disease (PD) is bradykinesia, baseline slowing of movement and progressive reductions in movement speed and amplitude with repetition.[1] The clinical definition of bradykinesia maps onto the neurobiological concept of vigor—the strength, speed, or amplitude of actions.[2-4] Ample evidence indicates that striatal dopaminergic transmission modulates willingness to exert effort in response to rewards and is hypothesized to mediate motivation-vigor coupling.[5-11] Prior studies demonstrated that PD subjects exhibit aberrant estimation of tradeoffs between effort and reward, and it was hypothesized that bradykinesia is a manifestation of impaired motivation, the process of motivation-vigor coupling.[12,13]

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*__Correspondence to:__ Prof. Taraz G. Lee, Department of Psychology, University of Michigan, 530 Church Street, Ann Arbor, MI 48109, USA; E-mail: tarazlee@gmail.com

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This inference is supported by parallel experiments in relevant animal models.[14] Optimal performance necessitates a cost–benefit analysis, encompassing the costs of action vigor.[15,16] Niv et al[15] proposed a reinforcement learning model incorporating action selection and vigor. This model requires a mechanism accounting for the long-term history of the average reward rate. Niv et al[15] proposed that tonic striatal dopamine signaling fulfills this function.

The clinical response to the mainstay of PD treatment, L-dopa, is multifaceted, comprising a short duration response (SDR) paralleling plasma levels, and a long duration response (LDR) that slowly increments over the course of days to weeks and likely recedes after therapy cessation over similar timescales.[17-23] The LDR accounts for ~60% of the total response to L-dopa.[23] The LDR is thought to account for the absence of motor fluctuations in early to moderate PD. Better understanding of the neural mechanisms underlying the LDR could lead to improved symptomatic therapy for PD. LDR induction by dopaminergic agonists implies that the LDR results from mimicry of tonic striatal dopaminergic signaling,[21,24-27] suggesting that the LDR might result from the type of motivational process predicted by the Niv et al[15] model.

Prior experiments examining motivation-vigor coupling in PD subjects did not take the LDR into account. These experiments exclusively examined chronically treated subjects[12,28] or compared performance after withholding dopamine replacement therapy (DRT) for 10 to 12 hours (practical "Off" state) and after resuming treatment (practical "On" state).[13,29] because of the LDR, these designs confound performance in the practical "Off" state with pre-treatment baseline performance. Properly evaluating the hypothesis that bradykinesia results from aberrant dopaminergic modulation of vigor requires better control of LDR effects.

We recruited newly diagnosed PD subjects who performed an incentivized movement task before treatment, after an acute dose of levodopa (L-dopa), and in both the practical "Off" (LDR) and "On" (SDR + LDR) states following chronic stable treatment. This design allowed us to disentangle the independent effects of SDR and LDR on motivation-vigor coupling. Our primary hypothesis was that the motivation-vigor relationship would be restored after chronic treatment despite overnight withdrawal of L-dopa, indicating an association between reward modulation of motor behavior and LDR induction. This hypothesis is consistent with the notion that the LDR is linked to mimicry of tonic striatal dopaminergic signaling, aligning with the Niv et al[15] model of motivation-vigor coupling. If subjects, however, exhibited improvement in bradykinesia dissociated from reward-vigor modulation, it would provide evidence against the hypothesis that bradykinesia is mainly secondary to impaired motivational processes.[12]

Materials and Methods

Participants

We recruited 12 participants with newly diagnosed PD from the Movement Disorders clinics at the University of Michigan. All research protocols were approved by the Health Sciences and Behavioral Sciences Institutional Review Board at the University of Michigan. This study was registered at ClinicalTrials.gov (NCT04821830). Participants met Movement Disorder Society (MDS) criteria for Clinically Probable Parkinson's Disease.[1] One subject started the study, but withdrew because of human subject restrictions during the coronavirus disease 2019 (COVID-19) pandemic, leaving 11 participants completing all sessions (6 male/5 female) (Table 1).

Table 1 *Features of PD participants at baseline*

Feature	No.	Mean	Range	SD
Participants (male/female)	11 (6/5)	–	–	–
Age	–	66.73	58–77	6.33
Lille Apathy Rating Scale	–	−10.45	(−16)–(−5)	2.88
PD-CRS	–	99.91	52–125	22.90
GDS	–	3.63	0–12	3.32
UPDRS total	–	43.64	34–59	8.23
SDR to LDR session interval (days)	–	62.73	27–112	32.89
L-Dopa daily dose* (mg/day)	–	395.45	300–900	192.94

*Refers to L-dopa daily dose at third visit (LDR session) following titration by referring clinicians. All participants received the same dose of L-dopa at the second visit (250 mg; SDR session).

Abbreviations: PD, Parkinson's disease; SD, standard deviation; PD-CRS, Parkinson's Disease-Cognitive Rating Scale; GDS, Geriatric Depression Scale; UPDRS, Unified Parkinson's Disease Rating Scale; SDR, short duration response; LDR, long duration response; L-dopa, levodopa.

Exclusion criteria included Montreal Cognitive Assessment score <24, stimulant use, dopamine agonist treatment, or confounding other neurologic or medical disorders. Because of technical difficulties, one participant was unable to perform the movement task for their first two sessions.

Procedures

There were four measurement states. First was a baseline session before chronic treatment initiation (baseline; "Off" state). The second session occurred shortly after the baseline evaluation and after an acute oral dose of L-dopa (25/250 carbidopa/L-dopa) with subjects evaluated within 2 hours of L-dopa ingestion to assess the SDR (acute "On" state). Participants were pre-treated for 24 hours with carbidopa, 25 mg every 6 hours, to reduce risk of nausea and orthostatic hypotension. Chronic treatment was subsequently initiated and titrated by referring clinicians. The study team had no input regarding treatment decisions. The third and fourth session were performed 2 to 3 months after initiation of chronic, stable L-dopa treatment. The third session measured the LDR. Participants abstained from L-dopa for 10 to 12 hours before evaluation (practical "Off" state). The final session, after subjects' usual L-dopa dose, measured the SDR + LDR (practical "On" state). Subjects were evaluated at each session with standard scales: parkinsonism, MDS-Unified Parkinson's Disease Rating Scale (UPDRS); mood, Geriatric Depression scale (GDS); apathy, Lille Apathy Rating Scale; cognition, PD-Cognitive Rating Scale (PD-CRS). A single experienced rater (R.L.A.) performed all UPDRS-III evaluations. Bradykinesia was also quantified with a tapping task previously used by Nutt et al[17,19] to characterize the LDR. Results of four tapping trials were averaged to generate a mean tapping speed (taps/min) for each subject in each session. Vigor modulation was examined using a joystick task that varied both the magnitude of prospective monetary incentives and motor force requirements (see below).

Stimuli and Experimental Paradigm

Stimuli were generated and presented using Python with the PsychoPy software package (Fig. 1).[30,31] This paradigm is a variant of a task initially developed by Panigrahi et al[12] to investigate movement vigor in mice. Participants sat in front of a computer screen with spring-loaded joystick that returned to a central position if no force was applied. Stimuli were presented on a light grey background spanning 30.43 × 30.43 cm. Each trial began with the presentation of an incentive value (3 seconds; $5, $10, or $20) and a large circular target stimulus. The target circle represented the movement goal for that trial and persisted throughout the remainder of each trial. The size of the target circle varied across trials (radius, 9.13, 11.41, or 13.69 cm),

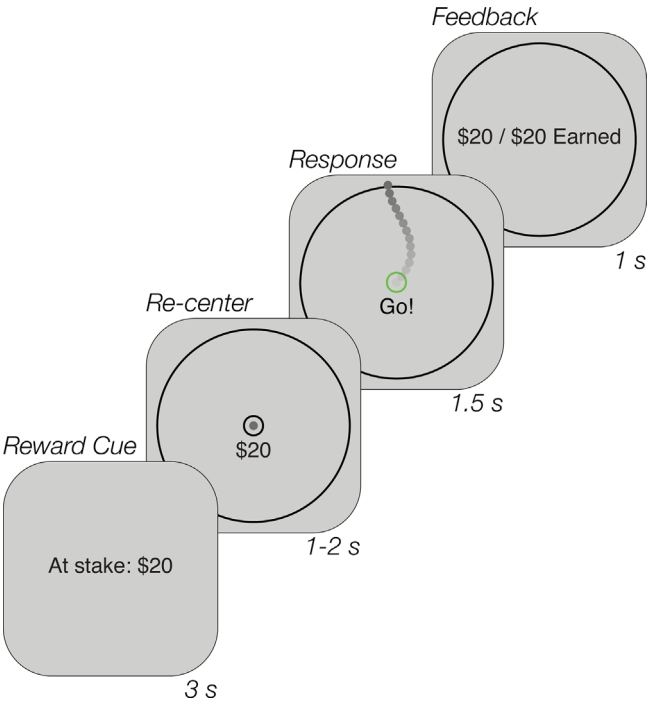


FIG. 1. Incentivized joystick paradigm. On each trial, participants were shown a reward cue ($5, $10, or $20) and given a movement goal (circle radius = 9.13, 11.41, or 13.69 cm). On receiving an initiation cue ("Go!"), participants were instructed to navigate the cursor beyond the specified boundary. Participants were then provided feedback reflecting the potential reward, which was determined proportionally to the maximum radius the participant managed to move the cursor. [Color figure can be viewed at wileyonlinelibrary.com]

modulating the amount of effort required to move the cursor beyond the edge of the target circle. Participants were instructed that at the session conclusion, a trial would be selected at random, and if they had reached the movement goal on that trial, they would receive the associated reward for that trial in addition to their base pay. This payoff scheme encouraged participants to evaluate individual trial incentives independent of other trials. Participants were then prompted to return a visual marker (radius, 0.76 cm) of the joystick position to the display center. A small circular stimulus surrounded the display center (radius, 0.99 cm). The origin circle color turned yellow if the marker was not sufficiently close to the display center (if any force was applied to the joystick in any direction). Once the marker was inside the origin circle, the color changed to black. To prevent anticipatory movements, participants were required to keep the marker within the origin circle for variable intervals for trial continuation. The interval was sampled from a uniform distribution over 1 to 2 seconds on each trial. If the participant deviated from the origin during this interval, the clock was reset. Once participants stayed at the center for the prespecified interval, the origin circle changed to green and the text "Go!" appeared. Participants were instructed to move the cursor past the edge of the target

circle and were given 1.5 seconds for each attempt. If the cursor crossed the edge of the target circle in any direction, the target circle color changed to green. Following the movement period, participants received feedback about the magnitude of potentially earned rewards. If the participant failed to reach the edge of the target circle, they received an amount proportional to the maximum radius achieved during the movement interval. For example, if the maximum eccentricity reached was 50% of the target circle radius on a $20 trial, the participant was presented with "$10/$20 earned." If that trial was selected randomly for reward at the end of the session, they would receive $10 rather than the amount indicated by the incentive cue (eg, $20) at the beginning of that trial.

Statistical Analysis

All statistical analysis was performed using R (R Core Team, 2022; Version 4.2.2). The incentivized joystick task produced three dependent measures: movement time, movement linearity, and a composite measure of speed and linearity that we describe as "movement efficiency" (see below and Supplementary Methods). We saved raw trial trajectories at the very end of each session. Movement time was calculated by subtracting the time it took to initiate the movement from the total time (relative to the "Go!" signal) it took to move the cursor to pass the target circle edge. Initiation time was defined as the time it took for the cursor to move past a threshold of 0.3 cm from the origin. Total movement time (initiation time + movement time) and movement error were saved at the end of each trial. We were able to decompose total movement time into initiation time and actual movement time from the raw trajectories. Because of the task unexpectedly aborting following the ninth block out of 10 for one participant and session (LDR session), we were unable to compute movement time for this participant/session. Prior research has demonstrated that point-to-point movement trajectories constrained by an external contact (eg, joystick) in healthy individuals follow approximately straight-line paths.[32-35] As a result, we examined the effect of L-dopa and reward on the linearity of participants' movements. Movement linearity was computed for each trial as the root mean square deviation from the most direct trajectory from the origin to the location along the target circle edge passed by the cursor. Performance improvements as measured by movement time or movement error alone may reflect a speed-accuracy tradeoff rather than true improvement.[36,37] To address this possibility, we computed a composite measure of overall performance, movement efficiency, approximately equivalent to the balanced integration score described previously (Supplementary Methods).[38,39]

To model the effect of incentives and session on the three measures, we fit a Bayesian hierarchical generalized linear model (GLM) (Supplementary Methods). For each comparison, we report the median, 95% highest density interval (HDI), and the probability of direction (pd). The HDI represents the interval for which all values within that interval have a higher probability density than points outside that interval. pd Is an index of effect existence (ranging from 50%–100%), which represents the probability that an effect goes in a particular direction (eg, effect x has a 99% probability of being negative). We consider a pd that is >95% to be strong evidence for the existence of an effect, a pd between 90% and 95% to provide some evidence for an effect, and a pd <90% to indicate limited evidence for an effect.

Results

L-Dopa Improves UPDRS-III Scores and Tapping Speed

L-Dopa elicited substantial improvement in motor performance across sessions (see Supplementary Table **S1**;

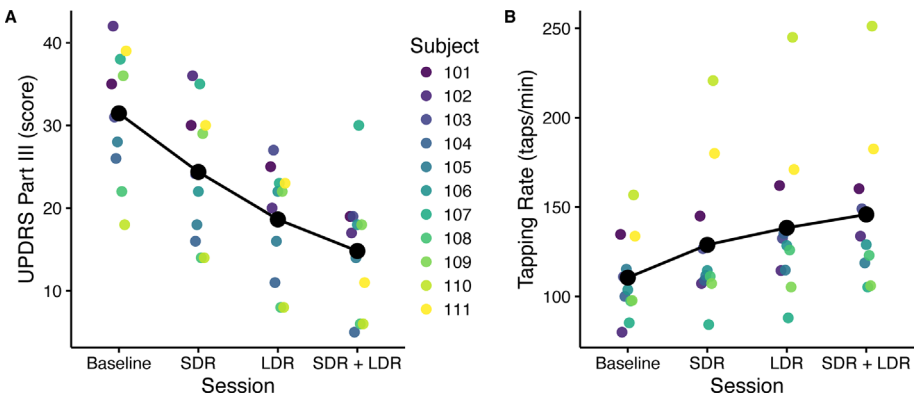


FIG. 2. Dopamine replacement therapy (DRT) improves Unified Parkinson's Disease Rating Scale III (UPDRS-III) scores and tapping speed. (**A**) The plot presents mean and individual UPDRS-III scores across sessions. Mean UPDRS-III scores for each session are represented by black dots and interconnecting lines. Individual participant UPDRS-III scores across sessions are illustrated by colored dots. (**B**) The plot presents both mean and individual finger tapping rate[17,19] across sessions. [Color figure can be viewed at wileyonlinelibrary.com]

Fig. 2). The initial dose of L-dopa (SDR session) produced a mean UPDRS-III score improvement of 22.5% relative to pre-treatment baseline (β_{SDR}: median [HDI] = −0.279 [−0.451, −0.094], pd = 100%). Finger tapping rates improved by 16.6% (β_{SDR}: median [HDI] = 0.134 [0.057, 0.207], pd = 100%). Following LDR induction, participants demonstrated further improvement in UPDRS-III scores (40.75%; β_{LDR}: median [HDI] = −0.568 [−0.750, −0.385], pd = 100%) and finger tapping rates (25.25%; β_{LDR}: median [HDI] = 0.205 [0.134, 0.280], pd = 100%). The combined treatment state (SDR + LDR) yielded further improvement (52.98% decrease [UPDRS-III]; $\beta_{SDR+LDR}$ [UPDRS-III]: median [HDI] = −0.830 [−1.013, −0.651], pd = 100%; 31.98% increase [finger tapping]; $\beta_{SDR+LDR}$ [finger tapping]: median [HDI] = 0.262 [0.188, 0.336], pd = 100%).

L-Dopa Improves Movement Speed, Linearity, and Efficiency

Mirroring changes in UPDRS-III scores and finger tapping rates, participants exhibited improvements in joystick measures across sessions (Supplementary Table S2). Improvements in movement time and movement error followed different time courses. Participants' movement times substantially improved relative to baseline following SDR induction (pd = 100%), with little evidence for improvements in movement error (pd = 64.98%). Movement times were similar between SDR sessions and LDR sessions (pd = 65.93%), with subjects exhibiting a marked improvement in movement error between these sessions (pd = 99.03%). The LDR + SDR sessions exhibited improvements in both movement time and accuracy relative to prior sessions (all pd > 98.43%). The movement efficiency measure revealed a steady improvement in performance across sessions (baseline vs. SDR: pd = 99.96%; baseline vs. LDR: pd = 100%; baseline vs. SDR + LDR: pd = 100%; SDR vs. LDR: pd = 92.5%; SDR vs. SDR + LDR: pd = 100%; LDR vs. SDR + LDR: pd = 99.91%). In contrast to movement speed, linearity, and efficiency, we found little evidence for a change in movement initiation time across sessions (Supplementary Table S3). A reliable difference was only observed when comparing the SDR + LDR session with baseline (pd = 97.79%).

Strong Relationship between Standard Motor Measures and Joystick Task Performance

Joystick outcome measures were highly correlated with both UPDRS-III scores and finger tapping rates. UPDRS-III scores strongly predicted movement time, linearity, and efficiency (time: median [HDI] = 0.012 seconds [0.006 0.017], pd = 100%; Spearman's $\rho = 0.298$, $P = 0.059$; linearity: median [HDI] = 0.122 [0.018, 0.226], pd = 98.94%; $\rho = 0.462$, $P = 0.002$; efficiency: median [HDI] = 0.013 [0.004, 0.023], pd = 100%; $\rho = 0.418$, $P = 0.006$). Finger tapping rates strongly predicted movement times (median [HDI] = −0.005 s [−0.007, −0.004], pd = 100%; $\rho = -0.733$, $P = 5e{-}08$). There was limited evidence for a relationship between finger tapping rates and movement linearity (median [HDI] = −0.0007 [−0.004, 0.002], pd = 69%; $\rho = -0.217$, $P = 0.173$). Reflecting this discrepancy, there was weak evidence for a relationship between finger tapping rate and the composite movement efficiency measure (median [HDI] = −0.001 [−0.004, 0.0004], pd = 93.43%; Spearman's $\rho = -0.275$, $P = 0.082$).

Combined SDR and LDR Effects Are Necessary for the Restoration of Motivation-Vigor Coupling

Participants exhibited no reward-related modulation of movement time, error, or efficiency across the baseline and SDR sessions (Table 2). We observed a robust difference in movement error between $20 and both $10 and $5 rewards in the SDR session. The direction of this effect, however, was opposite of that expected if participants were appropriately scaling their movement linearity with reward. Participants were less precise when the prospective reward was $20 than both $10 and $5. Rejecting our primary hypothesis, we found no modulation of motor performance by reward in the LDR session (all pd <86%). An effect of reward emerged in the final SDR + LDR session (Fig. 3). There was strong evidence that participants were both faster and more precise in their movement on high reward ($20) trials than low reward ($5) trials (all pd >95%). We found limited evidence for a consistent effect of reward on movement initiation time across all sessions (Supplementary Table S4). There was limited evidence for an effect of target circle radius on reward modulation of movement speed (Supporting Data).

Discussion

We investigated the relationship between distinct components of the response to L-dopa treatment and modulation of motor vigor and linearity by perceived rewards in PD. We observed compelling evidence for both an SDR and LDR in participants' motor performance, with further improvement in the combined SDR + LDR state. The SDR and LDR impacted different aspects of motor performance. The SDR substantially improved movement speed compared to the pre-treatment baseline with minimal change in motor linearity. After establishing the LDR, participants maintained the vigor improvement while also demonstrating enhanced motor linearity. We did not observe a restoration of the relationship between reward magnitude and motor vigor and linearity after an acute dose of L-dopa (SDR) nor in the practical "Off" state (LDR).

TABLE 2 *Posterior predictive summary for the effect of reward on motor performance for each session*

Measure	Session	Contrast	Median	95% HDI	pd (%)
Movement time	Baseline	$5 vs. $10	0.42 ms	−10.09 to 11.30	53.07
		$5 vs. $20	−6.23 ms	−17.28 to 4.57	87.08
		$10 vs. $20	−6.61 ms	−17.64 to 4.16	88.64
	SDR	$5 vs. $10	−1.43 ms	−9.63 to 6.91	63.53
		$5 vs. $20	−0.29 ms	−8.85 to 7.80	52.74
		$10 vs. $20	1.09 ms	−7.57 to 9.18	60.29
	LDR	$5 vs. $10	−0.48 ms	−8.58 to 7.37	54.61
		$5 vs. $20	2.53 ms	−5.49 to 10.41	73.77
		$10 vs. $20	3.01 ms	−4.69 to 11.17	77.36
	SDR + LDR	$5 vs. $10	3.42 ms	−3.73 to 10.85	82.32
		$5 vs. $20	**9.50 ms**	**2.25–16.80**	**99.53**
		$10 vs. $20	**6.08 ms**	**−0.85 to 13.53**	**95.51**
Movement linearity	Baseline	$5 vs. $10	0.009 cm	−0.003 to 0.021	93.40
		$5 vs. $20	0.004 cm	−0.007 to 0.017	76.74
		$10 vs. $20	−0.004 cm	−0.016 to 0.007	77.67
	SDR	$5 vs. $10	−0.002 cm	−0.013 to 0.009	61.51
		$5 vs. $20	**−0.012 cm**	**−0.024 to −0.001**	**98.62**
		$10 vs. $20	**−0.010 cm**	**−0.022 to 0.001**	**97.08**
	LDR	$5 vs. $10	−0.001 cm	−0.010 to 0.009	55.19
		$5 vs. $20	−0.002 cm	−0.012 to 0.008	65.63
		$10 vs. $20	−0.001 cm	−0.011 to 0.008	60.51
	SDR + LDR	$5 vs. $10	0.005 cm	−0.003 to 0.015	87.55
		$5 vs. $20	**0.008 cm**	**0–0.019**	**97.52**
		$10 vs. $20	0.003 cm	−0.005 to 0.012	77.51
Movement efficiency	Baseline	$5 vs. $10	0.046	−0.019 to 0.116	91.39
		$5 vs. $20	0.034	−0.034 to 0.104	83.95
		$10 vs. $20	−0.012	−0.083 to 0.053	63.01
	SDR	$5 vs. $10	−0.026	−0.092 to 0.036	79.30
		$5 vs. $20	−0.007	−0.075 to 0.057	58.33
		$10 vs. $20	0.020	−0.045 to 0.086	72.43
	LDR	$5 vs. $10	0.008	−0.051 to 0.071	60.46
		$5 vs. $20	−0.026	−0.087 to 0.035	79.38
		$10 vs. $20	−0.033	−0.094 to 0.030	85.74
	SDR + LDR	$5 vs. $10	0.025	−0.036 to 0.086	77.73
		$5 vs. $20	**0.068**	**0.007–0.132**	**98.25**
		$10 vs. $20	0.044	−0.021 to 0.104	91.02

Note: Bolded values indicate pd > 95%.
Abbreviations: HDI, highest density interval; pd, probability of direction; SDR, short duration response; LDR, long duration response.

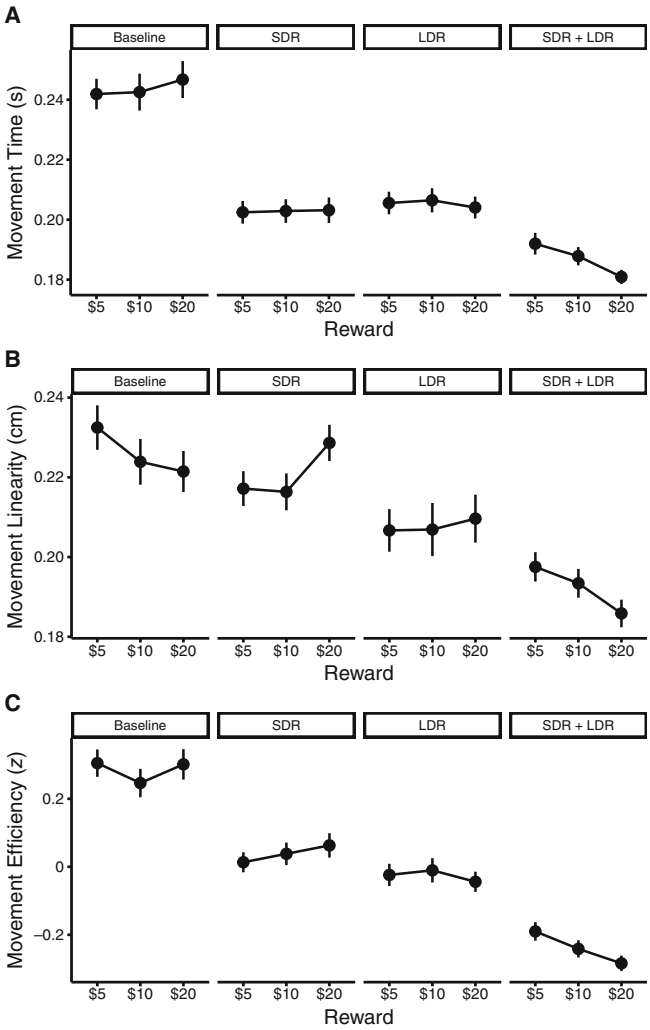


FIG. 3. Combined action of the short duration response (SDR) and long duration response (LDR) is necessary for the restoration of motivation-vigor coupling. (**A**) Mean movement speed across participants for each session and reward value. Error bars represent within-subject standard error of the mean (SEM).[62] (**B**) Mean movement linearity (± SEM) across participants for each session and reward value. (**C**) Mean movement efficiency (± SEM) across participants for each session and reward value.

Contrary to our primary hypothesis, neither the SDR nor the LDR alone sufficed to reinstate motivation-vigor coupling. An effect of reward emerged in the final SDR + LDR session, where patients demonstrated both faster and more linear movement on high reward trials compared to low reward trials.

The absence of motivational modulation of performance in the LDR session is consistent with prior work showing that PD subjects are less willing to exert effort for reward following overnight withdrawal of medication.[13] Our results are also consistent with prior work showing that chronically treated PD subjects in the practical "On" state exhibit modulation of response vigor in response to the prospect of rewards.[13,29,40] The comparison with the treated state in prior work matches the comparison of our LDR and LDR + SDR sessions. Prior research, however, could not determine whether reinstantiation of reward-effort coupling with treatment can be attributed to the SDR or a combined SDR + LDR effect. With the inclusion of a pre-treatment baseline, we were able to determine that the restoration of motivation-vigor coupling is associated with the combined action of the SDR and LDR.

Bradykinesia was previously characterized as a speed-accuracy tradeoff deficit, with slower movements hypothesized to compensate for increased movement variance.[41-45] The motivational explanation of Mazzoni and colleagues[12] largely supplanted this view.[46] Our result conflicts with both accounts. We observed concomitant improvements in both movement speed and linearity accompanying the LDR, consistent with a shift in the speed-accuracy tradeoff function rather than a shift along the same curve.[28] Our results challenge the notion that bradykinesia is mainly attributable to deficient modulation of motivational processes.[12] Although participants exhibited substantial improvement in bradykinesia accompanying both the SDR and LDR, restoration of motivational vigor was only observed in the combined SDR + LDR state. This finding implies that the abnormalities underlying bradykinesia in PD are more complex than previously believed and cannot solely be attributed to aberrant motor motivation. Our study highlights the importance of considering both the SDR and LDR effects of L-dopa when investigating motor dysfunction in PD. Further research is needed to fully elucidate the interplay between these responses and their impact on motor and motivational processes in PD.

A large body of research implicates dopamine in reward processing.[2-4,47] Phasic dopaminergic signaling figures prominently in reinforcement learning models, serving as a reward prediction error.[48-53] Phasic signaling, however, is degraded in PD because of nigrostriatal terminal denervation,[54,55] indicating that restored motor motivation with DRT must result from other components of striatal dopaminergic signaling. Tonic dopamine signaling was proposed to encode the average reward rate, providing a mechanism for modulating motor vigor by prospective rewards.[10,15] Recent work, however, points to a more nuanced relationship between dopamine and motivation. Grogan et al[29] found that chronically treated PD subjects modulated saccade vigor in response to performance-contingent rewards, but not guaranteed rewards. In contrast, subjects in the practical "Off" state (equivalent to our LDR session) were motivated by guaranteed rewards, but not performance-contingent rewards. As we used a contingent reward scheme, we cannot determine the impact of non-instrumental motivation on our subjects' performance across sessions. Nevertheless, we replicated their finding that PD patients on medication exhibit modulation of motor vigor in response to contingent rewards, but not in the practical "Off" state. Because we also did

not observe contingent reward modulation in the SDR session, our results further suggest that instrumental motivation is promoted by the synergistic action of SDR and LDR dopaminergic mechanisms.

The mechanisms underlying the SDR and LDR are unknown. The SDR parallels the plasma concentration of L-dopa. It is speculated that dopamine receptor activation elicited by the SDR is associated with maintenance of corticostriate plasticity.[25] The neural mechanisms underlying the LDR are even more cryptic. The fact that dopaminergic agonists elicit an LDR suggests that LDR induction is a consequence of partial restoration of tonic striatal dopamine signaling.[21,24-27] If the LDR is associated with a restoration of tonic dopaminergic signaling within the striatum, our result indicates that the restoration of striatal tonic dopaminergic signaling is not sufficient for the restoration of motivation-action coupling. Symptoms of PD such as the slowing of gait have been shown to be amplified when movements are not subject to attentional control.[56] As a result, it is possible that the observed change in reward sensitivity in the SDR + LDR session is attentional in nature. In other words, the combined action of the SDR and LDR may serve to reduce attentional load, and therefore, unmask latent motivation-vigor coupling that was previously suppressed by enhanced attentive control of movement across the first three sessions.

Our study has limitations. Our sample size was small because of the challenges of recruiting a large sample of de novo PD participants. This concern is somewhat mitigated by our use of a within-subject design, which substantially increased our statistical power. Furthermore, it is unclear whether our results will extend to alternative tasks with different motor requirements for successful performance. Future studies with larger sample sizes and variety of motor paradigms will be necessary to confirm and extend these findings. The current study examined two aspects of bradykinesia, slowing of movement and movement linearity. Bradykinesia also encompasses progressive decrements in movement speed and amplitude with repetition (ie, the sequence effect).[1] It is suggested that the sequence effect is resistant to treatment, although this conclusion flies in the face of clinical experience. The conclusion that the sequence effect is unresponsive to dopamine replacement rests on prior studies in chronically treated subjects, which did not isolate the SDR and LDR.[57-61] Examining whether our current findings extend to the sequence effect is an interesting avenue for future research.

Tasks such as the incentivized joystick task we used offer the possibility of collecting richer, but relatively interpretable datasets without over-burdening participants. Our incentivized joystick task results, notably movement time and movement efficiency, nicely paralleled the MDS-UPDRS-III results and had a broader dynamic range than the finger tapping measure.

We find that relationship between dopaminergic mechanisms and motivational processes is more complex than previously considered. We suggest that multiple mechanisms of dopaminergic signaling (ie, both the SDR and LDR) are required for participants to exhibit modulation of motor behavior by reward. Further research is necessary to elucidate the underlying mechanisms of the SDR, LDR, and their interactions. ■

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Data Availability Statement

The data and code that support the findings of this study are openly available on Open Science Framework at https://osf.io/tac5y/.

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Supporting Data

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