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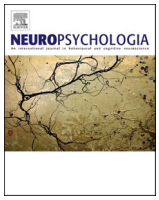

Side of motor symptom onset predicts sustained attention deficits and motor improvements after attention training in Parkinson's disease

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ABSTRACT

Objective: Parkinson's disease (PD) side of motor symptom onset has been associated with distinct cognitive deficits; individuals with left-side onset (LPD) show more visuospatial impairments, whereas those with right-side onset (RPD) show more verbal impairments. Non-spatial attention is a critical cognitive ability associated with motor functioning that is right hemisphere lateralized but has not been characterized with regard to PD side of onset. We compared individuals with LPD and RPD on non-spatial attention tasks and examined differential responses to a 4-week sustained attention training program.

Method: Participants included 9 with LPD and 12 with RPD, who performed both brief and extended go/no-go continuous performance tasks and an attentional blink task. Participants also engaged in an at-home sustained attention training program, Tonic and Phasic Alertness Training (TAPAT), 5 days/week for 4 weeks. We assessed cognitive and motor symptoms before and after training, and after a 4-week no-contact period.

Results: At baseline, participants with LPD exhibited worse performance than those with RPD on the extended continuous performance task, indicating specific deficits in *sustaining* attention. Poorer attention was associated with worse clinical motor scores. Notably, side of onset had a significant effect on clinical motor changes after sustained attention training, with only LPD participants improving after training, and 4/9 showing clinically meaningful improvements.

Conclusions: Compared to RPD, participants with LPD had poorer sustained attention pre-training and were more likely to improve on clinical motor functioning after sustained attention training. These findings support mechanistic differences between LPD and RPD and suggest potential differential treatment approaches.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the presence of resting tremor, bradykinesia, rigidity, and postural instability. These motor symptoms typically originate unilaterally, and the underlying neuropathological asymmetry persists long after symptoms become bilateral (Antonini et al., 1995; Booij et al., 1997; Kempster et al., 1989; Riederer et al., 2018). In line with this asymmetry, individuals with motor symptom onset or predominance on the left body side (LPD) and right body side (RPD) present with distinct cognitive deficit profiles (for reviews see Cronin-Golomb, 2010; Verreyt et al., 2011). Specifically, individuals with LPD have more compromised right-hemisphere processes, and demonstrate visuospatial deficits (Davidsdottir et al., 2005; Karádi et al., 2015; Laudate et al., 2013; Lee et al., 2001; Norton et al., 2015; Starkstein et al., 1987), whereas those with RPD have more impaired left-hemisphere processes, such as on verbally-mediated tasks (Amick et al., 2006; Foster et al., 2010; Huber et al., 1992; Starkstein et al., 1987). The side-of-onset groups may also respond differentially to cognitive rehabilitation (Ortelli et al., 2018) and dopamine replacement therapy (Hanna-Pladdy et al., 2015). It is currently unknown whether there are LPD and RPD differences in non-spatial attention, such as sustained and selective attention. The

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present study investigated whether the side of motor symptom onset critically influences sustained and selective attention and whether a validated sustained attention training program would produce differential outcomes in those with LPD vs. RPD.

Sustained attention is a core cognitive ability upon which many higher-level cognitive processes critically depend. It has been shown to be impaired in a range of neurodegenerative disorders (e.g., Hart et al., 2012; Huntley et al., 2017) and has also been related to motor function following age- or disease-related loss of automaticity. For example, sustained attention has positive correlations with gait speed (Killane et al., 2014; Park et al., 2021), negative associations with progression into frailty (O'Halloran et al., 2014), and is strongly predictive of motor recovery following stroke (Robertson et al., 1997). Sustained attention can influence mobility even in the absence of explicit motor impairments (i.e., "cognitive" gait disorders; Yogev-Seligmann et al., 2008). With respect to PD, basal ganglia dysfunction leads to a loss of automatic gait and increases dependence on cognitive resources to control movement (Chen et al., 2022; Gilat et al., 2017; Hung et al., 2020; Takakusaki et al., 2004; Wu et al., 2015). Sustained attention deficits in persons with PD predict decreased gait speed on a functional walking task (Lord et al., 2010), as walking effectively increases attentional load and exacerbates preexisting gait dysfunction (Hausdorff et al., 2008; Hausdorff and Yogev, 2006). Further, cognitive-motor dual-tasking in PD impairs not only the performance of the motor task (walking), but also impairs performance on the cognitive task (Salazar et al., 2017), alluding to the presence of a finite, depletable attentional resource that cognition and gait may simultaneously and unsuccessfully draw upon.

Beyond gait, studies have also found that attention in PD is related to performance on a number of motor tasks. Sustained attention increased upper limb rigidity (Mendonça and Jog, 2008). A concurrent verbal-cognitive test resulted in poorer hand dexterity (Proud and Morris, 2010), auditory input has been shown to cause attentional interference on an upper-limb functional task (Ma et al., 2009), and sustained auditory attention affects finger tapping (Martino et al., 2016). Reduction of attentional demands through external rhythmic auditory cueing improved drum tapping (Park and Kim, 2021). Further, individuals with PD and motor speech disorder, vs. those without, scored worse on attention/memory and perception items of the Non-Motor Symptoms Scale (Liu et al., 2019). To our knowledge, there are no published studies on the relation of sustained attention to tremor, bradykinesia or akinesia, or axial symptoms in PD.

It is apparent in PD that there is loss of motor automaticity and cognitive integrity, suggesting that efforts to compensate for diminished motor automaticity by drawing upon cognitive capacities are inclined to fail. Sustained attention has shown to be right-hemisphere lateralized (Coull et al., 1998; Mitko et al., 2019; for review see Langner and Eickhoff, 2013), particularly to inferior fronto-parietal networks (Sturm and Willmes, 2001). This suggests that those with more compromised right hemispheres, as in LPD, may be particularly impaired in this domain. Several studies have shown that sustained attention is responsive to rehabilitation (DeGutis et al., 2015; Jirayucharoensak et al., 2019; Van Vleet et al., 2016), particularly in those with right-hemisphere damage (DeGutis and Van Vleet, 2010; Van Vleet and DeGutis, 2013). Previous work has also demonstrated that sustained attention training increases activity in the right hemisphere (Sarter et al., 2001; Thimm et al., 2006), and these training benefits can generalize to improvements in motor functioning for those with right-hemisphere dysfunction (Van Vleet et al., 2020). Taken together, these findings suggest that training sustained attention is feasible and has important applications for motor and mobility improvement, particularly in those with right-hemisphere damage.

In the present study, we took an approach to cognitive training that targeted deficits in sustained attention to promote generalization to motor symptom improvement. Despite strong laterality effects, and evidence for beneficial motor outcomes in those with right-hemisphere dysfunction, no study to date has examined the potential of sustained attention training to differentially enhance motor function based on side of PD motor symptom onset. Given that previous work demonstrates variation in responses to treatment in persons with LPD and RPD (Hanna-Pladdy et al., 2015; Ortelli et al., 2018), collapsing across side of onset may mask evidence of subgroup effects. For these reasons, we aimed to assess whether differences in sustained attention related to side of onset, and further examined whether training preferentially benefitted LPD or RPD participants with respect to motor functioning. Our primary hypothesis was that enhancements in attentional resources would ameliorate attentional deficits in PD, potentially providing a compensatory mechanism to mediate the loss of motor automaticity, and thereby leading to improved gait-related outcomes. Additionally, due to the laterality of sustained attention, we hypothesized that training would preferentially benefit those with LPD.

2. Methods

2.1. Participants

Participants with idiopathic PD (UK Brain Bank criteria; Hughes et al., 1992) were recruited from the Boston University Parkinson's Disease and Movement Disorder Center at Boston Medical Center, the Fox Foundation Trial Finder, previous studies in the Vision and Cognition Laboratory of Boston University, and through other community outreach. Participants were excluded if they were not proficient in English, did not complete high school, reported a history of a traumatic brain injury, significant chronic illness (e.g., cardiac disease), comorbid psychiatric or neurological disorders (e.g., depression, intellectual disability, or dementia), eye disease or visual impairments (e.g., corrected binocular acuity poorer than 20/40), treatment with electroshock therapy, previous or current drug abuse, use of neuroleptic medication, or required a walking aid. Recruitment occurred in waves from April 2015 to July 2019, including non-randomized initial pilot study (12), randomized with exercise control (6), and randomized with waitlist control (17). The discrepancy in recruitment for exercise versus waitlist waves reflected difficulty enrolling participants who endorsed being sedentary.

Of the 35 participants enrolled, 14 either dropped out or were removed for the following reasons: change in medication across the study ($n = 4$), change in medical condition across the study, including problems with walking ($n = 2$), decided to not continue for personal reasons ($n = 5$), and persistent delays in training ($n = 3$). The final sample included participants from each wave as follows: 10 from the initial pilot wave (3 females; 5 RPD), 2 from the exercise control wave (2 females; 2 RPD), and 9 from the waitlist control wave (4 females; 5 RPD). All identified as White. Eleven identified as non-Hispanic; the rest either did not respond to this question or the data were otherwise unavailable.

Participants were evaluated for the following clinical characteristics: overall mental status with the Mini-Mental State Examination (MMSE), depression and anxiety symptoms with the Beck Depression Inventory 2nd edition (BDI-II; Beck et al., 1996) and Beck Anxiety Inventory (BAI; Beck et al., 1988), sleep and daytime sleepiness with the Parkinson's Disease Sleep Scale 2nd edition (PDSS-2; Trenkwalder et al., 2011) and Epworth Sleepiness Scale (ESS; Johns, 1991), levodopa equivalent dose (LED; Tomlinson et al., 2010), PD side of motor onset (LPD; RPD) and duration by self-report (corroborated by neurologist if available), and disease severity with the Unified Parkinson's Disease Rating Scale (UPDRS, Fahn et al., 1987) (Table 1).

2.2. Study design

We conducted assessments in the Vision and Cognition Laboratory of Boston University. Participants were instructed on equipment use, completed 4 weeks of computer-based attentional training at home, and returned for repeat assessments following training. To examine the

Table 1
Demographics, Clinical Characteristics, and Comparison of LPD vs RPD.

Sample Size	LPD	RPD	
	Mean (SD)		*p*-value
	$n = 9$ (8M, 1F)	$n = 12$ (4M, 8F)	
Age (years)	65.1 (6.2)	65.9 (7.7)	0.81
Education (years)	16.4 (2.1)	17.4 (2.0)	0.32
PD Duration (years)	4.1 (2.9)	5.7 (5.3)	0.46
H & Y Stage	2.0 (median)	2.0 (median)	0.67
UPDRS Total Score	27.7 (11.4)	22.7 (5.8)	0.22
UPDRS Motor Score	13.8 (8.8)	11.4 (4.9)	0.46
MMSE Score	28.2 (0.9)	28.7 (0.3)	0.18
BDI-II Score	8.2 (4.5)	6.3 (5.0)	0.39
BAI Score	4.4 (3.4)	5.6 (4.1)	0.53
LED (mg/day)	605.6 (255.7)	293.3 (305.0)	0.03*
PDSS-2	13.1 (8.2)	12.1 (7.1)	0.78
Epworth Sleepiness Scale	11.6 (5.2)	8.9 (4.8)	0.23
Day 1 TAPAT Commission Errors (%)	30.0 (12.5)	17.3 (9.9)	0.02*
Baseline Attentional Blink Lag 2 Accuracy (%)	57.2 (28.8)	55.4 (22.2)	0.74
Baseline gradCPT Accuracy (*d'*)	2.3 (1.1)	2.7 (1.1)	0.36
RAVLT Immediate Recall Total	44.7 (10.0)	49.2 (6.8)	0.26
RAVLT Delayed Recall	8.3 (3.9)	10.6 (2.5)	0.15

Note. * denotes $p < 0.05$
M: Male; F: Female; UPDRS: Unified Parkinson's Disease Rating Scale; MMSE: Mini-Mental State Examination; BDI-II: Beck Depression Inventory 2nd edition; BAI: Beck Anxiety Inventory; LED: Levodopa Equivalent Dose; PDSS-2: Parkinson's Disease Sleepiness Scale 2nd edition.

persistence of effects, an additional assessment was conducted after a 4-week no-contact period ($n = 17$). Though effects of this attentional training have previously been shown with only 2 weeks of training (e.g., spatial neglect, DeGutis and Van Vleet, 2010), longer 3-week (older adults, Van Vleet et al., 2016) and 12-week protocols have been well-tolerated and elicited more persistent effects (spatial neglect, Van Vleet et al., 2020). In persons with PD, who often need to change their medications (precluding commitment to a 12-week study period with no change in medications), we chose 4 weeks of training as a compromise between feasibility and persistence of training effects. Although we offered to conduct assessments at home if preferred, no participant selected this option. We provided a parking pass for each in-lab assessment.

The study protocol (#3966E) was approved by the Institutional Review Board of Boston University, and all participants provided informed consent prior to participation. All research was completed in accordance with the Helsinki Declaration.

2.3. Motor assessment

We examined clinical motor functioning with the UPDRS motor score. Minimal clinically meaningful differences in motor function were defined as a change in 2.3 points on UPDRS motor score (Shulman et al., 2010). Participants were in the ON medication state for in-lab assessments, including for the UPDRS.

2.4. Gradual onset continuous performance test (sustained attention)

The gradCPT (Esterman et al., 2013) is a well-validated and sensitive measure of sustained attention with established lifespan trajectories (Fortenbaugh et al., 2015). Gradual transitions between gray-scale scenes every 800ms eliminate the alerting and attention-engaging aspect of abrupt stimulus onsets and offsets and make the task more reliant on intrinsic sustained attention than sustained-attention-to-response (SART)-like tasks. In the gradCPT, participants make responses to frequent city scenes (90% of stimuli) and withhold responses to rare mountain scenes (10%) over 4 minutes. Accuracy (*d'*) is the primary measure of sustained attention on the gradCPT (Fortenbaugh et al., 2015). It is calculated using signal detection theory and based on miss rate (omission errors/failure to respond) and false alarm rate (commission errors/failure to withhold responses).

2.5. Go/No-Go continuous performance test (sustained attention) and Tonic and Phasic Alertness Training (TAPAT)

TAPAT is an adaptive cognitive training program that targets sustained attention by having participants practice focusing their attention and filtering out distractors. Previous work has demonstrated its effectiveness in improving attention in those with a history of stroke (DeGutis and Van Vleet, 2010) and in those with PD (DeGutis et al., 2015).

A single TAPAT session consisted of 3 × 12-min rounds with 1–2-min breaks between rounds. Each round contained 360 images shown for 500 ms/each, with a jittered inter-trial interval (e.g., 1000/1500/2000 ms). Participants responded to non-target images (90% of images) via spacebar presses, and withheld responses to rare, randomly presented target images (10% of images; go/no-go task). The target/non-target discrimination involved challenging within-category distinctions (Fig. 1). Because of the relatively low image rate (30/min vs. 75/min for gradCPT), non-target omission errors were quite rare (<3%) and we focused on target commission error rate as our measure of interest. The substantially lower image presentation rate for the TAPAT task compared to gradCPT made it relatively less intense, easier to perform reasonably well for a wide range of participants (<35% commission errors), and more tolerable and enjoyable to perform for 36 min/session.

To ensure task engagement, image sets changed each round, proceeding from easier to more difficult target/non-target discriminations. At the start of training, targets comprised 20% of trials and after each round performance-based adjustments were made. Following rounds with >90% accuracy, target frequency decreased by 5% to increase difficulty. After rounds with <75% accuracy, frequency increased by 5%, making it easier. As performance improved to <10% commission errors, the target frequency stayed the same but inter-trial intervals became less jittered and more consistent (e.g., 1000/1500/2000 ms to 1250/1500/1750 ms). This was motivated by previous studies showing that, compared to tasks with consistent intertrial intervals, tasks with more jittered intertrial intervals are easier to sustain attention and reduce lapses of attention in individuals with sustained attention difficulties (e.g., Ryan et al., 2010; Lee et al., 2015). That is, by making the intertrial intervals less jittered, we made the task more difficult. Participants completed TAPAT 5 days/week (36 min/day) for 4 weeks, and the trainer checked in regularly by phone.

2.6. Attentional blink (selective attention)

The attentional blink task was included to assess selective attention, an ability that is distinct from sustained attention. This allowed us to characterize the generality of non-spatial attention associations with motor symptoms and non-spatial attention differences between participants in the LPD and RPD groups. In this task, participants attempted to identify two target numbers (T1 and T2) embedded in a rapid visual serial stream of letter distractors. In healthy adults, accuracy is high on the first target (T1), and impaired on the second (T2) if it follows within approximately 200ms of T1 (i.e., lag 2); this impairment is referred to as the attentional blink. The attentional blink demonstrates temporal limitations of selective attention, which is exacerbated in populations with attention/visual working memory deficits (e.g., Lahar et al., 2001; Mathis et al., 2012). The attentional blink task was added to the study after data from 3 participants had already been collected.

2.7. Neuropsychological assessment

We administered a neuropsychological assessment examining

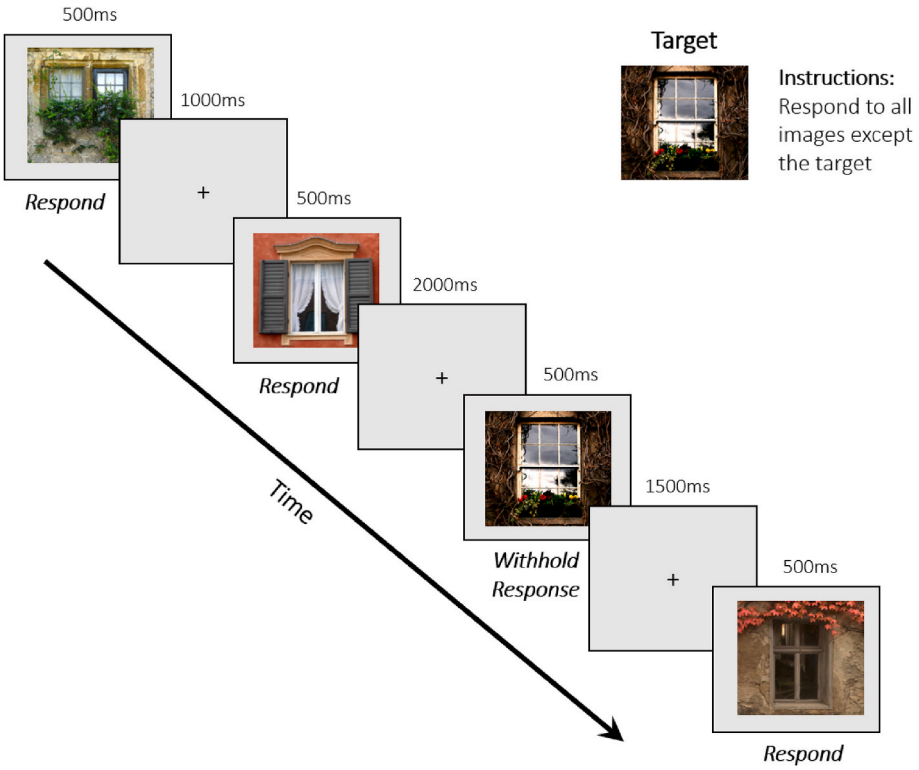

Fig. 1. Example trials from the Tonic and Phasic Alertness Training (TAPAT) task. Participants respond to frequent non-target images and withhold responses to rare, predetermined targets. Commission errors, our measure of interest, was the percentage of trials on which participants erroneously responded to the target images.

executive functioning with the Digit and Spatial Span tests from the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997), the Trail Making Test parts A and B (Tombaugh, 2004), the Stroop Color-Word Test (SCWT; Stroop, 1935), Serial 3's (counting backwards by 3's), and the Verbal Fluency test from the Delis-Kaplan Executive Function System (FAS, Animals, & Switching, D-KEFS; Delis et al., 2001). Visuospatial functioning was assessed with the Visual Dependence task (Danta and Hilton, 1975). Verbal learning and memory were measured with the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964), performance on which is typically impaired in those with left-hemisphere dysfunction (e.g., RPD; Verreyt et al., 2011).

2.8. Statistical analyses

We first examined whether poorer cognitive performance, particularly worse attention (Hausdorff et al., 2008; Hausdorff and Yogev, 2006; Killane et al., 2014; Park et al., 2021), predicted the degree of motor impairment indexed by the UPDRS motor score. We performed FDR-corrected correlations across the cognitive assessments. We next characterized whether individuals with LPD and RPD differed in their sustained attention ability, FDR-correcting for our two sustained attention measures. We additionally performed exploratory FDR-corrected LPD-RPD analyses across the rest of the cognitive tests. We examined pre- vs. post-TAPAT differences and pre- vs. post-TAPAT by side-of-onset interactions separately for our near-transfer sustained attention task, other cognitive assessments, and clinical motor functioning (UPDRS motor), FDR-corrected within each domain. Effect sizes were computed, and the recommended interpretations were used for small ($d = 0.20$; $\eta_p^2 = 0.01$), medium ($d = 0.50$; $\eta_p^2 = 0.06$), and large effects ($d = 0.80$; $\eta_p^2 = 0.14$) (Cohen, 1988).

2.9. Transparency and openness

All data, analysis code, and research materials are available from the corresponding author upon reasonable request. Data were analyzed using SPSS, version 27. The study design and analysis were not pre-registered.

3. Results

3.1. Participants

The following analyses were conducted with the data from the final sample of 21 participants, including 9 LPD and 12 RPD. The mean age was 65.6 years (SD = 7.1), mean education 17.0 years (SD = 2.1), Hoehn and Yahr median disease stage 2 (range 1–3, mild-moderate), mean UPDRS score 24.8 (SD = 9.0), and mean disease duration 5.0 years (SD = 4.5). LPD and RPD participants did not differ in demographics, except that the LPD subgroup had a higher ratio of males to females (LPD-8M:1F, RPD-4M:8F). The groups had similar PD symptom severity and duration. They differed only in levodopa equivalent dose (LED), with LPD participants taking higher doses. This imbalance was likely an artifact of the randomization process, considering that recent studies from our lab showed similar LED in RPD and LPD (e.g., Salazar et al., 2019). Of the 9 persons in the LPD group, 8 were taking levodopa/-carbidopa, 7 were taking DA agonists, and none anticholinergics. Of the 12 persons in the RPD group, 2 had levodopa/carbidopa, 9 DA agonists, and 2 anticholinergics. There was significant variability in the dosages of medications taken. No participants were diagnosed with impulse control disorder, and at no time did we suspect any of them of having such a disorder.

3.2. Correlations with motor deficits

We first examined whether poorer attention predicted the degree of motor impairment indexed by the UPDRS, collapsed across LPD and RPD (Table 2), similar to previous studies showing associations between attention and motor function in healthy aging (Hausdorff et al., 2008;

Hausdorff and Yogev, 2006; Killane et al., 2014; Park et al., 2021). We found a significant association between UPDRS motor score and attentional blink lag 2 accuracy ($n = 19$; $r = -0.73$, $p < 0.001$, $q = 0.006$) as well as trends towards significant associations between UPDRS motor score and TAPAT go/no-go commission errors ($r = 0.45$, $p = 0.04$, $q = 0.12$) and gradCPT *d*-prime ($r = -0.38$, $p = 0.09$, $q = 0.22$). We also found significant negative associations between UPDRS motor scores and both RAVLT immediate ($r = -0.67$, $p = 0.001$, $q = 0.008$) and delayed recall ($r = -0.62$, $p = 0.003$, $q = 0.02$). The overall regression predicting baseline UPDRS motor symptom score from TAPAT commission errors and lag 2 attentional blink accuracy was significant (adjusted $R^2 = 0.62$, $p = 0.0003$). While associations with baseline motor functioning on the UPDRS were present for MMSE ($r = -0.56$, $p = 0.008$, $q = 0.03$) as well as RAVLT immediate and delayed scores, including TAPAT commission errors and attentional blink performance significantly predicted additional variance in clinical motor deficits ($R^2 = 0.88$, R^2 change $= 0.27$), demonstrating an association between attention and motor functioning that extended beyond general cognitive status.

3.3. Cognitive differences by side of motor onset

We next examined whether the LPD and RPD groups differed on sustained and selective attention (Fig. 2). At baseline, LPD participants performed significantly worse than those with RPD ($t(19) = 2.48$, $p = 0.023$, FDR-corrected $q = 0.046$), as indexed by more TAPAT commission errors (go/no-go, measure of prolonged sustained attention), and the effect size was large ($d = 1.09$). Calculating the coefficient of variation on the TAPAT task (SD RT/Mean RT), we also observed that the LPD group had numerically greater RT variability ($M = .28$, $SD = .16$) than the RPD group ($M = .22$, $SD = .07$), though this difference was not significant ($p = .274$). There were no differences for the gradCPT ($t(19) = 0.93$, $p = 0.36$, $d = 0.41$). The greater sensitivity of the longer-duration sustained attention task to side of onset differences may be because longer vigilance tasks have been shown to be more dependent on the right hemisphere than shorter tasks (Langner and Eickhoff, 2013). To determine whether the observed effects were specific to sustained attention, we conducted exploratory analyses on group differences in selective attention, verbal memory abilities, and other cognitive measures. We found no side-of-onset differences in performance on the attentional blink (lag 2: $t(16) = 0.33$, $p = 0.74$, $d = 0.16$), RAVLT (immediate recall performance: $t(19) = 1.17$, $p = 0.26$, $d = 0.51$; delayed recall: ($t(19) = 1.52$, $p = 0.15$, $d = 0.67$), or any other neuropsychological measures (all *p*-values > 0.05).

Table 2
Correlations with Baseline Motor Score.

Sample Size	*Mean (SD)*	Pearson *r*	*p*-value	*q*-value
	$n = 21$			
Age (years)	65.6 (7.1)	−0.27	0.24	0.36
Side of Onset (LPD:RPD)	9:12	−0.17	0.46	0.63
Education (years)	17.0 (2.1)	−0.30	0.19	0.41
PD Duration (years)	5.0 (4.5)	0.09	0.71	0.89
UPDRS Motor Score	12.5 (7.0)	–	–	–
MMSE Score	28.5 (0.7)	−0.56	0.008**	0.03*
BDI-II Score	7.1 (4.9)	0.04	0.86	0.92
BAI Score	5.1 (3.9)	−0.02	0.95	0.95
LED (mg/day)	415.3 (308.9)	0.28	0.22	0.37
PDSS-2	12.5 (7.7)	−0.29	0.20	0.38
Epworth Sleepiness Scale	10.0 (5.1)	−0.07	0.78	0.90
Day 1 TAPAT Commission Errors (%)	23.0 (10.0)	0.45	0.04*	0.12
Baseline Attentional Blink Lag 2 Accuracy (%)	56.0 (24.9)	−0.73	<0.001***	0.006**
Baseline gradCPT Accuracy (*d'*)	2.5 (1.2)	−0.38	0.09	0.22
RAVLT Immediate Recall Total	47.2 (8.6)	−0.67	0.001**	0.008**
RAVLT Delayed Recall	9.6 (3.4)	−0.62	0.003**	0.02*

Note. * denotes p < 0.05, ** denotes p < 0.01, *** denotes p < 0.001.
UPDRS: Unified Parkinson's Disease Rating Scale; MMSE: Mini-Mental State Examination; BDI-II: Beck Depression Inventory II; BAI: Beck Anxiety Inventory; LED: Levodopa Equivalent Dose; PDSS-2: Parkinson's Disease Sleepiness Scale 2; TAPAT: Tonic and Phasic Alertness Training; gradCPT: Gradual Onset Continuous Performance Task; RAVLT: Rey Auditory Verbal Learning Test.

3.4. TAPAT: training

On average, participants completed 18.4 sessions of at-home sustained attention training (SD = 2.21), and there were no differences between the LPD and RPD subgroups in sessions completed ($t(19) = 0.30$, $p = 0.77$). On the first day of TAPAT, those with LPD performed worse than those with RPD ($t(19) = 2.09$, $p = 0.023$, $q = 0.046$, $d = 1.09$, as noted above). As shown in Fig. 3, throughout training the LPD subgroup generally did not achieve as high of difficulty levels (indicated by *lower* target percentages during the task) as the RPD subgroup. Final target percentages were higher for LPD than RPD, ($t(19) = 2.13$, $p = 0.046$) and the effect size was large ($d = 0.94$), demonstrating that LPD participants maintained lower sustaining attention performance throughout training. Due to the adaptive nature of TAPAT, commission errors did not differ on the final day of training ($t(19) = 1.34$, $p = 0.20$, $d = 0.59$; see Methods).

3.5. TAPAT: generalization to sustained attention and other cognitive measures

We first assessed whether TAPAT training generalized to cognitive improvements. Examining performance on our near-transfer sustained attention task, we found that gradCPT accuracy did not significantly improve ($F(1,19) = 1.92$, $p = 0.18$, $\eta_p^2 = 0.09$), and there was no effect of side of onset ($F(1,19) = 0.45$, $p = 0.51$, $\eta_p^2 = 0.02$).

When examining mid/far-transfer cognitive tasks, we found no significant improvements in attentional blink performance ($F(1,16) = 1.37$, $p = 0.26$, $\eta_p^2 = 0.08$), and no association with side of onset ($F(1,16) = 0.12$, $p = 0.73$, $\eta_p^2 = 0.01$). On the RAVLT, large effects were detected in follow-up immediate recall score improvement ($F(1,19) = 23.58$, $p < 0.001$, $q < 0.001$, $\eta_p^2 = 0.55$), with a trend as well for the side-of-onset interaction ($F(1,19) = 3.57$, $p = 0.07$, $q = 0.14$, $\eta_p^2 = 0.16$), with RPD exhibiting greater improvements. While a large effect was found for improvement in delayed recall ($F(1,19) = 20.27$, $p < 0.001$, $q < 0.001$, $\eta_p^2 = 0.52$), there was no association with side of onset ($F(1,19) = 0.81$, $p = 0.38$, $\eta_p^2 = 0.04$). After the 4-week no-contact period, performance on immediate recall was significantly better than baseline with a large effect size ($F(1,15) = 101.81$, $p < 0.001$, $\eta_p^2 = 0.87$), but no side-of-onset effects were present ($F(1,15) = 0.92$, $p = 0.35$, $\eta_p^2 = 0.06$). The same was true with improvements at the second follow-up relative to baseline delayed recall ($F(1,15) = 27.31$, $p < 0.001$, $\eta_p^2 = 0.65$), and no association with side of onset ($F(1,15) = 0.11$, $p = 0.74$, $\eta_p^2 = 0.01$). Similarly, Trails B performance improved significantly from the first assessment to the second follow-up, ($F(1,16) = 11.12$, $p = 0.004$, $\eta_p^2 = 0.41$) with a large effect, but there was no interaction with side of onset ($F(1,16) = 0.74$, $p = 0.40$, $\eta_p^2 = 0.04$).

The measures that showed no immediate improvements (i.e., gradCPT and attentional blink) also showed no effect at the 4-week follow-up assessment (all *p*-values > 0.05). There were no significant improvements in performance on any other neuropsychological measures immediately following training or after the 4-week no-contact period (all *p*-values > 0.05).

3.6. TAPAT: generalization to motor outcomes

We next investigated whether training sustained attention over 4 weeks generalized to improvements in motor symptoms. We had hypothesized that individuals with LPD would experience greater motor

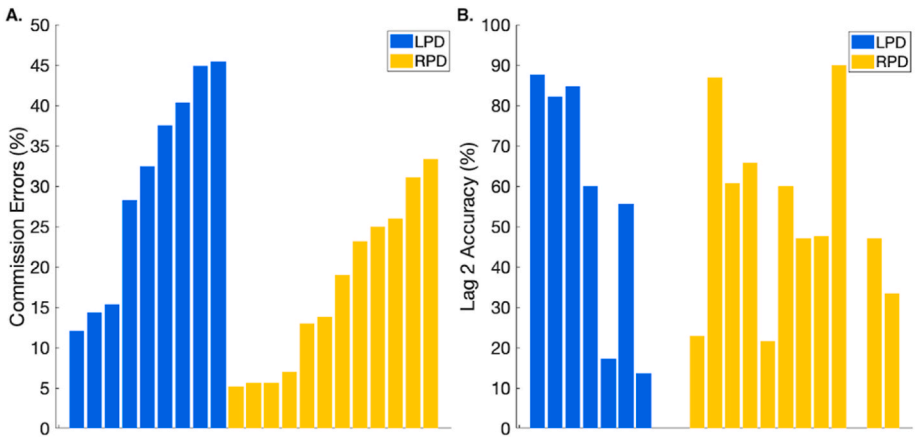

Fig. 2. Sustained and selective attention performance.
Note. Sustained attention was measured by the Day 1 TAPAT task commission errors (A), whereas the attentional blink lag 2 accuracy (B) was used to assess selective attention. The participants are arranged in the identical order across both figures for comparison. LPD = left-side motor symptom onset, RPD = right-side motor symptom onset.

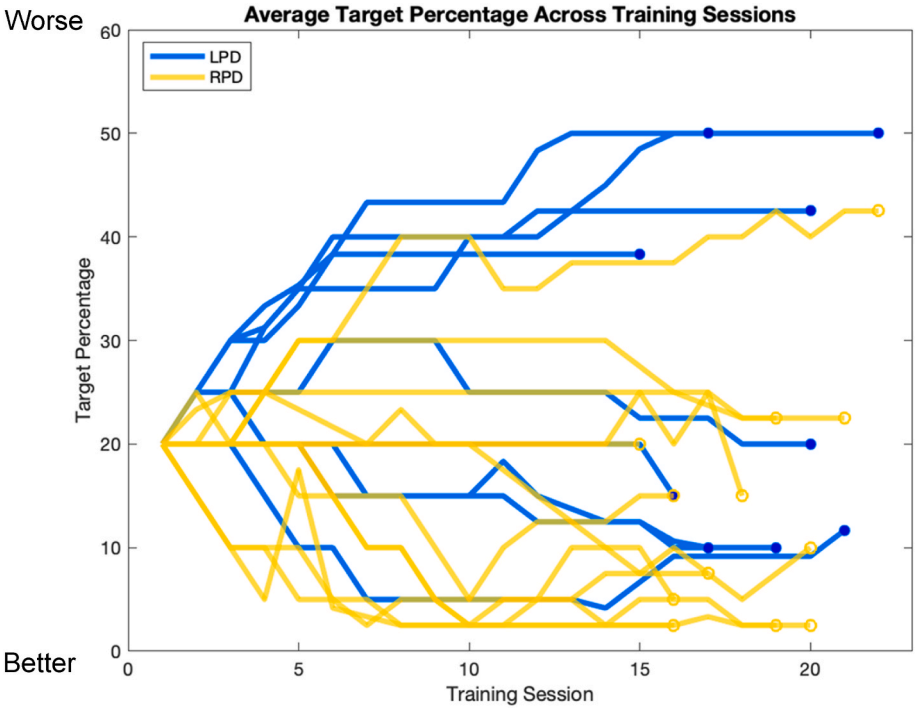

Fig. 3. Individual training trajectories.
Note. More difficult levels of the TAPAT task are reflected by lower target percentages (i.e., poorest performers are farthest from zero). All participants began TAPAT training at the same level of difficulty (target percentage). The target percentage decreased as participants achieved high levels of performance (>90% accuracy) or increased as participants performed poorly (<75% accuracy). LPD = left-side motor symptom onset, RPD = right-side motor symptom onset.

improvements than those with RPD, based on previous work showing that TAPAT enhanced sustained attention and benefitted motor function in individuals with hemispatial neglect following right-hemisphere brain injury (Van Vleet et al., 2020). Here, side of onset had a significant effect on change in motor symptom severity, with participants with LPD exhibiting greater improvements on UPDRS motor than those with RPD ($F(1,19) = 6.33$, $p = 0.02$; $\eta_p^2 = 0.25$) and this was consistent with a large effect. These differences remained significant with a large effect size after controlling for LED ($F(1,18) = 4.41$, $p = 0.05$; $\eta_p^2 = 0.20$), which was the only clinical characteristic on which the side-of-onset groups differed. Because the LPD subgroup had numerically (though not significantly) worse baseline UPDRS motor scores than RPD, LPD-RPD differences could possibly have been driven by regression to the mean. Considering this, we compared LPD and RPD post-training UPDRS motor scores while controlling for pre-training UPDRS motor scores using an ANCOVA and found that LPD participants still showed a large effect of greater motor improvements than RPD ($F(1,18) = 5.30$, $p = 0.03$; $\eta_p^2 = 0.23$), demonstrating that the results were not explained by regression to the mean. Finally, we quantified whether UPDRS changes were clinically meaningful and found that 4 of the 9 LPD participants showed clinically meaningful improvements, defined as a decrease in UPDRS motor score of at least 2.3 points (Shulman et al., 2010). By contrast, no RPD participant showed clinically meaningful improvements in motor scores (Fig. 4). When collapsing across LPD and RPD subgroups, no motor improvements were apparent in the overall sample ($t(20) = 0.14$, $p = 0.89$; $d = 0.03$). Motor improvements did not

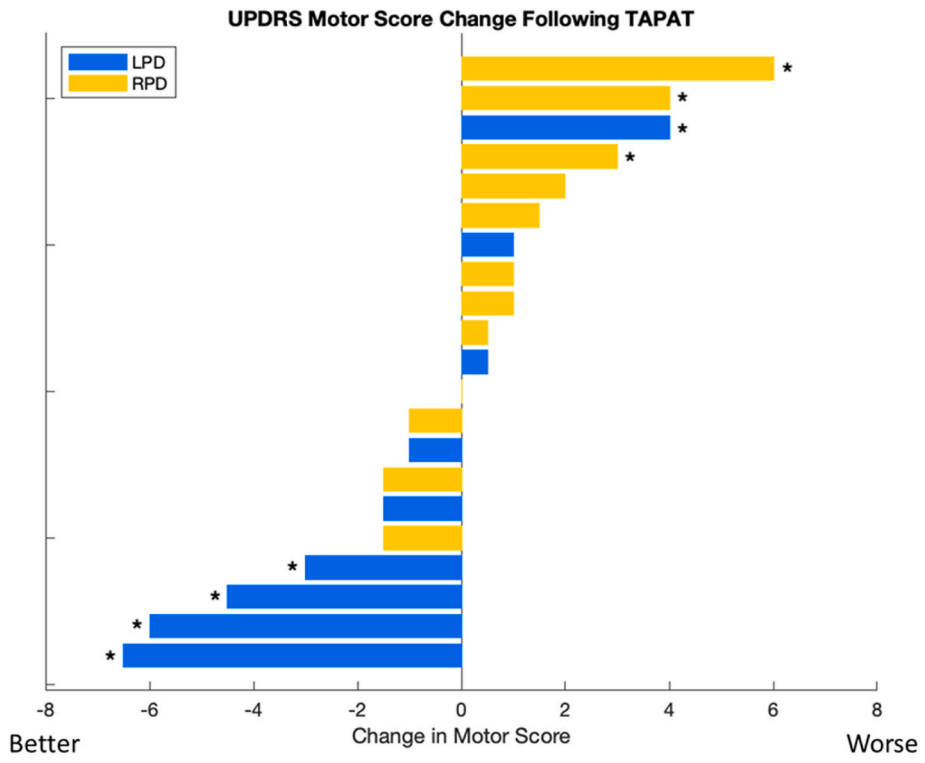

Fig. 4. Changes in UPDRS motor scores following TAPAT.
Note. *denotes a clinically meaningful difference in motor score; only individuals with LPD improved to this extent. UPDRS = Unified Parkinson's Disease Rating Scale, TAPAT = Tonic and Phasic Alertness Training, LPD = left-side motor symptom onset, RPD = right-side motor symptom onset.

significantly differ between men and women ($F(1,19) = 2.18$, $p = 0.16$; $\eta_p^2 = 0.10$). Of the 21 TAPAT participants, 17 returned for an additional motor assessment 4 weeks after completing training. There was still a trend toward an interaction between side of symptom onset and change in motor symptom severity with a large effect size, with LPD maintaining greater improvements on the UPDRS motor score ($F(1,15) = 3.70$, $p = 0.07$; $\eta_p^2 = 0.20$).

In addition to side of PD motor symptom onset, we also sought to determine if poorer baseline sustained attention performance predicted greater TAPAT-related motor improvements. We performed an exploratory correlation and found a robust relation between day 1 TAPAT commission errors and change in UPDRS motor scores ($r = 0.58$, $p = 0.006$).

4. Discussion

In this study, several important findings emerged regarding non-spatial attention in PD. First, we found that poorer non-spatial attentional abilities in individuals with PD, regardless of side of onset, were associated with worse clinical motor functioning on the UPDRS, the standard measure of disease severity in PD, extending previous work relating attention and motor performance in healthy older adults (Hausdorff et al., 2008; Hausdorff and Yogev, 2006; Killane et al., 2014; Park et al., 2021). We also demonstrated, for the first time, large PD side-of-onset effects in sustained attention, with participants with LPD exhibiting significantly worse sustained attention than those with RPD. Finally, clinically meaningful improvements in motor functioning were found in those with LPD compared to RPD, and these gains were maintained after a 4-week no-contact period. These findings highlight the importance of sustained attention for motor function in PD and suggest that modulating sustained attention has differential therapeutic effects depending on side of disease onset.

We found that non-spatial attention, as measured by the sustained attention tasks and attentional blink, predicted clinical motor deficits in PD. These relations were still significant after controlling for general cognitive functioning (MMSE and RAVLT), suggesting a specific association between non-spatial attention abilities and motor deficits. These findings are consistent with the "loss of automaticity" model of PD, where basal ganglia dysfunction leads to a reduction in automatic control of motor function and gait, which in turn leads to an increased reliance on attentional resources to control movement; e.g., dual-tasking consistently exacerbates motor and gait issues (Chen et al., 2022; Gilat et al., 2017; Hung et al., 2020; Salazar et al., 2017; Takakusaki et al., 2004; Wu et al., 2015). Unfortunately, in PD the loss of motor automaticity can often be accompanied by a reduction in attention abilities, therefore impeding the ability to compensate. Supporting this model, sustained attention deficits in people with PD have been associated with decreased gait speed on a functional gait task (Lord et al., 2010), and shown to predict future falling incidents (Allcock et al., 2009). Additionally, selective attention impairments have been associated with freezing of gait (Vandenbossche et al., 2013). The present results are consistent with these findings but are the first to demonstrate significant associations between both sustained and selective attention with clinical motor symptom severity on the UPDRS. Together, these associations and the results of TAPAT training (see below), suggest that enhancing non-spatial attention may be an important component of counteracting motor decline in PD.

Beyond demonstrating a clear association between non-spatial attention and clinical motor functioning, we also found that individuals with LPD had significantly worse sustained attention than those with RPD. In particular, we found this LPD-RPD difference with a longer, but not a shorter, continuous performance task, suggesting that these effects may be specific to time on task. In the present study, we employed two sensitive sustained attention measures: the short, well-validated 4-min gradCPT (Esterman et al., 2013; Fortenbaugh et al., 2015), and a longer, classic go/no-go sustained attention task (3 × 12 min, TAPAT; DeGutis and Van Vleet, 2010). The longer task was sensitive to side of onset, with LPD performing significantly more poorly than

RPD. Consistent with these findings, sustained attention has been shown to be lateralized to the right hemisphere (Coull et al., 1998; Mitko et al., 2019; for reviews see Langner and Eickhoff, 2013; Sturm and Willmes, 2001), suggesting that different patterns of deficits are to be expected depending on the location of the underlying disease pathology. While previous work has failed to identify PD side-of-onset differences in sustained attention performance (Bentin et al., 1981; Ortelli et al., 2018), this may be accounted for by discrepancies between methodologies in these studies and the present one. Specifically, the prior studies used non-standard measures of sustained attention, with a light sequence test (Bentin et al., 1981) and multiple-choice reaction time (Ortelli et al., 2018) as their measures. These tasks may less specifically require the 'constant vigilance' aspect of sustained attention that our CPTs require, instead reflecting more general aspects of cognitive functioning. In contrast to these findings, we provide evidence that side of PD motor symptom onset critically influences sustained attention in PD, supporting the notion that sustained attention particularly depends on the integrity of the right hemisphere.

Our current understanding of TAPAT's therapeutic effects comes from individuals with hemispatial neglect following right hemisphere brain injury (DeGutis and Van Vleet, 2010; Van Vleet et al., 2020). Two trials independently showed that TAPAT, compared to a waitlist and active control, improved spatial biases (e.g., DeGutis and Van Vleet, 2010) and enhanced everyday motor functioning (Van Vleet et al., 2020). Hemispatial neglect has been consistently associated with reduced sustained attention and damage to right fronto-parietal ventral attention network (VAN) regions (Clemens et al., 2013). Our mechanistic hypothesis of TAPAT results in persons with neglect is that it engages sustained attention and increases right VAN activity in perilesional regions. Greater right VAN activity may lead to increased right dorsal attention network (DAN) activation, a network involved in spatially-directed attention, allowing for better communication and competition between the right and left DAN. In neglect, better right and left DAN communication and competition has been associated with reduced spatial biases and improved recovery of motor functioning (Corbetta et al., 2005; Van Vleet et al., 2020). Our results suggest that a similar mechanism may be at work in PD. Specifically, TAPAT may engage right VAN regions, and this may result in increased right hemisphere DAN and motor region activation. This could result in a greater hemispheric balance in those with LPD, whose right hemispheres are particularly dysfunctional pre-training, but perhaps could result in more of an imbalance in those with RPD, as indicated by poorer motor performance in some of these individuals post-training (though see DeGutis et al., 2015 that showed benefits in both LPD and RPD). Notably, motor improvements after TAPAT were greatest in those with pre-training sustained attention deficits ($r = 0.58$, similar to DeGutis and Van Vleet, 2010), suggesting that TAPAT can be useful in persons with compromised sustained attention whose side of onset classified them as either LPD or RPD. Future studies including resting and task-related fMRI before and after TAPAT training in a larger sample of LPD and RPD would be useful to better understand the mechanism of this therapeutic effect and to show who is most responsive to TAPAT.

Regarding TAPAT training, it is notable that some participants showed inconsistent training trajectories and there was a high proportion of participants whose performance became worse with time. The inconsistent trajectories could reflect day-to-day attention and alertness fluctuations, as has been demonstrated when people with PD performed a working memory task several times over 10 days using smartphone-based ecological momentary assessment (Weizenbaum et al., 2022). Such fluctuations could also arise from any of a number of well-known disease correlates such as daytime sleepiness or fluctuations in medication effectiveness, or from contextual variables such as recent exercise. Fluctuations in non-motor symptoms including cognition and mood are recognized as an important component of daily function in PD (Caillava-Santos et al., 2015, Witjas et al., 2002). Finally, worse performance over time could be because all participants started at the same level and for some, especially in the LPD group, this was too difficult and over time they descended to easier levels.

The present study is not without limitations and additional work is needed to validate these findings. The sample is small ($N = 21$), and we divided it into motor subgroups (9 LPD, 12 RPD), which likely influenced the magnitude of effects detected in the present study. Replication in a larger sample will be necessary. That being said, we have previously demonstrated side-of-onset differences in similar-sized samples (e.g., Amick et al., 2006; Bogdanova and Cronin-Golomb, 2013; Davidsdottir et al., 2005; Laudate et al., 2013; Ren et al., 2015; Schendan et al., 2009; Seichepine et al., 2015; Stavitsky et al., 2008). Another limitation of the current study is that our subgroups differed in certain characteristics, with the LPD group having a higher ratio of men to women and a higher LED. The medication level difference could be related to the discrepancy in the sex ratio, with men requiring higher dosages, possibly due to lower bioavailability of levodopa (Shulman, 2007). These group differences cannot account for the pattern of response to training, however, as the association between sustained attention and motor symptom severity survived when controlling for LED, and there were no sex differences in motor symptom improvements when pooling across LPD-RPD subgroups. Moreover, it is important to note that the observed LPD-RPD differences are likely not due to general alertness variations, as subgroup scores on daytime sleepiness (ESS) and sleep (PDSS-2) were similar prior to training. Hence, despite these limitations, we suggest that this study provides compelling preliminary evidence for differential treatment responses based on side of PD motor symptom onset.

Constraints on generality. Despite efforts to recruit a diverse sample, participants in this study were White and those who identified their ethnicity (11/21) were non-Hispanic. The education level was high, with an average of 17 years**.** We excluded potential participants who were not proficient in English, did not complete high school, reported a history of or comorbidity with multiple traumas and disorders, or who required a walking aid. Hence, the results may not generalize to all individuals with PD. Another factor that may have affected the composition of the sample was the nature of the intervention study, which required multiple in-lab assessments (baseline, immediate post-intervention, 4-week no-contact post-intervention, with an additional baseline for waitlist participants) as well as a commitment to four weeks of attention training at home, five days per week. We did offer to conduct assessments at home if transportation to the lab was a problem, though no participants chose this option. Of those participants who initially enrolled but dropped out of the study, reasons including change in medication or medical condition, or decision to not continue for personal reasons; others were dropped from the study for persistent delays in training, possibly attesting to study demands.

Conclusions. The present results highlight the importance of considering attention as a contributor to motor dysfunction in PD, particularly in individuals with compromised right-hemisphere function. Our findings suggest that attentional training may preferentially benefit motor function in those with underlying right-hemisphere pathology (LPD), providing support for differential treatment plans based on PD motor subtype. Without examining the LPD and RPD subgroups, the positive effect of attentional training in the LPD subgroup would have been missed, and the intervention would have erroneously been seen as unsuccessful. Future work should more critically examine the relation between attention and motor function in PD, as well as the role of the side of predominant disease pathology in this association.

CRediT authorship contribution statement

Joseph DeGutis: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Courtney Aul:** Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Olivier J. Barthelemy:** Data curation, Formal analysis, Investigation, Visualization, Writing – review &

editing. **Breanna L. Davis:** Data curation, Investigation, Writing – review & editing. **Shaikhah Alshuaib:** Data curation, Investigation, Writing – review & editing. **Anna Marin:** Investigation, Writing – review & editing. **Shraddha B. Kinger:** Data curation, Investigation, Writing – review & editing. **Terry D. Ellis:** Conceptualization, Methodology, Writing – review & editing. **Alice Cronin-Golomb:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2023.108698.

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