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ORIGINAL PAPER

When is Higher Level Cognitive Control Needed for Locomotor Tasks Among Patients with Parkinson's Disease?

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Abstract Turning has been implicated as a complex task that requires both motor and cognitive resources. Accumulating evidence shows that patients with Parkinson's disease (PD) require more steps and more time to complete a turn, however, the role of the prefrontal cortex during turning is not clear. Forty nine patients with PD without freezing of gait (mean age 71.7 ± 1.0 years; 67% men, disease duration 9.7 ± 1.3 years) performed motor and cognitive tests. Prefrontal activation, specifically in Brodmann area 10 (BA10), during turning and usual walking was measured using functional near infrared spectroscopy (fNIRS). The patients with PD were further divided into two subgroups with high and low functional status based on limitations in community ambulation. General Linear Model analysis adjusted for age, gender, disease duration and turn duration was used to assess differences between tasks and subgroups of patients with PD. In addition, Pearson's correlation was performed to assess association between BA10 activation and motor and cognitive scores. Activation in BA10 increased during walking ($p < 0.001$), while it decreased during turning ($p = 0.006$). A comparison between the two subgroups of patients with PD revealed that patients with relatively better ambulation decreased prefrontal activation during turning, as compared to patients with relatively worse ambulation ($p < 0.001$). These findings are the first to show that BA10 plays a different role during turning and walking and that ambulation status may alter BA10 activation during turning. Higher prefrontal activation during turning in the subgroup of patients with relatively worse ambulation may reflect a compensatory attempt at improving performance.

Keywords Gait · Cognition · Parkinson's disease · BA10 · fNIRS

Introduction

Among patients with Parkinson's disease (PD), falls are highly prevalent and a significant cause of disability. One of the most common causes of falls in PD is turning, a complex task that involves shifting of the body weight while changing direction (Robinovitch et al. 2013; Weaver et al. 2016). Motor aspects of turning include inter-limb coordination, dynamic balance, and coupling between posture and gait. Recent work suggests that turning also utilizes cognitive resources such as attention, visual spatial function and executive function (Glaister et al. 2007; Herman et al. 2011; King et al. 2012; Mancini et al. 2016; Mellone et al. 2016; Mirelman et al. 2014b). While much is known about the motor and cognitive deficits that are common in PD, the mechanisms that contribute to impaired turning ability in PD have not yet been fully elucidated.

In a previous study among patients with PD, all of whom experienced freezing of gait (FOG), we investigated

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prefrontal activation during turns using functional near infra-red spectroscopy (fNIRS) (Maidan et al. 2015). During turns with freezing, i.e., unsuccessful turns, prefrontal cortex activation increased, compared to straight-line walking. In contrast, during turns without freezing, i.e., successful turns, prefrontal activation decreased, compared to straight-line walking. One explanation for these findings is that in PD patients who experience FOG, there is less reliance on prefrontal resources during successful turns, as compared to unsuccessful turns during which FOG occurs. This possibility is consistent with a recently proposed model of gait failures in PD including FOG (Sarter et al. 2014; Vandenbossche et al. 2012). The model posits that in the presence of reduced motor automaticity and poor gait, cognitive resources, in particular prefrontal regions, are called into play in attempt to compensate for these motor deficits. However, under challenging conditions (e.g., turns), the compensatory response is not sufficient, overloading occurs, and this leads to gait failure.

In PD, FOG generally occurs in the presence of relatively severe motor and cognitive deficits. Thus, it is not yet clear if the reduced prefrontal activation pattern observed during successful turns in patients with FOG is generalizable to patients with PD with less impaired motor and cognitive. Indeed, the motor properties of turning differ in patients with and without freezing; patients with freezing complete turns more slowly and take a higher number of steps, compared to PD non-freezers (Bengevoord et al. 2016; Bhatt et al. 2013; Spildooren et al. 2010). Thus, one could speculate that in PD patients without FOG, there will be less reliance on the prefrontal cortex and hence less recruitment of this brain region during turns, as compared to PD patients with FOG.

In contrast, the role of cognition in performing turns is more controversial. Intuitively and extending the models described above, one could suggest that turning ability and the recruitment of the prefrontal region would be mediated by cognitive abilities. Indeed, some evidence suggests that turns become slower and less efficient in the presence of a cognitive load (Porciuncula et al. 2016; Spildooren et al. 2010), supporting the idea that turns demand attention and prefrontal activation. In contrast, other work reports no association between measures of turns and executive function or attention in PD (Herman et al. 2011; Mancini et al. 2016; Mellone et al. 2016). Thus, the role of the prefrontal region during turns in patients with PD remains to be determined.

In the present study, we used fNIRS to examine the role of prefrontal cortex during turning in PD patients who do not experience FOG. We hypothesized that prefrontal activation during turns will be reduced, relative to usual walking, reflecting better motor ability and less reliance on cognitive resources during turns. To further examine this idea, we divided the PD subjects into two groups as a function of their gait. Based on the model of motor-cognitive compensation in PD described above, we speculated that patients with relatively worse mobility would have higher prefrontal activation during turns, as compared to patients with relatively better mobility. Finally, to further probe the model of gait failure and FOG, we also evaluated the relationship between cognitive ability and prefrontal activation during turns. Based on the previous reports of the impact of a dual task on turning in PD (Porciuncula et al. 2016; Spildooren et al. 2010), we postulated that cognition would modify the impact of turns on prefrontal activation.

Materials and Methods

Participants

The present work was a sub-study based on the baseline data of a randomized controlled trial, V-TIME (Mirelman et al. 2013). The sub-study included 49 patients with PD from one clinical site, Tel Aviv Medical Center, who performed the baseline gait evaluation with fNIRS. Inclusion criteria were (1) diagnosed with idiopathic PD, as defined by the UK Brain Bank criteria, (2) 60–90 years old, (3) in Hoehn and Yahr stage II-III, (4) able to walk at least 5 min unassisted, and (5) taking anti-Parkinsonian medication. Participants were excluded if they had: FOG episodes during the protocol, psychiatric co-morbidity, clinical diagnosis of dementia or other clinically significant cognitive impairment (Mini Mental State Exam score <24), a history of neurological disorder that could affect their performance (other than PD), any orthopedic problems that may affect their gait or had unstable medical condition including cardio-vascular instability (Mirelman et al. 2013). The study was approved by the local ethical committee and was performed according to the principles of the Declaration of Helsinki. All participants gave their written informed consent prior to participation.

Procedures

The protocol included: (1) cognitive and motor assessments, and (2) assessment of prefrontal activation during turning and usual walking using an fNIRS device. All tests were performed in the "ON" state, approximately 1 h after taking medications. The daily levodopa equivalent dosage (LEDD) was calculated for each patient as previously described (Tomlinson et al. 2010). The cognitive assessment included a computerized neuropsychological tests that generate index scores for executive function, attention, visual spatial, and global cognitive score (GCS) (Mindstreams, NeuroTrax Corp., Israel) (Doniger et al. 2006).

The motor assessment consisted of the 2 min walk test (Brooks et al. 2007; Rossier and Wade 2001) and the motor part of the Unified Parkinson's Disease rating scale (MDS-UPDRS) (Goetz et al. 2007). Walking tests were performed in a 30 m-long walkway that was marked with start and end lines. Subjects were asked to walk in their comfortable speed from the starting line to the end line. When they reached the end line, they were instructed to stop and stand for 20 s, then perform 180° turn to their preferred direction, stand again for another 20 s and then continue to walk. This procedure was repeated five times. Each of the walking trials was preceded by 20 s of quiet standing. Turns and walks with episodes of FOG, defined as paroxysmal absence or marked reduction of forward progression, despite the intention to walk (Giladi et al. 2013; Nutt et al. 2011) detected by an experienced assessor, were excluded from the analysis.

Functional Near Infrared Spectroscopy

Changes in oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (HHb) concentrations in the prefrontal cortex were measured with the PortaLite™ fNIRS system as previously described (Artinis Medical Systems, Elst, The Netherlands) (Maidan et al. 2016a; Mirelman et al. 2014a). The system uses near infrared light, which is transmitted at two wavelengths, 760 and 850 nm. Data was sampled with a frequency of 10 Hz. The PortaLite™ uses wireless technology (Bluetooth), allowing participants to walk without the restriction of wires. Two probes were placed on the right and left forehead of the participants. Probes were positioned at a height of 15% of the nasion-inion distance from nasion and at 7% of the head circumference to the left and right from midline, to avoid measuring the midline sinus. These locations roughly target left and right Brodmann's area (BA) 10, the dorsolateral and anterior prefrontal cortex (PFC) (Maidan et al. 2015; Okamoto et al. 2004). The probes were shielded from ambient light by covering the forehead with black fabric. Oxysoft version 3.0.52 (Artinis Medical Systems, Elst, The Netherlands) was used for data collection.

Based on different absorption spectra, concentration changes of HbO_2 and HHb in the targeted PFC were calculated from the changes in detected light intensity using the modified Lambert–Beer law, assuming constant scattering (Sakatani et al. 2006). The PortaLite™ has three transmitters and one receiver, with transmitter–receiver distances of 30, 35 and 40 mm. The concentrations of HbO_2 and HHb were exported to MATLAB (MATLAB and Statistics Toolbox Release 2012b, The MathWorks, Inc., Natick, MA) for further data processing. A bandpass filter with frequencies of 0.01–0.14 Hz was used to reduce physiological noise such as heart beat and drift of the signal. To remove motion artifacts, a wavelet filter was used (Brigadoi et al. 2014; Cooper et al. 2012), followed by correlation based signal improvement (Brigadoi et al. 2014; Cooper et al. 2012; Cui et al. 2010). HbO_2 concentration signals of the three channels of each probe were then averaged, resulting in an HbO_2 signal for the left and right PFC. For each trial, the average concentration of HbO_2 during task performance, and during the 5 s before the task (baseline) were calculated. The quiet standing period just before each task was considered as a baseline reference. Consistent with previous studies of fNIRS signals, each baseline concentration was subtracted from the average concentration during task performance to evaluate the relative change in HbO_2 concentration during specific tasks (Ferrari and Quaresima 2012; Holtzer et al. 2011, 2013, 2016a; Leff et al. 2011; Mirelman et al. 2014a). All trials were averaged per task, resulting in two HbO_2 concentrations for each task (left and right PFC). Since no left–right differences were present ($p > 0.376$), we averaged left and right PFC HbO_2 concentrations for further analyses.

Behavioural Task Performance

Gait was measured using an electronic walkway with embedded pressure sensors that were placed approximately 2 m after the start line. The walkway was connected to a personal computer using PKMAS software (ProtoKinetics, Havertown, PA) for processing and data storing. To characterize usual walking, two key measurements of walking, gait speed and stride length, were analyzed (Morris et al. 1998). The turns were performed at the end of each 30 m walking trial, not on the electronic walkway. The initiation and termination of each turn were marked in the fNIRS system by the assessor. These marks were used to calculate the duration of each turn.

Statistical Analyses

All variables were evaluated for normality and homogeneity using box plots and scatter plots. Means and standard errors were calculated for all dependent variables. The statistical analyses included two approaches to assess the association between motor and cognitive abilities and prefrontal activation in patients with PD: (1) assuming a continuous relationship, using Pearson correlations, and (2) dichotomous method in which the PD patients were divided into two subgroups: (a) gait speed lower than 1.0 m/s versus (b) gait speed equal or higher than 1.0 m/s. This threshold was used based on extensive previous work which showed that 1.0 m/s can be used to distinguish people with normal ambulation status from those with deficits in ambulation and mobility (Cesari et al. 2005; Studenski et al. 2011; Verghese et al. 2011). In addition, we divided the PD

patients based on the median GCS: 50% with the higher GCS versus 50% with the lower GCS, to evaluate the effect of cognitive abilities on prefrontal activation during turning. Differences between the subgroups in each category were assessed using General Linear Model analysis with covariates of age, gender, disease duration and turn duration. One sample *t* test was performed to compare between HbO_2 levels during turning and baseline (quiet standing) within each subgroup. Statistical significance was assumed when the p value was <0.05. Statistical analysis was performed using SPSS for Windows version 18.

Results

Participants

Table 1 summarizes the characteristics of the subjects. No significant differences were observed between patients with PD with higher or lower gait speed with respect to age, gender, disease duration, L-dopa equivalent daily dose (LEDD), and cognitive scores in the computerized test. In contrast, significant differences were found in UPDRS motor scores, gait speed, and stride length (Table 1).

Differences in Prefrontal Activation Between Walking and Turning

Among all subjects, prefrontal activation during walking significantly increased, as compared to baseline of quiet standing ($p < 0.001$). In contrast, during turning, prefrontal activation significantly decreased, as compared to quiet standing ($p < 0.001$). As shown in Fig. 1, HbO_2 level during walking was significantly higher than during turning ($p < 0.001$).

Prefrontal Activation During Turning in the Two Subgroups of Patients with PD

BA10 activation during turning was significantly different between those with limitations and normal community ambulation ($p = 0.02$) even after adjusting for age, gender, disease severity and turns duration (Table 2). The

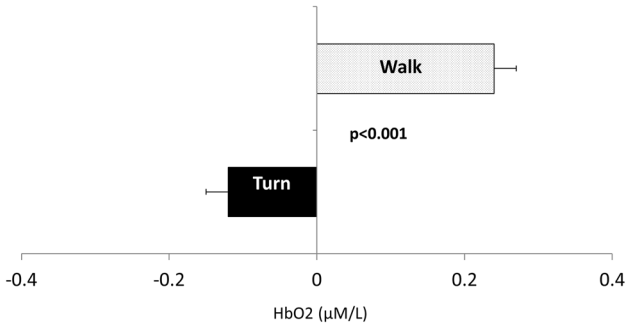

Fig. 1 HbO_2 levels during walking and turning, relative to quiet standing values. The *dotted bar* represents significant increase in HbO_2 during usual walking as compare to baseline in quite standing, while the *black bar* illustrates significant decrease in HbO_2 during turning as compare to baseline in quite standing

Table 1 Participant characteristics

Domain	Variable	All patients with PD (n = 49)	PD gait speed < 1 m/s[a] (n = 24)	PD gait speed ≥ 1 m/s[b] (n = 25)	p value between PD subgroups
Demographic	Age (years)	72.8 ± 1.0	72.0 ± 1.4	73.5 ± 1.5	0.467
	Gender (male/female)	33/16	16/8	17/8	0.921
	Education (years)	14.9 ± 0.6	14.0 ± 0.7	15.7 ± 0.9	0.170
	MMSE (score)	28.5 ± 0.2	28.2 ± 0.4	28.3 ± 0.2	0.726
Disease severity	LEDD (mg)	1005 ± 145	871 ± 143	1140 ± 254	0.362
	Disease duration (years)	9.7 ± 0.9	10.2 ± 1.4	9.2 ± 1.2	0.581
	UPDRS motor score	31.8 ± 2.1	38.5 ± 3.1	26.2 ± 2.0	0.002
Gait	Gait speed (m/s)	0.95 ± 0.04	0.72 ± 0.04	1.16 ± 0.02	<0.001
	Stride length (m)	1.07 ± 0.04	0.87 ± 0.04	1.25 ± 0.03	<0.001
Cognitive[c]	Global cognitive score	88.2 ± 1.5	87.4 ± 2.4	89.0 ± 1.8	0.929
	Executive function index	84.9 ± 1.6	85.0 ± 2.4	84.7 ± 2.0	0.910
	Visual spatial index	92.9 ± 2.4	91.0 ± 3.2	94.1 ± 3.2	0.489

PD Parkinson disease, *LEDD* L-dopa equivalent daily dose, *UPDRS* Unified Parkinson Disease Rating Scale

[a]Associated with limitations in community ambulation

[b]Associated with normal ambulation status

[c]A score of a 100 represents the age and education normed value. Entries are the mean ± standard error or ratio, as indicated

Table 2 Measures of turns in patients with limitations and normal community ambulation

	PD with normal community ambulation	PD with limitations in community ambulation	p value
Turn duration (s)	3.7 ± 0.2	4.7 ± 0.3	0.004
HbO_2 during turns (μM/L)	−0.23 ± 0.05	−0.01 ± 0.02	<0.001
HbO_2 during usual walking (μM/L)	0.25 ± 0.04	0.23 ± 0.04	0.898

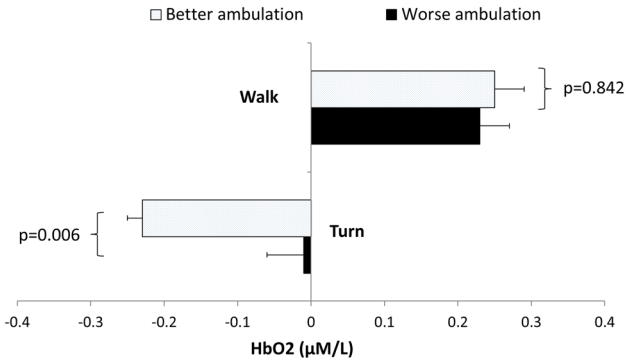

Fig. 2 HbO_2 level during turning and walking in patients with limitations and normal community ambulation. HbO_2 level during usual walking increased in both subgroups with no significant difference. In contrast, HbO_2 level during turning decreased specifically in patients with better community ambulation. No changes in HbO_2 level during turning were observed in patients with limitations in community ambulation

subgroup with limitations in community ambulation (lower than 1 m/s gait speed) had significantly higher BA10 activation during turning, as compared to the subgroup with normal community ambulation ($p=0.006$). In addition, as expected, patients with limitations in community ambulation had significantly longer turns duration, as compared to patients with normal community ambulation (Table 2). In contrast to prefrontal activation during turning, no significant differences between the two subgroups were observed in prefrontal activation during usual walking ($p=0.898$) (Fig. 2).

In contrast, when the subjects were divided into two subgroups based on the GCS, no significant differences in BA10 activation during turning were found ($p=0.646$). Similar results were obtained when subjects were divided into two subgroups based on executive function index ($p=0.705$) or visual spatial index (0.779).

Correlations Between Prefrontal Activation During Turning and Motor-Cognitive Scores

HbO_2 levels during turning were associated with gait speed ($r=-0.441$, $p=0.002$). Patients with lower gait speed had higher levels of HbO_2 during turning (Fig. 3). In contrast, HbO_2 concentration levels during turning were not associated with the global cognitive scores or any other cognitive indexes (Fig. 3).

Discussion

In this study, we used fNIRS technology to investigate the role of prefrontal cortex, specifically BA10, during turning, a motor task that is impaired in patients with PD. Our results reveal three main findings: (1) BA10 plays a different role during turning than during usual, straight-line walking; (2) the degree of BA10 activation during turning is related to background motor abilities, in particular ambulation function as measured using gait speed; and (3) global cognitive abilities are apparently not a contributor to BA10 activation during turning.

The increased activation that we observed in BA10 during usual walking is consistent with previous studies that showed the important role of the prefrontal cortex in healthy young, older adults and patients with PD (Holtzer et al. 2011, 2015; Maidan et al. 2016a; Mirelman et al. 2014a). However, this study is, to our knowledge, the first to report a different activation pattern during turning than during straight-line walking in patients with PD. Apparently, during turns, patients with PD use BA10 to a lesser extent than that seen during usual walking. Still, it is not clear and the methods used in the present study do not allow us to test if whether this reflects relative increased activation in other brain areas such as motor areas or not (Graziadio et al. 2015; Reuter-Lorenz and Cappell 2008). In addition, subgroup analysis based on level of community ambulation showed that activation in BA10 during turning was significantly lower in patients with relatively better community ambulation (gait speed ≥1 m/s), as compared to patients with relatively worse ambulation (gait speed <1 m/s). A priori, motor resources are considered essential for turning. In patients with worse ambulation, the motor system, at least aspects critical to turning, is probably more impaired and therefore requires compensatory strategies associated with executive functions, like attention and planning, that involve prefrontal regions such as BA10 (Holtzer et al. 2015, 2016b; Maidan et al. 2016a). Longer turn duration among the patients with worse ambulation may indicate that these compensatory strategies allow the performance of turning but they are less efficient.

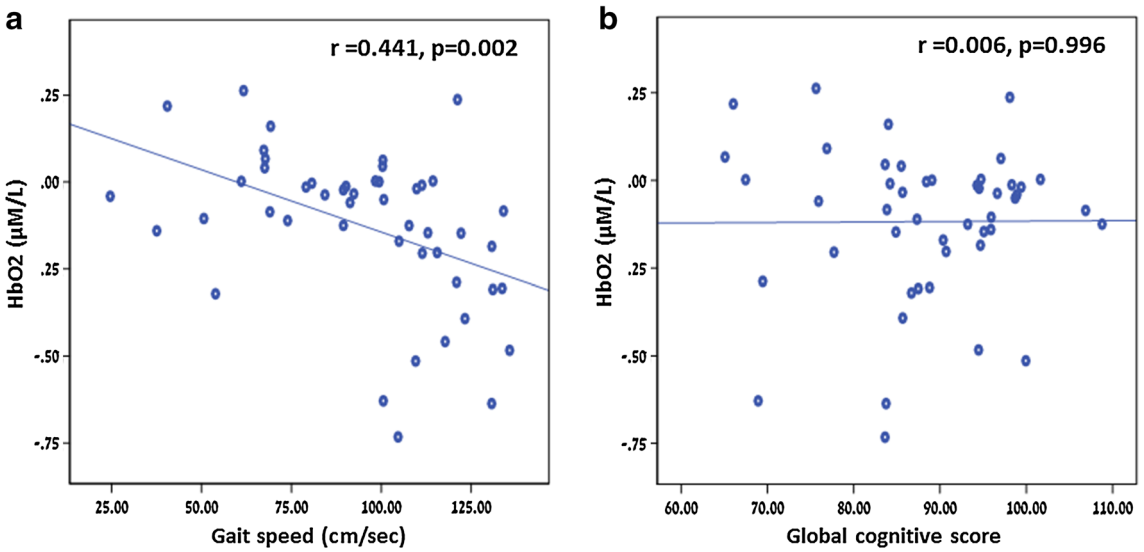

Fig. 3 Correlations between prefrontal activation during turning and motor and cognitive performance. **a** Inverse correlation was found between HbO_2 level and gait speed. Patients with higher gait speed (better ambulation) demonstrated lower levels of HbO_2 during turning. In contrast, **b** no correlation was shown between HbO_2 level and global cognitive score obtained from the neuropsychological battery test

These findings are in line with recent reports on the association between motor abilities and prefrontal activation during task performance (Holtzer et al. 2016b; Maidan et al. 2016a, b). In one study that included healthy elderly, increased prefrontal activation during walking was associated with lower gait speed, suggesting that subjects with lower motor abilities compensate via increased activation of prefrontal areas (Holtzer et al. 2016b). In other reports, patients with PD had higher prefrontal activation than healthy older adults during usual walking (Mahoney et al. 2016; Maidan et al. 2016a), suggesting that better motor status, as in healthy older adults, is associated with lower prefrontal activation during usual walking (Maidan et al. 2016a). In this study, we observed a negative association between levels of ambulation and BA10 activation during turning. In contrast, during usual walking, BA10 activation increased, related to quiet standing (recall Fig. 2), regardless of ambulation status.

Alterations in prefrontal activation during turning as a function of ambulation ability are consistent with previous reports that showed a different pattern of prefrontal activation during turns with and without FOG in PD patients who experience FOG (Maidan et al. 2015). The appearance of FOG during turns indicates a motor failure that can be explained by reduced automaticity of movement and higher reliance on cognitive resources. This shift from automated movement to higher level controlled movement reflects alterations in the activated brain networks, from networks controlled by the striatum to networks controlled by prefrontal cortex (Vandenbossche et al. 2012). The increased activation in prefrontal cortex may be a compensatory attempt to overcome this motor failure. In the current work, PD patients with better ambulation ability had lower prefrontal activation, suggesting that turning was a more automated movement. Based on this interpretation, one could argue that higher prefrontal activation during turns with FOG is a reflection of the compensatory mechanism in patients with PD with low motor abilities.

The two groups of PD patients, one with relatively better ambulation and one with relatively worse ambulation, differed in all motor measurements including UPDRS motor and gait assessments. However, no significant differences between the groups were observed in the computerized cognitive tests or in the global cognitive score. Although cognitive function was apparently not related to BA10 activation during turns, the present results suggest that during turning the role of BA10 is associated with ambulation level. These findings suggest that improving ambulation in patients with PD may increase the efficiency of brain activation by reducing prefrontal activation, a brain area that plays an important role in everyday life functions. In order to test these assumptions, further studies that measure activation in other brain regions during real walking and in response to specific interventions that target motor abilities are required. The results of the present study set the stage for those future investigations and suggest that interconnection between cognitive and motor abilities depends on the specifics of the motor task in patients with PD.

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