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Dopaminergic modulation of motor coordinaton in Parkinson's disease

Jaebum Park [a], Mechelle M. Lewis [b, c], Xuemei Huang [a, b, c, d, e], Mark L. Latash [a, *]

[a] Department of Kinesiology, The Pennsylvania State University, Rec. Hall-268N, University Park, PA 16802, USA
[b] Department of Neurology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA 17033, USA
[c] Department of Pharmacology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA 17033, USA
[d] Department of Radiology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA 17033, USA
[e] Department of Neurosurgery, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA 17033, USA

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ABSTRACT

Background: We applied the idea of synergies and the framework of the uncontrolled manifold hypothesis to explore the effects of dopamine replacement therapy on finger interaction and coordination in patients with early-stage Parkinson's disease (PD).
Methods: Eight patients performed single-finger and multi-finger force production tasks with both the dominant and non-dominant hand before (off-drug) and after (on-drug) taking their dopaminergic medications. Synergy indices were defined as co-varied adjustments of commands to fingers that stabilized the total force produced by the hand.
Results: PD patients showed significantly lower maximal finger forces off-drug compared to the on-drug condition, while indices of finger individuation (enslaving) were unchanged. The synergy indices were weaker during steady-state force production off-drug compared to on-drug. Anticipatory adjustments of synergies prior to the quick force pulse initiation were delayed and reduced off-drug as compared to the on-drug condition. These drug effects were observed in both the symptomatic and asymptomatic hands of the patients whose symptoms were limited to one side of the body.
Conclusions: The study demonstrates dopaminergic modulation of motor coordination in PD and supports that the analysis of different components of multi-finger synergies offers a set of indices sensitive to the effects of dopamine replacement therapy in early-stage PD. The results suggest an important role of the basal ganglia in synergy formation and in feed-forward synergy adjustments. Future studies using these methods may yield more objective, quantitative biomarker(s) of motor coordination impairments in PD, and better understanding of subcortical involvement in the neural control of natural actions.

1. Introduction

Although dopamine replacement is the most common pharmacological treatment of motor symptoms in Parkinson's disease (PD) [1,2], its effects on motor coordination remain largely unknown (although see Refs. [3,4]). In the current study, we applied the framework of a theory of synergies [5,6] to quantify the effects of dopaminergic medications on aspects of finger coordination. This theory assumes that the central nervous system organizes large sets of effectors (muscles, joint, digits, etc.) to stabilize important performance variables in a task-specific way [5,11]. We focus on finger coordination because problems with multi-finger action are common early signs of PD [7,8]. Recently, we used the framework of the uncontrolled manifold (UCM) hypothesis [11] to show that early-stage PD is associated with significantly reduced indices of multi-finger synergies and an impaired ability to modify the synergies in preparation to a quick self-paced action [9]. The latter aspect has been addressed as anticipatory synergy adjustments (ASAs, [10]). ASAs represent a drop in the synergy index prior to a quick action; their purpose is to decrease stability of a performance variable that the person plans to change.

While it is known that after overnight withdrawal dopaminergic medications have an acute positive effect on motor symptoms [13], their effect on different aspects of motor synergies involved in natural movements remains unknown. To address this, we tested three main hypotheses that followed rather directly from our previous work [9]. Hypothesis-1: Dopaminergic medications lead to higher magnitudes of the synergy index during steady-state

* Corresponding author. Tel.: +1 814 863 5374; fax: +1 814 863 4424.
E-mail address: mll11@psu.edu (M.L. Latash).

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accurate total force production with four fingers. Hypothesis-2: Dopaminergic medications lead to earlier and larger ASAs in preparation to self-paced pulse of total force. Hypothesis-3: An index of finger individuation (enslaving) will improve on dopaminergic medication.

2. Methods

2.1. Subjects

Eight patients with PD (age 66.6 ± 7.8 years; 4 males) at Hoehn-Yahr stage I or II (based on assessment in a practically defined "off" state) were recruited (demographic and clinical details in Table 1). All participants had a history of dramatic response to dopaminergic replacement treatment. Unified PD Rating Scale part III-motor scores (UPDRS-III) under off- and on-drug conditions had a mean ± SD of 14.4 ± 6.2 and 9.1 ± 7.1 (Cohen's $d = 0.79$), respectively. Disease duration from the time of diagnosis was 4.9 ± 3.4 years. Levodopa equivalent dose (LED) was estimated according to a published formula [14]. All non-dopaminergic drugs remained the same during the experiments. The study protocol was approved by the Institutional Review Board. Written consent was obtained from all subjects.

2.2. Apparatus

Details on the apparatus, procedures, and data analysis were published previously [9]. Briefly, four piezoelectric force sensors (Model 208A03, PCB Piezotronics Inc.) were attached to a customized flat wooden panel (Fig. 1A); the sensors measured vertical pressing forces exerted by the subject's fingers. The sensor positions were adjusted according to the individual hand anatomy. A wooden piece was placed underneath the palm in order to ensure constant hand and finger configuration (Fig. 1). Force signals were collected at 200 Hz with a 16-bit resolution.

2.3. Experimental procedures

Subjects were tested in the off- and on-drug conditions. The off-drug condition was obtained by overnight withdrawal of dopaminergic medication for at least 12 h before the first set of tests. Patients then took their prescribed dopaminergic medications (details in Table 1) and the second set of tests were initiated approximately 1 h after the medication was taken, when the patients reported clinical improvement.

Subjects sat in a chair facing a 19-inch monitor positioned at the eye level. Both hands were tested in a random order. The forearm was placed into the wrist-forearm brace and strapped using Velcro. Each task was explained and demonstrated by an experimenter, and subjects were given a 3–5 min practice session until they felt familiar with the task. Note that the tasks were very simple and took only a few trials to learn.

2.3.1. Maximal voluntary contraction (MVC) tasks

The subjects were instructed to press on the sensors with the four fingers simultaneously, to achieve maximal total force (F_{TOT}, shown on the screen) level within 8 s, and to relax immediately. The maximal total force (MVC_{TOT}) and the forces of individual fingers (MVC_i; i = I – index, M – middle, R – ring, and L – little) at the time of MVC were measured. The subjects performed two attempts, and the data from the attempt with the higher MVC level were selected.

2.3.2. Single-finger ramp tasks

The subjects were required to press with one of the fingers (the task finger) and match with its force the template shown on the screen (Fig. 1B). The 20-s template consisted of two horizontal segments, at zero force for the first 4 s and at 40% MVC_i for the last 4 s connected by a slanted line from 0% to 40% MVC over 12 s. One trial by each finger was performed, and the subjects were instructed to pay no attention to possible force production by non-task fingers.

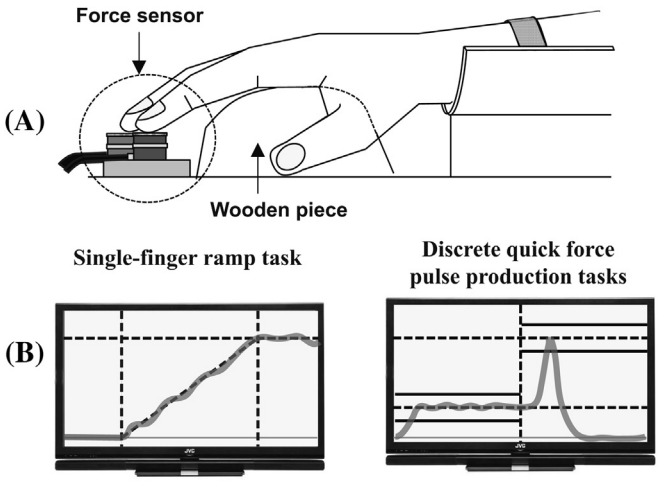

Fig. 1. A: The experimental setup. The subject's palm was supported by a wooden piece. The force sensors (gray cylinders) were attached to a wooden frame. B: The feedback screen during single-finger ramp tasks (left) and discrete quick force pulse production tasks (right).

2.3.3. Discrete quick force pulse production tasks

During each trial, the feedback on F_{TOT} was provided on the computer screen (Fig. 1C). A single trial consisted of two phases: 1) steady-state force production at 5% of MVC_{TOT}; and 2) quick pulse force production to 25 ± 5% of MVC_{TOT}. Two horizontal lines on the screen showed the initial and target force levels. The instruction was to match the initial level of F_{TOT} as accurately as possible for 5 s, and then to produce a very quick force pulse to the target at a self-selected time within the next 5 s. Each subject performed 25–30 trials with each hand. Additional trials were given if the subject made major mistakes (e.g., pressing before the cursor reached the vertical line, pressing several times, changing the baseline force in preparation to pressing, or trials with the time to peak force over 1 s).

2.4. Data analysis

The data were processed off-line using a customized Matlab (Matlab 7.4.0, Mathworks, Inc) program. The force data were digitally low-pass filtered at 10 Hz with zero-lag, 4th-order Butterworth filter.

2.4.1. Analysis of enslaving

Enslaving or lack of individuation is an index reflecting the fact that humans produce force (movement) by non-intended fingers when one or more fingers of the hand produce force (move) intentionally [15]. The enslaving matrix **E** (Eq. (2)) was used to quantify enslaving. For each single-finger ramp, linear regressions of the forces produced by individual fingers against F_{TOT} over a 10-s interval were computed. The first and last 1-s intervals were excluded to avoid edge effects. The regression coefficients (Eq. (1)) were used to construct **E** (Eq. (2)):

Table 1
Description of the participants.

Patient	Sex, M/F	HY stage	Height, cm	Weight, kg	Age, yr	Time since diagnosis, yr	Side of symptom onset	Total LED, mg/day	Type of dopaminergic replacements	Handedness, R/L	UPDRS score	
											Off med	On med
1	F	I	167.64	54.43	62.55	8.62	R	437	L-dopa, MAOI, DA	R	8	5
2	F	II	155.45	63.50	65.43	2.65	L	370	L-dopa, MAOI, DA	R	8	3
3	F	I	160.02	74.84	70.88	0.54	R	215	L-dopa, MAOI	R	8	2
4	F	II	152.40	68.98	65.76	2.51	L	500	L-dopa, MAOI, DA, amantadine	R	16	11
5	M	I	155.75	79.38	51.81	4.04	L	1150	L-dopa, MAOI, DA, amantadine, COMTI	R	16	13
6	M	II	179.83	81.65	77.88	9.63	R	2164	L-dopa, MAOI, DA, amantadine	R	23	21
7	M	I	173.74	68.04	72.99	6.62	L	625	L-dopa, DA, amantadine	R	14	8
8	M	II	155.75	87.54	65.82	0.08	L	700	L-dopa, MAOI, amantadine	R	25	7

Abbreviations: COMTI : catecholamine-o-methyltransferase inhibitors; DA: Dopamine agonists; L-dopa, levodopa; LED, levodopa equivalent dose; L/R, left/right; MAOI: Monoamine oxidase inhibitors; M/F, male/female; UPDRS, Unified Parkinson's Disease Rating Scale; HY – Hoehn and Yahr.

$$F_{i,j} = f_i^0 + k_{i,j} \times F_{TOT,j} \quad (1)$$

$$E = \begin{bmatrix} k_{I,I} & k_{I,M} & k_{I,R} & k_{I,L} \\ k_{M,I} & k_{M,M} & k_{M,R} & k_{M,L} \\ k_{R,I} & k_{R,M} & k_{R,R} & k_{R,L} \\ k_{L,I} & k_{L,M} & k_{L,R} & k_{L,L} \end{bmatrix} \quad (2)$$

where $i, j = \{I,M,R,L\}$; j represents a task finger. $F_{i,j}$ and $F_{TOT,j}$ indicate the individual i-finger force and F_{TOT}, respectively, when j-finger was the task-finger. In addition, we computed an enslaving index, EN_j, as the average $k_{i,j}$, $i \neq j$.

2.4.2. Analysis of multi-finger synergies

The time (t_0) of initiation of F_{TOT} change during a force pulse was defined as the time when the first derivative of force (dF/dt) reached 5% of its peak value in that particular trial. The accepted trials for each subject and each condition were aligned with respect to t_0. Finger force data were transformed into finger mode (**m**) data, computed based on the force magnitudes and the enslaving matrix **E** for each time sample. The variance in the mode space across trials was quantified separately in two sub-spaces for each time sample, variance within the UCM (V_{UCM}) that did not produce changes in F_{TOT}, and variance orthogonal to the UCM (V_{ORT}) that did.

An index of synergy (ΔV) has been computed reflecting the relative amount of V_{UCM} in the total variance for each time sample:

$$\Delta V(t) = \frac{V_{UCM}(t)/3 - V_{ORT}(t)/1}{V_{TOT}(t)/4} \quad (3)$$

where each variance index is normalized by the number of degrees-of-freedom in the corresponding spaces; V_{TOT} stands for total variance. Higher ΔV values are interpreted as stronger synergies stabilizing F_{TOT} (reviewed in Ref. [12]). ΔV was log-transformed (ΔV_Z) to avoid the ceiling effects for the statistical analysis [11,12]. The average value of ΔV_Z and its SD were computed for the steady-state (between −600 and −400 m before t_0). The time of anticipatory adjustment of ΔV_Z (t_{ASA}) was defined as the time when ΔV_Z dropped below its average steady-state value by more than two SDs. A synergy index change during the ASA (ΔV_{t_0-ss}) was quantified as the drop of ΔV_Z from the steady-state to t_0 [5,9,10,12].

2.5. Statistics

Standard descriptive statistics and mixed-design ANOVAs with repeated measures were used with the factors *Drug-state* (off- and on-drug), *Time* (t_{ASA} and t_0), *Hand* (left and right), and *Hand-2* (symptomatic and asymptomatic). The choices of factor combinations were based on particular comparisons. Variables with computational boundaries were transformed using adjusted Fisher's *z*-transformation to ensure normality prior to comparisons. For post-hoc comparisons, conservative non-parametric Mann–Whitney tests were used to explore significant effects with Bonferroni *p*-value adjustments for multiple comparisons. The statistical power for all comparisons was computed, and the power was >0.65 for all comparisons, while it was >0.8 for the main effect of *Drug-state*. The level of significance was set at $p < 0.05$.

3. Results

3.1. Performance indices

Subjects showed significantly lower MVC forces off-drug as compared to the on-drug condition, on average 11.67% and 9.97% less for the left and right hand, respectively (Table 2). There was no significant difference between the hands. A two-way ANOVA on MVC_{TOT} *Drug-state* × *Hand* showed only a main effect of *Drug-state* ($F\,[1,7] = 7.46$, $p < 0.05$).

During the single-finger ramp tasks, non-task fingers produced substantial finger forces. Whereas different fingers showed different amounts of enslaving ($EN_I < EN_M < EN_R$, EN_L; $p < 0.05$, Mann–Whitney tests), there was no significant difference in *EN* between the off- and on-drug states and no significant difference between the hands (Table 2).

The subjects performed the quick force pulse task with comparable accuracy during the on- and off-drug tests, with approximately the same percentages of trials rejected in both conditions (off-drug: 30.5 ± 4.6%; on-drug: 26.6 ± 10.7%, mean ± standard deviation). The average number of accepted trials was 17.8 ± 2.2 trials. The actual peak force was 26.6 ± 1.6% MVC off-drug and 25.2 ± 1.5% MVC on-drug for the 25% MVC target. Faster force pulses were produced in the on-drug state. The average time to peak force (t_{PEAK}) during the on-drug test was ~40 ms shorter than off-drug (0.18 s and 0.22 s, respectively, Table 2). Subjects were more consistent in the timing of the force pulses on-drug, as reflected by the lower standard deviation (SD) of t_{PEAK} across trials. These findings were supported by two-way ANOVAs *Drug-state* × *Hand* on t_{PEAK} and SD of t_{PEAK}, which showed a significant main effect of *Drug-state* ($F\,[1,7] > 19.0$, $p < 0.01$). There also was a significant *Drug-state* × *Hand* interaction for SD of t_{PEAK} ($F\,[1,7] = 8.67$, $p < 0.05$) reflecting the stronger effect of *Drug-state* in the right hand compared to the left hand.

3.2. Multi-finger synergies at the steady state

Multi-finger synergies in the steady-state reduced variance of the total force (F_{TOT}). This was reflected in positive synergy indices (ΔV) in both the off- and on-drug conditions (Fig. 2). The magnitude of ΔV_Z (*z*-transformed ΔV) was significantly higher on-drug as compared to the off-drug condition (by about 21%), and in the left hand as compared to the right hand (by about 20.5%). These results were supported by a two-way ANOVA on ΔV_Z that showed main effects of *Drug-state* ($F\,[1,7] = 27.67$, $p < 0.01$) and *Hand* ($F\,[1,7] = 11.29$, $p < 0.05$) without an interaction. The effects of dopaminergic medications on the synergy index were due primarily to the drug-induced drop in V_{ORT} (effect of *Drug-state*, $F\,[1,7] = 6.90$, $p < 0.05$), without a significant change in V_{UCM}.

3.3. Anticipatory synergy adjustments

The synergy index (ΔV_Z) showed a drop prior to the force pulse initiation (t_0 in Fig. 2). These anticipatory synergy adjustments (ASAs) started earlier (by about 61%) and were of a larger magnitude (by about 57%) in the on-drug condition than in the off-drug condition. These findings were supported by a two-way *Drug-state* × *Hand* ANOVA on t_{ASA} and ΔV_{t_0-ss}, which showed a significant main effect of *Drug-state* ($F\,[1,7] = 18.00$, $p < 0.01$ for t_{ASA}; $F\,[1,7] = 10.56$, $p < 0.05$ for ΔV_{t_0-ss}) without other effects. When changes in the two variance components (V_{UCM} and V_{ORT}) were analyzed separately, a significant increase in V_{ORT} was observed from t_{ASA} to t_0 (main effect of *Time*, $F\,[1,7] = 19.20$, $p < 0.01$) without significant change in V_{UCM}.

Table 2
Performance characteristics and main outcome variables.

		Performance variables						Enslaving		Synergy index and ASA			
		MVC (N)		Avg t_{PEAK}		SD t_{PEAK}		$EN_{fingers}$		t_{ASA}		ΔV_{t_0-ss}	
		off	on	off	on	off	on	off	on	off	on	off	on
Left hand	Mean	60	66	0.205	0.176	0.058	0.040	0.087	0.092	−0.076	−0.158	−0.117	−0.277
	SE	7.6	5.5	0.013	0.010	0.003	0.008	0.008	0.009	0.040	0.039	0.054	0.053
Right hand	Mean	61.4	66.5	0.233	0.189	0.099	0.052	0.070	0.074	−0.050	−0.173	−0.216	−0.505
	SE	5.3	6	0.024	0.012	0.010	0.008	0.007	0.008	0.024	0.049	0.074	0.152

Mean and standard error (SE) of maximal voluntary contraction (MVC) forces, the average (Avg t_{PEAK}) and SD (SD t_{PEAK}) of time to reach F_{PEAK}, average enslaving index across fingers ($EN_{fingers}$), the time of anticipatory synergy adjustment (t_{ASA}), a synergy index difference (ΔV_{t_0-ss}) in ΔV_Z at a steady-state and at t_0.

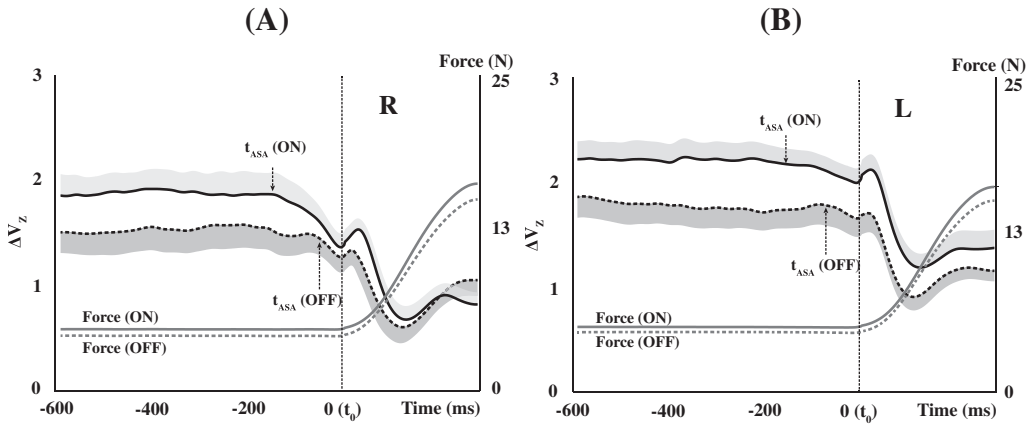

Fig. 2. The total force (gray lines) and synergy index (black line, z-transformed synergy index, ΔV_Z) of the **A** right **(R)** and **B** left hands **(L)** for the on-drug condition (ON, solid line) and off-drug condition (OFF, dashed line) during the discrete quick force production tasks. Average and standard error across subjects are presented for the variance (ΔV_Z), and the average across subjects is presented for the total force.

3.4. Symptomatic vs. asymptomatic hands

We compared the main outcome variables in the asymptomatic and symptomatic hands of the subjects whose clinical symptoms were limited to one arm ($n = 4$, Table 1). There were no significant differences between the hands ($p > 0.4$), while there were beneficial effects of the drug on both hands confirmed by two-way *Drug-state* × *Hand-2* (symptomatic vs. asymptomatic) ANOVAs. Significant main effect of *Drug-state* on ΔV_z at steady-state (off: 1.54 ± 0.22; on: 2.03 ± 0.16, $p < 0.01$) was observed, whereas changes in the ASA characteristics only approached significance despite their relatively large magnitude (nearly 100% change), ΔV_{t_0-ss} (off: −0.15 ± 0.06; on: −0.29 ± 0.04, $p = 0.059$), and t_{ASA} (off: −0.08 ± 0.23; on: −0.16 ± 0.03 s, $p = 0.1$). No interaction effects were found.

We compared changes in each of the mentioned synergy indices between the on-drug and off-drug states with changes in the UPDRS scores. While all the indices showed improvement on-drug, there was no significant correlation between their changes.

4. Discussion

This study is the first to demonstrate quantitatively the effects of dopaminergic medications on the indices of motor coordination using the idea of synergies. The first two specific hypotheses formulated in the Introduction have been supported by the results. Namely, the index of multi-finger synergies (ΔV) stabilizing total force during accurate force production was higher in the on-drug compared to the off-drug state. Moreover, PD subjects showed earlier and larger adjustments in multi-finger synergies (ASAs) in preparation to the quick force pulse [10]. In contrast, there were no significant drug-related changes in enslaving [15] thus disproving Hypothesis-3. Taken together, these findings suggest that PD medications may have different effects on different components of motor coordination.

Indices of enslaving and multi-finger synergic control show different patterns of changes across populations with impaired motor control. For example, healthy elderly persons show lower indices of enslaving (better individuation) and lower synergy indices compared to younger persons [16–18]. PD and multisystem atrophy-cerebellar type (MSA-C) lead to higher enslaving and lower synergy indices [9,19,20]. The current study demonstrated significant drug effects on the synergy indices, but not on the indices of enslaving. These observations lead to a hypothesis that indices of enslaving and synergic control may reflect changes at different levels of the neural hierarchy involved in hand control and can be differentially modulated by dopaminergic medications.

It is thought that enslaving results from two groups of factors, peripheral and neural (reviewed in Ref. [21]). The significantly higher indices of enslaving in patients with PD and MSA-C as compared to Controls [9,20] support the important role of central neural mechanisms in this phenomenon. The current study suggests that enslaving is a relatively stable characteristic of finger interaction that is independent of dopaminergic dysfunction in PD. Growing evidence suggests that PD affects many neural systems outside the dopaminergic system, ranging from lower brainstem to the cortex [22]. Thus, it is possible that the enslaving changes in PD originate from extranigral dysfunction. Unlike enslaving, synergy indices showed significant sensitivity to dopaminergic modulation. This result suggests that the nigrostriatal dopaminergic deficits may be responsible for changing synergy indices in PD patients.

Changes in the coordination of multi-element systems that take part in all natural actions have been quantified in PD only recently [9] based on the principle of motor abundance [23,24]. This approach links the neural impairment to loss of movement stability and adaptability to changes in external conditions. PD patients show impaired feed-forward control in both postural [25] and hand [26] tasks. Our recent observations of impaired ASAs document a novel aspect of motor dysfunctions in PD. Although the indices of synergies and ASAs were measured in the hands, these indices may reflect more general processes that bring about balance difficulty, freezing of gait, and fall risk in PD (cf. [27,28]). Because of their potential clinical importance for PD-related gait and postural disorders, the prospects of using ASA indices as early biomarkers in PD for predicting and preventing those events are exciting.

We would like to emphasize the similarity of the effects of dopaminergic medications on the symptomatic and asymptomatic hands of patients who showed clinical signs in one hand only. These observations tentatively suggest that the synergy indices may reflect a global dopamine deficiency and be sensitive to early, subclinical stages of PD. Potentially these indices may be used as biomarkers in persons with higher risk of PD due to a family history and/or occupation. A large cross-sectional study of such persons is needed to support this hypothesis.

Recent studies of patients with cortical and subcortical disorders suggest that overall performance relies more on cortical structures whereas synergy indices are more sensitive to dysfunction of subcortical pathways. In particular, Reisman and Scholz [29]

compared reaching movements by both arms after stroke. Whereas overall performance on the contralesional side was impaired significantly, there were no significant differences between the indices of kinematic multi-joint synergies on the two sides. In contrast, studies of PD and MSA-C patients demonstrate relatively mild differences in overall performance accompanied by significant changes in the synergy index [9,20].

The current study supports the hypothesis that subcortical circuits are important in the formation of synergies [30]. Note that, even when PD subjects were on-drug, these indices were lower than those in comparably aged healthy adults [9]. In contrast, overall MVC force levels showed only minor differences between the off- and on-drug states. Given that cortical stroke commonly leads to a dramatic drop in MVC force, particularly pronounced for finger tasks, our observations lend further support to the hypothesis suggesting contrasting roles for cortical and subcortical structures in the overall motor performance and synergic mechanisms.

We have to admit limitations of our study such as the small sample size and the lack of a control group (although a comparison with control subjects was done earlier, [9]). Despite these limitations, the study offers support for two non-trivial hypotheses: First, synergy indices may be sensitive to disorders of motor coordination in PD and drug therapy; and Second, subcortical structures play a major role in synergies stabilizing natural actions.

Disclosure

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Role of authors

Jaebum Park: Research Project (Organization, Execution); Statistical Analysis (Design, Execution), Manuscript Preparation (Writing of the first draft, Review and Critique).

Mechelle Lewis: Research Project (Organization); Statistical Analysis (Design, Review and Critique), Manuscript Preparation (Review and Critique).

Xuemei Huang: Research Project (Conception, Organization); Statistical Analysis (Review and Critique), Manuscript Preparation (Review and Critique).

Mark Latash: Research Project (Conception Organization, Execution); Statistical Analysis (Design, Review and Critique), Manuscript Preparation (Writing of the first draft, Review and Critique.

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