

Changes in multifinger interaction and coordination in Parkinson's disease

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Park J, Wu Y, Lewis MM, Huang X, Latash ML. Changes in multifinger interaction and coordination in Parkinson's disease. *J Neurophysiol* 108: 915–924, 2012. First published May 2, 2012; doi:10.1152/jn.00043.2012.—In this study, we tested several hypotheses related to changes in finger interaction and multifinger synergies during multifinger force production tasks in Parkinson's disease. Ten patients with Parkinson's disease, mostly early stage, and 11 healthy control subjects participated in the study. Synergies were defined as covaried adjustment of commands to fingers that stabilized the total force produced by the hand. Both Parkinson's disease patients and control subjects performed accurate isometric force production tasks with the fingers of both the dominant and nondominant hands. The Parkinson's disease patients showed significantly lower maximal finger forces and higher unintended force production (enslaving). These observations suggest that changes in supraspinal control have a major effect on finger individuation. The synergy indexes in the patients were weaker in both steady-state and cyclic force production tasks compared with the controls. These indexes also were stronger in the left (nondominant) hand in support of the dynamic-dominance hypothesis. Half of the patients could not perform the cyclic task at the highest frequency (2 Hz). Anticipatory adjustments of synergies prior to a quick force pulse production were delayed and reduced in the patients compared with the controls. Similar differences were observed between the asymptomatic hands of the patients with symptoms limited to one side of the body and matched hands of control subjects. Our study demonstrates that the elusive changes in motor coordination in Parkinson's disease can be quantified objectively, even in patients at a relatively early stage of the disease. The results suggest an important role of the basal ganglia in synergy formation and demonstrate a previously unknown component of impaired feedforward control in Parkinson's disease reflected in the reduced and delayed anticipatory synergy adjustments.

synergy; finger; uncontrolled manifold hypothesis; feedforward control

CHANGES IN MOTOR COORDINATION remain one of the most common and least understood consequences of neurological disorders. For example, several studies of patients with Parkinson's disease (PD) have reported impaired motor coordination (Bertram et al. 2005; Brown and Almeida 2011; Fradet et al. 2009), although it is not mentioned among the cardinal signs of this common neurological disorder. This lack of understanding has been due partly to the lack of a unifying theoretical approach that would allow quantifying coordination. Recent advances in the field of the control of redundant motor systems (reviewed

in Latash et al. 2007; Latash 2010) led to a method for quantifying motor synergies, defined as neural organizations of elemental variables (those produced by elements, for example, forces produced by individual digits) with the purpose of ensuring stable performance by the whole system (for example, total force and moment of force produced by the hand). The foundations of this approach are as follows: 1) all natural motor tasks are performed by redundant sets of elements (cf. the problem of motor redundancy; Bernstein 1967); 2) the central nervous system (CNS) facilitates families of solutions that can perform the task (principle of abundance; Gelfand and Latash 1998); and 3) the CNS manipulates elemental variables to ensure high stability (low variability) of important performance variables.

A particular method of quantitative analysis of synergies has been developed within the framework of the uncontrolled manifold (UCM) hypothesis (Scholz and Schöner 1999; reviewed in Latash et al. 2002a). According to this hypothesis, most variance of elemental variables is confined to a subspace (the UCM) compatible with a desired value of an important performance variable. This framework allows quantifying two components of motor variance, "good" and "bad," within (V_{UCM}) and orthogonal (V_{ORT}) to the UCM, respectively. "Bad" variance hurts accurate performance, whereas "good" variance does not and instead helps the CNS keep acceptable levels of performance in cases of unexpected perturbations and secondary motor tasks (Matos et al. 2011; Zhang et al. 2008).

Only a handful of studies to date have applied the aforementioned method for analyzing motor synergies during suboptimal motor performance, such as by persons with Down syndrome (Latash et al. 2002c; Scholz et al. 2003), stroke survivors (Reisman and Scholz 2003), healthy elderly (Olafsdottir et al. 2007; Shim et al. 2004), and young persons under fatigue (Singh et al. 2011). These studies have shown that the method is sensitive to subclinical, mild changes in motor coordination (we use this term to address covarying changes in elemental variables during voluntary actions). The main purpose of the current study is to expand further the application of the method by documenting and quantifying changes in multifinger synergies in patients with PD. The multifinger coordination paradigm has been chosen because it is vital for many activities of daily living. Moreover, hand function in PD is impaired (e.g., micrographia; McLennan et al. 1972; Viviani et al. 2009) and known as one of the early symptoms of PD.

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A drop in indexes of finger enslaving (unintended force production by fingers when other fingers produce force intentionally; Kilbreath and Gandevia 1994; Schieber and Santello 2004; Zatsiorsky et al. 2000) in healthy elderly persons has been reported and correlated with a drop in their ability to produce maximal voluntary contraction (MVC) finger forces (Shinohara et al. 2003). Our first hypothesis was that there would be changes in finger enslaving in PD that would parallel changes in their MVC force. The second hypothesis was that multifinger synergies that stabilize total force would be impaired in patients with PD. PD patients show impaired feedforward control in both postural (Bazalgette et al. 1986; Traub et al. 1980) and hand tasks (Albert et al. 2010; Muratori et al. 2008). Hence, the third hypothesis was that PD subjects would demonstrate deficits in the ability to adjust synergies in a feedforward manner in preparation to a quick action. Last, recent studies have reported involvement of the cerebellum in PD (cf. Lewis et al. 2007, 2011; Sen et al. 2010; Yu et al. 2007). Cerebellar disorders have been discussed as leading to problems with movement timing (reviewed in Ivry 1997) and impaired coordination (e.g., ataxia) ever since the pioneering studies of Babinski (1899), who described "asynergias" in movements by such patients. The current study tested the involvement of the cerebellum by determining whether the synergy changes in PD show frequency dependence in accurate cyclic force production tasks. The fourth hypothesis was that, at higher frequencies, PD patients would show larger differences from healthy subjects in the synergy indexes. We selected patients in the relatively early stages of PD that all were evaluated on their medications to test the sensitivity of the method to the mildest possible changes in motor coordination.

METHODS

Subjects

Ten patients with idiopathic PD (age 62.5 ± 10.2 yr; 5 males) and 11 control subjects (CS; age 64.3 ± 7.0 yr; 7 males) were tested. The participants were selected from a larger pool of subjects of an ongoing clinical and neuroimaging correlation study in which all PD subjects were recruited from a movement disorder clinic and diagnosed by movement disorders specialists. CS were recruited from spouses and friends of the patients, as well as through flyers posted in the local community. All participants were right-hand dominant as assessed by the Edinburgh Handedness Inventory (Oldfield 1971). None of the CS had any known neurological disorders or arthritis in their upper extremities.

Descriptive data for all subjects are presented in Table 1. For PD subjects, Unified Parkinson's Disease Rating Scale part III motor scores (UPDRS-III) were documented. Disease duration from time of diagnosis was recorded through PD subjects' history. The levodopa equivalent dose (LED) was estimated for PD subjects according to a published formula (Tomlinson et al. 2010). PD subjects were tested while on antiparkinsonian medication, with the exception of two very mild PD patients who were not taking any medication. All patients, with a possible exception of *patient 3*, were in the early stages of PD with total UPDRS scores ranging from 5 to 17 at the time of screening, immediately before the experiments. The median duration of symptoms was 2.9 yr; none of the patients showed signs of drug-induced dyskinesias, including the patient who took several medications, resulting in the high LED value (*patient 3* in Table 1). All the patients who were on PD medications showed a clinical history of improved motor function with medication. All subjects were negative for thyroid dysfunction, vitamin B₁₂, or folate deficiency and were free of kidney or liver disease as ascertained by relevant blood tests. The study protocol followed the Helsinki principles and was reviewed and approved by the Pennsylvania State University-Hershey Medical Center Institutional Review Board. Written informed consent was obtained from all subjects.

Table 1. Description of study participants

Patient	Sex, M/F	Age, yr	Height, cm	Weight, kg	On/Off Medication	Total LED, mg/day	UPDRS Score	Time Since Diagnosis, yr	Side of Symptom Onset, L/R	Handedness
<i>Patients with Parkinson's disease</i>										
1	M	63.7	155.75	87.54	Off	0	17	0	L	R
2	M	70.9	173.74	68.04	On	625	8	4.58	L	R
3	M	75.8	179.83	81.65	On	1,666	17	7.58	R	R
4	M	49.9	155.75	79.38	On	749	13	2.11	L	R
5	M	69.3	176.78	73.03	Off	0	14	0	R	R
6	F	43.9	164.59	71.21	On	200	11	0.3	R	R
7	F	60.8	167.64	54.43	On	187	5	6.87	R	R
8	F	63.7	155.45	63.5	On	89	8	0.92	Both	R
9	F	51	167.64	68.04	On	674	7	4.05	R	R
10	F	70.8	161.54	65.77	On	66	16	2.96	R	R
<i>Control subjects</i>										
1	F	65.8	161.54	76.66						R
2	F	54.3	155.45	57.61						R
3	F	64.1	173.74	86.18						R
4	F	69.1	155.75	88						R
5	M	53.9	182.88	84.82						R
6	M	58.4	179.83	89.81						R
7	M	59.8	155.75	91.63						R
8	M	73.7	155.45	78.93						R
9	M	66.9	176.78	88						R
10	M	74.3	155.75	92.99						R
11	M	67.3	176.78	90.72						R

LED, levodopa equivalent dose; L/R, left/right; M/F, male/female; UPDRS, Unified Parkinson's Disease Rating Scale.

Apparatus

Four piezoelectric force sensors (model 208A03; PCB Piezotronics, Depew, NY) were used to measure vertical forces produced by the fingers. The sensors were attached to a customized flat wooden panel (size: $140 \times 90 \times 5$ mm; Fig. 1A). Each sensor was covered with sandpaper (300 grit) to increase the friction between the fingertips and the top surface of the sensors. The positions of the sensors in the medial-lateral and anterior-posterior directions were adjusted according to the individual hand and finger anatomy to achieve a comfortable hand posture. A wooden piece was placed underneath the subject's palm to maintain a constant hand and finger configuration during the tests (Fig. 1A). The four force signals were digitized at 300 Hz with a 16-bit resolution with a customized LabView program.

Experimental Procedures

Subjects sat in a chair facing a 19-in. computer monitor positioned ~ 0.8 m away at the eye level. The monitor was used for setting tasks and real-time force feedback. The right or left upper arm was placed into the wrist-forearm brace. Velcro straps were used to prevent forearm and wrist movement during tests. Before each trial, the subject was asked to place the fingertips on the sensor centers and relax the hand; at that time, all sensor signals were set to zero. As a result, only active downward forces were measured by the sensors. The experiment consisted of four blocks including 1) MVC tasks, 2) single-finger ramp tasks, 3) quick force pulse production tasks, and 4) cyclic force production tasks. The subjects performed all four tasks with the left and right hands separately in a balanced-across-subjects order. The entire experiment lasted ~ 1 h. Before each block, subjects were given an instruction and a demonstration by an experimenter, and then they practiced for 1–3 min until they felt comfortable with the task.

MVC tasks. In the MVC task, subjects were instructed to press on the sensors with the four fingers together as hard as possible in a self-paced manner and achieve maximal total force level within 8 s. The subjects were instructed to relax immediately after reaching a maximal force. The feedback showed the sum of the four finger forces (F_{TOT}). 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 reaching MVC were measured and used to determine the target force levels for the next three tasks. The subjects performed two

consecutive attempts, and the data from the attempt with higher MVC level were used.

Single-finger ramp tasks. In these trials, 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 a horizontal segment at zero force for the first 4 s, followed by a slanted line from 0% to 40% of the force of the task finger measured in the MVC test over the next 12 s, and a horizontal segment at 40% of MVC_i for the last 4 s. Subjects were instructed to keep all fingers on the sensors at all times and to pay no attention to possible force production by non-task fingers.

Discrete quick force pulse production tasks. In this block, subjects were asked to produce quick force pulses to a target by pressing with all four fingers. During each trial, the feedback on F_{TOT} was provided on the computer screen (Fig. 1C). Two horizontal lines showed an initial force level (set at 5% of MVC_{TOT}) and a target level (set at 25% of MVC_{TOT} ; with $\pm 5\%$ error margins). The instruction was to press on the sensors with all four fingers and match F_{TOT} with the initial force level as accurately as possible. A vertical line was shown corresponding to 5 s after the trial initiation. Once the cursor crossed the vertical line, the subjects were required to produce a very quick force pulse to the target at a self-selected time within the next 5 s. Each subject performed 25–35 trials with each hand. Additional trials (over the minimum of 25) were given if the subject made a major mistake (for example, pressing before the cursor reached the vertical line, pressing several times within 1 trial, or changing the baseline force slowly in preparation to pressing).

Cyclic force production tasks. Subjects were asked to produce smooth sine-wave-like F_{TOT} for 20 s while being paced by a metronome (Fig. 1D). Two horizontal lines showed the required peak and trough levels of F_{TOT} ; they were set at 5% and 25% of MVC_{TOT} with $\pm 5\%$ of MVC_{TOT} error margins (dashed and solid lines in Fig. 1D). The subjects were instructed to time the peak forces with the “tick” sounds of the metronome. There were three metronome frequencies: 1 Hz (slow), 1.53 Hz (moderate), and 2 Hz (fast). Subjects performed two to three trials for each frequency, with the third trial given only in cases of major mistakes in one of the first two trials.

Data Analysis

The data were processed off-line using a customized Matlab program (Matlab 7.4.0; The MathWorks). The force data were digitally

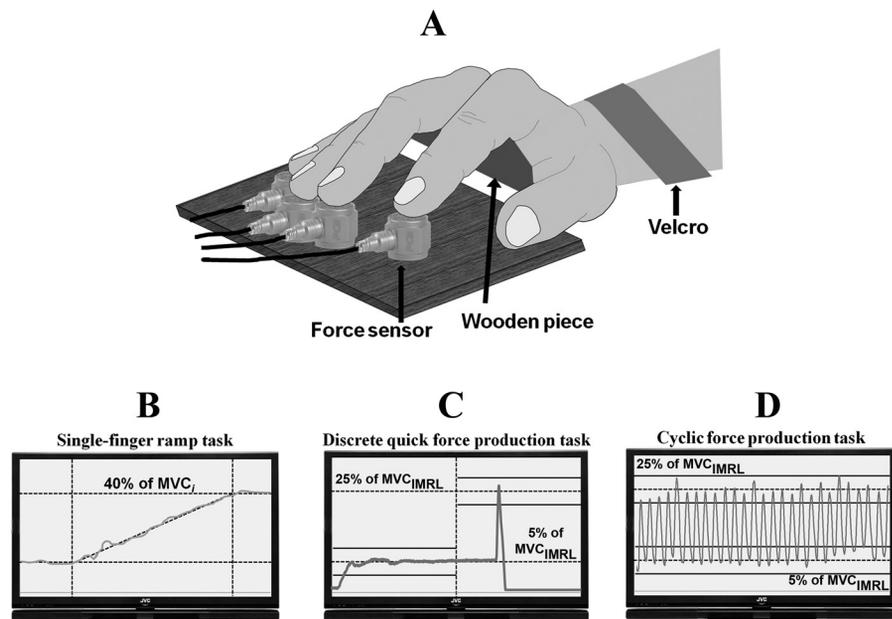


Fig. 1. A: the experimental setup. The subjects placed their palm on a wooden piece, and the forearm was held stationary with Velcro straps. The sensors (silver cylinders) were attached to a wooden frame. The feedback screens are shown during single-finger ramp tasks (B), discrete quick force pulse production tasks (C), and cyclic force production tasks (D) measuring forces of individual fingers at maximal voluntary contraction (MVC_i ; $i = I$, index; M , middle; R , ring; and L , little finger).

low-pass filtered with a zero-lag, fourth-order Butterworth filter at 10 Hz.

Single-finger ramp task: enslaving matrix. The enslaving matrix (**E**) reflects the involuntary force productions by non-task fingers when an instructed finger produces force. The **E** matrix was computed using the data from the single-finger ramp trials for each subject and each hand separately. For each single-finger trial, linear regressions of the forces produced by individual fingers against F_{TOT} over a 10-s time interval (starting 1 s after the ramp initiation and ending 1 s before the ramp termination to avoid edge effects) were computed. The regression coefficients (Eq. 1) were used to construct **E** (Eq. 2):

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

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

where $i = \{I, M, R, L\}$ and $j = \{I, M, R, L\}$; 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 index of overall enslaving, EN_j , as the average $k_{i,j}$ across the non-task fingers when j -finger was the task finger (Eq. 3):

$$EN_j = \sum_i k_{i,j}/3 \quad (i \neq j), \quad (3)$$

where $i, j = \{I, M, R, L\}$.

Discrete quick pulse force production tasks. Trials with the peak force (F_{peak}) that differed from the target level by more than $\pm 5\%$ MVC_{TOT} were excluded from further analysis. We also excluded the trials with the time to peak force over 1 s, because these trials were commonly accompanied by major mistakes (such as pressing several times). The time of initiation (t_0) of F_{TOT} change was defined as the time when the first derivative of force (dF/dt) reached 5% of its peak value in that particular trial. The time to reach F_{peak} (t_{peak}) was defined as the time of F_{peak} with respect to t_0 .

Further analysis used an index of multifinger force-stabilizing synergy computed within the framework of the UCM hypothesis (Scholz and Schöner 1999). We assumed that the CNS manipulated variables reflecting intended finger involvement in the task (finger modes, m_i). Each finger mode produced forces by all four fingers because of the aforementioned phenomenon of enslaving. The values of m_i were computed on the basis of the force magnitudes (F_i) and the enslaving matrix **E** for each time sample. All the accepted trials were aligned with respect to the time of initiation of F_{TOT} change, t_0 . After the trial alignment, variance in the m_i space across trials was quantified separately in two subspaces for each time sample. The first subspace (UCM) corresponded to a fixed value of F_{TOT} . The second subspace was the orthogonal complement to the first one. The computational details are presented in the APPENDIX. The variance components (V_{UCM} and V_{ORT}) were further combined into a single metric, a synergy index, ΔV , which was computed for each time sample and formed a time function:

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

where each variance index is normalized by the number of degrees of freedom in the corresponding spaces; V_{TOT} stands for total variance. For more detail, see Latash et al. 2001.

Note that $\Delta V > 0$ corresponds to proportionally more variance within the UCM, which is interpreted as a synergy-stabilizing F_{TOT} . Larger positive values of ΔV may be interpreted as reflecting a stronger synergy. Because ΔV could range from -4 (all variance is V_{ORT}) to 1.333 (all variance is V_{UCM}), for further statistical analysis, ΔV was log-transformed (Fischer transformation), resulting in an index ΔV_Z . The average value and standard deviation (SD) of ΔV_Z

were computed for the steady state (between -600 and -400 ms before t_0). The time of initiation of changes in ΔV_Z (time of anticipatory synergy adjustment, t_{ASA}) was defined as the time when ΔV_Z dropped below its average steady-state value by more than 2 SD. Negative values of t_{ASA} mean that ΔV_Z started to drop before the initiation of F_{TOT} changes.

Cyclic force production tasks. The force data during cyclic force production tasks were divided into the half-cycles of force increase and force decrease. Peak rate of force development, dF/dt_{max} , was measured in each half-cycle. Furthermore, the times when dF/dt dropped below 5% of dF/dt_{max} were defined both before and after the time of dF/dt_{max} . These were used as the times of half-cycle initiation and termination, respectively. The half-cycles with F_{TOT} peak or trough values outside the $\pm 5\%$ error margins, or with half-cycle duration deviating from the prescribed duration (as defined by the metronome beat) by over 15%, were excluded from further analysis.

For each half-cycle, the force data were resampled to 100 data points using cubic spline interpolation. Mode variance indices were computed for each sample across all the accepted half-cycles. The variance components and the synergy index (V_{UCM} , V_{ORT} , and ΔV) were computed for each time sample as described earlier. Furthermore, for comparisons across different phases of the force cycle, average ΔV_Z (the ΔV index after Fischer's transformation) was computed over three phase intervals: 1–20%, 41–60%, and 81–100%.

Statistics

Mixed-design ANOVAs with repeated measures were used. In particular, we explored how the main outcome variables (such as MVC, EN, V_{UCM} , V_{ORT} , ΔV_Z , and t_{ASA}) were affected by group (2 levels: PD and CS) and by other factors, such as hand (2 levels: left and right), frequency (3 levels: 1, 1.53, and 2 Hz), and phase (3 levels: 1–20%, 41–60%, and 81–100% of the half-cycle). Analyses were run separately for each of the variables, and the factors for particular comparisons are described in more detail in RESULTS. To explore possible effects of erratic trials, we performed some of the analyses both before and after screening the data for such trials with identical criteria applied to the PD and CS data. To compare effects of such a procedure, the factor "screen" was used with two levels (with and without). For post hoc comparison, Mann-Whitney tests were performed to explore significant effects with Bonferroni P -value adjustments for multiple comparisons ($P < 0.0083$ instead of the nominal $P < 0.05$). In addition, before ANOVAs were performed, variables with computational boundaries were transformed using Fisher's Z transformation according to the boundaries of each variable. The level of significance was set at $P < 0.05$.

RESULTS

Maximal Voluntary Contraction

PD subjects produced significantly lower peak forces in the MVC trials compared with CS. This was true for both hands and all four fingers. The difference between the PD and CS groups in the peak total force, MVC_{TOT} , was nearly 30%. The values (mean \pm SD) were 56.27 ± 16.54 and 58.31 ± 11.25 N for the left and right hand, respectively, of the PD group, whereas for the CS group these values were 79.42 ± 28.38 and 75.89 ± 25.16 N. A two-way repeated-measures ANOVA on MVC_{TOT} group \times hand showed a main effect of group [$F_{(1,19)} = 4.87$, $P < 0.05$] without other effects.

Enslaving

During the single-finger ramp force production tasks, unintended force production by non-task fingers (enslaving) was

seen in all participants. Overall, the enslaving (EN) was larger in the PD group compared with the CS group. Figure 2 illustrates the average EN indices for each task finger and hand. Note the larger values for the PD group (filled bars) and overall larger values for the ring (R) and little (L) fingers compared with the index (I) and middle (M) task fingers. There was no significant difference between the left and right hands. These observations were supported by a three-way repeated-measures ANOVA with factors finger, group, and hand, which showed significant main effects of finger and group [finger: $F_{(3,57)} = 42.95$, $P < 0.0001$; group: $F_{(1,19)} = 4.48$, $P < 0.05$] without other effects. Post hoc comparisons confirmed that $EN_I < EN_M < EN_L < EN_R$ ($P < 0.001$).

Discrete Quick Force Pulse Production Tasks

There were no significant differences between the PD and CS groups in the percentage of rejected trials (26.98 vs. 33.02% for the CS and PD groups, respectively) or the average F_{peak} and its SD (both expressed in %MVC) across subjects. This was true both before and after rejection of inaccurate trials based on the criteria described in METHODS.

PD subjects were relatively slow and showed higher SD of t_{peak} across trials compared with the CS group (Fig. 3). The group difference in SD of t_{peak} disappeared after screening out of inaccurate trials (Fig. 3B). The difference in t_{peak} , however, persisted (Fig. 3A), with the average t_{peak} for the CS group being ~ 150 ms shorter than for the PD group. These findings were supported by three-way repeated-measures ANOVAs on the average and SD of t_{peak} with factors group [main effects: $F_{(1,19)} = 9.10$, $P < 0.01$ for t_{peak} ; $F_{(1,19)} = 4.53$, $P < 0.05$ for SD of t_{peak}], hand (no main effect), and screen [main effects: $F_{(1,19)} = 45.36$, $P < 0.001$ for t_{peak} ; $F_{(1,19)} = 69.91$, $P < 0.001$ for SD of t_{peak}]. There also was a significant screen \times group interaction for both the mean and SD of t_{peak} [$F_{(1,19)} = 11.52$, $P < 0.01$ for t_{peak} ; $F_{(1,19)} = 11.06$, $P < 0.001$ for SD of t_{peak}], reflecting the fact that the group difference (PD $>$ CS) was attenuated by the screening process. Post hoc comparisons (Mann-Whitney tests) on t_{peak} confirmed that the group differences were significant both before and after screening ($P < 0.05$). For the SD of t_{peak} , the group effect was not significant after screening ($P > 0.05$; Mann-Whitney).

Synergy analysis of the quick pulse trials. During steady-state force production, both PD and CS groups showed positive

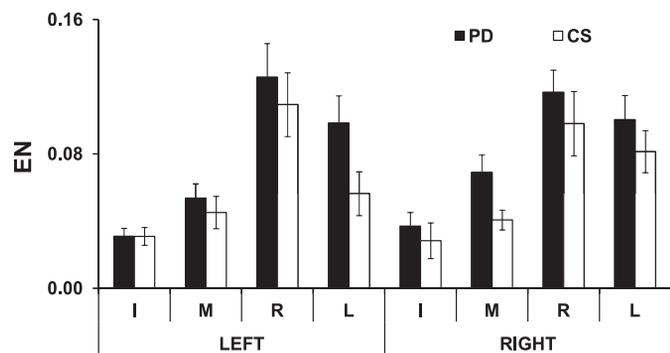


Fig. 2. Finger force enslaving (EN) of the index (I), middle (M), ring (R), and little (L) fingers of the left and right hands for the patients with Parkinson's disease (PD; filled bars) and sex- and age-matched control subjects (CS; open bars). Average values for PD and CS groups are presented with bars representing SE.

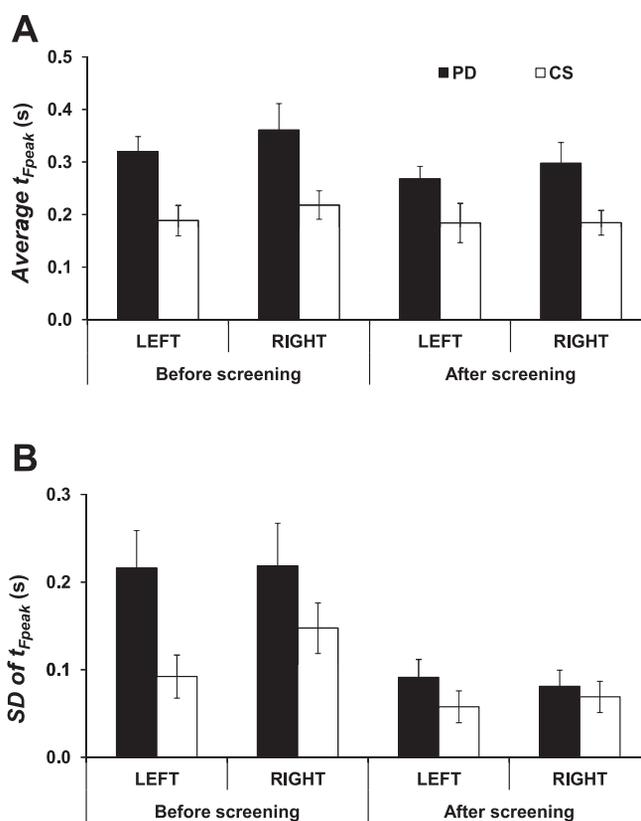


Fig. 3. Average (A) and SD values (B) for the time to peak force (t_{peak}), across trials for the PD (filled bars) and CS groups (open bars) during discrete pulse force production tasks. During the screening process, inaccurate trials based on the criteria described in METHODS were rejected for further analysis. Values are averages and SE across PD and CS groups.

ΔV indices, reflecting the fact that most variance in the space of commands to fingers (mode space) was compatible with the required constant F_{TOT} value. The magnitudes of the synergy index, however, showed significant differences between the groups and between the hands. As can be seen from Fig. 4, the CS group showed significantly higher ΔV_Z (Z-transformed ΔV) magnitudes at steady state compared with the PD group. There were also larger ΔV_Z magnitudes computed for the left hand compared with the right hand. These results were supported by a two-way repeated-measures ANOVA on ΔV_Z that showed main effects of group [$F_{(1,19)} = 12.83$; $P < 0.01$] and hand [$F_{(1,19)} = 7.57$; $P < 0.05$] without an interaction.

Before the initiation of the force pulse, there was a drop in the synergy index, which started earlier and was of a larger magnitude in the CS group compared with the PD group. This phenomenon, anticipatory synergy adjustment (ASA), was quantified using two indices, the difference in the synergy index between steady state and t_0 (ΔV_{t_0-ss}) and the time of initiation of the ΔV drop (t_{ASA} ; see METHODS). The ΔV_{t_0-ss} index was larger for the CS group than for the PD group and larger for the left hand than for the right hand. These findings were supported by a two-way group \times hand ANOVA on ΔV_{t_0-ss} , which showed significant main effects of both factors [group: $F_{(1,19)} = 13.46$, $P < 0.01$; hand: $F_{(1,19)} = 9.18$, $P < 0.01$] without an interaction.

The CS group showed an earlier drop in ΔV_Z (on average, by about 120 ms) compared with the PD group; there was no difference in t_{ASA} between the two hands. A two-way repeated-

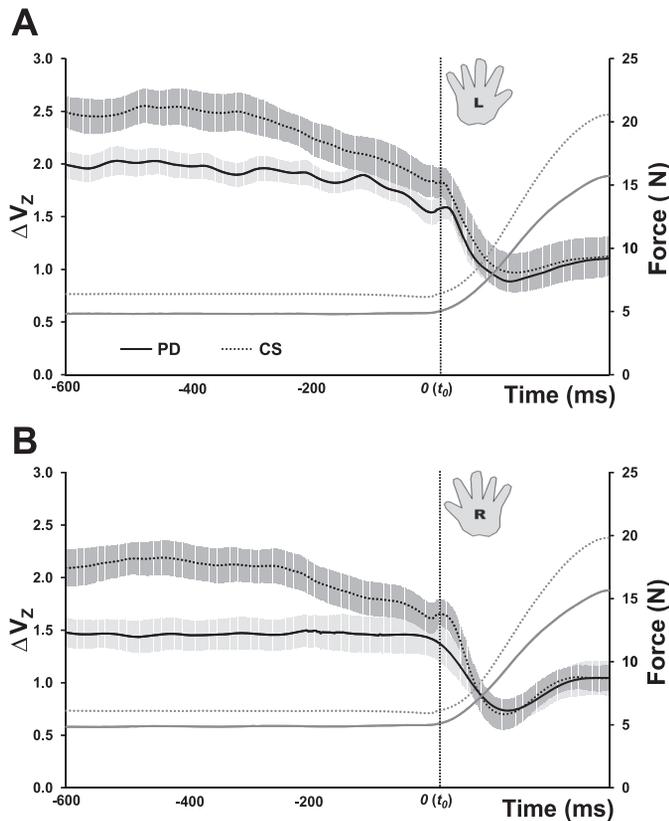


Fig. 4. Total force (gray lines) and variance of the total force (Z-transformed, ΔV_z) of the left (A) and right hands (B) for the PD (dashed line) and CS groups (dotted line) during discrete quick force production tasks. Averages and SE across PD and CS groups are presented for ΔV_z , and the average across each group is presented for the total force.

measures group \times hand ANOVA on t_{ASA} confirmed these findings by showing a significant main effect of group [$F_{(1,19)} = 4.46$, $P < 0.05$] without other effects.

We also compared the performance of the asymptomatic hands of the patients whose symptoms were limited to one side of the body ($n = 6$) with the performance of the symptomatic hands of the same patients and of the matched hands of the control subjects. For the latter comparison, each of the asymptomatic hands from the PD group was matched with a hand from the CS group with the same dominance, similar age, and same sex. The comparisons showed no differences in any of the outcome variables between the symptomatic and asymptomatic hands. In contrast, there were significant differences between the asymptomatic PD hands and matched CS hands in ΔV_z at steady state (1.79 ± 0.49 for PD vs. 2.58 ± 0.64 for CS, $P < 0.05$), t_{ASA} (-0.14 ± 0.12 s for PD vs. -0.31 ± 0.10 s for CS, $P < 0.05$), and ΔV_{t_0-ss} (-0.25 ± 0.11 for PD vs. -0.85 ± 0.63 for CS, $P < 0.05$).

Cyclic Force Production Tasks

All subjects within the CS group successfully completed the cyclic force production task in all frequency conditions (1, 1.53, and 2 Hz). In contrast, five PD patients could not perform the fast frequency condition (2 Hz). The average percentage of rejected cycles in those subjects who completed the tasks was similar between the groups, 29.65% for the CS group and 34.04% for the PD group. The groups performed similarly with

respect to the timing indices, such as average time of half-cycles and its SD computed across cycles ($P > 0.05$). Average peak (F_{peak}) and trough forces (F_{trough}) across multiple cycles for both groups were within the prescribed range even before the trial rejection process. Values of SD of F_{peak} and F_{trough} across cycles were similar for the PD and CS groups in the 1- and 1.53-Hz conditions. The five PD patients who were able to perform at 2 Hz showed a higher SD of F_{peak} and F_{trough} compared with the CS group for both hands. The group difference was still significant after inaccurate half-cycles were rejected, as confirmed by the three-way ANOVAs on group \times hand \times screen, which showed significant main effects of screen [$F_{(1,14)} > 23.67$, $P < 0.001$] and group [$F_{(1,14)} > 13.05$, $P < 0.01$] with no effect of hand and no interactions.

Synergy analysis of the cyclic force production trials. The synergy index ΔV was consistently positive for both groups, both hands, and all three frequencies. In other words, all subjects in all tasks showed force-stabilizing synergies.

Figure 5 illustrates the averaged time profiles across subjects of the synergy index after Fischer's transformation, ΔV_z . Note the pronounced modulation of the synergy index within each half-cycle (higher indices for higher forces) and the larger values of ΔV_z in the left hand (compare Fig. 5, A and B). The PD group showed smaller values of the synergy index at the higher forces, whereas the difference was absent at lower forces. These findings were supported by three-way repeated-measures ANOVAs run separately on ΔV_z for the force-increase and force-decrease half-cycles with factors group, hand, and phase (3 levels: 1–20%, 41–60%, and 81–100%). The ANOVA showed a significant main effect of hand [force increase: $F_{(1,19)} = 17.17$, $P < 0.01$; force decrease: $F_{(1,19)} = 8.96$, $P < 0.01$] and a significant group \times phase interaction [force increase: $F_{(2,38)} = 8.36$, $P < 0.01$; force decrease: $F_{(2,38)} = 8.08$, $P < 0.01$]. The interaction reflected the presence of group differences in the 81–100% phase only.

DISCUSSION

This is the first study that we know of to quantify the changes in motor coordination in Parkinson's disease using the uncontrolled manifold hypothesis framework. The results support two of the four hypotheses formulated in the Introduction, whereas the other two hypotheses received only partial support. First, PD subjects showed significantly higher indices of enslaving (lower individuation) compared with the control group (*hypothesis 1*). In contrast to our prediction, however, the higher enslaving with PD was associated with lower MVC forces. Second, PD subjects showed impairment of multifinger synergies stabilizing total force during steady-state force production and during certain phases in the cyclic force production (*hypothesis 2*). Third, PD subjects did show delayed, smaller adjustments of the multifinger synergies in preparation to a quick force pulse, thus supporting *hypothesis 3*. Equivocal results were obtained, however, when evaluating whether the synergy impairments in PD showed frequency dependence in accurate cyclic force production tasks. On the one hand, only half of the patients were able to complete the task at 2 Hz. On the other hand, smaller values of the synergy index in the PD group, compared with the CS group, at the higher forces within the cycle were seen during tasks at 1 and 1.5 Hz (cf. Spencer and Ivry 2005). Overall, the results suggest that PD is associ-

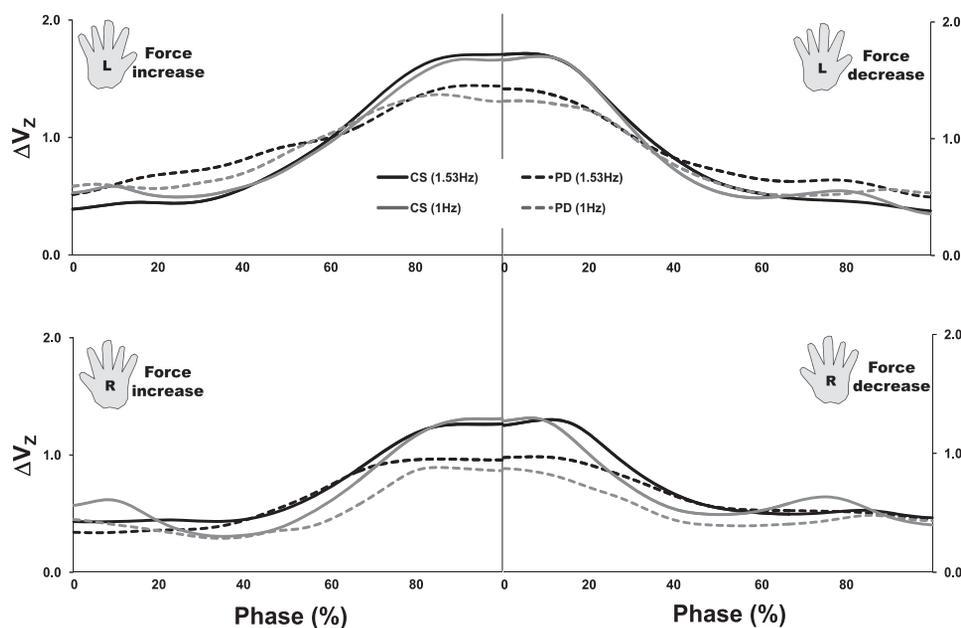


Fig. 5. Variance of the total force (Z -transformed, ΔV_z) of the left (A) and right hands (B) for the PD (dashed line) and CS groups (dotted line) during the cyclic force production tasks. Values are averages across PD and CS groups.

ated with significant impairments in multifinger synergies. The findings also demonstrate that quantitative analysis of multifinger synergies can provide indices sensitive to impairment of motor coordination in early-stage PD and may be used as a paradigm to address the underlying neurophysiological mechanisms of motor dysfunctions in PD. In the following, we address the implications of the results for such issues as the role of different brain structures in multifinger synergies and feedforward control in PD.

Loss of Finger Individuation in Parkinson's Disease

Healthy humans cannot move one finger at a time without moving other fingers or press with one finger without pressing with other fingers of the hand (Kilbreath and Gandevia 1994; Schieber and Santello 2004; Zatsiorsky et al. 2000). This phenomenon, addressed as lack of individuation, enslaving, or enslavement, gets contributions from several factors, including passive connections among fingers, the presence of multitendon extrinsic hand muscles, and overlapping cortical projections (reviewed in Schieber and Santello 2004; van Duinen and Gandevia 2011).

By itself, enslaving should not be viewed as a negative factor that puts constraints on finger coordination. It has been suggested, in particular, that typical enslaving patterns may help stabilize rotational action of the hand (Zatsiorsky et al. 2000). A drop in enslaving indices with healthy aging and fatigue (Danion et al. 2000; Shinohara et al. 2003) also suggests that a healthy amount of enslaving is in some sense optimal for everyday hand function. Nevertheless, increased enslaving should be viewed as detrimental for tasks that require flexible patterns of finger involvement, especially during precise manipulation tasks.

Patients with PD are known to demonstrate impaired hand function across a variety of tasks (Muratori et al. 2008; Prodoehl et al. 2009). Our results suggest that, at least partly, the impairment of the hand function may be due to the loss of finger individuation (higher enslaving). Previous studies have reported a positive correlation between MVC and enslaving

indices across a variety of comparisons such as young vs. elderly, males vs. females, and fatigued vs. nonfatigued subjects (Shinohara et al. 2003). In our study, the increased enslaving was accompanied by lower MVC forces in the PD group. Thus the higher enslaving cannot be attributed to the changed MVC forces but likely reflects changes in supraspinal control, in line with several studies that emphasized the role of neural factors in enslaving (Latash et al. 2002b; Schieber and Santello 2004).

Feedforward Control in Parkinson's Disease

Patients with PD are known to demonstrate impaired anticipatory postural adjustments (APAs; Bazalgette et al. 1986; Traub et al. 1980) as well as impaired feedforward control of hand actions (Albert et al. 2010; Muratori et al. 2008). In our study, we addressed a different mechanism of feedforward control, anticipatory synergy adjustments (ASAs). ASA may be viewed as a complementary mechanism to APA. ASAs reflect adjustments of synergies stabilizing a particular performance variable in preparation for a quick change in the variable (Olafsdottir et al. 2005). They are not seen in averaged performance but in the covariation of elemental variables across trials. In contrast, APAs reflect changes in the magnitude of a performance variable in preparation to a perturbation and/or action. They typically are studied in averaged across trials records. Recently, both ASAs and APAs have been documented in healthy persons who performed quick arm movements (Klous et al. 2011) or were subjected to an expected perturbation while standing (Krishnan et al. 2011).

Parallel changes in ASAs and APAs have been reported with healthy aging: Both indices show a delay and a drop in magnitude (Olafsdottir et al. 2007; Woollacott et al. 1988). Our observations in patients with PD (delayed initiation of ASAs and a drop in their magnitude) show similar parallels with earlier reports on delayed and reduced APAs in PD (Bazalgette et al. 1986). These observations suggest that the impaired feedforward control in PD may involve a previously unknown component reflected in the reduced and delayed ASAs.

Possible Neurophysiological Mechanisms of Impaired Synergies

Indices of synergies potentially can reflect neurophysiological processes at different levels of the neural axis. Our results suggest an important role of supraspinal processes. In particular, the differences between the synergy indices in the left and right hand during steady-state force production are compatible with the dynamic dominance hypothesis (Sainburg 2002; Schaefer et al. 2007), which is based primarily on cortical mechanisms. This hypothesis posits that the cortical mechanisms of the control of the dominant arm are specialized for trajectory control, whereas those mechanisms for the nondominant hand are specialized for the control of steady states: a typical example would be holding the nail with the left hand and hitting it with the hammer held by the right hand. The steady-state portion of the task with quick force pulse production may be viewed as analogous to holding an object steadily. We observed higher synergy indices in the left (nondominant) hand during steady-state force production in line with the Sainburg hypothesis. We did not focus on changes in the synergy index during the force pulse in this study. In an earlier study (Zhang et al. 2006), however, we observed a smaller drop in the synergy index in the right (dominant) hand, also in line with the dynamic dominance hypothesis. On the other hand, the differences between the subject groups suggest an important role of the basal ganglia in synergies. Note that there was no interaction between the hand and group factors, suggesting that PD is not associated with major changes in synergy-related cortical mechanisms that define handedness.

In the past, two potential sites of synergy formation have received much attention, the cerebellum and the cerebral cortex (reviewed in Amirkian and Georgopoulos 2003; Houk et al. 2005; Schieber 2001; Thach et al. 1992). It is noteworthy that the basal ganglia have been implicated in uniting the postural and locomotor synergies (Mori 1987) and in the grasp-lift synergy (Forsberg et al. 1999). Graybiel (1995) has suggested that the basal ganglia are involved in a brain-wide net of adaptive neural systems contributing to optimal motor and cognitive performance. Consistent with these previous studies, our results support the idea that broad networks within the CNS involving, among other structures, the basal ganglia may play an important role in the functioning of such synergies and in their adjustments in preparation for action.

The basal ganglia have been implicated in action initiation (Sanes 1985; Stelmach et al. 1986); in particular, episodes of freezing typical of PD have been interpreted as reflecting the impaired action preparation processes (Vercruyse et al. 2011). Our observations of the significantly reduced and delayed ASAs suggest a specific problem with action initiation in PD. The basal ganglia may be involved in anticipatory adjustments of synergies (without a change in overall performance) associated with the initiation of quick actions from steady state.

Several recent brain imaging studies have suggested cerebellar involvement in PD (Wu et al. 2011; Yu et al. 2007). In particular, weakened striatum-cerebellar connections have been documented (Wu et al. 2011), possibly related to problems with action initiation. It has been suggested that the cerebellum may play a compensatory role following primary basal ganglia dysfunction (Lewis et al. 2007; Sen et al. 2010). It is possible that some of the changes in synergy characteris-

tics observed in our study reflect the changes in networks involving both the basal ganglia and the cerebellum (cf. Spencer and Ivry 2005). The cyclic tasks were intended to probe the involvement of the cerebellum in synergies in patients with PD. With bradykinesia as one of cardinal signs of the disease, it is not surprising that half of the patients with PD were not able to complete the task at the higher frequency (2 Hz) used in our study. The fact that there were no significant differences between CS and PD subjects at lower frequencies suggests that the cerebellum and related neural networks may function or compensate well during slower actions.

We acknowledge that any conclusions from behavioral studies, such as the present one, have to be viewed as tentative. Behavioral studies of patients with disorders of specific brain structures produce only indirect information regarding the role of these structures in the functional behaviors. One reason is that such disorders are associated with secondary (frequently, adaptive) changes throughout the CNS. Adaptive changes may also be induced by antiparkinsonian drugs, although L-dihydroxyphenylalanine (L-DOPA)-induced dyskinesias are typically seen after much longer time compared with the median duration of PD in our group. We emphasize that none of our patients showed signs of dyskinesia at the time of testing. Nevertheless, since most patients were tested while on their antiparkinsonian medication, results of the tests reflected combined effects of the disease and the medication. In all those patients, the medications improved their clinical status; hence, we suggest that the observed differences between the PD and CS groups could be even larger if the patients were tested while off their medications. This is a hypothesis to be tested in a future study involving similar experimental procedures repeated both before the morning dose (off) and after the dose (on) of medication.

Concluding Comments

The main result of our study is the demonstration that the elusive changes in motor coordination in PD can be quantified objectively, even in patients at a relatively early stage of the disease. Significant changes in synergy indices were seen even in the asymptomatic hands of PD patients, that is, when clinical examination (such as UPDRS) fails to detect signs of PD. These results offer an exciting opportunity to use tests of motor synergies for early detection of PD and for tracking its progression and effects of treatment. They also suggest that the tests of motor synergies may be used in other cases of impaired coordination in neurological patients.

APPENDIX

Uncontrolled Manifold Analysis

For more details on the UCM analysis, see Scholz and Schönner (1999) and Latash et al. (2001).

The force data from multiple trials \mathbf{f} were converted into a mode vector \mathbf{m} by using the enslaving matrix \mathbf{E} , where $\mathbf{f} = [f_i, f_m, f_r, f_l]^T$ (\mathbf{T} represents a matrix transpose):

$$\mathbf{m} = [\mathbf{E}]^{-1} \cdot \mathbf{f} \quad (1)$$

For the total force (F_{TOT}) production, changes in F_{TOT} were a function of the changes in mode $d\mathbf{m} = [dm_i, dm_m, dm_r, dm_l]^T$:

$$dF_{TOT} = [1 \ 1 \ 1 \ 1] \cdot d\mathbf{f} = [1 \ 1 \ 1 \ 1] \cdot \mathbf{E} \cdot d\mathbf{m} \quad (2)$$

The UCM was approximated as a subspace defined by an orthogonal set of the vectors \mathbf{e}_i in the \mathbf{m} space satisfying

$$0 = [1 \ 1 \ 1 \ 1] \cdot \mathbf{E} \cdot \mathbf{e}_i \quad (3)$$

These vectors were found by computing the null space of the Jacobian of this transformation ($[1 \ 1 \ 1 \ 1] \cdot \mathbf{E}$). The mean-free modes were then projected onto these directions and summed to produce

$$\mathbf{f}_{\parallel} = \sum_i^{n-p} (\mathbf{e}_i^T \cdot d\mathbf{m}) \mathbf{e}_i \quad (4)$$

where $n = 4$ is the number of elemental variables (finger modes, \mathbf{m}) and $p = 1$ is the number of constraints defined by the performance variable (F_{TOT}). The orthogonal to the null-space projections was computed as

$$\mathbf{f}_{\perp} = d\mathbf{m} - \mathbf{f}_{\parallel} \quad (5)$$

The amount of variance per degree of freedom within the UCM is

$$V_{\text{UCM}} = \frac{\sum |\mathbf{f}_{\parallel}|^2}{(n-p)N_{\text{trials}}} \quad (6)$$

The amount of variance per degree of freedom orthogonal to the UCM is

$$V_{\text{ORT}} = \frac{\sum |\mathbf{f}_{\perp}|^2}{pN_{\text{trials}}} \quad (7)$$

The normalized difference between V_{UCM} and V_{ORT} (the synergy index) was quantified as

$$\Delta V = \frac{V_{\text{UCM}}/3 - V_{\text{ORT}}/1}{V_{\text{TOT}}/4} \quad (8)$$

where V_{TOT} is the total variance, also quantified per degree of freedom.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: J.P., Y.-H.W., X.H., and M.L.L. conception and design of research; J.P., Y.-H.W., and M.L.L. performed experiments; J.P., Y.-H.W., M.M.L., and M.L.L. analyzed data; J.P., M.M.L., X.H., and M.L.L. interpreted results of experiments; J.P. and Y.-H.W. prepared figures; J.P., X.H., and M.L.L. drafted manuscript; J.P., M.M.L., X.H., and M.L.L. edited and revised manuscript; J.P., Y.-H.W., M.M.L., X.H., and M.L.L. approved final version of manuscript.

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