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RESEARCH ARTICLE

Prehension synergies and hand function in early-stage Parkinson's disease

Hang Jin Jo · Jaebum Park · Mechelle M. Lewis · Xuemei Huang · Mark L. Latash

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Abstract We explored the multi-digit synergies and hand performance in object manipulations and pressing tasks in patients with early-stage Parkinson's disease (PD) and healthy controls. Synergies were defined as inter-trials co-variation patterns among forces/moments produced by individual digits that stabilized a resultant mechanical variable. The subjects performed three main tasks: pressing (steady-state force production followed by a force pulse into the target), prehension (manipulation of a handheld instrumented handle imitating the action of taking a sip from a glass), and functional object manipulation (moving a glass with water as quickly and accurately as possible along a chain of targets). The PD patients were slower compared to controls in all three tasks. Patients showed smaller synergy indices in the pressing and prehension tasks. In the prehension tasks, patients showed elevated grip force at steady states with smaller grip force modulation during the handle motion. PD patients showed smaller feed-forward synergy adjustments in preparation to the quick action in the pressing and (to a smaller degree) prehension tasks. Synergy indices correlated with the time index of performance in the functional glass-with-water task, whereas none of the indices correlated with the Unified PD Rating Scale part III—motor scores. We interpret the results as pointing at an important role of subcortical structures in motor synergies and their feed-forward adjustments to action.

Keywords Hand · Prehension · Parkinson's disease · Synergy · Finger · Uncontrolled manifold hypothesis · Feed-forward control

H. J. Jo · X. Huang · M. L. Latash (✉)
Department of Kinesiology, The Pennsylvania State University, Rec.Hall-268N, University Park, PA 16802, USA
e-mail: mll11@psu.edu

J. Park
Department of Health and Human Development, Montana State University, Bozeman, MT, USA

M. M. Lewis · X. Huang
Department of Neurology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA 17033, USA

M. M. Lewis · X. Huang
Department of Pharmacology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA 17033, USA

X. Huang
Department of Radiology, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA 17033, USA

X. Huang
Department of Neurosurgery, Pennsylvania State University-Milton S. Hershey Medical Center, Hershey, PA 17033, USA

Introduction

Although hand motor dysfunction is a well-documented early consequence of Parkinson's disease (PD, e.g., micrographia, McLennan et al. 1972; Viviani et al. 2009), problems with finger coordination are not mentioned among the cardinal signs of PD. A series of recent studies in patients with early-stage PD documented changes in finger interaction and coordination indices during isometric force production tasks (Park et al. 2012, 2013a, 2014). In particular, those studies reported lower maximal force, higher indices of unintentional force production by fingers that are not required to produce force (enslaving, Li et al. 1998; Zatsiorsky et al. 2000), and changes in indices of multi-finger synergies. According to the principle of abundance (Latash 2012), synergies were defined as co-variation among commands to elements (individual fingers) that stabilize

(reduces inter-trial variance of) total force. Patients with PD showed significantly reduced indices of synergies during steady-state force production and an impaired ability to adjust synergies in preparation to a quick force pulse (anticipatory synergy adjustments, ASAs, Olafsdottir et al. 2005). These results suggest impairments in both creating task-specific stability of salient variables (cf. Schöner 1995) and adjusting it in anticipation of a quick action. It has been hypothesized that the latter impairment may lead to problems with the initiation of various movements resulting, in particular, in episodes of freezing of gait common in PD (Park et al. 2014).

A study of patients on and off their PD medications has shown that both synergy indices and ASAs are sensitive to dopamine replacement therapy (Park et al. 2014). Although the early results suggest that synergy indices may be promising new measurements of PD-related motor dysfunction, only modest correlations of these indices with the Unified PD Rating Scale—motor subscales (UPDRS-III) were found. One reason may be the narrow range of UPDRS scores typical of early-stage PD (Park et al. 2012). Indeed, in a study of patients with multi-system brain degeneration leading to a combination of parkinsonian and cerebellar clinical signs, significant correlations were found between UPDRS scores and synergy indices (Park et al. 2013b).

The current study had two main goals. First, we quantified multi-digit synergies in a more ecologically relevant task, that is, manipulation of a handheld object. The prehensile manipulation was selected to mimic common everyday actions such as moving a glass of water to one's mouth and taking a sip. We also have added a functional hand task—the "glass-and-water" task—designed to detect impairments in an action relying on digit coordination in early-stage PD.

We expected patients with PD to perform slower than healthy controls (cf. bradykinesia) across all the tasks and show higher indices of enslaving (Hypothesis 1). Based on the aforementioned studies with pressing tasks, we expected patients to show lower indices of multi-digit synergies (Hypothesis 2). Note that this hypothesis is non-trivial: Several earlier studies have shown that faster actions are associated with lower synergy indices (Goodman et al. 2005; Friedman et al. 2009). We explored the second hypothesis at two levels of the hypothetical control hierarchy: At the upper level, the task is assumed to be shared between the thumb and a virtual finger (VF, an imagined digit with the mechanical action equal to the combined action of the four fingers, Arbib et al. 1985), whereas at the lower level, VF action is shared among the four fingers. We also expected PD patients to show reduced ASAs (Hypothesis 3), although the object manipulation task involved relatively slow force and moment of force changes as compared to the force pulse production tasks (see "Results").

To provide a link between the pressing task used in earlier studies (Park et al. 2012, 2013a, 2014) and the prehensile task, we also asked our participants to perform the accurate force and force pulse production during pressing tasks. We expected a correlation between the synergy indices recorded in the pressing and prehensile tasks (Hypothesis 4). We also explored correlations between the synergy indices, UPDRS scores, and performance indices in the glass-and-water test.

Methods

Subjects

Eight patients with PD (aged 63.93 ± 9.54 years; 7 males) and eight age-matched control subjects (CS; aged 63.97 ± 6.84 years; 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, diagnosed and managed by movement disorder specialists. CS were recruited from spouses and friends of the patients, as well as through fliers posted in the local community. All participants were right-handed according to their preferential hand use during writing and eating, and all the tests were performed with the right hand. 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 PD Rating Scale part III—motor scores (UPDRS-III) ranged between 6 and 34. Disease duration from time of diagnosis was between 0.7 and 10.3 years, with a median duration of 2.3 years. The levodopa equivalent daily dose (LEDD) was estimated for PD subjects according to a published formula (Tomlinson et al. 2010); none of the patients showed signs of postural instability or drug-induced dyskinesias. All PD patients had tremor scores of 1 or 0 (both for rest tremor and kinetic tremor) for their right hand. PD subjects were tested while on their prescribed antiparkinsonian medication. 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.

Apparatus

Pressing setup

This setup has been described in more detail in a previous publication (Park et al. 2012). Briefly, four piezoelectric force sensors (model 208A03; PCB Piezotronics, Depew,

Table 1 Description of study participants

Subject	Sex (M/F)	Age (year)	Handedness (R/L)	Symptom onset	Years since diagnosis	UPDRS motor score	Medication (on/off)	Total LEDD (mg)
PD group								
1	M	68	R	Bilateral	3.1	8	On	175
2	M	47	R	R	10.3	6	On	1,097.5
3	M	77	R	R	1.1	17	On	350
4	F	63	R	R	0.8	13	On	400
5	M	63	R	R	8.7	21	On	635
6	M	70	R	R	0.7	11	On	50
7	M	67	R	R	6.9	34	On	900
8	M	54	R	L	1.5	19	On	460
CS group								
1	M	60	R					
2	M	76	R					
3	M	59	R					
4	M	69	R					
5	M	54	R					
6	M	62	R					
7	M	61	R					
8	F	66	R					

M/F male/female, *R/L* right/left, *UPDRS* Unified Parkinson's Disease Rating Scale, *LEDD* levodopa equivalent daily dose

NY) were used to measure vertical forces produced by the fingers. The sensors were attached to a customized flat wooden panel. 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 help maintain a constant hand and finger configuration during the tests. The four force signals were digitized at 300 Hz with a 16-bit resolution using a customized LabView program.

Prehension setup

Five six-component force/moment transducers were mounted on a handle. A Nano-25 transducer (ATI industrial automation, Apex, NC, USA) was used for the thumb, and four Nano-17 transducers (ATI industrial automation, Apex, NC, USA) were used for the four fingers. The thumb transducer was mounted opposite to the transducers for the four digits (Fig. 1). The transducers were attached in such a way that the *X*-axes of all five transducers were parallel to the central vertical axis of the handle. The center points of the sensors for the index and middle fingers were 4.5 and 1.5 cm above

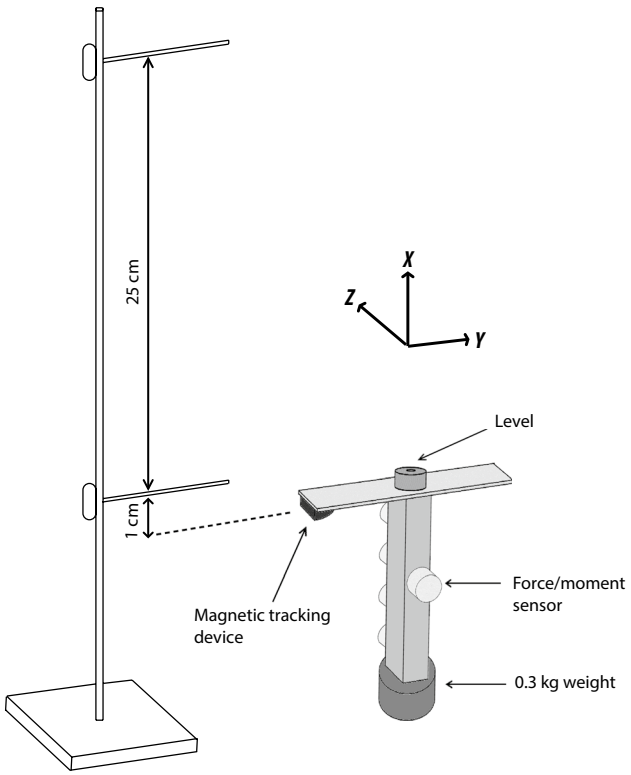

Fig. 1 The prehension setup included the customized handle with five force/moment sensors, a magnetic tracking sensor, and a level

the midpoint of the handle, respectively. The center points of the sensors for the ring and little finger were 1.5 and 4.5 cm below the midpoint of the handle, respectively. The thumb sensor was located at the midpoint of the handle. The horizontal distance between the sensor surfaces was 6 cm. The centers of all the sensors were within one plane referred to as the grasp plane. The total mass of the handle with five sensors and 0.3 kg weight attached was 0.619 kg. Sandpaper (100-grit) was attached to the contact surface of each sensor to increase the friction between the digits and the transducers. A six-component (three position and three angle components) magnetic tracking device (Polhemus FASTRAK, Rockwell Collins, Colchester, VT) was affixed to the top of the handle using a wooden base (2.5 × 15 × 0.2 cm). The tracking device samples the handle translation and rotational kinematics at 60 Hz. A circular level with 2° tolerance was attached at the center of wooden base and used as a feedback device for the subject to keep the handle orientation close to vertical at all times.

Experimental procedures

The experiment comprised five tasks: (1) maximal voluntary contraction (MVC) tasks, (2) single-finger ramp tasks, (3) quick force pulse production tasks, (4) prehension tasks, and (5) a glass-with-water test. The subjects performed all five tasks in the above order with their dominant (right) hand. The pressing setup was used for the first three tasks, and the prehension setup was used for the prehension task only. The entire experiment lasted for approximately 1 h. Before each task, subjects were given instructions and a demonstration by an experimenter, after which they practiced for 1–3 min.

Pressing tasks

For the tests performed using the pressing setup, subjects sat in a chair facing a 19-in. computer monitor positioned at eye level. The monitor showed real-time finger force feedback. The right forearm was strapped into a wrist–forearm brace to avoid forearm and wrist movement during trials. Prior to each trial, all sensor signals were set to zero when subjects placed their fingertips on the sensor centers and relaxed their hand. As a result, the sensors measured only active downward forces.

MVC task 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) were measured. The subjects performed two consecutive attempts and the trial with the higher MVC_{TOT} was selected to set further tasks with the pressing setup.

Single-finger ramp tasks Subjects were required to press with one of the fingers (the task finger) and match with its force the template shown on the screen. 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 asked to pay no attention to possible force production by other fingers (non-task fingers) and to keep all the fingers on the sensors at all times.

Accurate force pulse production task In this task, subjects were asked to produce quick force pulses into a target by pressing with all four fingers. During each trial, the feedback on F_{TOT} was provided on the computer screen. 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 ±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 at least 25 trials, and additional trials (over the minimum 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).

Prehension task

Subjects sat with an erect posture facing the prehension setup. They were asked to use their right hand to hold the handle with each digit tip placed on the center of the corresponding sensor. When holding the handle, the subject's right upper arm was abducted at approximately 45° in the frontal plane and internally rotated approximately 30°, the elbow was flexed at approximately 90°, and the wrist was in a neutral supination–pronation position. Subjects rested their left hand on their lap. A stand holding two horizontal wooden rods was used to indicate two targets, one lower and one higher (Fig. 1).

The prehension task was used to simulate component movements of taking a sip from a glass. Each trial consisted of five consecutive parts. Subjects were asked to: (1) lift the handle by about 1 cm in order to match the top of the handle to the lower target level, (2) lift the handle up to the higher target level (phase 1: vertical movement), (3)

move the handle horizontally toward their mouth and stop about 15 cm away from the face (phase 2: horizontal movement), (4) tilt the handle about 45° as if taking a sip (phase 3: tilting movement), and (5) return the handle back to the starting position. Each of the 5 parts lasted for about 4 s, and the experimenter verbally indicated when each part was to start. Subjects were asked to move fast during phases 1, 2, and 3. After each movement part, subjects were asked to keep the handle stationary without deviations from the vertical (keeping the air bubble in the center of the level), except for phase 3 when the handle rotated. Phases 1, 2, and 3 were used for the data analysis. Movement distances for both phase 1 and phase 2 were about 25 cm. Each subject performed 25 trials. Before each trial, the signals from the sensors were set to zero while the subjects were not touching the sensors.

Glass-with-water test

Subjects performed the glass-with-water test while standing in front of a table with a plastic tray (44.5 × 29.2 cm). Four target positions were marked on the four corners of the tray. A plastic glass (6.6 cm diameter on the bottom, 8.8 cm diameter on the top, and 15.2 cm in height, 70 g) full of water (the level of water 3 mm below the rim, 610 ml) was placed on one of the targets (the far right corner). Subjects were asked to move the glass from a target to the next target counterclockwise and complete three circles ending at the same target position where they started. They were instructed to perform the task as quickly as they could, just touching each of the targets with the bottom of the glass with no dwell time, and to spill as little water as possible. Movement time was measured with a stopwatch, whereas the amount of water spilled was measured using a scale.

Data analysis

The force data were digitally low-pass filtered with a zero-lag, fourth-order Butterworth filter at 10 Hz. The data processing was done using a customized MATLAB code.

Single-finger ramp tasks

The enslaving matrix (**E**) reflects the involuntary force productions by non-task fingers when an instructed finger produces force (Zatsiorsky et al. 2000). The **E** matrix was computed using the data from the single-finger ramp trials for each subject. For each single-finger trial, linear regressions of the force produced by individual fingers against F_{TOT} over a 10-s time interval were computed. The first and last 1-s intervals were excluded to avoid edge effects. The regression coefficients in $F_{i,j} = f_i^0 + k_{i,j} \times F_{TOT,j}$ were used to construct:

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

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. An overall index of enslaving, EN_j, was computed for each finger as the average $k_{i,j}$ across the non-task fingers when j-finger was the task finger: $EN_j = \sum k_{i,j}/3$ $(i \neq j)$.

Accurate force pulse production tasks

The trials with the following errors were excluded from further analysis: The peak force was outside the ±5 % error margins of the target force, the time-to-peak force was over 1 s, the baseline force was not stabilized prior to pressing, and/or the force pulse showed multiple peaks. Overall, the total number of excluded trials varied between 4 and 10 among subjects. The number of included trials was 20 ± 1 for all subjects since we collected extra trials (over the minimum 25) in case the subject made mistakes that could be recognized during the testing procedure. The following variables were computed only for the accepted trials.

The time (t_0) of initiation 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. All the accepted trials for each hand and each subject were aligned with respect to t_0.

An index of multi-finger force stabilizing synergy was computed within the framework of the uncontrolled manifold (UCM) hypothesis (Scholz and Schöner 1999; for computational details see Latash et al. 2001). Finger forces were transformed into finger modes (**m**) with the help of the **E** matrix. The variance in the mode space across all the accepted trials was quantified separately in two subspaces for each time sample. The first subspace (UCM) corresponded to no changes in F_{TOT}. The second subspace was the orthogonal complement (ORT) to the UCM; variance within ORT changed F_{TOT}. The two 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:

$$\Delta V = (V_{UCM} - V_{ORT})/V_{TOT},$$

where each variance index is normalized by the number of degrees-of-freedom in the corresponding spaces; V_{TOT} stands for total variance.

We interpret $\Delta V > 0$ as sign of a F_{TOT}—stabilizing synergy; a higher ΔV implies a stronger synergy. For further statistical analysis, ΔV was log-transformed (ΔV_Z) using

the Fischer transformation applied for the computational boundaries, from −4 to 1.333.

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

Prehension tasks

The movement times (MT) for each phase, tangential velocity in phases 1 and 2, and angular velocity about the *Y*-axis in phase 3 were computed for each phase. The initiation (t_{START}) and termination (t_{END}) of movement in each phase were defined as the points where the velocity (tangential velocity for phases 1 and 2; angular velocity for phase 3) first reached 5 % of its maximal value and dropped below 5 % of its maximal value in that trial, respectively. The data were quantified over three time periods in each phase, initial steady state (SS1), final steady state (SS2), and the movement duration, where SS1 refers to a 1-s interval starting 0.5 s before the movement initiation and SS2 refers to a 1-s interval starting 0.5 s after the movement termination. The trials were aligned by the $t_{START,}$ and time was normalized to 100 points over the movement duration. The intervals before and after the movement were not time normalized.

The data analysis was performed at two hierarchical levels (Arbib et al. 1985). At the upper level, the VF–TH level, the resultant force and moment components are shared between the thumb (TH) and virtual finger (VF, an imagined digit with the mechanical action equal to the combined actions of the four fingers). At the lower level, the IF level, VF action is shared among the four fingers. An index (ΔV) of synergy was calculated for several performance variables, which are the left-side variables in the following equations:

At the VF–TH level:

$$F^N = F^N_{TH} + F^N_{VF}$$
$$F^T = F^T_{TH} + F^T_{VF}$$
$$M_{TOT} = M_{TH} + M_{VF}$$

At the IF level:

$$F^N_{VF} = F^N_I + F^N_M + F^N_R + F^N_L$$
$$F^T_{VF} = F^T_I + F^T_M + F^T_R + F^T_L$$
$$M_{VF} = M_I + M_M + M_R + M_L$$

where subscripts at the force variables (*F*) and moment of force variables (*M*) refer to the digits (*I*—index; *M*—middle; *R*—ring; *L*—little) and TOT relates to the resultant moment of force produced by all five digits. Superscripts in the above equations refer to the normal force (*N*) or tangential force (*T*). At each level, ΔV was quantified for each of the force and moment variables. All trials were aligned for each phase starting 2 s before t_{START} and ending 2 s after t_{END} for each subject. The variances of each performance variable across trials were quantified separately in the UCM and ORT subspaces for each time sample. The synergy index, ΔV, was computed in the same way as in the force pulse production task. Note that $\Delta V > 0$ indicates a synergy stabilizing a certain performance variable at the selected level (Shim et al. 2005; Gorniak et al. 2009). This index was log-transformed (ΔV_Z) using a Fischer transformation applied to the boundaries of each level. Mean values of ΔV_Z for SS1 and SS2 were computed, and the mean value of ΔV_Z of these two steady states was used for statistical analysis. We also quantified the magnitude of the ΔV_Z drop ($\Delta\Delta V_Z$), which was defined as the difference in ΔV_Z between the mean value for SS1 and t_{START}, to investigate the modulation of ΔV_Z in preparation to quick action.

Safety margin (SM) is the proportion of normal force exerted beyond what is required to prevent object slipping (Burstedt et al. 1999); local SM was computed for the thumb as:

$$SM_{TH} = \frac{\left(F^N_{TH} - \left|F^T_{TH}\right| / \mu\right)}{F^T_{TH}}$$

where the superscripts *N* and *T* refers to normal and tangential forces of the thumb and μ is the coefficient of static friction between the finger and sandpaper interface that was about 1.4 (previously measured, Zatsiorsky et al. 2002).

Glass-with-water task analysis

The total time (T_{WATER}) of moving the glass with water three times around four targets was measured by a stopwatch. The weight of glass with water was measured before and after the test using a scale. For further comparisons, T_{WATER} was normalized by the amount of water remaining in the glass:

$$MT_{WATER} = T_{WATER}/W_{NS},$$

where W_{NS} stands for the amount of non-spilled water.

Statistics

Standard descriptive statistics were used, and the data are presented as means and standard errors. The MVC and outcome variables of the quick force pulse production task

(ΔV_{SS}, ΔV_{SS-t_0}, and t_{ASA}) were compared between groups using a *t* test. Mixed-design ANOVAs with repeated measures were used to explore how outcome variables (EN, MT, F_G, ΔSM_{TH}, V_{UCM}, V_{ORT} and ΔV_Z) were affected by factors *Group* (PD and CS), *Finger* (*I*, *M*, *R*, and *L*), and *Phase* (phases 1, 2, and 3; phases 1 and 2 for F_G and ΔSM_{TH} comparisons). The data were checked for violations of sphericity, and Greenhouse–Geisser criterion was used to adjust the degrees-of-freedom when necessary. Pair-wise comparisons were performed with Bonferroni corrections to explore significant effects of ANOVAs.

The relationship between ΔF_{TH}^N and ΔF_{TH}^T in PD and CS was explored by linear regression, with ΔF_{TH}^T as the dependent variable. The difference between the groups was tested using a dummy variable (0/1) identifying the PD subjects (Gujarati 1970). In the first multiple regression analysis, the dummy variable and ΔF_{TH}^N are independent variables. If the regression coefficient of the dummy variable is significant, the intercepts are significantly different between groups. To test slopes, the same analysis was done with the addition of the interaction term to the model. In these analyses, the slopes of the two lines are different if the regression coefficient of the interaction term is significant.

Pearson correlation coefficients were used to determine significant relationships between variables. For some analyses, we excluded phase 3 results for computational reasons. All statistical tests were performed with SPSS 19.0 (SPSS Inc, Chicago, IL, USA).

Results

Pressing tasks

Maximal voluntary contraction (MVC) and enslaving

Maximal force values (MVC) produced by the patients with PD were smaller than those produced by the healthy controls, on average by 24 % ($p < 0.05$). These data are presented in Table 2. Both groups showed substantial force production by the non-task fingers during single-finger ramp force production tasks. The enslaving index (*EN*) in the PD group was larger than in the CS group (Table 2). These findings were supported by a two-way repeated measures ANOVA on *EN* with factors *Group* (PD and CS) and *Finger* (*I*, *M*, *R*, and *L*), which showed significant main effects for *Group* [$F_{[1,14]} = 6.15$, $p < 0.05$] and *Finger* [$F_{[3,42]} = 21.17$, $p < 0.001$] without other effects. Post hoc comparisons confirmed that $EN_I < EN_M$, $EN_L < EN_R$ ($p < 0.05$).

Multi-digit synergies and ASA in quick force pulse production

During the steady-state phase of the pressing task, both PD and CS groups showed higher magnitudes of variance in the finger mode space compatible with unchanged total force (V_{UCM}) as compared with variance that affected total force (V_{ORT}). V_{UCM} was lower, and V_{ORT} was higher in the PD group. These effects were confirmed with a two-way repeated measures ANOVA with factors *Group* and *Variance*, which showed significant effects of *Variance* [$F_{[1,14]} = 52.16$; $p < 0.001$] and *Group* × *Variance* [$F_{[1,14]} = 4.83$; $p < 0.05$].

The difference between V_{UCM} and V_{ORT} differed between the two groups resulting in a significant group difference in the synergy index, ΔV. The magnitude of the log-transformed ΔV, ΔV_Z, at steady state in the PD group was smaller than in the CS group, on average by 28 % ($p < 0.05$; see Table 2).

Prior to the force pulse initiation, ΔV_Z showed a decline starting about 100–200 ms prior to t_0. The magnitude of the drop in ΔV_Z was smaller in the PD group, on average by 60 % ($p < 0.05$). The CS group showed an earlier initiation of the drop in ΔV_Z in preparation to the force pulse as compared to the PD group; this difference was on average about

Table 2 Performance characteristics for pressing tasks

	MVC	Enslaving				Quick force pulse				
	(*N*)	EN_I	EN_M	EN_R	EN_L	V_{UCM}	V_{ORT}	ΔV_{SS}	ΔV_{SS-t_0}	t_{ASA} (s)
PD										
Mean	68.9	0.041	0.070	0.103	0.052	0.12	0.03	1.68	0.30	−0.10
SE	7.7	0.009	0.016	0.015	0.014	0.04	0.02	0.11	0.10	0.05
CS										
Mean	90.8	0.014	0.036	0.065	0.038	0.17	0.01	2.33	0.76	−0.20
SE	6.4	0.005	0.012	0.010	0.006	0.03	0.00	0.10	0.09	0.02

Means and standard errors (SE) of maximal voluntary force (MVC), enslaving indices (EN), variance indices (V_{UCM}, V_{ORT}, and ΔV_Z) at steady state, magnitude (ΔV_{SS-t_0}), and time (t_{ASA}) of anticipatory synergy adjustments (ASA) are presented

I index, *M* middle, *R* ring, *L* little fingers, *PD* Parkinson's disease group, *CS* control group

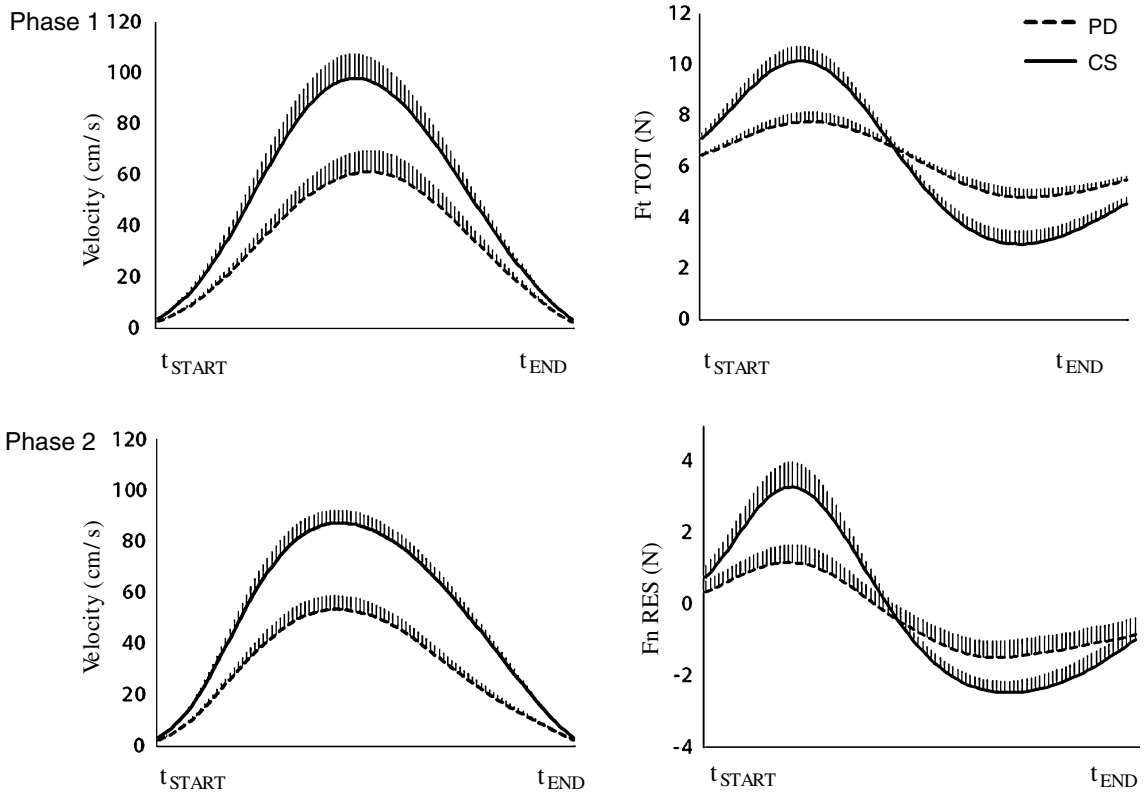

Fig. 2 Time profiles of movement velocity, sum of tangential forces ($F_{t\,\mathrm{TOT}}$) in *phase 1*, and resultant force ($F_{n\,\mathrm{RES}}$) in *phase 2*. Averaged values across subjects for the PD and CS groups are presented with standard error shades from the initiation (t_{START}) to the termination (t_{END}) of movement in each phase. The data between t_{START} and t_{END} were re-sampled to 100 points

50 %, but due to the large inter-subject variability the group effect was not significant.

Prehension task

Performance indices

Patients with PD performed the handle manipulation task slower than the CS group. Movement times (MT) in the PD group were longer than in the CS group, on average by 57 % for phase 1 (0.72 ± 0.06 s in PD and 0.46 ± 0.03 in CS), 83 % for phase 2 (1.06 ± 0.11 s in PD and 0.58 ± 0.05 in CS), and 83 % for phase 3 (0.75 ± 0.08 s in PD and 0.41 ± 0.04 in CS). These findings were supported by a two-way repeated measures ANOVA on *MT* with factors *Group* and *Phase*, which showed significant main effects of *Group* [$F_{[1,14]} = 25.22$, $p < 0.001$] and *Phase* [$F_{[2,28]} = 14.27$, $p < 0.01$] without interactions. Post hoc comparisons confirmed that MT in phase 2 was longer than MT in phases 1 and 3 ($p < 0.001$). The *MT* difference also was reflected in different magnitudes of the peak velocity in the two groups (Fig. 2, left panels).

During steady states, magnitude of grip force (F_{G}, estimated as the normal force produced by the thumb; $\Delta F^{N}_{\mathrm{TH}}$) was slightly higher in PD. For phase 1, F_{G} was 14.8 ± 1.1 N in the PD group and 13.7 ± 1.6 N in the CS group. For phase 2, F_{G} was 16.6 ± 1.3 N in the PD group and 15 ± 1.7 N in the CS group. These differences, however, were not statistically significant. Modulation of F_{G} during movements (ΔF_{G}) was significantly smaller in the PD group as compared to the CS group (Fig. 3). The modulation was quantified using peak-to-peak change of F_{G} during the movement in phases 1 and 2 for each trial. These observations were supported by a two-way repeated measures ANOVA with factors *Group* and *Phase* (phases 1 and 2), which showed significant main effects of *Group* [$F_{[1,14]} = 5.25$, $p < 0.05$] and *Phase* [$F_{[1,14]} = 19.89$, $p < 0.05$] without a significant interaction.

Further, we explored the relationship between ΔF_{G} and modulation of the thumb tangential force (ΔF^{T}) in the two groups. Phase 1 data averaged across trials within a subject were used for linear regression analysis. There was a significant correlation between ΔF_{G} and ΔF^{T} in each of the groups. The linear regression equations are shown with coefficients of determination in Fig. 4. Both slopes and intercepts of the regression lines were significantly different between the groups ($p < 0.05$).

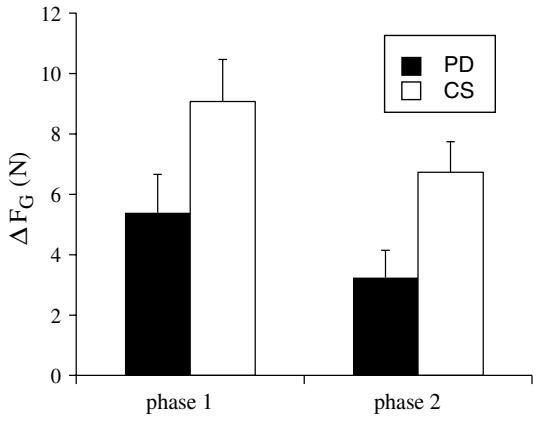

Fig. 3 Peak-to-peak grip force during the movement (ΔF_G) for phases 1 and 2 in control (CS, *white bars*) and Parkinson's disease (PD, *black bars*) groups. Group means are shown with standard errors

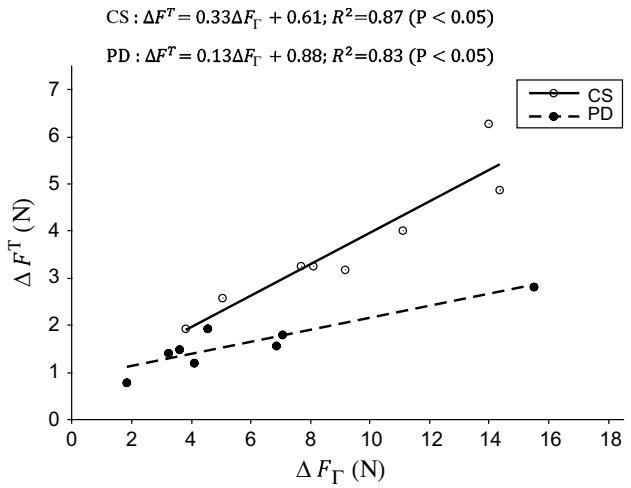

Fig. 4 The relationship between the changes in the grip force (ΔF_G) and thumb tangential force (ΔF^T) during phase 1 for the two groups, control (CS) and Parkinson's disease (PD). Each point represents the averaged value across trials within each subject. Linear regression equations are shown for the PD and CS groups separately, along with the coefficients of determination (R^2)

Safety margin

Local safety margin for the thumb (SM_{TH}) was computed for each subject, each trial, and at each time sample of phases 1 and 2. During SS1, the PD group showed overall higher SM_{TH} values as compared to the CS group. During the movement, however, the PD group showed a smaller modulation of SM_{TH} and, as a result, the peak SM_{TH} values were lower in PD subjects. The averaged across-subjects time profiles of SM_{TH} for phase 1 are presented in Fig. 5. The magnitude of change in SM_{TH} (ΔSM_{TH}) was computed within each phase; ΔSM_{TH} in the PD group was

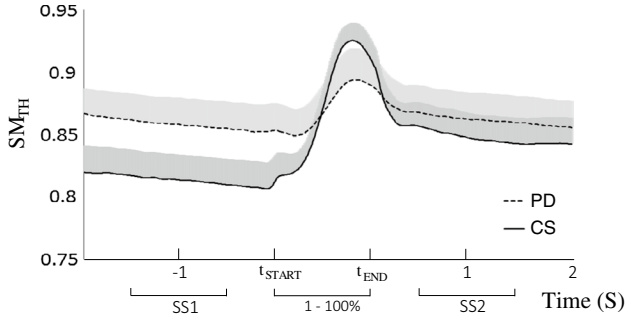

Fig. 5 Safety margin for the thumb plotted against time for the control (CS) and Parkinson's disease (PD) groups. Averaged values across subjects within each group are presented with standard error shades over the first steady state (SS1), between the initiation of movement (t_{START}) and the termination of movement (t_{END}) re-sampled to 100 points, and over the second steady state (SS2). Note the higher SM values and smaller magnitude of modulation in the PD group

lower by 71 % in phase 1 and by 69 % in phase 2. These findings were supported by a two-way repeated measures ANOVA on ΔSM_{TH} with factors *Group* and *Phase* (phases 1 and 2), which showed a significant main effect of *Group* [$F_{[1,14]} = 13.85$, $p < 0.05$] without other effects.

Multi-digit synergies and anticipatory synergy adjustments

Multi-digit synergies were quantified using an index (ΔV_Z) that was computed at each of two levels of hierarchy, the VF–TH and IF levels, for three performance variables, normal force ($\Delta V_Z F^N$), tangential force ($\Delta V_Z F^T$), and total moment of force ($\Delta V_Z M_{TOT}$). The mean ΔV_Z values of two steady states averaged across subjects within each group are shown in Fig. 6.

At the VF–TH level, the log-transformed synergy indices were positive for all three variables during steady states in all phases and in both groups. These indices were smaller in the PD group compared with the CS group, with particularly larger differences in $\Delta V_Z F^N$ and $\Delta V_Z F^T$. These findings were confirmed by a significant effect of *Group* in a two-way ANOVA on $\Delta V_Z F^N$ [$F_{[1,14]} = 7.34$, $p < 0.05$] and on $\Delta V_Z F^T$ [$F_{[1,14]} = 7.16$, $p < 0.05$]. The effects of *Phase* also were significant for both indices, [$F_{[2,13]} = 26.1$, $p < 0.001$] and [$F_{[2,13]} = 85.73$, $p < 0.001$], respectively. There were no interaction effects.

At the IF level, $\Delta V_Z F^T$ and $\Delta V_Z M_{TOT}$ were consistently positive, whereas there were some negative values for $\Delta V_Z F^N$ in both groups. The $\Delta V_Z F^T$ and $\Delta V_Z M_{TOT}$ indices in the PD group were smaller compared with the CS group, although $\Delta V_Z F^N$ was larger in PD subjects. ANOVAs showed a significant effect of *Group* only for $\Delta V_Z M_{TOT}$ [$F_{[1,14]} = 6.72$, $p < 0.05$]. The effects of *Phase* were significant for all variables; $\Delta V_Z F^N$ [$F_{[2.13]} = 9.07$,

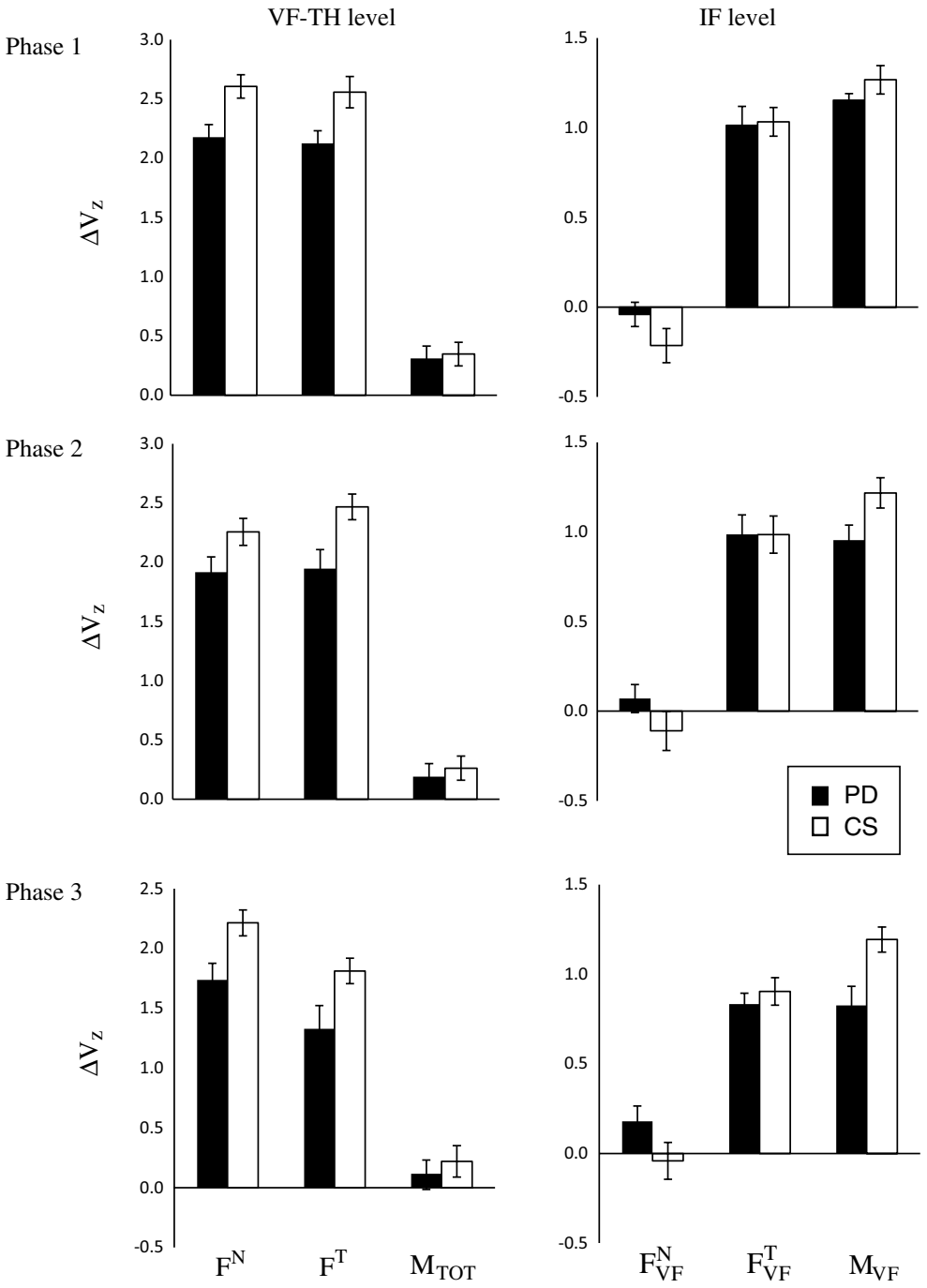

Fig. 6 The synergy index (ΔV_Z) during the steady states averaged across subjects within each group (*CS* control subjects; *PD* Parkinson's disease) at each of the two levels of hierarchy, the VF–TH level and IF level, for three performance variables: normal force (F^N), tangential force (F^T), and total moment of force (M_{TOT} and M_{VF}). Group means with standard *error bars* are shown

$p < 0.05$], $\Delta V_Z F^T$ [$F_{[2.13]} = 7.25$, $p < 0.05$], and $\Delta V_Z M_{TOT}$ [$F_{[2,13]} = 5.34$, $p < 0.05$]. There were no interaction effects.

The PD group showed signs of an impaired ability to adjust synergies in preparation to a quick action (ASA). For phase 1, the magnitude of drop in ΔV_Z before the vertical movement initiation ($\Delta\Delta V_Z$, see "Methods") was quantified for F^T at the VF–TH level. This index was lower in the PD group compared to the CS group by 59 % (0.40 ± 0.11 in PD; 0.97 ± 0.20 in CS, $p < 0.05$, t test). We also found a significant negative correlation between *MT* of phase 1 and $\Delta\Delta V_Z$ across all subjects ($r = -0.68$, $p < 0.05$).

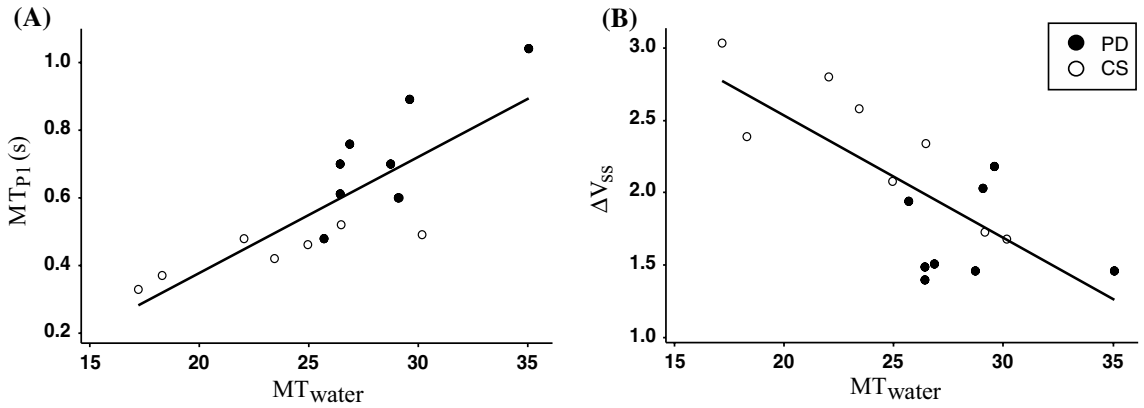

Fig. 7 The correlations between normalized movement time during the "glass-and-water" test (MT_{water}) and movement time during phase 1 (MT_{P1}) in the prehension task (**a** $r = 0.80$, $p < 0.001$), and also with the synergy index at the steady state (ΔV_{SS}) in the pressing task ($r = -0.74$, $p < 0.05$). The correlations were computed over all subjects from both groups, controls (CS) and Parkinson's disease (PD)

When synergy indices were compared between the pressing and prehension tasks, significant correlations were observed only between the indices in the pressing task computed for the normal finger force and in the prehension task for the tangential force ($\Delta V_Z F^T$). In particular, ΔV_Z in the pressing task showed positive correlations with $\Delta V_Z F^T$ computed at the VF–TH level in all three movement phases ($0.53 < r < 0.63$, $p < 0.05$). In contrast, when $\Delta V_Z F^T$ was computed at the IF level, the correlations with ΔV_Z in the pressing task were similar in absolute magnitude but negative. No significant correlation between ΔV_Z in the pressing task and ΔV_Z indices computed for the normal force and moment of force in the prehension task were observed.

Glass-with-water test

Movement time in the glass-with-water test was longer in PD subjects compared to CS (16.5 ± 0.7 and 13.0 ± 4.2 s, respectively), with the difference approaching significance ($p < 0.06$); the amount of water spilled was similar between the two groups, although slightly higher in PD (13.8 ± 1.0 ml) compared to the CS group (13.3 ± 5.9 ml). When movement time was normalized by the amount of water that was not spilled, the resulting index (normalized movement time, MT_{WATER}) was significantly longer in PD subjects (28.4 ± 1.1) compared to CS (23.9 ± 1.7, $p < 0.05$). There were significant correlations between MT_{WATER} and movement times recorded during the prehensile handle manipulation test. This was true for MT indices over all three phases: phase 1 (MT_{P1}) ($r = 0.80$, $p < 0.001$), phase 2 (MT_{P2}) ($r = 0.71$, $p < 0.05$), and phase 3 (MT_{P3}) ($r = 0.55$, $p < 0.05$). An example of this correlation is presented in Fig. 7a. Note that, whereas the data for all subjects fit the same regression line, the PD group data show consistently longer MT values.

MT_{WATER} also correlated negatively with synergy indices computed for the pressing task. In particular, significant correlations were observed between MT_{WATER} and the synergy index during steady state prior to force pulse production (ΔV_{SS}; illustrated in Fig. 7b; $r = -0.74$, $p < 0.05$) and with the overall drop in the synergy index during ASA (ΔV_{SS-t_0}; $r = -0.56$, $p < 0.05$). Whereas the indices of performance and synergy indices showed significant correlations, the UPDRS scores failed to show significant correlations with any of the measured and computed indices ($p > 0.4$ for Pearson's test; $p > 0.2$ for Spearman's test).

Discussion

The data provide support for most of the hypotheses formulated in the Introduction. In particular, patients with PD moved slower than the controls in the prehension test (the "glass-with-water" test produced results just under the significance level), reflecting bradykinesia typical of PD. The patients also showed lower finger force (MVC) and higher indices of enslaving, indicating impaired individualized control of fingers (similar to the results of Park et al. 2012). Taken together, these findings support our Hypothesis 1. The patients showed lower synergy indices during steady states in the pressing task and also for most analyses performed during the prehension task in support of Hypothesis 2. These differences were seen at both levels of the assumed hierarchy controlling the hand action (cf. Arbib et al. 1985; Zatsiorsky and Latash 2008) and with respect to both forces and moments applied to the handle.

Whereas anticipatory synergy adjustments (ASAs, Olafsdottir et al. 2005) were significantly delayed and reduced in the PD group in the pressing task, as expected based on earlier studies (Park et al. 2012, 2014), the findings in the

prehension task were less consistent. Only one variable, the tangential force, showed significantly reduced ASAs in the PD group, whereas analysis with respect to other variables showed no clear ASAs in either group. As a result, Hypothesis 3 has been supported in data from the pressing task, whereas the prehension task produced ambiguous findings.

Synergy indices correlated between the pressing and prehension tasks, as predicted by Hypothesis 4. The pattern of these correlations was unusual such that F^N in pressing correlated with F^T in prehension, although the correlation was positive at the task VH–TF level and negative at the IF level. We are encouraged particularly by the correlations between synergy indices in the pressing task with performance indices in both the prehension task (movement time) and the functional "glass-with-water" test (normalized movement time). These correlations suggest that a simple test of a multi-finger synergy in a constrained task and associated ASAs predicts changes in hand performance in object manipulation tasks. These results are in contrast to the lack of significant correlations of any of our indices with UPDRS scores.

Changes in motor synergies in PD

A number of studies on PD patients have reported impaired motor coordination in early PD, with some of the changes reflecting more general signs such as bradykinesia and tremor (Bertram et al. 2005; Fradet et al. 2009; Brown and Almeida 2011). One of the main goals of our line of research has been to introduce an objective, quantitative method for measuring impaired motor coordination. Based on recent data (Park et al. 2012, 2013a, 2014) and this work, we are confident that the analysis of motor synergies is such a method that is highly sensitive to effects of PD, even at its early stages and when the patients are on their prescribed medication.

The word *synergy* has been used in the movement science literature in at least three different ways. First, in clinical studies, particularly those of patients after stroke, synergy commonly means a stereotypical pattern of muscle activation (such as, flexor synergy and extensor synergy) interfering with the production of functional movements (Bobath 1978; DeWald et al. 1995). Second, frequently, this term implies groups of variables, kinematic, kinetic, or electromyographic, that show parallel changes over the task execution or over changes in task parameters (d'Avella et al. 2003; Ivanenko et al. 2004; Ting and Macpherson 2005). The organization of large sets of variables into synergies has been assumed to reduce the number of variables manipulated by the central nervous system and to alleviate the problem of motor redundancy (Bernstein 1967). Our third definition implies that synergy represents a neural organization providing for task-specific stability of actions by multi-element systems (Schöner 1995). Stability is paramount for everyday functional movements given that the external conditions of movement execution are never the same and frequently unpredictable. Hence, having appropriate synergies stabilizing salient performance variables is a prerequisite for successful movements (reviewed in Latash 2008).

Studies on the structure of variance in a redundant space of elemental variables (e.g., joint angles, digit forces, etc.) over repetitions of a motor task have been used to quantify synergies. This method, based on the uncontrolled manifold (UCM) hypothesis (Scholz and Schöner 1999), has been able to detect changes in motor synergies with atypical development, healthy aging, fatigue, and exercise (reviewed in Latash et al. 2007; Latash 2008).

A number of studies have linked PD to changes in movement variability and stability. In particular, the magnitudes of the variability measures were significantly correlated with the severity of PD in reach-to-grasp movements (Alberts et al. 2010; Rand et al. 2014). Our earlier studies have shown that changes in the magnitude of variability in PD are associated with significant changes in the structure of variance during a relatively artificial, constrained pressing task (Park et al. 2012, 2013a, b). The current study for the first time extends these findings to a less constrained object manipulation task designed to simulate motion of a handheld object (e.g., a glass with water). The new task was associated with expanding the analysis to more performance variables (normal force, tangential force, and moment of force) and also to two levels of analysis (VF–TH and IF levels) assumed based on earlier studies of the hand (reviewed in Arbib et al. 1985; Zatsiorsky and Latash 2008). Most of the analyses showed multi-digit synergies stabilizing relevant performance variables that were weaker in PD compared to control subjects. This was reflected in the smaller synergy indices (ΔV) computed for the performance variables.

Another major difference between the two subject groups was seen in task phases, which required the subjects to produce a quick action associated with a quick change in some of the performance variables. During the pressing task, a drop in the synergy index stabilizing total force was seen prior to the first detectable change in the force (ASA, Olafsdottir et al. 2005). This was true for both groups, but control subjects showed significantly earlier ASAs compared to the PD group (as in Park et al. 2012). In addition, the magnitude of the drop in the synergy index was larger in the control group. A similar group difference was seen in the prehension task but only for one of the three performance variables (tangential force) analyzed at the upper level of the assumed hierarchy (the VF–TH level). Other variables showed no clearly identifiable ASAs, possibly because the actions were not associated with fast enough

changes in those variables. Note that the assumed function of ASA is to phase out synergies stabilizing a variable in preparation to its quick change (Zhou et al. 2013); ASAs may not be needed if the variable does not change quickly.

The two main findings may be viewed as reflections of two components of the impaired control of stability in PD, weaker synergies reflecting lower stability of performance variables, and delayed (also reduced) adjustments in preparation to a quick action. Qualitatively similar (and, in some comparisons, correlated) findings in the pressing and prehensile tests suggest a general impairment that may be expected to lead to behavioral consequences across a range of motor tasks. Note that low postural stability is one of the cardinal features of PD and low movement stability also has been reported (Oates et al. 2013).

ASAs represent a specific example of feed-forward motor control. There have been reports on impaired feed-forward control in PD, including reduced anticipatory postural adjustments in postural tasks and during gait (Traub et al. 1980; Pieruccini-Faria et al. 2013; Fernandez et al. 2013) and reduced grip force adjustments in preparation to an action involving a quick motion of a handheld object (Gordon et al. 1997; Muratori et al. 2008). Significantly reduced ASAs in PD may have strong implications for some of the disabling features of this disease. For example, making a step requires destabilization of posture associated with a specific pattern of motion related to the center of pressure (Crenna and Frigo 1991). This loss of postural stability may be reflected formally in ASAs computed with respect to synergies stabilizing the center of pressure coordinate during quiet standing (Klous et al. 2011; Krishnan et al. 2011). Hence, reduced ASAs may lead to problems with step initiation reflected in episodes of freezing of gait typical of PD (Giladi et al. 1992). Note that "postural inflexibility" has been recently invoked as a possible contributor to freezing of gait (Smulders et al. 2014). *Inflexibility* in our framework implies reduced use of flexible involvement of the elements to perform the task and may be reflected in lower amounts of variance within the corresponding uncontrolled manifold (V_{UCM}) leading to lower synergy indices. As a result, both lowered synergy indices and reduced ASAs may be viewed as potential markers for episodes of freezing in PD (*vide infra*).

Neurophysiology of synergies is all but unknown. Several studies have emphasized the importance of subcortical structures in motor synergies, in particular of the loops involving the basal ganglia and cerebellum (reviewed in Wu and Hallett 2013) as well as of the brain stem (Hacker et al. 2012). Several recent brain-imaging studies have suggested cerebellar involvement in PD (Yu et al. 2007; Wu et al. 2011), as well as involvement of other brain structures including cortical areas (Planetta et al. 2014). 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). Consistent with this view, we found that patients with MSA-P (Park et al. 2013b) also display a significant reduction in synergy indices. Sensitivity of synergy indices to dopaminergic drugs (Park et al. 2014) supports the importance of cortico–striato–thalamo–cortical pathways in motor synergies. Our observations are compatible with the general view that PD leads to changes in the functioning of several loops involving subcortical structures, all contributing to loss of stability of motor actions.

Multi-digit synergy indices and the hand function

A number of changes in the indices of motor performance in our tasks may be viewed as potential contributors to the changed hand function. As in earlier studies (Park et al. 2012, 2013a, 2014), we saw decreased maximal finger forces and larger indices of unintentional force production in PD (larger enslaving, Zatsiorsky et al. 2000). Bradykinesia typical of PD (cf. Teo et al. 2013) was reflected in slower performance in both the prehension task and the "glass-with-water" test. In addition, our subjects showed a change in their use of grip force and its adjustments during object manipulation. These changes involved higher grip force and its poor modulation (cf. Gordon et al. 1997; Gorniak et al. 2013).

Whereas the mentioned changes may be specific to the pressing task and, by themselves, not limiting performance in everyday functional tasks, changes in the synergy indices observed in both pressing and prehension tasks potentially may reflect a global impairment within the central nervous system affecting a range of hand actions and potentially affecting performance of other tasks that do not rely on the hand function.

The first study reporting impaired multi-finger synergies in PD failed to find significant correlations between the indices of synergies, such as ΔV and indices of ASAs, and UPDRS scores. A later study of a group of patients with a mixture of parkinsonian and cerebellar signs (MSA-P) found rather strong correlations between the synergy indices and UPDRS scores (Park et al. 2013b), possibly due to the much broader range of UPDRS scores in these patients. It is also possible that involvement of cerebellar circuitry contributed to the significant correlations in that study. Our current study also used patients at a relatively early stage of PD (stage I–II according to the Hoehn and Yahr scale) tested on their optimal medications. Once again, we failed to detect any significant correlations between our outcome indices (both behavioral and synergic) and UPDRS scores. This may be due in part to the narrow range of UPDRS

scores and mild nature of motor disability in the study subjects, similar to our previous study (Park et al. 2012). In addition, UPDRS is a composite of several subjective evaluations of motor functions (from finger to whole body movements). Objective functional hands tests may be more relevant to our synergy indices.

Whereas there are several broadly used functional hand tests, these typically are sensitive to more serious impairment of hand function (such as the Jebsen–Taylor test) or reflect the ability to perform precision manipulations (such as the Pegboard test). We decided to introduce a test that would have several important features. First, we wanted it to reflect hand function in a typical everyday motion. Second, we designed the test to require stability of hand performance. Third, we intended it to be natural, easy to perform, and easy to quantify. Based on these requirements, we came up with the "glass-with-water" test. Note that this test requires stabilization of the glass in a vertical orientation at all times. Indeed, the performance index in this test (normalized movement time) correlated significantly with both performance indices in the tests (e.g., MT in the prehensile task) and the synergy and ASA indices (such as ΔV_Z and $\Delta\Delta Vz$) in the pressing task. We conclude that synergy and ASA indices are linked to changes in hand functional performance. This conclusion has to be viewed as tentative, until a broader range of tasks is studied.

Changes in multi-digit synergies as a potential biomarker of subcortical disorders

As mentioned in the Introduction, changes in hand function are among the relatively early symptoms of PD (McLennan et al. 1972; Viviani et al. 2009). Our previous studies showed significant changes in multi-finger synergy indices and ASAs during pressing tasks even in patients at stage-I PD (Park et al. 2012, 2014). In those patients, no clinical signs of PD could be identified on one side of the body during a clinical examination. The cited studies showed, however, significant changes in multi-finger synergies in the apparently unimpaired hand suggesting that indices of motor synergies may turn out to be highly sensitive, early behavioral biomarkers of PD.

In the current study, we also tested PD patients at stage-II (bilateral involvement). Overall, our data support using synergy indices as sensitive biomarkers of PD motor disability. In fact, the indices obtained in the constrained pressing task showed the most reproducible and significant group differences and correlations with performance indices in the other two tasks, prehensile and "glass-with-water." The constrained nature of the pressing task contributes to less within-subject variability, which could be the cause of more reproducible findings.

An important issue is whether the synergy changes are specific to PD or can be seen in other neurological disorders. So far, there is no unambiguous answer. One of our earlier studies of patients with multi-system brain atrophy with cerebellar involvement (Park et al. 2013b) documented changes in multi-finger synergies that were qualitatively similar to those observed in PD. Along similar lines, a recent study of hand force control deficits in individuals with various subcortical disorders including PD, multiple systems atrophy, and progressive supranuclear palsy has documented many similarities across these different patient populations (Neely et al. 2013). Taken together, these studies suggest that by itself changes in finger coordination (including those reflected in synergy indices) may be a common feature of subcortical disorders. The limited available reports of synergies after stroke suggest that, despite major changes in motor performance, synergy indices may remain unchanged (Reisman and Scholz 2003).

Searching for biomarkers of early PD has been a very active field of research. Indices based on mechanical (e.g., based on derivative of acceleration, Teulings et al. 1997; Dounskaia et al. 2009) and electromyographic variables (e.g., recorded during sleep—Chahine et al. 2014 or during writing movements—Rupasov et al. 2012) have been explored as possible early signs of PD. We believe that our approach has certain advantages such as the strong theoretical foundation (the theory of synergies), direct links to such a vitally important feature of movement as its stability, and the demonstrated sensitivity of the outcome measures to early-stage PD and dopamine replacement therapy (Park et al. 2014). As a result, we remain optimistic that our method can be developed into a valuable tool for early detection of PD, despite the mentioned concerns about the specificity of the method to PD, which we hope to address in future.

Concluding comments

We would like to acknowledge a number of limitations regarding the current study. We tested the patients in the on-medication state only. This was done on purpose, to focus on the differences between the indices of digit coordination and hand function that can be detected even when the patients were on their optimal medication. On the other hand, this could contribute to the lack of correlations between our outcome measures and UPDRS scores. Another limitation is using the same task order across all subjects. This was done to minimize spurious effects that could be induced by chance by different test orders in the two groups. On the other hand, this increased the chance that accumulation of fatigue could affect performance in later tests, such as the "glass-with-water" test. We would like to note, however, that all the pressing and handle-motion tests were not fatiguing, and the subjects always

had plenty of rest in-between tests. The "glass-with-water" test included only one trial involving three revolutions over the four targets. This was done for practical reasons, to limit the total testing time. More reliable results could be expected with multiple trials.

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