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Systemic effects of deep brain stimulation on synergic control in Parkinson's disease

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Abstract

Objective—We explored effects of deep brain stimulation (DBS) in patients with Parkinson's disease (PD) on the synergic control of fingers in a multi-finger force production task and of muscles in a task involving vertical posture.

Methods—The finger task involved the four fingers of a hand producing accurate total force followed by a targeted quick force pulse. The postural task involved releasing a load from extended arms. The analysis of synergies was performed within the framework of the uncontrolled manifold hypothesis.

Results—DBS led to no significant changes in indices of stability during steady-state phases. In contrast, DBS improved indices of agility, quantified as anticipatory synergy adjustments that reduced stability of salient performance variables in preparation to their quick change. There were moderate-to-strong correlations between indices of both stability and agility measured in the multi-finger force production and multi-muscle whole-body action.

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Disclosures

No conflicts of interest are claimed by any of the authors.

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Conclusions—Our results point at systemic changes in synergic control in PD. They show that DBS is effective in improving only one components of synergic control related to agility in performance being relatively ineffective for the stability component.

Significance—The results show systemic brain mechanisms of synergies and suggest differential effects of DBS on indices of stability and agility.

Keywords

Parkinson's disease; synergy; deep brain stimulation; stability; agility

Introduction

Deep brain stimulation (DBS) of nuclei within the basal ganglia, typically the subthalamic nucleus and globus pallidus, has been used as an effective treatment of Parkinson's disease (PD), commonly in combination with dopamine-replacement medications (reviewed in Kalia et al., 2013; DeLong and Wichmann, 2015). Many studies have reported significant positive effects of DBS on clinical indices such as Unified Parkinson's Disease Rating Scale (UPDRS) scores and general characteristics of movements such as maximal force, peak velocity, and movement time (Brown et al., 1999; Alberts et al., 2008; Daneault et al., 2016). In contrast, effects of DBS on motor coordination have been ambiguous, with some reporting positive effects, whereas others reporting negative or no effects (Alberts et al., 2008; Schettino et al., 2009; Israeli-Korn et al., 2013; Collomb-Clerc and Welter, 2015; Daneault et al., 2016). This controversy likely reflects a different understanding of coordination and methods of its assessment across studies.

Recently, a theory of synergic control of motor function has been developed (reviewed in Latash, 2016) that allows objective quantitative analysis of stability and agility of multi-effector movements, which both are impaired in PD (reviewed in Latash and Huang, 2015). In this context, stability of a performance variable refers to its relatively small deviations from a desired magnitude or time profile in the presence of relatively large deviations of the elements. Agility refers to an ability to change a performance variable quickly, which requires attenuating its stability in preparation to such an action. We assume that the central nervous system organizes multiple elements (e.g., muscles, joints, or digits) into task-specific groups, termed *synergies*, stabilizing the production of salient performance variables (e.g., center of pressure coordinate during standing, hand trajectory during reaching, and resultant force during pressing and prehensile tasks). The theory is based on a physical (physiological) approach to motor control; it accepts the principle of abundance (Gelfand and Latash, 1998; Latash, 2012), which views the apparently redundant sets of elements at any level of analysis of human movements not as a source of computational problems, but as a powerful design that allows ensuring task-specific stability of various salient performance variables.

Several recent studies have documented impaired synergies in early-stage PD even when the clinical examination failed to detect motor impairment (Park et al., 2012; Falaki et al., 2016). For example, impaired synergic control of both hands has been shown in patients with PD signs on only one half of the body (HY stage I, Hoehn and Yahr, 1979), whereas impaired

control of vertical posture has been documented in patients without clinically identifiable postural instability (HY stage II). Problems in synergic control of the hand also have been documented in healthy persons at elevated risk for parkinsonism (professional welders, Lewis et al., 2016).

Deficits in the synergic control in PD are two-faceted (reviewed in Latash and Huang, 2015). During steady-state tasks, PD patients typically show reduced synergy indices interpreted as decreased stability of the salient performance variables. During preparation to a quick action from steady state, PD patients show reduced adjustments in synergy indices (anticipatory synergy adjustments, ASAs, Olafsdottir et al., 2005) interpreted as reduced agility. Both types of impairment are sensitive to dopamine replacement drugs (Park et al., 2013; Falaki et al., 2017). These studies explored multi-finger and whole-body tasks, and showed improved indices of movement agility and stability on dopamine-replacement medication. The current study had two main aims.

First, we explored effects of DBS on indices of synergic control. We expected DBS to improve both stability of steady-state actions and agility in preparation to a quick action as reflected in the synergy index and ASAs (first hypothesis). To explore generality of the effects of DBS, we used two contrasting tasks, accurate force production by the hand and multi-muscle control of whole-body actions, performed in the DBS-on and DBS-off states.

The second aim was to explore indices of synergic control in a group of PD patients across dissimilar tasks that span the spectrum of everyday actions: multi-finger accurate force control and multi-muscle whole-body tasks involving vertical posture. We expected the deficits to be systemic based on the idea of distributed processing modules involving the basal ganglia (Houk, 2005) that likely are shared across effector systems and tasks. This prediction also is corroborated by earlier studies showing generality of the phenomena of freezing in PD (Nieuwboer et al., 2009; Vercruysse et al., 2014; Heremans et al., 2015); note that ASA deficits have been discussed as possible contributors to freezing (Latash and Huang, 2015). As such, our second hypothesis was that synergic indices of stability and agility would co-vary between the two tasks with and without DBS. Note that the second hypothesis is independent of the first one. Indeed, synergic indices measured in the two tasks can co-vary across participants without significant effects of DBS; if DBS is effective, by itself this does not ensure co-varied changes in the synergic indices between the two tasks.

To confirm the differences in the synergic control between PD patients with implanted DBS and healthy age-matched controls, we also compared indices of stability and agility obtained in the current study with similar indices obtained from healthy controls in previous studies (Jo et al., 2015; Falaki et al., 2016; Lewis et al., 2016). We expected reduced indices of both stability and agility in patients compared to controls.

Methods

Subjects

A group of 10 male PD patients (aged 61 ± 10 years, mean $\pm$ standard deviation), without any other known neurological disorders, volunteered to perform multi-finger hand tasks and

multi-muscle whole body postural tasks between 2015–2017. The modest number of participants is a reflection of our stringent inclusion criteria, in particular the ability of patients to perform the tasks (see below) in both the DBS-on and DBS-off states. We would like to admit upfront that the relatively small sample size makes the study prone to type-II statistical errors. Hence, comparisons that showed no statistically significant effects have to be viewed as preliminary and in need of confirmation in a larger study. Seven patients had bilateral DBS leads in the subthalamic nucleus and three had bilateral leads in the globus pallidus internus (see details on DBS parameters for each subject in Table 1). Patients were always on their routine schedule of oral medication and performed tasks in both DBS-on and DBS-off states (counter-balanced across patients). The levodopa equivalent daily dose (LEDD) was calculated according to a published article (Tomlinson et al., 2010) and handedness was decided upon the participants' preferential hand use during eating and writing. Only five patients were able to perform both hand and postural tasks satisfactorily because of excessive tremor preventing hand task performance and spinal deformity preventing postural task performance in some patients. Data on healthy controls who performed the same tasks in previous studies (Falaki et al., 2016; Jo et al., 2015; Lewis et al., 2016) were used. We tried to match the control and PD groups by age, as indices of synergies are affected by age (Olafsdottir et al., 2007; Shinohara et al., 2004). As far as gender matching is concerned, the previous postural study included only six men; as a result two women with the closest age to the patients were added for the comparisons. We did not expect any problems with respect to this selection, as no gender-related differences in indices of synergies were seen in previous studies of multi-finger and multi-muscle synergies. Table 1 presents the general description of patients, controls, and parameters of the DBS therapy when appropriate. All participants gave written informed consent according to the study protocol approved by the Pennsylvania State University-Hershey Medical Center Institutional Review Board.

Apparatus

Experiment 1: Hand setup—Participants sat comfortably behind a table facing a 19" monitor placed about 0.8 m away at their eye level. They rested the instructed forearm on a wooden wrist-forearm brace fixed to the table. Four PCB 208A03 single-axis piezoelectric force transducers (PCB Piezotronics, Depew, NY) were used to record vertical forces produced by the index (I), middle (M), ring (R), and little (L) fingers. Using an aluminum panel with four slots, 7.5 cm long and separated by 3 cm from each other in the medio-lateral direction, enabled adjustments of the sensor location in the anterior-posterior direction to provide comfortable positioning of the fingers for each subject and each hand. One of the two custom-made wooden pieces, designed for the left hand and the right hand, was placed underneath the palm to help maintain the inter-phalangeal joint configuration slightly flexed and constant during the course of the experiment. The top surface of each force sensor was covered with a round piece of sandpaper (300-grit) to increase friction. A velcro strap was used to hold the forearm on the wrist-forearm brace. PCB 484B06 signal conditioners (PCB Piezotronics, Depew, NY) were used to amplify force signals before sending them to a 16-bit analog-to-digital board (PCI-6225, National Instrument Corp., Austin, TX). A customized LabVIEW-based program (National Instruments Corp., Austin,

TX) was used to collect data at 200 Hz, and to provide real-time visual feedback for participants and the experimenter. Figure 1A represents an illustration of the hand setup.

Experiment 2: Postural setup—Participants stood barefoot on a force plate (OPTIMA AMTI, Watertown, MA) with their feet parallel and shoulder width apart. The foot position on the plate surface was marked and reproduced across tasks. Participants wore a safety harness affixed to the ceiling while standing on the force platform, and an experimenter stood nearby. Horizontal (F_X and F_Y) and vertical (F_Z) components of the ground reaction force and the three moments of force about the X , Y , and Z axes were recorded to compute the X - and Y -coordinates of the center of pressure (COP; Winters et al., 1996) using the force plate coordinate system (Figure 1B). Visual feedback on the COP coordinates in the anterior–posterior (COP_{AP}) and medial–lateral (COP_{ML}) direction was provided as a 0.5-cm white cursor presented on a 23" monitor mounted 1.3 m from the participants at eye level. COP_{AP} motion was shown as the up-down motion of the cursor and COP_{ML} motion was shown as the left-right motion of the cursor.

We used a 16-channel Trigno wireless system (Delsys Inc., MA) to record surface muscle electrical activity (electromyogram, EMG) of 13 leg and trunk muscles on the right side of the body: tibialis anterior (TA), soleus (SOL), gastrocnemius medialis (GM), gastrocnemius lateralis (GL), biceps femoris (BF), semitendinosus (ST), rectus femoris (RF), vastus lateralis (VL), vastus medialis (VM), tensor fasciae latae (TFL), lumbar erector spinae (ESL), thoracic erector spinae (EST), and rectus abdominis (RA). Rectangular shaped EMG sensors (37×26×15 mm, 14 g) with pre-amplifiers on the electrode heads were placed according to the published guidelines (Criswell and Cram 2011). Electrode placement was confirmed by asking participants to perform a set of isometric and isotonic contractions and observing the resulting EMG patterns. Figure 1B represent a schematic of the posture setup.

Analog EMG and force platform data were digitized at a 1 KHz sampling frequency using a PCI-6225 board and recorded by means of a customized LabVIEW-based program.

Procedures

Patients performed hand and postural tasks twice, in the DBS-on and DBS-off conditions. The order of performing hand tasks (Experiment 1) and postural tasks (Experiment 2) was counter-balanced across patients. After completing tasks in the initial DBS condition, participants were either provided with a 10-min break during which DBS state was changed or given a lunch break. A trained rater recorded Unified Parkinson's Disease Rating Scale motor scores (UPDRS-III) in both DBS conditions. The total experiment took approximately 5 hours including a lunch break in-between task conditions. Participants were encouraged to ask for additional rest intervals, drinks, and snacks as needed.

Experiment 1: Hand tasks—For each patient and DBS state, both the left hand and the right hand were tested in a random order. Prior to each trial, participants relaxed their fingertips on the sensors. During this period, sensor readings were set to zero to remove the weight of fingers from force measurements. There were three main tasks in the following order: maximal voluntary contraction (MVC), single-finger ramp force production, and quick force pulse production tasks. Prior to each task, participants performed practice trials

to get familiar with the task: typically one trial for the MVC task, 1–2 trials for the ramp task, and 5–8 trials prior to the force pulse production task. After testing one hand, there was a 5-min break before testing the other hand.

Experiment 1a: MVC task: Participants were asked to press as strongly as possible with all four fingers on the force sensors and given 8 s to reach peak force. After performing one practice trial, each participant performed two trials of the MVC task with visual feedback on the total force (F_{TOT}). There was a 30-s rest between the two trials. The trial with the higher peak force (MVC_{TOT}) was selected to define the maximal forces of individual fingers (MVC_i ; $i = I, M, R, L$). These values were used to adjust the force levels in subsequent tasks.

Experiment 1b: Single-finger ramp task: Participants pressed with one finger at a time to trace a ramp template shown on the screen while keeping all other fingertips on the sensors. This task was performed to quantify the finger force interdependence (enslaving, Zatsiorsky et al., 2000; Danion et al., 2003). The total template was 20 s long and consisted of three segments: (1) a horizontal segment for 4 s corresponded to zero force, (2) a slanted line that increased smoothly from 0% to 40% of MVC_i over 12 s, and (3) a horizontal segment for 4 s corresponding to 40% of MVC_i .

Experiment 1c: Quick force pulse production task: Each trial started by pressing and maintaining an initial force level, set at 8% of MVC_{TOT} , as steady as possible for 5 s. A vertical line at 5 s showed the point in time after which participants were allowed to produce the quick force pulse into the target set at $25 \pm 5\%$ of MVC_{TOT} in a self-paced manner. Visual feedback on the total force (F_{TOT}) was provided. The initial and target force levels were shown on the screen by two horizontal lines. Each trial lasted for 10 s with 10-s rest between trials. Participants were explicitly asked to pay attention to the quickness of the action rather than the accuracy of the force pulse level. In case of major errors such as pressing multiple times in one trial, obvious drift in force level prior to the pulse, or a very slow pulse production, the trial was repeated. A total of 24 trials were collected.

Experiment 2: Postural tasks—The postural experiment involved three main tasks in the following order: quiet standing (QS), continuous voluntary sway (VS), and load release (LR). Prior to each trial, participants were asked to stand on the force platform and maintain a standard initial foot position. Except for the QS task, participants performed a set of familiarization trials prior to each task: on average, 2–3 trials for the VS task and 4–6 trials for the LR task.

Experiment 2a: QS task: This task was performed to measure the background EMG activity of the recorded muscles during natural quiet standing. Each participant maintained the initial posture for 60 s with the arms crossed over the chest while looking at the screen without any visual feedback and trying to avoid body movements.

Experiment 2b: VS task: Each participant performed this task twice with visual feedback on both COP_{AP} and COP_{ML} . Each trial began with crossing the arms over the chest and maintaining the natural initial position, after which participants swayed at 0.5 Hz for 30 s mainly about the ankle joints in the anterior-posterior direction. A sound metronome was

used to pace the sways. Sway amplitude (6 cm peak-to-peak of COP_{AP} , centered about the initial position) was shown with two horizontal lines on the screen. There was a 30-s rest interval between trials. During each trial, participants were asked to keep their feet in full contact with the platform, avoid excessive hip and knee joints motion, and minimize movements in the medial-lateral direction as reflected by the COP_{ML} cursor motion on the screen. An experimenter always watched the performance of the participants to ensure minimal hip and knee joint involvement. Data from the VS trials were used to estimate a set of a muscle groups with co-varied EMG signals (M-modes; Krishnamoorthy et al., 2003a) and to relate changes in M-modes to COP_{AP} shifts (the Jacobian matrix; discussed in more details in data processing).

Experiment 2c: LR task: Participants held a brick-shaped load with fully extended arms (20 cm long; 1.5 kg for women and 2 kg for men) and leaned forward about the ankle joints to reach a target corresponding to a 3-cm shift of the COP_{AP} anterior to the neutral standing position. Subjects were asked to keep their posture at the target as stable as they could for about 2–3 s and then release the load in a self-paced manner by a quick, low-amplitude bilateral abduction of the arms (Aruin and Latash, 1995). Subjects repeated this task for 24 trials with 10-sec rest between trials and a 2–3 min break after each set of 12 trials.

Data processing

We processed data from the hand and postural tasks separately using customized Matlab (Mathworks Corp., Natick, MA) codes. First, we explain a general scheme of computing synergy indices. We then provide a more detailed description of the analysis for each of the experiments.

The method is based on the uncontrolled manifold (UCM) hypothesis (Scholz and Schöner, 1999); it includes computation of two components of inter-trial variance (V_{UCM} and V_{ORT}) that do and do not affect a specific performance variable (PV) produced by a set of elemental variables (EVs). Studies of multi-finger pressing tasks use finger modes as EVs and resultant force as a PV. Finger mode is a hypothetical variable reflecting a person's intent to change force by using only one digit. Because of the phenomenon of digit non-independence, such a command leads to force production by all the digits of the hand. Using modes allows removing effects of this interdependence of digit forces (Latash et al., 2001). Finger modes were defined using regression analysis across trials with accurate ramp force production while using one instructed finger at a time.

Studies of whole-body postural tasks used muscle modes (M-modes) as EVs and coordinate of the center of pressure as PV (Krishnamoorthy et al., 2003a,b). M-modes are hypothetical neural variables used for control of large muscle groups; changing a value (gain) of each M-mode leads to proportional changes in the activation levels of the involved muscles. M-modes were defined as eigenvectors in the space of muscle activations using principal component analysis with Varimax rotation and factor extraction.

The general logic of the inter-trial analysis of variance is as follows: Individual trials are aligned; variance in the space of the EVs is computed across trials for each time sample. The UCM is approximated as the null-space of the Jacobian ($\mathbf{J}$) that links small changes in EVs

to changes in the selected PV. For multi-finger tasks, $\mathbf{J}$ was computed taking into account the enslaving matrix ($\mathbf{E}$, see below). For multi-muscle tasks, $\mathbf{J}$ was found with a multiple linear regression technique. Variance in the space of EVs was computed within the UCM and within its orthogonal complement, V_{UCM} and V_{ORT} , respectively. Further, a metric (V) reflecting the difference between the two was computed: $V = (V_{UCM} - V_{ORT}) / V_{TOT}$, where V_{TOT} means the total variance and each value was quantified per degree-of-freedom in the corresponding spaces. Note that $V > 0$ implies presence of a synergy stabilizing the PV by co-variation of EVs. A larger V implies stronger synergies. $V = 0$ implies no synergy. Prior to running parametric statistics, V values were z-transformed (V_Z) to normalize the V distribution given the limits of this index imposed by its computation.

Anticipatory synergy adjustments (ASAs) were quantified using two indices, namely the magnitude of ASA (V_{ASA}) and the time of ASA initiation (t_{ASA}). The time interval between 600 to 400 ms prior to the task initiation (t_0) was considered as steady state (SS) and used to compute the mean and SD of V_Z . In Experiment-1, t_{ASA} was defined as the point in time prior to t_0 when V_Z dropped below its mean value during SS (V_{SS}) by two SDs, and V_{ASA} was defined as the difference between V_{SS} and the value of V_Z at t_0 : $V_{ASA} = V_{SS} - V_0$ for both experiments. Because of V_Z variations, t_{ASA} was defined in Experiment-2 as the point in time prior to t_0 when V_Z dropped below its mean and remained less than the mean until t_0 .

Experiment 1: Hand tasks—To avoid effects of tremor, especially in the DBS-off state, a fourth-order, zero-lag Butterworth filter was used to digitally low-pass filter the data at 4 Hz. Filtered data from the single-finger ramp task were used to define finger modes and data from the quick force pulse production task were used for variance analysis.

Defining the enslaving matrix and finger modes: Enslaving reflects the involuntary contraction of non-intended fingers when producing force with an instructed finger (Zatsiorsky et al., 2000). To quantify enslaving for each participant, a 4×4 $\mathbf{E}$ matrix was constructed using data from the single-finger ramp force production trials. In each trial, the force produced by non-intended fingers increased approximately in parallel with the force produced by the instructed finger. As a result, linear regression analysis was used for each trial to evaluate the contribution of each finger towards F_{TOT} :

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

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

where $i, j = \{I, M, R, L\}$, $F_{i,j}$ is the i -th finger force and $F_{TOT,j}$ is the total force when j represents the task finger. The first and last seconds of each trial were excluded from regression analysis to avoid potential edge effects. Finger modes can be subsequently computed as: $\mathbf{m} = [\mathbf{E}]^{-1} \mathbf{F}$, where $\mathbf{m}$ and $\mathbf{F}$ are vectors of modes and forces, respectively.

Analysis of variance using finger modes: For each trial of force pulse production, the onset of pulse initiation (t_0 , Figure 2) was defined as the time point when the first derivative of force (dF/dt) reached 5% of its maximum value in that trial. The time to peak force (T_{Peak}) was defined as the time, with respect to t_0 , when the F_{TOT} reached its maximum value during that trial. Trials with any of the following major errors were excluded from analysis: T_{Peak} was greater than 1 s, there were multiple peaks in the force pulse, and the total force was not stabilized prior to the pulse initiation. On average 18 ± 2 trials were accepted for the DBS-off condition and 21 ± 4 trials were accepted for the DBS-on condition.

After converting force data from the accepted trials into modes, $V_{UCM,F}$ and $V_{ORT,F}$ were quantified and used to compute V_F and ASA indices. A more detailed description of variance computation can be found in an earlier publication (Latash et al., 2001).

Experiment 2: Postural tasks—Data from the force platform were digitally filtered at 10 Hz using a low-pass, fourth-order, zero-lag Butterworth filter to compute COP_{AP} coordinates according to standard methods (Winter et al., 1996). The cut-off frequency was set to 4 Hz only for one participant because of significant tremor during the DBS-off state, which caused fluctuations in the F_Z component of the ground reaction force and erroneous trial alignment.

EMG signals were filtered between 20–350 Hz (fourth-order, zero-lag Butterworth filter), rectified, and low-pass filtered using a 100-ms moving average window to detect EMG envelopes. To account for the electromechanical delay (Corcos et al., 1992), EMG signals were shifted backward by 50 ms. EMG signals were normalized (EMG_{NORM}) by subtracting the background EMG activity—from the QS task—and then dividing by the maximal EMG levels:

$$EMG_{NORM} = \frac{EMG - EMG_{QS}}{EMG_{MAX}} \quad (2)$$

where EMG_{QS} is the averaged EMG level within the {5 s; 15 s} time period of the QS task and EMG_{MAX} is the maximal activity of individual muscles across VS trials. EMG data averaged over each 50-ms time-window were used for EMG_{PEAK} computation.

Defining muscle modes and the Jacobian matrix: For each participant, EMG data from the VS trials were used to identify M-modes and subsequently to find the mapping between M-mode changes and COP_{AP} shifts. The first 3-s and the last 2-s were removed from each trial to avoid effects of action initiation and termination. The period between two successive anterior-most COP_{AP} coordinates was defined as a sway cycle. COP and EMG data from the

beginning of the first cycle until the end of the last cycle were averaged over each 50-ms time window and were used for the analyses.

Based on the Kaiser criterion (Kaiser, 1960), the first four PCs with the greatest eigenvalues were selected as M-modes after applying PCA with Varimax rotation and factor extraction on the correlation matrix of the averaged EMGs. A fixed number of M-modes were selected across groups and states, because having variable mode numbers would change the dimension of UCM space without affecting the ORT space and affect the outcome variables. Considering loadings beyond ± 0.5 as significant, all M-modes had at least one significantly loaded muscle. EMG data were multiplied by M-modes, transforming the EMG signals into the four-dimensional mode space. For each participant, the $\mathbf{J}_M$ was reduced to a vector formed by coefficients of the regression analysis between small deviations of M-mode magnitudes ($\mathbf{M}$) and changes in COP_{AP} coordinates (COP_{AP}). To remove high frequency components of $\mathbf{M}$ and COP_{AP} unrelated to voluntary sway of the whole body, a fourth-order, zero-lag Butterworth filter with 2 Hz cut-off frequency was used prior to the analysis.

$$\Delta COP_{AP} = k_1 \Delta M_1 + k_2 \Delta M_2 + k_3 \Delta M_3 + k_4 \Delta M_4 \quad (3)$$

$$\mathbf{J} = [k_1 \ k_2 \ k_3 \ k_4]$$

Analysis of APA: Anticipatory postural adjustments (APAs; Belenkiy et al., 1967; Massion, 1992) were seen prior to the self-initiated LR task. APA initiation was defined based on two methods: (1) changes in the EMG envelopes ($t_{APA,m}$) and (2) changes in the magnitude of M-modes ($t_{APA,mode}$). For each participant, the mean value and SD of EMG and the first two M-modes (ventral and dorsal M-modes) were computed during the SS period. APA initiation was defined as the time point when the averaged across trial M-mode values or muscles activation levels deviated more than ± 2 SD from their respective mean values and this deviation remained until t_0 . The time when the earliest change happened across M-modes and across muscles were selected as $t_{APA,mode}$ and $t_{APA,m}$, respectively. These values were further confirmed visually.

Analysis of variance using muscle modes: LR trials were aligned by the time when the dF_Z/dt reached 5% of its minimum value. Trials in which COP_{AP} trajectory was not stabilized prior to t_0 (COP_{AP} coordinate within 200 ms interval prior to t_0 deviated from the initial target value by more than ± 2 SD; SD was computed during SS interval), and trials with faulty EMG signals were removed from the analysis. On average, 18 ± 1 trials were accepted for the analysis in both DBS conditions. In order to perform variance analysis, normalized EMGs were transformed into M-mode space. Residual mean-free vectors of M-mode changes ($\Delta \mathbf{M}_{demeaned} = \Delta \mathbf{M} - \overline{\Delta \mathbf{M}}$) were projected onto the UCM and the ORT spaces to compute V_{UCM} , V_{ORT} , V_Z , and ASA indices. To quantify the synergy index at t_0 , we used the average of V_Z within the 51-ms time window centered about t_0 ($\approx t_0 = \{t_0 - 25 \text{ ms}; t_0 + 25 \text{ ms}\}$). A more detailed description of the variance computation can be found in earlier publications (Klous et al., 2011; Singh et al., 2011).

Statistics

Results are presented as means $\pm$ standard error (SE), unless stated otherwise. SAS 9.4 (SAS Institute Inc, Cary, NC) with mixed linear model (PROC MIXED) and compound symmetrical covariance structure, and Minitab 17.3 (Minitab Inc, State College, PA), were used to perform statistical tests. For Experiment 1, mixed-design ANOVA with repeated measures was used to test effects of *DBS* (two levels; off and on), *Hand* (two levels; left and right), and *Space* (two levels; UCM and ORT) on the main outcome variables (MVC, T_{Peak} , variance components, $V_{\text{SS,F}}$, and ASA indices). For Experiment 2, a two-way repeated measures ANOVA was used to explore effects of *DBS* and *Space* on the inter-trial variance. For all significant contrasts related to the main hypotheses, effect sizes are reported using Cohen's d and η . All other outcome variables such as R^2 , t_{APA} , $V_{\text{SS,M}}$, and ASA indices were compared using Wilcoxon's signed-rank tests. All of the aforementioned statistical tests were performed using the data from eight participants who performed both DBS-on and DBS-off tests in Experiment 1 or Experiment 2. Correlations between hand and postural synergy indices were explored using Pearson correlation coefficients. ANCOVA statistics were used with the hand synergy index as the continuous variable to explore possible relations between hand and postural synergy indices in more detail. To compare the main outcomes of Experiment 1 and 2 with healthy controls, one-way ANOVAs with factor *Group* (three levels: DBS-off, DBS-on, and controls) were used. Data were checked to satisfy statistical assumptions of normality and were transformed accordingly if needed. When necessary, degrees of freedom were adjusted using the Kenward-Roger method according to sphericity assumptions. Pairwise comparisons with Bonferroni corrections were used to explore significant main effects. For all statistical tests, significance level was set at $p < 0.05$.

Results

Experiment 1: Hand tasks

MVC and T_{Peak} —During the MVC task, patients produced similar maximal forces in the DBS-off state (67.3 ± 4.7 N) compared with the DBS-on state (68.0 ± 5.5 N). There was no statistical difference in the magnitude of MVC forces produced by the left hand (65.6 ± 4.9 N) and the right hand (69.8 ± 5.2 N). A two-way repeated measures ANOVA with factors *DBS* and *Hand* showed no significant effects. These data are presented in Table 2.

Multi-finger synergies and ASAs—Figure 2 represents the mean performance of participants in the quick force pulse test, as well as the log-transformed synergy index averaged across all participants with standard error shades. There was no significant difference in the time (T_{Peak}) to reach the peak force between the two DBS conditions. In DBS-off, T_{Peak} values were 256 ± 20 ms (left hand) and 259 ± 24 ms (right hand), whereas in DBS-on the values were 244 ± 27 ms and 269 ± 37 ms, respectively.

Positive synergy indices during SS (V_{SS}) in Figure 2 confirmed larger amounts of inter-trial variance that did not change F_{TOT} (V_{UCM}) compared with the inter-trial variance that affected F_{TOT} (V_{ORT}). A three-way ANOVA with repeated measures using factors *DBS*, *Hand*, and *Space* on the log-transformed inter-trial variance showed significant main effects of *Space* [$F_{(1,49)} = 481.2$, $p < 0.001$; $d = 3.96$ ($\eta = 0.9$)] and *Hand* [$F_{(1,49)} = 8.3$, $p < 0.01$]

with no other main effect and no interactions. Pairwise comparisons confirmed that $V_{UCM} > V_{ORT}$ ($V_{UCM} = 1.23 \pm 0.39$; $V_{ORT} = 0.012 \pm 0.002$) in both hands and DBS conditions, and also a greater amount of total inter-trial variance in the left hand (0.96 ± 0.40) compared to the right hand (0.29 ± 0.09).

Although V_{SS} was slightly higher in the DBS-on state (2.72 ± 0.10) than in the DBS-off state (2.59 ± 0.12) during SS, this difference was not significant [$F_{(1,21)} = 1.5$, $p > 0.2$]. In contrast, the drop in the synergy index prior to the force pulse initiation (ASA) showed significant effects of DBS. In particular, ASA started earlier in the DBS-on condition ($t_{ASA} = -84 \pm 23$ ms in the DBS-off state and -174 ± 24 ms in the DBS-on state), on average a two-fold difference ($F_{(1,21)} = 12.2$, $p < 0.01$). The overall drop in V_Z during the ASA was larger in the DBS-on state than in the DBS-off state (0.48 ± 0.05 vs. 0.28 ± 0.07 ; $F_{(1,21)} = 8.1$, $p < 0.01$). There were no other effects in the *Hand* $\times$ *DBS* ANOVA. In the DBS-on vs. DBS-off comparison, Cohen's d was 1.07 for V_{ASA} ($\eta = 0.47$) and -1.18 for t_{ASA} ($\eta = 0.51$). Table 2 presents the synergy and ASA indices for both hand and postural experiments in each DBS condition.

Experiment 2: Postural tasks

Defining M-modes and the J_M matrix—Four M-modes were identified using the PCA with rotation and factor extraction procedure applied to integrated EMG indices (see Methods). On average, these M-modes accounted for similar amounts of variance in DBS-off ($75.3 \pm 2.9\%$) and DBS-on ($75.1 \pm 2.9\%$) states. The first two M-modes involved significantly loaded muscles on the ventral or dorsal side of the body, respectively, and will be addressed as “ventral M-mode” and “dorsal M-mode.” The composition of these M-modes was similar in all participants regardless of the DBS status.

To explore how changes in M-modes would affect COP_{AP} coordinates, linear regression analysis was run using M as predictors of COP_{AP} shifts for each participant and DBS status. All M-modes were significant predictors of COP_{AP} regardless of DBS status ($p < 0.001$), and there was no statistically significant difference between adjusted R^2 values computed for the regression analysis of DBS conditions (OFF: 0.70 ± 0.06 ; ON: 0.68 ± 0.07).

COP displacements, EMG patterns, and APA—Figure 3 illustrates the average time profile of COP_{AP} across participants, and the ventral and dorsal M-modes across all LR trials performed by a typical participant with standard error shades for the DBS-on (panel A) and DBS-off (panel B) conditions. EMG and M-mode time profiles were highly variable among participants, which made across participant averaging impractical. On average, significant modulation was observed about 115 ms prior to t_0 in EMG envelopes (DBS-off: -113 ± 15 ms; DBS-on: -123 ± 21 ms), and about 140 ms prior to t_0 in the magnitude of the dorsal and ventral M-modes (DBS-off: -137 ± 34 ms; DBS-on: -144 ± 40 ms). Neither ANOVA nor Wilcoxon signed-rank test showed statistically significant difference in t_{APA} between the DBS-on and DBS-off conditions.

Multi-muscle postural synergies and ASAs—Inter-trial variance within the M-mode space was quantified in two spaces, V_{UCM} and V_{ORT} . There was no statistically significant

difference during SS between the two DBS conditions in either V_{UCM} (DBS-off: 0.029 ± 0.009 ; DBS-on: 0.054 ± 0.026) or V_{ORT} (DBS-off: 0.029 ± 0.008 ; DBS-on: 0.048 ± 0.021). A two-way repeated measures ANOVA ($DBS \times Space$) showed no significant effects. Similar to the finger force pulse production task, V_{SS} was slightly higher in DBS-on (0.02 ± 0.05) compared to DBS-off (-0.02 ± 0.03), but this difference was not statistically significant (Wilcoxon signed-rank test).

There were, however, significant effects of DBS on ASAs. In particular, there was a drop in V_Z prior to t_0 in DBS-on ($V_{ASA} = 0.06 \pm 0.02$) that was absent in DBS-off ($V_{ASA} = -0.03 \pm 0.04$). This effect was confirmed by the Wilcoxon signed-rank test ($p < 0.05$). In addition, ASA in DBS-on was initiated, on average, earlier ($t_{ASA} = -81 \pm 21$ ms) compared to DBS-off ($t_{ASA} = -26 \pm 14$ ms; $p < 0.05$).

Comparison across the two experiments

Data from the five participants who performed both experiments were used for across-experiment comparisons. For this comparison, we used averaged values across the left and right hands with the equivalent values measured in the postural experiment using both Pearson correlation and ANCOVA. Figure 4 presents scatter plots of V_{SS} (panel A), t_{ASA} (panel B), and V_{ASA} (panel C) across participants with the least square lines of best fit. Note the correlations between the V_{SS} indices ($R^2 = 0.58$) and between the t_{ASA} indices ($R^2 = 0.57$). These correlations were confirmed by two ANCOVAs with DBS as the main factor and multi-finger index as the continuous variable that showed significant effects on V_{SS} [$F_{(1,7)} = 8.4$, $p < 0.05$] and t_{ASA} [$F_{(1,7)} = 6.9$, $p < 0.05$] with no other effects. The correlation coefficient for V_{ASA} was lower ($R^2 = 0.29$) and not statistically significant.

Comparing results with healthy subjects from earlier publications

Multi-finger synergies—MVC forces produced by patients (averaged across the DBS conditions; right: 70.0 ± 7.4 N; left: 65.6 ± 7.0 N) were slightly lower than the MVC forces produced by controls (right: 80.1 ± 6.4 N; left: 75.9 ± 5.8 N); the difference was non-significant. Since no effect of *Hand* was observed on T_{Peak} and multi-finger synergy indices, averaged data across both hands were used for the following comparison. In the quick force pulses, patients were about 40% slower in reaching the peak force ($T_{Peak} = 257 \pm 18$ ms and 257 ± 31 ms for the DBS-on and DBS-off, respectively) than controls ($T_{Peak} = 153 \pm 10$ ms; $F_{(1,14)} > 10.0$, $p < 0.01$). Compared to controls, Cohen's d was equal to 1.59 ($\eta = 0.62$) for DBS-on and 2.47 ($\eta = 0.78$) for DBS-off.

Patients showed similar amounts of the log-transformed synergy indices, V_Z , during SS (2.59 ± 0.15 and 2.72 ± 0.12 in the DBS-off and DBS-on, respectively) compared to controls (2.49 ± 0.09). In contrast, patients showed significantly smaller and delayed ASAs compared to controls in the DBS-off condition only: $t_{ASA} = -84 \pm 29$ ms and $V_{ASA} = 0.28 \pm 0.08$ in the patients compared to $t_{ASA} = -228 \pm 17$ ms and $V_{ASA} = 0.56 \pm 0.07$ in the controls. These differences were large, by about 63% and 50%, respectively, confirmed by the significant effect of *Group* on t_{ASA} ($F_{(1,14)} = 18.1$, $p < 0.001$) and on V_{ASA} ($F_{(1,14)} = 7.1$, $p < 0.05$); compared to controls, the effect size was $d = 2.13$ ($\eta = 0.73$) for t_{ASA} and $d = -1.33$

($\eta = 0.55$) for V_{ASA} . In the DBS-on state, both ASAs indices ($t_{ASA} = -174 \pm 25$ ms, $V_{ASA} = 0.48 \pm 0.06$) were not significantly different from those in controls.

Multi-muscle synergies—Patients showed significantly smaller indices of multi-muscle synergies stabilizing COP_{AP} during SS in both DBS-off (-0.02 ± 0.03 ; $d = -1.63$, $\eta = 0.63$) and DBS-on (0.02 ± 0.05 ; $d = -1.17$, $\eta = 0.51$) conditions compared to controls (0.22 ± 0.07). These differences were confirmed by one-way ANOVAs ($F_{(1,14)} > 5.4$, $p < 0.05$) on V_{SS} . There also were significant differences in the ASA parameters between the patients and controls. In particular, controls demonstrated significantly larger values of V_{ASA} (0.23 ± 0.04) compared to both DBS-off (-0.03 ± 0.04 ; $F_{(1,14)} = 20.5$, $p < 0.001$; $d = -2.26$, $\eta = 0.75$) and DBS-on (0.06 ± 0.02 ; $F_{(1,14)} = 13.1$, $p < 0.01$; $d = -1.81$, $\eta = 0.67$). The ASAs started earlier in controls ($t_{ASA} = -97 \pm 26$ ms) compared to DBS-off (-26.0 ± 14 ms) only ($F_{(1,14)} = 6.5$, $p < 0.05$; $d = -1.21$, $\eta = 0.52$). The difference between controls and DBS-on ($t_{ASA} = -81 \pm 21$) was non-significant.

Discussion

Our first hypothesis has been supported only partly. As expected, we saw an increase in indices of anticipatory synergy adjustments (ASAs, Olafsdottir et al., 2005) in the DBS-on state compared to the DBS-off state. On the other hand, effects of DBS on synergy indices computed over the steady-state phases of the tasks were weak and under the significance level. It is possible that chronic DBS, defined as >4 months treatment, normalized synergy indices because there were no significant differences between DBS-off patients and controls in the hand task. The second hypothesis has been supported by the findings: We observed moderate-to-strong correlations between synergic indices measured in the two tasks, multi-finger force production and multi-muscle whole-body action. This was true for both indices of ASAs, which showed significant effects of DBS, and synergy indices over steady-state task phases (V), which showed no significant effects of DBS.

Impaired control of stability in PD and the effects of DBS

Stability of most everyday actions is vital given the unpredictable changes in the environment and intrinsic body states. Indeed, when the brain generates descending signals to perform an action, it is unable to predict excitability of spinal neurons and reactive forces, e.g., if the foot is about to step on a pebble (cf. Bernstein, 1935, 1967). This means that all natural actions have to be dynamically stable, i.e. able to return close to a desired trajectory under unexpected changes in conditions. The idea of synergies as task-specific mechanisms ensuring action stability (Schöner, 1995) assumes that the central nervous system (CNS) is able to arrange multiple effectors contributing to any natural action into units that ensure such stable behaviors (reviewed in Latash et al., 2007).

There are, however, situations when high stability of an ongoing action is undesirable, e.g., when one plans to perform a quick change in a salient performance variable. The phenomena of ASAs show that the CNS indeed is able to attenuate synergies in preparation to quick actions (Olafsdottir et al., 2005; Shim et al., 2005). ASAs represent an example of feed-forward control with the purpose to ensure that the body does not have to fight its own synergies stabilizing a variable to be changed.

PD and a number of other neurological disorders are associated with significant changes in both synergies during steady-state tasks and ASAs, i.e. in action stability and agility (reviewed in Latash and Huang, 2015). In contrast, stroke survivors show only minor changes in the synergy index in multi-joint reaching and multi-finger pressing tasks (Reisman and Scholz, 2003; Jo et al., 2016), whereas ASAs are delayed and reduced significantly (Jo et al., 2016). These observations suggest that stability and agility, as reflected in indices of synergies and ASAs, involve different neurophysiological mechanisms. Our study corroborates this conclusion by showing differential effects of an acute change in the DBS status on the synergy index of stability (σ_V) and agility (ASAs). In the current study, this differential effect on synergy indices was similar in PD patients who had DBS leads placed in the GPi or STN. Further studies with larger samples sizes utilizing patients with both DBS targets might provide deeper insight on the contribution of the STN and GPi to synergic control.

Recent studies have shown positive effects of dopamine-replacement medication on indices of synergic control in both multi-finger force production (Park et al., 2014) and multi-muscle whole-body (Falaki et al., 2017a) actions. In both studies, patients showed significantly weaker synergies during steady-state following the overnight withdrawal of their prescribed medication (practical off-medication state). In the study of whole-body postural tasks, this effect was due to a significant drop in the component of the inter-trial variance that had no effect on the COP coordinate (V_{UCM}). This suggests that dopamine medication may lead to a more flexible behavior contributing to the action stability without negative impact on the accuracy of the performance in patients with PD. These previous studies also documented earlier and larger ASAs in preparation to a quick action (producing a quick force pulse in the multi-finger study and releasing a load in the postural study) on-medication compared to off-medication.

Earlier studies of PD patients led to a hypothesis that reduced ASAs may reflect mechanisms that also contribute to freezing of gait and other actions (Park et al., 2012; Falaki et al., 2016). Indeed, if a person is unable to destabilize a salient performance variable with ASA in preparation to action, this variable may be too stable to show a desired change. For example, step initiation is associated with a pattern of relatively quick COP shifts with the purpose to unload the stepping foot and generate moment of force contributing to the desired body motion (Breniere and Do, 1986; Crenna and Frigo, 1991; Halliday et al., 1998). These COP shifts are mechanically necessary to make a step. If the COP coordinate is stabilized by a strong multi-muscle synergy (e.g., Krishnamoorthy et al., 2003; Wang et al., 2006), the person may be unable to produce COP shifts unless the synergy is attenuated with ASA. As a result, the person may feel “glued” to the floor and unable to initiate the step. Indeed, young healthy persons show a reduction in the synergy index stabilizing COP coordinate about 200 ms prior to step initiation (Wang et al., 2006, 2007).

A number of studies reported strong positive effects of DBS on freezing in PD (Vercruysse et al., 2014; Sidiropoulos, 2015; Schlenstedt et al., 2017). Whereas other studies reported lack of such effects or even negative effects of DBS (Marconi et al., 2008; Rocci et al., 2012; Cossu and Pau, 2017), the differences likely were due to the location of the stimulation electrodes and frequency of stimulation (reviewed in Xie et al., 2017). Our observations

carry an optimistic message showing that a potential contributor to freezing (lack of proper ASAs) can be improved by DBS.

Chronic and acute effects of DBS

To our knowledge, this study is the first to explore the effects of DBS immediately after it is re-engaged on the control of action stability. Earlier studies provided conflicting evidence with respect to the DBS effect on motor coordination. Studies showing no effects of DBS on inter-limb coordination (Daneault et al., 2016) and visuo-motor coordination (Israeli-Korn et al., 2016) contrast with reports on improved digit coordination (Alberts et al., 2004, 2008; Schettino et al., 2009; Gorniak et al., 2013) and improved coordination between the upper and lower limbs (Carpinella et al., 2007). The conflicting reports may have reflected a number of factors including the different effectors and tasks, the ambiguous local effects of DBS on the stimulated structures, and the different definitions of coordination that could emphasize aspects of temporal, spatial, or force coordination. The lack of significant effects of DBS on the synergy index (ΔV) was unexpected and rejects our original hypothesis. This is consistent with several reports of weak or absent positive effects of DBS on such symptoms as postural stability and bradykinesia (Marconi et al., 2008; Collomb-Clerc and Welter, 2015).

One important factor to consider might be the effects of chronic vs. acute DBS (for a recent review see Ashkan et al., 2017). DBS is a chronic intervention, and our patients had it for 4–48 months. It might be expected to lead to relatively stable changes in the functioning of the neural circuitry affected by the structures with DBS. In such cases, acute DBS withdrawal is not expected to lead to significant effects in variables defined by those circuits. Other circuits, however, may require ongoing DBS to show changes in respective outcome variables. Significant effects of acute DBS withdrawal may be expected on those variables.

It has been reported that some DBS effects (particularly those for dystonic signs) (Merola et al., 2013) need chronic stimulation, whereas others (such as those for tremor) (Lilleeng et al., 2015) respond to DBS immediately. In the past, we demonstrated a significant synergy decrease (ΔV) in PD subjects without DBS treatment. In the current study, we observed this difference only in the postural and not hand tests, suggesting that chronic DBS treatment (>4 months) already may have normalized the ΔV for the hand. Further studies to test synergy indices immediately before and after DBS implantation, however, are needed to test this hypothesis.

Systemic effects of PD on motor synergies

Neurophysiological mechanisms of multi-finger and multi-muscle synergies are all but unknown. Several hypotheses have been suggested to account for the typical signatures of synergies, such as structure of inter-trial variance. These include computational schemes based on ideas of optimal feedback control (Todorov, 2004; Diedrichsen et al., 2010) and physiological schemes based on feedback loops within the central nervous system (Latash et al., 2005) and from peripheral receptors (Martin et al., 2009). Likely, synergies during natural actions reflect multiple mechanisms acting at different levels of the central nervous system. For example, the system of Renshaw cells may be seen as a tunable mechanism

stabilizing the output of a motoneuronal pool (cf. Mattei et al., 2003; Hultborn et al., 2004). Indeed, if, for any reason, an alpha-motoneuron stops generating action potentials, Renshaw cells excited by the collaterals of that motoneuron's axon would stop firing and hence reduce the overall amount of inhibition on all the neurons of the pool. This would compensate, partly, for the effect of turning the original motoneuron off, i.e. stabilize the output of the pool. Similarly, negative feedback effects that dominate most spinal reflex loops may be seen as contributors to a synergy stabilizing equilibrium state of the muscle against the external load (Latash, 2010).

A generic neural scheme has been suggested as a potential mechanism for tunable synergies based on the idea of local back-coupling loops within the CNS (Latash et al., 2005). The scheme is compatible with the widespread short-latency negative feedbacks leading to lateral inhibition and surround suppression leading to characteristic “Mexican hat” patterns of excitability within neuronal pools (Fukai, 1999; Lund et al., 2003; Schoppa and Urban, 2003; Wehr and Zador, 2003; Ozeki et al., 2004). This scheme allows, in particular, for changing stability of the outcome performance variable without a change in its magnitude, i.e. it offers a feasible mechanism for ASA.

The observations of impaired synergic control in patients with disorders affecting subcortical structures, such as the basal ganglia and the cerebellum (reviewed in Latash and Huang, 2010), suggest that a different mechanism may be involved in the unimpaired synergic control of voluntary movements. This mechanism is more likely to involve multiple brain structures shared among tasks and effectors, and united into what Bernstein (1935) called operators and Houk (2005) termed distributed processing modules (DPMs). Whereas stability of posture and movement have been linked to the cerebellum and trans-cerebellar loops (reviewed in Manzoni et al., 2004), our observations suggest that loops involving the basal ganglia also may play a crucial role in the neural control of action stability, including its feed-forward control reflected in ASAs. It is also possible that the documented changes in the functioning of cerebellar loops in PD (Yu et al., 2007; Lewis et al., 2007) play an important role in impaired synergic control.

The observations of correlated changes in the synergy indices between the multi-finger force production task and multi-muscle whole-body task are highly significant. Indeed, the neural control mechanisms of prehensile tasks and vertical posture traditionally have been thought to involve different neural mechanisms, with cortical control dominating the hand function but not the vertical posture. Moreover, the definition of a synergy as a task-specific neural mechanism that unites effectors to ensure proper stability of a salient performance variable makes synergies task- and effector system-specific.

The correlations between V and ASA indices (Figure 4) suggest that there are common mechanisms of synergic control shared among tasks and effector systems. Note that the correlation was not caused by similar effects of DBS across the two tasks: indeed, it was seen between the V indices, which showed no significant improvements under DBS. These observations suggest that indices of synergic control may show natural spread among humans and represent a person-specific “signature” reflected among a spectrum of actions.

This hypothesis remains speculative and needs confirmation in a large study of healthy participants.

We would like to emphasize the potential clinical importance of the correlation findings between synergic indices across dissimilar tasks. One of the obstacles on the way to turning studies of synergies into a broadly used and effective clinical tool is the relatively long testing procedure. This is particularly true for studies of multi-muscle synergies because of the requirement for electrode placement. Another problem is the necessity of collecting multiple trials to perform the inter-trial variance analysis. This issue may be resolved using a different proxy of action stability, the index of motor equivalence (Scholz et al., 2007; Mattos et al., 2011), which requires only a handful of trials. Note that the indices of inter-trial variance and motor equivalence show similar effects of PD, drug treatment, and correlated changes within a sway cycle (Falaki et al., 2017). Our study suggests that it may be possible to use a simple, less time-consuming task (e.g., multi-finger force production) to obtain indices of synergic control that are valid across other tasks, e.g. those involving postural control that may be more informative for clinicians.

Concluding comments

We would like to emphasize two important conclusions from our study. First, re-engaging DBS following a short withdrawal shows effectiveness with respect to indices of agility (ASAs) but not with respect to indices of stability (V), although we cannot rule out the possible influence of chronic DBS. Second, indices of both stability and agility correlate across dissimilar tasks such as multi-finger action and keeping vertical posture.

Two obvious drawbacks of the study are the modest number of participants and their clinical heterogeneity. This is in part due to our stringent inclusion criteria that required subjects who could perform the task in the “off” stimulation condition. Because DBS is often offered to more advanced PD patients, the criteria have hindered our ability to recruit more subjects. The current work represents our efforts over two years. Nonetheless, we have complete datasets from eight subjects in each experiment to test our Aim 1 hypothesis, and 10 complete datasets to compare the correlations between two different tasks to test our Aim 2 hypothesis. The clinical heterogeneity is another consequence of the same factor: We did not have the luxury of selecting subgroups of patients. Whereas the relatively small sample size of our study requires additional independent confirmation of these conclusions, the same small sample size may be viewed as an asset given the statistically significant findings. Indeed, it suggests that the observed statistically significant effects are not small and may be expected to be clinically significant. The small sample size, however, allowed us to detect only large effects leaving room for type-II errors. Hence the lack of significant effects of DBS on indices of stability in the current study does not rule out such effects. It has to be viewed as a preliminary finding limiting the clinical significance of the current dataset. With the growing trend of performing DBS at an earlier disease stage (Schuepbach et al., 2013; Charles et al., 2014), and individualization of DBS targeting STN versus GPi depending on patient needs (Okun et al., 2010; Martinez-Ramirez et al., 2015), future comparison studies with larger sample size are warranted and may yield information both clinically relevant and mechanistically important regarding effects of DBS therapy on motor coordination.

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Abbreviations

APA	anticipatory postural adjustment
ASA	anticipatory synergy adjustment
COP	center of pressure
DBS	deep brain stimulation
HY	Hoehn and Yahr
MVC	maximal voluntary contraction
PD	Parkinson's disease
UCM	uncontrolled manifold

References

- Ashkan K, Rogers P, Bergman H, Urghratdar I. Insights into the mechanisms of deep brain stimulation. *Nat Rev Neurol*. 2017; 13:548–554. [PubMed: 28752857]
- Alberts JL, Elder CM, Okun MS, Vitek JL. Comparison of pallidal and subthalamic stimulation on force control in patient's with Parkinson's disease. *Motor Control*. 2004; 8:484–499. [PubMed: 15585903]
- Alberts JL, Okun MS, Vitek JL. The persistent effects of unilateral pallidal and subthalamic deep brain stimulation on force control in advanced Parkinson's patients. *Parkinsonism Relat Disord*. 2008; 14:481–488. [PubMed: 18342565]
- Aruin AS, Latash ML. The role of motor action in anticipatory postural adjustments studied with self-induced and externally-triggered perturbations. *Exp Brain Res*. 1995; 106:291–300. [PubMed: 8566194]
- Belenkiy VY, Gurfinkel VS, Pal'tsev YI. Elements of control of voluntary movements. *Biofizika*. 1967; 10:135–141.
- Bernstein NA. The problem of interrelation between coordination and localization. *Arch Biol Sci*. 1935; 38:1–35. (in Russian).
- Bernstein, NA. *The Co-ordination and Regulation of Movements*. Oxford: Pergamon Press; 1967.
- Brown RG, Dowsey PL, Brown P, Jahanshahi M, Pollak P, Benabid AL, et al. Impact of deep brain stimulation on upper limb akinesia in Parkinson's disease. *Ann Neurol*. 1999; 45:473–488. [PubMed: 10211472]
- Breniere Y, Do MC. When and how does steady state gait movement induced from upright posture begin? *J Biomech*. 1986; 19:1035–1040. [PubMed: 3818673]
- Carpinella I, Crenna P, Marzegan A, Rabuffetti M, Rizzone M, Lopiano L, Ferrarin M. Effect of L-dopa and subthalamic nucleus stimulation on arm and leg swing during gait in Parkinson's disease. *Conf Proc IEEE Eng Med Biol Soc*. 2007; 2007:6665–6668. [PubMed: 18003554]
- Charles D, Konrad PE, Neimat JS, Molinari AL, Tramontana MG, Finder SG, et al. Subthalamic nucleus deep brain stimulation in early stage Parkinson's disease. *Parkinsonism Rel Disord*. 2014; 20:731–737.

- Collomb-Clerc A, Welter ML. Effects of deep brain stimulation on balance and gait in patients with Parkinson's disease: A systematic neurophysiological review. *Neurophysiol Clin.* 2015; 45:371–388. [PubMed: 26319759]
- Corcos DM, Gottlieb GL, Latash ML, Almeida GL, Agarwal GC. Electromechanical delay: An experimental artifact. *J Electromyogr Kinesiol.* 1992; 2:59–68. [PubMed: 20719599]
- Cossu G, Pau M. Subthalamic nucleus stimulation and gait in Parkinson's disease: a not always fruitful relationship. *Gait Posture.* 2017; 52:205–210. [PubMed: 27915226]
- Crenna P, Frigo C. A motor programme for the initiation of forward-oriented movements in humans. *J Physiologie.* 1991; 437:635–653.
- Criswell, E., Cram, JR. *Cram's introduction to surface electromyography.* 2. Jones and Bartlett; Sudbury, MA: 2011.
- Daneault JF, Carignan B, Sadikot AF, Duval C. Subthalamic deep brain stimulation and dopaminergic medication in Parkinson's disease: Impact on inter-limb coupling. *Neurosci.* 2016; 335:9–19.
- DeLong MR, Wichmann T. Basal ganglia circuits as targets for neuromodulation in Parkinson disease. *JAMA Neurol.* 2015; 72:1354–1360. [PubMed: 26409114]
- Diedrichsen J, Shadmehr R, Ivry RB. The coordination of movement: optimal feedback control and beyond. *Trends Cogn Sci.* 2010; 14:31–39. [PubMed: 20005767]
- Falaki A, Huang X, Lewis MM, Latash ML. Impaired synergic control of posture in Parkinson's patients without postural instability. *Gait Posture.* 2016; 44:209–215. [PubMed: 27004660]
- Falaki A, Huang X, Lewis MM, Latash ML. Dopaminergic modulation of multi-muscle synergies in postural tasks performed by patients with Parkinson's disease. *J Electromyogr Kinesiol.* 2017a; 33:20–26. [PubMed: 28110044]
- Falaki A, Huang X, Lewis MM, Latash ML. Motor equivalence and structure of variance: Multi-muscle postural synergies in Parkinson's disease. *Exp Brain Res.* 2017b; 235:2243–2258. [PubMed: 28455740]
- Fukui T. Sequence generation in arbitrary temporal patterns from theta-nested gamma oscillations: a model of the basal ganglia-thalamo-cortical loops. *Neural Netw.* 1999; 12:975–987. [PubMed: 12662640]
- Gelfand IM, Latash ML. On the problem of adequate language in movement science. *Motor Control.* 1998; 2:306–313. [PubMed: 9758883]
- Gorniak SL, McIntyre CC, Alberts JL. Bimanual force coordination in Parkinson's disease patients with bilateral subthalamic deep brain stimulation. *PLoS One.* 2013; 8:e78934. [PubMed: 24244388]
- Halliday S, Winter D, Frank J, Patla A. The initiation of gait in young, elderly, and Parkinson's disease subjects. *Gait Posture.* 1998; 8:8–14. [PubMed: 10200394]
- Heremans E, Nackaerts E, Vervoort G, Vercruysse S, Broeder S, Strouwen C, Swinnen SP, Nieuwboer A. Amplitude manipulation evokes upper limb freezing during handwriting in patients with Parkinson's disease with freezing of gait. *PLoS One.* 2015; 10:e0142874. [PubMed: 26580556]
- Hoehn M, Yahr M. Parkinsonism: onset, progression and mortality. *Neurology.* 1967; 17:427–442. [PubMed: 6067254]
- Houk JC. Agents of the mind. *Biol Cybern.* 2005; 92:427–37. [PubMed: 15915357]
- Hultborn H, Brownstone RB, Toth TI, Gossard JP. Key mechanisms for setting the input-output gain across the motoneuron pool. *Prog Brain Res.* 2004; 143:77–95. [PubMed: 14653153]
- Israeli-Korn SD, Hocherman S, Hassin-Baer S, Cohen OS, Inzelberg R. Subthalamic nucleus deep brain stimulation does not improve visuo-motor impairment in Parkinson's disease. *PLoS One.* 2013; 8:e65270. [PubMed: 23776460]
- Jo HJ, Park J, Lewis MM, Huang X, Latash ML. Prehension synergies and hand function in early-stage Parkinson's disease. *Exp Brain Res.* 2015; 233:425–440. [PubMed: 25370346]
- Jo HJ, Maenza C, Good DC, Huang X, Park J, Sainburg RL, Latash ML. Effects of unilateral stroke on multi-finger synergies and their feed-forward adjustments. *Neurosci.* 2016; 319:194–205.
- Kalia SK, Sankar T, Lozano AM. Deep brain stimulation for Parkinson's disease and other movement disorders. *Curr Opin Neurol.* 2013; 26:374–380. [PubMed: 23817213]

- Klous M, Mikulic P, Latash ML. Two aspects of feed-forward postural control: Anticipatory postural adjustments and anticipatory synergy adjustments. *J Neurophysiol.* 2011; 105:2275–2288. [PubMed: 21389305]
- Krishnamoorthy V, Goodman SR, Latash ML, Zatsiorsky VM. Muscle synergies during shifts of the center of pressure by standing persons: Identification of muscle modes. *Biol Cybern.* 2003a; 89:152–161. [PubMed: 12905043]
- Krishnamoorthy V, Latash ML, Scholz JP, Zatsiorsky VM. Muscle synergies during shifts of the center of pressure by standing persons. *Exp Brain Res.* 2003b; 152:281–292. [PubMed: 12904934]
- Latash ML. Motor synergies and the equilibrium-point hypothesis. *Motor Control.* 2010; 14:294–322. [PubMed: 20702893]
- Latash ML. The bliss (not the problem) of motor abundance (not redundancy). *Exp Brain Res.* 2012; 217:1–5. [PubMed: 22246105]
- Latash ML. Towards physics of neural processes and behavior. *Neurosci Biobehav Rev.* 2016; 69:136–146. [PubMed: 27497717]
- Latash ML, Huang X. Neural control of movement stability: Lessons from studies of neurological patients. *Neurosci.* 2015; 301:39–48.
- Latash ML, Scholz JF, Danion F, Schöner G. Structure of motor variability in marginally redundant multi-finger force production tasks. *Exp Brain Res.* 2001; 141:153–165. [PubMed: 11713627]
- Latash ML, Shim JK, Smilga AV, Zatsiorsky V. A central back-coupling hypothesis on the organization of motor synergies: a physical metaphor and a neural model. *Biol Cybern.* 2005; 92:186–191. [PubMed: 15739110]
- Latash ML, Scholz JP, Schöner G. Toward a new theory of motor synergies. *Motor Control.* 2007; 11:276–308. [PubMed: 17715460]
- Lewis MM, Lee E-Y, Jo HJ, Park J, Latash ML, Huang X. Synergy as a new and sensitive marker of basal ganglia dysfunction: A study of asymptomatic welders. *Neurotoxicol.* 2016; 56:76–85.
- Lewis MM, Slagle CG, Smith AB, Truong Y, Bai P, McKeown MJ, Mailman RB, Belger A, Huang X. Task specific influences of Parkinson's disease on the striato-thalamo-cortical and cerebello-thalamo-cortical motor circuitries. *Neurosci.* 2007; 147:224–35.
- Lilleeng B, Gjerstad M, Baardsen R, Dalen I, Larsen JP. Motor symptoms after deep brain stimulation of the subthalamic nucleus. *Acta Neurol Scand.* 2015; 131:298–304. [PubMed: 25346142]
- Lund JS, Angelucci A, Bressloff PC. Anatomical substrates for functional columns in macaque monkey primary visual cortex. *Cereb Cortex.* 2003; 13:15–24. [PubMed: 12466211]
- Manzoni D, Andre P, Bruschini L. Coupling sensory inputs to the appropriate motor responses: new aspects of cerebellar function. *Arch Ital Biol.* 2004; 142:199–215. [PubMed: 15260377]
- Marconi R, Landi A, Valzania F. Subthalamic nucleus stimulation in Parkinson's disease. *Neurol Sci.* 2008; 29(Suppl 5):S389–91. [PubMed: 19381771]
- Martin V, Scholz JP, Schöner G. Redundancy, self-motion, and motor control. *Neural Comput.* 2009; 21:1371–1414. [PubMed: 19718817]
- Martinez-Ramirez D, Hu W, Bona AR, Okun MS, Shukla AW. Update on deep brain stimulation in Parkinson's disease. *Transl Neurodegen.* 2015; 4:12.doi: 10.1186/s40035-015-0034-0
- Massion J. Movement, posture and equilibrium: Interaction and coordination. *Prog Neurobiol.* 1992; 38:35–56. [PubMed: 1736324]
- Mattei B, Schmied A, Mazzocchio R, Decchi B, Rossi A, Vedel JP. Pharmacologically induced enhancement of recurrent inhibition in humans: effects on motoneurone discharge patterns. *J Physiol.* 2003; 548:615–629. [PubMed: 12611926]
- Mattos D, Latash ML, Park E, Kuhl J, Scholz JP. Unpredictable elbow joint perturbation during reaching results in multijoint motor equivalence. *J Neurophysiol.* 2011; 106:1424–1436. [PubMed: 21676927]
- Merola A, Zibetti M, Artusi CA, Rizzi L, Angrisano S, Lanotte M, Lopiano L, Rizzone MG. 80 Hz versus 130 Hz subthalamic nucleus deep brain stimulation: effects on involuntary movements. *Parkinsonism Relat Disord.* 2013; 19:453–456. [PubMed: 23395217]

- Nieuwboer A, Vercruyssen S, Feys P, Levin O, Spildooren J, Swinnen S. Upper limb movement interruptions are correlated to freezing of gait in Parkinson's disease. *Eur J Neurosci*. 2009; 29:1422–1430. [PubMed: 19309319]
- Okun MS, Foote KD. Parkinson's disease DBS: what, when, who and why? The time has come to tailor DBS targets. *Expert Rev Neurother*. 2010; 10:1847–1857. [PubMed: 21384698]
- Olafsdottir H, Yoshida N, Zatsiorsky VM, Latash ML. Anticipatory covariation of finger forces during self-paced and reaction time force production. *Neurosci Lett*. 2005; 381:92–6. [PubMed: 15882796]
- Olafsdottir H, Yoshida N, Zatsiorsky VM, Latash ML. Elderly show decreased adjustments of motor synergies in preparation to action. *Clin Biomech*. 2007; 22:44–51.
- Ozeki H, Sadakane O, Akasaki T, Naito T, Shimegi S, Sato H. Relationship between excitation and inhibition underlying size tuning and contextual response modulation in the cat primary visual cortex. *J Neurosci*. 2004; 24:1428–1438. [PubMed: 14960615]
- Park J, Lewis MM, Huang X, Latash ML. Dopaminergic modulation of motor coordination in Parkinson's disease. *Parkinsonism Relat Disord*. 2014; 20(1):64–68. [PubMed: 24090949]
- Park J, Lewis MM, Huang X, Latash ML. Effects of olivo-ponto-cerebellar atrophy (OPCA) on finger interaction and coordination. *Clin Neurophysiol*. 2013; 124:991–998. [PubMed: 23182835]
- Park J, Wu Y-H, Lewis MM, Huang X, Latash ML. Changes in multi-finger interaction and coordination in Parkinson's disease. *J Neurophysiol*. 2012; 108:915–924. [PubMed: 22552184]
- Reisman D, Scholz JP. Aspects of joint coordination are preserved during pointing in persons with post-stroke hemiparesis. *Brain*. 2003; 126:2510–27. [PubMed: 12958080]
- Rocchi L, Carlson-Kuhta P, Chiari L, Burchiel KJ, Hogarth P, Horak FB. Effects of deep brain stimulation in the subthalamic nucleus or globus pallidus internus on step initiation in Parkinson disease: laboratory investigation. *J Neurosurg*. 2012; 117:1141–1149. [PubMed: 23039143]
- Schettino LF, Van Erp E, Hening W, Lessig S, Song D, Barba D, Poizner H. Deep brain stimulation of the subthalamic nucleus facilitates coordination of hand preshaping in Parkinson's disease. *Int J Neurosci*. 2009; 119:1905–1924. [PubMed: 19922392]
- Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, et al. EARLYSTIM Study Group. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med*. 2013; 368:610–622. DOI: 10.1056/NEJMoa1205158 [PubMed: 23406026]
- Schlenstedt C, Shalash A, Muthuraman M, Falk D, Witt K, Deuschl G. Effect of high-frequency subthalamic neurostimulation on gait and freezing of gait in Parkinson's disease: a systematic review and meta-analysis. *Eur J Neurol*. 2017; 24:18–26. [PubMed: 27766724]
- Scholz JP, Schöner G, Hsu WL, Jeka JJ, Horak F, Martin V. Motor equivalent control of the center of mass in response to support surface perturbations. *Exp Brain Res*. 2007; 180:163–179. [PubMed: 17256165]
- Scholz JP, Schöner G. The uncontrolled manifold concept: Identifying control variables for a functional task. *Exp Brain Res*. 1999; 126:289–306. [PubMed: 10382616]
- Schöner G. Recent developments and problems in human movement science and their conceptual implications. *Ecol Psychol*. 1995; 8:291–314.
- Schoppa NE, Urban NN. Dendritic processing within olfactory bulb circuits. *Trends Neurosci*. 2003; 26:501–506. [PubMed: 12948662]
- Shim JK, Olafsdottir H, Zatsiorsky VM, Latash ML. The emergence and disappearance of multi-digit synergies during force production tasks. *Exp Brain Res*. 2005; 164:260–270. [PubMed: 15770477]
- Shinohara M, Scholz JP, Zatsiorsky VM, Latash ML. Finger interaction during accurate multi-finger force production tasks in young and elderly persons. *Exp Brain Res*. 2004; 156:282–292. [PubMed: 14985892]
- Sidiropoulos C. Low-frequency stimulation of STN-DBS reduces aspiration and freezing of gait in patients with PD. *Neurology*. 2015; 85:557.
- Singh T, Latash ML. Effects of muscle fatigue on multi-muscle synergies. *Exp Brain Res*. 2011; 214:335–350. [PubMed: 21842189]
- Todorov E. Optimality principles in sensorimotor control. *Nat Neurosci*. 2004; 7:907–915. [PubMed: 15332089]

- Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Move Disord*. 2010; 25:2649–53.
- Vercruysse S, Vandenberghe W, Müinks L, Nuttin B, Devos H, Nieuwboer A. Effects of deep brain stimulation of the subthalamic nucleus on freezing of gait in Parkinson's disease: a prospective controlled study. *J Neurol Neurosurg Psychiatry*. 2014; 85:871–877. [PubMed: 24396010]
- Wang Y, Zatsiorsky VM, Latash ML. Muscle synergies involved in shifting center of pressure during making a first step. *Exp Brain Res*. 2005; 167:196–210. [PubMed: 16034579]
- Wang Y, Zatsiorsky VM, Latash ML. Muscle synergies in preparation to a step made under self-paced and reaction-time instructions. *Clin Neurophysiol*. 2006; 117:41–56. [PubMed: 16364687]
- Wehr M, Zador AM. Balanced inhibition underlies tuning and sharpens spike timing in auditory cortex. *Nature*. 2003; 426:442–446. [PubMed: 14647382]
- Winter DA, Prince F, Frank JS, Powell C, Zabjek KF. Unified theory regarding A/P and M/L balance in quiet stance. *J Neurophysiol*. 1996; 75:2334–2343. [PubMed: 8793746]
- Xie T, Padmanaban M, Bloom L, MacCracken E, Bertacchi B, Dachman A, Warnke P. Effect of low versus high frequency stimulation on freezing of gait and other axial symptoms in Parkinson patients with bilateral STN DBS: a mini-review. *Transl Neurodegener*. 2017; 6:13. [PubMed: 28529730]
- Yu H, Sternad D, Corcos DM, Vaillancourt DE. Role of hyperactive cerebellum and motor cortex in Parkinson's disease. *Neuroimage*. 2007; 35:222–33. [PubMed: 17223579]
- Zatsiorsky VM, Li Z-M, Latash ML. Enslaving effects in multi-finger force production. *Exp Brain Res*. 2000; 131:187–195. [PubMed: 10766271]

Highlights

- Deep brain stimulation affects indices of agility in Parkinson's disease.
- Indices of synergic control correlate between dissimilar multi-finger and whole-body tasks.
- Deep brain stimulation may have both acute and chronic effects on synergy indices.

A: Hand setup **B: Postural setup** **Figure 1.**

Experimental setup. **A**, a schematic of the hand setup. The wooden piece was customized separately for the left hand (L) and the right hand (R) to keep the inter-phalangeal joints slightly flexed during the course of the experiment. **B**, a schematic of a participant holding the load with extended arms. X, Y, and Z axes represents the force plate coordinate system. Participants wore a safety harness (not shown) while standing on the force plate.

Figure 2.

Performance of the quick force pulse production task. Averaged (across participants) time profiles of the total force (F_{TOT}) and the log-transformed synergy index (ΔV_Z) are shown for the DBS-off condition (dashed line) and DBS-on condition (solid line) with standard error shades. t_0 represents the task initiation and vertical arrows represent the initiation of anticipatory synergy adjustments (ASAs).

Figure 3.

Load release task performance for the DBS-on (**A**) and DBS-off (**B**) conditions. The solid line represents the time profile of averaged center of pressure coordinates across participants in the anterior-posterior direction (COP_{AP}). Dashed and dashed-dotted lines represent time profiles of the first two M-modes, averaged across trials performed by a representative participant. Shaded area demonstrates one-sided standard errors. t_0 represents the task initiation and vertical arrows represent the initiation of anticipatory postural adjustments (APAs).

Figure 4.

Scatter plots of multi-finger synergy indices and multi-muscle synergy indices with the least squares line of best fit. **A**, Regression between multi-finger log-transformed synergy index (ΔV_Z) and multi-muscle one during the steady state time interval. **B**, Regression between the initiation of multi-finger anticipatory synergy adjustment (t_{ASA}) and multi-muscle one. **C**, Regression between the magnitude of multi-finger anticipatory synergy adjustment ($\Delta\Delta V$) and multi-muscle one. Data points for the DBS-on condition are shown with a '+' and those for the DBS-off condition are shown with a '●'.

Table 1

Description of the participants

Patients														
SID	Sex	Age (y)	Onset side	Disease duration	DBS target	DBS duration	DBS parameters	UPDRS III (Off)	UPDRS III (On)	H&Y (Off)	H&Y (On)	LEDD (mg)	Hand task	Postural task
P01	M	74	L	9 y	GPI	30 Mo	3-C+ 5.5V 90PW 130Freq 11-C+ 5.5V 90PW 130Freq	26	17	2	2	650	✓	✓
P02	M	48	B	12 y	STN	4 Mo	Not available	16	15	2	2	767.5	✓	✓
P03	M	58	R	6 y	STN	30 Mo	Not available	79	27	3	2	0		✓
P04	M	55	L	16 y	STN	21 Mo	1-C+ 2.8V 90PW 130Freq 1-C+ 3.5V 60PW 150Freq	59	19	3	3	200	✓	✓
P05	M	58	R	8 y	GPI	4 Mo	3-C+ 2.8V 90PW 130Freq 9-C+ 1.5V 90PW 130Freq	49	38	2	2	1200	✓	
P06	M	73	R	22 y	GPI	10 Mo	1-C+ 2.5V 90PW 130Freq 10-C+ 2.4V 90PW 130Freq	12	13	2	2	780		✓
P07	M	50	L	3 y	STN	7 Mo	3-2+ 3.1V 90PW 180Freq 11-10+ 3.7V 90PW 180Freq	44	42	2	2	1250	✓	✓
P08	M	64	R	9 y	STN	48 Mo	Not available	17	28	3	4	292.5	✓	✓
P09	M	55	R	11 y	STN	8 Mo	2-C+ 2.8V 60PW 130Freq 9-10+ 3.4V 60PW 130Freq	21	23	2	2	1250	✓	
P10	M	75	R	14 y	STN	5 Mo	1-C+ 2.5V 90PW 130Freq 10-C+ 2.6V 90PW 130Freq	47	49	2	3	755	✓	✓
Controls														
Hand Task					Postural Task									
SID	Sex	Age (y)	SID	Sex	Age (y)									
C01	M	59	C09	M	56									
C02	M	41	C10	M	77									
C03	M	67	C11	M	78									
C04	M	57	C12	M	69									
C05	M	58	C13	M	64									
C06	M	59	C14	M	63									
C07	M	74	C15	F	60									
C08	M	57	C16	F	58									

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SID, subject identification number; DBS, deep brain stimulation; UPDRS III, unified Parkinson’s disease rating scale-part III (motor scores); H&Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; M/F, male/female; R/L/B, right/left/both sides; GPi, globus pallidus internus; STN, subthalamic nucleus. All the subjects were right-handed with the exception of P10 (left-handed) and C12 (ambidextrous).

Table 2

Performance and synergy indices for hand and postural experiments

Hand tasks		MVC (N)	T_{Peak} (ms)	V_{SS,F}	V_F	t_{ASAF} (ms)
PD (DBS-off)	Right	68.9 ± 6.9	259 ± 24	2.44 ± 0.14	0.20 ± 0.09	-89 ± 43
	Left	65.8 ± 6.7	256 ± 20	2.73 ± 0.20	0.36 ± 0.10	-79 ± 21
PD (DBS-on)	Right	70.6 ± 8.3	269 ± 37	2.62 ± 0.10	0.50 ± 0.06	-219 ± 38
	Left	65.4 ± 7.8	244 ± 27	2.83 ± 0.18	0.46 ± 0.09	-130 ± 22
Controls	Right	80.1 ± 6.4	144 ± 12	2.3 ± 0.10	0.48 ± 0.06	-226 ± 30
	Left	75.9 ± 5.8	163 ± 10	2.68 ± 0.13	0.64 ± 0.11	-231 ± 22

Postural tasks		APA_{EMG} (ms)	APA_{M-mode} (ms)	V_{SS,P}	V_P	t_{ASAP} (ms)
PD (DBS-off)		-113 ± 15	-137 ± 34	-0.02 ± 0.03	-0.03 ± 0.04	-26 ± 14
PD (DBS-on)		-123 ± 21	-144 ± 40	0.02 ± 0.05	0.06 ± 0.02	-81 ± 21
Controls		-122 ± 14	-125 ± 31	0.22 ± 0.07	0.23 ± 0.04	-97 ± 27

Mean ± SE of performance and synergy indices for the fingers (F) and posture (P) are presented. MVC, maximum voluntary contraction force; T_{Peak}, time to peak force; V_{SS}, synergy index averaged over the steady-state period (600 to 400 ms prior to task initiation); V_P, magnitude of anticipatory synergy adjustments; t_{ASA}, time of anticipatory synergy adjustments; APA, time of anticipatory postural adjustments identified based on changes in muscles activity (EMG) or in the magnitude of muscle groups (M-mode)