Effects of deep brain stimulation and medication on bradykinesia and muscle activation in Parkinson’s disease

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Summary
Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and antiparkinsonian medication (Meds) have proved to be effective therapies for treating bradykinesia in Parkinson’s disease. However, it is not currently known how or to what extent STN stimulation alters the control signals to agonist and antagonist muscles to change movement speed. Our objective was to investigate movement speed along with the amplitude and temporal features of EMG activity to determine how and to what extent these parameters are changed by DBS and medication. Nine patients with Parkinson’s disease were studied following neurosurgery that implanted high-frequency stimulating electrodes in the STN. The experiments for the patients were performed in each of four treatment conditions: (i) OFF treatment; (ii) STN DBS; (iii) Meds; and (iv) Meds plus STN DBS. Also, a group of age- and gender-matched control subjects were examined. Medication and DBS had similar effects in that both treatments increased movement speed, increased the amplitude of the first agonist burst, increased burst duration, reduced the number of agonist bursts, reduced cocontraction, increased the size of the antagonist EMG, and reduced the centroid time of the antagonist EMG. When DBS and medication were combined, only temporal measures of burst duration and the number of agonist bursts were different from the medication alone condition. There was a positive association between the level of bradykinesia OFF treatment and the level of bradykinesia following DBS and medication. The movement speed of neurologically normal control subjects’ was over 40% higher during both flexion and extension movements when compared with the patients during Meds plus STN DBS. The changes in the muscle activation patterns provide a mechanism of action for the pharmacological and surgical interventions used to treat bradykinesia in Parkinson’s disease. However, despite the success of medication and DBS at improving bradykinesia in patients with Parkinson’s disease, patients’ movement speed was not restored to normal due to limitations in the amplitude and temporal scaling of the agonist and antagonist bursting pattern. These findings suggest a link between basal ganglia function in scaling both the amplitude and temporal parameters of the input to the motor neuron pool.

Keywords: deep brain stimulation; subthalamic nucleus; bradykinesia; EMG; Parkinson’s disease

Abbreviations: ANOVA = analysis of variance; DBS = deep brain stimulation; Meds = medication; STN = subthalamic nucleus; UPDRS = Unified Parkinson’s Disease Rating Scale


Introduction
The EMG pattern during ballistic movements of healthy individuals includes a phasic agonist burst that accelerates the limb to its destination. In both humans and primates the greater the amplitude of the first agonist burst the faster the movement (Anderson and Horak, 1985; Corcos et al., 1989). Quasi-electrical silence follows the first agonist burst and a
phasic agonist burst decelerates the limb. A second phasic agonist burst damps out the limb oscillations at the end of movement (Hannaford and Stark, 1985). This sequence of events has been termed the triphasic EMG pattern and has been well studied in humans (Hallett et al., 1975; Gottlieb et al., 1989) and primates (Horak and Anderson, 1984b; Sergio and Kalaska, 1998).

Patients with Parkinson’s disease no longer exhibit the triphasic agonist and antagonist burst pattern—instead they exhibit a fractionated bursting pattern (Hallett and Khoshbin, 1980; Berardelli et al., 1996). In particular, the amplitude of the agonist and antagonist bursts are reduced, the duration of the agonist bursts become shorter, and there are more agonist bursts prior to peak velocity (Teasdale et al., 1990; Pfann et al., 2001). While antiparkinsonian medication (Meds) in Parkinson’s disease alters basal ganglia output from the internal globus pallidus leading to increased movement speed, medication alone does not restore normal movement speed nor the triphasic EMG pattern (Robichaud et al., 2002). Also, pallidotomy has failed to normalize movement speed and muscle activation patterns (Pfann et al., 1998). While deep brain stimulation (DBS) of the subthalamic nucleus (STN) increases movement speed (Brown et al., 1999), it is not currently known how or to what extent DBS alters the control properties of the agonist and antagonist muscle to change movement speed.

The present study investigated five questions regarding STN DBS, medication, and bradykinesia: (i) how STN DBS and medication change both the amplitude and temporal profile of the agonist and antagonist bursts; (ii) whether STN DBS and medication alters the cocontraction between the agonist and antagonist muscles was examined; (iii) whether patients with resting tremor and those patients without a resting tremor receive similar beneficial effects of DBS and medication; (iv) if bradykinesia OFF treatment could predict bradykinesia when the patients received both Meds and STN DBS; and (v) the extent to which movement speed and muscle activation patterns are restored to normal by means of medication and STN DBS. These questions were examined in patients with Parkinson’s disease following neurosurgery that implanted high frequency stimulating electrodes into the STN. Patients were examined in four treatment conditions: (i) OFF treatment; (ii) STN DBS; (iii) Meds; and (iv) Meds plus STN DBS. An age- and gender-matched control group was also examined and their movement speed and muscle activation patterns were compared with the patients during Meds plus STN DBS. Additionally, to determine the general-ality of the findings in muscle activation across muscle groups, patients and controls were examined in both flexion and extension movements. The findings demonstrate the mechanisms by which DBS affects muscle activation patterns, and provides the first evidence on whether the combination of medication and DBS restore the normal triphasic EMG pattern.

Subjects and methods

Subjects and stimulation parameters

Nine patients (mean age: 55.3 years ± SD 6.12 years) diagnosed with idiopathic Parkinson’s disease participated in the study 3–6 months after quadripolar stimulating electrodes (Medtronic Inc., Minneapolis, MN, USA) were implanted unilaterally in the STN during stereotactic neurosurgery. Intraoperative microelectrode recording and a postoperative MRI scan confirmed electrode placement in the STN. Table 1 shows the descriptive characteristics of each patient. The stimulator pulse width was always 60 μs and the frequency was 185 Hz. The voltage level varied across subjects (mean: 2.35 V ± SD 0.52 V) and these parameters were set based on neurological evaluation for optimal functional status. Also, nine age- and gender-matched control subjects were examined (mean age: 54.7 years ± SD 7.42 years). A two-tailed t-test showed no significant age differences between groups (P > 0.05).

Patients were included in the study if they had a positive clinical improvement [greater than a 15% reduction in the Unified Parkinson’s Disease Rating Scale (UPDRS) motor section scores] from the unilateral STN DBS in the OFF treatment condition compared with the STN DBS condition. This comparison was performed postoperatively. The UPDRS motor scores are in Table 1 (preoperative mean: OFF meds = 40.3; postoperative means: OFF treatment = 37; STN DBS = 27.7; Meds = 14.8; Meds plus STN DBS = 12.8). This indicates an average reduction of 31% for the UPDRS pre-surgery OFF Meds to the post-surgery DBS alone condition. Because the surgery was unilateral we expected a lower percentage improvement than what has been reported for bilateral STN DBS (Deep-Brain Stimulation for Parkinson’s Disease Study Group, 2001). On a rating scale of 0–4 where the total average of axial and appendicular dyskinesia ratings was considered, the Meds condition equalled 1.3 ± 0.67 and Meds plus STN DBS was 1.2 ± 0.91. All subjects gave informed consent to all experimental procedures, which were approved by the local Institutional Review Board.

Experimental setup

Since electrode implantation may produce a microlesion effect, the testing took place at least 3 months following surgery. The experiments for the patients were performed on two consecutive days in each of four treatment conditions: (i) OFF treatment; (ii) STN DBS; (iii) Meds; and (iv) Meds plus STN DBS. On day 1, testing of condition 1 took place between 09.00 and 11.00 and condition 2 occurred between 13.00 and 15.00. On day 2, the same testing schedule as day 1 was set for conditions 3 and 4, respectively. The control subjects were tested on 1 day only.

To ensure that each Parkinson patient was ‘off’ their treatment, patients were always tested in the OFF condition following 12 h withdrawal from the specific treatment (Langston et al., 1992). For instance, the night prior to day 1 patients were off both treatments, whereas patients were only off DBS for the night prior to day 2. Each patient stayed in a hotel close to the laboratory and was examined using a Medtronic Console Programer (Model 7432) on each night prior to days 1 and 2 to make certain that the stimulator was off. To ensure that each Parkinson patient was ‘on’ their treatment, subjects were always tested 90 min following either turning the stimulator on or administering the medication. The patient specific dose of medication, as shown in Table 1, was administered to each patient prior to the testing. During experimental testing, all but two of the patients took their pre-surgery medication dosage (i.e. optimal
levodopa treatment). Optimal levodopa treatment was defined as the clinically determined preoperative medication dosage (Kumar et al., 1998).

Motor control testing
The subject viewed a computer monitor that displayed a vertical cursor and a vertical target that were positioned along the horizontal axis. The cursor represented the angular position (measured in degrees). The starting position was shown as a stationary bar on the monitor and target position was always placed at a set distance in a one-to-one correspondence with the direction of motion. The monitor distance was set to 110 cm from the subject and this distance remained constant across experimental sessions. The height of the monitor was set level to the eyes of each individual subject and also remained constant across testing sessions.

The subject was seated with the arm abducted between 75° and 90° depending on the comfort of each subject (Fig. 1A). The arm examined in this study was always contralateral to the placement of the unilateral DBS electrode. The chair height was set during the first testing session and, along with the arm abduction angle, remained constant across all experimental testing sessions. The forearm rested on a rigid, lightweight manipulandum that could freely rotate only in the horizontal plane. The axis of rotation was aligned with the elbow joint. Full extension of the tested limb was defined as 0°. Joint angular position was measured by a capacitive transducer mounted on the shaft at the axis of rotation. Velocity was obtained by differentiating the angle signal by a custom-built analogue differentiator. Joint acceleration was measured by an accelerometer mounted 47.6 cm from the centre of rotation. Surface EMG was used to assess neuronal function. Surface electrodes were placed on the biceps and lateral head of the triceps muscle. The EMG signals were amplified (gain = 1000) and bandpass filtered between 20 and 450 Hz (Delsys Inc., Boston, MA, USA). All kinematic and EMG signals were digitized at 1000 Hz using a 12-bit analogue to digital converter.

The experimental task was a single-joint movement in both elbow flexion and elbow extension over a 72° distance. The elbow movements were performed while the patient was under each specific medication and stimulation treatment condition. The subjects were instructed to perform the elbow movements ‘as fast and accurately as possible’ to a 6° target. Ten trials were performed in each direction (flexion and extension) during each of the four treatment conditions. The flexion/extension movements were performed in a random order. Prior to beginning the 10 experimental trials, 10 practice trials were given to the subject to become acquainted with the new condition.

Data processing and analysis
Figure 1(B–E) depicts examples of the analyses performed on the kinematic and EMG records. The kinematic signals were lowpass

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M = male; F = female; tab = tablet.
The EMG records were first rectified and then lowpass filtered at 50 Hz (Butterworth 2nd order filter dual pass) (McAuley et al., 1997; Vaillancourt et al., 2003). Peak velocity was marked using an automated algorithm (Fig. 1B) and the EMG agonist bursts were marked by the following procedure.

First, movement onset was identified from the acceleration signal. This was accomplished by finding peak acceleration and then searching backwards to locate the first acceleration data sample that fell below 5% of peak acceleration. Secondly, due to the well-known electromechanical delay (~30 ms) between EMG and kinematic signals (Corcos, 1992), the algorithm searched for the onset of the EMG signal before the onset of acceleration. Each data sample from the EMG during that period was compared with the baseline EMG activity (mean EMG activity for 1 s before acceleration onset). If the EMG data sample was greater than a threshold (4 times the standard deviation of EMG activity calculated 1 s before acceleration onset added to the baseline EMG level) this was marked as the onset of the EMG burst. Thirdly, the algorithm searched forward to find when the EMG signal fell below the threshold value for 10 consecutive samples and this time point was set to the offset of the EMG burst.

Fourthly, steps 2 and 3 were repeated to mark any additional EMG bursts that occurred before peak velocity. Following algorithm marking, each trial was visually inspected to ensure burst marking accuracy and adjustments were made if necessary.

After the kinematic and EMG signals were marked, analysis focused on the velocity of movement, and on the agonist and antagonist burst pattern. The following variables were calculated.

(i) Peak velocity (°/s): the largest value of movement velocity (Fig. 1B).

(ii) Agonist burst amplitude (mV): the average EMG activity during the first agonist burst. A burst could occur at any time from the marked onset to the time of peak velocity for each trial. This parameter is used to characterize the size of the first agonist EMG burst which is responsible for the limb accelerating towards the target (Fig. 1C).

(iii) Agonist burst duration (s): time period between the marked onset of the first agonist burst until its offset.

(iv) Number of agonist bursts: a count of the agonist bursts that begin prior to peak velocity (Fig. 1C).

(v) Antagonist burst amplitude (mV): the average of the antagonist EMG signal (lateral head of triceps) for each trial from the marked onset of the agonist burst to the end of the movement (the time at which acceleration drops below 5% of maximum).

(vi) $C_{\text{cent}}$ (ms): the centroid of the antagonist burst represents the temporal event when the bulk of antagonist activation occurred and is used as a measure of the timing of antagonist activation. The centroid was calculated by the following equation (Fig. 1D):

$$Centroid = \frac{\int_{0}^{MT} t \cdot EMG(t) \cdot u(t) dt}{\int_{0}^{MT} EMG(t) \cdot u(t) dt}$$

where $u(t) = 1$ if $EMG(t) \geq K$ EMGmax or $u(t) = 0$ if $EMG(t) < K$ EMGmax. $MT$ is movement time, $t_0$ is the time of the start of acceleration, $EMG(t)$ is the EMG signal in the antagonist muscle, $K$ is 0.75, EMGmax is the peak EMG of the antagonist signal (Gottlieb, 1996).

(vii) Cocontraction: the degree of cocontraction from movement onset up to peak acceleration was calculated according to the algorithm by Winter (1990). We chose to calculate cocontraction over the time interval of acceleration because we were interested in muscle cocontraction associated with limb acceleration. Integration
over a longer period would include analysis of muscle activation associated with limb deceleration. In Fig. 1E, the cocontraction was calculated between the two dashed lines. The equation assesses the percentage of overlapping area (light gray between dashed lines in Fig. 1E) in each EMG pair:

\[
\% \text{Concon} = 2 \cdot \frac{\int \min(EMG_i(t), EMG_j(t)) dt}{\int EMG_i(t) dt + \int EMG_j(t) dt}
\]

where \(\min\) is the minimum between two signals at time \(t\).

**Statistical analysis**

The influence of direction, medication, DBS, and the combination of DBS and medication on each dependent variable for Parkinson’s subjects was examined in two separate repeated measures analyses of variance (ANOVA). A third ANOVA compared Parkinson’s subjects in the Meds plus STN DBS condition to the control subjects in a mixed ANOVA. Specifically, these were organized as follows:

(i) three-way repeated measures ANOVA: repeated factors for direction [flexion (F) and extension (E)] \(\times\) medication (ON and OFF) \(\times\) DBS (ON and OFF);

(ii) two-way repeated measures ANOVA: repeated factors for direction \(\times\) DBS when ON meds;

(iii) two-way mixed ANOVA: between subject factor of group (Parkinson and control) \(\times\) repeated factor for direction when patients were ON Meds plus STN DBS

Each ANOVA was interpreted as significant when there was less than a 5% chance of making a type I error (\(P < 0.05\)). All statistical analyses were completed using Statistica (StatSoft Inc., OK, USA).

In some instances, it is difficult to make within and between subject comparisons using surface EMG because of the other factors that influence EMG voltage levels, such as sub-cutaneous tissue properties, surface moisture, temperature, and electrode placement (Winter, 1990). The current study used meticulous experimental procedures to minimize the above-mentioned influences on the EMG recordings. To minimize variability of electrode placement between subjects, we used careful measurements from easily identifiable anatomical markers to ensure electrode placement accuracy. To minimize variability of electrode placement across testing sessions within a subject, we carefully used a permanent marker to outline the Bagnoli surface electrodes. The permanent marker was visible across each day of testing for each subject, and electrodes were always placed in the same spot outlined by the permanent marker. Therefore, there was very little change in placement within each subject. We also took great care to match the morphological characteristics between our patients and control subjects. The two-tailed \(t\)-tests revealed no difference in the height or weight between groups. Finally, the peak velocity difference between groups was greater than 40% and the average agonist EMG difference was over 100%. While a portion of the 100% between-group EMG amplitude difference may have been due to other factors, a clear and dominant component was due to differences in the neural drive to the muscle.

**Results**

**Peak velocity and individual EMG patterns**

Figure 2 shows kinematic and EMG patterns of a 52-year-old, healthy control subject during a single trial 72° flexion movement. The maximal velocity occurred within 140 ms at 545 °/s. The first agonist EMG burst lasted 152 ms reaching an average amplitude of 0.66 mV. The antagonist EMG turned on shortly after the initial agonist burst and remained active throughout the movement. The agonist and antagonist cocontraction was 9%. The second agonist EMG burst increased considerably near the end of the first agonist burst to damp potential oscillations at the end of movement.

Figure 3 depicts a moderately bradykinetic patient with Parkinson’s disease (Subject 9; values of 2–3 from UPDRS questions 23–26) performing 72° flexion movements under...
each of the four treatment conditions. OFF treatment the patient moved very slowly. Peak velocity occurred 603 ms after movement onset reaching a peak velocity of 111°/s. The agonist bursts were fractionated with the first agonist burst average amplitude of 0.002 mV and cocontraction was 66%. STN DBS resulted in a substantial increase in the agonist burst amplitude. Similarly, the antagonist burst (triceps) increased its amplitude considerably, and cocontraction decreased to 62%. Peak velocity now occurred within 298 ms at 216°/s. During the Meds condition, the patient moved at a maximal velocity of 183°/s, which was a 65% increase compared with the OFF treatment condition. The average first agonist amplitude reached 0.01 mV and was less fractionated as compared with the OFF treatment condition. The antagonist burst amplitude also increased considerably, with cocontraction at 53%. Finally, the Meds plus STN DBS condition led to the greatest maximal velocity and largest agonist burst amplitude. Maximal velocity occurred within 253 ms and reached a peak value of 246°/s. Average amplitude of the first agonist EMG burst was 0.012 mV, which was a robust increase compared with the OFF treatment condition. Additionally, the antagonist EMG burst increased compared with the OFF treatment condition, and cocontraction was 43%.

Figure 4 depicts a mildly bradykinetic patient with Parkinson’s disease (Subject 4; values of 1 from UPDRS questions 23–26) under each treatment condition. Off treatment the patient moved at a maximal velocity of 268°/s, which was close to the velocity of the Meds plus STN DBS condition for the patient depicted in Fig. 3. Average amplitude of the first agonist burst was 0.09 mV, the bursting pattern was fractionated with multiple agonist bursts, and the cocontraction was 40%. During the STN DBS condition, the patient moved at 390°/s and the first agonist burst maximum reached average amplitude of 0.29 mV. There was reduced fractionation in the agonist burst pattern and the antagonist burst increased in amplitude. Cocontraction was at 23%. For the Meds condition the patient moved at 333°/s and the first agonist burst reached average amplitude of 0.27 mV. The antagonist burst did not significantly change when compared with the OFF treatment condition, and cocontraction was 35%. Meds plus STN DBS allowed the patients to move at a
maximal velocity of 496°/s. The first agonist burst was at an average amplitude of 0.32 mV and cocontraction was 31%. Qualitatively, the triphasic EMG pattern appeared relatively normal, and only further quantitative analyses can discern whether medication and DBS normalized the muscle activation patterns.

Quantitative assessment of the EMG burst pattern
Table 2 shows the results from the ANOVA for peak velocity. Both medication and DBS increased peak velocity. There was an interaction between Meds and DBS, and post hoc analyses indicated that this interaction occurred because DBS had a greater effect on peak velocity OFF Meds compared with ON Meds. Also, during Meds plus STN DBS the Parkinson’s patients moved faster than when ON Meds. An additional finding was that flexion movements were consistently faster than extension movement. Although medication and DBS were effective in increasing movement speed, the patients continued to have 40% lower velocity under Meds plus STN DBS compared with the healthy control group. To determine how practice may have influenced the additive effect, we asked one patient to stay for a third consecutive day and tested the individual OFF treatment again. This patient increased peak velocity in the range of 5% when compared with the first OFF treatment session. This 5% change was accrued over the prior four testing sessions that spanned 2 days. However, the patient showed a 20% increase in peak velocity observed for the additive effect accrued over two testing sessions within 1 day. Thus, while practice had some influence on the additive effect shown for peak velocity in this subject, it cannot account for most of the changes in the additive effect of STN DBS and medication on bradykinesia.

Figure 5 depicts the across subject average (± SEM) of six measures quantified from the agonist and antagonist burst pattern during flexion movement (see Fig. 1 and Subjects and methods for description). Each measure was plotted against the corresponding averaged peak velocity (± SEM) from the specific treatment condition. In Fig. 5A, the average EMG of the first agonist burst scaled with increased peak velocity.

Fig. 4 Kinematic and EMG time series from a mildly bradykinetic patient with Parkinson’s disease (subject 4; values of 1 from UPDRS questions 23–26). Each trace shows data from a single trial of a 72° flexion movement. From left to right, the panels represent the four post-surgery medication-stimulation conditions: OFF treatment, STN DBS, Meds and Meds plus STN DBS. From top to bottom, the traces represent position, velocity, acceleration, agonist EMG and antagonist EMG.
Table 2 ANOVA results

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<th>Cocontraction</th>
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F = flexion; E = extension; Int = interaction; ns = not significant. *ON and OFF DBS while ON Meds.

There was a significant difference in the first agonist EMG for flexion greater than extension (see Table 2). Importantly, Meds increased the first agonist EMG, and STN DBS also increased the first agonist EMG voltage levels (Table 2). However, there was no significant difference between Meds and Meds plus STN DBS. Figure 5A and Table 2 also demonstrate that the healthy control subjects had much greater first agonist EMG values compared with the Meds plus STN DBS condition for the Parkinson’s disease patients. Figure 5B shows the first agonist burst duration plotted against movement speed. Figure 5B indicates that the burst duration increased across movement speed in the parkinsonian subjects, and fell back to a shorter duration in the control group. Table 2 indicates that Meds had longer bursts than OFF treatment, and STN DBS had longer burst duration than OFF treatment. Additionally, the burst duration in the Meds plus STN DBS condition was greater than Meds. The burst durations of the patients under Meds plus STN DBS were significantly longer than the control group.

Figure 5C depicts the number of agonist bursts during flexion prior to peak velocity. OFF treatment the patients (on average) generated 2.7 bursts and this value was significantly reduced to two bursts during STN DBS. The number of bursts significantly dropped to 1.8 when ON Meds and dropped even further to 1.6 bursts for Meds plus STN DBS. The number of bursts was lower in the control subjects (1.3 bursts) compared with the patients during Meds plus STN DBS, but the difference was non-significant. Figure 5D indicates that the percent cocontraction was on average 42% for the Parkinson’s disease patients when OFF treatment. The cocontraction systematically decreased with increased movement speed. The analysis of variance from Table 2 demonstrates that Meds significantly reduced cocontraction to 37% and that STN DBS also significantly reduced cocontraction to 37%. Although Table 2 indicates the comparisons were non-significant, Meds plus STN DBS together led to cocontraction values equal to 35%, and the control subjects had cocontraction values of 26%.

The mean antagonist EMG during flexion is shown in Fig. 5E. The antagonist EMG was 0.003 mV OFF treatment and significantly increased to 0.01 mV on STN DBS and 0.010 mV when ON Meds (Fig. 5E). The Meds plus STN DBS condition increased the antagonist EMG values to 0.016 mV, but this difference was not significantly different from the Meds condition. There was a further increase in the antagonist EMG values for the healthy control subjects (0.025 mV), but this difference was not significantly different from the patients during Meds plus STN DBS (Table 2). Figure 5F depicts the antagonist centroid time. The centroid time was equal to 380 ms for the patients when OFF treatment and the centroid time decreased linearly across peak velocity. The STN DBS, Meds, and Meds plus STN DBS conditions had centroid times of 284, 298, and 277 ms respectively, and the control subjects had significantly lower centroid times equal to 160 ms. The data presented in Fig. 5F for the centroid measure and in Fig. 5D on cocontraction may appear contradictory since earlier muscle activation could imply increased muscle cocontraction. However, they are not contradictory because the centroid measure represents the time point where the bulk of the antagonist EMG activity occurred (Equation 2), and does not include the early antagonist (see Fig. 1D). The shortest centroid time was at 160 ms for the control subjects, whereas cocontraction was calculated over the initial 100 ms of the movement depending on the time interval between movement onset and peak acceleration.
Although not depicted, the relationship between peak velocity and the same six dependent measures during extension contractions produced similar results as seen in Fig. 5. In summary, either STN DBS or Meds increased the mean EMG of the first agonist burst, increased agonist burst duration, reduced the number of agonist bursts, reduced cocontraction, increased the mean antagonist EMG, and reduced the antagonist centroid time. These findings point to changes in the amplitude and temporal features of both the agonist and antagonist muscles following DBS and medication. When both treatments were on together, only the temporal features (agonist burst duration and number of agonist bursts) were different between the Meds plus STN DBS condition compared with Meds. This indicates a reduction in burst fractionation. These findings were consistent for both flexion and extension contractions. Finally, control subjects continued to have significantly faster movements, greater mean EMG of the first agonist burst, reduced agonist burst duration, and reduced centroid times compared with the patients under Meds plus STN DBS.

Off treatment velocity predicts Meds plus STN DBS velocity

Figures 3 and 4 depicted moderate and mild bradykinetic patients with Parkinson’s disease. The peak velocity values suggested that the initial velocity OFF treatment might predict the velocity of the patients during Meds plus STN DBS. Indeed, Fig. 6 shows the linear regression between peak velocity of each patient OFF treatment and peak velocity during Meds plus STN DBS. The peak velocity values OFF treatment significantly predicted the peak velocity during Meds plus STN DBS. The peak velocity values OFF treatment significantly predicted the peak velocity during Meds plus STN DBS for both flexion ($R^2 = 0.68$, $P < 0.05$) and extension ($R^2 = 0.47$, $P < 0.05$) contractions. The slope and y-intercept values were 1.57 and 43.13 for flexion, and 1.14 and 149.24 for extension. Thus, the patients’ movement speed prior to the pharmacological and surgical intervention provides good prediction of how they will function after the intervention.

Effects of DBS on patients with and without Parkinsonian tremor

Figure 7 shows the kinematic and EMG recordings of elbow flexion movements made over a 72° distance from two unmedicated, male patients with Parkinson’s disease OFF treatment and on STN DBS (left: Patient 1; right: Patient 8). Figure 7 shows that the movements performed by both patients had a greater maximal velocity for STN DBS compared with OFF treatment. The primary difference between these two patients is that Patient 1 (left panel) has a normal 10 Hz physiological resting tremor as determined from the acceleration power spectrum prior to movement initiation. Also, the UPDRS from this patient

![Fig. 5](image-url)  
**Fig. 5** Across subject average (± SEM) of EMG measures for 72° flexion movements by Parkinsonian patients across the four postsurgery medication-stimulation conditions and by healthy control subjects. Data are plotted against the corresponding across subject average peak velocity. Part (A) shows amplitude of the agonist EMG burst, part (B) first agonist burst durations, part (C) the number of agonist bursts, part (D) the percentage of agonist-antagonist cocontraction, part (E) the amplitude of the antagonist EMG burst and part (F) the centroid of the antagonist.

![Fig. 6](image-url)  
**Fig. 6** Linear regression of average peak velocity for nine patients with Parkinson’s disease when OFF treatment in relation to peak velocity during Meds plus STN DBS for flexion movements (left panel) and extension movements (right panel).
D. E. Vaillancourt et al.
Physiological studies of bradykinesia demonstrate that patients with Parkinson’s disease have abnormal muscle activation patterns that fail to adequately ‘energize’ agonist muscles (Hallett and Khoshbin, 1980). Patient’s exhibit low amplitude fractionated bursting patterns that significantly depart from the healthy triphasic EMG pattern. Specifically, the amplitude of the agonist and antagonist bursts are reduced, the duration of the agonist bursts become shorter, and there are more agonist bursts prior to peak velocity (Hallett and Khoshbin, 1980; Pfann et al., 2001). The multibursting pattern may be a form of action tremor of Parkinson’s disease, which has been postulated to play a fundamental role in bradykinetic movements (Brown et al., 1997; Carboncini et al., 2001). The altered amplitude and temporal features of muscle activation directly limit patients’ movement speed providing a physiological mechanism for bradykinesia in Parkinson’s disease.

Discussion
Physiological studies of bradykinesia demonstrate that patients with Parkinson’s disease have abnormal muscle activation patterns that fail to adequately ‘energize’ agonist muscles (Hallett and Khoshbin, 1980). Patient’s exhibit low amplitude fractionated bursting patterns that significantly depart from the healthy triphasic EMG pattern. Specifically, the amplitude of the agonist and antagonist bursts are reduced, the duration of the agonist bursts become shorter, and there are more agonist bursts prior to peak velocity (Hallett and Khoshbin, 1980; Pfann et al., 2001). The multibursting pattern may be a form of action tremor of Parkinson’s disease, which has been postulated to play a fundamental role in bradykinetic movements (Brown et al., 1997; Carboncini et al., 2001). The altered amplitude and temporal features of muscle activation directly limit patients’ movement speed providing a physiological mechanism for bradykinesia in Parkinson’s disease.

Effects of DBS and medication: movement speed and muscle activation patterns
The first and second questions of the study examined the amplitude and temporal features of agonist and antagonist activation to determine how STN DBS and medication cause increases in movement speed. The findings demonstrated that with increased movement speed there was: (i) increased size of the first agonist burst; (ii) increased burst duration in the patients; (iii) reduced number of agonist bursts; (iv) reduced cocontraction; (v) increased size of the antagonist EMG; and (vi) reduced centroid time of the antagonist EMG. Either DBS or medication alone caused these changes in movement speed and muscle activation. Moreover, the relationship between movement speed and each parameter of muscle activation following DBS and medication was found for both flexion and extension contractions. When both DBS and medication were combined, only the temporal measures of burst duration and the number of agonist bursts were different from the medication alone condition. It should be noted that some of the improvements observed for bradykinesia may be secondary to changes in rigidity. For instance, EMG cocontraction is related to limb stiffness (i.e. rigidity) and this variable was reduced by both treatments. Collectively, these findings support three important conclusions: (i) either DBS or medication alone change both the amplitude and temporal features of the agonist and antagonist muscle activation; (ii) either DBS or medication alone reduce cocontraction between muscles; and (iii) the additive effects of DBS and medication on bradykinesia are mediated through increased agonist burst duration accompanied by a reduction in the number of agonist bursts.

With the exception of the agonist burst duration, the findings on the muscle activation patterns found for DBS of the STN are consistent with previous work examining the effects of levodopa. There were slight quantitative differences between medication and DBS, but overall these differences were small. A disparity found in this study from previous work was the previously reported finding that the agonist burst duration was constant on and off antiparkinsonian medication (Berardelli et al., 1986; Robichaud et al., 2002). The present study found that either medication or DBS alone increased the agonist burst duration, and that both treatments together produced an even greater increase in burst duration. The discrepancy regarding the effects of medication could be due to several factors.

One potential factor that could have contributed to the effects of medication on burst duration was that the DBS electrode was in the patients’ STN for over 3 months, and in previous work there was no DBS surgery (Berardelli et al., 1986; Robichaud et al., 2002). The continuous high frequency stimulation could have altered the way in which the basal ganglia responded to levodopa. Also, the DBS could have changed the way that other neural structures respond to basal ganglia output. Another clear difference between this study and the previous work was the differences in age, disease duration, and dyskinesias. Disease duration in the study of Berardelli et al. (1986) ranged from 2 to 21 years with a mean of 9 years, in Robichaud et al. (2002) it ranged from 2 to 20 years with a mean of 10.3 years, and in the present study it ranged from 5 to 21 years with a mean of 13.7 years. Also, the patients in this study were younger than in previous work [current study = 55.3 years; Berardelli et al. (1986) = 59.9 years; Robichaud et al. (2002) = 64.6 years]. The study by Berardelli et al. (1986) did not report on dyskinesias and that by Robichaud et al. (2002) had only two patients with minor dyskinesias. In the present study each patient experienced between mild and moderate dyskinesias. Finally, while not all of the UPDRS scores are available from each of the two.
studies above, there does appear to be significant overlap in the severity of the patients, indicating that disease severity may not have been a factor. Thus, one or a combination of factors that included chronic DBS, age, disease duration and dyskinesias may have contributed to the findings regarding the differential effects of medication on agonist burst duration.

Two findings regarding agonist burst duration ON and OFF treatment draws comparison to the data reported on Huntington’s disease. Huntington’s disease results in a preferential loss of striatal neurons of the indirect pathway that leads to excessive inhibition of the STN thereby reducing STN output (Wichmann and DeLong, 1996). Huntington’s disease patients move slowly and their agonist burst duration is prolonged (Thompson et al., 1988). In contrast, Parkinson’s disease patients OFF treatment have increased STN output with slow movement and reduced agonist burst duration. DBS of the STN and drug therapy reduces the excessive output from the STN (Hutchison et al., 1997; Beurrier et al., 1999). In addition, the current findings indicate that under Meds plus STN DBS patients still moved slowly, but that the agonist burst duration was longer than normal—a finding consistent with those on Huntington’s disease (Thompson et al., 1988). These data raise the possibility that the pathophysiology of the pharmacologically and surgically induced agonist burst duration in patients with Parkinson’s disease may be in part similar to the prolonged agonist burst duration of Huntington’s disease.

**DBS, tremor, and muscle activation**

Previously, DBS of the STN in patients with Parkinson’s disease has been shown to reduce bradykinesia, tremor and rigidity (Limosin et al., 1998; Deep-Brain Stimulation for Parkinson’s Disease Study Group, 2001; Rocchi et al., 2002). Prior to this study, it has been unclear as to whether DBS improves bradykinesia similarly in patients with and without a parkinsonian rest tremor, and this gave rise to our third question. The observation from this study was that DBS and medication improved movement speed and muscle activation in patients with and without a parkinsonian rest tremor.

**Degree of improvement related to initial status**

The fourth question of the study examined the relationship between OFF treatment movement speed and on treatment movement speed. The movement speed in the no treatment condition significantly predicted (68% for flexion and 47% for extension) a considerable portion of the variance for movement speed when patients were on both medication and DBS. Currently most of the patients treated with DBS surgery have advanced Parkinson’s disease. Because the degree of improvement in bradykinesia was related to the initial level of bradykinesia, then the patients who have the greatest potential to function normally following DBS have the lowest probability of receiving DBS surgery. Finally, the data clearly imply that, in some instances, patients who move at speeds of ~300°/s OFF treatment will approach normal speed of movement following surgery.

Is the triphasic EMG pattern restored by DBS and medication?

The fifth question of the study determined the extent to which movement speed and muscle activation patterns are restored to normal by means of medication and STN DBS. Control subjects’ movement speed was over 40% higher during both flexion and extension contractions when compared with the patients on both medication and DBS. Additionally, compared with the patients, healthy control subjects had a larger agonist burst, a shorter agonist burst duration, and reduced centroid time of the antagonist burst. Thus, in patients with Parkinson’s disease on both medication and DBS of the STN, movement speed and the triphasic EMG pattern are not restored to normal. Furthermore, the limitations in achieving normal movement speed reside in the amplitude and temporal scaling of the agonist and antagonist bursting pattern.

**Implications for basal ganglia contributions to pulse height and pulse width control**

The findings regarding the amplitude and temporal features of the agonist burst have implications on models of motor control and basal ganglia function. One such model of motor control proposed to account for the shape of the recorded agonist EMG burst includes two different types of input to the motor neuron pool: pulse height and pulse width control. Pulse height control postulates that the input to the motor neuron pool is of constant duration and the height of the excitation pulse scales to provide impulsive force to move the limb for movements of different speeds (Corcos et al., 1989). Pulse width control proposes an excitation of fixed amplitude where the duration scales for different distances and loads (Gottlieb et al., 1989). In both pulse height and pulse width control the input to the motor neuron pool is lowpass filtered by the neuromuscular system. When measured in the EMG signal, the lowpass filtering causes an excitation pulse using pulse height control to slightly change in duration, and for an excitation pulse using pulse width control to have small changes in its height. Thus far, the literature has supported a role of the basal ganglia in pulse height control and little attention has been paid to its possible contribution in pulse width control.

For instance, evidence from primates demonstrated that an imbalance in the output from basal ganglia neurons altered movement velocity and scaled agonist burst amplitude. In primates, cooling the external segment of the globus pallidus caused a decrease in movement speed, a loss of the phasic EMG burst, an increase in cocontraction, and an increase in movement variability (Hore and Vilis, 1980). In the primate, kainic acid-induced or muscimol-induced lesions of the globus pallidus lead to slower movements and a reduction in
the EMG burst amplitude (Horak and Anderson, 1984a; Mink and Thach, 1991). Single-cell discharge from the primate globus pallidus correlated with the velocity of horizontal arm movement (Anderson and Horak, 1985). Similar to the work on primates, there is evidence in humans linking basal ganglia output to movement velocity and pulse height control. In Parkinson’s disease, patients move abnormally slowly during ballistic movement tasks (Flowers, 1976) and the amplitude of the agonist bursts are reduced (Hallett and Khoshbin, 1980). Either injecting muscimol or lesioning the internal globus pallidus of Parkinson’s disease patients reduced the inhibitory output and increased movement velocity (Penn et al., 1998; Limousin et al., 1999). In addition, direct evidence from a PET study in humans showed that the regional cerebral blood flow of the internal globus pallidus scaled directly with movement speed (Turner et al., 1998). In their review of single-joint movement control, Berardelli et al. (1996) concluded that the basal ganglia play a role in scaling the amplitude of the agonist burst.

In support of Berardelli et al. (1996), the findings from the current paper have shown that the size of the first agonist burst increased linearly across changes in movement speed, and these changes were mediated by medication or DBS of the STN. Administering either medication or DBS of the STN directly changes the firing pattern of the output from the globus pallidus (Hutchison et al., 1997; Hashimoto et al., 2003). Current models of the basal ganglia predict that medication acts at the striatum thereby affecting the direct and indirect pathway, whereas STN DBS acts through the indirect pathway. The similar effects of the two treatments on scaling the amplitude of the agonist burst suggest that Parkinson patients will benefit as long as the firing pattern in the deficient common output from the direct and indirect pathway (i.e. globus pallidus internus/substantia nigra pars reticulata) is altered.

The findings from the present study suggest a role for the basal ganglia in not only pulse height control, but also in pulse width control (i.e. scaling burst duration). Either medication or DBS were shown to substantially increase the duration of the first agonist burst. Furthermore, the addition of DBS in the medicated state increased burst duration beyond the burst duration due to medication alone. Although the lowpass filtering properties of the neuromuscular system can alter the duration of a burst when pulse height control is used, the changes in the burst duration would be much smaller than the two-fold increase in burst duration observed in the Parkinson’s disease patients in this study. Therefore, the increased duration represents a role for the basal ganglia in pulse width control. Further support for this conclusion comes from two previous observations: (i) patients with Parkinson’s disease have shorter, fractionated bursts than healthy control subjects (Hallett and Khoshbin, 1980; Pfann et al., 2001), and (ii) patients with Huntington’s disease have a prolonged agonist burst duration (Thompson et al., 1988).

In conclusion, the evidence presented suggests a link between basal ganglia function with both pulse height and pulse width control. The changes in the amplitude and temporal features of the muscle activation patterns provide a mechanism of action for the pharmacological and surgical interventions used to treat bradykinesia in Parkinson’s disease. However, despite the ability of the combination of medication and DBS at improving bradykinesia in patients with Parkinson’s disease, patients’ movement speed is not restored to normal, presumably because the firing patterns within and between basal ganglia neurons remains abnormal.

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