Effects of subthalamic nucleus stimulation and medication on resting and postural tremor in Parkinson’s disease

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Summary
Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and antiparkinsonian medication have proved to be effective treatments for tremor in Parkinson’s disease. To date it is not known how and to what extent STN DBS alone and in combination with antiparkinsonian medication alters the pathophysiology of resting and postural tremor in idiopathic Parkinson’s disease. The purpose of this study was to examine the effects of STN DBS and antiparkinsonian medication on the neurophysiological characteristics of resting and postural hand tremor in Parkinson’s disease. Resting and postural hand tremor were recorded using accelerometry and surface electromyography (EMG) from 10 Parkinson’s disease patients and 10 matched control subjects. The Parkinson’s disease subjects were examined under four treatment conditions: (i) off treatment; (ii) STN DBS; (iii) medication; and (iv) medication plus STN DBS. The amplitude, EMG frequency, regularity, and 1–8 Hz tremor–EMG coherence were analysed. Both STN DBS and medication reduced the amplitude, regularity and tremor–EMG coherence, and increased the EMG frequency of resting and postural tremor in Parkinson’s disease. STN DBS was more effective than medication in reducing the amplitude and increasing the frequency of resting and postural tremor to healthy physiological levels. These findings provide strong evidence that effective STN DBS normalizes the amplitude and frequency of tremor. The findings suggest that neural activity in the STN is an important modulator of the neural network(s) responsible for both resting and postural tremor genesis in Parkinson’s disease.

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

Abbreviations: ANOVA = analysis of variance; ApEn = approximate entropy; DBS = deep-brain stimulation; RMS = root mean square; STN = subthalamic nucleus; UPDRS = Unified Parkinson’s Disease Rating Scale; VIM = Ventral intermediate

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Introduction
Tremor is one of three cardinal signs of idiopathic Parkinson’s disease, and individuals with the disease often exhibit both resting and postural tremor (Deuschl et al., 1998). Tremor in either form can be a debilitating neurological symptom because its presence severely disrupts activities of daily living, especially self-care tasks (Wasielewski et al., 1998). Deep brain stimulation (DBS) of the subthalamic nucleus (STN) (Deep Brain Stimulation for Parkinson’s Disease Study Group, 2001; Benabid, 2003; Krack et al., 2003) and antiparkinsonian medication (Cotzias et al., 1969; Yahr et al., 1969) are effective treatments for Parkinson’s disease. The extent to which STN DBS and medication change the neurophysiology of bradykinesia (Vaillancourt et al., 2004), gait (Faist et al., 2001; Bastian et al., 2003) and postural instability (Maurer et al., 2003) in Parkinson’s disease to healthy levels have been established. While STN DBS and medication reduce tremor rating scales (Olanow et al., 1991; Friedman et al., 1997; Krack et al., 1998; Rodriguez et al., 1998), it is not currently known how or to what extent STN DBS alters the pathophysiology of resting and postural tremor in Parkinson’s disease.

Previous research has used multiple dependent measures to study the neurophysiological mechanisms of tremor in Parkinson’s disease. These include measures of tremor amplitude, frequency, regularity and tremor–EMG coherence (Vaillancourt et al., 2004). Tremor–EMG coherence is the correlation between tremor and EMG activity recorded from the muscle groups responsible for tremor generation (Maurer et al., 2003). The coherence between tremor and EMG activity is a measure of how much of the tremor is generated by neural activity in the muscle group(s) responsible for tremor. Previous studies have shown that tremor–EMG coherence is increased in Parkinson’s disease compared to healthy controls, and that tremor–EMG coherence decreases with effective treatment (Vaillancourt et al., 2004). The purpose of this study was to examine the effects of STN DBS and antiparkinsonian medication on the neurophysiological characteristics of resting and postural hand tremor in Parkinson’s disease. Resting and postural hand tremor were recorded using accelerometry and surface electromyography (EMG) from 10 Parkinson’s disease patients and 10 matched control subjects. The Parkinson’s disease subjects were examined under four treatment conditions: (i) off treatment; (ii) STN DBS; (iii) medication; and (iv) medication plus STN DBS. The amplitude, EMG frequency, regularity, and 1–8 Hz tremor–EMG coherence were analysed. Both STN DBS and medication reduced the amplitude, regularity and tremor–EMG coherence, and increased the EMG frequency of resting and postural tremor in Parkinson’s disease. STN DBS was more effective than medication in reducing the amplitude and increasing the frequency of resting and postural tremor to healthy physiological levels. These findings provide strong evidence that effective STN DBS normalizes the amplitude and frequency of tremor. The findings suggest that neural activity in the STN is an important modulator of the neural network(s) responsible for both resting and postural tremor genesis in Parkinson’s disease.
Parkinson’s disease. These measures include frequency (Homberg et al., 1987), amplitude (Stiles and Pozos, 1976), regularity (Vaillancourt and Newell, 2000) and tremor–electromyogram (EMG) coherence (Brown et al., 1997; Vaillancourt and Newell, 2000). In contrast to the 8–12 Hz frequency of healthy physiological tremor (Halliday and Redfearn, 1956; Lakie et al., 1986), the frequency of resting and postural tremor in Parkinson’s disease is reduced to 3–6 and 4–12 Hz, respectively (Findley et al., 1981; Elble and Koller, 1990; Deuschl et al., 1998). There is a negative relation between the frequency and amplitude of tremor oscillations, such that if the frequency decreases the amplitude increases (Stiles and Pozos, 1976). The degree of rhythmicity in tremor, assessed using approximate entropy (ApEn) (Pincus and Goldberger, 1994), is greater and more regular in patients with Parkinson’s disease compared with healthy control subjects (Vaillancourt and Newell, 2000). In addition, the amount of squared correlation between the tremor and EMG signals (tremor–EMG coherence) in patients with Parkinson’s disease is increased in the low-frequency bands (Vaillancourt and Newell, 2000).

The purpose of this study was to examine the effects of therapeutic doses of medication and STN DBS on the neurophysiological characteristics of resting and postural hand tremor in patients with idiopathic Parkinson’s disease. The study had three main objectives. First, we examined whether STN DBS and medication reduced resting and postural tremor amplitude, regularity and tremor–EMG coherence, and whether the treatments increased resting and postural tremor EMG frequency. Secondly, the study directly compared the effects of STN DBS with those of medication on the neurophysiology of resting and postural tremor. The third objective was to determine the extent to which STN DBS alone, medication alone, or the combination of STN DBS and medication altered the neural control of resting and postural tremor to healthy physiological levels. Ten individuals diagnosed with Parkinson’s disease who received STN DBS participated in the study. The patients’ hand tremor data were compared with data from neurologically healthy control subjects who were matched according to age and gender. Patients were tested in four treatment conditions: (i) off treatment; (ii) STN DBS; (iii) medication; and (iv) medication plus STN DBS. Each patient and control subject was examined during resting and postural hand tremor conditions. The findings from this study establish neurophysiological correlates underlying the clinical efficacy of medication and STN DBS in the treatment of resting and postural hand tremor in Parkinson’s disease. Furthermore, the first evidence is presented on whether STN DBS and/or medication restore the neurophysiology of tremor to healthy physiological levels.

Methods

Subjects

Ten patients with Parkinson’s disease, aged 52.9 years (SD = 8.03), and 10 age- and gender-matched control subjects, aged 52.7 years (8.26), participated in the study. A paired t test confirmed that there were no statistically significant differences in age between the patient and control groups. All clinical and motor control evaluations for all of the patients were performed an average of 6.7 months after surgery and after optimization of DBS parameters had occurred. A priori inclusion criteria were established for the study, and the first 10 Parkinson’s disease patients who received STN DBS and met the criteria were chosen for the study. Patients were examined by a movement disorders neurologist and included in the study if they: (i) had idiopathic Parkinson’s disease as outlined by the Parkinson’s Disease Society Brain Bank diagnostic criteria (Hughes et al., 1992a, b); (ii) were deemed to have resting and/or postural tremor which was consistent with the Movement Disorders Consensus Statement on Tremor Type I or Type II classification (Deuschl et al., 1998); (iii) had a resting and/or postural tremor which both responded positively to levodopa therapy; and (iv) had a positive clinical improvement [greater than a 15% reduction in scores from the entire motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS)] from the off-treatment condition compared with the on STN DBS condition. All subjects gave informed consent to all experimental procedures, which were approved by the local institutional review board at The University of Illinois at Chicago, USA.

In all cases a quadripolar stimulation electrode was placed in the STN opposite to the most severely affected body side. Surgery was performed as part of clinical care according to standard procedures (Deep Brain Stimulation for Parkinson’s Disease Study Group, 2001; Starr et al., 1998). Briefly, the anatomical target was based on standard stereotactic coordinates while the patient was in the MRI scanner with a Leksell stereotactic head frame in place (Cohn et al., 1998). MRI images were subsequently reformatted and coordinates refined using a Stealth system. Intra-operatively, microelectrode penetrations were made through a burr hole to verify the neurophysiological target (Starr et al., 1998, 2000; Vitek et al., 1998). Responses to sensory stimuli (passive movements of upper and lower limbs) were sought to identify the sensorimotor portion of the STN, where the DBS lead was subsequently placed. Postoperatively, MRI demonstrated appropriate placement of the DBS lead.

The same movement disorders neurologist administered the entire motor section of the UPDRS to each patient before (pre) and after (post) surgery, and these scores are reported bilaterally. Following surgery, stimulation parameters were optimized in order to reduce presurgery scores on the motor section of the UPDRS. Optimization took place during several visits over the ensuing months. At the time of the experiments, in each case the pulse width and frequency were 60 µs and 185 Hz, respectively. The stimulation intensity varied from 1.8 to 3.1 V (mean = 2.26 V, SD = 0.42), and stimulation was delivered in a monophasic fashion (Table 1).

The average presurgical motor UPDRS score was 46.05 (SD = 12.90) off medication. Average postsurgical UPDRS scores were 37.85 (11.88) off treatment, 14.2 (10.42) on medication, 24.17 (11.51) on STN DBS, and 10.75 (8.98) on medication plus STN DBS. Presurgery UPDRS scores were significantly different from postsurgery off-treatment scores using a Wilcoxon matched pairs test (Z = 2.29, P < 0.05).

Experimental setup

The experiments for the patients were performed on two consecutive days in each of four treatment conditions: (i) off treatment; (ii) STN DBS; (iii) medication; and (iv) medication plus STN DBS. Examination of Figs 1–6 does not show trends in the data, suggesting that test order was not a limitation in the study. On day 1, testing of condition 1 took place between 9 and 11 a.m. and condition 2 occurred between 1 and 3 p.m. On day 2, the same testing schedule as day 1 was set for...
After the 9 a.m. dose, the motor section of the UPDRS was administered 90 min after activation of the stimulator. The patients' normal medication dose schedule was withheld, and the night prior to day 2 only STN DBS was withheld. Each patient stayed in a hotel close to the laboratory and was examined using a Medtronic Console Programmer (Model 7432 Minneapolis, Minnisota, USA) on each night prior to days 1 and 2 to ensure that medication efficacy was optimized. All patients had reduced UPDRS values 90 min following reactivation of the stimulator. The patients’ normal medication dose schedule was restarted on day 1 after tremor testing was completed. For all patients, resumption of optimal levodopa therapy began at 3 p.m. on day 1 and continued through day 2 of testing. On day 2, all patients took medication between 6 and 7 a.m. and then again at 9 a.m. Forty-five minutes after the 9 a.m. dose, the motor section of the UPDRS was administered to ensure that medication efficacy was optimized. All patients responded to levodopa therapy, so tremor testing proceeded 50 min after administration of the 9 a.m. levodopa dose. For the afternoon session on day 2, patients took medication at 12:30 p.m., and the same protocol for the morning session was followed. For all patients in this study, the afternoon tremor testing commenced 50 min later. At each dose, patients took the medications listed in Table 1.

### Table 1 Profile of each subject

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Post-surgical UPDRS off treatment Item 20</th>
<th>Deep brain stimulation parameters Item 21</th>
<th>Anti-parkinsonian medications</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>43</td>
<td>F</td>
<td>3</td>
<td>2.8 Monopolar: 0° C +</td>
<td>Carbidopa/levodopa 25/100 0.5 tab</td>
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<tr>
<td>2</td>
<td>49</td>
<td>F</td>
<td>0</td>
<td>2.6 Monopolar: 1° C +</td>
<td>Carbidopa/levodopa 25/100 0.5 tab</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>F</td>
<td>3</td>
<td>2.0 Monopolar: 1° C +</td>
<td>Carbidopa/levodopa 25/100 1 tab</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>F</td>
<td>3</td>
<td>2.2 Monopolar: 0° C +</td>
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</tr>
<tr>
<td>5</td>
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<td>F</td>
<td>3</td>
<td>1.8 Monopolar: 2° C +</td>
<td>Carbidopa/levodopa CR 25/100 1 tab</td>
</tr>
<tr>
<td>6</td>
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<td>3</td>
<td>2.1 Monopolar: 1° C +</td>
<td>Carbidopa/levodopa 25/100 3 tabs</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>M</td>
<td>1</td>
<td>2.0 Monopolar: 1° C +</td>
<td>Carbidopa/levodopa 25/100 1.5 tab</td>
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<td>3.1 Monopolar: 0° C +</td>
<td>Carbidopa/levodopa CR 25/100 1 tab</td>
</tr>
</tbody>
</table>

To ensure that each patient was on STN DBS, the motor section of the UPDRS was administered 90 min after activation of the stimulator. All patients had reduced UPDRS values 90 min following reactivation of the stimulator. The patients’ normal medication dose schedule was restarted on day 1 after tremor testing was completed. For all patients, resumption of optimal levodopa therapy began at 3 p.m. on day 1 and continued through day 2 of testing. On day 2, all patients took medication between 6 and 7 a.m. and then again at 9 a.m. Forty-five minutes after the 9 a.m. dose, the motor section of the UPDRS was administered to ensure that medication efficacy was optimized. All patients responded to levodopa therapy, so tremor testing proceeded 50 min after administration of the 9 a.m. levodopa dose. For the afternoon session on day 2, patients took medication at 12:30 p.m., and the same protocol for the morning session was followed. For all patients in this study, the afternoon tremor testing commenced 50 min later. At each dose, patients took the medications listed in Table 1.

### Tremor testing

Subjects were positioned in a 42 cm high straight-back chair with an arm that was 43 cm in length and 58 cm from the ground. The arm of the chair supported the subject’s forearm, with the ulnar styloid process aligned with the end of the chair. The elbow joint was flexed to approximately 90°, the shoulder joint was slightly abducted, and the forearm was pronated. A small table was positioned 30 cm in front of the subject. The height of the table was adjusted to be level with the tip of the subject’s hand when the wrist and fingers were extended parallel with the floor. The table served as the visual target to enable the subject to maintain the wrist in a neutral position. The width of the table edge was 0.5 inches.

A calibrated Coulbourn type V 94–41 (Allen town Pennsylvania, USA) miniature solid-state piezoresistive accelerometer was taped to the hand (2 cm proximal to the middle of the second metacarpophalangeal joint). A Coulbourn Lab Linc V System V72-25A resistive bridge strain gauge transducer with an excitation voltage of ±5 V amplified the acceleration signal. The accelerometer’s resolution was 0.01 m/s², and a 12-bit analogue–digital converter sampled the signal at 1000 samples per second. To remove the DC effects of gravity, all accelerometry data were collected in AC mode with a 1 Hz analogue high-pass filter (Elble and Koller, 1990).

Surface EMG was used to measure the neuromuscular activity in the extensor digitorum and the flexor digitorum superficialis. Electrode placement was determined by muscle palpation during active finger extension and flexion with the wrist in a neutral, extended position. The EMG signal was amplified (gain = 1000) and band-pass-filtered between 20 and 450 Hz (Delsys, Boston, MA, USA).

The study examined two types of tremor. In the resting tremor condition, subjects were instructed to relax their forearm and hand muscles and allow the wrist to dangle unsupported over the edge of the supportive surface for 30 s (Marsden et al., 1969; Burne et al., 1984;
Henderson et al., 1994; Raethjen et al., 2000). In the postural tremor condition, subjects were asked to maintain their wrist and hand in a neutral, extended position while keeping it level with the target for 30 s (Elble and Randall, 1976; Homberg et al., 1987; Henderson et al., 1994; Raethjen et al., 2000). Subjects performed three trials at each respective condition and were explicitly instructed throughout each trial not to suppress resting or postural tremor.

Data analysis
Before performing all data analyses, the acceleration and EMG data were conditioned by the following methods. The EMG data were digitally rectified, and the acceleration and EMG data were downsampled to 200 Hz (Vaillancourt and Newell, 2000). The acceleration and EMG data were digitally filtered using a fourth-order Butterworth filter with a low-pass cutoff frequency of 60 Hz for the EMG signals and 30 Hz for the acceleration signals. All data analyses were performed on the entire 30 s data segment—the same for each subject, trial, and condition. The dependent measures were averaged across the three trials for each condition. All data processing and subsequent time and frequency analyses were performed using software written in Matlab (MathWorks, Natick, MA, USA).

Amplitude and regularity of tremor
The amplitude and regularity of hand tremor were quantified in the same way as in our study of essential tremor (Vaillancourt et al., 2003). The amplitude of tremor was calculated using a method in which spectral analysis is used to extract the root mean square (RMS) tremor displacement from the dominant frequency of tremor (Stiles, 1976). The RMS displacement is obtained as if it had resulted from a single-frequency, periodic oscillation. This assumption is reasonable when examining hand tremor because the 5–10 Hz peak dominates the spectrum (Elble and Koller, 1990). First, the spectrum of the tremor acceleration is calculated. Second, the sum of the central three spectral values of the principal band from the spectrum is taken as the variance of the tremor oscillations at the dominant frequency (f). Thirdly, the RMS acceleration at this frequency (f) was obtained as the square root of this sum and then converted to units of displacement by dividing by the square of ω (ω = 2πf). The RMS displacement value is reported in centimetres.

The degree of rhythmicity or regularity of hand tremor was calculated using approximate entropy (ApEn), a measure of the time-dependent structure of the signal (Pincus, 1991). ApEn returns a value in the approximate range of 0–2, and it reflects the predictability of future values in a time series based on previous values. For example, a sine wave has accurate short- and long-term predictability, and this corresponds to an ApEn value near 0. If varying amplitudes of white Gaussian noise are added to a sine wave, then the ApEn value will increase. This increases the uncertainty of making future time series predictions when random elements are added. For a completely random signal (viz., white Gaussian noise), each future value in the time series is independent and unpredictable from previous values, and the ApEn value tends towards 2. Because ApEn is influenced by filtering characteristics, data length, and other factors (Pincus and Goldberger, 1994), the same algorithm and parameter settings (m = 2; r = 0.2 × SD of the signal) were used to be consistent with previous work (Pincus and Goldberger, 1994; Vaillancourt et al., 2003).

Coherence between acceleration and extensor EMG activity
The coherence between the acceleration and EMG signals estimates the degree of motor unit entrainment affecting the acceleration signal (Elble and Randall, 1976). The cross-spectrum was calculated using Welch’s averaged periodogram method (bin width = 0.7813 Hz). Coherence between the acceleration and extensor EMG signals (tremor–EMG coherence) was calculated, and a 95% confidence interval was determined based on the number of disjoint sections from the sample record (Rosenberg et al., 1989; Farmer et al., 1993). This method revealed a broad band of significant coherence. Next, we determined the peak coherence value in the coherence spectrum in the 1–8, 9–15, 15–30 and 35–50 Hz bins.

Frequency
The dominant frequency in the EMG spectrum recorded during resting and postural hand tremor was examined using autospectral analysis of the extensor EMG signal between 3 and 15 Hz.

Statistical analysis
The dependent variables described in the preceding sections were evaluated by analysis of variance (ANOVA). First, the effects of medication and STN DBS on tremor were evaluated using a three-way ANOVA: medication (off versus on) × STN DBS (off versus on) × tremor type (resting versus postural). Secondly, a direct comparison between medication and STN DBS was performed using a one-way ANOVA: treatment (on medication versus on STN DBS). Thirdly, a comparison of each treatment alone and the combination of both treatments with healthy tremor was performed using a two-way ANOVA: group (Parkinson’s disease versus control) by tremor type (resting versus postural).

The clinical postsurgical UPDRS hand tremor data were evaluated using a non-parametric Wilcoxon matched pairs test. Postsurgical, off-treatment, unilateral UPDRS hand tremor scores (Table 1) were compared with scores on medication, STN DBS, and medication plus STN DBS. UPDRS hand tremor scores were considered unilaterally because patients received unilateral STN DBS, and the dependent measures quantified hand tremor unilaterally. All statistical analyses were interpreted as significant when there was no more than a 5% chance of making a type I error. For important statistical comparisons, we wanted to protect against making a type II error. Therefore, additional power analyses were conducted for non-significant findings when comparing between medication and STN DBS, and comparing between each treatment and control subjects. The results from this power analysis are reported after the F values in two ways. Both the percentage of power in the current study with the current sample size and the sample size required to achieve 90% power are reported. All statistical analyses were completed using Statistica (StatSoft, Tulsa, OK, USA).

Results
Clinical effects
All 10 patients demonstrated positive clinical benefits from either medication or STN DBS. Postsurgical, unilateral UPDRS resting hand tremor scores (item 20) averaged across subjects were 2.2 (SD = 1.32) off treatment, 1.4 (1.26) on medication, 0.80 (0.92) on STN DBS, and 0 (0)
on medication plus STN DBS. Compared with off treatment, medication \((Z = 2.2, P < 0.05)\), STN DBS \((Z = 2.37, P < 0.01)\) and medication plus STN DBS \((Z = 2.52, P < 0.01)\) reduced unilateral hand tremor UPDRS scores for item 20. For postural tremor (item 21), the average postsurgical unilateral hand tremor UPDRS scores were 1.90 (1.10) off treatment, 1.1 (1.10) on medication, 1.1 (0.99) on STN DBS, and 0.2 (0.42) on medication plus STN DBS. Compared with off treatment, medication \((Z = 2.37, P < 0.01)\), STN DBS \((Z = 2.03, P < 0.05)\) and the combination of medication plus STN DBS \((Z = 2.52, P < 0.01)\) reduced postsurgical unilateral hand tremor UPDRS scores. Furthermore, patient reports concurred with UPDRS scores that both treatments reduced the amount of tremor experienced by the patients.

**Characterization of resting and postural tremor in individual subjects**

Figure 1 depicts acceleration, extensor EMG and flexor EMG signals from a patient with Parkinson’s disease (Case 6, Table 1) and a control subject during the resting tremor condition. Off treatment (Fig. 1A), the Parkinson’s disease subject had a high-amplitude tremor \((RMS = 11.05 \text{ cm})\) with a high degree of regularity, which corresponded to a low ApEn value equal to 0.50. The EMG revealed the pattern characteristic of Parkinson’s disease resting tremor—alternating bursts of flexor and extensor EMG activity. In Fig. 1B, medication decreased the amplitude of tremor to 1.33 cm and increased ApEn to 0.58. On STN DBS (Fig. 1C), the amplitude of the tremor also decreased to 0.03 cm and ApEn increased to 0.60. Resting physiological tremor data collected from a representative control subject (Fig. 1D) had a minute amplitude of 0.008 cm and ApEn equal to 0.66. In contrast to the bursting
EMG pattern in Fig. 1A, the EMGs depicted in Fig. 1B–D show a small, evenly dispersed amount of EMG activity consistent with a resting limb state.

Figure 2 shows time series data from the postural tremor condition. Off treatment (Fig. 2A), the Parkinson’s disease patient (Case 3, Table 1) had a high-amplitude tremor of 18.95 cm with ApEn equal to 0.46. Similar to resting tremor, postural tremor for the Parkinson’s disease patient off treatment presented with alternating bursts of flexor and extensor EMG activity. Medication (Fig. 2B) reduced the amplitude of postural tremor to 1.32 cm and increased ApEn to 0.58. STN DBS (Fig. 2C) reduced the amplitude of
postural tremor to 0.18 cm and increased ApEn to 0.63. Both treatments reduced the prominent alternating bursts of EMG activity that occurred off treatment. In Fig. 2D the representative control subject’s postural tremor had an amplitude of 0.03 cm. The control subject’s physiological postural tremor had an ApEn value of 0.76, which was higher than the value for the Parkinson’s disease patient on each treatment independently or in combination.
Amplitude of tremor

Effects of medication and STN DBS

Figure 3A and B depict across-subject average RMS displacements for resting and postural tremor from Parkinson’s disease patients and control subjects. The within-subject ANOVA revealed that postural tremor displacement was greater than resting tremor displacement for the Parkinson’s disease subjects \( F(1,9) = 5.76, P < 0.05 \). There was no interaction between medication and/or STN DBS and tremor type. However, there was a significant interaction between medication and STN DBS \( F(1,9) = 9.59, P < 0.01 \). Because of the interaction, one-way ANOVAs were conducted on the medication and STN DBS data separately. Medication significantly reduced displacement when patients were off STN DBS \( F(1,9) = 10.80, P < 0.01 \). Medication did not affect displacement when patients were on STN DBS \( F(1,9) = 1.42, P = 0.26, 10\% , n = 168 \). STN DBS reduced displacement when patients were either off medication \( F(1,9) = 13.02, P < 0.01 \) or on medication \( F(1,9) = 7.15, P < 0.05 \).

In order to determine directly which of the two treatments was more efficacious, tremor amplitude of Parkinson’s disease patients on medication was compared with amplitude on STN DBS. STN DBS reduced tremor amplitude below that of medication \( F(1,9) = 6.71, P < 0.05 \). These results show that each treatment reduces tremor, but that STN DBS is more effective than medication for tremor amplitude reduction.

Fig. 6 Resting and postural 1-8 Hz tremor-EMG coherence between the acceleration and extensor EMG of Parkinson’s disease patients \( (n = 10) \) and control subjects \( (n = 10) \), patients off medication (closed hexagons), patients on medication (open triangles) and control subjects (closed squares). (A) Resting tremor–EMG coherence from a Parkinson’s disease patient off treatment (dotted line) and on STN DBS (solid line). (B) Postural tremor–EMG coherence from the same Parkinson’s disease patient shown in A off treatment and on STN DBS. (C) Resting tremor–EMG coherence averaged across subjects (mean ± SE). (D) Postural tremor–EMG coherence averaged across subjects (mean ± SE). The thick dotted line in A and B is the 95% confidence line for significant coherence. Refer to text for significant differences.
Comparison of each treatment with controls

Figure 3A and B also illustrate that resting and postural tremor amplitude for control subjects was similar to Parkinson’s disease patients when on STN DBS \( [F(1,18) = 1.51, P = 0.23, 9\% , n = 272] \) alone, and under the combination of medication plus STN DBS \( [F(1,18) = 3.37, P = 0.08, 11\% , n = 108] \). However, patients in the medication-alone condition had greater tremor amplitude compared with control subjects \( [F(1,18) = 7.15, P < 0.01] \). The results from the three between-group ANOVAs showed non-significant interactions between group and tremor type, and non-significant main effects for tremor type. These findings demonstrate that only STN DBS normalized the amplitude of tremor.

Approximate entropy of tremor

Effects of medication and STN DBS

Figure 4A and B and statistical analysis revealed that medication \( [F(1,9) = 15.45, P < 0.01] \) and STN DBS \( [F(1,9) = 15.04, P < 0.01] \) increased ApEn (reduced regularity) during resting and postural tremor conditions. There were no differences in ApEn between resting and postural tremor, and no significant interactions with the treatment conditions. Furthermore, there was no difference between the medication alone and STN DBS alone conditions \( [F(1,9) = 0.00, P = 0.99, 9\% , n = 250] \). These findings show that medication and STN DBS equally reduce the regularity of tremor.

Comparison of each treatment with controls

When comparing Parkinson’s disease patients under each treatment condition with control subjects, Parkinson’s disease patients always had lower ApEn values (Fig. 4A and B) [medication alone, \( F(1,18) = 9.29, P < 0.01; \) STN DBS alone, \( F(1,18) = 11.53, P < 0.01; \) medication + STN DBS, \( F(1,18) = 6.52, P < 0.01 \)]. For each of the three between group comparisons, there was a main effect of tremor type \( (P < 0.05, \) with ApEn values greater for postural tremor than for resting tremor. These analyses show that the tremor of Parkinson’s disease patients is still more regular than that of control subjects regardless of treatment interventions.

Frequency of tremor

Effects of medication and STN DBS

Figure 5A and C depict the EMG spectrum during resting tremor from a representative Parkinson’s disease patient (Case 8, Table 1) off treatment and on STN DBS. Figure 5B and D show the EMG spectrum during postural tremor from the same Parkinson’s disease patient off treatment and on STN DBS. In the off-treatment condition (Fig. 5A and B), the peak frequency in the EMG spectrum is below 10 Hz, and there is high peak power in the spectrum in the low peak frequency range. In the on STN DBS condition, the peak frequency in the EMG spectrum is at a greater frequency \( (~10 \text{ Hz}) \), and the amount of power in the spectrum is reduced for both resting (Fig. 5C) and postural (Fig. 5D) tremor.

The statistical analysis resulted in a main effect for medication \( [F(1,9) = 10.48, P < 0.01] \) and STN DBS \( [F(1,9) = 19.17, P < 0.01] \) on resting and postural tremor EMG frequency (Fig. 5E and F). There was also a main effect of tremor type \( [F(1,9) = 14.05, P < 0.01] \). Figure 5E and F present group data, which show that postural tremor EMG frequency is greater than resting tremor EMG frequency. There were no significant interactions between treatment condition and tremor type. When directly comparing the two treatments, Fig. 5E and F and the statistical analysis show that Parkinson’s disease patients on STN DBS had greater EMG frequencies compared with the on-medication condition \( [F(1,9) = 9.28, P < 0.01] \). Thus, both medication and STN DBS increased tremor frequency, yet STN DBS had a greater effect on frequency than medication.

Comparison of each treatment with healthy controls

Effects of STN DBS/medication on tremor in PD

Effects of medication and STN DBS

Figure 5E and F present mean EMG frequencies from healthy subjects for resting tremor and postural tremor. Patients on medication alone had lower EMG frequencies than healthy subjects \( [F(1,18) = 23.65, P < 0.01] \). However, EMG frequencies of Parkinson’s disease patients on STN DBS alone \( [F(1,18) = 2.72, P = 0.12, 12\% , n = 102] \) and the combination of medication plus STN DBS \( [F(1,18) = 2.81, P = 0.11, 12\% , n = 105] \) were statistically indistinguishable from those of control subjects. For each of the three between-group comparisons there was a main effect of tremor type \( (P < 0.01, \) such that postural tremor EMG frequency was greater than resting tremor EMG frequency. In summary, STN DBS was the only treatment that normalized tremor EMG frequency.

Tremor–EMG coherence

Effects of medication and STN DBS

Figure 6A depicts resting tremor from a Parkinson’s disease patient (Case 4, Table 1) showing a reduction in 1–8 Hz resting tremor–EMG coherence from 0.70 to 0.32 as a result of STN DBS. Similarly, in the same patient during postural tremor, STN DBS (Fig. 6B) decreased tremor–EMG coherence in the 1–8 Hz bin from 0.75 to 0.42. We also examined resting and postural tremor–EMG coherence between 9 and 15 Hz, 15 and 30 Hz, and 35 and 50 Hz using exactly the same methods as described for the 1–8 Hz bin (see Method’s section: Coherence between acceleration and extension EMG activity). However, we did not find statistically significant differences between treatment conditions in these higher frequency bins.

Figure 6C and D depict across subject average resting and postural tremor–EMG coherence for Parkinson’s disease patients and control subjects. From the within-subject ANOVA, there was no effect of tremor type on tremor–EMG coherence, and no interactions between the treatments and tremor type. Conversely, there was a significant interaction between medication and STN DBS \( [F(1,9) = 5.12, P < 0.05] \). Due to this interaction, one-way ANOVAs were conducted on the medication and STN DBS data separately. STN DBS reduced tremor–EMG coherence both when patients were...
off medication \( [F(1,9) = 23.42, P < 0.01] \) and when they were on medication \( [F(1,9) = 6.42, P < 0.05] \). Medication also significantly reduced tremor–EMG coherence when patients were off STN DBS \( [F(1,9) = 10.48, P < 0.01] \). However, when patients were on STN DBS the addition of medication did not affect tremor–EMG coherence \( [F(1,9) = 0.87, P = 0.37, 9\% , n = 150] \). Finally, when medication and STN DBS were compared directly, tremor–EMG coherence for the STN DBS condition was lower than for the medication condition, yet the analysis did not reach statistical significance \( [F(1,9) = 3.61, P = 0.09, 29\%, n = 41] \). In summary, medication and STN DBS reduced tremor–EMG coherence compared with off treatment, but only STN DBS provided additional reductions in coherence when on medication.

**Comparison of each treatment with healthy controls**

Mean resting (Fig. 6C) and postural (Fig. 6D) tremor–EMG coherence for control subjects was lower than tremor–EMG coherence for patients in each treatment condition. The statistical analysis confirmed the observation from Fig. 6C and D. Medication \( [F(1,18) = 15.10, P < 0.01] \), STN DBS \( [F(1,18) = 5.80, P < 0.05] \) and the combination of medication plus STN DBS \( [F(1,18) = 7.85, P < 0.01] \) did not reduce tremor–EMG coherence in Parkinson’s disease patients to healthy physiological levels. The results from the three between-group ANOVAs also showed non-significant interactions between group and tremor type, and non-significant main effects for tremor type. These analyses demonstrate that the treatment interventions did not normalize tremor–EMG coherence.

**Discussion**

The purpose of this study was to examine the effects of therapeutic doses of medication and STN DBS on the neurophysiological characteristics of resting and postural hand tremor in patients with Parkinson’s disease. Consistent with previous work on essential tremor (Vaillancourt et al., 2003), the tremor amplitude, regularity, tremor–EMG coherence and EMG frequency were quantified. There were three important findings from this study. First, medication and STN DBS reduced resting and postural tremor amplitude, regularity and tremor–EMG coherence while increasing tremor frequency. Secondly, STN DBS was more effective than medication in reducing the amplitude and increasing the frequency of resting and postural tremor. Thirdly, STN DBS caused resting and postural tremor amplitude and frequency to approximate healthy physiological tremor, but medication did not. This is similar to the normalizing effect of STN DBS on gait stride length and gait velocity during treadmill walking in Parkinson’s disease patients (Faist et al., 2001). In contrast, STN DBS did not normalize tremor regularity and 1–8 Hz tremor–EMG coherence, which is comparable to the effects of STN DBS on self-paced, overground walking (Bastian et al., 2003), postural control (Maurer et al., 2003) and bradykinesia (Vaillancourt et al., 2004). These differences are important because they suggest that STN DBS operates with different magnitudes of clinical efficacy based on the task and/or the specific motor deficit. Our results are discussed in terms of the clinical significance and insight they provide for the central oscillator(s) of resting and postural tremor in Parkinson’s disease.

**Tremor amplitude**

The finding that medication (Koller, 1986; Koller et al., 1989; Henderson et al., 1994) and STN DBS (Krack et al., 1998; Rodriguez et al., 1998) reduced the amplitude of resting and postural hand tremor in patients with Parkinson’s disease is consistent with previous literature. However, the results from this study are the first to determine the extent to which STN DBS normalizes resting and postural tremor to healthy levels. Specifically, we found that the resting and postural tremor amplitude of Parkinson’s disease patients on STN DBS alone were both similar to the tremor amplitude of control subjects. In contrast, medication alone did not reduce tremor amplitude to the level of control subjects. While it is possible that suprathreshold doses of medication could have further reduced tremor, such doses would also cause dyskinesias, thereby compromising the clinical benefits of medical therapy.

Previous reports demonstrate that DBS of the ventral intermediate (VIM) thalamic nucleus reduces postural tremor amplitude in patients with Parkinson’s disease (O’Suilleabhain et al., 2003), but the extent to which VIM DBS restores tremor to control levels remains unclear. Nevertheless, clinical reports indicate that STN DBS also reduces rigidity, bradykinesia, and postural instability in patients with Parkinson’s disease (Deep-Brain Stimulation for Parkinson’s Disease Study Group, 2001; Benabid, 2003), supporting the current view that the STN rather than the VIM thalamic nucleus may be the preferred neurosurgical target for the treatment of parkinsonian patients exhibiting the classic triad of abnormal motor signs.

**Tremor regularity, frequency and coherence**

Increased regularity from physiological output is considered a biomarker for ageing and disease in the cardiovascular, endocrine and nervous systems (Lipsitz and Goldberger, 1992; Vaillancourt and Newell, 2002). Previous research has shown that Parkinson’s disease patients have more regular tremor compared with control subjects during resting and postural tremor (Vaillancourt and Newell, 2000). Our findings of reduced tremor regularity following STN DBS and medication are consistent with the effects that DBS of the VIM thalamic nucleus has on the regularity of essential tremor (Vaillancourt et al., 2003). The decrease in regularity demonstrates that STN DBS and medication actually change the time-dependent structure of tremor in patients with Parkinson’s disease rather than merely suppressing the amplitude of the pathological oscillations. It is important to note that neither treatment alone or in combination decreased resting and postural tremor regularity to control levels.
Medication and STN DBS also reduced the pathological 1–8 Hz tremor–EMG coherence in Parkinson’s disease patients. Due to the established relation between tremor–EMG coherence and motor unit synchronization (Halliday et al., 1999), the reduction in tremor–EMG coherence suggests that either treatment reduced motor unit synchronization. Primate electrophysiology has shown that STN lesions can desynchronize oscillatory neural activity in the STN while simultaneously reducing the amount of limb tremor (Wichmann et al., 1994). Similarly, dopamine and dopamine receptor agonists have been shown to reduce the 3–8 Hz oscillatory activity (Levy et al., 2001), and the coherence between these oscillatory neurons in the STN (Brown et al., 2001). This suggests that when previously synchronized basal ganglia oscillations become desynchronized, motor units are allowed to fire more independently rather than in synchrony. Since STN DBS and medication reduced tremor–EMG coherence, we postulate that motor units fired more independently, which also reduced tremor regularity and tremor amplitude.

An important finding from this study was that STN DBS and medication altered the EMG frequency of resting and postural tremor. In addition, STN DBS operated with sufficient efficacy such that resting and postural tremor EMG frequency in Parkinson’s disease patients was similar to that in control subjects. While previous studies have found that medication did not affect the frequency of tremor in Parkinson’s disease (Koller et al., 1989; Henderson et al., 1994), we found that medication did alter the frequency of tremor. These earlier studies determined the frequency of tremor by analysing the acceleration signal, which includes contributions from both the mechanical and the central oscillator(s). In contrast, the present study examined the EMG spectrum to determine the frequency of tremor, thereby focusing on the effect of treatment on the pathological central oscillator(s). Differences in disease severity and medication dosage between the Parkinson’s disease patients in our study and the Parkinson’s disease patients in previous studies may also explain the null effect medication had on tremor frequency in the preceding literature.

The mechanisms responsible for the increases in resting and postural tremor EMG frequencies are unclear. One possible mechanism is that the treatments directly changed the frequency of the central oscillator(s). While this explanation is plausible, we prefer the hypothesis that STN DBS and medication suppressed the pathological central oscillator(s), which would allow input from other oscillators (mechanical-reflex) to become more dominant in the system. The fact that the EMG frequency of tremor following STN DBS was similar to that in control subjects strengthens the argument that STN DBS unmasked oscillations which are characteristic of physiological tremor. Further study is necessary to determine if STN DBS resets or suppresses the central oscillator(s) frequency, thus allowing mechanical-reflex factors to play a larger role in the genesis of tremor.

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