INTRODUCTION

Dystonia is characterized by sustained co-contractions of agonist and antagonist muscles that lead to abnormal posture and movement. Although the underlying pathophysiology is unclear, it has been proposed that the hyperkinetic symptoms seen in dystonia arise from abnormally low firing rates of the neurons in the globus pallidus internus (GPI), leading to decreased inhibition of thalamic activity and consequently to increased excitability of the motor cortex (Vitek 2002). Neuronal recordings in the GPs obtained during functional stereotactic surgery for the implantation of deep brain stimulating (DBS) electrodes in dystonia patients have provided the opportunity to determine the firing rates of the neurons in these patients. Most of the published studies have reported low firing rates (Lenz et al. 1998; Merello et al. 2004; Starr et al. 2005; Vitek 2002; Vitek et al. 1998, 1999; Zhuang et al. 2004), confirming the predictions of the model. However, Hutchison et al. (2003) reported that the firing rates in the GPs of dystonia patients were high and not significantly different from those recorded in Parkinson’s disease (PD) patients except in patients under propofol anesthesia whose firing rates were low. Furthermore, the mean firing rate of neurons within the motor thalamus was found to be reduced in dystonia (Lenz et al. 1999) rather than the predicted increase. The model also fails to explain the therapeutic effects of pallidotomy for dystonia (Ford 2004; Imer et al. 2005; Lozano et al. 1997; Ondo et al. 1998; Vitek et al. 1998; Yoshor et al. 2001).

DBS of the GPI is also an effective treatment for PD (Alberts et al. 2004; Anderson et al. 2005; Loher et al. 2002; Rodriguez-Oroz et al. 2005; Weaver et al. 2005), a neurodegenerative disorder in which tremor, rigidity, and akinesia are the most relevant motor signs. The now classical basal ganglia–thalamic–cortical circuitry model explains the pathogenesis of hypokinetic symptoms in PD by an imbalance of the D1-mediated direct and D2-mediated indirect pathways (Albin et al. 1989; DeLong 1990). Such alterations were proposed to increase transmission through the indirect pathway while decreasing transmission through the direct pathway, resulting in increased neuronal firing in the GPI and decreased firing in the globus pallidus externus (GPe). Indeed, elevations in GPe firing rates have been shown to occur after administration of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) in nonhuman primates (Boraud et al. 1998; Drouot et al. 2004; Filion and Tremblay 1991; Miller and DeLong 1987), although there have also been other reports demonstrating a lack of difference between the two states (Bergman et al. 1994; Raz et al. 2000; Wichmann et al. 1999). In addition to changes in firing rates, GPe firing patterns were found to be more bursty (Boraud et al. 1998; Filion and Tremblay 1991) and displayed an increase in synchronous rhythmic activity (Bergman et al. 1998; Nini et al. 1995; Raz et al. 1996, 2000). Similarly, neuronal recordings in the GPs of PD patients show high firing frequencies and bursty, sometimes synchronously rhythmic, activity between GPe neurons (Hutchison et al. 1994; Levy et al. 2002; Magnin et al. 2000).

The varied and sometimes conflicting results from the previous dystonia studies might be related to the fact that the findings from patients with diverse manifestations of dystonia were pooled together in the analysis. To avoid this possible confound, the present study was limited to patients with a focal form of dystonia—cervical dystonia (CD)—that primarily af-
ffects the neck in comparison to a group of PD patients. Our results show that in the ventral portion of the GPi, the neuronal firing rates were significantly lower and more bursty in the CD group compared with the PD group. Some of the data presented here were briefly reported in Tang et al. (2005b).

**METHODS**

Neuronal recordings were obtained from seven idiopathic CD patients undergoing stereotactic surgery for bilateral implantation of DBS electrodes in the GPi. At the time of surgery, their mean age was 49 yr and the mean duration of symptoms was 10 yr. Further details of clinical symptoms and medications are provided in Table 1. Presurgical clinical assessments of all patients were performed by movement disorder specialists at the Toronto Western Hospital. The degree of disability was quantified according to the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS; Comella et al. 1997) and the scores are detailed in Table 2. No sedatives or anesthetics (e.g., propofol) were administered during or before the neuronal recordings. All of the CD patients had prior botulinum toxin injections in the affected muscles but had failed to obtain significant relief. Four of the CD patients received initial benefit from botulinum toxin injections (secondary nonresponders), whereas the other three never received any benefit from the injections (primary nonresponders).

Fourteen PD patients (nine males and five females) undergoing stereotactic surgery for the placement of bilateral DBS electrodes in the GPi or a unilateral lesion in the GPi (pallidotomy) were also included in this study for comparison purposes. These patients were previously reported in Tang et al. (2005a); however, the number of cells included in the present study is smaller because of a stricter inclusion criterion with respect to duration of recordings and additional analyses were performed on the data. All patients in this group were responsive to levodopa [L-DOPA (3,4-dihydroxy-L-phenylalanine)] and had L-DOPA–induced dyskinesia and motor fluctuations. Their mean age at the time of surgery was 62 yr. Medications were withheld overnight before the surgery and all PD patients manifested overt parkinsonian symptoms without dyskinesia during the procedure.

The methods of microelectrode-guided stereotactic surgery for the implantation of DBS electrodes into the GPi or pallidotomy have been previously described (Lozano and Hutchison 2002; Lozano et al. 1996). Briefly, recordings were made using parylene-coated tungsten microelectrodes with an exposed tip size of 15–25 μm. Microelectrode tips were plated with gold and platinum to reduce impedance to approximately 0.2 MΩ at 1 kHz. In five CD patients and six PD patients, simultaneous recordings from pairs of neurons were made using a pair of closely spaced (250 or 600 μm apart) microelectrodes. Signals were amplified and filtered using two Guideline System GS3000 modules (Axon Instruments, Foster City, CA). Action potentials arising from a single neuron were discriminated using template-matching, spike-sorting software (Spike2; Cambridge Electronic Design, Cambridge, UK). Only well-isolated single-cell recordings that were >18 s in duration while the patient was at rest were included in the analysis. Interspike interval (ISI) histograms to confirm a refractory period and power spectral analysis of the spike recordings to rule out cardiac pulsation-mediated oscillations or 60-Hz power line artifacts were performed on all recordings. Peripallidal recordings of border cells were identified and excluded from the analysis.

Locations of recording sites were reconstructed from the predicted electrode trajectory using the stereotactic atlas of Schaltenbrand and Wahren (1977). The atlas map was scaled to fit the patient’s anterior and posterior commissures and adjusted if necessary to correspond with the physiologically determined landmarks. These landmarks were obtained from single-cell recordings and microstimulation data that allowed identification of regions with or without cellular activity (gray vs. white matter), peripallidal border cells, the optic tract, and the internal capsule (Lozano and Hutchison 2002; Lozano et al. 1996). From these reconstructions, neurons were determined to be in the GPe or the GPi. Furthermore, to determine the approximate locations of GPi recordings within the structure (such as dorsal vs. the ventral part of the GPi), distances of the recordings to the dorsal border of the optic tract, which lies close to the ventral border of GPi, were calculated.

To characterize the firing activity of GPi neurons in the two patient groups, mean firing rates and several measurements of firing patterns were obtained. For the quantification of firing irregularity and burstiness the following were measured: 1) the burst index (a ratio of mean ISI to the mode ISI); 2) the coefficient of variation; 3) the kurtosis and skewness of the distribution of ISIs; 4) a modification of the Kaneoke and Vitek (1996) method, which uses discharge density to categorize firing patterns into bursts (a cell with frequent intervals of elevated instantaneous firing rates compared with other intervals of the spike train), random or regular (Levy et al. 2001); 5) percentage of spikes participating in bursts, number of bursts per 1,000 spikes, and intraburst rate, as determined by the use of a burst-detecting algorithm called the “Poisson surprise,” as described by Legendy and Salcman (1985). In the surprise method, only epochs of elevated discharge rate in a spike train with a surprise value ≥5 were considered to be bursts.

Previous studies have highlighted the possible significance of pauses in GPi activity in the pathophysiology of dystonia (Vitek et al. 1999; Zhuang et al. 2004). To more directly study pauses in the spike train, we have adapted the definition of Poisson surprise to identify pauses in GPi activity in the pathophysiology of dystonia (Vitek et al. 1999; Zhuang et al. 2004). To identify pauses in activity, we have also assumed a Poisson distribution of ISIs, which under these conditions would closely approximate an exponential distribution. The probability of finding a specific ISI in the distribution would be \( P_{pause} = e^{-x/P} \) and its surprise

<p>| Table 1. Clinical descriptions of the cervical dystonia patients at the time of surgery |
|---------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age, yr</th>
<th>Duration of Symptoms, yr</th>
<th>Symptom</th>
<th>Nonresponsiveness to Botulinum Toxin Injection</th>
<th>Medication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>M</td>
<td>50</td>
<td>10</td>
<td>Left</td>
<td>Present</td>
<td>Clonazepam</td>
</tr>
<tr>
<td>B</td>
<td>M</td>
<td>37</td>
<td>4</td>
<td>Right</td>
<td>Absent</td>
<td>Secondary</td>
</tr>
<tr>
<td>C</td>
<td>M</td>
<td>37</td>
<td>11</td>
<td>Right</td>
<td>Absent</td>
<td>Secondary</td>
</tr>
<tr>
<td>D</td>
<td>F</td>
<td>62</td>
<td>5</td>
<td>Right and Anterocollis</td>
<td>Absent</td>
<td>Primary</td>
</tr>
<tr>
<td>E</td>
<td>F</td>
<td>67</td>
<td>15</td>
<td>Left</td>
<td>Present</td>
<td>Primary</td>
</tr>
<tr>
<td>F</td>
<td>M</td>
<td>33</td>
<td>11</td>
<td>Retrocollis</td>
<td>Absent</td>
<td>Secondary</td>
</tr>
<tr>
<td>G</td>
<td>F</td>
<td>59</td>
<td>11</td>
<td></td>
<td></td>
<td>Clonazepam, baclofen, amitriptyline</td>
</tr>
</tbody>
</table>
RESULTS

Recordings from 173 GPe cells were analyzed (mean duration 29.4 s) along 23 tracks in seven CD patients and 168 (mean duration 34.9 s) along 23 tracks in 14 PD patients (12 of the 14 patients underwent unilateral pallidotomy); 39 GPe cells were recorded from six of the CD patients (except from patient D) and 58 from the PD patients. Figure 1A shows the trajectory of a typical electrode penetration through the GPe and GPe.

Firing rates

Results of rate analysis are summarized in Table 3. No significant difference was found in comparing the mean firing rates of GPe neurons between the CD and PD groups (t-test; \( P = 0.38 \); 62.6 ± 4.8 and 56.7 ± 4.4 Hz, respectively), whereas the mean firing rate of GPe neurons recorded from CD patients was significantly lower than that from the PD patients (Mann–Whitney rank-sum test; \( P < 0.001 \); 71.4 ± 2.2 and 91.7 ± 3.0 Hz, respectively; Table 3; Fig. 1B). When comparing GPe and GPe neuronal firing rates within the same patient group, firing rates of GPe and GPe neurons were similar in the CD patients (t-test; \( P = 0.09 \)), but firing rates of GPe neurons were significantly lower than those of GPe neurons in the PD group (t-test; \( P < 0.001 \)). Figure 1C plots the mean firing rates of GPe neurons recorded in 2-mm intervals dorsal to the physiologically identified optic tract. This plot demonstrates that the difference in mean firing rates occurred in the ventral portion of the GPe (two-way ANOVA; \( P < 0.001 \) for both 1.0- to 2.9 and 3.0- to 4.9-mm intervals, \( P = 0.01 \) for 5.0- to 6.9-mm intervals).

Firing patterns

The results of firing pattern analyses are summarized in Table 3. Comparisons of burst indices, coefficients of variation, percentages of spikes participating in bursts, and kurtosis

<table>
<thead>
<tr>
<th>Torticollis Severity Scale</th>
<th>Maximum Score</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Maximal Excursion</td>
<td></td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>1. Rotation</td>
<td></td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>2. Laterocollis</td>
<td></td>
<td>3</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3. Anterocollis or Retrocollis</td>
<td></td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B. Duration Factor (×2)</td>
<td></td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>4.5</td>
<td>4.5</td>
<td>3.5</td>
</tr>
<tr>
<td>C. Effect of Sensory Tricks</td>
<td></td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>D. Shoulder Elevation</td>
<td></td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>E. Range of Motion</td>
<td></td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>F. Time</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 3. Comparisons of burst indices, coefficients of variation, percentages of spikes participating in bursts, and kurtosis.
and skewness of ISI distributions showed that there was no significant difference in the firing pattern in the GPe between the two groups (Mann–Whitney rank-sum tests; Table 3, Fig. 2A). On the other hand, comparisons of these values for the GPi recordings demonstrated that GPi activity recorded from the CD group was remarkably more bursty, as demonstrated by significantly higher means of burst index, coefficient of variation, and percentage of spikes participating in bursts, as well as higher kurtosis and skewness in ISI distributions, signifying a higher dispersion of ISIs away from the mean ISI in their distributions (Mann–Whitney rank-sum tests; *P < 0.05; **P < 0.001). Figure 2C plots the mean values for each of the measures for GPi neurons recorded in 2-mm intervals as a function of their locations dorsal to the physiologically identified optic tract. This plot demonstrates that the differences in mean burst index, coefficient of variation, and percentages of spikes in bursts occurred in the ventral portion of the GPi (two-way ANOVA; *P < 0.05), whereas differences in kurtosis and skewness of ISI distributions occurred in the dorsal portion of the GPi (two-way ANOVA; **P < 0.001). Comparison of proportions of neurons exhibiting regular, random, or bursty firing patterns as determined by the Kaneoke and Vitek (1996) method demonstrated a statistically significant difference between the CD and PD groups in the GPi (chi-square = 16.6, *P < 0.005).

TABLE 3. Summary of measurement outcomes from rates and pattern analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cervical dystonia (n = 39)</th>
<th>Parkinson’s disease (n = 58)</th>
<th>Cervical dystonia (n = 173)</th>
<th>Parkinson’s disease (n = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firing rate, Hz</td>
<td>62.6 ± 4.8</td>
<td>56.7 ± 4.4</td>
<td>71.4 ± 2.2**</td>
<td>91.7 ± 3.0</td>
</tr>
<tr>
<td>Burst index</td>
<td>3.5 ± 0.1</td>
<td>2.6 ± 0.1</td>
<td>3.5 ± 0.1**</td>
<td>2.6 ± 0.1</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.04</td>
<td>1.0 ± 0.02**</td>
<td>0.9 ± 0.03</td>
</tr>
<tr>
<td>% Spikes in bursts</td>
<td>20.2 ± 2.9</td>
<td>18.8 ± 1.7</td>
<td>16.3 ± 1.0*</td>
<td>13.1 ± 1.0</td>
</tr>
<tr>
<td>Kurtosis of ISI distribution</td>
<td>50.9 ± 12.4</td>
<td>40.0 ± 5.0</td>
<td>32.5 ± 2.9*</td>
<td>26.2 ± 2.1</td>
</tr>
<tr>
<td>Skewness of ISI distribution</td>
<td>4.9 ± 0.5</td>
<td>4.3 ± 0.3</td>
<td>4.1 ± 0.1**</td>
<td>3.5 ± 0.1</td>
</tr>
<tr>
<td>Intraburst firing rate, Hz</td>
<td>123.8 ± 10.6</td>
<td>127.1 ± 11.0</td>
<td>113.4 ± 4.9**</td>
<td>141.1 ± 6.4</td>
</tr>
<tr>
<td>Number of bursts per 1,000 spikes</td>
<td>5.5 ± 1.0</td>
<td>7.4 ± 1.0</td>
<td>7.0 ± 0.7*</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>Number of pauses per 1,000 spikes</td>
<td>2.0 ± 1.4</td>
<td>0.04 ± 0.003</td>
<td>40.8 ± 1.4**</td>
<td>29.0 ± 1.4</td>
</tr>
<tr>
<td>Pause duration, ms</td>
<td>107.4 ± 14.2</td>
<td>157.8 ± 30.5</td>
<td>81.6 ± 4.1*</td>
<td>65.8 ± 4.1</td>
</tr>
</tbody>
</table>

Values are means ± SE; n values in parentheses. Asterisks denote significant differences (Mann–Whitney rank-sum tests or t-tests. *P < 0.05; **P < 0.001).
df = 2; P < 0.001) but not in the GPe (chi-square = 3.3, df = 1; P = 0.07; Fig. 2D).

Detailed characterization of bursts detected by the surprise method revealed that intraburst firing rates were significantly higher (Mann–Whitney rank-sum test; P < 0.001) in the GPi neurons of the PD group; on the other hand, the number of bursts per 1,000 spikes was higher in the CD group (Mann–Whitney rank-sum test; P < 0.05; Fig. 3A). The difference in intraburst rate occurred in both the ventral and dorsal parts of the GPi, whereas the difference in burst frequency occurred in only the ventral part of the GPi (two-way ANOVA; P < 0.05; Fig. 3B).

The use of the modified Poisson surprise method to identify pauses in activity showed that there was no significant difference in the frequency and duration of pauses in the GPe of the two groups (t-test; P values of 0.8 and 0.5 respectively; Fig. 3C). However, in the GPi the occurrences of pauses and pause durations were higher in CD patients (t-test; P < 0.05; Fig. 3C). Furthermore, the differences were limited to the ventral region of the GPi (two-way ANOVA; P < 0.05, Fig. 3D).

Spearman rank-order correlation was performed on pause measurements, firing rate, and burst measurements to determine whether the variables were correlated. The two pause measurements were significantly (P < 0.05) but weakly correlated (low correlation coefficients) with rate and burst measurements (Table 4).

**Rhythmic activity**

Spectral analyses of the data demonstrated a significant peak in the very low frequency (VLF; <3.0 Hz; e.g., see Fig. 4Ai) band in 25/39 of the GPe recordings and 169/173 of the GPi recordings in the CD group. Similar peaks were found in 31/58 of the GPe recordings and 163/168 of the GPi recordings in the PD group (Fig. 4Aii). The proportions of recordings with significant peaks at VLF were not significantly different between CD and PD patients in either the GPe or the GPi (Fisher exact tests; P values of 0.68 and 0.71 for GPe and GPi,
respectively). However, the proportions of recordings with significant peaks were remarkably lower in the GPe than in the GPi in both groups (Fisher exact test; \( P < 0.001 \)). Average frequencies of the peaks in the VLF band were lower in the GPi than in the GPe (two-way ANOVA; \( P < 0.001 \)) in the CD and the PD groups; however, there was no significant difference in mean peak frequency between the two patient groups (Fig. 4Aiii).

In addition to the presence of peaks in the VLF band, significant peaks were also found in the slow (3–6 Hz), mu-like (6–15 Hz), beta (15–35 Hz), and gamma (>35 Hz) ranges for some neurons in the GPe and GPi of both groups (see Fig. 4Bi for examples). The percentages of neurons in each of these frequency bands are displayed in Fig. 4Bi and their specific frequencies in Fig. 4Bii. Locations of the identified rhythmic cells and their oscillatory frequency are displayed in Fig. 4C, which shows that the distributions of oscillation frequencies were similar between the two groups at different depths.

**Correlated activity between pairs of neurons**

Simultaneous recordings were obtained from 39 pairs of neurons in the CD group and 40 pairs in the PD group. In the CD group, 24 pairs were recorded with both electrodes inside the GPi, 12 pairs were recorded in the GPe, and three pairs were recorded with one electrode in the GPi and the other in the GPe. None of the simultaneously recorded pairs of neurons from CD patients showed significant correlation of firing activity. Cross-correlations of GPi neuronal pairs (\( n = 28 \)) recorded from the PD patients revealed one pair exhibiting a short-latency inhibitory interaction and one pair with synchronized oscillatory firing at 17 to 20 Hz. In the cross-correlations of GPe pairs (\( n = 12 \)) recorded from the PD group, a short-latency inhibitory interaction was found for one pair and oscillatory synchronization at 17 to 22 Hz was found in a second pair.

**Relationship between firing activity and motor symptoms**

No significant relationship was found between the TWSTRS severity subscores and GPi firing rates (Pearson product moment correlation; \( P = 0.2 \); Fig. 5A) or patterns (Pearson product moment correlations; burst index, \( P = 0.3 \); coefficient of variation, \( P = 0.4 \); participation of spikes in bursts, \( P = 0.9 \); occurrences of pauses in activity, \( P = 0.8 \); duration of pauses in activity, \( P = 0.1 \)). In patients with head turn or torticollis, the mean neuronal firing rate of the GPi on the side ipsilateral to the direction of head deviation was not significantly different from that on the other side (Mann–Whitney rank-sum test; \( P = 0.7 \)) and no significant difference was found when the comparison was done for each patient individually (Fig. 5B). Similarly, no significant difference in firing pattern indices was found between the two sides (Mann–Whitney rank-sum test; \( P = 0.8 \)).

**FIG. 3.** Comparisons of outcomes from detailed burst and pause analyses. A and C: log-scaled box plots of burst and pause measurements, respectively, in GPe and GPi of CD (open boxes) and PD (filled boxes) patients. Distribution of these indices (means for 2-mm segments) as a function of distance dorsal to the optic tract is shown in B and D. Asterisks denote comparisons where statistical significance was reached (*\( P < 0.05 \); **\( P < 0.001 \)).

**TABLE 4.** Spearman rank-order correlation of pause, rate, and burst measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pause Duration</th>
<th>Firing Rate</th>
<th>Burst Index</th>
<th>Coefficient of Variation</th>
<th>% Spikes in Bursts</th>
<th>ISI Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pauses/1,000 spikes</td>
<td>0.56**</td>
<td>-0.41**</td>
<td>0.53**</td>
<td>0.57**</td>
<td>0.49**</td>
<td>0.22**</td>
</tr>
<tr>
<td>Pause duration</td>
<td>-0.63**</td>
<td>-0.35**</td>
<td>-0.51**</td>
<td>0.40**</td>
<td>0.33**</td>
<td>0.14*</td>
</tr>
<tr>
<td>Firing rate</td>
<td>-0.63**</td>
<td>0.40**</td>
<td>0.55**</td>
<td>0.72**</td>
<td>0.57**</td>
<td>0.0041</td>
</tr>
<tr>
<td>Burst index</td>
<td>-0.46**</td>
<td>-0.41**</td>
<td></td>
<td></td>
<td></td>
<td>0.034</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>0.72**</td>
<td>0.55**</td>
<td>0.72**</td>
<td></td>
<td></td>
<td>0.42**</td>
</tr>
<tr>
<td>% Spikes in bursts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.30**</td>
</tr>
<tr>
<td>Kurtosis of ISI distribution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.98**</td>
</tr>
</tbody>
</table>

Positive correlation coefficient represents direct proportional relationship; negative correlation represents inversely proportional relationship. *\( P < 0.05 \); **\( P < 0.001 \).
tests; burst index, $P = 0.7$; coefficient of variation, $P = 0.8$; participation of spikes in bursts, $P = 0.2$; occurrences of pauses in activity, $P = 0.4$; duration of pauses in activity, $P = 0.6$).

**DISCUSSION**

**GPi firing rates**

Consistent with the prediction of the rate model of basal ganglia function for dystonia (Vitek 2002), the firing rates of GPi neurons were found to be significantly lower in CD than in PD patients. [A previous study from our group reported a lower mean PD GPi firing rate (74 Hz; Hutchison et al. 1994) possibly as a result of using a different spike-discrimination method and/or systematic differences in the patients in the two studies.] However, in the absence of control data it is not possible to determine whether the firing in the CD patients was lower than normal and/or whether the firing in the PD patients was higher than normal. The mean firing rate in the GPi of normal monkeys (Filion and Tremblay 1991; Starr et al. 2005) is similar to the mean rate of 71 Hz in the CD patients and the difference in firing rates between the two groups (22%) is similar to the increase in GPi firing rates reported in some studies that compared normal and MPTP-treated monkeys (Filion and Tremblay 1991), thus suggesting that the firing rates we observed in the CD patients are close to normal. However, the mean firing rates of GPi neurons reported in previous studies for dystonia patients (mostly with generalized dystonia) are substantially lower, ranging from 20 to 60 Hz (Lenz et al. 1998; Merello et al. 2004; Sanghera et al. 2003; Starr et al. 2005; Vitek et al. 1998, 1999). Because CD is a focal disorder, it is possible that only a small portion of the GPi in CD patients is affected and thus that many of the recordings were made in the relatively unaffected parts of the GPi. This

![FIG. 4.](image)

**FIG. 4.** A: examples of power spectra showing peaks at very low frequencies (VLFs: <3 Hz). Dashed lines represent power spectra of raw data; solid lines represent corrected power spectra (see METHODS). Shaded bands show the 99.5% confidence intervals. Note that correction of the power spectra can either decrease (top right and bottom left), increase (bottom right), or result in no change (top left) to the power of a peak. Aii: proportions of recordings obtained from PD and CD patients with or without significant VLF peaks in their corrected power spectra. Aiii: comparison of distribution of the peak frequencies. B: examples of corrected power spectra with peaks in non-VLF frequencies. Bi: stacked bar graphs representing the proportion of neurons with significant peaks at the slow (3–6 Hz), mu-like (6–15 Hz), beta (15–35 Hz), and gamma (>35 Hz) bands in their corrected power spectra. Numbers of neurons contributing to each portion are numbered within the corresponding bar. Biii: scatterplot of the distribution of peak frequencies of neurons with rhythmic activity as a function of their depth in the 2 patient groups. Each plotted cell had only one significant peak >3 Hz.

**FIG. 5.** Lack of correlation between motor symptoms and electrophysiological recordings within the GPi. A: comparison of symptom severity and GPi neuronal firing rates in CD patients. Severity scores were assessed according to the Toronto Western Spasmodic Torticollis Rating Scale (scores proportional to severity; Comella et al. 1997). B: in patients with torticollis (head turn), firing rates of neurons recorded from the side ipsilateral to the direction of head turn were compared with those on the contralateral side. No significant difference was found between the 2 sides either when compared in groups (i) or individually (ii).
might explain the difference between our findings and those of the previous studies that included largely or only generalized dystonia patients. This interpretation might also explain the lack of significant correlation between severity and firing properties, as well as the lack of lateralized differences.

**GPI firing patterns**

The GPI neurons in CD patients were found to fire in a more bursty fashion compared with those recorded in PD patients. A similar finding was reported by Starr et al. (2005) in their burst index measurement for a group of dystonic patients that included some CD patients. Most studies in monkeys have reported increased burstiness in GPI activity in MPTP-treated monkeys compared with normal monkeys (Bergman et al. 1994; Boraud et al. 1998; Filion and Tremblay 1991; Filion et al. 1991; Wichmann et al. 1999) and that dopamine agonists decrease this burstiness (Boraud et al. 1998, 2001; Filion and Tremblay 1991), thus suggesting that the increased burstiness observed in the CD (and PD) patients is related to their pathology. We also found significantly more frequent and longer pauses in the GPI of CD compared with PD patients. Previous studies have qualitatively commented on the presence of frequent pauses in GPI activity in dystonia or hemiballism, another type of hyperkinetic disorder (Hutchison et al. 2003; Lenz et al. 1998; Sanghera et al. 2003; Vitek et al. 1999; Zhuang et al. 2004) and an association between pauses and onset of involuntary muscle contractions was reported in two studies (Vitek et al. 1999; Zhuang et al. 2004). It is possible that some of the pauses we observed in the CD patients may have been related to dystonic contractions.

**Localized changes within the GPI**

We found that the differences in GPI firing rates and patterns between CD and PD patients occurred primarily in the ventral region of the GPI, consistent with our previous findings showing that the differences in firing rates and patterns between various different types of movement disorders occur primarily in the ventral portion of GPI (Hutchison et al. 1994; Pereira et al. 2004; Tang et al. 2005b). Anatomical studies in nonhuman primates have shown that sensorimotor input is confined to the ventrolateral two thirds of the GPI (Flaherty and Graybiel 1991, 1993; Nakano 2000), suggesting that the differences in activity in the ventral portion might reflect localized pathophysiological changes in the motor region of the basal ganglia in PD and CD. Our finding of regional differences in firing rates and patterns suggests that mean results of pooled data from the whole nucleus can vary in different studies if the distribution of recording sites within GPI differs systematically.

**Similarity in GPe properties between the two groups**

According to the rate model of the pathophysiology of dystonia (Vitek 2002), the striatal inhibitory input to both pallidal segments is hyperactive so that both the GPe and GPI become hypoactive. Similarly, the rate model explains the pathophysiology of PD partially by a suppressed GPe output (Albin et al. 1989; DeLong 1990). Thus according to these models GPe activity is reduced in both dystonia and PD. This has been confirmed in MPTP-treated monkeys (Boraud et al. 1998; Filion and Tremblay 1991; Heimer et al. 2002; Raz et al. 2000) and is consistent with the findings of similar GPe and GPI firing rates in our study and that of Starr et al. (2005). However, the similarity in GPe firing patterns was a surprising finding given the very different GPI firing patterns between the two groups. The lack of a significant difference in GPI firing rates and patterns between the two groups suggests that the differences in GPI activity may be explained by changes in the direct pathway rather than the GPe-mediated indirect pathway (Kita et al. 2005) and/or pathology within GPI. Another possibility is that the region of GPI sampled in this study is not the motor region of the GPe.

**Oscillation and synchronization**

VLF (<3 Hz) oscillations were present in the majority of pallidal neurons, in both groups. VLF oscillations could possibly be generated by coupling between GPe and STN as previously shown in cortex-striatum-STN-GPe organotypic cultures (Plenz and Kitai 1999), although the source of oscillations in vivo may be different especially because the VLF oscillations were less frequent in the GPe than in the GPI. Another potential source for the generation of VLF oscillations in GPI neuronal activity is the striatum, which is known to oscillate between “up” and “down” states (Plenz and Kitai 1998; Tseng et al. 2001; Yasumoto et al. 2002) at approximately 1 Hz in vivo in rats with (Plenz and Kitai 1998; Tseng et al. 2001) and without (Stern et al. 1997) nigrostriatal lesions.

Consistent with previous findings from local field potential (LFP) recordings made in dystonic patients (Chen et al. 2006; Liu et al. 2006; Silberstein et al. 2003), we have found oscillatory activity in the slow, mu-like, and both beta and gamma ranges in single-unit recordings made in PD patients. However, similar oscillatory patterns were also present in the PD group and with a higher incidence of occurrence. This contrasts with the results of a previous study comparing recordings in the GPi of patients with different forms of dystonia and PD, which failed to find a significant difference in the proportion of oscillatory cells (~25% in patients with primary dystonia) (Starr et al. 2005). An increase in oscillatory activity has been suggested to be pathological in PD because MPTP-treated primates have demonstrated a marked increase in the occurrence of oscillatory and synchronized firing compared with normals (Bergman et al. 1994; Raz et al. 2000; Soares et al. 2004). In this study, some synchronous activity was found in the pairs of recordings made in PD patients, whereas no significant correlated activity was found between neuronal pairs recorded in the GPe or the GPI of CD patients, which is also consistent with the low occurrence of oscillatory cells in the CD patients (Levy et al. 2002). This suggests that increased synchronization and a breakdown in the segregation of subcircuits, which has been proposed as a pathological feature in PD (Bergman et al. 1998; Filion et al. 1994; Nini et al. 1995; Raz et al. 1996), may not be a feature of the pathophysiology in CD.

**Implications to the current model of dystonia and PD pathophysiology**

In conclusion, our finding of decreased GPI neuronal firing rates in CD patients compared with PD patients is consistent
with the predictions of the rate models. However, the firing rates in the CD patients were not as low as those reported in most previous studies of dystonia and may be close to normal. However, in view of the findings of other recent studies (Anderson et al. 2003; Bergman et al. 1994; Garcia et al. 2003; Hutchison et al. 2003; Lozano and Hutchison 2002; Raz et al. 2000; Tang et al. 2005a; Wichmann et al. 1999), it appears that alterations in GPi firing rates may not be the main cause of the dystonic or parkinsonian symptoms. We have also found a substantial difference in burstiness partly arising from a difference in the pauses in firing between the two groups; moreover, theta and beta oscillatory activity were more commonly found in PD, thus suggesting that changes in firing patterns and oscillatory activity play a significant role in the pathophysiology of both disorders (Brown 2003). The preferential changes in ventral GPi identified in this study suggest that future studies of GPi pathophysiology should take into account the locations of the recordings within the nucleus.

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REFERENCES


