Neuronal Firing Rates and Patterns in the Globus Pallidus Internus of Patients with Cervical Dystonia Differ from Those with Parkinson's Disease

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Running Head: Pallidal neuronal activity in CD

Abstract

Cervical dystonia (CD) is a movement disorder that involves involuntary turning and twisting of the neck caused by abnormal muscle contraction. Deep brain stimulation (DBS) in the globus pallidus internus (GPi) is used to treat both CD and the motor symptoms of Parkinson's disease (PD). It has been suggested that the differing motor symptoms in CD and PD may be due to a decreased GPi output in CD and elevation of output in PD. To test this hypothesis, extracellular recordings of GPi neuronal activity were obtained during stereotactic surgery for the implantation of DBS electrodes in seven idiopathic CD and 14 PD patients. The mean GPi neuronal firing rate recorded from CD patients was lower than in PD patients ($P < 0.001$; mean $\pm$ SEM: 71.4 ± 2.2 and 91.7 ± 3.0 Hz respectively). Furthermore, GPi neurons fired in a more irregular pattern consisting of more frequent and longer pauses in CD compared to PD patients. When comparisons were done based on locations of recordings, these differences in firing rates and patterns were limited to the ventral portion of the GPi. In contrast, no difference in firing rate or pattern was observed in the globus pallidus externus between the two groups. These findings suggest that both alterations in firing rate and firing pattern may underlie the differing motor symptoms associated with these two movement disorders.

Keywords

Basal Ganglia, Movement Disorders, Spasmodic Torticollis, Single-Unit Recording

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 are due to 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 GPi 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 et al., 1999; Vitek, 2002; Vitek et al., 1998; Zhuang et al., 2004), confirming the predictions of the model. However, Hutchison et al. (2003) reported that the firing rates in the GPi 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 Parkinson's disease (PD) (Alberts et al., 2004; Anderson et al., 2005; Lohr 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-thalamo-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 GPi firing rates have been shown to occur after administration of MPTP in non-human 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, GPi 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., 2000; Raz et al., 1996). Similarly, neuronal recordings in the GPi of PD patients show high firing frequencies and bursty, and sometimes synchronously rhythmic activity between GPi 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 affects 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 to 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 years and the mean duration of symptoms was 10 years. Further details of clinical symptoms and medications are provided in Table 1. Pre-surgical 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 prior to 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 non-responders) while the other three never received any benefits from the injections (primary non-responders).

Fourteen PD patients (9 males and 5 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 have previously been reported in Tang et al. (2005a), but the number of cells included in the present study is smaller due to a stricter inclusion criterion with regards to duration of recordings and additional analyses were performed on the data. All patients in this group

were Levodopa-responsive and had Levodopa-induced dyskinesia and motor fluctuations. Their mean age at the time of surgery was 62 years. 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 et al., 1996; Lozano and Hutchison, 2002). 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 $\sim 0.2 \text{ M}\Omega$ at 1 kHz. In 5 CD patients and 6 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 longer than 18 seconds in duration made while the patient was at rest were included in the analysis. Interspike interval histograms to confirm a refractory period and power spectral analysis of the spike recordings to rule out cardiac pulsation-mediated oscillations or 60Hz 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 Schaltenbrand and Wahren stereotactic atlas (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 et al., 1996; Lozano and Hutchison, 2002). From these reconstructions, neurons were determined to be in the GPe or the GPi. Furthermore, in order to determine the approximate locations of GPi recordings within the structure (such as dorsal versus 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 inter-spike interval to the mode inter-spike interval), 2) the coefficient of variation 3) the kurtosis and skewness of the distribution of inter-spike intervals (ISIs), 4) a modification of the Kaneoke and Vitek (1996) method, which uses discharge density to categorize firing patterns into bursty (a cell with frequent intervals of elevated instantaneous firing rates compared to other intervals of the spike train), random or regular (Levy et al., 2001), 5) percentage of spikes participating in bursts, number of bursts per 1000 spikes and intra-burst 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 greater than or equal to 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 the occurrences of pauses. The original Poisson surprise value was defined to be $-\log(P)$, where P is the probability that the spike density is similar to that of a Poisson distribution (Legendy and Salcman, 1985). 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 $P_{\text{pause}} = e^{-x/\mu}$ and its surprise value would become $S_{\text{pause}} = -\log(P) = -\log(e^{-x/\mu}) = x/\mu$. Here, we have used a minimum S_{pause} value of 3 as it identified most of the visually identifiable pauses in activity. An ISI, x , with a S_{pause} value of 3 is equivalent to a 0.05 probability of finding x in a random distribution. After the identification of pauses, the frequency of pause occurrences and average duration of pauses were determined.

To determine rhythmicity of activity, auto-correlograms and power spectra were constructed. Details regarding the use of auto-correlograms for identifying rhythmic activity have been previously described in Levy et al. (2002). As for the use of time-frequency analysis, power spectra were constructed based on a method akin to the global shuffling method described in Rivlin-Etzion et al. (2006) that removes the effect of mean neuronal firing frequency on the power spectrum. Data were bootstrapped on the basis of shuffling the ISIs 40 times, and a power spectrum was constructed after each shuffling. The 40 power spectra were then averaged, smoothed and subtracted from the power spectrum derived from the original data. The 99% confidence intervals (CI) were

calculated based on the Chi-square distribution of the ISIs and a non-overlapping window of Fourier transform analysis to give the minimal degrees of freedom, and a more conservative estimate of the intervals. In addition, cross-correlations were performed for simultaneously recorded neurons for the detection of synchronicity between pairs of neurons (Karmon and Bergman, 1993; Levy et al., 2002).

Offline data analysis was performed in Spike2 (Cambridge Electronic Design, England) and Matlab (The MathWorks, Natick MA). Comparisons were performed by the use of the SigmaStat software (version 3.00, SPSS Inc.). To detect differences in firing rate and pattern of activity between PD and CD, measurements were subjected to student t-tests if the data were normally distributed; otherwise, Mann-Whitney rank sum tests were performed. For comparisons of means at different distances from the optic tract, two-way ANOVA followed by Dunn's method of all pairwise multiple comparison were used. Chi-square comparisons were performed to compare proportions of observations of different categories and Fisher exact-tests were employed if one or more of the categories consisted of 5 or less expected observations. Lastly, the Spearman rank order correlation was done for detecting possible correlation between various measurements. In this study, a *p* value less than 0.05 was considered to be significant. All values are expressed as the mean $\pm$ SEM.

Results

Recordings from 173 GPi 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 6 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 GPi.

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 GPi 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 GPi neuronal firing rates within the same patient group, firing rates of GPe and GPi neurons were similar in the CD patients (t-test; $p=0.09$), but firing rates of GPe neurons were significantly lower than those of GPi neurons in the PD group (t-test; $p<0.001$). Figure 1C plots the mean firing rates of GPi 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 GPi (two-way ANOVA; $p<0.001$ for both 1.0-2.9 and 3.0-4.9 mm intervals, $p=0.01$ for 5.0-6.9 mm interval).

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 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; $p < 0.05$; Table 3, Fig. 2B). 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 with 2 degrees of freedom; $p < 0.001$) but not in the GPe (Chi-square=3.3 with 1 degree of freedom; $p = 0.07$; Fig. 2D).

Detailed characterization of bursts detected by the surprise method revealed that intra-burst 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 1000 spikes was higher in the CD group (Mann-Whitney rank sum test; $p < 0.05$; Fig. 3A). The difference in intra-burst rate occurred in both the ventral and dorsal parts of the GPi,

whereas the difference in burst frequency occurred only in 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-tests; $p = 0.8$ and 0.5 respectively; Fig. 3C). However, in the GPi the occurrences of pauses and pause durations were higher in CD patients (t-tests; $p < 0.05$; 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; see Fig. 4Ai for example) 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; $p = 0.68$ and 0.71 for GPe and GPi respectively). However, the proportions of recordings with significant peaks were remarkably lower in the GPe than 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 (3-6Hz), mu-like (6-15Hz), beta (15-35Hz) and gamma (>35Hz) 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 Figure 4Bii and their specific frequencies in Figure 4Biii. The locations of the identified rhythmic cells and their oscillatory frequency are displayed in Figure 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 sub-scores 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 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 (74Hz; Hutchison et al 1994) possibly due to the use of 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 rates in the GPi of normal monkeys (Filion and Tremblay, 1991; Starr et al., 2005) is similar to the mean rate of 71Hz 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 60Hz (Vitek et al., 1998; Vitek et al., 1999; Lenz et al., 1998; Merello et al., 2004; Sanghera et al., 2003; Starr et al., 2005). Since 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 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 to 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 to normal monkeys (Bergman et al., 1994; Boraud et al., 1998; Fillion et al., 1991; Fillion and Tremblay, 1991; Wichmann et al., 1999) and that , dopamine agonists decrease this burstiness (Boraud et al., 2001; Boraud et al., 1998; Fillion 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 to 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, and is 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,(Pereira et al., 2004; Tang et al., 2005b, Hutchison et al., 1994). Anatomical studies in non-human primates have shown that sensorimotor input is confined to the ventrolateral two-thirds of the GPi (Flaherty and Graybiel, 1993; Flaherty and Graybiel, 1991; 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 suggest 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 GPe firing rates and patterns between the two groups suggests that the differences in GPi activity may be due to 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 GPe sampled in this study is not the motor region of the GPe.

Oscillation and synchronization

VLF (<3Hz) 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), but the source of oscillations *in vivo* may be different especially since 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 ~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, beta and gamma ranges in single unit recordings made in CD 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 as MPTP-treated primates have demonstrated a marked increase in the occurrence of oscillatory and synchronized firing compared to 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 while 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; Fillion 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 to 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 due to a difference in the pauses in firing between the two groups, and 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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Table 1. Clinical descriptions of the cervical dystonia patients **at the time of surgery**

	Gender	Age (years)	Duration of Symptoms (years)	Symptoms		Non-responsiveness to botulinum toxin injection	Medications
				Side at which the Head is Deviated Towards	Head Tremor		
A	M	50	10	Left	Present	Secondary	Clonazepam
B	M	37	4	Right	Absent	Secondary	Lorazepam
C	M	37	11	Right	Absent	Primary	Gabapentin
D	F	62	5	Right and Anterocollis	Absent	Primary	Lorazepam
E	F	67	15	Left	Present	Secondary	Nil
F	M	33	11	Right	Present	Primary	Diazepam, cyclobenzaprine
G	F	59	11	Retrocollis	Absent	Secondary	Clonazepam, baclofen, amitriptyline

Table 2. Breakdown of dystonia severity scores according to the Toronto Western Spasmodic Torticollis Rating Scale(Comella et al., 1997) assessed at the time of the last preoperative visit of the cervical dystonia patients

Torticollis Severity Scale	Max Score	Patients						
		A	B	C	D	E	F	G
A. Maximal Excursion								
1. Rotation	4	2.5	2	2.5	4	4	3	1
2. Laterocollis	3	1	2	2	2.5	0.5	1	0
3. Anterocollis or Retrocollis								
a. Anterocollis	3	0.5	1	0	3	0.5	0	0
b. Retrocollis	3	0	0	0	0	1	0	3
4. Lateral Shift	1	0	0	1	0.5	0	0	0
5. Saggittal Shift	1	0	0	0	0	0	0	1
B. Duration Factor (x2)	5	4	5	4.5	4.5	3.5	5	5
C. Effect of Sensory Tricks	2	1.5	0.5	1	0.5	0.5	1	1
D. Shoulder Elevation/ Anterior Displacement	3	1	2.5	1	1	1	0	1
E. Range of Motion	4	0	1.5	1	4	-	2	1
F. Time	4	0	4	4	4	4	4	4
Total Score	38	14.5	23.5	21.5	28.5	18.5	16	17
Ranking (1=most severe)		7	2	3	1	4	6	5

Table 3. Summary of measurement outcomes from rates and pattern analyses. Asterisks denote significant differences (Mann-Whitney rank sum tests or t-tests; * $p < 0.05$; ** $p < 0.001$).

	Globus Pallidus Externus		Globus Pallidus Internus	
	Cervical Dystonia (n = 39)	Parkinson's Disease (n = 58)	Cervical Dystonia (n = 173)	Parkinson's Disease (n = 168)
Firing Rate (Hz)	62.6 ± 4.8	56.7 ± 4.4	$71.4 \pm 2.2^{**}$	91.7 ± 3.0
Burst Index	3.5 ± 0.1	2.6 ± 0.1	$3.5 \pm 0.1^{**}$	2.6 ± 0.1
Coefficient of Variation	1.1 ± 0.1	1.0 ± 0.0	$1.0 \pm 0.0^{**}$	0.9 ± 0.0
% Spikes in Bursts	20.2 ± 2.9	18.8 ± 1.7	$16.3 \pm 1.0^{*}$	13.1 ± 1.0
Kurtosis of ISI Distribution	50.9 ± 12.4	40.0 ± 5.0	$32.5 \pm 2.9^{*}$	26.2 ± 2.1
Skewness of ISI Distribution	4.9 ± 0.5	4.3 ± 0.3	$4.1 \pm 0.1^{**}$	3.5 ± 0.1
Intra-Burst Firing Rate (Hz)	123.8 ± 10.6	127.1 ± 11.0	$113.4 \pm 4.9^{**}$	141.1 ± 6.4
Number of Bursts per 1000 Spikes	5.5 ± 1.0	7.4 ± 1.0	$7.0 \pm 0.7^{*}$	4.4 ± 0.4
Number of Pauses per 1000 Spikes	2.0 ± 1.4	0.04 ± 0.0	$40.8 \pm 1.4^{**}$	29.0 ± 1.4
Pause Duration (ms)	107.4 ± 14.2	157.8 ± 30.5	$81.6 \pm 4.1^{*}$	65.8 ± 4.1

Table 4. Spearman rank order correlation of pause, rate and burst measurements

	Pause Duration	Firing Rate	Burst Index	Coefficient of Variation	% Spikes in Bursts	Kurtosis of ISIs Distribution	Skewness of ISIs Distribution
Pauses / 1000 Spikes	0.56**	-0.41**	0.53**	0.57**	0.49**	0.22**	0.29**
Pause Duration		-0.63**	0.35**	0.40**	0.33**	0.14*	0.19**
Firing Rate			-0.51**	-0.46**	-0.41**	0.0041	-0.059
Burst Index				0.72**	0.55**	0.034	0.12*
Coefficient of Variation					0.72**	0.42**	0.52**
% Spikes in Bursts						0.30**	0.38**
Kurtosis of ISI Distribution							0.98**

* $P < 0.05$ ** $P < 0.001$

Positive correlation coefficient represents direct proportional relationship; negative correlation coefficient represents inversely proportional relationship.

Figure 1. Firing rates of pallidal neurons in cervical dystonia (CD) and Parkinson's disease (PD) patients. A: Depiction of a typical track penetrating through the globus pallidus with the globus pallidus internus shaded in grey; The distance between the small ticks on the electrode track is 1mm. B: Box plots (span of box represents data within the 25th to 75th percentile) of neuronal firing rates recorded from the globus pallidus externus (GPe) and internus (GPi) of CD and PD patients with. Filled boxes represent data from the PD group and open boxes represent those from the CD group. The medians are marked by horizontal lines within the boxes. C. Firing rates are plotted as a function of depth of neuronal recordings in 2-mm intervals. The numbers of cells included in each plot are labeled above or below the corresponding circle. Asterisks denote comparisons where statistical significance was reached (* $P < 0.05$ and ** $P < 0.001$).

Figure 2. Comparisons of firing pattern indices. **B** Box plots of measurements obtained from neurons in GPe (A) and GPi (B) in the CD (represented by open boxes) and PD (filled boxes) groups. In part C, the mean values for each of the firing pattern indices of neurons in 2 mm intervals in GPi are plotted as a function of distance dorsal to the optic tract in 2 mm intervals. Stacked bar graphs of percentages of GPe and GPi cells in CD and PD that were categorized into the three different firing patterns by the use of the modified Kaneoke and Vitek method (1996) are displayed in D. Asterisks denote comparisons where statistical significance was reached (* $P < 0.05$ and ** $P < 0.001$).

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

Figure 4. Examples of power spectra showing peaks at very low frequencies (VLF; < 3 Hz) are depicted in A(i). Dashed lines represent power spectra of raw data whereas 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 (upper right and lower left), increase (lower right) or result in no change (upper left) to the power of a peak. A(ii) shows the proportions of recordings obtained from PD and CD patients with or without significant VLF peaks in their corrected power spectra. The distribution of the peak frequencies are compared in A(iii). Examples of corrected power spectra with peaks in non-VLF frequencies are displayed in B(i). 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 are depicted in B(ii). The numbers of neurons contributing to each portion are numbered within the corresponding bar. The scatter plot (Biii) shows the distribution of peak frequencies of neurons with rhythmic activity as a function of their depth in the two patient groups. Each plotted cell had only one significant peak above 3 Hz.

A Very Low Frequencies (VLF)

B Other Frequencies

C Locations of Rhythmic cells

Figure 5. Lack of correlation between motor symptoms and electrophysiological recordings within the globus pallidus internus (GPi). Comparison of symptom severity and GPi neuronal firing rates in cervical dystonia patients is displayed in A. Severity scores were assessed according to the Toronto Western Spasmodic Torticollis Rating Scale (scores proportional to severity; [Comella et al., 1997](#)). In patients with torticollis (head turn), firing rates of neurons recorded from the side ipsilateral to the direction of head turn were compared to those on the contralateral side (B). No significant difference was found between the two sides either when compared in groups (i) or individually (ii).