Spontaneous pallidal neuronal activity in human dystonia: comparison with Parkinson’s disease and normal macaque

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Running title: Pallidal single unit activity in dystonia
Abstract

Dystonia is a movement disorder defined by sustained muscle contractions, causing twisting and repetitive movements and abnormal postures. To understand the abnormalities in pallidal discharge in dystonia, we have analyzed the spontaneous activity of 453 neurons sampled from the internal or external pallidum (GPi or GPe, respectively) of 22 patients with dystonia, 140 neurons from eleven patients with Parkinson’s disease (PD), and 157 neurons from two normal nonhuman primates (NHPs) (*Macacca mulatta*). All recordings were performed without systemic sedation. Mean GPi discharge rate (+/-SEM) in dystonia was 55.3 +/- 1.3 Hz. This was significantly lower than in the normal NHP (82.5 +/- 2.5 Hz) and lower than in PD patients (95.2 +/- 2.3 Hz). Mean GPe discharge rate in dystonia (54.0 +/- 1.9 Hz) was lower than in the normal NHP (69.7 +/- 3.3 Hz) and was indistinguishable from that in PD (56.6 +/- 3.5 Hz). Mean GPi discharge rate was inversely correlated with dystonia severity. GPi showed increased oscillatory activity in the 2-10 Hz range and increased bursting activity in both dystonia and PD as compared with the normal NHP. Since the abnormalities in discharge patterns were similar in dystonia compared with PD, we suggest that bursting and oscillatory activity superimposed on a high background discharge rate are associated with parkinsonism, while similar bursting and oscillations superimposed on a lower discharge rate are associated with dystonia. Our findings are most consistent with a model of dystonia pathophysiology in which the two striatal cell populations contributing to the direct and indirect intrinsic pathways of the basal ganglia both have increased spontaneous activity.

Keywords: Dystonia, electrophysiology, globus pallidus, Parkinson’s disease
Introduction

Dystonia is a movement disorder defined by sustained muscle contractions, causing twisting and repetitive movements and abnormal postures. The pathophysiology of dystonia is incompletely understood, but it is thought to involve the loop circuit from sensorimotor cortices (SMC), through parts of the basal ganglia and ventrolateral thalamus, and back to cortex (Marsden et al. 1985; Vitek et al. 1999). The globus pallidus internus (GPi) occupies a critical position in this circuit, being the major output structure of the basal ganglia “motor” territory (Alexander et al. 1990). Decreases and increases in discharge of the GABAergic neurons of GPi are believed to facilitate and suppress, respectively, the activity of recipient thalamocortical circuits and, eventually, muscle activity (Wichmann and DeLong 1998). Hypo- and hyperkinetic movement disorders have been modeled as imbalances in the suppressive or facilitatory effects of pallidal output (Bergman et al. 1990; Mink 2003; Wichmann and DeLong 1998).

The resurgence of microelectrode-guided basal ganglia surgery for movement disorders affords the opportunity to study pallidal electrophysiology in a variety of disease states. Pallidal single cell discharge characteristics are best documented in Parkinson’s disease (PD). PD in the off-medication state has been found to be associated with excessive and abnormally patterned neuronal activity in the motor territory of the GPi (Hutchison 1998; Levy et al. 2001; Magnin et al. 2000; Sterio et al. 1994).

Several groups have described single unit microelectrode recordings in dystonic humans in the awake state, but unresolved questions remain. Four reports, describing data collected from a total of 16 patients, reported that the mean spontaneous GPi discharge rate is abnormally low in dystonia (Lenz et al. 1998; Merello et al. 2004; Sanghera et al. 2003; Vitek et al. 1999). In contrast, Hutchison et al. (2003) showed that in seven dystonic patients, GPi discharge was not reduced and was in fact similar to the hyperactive pallidal discharge of Parkinson’s disease. Given the heterogeneity in the type and severity of dystonia represented in prior series, analysis of a larger number of cases, controlling for disease type and severity, is needed to resolve the discrepancies.

Vitek et al. (Vitek 2002; Vitek et al. 1999) have focused on patterns of discharge in the dystonic GPi, proposing that intermittent bursts of high frequency discharge are a prominent feature of dystonia. It is unclear, however, if bursts in single unit discharge occur in a periodic manner and, if so, in what frequency range. Abnormal oscillatory activity in specific frequency bands has been proposed to be a fundamental feature of disordered basal ganglia function (Bergman et al. 1994; Brown 2003; Ruskin et al. 2002; Silberstein et al. 2003). This motivates a closer investigation of oscillatory activity in single unit data in dystonia.

When the dystonic state is studied in isolation, it is difficult to determine which of the electrophysiologic characteristics are actually abnormal and which abnormalities are unique to the dystonic state. The optimal control group would be normal humans, but
single unit recording in normal humans cannot be performed due to the invasiveness of the technique. Of note, many similarities have been found between GPi recording obtained from nonhuman primates (NHPs) in the parkinsonian state (Filion and Tremblay 1991; Miller and DeLong 1987; Wichmann et al. 1999) and those from humans with PD (Hutchison 1998; Levy et al. 2001; Magnin et al. 2000; Sterio et al. 1994). This suggests that pallidal physiology of the NHP will provide a reasonable approximation to what would be observed in the normal human. A direct comparison of GPi discharge in human dystonia with that of the normal nonhuman primate, using similar methodology, however, has not been performed previously.

To clarify the nature of abnormal basal ganglia output in dystonia, we have analyzed the spontaneous activity of 453 pallidal neurons sampled from 22 patients with dystonia, 140 neurons from eleven patients with Parkinson’s disease, and 157 neurons from two normal NHPs (Macaca mulatta). We used identical recording and analysis methods for all subjects. Recordings were obtained without systemic anesthetics or sedatives.

Methods

Patient population

Single unit recording in GPi and GPe was performed in awake patients undergoing physiologic mapping for placement of DBS electrodes. Of 28 dystonia patients mapped between 1999 and 2004, 22 were included in this study. All subjects gave informed consent according to a protocol approved by the Institutional Review Board. Patients were excluded from this study if physiological mapping had to be performed with general anesthesia or intravenous sedation, or if recordings from fewer than 5 units from GPi or GPe were amenable to analysis. A quantitative measure of dystonia severity was obtained in the month prior to surgery, using a standard clinical rating scale, the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) (Burke et al. 1985), by a movement disorders neurologist (WJM or JLO). All patients underwent magnetic resonance imaging (MRI) of the brain prior to surgery, and all juvenile onset dystonia patients had genetic testing for the presence of a mutation at the DYT-1 locus (Ozelius et al. 1997). We also studied eleven patients undergoing pallidal DBS implantation for PD, who were rated preoperatively with the motor scale (Part III) of the Unified Parkinson’s Disease Rating Scale (UPDRS).

Surgical procedures and data recording: human

Procedures for pallidal localization and electrophysiology were similar to those documented in recent publications (Lozano et al. 1996; Starr 2003; Starr et al. 2004; Vitek et al. 1998). Most patients required sedation with propofol for placement of the stereotactic headframe and stereotactic MRI, due to involuntary muscle spasms. All patients, including PD patients, received propofol for placement of a foley catheter immediately prior to surgery, and for the surgical incision. In all cases, propofol was stopped at least 30 minutes prior to the start of pallidal recording, and the total dose of
propofol given did not exceed 200 mg. All patients were alert and oriented at the start of microelectrode recording. Patients were instructed to make no voluntary movements during the recording, although most patients with dystonia at rest did experience spontaneous dystonic spasms during the recording.

For a subset of patients, four channels of surface electromyographic (EMG) data were collected (Delsys, Inc., Boston, MA) at 1000× gain, filter band pass of 100 Hz - 800 Hz, and sampling rate of 20 kHz. For patients with generalized dystonia, EMG data were recorded from the contralateral biceps, triceps, rectus femoris, and hamstrings. For patients with cervical dystonia, EMG data were recorded from the contralateral biceps, triceps, trapezius, and sternocleidomastoid. Summed triaxial acceleration was recorded from the contralateral wrist. These signals were used to document any spontaneous movement that occurred during the recording period, as well as for statistical correlation with neuronal activity.

Single unit discharge was recorded with glass-coated platinum/iridium microelectrodes, impedance 0.4-1.0 Mohm at 1000 Hz (Microprobe, Inc., Gaithersburg, MD or FHC, Inc., Brunswick, ME). Recordings were filtered (300 Hz-5 KHz), amplified, played on an audio monitor, and digitized (20 kHz sampling rate) using the Guideline System 3000 (Axon Instruments, Foster City, CA, now distributed by FHC, Inc., Brunswick, ME). Microelectrodes were advanced into the brain using a motorized microdrive (Axon Instruments clinical micropositioner or FHC microdrive).

In a typical surgical case, 3-4 parallel parasagittal microelectrode penetrations were made serially through GPe and GPi on each side, separated by 2-3 mm, in 1-2 parasagittal planes. All except two patients were operated bilaterally, and neuronal data collected from both hemispheres were pooled. The optic tract (OT) was detected by light-evoked action potential discharge at the pallidal base. Cells were recorded at approximately every 300-800 microns along each trajectory. Somatosensory examination was performed during all recordings to detect cells responsive to movement, so as to determine whether the region recorded was within the motor territory of the relevant nucleus. Neuronal activity was collected for a minimum of 20 seconds. Prior to recording, subjects were asked to remain as still as possible during these periods of recording. The location and discharge characteristics of cells along each microelectrode track were plotted on scaled drawings, noting also the locations of white matter laminae and the OT. The tracks were superimposed on drawings of parasagittal sections from the Schaltenbrand and Warren human brain atlas, according to a visual judgment of “best fit” of the tracks to the atlas. Cells encountered between the internal medullary lamina and the optic tract were considered internal pallidal cells, while those between the striatum and the internal medullary lamina were considered external pallidal cells. Cells near the presumed GPe-GPi border, on a track where a definite white matter boundary was not identified, were excluded from analysis due to their uncertain localization.

**Surgical procedures and data recording: NHP**

Two rhesus macaques (male, 10 kg and female, 6 kg) were surgically prepared for recording using aseptic surgery under isoflurane inhalation anesthesia. All aspects of
animal care were in accord with the “Guide for the Care and Use of Laboratory Animals” (National Academy Press, 1996), and all procedures were approved by the UCSF Institutional Animal Care and Use Committee. A cylindrical stainless steel chamber (18 mm internal diameter) was implanted with stereotaxic guidance over a burr hole allowing access to nuclei of the posterior basal ganglia [centered on Horsley-Clark anterior 10, lateral 20, depth 20 (Winters et al. 1969)]. The chamber was oriented parallel to the coronal plane at an angle of 35 degrees from vertical. The chamber was fixed to the skull with bone screws and dental acrylic. Bolts were embedded in the acrylic to allow fixation of the head during recording sessions.

After a minimum interval of one month following placement of recording chambers, serial microelectrode penetrations through the globus pallidus were performed along parallel coronally oriented trajectories, separated by 1.0 mm. No sedative agents were used for the recording sessions. Microelectrodes were identical to those used in the human. The electrodes were advanced into the brain using a hydraulic microdrive (MO-95, Narishige International, Tokyo). Neuronal signals were amplified (10,000×), filtered (150 Hz – 8 kHz band pass), and digitized (40 kHz) using one channel of a Multichannel Acquisition Processor (Plexon, Inc., Dallas, TX). A 2-minute record of continuous data was collected for each neuron while the animal rested quietly in a sound- and light-shielded chamber. Neurons were then examined for responses to experimenter-imposed manipulations of leg and arm joints, the trunk, and face.

**Analysis of spontaneous activity**

Digitized spike trains were imported into off-line spike sorting software (Plexon, Inc.) for discrimination of single populations of action potentials by principal components analysis. This software generated a record of spike times (subsequently reduced to millisecond accuracy) for each action potential waveform detected. The interspike intervals (ISIs) between successive spike times were used to evaluate stationarity of discharge, to calculate parameters of the ISI distribution, to construct autocorrelograms, and to evaluate the data stream for the occurrence of bursting or irregularity in discharge (see below). Analyses were performed in Labview and Matlab programming environments.

Neuronal data were included in this study only if action potentials could be discriminated with a high degree of certainty, if the complete record of ISIs fulfilled statistical criteria for stationarity of discharge (as tested off-line with the runs-test (Tuckwell 1988)), if the number of recorded action potentials exceeded 800, and if the spontaneous activity of the neuron was recorded for at least 20 seconds (human) or 60 seconds (NHP). (For the units which met these criteria, the mean stationarity (+/- standard deviation) was 0.37 +/- 0.17).

Non-oscillatory bursting. The data were submitted to a variety of pattern detection algorithms to assess non-oscillatory bursting. To facilitate comparison of our data with other publications on discharge abnormalities in movement disorders, three methods for burst detection described in other studies were used here: the “L” statistic, after Kaneoke and Vitek (Kaneoke and Vitek 1996) and Goldberg et al. (Goldberg et al. 2002); the
“burst index” (Hutchison et al. 2003), defined as the mean ISI divided by the modal value; and the Poisson “surprise” method of Legendy and Salcman (Legendy and Salcman 1985; Wichmann et al. 1999). In this latter method, bursts in the discharge stream are defined as segments of data with a Poisson surprise value of greater than ten. The minimum number of spikes that can constitute a burst in this method was four. The resulting data were tabulated as the proportion of ISIs within bursts compared to the total number of ISIs in the entire data stream.

Oscillatory activity. Autocorrelograms were used to detect oscillatory activity. Autocorrelation functions were calculated from the ISI data for lags of -500 to +500 ms, low-pass filtered (100 Hz cutoff, Remez FIR method), and plotted for visual inspection. The functions were statistically evaluated following methods modified slightly from Raz et al. (Raz et al. 1996). First, the central trough associated with the refractory period of a cell was removed from the autocorrelation to reduce high frequency noise. The mean of the autocorrelogram was subtracted and the autocorrelogram was resampled to 5 ms bins so as to improve the resolution of low frequency oscillations. A power spectrum was computed from the rebinned autocorrelogram (±500 ms in 5 ms bins), providing a 0.4 Hz resolution of frequencies. The fast Fourier transform for this analysis was calculated using non-overlapping segments of 512 data points and a boxcar window of the same length. The activity of a cell was considered to have a significant oscillatory component if the power spectrum had one or more significant peaks between 2 and 30 Hz. A peak in the spectrum was considered significant if either of the following two criteria were met: 1) Peak signal-to-noise ratio (SNR) exceeded 7 SD. Peak SNR was computed as the difference of peak power and mean power (2-30 Hz) divided by SD of the entire power spectrum (0-100 Hz). 2) Oscillation index (OI) of the peak exceeded 10%. Peak OI reflected the area under a spectral peak and above mean power (2-30 Hz) divided by the total power under the spectrum. These thresholds for statistical significance of SNR and OI were established empirically according to a Monte Carlo analysis in order to avoid assumptions about the population statistics of those measures (Tsau and Chen 1989). In this analysis, SNR and OI measurement were computed for 10,000 synthetic "random" spike trains generated assuming Poisson firing statistics and a mean firing rate of 50 Hz. The thresholds cited above were found to reject false positives within these synthetic spike trains with 95% accuracy.

Analysis of spike-EMG coherence

For data sets that included EMG and accelerometer recordings, the EMG data were rectified, smoothed (100 Hz low-pass, zero phase lag Remez FIR method), and sub-sampled to a 200 Hz sampling rate. A spike density function (SDF) was constructed from the neuron’s spike train as the sum of Gaussian functions (unit area, 10 ms variance) centered on individual spike times. (For a detailed justification and description of this method, see (Szucs 1998)). The SDF was then low-pass filtered (100 Hz cut-off) and sub-sampled to a 200 Hz sampling rate. Cross-correlograms and coherence functions were computed for all SDF–EMG or SDF–acceleration combinations according to the methods of Halliday et al. (1995). Instances of significant coherent oscillation in neuronal activity and EMG/acceleration were detected as peaks in the coherence function below 30 Hz that had a raw probability of $p<0.0002$. This threshold was determined to reject false
positives in 95% of cases in Monte Carlo analyses of identically processed random synthetic data.

Hypothesis testing

Hypothesis testing was performed using the SPSS statistical package (SPSS, Chicago, Illinois). We tested the hypothesis that mean spontaneous pallidal discharge parameters in patients with dystonia, patients with PD, and normal NHP are different, using the independent sample t-test (for continuous data) or the chi-square test (for categorical data). We tested the hypothesis that mean pallidal discharge rate in dystonia correlates with dystonia severity, using Spearman’s rho. Difference in severity and discharge rate between subtypes of dystonia was tested using the Kruskall Wallis exact test, two sided.

Results

Patient characteristics

Characteristics of the 22 dystonia patients (labeled cases A-V) are presented in Table 1. Since dystonia is a heterogeneous disorder, different etiologies were represented in this series: idiopathic dystonia (14 cases), tardive dystonia (three cases), and secondary dystonia (three cases). Two cases were classified as unknown etiology, since the patients were adopted at age two and age five, with a movement disorder already present, normal MRI scans of the brain, and an unknown prior medical history. In these two cases, secondary dystonia from perinatal or early childhood brain injury cannot be ruled out. The three patients with secondary dystonia had definite structural brain abnormalities on MRI, as follows: bilateral parietal encephalomalacia (case R, post-traumatic dystonia), T-2 hyperintensity in the lentiform nuclei (case S, pantothenate-kinase associated neurodegeneration), and a focal left posterior thalamic T1 hypointensity (case T, post-stroke dystonia). All other patients had normal brain MRIs. The idiopathic dystonias were further characterized as juvenile onset, positive for the DYT-1 mutation (Ozelius et al. 1997) (four cases); juvenile onset, negative for the DYT-1 mutation (four cases); or adult onset (six cases). Two patients (cases E and T) had a visible dystonic tremor during surgery (Svetel et al. 2004). Three cases (A, F, and O) had minimal dystonia at rest, but had action-induced dystonia that produced severe disability, including inability to use the arms for any skilled activities (case A) and inability to walk (case O). Clinical characteristics of the eleven PD patients were as follows (mean +/- SD): age at surgery = 59 +/- 8 years; duration of symptoms = 15 +/- 5 years; baseline UPDRS motor subscore in the off medication state = 43 +/- 8, daily levodopa dosage = 980 +/-390 mg. All PD patients manifested prominent bradkinesia during surgery, while none manifested obvious dystonia. Only one of the PD patients had tremor during surgery.

Pallidal discharge rate in dystonia, normal NHP, and PD

Summary data, in which all units recorded in each condition (dystonia, normal NHP, and PD) are pooled, are shown in Table 2. Mean GPi discharge rate in dystonia
was lower than that in the normal NHP and in Parkinson’s disease patients ($p<0.001$ for both comparisons, 2-sample independent t-test). Mean GPe discharge rate in dystonia was lower than in the normal NHP, but it was statistically indistinguishable from that in PD. (The infrequently recorded, low-frequency GPe bursting cells were deliberately excluded from the analysis.)

GPI and GPe discharge rates for the individual cases of dystonia, compared with NHPs and patients with PD, are illustrated in boxplots in Figure 1. All dystonic patients had lower median GPI discharge rates than all of the PD patients. Median discharge rates in dystonia were generally lower than those in the normal NHPs, but several dystonic patients (cases C, H, M, N, and O) had median discharge rates in the same range as those of the normal NHPs.

To better understand the variability in GPI discharge rates between dystonia patients, mean GPI discharge rates for all cases of dystonia were plotted as a function of dystonia severity and etiology (Figure 2). Statistical comparison of group means for dystonia subtypes are provided in Table 3. GPI discharge rates were found to be significantly higher for patients with primary dystonia (57.8 +/- 1.5 Hz) and tardive dystonia (54.6 +/- 3.1 Hz) versus those with secondary dystonia (34.0 +/- 3.5 Hz) (Kruskall Wallis exact test, two-sided, $p=0.05$). For patients with primary dystonia there was a significant inverse correlation of GPI neuronal discharge rate with the severity of dystonic symptoms ($p=0.028$, Spearman’s rho), and this correlation accounted for 33% of the variability in discharge rate. GPe discharge rate was not correlated with dystonia severity or type.

Pallidal discharge rate as a function of time elapsed from administration of sedative agents

All patients in both disease groups received propofol for sedation during stereotactic frame placement and MRI, halted at least 30 minutes prior to the start of recording. The NHPs received no anesthetic in the days prior to recording. To determine if discharge rates in patients were affected by lingering effects of the anesthetic agent, we examined neurons recorded in a subset of cases where the total duration of microelectrode mapping was relatively long (greater than three hours). The mean GPI discharge rates recorded during the first half of those sessions were statistically indistinguishable from those recorded during the last half ($p=0.72$, independent sample t-test), reinforcing the view that anesthetic dosing cannot account for the differences between groups in neuronal firing.

Measures of bursting or irregular discharge

Group means for the various measures of discharge pattern in dystonia, normal NHP, and PD are given in Table 2. In GPI, all three measures of bursting and discharge irregularity (the L-statistic, burst index, and proportion of burst discharges by the “Poisson Surprise” method) were significantly higher in dystonia than in the normal NHP ($p<0.001$, independent sample t-test). The parkinsonian GPI had a similarly high proportion of burst discharges by the “Poisson Surprise” method, and this was also
significantly different from the normal NHP ($p<0.001$). It is worth noting that both L-statistic and Poisson surprise statistics were found to be sensitive to GPi firing rates, the former negatively and the latter positively correlated ($p<0.001$ Spearman's rho; for separate comparisons within the dystonic, NHP, and PD datasets). The increased prevalence of burst discharges in the dystonic GPi, however, was found independent of which burst statistic was used. GPi bursting was not consistently different between dystonia subtypes (Table 3), although one measure of bursting, (Poisson “surprise” method) did show a higher proportion of burst discharges in tardive dystonia compared to primary dystonias.

Bursting discharge in GPe cells did not differ greatly between dystonia and normal NHP. Two of the measures of bursting (the L-statistic and the proportion of burst discharges by the Poisson surprise method) were statistically indistinguishable. The third measure, the burst index, was significantly higher (indicating greater burstiness) for dystonia, at the threshold of significance, $p=0.05$ (Table 2). GPe bursting did not differ between dystonia subtypes.

Raster diagrams showing the pattern of discharge of GPi cells exhibiting notably abnormal behavior are shown in Figure 3. Since increased burstiness was a feature of both dystonia and PD, we performed a more detailed comparison of intra-burst properties (detected by the Poisson surprise method) between these two conditions. The mean frequency within the burst (206 +/- 3 Hz for dystonia and 236 +/- 4 Hz for PD) were higher in PD than in dystonia (independent sample t-test, $p<0.001$), although the quantitative difference was small and may reflect the difference in the underlying discharge rate. The mean burst duration, number of spikes per burst, and maximum frequency within the bursts did not differ.

Oscillatory neuronal activity

An example of a GPi unit with oscillatory discharge in dystonia is shown in Figure 4A (neuronal recording) and 4B (frequency spectrum of the autocorrelogram). Group statistics for oscillatory activity are provided in Table 2 (bottom two rows). In the dystonic state, 85 of 302 GPi neurons and 20 of 151 GPe neurons had oscillatory activity according to autocorrelation analysis. In PD, 18 of 101 GPi neurons and 7 of 39 GPe neurons were oscillatory. For both nuclei, the proportion of neurons with oscillatory activity was significantly higher in dystonia than in the normal NHP. For both nuclei in all conditions, the mean frequency of oscillations was between 3 and 8 Hz, and the distribution of frequencies was unimodal (shown for GPi in Figure 4D, left column). Thus, the only significant difference in single unit discharge between PD and dystonia was in mean GPi discharge rate, not in oscillatory activity, bursting, or mean GPe discharge rate. Oscillatory activity did not differ between subtypes of dystonia.

Mean GPi discharge rate did not differ between oscillatory and nonoscillatory neurons, in either dystonia or PD. For the dystonic GPi, oscillatory neurons were significantly more bursty, by all three measures of bursting, than nonoscillatory neurons ($p<.005$ for all measures). Nevertheless, the proportion of burst discharges (Legendy method) remained significantly higher for nonoscillatory dystonic units ($0.22 +/- 0.016$)
compared with normal macaque (0.17 +/- 0.002). For PD, GPi bursting did not differ between oscillatory versus nonoscillatory units. Thus, the bursting discharge in dystonia and PD was not strictly periodic.

Correlations of involuntary muscle activity with neuronal discharge

A total of 169 GPi neurons in 15 dystonic patients and 72 GPi neurons in 8 PD patients were recorded simultaneously with 4 channels of EMG. In patients with dystonic spasms or tremor at rest, EMG recording from the affected muscle groups showed involuntary activity at rest. For 45 (27 %) GPi cells in dystonia there was at least one significant peak in the SDF-EMG coherence function for at least one of the EMG channels. For cells showing SDF-EMG coherence the mean number of significant peaks was 1.4. For 11 (15 %) GPi cells in PD there was at least one significant peak, and for these the mean number of significant peaks was 1.9.

Figure 4-C shows the SDF-EMG coherence function for the neuronal discharge and EMG in Figure 4-A. The distribution of SDF-EMG coherence frequencies in GPi for dystonia and PD are shown in Figure 4D (right hand histograms). The distribution is bimodal in both cases, with peaks in the 2-10 Hz range and in the 20-30 Hz range. For the dystonic GPi, the median frequency of coherence was 16.4 Hz (range, 0.4-29 Hz), while for the parkinsonian GPi the median was 19.1 (range 0.7-29). In both disease states, there were approximately equal numbers of SDF-EMG pairs with positive phase delays as there were pairs with negative phase delays.

Of the 85 GPi units in dystonia that manifested oscillatory activity (by autocorrelation analysis), only 5 of the units showed significant coherence with at least one of the recorded EMG channels at the same frequency (The unit in Fig 5 A-C is one such unit). This was in spite of the fact that EMGs were recorded from the most affected muscle groups. Four of the five units were in the two patients with overt dystonic tremor present during surgery (case E and T). Of the 18 GPi units in PD patients with oscillatory activity, only one unit showed EMG coherence at the same frequency, and this was in the one patient with tremor during surgery. Figure 4D shows that the frequency distributions of neuronal oscillations are dissimilar to the distributions of SDF-EMG coherence. Thus, for the majority of units in the majority of patients, there was no consistent relationship between the presence or absence of oscillatory neuronal discharge and the presence or absence of SDF-EMG coherence, and where both were present, no consistent relationship in their frequencies was found.

For GPe, The smaller number of units with coherent SDF-EMG oscillations in (15 in dystonia, zero in PD) precluded detailed analysis. The median frequency of coherence was 13.5 Hz (range, 2-30 Hz) for dystonia.

Discussion

The major findings of this study were that mean spontaneous GPi discharge rate in human dystonia was lower than that of the normal NHP, and that in primary dystonia,
it was inversely correlated with dystonia severity. Mean GPi discharge in PD was higher than in the normal NHP. In both dystonia and PD, non-oscillatory bursting and oscillatory activity were increased compared with the normal NHP. Oscillations occurred predominantly in the 2-10 Hz range, were seen in all dystonia subtypes, and in most cases were not associated with tremor.

Comparison with prior studies of GPi discharge rate in dystonia

A handful of studies have been published on pallidal neuronal physiology in awake humans with dystonia (23 cases total) (Hutchison et al. 2003; Lenz et al. 1998; Merello et al. 2004; Sanghera et al. 2003; Vitek et al. 1999). These series focused primarily on spontaneous discharge rates. Four studies of 16 total awake patients did show a reduced GPi discharge rate in the majority of dystonia cases, but this was not true for the seven cases presented by Hutchison et al. (Hutchison et al. 2003). This discrepancy might be accounted for by variations in symptom severity of the dystonic patients studied. In the study of Hutchison et al. (Hutchison et al. 2003), five patients had BFMDRS severity scores reported, and two of these were less than 15. In our series, such patients had higher pallidal discharge rates, indistinguishable from the normal NHP and only 10-20 Hz lower than in PD. We also found that patients with secondary dystonias associated with abnormal MRI findings had lower GPi discharge rates than patients with primary or tardive dystonia of similar severity. Thus, heterogeneity in dystonia subtype could also account for variability in published physiological data.

The finding that symptom severity influences GPi discharge rate is supported by Lenz et al. (Lenz et al. 1998), who showed in a single case that pallidal discharge rate decreased as the severity of dystonic spasms increased. Reduced pallidal outflow in dystonia is also consistent with studies in a rodent model of genetic dystonia, the dt-sz hamster, in which spontaneous discharge in the entopendular nucleus (rodent homologue of GPi) was reduced in the dystonic state compared with the normal state (Bennay et al. 2001).

Implications for alterations in the direct and indirect pathways

Models of the contribution of the basal ganglia to the control of movement have emphasized two major intrinsic pathways linking the basal ganglia input (striatum) to the basal ganglia outputs, GPi and SNr. A variety of derangements in these pathways have been proposed as the basis for dystonia (Hallett 1998; Perlmutter et al. 1997; Vitek 2002). In the model of Vitek, striatal inputs to both pallidal segments are hyperactive. GPe then becomes hypoactive, and the STN becomes hyperactive. The GPi is subjected to conflicting influences from the direct and indirect pathways, but the net result is suppression of GPi discharge, due to a greater influence of the direct pathway. Since we found that both GPe and GPi have reduced activity in dystonia, our data are most consistent with this model. Our results suggest that abnormal basal ganglia discharge rates are present at rest as well as during movement, since the rate abnormalities were present in two of three patients who did not have involuntary muscle activity at rest in the operating room. Hyperactivity in striatal projection neurons that innervate both GPe and
GPe could account for simultaneous reductions in firing rates in both pallidal segments (Parent et al. 1995).

Oscillations and bursts in pallidal discharge are prominent features of dystonia

Abnormal oscillations in pallidal single unit activity have been well documented in PD (Hurtado et al. 1999; Hutchison et al. 1997; Levy et al. 2001; Levy et al. 2002) and in animal models of parkinsonism (Bergman et al. 1994; Ruskin et al. 2002). In this paper, we show that oscillations in single unit activity in both pallidal segments are also a prominent feature of dystonia, and occur predominantly in the 2-10 Hz range. Oscillatory pallidal activity in human dystonia has previously been documented in local field potential (LFP) recordings (Silberstein et al. 2003), which reflect synchronized activity across many neurons. LFP oscillations occurred in the same 2-10 Hz frequency range as the single unit oscillations reported here, and thus may reflect the same underlying signal.

The presence of tremor can lead to neuronal oscillations in motor areas of basal ganglia nuclei, via proprioceptive sensory feedback. It is unlikely that the oscillatory activity we recorded in dystonia was due exclusively to sensory feedback from joint or muscle, since it was present in those patients who did not have dystonic tremor or spontaneous muscle spasms while at rest (cases A, F, and O). Furthermore, even in patients with dystonic spasms at rest, only a small percentage of oscillatory neurons in dystonia showed coherent EMG activity at the same frequency. Thus, 2-10 Hz single unit pallidal oscillations in dystonia probably reflect an abnormal “idling rhythm” rather than a sensory response to abnormal spontaneous movements (Brown 2003).

Bursting is a type of temporal ordering of short and long ISIs such that short ISIs tend to occur in clumps (Ruskin et al. 2002). Bursting may be oscillatory or non-oscillatory. GPi bursting in human dystonia has been reported previously (Hutchison et al. 2003; Merello et al. 2004; Vitek et al. 1999). However, descriptions of discharge pattern are difficult to interpret in the absence of comparison data from non-dystonic subjects, and only one study (Hutchison et al. 2003) provided a quantitative statistical measure of bursting. Here, we show using multiple statistical measures of bursting activity that both dystonia and PD are characterized by increased bursting activity in comparison to the NHP. While oscillatory units contained a higher proportion of burst discharges than non-oscillatory units, pallidal bursting in both dystonia and PD was not exclusively limited to oscillatory cells. That bursting is a prominent feature of dystonia is also supported by studies in the dt-sz hamster model of dystonia, in which bursting in the entopeduncular nucleus was observed only during the dystonic phase of the animal’s ontogeny (Gernert et al. 2002). The finding of pallidal neuronal synchrony in dystonia (Silberstein et al. 2003) and in PD (Hurtado et al. 1999; Levy et al. 2002; Silberstein et al. 2003) suggests a potential mechanism for GPi bursting in movement disorders. If the GPe “pauser” cells providing convergent input onto an individual GPi cell produced synchronized pauses, then GPi bursts would result from the brief periods of excessive disinhibition. Investigation of this possibility will require simultaneous recording from multiple neurons.
Neuronal correlates of dystonia in relation to other movement disorders

We found that the abnormal bursting and oscillatory activity seen in dystonia is remarkably similar to that of PD patients with predominant bradykinesia and rigidity, but that the two conditions differed in mean GPi discharge rates. Similarities in the discharge pattern abnormalities between dystonia and PD is not surprising, given that dystonia can occur as a symptom of PD, and it also occurs transiently in the MPTP treated NHP prior to the appearance of parkinsonian bradykinesia and rigidity (Perlmutter et al. 1997). Unlike discharge rate, statistical measures of bursting and oscillation did not correlate with disease severity, arguing that the observed firing pattern abnormalities do not “encode” dystonia. These observations suggest that abnormally patterned activity in the GPi superimposed on a low discharge rate produces dystonia, while similar abnormalities superimposed on a higher mean rate produce bradykinesia. In support of this concept, Hashimoto et al. (Hashimoto et al. 2001) measured GPi discharge rate in a PD patient during a dystonic phase and a non-dystonic phase and showed a much lower discharge rate in the dystonic phase.

Like idiopathic dystonia, levodopa-induced dyskinesias in PD are associated with reduced GPi firing rates and abnormal bursting discharge (Levy et al. 2000; Merello et al. 1999), yet these two conditions are phenotypically distinct. Differences in interneuronal synchronization, which was not studied here, might provide the physiologic correlate for this distinction. In addition to lowering mean GPi discharge rate, levodopa treatment in PD reduces neuronal synchronization (Brown et al. 2001; Silberstein et al. 2003). Thus, dyskinesias occurring at peak levodopa dosage in PD are probably the result of unsynchronized, low frequency pallidal activity. Our findings, taken together with those of Silberstein et al (2003), suggest that if pallidal outflow is both decreased and synchronized, dystonia rather than dyskinesia may result.

Other pallidal abnormalities could be important in dystonia. Enlarged neuronal receptive fields have been observed in the thalamus (Lenz et al. 1999) and cortex (Sanger et al. 2001) in human dystonia, and in the cortex in a primate model of dystonia (Byl et al. 1996). There are conflicting data on whether or not this is the case in the dystonic GPi (Hutchison et al. 2003; Lenz et al. 1998), and we did not systematically examine receptive field size of movement related cells.

Pitfalls in interpretation

In this study, discharge rate and pattern in dystonia and PD were defined as “abnormal” in relation to single unit discharge in the normal Rhesus macaque, collected and analyzed by identical methods. The use of a different species as a control group could be seen as problematic, but single unit data from normal humans cannot be obtained. Cross-species comparisons of pallidal physiology in the parkinsonian state, however, support the similarity of pallidal physiology between humans and NHPs. The discharge rates of GPi and STN neurons are very similar for NHPs in the parkinsonian state and for human with PD (Hutchison 1998; Hutchison et al. 1998; Sterio et al. 1994). In addition, the prevalence of burst discharges observed here in the GPi in PD is nearly identical to that reported previously for parkinsonian NHPs using the same statistical analysis.
Given the similarity of pallidal physiology in NHPs and humans in the parkinsonian state, it is reasonable to assume this would also be the case for the normal state.

Due to the fact that MER in humans was performed along nearly parasagittal trajectories, the part of the GPe explored was not in the center of the motor territory, which is dorsolateral (Francois et al. 2004; Hedreen and DeLong 1991) and not immediately dorsal, to the GPi. Thus, the GPe physiology we studied in the human may not fully reflect abnormalities that could be present in a more central region of the motor sub-territory. This difficulty does not affect the GPi recordings, because the trajectory was designed to traverse only the posterior (motor) GPi, and because cells responsive to passive joint movements were found throughout the regions of GPi explored in each case.

Sampling bias may have affected our results. We attempted to minimize this by collecting data from dystonia and PD patients, as well as NHPs, using similar methodology. Finally, lingering effects of propofol sedation given prior to neuronal recording could have suppressed pallidal discharge rates, in spite of starting the recording after at least a 30 minute sedative free interval. Three half lives are used to characterize the pharmacokinetic elimination of propofol, but the longest half-life (approximately 12 hours) is only relevant at very low plasma concentrations, in the range of 0.01 mgrams/ml (Fechner et al. 2004). This is well below the levels shown to influence neuronal recording in laboratory animals (Fechner et al. 2004). Several results argue against an effect of propofol in this study. The mean GPi discharge rate for PD patients was elevated (close to 100 Hz), despite having received similar doses of propofol in a similar time frame as the dystonia patients. In addition, one would expect a residual propofol effect to gradually decrease during a recording period lasting several hours, whereas we found no difference in discharge rates for neurons recorded early in the case versus late in the case.

**Conclusions**

Human dystonia is associated with abnormal oscillatory activity and abnormal bursting activity in comparison with the normal NHP. Severe dystonia is also associated with reduced mean GPi discharge rate, in contrast to the rigid-akinetic form of PD, which is associated with an increased mean rate. Discrepancies in prior studies of pallidal physiology in dystonia probably reflect heterogeneity in disease severity and subtype. Differences in mean discharge rate and/or neuronal synchrony may determine whether abnormally patterned pallidal activity is manifested as dystonia, parkinsonism, or dyskinesia. Our data are consistent with a model in which both direct and indirect basal ganglia intrinsic pathways are overactive.

**Acknowledgments:** Matthew Mori contributed to early data analysis for this project. Susan Heath contributed to data collection.
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# Tables

## Table 1: Characteristics of dystonia patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Type of dystonia</th>
<th>Baseline BFMDRS severity score</th>
<th>Affected body regions</th>
<th>Age at onset (years)</th>
<th>Age at surgery (years)</th>
<th>Medications (total daily dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Idiopathic Juvenile DYT 1+</td>
<td>52</td>
<td>Cervical, trunk, arms</td>
<td>8</td>
<td>17</td>
<td>Trihexyphenidyl 40 mg</td>
</tr>
<tr>
<td>B</td>
<td>Idiopathic Juvenile DYT 1+</td>
<td>74</td>
<td>Generalized</td>
<td>5</td>
<td>27</td>
<td>Trihexyphenidyl 30 mg Diazepam 100 mg Baclofen (oral) 80 mg Carbamazepine 700 mg</td>
</tr>
<tr>
<td>C</td>
<td>Idiopathic Juvenile DYT 1+</td>
<td>58</td>
<td>Generalized</td>
<td>9</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td>D</td>
<td>Idiopathic Juvenile DYT 1+</td>
<td>49.5</td>
<td>Cervical, trunk</td>
<td>12</td>
<td>17</td>
<td>Baclofen (intrathecal)</td>
</tr>
<tr>
<td>E</td>
<td>Idiopathic Juvenile DYT 1 -</td>
<td>19</td>
<td>Cervical, face, shoulders</td>
<td>5</td>
<td>42</td>
<td>None</td>
</tr>
<tr>
<td>F</td>
<td>Idiopathic Juvenile DYT 1 -</td>
<td>35.3</td>
<td>Left hemibody</td>
<td>9</td>
<td>28</td>
<td>Clonazepam 2 mg Trihexyphenidyl 6 mg Gabapentin 900 mg</td>
</tr>
<tr>
<td>G</td>
<td>Idiopathic Juvenile DYT 1 -</td>
<td>94</td>
<td>Generalized</td>
<td>6</td>
<td>28</td>
<td>Trihexyphenidyl 35 mg Clorazepate 25 mg Baclofen 80 mg</td>
</tr>
<tr>
<td>H</td>
<td>Idiopathic Juvenile DYT 1 -</td>
<td>40</td>
<td>Cervical, right shoulder, right arm</td>
<td>14</td>
<td>18</td>
<td>None</td>
</tr>
<tr>
<td>I</td>
<td>Idiopathic Adult</td>
<td>20</td>
<td>Cervical</td>
<td>37</td>
<td>50</td>
<td>None</td>
</tr>
<tr>
<td>J</td>
<td>Idiopathic Adult</td>
<td>36</td>
<td>Cervical</td>
<td>27</td>
<td>29</td>
<td>Baclofen (oral) 30 mg Amitryptyline 25 mg Clonazepam 0.5 mg Benztropine 7.5 mg</td>
</tr>
<tr>
<td>K</td>
<td>Idiopathic Adult</td>
<td>28</td>
<td>Cervical, face, arms</td>
<td>55</td>
<td>58</td>
<td>Lorazepam 8 mg Hydrocodone 30 mg Temazepam 30 mg</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td>---</td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>Idiopathic Adult</td>
<td>41</td>
<td>Cervical, arms</td>
<td>29</td>
<td>42</td>
<td>Baclofen (oral) 60 mg Gabapentin 900 mg Inderal 240 mg</td>
</tr>
<tr>
<td>M</td>
<td>Idiopathic Adult</td>
<td>30</td>
<td>Cervical, face</td>
<td>58</td>
<td>63</td>
<td>None</td>
</tr>
<tr>
<td>N</td>
<td>Idiopathic Adult</td>
<td>17</td>
<td>Cervical</td>
<td>18</td>
<td>50</td>
<td>Neurontin 1800 mg</td>
</tr>
<tr>
<td>O</td>
<td>Tardive</td>
<td>11</td>
<td>Legs</td>
<td>29</td>
<td>36</td>
<td>Divalproex sodium 1000 mg Risperidone 8 mg Trazadone 50 mg Benztropine 16 mg</td>
</tr>
<tr>
<td>P</td>
<td>Tardive</td>
<td>20</td>
<td>Face, arms</td>
<td>49</td>
<td>59</td>
<td>Clonazepam 3 mg Temazepam 30 mg</td>
</tr>
<tr>
<td>Q</td>
<td>Tardive</td>
<td>80</td>
<td>Generalized</td>
<td>26</td>
<td>36</td>
<td>Gabapentin 1800 mg Benztropine 6 mg Tizanidine 18 mg Lorazepam 8 mg Diphenhydramine 150 mg</td>
</tr>
<tr>
<td>R</td>
<td>Secondary (Post-traumatic)</td>
<td>54</td>
<td>Cervical, trunk, arms</td>
<td>26 (following trauma at 22)</td>
<td>29</td>
<td>Trihexyphenidyl 10 mg Pergolide 1.5 mg Levodopa 500 mg</td>
</tr>
<tr>
<td>S</td>
<td>Secondary (PKAN)</td>
<td>30</td>
<td>Arms</td>
<td>30</td>
<td>43</td>
<td>Levodopa 300 mg Amantadine 200 mg Gabapentin 900 mg</td>
</tr>
<tr>
<td>T</td>
<td>Secondary (Post-stroke)</td>
<td>32</td>
<td>Right hemibody</td>
<td>69</td>
<td>74</td>
<td>None</td>
</tr>
<tr>
<td>U*</td>
<td>Very early onset, type unknown</td>
<td>89</td>
<td>Generalized</td>
<td>&lt;5</td>
<td>18</td>
<td>Trihexyphenidyl 4 mg Diazepam 10 mg Pramipexole 0.375 mg</td>
</tr>
<tr>
<td>V*</td>
<td>Very early onset, type unknown</td>
<td>81</td>
<td>Generalized</td>
<td>&lt;2</td>
<td>28</td>
<td>Diazepam 15 mg</td>
</tr>
</tbody>
</table>

Abbreviations: BFMDRS=Burke-Fahn-Marsden Dystonia Rating Scale, PKAN=Pantothenate Kinase Associated Neurodegeneration

* Patients U and V were adopted at an early age, with dystonia already present. These may represent cases of dystonic cerebral palsy (secondary dystonia), but medical history prior to adoption is unknown. MRI scans were normal.
Table 2: Spontaneous pallidal discharge parameters in dystonia, normal NHP, and PD (error values are standard error of the mean)

<table>
<thead>
<tr>
<th></th>
<th>GPi</th>
<th>GPe†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dystonia</td>
<td>Normal macaque</td>
</tr>
<tr>
<td># subjects</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td># units</td>
<td>302</td>
<td>96</td>
</tr>
<tr>
<td>Mean rate (Hz)</td>
<td>55.3 +/- 1.3</td>
<td>82.5 +/- 2.5</td>
</tr>
<tr>
<td></td>
<td>*p&lt;0.001</td>
<td>**p&lt;0.001</td>
</tr>
<tr>
<td>Mean proportion of</td>
<td>0.026 +/- 0.001</td>
<td>0.017 +/- 0.002</td>
</tr>
<tr>
<td>burst discharges</td>
<td>*p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>(Legendy method)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean L-statistic</td>
<td>5.9 +/- 0.08</td>
<td>5.1 +/- 0.08</td>
</tr>
<tr>
<td></td>
<td>*p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>**p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean burst index of</td>
<td>3.7 +/- 0.1</td>
<td>2.3 +/- 0.2</td>
</tr>
<tr>
<td>normalized ISI</td>
<td>*p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>**p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Proportion of units</td>
<td>0.282 (85/302)</td>
<td>0.114 (11/96)</td>
</tr>
<tr>
<td>with significant</td>
<td>*(χ² =14.1, p&lt;0.0001)</td>
<td>(χ² =3.1, p&lt;0.6)</td>
</tr>
<tr>
<td>oscillations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean frequency of</td>
<td>6.0 +/- 0.5</td>
<td>4.8 +/- 1.1</td>
</tr>
<tr>
<td>significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oscillations (Hz)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*indicates a value that was significantly different from that for normal macaque by t-test; **indicates a value that was significantly different between dystonia and PD by t-test; †GPb burster cells not included in this analysis; Abbreviations: ISI = interspike interval
Table 3: Spontaneous discharge parameters in subtypes of dystonia (error values are standard error of the mean)

<table>
<thead>
<tr>
<th></th>
<th>GPi</th>
<th>GPe†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary dystonia</td>
<td>Tardive dystonia</td>
</tr>
<tr>
<td># subjects</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td># units</td>
<td>225</td>
<td>50</td>
</tr>
<tr>
<td>Mean rate (Hz)</td>
<td>57.8 +/- 1.4</td>
<td>54.6 +/- 3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean proportion</td>
<td>0.024 +/- 0.001</td>
<td>0.032 +/- 0.003</td>
</tr>
<tr>
<td>of burst</td>
<td></td>
<td></td>
</tr>
<tr>
<td>discharges</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Legendy method)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean L-statistic</td>
<td>5.8 +/- 0.10</td>
<td>6.0 +/- 0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean burst</td>
<td>3.4 +/- 0.13</td>
<td>3.6 +/- 0.2</td>
</tr>
<tr>
<td>index of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>normalized ISI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of</td>
<td>0.257 (58/225)</td>
<td>0.360 (18/50)</td>
</tr>
<tr>
<td>units with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oscillations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean frequency</td>
<td>5.8 +/- 0.5</td>
<td>5.4 +/- 0.8</td>
</tr>
<tr>
<td>of significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oscillations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Hz)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* denotes significant difference from primary dystonia, by t-test; †GPe burster cells were excluded from this analysis; Abbreviations: ISI = interspike interval
**Figure Legends**

1.) Boxplots of the distribution of pallidal neuronal discharge rates for all subjects with dystonia (shaded boxes), PD (open boxes), and normal NHP (hatched boxes). Upper plot, GPi. Lower plot, GPe. Each box represents the range of values within the middle two quartiles of the data distribution. The horizontal black line is the median value. Open circles are outlying values and asterisks are extreme values. The numerals below each box in the discharge rate plots give the number of units analyzed, and the letters designate the case. Clinical histories for each dystonia case are provided in Table 1. (The numbers of subjects differ for GPi versus GPe boxplots since not all patients had sufficient numbers of units recorded to contribute data for both nuclei.)

2.) Scatterplot of mean GPi neuronal firing rates as a function of baseline Burke-Fahn-Marsdon Dystonia Rating Scale score. Presumed idiopathic dystonias are represented as circles, secondary dystonias as triangles, and tardive dystonias as asterisks. The square shows the mean GPi discharge rate for the normal NHP.

3.) Raster diagrams of illustrative GPi neurons in dystonia (A), PD (B), and normal NHP (C). The width of each raster is 500 msec, and 30 seconds of data are shown.

4.) Oscillatory neuronal activity and SDF-EMG coherence in the dystonic GPi. A, example of neuronal discharge (top trace) and simultaneously-recorded trapezius EMG (lower trace), over a five second interval. The EMG has been rectified and filtered. From Case E (see Table 1), a patient with dystonic tremor of the shoulder and neck. B, spectral power of the autocorrelogram between 0 and 30 Hz for the unit shown in (A). There is a single significant peak (arrow) at 2.3 Hz. C, SDF-EMG coherence function for the unit and EMG shown in (A). The dotted line shows the significance threshold. There are two significant peaks (arrows) at 2.3 Hz and 5.5 Hz. The coherence peaks were calculated to have a phase lag of -55 msec (that is, the EMG lagged behind the spike density function) for the first peak and +5 msec for the second peak. D, Distribution of frequencies of significant neuronal oscillations (left column) and significant peaks in the SDF-EMG coherence function (right column) for all GPi cells, in dystonia (top row), and Parkinson’s disease (bottom row).

**References**


FIGURES

Figure 1

Dystonia = □
Normal Macaque = □
Parkinson's Disease = □

GPI Discharge Rate (Hz)

Case = A B C D E F G H I J K L M N O P Q R S T U V

N = 33 15 11 10 11 10 6 14 26 25 5 11 10 10 28 12 9 11 11 7 20

GPe Discharge Rate (Hz)

Case = A B I J K L N O P Q R S T U V

N = 18 13 10 12 8 0 5 5 5 9 5 12 0 11 13 16 34 27 9 7 12 5 6
Figure 2

Mean GPi discharge rate vs Baseline dystonia severity score.
Figure 4

A

0.1 mV

1 sec

B

C

D

Dystonia

Number of Occurrences

Frequency of peaks in ACF

PD

Frequency of coherent oscillations