The subthalamic nucleus in primary dystonia: single unit discharge characteristics

Lauren E. Schrock\textsuperscript{1,3}, Jill L. Ostrem\textsuperscript{1,3}, Robert S. Turner\textsuperscript{4}, Shoichi A. Shimamoto\textsuperscript{2}, Philip A. Starr\textsuperscript{2,3}

\textsuperscript{1}Department of Neurology
University of California, San Francisco
San Francisco, California 94122

\textsuperscript{2}Department of Neurological Surgery
University of California, San Francisco
San Francisco, California 94122

\textsuperscript{3}Parkinson’s Disease Research, Education, and Clinical Center
San Francisco Veterans Affairs Medical Center
San Francisco, California 94121

\textsuperscript{4}Dept. of Neurobiology and Center for the Neural Basis of Cognition
University of Pittsburgh
Pittsburgh, PA 15261, USA

Running Title: STN physiology in primary dystonia

Corresponding Author:
Philip Starr MD, PhD
Department of Neurological Surgery
University of California, San Francisco
533 Parnassus Avenue Box 0445
San Francisco, California 94143
Telephone: (415) 353-3489
Fax: (415) 502 4276
Email: starrp@neurosurg.ucsf.edu

Copyright © 2009 by the American Physiological Society.
Abstract

Most models of dystonia pathophysiology predict alterations of activity in the basal ganglia thalamocortical motor circuit. The Globus Pallidus interna (GPi) shows bursting and oscillatory neuronal discharge in both human dystonia and in animal models, but it is not clear which intrinsic basal ganglia pathways are implicated in this abnormal output. The subthalamic nucleus (STN) receives prominent excitatory input directly from cortical areas implicated in dystonia pathogenesis and inhibitory input from the external globus pallidus. The goal of this study was to elucidate the role of the STN in dystonia by analyzing STN neuronal discharge in patients with idiopathic dystonia. Data were collected in awake patients undergoing microelectrode recording for implantation of STN DBS electrodes. We recorded 62 STN neurons in 9 patients with primary dystonia. As a comparison group, we recorded 143 STN neurons in 20 patients with Parkinson’s disease (PD). Single unit activity was discriminated off-line by principal component analysis and evaluated with respect to discharge rate, bursting, and oscillatory activity. Mean STN discharge rate in dystonia patients was 26.3 Hz (SD 13.6). This was lower than in the PD patients (35.6 Hz, SD 15.2), but higher than published values for subjects without basal ganglia dysfunction. Oscillatory activity was found in both disorders, with a higher proportion of units oscillating in the beta-range in PD. Bursting discharge was a prominent feature of both dystonia and PD, while sensory receptive fields were expanded in PD compared with dystonia. The STN firing characteristics, in conjunction with those previously published for GPi, suggest that bursting and oscillatory discharge in basal ganglia output may be transmitted via pathways involving the STN, and provide a pathophysiologic rationale for STN as a surgical target in dystonia.
Introduction

Dystonia is a movement disorder defined by sustained muscle contractions resulting in involuntary twisting and repetitive movements and abnormal postures (Fahn et al. 1998). Several lines of evidence implicate the basal ganglia as key structures in the pathophysiology of dystonia (Chiken et al. 2008; Dang et al. 2005; Marsden et al. 1985; Perlmutter et al. 1997a; Perlmutter et al. 1997b; Playford et al. 1993). Early models of dystonia pathophysiology focused on changes in the relative contributions of the ‘direct’ and ‘indirect’ intrinsic BG pathways (Mink 2003; 1996; Sanger 2003; Vitek 2002; Vitek et al. 1999). In human dystonia patients undergoing microelectrode-guided pallidal surgery in the awake state, GPi neurons show bursting discharge and 2-30 Hz oscillations that are also seen in Parkinson’s disease (Hutchison et al. 2003; Merello et al. 2004; Starr et al. 2005; Tang et al. 2007; Vitek et al. 1999). The GPi, however, reflects the final stage of basal ganglia processing. Thus, GPi recording cannot distinguish the relative contributions of intrinsic basal ganglia pathways to basal ganglia output.

Several lines of evidence prompt a re-examination of the role of STN in dystonia. First, the STN in primates receives substantial direct cortical projections, via the “hyperdirect” pathway (Nambu et al. 2002), from wide areas of the frontal lobe (Kitai and Deniau 1981; Monakow et al. 1978; Nambu et al. 1996; Nambu et al. 1997). Cortical areas projecting to the STN have been implicated in dystonia pathophysiology (Carbon and Eidelberg 2009; Draganski et al. 2003; Garraux et al. 2004; Ikoma et al. 1996; Quartarone et al. 2003; Quartarone et al. 2008; Toro et al. 2000). Second, the STN has strong reciprocal connections with the globus pallidus externus (GPe), which in turn is modulated by D2 receptor-positive striatal cells. Human functional imaging has demonstrated abnormal striatal D2 binding in patients with idiopathic focal and segmental dystonia using [123I]-iodobenzamide, [123I]-epidepride, and [123I]-beta-CIT SPECT (Hierholzer et al. 1994; Naumann et al. 1998) and [18F]-
spiperone PET imaging (Perlmutter et al. 1997a), as well as in asymptomatic carriers of the DYT1
primates (NHPs) have found decreased striatal D2-like specific binding sites during the temporary
dystonic phase following treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)
(Perlmutter et al. 1997b). These findings suggest that striatal abnormalities in dystonia may be
transmitted to the GPe-STN network (Sani et al. 2008).

Single unit physiology in the STN has been studied in detail in Parkinson’s disease (Hutchison et
Rodriguez-Oroz et al. 2001; Romanelli et al. 2004; Theodosopoulou et al. 2003), but only one study to-
date has reported single-unit recordings from the STN in patients with dystonia (Zhuang et al. 2004).
However, this study did not include a non-dystonic comparison group, and did not analyze oscillatory
activity or bursting behavior quantitatively.

Expanded somatosensory receptive fields in the STN are a well documented feature of the
parkinsonian state (Rodriguez-Oroz et al. 2001; Vitek et al. 1998). GPi recording in dystonia animal
models (Chiken et al. 2008) and in some human subjects (Lenz et al. 1998; Magarinos-Ascone et al.
2008; Vitek et al. 1999) suggests that the same is true for dystonia, but no studies of STN physiology in
humans have addressed this. Here, we study STN single unit discharge in awake patients with primary
dystonia and PD. We test the hypothesis that spontaneous and movement-related discharge rates,
bursting discharge, oscillatory activity, and sensory receptive fields distinguish dystonia from PD, and
utilize these data to re-assess current models of the contribution of STN to the pathophysiology of
dystonia and PD.
Methods

Patient population

Single unit recordings in the STN were obtained from patients with primary dystonia undergoing physiologic mapping for placement of STN DBS electrodes. All of the dystonia patients had significant disability, failed medical therapy, and received prior botulinum toxin injections but no longer obtained significant relief. All subjects provided written informed consent to participate in a protocol approved by the Institutional Review Board and all research-related activities were performed in compliance with national legislation and the World Medical Association Declaration of Helsinki. A subset of subjects simultaneously participated in a clinical study of STN DBS for adult-onset primary dystonia (Ostrem et al. 2008). Presurgical clinical evaluations were obtained by movement disorders neurologists (JLO, LES) in the month prior to surgery, and the severity was quantified according to two standard clinical rating scales: (1) the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) (Burke et al. 1985), and (2) the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) (Comella et al. 1997).

As a comparison group, patients with Parkinson’s disease undergoing microelectrode-guided stereotactic surgery for the placement of STN DBS electrodes were studied. All patients in this group were responsive to levodopa (3,4-dihydroxy-L-phenylalanine) and had either levodopa-induced dyskinesias, motor fluctuations, or medically intractable tremor. The severity of disease was assessed prior to surgery according to the Hoehn and Yahr Parkinson’s disease staging system. Antiparkinsonian medications were withheld for at least 12 hours before the surgery and all PD patients displayed overt
parkinsonian symptoms without dyskinesias during the procedure. PD patients with off-period dystonia were excluded from study.

Surgical procedures and data collection

The methods of microelectrode-guided stereotactic surgery for the implantation of DBS electrodes in the STN were similar to those previously described (Starr 2002; Starr et al. 2002). Single-unit recordings were obtained using glass-coated platinum/iridium microelectrodes with impedance 0.4 – 1.0 MΩ (Microprobe, Gaithersburg, MD, or FHC, Inc., Bowdoin, ME). Signals were bandpass filtered (300 Hz to 5 kHz), amplified, played on an audio monitor, displayed on an oscilloscope, and digitized (20-kHz sampling rate) using the Guideline System 3000 or 4000 (FHC, Inc.), or the Microguide system (Alpha Omega Inc., Israel). Microelectrodes were advanced into the brain using a motorized or manual microdrive (FHC, Inc., Alpha Omega, Inc., or Elekta, Inc, Stockholm, Sweden). In a typical surgical case, one to two microelectrode penetrations were made serially through the STN on each side, separated by 2-3 mm. Cells were recorded at approximately every 300-800 µm along each trajectory. For well isolated cells, spontaneous neuronal activity was collected for a minimum of 20 seconds.

Neurons were screened for movement-related activity based on audible changes in action potential discharge evoked by passive (investigator-initiated) contralateral limb movements (i.e., shoulder, elbow, wrist, hip, knee, and ankle joints). Proprioceptive responsiveness of a neuron in relation to movements of one or more joints was determined by concurrence between the examiner and one or more operating room staff based on audiovisual assessments of the response.

When single cell isolation could be maintained, neurons that showed a reproducible response to passive movement in the initial multi-joint screening were selected for quantitative investigation, focusing only on movement of the joint that produced the maximal modulation of discharge (i.e., a
transient increase or decrease in action potential firing that is time-locked with movement) on the initial
screen. A triaxial accelerometer (FHC) was strapped to the limb distal to the joint being assessed to
indicate the timing of movement onset. Each passive movement (alternating between flexion and
extension or internal and external rotation) was followed by 3-5 s of immobility and repeated 6-18
times. Some neurons were also studied while subjects performed voluntary flexion and extension of the
identified joint, in alternating fashion at a rhythm of approximately one cycle per second. Subjects were
prompted verbally to begin making the train of movements, but no external cues or commands were
provided during their execution.

Prior to recording all patients were sedated with propofol for the surgical incision and skull
opening. Propofol was stopped at least 30 minutes prior to neuronal recording, which is sufficient to
wash out its known effect on STN single unit discharge (Raz et al. 2008). All patients were awake and
alert for physiologic mapping, and were asked to remain as still as possible with eyes open during
periods of neuronal recording.

Data analysis

Digitized spike trains were imported into off-line spike sorting software (Plexon, Inc., Dallas
TX) for discrimination of single populations of action potentials by principal components analysis. The
software provided a 2-dimensional representation of neuronal waveforms, allowing visual separation of
distinct waveform morphologies. This software generated a record of spike times (subsequently reduced
to millisecond accuracy) for each action potential waveform detected. The spike times were used to
calculate discharge rate, bursting, and oscillatory activity in the 0-200 Hz range (see following text).
Analyses were performed using Matlab software (The Mathworks, Natick, Massachusetts). Neuronal
data were included in this study only if action potentials could be discriminated with a high degree of
certainty, as indicated by the presence of a clear refractory period in the interspike interval (ISI) histogram (> 3msec, as illustrated in Figure 1), and if the spontaneous activity of the neuron was recorded for greater than 20 seconds. Neurons whose action potential morphology varied greatly in synchrony with the cardiac cycle were excluded. In addition, only cells recorded in the dorsal 3 mm of the STN were analyzed, based on prior studies indicating that movement-related activity is generally restricted to the dorsal 3 mm (Rodriguez-Oroz et al. 2001; Romanelli et al. 2004; Theodosopoulos et al. 2003).

**Bursting**

For the quantification of bursting discharge, three methods for burst detection that have been previously described were used: (1) The “burst index” (Hutchison et al. 2003), (2) the “L” statistic (Goldberg et al. 2002; Kaneoke and Vitek 1996), and (3) the Poisson “surprise” method (Legendy and Salcman 1985; Wichmann et al. 1999). The burst index is defined as the mean ISI divided by the modal value. To calculate the “L” statistic, the spike train is rebinned into segments of duration equal to the ISI. “L” is defined as the number of distinct values taken on by the rebinned spike train. In the “surprise” method, bursts in the spike train were defined as segments of data with a Poisson surprise value of >5. The minimum number of spikes that can constitute a burst in this method was 2. The resulting data were tabulated as the proportion of ISIs within bursts compared with the total number of ISIs in the entire data stream.

**Oscillatory activity**

Oscillations in the spike train at 0-200 Hz were evaluated using the “global spike shuffling” method (Rivlin-Etzion et al. 2006) in order to eliminate the artifactual autocorrelations that arise from the neuronal refractory period. Spike shuffling is a process in which the order of ISIs is randomized.
Spike timestamps were converted to a data stream consisting of 1 ms bins in which the occurrence or absence of a spike was represented by 1 or zero, respectively, in that bin (Halliday et al. 1995). A 2048 point fast Fourier transform with Hanning window was used, resulting in a spectral resolution of 0.5 Hz. Similar analysis was performed on “control” data in which ISIs had been randomly shuffled 100 times (Rivlin-Etzion et al. 2006). Twenty shuffles have been reported to yield a good estimate of the “control” spectrum; we increased the number of shuffles by 5 times to ensure the accuracy of the estimates. Statistically significant peaks in the spike train data (after normalization with the spectrum of the shuffled data) were determined by using the 300-500 Hz part of the spectrum as the control segment and its standard deviation was used as a measure of random fluctuations in the spectrum. Each frequency point between 0 and 200 Hz was then checked for deviation from the expected power, at a significance level of p < 0.01, after correction for multiple (400) comparisons.

The spike shuffling method for detecting oscillatory activity would not detect first-order oscillations, which can arise when neuronal discharge is very regular with a narrow range of interspike intervals (Rivlin-Etzion et al. 2006). In such cases, the oscillation frequency is equal to the mean discharge rate. To ensure that no such first-order oscillations were missed, oscillations analysis was also performed without normalizing by the shuffled spectrum, and significant oscillations at frequencies at or near the neuron’s mean firing frequency were noted.

Quantitative analysis of peri-movement discharge

Methods for quantitative analysis of peri-movement discharge are as described by Chang et al. (Chang et al. 2007). Neuronal data were quantitatively analyzed for passive movement responses only if at least 6 movement trials in each direction were successfully completed. The onsets of investigator-imposed passive joint movements were detected by manual inspection of individual accelerometer
traces. The time of initial deflection in acceleration from baseline was taken as the onset of movement. For each cell tested, there were only two directions about a single joint. For flexion/extension pairs, movement occurred in the same plane but in opposite directions. For ball-and-socket joints (hip and shoulder), care was taken by the examiner to ensure that flexion and extension movements took place in the same plane given the larger degree of freedom at these joints.

Peristimulus mean spike density functions (SDFs; i.e., 1-ms resolution spike delta functions) smoothed with a 50-ms sigma Gaussian) (Szucs 1998) were averaged across trials aligned with movement onsets. Statistically significant increases or decreases in neuronal activity were determined by comparison with the mean and variance of the SDF in a prestimulus baseline period. With movement onset defined as time 0, the prestimulus baseline period was from 1.5 to 0.5s, and the analysis period lasted 1500 ms from -0.5 to 1.0s. A significant response was defined as a deviation from the mean baseline firing rate that exceeded three times SD of the baseline for 50 ms. The beginning of the response corresponds to the first millisecond of the SDF, the value of which falls outside of the 3 x SD threshold. This threshold provided an omnibus sensitivity of p < 0.05 after correcting for multiple comparisons (actual p = 0.05/30 comparisons), where the number of independent comparisons was estimated from the duration of the analysis period divided by the degree of smoothing (i.e., 1500 ms/50 ms). For each neuronal response that was significant, the type of response (i.e., increase, decrease, or combinations of both) was identified by visual inspection of the SDF, and the duration of significant response for each neuron was calculated.

Confirmation of electrode location

STN lead placement was verified by post-operative magnetic resonance imaging (MRI) using a transmit-receive headcoil in accordance with the device manufacturer recommendations. The MR
Images were transferred to an image-processing station (Framelink version 4.1; Medtronic) for analysis. Images were computationally reformatted into standard anatomic planes orthogonal to the intercommisural line and midsagittal plane. Lateral (x), vertical (z), and anterior-posterior (y) coordinates of the distal tip of the DBS lead were measured with respect to the midpoint of the line between the anterior commissure (AC) and the posterior commissure (PC).

Statistical analysis

The distributions of discharge rates, measures of bursting, and lead locations were checked for normality using the Kolmogorov-Smirnov test (‘kstest’ command from the Matlab statistics toolbox; The Mathworks, Inc.). Since they were not normally distributed, comparisons between disease states were performed using the Wilcoxon rank-sum test for unpaired data. Paired comparisons of discharge parameters between rest and movement were performed using the Wilcoxon sign-rank test. The chi-squared test was used for categorical data (proportions of cells with oscillatory activity).

Results

Patient characteristics

Nine patients with adult or late juvenile-onset dystonia (5 males, 4 females) were included in the study. All dystonia patients had primary dystonia. Three patients had only cervical involvement, whereas the remaining patients had cranial dystonia (i.e., eyes, mouth, or speech/swallow involvement) in addition to prominent cervical dystonia. Three of the six patients with cranial-cervical dystonia also had dystonia involving one or both arms. Two patients also had truncal involvement. There were no patients with generalized dystonia. At the time of surgery, the mean age of the dystonia patients was 46.7 years (SD 14.1) and the mean duration of symptoms was 11.0 years (SD 9.8). Further details of clinical symptoms and rating scores are provided in Table 1.
As a comparison group, 20 patients with PD (17 males and 3 females) were studied. Thirteen of 20 were of the akinetic-rigid subtype and suffered from motor fluctuations or dyskinesias, whereas 7 had tremor as the major component of their disease. All patients were off of anti-parkinsonian medications for > 12 hours prior to surgery, and experienced their typical off-medication symptoms during the procedure. No PD patient had off-period dystonia. The mean age at the time of surgery was 60.3 years (SD 9.0), the mean duration of symptoms was 10.4 years (SD 3.8), and all patients had a Hoehn and Yahr score of at least Stage 2 (mean 2.6, SD 0.6).

**Spontaneous discharge parameters – rate and bursting**

In the “resting state” (no attempted voluntary movement), we recorded 62 STN neurons from dystonia patients and 143 STN neurons from PD patients. All recorded cells were considered to be within the motor territory of the nucleus based on the detection of movement-related changes in neuronal discharge in the region of the recording, and the fact that recording was restricted to the dorsal 3 mm of the nucleus (Rodriguez-Oroz et al. 2001; Romanelli et al. 2004; Theodosopoulos et al. 2003). (26% of these dystonia neurons and 39% of these PD neurons showed discharge modulation in response to passive movement, and these units form a subset of all neurons screened for responses to passive movement as described further below). Mean recording duration was 33.2 seconds (SD 13.6, range 10.6 – 75.0) in dystonia patients and 39.0 seconds (SD 15.5, range 2.7 – 118.6) in PD patients. Firing characteristics of a typical dystonia and PD STN neuron are shown in Figure 1. Group statistics for neuronal firing rates and bursting analysis are provided in Table 2. STN neuronal discharge rate was significantly lower in dystonia patients (26.3 Hz, SD 13.6, p = < .001) than PD patients (35.6 Hz, SD 15.2), as shown in Figure 2. Bursting was a prominent feature in both conditions, but STN neurons in patients with dystonia were significantly more bursty than in PD patients by two of three measures of burstiness (See Table 2). These distinctions between dystonia and PD were also present when neurons...
from PD patients were subgrouped into akinetic-rigid versus tremor dominant subtypes, as shown in Table 3. There were no significant differences in spontaneous discharge parameters between the two subtypes of PD. Subgroup analysis of dystonia patients showed no significant differences in spontaneous discharge parameters between focal cervical and segmental dystonia patient groups.

Oscillatory activity

Results of oscillation analysis are shown in Tables 2 and 3, as well as in Figure 3. STN oscillatory activity in the 0-200 Hz range was a prominent feature of both PD (40% of recorded units showed oscillatory activity) and of dystonia (32% with oscillatory activity). 10.5% of PD neurons and 6.5% of dystonia neurons oscillated at more than one frequency. Where multiple oscillation frequencies were detected in a single neuron, they were not in a harmonic relationship. There was a greater incidence of oscillatory activity in low frequency bands (3-30 Hz) in PD than dystonia (20.3% vs. 6.5%, p = .01). Oscillatory activity in the beta band (13-30 Hz) was found only in PD (6.3% vs. 0%, p = .03). When PD patients were subdivided into tremor dominant versus akinetic-rigid subtypes based on clinical features, there were no significant differences between oscillatory activity in dystonia versus PD patients of either subtype. Subgroup analysis of dystonia patients did not reveal significant differences in oscillatory activity between focal cervical and segmental dystonia patients. We also looked for first-order oscillations that could occur near the mean firing frequency in neurons with very regular firing patterns, by performing the analysis on spike trains without normalization by the power spectrum of the shuffled spike train (see Methods). There were no units in any group oscillating at or very near the mean firing frequency, showing that all oscillatory activity detected reflected second- or higher-order properties of the spike train.

Neuronal responses to passive movement
Details of somatosensory responses found during the initial screen are shown in Table 4. During the initial intra-operative screen of responses to passive movement based on audiovisual monitoring, 100 STN neurons in 9 dystonia patients and 180 STN neurons in 17 PD patients were tested. A greater proportion of passive joint responses was found in PD than dystonia (64% vs. 46%, chi-squared = .002). Of those units that were responsive to passive movement, 33% were multi-joint responsive in PD versus 15% in dystonia (chi-squared = .02). Of these multi-joint responsive cells, four out of 38 in PD and one out of seven in dystonia were responsive to both upper and lower limb movements. Thirty-four of 46 movement-responsive cells in dystonia patients involved passive movement responses in limbs that did not have clinical dystonia based on their preoperative BFMDRS limb scores. Differences in somatosensory responses between dystonia and PD were maintained when PD patients were divided into akinetic-rigid and tremor dominant PD subtypes. There was no difference in the proportion of cells responsive to passive movement between akinetic-rigid and tremor dominant PD subtypes (67% and 57%, respectively; chi-squared = .17).

Responses to passive movement were quantitated using peri-event spike density functions in 6 cells in 3 dystonia patients and 12 cells in 4 PD patients. Examples of various response patterns are shown in Figure 4. Neuronal response to only one movement phase was more common in dystonia than PD (chi-squared = .03). However, there were no significant differences in the proportion of movement responses that were positive (increased firing rate), negative (decreased firing rate), or biphasic (increased followed by decreased firing rate) between PD and dystonia (chi-squared = .16), as detailed in Table 5. The mean duration of significant response was 0.43 seconds (SD 0.28) for dystonia and 0.37 seconds (SD 0.23) for PD.

Movement-related discharge
Nine cells in dystonia and 19 cells in PD were recorded both at rest and during repetitive, voluntary flexion/extension movements of a contralateral limb joint, using the joint that was found to modulate discharge rate during the passive movement screening. Voluntary movement produced a non-significant increase in discharge rate in both disease states (Table 6). During movement, in this small sample size, there was a trend toward increased mean STN discharge rate in PD compared to dystonia.

Confirmation of electrode location

All microelectrode recordings were made within 2 mm of the final DBS electrode trajectory. Thus, DBS electrode locations provided an anatomic confirmation of the general region in which cells were recorded, and controlled for any systematic difference in the targeted region in dystonia versus PD patients. All DBS leads traversed the dorsolateral STN based on their AC-PC coordinates as mapped to standard brain atlases (Schaltenbrand and Walker 1982; Talairach 1967). There was no significant difference between lead tip locations in dystonia and PD with respect to the midcommissural point, as measured by postoperative MRI (X [mean]: 11.0 mm [SD 1.3] vs. 11.1 mm [SD 1.1]; Y: 3.5 mm [SD 0.9] vs. 4.1 mm [SD 1.7]; Z: 7.2 mm [SD 1.2] vs. 5.9 mm [SD 2.0]). Methods for confirming electrode location do not allow unambiguous verification of recording location, due to the possibility of misregistration between microelectrode recording and DBS lead placement and the intrinsic MRI error.

Discussion

We compared STN single unit activity in patients with primary dystonia and Parkinson’s disease, and found that: (1) mean STN discharge rate in dystonia patients (26.3 Hz, SD 13.6) was lower than in PD patients (35.6 Hz, SD 15.2); (2) bursting discharge was prevalent in both conditions but even more common in dystonia than PD; (3) single unit oscillatory activity was a prominent feature in both dystonia and PD; (4) beta-range oscillatory activity was more prominent in PD than dystonia; (5)
dystonia patients had more restricted somatosensory receptive fields in STN neurons, compared with PD; (6) Subgroup analysis of both PD (akinetic-rigid vs. tremor-predominant PD) and dystonia (focal cervical vs. segmental dystonia) revealed no significant differences in STN discharge rate, bursting, oscillatory activity, or receptive field size between disease subtypes.

One previous study has reported single-unit recordings from the STN in patients with dystonia (Zhuang et al. 2004). The STN mean discharge rate in this mixed population of primary and secondary dystonia patients was found to be 31.5 Hz. Unlike our study, this study did not include a non-dystonic comparison group, and did not analyze oscillations and bursting behavior quantitatively.

STN discharge rates distinguish different movement disorders

Spontaneous STN discharge rates in the awake state have been measured in several disease states in humans, in the normal state in non-human primates (NHPs), and in MPTP-induced parkinsonism in NHPs. Although we do not have normal control data from humans, Steigerwald et al. (Steigerwald et al. 2008) recently studied STN neuronal discharge in patients with essential tremor (a disorder thought to not involve the basal ganglia (Lorenz and Deuschl 2007)) and found the mean firing rate to be 19.3 Hz. Similarly, most measures of spontaneous discharge rates reported for the STN motor territory in awake normal macaques are close to 20 Hz (Bergman et al. 1994; DeLong et al. 1985; Georgopoulos et al. 1983; Wichmann and Soares 2006). In contrast, STN discharge rates in the off-medication parkinsonian state in humans and MPTP-treated NHPs are usually reported as >30 Hz (Hutchison et al. 1998; Magarinos-Ascone et al. 2000; Magnin et al. 2000; Rodriguez-Oroz et al. 2001; Steigerwald et al. 2008; Theodosopoulos et al. 2003). In this context, our findings suggest that spontaneous STN discharge rate in dystonia (26.3 Hz) is likely to be higher than normal, though less elevated than in the parkinsonian state. Rodent studies suggest that STN firing rate and pattern are determined in part by a driving influence of the cortico-subthalamic pathway, and this influence is modulated by dopamine (Bevan et al. 2003).
An additional strong influence on STN firing is the GPe, which in turn is inhibited by D2 receptor-positive striatal cells. Functional imaging studies show reduced D2 receptor activation in a variety of dystonic conditions (Asanuma et al. 2005; Naumann et al. 1998; Perlmutter et al. 1997a), which could suppress GPe discharge and elevate STN discharge. However, a profound elevation in STN discharge rate (>30 Hz) appears to be uniquely associated with PD.

Bursting discharge in the STN

Bursting discharge in the basal ganglia nuclei has been considered to be characteristic of the parkinsonian state, based on an increase in bursting in nonhuman primate and rodent models of PD when compared to the normal state (Bergman et al. 1994; Hassani et al. 1996). Pallidal recordings in humans show that primary dystonia is similarly associated with bursting (Starr et al. 2005; Tang et al. 2007; Vitek et al. 1999). This has been confirmed in rodent models of dystonia (Chiken et al. 2008; Gernert et al. 2002). Here, we show that in the STN, bursting discharge is not only present in dystonia, but it is in fact even more prominent than in PD. This suggests that bursting discharge in basal ganglia output in dystonia is transmitted via the STN. The increased burstiness of STN in dystonia compared to PD is consistent with the recent finding that pauses in GPe activity are more prominent in primary dystonia than in PD (Sani et al. 2008). Since the GPe provides tonic inhibition to the STN, a pause in GPe activity should result in a burst in STN activity. The ultimate effect of basal ganglia bursts on cortical activity is uncertain. Bursts in the activity of basal ganglia inhibitory output neurons may actually facilitate thalamocortical activation and the excessive motor outflow of dystonia by a process of disinhibition (Person and Perkel 2005). Transient reduction in basal ganglia output (such as occurs between bursts) could also paradoxically decrease cortical excitability, as demonstrated in a rodent model of epilepsy (Paz et al. 2007).

Oscillatory activity in the STN
Basal ganglia oscillations have been extensively characterized in the parkinsonian state. Three to 30 Hz oscillations are present at many points in the basal ganglia-thalamocortical network, in both single unit and local field potential (LFP) recordings (Hammond et al. 2007). In particular, a pathological role of oscillatory activity in the beta band (13-30 Hz) in the parkinsonian state has been suggested (Brown 2003). In the STN of normal non-human primates, very few STN single neurons show oscillatory activity, whereas 27% of neurons show oscillatory activity in MPTP-treated parkinsonian monkeys (Bergman et al. 1994; Wichmann et al. 1994). Induction of parkinsonism in rodents also increases STN single unit oscillations (Mallet et al. 2008). Although we do not have normal data from humans, patients with a movement disorder not involving the basal ganglia (essential tremor) have fewer 3-30 Hz oscillations than PD patients (Steigerwald et al. 2008). Thus, it seems likely that the oscillatory activity shown here in 32% of STN single units in dystonia patients is a manifestation of the disease state. Since this is a similar proportion as seen in GPi neurons in dystonia patients (Starr et al. 2005), it is also plausible that excitatory inputs from the STN contribute directly to pallidal oscillations. Of note, a mathematical model of dystonia pathophysiology predicts oscillatory activity in structures contributing to the indirect striato-pallidal pathway (Sanger 2003).

GPi oscillation frequencies in LFP recordings have been shown to distinguish PD and dystonia, with predominant beta band oscillations in PD, in contrast to predominant theta-alpha band oscillations in dystonia (Silberstein et al. 2003). Consistent with this, we found a higher proportion of beta oscillations in spontaneous single unit STN discharge in PD. Single unit recording and LFP recording represent different aspects of neuronal activity, since the latter reflects synchronized activity across many neuronal elements and also includes subthreshold synaptic potentials (Chen et al. 2006). Some studies have shown coherence of single neurons with the LFP (Goldberg et al. 2004; Weinberger et al. 2006), whereas others have not (Heimer et al. 2002). Moran et al. have suggested that there may be two
distinct neuronal populations with oscillatory activity in PD, tremor frequency (3-7 Hz) and high
frequency (8-20 Hz) neurons, which can be distinguished by their degree of synchronized activity with
surrounding neurons (Moran et al. 2008).

Responses to passive movement

Widened receptive fields of basal ganglia neurons are a well documented characteristic of the
parkinsonian state (Bergman et al. 1994; Boraud et al. 2000; Rodriguez-Oroz et al. 2001; Vitek et al.
1998), and have been shown in a model of DYT1 dystonia (Chiken et al. 2008). Here, somatosensory
receptive fields were widened in PD as compared to dystonia. Of note, most passive movement
responses in dystonia were tested in limbs that did not clinically have dystonia; thus it is possible that
widened receptive fields might be more prominent in patients with generalized dystonia. Most of the
multi-joint movement-responsive cells in dystonia patients, however, involved passive movement
responses in limbs that did not have clinical dystonia. Thus, some alteration in STN receptive field
properties could represent a dystonic endophenotype (Quartarone et al. 2003; Quartarone et al. 2008).
Quantitative study of neuronal responses to passive movement at a single joint showed that response to
only one movement phase was more common in dystonia than PD, whereas direction and duration of
response did not distinguish PD from dystonia. Responses to passive joint manipulation in our study
were similar to those previously described in the GPi in dystonic patients (Chang et al. 2007). Almost all
responses to passive movement were increases in discharge, in both PD and dystonia.

Implications for current models of basal ganglia function

Early models of the functional organization of the basal ganglia (Albin et al. 1989; DeLong
1990) emphasize two distinct intrinsic pathways linking the basal ganglia input (striatum) to the basal
ganglia outputs (GPI and SNr), which require a balance for normal motor function. Vitek et al. (Vitek
2002) have extended this concept to primary dystonia, proposing that striatal cells originating both the direct and indirect pathways are overactive. This is in contrast to parkinsonism, in which only the striatal cells originating the indirect pathway are overactive. Our findings are consistent with Vitek’s model, but indicate that the extent of indirect pathway activation is less than that present in PD. Furthermore, it is now recognized that the corticosubthalamic pathway has a prominent excitatory influence on STN activity (Bevan et al. 2007; Magill et al. 2001), thus our findings would also be consistent with hyperactivity in this pathway in dystonia.

Mink (Mink 2003; 1996) has proposed a “center-surround” organization of the basal ganglia intrinsic pathways. In the normal state, the inhibitory direct pathway or “center” selects a desired motor program via focal disinhibition of GPi output, whereas the divergent excitatory STN-GPi activity provides a broad “surround” inhibition of unwanted motor programs. Nambu et al. have modified this model to emphasize the “hyperdirect” cortex-STN-GPi pathway as the major source of surround inhibition (Nambu 2004; Nambu et al. 2002). When applied to dystonia, this model predicts that deficient surround inhibition via the STN, or excessive center excitation, results in incomplete suppression of motor pattern generators (Mink 2003). Our results do suggest a relative decrease in surround inhibition in dystonia compared with PD. However, our finding of relatively high spontaneous STN discharge rate in dystonia does not support an absolute decrease in surround inhibition. Further, our limited data on movement-related activity produced no evidence for a movement-related decrease in surround inhibition, since voluntary movement tended to produce an increase in STN firing in both dystonia and PD. Thus, the center-surround framework, if applicable to dystonia, would need to emphasize an expanded “center” rather than a deficient “surround”, or would need to invoke bursting discharge rather than discharge rate as the mechanism for excessive thalamocortical activations in “surround” channels (Person and Perkel 2005).
Implications for surgical target choice

At most centers performing movement disorders surgery, the STN is the preferred target for PD while GPi is preferred for dystonia. This distinction is largely based on empiric findings rather than physiological principles. It has been hypothesized that the therapeutic effect of DBS may be related to the attenuation of abnormal firing patterns in the basal-ganglia thalamocortical circuit. Here, we show that the major features of pallidal discharge in dystonia that were documented in prior studies are also found in the STN. This provides a physiological basis for the STN as an alternative therapeutic DBS target for the treatment of dystonia. Several cases of STN DBS for the treatment dystonia have been reported in the literature with beneficial effects in most cases of cervical (Chou et al. 2005; Ostrem et al. 2008), segmental (Kleiner-Fisman et al. 2007; Ostrem et al. 2008), primary generalized (Detante et al. 2004; Kleiner-Fisman et al. 2007; Novak et al. 2008; Sun et al. 2007), and tardive dystonia (Sun et al. 2007; Zhang et al. 2006), whereas outcomes in secondary dystonia patients have not been favorable (Detante et al. 2004; Zhang et al. 2006). Recently, interest in exploring alternative targets for treatment of cervical and segmental dystonia has been spurred by the report that prolonged GPi DBS may cause reversible stimulation-induced bradykinesia in previously non-dystonic limbs that cannot be attributed to spread of stimulation to surrounding corticospinal fibers (Berman et al. 2009; Hubl et al. 2009; Ostrem et al. 2007; Zauber et al. 2008).

Pitfalls in interpretation

The present study has some limitations. First, isolation of single units in the human STN is challenging due to high neuronal density and periodic loss of unit isolation in synchrony with the cardiac cycle. As a result, the number of stable, well isolated units recorded from each study subject was small. Also, the dystonia patients in this study had focal or segmental rather than generalized dystonia. The
differences between PD and dystonia found here might have been accentuated in generalized dystonia patients. Nonetheless, even patients with focal dystonia (Garraux et al. 2004; Peller et al. 2006; Quartarone et al. 2008) or non-manifesting DYT1 gene carriers (Asanuma et al. 2005; Carbon et al. 2008; Eidelberg et al. 1998; Ghilardi et al. 2003; Trost et al. 2002) have global network abnormalities. Additionally, in GPi, similar oscillatory activities are seen in generalized and cervical dystonia patients (Liu et al. 2008).

Conclusions

Spontaneous STN single unit discharge in humans with primary dystonia shows many of the same features as in PD: prominent bursting and oscillatory discharge. However, oscillatory activity in the beta range is greater in PD than dystonia, supporting a current hypothesis that increased beta band oscillations play a role in the pathophysiology of PD. Although sensory receptive fields are widened in PD compared with dystonia, the direction and duration of responses to passive movements are similar in the two conditions. Our findings provide a physiological basis for surgical intervention in STN in primary dystonia.

Figure legends

Figure 1. Examples of single-unit activity from a typical STN neuron in a patient with cranial-cervical dystonia (left column) and a patient with the akinetic-rigid subtype of Parkinson’s disease (right column). A: Neuronal recordings. A two-second interval is shown. B: Interspike interval histograms, bin size of 1 msec. Inset shows an expanded timescale demonstrating the absence of interpike intervals of
less than 3 msec duration, consistent with the neuronal refractory period. C: Raster diagrams showing bursting discharge. Bursts as defined by the Poisson “surprise” method (surprise value > 5) are labeled with a black bar above spikes that constitute a burst. Note the higher proportion of bursts per total number of spikes shown in the dystonia neuron (0.40 versus 0.26 in the PD neuron). Consecutive rows (3 seconds of data per row) from bottom to top represent continuous 36 second recordings. D: Autocorrelograms. The right autocorrelogram shows oscillatory activity ~11 Hz. The unit on the left was not found to have significant oscillations.

Figure 2. Histograms of spontaneous STN discharge rates in PD (black bars) and dystonia (grey bars). Bin size is 10 Hz. X-axis labels indicate the bin midpoint (i.e., 5 refers to 0 – 9.99, 15 refers to 10 – 19.99, 25 to 20 – 20.99, etc.). Bars are slightly off-set for visual clarity. STN neuronal discharge rate was significantly lower in dystonia patients than in PD patients (p < .001).

Figure 3. A: Distribution of frequencies of significant oscillations in spontaneous STN activity in dystonia (upper graph) and Parkinson’s disease (lower graph). Bins are left-inclusive, except for the first bin, which starts at 0.4 Hz since the lower limit of oscillatory activity was 0.49 Hz. (i.e., the bins represent 0.4-2.99, 3-7.99, 8-12.99, 13-29.99, 30-59.99, 60-99.99, and 100-199.99 Hz.). Several cells oscillated at more than one frequency (see Results). There was a greater incidence of oscillatory activity in low frequency bands (3-30 Hz) in PD than dystonia (p=.01). Oscillatory activity in the beta band (13-30 Hz) was found only in PD (p = .03). B: Top: The power spectra of spike trains generated by the global spike shuffling method between 0 and 30 Hz for a patient with the akinetic-rigid subtype of PD. This is the same PD cell displayed in Figure 1. There is a single significant peak at 11 Hz. Middle: The power spectra between 0 and 30 Hz for a patient with cranial-cervical dystonia. There is a single significant peak at 3.9 Hz. Bottom: The power spectra between 0 and 115 Hz for a patient with akinetic-rigid PD. There are 2 significant peaks at 3.4 Hz and 90.3 Hz.
Figure 4. Representative STN neuronal responses to passive limb movement in dystonia and Parkinson’s disease. For each example, neuronal responses for reciprocal movements are shown in left and right columns. For each neuron, top panel shows a mean spike density function centered at the initial deflection in limb acceleration (time = 0s). The dotted line shows the thresholds for significant changes in mean discharge rate. The bottom panel shows a raster display of neuronal responses to each individual trial. A: Neuronal response to passive knee movement in a dystonia patient: flexion (left) evoked a brisk increase response, but extension (right) resulted in no appreciable change in firing. B: Neuronal response to passive knee movement in a patient with Parkinson’s disease: flexion (left) and extension (right) both resulted in firing increases. C: Neuronal response to passive wrist movement in a patient with Parkinson’s disease: flexion (left) resulted in increased firing and extension (right) evoked a decrease in firing. D: Neuronal response to passive shoulder movement in a patient with Parkinson’s disease: both external rotation (left) and internal rotation (right) evoked a brisk biphasic response of increased neuronal firing followed by decreased firing.

References


Sanger TD. Childhood onset generalised dystonia can be modelled by increased gain in the indirect basal ganglia pathway. *Journal of neurology, neurosurgery, and psychiatry* 74: 1509-1515, 2003.


<table>
<thead>
<tr>
<th>Subject</th>
<th>Dystonia type</th>
<th>Gender</th>
<th>Age at surgery (years)</th>
<th>Duration of symptoms (years)</th>
<th>Body parts involved (BFMDRS score &gt;0)</th>
<th>Baseline BFMDRS Movement score</th>
<th>Baseline TWSTRS score (total)</th>
<th>Preoperative medications (total mg per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Seg</td>
<td>F</td>
<td>45</td>
<td>2</td>
<td>M, S, A (both), N, T</td>
<td>30</td>
<td>60</td>
<td>intrathecal baclofen (545mcg), oxycodone (15)</td>
</tr>
<tr>
<td>2</td>
<td>Seg</td>
<td>F</td>
<td>47</td>
<td>2</td>
<td>E, M, S, N</td>
<td>20</td>
<td>41</td>
<td>diazepam (10), baclofen (40), levetiracetam (1000)</td>
</tr>
<tr>
<td>3</td>
<td>Foc</td>
<td>F</td>
<td>51</td>
<td>10</td>
<td>N</td>
<td>4</td>
<td>53</td>
<td>oxycodone ER (190), escitalopram (20), clonazepam (2), tizanidine (100), nortriptyline (25), gabapentin (1800), amlodipine/benazepril (10/20)</td>
</tr>
<tr>
<td>4</td>
<td>Seg</td>
<td>M</td>
<td>23</td>
<td>11</td>
<td>M, S, N, A (right)</td>
<td>32</td>
<td>56.75</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>Foc</td>
<td>M</td>
<td>48</td>
<td>7</td>
<td>N, T</td>
<td>20</td>
<td>53.5</td>
<td>clonazepam (1.5), morphine sr (90), acetaminophen/hydrocodone (1500/15)</td>
</tr>
<tr>
<td>6</td>
<td>Seg</td>
<td>M</td>
<td>61</td>
<td>7</td>
<td>E, M, S, N</td>
<td>22.5</td>
<td>61.25</td>
<td>morphine sr (90), sertraline (200)</td>
</tr>
<tr>
<td>7</td>
<td>Seg</td>
<td>M</td>
<td>34</td>
<td>17</td>
<td>M, S, N, A (both)</td>
<td>40</td>
<td>53.5</td>
<td>trihexyphenidyl (6), clonazepam (3), topiramate (25)</td>
</tr>
<tr>
<td>8</td>
<td>Foc</td>
<td>F</td>
<td>40</td>
<td>9</td>
<td>N</td>
<td>8</td>
<td>64</td>
<td>clonazepam (1), lexapro (40), tramadol (150), acetaminophen/hydrocodone (3000/30)</td>
</tr>
<tr>
<td>9</td>
<td>Seg</td>
<td>M</td>
<td>71</td>
<td>34</td>
<td>E, M, N</td>
<td>13</td>
<td>58.5</td>
<td>lorazepam (9)</td>
</tr>
</tbody>
</table>

Mean (SD)

<table>
<thead>
<tr>
<th>BFMDRS Movement score</th>
<th>Baseline TWSTRS score (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>46.7 (SD 14.1)</td>
<td>11.0 (SD 9.8)</td>
</tr>
</tbody>
</table>

Abbreviations: A=arm; BFMDRS=Burke-Fahn-Marsden Dystonia Rating Scale; E=eyes; Foc=focal; Seg=segmental; M=mouth; N=neck; S=speech/swallow; SD = standard deviation; T=trunk; TWSTRS=Toronto Western Torticollis Rating Scale
<table>
<thead>
<tr>
<th></th>
<th>Dystonia</th>
<th>Parkinson’s disease (all units)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of neurons</td>
<td>62</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>Mean firing rate (Hz)</td>
<td>26.3 (SD 13.6)</td>
<td>35.6 (SD 15.2)</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Burst index</td>
<td>7.2 (SD 4.0)</td>
<td>4.7 (SD 2.6)</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Proportion of discharges in bursts§</td>
<td>0.26 (SD 0.14)</td>
<td>0.19 (SD 0.14)</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>L-statistic</td>
<td>7.1 (SD 1.5)</td>
<td>6.7 (SD 1.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Proportion of cells with significant oscillations 0-200 Hz</td>
<td>32.3%</td>
<td>39.9%</td>
<td>0.35</td>
</tr>
<tr>
<td>Proportion of cells with significant oscillations 3-30 Hz</td>
<td>6.5%</td>
<td>20.3%</td>
<td>0.01*</td>
</tr>
<tr>
<td>Proportion of cells with significant oscillations 13-30 Hz</td>
<td>0%</td>
<td>6.3%</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

Values are mean and standard deviation (SD) of mean
* denotes statistically significant difference between dystonia and PD by Wilcoxon ranksum test or chi-squared test
§ As determined using the Poisson ‘surprise’ method
Table 3. Electrophysiological characteristics of STN neurons in dystonia and PD subtypes

<table>
<thead>
<tr>
<th></th>
<th>Dystonia</th>
<th>Parkinson’s disease (akinetic-rigid)</th>
<th>p-value</th>
<th>Parkinson’s disease (tremor dominant)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of neurons</td>
<td>62</td>
<td>93</td>
<td></td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Mean firing rate (Hz)</td>
<td>26.3 (SD 13.6)</td>
<td>35.0 (SD 15.2)</td>
<td>&lt; .001*</td>
<td>36.7 (SD 15.1)</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Burst index</td>
<td>7.2 (SD 4.0)</td>
<td>4.7 (SD 2.5)</td>
<td>&lt; .001*</td>
<td>4.7 (SD 2.7)</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Proportion discharges in bursts§</td>
<td>0.26 (SD 0.14)</td>
<td>0.19 (SD 0.13)</td>
<td>.001*</td>
<td>0.20 (SD 0.51)</td>
<td>.02*</td>
</tr>
<tr>
<td>L-statistic</td>
<td>7.1 (SD 1.5)</td>
<td>6.7 (SD 1.7)</td>
<td>.05</td>
<td>6.8 (SD 1.7)</td>
<td>.28</td>
</tr>
<tr>
<td>Proportion of cells with significant oscillations 0-200 Hz</td>
<td>32.3%</td>
<td>39.8%</td>
<td>.64</td>
<td>40%</td>
<td>.64</td>
</tr>
<tr>
<td>Proportion of cells with significant oscillations 3-30 Hz</td>
<td>6.5%</td>
<td>20.4%</td>
<td>.05</td>
<td>20.0%</td>
<td>.05</td>
</tr>
<tr>
<td>Proportion of cells with significant oscillations 13-30 Hz</td>
<td>0%</td>
<td>6.5%</td>
<td>.09</td>
<td>6.0%</td>
<td>.09</td>
</tr>
</tbody>
</table>

Values are mean and standard deviation (SD) of mean

* denotes statistically significant difference between dystonia and PD subtype identified in preceding column by Wilcoxon ranksum test or chi-squared test.

§ As determined using the Poisson ‘surprise’ method
Table 4. Responses to passive movement on initial intraoperative screen of contralateral joint movements

<table>
<thead>
<tr>
<th></th>
<th>Parkinson’s disease</th>
<th>Dystonia</th>
<th>p-value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cells tested</td>
<td>180</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Movement-responsive</td>
<td>64%</td>
<td>46%</td>
<td>0.002</td>
</tr>
<tr>
<td>Multi-joint responsive*</td>
<td>33%</td>
<td>15%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Proportion of movement-responsive cells with responses to multiple joints

§chi-square test
<table>
<thead>
<tr>
<th>Response Type</th>
<th>Parkinson’s Disease</th>
<th>Dystonia+</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cells analyzed</td>
<td>12</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Response to one movement phase only</td>
<td>2/12</td>
<td>4/6</td>
<td>0.03*</td>
</tr>
<tr>
<td>Response to both movement phases</td>
<td>10/12</td>
<td>2/6</td>
<td></td>
</tr>
<tr>
<td>Increase response≠</td>
<td>18/24</td>
<td>7/12</td>
<td></td>
</tr>
<tr>
<td>Decrease response≠</td>
<td>2/24</td>
<td>0/12</td>
<td>0.16*</td>
</tr>
<tr>
<td>Biphasic response≠</td>
<td>2/24</td>
<td>1/12</td>
<td></td>
</tr>
<tr>
<td>No response≠</td>
<td>2/24</td>
<td>4/12</td>
<td></td>
</tr>
<tr>
<td>Duration of response (mean and SD)</td>
<td>0.37s (SD 0.23)</td>
<td>0.43s (SD 0.28)</td>
<td>0.56§</td>
</tr>
</tbody>
</table>

+ Sample include four cells from two patients with focal cervical dystonia and two cells from a patient with cranial-cervical dystonia. No cells from patients with arm involvement were included.

*chi squared test

§Wilcoxon rank-sum test

#Response proportion calculated using both movement phases
Table 6. Electrophysiological characteristics of STN neurons with subjects at rest and with voluntary movement. Only neurons studied both at rest and during voluntary movement are included in this comparison.

<table>
<thead>
<tr>
<th></th>
<th>Dystonia</th>
<th>PD</th>
<th>PD vs. Dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Movement</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Number of neurons</strong></td>
<td>9</td>
<td>9</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Mean firing rate</strong></td>
<td>23.7 (SD 6.3)</td>
<td>26.6 (SD 13.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Burst index</strong></td>
<td>7.2 (SD 1.8)</td>
<td>7.7 (SD 3.9)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Proportion of spikes in bursts</strong></td>
<td>0.20 (SD 0.08)</td>
<td>0.29 (SD 0.11)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>L-statistic</strong></td>
<td>7.0 (SD 0.9)</td>
<td>7.2 (SD 1.4)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Values are mean and standard deviation (SD) of mean

* Denotes statistically significant difference between rest and voluntary movement by Wilcoxon paired sample test.
A

Dystonia

PARKINSON'S DISEASE

100 mV

500 msec

Counts/bin

0 0 50 200

20 60 40

150

100

50

TIME (sec)

B

Counts/bin

0 0 50 100

200 250

150

100

50

TIME (sec)

C

Time (sec) 0 3

Frequency (Hz)

0 0 0.5 1

20 40 60 80

D

Frequency (Hz)

0 0 0.5 1
Dystonia

Number of units studied = 62
% with significant oscillations = 32

Oscillation frequencies (Hz)

Parkinson’s disease

Number of units studied = 143
% with significant oscillations = 40

Oscillation frequencies (Hz)