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Subthalamic Nucleus Discharge Patterns during Movement in the Normal Monkey and Parkinsonian Patient

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Abstract

The pathophysiology of Parkinson disease (PD) is characterized by derangements in the discharge rates, bursting patterns, and oscillatory activity of basal ganglia (BG) neurons. In this study, subthalamic nucleus (STN) neuronal activity patterns in humans with PD was compared with that in the normal monkey during performance of similar volitional movements. Single-unit STN recordings were collected while PD patients and animals moved a joystick in the direction of targets presented on a monitor. When discharge rates in all PD human and normal monkey neurons were compared, no significant differences were observed. However, when neurons were classified by peri-movement response type (i.e., excited, inhibited, or unresponsive to movement) statistical differences were demonstrated – most significantly among PD excited neurons. Analysis of burst activity demonstrated inter- and intra-burst activities were greater in the PD human compared to the monkey irrespective of neuronal response type. Moreover, simultaneously recorded neurons in the human demonstrated consistent oscillatory synchronization at restricted frequency bands, whereas synchronized oscillatory neurons in the monkey were not restricted to distinct frequencies. During movement, discharge and burst rates were positively correlated, independent of subject or neuronal response type; however, rates and oscillatory activity were more strongly correlated in the PD human than the normal monkey. Interestingly, across all domains of analysis, STN neurons in PD demonstrated reduced response variability when compared to STN neurons in the normal monkey brain. Thus, the net effect of PD may be a reduction in the physiological degrees of freedom of BG neurons with diminished information carrying capacity.

Keywords

Parkinson disease; subthalamic nucleus; basal ganglia; movement; oscillations

1. Introduction

Basal ganglia (BG) structures are involved in multiple, partially segregated parallel loops that modulate cortical activity (Alexander et al., 1986; Alexander and Crutcher, 1990; Alexander, 1994; Hoover and Strick, 1999). Various circuits have been characterized including oculomotor, prefrontal, limbic, and motor loops (Alexander and Crutcher, 1990). These circuits include convergent inputs from the cortex to the striatum before proceeding through different

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pathways to the output nuclei, the globus pallidus internus (GPi) or substantia nigra pars reticularis (SNpr), which project to the thalamus or other brainstem nuclei. Specific motor loop nuclei include the striatum, globus pallidus externus, GPe, substantia nigra, subthalamic nucleus (STN), and thalamic motor nuclei.

The primary models of BG physiology include the rate (Albin et al, 1989; DeLong, 1990), selectivity (Mink, 1996), oscillatory (Brown, 2003) and pattern models (Bergman et al., 1994; Soares et al., 2004; Beurrier et al., 1999; Bevan et al., 2000). The rate and selectivity models posit that the BG encode information based on neuronal firing rates, while the oscillatory model suggests information is encoded in specific frequency bands. The pattern model suggests that burst patterns of BG neurons interrupt information transfer in Parkinson disease (PD). Each of these models is supported by a specific derangement in neuronal activity (i.e., discharge rates, oscillatory activities and bursting pattern) in various BG pathologies; however, the nature of these processes during volitional movements in the normal and pathologic conditions is poorly understood.

The primary goal of this study was to contrast neuronal firing rates, oscillatory activity, and bursting patterns of STN neurons during the performance of volitional movements in normal monkeys and Parkinsonian humans. The results demonstrate STN neurons in PD humans have less response variability across multiple dimensions, and suggest that the aggregate effect of PD is a reduction in the information carrying capacity of BG neurons.

2. Results

Neuronal Discharge Rates

One-hundred Parkinsonian human and 101 normal monkey STN neurons were isolated. Examination of peri-movement histograms demonstrates considerable differences between PD humans and normal monkeys. Fig. 1 illustrates the peri-movement neuronal rates for neurons classified as either excited, inhibited, or unresponsive for both the PD human (left panel) and the normal monkey (right panel). Peri-movement rates were aligned to the peak velocity in the joystick voltage (grey lines), and the median value was taken across all neurons for each classification. Additionally, all traces were temporally adjusted to account for one-half the window size of the statistical analysis. Due to time differences in the behavioral tasks between the human and animal experiments variations in the onset of neuronal changes were not analyzed. Moreover, the temporal change from the period of rest to the peak velocity of the movement in the PD human is nearly twice as long as that seen in the normal monkey (Fig. 1, gray lines). However, interpretation of this observation must be undertaken with considerable caution, as parameters of movement (e.g. reaction and movement times) are considerably different between monkeys and humans. Furthermore, variations in experimental conditions such as room illumination, handedness, and fatigue can contribute to variations in movement parameters.

The median baseline (pre-movement) discharge rate for the PD human (23.8 Hz) was greater than that of the normal monkey (19.1 Hz), although significant changes were only observed by comparing the interactions between neuronal response types. For example, firing rates between human excited (32.3 Hz) and human unresponsive (20.4 Hz) neurons were statistically significant. Comparisons between human excited (32.3 Hz) and monkey excited (14.3 Hz) as well as monkey unresponsive (19.2 Hz) neurons were also significantly different (corrected multiple comparisons Kruskal-Wallis analysis of variance; $p < 0.05$, bonferroni correction). The percent difference between excited neurons between monkey and human subjects was not shown to be significant. Thus, the identification of neuronal response type appears critical for such comparisons of discharge rates between individuals.

Burst Activity

At rest, both the burst rate (burst/second) and intra-burst frequencies (Hz/Burst) were significantly higher in the PD human than in the normal monkey (Fig. 2). Thus, both the percentage of time in burst mode and firing rate within a burst appears to be greater in the PD human.

Peri-movement histograms were constructed based on the inter- and intra-burst activity in order to examine changes during movement. Inter-burst rate increased relative to movement in excited, decreased in inhibited neurons, and remained unchanged in unresponsive neurons (Fig. 3). Changes in peri-movement burst rates for the excited and inhibited neuronal populations were statistically significant relative to pre-movement inter-burst rates (Kruskal-Wallis analysis of variance; $p < 0.05$). Unlike the number of bursts per second, intra-burst spike frequency remained unchanged during movement (Kruskal-Wallis analysis of variance; $\alpha = 0.05$).

Oscillatory Synchronization

Twenty-eight percent (27/97 pairs) of simultaneously recorded neurons in the human demonstrated synchronized oscillatory activity. Similarly, 31% (23/74) of simultaneously recorded neurons in the normal monkey exhibited synchronized oscillatory activity. However, in the PD human, oscillatory activities were constricted to discrete frequency bands (21, 29 and 43Hz) (red arrows) in contrast to non-specific oscillatory activities in the normal monkey (Fig. 4A, B). Hence, synchronization was greater in the PD human in specific frequency bands.

Peri-movement Oscillatory Activities

As a means of examining potential changes in oscillatory activities relative to movement, spectral analysis was performed on the spike activities aligned to the peak velocity of the movements. Spectral estimates were calculated at 100 ms intervals using a 500 ms sliding window, starting 1.5 seconds before and ending 0.5 seconds after movement (refer to methods “4.9. Peri-movement Oscillatory Activity”). Since a 500 ms window size was used, frequencies less than 4 Hz were beyond the resolution of this analysis. Although PD patients can have tremor related neuronal oscillation in the 2-4 Hz frequency range (Rodriguez et al., 1998; Magarrinoc-Ascone et al., 2000; Levy et al., 2001), it was decided that an analysis window greater than 500 ms would significantly distort the resolution between movement and frequencies in the 5-40 Hz band. Hence, we chose to preserve the resolution, and focus on frequencies above 4 Hz that modulated relative to movement.

During movement, oscillatory activities in the PD human and normal monkey were modulated at various frequency bands for both excited (Fig. 5) and inhibited (Fig. 6) responsive neurons. Furthermore, there were significant correlations between the changes in neuronal spike/burst rates and oscillatory activities.

The most prominent changes in oscillatory activity occurred in excited responsive neurons at 5-40 Hz in PD humans (Fig. 5). Specifically, excited responsive neurons demonstrated a significant increase in oscillatory power relative to the peak velocity of movement (paired t test; $p = 0.03$), and positively correlated with firing rates. This was also observed in the normal monkey (paired t test; $p = 0.01$). In frequencies above 10 Hz, no significant changes were observed in the normal monkey, while in the PD human oscillatory power was significantly (paired t test; $p = 0.02$ at 10-25 Hz and $p = 0.04$ at 25-40Hz) decreased relative to movement (Fig. 5).

With regard to inhibited neurons, no significant changes were found in the normal monkey relative to movement (Fig. 6). In the PD Human, a significant decrease in oscillatory power

was observed in the 5-10 Hz range (paired t test; $p=0.02$), but not at higher frequency ranges. In addition, no significant changes were noted in unresponsive neurons relative to movement.

Variance Analysis

The variance in peri-movement neuronal activity was significantly different between STN neurons of the PD human and normal monkey for all modes of neuronal analysis (Fig. 7). The magnitude of peri-movement changes in STN firing rates, burst rates (0.28; 0.33), and SNR of the 15-35 Hz range relative to baseline activities showed significantly more variance in the monkey than in the PD human (Ansari-Bradley test for variance, $p < 0.01$ in each analysis).

3. Discussion

Abnormal activity patterns of STN neurons play an important role in the pathophysiology of PD. As these patterns change with different phases of movement, it is important that they be assessed using active, reproducible tasks as described above. However, discerning which patterns are pathological is limited by the inability to record STN activity in normal humans. In addition to normal monkeys, STN activity can be evaluated in primates rendered Parkinsonian by the administration of 1-methyl-4-phenyl-2,3,6-tetrahydropyridine (MPTP). However, this approach has limitations in that MPTP-treated animals only approximate human PD, and such animals are frequently unable to perform complex behavioral tasks. An alternative comparison involves administration of dopaminergic agonists to human subjects intra-operatively; however, this prolongs surgery time and does not restore a normal state since long-term processes such as changes in receptor density are still present. Hence, no single comparison is perfect, but all have the potential to yield important insights in relation to the primary models of BG physiology.

The rate model posits that information is encoded by neuronal firing rates. In accordance with the rate model, the direct pathway is thought to facilitate movement, while the indirect pathway is thought to suppress movement. The antagonistic relationship between these pathways is governed by differential responses of striatal neurons to dopamine, with D1- direct pathway neurons being excited by dopamine, while D2-striatal neurons of the indirect pathway are inhibited. Thus in PD, the loss of dopamine results in less direct pathway activation and more indirect pathway activation – resulting in disinhibition of the GPi, suppression of the thalamus, and decreased cortical activity. Moreover, the extent and duration of movement-related increases in firing rates and periodic bursting patterns are altered with placement of lesions in the STN of normal monkeys (Wichmann et al., 1994b). However, the power of oscillatory activity observed in GPi did not diminish with STN lesioning despite symptomatic tremor changes. During torque movement, Wichmann and colleagues found 40% of STN arm cells demonstrated significant activity changes (of which 90% were increased discharge rates) (Wichmann et al., 1994a). By comparison the present study observed a similar 44% change in neuronal activity; however, in contrast we observed 57% of these neurons with increased discharge rates. The rate model has thus been used to describe hypokinetic aspects in PD, although other features such as tremor and dystonia are less clearly explained. The data presented above supports the basic prediction of the rate model in that the firing rate of STN excited neurons is greater in human PD patients compared to other neuron types in normal monkeys. Thus, the above data illustrates the importance of determining neuron response type (i.e., excited or inhibited) before a direct comparison can be made between individuals. Although the overall trend is consistent with the model, direct comparisons of firing rates between humans and primates must be interpreted with caution. However, comparisons between the distribution of different response types (i.e., the proportion of inhibited and excited neurons) may be more meaningful.

Like the rate model, the selectivity model predicts that information is encoded by neuronal rates. However, the selectivity model suggests that inputs to the GPi form a center-surround organization wherein direct pathway activity facilitates desired movements while STN activity (of the indirect pathway) inhibits unwanted behaviors. Dysregulation or depletion of dopamine may result in an inability to select desired or inhibit unwanted behaviors. Although this is an intriguing idea, there is little physiological data to support a center-surround organization in the GPi. Furthermore, the model suggests that for any movement, there are many competing movement programs, although this has not been clearly demonstrated.

The pattern model suggests that BG neuronal burst patterns differ between normal and pathological conditions. In the BG of animals given MPTP, burst occurrence and duration are often greater than that in normals (Wichmann and Soares, 2006). Thus, interactions between both burst length and intra- and inter-burst intervals are believed to alter information processing in the pallidum and subthalamic nucleus in Parkinsonian states (Beurrier et al., 1999; Bevan et al., 2000). The data presented here are consistent with the pattern model since mean burst rate and intra-burst frequencies were greater in the PD human than the normal monkey.

The oscillatory model suggests that BG nuclei encode information in specific frequency bands. The present study suggests that some degree of oscillatory changes relative to movement is present in the normal STN – possibly a normal property of the BG-cortical network. For example, Courtenmanche et al. (2003) reported widespread coherent beta-band oscillations in the striatum of normal behaving monkeys. However, there is considerable evidence that excessive oscillatory activity in BG neurons may contribute to the pathophysiology of PD. Abnormal oscillations of the BG are not limited to a single frequency, but instead appear to span a number of distinct frequency bands. Of note, previous studies suggest dopamine levels may play a role in regulating oscillatory activity in the BG as dopamine depletion has been shown to increase oscillatory power in the beta band (Sharotta et al., 2005; Brown, 2002). This is reversible by administration of dopamine agonists. The identification of abnormal oscillatory activity in the BG was described in both the PD human and the MPTP monkey (Miller and DeLong, 1987; Fillion and Tremblay 1991). The relationship between oscillations and tremor is complex, such that beta-band oscillations can be observed in the presence and absence of tremor. Moreover, the frequency of beta-band oscillations is greater than the commonly observed 5 Hz tremor frequency. Hence, it has been suggested that abnormal beta-band oscillatory patterns may disrupt thalamo-cortical processing, resulting in akinesia (Rivlin-Etzion et al., 2006). Moreover, the observed ~300 Hz inter-burst frequency in PD humans may account for the observations of Foffani and colleagues who reported 300 Hz oscillatory activity in the local field potentials of the Parkinsonian STN (Foffani et al., 2003). Although not examined in this study due to analysis limitations, considerable attention has been paid to tremor related oscillatory activity of STN neurons in the range of 2-4 Hz (Rodriguez et al., 1998; Magarrinoc-Ascone et al., 2000; Levy et al., 2001). Importantly, Levy et al. (2001) demonstrated in the PD human that both the tremor and the 2-4 Hz STN oscillatory activity are concurrently attenuated with the administration of apomorphine. Tremor-related oscillations can be observed in single neurons (either alone or in the presence of beta-band oscillations) and may significantly contribute to the abnormal oscillatory activities seen in PD (Levy et al., 2001).

Current models of BG physiology and pathophysiology have been useful in explaining specific attributes of PD such as tremor, bradykinesia and dystonia. However, no single model captures all physiological and clinical attributes observed in PD since specific studies refute various aspects of each model (Gale et al., 2007). One explanation for this shortcoming may be that each model tends to focus on a single characteristic of neuronal activity, such as firing rates, oscillatory characteristics, or burst patterns. Indeed, the findings of this study can be consistent with each model when the analysis is considered in isolation. However, as demonstrated by

examining the variance in each measure of neuronal activity, a consistent pattern emerges. Specifically, across all modes of analysis (i.e. firing rate, burst rate, directional selectivity and spectral analysis), STN neurons in PD demonstrate less variability than do STN neurons of the normal primate.

We present the following hypothesis to account for these observations. In the normal condition, the BG-thalamic-cortical network dynamically modulates neuronal activity, and possibly the degree of correlation, in order to appropriately select or facilitate motor behavior. PD results in a multifactorial disruption of activity leading to a saturation of global and/or local neuronal patterns such as oscillations, synchronicity, firing rates, and bursting. The net effect is a reduction in the dynamic range of the affected neurons across multiple dimensions, which effectively reduces their information carrying capacity. Deep brain stimulation may work by either reducing these pathologic effects (allowing the neurons to have a more normal dynamic range), or by functionally taking the circuit off-line. Understanding which of these mechanisms is at play, should be an important component of future research, and will hopefully allow for the continued rational evolution of DBS therapies. Direct comparisons will therefore be required (between neurons with identical response types) between normal and MPTP monkeys during motor behaviors to support the above findings. Of note, the most salient implication of these findings for neurophysiologists is the various responses of neurons observed during microelectrode recording sessions. Before neuronal dynamics can be fully assessed in Parkinsonian patients or animals, the response to movement (excited, inhibited, or unresponsive) should be determined in each cell to avoid investigator bias or misinterpretation.

4. Experimental Procedure

4.1. Patient Selection

Human Research conducted in this study was performed in accordance with a protocol approved by the Massachusetts General Hospital Institutional Review Board and was in accordance with appropriate NIH guidelines. The research purpose and potential risks associated with participation in the clinical studies were explained to the human subjects by study personnel other than the operating surgeon, and signed consents for participation were obtained before surgery. Surgical decisions in human subjects were based on clinical indications, and were not related to participation in the study. All animal studies were conducted under a protocol approved by the Animal Care and Use Committee, and were in accordance with all applicable USDA guidelines.

All 23 human subjects (84 recording sessions with at least 60 trials each) included in this study had a pre-surgical diagnosis of idiopathic PD for a minimum of four years and a Hoehn and Yahr score of three or greater. Furthermore, all patients had a documented therapeutic response to l-3,4-dihydroxyphenylalanine (L-Dopa). Patients who demonstrated a lack of response to typical medication regimens and those who presented with specific symptoms such as autonomic dysfunction, ataxia, and supranuclear palsy were excluded from this study. Prior to surgery, subjects underwent neuropsychiatric testing to detect any cognitive impairment or active psychiatric disorders.

4.2. Animals

Two juvenile male non-human primates (*macaca mulatta*) were used in this study. Between research sessions, the animals were individually housed in a climate and light (12 hour on/off) controlled environment, and provided a balanced primate diet with supplemental fruits and treats. Water intake and animal weights were monitored on a daily basis. Mean weight during the study was 8.2 and 6.3 Kg.

4.3. Human Surgeries and Localization of the STN

Starting at midnight prior to surgery, anti-Parkinsonian medications were withheld. Surgeries were performed using stereotactic techniques and electrophysiological localization of the STN as previously described (Amirnovin et al., 2004). In addition to pre-surgical MRI and CT studies, intra-operative electrophysiological recordings were performed to define the STN boundaries. Somatosensory regions were identified by neuronal responsiveness to active and passive movements of the extremities. Electrophysiological recordings were obtained using three tungsten microelectrodes (300-500 kOhm impedance, FHC, Bowdoinham, ME) spaced 2 mm apart in the parasagittal plane. Electrodes were simultaneously advanced through the brain by a motorized microdrive at 20-50 μ m increments. The analog neuronal signal from each electrode was amplified, band-pass filtered (300 Hz to 6 kHz), and digitized at 20 kHz by an FDA approved system (Alpha-Omega Engineering, Nazareth, Israel).

4.4. Localization of the STN in the monkey

Prior to recording sessions, each primate was implanted with a standard recording chamber (Crist Instrument Co., Bethesda, MD). The chamber position was calculated based on MR (1.5 tesla) images referenced to stereotactic atlas coordinates (Paxinos et al., 2000). Postoperatively, animals were re-scanned to verify chamber placement. Once the animals recovered (~2 weeks), STN borders were mapped using electrophysiological recordings (Williams et al., 2005). Briefly, a single microelectrode (300-500 kOhm impedance @ 1 KHz; FHC, Bowdoinham, ME) were inserted in the brain during each recording session via a grid with holes spaced at 2 mm intervals, using a microelectrode manipulator (David Kopf Instruments, Tujunga, CA) mounted to the recording chamber. Analog extracellular signals were band-pass filtered at 0.3 to 6 kHz, amplified (MDA-4I, BAK Instruments, Mount Airy, MD) and digitized at 20 kHz (Cambridge Electronic Design, Cambridge, England) for offline processing.

4.5. Behavioral Task

After microelectrode placement in the STN, both primate and human subjects viewed a computer monitor and performed the behavioral task by moving a joystick with the contralateral hand. Each trial began with the presentation of a small central fixation point. After a brief delay (250 ms), four small gray targets appeared in a circular array around the fixation point. Following a 500-1500 ms delay, a randomly selected target turned green. At this point, subjects used the joystick to guide a cursor from the center of the monitor toward the green target. A tone sounded once the target was reached, indicating successful task completion. Subjects were required to reach the target within 3/5 sec (monkey/human) of the green cue presentation, and to return the joystick to the center position before a new trial started. This was followed by an inter-trial interval of 1000-1500 ms. If the subject prematurely moved the joystick, strayed beyond the confines of an invisible corridor, failed to reach the target, or failed to return the joystick to its central position the trial was aborted. The movement directions were pseudo-randomized to ensure an equal number of trials in each direction. Monkeys were required to maintain eye fixation on the center fixation point throughout the task. Failure to maintain eye fixation during the task sequence resulted in an aborted trial.

4.6. Data Acquisition and Conditioning

All behavioral and electrophysiological data was captured on a single computer acquisition system (Spike 2, Cambridge Electronic Design, UK). Analog electrophysiological and joystick data were simultaneously digitized at 20 kHz and 1 kHz, respectively. Once digitized, all data was archived for post-hoc conditioning. Electrophysiological data for the human and primate were sorted into individual unit activities using software packaged with the Spike2 acquisition system. Great care was taken to ensure that single and stable neurons were used for the analysis. Therefore, only neurons with sufficient and stable signal-noise ratios (SNR) were used for

subsequent analysis. Furthermore, the autocorrelograms and crosscorrelograms of the isolated neurons were reviewed to ensure that the resultant unit activity was consistent with the characteristics of a single neuron.

4.7. Movement Detection

Movement events were detected by examining joystick voltages acquired during the behavioral task. The peak velocity of each movement was detected by first calculating the Pythagorean distance ($c = (X^2 + Y^2)^{1/2}$) of the X and Y joystick voltages. Once calculated, the peak velocity was determined to be the maximum value of the derivative of the Pythagorean distance following the start of each movement. Timestamps for each movement event were then stored for subsequent analysis. In order to facilitate comparisons between neurons and subjects, 60 movements were randomly selected from the pool of detected movements for each recording session and used for all peri-movement analysis. Recording sessions with less than 60 movements were discarded.

4.8. Peri-movement Discharge Rates

Peri-movement rasters and histograms were constructed for each neuron, and aligned to 1.5 seconds before and 0.5 seconds after each movement. Discharge rate histograms were binned in 100 ms intervals using a 500 ms sliding window (Fig. 8a). Neurons were then divided by their peri-movement rate responses, which were classified as excited, inhibited or unresponsive to movement. These rate classifications were based on comparisons between the pre-movement (500 ms) baseline activities to the activities that occurred during movement (500 ms; centered on peak movement velocity). Inclusion into either the excited or inhibited groups was determined by a multiple comparison ANOVA ($p < 0.05$) of baseline activity relative to each 100 ms bin during movement.

4.9. Peri-movement Oscillatory Activity

Using methods previously described, autocorrelograms were constructed for each window of the raster with a resolution of 1ms (Fig. 8a,c) (Amirnovin et al., 2004; Raz et al., 2000). After subtracting the mean, the power spectrum of each autocorrelogram was calculated by the Fast Fourier Transform (FFT, 512 point based; MatLab, The MathWorks Inc., Natick, MA) (Fig. 8d,e). Since a 500 ms window size was used, frequencies less than 4 Hz were beyond the resolution of this analysis. The SNR was computed for each power spectra using the formula: $((\text{current frequency}) - (\text{mean of all frequencies})) / (\text{standard deviation of all frequencies})$. The power of the SNR was then averaged across different frequency bands.

4.10. Synchronized Oscillatory Activity

Synchronized oscillatory activity was determined by first constructing cross-correlograms for pairs of recorded neurons 500 ms before and after the reference spike in 1 ms bins. Neuron pairs that crossed the cross-correlogram SNR by 2.5 standard deviations in two consecutive bins either 100 ms before or after the reference were further frequency analyzed. The power spectrum for synchronized pairs was calculated from the complete cross-correlogram (FFT; 512 point based). Neuron pairs were considered to have significant synchronized oscillatory activity if 3 consecutive bins crossed the power spectrum SNR by 2.5 standard deviations.

4.11. Burst Activity

Burst activity of all spike trains was quantified using a variant of the Poisson-surprise method described by Legendy and Salcman (1985). The surprise value is calculated by:

$$\text{Surprise} = \log(e^{-rT} \sum_{i=n}^{\infty} (rT)^i / i!);$$

$T = \Delta \text{ time (current spikes)}$
 $i = \text{number of spikes}$
 $r = \text{mean spike rate (5 second window around first spike)}$

Briefly, the surprise value (S) is the negative log of the probability that a set of spikes (i), over their time period (T), follows a Poisson distribution for a train of spikes that have a specific average firing rate (r). A low probability or high surprise value is consistent with a burst of neuronal spike trains. One assumption of this method is that the average firing rate of the spike train is stationary over the time-course of the analysis. However, this is unlikely with neurons from the STN (Wichmann et al., 2001). In order to account for this limitation, some have chosen not to include neurons that have non-stationary firing rates for subsequent burst analysis (Wichmann and Soares, 2006). However, because non-stationary firing rates are a significant feature of STN neuronal activity, we substituted a local spike rate value (5 second window around the first spike) for the variable r in the Poisson-surprise formula to avoid bias by exclusion of neurons. Spike activities were accepted as bursts when $S > 2$. The location and inter-burst frequencies for spikes that reached the surprise criterion were stored for further analysis.

4.12. Variance Analysis

The variance of neuronal firing rates, burst rates, and mean SNR (15-35 Hz range) were examined by calculating the percent change of the peri-movement activity (± 250 ms from peak movement velocity) relative to baseline activity (500 ms pre-movement) for each STN neuron that demonstrated peri-movement modulation (e.g. excited or inhibited). Statistically significant variance differences between the PD human and non-human primates were determined by performing the non-parametric Ansari-Bradley test for variance for each mode of neuronal activity (median values were subtracted from each group in order to facilitate comparisons).

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FIG 1.
 Peri-Movement spike rates of normal monkey and PD human excited, inhibited, and unresponsive neurons. Values represent medians of the respective neuronal populations.

FIG 2.

Comparisons between inter- and intra-burst frequencies in the PD human and normal monkey. Asterisks designate statistical significance between the PD human and monkey (Kruskal-Wallis; $p < 0.001$). Values represent medians, and error bars represent 25th and 75th percentiles.

FIG 3.
 Peri-Movement burst rates of normal monkey and PD human excited, inhibited, and unresponsive neurons. Values represent medians of the respective neuronal populations.

FIG 4.

Frequency components of correlated neurons in (A) PD humans and (B) normal monkeys. Red lines represent a boxcar-average (3 bin) of each histogram. Red arrows indicate specific peaks in the frequency analysis.

FIG 5.

Time frequency spectrograms of excited neurons in the PD human (upper left panel) and normal monkey (upper right panel). Lower panel illustrate median SNR of 5-10 Hz, 10-25 Hz and 25-40 Hz frequency bands. Note the difference in scale of SNR for each spectrogram.

FIG 6. Time frequency spectrograms of inhibited neurons in the PD human (upper left panel) and normal monkey (upper right panel). Lower panel illustrate median SNR of 5-10 Hz, 10-25 Hz and 25-40 Hz frequency bands. Note the difference in scale of SNR for each spectrogram.

FIG 7.

Percent changes in peri-movement spike-rates, burst-rates and mean SNR (15-35 Hz) of modulated neurons relative to baseline activities. Values represent medians, and error bars represent 10th and 90th percentiles. Black circles represent individual neurons in the normal monkey, while red circles represent individual neurons in the PD human.

FIG 8.

Illustration of rate and frequency analysis methodology of peri-movement activities showing the construction of (a) peri-movement rasters, (b) histograms, (c) autocorrelograms, (d) mean subtracted autocorrelograms, and (e) resultant FFT of two adjacent bins of peri-movement activity.