Neuronal Activity of the Human Subthalamic Nucleus in the Parkinsonian and Nonparkinsonian State

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INTRODUCTION

Several lines of evidence indicate that abnormal neuronal activity of the subthalamic nucleus (STN) plays a pivotal role in the pathophysiology of parkinsonian motor symptoms: lesioning or deep brain stimulation (DBS) of the STN dramatically reduces akinesia, tremor, and rigidity in 1,2,3,6-tetrahydro-o-pyridine (MPTP)-treated monkeys (Benazzzou et al. 1993; Bergman et al. 1990) and patients with Parkinson’s disease (PD) (Volkmann 2007). Recordings from the STN in MPTP monkeys, on the other hand, exhibit characteristic changes in the firing behavior of STN neurons with the appearance of parkinsonian symptoms after striatal dopamine depletion. The mean firing rate of STN neurons increases from about 20 to 30–40 Hz after MPTP intoxication (Bergman et al. 1994; Wichmann and Soares 2006; Wichmann et al. 1994b) in keeping with the popular rate model of the basal ganglia (Albin et al. 1995; DeLong 1990).

However, several clinical observations, in particular the effects of functional stereotactic procedures (Marsden and Obeso 1994), are difficult to reconcile with an exclusive role of firing rate in the pathophysiology of movement disorders. Other features such as the firing pattern (Boraud et al. 2002) or interneuronal synchronization (Bergman and Deuschl 2002; Bergman et al. 1998) may be more important for a normal flow of information through the basal ganglia and for determining pathological states (Hammond et al. 2007). The most prominent abnormalities in the discharge pattern of MPTP monkeys are the development of periodic bursting or oscillatory activity in STN and internal globus pallidus (GPi) (Bergman et al. 1994; Wichmann et al. 1994a) and the increase of synchronous firing in simultaneously recorded neurons (Nini et al. 1995; Raz et al. 2000).

Microelectrode recordings are routinely performed during functional neurosurgery and provide a unique opportunity to confirm the observations from the primate MPTP model in patients with PD. The reported mean firing rates of subthalamic neurons between 33 and 64 Hz in awake and unmedicated PD patients (Hutchison et al. 1998; Magarinos-Ascone et al. 2000; Magnin et al. 2000; Rodriguez-Oroz et al. 2001) lie roughly within the range observed in MPTP-treated monkeys. Most neurons exhibit an irregular discharge pattern. Oscillatory single-cell activity was described as tremor-locked 3–7–Hz bursting of STN or GPi neurons (Hutchison et al. 1997, 1998; Rodriguez-Oroz et al. 2001), but also as beta-band oscillations (15–30 Hz), which were modified by voluntary movements or dopaminergic medication (Levy et al. 2002a). Microelectrode and local field potential recordings in unmedicated PD patients have demonstrated the synchronization of this oscillatory activity not only within but also between basal ganglia nuclei (Brown et al. 2001; Levy et al. 2002b).

In summary, these data suggest that the electrophysiological activity of the STN in PD is similar to that described in MPTP monkeys. The pathophysiological interpretation of microelectrode recordings in parkinsonian patients, however, has so far been limited by the lack of a control group. For obvious reasons invasive recordings from normal humans without any disease will never be available for comparison.
In our center microrecordings are routinely performed to explore the ventrolateral thalamus and subthalamic area of patients with essential tremor, before implanting therapeutic DBS electrodes into the thalamic ventrointermediate (VIM) nucleus and underlying subthalamic fiber tracts (Herzog et al. 2007). During these explorations we were able to record from a limited number of subthalamic neurons in ET patients and to compare their activity to recordings from patients with PD undergoing implantation of DBS electrodes into the STN. Classical essential tremor is one of the most prevalent neurological disorders and is clinically defined by a slowly progressive action tremor in the absence of other neurological symptoms, especially parkinsonian features (Deuschl et al. 1998). In almost half of the patients intention tremor evolves together with other subtle signs of cerebellar dysfunction such as ataxia and movement overshoot over many years. The motor impairment imposed by intention tremor is typically the reason for patients to seek surgical treatment, once medical alternatives have failed. ET is most likely caused by abnormal functioning of the olivocerebellar motor pathways (Deuschl and Bergman 2002; Deuschl and Volkmann 2002). Although this classical view of ET as a pure functional-metabolic disorder without any structural abnormality has recently been challenged by more rigorous neuropathological studies reporting signs of neurodegeneration in the cerebellum and brain stem (Louis and Vonsattel 2008), there has never been any evidence for an involvement of dopaminergic pathways or basal ganglia nuclei in the disease. We thus considered ET an appropriate nonparkinsonian control condition for characterizing resting state neuronal activity of the human STN in comparison to PD.

**Methods**

Intraoperative microelectrode recordings were obtained from 65 patients suffering from advanced PD (mean age 60 ± 8.6 yr; disease duration 16 ± 6.7 yr; 41 male/24 female) and 9 patients (mean age 70 ± 4 yr; disease duration 34 ± 16.2 yr; 7 male/2 female) with medically intractable essential tremor. All PD patients suffered from severe akinetic-rigid motor symptoms in the medication-off state (Unified Parkinson’s Disease Rating Scale [UPDRS] motor score: 46 ± 15 points in the off-state), which were highly levodopa sensitive (UPDRS motor score: 20 ± 11 points in the best-on-state). They had been selected for surgery to treat drug-refractory hypokinetic fluctuations or dyskinesias according to the established inclusion and exclusion criteria for DBS (Lang et al. 2006). Thirty-one patients suffered from a moderate to severe (UPDRS item 20 ≥2) off-period resting tremor in at least one extremity. ET patients had been selected for VIM–DBS to treat a severe, drug-refractory kinetic tremor in at least one extremity (Raethjen and Volkmann 2004) as defined by a score of ≥2/4 on the postural and intention tremor items of the Fahn–Tolosa–Marin tremor rating scale (TRS). None of them suffered from a resting tremor or had clinical signs of parkinsonism. The average severity of tremor as assessed by the TRS (part A) was 18 ± 7 points. Clinical scores were obtained during a standardized and videotaped neurological examination within 1 wk before surgery.

The decision to perform surgery was not influenced by the participation within this study. The protocol had been approved by the local ethics committee and all patients gave informed consent.

**Surgical and microrecording procedure**

Details of the stereotactic procedure and the intraoperative microrecordings have been reported previously (Herzog et al. 2007; Steigerwald et al. 2005). In all patients antiparkinsonian or antitremor medication were withheld for ≥12 h before surgery. The entire neurophysiological mapping procedure was performed under local anesthesia without sedatives. We used stereotactic magnetic resonance imaging (MRI) and a combination of landmark-based and direct imaging for target and trajectory planning. After a burr hole anterior to the coronal suture was prepared according to the planned entry point, up to five parallel rigid cannulas were inserted into a BenGun microelectrode holder and microdrive. The central trajectory of the BenGun holder was directed at the anatomical target, whereas the other four were equally spaced around with a center-to-center distance of 2.0 mm. Up to five stainless microelectrodes (FHC, Bowdoinham, ME) were simultaneously advanced in increments of ≤0.5 mm. Amplification, visual display, and audio-monitoring of the signal were handled by the Leadpoint microrerecording system (Medtronic, Minneapolis, MN). The analog output of this system was fed into a second-stage biosignal amplifier (TPM, Lüneburg, Germany) for band-pass filtering (0.3–10 kHz) with a gain of 100. Recordings were digitized using the CED 1401 system (sampling rate of 25 kHz; Cambridge Electronic Design [CED], Cambridge, UK) and stored for off-line analysis on a personal computer.

The theoretical coordinates of the STN were 11–13 mm lateral to the intercommisural line, 4–6 mm below and 2–3 mm behind the midcommissural point (MCP). In patients with ET we targeted the subthalamic area below the ventrointermediate thalamic nucleus (VIM: 14–15 mm lateral to the intercommisural line, 0 mm below and 6 mm behind the MCP). From these coordinates it is evident that depending on the individual angulation of the trajectory the anterior or medial electrode within the “BenGun” arrangement could possibly enter into the STN, which forms the ventral border of the subthalamic area. Identifying typical STN discharges when slowly advancing the microelectrodes beyond the anatomical target helps to delineate the boundary of the subthalamic white matter tracts that, in our experience, represent the optimal target for treating intention tremor in ET (Herzog et al. 2007). Only in those ET patients for whom the stereotactic planning suggested that at least one of the trajectories would also pass through the more ventromedial STN without a risk of injuring vessels, the recordings were extended to neurophysiologically identify the depth of the STN. After the microelectrode mapping of the STN region the electrodes were pulled back to the subthalamic area or the thalamus in ET patients to perform test stimulations. We did not implant therapeutic electrodes into the subthalamic nucleus, nor did we perform test stimulations within this region in ET patients, because the intended target, which most likely corresponds to the zona incerta and prelemniscal radiation, lies dorsal to the nucleus (Herzog et al. 2007). A MATLAB (The MathWorks, Munich, Germany) routine was programmed to reconstruct the anterior commissural–posterior commissural (AC–PC)-based coordinates of all neuronal recording sites based on the depth of the microelectrode tip (readings from the microdrive), the stereotactic MRI coordinates of the AC and PC, and the anteroposterior and mediolateral angulation of the trajectory. Only those neurons in ET whose stereotactic position fell within the 95% confidence interval of the recordings sites in PD patients were included in the comparative analysis. The stereotactic coordinates of each recording site were transferred into the corresponding plates of the Schaltenbrand–Wahren atlas (Schaltenbrand and Wahren 1977). The fusion of atlas and recording sites was strictly based on standard stereotactic techniques and no corrections were made for the individual boundaries of nuclei determined by neurophysiological methods or interindividual differences in scaling. Thus possible deviations between the intended and the true stereotactic position of the microelectrode tip, brain shift after opening the dura, and the variability between the individual brain and the atlas morphology cause uncertainties with respect to the true localization of the recording sites. The goal of this analysis, however, was not a precise anatomical superimposition onto a standard atlas brain but rather a comparison of the recording sites of ET and PD patients. Such a comparative analysis...
should be able to detect possible anatomical biases despite the localization errors because they should equally affect both groups.

Intraoperatively, the dorsal border of the STN was identified by an increase of background noise and typical large-amplitude irregular spike activity after passing the subthalamic white matter and zona incerta. Neuronal activity was recorded for \( \geq 30 \) s at each depth while the patients were lying relaxed with their eyes open and without performing voluntary movements. Resting tremor was infrequently seen under this condition in PD patients because we selected patients with predominantly akinetic symptoms and severe off-period rigidity counteracting tremor.

Analysis of neuronal activity and statistics

The recordings were analyzed off-line using the Spike2 software version 5 (CED, Cambridge, UK). Given the high cellular density of the STN, we restricted the spike-sorting procedure to those recordings with stable single- or multiunit activity that clearly exceeded the amplitude of the background noise. Single-unit activity (SUA) was discriminated by threshold spike detection and template matching, controlled by cluster analysis with principal component analysis and final visual inspection. Only SUAs, which could be recorded for \( \geq 20 \) s or with \( \geq 350 \) spikes, were further analyzed.

The statistical characterization of SUAs included instantaneous and mean firing rate (1 s bins), interspike interval (ISI) histogram, autocorrelation, and cross-correlation of simultaneously recorded units (1 ms bin).

The firing pattern of each neuron was predetermined based on the visual inspection of the spike train and the ISI histogram (ISIH). The final classification was observer independent and relied on several statistical parameters of the ISI distribution (Gernert et al. 1999; Hassani et al. 1996): The asymmetry index (AI), which is the ratio of the mode to the mean ISI, provides information on the shape of the ISIH, the variance, and the coefficient of the variance (CV) of ISIs. According to these variables the firing patterns were classified into the

![FIG. 1](http://jn.physiology.org/FIG1.jpg)

**FIG. 1.** Example of spike sorting and postprocessing of single-unit activity (SUA) in a recording sweep from a Parkinson’s disease (PD) patient. **A:** template matching and principal component analysis (PCA) identified the activity of 2 units with different spike shape and separate clusters in the PCA (**top panels**) from the raw recording (**bottom trace**). The sorted spikes are displayed above the raw trace. **B** and **C:** for each unit the interspike interval histogram (ISIH, **top graph**) and the autocorrelation (**middle**) graph is calculated. The power spectrum of the autocorrelation (**bottom graph**) indicates significant oscillatory activity in the theta band for both units. **D:** for pairs of simultaneously recorded units the cross-correlation is computed (**left**), which also exhibits a significant peak within the theta band of the power spectrum (**right**).
following three types. 1) A bursting or burst-like firing pattern consisting of intermittent grouped firing separated by periods of pauses or low-frequency tonic activity. The ISIHs of these neurons were characterized by a positively skewed distribution (AI < 0.75), i.e., by a large fraction of short ISIs representing “intraburst” firing overlapping with variably longer “interburst” intervals. With more regular bursting activity the shape of these ISIH was shifted to a double-peaked (bimodal) distribution representing the short regular intraspike intervals and longer regular interburst intervals. 2) An irregular firing pattern characterized by a flat and broad-based, random distribution of the ISI (CV > 85), which sometimes showed mild positive skewness. 3) Regular tonic firing characterized by ISIHs with a typical bell-shaped distribution and a small variance as indicated by an AI close to unity and a CV of the ISI < 90. SUAs classified as bursting were further analyzed for their burst features by the burst surprise method (Legendy and Salcman 1985) with a burst surprise value ≥ 5.

Auto- and cross-correlation functions (1000 ms window, bin size 1 ms, offset 500 ms) were reconstructed for each SUA and neuronal pairs and analyzed by the method of Raz et al. (2000) to detect significant oscillations and synchrony. In brief, correlations (in the case of autocorrelation the trough of the refractory period ± 10 ms around time 0 was removed first to reduce high-frequency noise) were low-pass filtered (100 Hz) and the DC offset was removed. Only peaks between 1 and 100 Hz of the power spectra (fast Fourier transformation, 1.953 Hz resolution, Hamming window) exceeding fivefold the SD around the mean power were considered significant (Fig. 1). The oscillatory activity detected by this method was classified according to the peak frequency of the power spectrum into theta

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**FIG. 2.** The stereotactic positions of the recording sites of SUA in patients with Parkinson’s disease (crosses) and essential tremor (ET, boxes) are superimposed onto the corresponding coronal (left) and sagittal (right) section of the Schaltenbrand–Wahren atlas.

**FIG. 3.** Discharge patterns of subthalamic neurons (STNs) of PD and ET patients. Trains of discriminated spikes drawn as raster plots (50 spikes for each, resulting in different time bars shown under the raster plot) and, below, ISIHs illustrate the 3 different types of discharge patterns.
resulting in a small AI and intermediate CV (n = 258, 67.2%; AI = 0.58 ± 0.11; CV = 133.9 ± 2.44). 126 neurons (32.8%) had nonbursting activity. Among these, 60 SUAs (15.6%; AI = 0.4 ± 0.17; CV = 185.9 ± 5.07) were characterized by a high CV and broad, random ISI distribution reflecting irregular activity and 66 neurons (17.2%, AI = 0.83 ± 0.05; CV = 73.3 ± 4.83) by the bell-shaped ISI distribution of tonic activity with a very low CV.

The relative proportion of these discharge patterns differed significantly between the PD and the ET groups (χ² test, P < 0.001; see Fig. 4). Burstlike activity dominated in PD (70%), whereas the proportion of burstlike versus nonbursting SUAs was reversed in ET (36 vs. 64%). Because we did not find a particular topographical distribution of the different discharge patterns within the subthalamic nucleus of PD patients (see Fig. 6, C and D), the group differences were unlikely the result of a recording bias within STN. The burst characteristics of neurons with burstlike discharge in PD did not differ significantly from burstlike neurons in ET (Table 1). Only a trend was seen toward longer interburst intervals in ET.

An overall ANOVA with the factors disease (PD vs. ET) and pattern (bursting vs. nonbursting) was conducted on the mean discharge rate of all SUAs, which indicated significant independent effects of both factors on the mean firing rate, with SUAs in ET firing at a significantly lower rate than that in PD and bursting cells having in general higher discharge rates than those of nonbursting cells (disease, P < 0.0005; pattern, P < 0.001; pattern × disease, P = 0.0107). Whereas SUAs in PD patients had a mean frequency of 40.5 ± 23.3 Hz, the average discharge rate in ET was only 19.3 ± 20.1 Hz (Table 2, Fig. 5). Again, topographical analysis ruled out that the group differences resulted from a sampling bias due to an uneven spatial distribution of firing rates within the STN (see Fig. 6, A and B).

**Oscillation and synchronization**

SUAs with significant peaks in the power spectrum of their autocorrelation (see Methods and Fig. 1, B and C), were referred to as oscillatory. When we considered the entire analyzed bandwidth from 1 to 100 Hz the proportion of oscillatory SUAs was almost equal in PD and ET (25.1 vs. 18.2%). Table 3 summarizes the distribution of significant oscillations across the theta, alpha, beta, and gamma bands. This distribution differed between ET and PD as indicated by a strong trend in Fisher’s exact test (P = 0.05). Oscillations in the theta band were common in either group (PD 79.5%; ET 50.0%). However, oscillations within the alpha and beta bands were found only in PD and the relative proportion of gamma-band oscillations was markedly lower in PD (9.1%) than that in ET (50.0%). In both groups significant oscillations within the gamma band were restricted to frequencies >60 Hz; no significant peaks were found in the lower-frequency range. When

![Image of bar graph showing relative proportion of discharge patterns in PD and ET](http://jn.physiology.org/DownloadedFrom/http://jn.physiology.org/)

**Discharge pattern and frequency**

Spikes recorded from the STN had a characteristic biphasic shape with an initial negative phase. Based on the ISI distribution three main patterns of neuronal discharges were differentiated (Fig. 3): The majority of neurons exhibited a burstlike firing pattern with a positively skewed distribution of the ISI,
recorded neurons using cross-spectral analysis. Overall, we
presence of synchronization within pairs of simultaneously
activity within the STN neuronal network, we looked for the
phenon of single-cell activity or rather represented synchronized
from the AC–PC plane; 12.2
mm sagittal distance from MCP; the dorsal portion of the STN (average coordinates:
Oscillatory activity in general was equally distributed throughout
were commonly found in nonbursting cells (n = 8/11; 72.7%).
stratifying by discharge pattern, it became apparent that in
neurons with theta and beta oscillations bursting characteristics predominated (n = 71/81; 87.6%), whereas gamma oscillations
were commonly found in nonbursting cells (n = 8/11; 72.7%).
Oscillatory activity in general was equally distributed throughout
the STN, but beta oscillatory SUAs were exclusively found within
the dorsal portion of the STN (average coordinates: −1.9 ± 1.0
mm sagittal distance from MCP; −1.6 ± 1.2 mm vertical distance
from the AC–PC plane; 12.2 ± 1.2 mm lateral to MCP).

To evaluate whether these oscillations were a mere phenomenon of single-cell activity or rather represented synchronized activity within the STN neuronal network, we looked for the presence of synchronization within pairs of simultaneously recorded neurons using cross-spectral analysis. Overall, we
were able to simultaneously record from 93 pairs of SUAs in
PD patients (see Fig. 1D; 25 from the same, 68 from different electrodes) and 17 pairs in ET (5 same, 12 different electrodes).
In all, 17 of 93 (18%) of these pairs in PD and 2 of 17 (12%) in ET exhibited significant synchronization of their activity
within the entire bandwidth from 1 to 100 Hz. The small number of synchronized pairs did not allow any meaningful statistical analysis on their distribution across frequency bands, but similar to the autocorrelation analysis we found synchronized beta activity only in SUAs recorded from PD patients (Table 3).

Relation between neuronal discharge properties and clinical symptoms

To relate the severity of parkinsonian symptoms to neuronal discharge properties we calculated the average frequency of all
SUAs and an oscillation index (number of SUAs with oscillation/total number of SUAs) for each individual patient. Only those PD patients with more than five isolated SUAs were included in this analysis (n = 26). We did not find any significant correlation between the total UPDRS motor score (part III) or symptom subscores for tremor, rigidity, or akinesia with the frequency of neuronal discharges or the oscillation index. Oscillatory SUAs were not more frequent in PD patients with resting tremor than in those without. Neither did we find a difference between PD patients with or without resting tremor in the frequency distribution of oscillatory SUAs or in the relative proportion of the discharge patterns.

**TABLE 2. Temporal characteristics of neuronal discharges in the subthalamic nucleus**

<table>
<thead>
<tr>
<th>Discharge Pattern</th>
<th>n</th>
<th>(%)</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bursting</td>
<td>246</td>
<td>(70)</td>
<td>42.9 ± 20.0</td>
<td>(11–123)</td>
<td>1.34 ± 0.39</td>
<td>(0.8–3.3)</td>
</tr>
<tr>
<td>Nonbursting</td>
<td>43</td>
<td>(12)</td>
<td>13.9 ± 5.6</td>
<td>(1–25)</td>
<td>2.04 ± 0.52</td>
<td>(0.9–2.9)</td>
</tr>
<tr>
<td>Irregular</td>
<td>62</td>
<td>(18)</td>
<td>49.2 ± 29.7</td>
<td>(5–135)</td>
<td>0.74 ± 0.16</td>
<td>(0.3–1.4)</td>
</tr>
<tr>
<td>Tonic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>351</td>
<td></td>
<td>40.5 ± 23.3</td>
<td>(1–135)</td>
<td>1.327 ± 0.52</td>
<td>(0.8–3.3)</td>
</tr>
<tr>
<td>ET</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bursting</td>
<td>12</td>
<td>(36)</td>
<td>38.4 ± 23.1</td>
<td>(11–88)</td>
<td>1.32 ± 0.39</td>
<td>(0.9–2.0)</td>
</tr>
<tr>
<td>Nonbursting</td>
<td>17</td>
<td>(52)</td>
<td>7.3 ± 2.4</td>
<td>(4–11)</td>
<td>1.41 ± 0.39</td>
<td>(0.9–2.5)</td>
</tr>
<tr>
<td>Irregular</td>
<td>4</td>
<td>(12)</td>
<td>12.9 ± 2.5</td>
<td>(10–16)</td>
<td>0.71 ± 0.10</td>
<td>(0.6–0.8)</td>
</tr>
<tr>
<td>Tonic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td></td>
<td>19.3 ± 20.1</td>
<td>(4–88)</td>
<td>1.29 ± 0.43</td>
<td>(0.6–2.5)</td>
</tr>
</tbody>
</table>

To relate the severity of parkinsonian symptoms to neuronal discharge properties we calculated the average frequency of all
SUAs and an oscillation index (number of SUAs with oscillation/total number of SUAs) for each individual patient. Only those PD patients with more than five isolated SUAs were included in this analysis (n = 26). We did not find any significant correlation between the total UPDRS motor score (part III) or symptom subscores for tremor, rigidity, or akinesia with the frequency of neuronal discharges or the oscillation index. Oscillatory SUAs were not more frequent in PD patients with resting tremor than in those without. Neither did we find a difference between PD patients with or without resting tremor in the frequency distribution of oscillatory SUAs or in the relative proportion of the discharge patterns.

**FIG. 5. Distribution of the mean frequencies of all STN neurons in patients with PD and ET. Each dot represents the mean frequency of an individual SUA. The box plots summarize the distribution with the ends of the box indicating the 25th and 75th quantiles and the line across the middle of the box identifying the median sample value. The whiskers extend to the 95% confidence limits. The mean discharge rate of single units recorded in PD was significantly higher than that in ET (Mann–Whitney U test, P < 0.001).**

**DISCUSSION**

The present study describes the characteristics of resting-state neuronal activity in the STN of patients with PD and ET. It is unique in using for the first time recordings from the STN of patients not affected by PD as control data, which allows verification of the concepts of basal ganglia dysfunction derived from primate models of parkinsonism in the human disease state.

In agreement with the rate model of basal ganglia function, which predicts a disinhibition of the STN in the parkinsonian state (Alexander et al. 1990; Bergman et al. 1994), we found significantly higher firing rates of STNs in PD compared with ET. Our mean discharge frequency of 40.5 Hz in PD patients lies within the range of previous reports (Hutchison et al. 1998; Magarinos-Ascone et al. 2000; Magnin et al. 2000; Rodriguez-Oroz et al. 2001) and roughly doubles the rate found in ET (19.3 Hz). The possibility that the lower mean frequency in ET
is an artifact by recording from a circumscribed part of the STN with a lower discharge rate is very unlikely. A previous report described a lower discharge rate in the ventral portion of the STN (Rodriguez-Oroz et al. 2001). We were not able to reproduce this result in our topographical analysis. However, even if the discharge rate had a rostrocaudal gradient, we should have recorded predominantly from the faster discharging, dorsal regions of the STN in ET because the STN marks the lower border of the subthalamic area, which we explored electrophysiologically to delineate the target for optimal tremor control (Herzog et al. 2007).

Another hallmark of the parkinsonian state was a relative increase of burstlike activity in the STN compared with ET. Based on the ISI distribution we classified 70% of single-unit activities in PD as bursting; using a different analysis approach and terminology, Rodriguez and colleagues (2001) described “irregular discharges with silent periods or pauses” in 60.5% and tonic discharges in 24% of STN neurons recorded from PD patients. The properties of the first type match our group of “burstlike” activity. This close coincidence in the relative proportion of different discharge types supports the validity of our findings in PD. The shift from nonbursting to bursting activity in PD most likely reflects a change in the preferred functional state of a single neuronal population because histological differences in the STN of PD and ET patients have not been described and the neuronal morphology and structure of the STN are relatively homogeneous in monkeys (Parent and Hazrati 1995), rendering an anatomical sampling bias implausible.

Interestingly, we found specific features of intrinsic oscillatory activity associated with the bursting and tonic discharge mode: gamma-band oscillations dominated in nonbursting SUAs, whereas beta-band and lower-frequency oscillations were linked to the bursting pattern. This could explain the higher proportion of SUAs with gamma-band oscillations in ET and the exclusive finding of alpha- and beta-band oscillations in neuronal activity recorded from PD patients. Previous studies using LFP recordings from the human basal ganglia have emphasized two distinct operating modes characterized by the dominance of either synchronized beta- (<30 Hz) or gamma-band (>60 Hz) oscillations (Brown and Williams 2005). The two frequency bands are inversely affected by the execution or inhibition of movement and differentially expressed according to the prevailing level of dopaminergic activity. Levodopa shifts the peak frequency of LFPs in PD from <30 to >70 Hz (Brown et al. 2001). During voluntary movements gamma-band activity is enhanced and 8- to 30-Hz activity is suppressed (Cassidy et al. 2002; Levy et al. 2002a), suggesting prokinetic (movement facilitating) and antikinetic
(movement inhibiting) functions of the two bands. The differential distribution of neuronal oscillations across frequency bands in our study of ET and PD patients, in principle, supports the concept of abnormal oscillatory binding in PD. However, the relative proportion of cells exhibiting intrinsic oscillations or interneuronal synchronization within the beta band was much smaller in this study compared with previous reports (Levy et al. 2000, 2002a,b). Levy and colleagues observed synchronized 15- to 30-Hz oscillations in 28 of 82 pairs (34%) of simultaneously recorded STN units in PD. The authors emphasized the importance of tremor for the emergence of beta-band oscillations because the majority of synchronous cells were recorded from five patients with resting tremor in the operating room, whereas no synchronous pairs were found in nontremulous patients. In our group of patients moderate to severe resting tremor was relatively infrequent, with only 31 patients (47%) exhibiting a score $\geq 2$ on item 20 of the UPDRS for any body segment and 25 patients having a total score $\leq 2$ on item 20, indicating a pure akinetic-rigid type of parkinsonism. The 139 units recorded from these 25 patients without tremor did not differ from the remaining group in the prevalence of bursting activity and theta or beta oscillations. This is in accordance with a recent study of the same group, which also found beta oscillations in PD patients without tremor (Weinberger et al. 2006).

A limitation of our study, however, is the lack of tremor recordings during surgeries. We were therefore not able to determine the amount of tremor-locked activity within the 3- to 10-Hz or transient changes of the neuronal discharge pattern in relation to intermittent tremor. In addition, methodological issues in detecting oscillatory single-unit activity (Rivlin-Etzion et al. 2006) and in particular the very conservative statistical threshold for significant spectral peaks in the auto- and cross-correlations (which, however, was also used in studies by other groups, e.g. Raz et al. 2000) may have caused an underestimation of oscillatory and synchronous discharge behavior in this study. Although this could compromise the comparability of the results with previous studies, it should not affect our internal comparison of the physiological characteristics in PD and ET because the same criteria were applied to both groups.

Another important methodological issue that needs to be considered in the comparison of human and animal recordings is the behavioral context of the experiments. We recorded neuronal activity intraoperatively in the resting state, after instructing the patient to withhold any voluntary movements. Moreover, we did not specifically monitor the level of attention during the recordings such that drowsiness may have occurred. In contrast, most studies in the monkey report recordings in unrestrained animals or even during the performance of trained motor tasks (Raz et al. 2000). Other limitations of our study include the relatively small sample of neurons recorded in ET, which has to be attributed to the small number of patients, in whom the stereotactic trajectories led into the STN region without risk of injuring blood vessels, the possible impact of an anatomical recording bias, and the fact that we were comparing two disease states, although ET has never been associated with abnormal basal ganglia function.

Despite these limitations, our study confirms several predictions of the MPTP model of parkinsonism: firing rates of STN neurons were increased in PD compared with ET patients, closely matching the frequency ranges observed in monkeys before and after MPTP intoxication (Bergman et al. 1994; Wichmann and Soares 2006). Likewise, we found a shift toward bursting-type activity in PD, which was also described in recordings from GPi or STN of the primate model (Bergman et al. 1994; Wichmann and Soares 2006; Wichmann et al. 1994a). Our ANOVA analysis with independent effects of disease and discharge type on firing rate corroborates recent identical findings in several extratrigeminal basal ganglia nuclei of monkeys by Wichmann and Soares (2006) who also emphasized the complexity of changes in the timing of cellular activity after MPTP intoxication. In contrast to the animal

### TABLE 3. Distribution and mean frequency of significant peaks in the power spectral analysis of autocorrelations and cross-correlations of single-unit activity

<table>
<thead>
<tr>
<th>Bandwidth, Hz</th>
<th>Theta</th>
<th>8–12</th>
<th>12–35</th>
<th>$\geq$35</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>n</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>n</td>
<td>70</td>
<td>(79.5)</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>(2.3)</td>
<td>(9.1)</td>
<td></td>
<td>(9.1)</td>
</tr>
<tr>
<td>Peak frequency, Hz (mean ± SD)</td>
<td>4.2 ± 1.4</td>
<td>9.7 ± 0.1</td>
<td>17.9 ± 6.0</td>
<td>84.9 ± 6.5</td>
</tr>
<tr>
<td>ET</td>
<td>n</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>n</td>
<td>3</td>
<td>(50.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>(0)</td>
<td>(0)</td>
<td></td>
<td>(0)</td>
</tr>
<tr>
<td>Peak frequency, Hz (mean ± SD)</td>
<td>4.0 ± 0.4</td>
<td>—</td>
<td>—</td>
<td>82.7 ± 12.8</td>
</tr>
<tr>
<td>PD</td>
<td>n</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>n</td>
<td>8</td>
<td>(47.1)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>(0)</td>
<td>(11.8)</td>
<td></td>
<td>(41.2)</td>
</tr>
<tr>
<td>Peak frequency, Hz (mean ± SD)</td>
<td>5.6 ± 1.4</td>
<td>—</td>
<td>18.4 ± 4.4</td>
<td>75.9 ± 15.2</td>
</tr>
<tr>
<td>ET</td>
<td>n</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>n</td>
<td>1</td>
<td>(50.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>(0)</td>
<td>(0)</td>
<td></td>
<td>(50.0)</td>
</tr>
<tr>
<td>Peak frequency, Hz</td>
<td>4.5</td>
<td>—</td>
<td>—</td>
<td>66.5</td>
</tr>
</tbody>
</table>

**A. Oscillatory activity in autocorrelation**

**B. Oscillatory activity in cross-correlation**
model, however, we did not find global differences in the proportion of neurons exhibiting intrinsic oscillatory activity or internu- ronal synchronization (Nini et al. 1995; Raz et al. 2000) in PD or ET. Both disease states rather differed in the relative fraction of neurons with theta-, alpha-, beta-, or gamma-band activity. The large proportion of neurons exhibiting theta-band activity around 4 Hz in PD patients in our study has not been described in the MPTP monkey, where 10-Hz activity dominates (Nini et al. 1995; Raz et al. 2000; Wichmann and Soares 2006).

In summary, we were able to confirm several predicted key features of abnormal subthalamic neuronal activity in the parkinsonian state compared with patients without any symptoms of parkinsonism, which consist in an overall increase in discharge rate and complex changes in the patterning and dynamics of neuronal firing.

GRANTS

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REFERENCES


