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Characteristics of oscillatory pallidal neurons in patients with Parkinson's disease

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Abstract

Background: Excessive neuronal activity in the globus pallidus internus (GPi) is believed to promote parkinsonian akinesia/bradykinesia, but not tremor. Parkinsonian tremor is thought to result from dysfunction in the basal ganglia and cerebello-thalamo-cortical circuits. Whether the GPi is involved in tremorgenesis has not been fully elucidated. This study was designed to quantify the characteristics of oscillatory GPi neurons in patients with Parkinson's disease.

Methods: Nine patients undergoing surgery were studied. Microelectrode recordings in the GPi and electromyographic (EMG) activity in the limbs were recorded and the mean spontaneous firing rates (MSFRs) were calculated. Spectral analysis was used to assess neuronal oscillatory patterns. Coherence analysis was applied to explore the relationship between oscillatory neurons and EMG.

Results: Of 79 GPi neurons, 50.6% oscillated at the tremor frequency; 25.3% oscillated at β frequency, and 24.1% did not oscillate. The MSFR of all neurons was 81.5 ± 7.4 spikes/s. Among neurons oscillating at tremor frequency, 40% were coherent with the tremor. In four neurons, the pattern changed from tremor frequency to β frequency or *vice versa*. It appeared that the tremor began before the GPi fired bursts.

Conclusion: Some neuronal activity in the GPi correlates with tremor and this correlation might be due to either feedback, maintenance, or initiation. Since there were examples of EMG tremor prior to GPi activity, initiation seems least likely. The data further support the prediction of the classic pathophysiology model of Parkinson's disease.

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Declaration of Competing Interest

The authors declare no competing interests. MH has no relevant disclosures to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jns.2019.116661>.

Keywords

Parkinson's disease; Globus pallidus internus; Oscillation; Single unit; Microelectrode recording

1. Introduction

Parkinson's disease (PD) is characterized by bradykinesia, rigidity, and resting tremor. The symptoms are mainly caused by the degeneration of dopamine neurons in the substantia nigra pars compacta [1,2]. The relief afforded by pallidotomy and stimulation of the internal globus pallidus (GPi) imply a key role of the GPi in the control of movement [3]. It is one of the two output nuclei of the basal ganglia (GPi and substantia nigra pars reticulata), receives inputs from pathways in the basal ganglia, and projects primarily to the motor thalamus, indirectly influencing the cortex [4,5]. Although the clinical importance of the GPi in PD is clear, its role in relation to the motor symptoms (bradykinesia, rigidity, and tremor) is still poorly understood.

Pathological neuronal activity in the basal ganglia is associated with the motor symptoms of PD [4]. The GPi projects to the pallidal receiving area of the motor thalamus through inhibitory connections mediated by γ -aminobutyric acid [4,5]. According to the classical model of the pathophysiology of PD, the inhibitory projections are overactive, excessively inhibiting thalamic neurons to produce slowness and bradykinesia [5,6]. However, their relationship with resting tremor remains elusive [7–9]. Rather, parkinsonian tremor has been hypothesized to result from malfunctions in both the basal ganglia and cerebello-thalamo-cortical circuits [9,10]. Evidence has shown that the basal ganglia circuit evokes the onset of tremor and the cerebellar circuit determines its amplitude [9–11], but how the interplay of neuronal activity between basal ganglia and cerebellar circuits promotes parkinsonian tremor remains unclear.

In accordance with the “rate model”, an enhanced rate of neuronal discharge in the GPi has been reported in animal models of PD [12,13] and in parkinsonian patients during stereotactic neurosurgery [14,15]. These findings indicate that the firing rates are elevated in the parkinsonian state, though not all studies have shown the predicted changes in firing rate [16–18].

In addition, the increased neuronal bursting in the GPi and the subthalamic nucleus (STN) has provided an alternative theory for the manifestations of PD [19,20]. These studies also found neurons oscillating at the tremor frequency in the GPi [16,20,21], the STN [22,23], and the thalamus [24,25]. These neurons fired at the same frequency as the tremor, were often correlated with the muscular activity of the tremor [20,21,23], and were mostly found in the ventral oral anterior (Voa), ventral oral posterior (Vop), and ventral intermediate (Vim) nuclei of the thalamus [24,25]. The Voa and Vop nuclei receive major input from the GPi, whereas the Vim nucleus, an excellent target for the relief of tremor, receives primary input from the cerebellum. Interference with all these regions can effectively improve tremor. These results support the idea that PD tremor is due to an abnormal interaction between the basal ganglia and cerebellothalamic circuits [8, 9, 10, 11]. A more recent hypothesis has been proposed, that decreased dopamine in the GPi triggers

hyperactivity in the cerebellothalamic circuit, producing resting tremor [10,11]. Although a recent study [26,27] has provided data on how deep brain stimulation (DBS) of the GPi modulates thalamic neuronal activity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model of PD, it remains unknown how the interplay between these two circuits might result in parkinsonian tremor.

Numerous local field potential and microelectrode recording studies have explored the causal relationship between β oscillation and parkinsonian symptoms. These studies have revealed neurons with oscillating bursts in the β range (10–30 Hz) in the STN and GPi [15,28–30]. The pathological β oscillations have been reported to be inhibited by volitional movement [31,32], dopamine administration [28,29,33,34], and STN stimulation in some studies, but not in others (30, 35, 36, 37). Some studies have also demonstrated that STN neurons with β oscillation are directly correlated with akinesia/rigidity [30–32,38]. Moreover, the level of inhibition of β oscillations during dopamine therapy is correlated with improvement of the hypokinetic symptoms, such as akinesia/bradykinesia and rigidity, but not tremor [3,30,38]. These data suggest that the abnormal β oscillation is a result of dopamine depletion in the basal ganglia [32,33] and is tightly correlated with akinesia/bradykinesia and rigidity.

Although the bulk of evidence demonstrates increased neuronal firing rates and pathological oscillatory patterns in the basal ganglia, the role of the GPi in parkinsonian rigidity, bradykinesia, and tremor remains unclear. The aim of this study was to quantify the characteristics of oscillatory neurons in the GPi in relation to parkinsonian symptoms. In particular, we addressed whether the GPi plays an important role in tremorgenesis.

2. Materials and methods

2.1. Patients

We investigated 9 PD patients (4 females and 5 males, aged 58.11 ± 5.53 years) who underwent electrode implantation for GPi stimulation or pallidotomy. PD was diagnosed based on disease history, physical tests, and the L-dopa response; laboratory examinations and MRI were used to exclude other neurological disorders. The mean disease duration in these patients was 6.3 ± 1.3 years (range, 5–9 years) and the mean dose of L-dopa was 590.4 ± 153.2 mg/day (range, 350–800 mg/day). Their mean “OFF” total score was 44.0 ± 10.6 (range, 32.5–60) on the Unified Parkinson's Disease Rating Scale (UPDRS) III (Motor), and the mean Hoehn and Yahr score was 2.7 ± 0.3 (range, 2.5–3) at the time of surgery. All patients were evaluated before and a month after operation while “on” and “off” medication. In patients with DBS treatment, stimulation was “on” for the post-operative assessments.

According to their UPDRS III sub-scores and clinical features, the patients presented mixed rigidity, bradykinesia, and tremor with significant “ON and OFF” fluctuation, but without dyskinesia. These patients did not have dyskinesia that might be due to under-medication with levodopa.

The details of their demographic and clinical features are shown in Table 1. The conduct of this research adhered to the Declaration of Helsinki and was approved by the Xuanwu Hospital Ethics Committee, Capital Medical University. Patients gave written informed consent.

UPDRS III, Unified Parkinson's Disease Rating Scale Part III (motor section); LEDD, L-Dopa equivalent daily dose; L, left; R, right; GPi, globus pallidus internus; Pre, before operation; Post, after operation; Pvp: posteroventral pallidotomy.

2.2. Stereotactic surgery and electrophysiology

Detailed descriptions of the surgical and microelectrode recording techniques have been reported in previous studies [20,39]. Briefly, after local anesthesia at the four pin sites, a CRW frame (Radionics, Burlington, MA, USA) was mounted on the head. Sagittal MRI sequences of the brain (Siemens 1.5 Tesla Sonata, Erlangen, Germany) were collected and fused with a CT scan using Framelink software (Medtronic StealthStation S7, Medtronic Navigation Inc., Louisville, KY, USA). Both commissures, the GPi, and vessels were determined with high resolution. After setting a reference line linked to the anterior-posterior (AC-PC) line, the GPi was targeted 18–25 mm lateral to the midline, 2–3 mm anterior to the midpoint of the AC-PC line, and 4–6 mm inferior the AC-PC line [20,39].

The GPi was physiologically localized using microelectrode recording. The microelectrode trajectory traversed the external and internal divisions of the GPi directly to its posteroventral portion. The final target was confirmed based on anatomical landmarks, including the location of the optic tract and internal capsule, as detected using strobe light stimulation and macrostimulation. The occurrence of 'border cells' marked the boundaries of nuclear segments with the relatively 'silent' white matter laminae. The neuronal firing patterns in the GPi and surrounding areas and the numbers of multiple units and background noise (cell-dense *versus* cell-sparse zones) allowed discrimination of the different pallidal segments. Typical neurons with overactive discharges were detected in the GPi. Recording began at a distance of 10 mm from the final target and a tungsten microelectrode (10–20 μm at the tip and resistance 0.5–1 M Ω , Alpha Omega Engineering, Nazareth, Israel) was advanced in 0.5-mm increments.

All extracellular action potential signals were amplified ($\times 20,000$) and filtered (bandpass, 200 Hz to 10 kHz). Only well-isolated single units were selected for periods of 15 s to several minutes to explore neuronal firing rates and oscillatory patterns. The neuronal signals were sampled at 12 kHz. We simultaneously recorded one channel of microelectrode recording in the GPi with three channels of electromyograms (EMGs) from the muscles of the contralateral limbs. The EMG recordings, using surface electrodes, were from the extensor carpi radialis (ECR) and flexor carpi radialis (FCR) of the upper limb, and tibialis anterior (TA) of the lower limb. The EMG activity was amplified and sampled at 3 kHz. Four-channel recording using the MicroGuide recording navigation system (AlphaOmega Engineering) was done while patients were at rest. The patients were encouraged not to suppress tremor if it occurred.

Patients were required to withdraw from medications overnight before the operation and were completely awake during the surgery to allow cooperation.

2.3. Data analysis

Neuronal and EMG signals were transformed into Spike2 format (Cambridge Electronic Design, Cambridge, UK) for discrimination [40]. Only stable, well-isolated single-unit recordings longer than 15 s without any movements and artifacts were analyzed. Spikes with a signal-to-noise ratio > 2:1 were studied. The interspike intervals (ISIs) and ISI histograms were used to calculate the mean spontaneous neuronal firing rate (MSFR) and the distribution of firing rates. The coefficient of variation (CV) of ISIs was calculated to assess the regularity of the neuronal discharge patterns.

All neuronal and EMG signals were rectified and converted into MatLab 7 files (The MathWorks, Natick, MA, USA). Power spectrum density analysis was used to determine the oscillatory patterns of neurons. A Hanning window 2 s wide with a 50% overlap between windows was applied. Significant oscillatory frequencies were identified if the frequencies exceeded a threshold of 5 SD above the mean power in the 30–70 Hz band [22]. In this study, three patterns of oscillatory neuronal activity were classified: (1) neurons with oscillatory activity at the tremor frequency with bursting concurrent with the tremor EMG, defined as tremor frequency oscillatory neurons. Their mean oscillation frequency of peak power was in the range of 3–6 Hz [16]; (2) neurons with high-frequency (> 8 Hz) oscillations, defined as β frequency oscillatory neurons. Their mean frequency of peak power was in the range of 8–30 Hz [41]; and (3) neurons without any oscillation, defined as non-oscillatory neurons. If a neuron showed different behaviors during the recording, it was classified according to its predominant pattern. The proportion of different oscillatory neurons was calculated based on number of oscillatory neuron divided by total number of neurons collected.

The relationship between oscillatory neuronal activity and EMG activity was determined using a coherence algorithm. A coherence of 0.42 at a given frequency suggested that the two signals were most likely to be linearly related at that frequency ($p < .05$). Data processing and analysis was carried out using Spike II 7.02 (Cambridge Electronic Design), MatLab 7.0 (The MathWorks), and Origin 7.5 (OriginLab Corp., Northampton, MA, USA).

2.4. Statistical analysis

Differences between neuronal patterns were analyzed using one-way ANOVA with the Bonferroni comparison *post hoc* test, with a level of significance $\alpha = 0.05$. The differences in MSFRs and the CVs of the ISIs between neuronal pattern groups were compared. Student's *t*-test was used to compare the means of two independent samples. All data are shown as the mean $\pm$ standard deviation.

Comparison of the proportion of differences in neuronal patterns used χ^2 analysis with the null hypothesis that the proportions were the same.

Statistical significance was set at $p < .05$. SPSS 17.0 (SPSS, Chicago, IL, USA) and Origin 7.5 (OriginLab Corp.) were used for analysis.

3. Results

Seventy-nine GPi neurons were identified in the 9 PD patients. Among these neurons, 40 (50.6%) oscillated at the tremor frequency and were classified as tremor frequency oscillatory neurons; 20 (25.3%) oscillated at β frequency and were classified as β frequency oscillatory neurons, and the remaining 19 (24.1%) did not oscillate and were classified as non-oscillatory neurons. We focused analysis on the oscillatory neurons, particularly those oscillating at the tremor frequency.

3.1. Oscillatory neuronal patterns and firing rates in the GPi

Further analysis showed that of 40 tremor frequency oscillatory neurons, their mean oscillatory frequency was 4.7 ± 0.7 Hz (range, 3–6 Hz). Of 20 β frequency oscillatory neurons, their mean oscillatory frequency was 20.5 ± 8.7 Hz (range, 8–30 Hz) and the rest of 19 non-oscillatory neurons did not present any oscillation. Typical examples are shown in Fig. 1A–C.

Further ISI analysis demonstrated that the MSFR of the 79 neurons was 81.5 ± 7.4 spikes/s (range, 65.2–104.8; median, 81.1). ANOVA demonstrated significant differences in MSFR among tremor frequency oscillatory neurons (81.8 ± 7.0 spikes/s), β frequency oscillatory neurons (86.0 ± 8.3 spikes/s), and non-oscillatory neurons (77.8 ± 7.3 spikes/s) ($F = 6.04$, $P < .004$). The Bonferroni test revealed a significant difference in MSFR between β frequency oscillatory neurons and non-oscillatory neurons (86.0 ± 8.3 versus 77.8 ± 7.3 spikes/s, $P < .05$). In addition, significant differences in CV were also found among the three types of neuron ($F = 5.62$, $P < .005$). The Bonferroni test indicated significant differences in CV between neurons with tremor frequency and those with β frequency oscillation (1.07 vs 0.96 , $P < .05$) as well as between neurons with β frequency oscillation and non-oscillating neurons (0.96 vs 1.04 , $P < .05$) (Fig. 1D).

3.2. Neurons with tremor frequency oscillatory activity coherent with the tremor

To determine whether the neurons oscillating at the tremor frequency were associated with the tremor, the relationship between the GPi and EMG spectra was assessed using coherence analysis. Coherence is a statistical function used to estimate the probability that two signals are correlated at a given frequency. As computed in the current study, a coherence 0.42 indicated a significant probability of a linear relationship between GPi neurons and tremor EMG. Of the 40 tremor frequency oscillatory neurons, 16 (40%) were highly coherent with the tremor EMG, and were defined as tremor-related neurons. These neurons were significantly coherent with EMG activity in the FCR, ECR, or TA, with a linear relationship. The average coherence coefficient was 0.70 ± 0.21 (median, 0.7; range, 0.44–0.92; Table 2). However, no tremor-related neurons were coherent with EMG activity in both the upper and lower limbs.

While some neurons oscillating at the tremor frequency were not coherent with the tremor (Fig. 2A and A1), the tremor-related oscillatory neurons were significantly coherent with the tremor. For example, we found a coherence coefficient of 0.9 at 5 Hz in the FCR (Fig. 2B and B1); a coherence coefficient of 0.75 at 5 Hz in both the FCR and ECR but not in the TA

(Fig. 2C, C1, and C2); and a coherence coefficient of 0.9 at 5.5 Hz in the TA but not in the ECR and FCR (Fig. 2D, D1, and D2).

3.3. GPi oscillatory neurons can transiently change their patterns associated with EMG activity during tremor

During targeting, we found that in some oscillatory neurons the pattern associated with tremor transiently appeared or diminished. For example, one neuron oscillated at the tremor frequency (peak power at 5.1 Hz) at the beginning of the recording, then it switched to β oscillatory activity (peak power at 12 Hz and 4.4 Hz), while another neuron showing β oscillation (peak power at 23.5 Hz) at the beginning of the recording changed to tremor oscillation (peak power at 5.1 Hz) (Fig. 3A and B). Clearly, the presence of limb tremor was associated with neurons oscillating at the tremor frequency, whereas a decline in tremor was associated with neurons oscillating at β frequency (Fig. 3A1, A2, B1, and B2). In accordance with these firing patterns, the ISI histograms further illustrated their distribution patterns (Fig. 3A4 and B4). Significant differences in the MSFRs and CVs of ISIs were also found between neurons with the tremor frequency pattern and those with the β frequency pattern (Fig. 3A3 and B3). Although the changes in neuronal oscillatory pattern illustrated in Fig. 3 appeared to be associated with changes in the tremor EMG, there was no significant correlation between the neuronal firing pattern and the EMG pattern. There are three possible explanations for this phenomenon. A neuron may be related to muscles other than those recorded. It seems that some related neurons are coherent with the EMG and some are not. Alternatively, it may be that some time is needed for neurons and EMG to synchronize. One of the neurons shown in Fig. 3 was classified as a tremor frequency oscillatory neuron and the other as a β oscillatory neuron, based on their oscillatory patterns at the beginning of the recording. With these caveats, it is of note that the tremor began before the GPi neurons began to fire bursts (see Fig. 3B; arrows indicate the tremor onset).

We also investigated variability of the firing patterns over time. We examined neurons with 15 s of recording ($n = 56$) and found that 5 neurons varied patterns within the time of recording. We show 3 examples of neurons varying their pattern within 30 s recordings (see supplementary material). Power spectral and histograms of ISI of these neurons further confirm their variability of firing pattern. However, these neuronal activities did not correlate with limb EMG activity. These neurons were classified by their dominant behavior.

3.4. Localization of oscillatory and non-oscillatory neuron within the GPi

We analyzed the stereotactic locations of the neurons along the trajectories in the external and internal GPi. The depths of the tremor frequency, β frequency, and non-oscillatory neurons along each trajectory were noted and normalized to the dorsal border of the optic tract. Plotting their locations, we found that most of the tremor frequency (Fig. 4A1 and B1), tremor-related (Fig. 4A2 and B2), and β frequency (Fig. 4A3 and B3) neurons were localized at 3.0–6.5 mm anterodorsal to the optic tract (means: 4.21 ± 2.41 , 4.72 ± 2.22 , and 4.57 ± 2.40 mm; medians: 4.49, 4.75, and 4.75 mm, respectively). Furthermore, the majority of the non-oscillatory neurons were localized 5.23 mm $\pm$ 2.23 mm anterodorsal to the optic tract (median: 4.64 mm) (Fig. 4A4 and B4). However, ANOVA demonstrated no difference

in the localization of the four types of neuron ($F=0.98$, $P=.4$), but the sample size was small.

Consistent with a previous report [20], our findings further confirm that tremor frequency and tremor-related oscillatory neurons are localized in the ventral portion of the GPi which seems to delineate the sensorimotor portion that might be optimal for the placement of lesions or the implantation of stimulating electrodes to treat PD.

4. Discussion

In this study, we not only recorded high firing rates in all types of GPi neurons, but also found a large proportion of tremor-related neurons with high levels of coherence. In addition, we found a relatively large percentage of β oscillatory neurons in the GPi. The oscillatory neurons were mainly localized in the ventral portion, where lesions or stimulation produces the greatest improvement in parkinsonian motor symptoms. These findings confirm and extend previous reports [16,20], further supporting the view that excessive oscillatory activity in GPi neurons not only promotes parkinsonian bradykinesia and rigidity, but also participates in tremor [4,5]. It is interesting that four neurons changed their pattern from tremor frequency to β frequency oscillation or *vice versa* in relation to changes in the tremor. Although these are minimal data, they contradict the hypothesis suggested by Helmich [11], since the GPi neurons began to fire bursts only after EMG tremor activity.

High average spontaneous firing rates have also been reported in GPi neurons of MPTP monkeys [12,17,42] and PD patients [15,16,20]. The mean spontaneous firing rate of GPi neurons in the present study of patients with PD (82 spikes/s) is similar to the values in MPTP monkeys (77–100 spikes/s) but higher than those in normal monkeys (48–79 spikes/s) [13,43]. This finding is consistent with the classic “rate model” of PD, which predicts the development of hypokinetic features. In accordance with the model, the increased activity of inhibitory pallidal projection results in weaker neuronal discharges in the pallidal receiving zones of the thalamus, giving rise to akinesia and rigidity [4,5,44].

We also found 20 neurons with a marked β frequency oscillation in the GPi of patients with PD, indicating that exaggerated β oscillatory activity is prominent in the parkinsonian basal ganglia [28,29]. This finding is consistent with prior results obtained from large-contact DBS macroelectrode [33–37] and microelectrode recordings [22,23]. These studies paid close attention to the role of β oscillatory activity in bradykinesia and rigidity based on local field potential [37,41] and single-unit recordings [38,45]. Some studies have shown that the proportion of β oscillatory neurons is significantly higher in the akinetic-rigid type than the mixed type of PD [38,45]. Without levodopa administration, the cortico-basal ganglia loop tends to synchronize within the β band range in PD. Following levodopa replacement, the activity tends to synchronize at a higher frequency [28,41]. In the present study, we found oscillatory neurons that changed their patterns from tremor frequency to β frequency or *vice versa* during tremor. Clearly, tremor-frequency oscillatory behavior was associated with tremor whereas β frequency oscillatory behavior was not. It is known from prior studies that β oscillatory activity is associated with bradykinesia, but not tremor. This finding makes it

clear that neuronal activity is not fixed in type, but changes with behavior. It is possible that most neurons can display any of the various firing patterns at different times, but this would just be speculation.

The current findings are consistent with previous reports of tremor frequency activity in the GPi correlated with limb tremor in animal models [46,47] and patients with PD [15,16,20,21]. Evidence favoring the idea that the basal ganglia participate in tremor comes from studies by Bergman's group [17,46,47], who reported that GPi neurons oscillate at tremor frequency in MPTP models with both rhesus monkeys and African green monkeys. Neurons with tremor frequency activity in the GPi were found in the early studies of Umbach and Erhardt [48] and Jasper and Bertrand [49]. Although Raeva [50] reported rhythmic oscillations in pallidal neurons in PD, she did not find oscillations associated with the tremor itself. It is possible that tremor was not identified in those studies because the recordings might have been too short or the pattern of firing was not stable, or the patients were predominantly akinetic-rigid without tremor. Following these studies, Hutchison's group [20] demonstrated a general correlation of single pallidal tremor cell frequency with limb tremor frequency. Lenz's group [16] reported a number of tremor-frequency (3–6 Hz) neurons in the GPi, but only one of these neurons was correlated with limb tremor. Hurtado and colleagues [21] reported the presence of transient limb–GPi synchronization and this was not dependent on tremor-related activity in the GPi. The present results together with previous findings strongly support an important role of the GPi in tremor.

Another line of study focused on how the motor thalamus participates in the pathogenesis of tremor [24,25]. Tremor frequency activity and tremor-related activity have been found not only in the pallidal thalamus (Voa and Vop nuclei), but also in the cerebellar thalamus (Vim nucleus) [24,25]. In the latter, these “tremor cells” are mainly located anterior to the border of the ventral caudal nucleus, presumably in the Vim nucleus. Neurons in this region fire in advance of the tremor burst measured by EMG [16,25]. In addition, it is well established that stereotactic lesions or stimulation of the Vim nucleus are superior to those in the Voa/Vop nuclei for relieving tremor [51–53], which suggest that reduction of pallidal outflow to the thalamus is not as important as the reduction of cerebellar flow in treating tremor. Because the Vim nucleus is a principal component of the tremor circuit due to its large kinesthetic input and projection to the motor cortex [53,54], a lesion or stimulation must be highly effective in reducing tremor. Thus, the pathological signals from the GPi may be transmitted to the cerebello-thalamo-cortical circuit *via* the motor cortex [53,54]. Furthermore, recent evidence indicates more direct pathways from the cerebellum to the basal ganglia [55]. Supporting data come from two recent studies. In a study of the mechanisms by which Vim stimulation suppresses tremor in patients with essential tremor and PD tremor, Hutchison's group found that inhibition of the thalamus is likely necessary for reducing tremor and may function in effect as a filter to uncouple thalamo-cortical from cortico-spinal reflex loops [56]. This finding indicates possible gating properties of the Vim within the cerebello-thalamo-cortical tremor network. Vitek's group [26] explored changes in the neuronal activity in the motor thalamus in an MPTP nonhuman primate model of PD with GPi stimulation and found that this intervention produced widespread changes in both the pallidal and cerebellar thalamo-cortical circuits.

In the present study, we found that tremor-related oscillatory neurons were not only coherent with EMG activity in the upper limb ($n = 14$), but also with EMG activity in the lower limb ($n = 2$). These results suggest that, while distinct body parts have a similar tremor frequency, they are generally not exactly the same and not phase-locked. This phenomenon suggests a separate tremor generator for each part of the body. Thus, when a GPi tremor cell is uncorrelated with tremor that cell might not involve the relevant body part [5,6,8].

A limitation of this study was that we studied only a small sample of 9 patients with mixed-type PD presenting tremor, bradykinesia, rigidity, and “ON” and “OFF” fluctuation who were selected for pallidotomy or DBS. Another limitation was that we only recorded UPDRS III data before and a month after surgery, so the long-term follow-up clinical outcome could not be reported. Additional investigations with larger patient populations are needed to confirm these results.

5. Conclusions

We have found a large number of tremor-frequency neurons as well as β frequency oscillatory neurons in the GPi of patients with PD. Coherence analysis showed that many of the tremor-frequency neurons were highly coherent with tremor EMG in the limbs, either upper or lower, but not both. Thus, each body part appears to have a separate oscillator. We also found the MSFRs of all types of GPi neurons to be significantly higher than the firing rates in the GPi in normal nonhuman primates. These findings reflect the rate theory of PD and support the prediction that altered neuronal activity in the GPi not only promotes slowness and bradykinesia but also participates in tremor. The high values of the coherence between GPi tremor-frequency neurons and the tremor EMG suggests that the pallidum is involved in the pathophysiology of parkinsonian resting tremor. Although the data are preliminary, the novelty of the present finding is that tremor appears to precede some bursting GPi cells, and this is not consistent with the idea that the GPi triggers the onset of parkinsonian tremor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

Characteristics of oscillatory and non-oscillatory neurons in the GPI.

A. Patterns typical of a tremor frequency oscillatory neuron, a β frequency oscillatory neuron, and a non-oscillatory neuron. Each upper trace shows the raw data, and below is the spike train. B. Example interspike interval (ISI) histograms of the three neurons and their mean spontaneous firing rates (MSFRs). C. Power density spectra of the three neurons at 4 Hz, 16 Hz, and no power (horizontal line indicates the significant oscillatory level of the power of the spike train signal). D. Comparisons of MSFR, coefficient of variation of ISIs (CV), and percentages of tremor frequency, β frequency, and non-oscillatory neurons. The histograms include the MSFRs of all 79 GPI neurons (* $P < .05$).

Fig. 2.

Analysis of tremor frequency and tremor-related oscillatory neurons recorded in the GPi during tremor.

A. A tremor frequency oscillatory GPi neuron not correlated with the tremor (upper trace, raw data; middle trace, spike train; lower trace, EMG). A1. The neuron in A had a peak frequency at 4 Hz (left panel) while the FCR EMG had a peak at 5 Hz (middle panel), and neuron $\times$ FCR showed no coherence (right panel). B. A GPI tremor-related oscillatory (TRO) neuron coherent with FCR (traces arranged as in A). B1. The neuron and FCR EMG in B had peak frequencies at 5 Hz, and neuron $\times$ FCR showed coherence at 5 Hz. C. A GPI TRO neuron coherent with FCR and ECR EMGs (traces arranged as in A). C1. The TRO neuron in C had a peak at 5 Hz, the FCR and ECR two peaks at 5 and 10 Hz, and the TA a peak at 5 Hz. C2. Neuron $\times$ FCR and neuron $\times$ ECR were coherent at 5 Hz, but neuron $\times$ TA showed no coherence. D. A GPI TRO neuron coherent with TA (traces arranged as in A). D1. The neuron in D had a peak at 3.5 Hz, FCR at 5 Hz, ECR at 5.5 Hz, and TA at 3.5 Hz. D2. Neuron $\times$ FCR and ECR showed no coherence, but neuron $\times$ TA was coherent at 3.5 Hz. FCR, flexor carpi radialis; ECR, extensor carpi radialis; TA, tibialis anterior. Horizontal lines in C1 and D1 indicate the significant level of power, and in C2 and D2 indicate a significant coherence level at 0.42 ($P < .05$).

Fig. 3.

Examples of GPi oscillatory neurons whose oscillatory patterns changed during tremor. A and B. Raw data from two neurons, one showing a pattern of tremor frequency oscillation (A) and the other showing a β frequency oscillation pattern (B) at the beginning of traces, that changed to β frequency and tremor frequency, respectively (arrows indicate the starting point of the neuronal and EMG pattern changes; brackets indicate periods with/without tremor in A and minor/severe tremor in B). A1 and A2. Spectral analysis confirming that the peak power for the neuron in A changed from 5.1 Hz (A1) to 12.5 Hz and 4.4 Hz (A2). B1 and B2. The peak power of the neuron in B changed from 23.5 Hz (B1) to 5.1 Hz (B2). A3 and B3. The MSFRs and CVs of the neurons in A and B during periods of tremor frequency oscillation and β frequency oscillation ($*p < .05$). A4 and B4. ISI histograms showing the pattern changes in the neurons in A and B (upper panels, before the change; lower panels, after the change).

ISI, interspike interval; CV, coefficient of variation of ISI; MSFR, mean spontaneous firing rate. FCR, flexor carpi radialis; ECR, extensor carpi radialis; EMG, electromyogram. These two neurons were recorded from patients 3 and 7.

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Fig. 4.

Sagittal maps of the locations of pallidal neurons with different patterns.

A1–A4. Sagittal maps with reconstruction of the microelectrode tracks through the GPi (12 trajectories in 9 patients). The typical trajectory is plotted at 20 mm from the midline of the globus pallidus from the Schaltenbrand and Wahren atlas (Schaltenbrand and Wahren, 1977). Each small division is 1 mm. The histograms show the distribution of tremor frequency, tremor-related, β frequency, and non-oscillatory neurons. Arrows, direction of trajectory. B1–B4. Box plots of distance from the border of the optic tract for the corresponding type of neuron (squares, median; circles, standard deviation). AC–PC, anterior–posterior line; GPie, external globus pallidus internus; GPii, internal globus pallidus internus; OT, optic tract.

Table 1

Details of the demographics and clinical characteristics of patients.

Patient/ Disease duration (years)	UPDRS III			LEDD (mg/day)	Type of operation and side of microelectrode recording	No. of neurons			
	Off pre/ post	On pre/ post	Off pre/post			On pre/post	Tremor frequency oscillatory neurons	β frequency oscillatory neurons	Non- oscillatory neurons
Total score	Total score	Rest tremor	Postural tremor	Rest tremor	Postural tremor				
1/6	32.5/18.5	12/12	9/3	0/0	4/1	0/0	5 (45.5%)	3 (27.3%)	
2/6	33.5/18	14/14	9/3	2/0	3/1	1/0	8 (80.0%)	2 (20.0%)	0
3/5	41/22	23.5/20	5/1	0/0	1/0	0/0	5 (45.5%)	1 (9.1%)	5 (45.5%)
4/5	33/18.5	19.5/14.5	5/1	2/0.5	4/1	1/0.5	3 (33.3%)	3 (33.3%)	3 (33.3%)
5/7	39.5/18.5	21/18	11/3	0/0	5/0	0/0	5 (83.3%)	0	1 (16.7%)
6/7	47/22.5	33.5/22.5	11.5/4	2/0	3/1	1/0	6 (75.0%)	0	2 (25.0%)
7/5	60/37	37.5/30.5	11/3	3/1	4/3	2/1	3 (37.5%)	5 (62.5%)	0
8/7	52.5/30	26.5/24.5	5/1	2/1	1/1	1/1	2 (25.0%)	4 (50.0%)	2 (25.0%)
9/9	57/32	27/26.5	8/2	3/0	3/0.5	0/0	3 (37.5%)	2 (25.0%)	3 (37.5%)

Table 2

Tremor frequency oscillatory neurons and tremor-related oscillatory neurons in the globus pallidus internus.

GPI oscillatory neurons (number)	Tremor frequency oscillatory neurons (number)	Tremor-related oscillatory neurons (%)	Related muscle activity	Range of coherence magnitude	Mean coherence magnitude (mean $\pm$ SD)	Median coherence magnitude
60	40	14/40 (35.0%) 2/40 (5.0%)	ECR/FCR TA	0.44–0.92 0.63–0.80	0.70 $\pm$ 0.14 0.72 $\pm$ 0.12	0.7

GPI, globus pallidus internus; FCR, flexor carpi radialis; ECR, extensor carpi radialis; TA, tibialis anterior.