Computer Analysis of the Tonic, Phasic, and Kinesthetic Activity of Pallidal Discharges in Parkinson Patients

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OBJECTIVE
Intraoperative analysis of microrecording data during pallidotomy often depends on subjective interpretation of the oscilloscope signal, especially during the analysis of phasic activity. The goals of this project were: 1) to develop an inexpensive system that allowed online, objective characterization of single-unit pallidal discharges, and 2) to have objective criteria to differentiate the internal part (GPi) from the external part (GPe) of the globus pallidus.

METHODS
A computer program was developed that allowed the analysis of firing rates (mean, median, and quartiles), spike count per unit time, and interspike interval (ISI) histograms with Chi-square statistical evaluation. Indices were developed that measured phasic activity, including burst index (BI) for the measurement of bursts, pause index (PI) for the measurement of pauses, and pause ratio (PR) for analysis of time spent in pauses. Single-unit activity of 152 GPe and 203 GPi cells in 47 Parkinson patients were digitized using the computer soundcard during pallidotomy and analyzed using this software.

RESULTS
GPe discharges had a mean firing rate = 42 Hz, BI = 0.81, PI = 0.21, and PR = 1.41. GPi had a mean firing rate = 81, BI = 1.61, PI = 0.04, and PR = 0.21. The PR was the best index that differentiated GPe from GPi, followed by PI, BI, and firing rates, in that order. Kinesthetic cells were recorded equally in GPe from GPi, and their responses to generalized movements were not significantly different.

CONCLUSION
(1) Signal analysis using the digitization process of a computer sound card and dedicated software is satisfactory for the objective “on-line” and “off-line” analysis of microrecordings (including phasic activity); (2) PI and PR are most helpful in differentiating neurons of GPi from those of GPe; (3) no single parameter can differentiate GPe from GPi activity in all cases; and (4) unlike the findings in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys, GPe and GPi of Parkinson patients have similar prevalence of kinesthetic cells and similar responses to generalized somatotopic effects. © 1999 by Elsevier Science Inc.

KEY WORDS
Microrecording, pallidotomy, Parkinson, globus pallidus, stereotaxy

In both experimental and clinical studies, pallidal neuronal discharges have been characterized by analyzing three parameters: tonic activity (firing rate), phasic activity (spike pattern), and kinesthetic activity (response to movement) [1–4]. Both tonic and kinesthetic activities are easily and objectively analyzed by evaluating the distribution of firing rates and by evaluating graphs of spike count per unit of time, respectively. The phasic activity, on the other hand, has largely been analyzed based on subjective description of the firing pattern, binary plot of spike activity, and evaluation of interspike interval histograms. The former two methods depend largely on human interpretation and on observer experience, which introduce an element of human error and which cannot form a basis for comparison between different intracranial structures or between different researchers. The latter method objectively characterizes spike patterns; however, this technique requires a large number of spikes (i.e., longer recording time) to achieve practically useful results and is therefore better suited...
for laboratory recordings than for surgical recordings. In addition, subtle information in the interspike interval histograms may be more easily described by a limited set of indices.

The goal of this project was to create a computer program that analyzes the tonic, phasic, and kinesthetic activity of pallidal recordings objectively and that can be used for both on-line and off-line analysis. In specific, we established methods for the statistical analysis of interspike interval histograms and created indices that objectively characterize the phasic activity of neuronal discharges intraoperatively and that can be used as a basis of comparison between different intracranial structures and between different researchers.

**MATERIALS AND METHODS**

Between March 1995 and March 1996, 47 patients with Parkinson’s disease underwent single-unit microrecording during pallidotomy at the Oregon Health Sciences University. There were 24 males and 23 females, ages 42 to 78 years. All patients had poor control of the disease with dopaminergic medications because of either decreased efficacy, severe fluctuations of “on/off” cycles, or drug-induced dyskinesia. Extracellular, single-unit discharges were recorded from the left globus pallidus in 27 patients and from the right in 20 patients. All 47 patients had their single-unit discharges tested for responses to passive movement of the contralateral limbs. In the last 15 patients, single-unit discharges were systematically tested for responses to passive movement of ipsilateral limbs as well. Responses to orofacial movements were not tested in this series.

**SURGICAL TECHNIQUE**

Pallidotomy was performed using the Leksell stereotactic system (Elekta, Sweden), guided by magnetic resonance imaging (MRI). All surgical procedures were performed under local anesthesia, without intraoperative sedation, and with the patients in the “off” cycle. The Leksell stereotactic frame was fixed to the patient’s head, guided by the Leksell ear bars and known external landmarks [5] to position the frame parallel to the intercommissural plane. MRI was performed using a 1.5 T GE-Signa scan (General Electric, Wisconsin). Sagittal, coronal, and axial images parallel to the intercommissural plane were obtained. Proper frame placement and imaging planes (i.e., orthogonal to the midsagittal plane and parallel to the intercommissural line) were verified on axial and coronal MR images. Errors were corrected using the appropriate mathematical formulas. The pallidal target was measured 2 mm anterior to the midcommissure, 3 to 6 mm below the intercommissural plane, and 19 to 22 mm lateral to the midline, just superolateral to the optic tract.

After assembling the Leksell stereotactic arc system on the stereotactic frame, a 3 mm twist-drill hole was created, approximately 2 cm lateral to the midline, just anterior to the coronal suture. The trajectory to the pallidal target in the sagittal plane was 63 ± 14 degrees to the intercommissural line; the trajectory in the coronal plane was 90 ± 2 degrees to the midsagittal plane. Extracellular single-unit discharges were recorded starting 10 mm above the calculated pallidal target and through the pallidal base. Microrecordings were obtained through one to three tracks for each patient.

**MICRORECORDING TECHNIQUE**

Single unit discharges were recorded extracellularly using specially designed, monopolar, tungsten microelectrodes that had diameter tips of 1 to 2 micrometers and impedances of 1.1 to 1.4 megohm at 1000 Hz [6]. The microelectrode sliding cannula was used as the indifferent electrode. The microelectrode was advanced in micrometer increments, using a manual hydraulic microdrive (Trent-Wells, Stolting, IL). A unity-gain preamplifier (High Impedance Probe, Grass-Astromed, RI) was fixed to the Leksell stereotactic arc and attached to an A.C.-coupled differential amplifier (P511, Grass-Astromed). The recorded signal was filtered using a bandwidth of 300 to 10,000 Hz and a 60 Hz filter, and amplified ten thousand times. The signal was displayed on an oscilloscope with Schmidt-trigger capabilities (Tektronix, Beaverton, OR) and stored on magnetic tape. The signal was also connected to an audio monitor. The patient’s movements during microrecording were continuously monitored using a video camera.

Single-unit discharges were identified intraoperatively by their firing patterns, frequencies, and amplitudes and verified using Schmidt-triggering techniques. Neurons of GPe were identified by their typical irregular and/or short-burst activity, whereas neurons of GPI were identified by their typical sustained, high-frequency discharges and correlated with the depth of the recording electrode [3,4]. The pallidal base was identified by the lack of GPI cell activity and the sudden change in neuronal background noise. In the last 16 patients, the optic tract was identified by recordings of extracellular axonal discharges that were evoked using a strobe light (Grass-Astromed). After each
track, cells were plotted on a map of the corresponding sagittal sections of the globus pallidus, which was obtained from the Schaltenbrand and Bailey stereotactic atlas [7].

Single-unit activity was recorded during spontaneous neuronal discharges and during the following contralateral passive joint movements: shoulder flexion and extension, shoulder abduction and adduction, elbow flexion and extension, elbow pronation and supination, wrist flexion and extension, finger flexion and extension (including metacarpophalangeal and proximal interphalangeal joints), hip flexion and extension, knee flexion and extension, ankle dorsiflexion and plantarflexion, and big toe flexion and extension (metacarpophalangeal joint). In the last 15 patients, responses to ipsilateral passive joint movements were also recorded. Responses to orofacial movements and active limb movement were not tested in this series.

**SIGNAL ANALYSIS**

The signal was digitized using the sound card of a computer (Ensoniq Soundscape, Gateway, North Sioux City) that allowed a sampling rate of 11, 22, or 44 kHz and has a 16-bit linear serial sigma-delta A/D converter. The line audio input (nominal input level = 1 V and nominal impedance = 100 K Ohms) of the soundcard was connected directly to the amplifier (P511, Grass-Astromed). The signal was optimally digitized on 16 bits using a sampling rate at 22 kHz, without noticeable change of the signal/noise ratio or loss of the dynamic of the signal. The software, which was written using Delphi for Windows (Borland International), allowed the following: (1) display of the signal in both spike or binary plot forms; (2) spike amplitude-discriminating capabilities; (3) stereo acquisition for analysis of multiple data (e.g., microrecording data with accelerometer signal); (4) evaluation of the tonic activity of the signal, such as duration of recording; number of spikes; and mean, median, and quartiles (P25 and P75) and extremes (P10 and P90) frequencies; (5) evaluation of phasic activity, using the following parameters: (a) a statistical comparison of interspike interval (ISI) histograms, using Chi-square analysis; (b) calculation of a modified Burst Index (BI) [8,9], defined as the number of ISI < 10 ms divided by the number of ISI > 10 ms; (c) calculation of pause index (PI), defined as the number of ISI > 50 ms divided by the number of ISI < 50 ms; (d) calculation of a pause ratio (PR), defined as the total duration of pauses (ISI > 50 ms) divided by the total duration of “non-pauses”; (6) evaluation of kinesthetic activity using graphs of the number of spikes per unit of time; and (7) evaluation of evoked potentials that allow the analysis of optic tract recordings. The thresholds of 10 ms for the BI and 50 ms for the PR were chosen empirically using the information gathered from the ISI histograms and can be set up at different values. The data analysis was performed on a PC (P5 120XL, Gateway) operated by a 120-MHz Pentium processor (Intel) and lasted about 2 minutes for each cell. All cells were plotted on the corresponding sagittal sections of the globus pallidus obtained from the Schaltenbrand and Bailey stereotactic atlas [4]. Spatial localization was verified and compared to the rostrocaudal dimensions of GPe and GPi (estimated by intraoperative microrecordings), pallidal base, and the location of the optic tract and the internal capsule (localized by evaluation of microrecording data, optic tract recordings, and macrostimulation).

**DATA ANALYSIS**

Parameters that have been analyzed previously in the literature for primate GPe and GPi cells were analyzed in this study for human GPe and GPi cells. These parameters included the tonic, phasic, and kinesthetic activity of pallidal neuronal activity. Evaluation of tonic activity included the analysis of the mean firing rates and analysis of the distribution of neuronal firing rates, which was evaluated by calculating the range and the 10th (P10), 25th (P25), 50th (P50), 75th (P75), and 90th (P90) percentiles. Evaluation of phasic activity included the analysis of the bursting patterns, statistical comparison of interspike interval histograms using Chi-square analysis, and analysis of parameters that objectively define the temporal pattern of phasic activity (i.e., BI, PI, PR). Evaluation of kinesthetic activity included the analysis of both the prevalence of kinesthetic cells as well as the analysis of responses to nonspecific joint movements (i.e., arm and leg, contralateral and ipsilateral, multiple joints, bidirectional joint movement). All distributions were statistically analyzed using Chi-square analysis with Yates correction for data values greater than 5 and the Fisher exact test for data values ≤ 5 [10]. Mean firing rates, BI, PI, and PR were compared using two tailed Student’s t-test. Significance was accepted for P < 0.05 [10].

**Results**

From 3 to 14 neurons (median, 9) were isolated for every patient and studied for spontaneous and movement-related activity. Of the 356 cells ana-
The firing rate of GPe cells ranged from 11 to 108 Hz (mean, 42 Hz, P10 = 17 Hz, P50 = 42 Hz, P90 = 65 Hz). The firing rate of GPi cells ranged from 42 to 201 Hz (mean, 81 Hz, P10 = 38 Hz, P50 = 77 Hz, P90 = 120 Hz). The mean firing rates of GPe and GPi cells were significantly different; however, overlap in the firing rate existed between GPe and GPi cells (Figure 1).

**Tonic Activity**

The firing rate of GPe cells ranged from 11 to 108 Hz (mean, 42 Hz, P10 = 17 Hz, P50 = 42 Hz, P90 = 65 Hz). The firing rate of GPi cells ranged from 42 to 201 Hz (mean, 81 Hz, P10 = 38 Hz, P50 = 77 Hz, P90 = 120 Hz). The mean firing rates of GPe and GPi cells were significantly different; however, overlap in the firing rate existed between GPe and GPi cells (Figure 1).

**Phasic Activity**

The typical GPe cell fired irregularly with spikes and short bursts interposed by short or long pauses (Figure 2). The typical GPi cell fired more rapidly, with longer bursts and less irregularity (Figure 2). Ten percent of GPe cells fired at repeated short bursts were occasionally interposed by single spike activity (Figure 2). The latter cells were similar to the low frequency bursting (LFB) cells described in primates [2].

The interspike interval distributions of the overall GPe and GPi cells were significantly different; however, some GPe and GPi cells had similar interspike interval histograms (Figure 3).

The burst index (BI) of GPe cells ranged from 0 to 2.88 (mean, 0.89, P10 = 0.05, P50 = 0.76, P90 = 2.32). BI of GPi cells ranged from 0.47 to 7.7 (mean, 1.97, P10 = 0.63, P50 = 1.43, P90 = 4.36). The mean BI of GPe and GPi cells were significantly different; however, some GPe and GPi cells had similar BI (Figure 1).

The PI of GPe cells ranged from 0 to 0.84 (mean, 0.2, P10 = 0.02, P50 = 0.11, P90 = 0.12). PI of GPi cells ranged from 0 to 0.23 (mean, 0.04, P10 = 0, P50 = 0.02, P90 = 0.12). The mean PI of GPe and GPi cells were significantly different, with minimal overlap in the distribution of their values (Figure 1).

The PR of GPe cells ranged from 0 to 11.08 (mean, 1.41, P10 = 0.08, P50 = 0.71, P90 = 4.04). PR of GPi cells ranged from 0 to 0.92 (mean, 0.21, P10 = 0.27, P50 = 0.09, P90 = 0.74). The mean PR of GPe and GPi cells were significantly different, with minimal overlap in the distribution of their values (Figure 1).

**Kinesthetic Activity**

Of the 356 pallidal cells, 75 (21%) changed their firing rate in response to passive movement of contralateral limbs (i.e., kinesthetic). Kinesthetic cells were identified in 32 (21%) of 152 GPe cells and in 43 (21%) of 204 GPi cells. The difference was not statistically significant.

Kinesthetic cells that responded to nonspecific stimuli were isolated in both GPe and GPi segments and are summarized in Table 1.

- Cells responding to upper and lower limb movements. Of the 75 pallidal kinesthetic cells, 8 (11%) changed their firing rate in response to contralateral passive upper and lower limb movements. These cells were not recorded significantly more in GPe versus GPi (p = 0.72).
- Cells responding to contralateral and ipsilateral limb movements. Of the 26 kinesthetic cells
tested (15 GPe and 11 GPi cells), 11 (42%) responded to both contralateral and ipsilateral limb movements. These cells were not recorded significantly more in GPe versus GPi.

- Cells responding to multiple joint movements. Of the 75 pallidal kinesthetic cells, 23 (31%) responded to multiple joint movements. These cells were not recorded significantly more in GPe versus GPi.

- Cells responding to bidirectional limb movements. Of the 75 pallidal kinesthetic cells, 27 (36%) responded to limb movements in more than one direction. These cells were not recorded significantly more in GPe versus GPi.

**DISCUSSION**

The results of this study demonstrate notable similarities between the pallidal neuronal firings of Parkinson patients and those of MPTP-treated monkeys [1,2,11,12]. These results support the contention that the model of Parkinson disease, which has been based on animal findings, largely applies to humans. However, the results also demonstrate that some differences exist between the human and the animal models. The following is analysis of signal characteristics of pallidal discharges in our series:

**TONIC ACTIVITY**

Mean firing rates do not accurately characterize neuronal discharges (Figure 4); however, most studies on primates and Parkinson patients emphasize mean firing rates as an important parameter for differentiating GPe from GPi cells [1–4,13]. Our study confirms that the mean firing rates of GPe (47 Hz) and GPi (93 Hz) cells of Parkinson patients are similar to the respective mean firing rates of GPe and GPi cells of MPTP-treated monkeys [1,2]; however, our study also confirms that many GPe cells have firing rates as high as GPi cells (Figure 1). High mean firing rates of GPe cells could represent normal GPe cells that have not been affected by the pathophysiological changes of Parkinson disease; typical Parkinson GPe cells that have excessively increased their phasic activity; or atypical Parkinson GPe cells that behave similar to Parkinson GPi cells and, as such, play a similar role in the pathophysiology of Parkinson symptoms.

**Characteristics of Responses of 32 GPe and 43 GPi Kinesthetic Cells**

<table>
<thead>
<tr>
<th></th>
<th>GPe</th>
<th>GPi</th>
<th>SIGNIFICANCE</th>
</tr>
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<tbody>
<tr>
<td>Upper and lower limb movements</td>
<td>4 (13%)</td>
<td>4 (9%)</td>
<td>p = 0.72</td>
</tr>
<tr>
<td>Contralateral and ipsilateral limbs*</td>
<td>7 (47%)</td>
<td>4 (33%)</td>
<td>p = 0.71</td>
</tr>
<tr>
<td>Multiple joint movements</td>
<td>11 (34%)</td>
<td>12 (28%)</td>
<td>p = 0.55</td>
</tr>
<tr>
<td>Bidirectional movements</td>
<td>12 (38%)</td>
<td>15 (35%)</td>
<td>p = 0.8</td>
</tr>
</tbody>
</table>

*Response to contralateral and ipsilateral limb movements were tested for 26 kinesthetic cells (GPe = 15, GPi = 11). Corresponding percentages relate to the tested cells and not to the total number of GPe and GPi kinesthetic cells.
PHASIC ACTIVITY

In our study, statistical analysis of pallidal interspike interval histograms demonstrated significant differences between the overall GPe and GPi neurons; however, some GPe and GPi cell ISI histograms were not significantly different (Figure 2). Indices such as BI, PI, and PR proved valuable in objectively differentiating GPe and GPi cells. The overlap in the distribution of these indices between GPi and GPe were least with PR, followed by PI and BI, in that order. The advantage of these indices is that they allow objective evaluation of pallidal discharges and can be used as reference values for comparison purposes between different structures, researchers, or treatment modalities.

KINESTHETIC ACTIVITY

After the administration of MPTP to monkeys, kinesthetic cells doubled in GPe and quadrupled in GPi [11]. In addition, kinesthetic cells generalized their somatotopic effect by responding to movement of both upper and lower limbs, contralateral and ipsilateral limb movement, movement of more than one joint, and movement in more than one direction [1,11,12,14–16]. These cells were found more often in GPi of MPTP-treated monkeys than in GPe.
In our study, kinesthetic cells were identified in 21% of pallidal neurons of Parkinson patients. Unlike the findings in MPTP-treated monkeys, kinesthetic cells were equally recorded in GPe and GPi of Parkinson patients. In addition, unlike the case in MPTP-treated monkeys, cells that generalized their somatotopic effect were similarly recorded in GPi and GPe of Parkinson patients. These differences could represent species differences, differences in the projections to the globus pallidus in humans, or differences in the pathophysiology of limb movements in Parkinson patients.

The results of our study document that the model for Parkinson’s disease, which has been based on animal findings, largely applies to humans. In this study, we demonstrated that all tonic, phasic, and kinesthetic activities of pallidal discharges can be analyzed objectively. Although most GPe and GPi cells can be separated by human and computer analysis, some GPe and GPi cannot be differentiated. Analysis of neighboring cells can help define these cells.

**Conclusion**

Based on our results, we conclude the following: (1) signal analysis using the digitization process of a computer sound card and dedicated software is satisfactory for the objective “on-line” and “off-line” analysis of microrecordings. The software eliminates observer subjectivity that results in more accurate interpretation of the data; (2) using this computer software, the phasic activity can be defined objectively, including the temporal behavior of spike activity; (3) the PI and PR are most helpful in differentiating neurons of GPi from those of GPe; (4) no single parameter can differentiate GPe from GPi activity in all cases; and (5) unlike the findings in MPTP-treated monkeys, GPe and GPi of Parkinson patients have similar prevalence of kinesthetic cells and similar responses to generalized somatotopic effects.

**REFERENCES**


**COMMENTARY**

Palidotomy is now a commonly practised procedure for the amelioration of many of the features of Parkinson’s disease. Though the structure can be visualized with MRI, I have never found these images sharply defined enough to act as anything more than a general guide to the location of the target in GPi; others might disagree with this point of view. Failing direct imaging localization, functional corroboration of the target site is necessary, for which we have found microelectrode recording and microstimulation the most useful and precise technique. As the microelectrode data are collected, the surgeon must look for cellular activity typical of GPe and GPi with border cells in between and surrounding the GPi neurons. This is a subjective assessment based upon which the surgeon places a lesion of a certain size in a particular portion of GPi based on his judgment and opinion as to the lesion that gives optimal results. The identification of recording silence surrounding GPi identifies nuclear margins occupied by fibre tracts, of which the internal capsule can be recognized by inducing muscle contractions with microstimulation, and the optic tract by eliciting contralateral colored phosphes or by recording axonal evoked potentials in response to light.

Though this subjective assessment of these data has worked well in our hands, Favre and his colleagues provide a software program that objectively analyzes the physiological data, giving the surgeon objective evidence for choice of target site. I would suspect that in those patients where the physiological data are of inferior quality, the computer program might also face difficulties in giving the surgeon clear direction. Furthermore, despite what the surgeon’s subjective assessment or the computer’s objective review suggests, maximum weight needs to be placed on the data demarcating optic tract and internal capsule no matter what the recordings show.

I think this program would be a useful adjunct to microelectrode-guided pallidotomy with the caveat that a neurosurgeon who has had a satisfactory experience with the procedure should at first carefully compare target localization using his own established technique and that dictated by the computer program when he first starts to use the computer program.

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However, the authors’ program provides a “better than you can see or hear” analysis of firing that has a probability attached to it that puts any given cell into a GPi or GPe cell category. Individual surgeons will have to try the program out in their own operating rooms to determine how much value it has in their environment. Generously, Favre will make the program available on his home page.*

A basic supposition of this paper is that GPi and GPe cells have been correctly identified before computer analysis, so that the program can compare their characteristics. Unfortunately, this cannot be done with precision unless we have histological confirmation of the tracts, an impossibility with patients. An atlas is only an approximation. In fact, if an atlas were precise, we would not need recording. Some of the seeming overlap of GPe and GPi cells in humans may come about from improper initial identification of cell type. There is also the likelihood that cell-firing patterns are much more complex, especially in an awake Parkinsonian patient. The elegant diagrams of the succession of firing patterns shown in some neurophysiology papers exaggerate the real patterns of cell firing. The “best examples” are used. Surgeons who are beginning to use electrical recording in the operating room need to know that, just like MRI or responses to electrical stimulation, electrical recordings are simply another bit of important information to be considered before making a permanent lesion in a patient.

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Of all the creatures that were made [man] is the most detestable. Of the entire brood he is the only one—the solitary one—that possesses malice. That is the basest of all instincts, passions, vices—the most hateful. . . . He is the only creature that inflicts pain for sport, knowing it to be pain. . . . Also, in all the list he is the only creature that has a nasty mind.

—Mark Twain
"Autobiography"