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Quantitative Digitography (QDG): A Sensitive Measure of Digital Motor Control in Idiopathic Parkinson's Disease

*Helen M. Bronte-Stewart, MSE, MD, †Long Ding, MS, *Corinne Alexander, BA, ‡Yi Zhou, PhD, and *George P. Moore, PhD

**Department of Neurology and Neurological Sciences, Stanford University Medical Center, Stanford, California; †Department of Neuroscience, University of Pennsylvania, Philadelphia, Pennsylvania; and ‡Kaiser Foundation Health Plan, Oakland, California, U.S.A.*

Summary: This study introduces a new method for studying, quantitatively, the dynamics of finger movement using data obtained from sequences of key strikes on a computer-interfaced piano keyboard. We have called this quantitative digitography (QDG). This initial article introduces the method in a group of patients with Parkinson's disease and in a group of healthy subjects using simple, repetitive, alternating finger-tapping for 60 seconds. Patients with idiopathic Parkinson's disease (IPD) were studied "ON" and "OFF" dopaminergic medication before and after pallidotomy. Customized software allowed the independent analysis of key strike velocity, duration of key strike, and frequency of tapping along with a quantitative measure of the regularity of performance. Quantitative measures of the improvement in performance after medication are presented for each parameter of movement. The technique also reveals correlates of some clinical phenomena of the temporal disturbances of repetitive motion in IPD, such as fatigue, tremor, freezing, and festination. We demonstrate that the performance of 60 seconds of alternating finger tapping on a computerized keyboard yields objective measures of motor performance that are significantly different in patients with IPD "OFF" when compared with "ON" medication and when compared with healthy subjects. This is the first time that such a method has been used in the measurement of specific kinematics of digital motion in Parkinson's disease. The equipment is inexpensive and portable and the data are rapidly and easily collected, making it suitable for the outpatient setting. **Key Words:** Parkinson's disease—Quantitative digitography—QDG—Finger tapping—MIDI—Quantitative measures–Repetitive movement.

At any point in time, the clinical signs in idiopathic Parkinson's disease (IPD) vary among a population of patients and they can vary in the same patient from day to day. Methods of assessment have traditionally relied on either clinical rating scales of motor dysfunction, based on the examiner's judgment, or on disability scales based on the patient's judgment.[1] Clinical rating scales such as the Webster scale, the Columbia scale, and the Unified Parkinson's Disease Rating Scale (UPDRS) were carefully developed and validated to encompass the wide spectrum of clinical signs seen in Parkinson's disease (PD).[2–4] The interpretation of the motor examination is subjective and has resulted in significant differences in the scores given to the same patient, even among experienced movement disorder specialists.[5] Objective measurement has not been as widely used mainly as a result of the limited availability of quantitative assessment tools that are quick to administer, appropriate for the office setting, and inexpensive. Nevertheless, the need for reliable, reproducible, and objective outcome studies has become even more important to document the efficacy of pallidotomy and deep brain stimulation as treatment options for patients with PD. Several outcome-based studies[6–12] have reported varying degrees of improvement after pallidotomy. Part of this variability may be the result of different methods of data collection[13] and of interrater variability in assessment.

Recent advances in electronic music technology have led to the development of piano keyboards equipped with optical sensors and a computer interface called MIDI (Musical Instrument Digital Interface) which have the

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Address correspondence and reprint requests to Helen M. Bronte-Stewart, MSE, MD, Department of Neurology and Neurological Sciences, RM. A343, Stanford University Medical Center, 300 Pasteur Dr., Stanford, CA 94305-5235, U.S.A.

temporal resolution appropriate for the study of digital movement.[14] These keyboards have been used in several neurologic studies to measure errors in finger movements in healthy subjects during transcranial magnetic stimulation[15,16] or to study musicians with focal dystonias and other hand control disorders.[17,18] This is the first study to use this technology and analysis to quantify the abnormalities of digital movement in IPD. Earlier Wilson demonstrated qualitatively the improvement seen in the performance of a musician with PD on an MIDI keyboard after treatment with L-dopa.[19]

As part of the development of a neurosurgical program for patients with PD, we incorporated several quantitative measures of motion, using computerized technology, to supplement the CAPIT (Core Assessment Program for Intracerebral Transplantation),[20] which is the international, methodologic standard for the longitudinal assessment of patients with PD undergoing any neurosurgical intervention. In this article we report the results of a quantitative test of repetitive finger tapping similar to the repetitive finger tapping task in the UPDRS Motor subscale (no. 23). The task we have chosen is simple, repetitive, alternating finger tapping of adjacent keys (or a "trill"), which can be performed easily by subjects without formal musical training. We introduce the technique in a group of patients with IPD, off and on medication and before and after pallidotomy in one patient. We demonstrate that kinematics of motor control, such as the velocity and duration of finger strike and the frequency and regularity of tapping, can be independently analyzed. From the analysis of 60-second recordings of alternating finger tapping, we have identified the manifestations corresponding to several well-known disturbances of motion in PD, such as tremor, fatigue, freezing, and festination.

MATERIALS AND METHODS

Patients and Experimental Protocol

Sixteen patients with IPD and 11 age-matched normal subjects performed repetitive, alternating finger tapping on a computer-interfaced keyboard.

All patients and normal subjects gave informed consent and the study was approved by the local ethics committee. All patients had been accepted for surgery and had IPD without evidence of dementia. Normal subjects had no evidence of neurologic disease. No patient or normal subject was a professional keyboard player. This study was added to the standard CAPIT. All patients were examined first on one morning in their "best on" state and again the next morning in the "practically defined off" state. This is defined as the clinical state 12 hours after the last dose of dopaminergic medication.[20] We withdrew all long-acting medication at least 18 hours before the "off"-state testing. The testing was done at the same time each morning.

Patients were seated comfortably on an armless chair at the keyboard with their arm flexed at the elbow to approximately 90° and with their wrist resting on a firm rubber pad that was level with the keys. The patients were instructed to perform 60 seconds of alternating finger tapping of consecutive keys with the index and middle fingers of each hand without stopping and without taking the wrist off the pad. They were instructed to begin immediately after they were given a "start" command, and they were told to perform the movement as fast as possible while keeping the alternating movement as regular as possible. No external pacing was provided. All patients were given a short period of practice before the test began. All trials were videotaped. If patients stopped voluntarily or if their fingers moved to different keys the trial was aborted. Subjects were examined without auditory or visual feedback. For withdrawal of visual feedback the subjects wore a blindfold. The keys do not produce audible notes but a sound is produced by the finger striking the key. To mask the sound of the finger strike, that is, for withdrawal of auditory feedback, subjects wore headphones through which static or "white noise" was transmitted.

MIDI Keyboard Technology

Rapid, alternating finger tapping was performed on an inexpensive, portable, two-octave, MIDI-equipped keyboard (Novation Electronic Music Systems MM10-X, Buckinghamshire, England); a number of manufacturers make comparable devices. The mechanical components of the keys are interfaced to electronic circuits that generate and transmit a digital MIDI message to a host computer. Each key-strike transmits a code that identifies the note struck, the time of strike, and the velocity of strike. When that key is released, another MIDI signal is sent, which identifies the note and the time of release. From these two MIDI messages, the identity, time of onset, duration, and the velocity with which the key was struck are recorded for each note played. The note-interval is the time between successive strikes for each finger. We represent the information about each note as an L-shaped symbol whose horizontal base elevation, in relation to a graphic representation of the keyboard, indicates the identity of the note; the length of the base indicates the note duration, and the height of the symbol is proportional to the velocity of the key-strike (Fig. 1). On a traditional piano a certain force of strike and displacement of the key is required to produce a note. On the

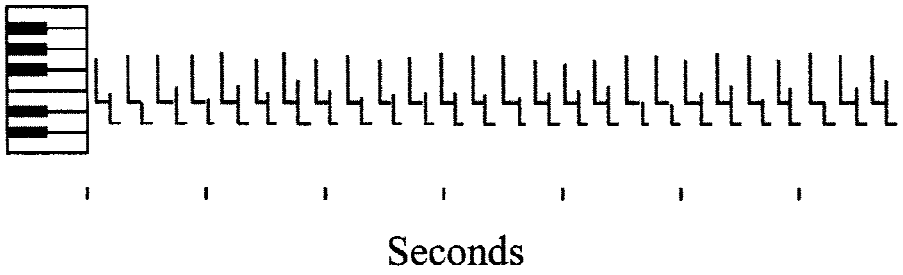

FIG. 1. Sequence of 26 notes played by the middle finger of the right hand of a normal subject (the keyboard alignment indicates it was note E) alternating with 26 notes played by the index finger (note D). Each strike of the key is recorded as a mark in the shape of an "L" with the vertical component indicating the time of note onset. The height of the L is proportional to the velocity of finger strike and the length of the horizontal bar indicates the duration of the note. The data show that the upper note (E) is released at almost exactly the same time that note D is struck but the converse is not true.

Novation keyboard, however, the MIDI code is activated with only a slight depression of the key (1–2 mm) and with little force. We do not measure the actual displacement of the key.

The temporal resolution of the MIDI clock is approximately 5 msec. The digital velocity code has a numeric value in the range of 0–127, but these are effectively uncalibrated in terms of primary physical variables. The higher the value (that is, the faster the key deflection), the louder the note, so an ordinal scale is preserved, thus making it possible to determine whether notes from the same key were struck with greater or less force. Different keys may not have exactly identical codes for identical velocities, which limits the validity of quantitative comparisons between notes or between keyboards. The data for this study were obtained from a single keyboard. The notes to be used were marked in all but the earliest trials.

Data Analysis

Customized software was developed for processing and displaying the MIDI data and was used to produce the figures shown in this article.[14] The coefficient of variation (CV), defined as the standard deviation divided by the mean, was computed over 60 seconds for each performance variable and expressed as a percentage. This is a measure of the regularity of performance. The improvement of any component of performance after therapeutic interventions, such as medication and/or surgery, was analyzed by calculating the ratio of the means and the CVs before and after the intervention. These are expressed as a percentage with respect to the state before intervention, whether that is medication, stereotactic surgery, or something else, similar to the method of expression for the percentage improvement in UPDRS scores following therapeutic interventions. For the case of the duration of strike, in which a better performance is reflected by a shorter duration, the ratio was inverted.

To compare performance within patients on and off medication, two tests were used. When a variable, such as strike velocity, was normally distributed, a paired Student's *t* test was used to assess the statistical significance of any differences in the mean. Otherwise, as in the case of note duration and note interval, a Wilcoxon signed rank test was used to test the statistical significance of the differences in median values. To compare the difference in performance between patients (on or off medication) and normal subjects, an independent Student's *t* test was used to determine the statistical significance of differences in mean velocity. A Wilcoxon rank sum test was used to assess the statistical significance of the difference in median note duration or median interval.

RESULTS

Figure 2 displays the data from 60 seconds of alternating finger tapping performed by one of the normal subjects. The performance of the subject was consistent during the 60 seconds and finger tapping alternated in a regular manner. The subject struck a total of 475 notes in 60 seconds. Figure 2B reveals the sequences of velocity of finger strike and duration of each note (top and middle trace, respectively) for each finger. The lowest trace represents the interval between successive strikes for each finger. The interval between successive strikes is the inverse of the frequency of tapping. The normal subject maintained a nearly constant velocity of finger movement, duration of strike, and frequency of tapping throughout the 60 seconds, showing no sign of fatigue or hesitation. The mean duration of strike was consistently low, which demonstrates that the subject was able to tap and withdraw each finger rapidly without lingering on the key. The normal subject tapped at a rapid rate (mean of four strikes per second per finger) and maintained a regular rate ($CV_{frequency} = 9\%$).

Figures 3 and 4 contrast the performance of a 51-year-old patient with IPD in the "best on" and in the "practi-

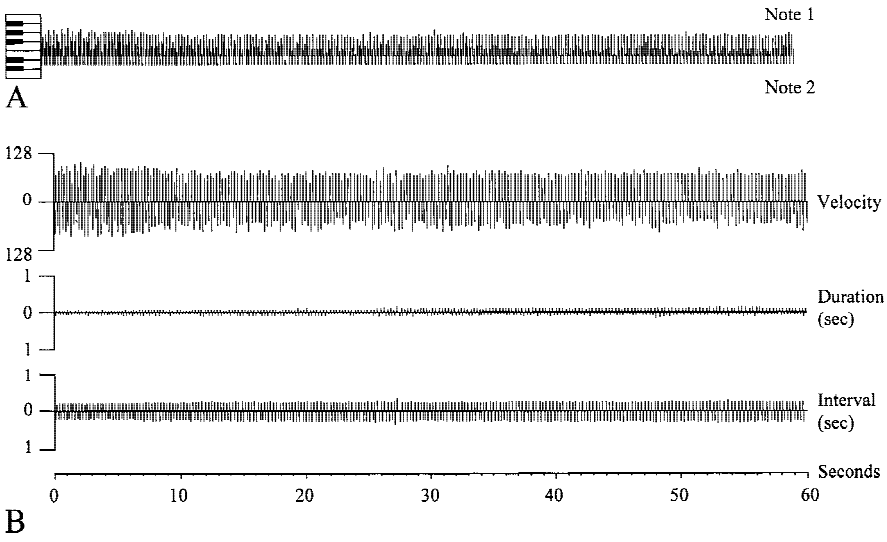

FIG. 2. (**A** and **B**) A normal subject performing 60 seconds of alternating finger tapping. The raw data trace (**A**) shows every recorded note aligned with the notes of the keyboard. (**B**) Specific traces showing velocity of finger strike (upper), duration of strike (middle), and interval (lower) between finger strikes. Values for note 1 are oriented upward and for note 2 downward. The mean and CV for velocity were 77 and 12% for note 1 and 61 and 22% for note 2. For duration of strike the means and CVs were 104 msec and 23% and 84 msec and 21%, respectively, and for interval they were 253 msec and 9% and 253 msec and 10%, respectively.

cally defined off" states. The differences between the "best" performance of this patient and that of the normal subject in Figure 2 will be clear. In the on state the patient's estimated clinical disease stage was Hoehn and Yahr stage III and the UPDRS III Finger Tapping (FT) score was 1. The patient's performance was clearly slower than that of the normal subject (mean frequency = 1.2 strikes per second) but she maintained the motor task throughout the 60 seconds (Fig. 3A, B). The records and comparison of the CVs (Figs. 2B and 3B) demonstrate that although the performance of the patient on medication was consistent, it was less regular than the normal subject.

The performance of the same patient in the "practically defined off" state is shown in Figure 4. In the off state her estimated Hoehn and Yahr stage was III and her UPDRS III FT score was 2. The data in Figure 4A shows that, off medication, the patient's performance was not consistent and deteriorated over the course of the record. The patient maintained the desired motor task for 60 seconds (Fig. 4B) except for a period between 18 and 28 seconds when she abruptly slowed in frequency and lost the rhythm of alternating tapping (interval trace). When she resumed the motor task, her frequency was much slower. The other striking aspect of this record is the early deterioration in finger velocity. After the period of movement arrest and loss of rhythm, the velocity never recovered. We define fatigue as the occurrence of a progressive and consistent decrease in the patient's keystrike velocity and/or increase in the interval between

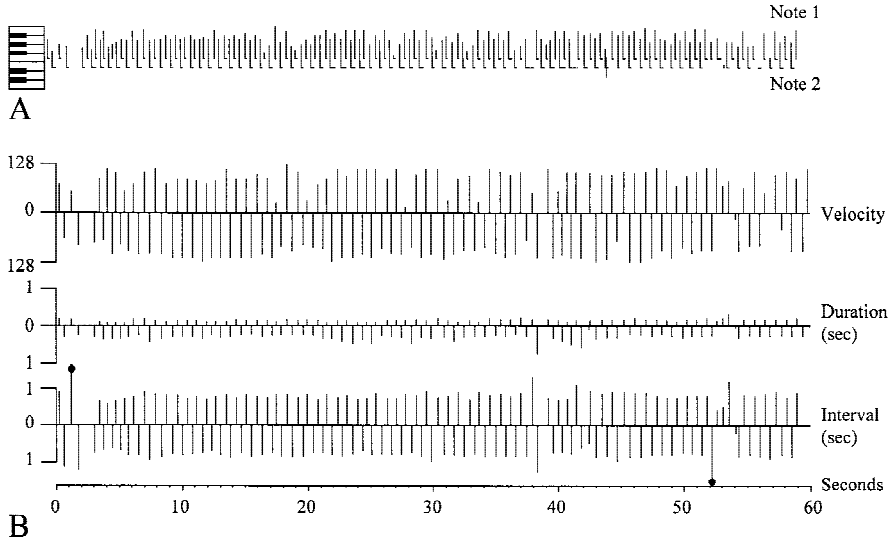

FIG. 3. (**A** and **B**) The performance of a patient with idiopathic Parkinson's disease in the "best on" state with the same data representation as in Figure 2. The filled circles on the strikes in the interval trace (**B**, lowest trace) indicate intervals between strikes that are greater than 1 second. The mean and CV for velocity were 94 and 27% for note 1 and 101 and 25% for note 2. For duration of strike the means and CVs were 177 msec and 20% and 303 msec and 26%, respectively, and for interval they were 839 msec and 22% and 827 msec and 22%, respectively.

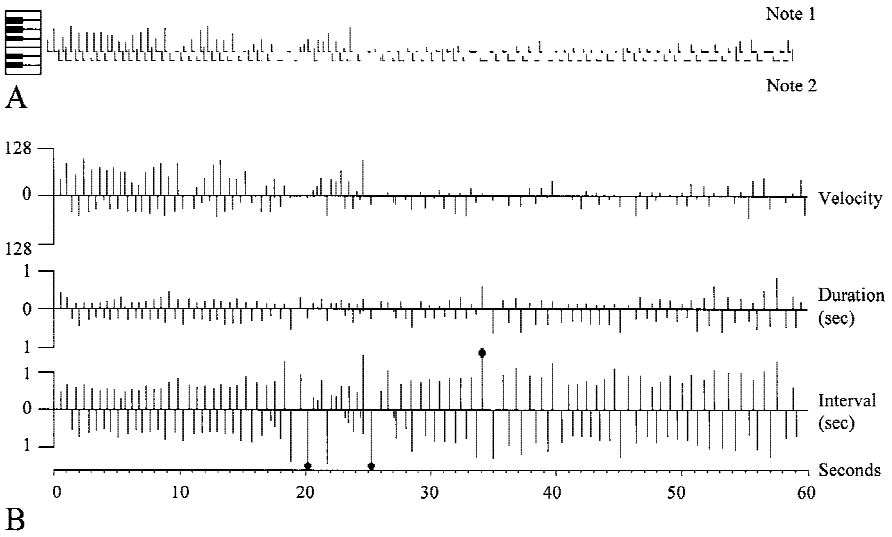

FIG. 4. (**A** and **B**) The performance of the same patient as in Figure 3 but in the "practically defined off" state. Many strikes in the raw data trace (**A**) appear to have only a horizontal component when the velocity of strike becomes very small (**B**, upper trace). The mean and CV for velocity were 36 and 82% for note 1 and 26 and 63% for note 2. For duration of strike the means and CVs were 240 msec and 40% and 322 msec and 35%, respectively, and for interval they were 775 msec and 32% and 799 msec and 38%, respectively.

strikes from the start of the record, both of which are demonstrated by this patient. We propose a quantitative definition of fatigue in a separate paper. This record substantiates the description of choice "2" of UPDRS III 23—"moderately impaired. Definite and early fatiguing. May have occasional arrests in movement."

This patient's performance in the off state was also more irregular in all QDG parameters of performance. The differences in the performance off versus on medication are summarized in Table 1 in which the improvement is demonstrated for six different variables: the improvement in the means of each QDG variable is termed IM, and the improvement in the regularity of performance is termed IR. The means have been calculated for finger 1 only and the same key was used by this patient in the on and off state.

Figure 5A–C summarizes the means of velocity of finger strike, note duration and interval between strikes for 15 patients in the off and the on state (mean age = 58 yrs; nine men, six women); mean Hoehn and Yahr stage III.4—off and II—on and for 11 normal subjects (mean age = 56 yrs; eight men, three women). Significant differences were found between patients off and on medication in all kinematic variables. The patient group, after medication, showed a 196% improvement in velocity, a 47% improvement in duration of strike, and a 41% improvement in frequency of tapping. These measurements demonstrate that this group had levodopa-responsive PD. As a group, the normal subjects performed better than the group of patients on medication but this was statistically significant only in the frequency of tapping.

Patients off medication were more irregular in their performance of a repetitive, alternating finger tapping task than when on medication and compared with normal subjects in every parameter of movement (Fig. 6). All normal subjects had CVs of velocity, note duration, and frequency of tapping less than 30%. All patients off medication had CVs of velocity greater than 30%. A $CV_{velocity} = 30\%$ in this database thus distinguishes normal subjects from patients off medication. After medication the patient group showed a 229% improvement in the $CV_{velocity}$, an 88% improvement in the $CV_{duration}$, and a 68% improvement in the $CV_{frequency}$. This was especially notable in the velocity of finger strike and may reflect partly the medication responsiveness of fatigue in IPD. Because the CV is a ratio, it is independent of any difference in velocity measurement from one key to an-

TABLE 1. *Improvement factors in performance after dopamimetic medication*

Variable	Mean off	Mean on	Improvement in the mean, IM_{med} (%)	CV_{off} (%)	CV_{on} (%)	Improvement in regularity, IR_{med} (%)
Velocity	36	94	161	82	27	67
Duration (msec)	240	180	40	40	20	50
Frequency (notes/sec)	1.29	1.19	−8	32	22	31

Data are from the patient shown in Figures 3 and 4.

other. The group average of the performance of patients on medication was less regular than the normal subjects in all kinematic variables. Although the differences are less pronounced between patients on medication and normal subjects, Figures 5 and 6 demonstrate that even when medicated, patients with IPD did not achieve the performance regularity of the normal subjects.

In addition to accurately measuring the abnormalities of motor control in a group of patients with IPD off and on medication and compared with normal subjects, QDG also documents manifestations of some of the clinical phenomena of temporally dependent motor dyscontrol that are seen clinically. These include tremor, freezing, bradykinesia, and, as shown already, fatigue.

Fatigue and Freezing

Figure 7 displays the velocity, duration, and interval sequences of the performance of a patient, aged 71 years, with IPD in the practically defined off state (Hoehn and Yahr stage III and UPDRS [III] FT score = 3). This record demonstrates some of the clinical phenomena seen in PD, such as fatigue, freezing, tremor, and festination. The performance progressed from rapid, regular, rhythmic tapping to a slower, more disordered movement with significant reductions in velocity of finger strike and in frequency of tapping. These are the hallmarks of fatigue. Within the record there were four clear periods or "epochs" (indicated by the vertical, dashed lines) separated by "freezes." We define a "freeze" as the complete cessation of activity in one or both fingers in all kinematic variables that lasts longer than the mean interval between finger strikes of the preceding 5 seconds plus two standard deviations. This reflects a cessation in activity that interrupts the periodicity of the repetitive action. After each freeze there seemed to be a fundamentally different organization of the sequence pattern with a stepwise increase in note durations and in interstrike intervals. Within epochs 1, 3, and 4, the "new" duration and interval were relatively well maintained.

During the second epoch the frequency of tapping began to increase progressively and the duration of finger strike decreased until the patient froze again for more than 1 second. This "festination" of digital tapping may be analogous to festination seen in gait, in which the stride frequency becomes progressively more rapid. In the final 20 seconds of performance the patient produced a slower, lower velocity movement, in which the fingers remained on the keys for up to 800 msec between strikes. Given the interval between note onsets, this means that one finger was lifted after the time of onset of the other note, that is, at times both fingers were in the depressed position. This important aspect indicates that strict alternation of finger tapping was not maintained and the patient was unable to sustain the chosen motor sequence of repetitive, alternating finger tapping.

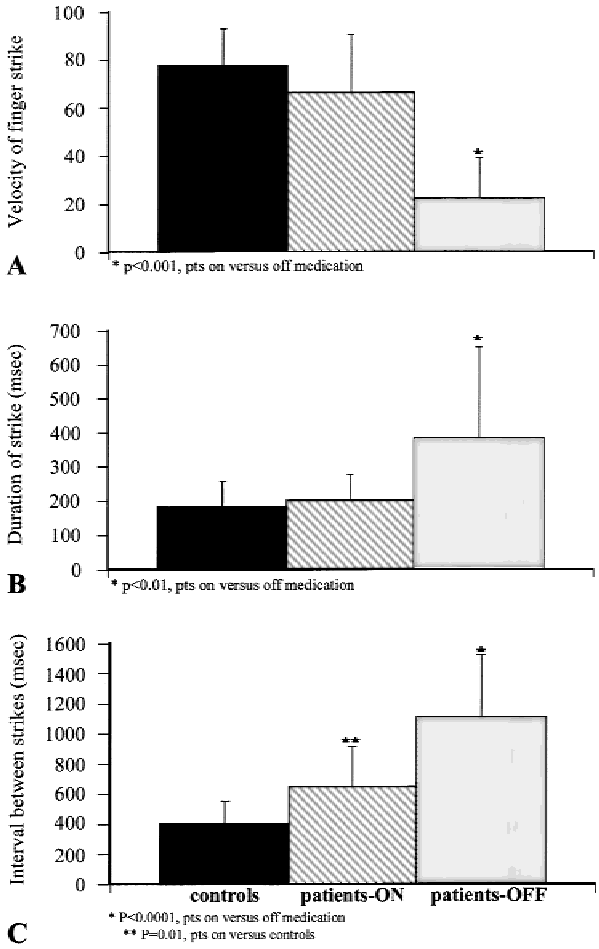

FIG. 5. (**A–C**) Group means and standard deviation of the velocity of finger strike (**A**), duration of strike (**B**), and interval between strikes (**C**) of the normal subjects, the patients on medication, and the patients off medication.

Akinesia and Tremor

Figure 8 displays the performance of another patient with IPD, aged 38 years, in the practically defined off state (Hoehn and Yahr stage IV, UPDRS [III] FT = 4). The performance demonstrated only akinesia or tremor. No voluntary alternating movement was achieved. During the first 9 seconds after the command to start the patient was akinetic and unable to perform any voluntary tapping. Instead a tremor developed. When his fingers did touch the keys he was unable to override the tremor, and the analysis revealed single or simultaneous digit tapping at high velocities and frequencies with short durations of strike. When both fingers touched the keys, the movements were revealed as synchronous, non-

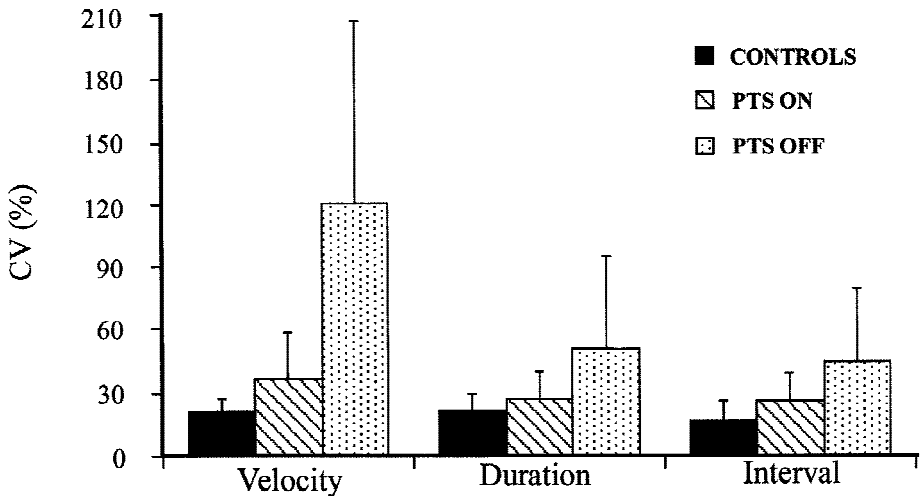

FIG. 6. Group means of the coefficients of variation (CV) of velocity, duration and interval of the normal subjects, the patients on medication, and the patients off medication.

alternating key strikes, that is, tremor (see insert at the top right hand corner of Fig. 8). We recognize tremor in QDG data as synchronized, non-alternating tapping, with short durations of strike (<100 msec) and with frequencies in the range of those of parkinsonian tremor (4–7 Hz). This tapping rate is significantly faster than that of voluntary, alternating finger tapping that the patient is able to perform. For instance, the mean frequency of tapping for the group of patients when off medication was 0.9 Hz and when on medication it was 1.5 Hz. This patient's tremor frequency as measured from these data was 5.5 Hz.

Bradykinesia

The performance of a fourth patient in the practically defined off state is shown in Figure 9 and demonstrates bradykinesia and the sensitivity of the MIDI keyboard in detecting finger strikes of very low velocity. The age of this patient is 35 years with Hoehn and Yahr stage II.5 and UPDRS (III) FT = 2, the same score as the patient in Figure 4. Compared with the performances of the patients in Figures 4 and 7, this patient was bradykinetic but very regular. The mean frequency was only 0.5 strikes per second with a clear demonstration of fatigue. Although the patient's velocity of finger strike was very low and his movements were scarcely visible, the keyboard's sensitivity to slow deflections is such that each movement was recorded showing that the patient actually maintained the correct motor task for the full 60 seconds. Despite the bradykinesia, the patient still lifted each finger off the key before the other finger struck.

Improvement After Pallidotomy

Figure 10 demonstrates the performance of a fifth patient, off medication, 1 week before (Fig. 10A) and 3 months after (Fig. 10B) a successful, microelectrode-guided pallidotomy. The records are from the hand contralateral to the operated hemisphere. Pre-pallidotomy the patient's Hoehn and Yahr stage was III in the off state and post-pallidotomy it was II.5. The patient's UPDRS (III) FT score was 3 preoperatively and 1 postoperatively.

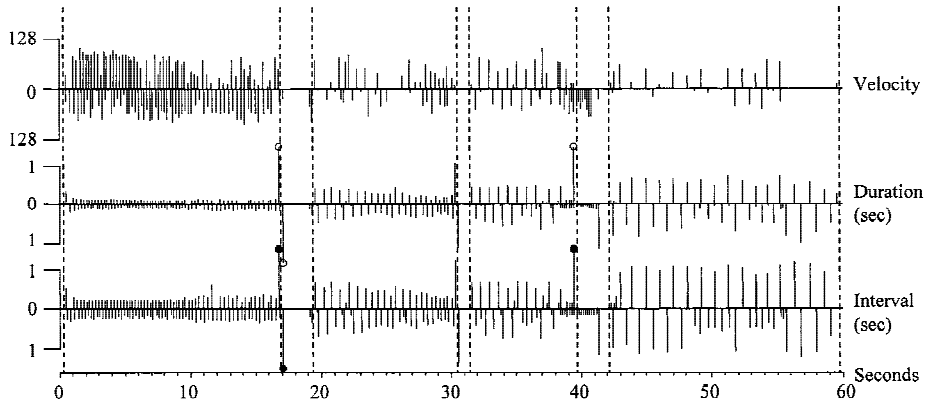

FIG. 7. Velocity, duration, and interval traces from a patient with Parkinson's disease in the "off" state. The vertical dashed lines indicate the boundaries of successive epochs, which are defined by the freezes. The open and closed circles in the duration and interval traces, respectively, represent durations and intervals longer than 1 second.

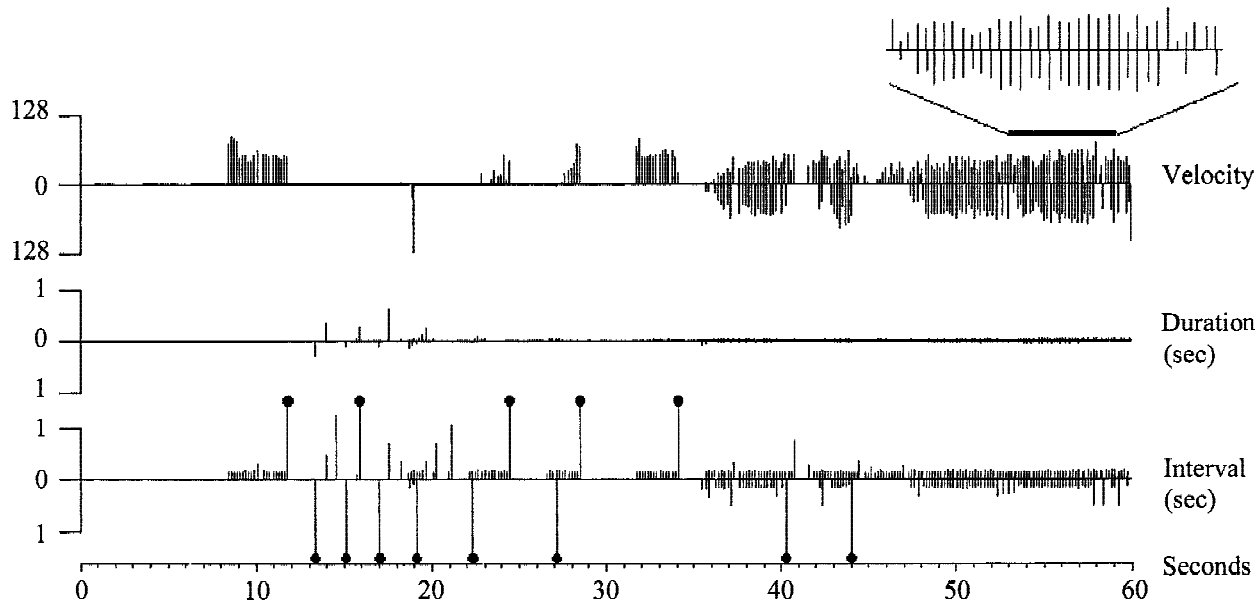

FIG. 8. Akinesia and tremor in a patient with Parkinson's disease off medication.

Preoperatively (Fig. 10A) the patient's performance was irregular and disordered. There were six freezes in the record, the first occurring only 7 seconds after the command to start. After each freeze there were attempts at alternating finger movement but these were not sustained for more than 10 seconds before the patient exhibited fatigue and/or the motor sequencing broke down. The rhythm was poor, which was reflected by the $CV_{frequency}$ of 84%. Three months after pallidotomy the performance had improved dramatically and demonstrated regular, rhythmic, alternating finger tapping without evidence of fatigue or freezing (Fig. 10B; $CV_{frequency}$ = 16%). The mean frequency improved to four strikes per second, similar to the normal subject (Fig. 2).

DISCUSSION

This report introduces quantitative digitography (QDG), a technique for measuring the kinematics of finger movement in PD. The initial task that we have chosen is repetitive, alternating finger tapping. The analysis of 60 seconds of alternating finger tapping on a portable keyboard yields objective data that are accurate and independent measurements of digital motor performance in patients with IPD. Improvements in the performance af-

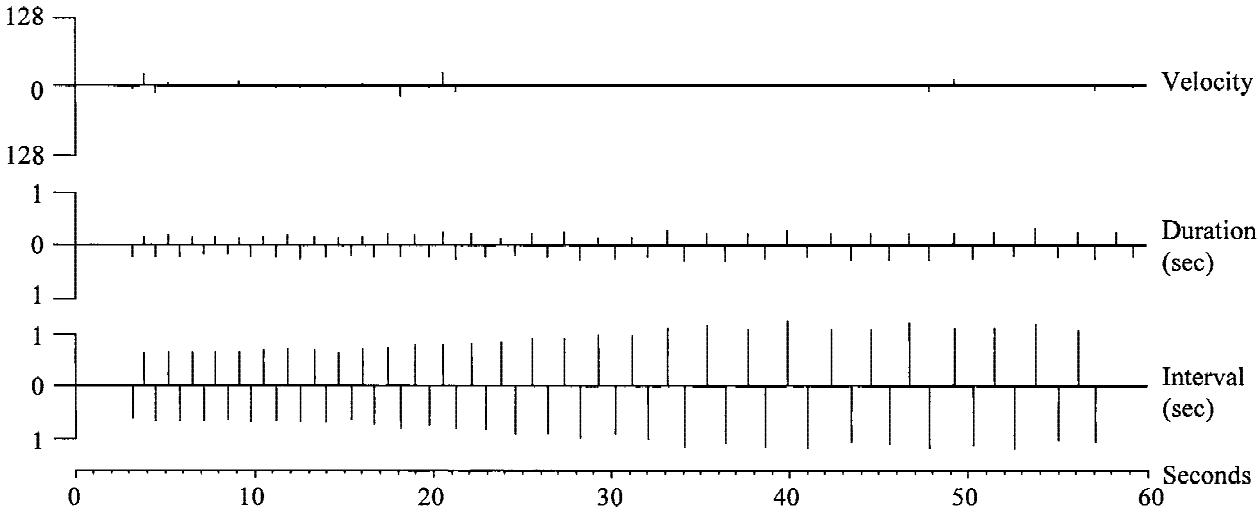

FIG. 9. Bradykinesia and low-velocity finger strikes in a patient with Parkinson's disease off medication.

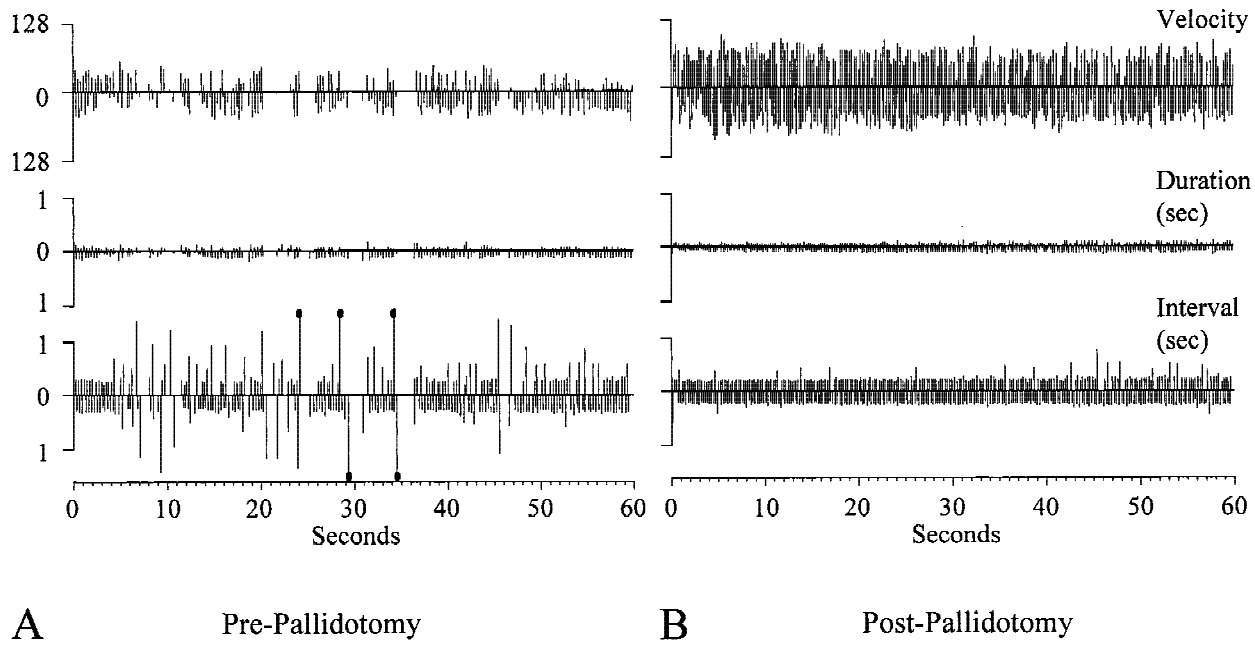

FIG. 10. (**A** and **B**) The performance of a patient with Parkinson's disease off medication 1 week before (**A**) and 3 months after (**B**) microelectrode-guided pallidotomy.

ter medication and after surgery can be quantified and can also be compared with data from normal subjects. Separate parameters of movement, such as the velocity of finger strike, the note duration, and the frequency of tapping, are independently measured. The regularity of repetitive movement is measurable from the CV of each parameter. Clinically important disturbances of repetitive motion in PD, such as fatigue, freezing, festination, and tremor, are demonstrated here and can also be measured by the analysis.

QDG Correlates of Parkinsonian Motor Signs

Clinical scales such as the Webster scale, the Columbia scale, and the UPDRS have been carefully designed to take into account the phenotypic heterogeneity of signs in IPD.[2–4] However, these descriptions are subjective. One has the choice of five integers, in the case of the UPDRS, to describe each feature. For the feature of repetitive finger tapping in the UPDRS section III, no. 23, there are three qualitative areas of motor dyscontrol that may be noted for the choice of one integer: choice "2" = "moderately impaired. Definite and early fatiguing. May have occasional arrests in movement." For the repetitive movement tasks, patients who are moderately bradykinetic but who maintain the rhythm may be given the same score as patients who can perform the repetitions more rapidly but with several pauses or freezes in the ongoing movement. Moreover, the difference among patients in the frequency or in the amplitude of the repetitive task cannot be quantified.

A more specific and quantitative analysis of digital motor control is possible using QDG, thus providing a more sensitive record of the progression of motor dyscontrol and a more specific description of each patient's unique profile of motor signs. In our experience QDG has revealed consistent differences among some patients in their motor profile. For instance, the patient in Figure 7 was able to initiate rapid movement sequences but was unable to maintain the rhythm for longer than 10 seconds at a time before the motor sequence froze. This patient was unable to maintain the correct motor task in the latter part of the record. On the other hand, the patient in Figure 9 was very bradykinetic but maintained the rhythm and correct motor task for the full 60 seconds. These two patients were consistent in their motor profile among three separate evaluations spaced 1 month apart. Most patients show a combination of motor deficits that are reflected in QDG and can be independently analyzed. Using multiple regression analysis it will be interesting to look at the correlation between different motor profiles and other signatures of the disease to see if any patterns emerge of subgroups of patients having similar motor profiles that may suggest specific pathophysiological roots. On the other hand, the varied phenotypic expression of the disease may have little correlation with

genetic or pathologic substrate, like that seen in the hereditary ataxias.

Temporal Disorders of Digital Motion

The subjects of this study were given a "start" command and were told to perform the task as rapidly as possible without external sensory cues. Thus, the movement was self-paced. With a self-paced, repetitive task we have found a spectrum of deficits in digital motor timing in patients with PD. Some are similar to those seen in digital movements in the clinical setting, such as fatigue and tremor, and some are more often described in terms of gross movements, such as freezing and festination.

A decrease in velocity of finger strike over time may be related to the progressive hypometria of repetitive finger tapping, usually assessed as fatigue. Fatigue in this task may also be manifest as a slowing of the repetitive movement. In QDG this is measured in terms of the increasing interval between strikes. We have observed that these two parameters may be independent; one patient may only show a decrease in velocity whereas another may maintain the velocity of strike but exhibit a progressive decrease in the frequency of strike. In any one record an exact, quantitative assessment of fatigue is possible.

We did not detect fatigue in any normal subject during 60 seconds of performance, and this is reflected in the fact that the CVs of all their kinematic parameters remained less than 30%. However, repetition of the task for 60 seconds was challenging for the patients with IPD, especially off medication. Almost all the patients, on and off medication, were able to maintain regular, alternating finger tapping for approximately 10 seconds. After that their performance became progressively more disordered and patients clearly found it harder to maintain the rhythm, especially in the "off" state. Our observations suggest that the assessment of repetitive tasks in clinical scales should be made only after 20–30 seconds to document accurately disorders such as fatigue and freezing.

Finger tremors may be measured in QDG. Tremors are characterized by regular, repetitive, non-alternating, that is, synchronized, finger tapping at frequencies greater than 4 Hz with note durations of less than 100 msec and with CVs less than 30% (Fig. 8). The non-alternating component will differentiate tremor from the performance of trills that may be seen from some highly skilled musicians who have been trained to release one finger as the other finger strikes the key (legato) and who may have a duration of strike as short as 100 msec[14] and frequencies of 4–5 Hz. Although a few of the normal subjects in this study could maintain the motor sequence of alternating finger tapping at frequencies up to 4 Hz, their average duration of strike was 186 msec, well above the durations we observed for tremor. Logigian et al.[21] proposed that central pattern generators, which generate voluntary rhythmic movement, may synchronize with neural oscillators, which generate the characteristic parkinsonian tremor, making it difficult for some patients to produce repetitive voluntary movements at frequencies different from their tremor. We show here, however, that the frequency of alternating voluntary movement is different from the tremor frequency.

Our definition of digital freezing in QDG allows us to count the number of freezes per record and to compare this variable to other parameters of performance and to the clinical stage of disease. We also observed a type of "digital festination" in QDG with several patients in whom the tapping frequency increased rapidly and the duration of strike decreased until a freeze occurred; we have likened this to the festination that may occur prior to a freeze in gait (Fig. 5). Nakamura et al. described a characteristic disturbance of rhythm formation of finger tapping in patients with PD in response to auditory cues[22] and referred to it as "the hastening phenomenon." They suggested that the "hastened tapping" represented an intrinsic oscillation of 5–6 Hz in the nervous system that can be damped in normal subjects but is released in patients with PD. Tapping frequencies during what we call festination in our patients, who were performing a self-paced task, were usually below tremor frequencies.

Complex Motor Sequences

Clinical studies suggest that the basal ganglia are involved in complex motor sequences.[23,24] Extracellular recordings from pallidal neurons in primates also support the role of the pallidum in sequential movements and suggest that the magnitude and timing of their output provides an internal cue for switching from one movement sequence to another. These neurons also show more prominent responses to predictable rather than novel movements.[25,26]

QDG can be used for many different combinations of finger tapping tasks. We have chosen alternating finger tapping with two adjacent fingers for this initial study. Tapping with alternate fingers introduces some strategy and complexity to the motor plan but is simple enough to be performed correctly by non-musicians and learning is not a significant variant among subjects without dementia or apraxia. It is easily measured and analyzed from the keyboard data. It consists of sequential but roughly identical movements from two adjacent fingers. A perfect performance of alternating tapping results in little "switching" time between sequential finger strikes and

thus the time that the finger rests on the key, the note duration, is short and consistent as shown by the normal subject in Figure 2. The note duration may therefore be a peripheral indicator of the central switching time needed to move from one sequence to another. This article demonstrates that the note duration was longer in patients with PD off medication than in normal subjects. In some patients the note duration became so long that one finger failed to be released from the key before the other finger struck its key and the motor sequence broke down. In other patients the prolonged note duration of one finger was associated with a freeze in ongoing movement. In both cases the increased note duration appeared to lead to a fragmentation of the motor plan (Figs. 7 and 10A). It remains to be seen whether the note duration is an important peripheral marker of central pathophysiology in the errors of timing seen in PD. We are currently expanding the complexity of the QDG task to examine this further.

QDG Sensitivity to Therapeutic Interventions

The change in neurologic function after different therapeutic interventions is accurately measured with QDG. Taken as a group, there was a significant difference in all parameters of digital motion between patients with IPD off and on medication and compared with normal subjects. The regularity of each parameter also improved after dopaminergic medication, which resulted from a reduction in the number of freezes and from a decrease in fatigue. Similarly, in the single example of QDG analysis pre- and post-pallidotomy, our data show that the patient improved in all parameters of performance and that this was most notable in the "smoothing out" of the irregularity in performance and in the reduction of the number of freezes.

The improvement after pallidotomy and/or deep brain stimulation varies among patients.[13,27] Patient selection is an important determinant of surgical outcome, and the current selection criteria require patients with dopa-responsive PD without dementia. A recent data-driven subclassification of IPD grouped patients into three types: motor only IPD, motor and cognitive IPD, and rapidly progressive IPD.[28] Subgrouping of the motor type traditionally was based on the predominance or not of tremor. Our analysis would suggest that, in addition, patients with IPD display a heterogeneous set of motor profiles under the domains of bradykinesia and fatigue. Within the bradykinesia domain there may be profiles such as "bradykinesia-regular" versus "bradykinesia-fatigue" versus "bradykinesia-freezing." Within the domain of fatigue there are those who fatigue mainly in the velocity domain and those who fatigue mainly in the frequency domain. QDG can separate and measure these profiles independently, unlike scales such as the UPDRS in which a potentially heterogeneous motor profile is lumped under one integer option. Different motor profiles may show different responses to medications and/or surgical interventions, and therefore by testing the response of each it may be possible to develop "cocktails" of therapy more specifically targeted to cover the spectrum of motor profiles.

QDG, using a non-invasive, inexpensive, and office-based device, has proven to be useful for quantifying abnormalities of repetitive movement in IPD. The task should have a duration of at least 30 seconds but a full set of data can be acquired in less than 5 minutes. The device is portable and suitable for the outpatient setting. Because it will not interfere with electrophysiological recording, it also may be useful for intraoperative neurologic testing. Its clinical use remains to be demonstrated with future studies correlating QDG parameters with the current standard methods of patient assessment such as UPDRS.

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