Movement Disorders
Vol. 20, No. 10, 2005, pp. 1286–1298

Quantitative Measurements of Alternating Finger Tapping in Parkinson's Disease Correlate With UPDRS Motor Disability and Reveal the Improvement in Fine Motor Control From Medication and Deep Brain Stimulation

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Abstract: The Unified Parkinson's Disease Rating Scale (UPDRS) is the primary outcome measure in most clinical trials of Parkinson's disease (PD) therapeutics. Each subscore of the motor section (UPDRS III) compresses a wide range of motor performance into a coarse-grained scale from 0 to 4; the assessment of performance can also be subjective. Quantitative digitography (QDG) is an objective, quantitative assessment of digital motor control using a computer-interfaced musical keyboard. In this study, we show that the kinematics of a repetitive alternating finger-tapping (RAFT) task using QDG correlate with the UPDRS motor score, particularly with the bradykinesia subscore, in 33 patients with PD. We show that dopaminergic medication and an average of 9.5 months of bilateral subthalamic nucleus deep brain stimulation (B-STN DBS) significantly improve UPDRS and QDG scores but may have different effects on certain kinematic parameters. This study substantiates the use of QDG to measure motor outcome in trials of PD therapeutics and shows that medication and B-STN DBS both improve fine motor control. © 2005 Movement Disorder Society

Key words: Parkinson's disease; deep brain stimulation; Unified Parkinson's Disease Rating Scale; repetitive alternating finger-tapping task; quantitative digitography; musical instrument digital interface

The motor phenotype of Parkinson's disease (PD) is characterized by slowness, paucity of spontaneous movement, rigidity, and tremor. Reliable and objective clinical assessments are particularly useful in PD as patients are followed frequently for many years with progressive treatment adjustments, pharmacologic and surgical, that are superimposed on a variable rate of disease progression and side effect profile.

The Unified Parkinson's Disease Rating Scale (UPDRS) was developed as a standardized test that has proved very useful as a global measure of function.[1] The UPDRS is straightforward to assess in the clinic, although the assessment is subjective and requires considerable experience and monitoring to minimize interrater variability. The UPDRS III (motor) subscale represents a coarse-grained scale of motor function with which a clinical evaluation is made of normal (0) performance, mild (1), moderate (2), or severe (3) impairment, or incapacity to perform the task (4). As such, this scale represents a comprehensive but not specific evaluation of motor disability. The UPDRS cannot differentiate specific kinematics of digital, limb, or axial movement, or the aspect of sensorimotor processing.

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Received 19 November 2004; Revised 26 December 2004; Accepted 21 January 2005

Published online 6 July 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.20556

With the advance of potential neuroprotective therapies, designed to slow or prevent the progression of disease, there is a compelling need to develop objective and sensitive tests of motor function in PD. Abnormalities of fine motor control are often among the first signs of motor impairment in patients with PD, so a tool that is sensitive to measuring fine motor control would be useful in such studies.[2,3] Ideally, an appropriate tool would have better resolution than the UPDRS does for detecting small changes in motor function in early-stage disease. This would increase the power of any individual trial, thereby reducing patient number, trial duration, and total cost.

Musical Instrument Digital Interface Technology

Musical instrument digital interface (MIDI) was developed 20 years ago for use by musicians and was designed originally to enable the combining of sounds produced by different instruments. This is achieved in part by attributing to each note a set of standardized characteristics including time of note onset, time of offset, and loudness (or key-strike velocity). This has made MIDI technology attractive for the study of movement and has been employed in kinematic studies of normal subjects,[4,5] pianists,[6,7] pianists with focal dystonia,[8] and patients with idiopathic PD.[9–11] The test–retest reliability of the MIDI keyboard was shown to be very high (correlation coefficients $\geq$0.94 for all kinematic variables) when tested with a group of professional pianists playing scales and trills.[8]

Kinematics of Repetitive Alternating Finger Tapping Using Quantitative Digitography

In a previous study, we described the kinematics of digital movement using a MIDI interfaced keyboard and we named this technique quantitative digitography (QDG).[10] From a repetitive alternating finger-tapping (RAFT) task over 30 seconds, we initially chose to study six kinematic measures. We calculated for each finger the means of key-strike velocity, duration of finger strike, and the interval between strikes. We also computed a measure of regularity of each kinematic over the duration of the task, using the coefficient of variation (CV). These six separate measures are similar to the components assessed in repetitive motor tasks in the UPDRS III, such as finger tapping, where descriptions of amplitude, frequency, and temporal variation of performance are included to decide on a single integer rating of disability.

Key-strike velocity is the downstroke velocity of the finger and key after the finger makes contact with the key. The duration of keystrike (Dur) is the time that the key is in the depressed state. The interval between successive keystrikes of each finger (Int) can be used to compute the mean frequency of tapping, a widely used measure in clinical assessments for bradykinesia. A signature of abnormal motor control in PD is the temporal aspect of repetitive movements. The loss of movement speed and amplitude over time is identified clinically as fatigue. In addition, rhythmic movement becomes irregular with complete interruptions in ongoing movement, which have been referred to as freezes when discussed in relation to walking. Various quantitative measures, such as variance, standard deviation, or CV have been used to measure temporal abnormalities of repetitive digital movement in QDG.[10,11]

Few studies have looked specifically at the effects of symptomatic therapies on quantitative measures of finger movement and debate continues whether medication or DBS is superior in improving fine motor control in PD.[12–18]

In this study, we validate QDG as a measure of motor function in patients with PD by demonstrating that certain QDG scores are strongly correlated with the UDPRS III score. Examination of UPDRS subscore correlations suggests that QDG most closely reflects clinical measures of bradykinesia. We also show that QDG can be used to assess the effects of medication and STN DBS on fine motor control in PD.

SUBJECTS AND METHODS

Subjects

From 62 patients with PD who received B-STN DBS implants at Stanford between September 1999 and August 2003, 33 were included in a study to investigate the effects of B-STN DBS on different aspects of motor control. The study was approved by the local Institutional Review Board. Of 29 not included in the study, 15 declined and 14 were excluded for reasons of previous surgery, concurrent other medical conditions, or being lost to follow-up. This study was part of a broader outcome study and all patients were screened extensively before surgery (see Surgery section). Of 33 patients included in the preoperative group, a subgroup of 17 patients was studied at a mean of 9.7 months (range, 5.3–25.5 months) after the onset of B-STN DBS. Of 16 who were not included in the postoperative group, 3 patients had difficulties with travel or with the length of the protocol, 6 patients had not reached the 6-month postoperative date, and 7 had incomplete data or protocol violations.

Preoperative patients had QDG evaluations (see Task section) and UPDRS scores in their *on* and *off* medica-

tion states; testing was either done on the same day (11/33 patients) or on 2 consecutive days (22/33). Before *off* medication testing, all long-acting dopaminergic medication was stopped for 24 hours and short-acting medication for 12 hours. Patients were tested in their *on* state 1 to 2 hours after taking their morning medication; some patients were given an additional dose of liquid levodopa (L-dopa)-carbidopa if they were not in their best *on* state on the morning of the evaluation, after which time they and the examiner determined that they were at their best *on* medication state. Assessments of the effect of medication compared patients' performances *on* versus *off* medication, preoperatively.

Postoperative QDG and UPDRS testing was carried out on 3 consecutive workdays in 3 respective states: on medication/on DBS (*on*/ON), off medication/on DBS (*off*/ON), and off medication/off DBS (*off*/OFF).* *On*/ON testing was carried out with clinically optimized medication and DBS parameters. After *on*/ON testing, long-acting medication was stopped for 24 hours and short-acting medication for 12 hours before the *off*/ON condition. After *off*/ON testing, DBS was turned off so that by *off*/OFF testing the following day, patients had been off DBS for between 17 and 23 hours and off long-acting and short-acting medication for 48 and 36 hours, respectively. This work addresses the effect of DBS by comparing patients' performances in the *off*/OFF to that in the *off*/ON evaluation. The *on*/ON data is not included in this work.

Each evaluation consisted of a series of quantitative and clinical tests, including QDG and the full UPDRS. The UPDRS III total was 100. We did not include tremor at rest of the head and rigidity of the neck. We refer to the UPDRS III total therefore as the modified UPDRS III score. Ages at evaluation (mean $\pm$ standard deviation) were 59.9 $\pm$ 8.8 years for the presurgery group (n = 33) and 59.6 $\pm$ 8.8 years for the postsurgery subgroup (n = 17).

Surgery

Selection Criteria.

The main indication for STN DBS was a diagnosis of idiopathic PD in patients who had developed motor response complications such as dyskinesias, on–off phenomena, and freezing. Preoperative screening included UPDRS assessment of L-dopa–responsive PD, comprehensive neuropsychological testing, and magnetic resonance imaging (MRI) of the brain. Contraindications to surgery included a poor response to dopaminergic therapy, cognitive deterioration, neuroimaging abnormalities, major psychiatric illness, and general surgical/anesthetic contraindications. A multidisciplinary team including a neurosurgeon, neurologist, psychiatrist, neuropsychologist, and nurse specialists evaluated each candidate's suitability for surgery and came to a consensus agreement.

Operative Technique.

Stereotactic coordinates were identified by preoperative MRI and intraoperative ventriculography.[19] Microelectrode mapping was used to investigate the somatotopic organization of the laterodorsal STN before implantation of the DBS electrode, which was based on electrophysiological and anatomical parameters. X-ray imaging was carried out to confirm correct positioning after each microelectrode track and upon placement of the final DBS electrode. All patients but one in our study had two separate procedures to implant the right and left DBS electrodes, on average 1 month apart, with implantable pulse generator (IPG) placement under general anesthetic the same day. One patient had bilateral implants done on the same day and one patient had two separate procedures 6 months apart. DBS stimulators were programmed approximately 1 month after implantation of the second electrode. Two patients had to have one side redone 4 months after original implantation due to infection.

QDG Task

All testing was done on a portable, 2-octave, MIDI-equipped keyboard (MM10-X; Novation Electronic Music Systems, Buckinghamshire, UK). Patients were seated in an armless chair in front of the keyboard with their wrist resting comfortably on a rubber pad level with the keys (see Fig. 1a). Each patient was instructed to perform RAFT as fast as possible with their index and middle fingers, first with their right hand and then with their left. Patients with PD usually demonstrate their most affected performance of sensorimotor tasks if sensory feedback is minimized, therefore patients were assessed both with and without visual and auditory feedback. In the condition without feedback, which was used for data analysis herein, they closed their eyes, the keyboard volume was turned off, and white noise was delivered through headphones to mask the tapping sound caused by striking the keys. In all except one (131/132) of the presurgery trials, patients were asked to play for 60 seconds but only the first 30 seconds has been for analysis. All postsurgery trials were done for 30 seconds. An instruction to start was given and recording commenced

*Lowercase terms refer to the medication state and upper case terms refer to the state of DBS.

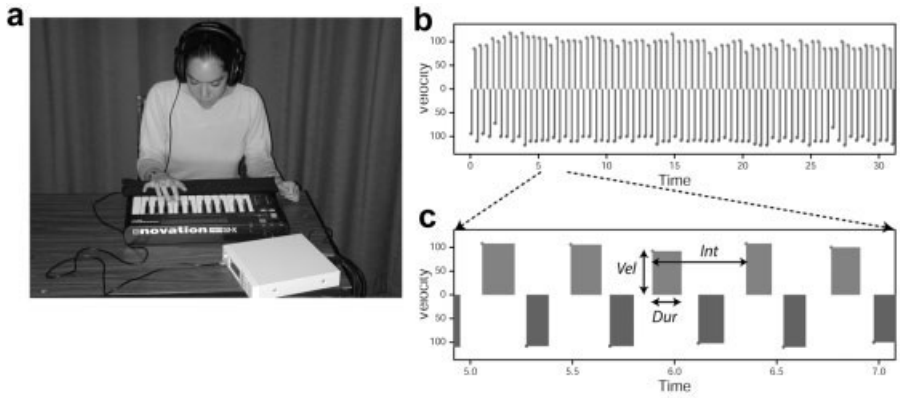

FIG. 1. QDG: repetitive alternating finger-tapping task. **a:** Demonstration of alternating two-digit finger tapping task on marked keys of a MIDI-equipped musical keyboard. In this example the subject is playing with their right hand, with visual and auditory feedback (the musical notes are played through the headphones). **b:** Example trace from a control subject: Right hand without vision/sound (the eyes are closed and white noise is delivered through headphones to mask the tapping of the keys). The upper note is depicted on the upper y-axis and the lower note on the lower y-axis. The y-axis corresponds to the velocity of key strike (which is positive in both directions) and the x-axis to time in seconds (for a 30-second trace). The start of each key-strike is represented by a dot. **c:** Two seconds from the above trace (5–7 seconds) demonstrating some of the parameters that can be studied with this output. Duration (Dur) of individual key strikes corresponds to the width of the bars. Interval (Int) corresponds to the time between successive key strikes for the same key.

once the patients had begun playing (so the delay between the start instruction and actual playing was not captured). No external pacing was provided and the trial was aborted if the patient stopped voluntarily or their fingers moved to different keys.

Data Capture

The four tests in a standard trial were each captured by a dedicated PC workstation attached to the Novation keyboard via a MIDI. Each note played was transmitted to the PC as two MIDI events, an ON event (key down) and an OFF event (key up). Each event contained a time stamp indicating the amount of time elapsed since the last event, the identity of the key being pressed or released, and a key-strike velocity (which is only meaningful for the ON event). The time stamp was expressed in MIDI ticks, which in our experiments corresponded to either 1/192 or 1/120 of a second, the fundamental temporal resolution of the recording. These MIDI events were captured on the PC with Cakewalk MIDI software (Cakewalk, Boston, MA) and subsequently saved as a binary Standard MIDI File (SMF) consisting of the MIDI events and meta-information to identify the patient, date, and nature of the test.

Keyboard Calibration

The key-strike velocity was recorded as an integer in the range 1 to 127 on a MIDI "loudness" scale. We carried out a detailed calibration study of the keyboard comparing the loudness values to metric velocity (cm/sec). We discovered that there was a truncation at each end of the MIDI scale, such that all very low velocities ($<$6.5 cm/sec) are coded as 1 and all very large velocities ($>$98.2 cm/sec) are coded as 127. In this study, $\leq$0.5% of events fell in the upper category and up to 8% fell in the lower category, predominantly when patients were off therapy (70% of those events). The MIDI loudness scale is a monotonically increasing function of key-strike velocity. It is approximately linear over its midrange but there is no systematic physical relationship between subsequent values of the loudness scale. Although all keys tested had the same shape of the calibration curve, these curves could vary by a constant multiplicative factor. In most trials (176/200 = 88%), including all of the post-operative data, the two keys to be played were marked (first with stickers and subsequently with rubber half O-rings; see Data Capture section). The first 24 trials were carried out on a different pair of keys.

Data Analysis

The MIDI files were converted to a text representation using a custom tool written in the Java programming language making use of the standard *javax.sound.midi* package (Sun Microsystems, http://java.sun.com). These MIDI text files were then imported into the statistical environment R (http://www.r-project.org), which was used for all subsequent analysis. Custom routines were written in R to calculate, from the MIDI text files, five quantities for each note: Time, Key, Velocity (Vel), Duration (Dur), and Interval (Int; (Fig. 1c). Each MIDI file could be used to produce raw data plots for visual inspection (e.g., Fig. 1b) and to calculate summary sta-

tistics for individual MIDI traces. We noticed that the keyboard occasionally generated additional notes (artifacts) as a key was released, producing a second note of or less than 1 MIDI tick after the termination of the first. These additional notes (169 artifacts/27,376 total notes ~ 0.6%) were therefore removed in R before any further processing.

Statistical Analysis

Individual Traces.

Each MIDI record was statistically summarized by mean key-strike Vel, Dur, and Int calculated using the notes played on both keys. To give an indication of the regularity of playing during an individual test we calculated a measure of their variability for each of these three variables. For Vel we calculated the standard deviation (SDVel). For Dur and Int, the variance increased with increasing magnitude of the respective variables and we therefore normalized for this common effect by calculating their CVs (CVDur and CVInt), corresponding to the standard deviation divided by the mean.

Group Data.

To make comparisons among patients, each QDG evaluation was summarized by pooling upper and lower notes for each hand, calculating Vel, Dur, Int, SDVel, CVDur, and CVInt as described above. We then calculated the mean of the left and right scores for each of these six statistics. Dur and Int were not normally distributed, but showed a substantial rightward skew typical of many physical variables in which variance increases with the magnitude of the observed values. These variables (Dur, Int, CVDur, and CVInt) were therefore $\log_{10}$-transformed to give a symmetrical and approximately normal distribution. All subsequent occurrences of these variables refer to the $\log_{10}$ transform.

Pearson's correlation coefficients were calculated for the individual correlations between QDG variables and the UPDRS III and subscores. Linear models were used to assess: (1) which combination of QDG variables could best predict UPDRS III scores; and (2) which UPDRS subscores were most related to the combination of QDG variables selected in (1) that best predicted UPDRS III. One specific advantage of the use of linear models over multiple separate tests on individual variables is that the model corrects for the correlations among variables. Where appropriate, linear models were simplified to reduce the number of predictive variables. This simplification was carried out in an automated fashion by application of the step AIC function of the MASS library in R, which implements a selection based on Akaike's Information Criterion.[20] This procedure searches for the model with the smallest number of variables that still minimizes the error in predicting UPDRS III. The variables selected by the automatic search were confirmed manually using the traditional *t* test.

Paired *t* tests were run to assess the effects of medication (presurgery) and B-STN DBS (postsurgery) on individual variables. A correction for multiple comparisons was not applied as the QDG variables were not independent.

A linear mixed-effects model[21] was used to compare the effect of medication and DBS on QDG variables and UPDRS III; therapy type (medication or DBS) and therapy status (on or off) were fixed effects and patient identity a random effect. Mixed-effects models are used when repeated measurements are made on the same patient.

RESULTS

RAFT Scores Measured With QDG Are Correlated With UPDRS III Motor Total Scores Off Medication

In assessing the relevance of QDG and specifically the RAFT task for the motor evaluation of patients with PD, we first asked whether these measures of digital motor function reflected the clinical assessment of motor function. Initial comparison of these tests was carried out in the presurgery group off medication, because this represented the patient group with the least intervention. In this group we found that modified UPDRS III scores and QDG scores were indeed strongly related.

In the off-medication condition before surgery, four of six parameters studied were correlated with the modified UPDRS III score (Fig. 2). The strongest correlation was for CVDur ($r = 0.66$; $P < 0.001$) followed by Vel ($r = -0.61$; $P < 0.001$), which was negatively correlated because higher velocities and lower UPDRS scores indicate better motor function. There was only one patient who had more than four notes, whose velocity was coded as 127 (the upper limit of the velocity scale). This patient's modified UPDRS III score was 26, off medication, which was the third lowest of the group. At the lower limit of the scale, the patient with the largest number of notes whose velocity was coded as 1, had a modified UPDRS III score of 63 off medication, which was the second highest of the group. CVInt, which is high when patients have an irregular rhythm, and Int also correlated with UPDRS III ($r = 0.56$, $P < 0.001$ and $r = 0.50$, $P < 0.01$, respectively).

Because we intended to study the utility of these individual QDG variables as clinical indicators in this

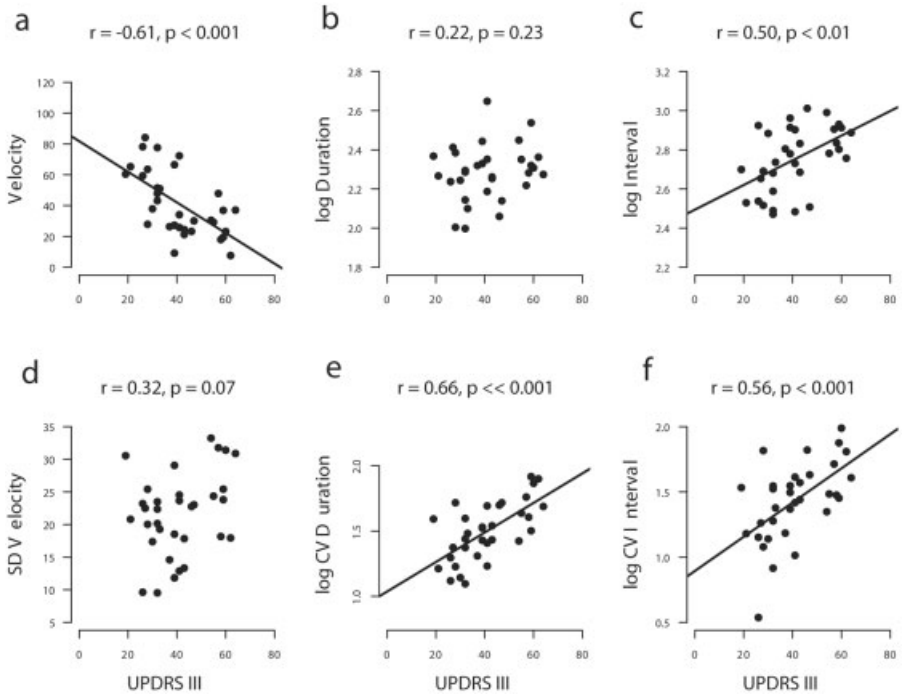

FIG. 2. QDG scores correlate with the modified UPDRS III scores. In the off-medication condition before surgery (n = 33), CVDur, Vel, Int, and CVInt were correlated with the UPDRS III.

study, we checked to see if they were related to each other. Table 1 shows that there were significant correlations among QDG variables. For instance, Vel was related to Int, CVDur, and CVInt. Dur was only related to Int. Where there was a significant relationship, one variable only explained about 18 to 35% of the variance in the other variable. However, CVDur and CVInt were very strongly related (explaining 81% of the variation of each other). In other words, the regularity of note spacing and note length were very dependent.

We asked whether a combination of QDG scores might be better than any individual parameter to predict the modified UPDRS III. We constructed a linear regression model in which all six QDG variables were used to predict the modified UPDRS III. The model searched for the best combination of parameters and discarded those that were not useful. We found that a model using a combination of three QDG variables, Vel, Int and CVDur, best predicted modified UPDRS III scores (adjusted $r = 0.704$; $P << 0.001$). This combination was significantly better at predicting the modified UPDRS III than was any single parameter ($F = 3.79$; $P = 0.034$). At least one other combination was almost as good: Dur could substitute for Int in our model with little effect on predictive power, indicating that Dur and Int are approximately equally useful predictors of UPDRS III when combined with Vel and CVDur.

One additional benefit of the construction of this linear model is that the resultant number, which we shall define as the QDG composite score, can be used to summarize

TABLE 1. *QDG variables are correlated*

	Vel		Dur		Int		SDVel		CVDur		CVInt	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Vel	—	—	−0.15	0.40	**−0.51**	0.00	−0.10	0.50	**−0.56**	0.00	**−0.56**	0.00
Dur	−0.15	0.40	—	—	**0.57**	0.00	0.10	0.57	−0.02	0.91	−0.13	0.48
Int	**−0.51**	0.00	**0.57**	0.00	—	—	0.25	0.17	**0.35**	0.05	0.27	0.12
SDVel	−0.10	0.58	0.10	0.57	0.25	0.17	—	—	**0.53**	0.00	**0.54**	0.00
CVDur	**−0.56**	0.00	−0.02	0.91	**0.35**	0.05	**0.53**	0.00	—	—	**0.87**	0.00
CVInt	**−0.56**	0.00	−0.13	0.48	0.27	0.12	**0.54**	0.00	**0.87**	0.00	—	—

Total N = 33.
QDG, quantitative digitography; Vel, key-strike velocity; Dur, duration of key strike; SD, standard deviation; CV, coefficient of variation.

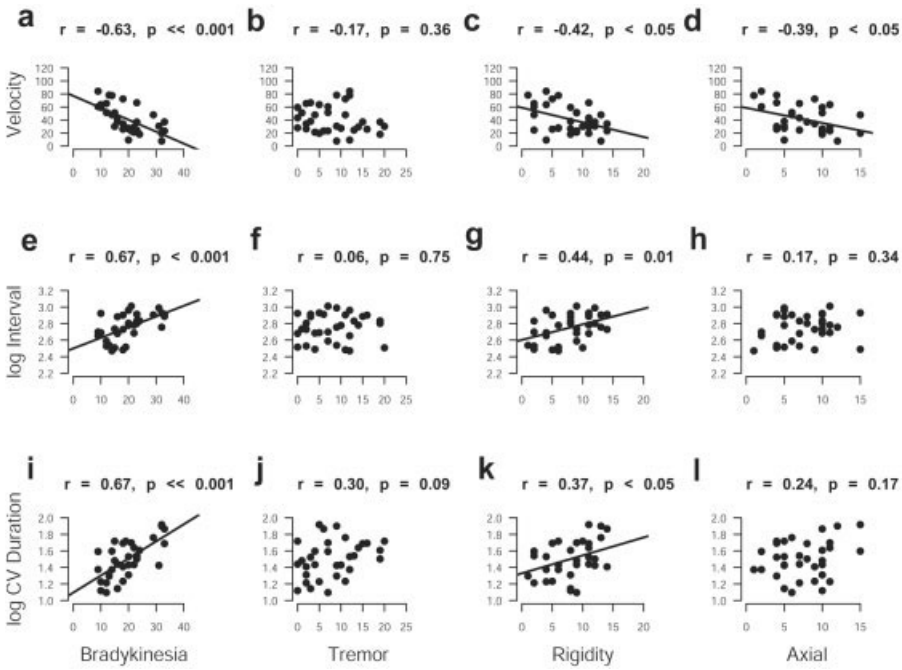

FIG. 3. QDG scores correlate with bradykinesia subscores. In the off-medication condition before surgery (n = 33), the mean velocity (Vel; **a–d**), log CV Int (**e–h**), and log CVDur (**i–l**) were compared to four sections of the modified UPDRS III: bradykinesia, tremor, rigidity and axial subscores. Vel, Int and CVDur were all correlated most strongly with the bradykinesia subscore (a, e, and i).

any particular QDG evaluation. Although this can hide some of the distinctive features of each individual QDG variable, this can be statistically convenient and may provide a more sensitive and reliable global score than does the UPDRS III subscore.

QDG Scores for RAFT Are Correlated With Bradykinesia Subscores

The UPDRS III rates 14 distinct aspects of motor function; these ratings can be combined into the subscores bradykinesia, tremor, rigidity, and axial. Are QDG parameters more closely correlated with certain subscores of the UPDRS III? We chose to look at the three variables that best predicted the modified UPDRS III score. In Figure 3, we show plots for the individual correlations between Vel, Int, and CVDur and the four UPDRS III subscores in the off-medication condition before surgery. The three variables were correlated most strongly with bradykinesia scores (CVDur, $r = 0.67$; Int, $r = 0.67$; Vel, $r = -0.63$; $P < 0.001$). Vel and Int also showed a moderate correlation with rigidity ($r = -0.42$, $P < 0.05$ and $r = 0.44$, $P < 0.01$, respectively). None of the variables was related to tremor.

Effect of Therapy (Medication and DBS) on Clinical Assessment of Motor Disability

Figure 4 shows that medication (Fig. 4a) and STN DBS (Fig. 4e) both improved total motor disability as assessed by the UPDRS III. The mean preoperative UPDRS III score improved with medication from 40.9 to 22.5 (a change of 45.0%) for the total group of patients; the improvement was from 40.5 to 21.0 (48.0%) for the subgroup of patients that were also tested postoperatively. In this subgroup, the mean postoperative improvement from STN DBS, comparing the *off*/OFF to the *off*/ON state, was from 33.9 to 9.4 (72.3%). Both medication and DBS improved the clinical assessment of tremor, rigidity, and bradykinesia (Fig. 4b–d 4f–h, respectively).

Effect of Therapy (Medication and DBS) on QDG Measures of Fine Motor Control

Figure 5 and 6 demonstrate the effect of medication and DBS on each of the six QDG variables for the presurgery group and the postsurgery subset. Figure 5 demonstrates that medication improved three of six QDG variables. Vel was highly significantly improved with medication ($P << 0.001$); no patient had a worse velocity on medication than off. Int, an inverse measure of the frequency of tapping, and CVDur also improved ($P < 0.001$ and $P < 0.05$ respectively). For this group of patients, SDVel, Dur, and CVInt were not significantly changed with medication. Figure 4 and 5 thus show that both the clinical (UPDRS) and quantitative (QDG) measurements of overall and fine motor control, respectively, are sensitive to improve-

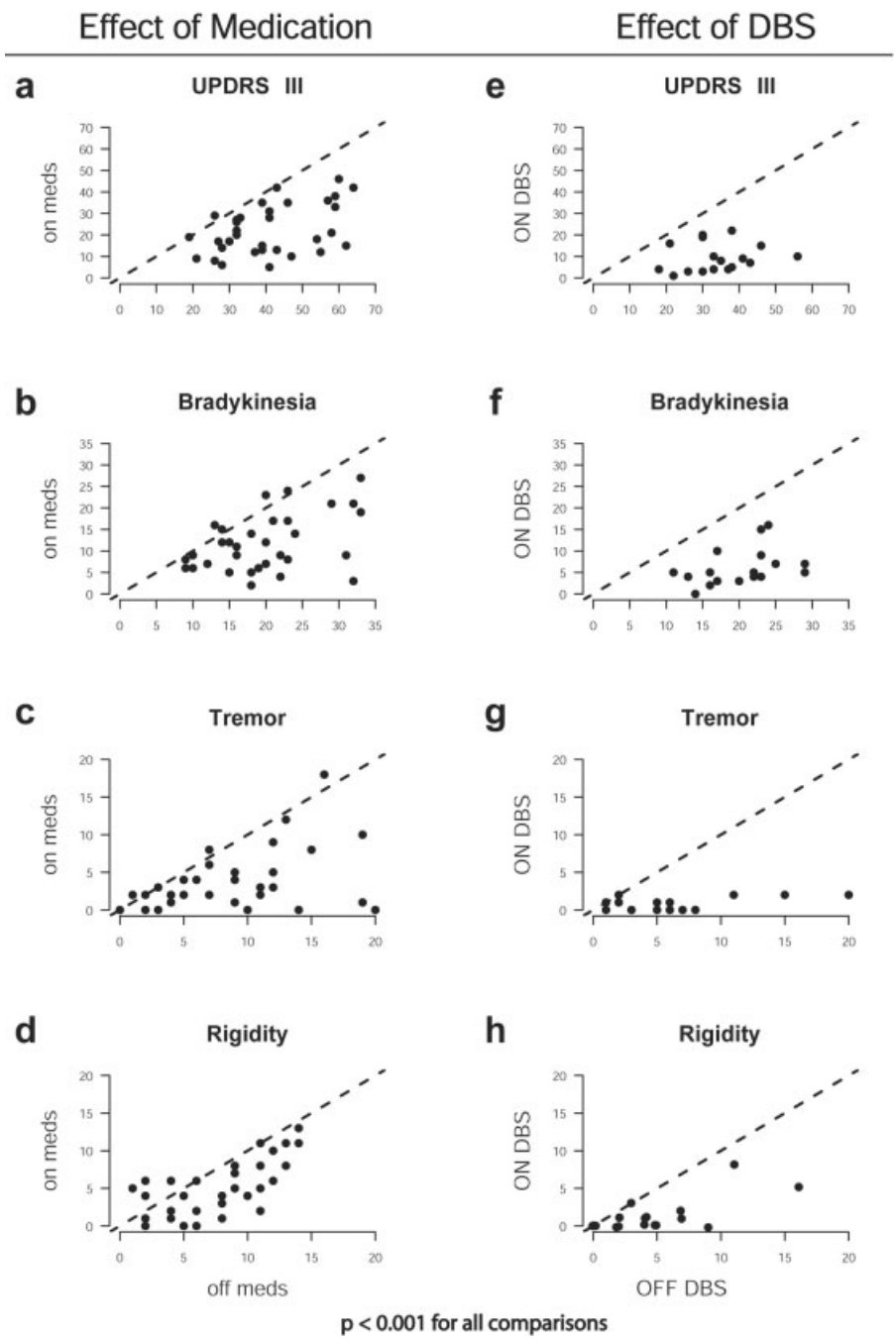

FIG. 4. Effect of medication and STN DBS on the modified UPDRS III score (**a, e**) and subscores of bradykinesia (**b, f**), tremor (**c, g**), and rigidity (**d, h**). The dashed line corresponds to y = x and improvement from either therapy is reflected by points lying below the line.

-ment with medication; however, there seemed to be specific kinematic parameters of fine motor control in PD that were dopamine responsive and others that were not.

Effects of DBS

Figure 4e–h demonstrated that DBS alone improved the UPDRS III and all its subscores in our postoperative subgroup. Figure 6 shows that fine motor control, as measured by QDG, was also significantly improved by DBS. In a similar fashion to the effect of medication, the improvement from STN DBS in Vel and Int was highly significant ($P << 0.001$); only 1 patient had a worse Vel or Int ON DBS than OFF. DBS also showed significant improvement in Dur and CVInt, which was not seen with medication (Fig. 5b,f), and a more robust improvement in CVDur. We verified that the subgroup (n = 17) of patients who were

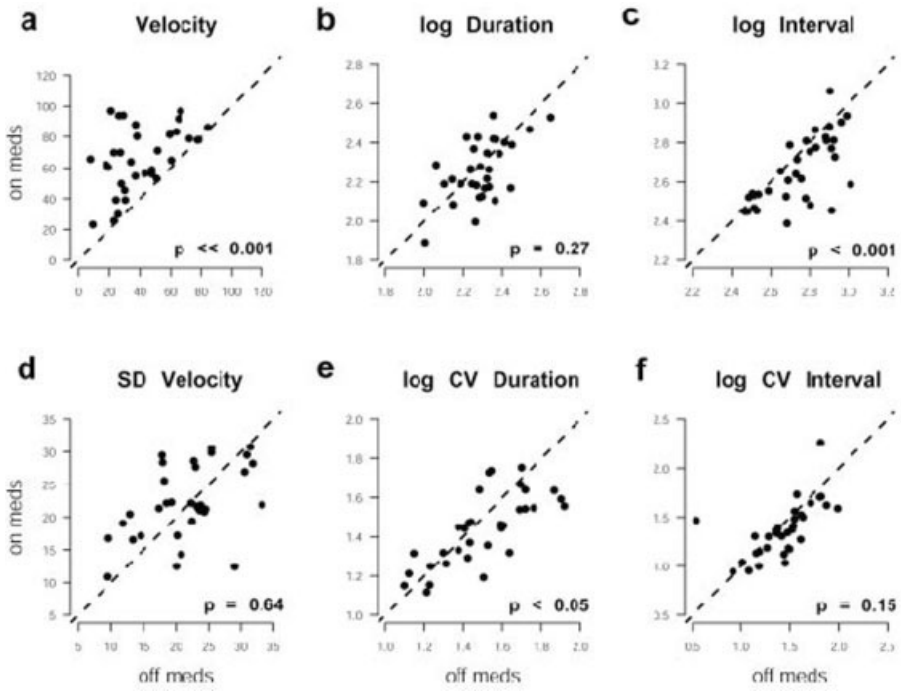

FIG. 5. Effect of medication on QDG scores. The six QDG variables in the RAFT task are compared before surgery (n = 33) by plotting off-medication scores on the x-axis and on scores on the y-axis. The dashed line corresponds to y = x, so improvement with medication results in points lying above the line for velocity and points below the line for the other five variables.

studied pre- and postsurgery showed a similar presurgery effect of medication as the larger (n = 33) group (data not shown) supported the observation that medication and STN-DBS may exert different effects on different aspects of fine motor control as measured by QDG.

Comparing Effects of Medication With Effects of B-STN DBS

A more direct comparison was required to ascertain whether medication and STN-DBS were truly having

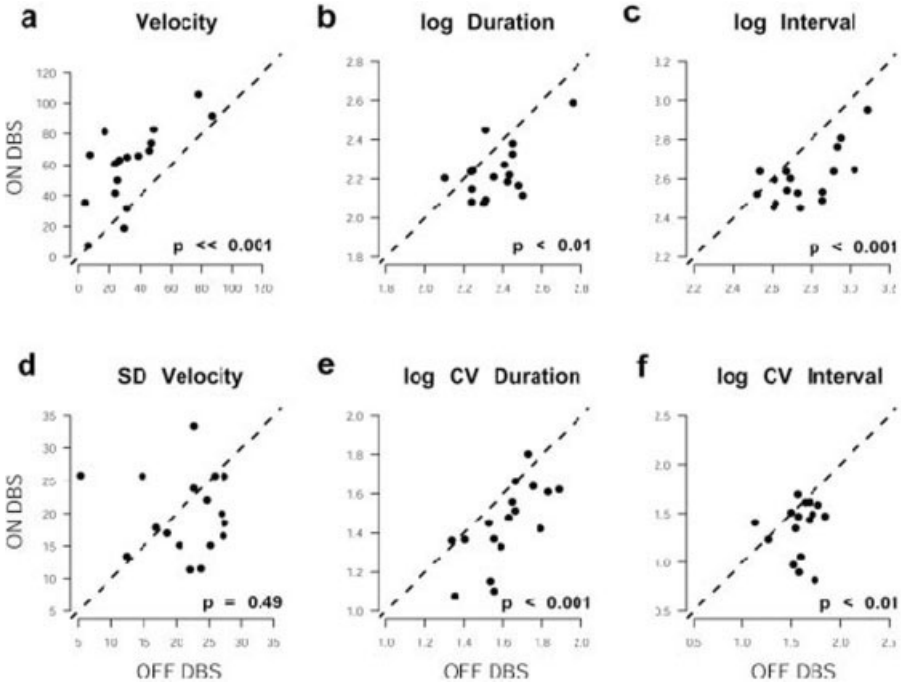

FIG. 6. Effect of DBS on QDG scores. The same six variables are compared after surgery (n = 17, subset of the before surgery group) by plotting *off*/OFF scores on the x-axis and *off*/ON scores on the y-axis. The dashed line corresponds to y = x, so improvement with DBS results in points lying above the line for velocity and points below the line for the other five variables.

different effects on these six QDG variables. Therefore, we tested whether there was a significant difference between therapies (i.e., off versus on medication, before surgery compared with OFF versus ON STN DBS, and after surgery) using our predicted QDG composite score (based on the three QDG variables Vel, Int, and CVDur). We found that there was a difference between treatments ($P < 0.05$). Having found a significant difference, we then investigated its origin by testing whether there was a significant difference between therapies for each of the six QDG variables, using the mixed-effects model. For Vel and SDVel, there was no difference between treatments (Vel, $P = 0.87$ and SDVel, $P = 0.42$). There was a significant difference for Dur and CVDur ($P < 0.05$ for both). There was no significant effect for Int ($P = 0.08$) but there was for CVInt ($P < 0.05$). This confirmed the differences between the effects of medication and DBS that were seen in Figures 5 and 6: Vel and Int were improved by both, SDVel did not improve with either, and DBS seemed to be more efficacious for Dur, CVDur, and CVInt. We carried out the same analysis for UPDRS III scores and found that there was not a significant difference between treatments (medication or DBS) on actual motor total scores ($P = 0.08$). Therefore, we were able to demonstrate with QDG a significant difference in the effect of two different therapies that was not detectable using the UPDRS.

DISCUSSION

This study has shown that the quantitative measurement of RAFT on a MIDI keyboard is a valid measure of motor disability in PD. We have termed this technology quantitative digitography (QDG).

In the baseline (untreated state), several individual QDG measures (Vel, Int, CVDur, and CVInt) correlated with motor disability (UPDRS III). CVDur was the individual variable that showed the strongest correlation. A combination of Vel, Int, and CVDur, however, predicted total motor disability more accurately than did any individual parameter. The duration of key-strike (Dur) could be substituted for Int in the combination with equal power, even though it was not itself significantly correlated with the UPDRS III subscore. This was not altogether surprising, as it is known that individual measures may have enough interdependence that their correlation with another variable (here the modified UPDRS III) may not be significant when compared separately but when combined, their mutual dependence is eliminated and the underlying correlation with the modified UPDRS III is exposed.

It seemed that total motor disability of PD was best predicted from quantitative measurements of fine motor control if these measurements included measures of the temporal variation of ongoing movement as well as the means of specific kinematic parameters. These findings are not altogether surprising as the UPDRS uses subjective assessments of temporal variation in amplitude and frequency in the assessment of repetitive movements. What was surprising was the importance of CVDur, which was the best single predictor of UPDRS III. This may be task specific, as the RAFT task comprises repetitive switching from one finger to another when tapping, also known as a trill. Highly skilled musicians will minimize Dur and CVDur in this task; one finger must be released as the other is being pressed down, with the goal of playing the alternating notes as regularly as possible. We have shown that CVDur, a measure of regularity, is increased significantly in patients with PD when compared to that in age-matched controls.[10] In this task, patients with PD seem to have difficulty switching from one motor act to the other and in controlling the regularity of this switching over time. This supports other studies, which have shown that PD patients have particular difficulty carrying out sequential motor acts.[22,23]

Many other studies have used repetitive finger tapping to measure abnormalities of timing and kinematics of fine motor control in PD.[11,24–35] These studies used either single digit tapping, alternating index-middle finger tapping, finger to thumb opposition and self-paced or externally paced timing. Measurements were made using electrical switches, metal loops, optoelectronic cameras, magnetic sensors, and computerized keyboards. Our finding that RAFT as measured by QDG can be a good indicator of overall disease severity confirms one previous study, which showed that an objective measurement of RAFT with contralateral hand activation was more sensitive than single digit tapping in both the assessment of disease severity in PD and fluorodopa uptake abnormalities on positron emission tomography (PET).[36]

The RAFT Task of QDG Is Correlated With Bradykinesia Subscores of the UPDRS

The UPDRS III measures different aspects of motor function, which can be broadly categorized into tremor, rigidity, bradykinesia, and axial motor control. The QDG variables Vel, Int, and CVDur, which best predicted UPDRS III scores, were all strongly correlated with the bradykinesia subscore of UPDRS III. No variable was correlated with tremor or axial scores of the UPDRS. The RAFT task of QDG thus seems to be most sensitive for the assessment of bradykinesia. Repetitive finger tapping has been shown to be the most challenging of the repetitive movement tasks that assess bradykinesia in the

UPDRS for patients with PD and its clinical assessment was a good indicator of overall motor disability.[30]

Effect of Medication and B-STN DBS on UPDRS and RAFT

This study has shown that both medication and B-STN DBS improve the clinical assessment of motor disability using the UPDRS and a quantitative measure of fine motor control using QDG.

Dopaminergic medication improved certain aspects of fine motor control as measured by QDG, such as key-strike velocity and the frequency of tapping. The improvement in the temporal variation of strike duration was significant but not as robust as that for velocity or frequency. In contrast, the duration of strike and the temporal variability of velocity and frequency were not improved with medication. Postoperatively, DBS alone improved all kinematic parameters of RAFT except for SDVel.

Comparison of the QDG data from Figures 5 and 6 suggested that DBS was more efficacious than medication in improving mean duration of strike, and the temporal variation in frequency and duration. This was confirmed by a comparison using the mixed-effects model. This dissociation of the effect of each therapy on fine motor control was not detected by the UPDRS. As the effect of each therapy was assessed at a different time point, preoperatively for medication and postoperatively for DBS, other variables might have contributed to this difference such as disease progression, surgical intervention, optimization variability of medication and DBS, and the effect of DBS on individual hands. The results here are averaged for both hands.

It is interesting that the dissociation of effect of DBS versus medication was mainly in their effect on temporal variation of the kinematics of RAFT. DBS made the alternating tapping rhythm more regular. It has been shown in animals and in humans that the electrical activity of neurons of the basal ganglia motor circuitry changes from a regular to irregular firing pattern in the Parkinsonian state.[38–47] Intraoperative administration of dopaminergic medication can make neuronal firing patterns even more irregular whereas DBS may restore a more regular firing pattern within basal ganglia circuits.[48–52] Whether the temporal behavior of neurons within extrapyramidal brain circuitry directly affects the temporal variation in motor behavior is unknown, but it is interesting that the dissociation between the effects of dopaminergic medication and DBS on firing patterns is paralleled by the dissociation of the effect of medication and DBS on the rhythm of fine motor control of repetitive movements. We have reported a similar dissociation between the effect of medication and surgery on sensory aspects of postural instability.[52]

Few studies have used quantitative measures of finger tapping to study the effect of DBS on fine motor control. Unilateral pallidotomy was shown not to improve finger tapping and pegboard tasks in one study[13] off medication but was shown to improve repetitive finger tapping in another that was performed on medication.[14] Both studies were carried out 2 to 3 months after surgery. Bilateral STN DBS has been shown to improve the movement speed of elbow flexion and extension.[53] Using quantitative electromyogram (EMG) analysis, the authors found that this was achieved in part with an increase in the amplitude of the first burst of muscle activity in the agonist muscle and with a reduction in co-contraction of the agonist–antagonist muscle pairs in the acceleration phase. This also suggested that rigidity was contributing to bradykinesia in arm movements. Whether these physical aspects of motor control are linked in central nervous system circuitry remains to be determined.

Future Directions

Specific Kinematics of RAFT Using QDG.

QDG is a useful measure of overall motor disability and it can separately measure specific kinematics such as key-strike velocity, duration of strike, frequency of tapping, fatigue, rhythm, and switching times. In the UPDRS finger-tapping score, velocity, amplitude of tapping, frequency, and their temporal variations are included into one integer value. QDG thus offers both high sensitivity and specificity for measuring motor impairment in PD.

Clinical assessment of patients with PD suggests that fatigue, freezing, and irregularities of performance of repetitive movements become worse as the disease progresses. With quantitative tools such as QDG, these could be measured independently over large populations for markers of early (or preclinical) disease or as markers of disease progression. It remains to be seen, by looking at larger groups of patients in detail, whether each patient may have a certain signature of kinematic abnormalities.[10]

Effect of Different Therapies on Specific Kinematics of Fine Motor Control.

This study did not separate out the effect of different types of medication or the effect on the more- versus less-affected hand. It will be interesting to measure quantitatively the effect of different therapeutics on fine motor control by individually studying the more- or less-affected hand or specific kinematic parameters and their

temporal patterns. Quantitative assessments of motor control may yield differences in the effects among therapeutics on specific kinematics and may result in more effective "cocktails" of therapy designed for individuals, as have been used in other diseases.

Acknowledgments: We thank K. McGuire, G. Fujikami, and T. Courtney for patient testing and data input. The study was supported by the Kinetics Foundation and the Vincent Coates Foundation (to H.B.S.) and by a Stanford University Dean's Postdoctoral Fellowship (to A.L.T.T.).

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