Research Report – Research Article

Tablet-Based Application for Objective Measurement of Motor Fluctuations in Parkinson Disease

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Abstract

Background: The motor subscale of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) has limited applicability for the assessment of motor fluctuations in the home setting. ***Methods:*** To assess whether a self-administered, tablet-based application can reliably quantify differences in motor performance using two-target finger tapping and forearm pronation-supination tasks in the ON (maximal dopaminergic medication efficacy) and OFF (reemergence of parkinsonian deficits) medication states, we recruited 11 Parkinson disease (PD) patients (age, 60.6 ± 9.0 years; disease duration, 12.8 ± 4.1 years) and 11 healthy age-matched controls (age, 62.5 ± 10.5 years). The total number of taps, tap interval, tap duration, and tap accuracy were algorithmically calculated by the application, using the more affected side in patients and the dominant hand in healthy controls. ***Results:*** Compared to the OFF state, PD patients showed a higher number of taps (84.2 ± 20.3 vs. 54.9 ± 26.9 taps; p = 0.0036) and a shorter tap interval (375.3 ± 97.2 vs. 708.2 ± 412.8 ms; p = 0.0146) but poorer tap accuracy (2,008.4 ± 995.7 vs. 1,111.8 ± 901.3 pixels; p = 0.0055) for the two-target task in the ON state, unaffected by the magnitude of coexistent dyskinesia. Over-

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all, test-retest reliability was high (r >0.75) and the discriminatory ability between OFF and ON states was good (0.60 ≤ AUC ≤ 0.82). The correlations between tapping data and MDS-UPDRS-III scores were only moderate (−0.55 to 0.55). **Conclusions:** A self-administered, tablet-based application can reliably distinguish between OFF and ON states in fluctuating PD patients and may be sensitive to additional motor phenomena, such as accuracy, not captured by the MDS-UPDRS-III.

Introduction

A growing body of evidence suggests that biometric monitoring using technology-based objective measures will become a valuable supplement to routine neurological evaluations [1–6]. Technology-based objective measures can reduce rater bias and interrater variability and increase sensitivity, elucidating important subclinical changes [4, 7, 8]. As of November 2015, there were at least 73 different devices (22 wearable, 38 nonwearable, and 13 hybrid) developed to assess Parkinson disease (PD) [9], and, as of October 2016, at least 47 assessed limb bradykinesia specifically [10]. Among the wearable devices, only Kinesia [11], a hybrid device, and 6 other wearable devices have been used to assess PD by groups other than the developers [12–17]. Besides a lack of validation, additional reasons that may contribute to the limited use of these technologies include skepticism about the usefulness of data, a perception of a high burden required for adoption, unsustained adherence, a discrepancy between research and clinical utility, the unclear value for informing management decisions, and a lack of compatibility between systems, which affect data integration and analytics [4, 18].

Finger tapping data have been successfully used to evaluate motor function in PD [19–21]. Individuals with PD often have motor fluctuations in response to commonly used medications for the condition. These fluctuations, termed "ON" and "OFF" states, are closely monitored in clinical care and PD clinical trials. We sought to assess whether a tablet-based application (iMotor; Apptomics Inc., Wellesley Hills, MA, USA) can reliably detect and quantify differences in motor performance in PD-associated OFF (reemergence of parkinsonian deficits) and ON (maximal dopaminergic medication efficacy) medication states using a standard finger tapping test.

Methods

Study Population and Design

We prospectively enrolled consecutive PD patients undergoing assessment eligibility for deep-brain stimulation from December 2015 to March 2016. Inclusion criteria were the diagnosis of idiopathic PD according to UK Brain Bank criteria [22]; Hoehn and Yahr stage I–III in the ON state [23]; and an age of 18–75 years. Excluded were any patients with history or clinical features suggestive of an atypical parkinsonian syndrome and any comorbid central nervous system disorder which could contribute to motor impairment. Healthy spouses and caregivers of PD patients were enrolled and matched for age as healthy controls. The University of Cincinnati institutional review board approved the study, and all participants gave written informed consent.

OFF/ON Assessment

The participants provided demographic information and their medical history in a structured interview on the day of their OFF/ON assessment for deep-brain stimulation eligibility.

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Fig. 1. Screenshots of iMotor-based tapping tests. **a** Two-target test: the participants alternatingly tapped with the index finger, as fast and as accurately as possible, the centers of two concentric circles on the tablet screen. **b** Pronation-supination test: the participants alternatingly tapped the palmar and dorsal surfaces of their hand as fast as possible on the tablet screen. **c** Sample patient score report, available immediately to the patient.

Motor subscale scores on the Movement Disorder Society version of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) and iMotor tapping data were collected during both medication states. Clinical assessment, scale administration, and iMotor testing were performed in the practically defined OFF state, i.e., after withholding all dopaminergic medications for ≥12 h, and again in the ON state, i.e., after the usual dopaminergic regimen had become clinically most effective. The maximum dopaminergic medication effectiveness was determined by the combined judgment of the patient and a movement disorder specialist through a semi-structured interview and documented by a reduction in the MDS-UPDRS-III score within 60 min after medication administration.

Tablet App Testing

Site personnel trained the participants to follow the screens of the iMotor tablet app (Fig. 1) to perform the following tests during their OFF and ON states:

1. Two-target finger tapping test: the participants were prompted to alternatingly tap the centers of two concentric circles with the index finger, as fast and accurately as possible; double and mis-taps due to tremor, dyskinesia, or touch screen errors were not recorded by the application in order to minimize errors in tapping data collection
2. Pronation-supination test: the participants were prompted to alternatingly tap the palmar and dorsal surfaces of their hand on the tablet screen as fast as possible

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The total number of taps, tap interval (time [ms] between two consecutive finger/hand screen taps), tap duration (time [ms] the index finger/hand touches the screen per tap), and tap accuracy (tap distance [pixels] from the center of the target) were recorded.

The duration of each test was 30 s. User fatigue was assessed retrospectively using the patient score report (Fig. 1c). The total duration of the patient interface with the application was, on average, 5 min. The patients performed each test twice with their more affected hand (as assessed by the investigator), the controls with their dominant hand. All tests were performed with the tablet resting flat on a table in front of the patient. The tablet was in portrait orientation during the two-target test and in landscape orientation during the pronation-supination test.

Blinded Video Analysis

Videos of the patients at rest and while performing the MDS-UPDRS-III finger tapping and pronation-supination tasks, taken in the OFF and ON states, were randomized for later blinded rating. Senior Movement Disorder Fellows (F.R.-P., J.V., and L.L.) blindly rated the dyskinesia severity during each activity (0 = absent; 1 = mild/no interference with activity; 2 = severe/interferes with activity). The dyskinesia distribution was categorized into: (1) any; (2) axial; (3) appendicular in the active limb; and (4) appendicular in the nonactive limb. The dyskinesia severity ratings were then compared with the tapping accuracy scores.

Statistical Analysis

It was estimated that a sample size of 11 was needed to detect between-group differences in motor performance with 80% power and a 1% level of significance, adjusted due to multiple tests, assuming at least a 20% mean difference in each test with a 15% standard deviation (SD), estimated based on a previous study using tapping tests that compared PD patients with controls [21], using a paired t test. Data are reported as means ± SD, where applicable. Categorical variables were compared using Fisher's exact test, while quantitative variables were compared using the t test between controls and PD cases. Test-retest reliability and MDS-UPDRS-III score correlations were measured using a concordance correlation coefficient (r). Tapping data were averaged across multiple readings and compared between the OFF and the ON state. Between the OFF and the ON state, all data were compared using paired t tests. Ordinal survey satisfaction data were compared using the Wilcoxon rank-sum test between controls and PD cases. The presence of dyskinesia was compared between the OFF and the ON state using McNemar's test in each condition. Tapping accuracy was compared according to dyskinesia status and for different types using the Wilcoxon rank-sum test. Paired t test results were summarized using mean changes along with 95% confidence intervals and p values. Further, logistic regression models were performed to evaluate the individual discriminatory performance of each test in differentiating between PD-ON and PD-OFF after adjusting for clustering effects. The results were summarized using AUC (area under the receiver operating characteristic curve) and CC (correct classification) accuracy. p values <0.05 were considered significant results. All statistical analyses were carried out using SAS 9.3 and STATA 13.

Results

Patients

The cohort included 11 PD patients (73% men; 60.6 ± 9.0 years old) and 11 controls (46% men; 62.5 ± 10.5 years old) (Table 1). The patients' mean MDS-UPDRS-III score was 48.6 ± 8.2 in the OFF state and 23.0 ± 6.1 in the ON state (p < 0.0001).

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Table 1. Demographics

	Controls ($n = 11$)	PD patients ($n = 11$)	p value
Age, years	62±11	61±9	0.65
Male	5 (46)	8 (73)	0.19
Education, years	16±3	17±2	0.6
White	10 (91)	10 (91)	1
Disease duration, years	–	13±4	–
MDS-UPDRS-III OFF score	–	49±8	–
MDS-UPDRS-III ON score	–	23±6	–
Dyskinesia (OFF state)	–	0	–
Dyskinesia (ON state)	–	10 (91)	–
Dyskinesia interfered with UPDRS ratings (ON state)	–	2 (18)	–
LEDD, mg	–	2,199±992; 1,200–3,920	–

Data are reported as n (%) or mean ± SD; range. PD, Parkinson disease; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose.

Tablet App Results

Two-Target Finger Tapping Test

Compared to the OFF state, there were more total taps (84.2 ± 20.3 vs. 54.9 ± 26.9 taps; $p = 0.0036$) and shorter tap intervals in the ON state (375.3 ± 97.2 vs. 708.2 ± 412.8 ms), but with a lower tapping accuracy (2,008.4 ± 995.7 vs. 1,111.8 ± 901.3 pixels; $p = 0.0055$) (Table 2). The controls tended to tap more accurately and had more total taps than the PD patients in the ON state ($p = 0.1828$ and $p = 0.1517$, respectively).

Pronation-Supination Test

Compared to the OFF state, there were more total taps (78.1 ± 20.2 vs. 54.9 ± 20.8 taps; $p = 0.0027$) and shorter tap intervals in the ON state (408.6 ± 112.2 vs. 649.9 ± 386.5 ms; $p = 0.0315$). Accuracy was not measured during the pronation-supination test.

Tablet App Performance

With the exception of tap duration, the other iMotor-measured tasks distinguished PD-OFF from PD-ON (AUC = 0.75–0.82; CC = 64–77%) (Table 2). Test-retest reliability was high in both the ON state ($r = 0.85 ± 0.07$; r range, 0.75–0.95) and the OFF state ($r = 0.71 ± 0.31$; r range, 0.06–0.96). Two-target and pronation-supination tapping test data correlated only moderately with MDS-UPDRS-III scores (–0.55 to 0.51).

Dyskinesia and Accuracy

Dyskinesia severity did not affect tapping accuracy (Table 3). Tapping accuracy tended to be lower in patients who were dyskinetic at rest ($p = 0.1709$), but this trend did not persist during the two-target tapping and pronation-supination tasks.

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Table 2. iMotor testing and reliability

	Controls	PD-OFF			PD-ON			p value[a]	p value[b]	p value[c]	AUC	CC, %
	mean ± SD	mean ± SD	reliability	UPDRS correlation	mean ± SD	reliability	UPDRS correlation					
Two-target test												
Total taps	101±32	55±27	0.96	−0.55	84±20	0.85	−0.53	0.002	0.15	0.004	0.82	73
Tap interval, ms	324±93	708±413	0.92	0.51	375±97	0.75	0.41	0.01	0.22	0.01	0.80	77
Tap duration, ms	113±120	74±65	0.88	0.35	108±158	0.95	−0.40	0.36	0.94	0.55	0.60	46
Tap accuracy, pixels	1,515±646	1,112±901	0.77	−0.51	2,008±996	0.90	−0.46	0.24	0.18	0.006	0.78	73
Pronation-supination test												
Total taps	84±21	55±21	0.60	−0.31	78±20	0.83	−0.55	0.006	0.54	0.003	0.77	68
Tap interval, ms	377±92	650±387	0.81	0.27	409±112	0.76	0.42	0.04	0.50	0.03	0.75	64
Tap duration, ms	4±2	3±1	0.06	0.10	3±2	0.88	0.20	0.26	0.89	0.46	0.45	50

Data are reported as the mean ± SD unless specified otherwise. Data were collected for most affected side and dominant hand for p and controls, respectively. PD-OFF/ON, Parkinson disease patients in the OFF state (reemergence of parkinsonian deficits)/ON state (maximal dopaminergic medication efficacy); UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; AUC, area under the curve for PD-OFF vs. PD-ON; CC, correct classification. [a] Unpaired/Satterthwaite t test between controls and PD-OFF. [b] Unpaired/Satterthwaite t test between controls and PD-ON. [c] Paired t test between PD-OFF and PD-ON.

Table 3. Tapping accuracy categorized by the presence of dyskinesia according to blinded video ratings

Dyskinesia type	No dyskinesia	Dyskinesia	p value	κ
At rest				
any	1,668±884	2,293±713	0.17	0.32
limb	1,701±1,126	2,378±762	0.17	0.63
axial	1,824±1,187	2,230±778	0.41	0.88
Finger tapping				
any	2,691±1,664	1,857±867	0.41	0.31
axial	2,663±1,178	1,763±876	0.18	0.27
active limb	2,043±1,089	1,915±890	1	0.27
nonactive limb	2,642±1,130	1,646±770	0.16	0.26
Pronation-supination				
any	2,453±1,498	1,842±812	0.61	0.39
axial	2,218±1,310	1,888±865	0.78	0.74
active limb	2,072±1,073	1,723±712	0.91	0.24
nonactive limb	2,243±1,241	1,727±612	0.65	0.02

Data reported are pixels away from the center of the target (less is more accurate). Patients were categorized as having dyskinesia vs. no dyskinesia by blinded video analysis. Dyskinesias were further defined as: any; axial; active limb (extremity associated with the task); and nonactive limb (extremities not associated with the task). κ values represent slight (0.01–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect agreement (0.81–0.99) [28].

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Discussion

The tablet-based application captured an increase in the total number of taps and a corresponding reduction in the tap interval in the ON state compared to the OFF state, reliably distinguishing these two states. Notably, motor accuracy, a feature not readily measurable with clinical scales, lowered with an increased tapping frequency in the ON state. This reduction in motor accuracy was not affected by (or due to) any coexistent dyskinesia. Finally, the results were consistent between the two tapping tests, and repeatable within each test for both medication states.

An increased tapping speed may require sacrificing accuracy, or speed and accuracy may be modulated by separate mechanisms. The lower tapping accuracy in the ON (hyperdopaminergic) state may be due to the hypothesis of Vaillancourt et al. [24]: a dopamine overdose effect in the ventral and anterior striatum could negatively affect the cognitive challenge of tapping both quickly *and* accurately. In fact, multiple cognitive domains may be adversely affected by dopamine flooding [25]. The blinded video analysis suggested dyskinesia did not affect accuracy, regardless of the presence of dyskinesia in the upper or lower extremity. Voluntary movement during the tapping tests may have overridden dyskinetic movement. Tremor could have influenced tapping accuracy, but it is unlikely to fully account for the observed reduction, since PD patients in the OFF state tended to be more accurate than controls.

It is important to note that tapping tasks are widely used by clinicians as methods of assessing bradykinesia, a core element of PD. However, total taps and tap accuracy are not properly captured by the MDS-UPDRS-III, which focuses on rhythm, interruptions, slowing, and decrements in amplitude. These differences may have contributed to what represents only a moderate correlation with MDS-UPDRS-III scores. As subjective scales are limited in accuracy and reliability [1], a moderate correlation suggests a tablet-based application may be capable of detecting differences in motor function beyond those probed by the MDS-UPDRS-III. In fact, the test-retest reliability for both medication states was higher than that reported for the MDS-UPDRS-III (0.60–0.71) [26]. Thus, a "perfect" correlation of any technology-based objective measure with MDS-UPDRS-III scores may not be achievable or even desirable if objective measures capture motor data more accurately and reliably.

PD-specific motor scales also have limitations in logistic deployment, reliability, and spatial resolution [1, 2, 27]. These shortcomings may lower the signal-to-noise ratio in the measurement of relevant endpoints in clinical trials, lowering the ability of finding statistically significant differences between interventions of interest. On the other hand, technology-based objective measures can detect functional abnormalities without reliance on skilled administrators, and the results can be comparable across centers, understood by patients, and readily integrated into medical records. Importantly, technology-based objective measures can be easily deployed in the home setting, capture different time points in the dopaminergic cycle, cover a larger spectrum of motor behaviors, and aid in decision-making and response monitoring. Within this context, assessment of motor fluctuation with technology-based objective measures, both in clinical trials and in daily monitoring, offers potential improvement in PD and other movement disorders.

Some limitations need to be acknowledged with regard to the study design and the tablet-based application. The small sample size does not allow robust generalizations. However, there was sufficient power for the relatively large effects between the OFF and the ON medication state to be significant. Also, dopaminergic states were considered binary rather than continuous, as is common in clinical trials. Recording motor function at multiple levels of dopaminergic stimulation would have been optimal, but it is methodologically more complex and time-consuming. Additionally, upon conducting our analysis, the variation

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observed in some measures was higher than the predicted SD of 15%. However, robust statistical significance was still met for the primary outcome measures, and, therefore, enrollment was stopped. Further, the tablet-based application relied on tapping tests as a proxy for motor function, largely by virtue of its widespread use as part of the MDS-UPDRS-III. It may not be the task best reflective of global movement, which was not characterized by complementary measures. Finally, there could have been touch screen errors that were not observed by the study personnel monitoring the test and that were not recorded by the application.

Conclusions

A tablet-based application reliably captured differences in motor performance between the OFF and the ON state of PD patients, identifying a tradeoff between velocity and accuracy for tapping. The moderate correlation between iMotor and MDS-UPDRS scores suggests that tablet-based applications may be more sensitive and accurate at measuring performance than clinical scales, and that they could serve as useful adjuncts in clinical trials and home-based assessments.

Statement of Ethics

The authors confirm that all subjects gave written, informed consent. The study protocol was approved by the University of Cincinnati Institutional Review Board (#2014-0626).

Disclosure Statement

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Author Contributions

1. Research project: (A) conception; (B) organization; (C) execution
2. Statistical analysis: (A) design; (B) execution; (C) review and critique
3. Manuscript preparation: (A) writing of the first draft; (B) review and critique
B.D.W.: 1B, 1C, 2C, and 3A
G.M.: 1B, 1C, 2C, and 3B
A.K.D.: 1C, 2A, 2B, 2C, and 3B
S.P., S.L., J.R.L.C., E.S., A.P.D., F.R.-P., J.V., L.L., I.T., and A.S.: 1C and 3B
A.J.E.: 1A, 1B, 1C, 2C, and 3B

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