Journal of Neural Transmission
https://doi.org/10.1007/s00702-023-02659-w

NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

A smartphone-based tapping task as a marker of medication response in Parkinson's disease: a proof of concept study

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Received: 13 April 2023 / Accepted: 24 May 2023

Abstract

Tapping tasks have the potential to distinguish between ON–OFF fluctuations in Parkinson's disease (PD) possibly aiding assessment of medication status in e-diaries and research. This proof of concept study aims to assess the feasibility and accuracy of a smartphone-based tapping task (developed as part of the cloudUPDRS-project) to discriminate between ON–OFF used in the home setting without supervision. 32 PD patients performed the task before their first medication intake, followed by two test sessions after 1 and 3 h. Testing was repeated for 7 days. Index finger tapping between two targets was performed as fast as possible with each hand. Self-reported ON–OFF status was also indicated. Reminders were sent for testing and medication intake. We studied task compliance, objective performance (frequency and inter-tap distance), classification accuracy and repeatability of tapping. Average compliance was 97.0% (±3.3%), but 16 patients (50%) needed remote assistance. Self-reported ON–OFF scores and objective tapping were worse pre versus post medication intake ($p < 0.0005$). Repeated tests showed good to excellent test–retest reliability in ON ($0.707 \leq ICC \leq 0.975$). Although 7 days learning effects were apparent, ON–OFF differences remained. Discriminative accuracy for ON–OFF was particularly good for right-hand tapping ($0.72 \leq AUC \leq 0.80$). Medication dose was associated with ON–OFF tapping changes. Unsupervised tapping tests performed on a smartphone have the potential to classify ON–OFF fluctuations in the home setting, despite some learning and time effects. Replication of these results are needed in a wider sample of patients.

Keywords Dopaminergic medication · Parkinson's disease · Smartphone · Finger tapping · Fluctuation · Feasibility · Repeatability

Introduction

Parkinson's disease (PD) is characterized by disturbances of repetitive movement, reflecting the cardinal symptom of bradykinesia (Bologna et al. 2020). Until now, dopaminergic replacement is considered the gold standard treatment of motor symptoms in PD (Poewe and Antonini 2015). However, disease progression and the prolonged intake of levodopa are associated with several side effects including response fluctuations, peak-dose dyskinesias and wearing-OFF (Pahwa and Lyons 2009; Pandey and Srivanitchapoom 2017; Salat and Tolosa 2013). A wearing-OFF period is defined as the recurrence of PD symptoms before the next scheduled dose (Salat and Tolosa 2013; Stocchi et al. 2014). Daily fluctuations greatly affect patients' quality of life, as was assessed by the 8-item Parkinson's Disease Questionnaire (PDQ-8) (Stocchi et al. 2014) and, especially when OFF-periods manifest unpredictably. They also affect the reliability of research outcomes acquired over long periods of time in the clinic as well as in the home setting. Methodologies for monitoring symptoms, adherence to medication and motor performance in free-living circumstances, are increasingly

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Published online: 02 June 2023

being developed under the impetus of advancing technology (Debelle et al. 2023; Palmerini et al. 2023), thereby avoiding the infamous 'white coat effect'.

Electronic and paper diaries filled in the home situation were reported to provide valid and reliable information about fluctuations and dyskinesias (Hauser et al. 2004; Lyons and Pahwa 2007; Reimer et al. 2004; Stacy and Hauser 2007; Terroba-Chambi et al. 2018). However, home diaries rely on patients' self-perceived response to dopaminergic therapy, usually calibrated against standardized definitions of the OFF and ON state (Antonini et al. 2011). Wearable technology is becoming increasingly available for objective assessment of medication responsiveness and adherence derived from mobility data in the clinic and the home setting (Akram et al. 2022; Debelle et al 2023; Habets et al. 2021; Hasan et al. 2017; Rissanen et al. 2021; Simonet et al. 2021). Yet, feasible procedures for obtaining a valid ON–OFF classification are still lacking (Barrachina-Fernandez et al. 2021). Therefore, tracking patients' medication response using simple and objective motor tests may complement 'subjective' electronic diaries and protocols. On the downside, performance tests may be prone to learning effects, whereas free-living activity tracking with wearables may be subject to other sources of variability than those induced by medication.

In this study, we aimed to investigate the validity of a finger tapping task on a smartphone (Stamate et al. 2018) as a marker of patients' medication status at home. We selected finger tapping because it provides an objective measure of hand bradykinesia (Alberts et al. 2021; Lipsmeier et al. 2021; Omberg et al. 2021; Pal et al. 2001; Surangsrirat et al. 2022), has some diagnostic value (Akram et al. 2022; Goñi et al. 2021, 2020; Lee et al. 2016a, b; Lipsmeier et al. 2018; Noyce et al. 2014; Omberg et al. 2021; Sahandi Far et al. 2021; Simonet et al. 2021; Trager et al. 2020) and can be captured easily and safely in an unsupervised setting. As well, several studies on repetitive and alternating tapping using a keyboard, a tablet, or other forms of motion analysis found differences in ON–OFF states (Akram et al. 2022; Bologna et al. 2018; Hasan et al. 2019; Simonet et al. 2021; Thijssen et al. 2022; Wissel et al. 2017). The tapping test application is part of the cloudUPDRS project (Stamate et al. 2018), a Class I Medical Device registered with the Medicines and Healthcare products Regulatory Agency (MHRA) (Reference Number 5903). In this study we wanted: (1) to examine the feasibility of performing an unsupervised tapping protocol at home focusing on overall compliance, delay after an electronic reminder and subjective experience; (2) to test whether tapping performance was different in ON and Off and explore ON–OFF classification accuracy in comparison to a self-reported ON–OFF scores; (3) to determine test–retest reliability and possible learning effects over 7 days of testing; (4) to correlate ON–OFF tapping changes with medication dosage and measures of disease severity and dyskinesias.

Methods

Participants

In this study, 33 participants with PD were included. Inclusion criteria were: (i) a diagnosis of PD, based on the UK brain bank criteria (Hughes et al. 1992); (ii) pharmacological treatment with levodopa; (iii) Hoehn and Yahr (H&Y) stage I-III; (iv) Mini Mental State Examination (MMSE) score ≥ 24 (Folstein et al. 1975); (v) absence of other disorders that would interfere with tapping; and (vi) right-handedness.

The protocol (S62564) was approved by the local Ethics Committee Research UZ/KU Leuven. Written informed consent was obtained prior to participation. The study was registered as ClinicalTrials.gov Protocol Record NCT04185740.

Experimental design

The study design consisted of three consecutive tapping tests per day for seven days (Fig. 1A) in unsupervised circumstances. At baseline and in the patient's home (ON medication), the researcher administered the Movement Disorders Society sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)(Goetz et al. 2008) part III and recorded data on demographics, clinical descriptors, and medication intake. Disease dominance was calculated as the difference between left and right MDS-UPDRS part III upper limb scores (items 3.3–3.6 and 3.15–3.17). Levodopa Equivalent Daily Dose (LEDD) (Schade et al. 2020) was based on the daily medication schedule of the participant. The researcher demonstrated the use of the application to participants as well as set personalized reminders for the tapping task execution and medication intake in the smartphone (Samsung Galaxy Xcover 4, Android version 9). Participants were not allowed to train the task to avoid learning effects at the start of the trial as we wanted to investigate this question. The following 7 days, the participant performed the tapping task 3 times daily on the smartphone positioned on a table without a video camera or a researcher being present. Taking into account an estimated average levodopa response of four hours for mid-stage PD, all tapping tests were performed in the morning (Armstrong and Okun 2020). The first test was performed in OFF, half an hour before the earliest PD medication intake of the day. The next two tests were performed in ON, 1 and 3 h after levodopa intake (Fig. 1B).

For compliance, the number of trials and time points were registered and automatically saved on a secured cloud drive. The researchers checked the data input daily. In case

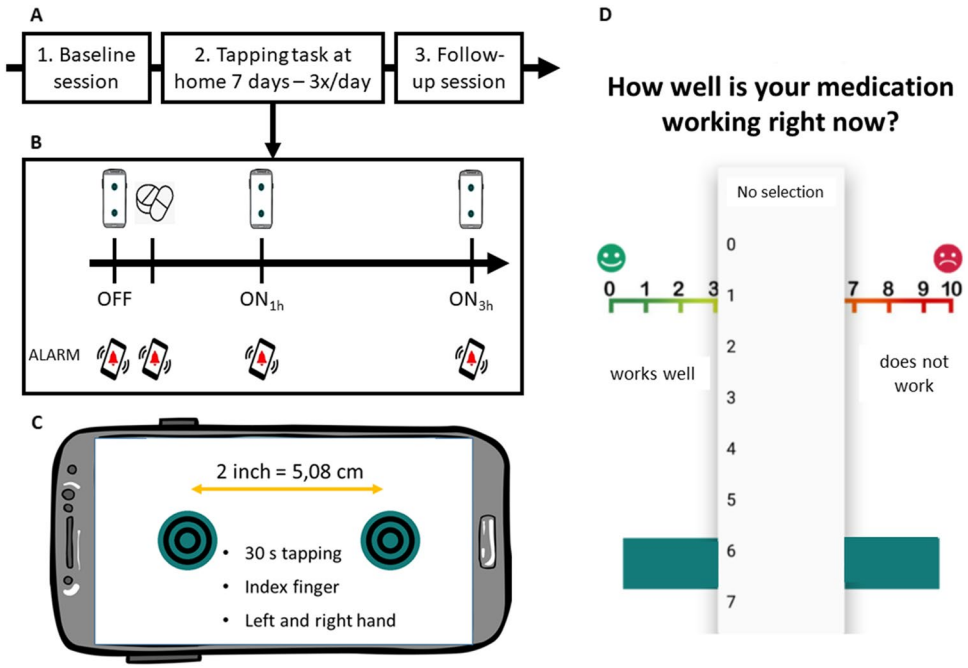

Fig. 1 **A** The study design included 3 test periods: (1) Baseline assessment, (2) Test phase and (3) Follow-up session. **B** Time schedule during one day with tapping performance before (OFF) as well as 1 h and 3 h after medication intake. **C** Timed tapping task display on the smartphone. **D** Visual analogue scale (VAS) assessing the self-perceived medication response

of non-compliance, they called the patient and provided support if needed. A follow-up visit took place after completion of the 7-day protocol to evaluate user-experience and feasibility of the protocol using a custom-made exit questionnaire of twelve questions with a five-point Likert scale (ranging from 1 = totally disagree to 5 = totally agree).

Smartphone tapping task and outcome measures

The tapping task consisted of two targets with a diameter of 0.6 inch (1.5 cm) positioned at a fixed distance of 2 inch (5.1 cm) and presented on the screen of a smartphone. The cloudUPDRS application (version 1.3.0) was developed by GR and colleagues (Fig. 1C) (Stamate et al. 2018). For the current study, participants only had access to the finger tapping paradigm. Test instructions (translated in Dutch) stipulated that patients had to tap as fast and as accurately as possible for 30 s between the two targets using their index finger. This movement was also shown in a video before each tapping session. The task was performed with a fixed order starting with the left before the right hand to make the test intuitive for patients. The touch-sensitive screen (i.e. IPS LCD display) of the smartphone measured the timing of each touch event and its coordinates. Outcomes measures were tap frequency (taps per second) and the inter-tap distance (in number of pixels), shown earlier to be sensitive to Levodopa (Thijssen et al. 2022). After completion of the tapping task with each hand, participants had to indicate the hour of their last medication intake, the presence of dyskinesias and their self-perceived medication response on a visual analogue scale (VAS). Lower VAS-scores indicated that medication was working well (Fig. 1D) (Terroba-Chambi et al. 2018).

Data processing and statistical analysis

Data processing and extraction of the dependent variables were executed via an open source Python toolkit (https://github.com/pdkit/) (Stamate et al. 2021). Due to the known difficulties in terminating movements in PD (Warabi et al. 2011) and based on pilot tests, the last tap was removed from all trials. Test sessions performed with a delay of more than 60 min were deleted (data loss: 3 test sessions, 0.46%). Statistical analyses were conducted using SPSS (version 28 SPSS, Inc., USA) or SAS software (Version 9.4_M6 of the SAS System for OnDemand for Academics, USA) with significance levels set to $p < 0.05$. The Shapiro–Wilk test, complementary histograms and Q-Q plots were used to check for normality. Cohen's d based on pooled standard deviations was used to calculate effect sizes. Compliance was captured as the percentage of actual versus expected tests performed. Compliance delay was computed as the time span between the automatic reminder to perform the test and actual test performance in minutes. Both metrics were analyzed by Friedman's test. Post hoc comparisons were carried out using the paired Wilcoxon test with Bonferroni's correction. Tapping performance was analyzed using linear mixed effect models with the most optimal residual covariance structure based on the Akaike and Bayesian information criteria and with participant as a random effect. Fixed factors varied in function of the analysis. Statistical comparisons of average tapping performance were executed using models

with HAND and TIME as fixed factors. DISEASE DOMINANCE, nested within HAND, was included as a random factor. Mixed model comparisons to investigate the repeated performance per day were conducted with HAND (left or right), TIME (OFF, ON_{1h} or ON_{3h}) and DAY (day 1, 2, 3, 4, 5, 6 or 7) as fixed factors. Self-reported ON–OFF status (VAS-scores) were compared using a model with TIME as fixed factor. Significant interactions were explored by Bonferroni multiple comparison post-hoc tests. Classification of ON–OFF status based on tapping was explored with multiple logistic regression and receiver operating characteristic (ROC) curves for each day separately and combining tapping frequency and inter-tap distance variables. An FDR-correction for multiple comparisons was applied for this analysis. Binary classification was based on the VAS change scores (OFF-ON_{1h} and OFF-ON_{3h}), with ON if >0 and OFF if ≤ 0. Area under the curve (AUC) values of >0.7 were considered as good discriminative ability, according to the COSMIN criteria (Mokkink et al. 2016).

Test–retest reliability of repeated measurements during ON (ON_{1h} versus ON_{3h}) was examined by Intraclass Correlation Coefficients (ICC) in a two-way random effects model with absolute agreement for tapping data. The following criteria were used for interpretation: <0.40 as poor, 0.40–0.75 as fair to good and >0.75 as excellent reliability (Shrout and Fleiss 1979). Finally, an analysis of covariance was conducted to estimate whether clinical outcomes and dyskinesias were associated with ON–OFF changes in tapping outcomes (described in detail in the supplementary materials).

Results

Participants and feasibility of tapping task

Demographics and clinical characteristics of 32 out of the 33 participants are specified in Table 1. One PD patient experienced insurmountable difficulties with the autonomous use of the smartphone and dropped out after day 2. Three of the remaining patients did not have prior experience with a smartphone. Eleven patients (34.4%) experienced dyskinesias during both OFF and ON tapping (OFF: 11 tests, ON_{1h}: 20 tests and ON_{3h}: 22 tests). Five patients (15.6%) indicated that the dyskinesias interfered with tapping. Sixteen patients (50%) needed remote guidance to comply with the procedures at the end of day 1, provided via phone calls or text message. This remote problem solving addressed participants' insecurities about task performance and the time schedule.

As for overall compliance, 28 participants (87.5%) performed three correct tests on all 7 days with less than 40 min delay. Four patients (12.5%) showed consistent difficulties with task compliance, accounting for 20 missing test session. Average tapping task-compliance (i.e., percentage of actual versus expected tests performed) per patient was 97.0% ($\pm$3.3%). The lowest compliance of 92.7% was found at day 6 and day 7. The delay between the reminder to do the test and the start of the tapping differed significantly for the 3 test moments ($X^2(2) = 8.683$, $p = 0.013$) (Figure S1), indicating longer delays when testing later in the day. More specifically, during OFF, 72% of participants had an average delay of below 5 min (median: 2.8 min. (1.1–5.4), compared to 53% during ON_{1h} (median: 4.1 min. (2.1–8.3)) and ON_{3h} (median: 4.8 min. (2.8–8.6) (Wilcoxon post hoc test: resp.p = 0.021 and p = 0.012). As for compliance with assigning the VAS scores, 13 patients (40.6%) missed these self-reported assessments, despite the fact that participants were required to give the scores immediately after tapping. In total, there were 59 missing VAS values (8.8%), the highest numbers of which were found at day 5, 6 and 7 (around 12% missing values).

Responses to the exit questionnaires are summarized in Figure S2 and show that 85% of the PD patients considered the tapping task as user-friendly (question 4). However, 48% of participants denoted that long-term performance would be difficult (question 5). Only 53% experienced a difference in tapping performance between OFF and ON medication (question 11). In addition, a substantial number of participants indicated difficulties with the VAS-scale and suggested that this part of the application should be improved in future versions.

Discriminative ON–OFF ability of the tapping task

Average tapping performance over the seven days was significantly different across the 3 time points (main effect TIME for frequency: $F(2, 31) = 17.703, p < 0.0005$ and for inter-tap distance: $F(2, 145) = 15.797, p < 0.0005$). Post hoc analysis revealed that patients ON medication (ON_{1h} and ON_{3h}) tapped significantly faster and with larger movement amplitudes compared to the OFF assessment (all $p < 0.0005$). Also, performance with the right hand was significantly better, compared to left (main effect HAND for frequency: $F(1, 14) = 40.565, p < 0.0005$ and for tapping distance: $F(1, 10) = 7.324, p = 0.023$) (Fig. 2A and B and Table S1). Figure 2 also shows that patients scored their subjective ON-state as significantly different compared to the OFF state with the VAS methodology (main effect TIME: $F(2, 31) = 15.548, p < 0.0005$, post hoc tests: both OFF vs. ON_{1h} and OFF vs. ON_{3h} $p < 0.0005, d \geq 0.9$) (Fig. 2C and Table S1).

Multiple logistic regression, using the first tapping session in ON (ON_1) compared to OFF, revealed that right hand tapping showed good AUC values to classify patient as being ON or OFF. AUC-values ranged between 0.72 and

Table 1 Demographic and clinical data of participants

Patient ID	Age (years)	Gender	MMSE (0–30)	Disease duration (years)	Disease dominance	MDS-UPDRS III ON(0–132)	H&Y stage (1–5)	LEDD (mg/24 h)
1	72	F	29	5	R	23	2	426
2	73	M	28	8	R	20	2	810
3	77	M	30	1,5	L	18	2	250
4	43	M	29	4	L	5	2	898
5	70	M	30	5	R	22	1	510
6	70	M	26	13	B	12	2	860
7	76	M	27	6	R	31	2	400
8	59	M	30	4	R	14	2	750
9	68	M	28	12	L	8	2	710
10	64	M	30	9	R	10	2	300
11	72	F	30	10	L	12	2	500
12	78	F	29	14	L	33	3	610
13	45	M	28	5	R	12	2	710
14	59	F	30	3	R	4	2	500
15	64	M	28	7	R	9	2	566
16	69	M	30	7,5	B	16	2	842
17	61	F	30	10	B	12	2	791
18	43	M	29	1	R	13	1	400
19	61	F	30	15	R	33	2	850
20	72	F	29	6	R	20	2	560
21	63	F	28	5	R	57	3	810
22	60	M	27	16	L	30	3	1512
23	61	M	30	8	R	33	2	1120
24	57	M	30	3	R	25	2	300
25	59	F	30	10	R	17	2	915
26	73	F	30	14	L	23	3	710
27	60	M	28	5	R	30	3	550
28	58	M	25	9	L	46	3	1403
29	63	M	30	10	B	33	3	1241
30	69	F	29	10	R	28	2	460
31	82	F	27	7	L	51	3	450
32	70	M	27	9	L	34	3	560
Mean ± SD	64.7 ± 9.5	20 M, 12 F	28.8 ± 1.4	7.9 ± 3.9	10 L, 18 R, 4 B	22.9 ± 13.0	2.2 ± 0.6	696.1 ± 306.5

B both hands, *H&Y* stage Hoehn and Yahr stage, *L* left hand, *LEDD* Levodopa Equivalent Daily Dose, *MDS-UPDRS* Movement Disorders Society Unified Parkinson's disease rating scale, *MMSE* Mini Mental State Examination, *R* right hand, *SD* standard deviation

0.80 from day 2 till day 6 (Fig. 3, Table S2). Interestingly, the ranges of the AUC values for right hand tapping during the second ON session compared to OFF (ON_{3h}) only fell between 0.63 and 0.7. For the left hand, AUC-values were also smaller, ranging between 0.58 and 0.73. Thus, tapping with the right hand, assessed 1 h after medication intake, displayed the strongest ON–OFF discriminative ability.

Test–retest reliability

Good to excellent test–retest reliability during ON was found for both frequency ($0.733 \leq ICC \leq 0.971$) and inter-tap distance of the tapping task ($0.707 \leq ICC \leq 0.975$) (Table S1). The ICCs of the VAS-scores showed fair test–retest reliability ($0.481 \leq ICC \leq 0.653$).

Learning effects

Repeated tapping over 7 days revealed a significant increase in frequency during the first 3 days, indicating a learning effect in both medication states (main effect DAY: $F(6, 1278) = 48.157, p < 0.0005$, post hoc tests: day 1, 2 and 3 vs. other days all $p \leq 0.030$) (Figure S3). Tapping frequencies were significantly lower during OFF compared

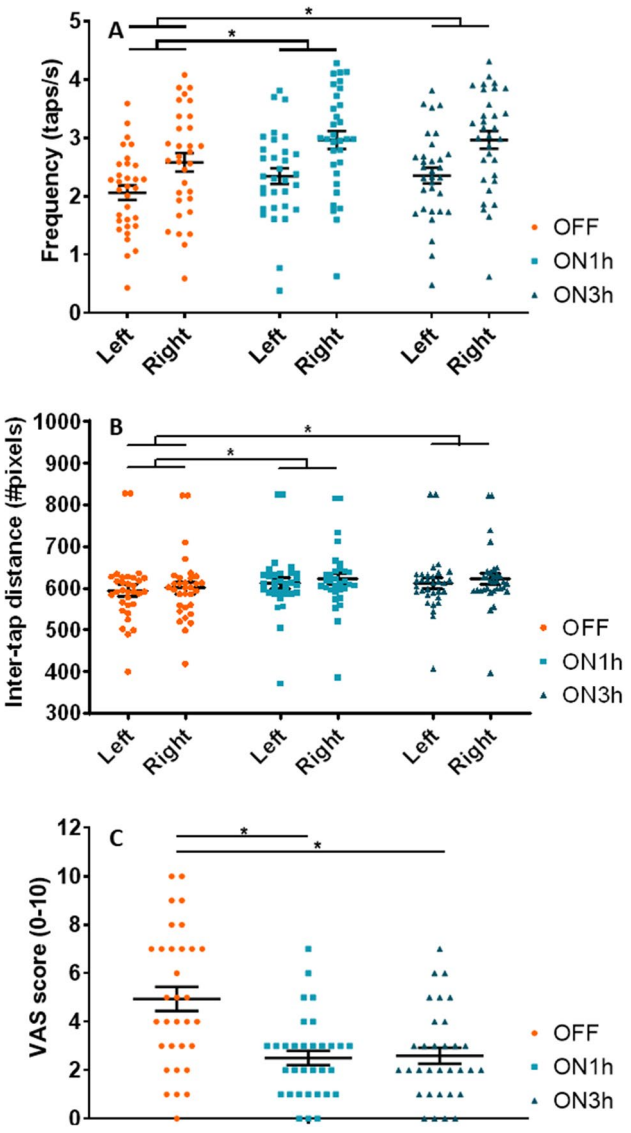

Fig. 2 Tap frequency in taps per second (**A**), inter-tap distance in centimeters (**B**) and self-reported ON–OFF (**C**) during OFF, ON1h and ON3h (dots, squares and triangles, respectively). Data (the average over 7 days) are presented as group means (± standard error) as well as individual data points. *Indicates p value < 0.05 (post hoc)

to ON (main effect TIME: $F(2, 1217) = 96.862, p < 0.0005$, post hoc tests: both OFF vs. ON_{1h} and OFF vs. ON_{3h} $p < 0.0005$). Right hand tapping was better than left hand performance across the seven days (main effect HAND: $F(1, 14) = 41.712, p < 0.0005$). The inter-tap distance did not change over days, though the distance during OFF was significantly smaller compared to ON performance (main effect TIME: $F(2, 742) = 10.397, p < 0.0005$, post hoc tests: both OFF vs. ON_{1h} and OFF vs. ON_{3h} $p < 0.0005$). We also analyzed the differences across the 7 days of the ON–OFF VAS scores. No differences were found, except that global scores in ON were lower than in OFF (main effect TIME: $F(2, 447) = 61.499, p < 0.0005$, post hoc tests: both OFF vs. ON_{1h} and ON_{3h} $p < 0.0005$).

Correlational analysis

Exploratory correlation analysis showed that the change in ON–OFF tapping outcomes were positively correlated to LEDD (tapping frequency—right hand ON_{1h}: $\beta = 0.218$, $p = 0.007$; ON_{3h}: $\beta = 0.222$, $p = 0.01$ and left hand ON_{3h}: $\beta = 0.185$, $p = 0.023$. Inter-tap distance – right hand ON_{1h}: $\beta = 0.217$, $p = 0.005$; ON_{3h}: $\beta = 0.265$, $p = 0.001$ and left hand ON_{1h}: $\beta = 0.138$, $p = 0.036$; ON_{3h}: $\beta = 0.119$, $p = 0.032$). Correlations with age and disease duration were moderate and no other clinical variables showed meaningful associations with tapping gains (see Supplementary Material A for details).

Discussion

This study aimed to validate the ability of a smartphone-based tapping task, performed in the home setting for 7 days without supervision, to quantify differences in hand bradykinesia measured in the pragmatically defined OFF- and ON-status of people with PD. As a proof of concept, we showed that tapping outcomes were significantly different in OFF and ON at 1 and 3 h after medication intake. We also could establish that tapping had good ON–OFF classification ability for the right hand, specifically for test days 2 to 5. During the ON-period, the test–retest reliability within one day was excellent, but tapping showed a learning effect over the 7 days for frequency only. However, the detected ON–OFF differences remained discernable throughout this period. As such, and together with the satisfactory patient compliance and subjective ratings, this study underscores the potential of using a smartphone-based tapping test as a marker of daily ON–OFF fluctuations in free-living conditions (Akram et al. 2022; Hasan et al. 2019; Simonet et al. 2021; Wissel et al. 2017).

Emerging technology solutions enable remote patient monitoring and telehealth, a trend which is rapidly expanding since the COVID-19 pandemic. The advantages of home-based assessments include increased patient comfort, reduced costs, access to accurate data in a large population and prevention of 'white coat-induced' performance bias (Lipsmeier et al. 2018; Wilkinson et al. 2009). On the other hand, there are also many challenges to unsupervised methodologies (Shivkumar et al. 2021; van den Bergh et al. 2021). First, our group showed that adequate use of smartphone or tablet technologies cannot be assumed due to dexterity deficits in PD. Indeed, in the present study one patient dropped out because of these difficulties (De Vleeschhauwer et al. 2021). Second, we highlighted the importance of

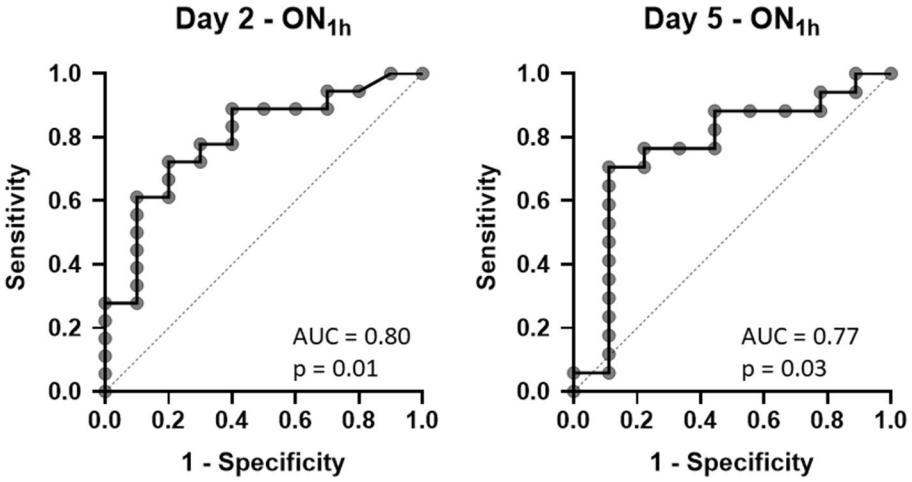

Fig. 3 Receiver operating curves for combined tapping frequency and inter-tap distance values with the right hand assessed 1 h after medication intake (ON1h) at day 1 and day 5

providing remote backup support for testing done at home. In this study, support was needed in 16 patients. Third, we noticed time effects in our home-recorded tapping data indicating that the first test showed less reliable ON–OFF classification. This points to the importance of incorporating a familiarization period for motor tests involving technology in unsupervised settings.

Nevertheless, the current study showed that PD patients were able to perform the smartphone-based tapping task independently at home with a high average task compliance (97%). Previous studies showed more variable compliance with smartphone assessments, ranging from 30 to 96% in PD (Gatsios et al. 2020; Horin et al. 2019; Lee et al. 2016a, b; Motolese et al. 2020). To our knowledge, this study is the first to investigate the response to reminders set at fixed hours to control for the time between medication intake and task performance (Akram et al. 2022). We found that compliance delays were longer for the assessments scheduled later in the day, i.e., 3 h instead of 1 h after medication intake. We interpret this result as possibly due to the interference of daily activities undertaken later in the day compared to in the early morning. Also, compliance rates were lower at the end of the 7-day monitoring period (i.e., day 6 and 7), especially for the subjective VAS-scores but also for the tapping test. What is more, almost half of the patients were not keen to continue the procedure after the 7-day testing period. Therefore, we recommend to enhance the feasibility of the home tapping protocol by comparing early ON versus OFF tests only, by keeping the monitoring period under 7 days, repeat this short monitoring period regularly over several months and by ensuring remote troubleshooting. This will support the development of feasible procedures for obtaining a valid ON–OFF classification for clinical and research purposes, complementary to 'subjective' electronic diaries and protocols.

Wearable technology is becoming increasingly available for objective assessment of medication responsiveness and adherence derived from mobility data in the clinic and the home setting (Akram et al. 2022; Debelle et al 2023; Habets et al. 2021; Hasan et al. 2017; Rissanen et al. 2021; Simonet et al. 2021). Yet, feasible procedures for obtaining a valid ON–OFF classification are still lacking (Barrachina-Fernandez et al. 2021). Therefore, tracking patients' medication response using simple and objective motor tests may complement 'subjective' electronic diaries and protocols.

The finding that tapping performance was enhanced by levodopa intake is in accordance with previous studies using comparable tasks (Akram et al. 2022; Hasan et al. 2019; Noyce et al. 2014; Simonet et al. 2021; Thijssen et al 2022; Wissel et al. 2017). The most well-known and validated tapping task is the Bradykinesia Akinesia Incoordination (BRAIN) tap test, consisting of alternating finger-tapping on a keyboard (Akram et al. 2022; Hasan et al. 2019; Noyce et al. 2014). For this task, the distance between tapping targets is relatively large, also requiring proximal movements (Noyce et al. 2014). As such, the BRAIN test may be less sensitive to subtle motor fluctuations evoked by the small sequential movements needed for the Cloud-UPDRS tapping task (Akram et al. 2022). Other studies using repetitive or two-finger paradigms required tapping on the spot or on different keys, included no distance component (Akram et al. 2022; Arora et al. 2015; Goñi et al. 2021, 2020; Lipsmeier et al. 2018, 2021; Omberg et al. 2021; Sahandi Far et al. 2021; Simonet et al. 2021; Surangsrirat et al. 2022). Here, we found, similar to a recent study (Thijssen et al. 2022), that the average frequency and the inter-tap distance improved with levodopa, with a few exceptions. This confirms that tapping between two dots is suitable for estimating ON–OFF fluctuations of hand bradykinesia at the group level. In addition, greater changes in tapping performance were correlated to higher LEDDs confirming the validity of tapping as a marker of medication response. Other baseline disease characteristics showed no or weaker correlations.

This was the first study that demonstrated excellent test–retest reliability of tapping when tested twice on the same day when ON-medication in a free-living setting. In contrast, subjective VAS-scores of these two time points lacked adequate test–retest reliability. However, when analyzing performance over 7 days, we found a learning effect for tapping frequency, which reached a 'ceiling' after 5 days. No learning effect was revealed for the subjective VAS-scores. Although learning constituted a disadvantage of tapping, the distinctions between ON–OFF remained similar across the 7 days. Also, learning effects were not meaningful for inter-tap distance, which may be explained by the use of visual targets (Almeida and Brown 2013; Makai-Boloni et al. 2021). In addition, performance with the dominant hand proved the most accurate, possibly because greater tapping variability when conducted with the non-dominant hand. Even though disease dominance was accounted for in the statistical analysis, a more detailed analysis of the interactions between handedness, and disease dominance would be of benefit to further develop tapping as marker of ON–OFF status. Based on these results and the fact that the discriminative ability for tapping was most accurate for day 2 and 5, we recommend to include a longer familiarization period in future home protocols. However, familiarization should fall outside the formal testing period to reduce the test-burden as compliance tailed off after 7 days. In addition, reward-based strategies to improve compliance during prolonged free-living test protocols warrant further investigation.

The self-reported VAS scores showed that patients were able to differentiate between OFF and ON adequately. Yet, the VAS-scores were less reliable during repeated measures in ON. Subjective rating scales are possibly more useful for detecting general states and changes in a person's well-being (Heldman et al. 2014). Objective tests, such as tapping, could play a complementary role, providing a more specific and reliable detection of ON–OFF states in a well-defined motor domain.

The current findings have to be interpreted against a number of drawbacks. Eleven patients reported dyskinesias during tapping. Previous blinded video analysis showed that in general dyskinesia's do not affect tapping performance (Wissel et al. 2017), limiting the utility of tapping to gaining a full picture and extent of motor fluctuations in PD. Also, the long-duration response to levodopa could have affected the OFF-state results in this study (Cilia et al. 2020). Further, the VAS-scale was always assessed after tapping, which may have influenced the results. Therefore, future study on the criterion validity of home tapping for ON–OFF classification needs to be based on an independent gold standard, such as a video-taped UPDRS-bradykinesia scores obtained at the same time. Patients with a longer disease duration and freezing of gait were under-represented in our cohort (66% in H&Y stage II). Capturing freezing episodes during finger tapping (not detected in this study) could be influenced by medication response (D'Cruz and Nieuwboer 2021). Also, people with tremor or cognitive decline could have compromised test–retest reliability and were not included in the current analysis. Future studies need to address these sources of spectrum bias by including a wider cohort of patients.

Conclusion

Repeated tapping tests performed on a smartphone in the home setting were able to discriminate between ON–OFF states and also proved reliable when repeated within the ON-state. Tests took only 30 s, were conducted without supervision, but were supported by reminders sent from the smartphone. Despite some learning and time effects, most patients were able to adhere to this protocol for the required 7 days, but about half of patients were reluctant to continue it for longer. Replication of these results in a wider sample, as well as criterion validity against a gold standard are needed before wide implementation in future home-based studies can be considered.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00702-023-02659-w.

Author contributions SB: Design: Conception, Organization, Execution; Data: Acquisition, Processing; Analysis: Design, Execution; Manuscript: Writing of the first draft. GR: Design: Conception, Organization; Data: Processing; Analysis: Design, Review and Critique; Manuscript: Review and Critique. JDV: Analysis: Review and Critique; Manuscript: Review and Critique. NDC: Analysis: Design, Execution, Review and Critique; Manuscript: Review and Critique. JO: Design: Conception, Organization, Execution; Analysis: Design, Review and Critique; Manuscript: Review and Critique. AN: Design: Conception, Organization, Execution; Analysis: Design, Review and Critique; Manuscript: Review and Critique.

Funding Internal Funds of the KU Leuven (C14/17/115) and the Research Foundation Flanders (FWO) supported this study; SB and JDV are FWO doctoral researchers (resp. FWO grant numbers 1167419N and 11N5622N). All funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data availability statement The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors have no conflict of interest to report.

Ethical approval The protocol (S62564) was approved by the local Ethics Committee Research UZ/KU Leuven. Written informed consent was obtained prior to participation. The study was registered as ClinicalTrials.gov Protocol Record NCT04185740. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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