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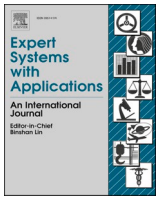

Estimation of motor severity scales in Parkinson's disease by linear models of bimanual non-alternating index finger tapping features

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ABSTRACT

Background and Objective: Clinical scales used by well-trained clinicians to assess motor symptoms in patients with Parkinson's Disease (PD) allow to establish the patients' medical therapy and follow-up their response. However, these assessments are subjective and their application to patients requires experienced and qualified operators. This study analyzes the role of the kinematic patient's features, captured by a simple computer keyboard paradigm, in predicting the scores prescribed by an experienced neurologist.
Methods: A total of 47 patients in their ON medication state participated in this study. Their motor capacity was assessed by an experienced neurologist with several standardized clinical scales. The patients also performed 5 consecutive trials of 10 s of a computerized finger tapping task by pressing with their index the space bar, first with their dominant hand and then with the other hand. 270 tapping-related features were extracted from the tapping task data for each participant and linear regression multivariate models for each clinical variable were built by using these features.
Results: The best resulting models were for the motor capacity (Unified Parkisnon Disase Scale Revised – MDS-UPDRS Part III), years from disease onset and balance scores (Limit of Stability – LoS), with root mean squared errors (RMSE) of 0.268, 0.254 and 0.150, respectively, all bellow their corresponding minimal clinically important differences. Those models included variables from both hands and from all trials, mainly regarding slow and fast tapping-related variables in different degrees.
Conclusions: A simple bimanual non-alternating finger tapping task has shown to foresee motor capacity and balance scores by using statistical and machine learning methods. This easy and quick task could be performed periodically in the medical office or at home helping the clinician to know the patients' motor state and temporary alterations in that way and to make finer clinical decisions about the proper pharmacological treatment of every patient.

1. Introduction

Motor symptoms in Parkinson's Disease (PD) patients is the result of the degeneration of dopaminergic neurons in the substantia nigra (Foffani and Obeso, 2018). The progress of the disease lies in the dysfunctional interactions between this basal ganglion and motor cortical areas (Poewe et al., 2017). In addition to bradykinesia (Postuma et al., 2015), the clinical characterization of PD can exhibit diverse motor signs as impaired gait, postural instability, tremor or a mixed manifestation of several of them. These motor phenotypes are highly individual and variable, depending on the disease course, response to drugs, or age (Herb et al., 2016).

PD symptoms, especially bradykinesia, impact in several domains of action of the patients like activities of daily living and cognitive and motor skills. The assessment of motor and physical disabilities includes the evaluation of balance and control of posture, gait, and arm and hand function (Opara et al., 2017). The standardized clinical evaluation scales commonly used include the Hoehn & Yarh (Hoehn and Yahr, 1967), the

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Table 1
Demographics and clinical variables of the participants included in the study.

(n = 47)	Avg. (std.); min. - max. # (%)
Age (years)	63.30 (8.80); 44.00—80.00
Sex	
Female	16 (34.00 %)
Male	31 (66.00 %)
Dominance	
Right	45 (95.70 %)
Left	2 (4.30 %)
Time from disease onset (years)	6.06 (3.89); 0.00—21.00
Side of symptoms onset	
Right	27 (57.40 %)
Left	20 (42.60 %)
Levodopa Equivalent Dose (LED) (mg)	587.51 (411.07); 0.00—1717.00
Hoehn & Yahr	1.94 (0.67); 1.00—3.00

Modified Bradykinesia Rating Scale (MBRS) (Kishore et al., 2007), the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987) and its modified version, the Movement Disorder Society (MDS)-UPDRS (Goetz et. al, 2008). Parts II and III of UPDRS and MDS-UPDRS subjectively assess motor alterations in all domains in PD. Besides, there exist well-known tests for evaluating balance and posture like the Timed Up&Go test (Podsiadlo and Richardson, 1991), different timed walking tests for gait, and the Fugl-Meyer Motor Assessment Scale (Fugl-Meyer et al., 1975) and Finger Tapping Test (FTT) (Shimoyama et al., 1990) for arm and hand motor skills.

The success of a medical treatment in handling motor symptoms is strongly conditioned by a precise and regular clinical evaluation. Even though, once the pharmacological treatment has been established after the clinical assessment, the functional state of patients and the severity of their symptoms are quite variable as a consequence of the pharmacokinetics of the medication, which leads to switch between ON medication and OFF medication states in an unforeseen manner (Kleinholdermann et al., 2021). So, a precise and periodic testing (several times a day) of patient's symptoms could support the clinician to fit a personalized and effective therapy.

One of the earliest motor impairments of the disease is located at the hands (Agostino et al., 2003; Lanciego et al., 2012) while performing fine motor tasks, that is evidenced at the disease onset in an asymmetric way (Hanna-Pladdy et al., 2015). Finger-to-thumb tapping, as a self-cued repetitive opposition of thumb and index of each hand, is considered the most suited task to measure fine motor skills and bradykinesia (Williams et al., 2020a). The assessment of this neurophysiological motor dysfunction is usually included in the UPDRS and MDS-UPDRS Part II and III and also by the dedicated FTT clinical rating scales, which are administered by well-trained and experienced neurologists (Goetz and Stebbins, 2004). Despite these scales have been extensively validated and improved in clinical terms along the past decades they need to be applied by trained professionals to be reliable. These tests are subjective, not suitable to be applied several times a day and their results depend largely on the time the patients took their last medication dose, whose absorption and effects are often unpredictable, resulting in a suboptimal procedure (Kim et al., 2021).

The emergence of new technologies has allowed to develop techniques to quantify motor symptoms and disease state in PD (Hasan et al., 2017; Merola et al., 2018). Regarding bradykinesia, the technology has provided approaches for quantitatively assessing finger tapping in patients by means of sensors like accelerometers, gyroscopes, and magnetometers (Li et al., 2020), light-diode finger tappers (Roalf et al., 2018), kinematic motion analysis systems (Bologna et al., 2018) and conventional video devices (Monje et al., 2021). Likewise, mobile smart devices endowed with sensors help to capture and store movement data in an unobtrusive and wearable fashion (Rovini et al., 2017; Ancona et al., 2021), that is welcomed by patients (AlMahadin et al., 2020).

Although both evaluation approaches, subjective and quantitative, can be used to detect typical motor symptoms in PD (Camicioli, 2002), objective procedures offer data whose analysis can help to determine impaired profiles of motion and/or temporary alterations in the disease state and even the effects of the applied therapy in a more precise and finer way. But, to what extent these technologies and techniques provide with reliable information that can be compared to the outcomes of gold standard rating scales? (Ghoraani et al., 2021). Some research works have found features that correlate or predict some MDS-UPDRS Part III subitem scores (ranging from 0 to 4) and the medication state (OFF/ON) from electromyography recordings (Kleinholdermann et al., 2021) with a coefficient of determination (R^2) of 0.546 between true and predicted scale scores, wearable devices (Ancona et al., 2021) with an accuracy in the detection of the presence of bradykinesia and tremor between 70 % and 88 %, and contactless sensors (Williams et al., 2020b; Sibley et al., 2021; García-Agundez and Eickhoff, 2021) with R^2 between 0.291 and 0.736 and best Root Mean Standard Error (RMSE) of 4.37 between true and predicted scale scores, or just detected early-stage PD based on the computer keystroke dynamics while typing (Adams, 2017; Giancardo et al., 2016; Lan and Yeo, 2019) with Areas Under Curve (AUC) between 0.670 and 0.980. Computer keyboard-based assessments offer a simple, comfortable, cost-effective, maintenance-free, untethered, remote and patient-centered means to assess Parkinson's symptoms through a horizontal task, with hands on a desktop.

Previous computer keystroke-based assessment approaches are either based on typing (Giancardo et al., 2016; Adams, 2017; Lan and Yeo, 2019), an infrequent skill in elder people, which is also affected by a learning component, or on bimanual alternation with engineered keyboards designed ad hoc (Tavares et al., 2005; Trager et al., 2020). However, it has been already evidenced that PD is symptomatically asymmetric and simple unimanual tasks yield more representative and less confounding results of the motor disorders (Trager et al., 2015).

Our aim is to predict for the first time several clinically meaningful motor-related scores and variables, either from upper or lower limbs, or for symptomatic or functional factors, reported by several neurologists experienced in the assessment of movement disorders in their medical consultation, just from patients' computer spacebar taps with the index fingers. We hypothesise that the scores of different movement- and balance-related clinical scores can be foreseen from features obtained while patients perform simple unimanual non-alternating index finger taps by using statistical analysis and machine learning methods. The automatic prediction of these variables through the computer keyboard paradigm proposed may be a very valuable asset in clinical assessments of motor disability for PD patients both in the medical office and remotely at home. It is an objective, unobtrusive, cost-effective, available and simple paradigm to quantify and assess motor symptoms by the neurologist. Besides, it can be dispensed by an easy and quick task in a periodic way in order to help to design the tailored pharmacological therapy and fasten the achievement of the optimum state of the patients.

2. Methods

2.1. Participants

Forty-seven PD patients were recruited for the study according to the next inclusion criteria: over 18 years old, diagnosed with idiopathic PD according to the London Brain Bank, Hoehn-Yahr score between I and III, no modifications of dopaminergic medication and psychotropic drug intake in the previous 30 and 90 days, respectively, and not demented (Minimental State Examination -MMSE- score < 25). Demographics and clinical characteristics are shown in Table 1. As derived from the data in Table 1, the participants were predominantly men and right-handed with the most-affected side slightly unbalanced to the right. The duration of the disease among the participants ranged from recently diagnosed to 21 years of development. However, according to the Hoehn and Yahr scores the participants suffered from mild to moderate disease severity. The average age was 63 years, but the range of age among

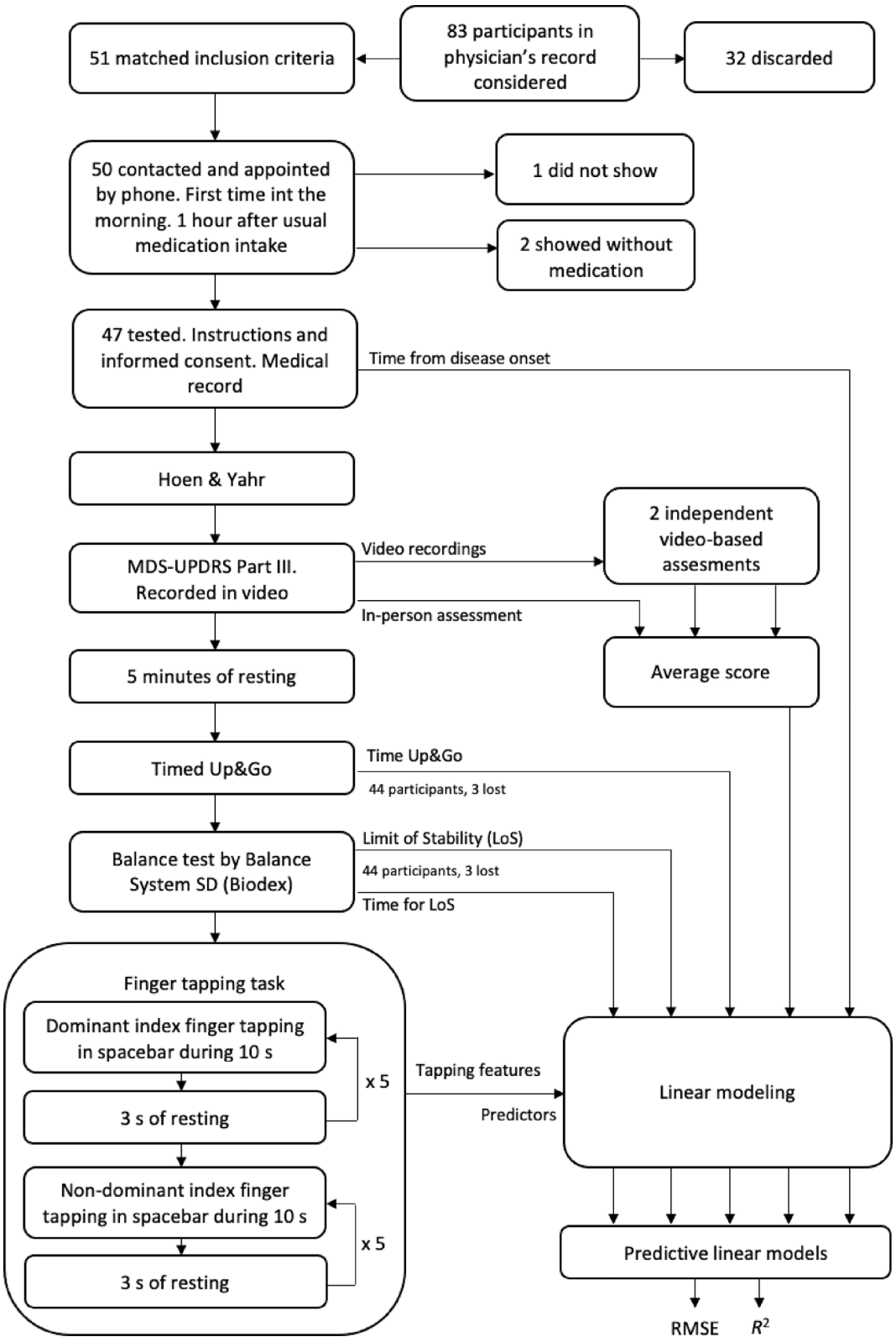

Fig. 1. Scheme of the complete methodology of the present study.

participants was 36 years, from the youngest 44-year-old participants to the oldest 80-year-old participant.

2.2. Materials

The participants' motor capacity was assessed by an experienced neurologist (J.P.R.) with the MDS-UPDRS Part III (motor examination) (Goetz et al., 2008), the Hoehn & Yahr scale (Hoehn and Yahr, 1967) and the timed Up & Go test (Podsiadlo and Richardson, 1991). The standing balance control of the participants was also assessed by a Balance System SD (Biodex Medical Systems Inc., USA) with the Limit of Stability (LoS) test (Azarpaikan,Torbati,and Sohrabi, 2014). The

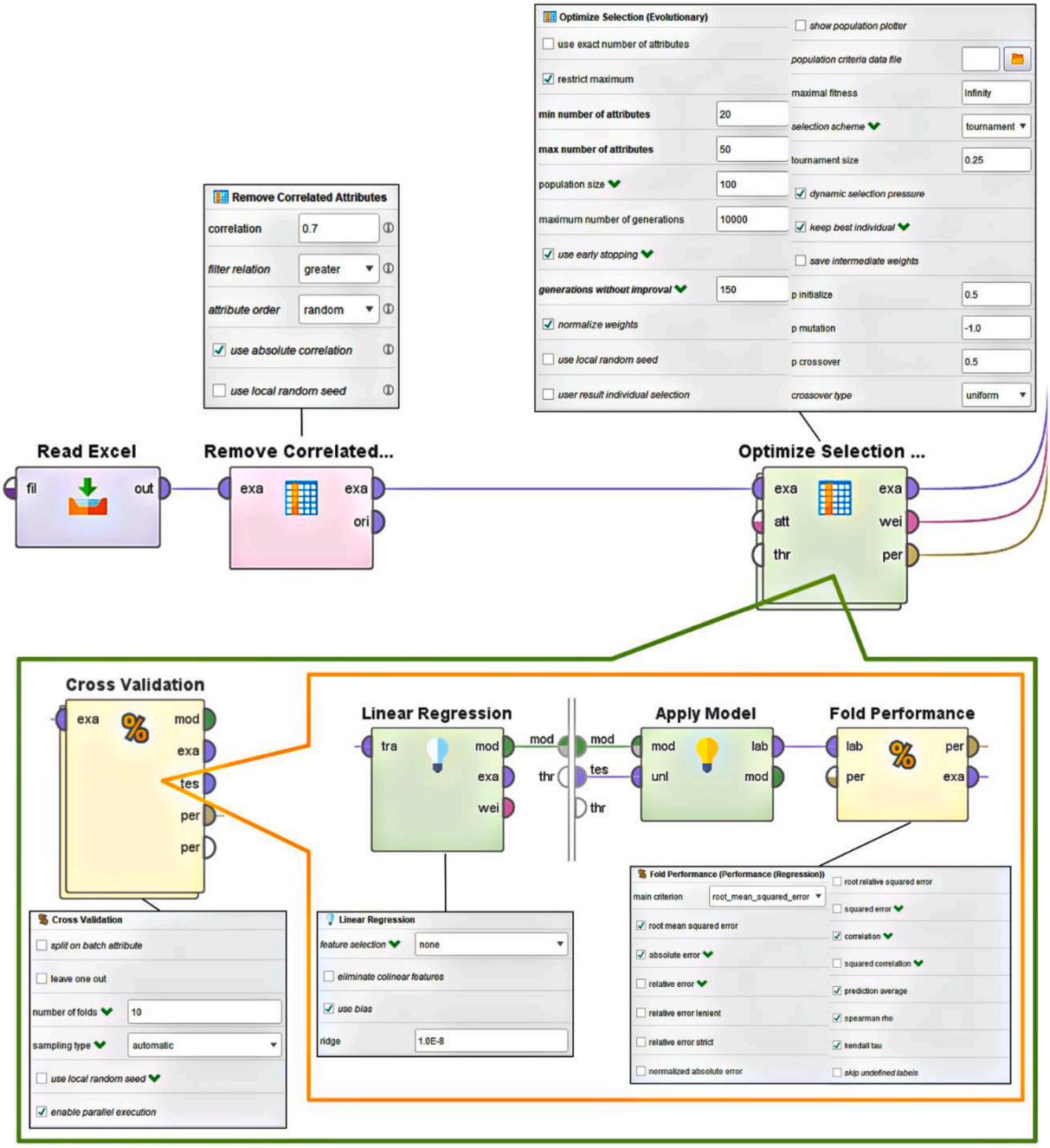

Fig. 2. RapidMiner Studio complete process model, with all operators and parameters, of the linear model optimization. Exa: Dataset; wei: Weights; per: Performance; mod: Model; tra: Training set; tes: Test set: unl: Dataset unlabeled; lab: Dataset labeled; p: Probability. Note that mutation probability ('p mutation') of −1.0 means 1/number of attributes in the individual.

Table 2
Results from the clinical testing of the participants.

	Avg. (std.); min. - max.
MDS-UPDRS Part III* - In-person assessment	14.70 (7.75); 0.00—32.00
MDS-UPDRS Part III* - video-based assessment 1	18.42 (5.12); 8.00 – 30.00
MDS-UPDRS Part III* - video-based assessment 2	21.77 (7.67); 1.00 – 38.00
MDS-UPDRS Part III* - Average of all assessments	18.29 (5.17); 6.00 – 29.00
Limit of Stability (LoS)**	34.58 (16.50); 10.00—69.00
Time for Limit of Stability (s) **	68.39 (20.70); 42.00—135.00
Up & Go (s)**	10.36 (2.70); 0.00—15.59

* n = 47.
** n = 44.

outcome of the LoS test was the overall score plus the time to complete the test in the level 12 totally stable platform, following the default manufacturer instructions and settings for the LoS test (Biodex Medical Systems, 2021).

The participants also performed a computerized finger tapping task (Strauss et al., 2006). To this end, the participants comfortably sat in front of a screen and a keyboard with the wrists resting in the table right before the keyboard. Then, they were asked to perform taps with the index finger on the space bar as fast as they could during time intervals (trials from now on). They perform five consecutive trials of 10 s each interleaved with 3-second resting periods (Strauss et al., 2006), first with the dominant hand and then with the other hand. The times between consecutive taps in each 10 s trial were recorded for further

Table 3
Adjustment parameters and statistics (F-ratio and p-value) of the clinical predictions of the best multivariate linear regression models composed of tapping variables.

Clinical variable predicted	RMSE GA 10 executions Avg. (std)	Best from GA 10 runs		
		RMSE Avg. (std.)	R^2	Statistics
Time from onset (years)	0.801 (0.359)	0.254 (0.104)	0.995	F(46) = 1411.938; p <.0005
MDS-UPDRS Part III	1.516 (1.249)	0.268 (0.128)	0.997	F(46) = 15806.059; p <.0005
Up & Go (s)	0.442 (0.389)	0.150 (0.041)	0.995	F(43) = 816.782; p <.0005
LoS	2.405 (1.107)	1.454 (0.551)	0.991	F(43) = 1970.870; p <.0005
Time for LoS (s)	0.692 (0.394)	2.977 (2.332)	0.999	F(43) = 8789.274; p <.0005

RMSE: Root Mean Squared Error; R^2: Coefficient of determination; GA: Genetic Algorithm; LoS: Limit of stability; Avg.: Average; Std: Standard deviation.

processing and analysis.

2.3. Procedure

Fig. 1 depicts the complete methodology of the present study. Patients successfully contacted who met the inclusion criteria (>18 years old, idiopathic PD, Hoehn & Yahr stage I-III, no modifications in dopaminergic medication in the previous 30 days, no modifications in psychotropic drugs medication in the previous 90 days) were appointed for testing in the morning, one hour after their usual dopaminergic medication intake to guarantee that they performed the tests in the ON-medication state. They were instructed about all the procedure and data management and signed the informed consent. All the procedure was carried out according to the Declaration of Helsinki and approved by the Ethical Committee Review Board of Hospital Beata María Ana.

The participants were first assessed by the MDS-UPDRS Part III and Hoehn & Yarh examinations. After five minutes of resting, they performed the timed Up & Go test. Then, their limit of stability was assessed in the balance system. Finally, they performed the finger tapping task. The MDS-UPDRS Part III was recorded in video and two additional video-based assessments by two additional neurologists were collected.

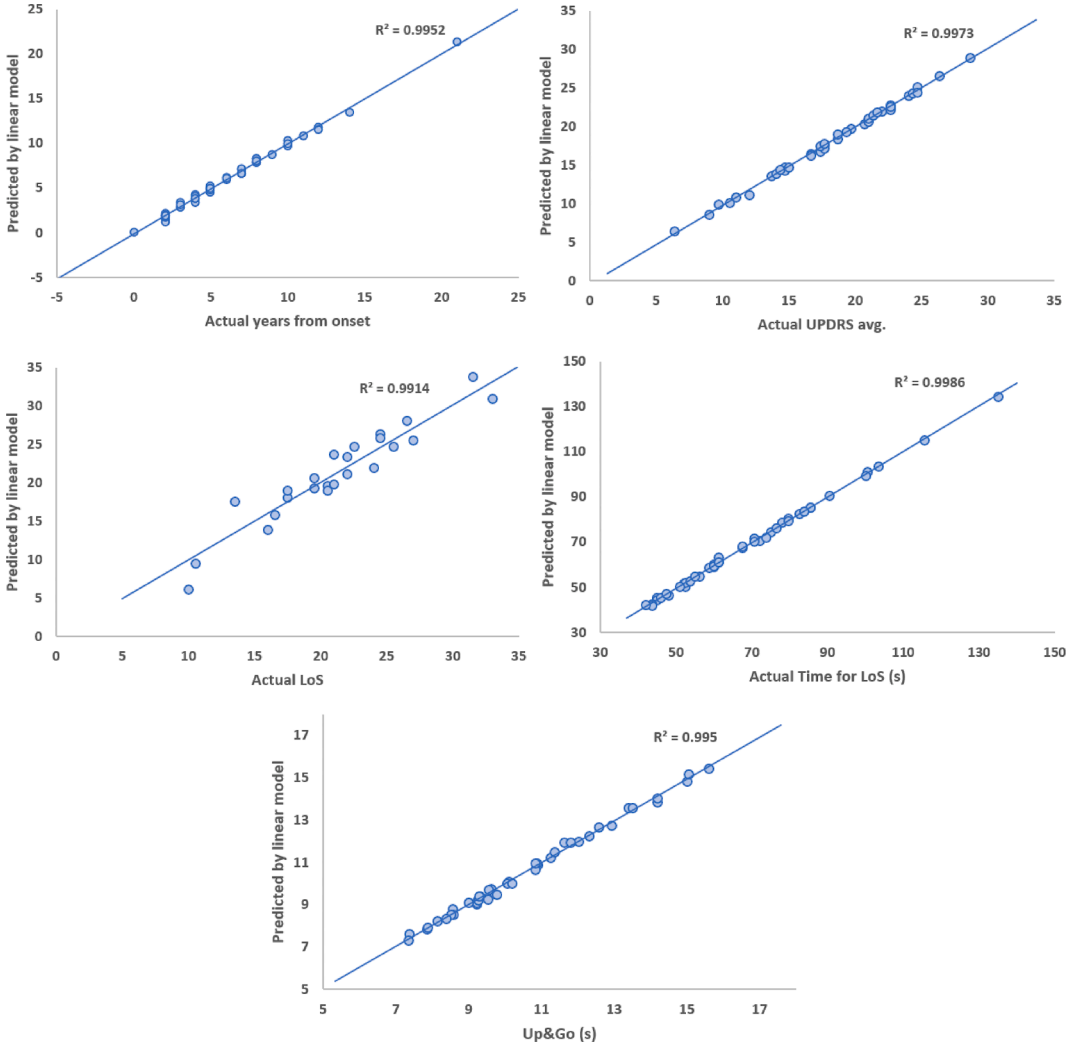

Fig. 3. Scatter plot and linear adjustments for the clinical variables considered and the corresponding prediction from the multivariate linear models composed of tapping features. MDS-UPDRS: Modified version of the Movement Disorder Society - Unified Parkinson's Disease Rating Scale; LoS: Limit of Stability.

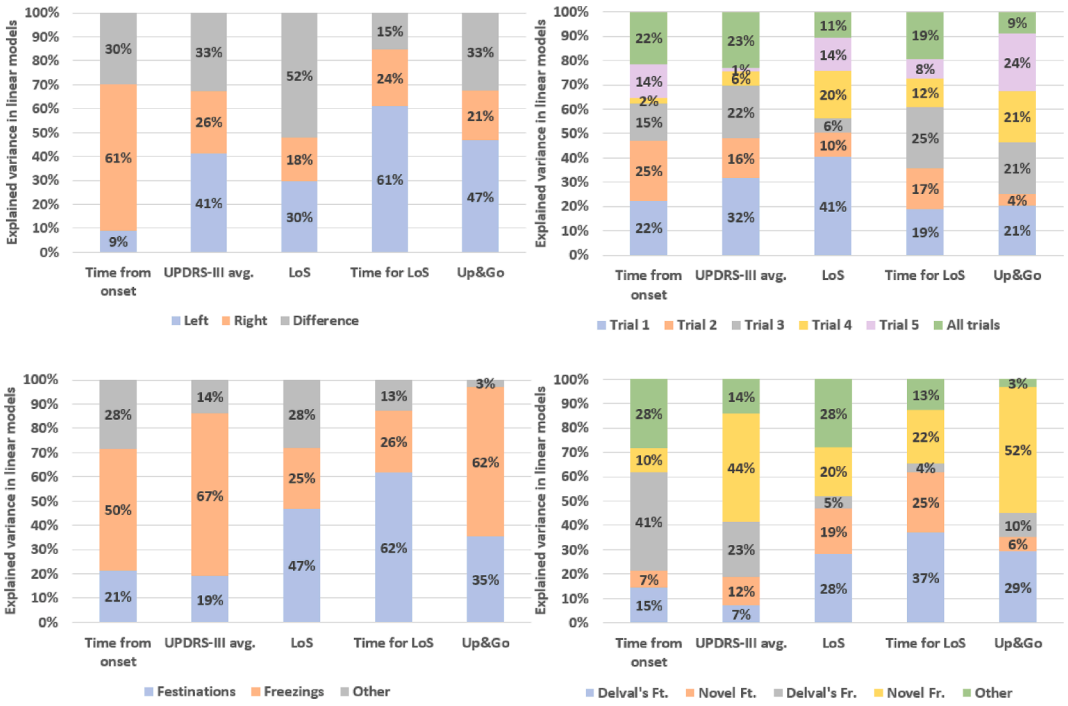

Fig. 4. Distribution of the variance explained by left side, right side and side difference (topleft), festination-related and freezing-related (bottom-left), Delval's festination- and freezing-related, novel festination- and freezing-related (bottom-right), and trials (top-right) among the finger-tapping variables in each multivariate linear regression model for each clinical variable. Ft.: Festinations; Fr. Freezings.

2.4. Data processing and analysis

All data was anonymized by identifying each participant with a code composed of two random capital letters and two random numbers. Date of testing was never recorded. The names of the recorded video files were only identified with each participant code. Each participant code was associated with the corresponding MDS-UPDRS Part III scores, Hoehn & Yarh stage, Up & Go time in seconds, LoS, time in seconds for complete the LoS task, and the features extracted from the finger tapping task.

From the times between consecutive taps recorded during each 10 s trial for each hand, the next features were extracted for each participant: the number of taps, the average time between taps and the uniformity of tapping cadence (as the coefficient of variation of the time between taps, i.e., the ratio of the standard deviation to the average). In addition, features from freezings (abnormally slower) and festination (abnormally faster) taps were also extracted: the number, the percentage with respect to the total taps in the trial and the average duration. We used two different concepts of freezing and festination. The first one is an adaptation of the concept used in Delval et al. (2016). According to it, a freezing tap is the one that lasts more than 0.5 s. A festination tap is defined as the one that lasts less than two standard deviations from the average duration of the first five taps of the trial. Since we think these definitions are somewhat arbitrary and not very robust, we also extracted features of freezing and festination based on the statistical outlier concept. In this sense, we also consider a freezing tap the one that lasts more than 1.5 times the interquartile range over the 3rd quartile (considering all the taps in a trial), i.e. a high outlier. Analogously, we consider a festination tap the one that lasts less than 1.5 times the interquartile range below the 1st quartile, i.e. a low outlier. Given the extracted features mentioned, each trial of tapping will be characterized by 15 variables (3 from taps, 3 from each of the two concepts of freezing, and 3 from each of the two concepts of festination). Since there are 5 trials for each hand, it accumulates 150 variables. We also considered the same mentioned variables accumulated, i.e., grouping all 5 trials for each hand, which adds another 30 variables. Finally, we also considered the difference between hands of each variable in each trial and in the accumulated trial. This results in a total number of 270 variables describing the finger tapping task for each participant. Other typical features could have been extracted from the tapping series for each trial and side, such as kurtosis, skewness, entropy or Lyapunov exponents. However, their meaning and interaction with the other variables would be hard to explain in clinical terms, thus undermining the clinical validity of the models.

Using those 270 tapping-related variables, we attempted to construct optimal linear regression models able to predict the corresponding clinical variables (years from the disease onset, MDS-UPDRS Part III, timed Up & Go, LoS and time of LoS). Other suitable models such as Regression Trees (Jiao et al., 2020) or Neural Networks (Specht, 1991) are less explainable, more conditioned by hyperparameter tunning and could have found complex non-linear relationships clinically hard to explain. For that purpose, we first remove the tapping-related variables that were highly correlated (Pearson's rho higher than 0.7). Then, a genetic algorithm (GA) was applied to find the subset from the remaining tapping-related variables that produce the linear model with the lowest RMSE. GAs are the most suitable method when the solution space is high-dimensional, such as all subsets from 270 variables. The applied core GA algorithm was the one implemented in the Optimize Selection (Evolutionary) operator of RapidMiner Studio version 9.10.011 (RapidMiner GmbH, Dortmund, Germany). The GA parameters were set to a population size of 100 individuals and a number of generations without improvement of 150 (to guarantee convergence), with a tournament selection scheme with size 0.25 and dynamic selection pressure, and probabilities of initialization, mutation and shuffle-crossover of 0.5, 1/number of features and 0.5, respectively, keeping the best individual of each generation for the next one. The individuals in the population were subsets of size between 20 and 50 variables from the remaining tapping-related variables considered, to obtain accurate but informative linear models without overfitting. Each individual was scored by the average RMSE on the validation parts from a 10-fold cross-validation on the entire dataset. Given the random nature of genetic algorithms, the GA was run ten times for each clinical variable. Average

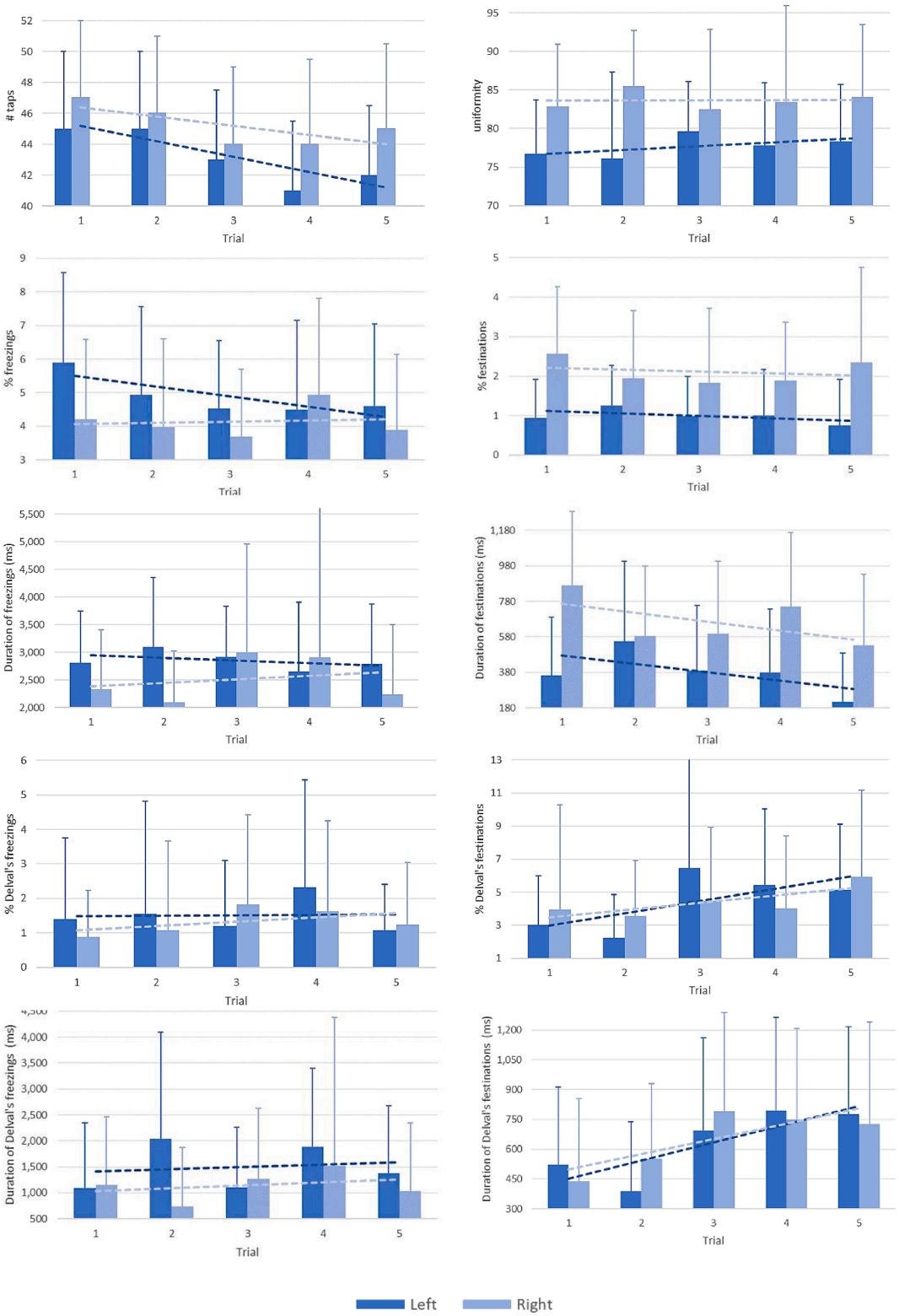

Fig. 5. Average values (and standard deviations multiplied by 0.5) of the different tapping variables considered along the five trials, together with the corresponding linear approximations (dotted lines) for the left and right sides.

(and standard deviation) of the best RMSEs from each of the 10 executions of the GA was reported. The average RMSE and R^2 over the 10 validation parts from the 10-fold cross-validation of the best individual from the 10 runs of the GA was also reported as prediction accuracy outcomes. Mean Squared Error (MSE) could have also been used, but the units of this error are not the same as the modeled variable and, consequently, it is harder to explain in clinical terms. Mean Absolute Error (MAE) is other feasible metric, but the error here is lineal and large individual errors might be somewhat compensated with perfect matches, what is not acceptable for clinical use. The whole feature subset process was carried out by RapidMiner Studio version 9.10.011 (RapidMiner GmbH, Dortmund, Germany). Fig. 2 shows the complete

Table 4
Correlations between clinical variables considered in the study.

		MDS-UPDRS Part III	Up&Go	LoS	Time for LoS
Time from onset	Pearson's ρ	0.022	0.477*	-0.395*	0.264
	(p-value)	(0.893)	(0.001)	(0.008)	(0.083)
	R^2	0.001	0.228	0.156	0.070
MDS-UPDRS Part III	Pearson's ρ		0.355*	0.338*	-0.256
	(p-value)		(0.029)	(0.038)	(0.120)
	R^2		0.126	0.114	0.066
Up&Go	Pearson's ρ			-0.420*	0.370*
	(p-value)			(0.007)	(0.019)
	R^2			0.176	0.137
LoS	Pearson's ρ				-0.678*
	(p-value)				(<0.0005)
	R^2				0.460

ρ: Pearson's rho; R^2: Coefficient of determination;* Statistically significant correlations (p <.05).

Table 5
Variance of the model in the rows explained by the variables shared with the models in the columns.

	Time from onset	MDS-UPDRS Part III	Up&Go	LoS	Time for LoS
Time from onset		8.50 %	2.70 %	7.20 %	23.10 %
MDS-UPDRS Part III	4.40 %		1.90 %	15.00 %	27.00 %
Up&Go	27.10 %	2.50 %		6.80 %	19.00 %
LoS	20.20 %	14.00 %	29.10 %		18.30 %
Time for LoS	14.00 %	15.20 %	35.80 %	48.10 %	

LoS: Limit of Stability test.

RapidMiner process model, with all operators and parameters used.

After that, the best subset of variables from the ten runs of the GA was used to build a linear regression model of each clinical variable on the whole dataset, in order to study the contribution of each tapping variable to the corresponding model (the RapidMiner model as well as the raw and processed data are accessible through: https://g-nec.car.upm-csic.es/NeuroMOD/data/). Analysis of variance (ANOVA) was applied to test for statistical significance of the linear models fitting. In addition, for each predictor in the linear models, the corresponding explained variance was calculated as the normalized residual sum of squares (nRSS) with the predictor removed from the model, that is, how much the model deviates from the real data without the removed predictor. Consequently, the higher the nRSS the more important the predictor. Also, the statistical significance of each predictor was calculated by a *t*-test checking whether the corresponding coefficient is different from 0. These statistical analyses were performed by IBM SPSS Statistics v28.0 (IBM Corp., Armonk-NY, USA) with the default parameters.

3. Results

3.1. Clinical testing

Table 2 shows the results of the clinical testing of the participants. According to the average MDS-UPDRS Part III scores the participants showed a mild-to-moderate motor impairment. However, the balance was moderately affected in most participants, where 65 is the bottom limit for LoS normality. Gait affection was just mild or inexistent according the timed Up & Go results. Data from Up & Go and LoS tests (both limit and time) of 3 participants were lost, so the final sample size for these tests was 44. It is also noticed that the subjectivity between evaluators in MDS-UPDRS Part III scores is explicit, with an intraclass correlation coefficient (ICC) with absolute agreement definition of ICC

Table A1
Linear model for years from onset.

Tapping-related variable	Non-standarized coefficients	Stdandarized coefficients	t	p-value
(Intercept)	27.992		54.203	<0.0005
Festinations mean time L T1	0.000	−0.066	−7.046	<0.0005
Festinations mean time R T2	−0.001	−0.224	−24.277	<0.0005
# Festinations R T1	0.736	0.321	29.120	<0.0005
% Festinations L-R Diff. T4	−0.144	−0.113	−12.988	<0.0005
% Festinations L-R Diff. T5	−0.082	−0.106	−11.638	<0.0005
Freezings mean time L T4	0.000	−0.101	−9.366	<0.0005
Freezings mean time R T1	0.000	0.152	13.542	<0.0005
Freezings mean time R All trials	0.000	−0.071	−5.140	<0.0005
# Freezings R T2	0.742	0.472	46.854	<0.0005
# Freezings R T3	−0.133	−0.059	−5.096	<0.0005
# Freezings R T4	−0.163	−0.100	−7.709	<0.0005
Mean time R T3	−0.006	−1.035	−42.146	<0.0005
Delval's Festinations mean time R T1	0.001	0.185	14.610	<0.0005
Delval's Festinations mean time R T2	−0.001	−0.188	−13.595	<0.0005
Delval's Festinations mean time R All trials	0.000	−0.054	−3.298	0.007
Delval's Festinations mean time L-R Diff. T2	−0.003	−0.502	−56.208	<0.0005
Delval's Festinations mean time L-R Diff. All trials	0.000	0.058	4.671	0.001
# Delval's Festinations L T4	−0.057	−0.063	−6.808	<0.0005
# Delval's Festinations L T5	0.088	0.078	8.267	<0.0005
# Delval's Festinations R T4	0.061	0.062	7.752	<0.0005
% Delval's Festinations L-R Diff. All trials	0.026	0.101	8.738	<0.0005
Delval's Freezings mean time R T1	−0.001	−0.998	−66.821	<0.0005
Delval's Freezings mean time R All trials	0.002	1.515	69.678	<0.0005
Delval's Freezings mean time L-R Diff. T2	0.000	0.033	2.339	0.039
# Delval's Freezings L All trials	0.566	0.614	25.261	<0.0005
# Delval's Freezings R T3	1.103	0.354	20.337	<0.0005
# Delval's Freezings R T4	−1.201	−0.312	−14.742	<0.0005
% Delval's Freezings L-R Diff. T1	0.206	0.184	11.045	<0.0005
Uniformity L T1	0.000	−0.033	−2.262	0.045
Uniformity L T2	−0.002	−0.304	−18.276	<0.0005
Uniformity L T3	0.003	0.287	13.055	<0.0005
Uniformity L T4	0.000	0.045	2.191	0.051
# taps L T5	−0.176	−0.387	−31.155	<0.0005
# taps L-R Diff. T5	−0.304	−0.482	−49.714	<0.0005
Uniformity L-R Diff. T3	−0.092	−0.423	−40.966	<0.0005

L: Left finger; R: Right finger; Ti: Trial i. Diff.: Difference.

(2,3) = 0.493 (0.160-0.712). This might be due in part to the heterogeneous modalities of assessment (in-person vs video-based). However, the intraclass correlation coefficient of only the two video-based evaluators, ICC(2,2) = 0.671 (0.298-0.838), although higher, still indicates a moderate inter-evaluator variability. Consequently, the average score of the three evaluators was taken as the MDS-UPDRS Part III variable to be modeled, thus collecting the subjectivity of the test.

3.2. Clinical prediction from tapping variables

Table 3 shows the average of the best RMSEs (standard deviation) over the 10 runs of the GA. For of the best result from the 10 GA runs, Table 3 also reports the average RMSE (standard deviation) from the 10-fold cross-validation and the coefficient of determination (R^2) of the validation parts, and the F-ratio (ANOVA) of the multivariate linear regression model for each clinical variable.

All clinical variables obtained a statistically significant multivariate linear regression model (Appendix I). In prediction terms, Fig. 3 shows the scatter plots of the relation between the actual values of the clinical variables (x-axis) and the predicted values from the multivariate linear regression models of tapping features on the validation folds. All variables were significantly predicted by well-fitted models with a low prediction error and a high coefficient of determination.

Besides, all linear models included variables from both sides and side differences, and from all trials, included the accumulated trial. Fig. 4 shows a summary of the distributions of the variance explained by finger tapping variables of all linear models grouped by side, type and trial. The data in Fig. 4 suggest that the Time from onset is mainly predicted by freezing-related tapping features of the dominant hand (right). The MDS-UPDRS Part III and Up&Go variables are also mainly predicted by freezing-related features, but from the non-dominant hand (left) or the difference between sides. LoS and time for LoS are mainly predicted by festination-related variables of the difference between sides and non-dominant hand, respectively. Nevertheless, the percentage of the variance explained by festination- plus freezing-related features of the prediction models was 71.70 %, 86.00 %, 72.10 %, 87.40 % and 97.00 % for the clinical variables in the columns of Table 3, respectively.

With respect to the two concepts of freezing and festination, the models contained a higher explained variance by the concepts proposed in the present work than from the Delval's et al. (2016) concepts, except for the Time from onset model. With respect to the trials, the variables acquired in the first three trials provided more than the 50 % of explained variance in all models, except for the Up&Go model, where the variables from the rest of the trials and the accumulation variables (sum from all trials) explained more than the 50 % of the variance.

Regarding the repeatability among the different trials, Fig. 5 shows the average values along the trials of the different tapping variables for the two sides. Although the high variability among participants prevents statistically significant differences among the different trials in all variables from appearing, Fig. 5 shows trends over the trials, either positive or negative, for many of the variables and sides, pointing to tentative effects of fatigue and/or habituation the task. This supports the inclusion of the variables from all trials in the analyses.

Finally, Table 4 reports the statistically significant correlations among the clinical variables.

Although the results in Table 4 shows some highly significant correlations such as LoS with Up&Go and Time for LoS, the Pearson's coefficients indicate just low or low moderate correlations (Mukaka, 2012). Moreover, the dispersion of the correlated data, given that R^2 is a normalization of the residuals of the model, is high overall. These numbers explain why the variance in the models, explained by the predictors shared with the others models of the correlated variables, is relatively low, as shown in Table 5.

Table A2
Linear model for MDS-UPDRS Part III.

Tapping-related variable	Non-standarized coefficients	Stdandarized coefficients	t	p-value
(Intercept)	−17.236		−111.109	<0.0005
Festinations mean Time L T1	0.001	0.116	28.063	<0.0005
Festinations mean time L T2	−0.004	−0.655	−159.546	<0.0005
Festinations mean time R T5	−0.001	−0.136	−53.624	<0.0005
Festinations mean time L-R Diff. T1	0.002	0.229	77.554	<0.0005
# Festinations L T1	0.855	0.173	41.836	<0.0005
# Festinations L T4	−2.782	−0.521	−162.582	<0.0005
# Festinations R T2	0.201	0.074	25.495	<0.0005
# Festinations R T4	0.392	0.105	44.156	<0.0005
# Festinations R All trials	−1.106	−0.591	−143.029	<0.0005
Freezings mean time L T1	0.004	1.233	296.890	<0.0005
Freezings mean time L T3	0.001	0.314	134.950	<0.0005
Freezings mean time L All trials	0.004	1.352	233.151	<0.0005
Freezings mean time R T5	−0.001	−0.316	−69.386	<0.0005
Freezings mean time L-R Diff. T3	0.002	1.641	294.389	<0.0005
Freezings mean time L-R Diff. T5	0.000	−0.139	−35.160	<0.0005
# Freezings L T1	−1.723	−0.787	−189.616	<0.0005
# Freezings R T2	−2.527	−1.293	−176.153	<0.0005
Mean time L-R Diff. T3	−0.511	−1.051	−164.817	<0.0005
Delval's Festinations mean time R 1	0.004	0.680	173.714	<0.0005
Delval's Festinations mean time L-R Diff. T3	−0.001	−0.094	−31.726	<0.0005
Delval's Festinations mean time L-R Diff. T4	0.002	0.257	82.460	<0.0005
# Delval's Festinations L1	0.023	0.014	4.852	0.008
# Delval's Festinations R 1	1.028	0.831	118.340	<0.0005
Delval's Freezings mean time R 1	0.000	−0.018	−3.894	0.018
Delval's Freezings mean time R 2	−0.004	−1.805	−216.133	<0.0005
Delval's Freezings mean time L-R Diff. T3	−0.002	−0.870	−155.167	<0.0005
Delval's Freezings mean time L-R Diff. All trials	−0.001	−0.650	−183.647	<0.0005
# Delval's Freezings R T	1.981	1.597	191.082	<0.0005
% Delval's Freezings L-R Diff. All trials	3.098	1.052	151.217	<0.0005
Uniformity L4	−0.003	−0.253	−79.515	<0.0005
# taps L1	0.628	1.295	203.179	<0.0005
# taps L-R Diff. T1	0.056	0.056	15.594	<0.0005
# taps L-R Diff. T2	−0.804	−0.848	−123.695	<0.0005
Uniformity L-R Diff. T1	−0.155	−0.327	−105.609	<0.0005

L: Left finger; R: Right finger; Ti: Trial i. Diff.: Difference.

Table A3
Linear model for LoS.

Tapping-related variable	Non-standarized coefficients	Stdandarized coefficients	t	p-value
# Delval's Freezings L All trials	18.388	0.404	47.453	<0.0005
Festinations mean time L T1	−0.002	−0.095	−13.847	<0.0005
Festinations mean time R T3	−0.004	−0.209	−17.248	<0.0005
Festinations mean time L-R Diff. T3	0.002	0.083	7.187	<0.0005
# Festinations L T2	6.569	0.369	48.546	<0.0005
# Festinations L T4	0.585	0.033	3.827	0.005
# Festinations R T1	−4.931	−0.514	−65.221	<0.0005
# Festinations R T3	2.536	0.244	21.306	<0.0005
# Festinations R All trials	0.470	0.076	10.530	<0.0005
Freezings mean time L T4	0.003	0.449	38.784	<0.0005
Freezings mean time L-R Diff. T5	0.004	0.440	38.931	<0.0005
Freezings mean time L-R Diff. All trials	−0.007	−0.493	−52.175	<0.0005
# Freezings L T1	1.776	0.264	40.604	<0.0005
# Freezings L All trials	−0.923	−0.577	−26.768	<0.0005
% Freezings L-R Diff. T1	0.398	0.119	11.773	<0.0005
% Freezings L-R Diff. T4	−0.486	−0.176	−12.974	<0.0005
Mean time R T2	−0.012	−0.381	−19.557	<0.0005
Mean time L-R Diff. T1	−1.488	−0.870	−46.813	<0.0005
Mean time L-R Diff. T4	1.375	1.216	48.053	<0.0005
Delval's Festinations mean time L T2	0.003	0.113	13.764	<0.0005
Delval's Festinations mean time L-R Diff. T1	−0.012	−0.613	−90.503	<0.0005
Delval's Festinations mean time L-R Diff. T4	−0.008	−0.391	−47.292	<0.0005
# Delval's Festinations L T3	−0.701	−0.269	−18.821	<0.0005
# Delval's Festinations L All trials	0.613	0.456	28.135	<0.0005
% Delval's Festinations L-R Diff. T2	−0.256	−0.109	−11.556	<0.0005
Delval's Freezings mean time L-R Diff. T3	0.001	0.135	13.240	<0.0005
% Delval's Freezings L-R Diff. T4	−2.990	−0.796	−44.926	<0.0005
Uniformity L T2	−0.009	−0.270	−13.866	<0.0005
Uniformity L T5	0.033	0.586	35.044	<0.0005
Uniformity L All trials	−0.019	−0.407	−11.218	<0.0005
Uniformity R T5	−0.008	−0.303	−25.855	<0.0005
# taps L T2	−0.749	−0.403	−27.879	<0.0005
# taps R T1	0.728	0.431	17.927	<0.0005
# taps R T3	−1.321	−0.760	−34.357	<0.0005
# taps L-R Diff. All trials	−0.088	−0.157	−4.878	0.001

L: Left finger; R: Right finger; Ti: Trial i. Diff.: Difference.

Table A4
Linear model for the time for LoS.

Tapping-related variable	Non-standarized coefficients	Stdandarized coefficients	t	p-value
(Intercept)	92.968		206.302	< 0.0005
# Delval's Freezings L All trials	−29.995	−0.525	−139.936	< 0.0005
Festinations mean time L T4	−0.017	−0.587	−117.744	< 0.0005
Festinations mean time R T2	0.013	0.491	123.774	< 0.0005
Festinations mean time L-R Diff. T1	0.001	0.022	5.628	< 0.0005
Festinations mean time L-R Diff. T2	−0.009	−0.309	−74.619	< 0.0005
Festinations mean time L-R Diff. T5	−0.001	−0.037	−11.459	< 0.0005
# Festinations L T1	5.558	0.268	81.065	< 0.0005
# Festinations L T4	10.945	0.489	98.376	< 0.0005
# Festinations L T5	−1.074	−0.047	−14.635	< 0.0005
# Festinations R All trials	−4.290	−0.551	−118.750	< 0.0005
Freezings mean time L T2	0.009	1.083	143.067	< 0.0005
Freezings mean time L T3	−0.004	−0.334	−61.595	< 0.0005
# Freezings L All trials	−1.008	−0.501	−101.210	< 0.0005
% Freezings L-R Diff. All trials	4.561	1.138	153.953	< 0.0005
Mean time L-R Diff. T2	−0.027	−0.012	−2.016	0.079
Mean time L-R Diff. T4	−0.063	−0.045	−7.814	< 0.0005
Delval's Festinations mean time R T4	0.002	0.100	26.246	< 0.0005
Delval's Festinations mean time R T5	0.003	0.111	38.473	< 0.0005
Delval's Festinations mean time L-R Diff. All trials	0.003	0.118	33.646	< 0.0005
# Delval's Festinations L T1	3.533	0.523	124.042	< 0.0005
# Delval's Festinations L T3	2.644	0.809	249.404	< 0.0005
# Delval's Festinations R T1	−1.353	−0.453	−106.832	< 0.0005
% Delval's Festinations L-R Diff. T4	0.509	0.275	80.993	< 0.0005
Delval's Freezings mean time R All trials	0.000	−0.061	−7.409	< 0.0005
Delval's Freezings mean time L-R Diff. T3	0.001	0.086	11.086	< 0.0005
Delval's Freezings mean time L-R Diff. T5	0.001	0.094	18.838	< 0.0005
Delval's Freezings mean time L-R Diff. All trials	−0.002	−0.274	−43.403	< 0.0005
# Delval's Freezings R T1	−15.595	−0.624	−90.636	< 0.0005
Uniformity L T2	0.002	0.045	3.169	0.013
Uniformity L T5	−0.010	−0.146	−18.711	< 0.0005

(*continued on next page*)

Table A4 (*continued*)

Tapping-related variable	Non-standarized coefficients	Stdandarized coefficients	t	p-value
Uniformity R T2	−0.024	−0.392	−56.272	< 0.0005
# taps R T1	−0.832	−0.393	−90.814	< 0.0005
# taps L-R Diff. T1	0.244	0.067	13.102	< 0.0005
Uniformity L-R Diff. T2	0.102	0.102	9.293	< 0.0005
Uniformity L-R Diff. T3	−0.413	−0.362	−41.388	< 0.0005

L: Left finger; R: Right finger; Ti: Trial i. Diff.: Difference.

The only moderately strong correlation found was the one between Time for LoS and LoS (Table 4). In this case, the 48.10 % of the variance of the Time for LoS models is explained by the predictors shared with the LoS model (Table 5). Nevertheless, the correlation between the Pearson's rho and shared explained variance between every pair of models is 0.451, which indicates that the higher correlated the variables the higher explained variance by the shared predictors in the corresponding models.

4. Discussion

Our results showed for the first time that the linear combination of unimanual and bilateral index finger tapping features could characterize and predict the MDS-UPDRS-III score with an RMSE of 0.268 (±0.128), which is lower than any of the minimal clinically important differences (CID) estimated in the literature (Shulman et al., 2010; Horváth et al., 2015; Sánchez-Ferro et al., 2018). In addition, the coefficient of determination between the MDS-UPDRS-III model and the scale score was R^2 = 0.997, is higher than the maximum comparable reported in the literature of R^2 = -0.690 (RMSE of 4.37) with a model of variables obtained from video recordings of classical finger tapping (index to thumb) (Williams et al., 2020b). It is also higher than other R^2 = 0.546 (Kleinholdermann et al., 2021) and R^2 = 0.736 (García-Agundez and Eickhoff, 2021) results obtained from models of electromyography (EMG) and contactless sensors features, respectively. It is even higher than the AUC of 0.980 from just a classifier between healthy and early-stage PD subjects built from keystroke dynamics while typing (Lan and Yeo, 2019). Similarly, the Time from disease onset could be also predicted with an RMSE of 0.254 (±0.104) years and R^2 = 0.995. With respect to the balance scales the LoS was predicted with a RMSE of 1.454 (±0.551) and R^2 = 0.991, and the Time for LoS with a RMSE of 2.977 (±2.332) seconds and the highest R^2 of 0.999, both also lower than the corresponding minimal CID (Pickerill and Harter, 2011). Finally, the scale mostly related with the lower limbs, the Up&Go test, was also accurately predicted from the finger tapping variables with a RMSE of 0.150 (±0.041) and R^2 = 0.995 below the minimal detectable change (Huang et al., 2011). Taken together, the mentioned results constitute the main contribution of the present work: the validation of the use of the estimations from index finger tapping features as easily and remotely measurable, ecological clinical markers of motor symptoms in PD.

Most of the tapping features used to characterize the former clinical variables were related to either freezings or festinations rather than to cadence or velocity. On the one hand, bradykinesia symptoms are expected to contribute, since they are cardinal motor manifestations of PD. Given that the participants were in the ON-medication state, an alleviation and improvement of bradykinetic symptoms would be also expectable. However, even though levodopa actually ameliorates bradykinesia it does not make a difference in the sequence effect, i.e. decrement in amplitude or speed (or progressive hesitations/halts) as movements are continued (Postuma et al., 2015; Bologna et al., 2019). On the other hand, symptoms like festinations are plausibly explained by

Table A5
Linear model for the Up & Go test.

Tapping-related variable	Non-standarized coefficients	Stdandarized coefficients	t	p-value
(Intercept)	7.211		41.436	<0.0005
Festinations mean time L T3	0.001	0.328	23.417	<0.0005
Festinations mean time L T4	0.000	0.064	7.062	<0.0005
Festinations mean time R T1	0.000	−0.059	−5.534	<0.0005
# Festinations L T3	−0.574	−0.208	−19.994	<0.0005
# Festinations R T2	0.104	0.071	5.383	<0.0005
% Festinations L-R Diff. T2	0.134	0.171	11.998	<0.0005
Freezings mean time R T1	0.000	0.068	5.227	0.001
Freezings mean time R T2	0.000	−0.326	−20.705	<0.0005
Freezings mean time R All trials	0.001	0.881	40.170	<0.0005
Freezings mean time L-R Diff. T1	0.001	0.741	54.748	<0.0005
Freezings mean time L-R Diff. T5	0.000	−0.064	−6.634	<0.0005
# Freezings L T5	−0.978	−0.698	−80.105	<0.0005
% Freezings L-R Diff. T1	0.010	0.018	1.151	0.279
% Freezings L-R Diff. T3	0.163	0.221	18.098	<0.0005
Delval's Festinations mean time L-R Diff. T1	0.000	−0.097	−8.606	<0.0005
Delval's Festinations mean time L-R Diff. T3	0.000	−0.084	−8.276	<0.0005
Delval's Festinations mean time L-R Diff. All trials	0.000	0.022	1.210	0.257
# Delval's Festinations L T2	−0.121	−0.094	−13.217	<0.0005
# Delval's Festinations L T3	0.248	0.530	32.659	<0.0005
# Delval's Festinations L T4	−0.416	−0.585	−50.906	<0.0005
# Delval's Festinations R T1	−0.108	−0.159	−18.811	<0.0005
% Delval's Festinations L-R Diff. T3	−0.015	−0.074	−4.324	0.002
% Delval's Festinations L-R Diff. T4	0.093	0.369	44.011	<0.0005
Delval's Freezings mean time L T3	0.000	0.151	12.825	<0.0005
Delval's Freezings mean time L All trials	0.000	−0.047	−3.900	0.004
# Delval's Freezings R T3	−1.334	−0.636	−41.650	<0.0005
% Delval's Freezings R T1	−0.151	−0.156	−7.902	<0.0005
% Delval's Freezings L-R Diff. T4	0.092	0.153	10.738	<0.0005
% Delval's Freezings L-R Diff. T5	0.128	0.199	12.135	<0.0005
Uniformity L T1	0.000	−0.039	−2.814	0.020
# taps L T3	−0.038	−0.123	−10.276	<0.0005
# taps L-R Diff. T1	0.060	0.122	16.513	<0.0005
Uniformity L-R Diff. T1	0.032	0.136	10.266	<0.0005
Uniformity L-R Diff. T2	0.019	0.149	11.866	<0.0005

L: Left finger; R: Right finger; Ti: Trial i. Diff.: Difference.

a defective cue production by the basal ganglia that have been described mostly in gait but also in upper limbs (Iansek et al., 2006; Freeman and Cody, 1993). These results point that most motor symptoms and severity in PD come from the pathological central mechanisms causing freezings and festinations. This knowledge might contribute to the design of more targeted drugs or neuromodulation treatments.

Regarding lateralisation, the prediction models for MDS-UPDRS Part III, Time for LoS and Up&Go are mostly composed of left (non-dominant side in our study) and bilateral difference-related tapping features, pointing to the lateralised nature of the PD symptom severity. However, the Time from onset model was mainly composed of right (dominant side in our study) tapping features, indicating an opposite lateralization of the disease progression. This knowledge might contribute to a finer prescription of the medication depending on the disease duration.

With respect to the timing, the first three trials are the one with more tapping features in all models, suggesting a possible effect of the fatigue in finger tapping not strongly related to the clinical scales. The only exception to this is Up&Go, where the variables of the corresponding linear model belong to all trials (excluding trial 2) in an equally distributed manner. Nevertheless, all trials showed informative for the linear models.

Finally, the finger tapping features were also determinants of the lower limb motor capacity, as measured with the timed Up&Go test and LoS balance tests, which also comprises lower limb function. This is also the first time that lower limb and core-related function capacity are predicted from just upper limb features in PD, which points to a common central cause for most motor symptoms in PD.

Besides, the parameters and hyperparameters selected for all algorithms and methods were the default ones in the software used, except for the number of generations and the number of generations without improvement of the GA, since we were concerned about convergence. Once we confirmed that the GA converged with this set of parameter values and that we obtained a valid performance, different combinations were discarded. Other values could have just made the GA converge faster or reach better performance, although the margin of improvement is marginal given the current results.

The present study carries some limitations to be considered. The first one is related to the sample. The sample size should be larger to better generalize the findings to the majority of the pathological population. In addition, left-handed participants should be also recruited. Nevertheless, the size was enough to yield significant statistical results and avoid overfitting. In addition, the results must be interpreted taking into account that they are derived from mild-to-moderate PD participants in the ON state and cannot be extrapolated to participants in an advanced stage of the disease or in the absence of the effects of dopaminergic therapy. Other limitation of the study is the determination of the MDS-UPDRS Part III score by different modalities (in-person and video-based), which likely introduces variability not due to the evaluator subjectivity. However, the introduced variability is not significative since there is evidence supporting a moderate-good agreement between the two modalities with ICC between 0.53 and 0.78 (Sibley et al., 2021). Moreover, it is also worth considering the video-based modality since it is becoming a common practice since the Covid-19 pandemic (Myers et al., 2021).

5. Conclusion

In this paper, we have shown how the use of a simple computer keyboard paradigm can facilitate clinically valid knowledge about the motor state of a sample of 47 right-handed idiopathic PD patients in the ON-medication state, overcoming the time and periodicity limitations of a standardized clinical evaluation for daily assessment. This paradigm represents a simple, easy and proper method to capture kinematic patients' features that allows clinicians to quantitatively monitor patients' status and progression and assess their motor symptoms and fluctuations unobtrusively, rapidly and even remotely. This information is especially useful when a pharmacological treatment has been prescribed and may provide a more comprehensive vision of the disease and the immediate therapy consequences. Next step involves further validating the approach with more patients in daily real-life settings. Future research will focus on testing the same approach using the touchscreens of common devices, such as smartphones and smartwatches.

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CRediT authorship contribution statement

J. Ignacio Serrano: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Juan P. Romero:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Aida Arroyo-Ferrer:** Investigation, Methodology, Resources, Supervision, Validation, Writing – review & editing. **M. Dolores del Castillo:** Conceptualization, Formal analysis, Funding acquisition, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

A link has been provided inside de manuscript to access models and data used, under a license agreement.

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Appendix

Linear model equations of the study

References

Adams, W. R. (2017). High-accuracy detection of early Parkinson's Disease using multiple characteristics of finger movement while typing. *PloS one, 12*(11), e0188226.

Agostino, R., Currà, A., Giovannelli, M., Modugno, N., Manfredi, M., & Berardelli, A. (2003). Impairment of individual finger movements in Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society, 18*(5), 560–565. https://doi.org/10.1002/mds.10313

AlMahadin, G., Lotfi, A., Zysk, E., Siena, F. L., Carthy, M. M., & Breedon, P. (2020). Parkinson's disease: current assessment methods and wearable devices for

evaluation of movement disorder motor symptoms - a patient and healthcare professional perspective. *BMC neurology, 20*(1), 419. https://doi.org/10.1186/s12883-020-01996-7

Ancona, S., Faraci, F. D., Khatab, E., Fiorillo, L., Gnarra, O., Nef, T., Bassetti, C., & Bargiotas, P. (2021). Wearables in the home-based assessment of abnormal movements in Parkinson's disease: a systematic review of the literature. *Journal of Neurology*. https://doi.org/10.1007/s00415-020-10350-3

Azarpaikan, A., Torbati, H. T., & Sohrabi, M. (2014). Neurofeedback and physical balance in parkinson's patients. *Gait & Posture, 40*(1), 177–181. https://doi.org/10.1016/j.gaitpost.2014.03.179

Biodex Medical Systems, Inc. (2021). Balance System SD (version 4.x) – Instructions for Use and Assembly. Accessed in July 2nd 2021 through https://www.biodex.com/sites/default/files/950440man_10205revd.pdf.

Bologna, M., Guerra, A., Paparella, G., Giordo, L., Alunni Fegatelli, D., Vestri, A. R., Rothwell, J. C., & Berardelli, A. (2018). Neurophysiological correlates of bradykinesia in Parkinson's disease. *Brain: a journal of neurology, 141*(8), 2432–2444. https://doi.org/10.1093/brain/awy155

Bologna, M., Paparella, G., Fasano, A., Hallett, M., & Berardelli, A. (2019). Evolving concepts on bradykinesia. *Brain*, *143*(3), 727–750.https://doi.org/10.1093/brain/awz344.

Camicioli R. (2002). Identification of parkinsonism and Parkinson's disease. *Drugs of today (Barcelona, Spain: 1998)*, *38*(10), 677–686. https://doi.org/10.1358/dot.2002.38.10.740195.

Delval, A., Rambour, M., Tard, C., Dujardin, K., Devos, D., Bleuse, S., Defebvre, L., & Moreau, C. (2016). Freezing/festination during motor tasks in early-stage Parkinson's disease: a prospective study. *Movement Disorders: Official Journal of the Movement Disorder Society, 31*(12), 1837–1845. https://doi.org/10.1002/mds.26762

Fahn S, Elton RL. UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Recent Developments in Parkinson's Disease. 2nd edn Macmillan Healthcare Information; Florham Park, NJ: 1987. pp. 153–163. pp. 293–304.

Foffani, G., & Obeso, J. A. (2018). A cortical pathogenic theory of parkinson's disease. *Neuron, 99*(6), 1116–1128. https://doi.org/10.1016/j.neuron.2018.07.028

Freeman, J.S., Cody, F., W, Schady, W. (1993). The influence of external timing cues upon the rhythm of voluntary movements in Parkinson's disease. *J Neurol Neurosurg Psychiatry* Oct;56(10):1078-84. doi: 10.1136/jnnp.56.10.1078.

Fugl-Meyer, A. R., Jääskö, L., Leyman, I., Olsson, S., & Steglind, S. (1975). The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scandinavian Journal of Rehabilitation Medicine, 7*(1), 13–31.

García-Agundez, A., & Eickhoff, C. (2021). Towards objective quantification of hand tremors and bradykinesia using contactless sensors: a systematic review. *Frontiers in aging neuroscience, 13*, Article 716102. https://doi.org/10.3389/fnagi.2021.716102

Ghoraani, B., Galvin, J. E., & Jimenez-Shahed, J. (2021). Point of view: wearable systems for at-home monitoring of motor complications in parkinson's disease should deliver clinically actionable information. *Parkinsonism & related disorders, 84*, 35–39. https://doi.org/10.1016/j.parkreldis.2021.01.022

Giancardo, L., Sánchez-Ferro, A., Arroyo-Gallego, T., Butterworth, I., Mendoza, C. S., Montero, P., Matarazzo, M., Obeso, J. A., Gray, M. L., & Estépar, R. S. (2016). Computer keyboard interaction as an indicator of early parkinson's disease. *Scientific reports, 6*, 34468. https://doi.org/10.1038/srep34468

Goetz, C. G., & Stebbins, G. T. (2004). Assuring interrater reliability for the UPDRS motor section: utility of the UPDRS teaching tape. *Movement disorders: Official journal of the Movement Disorder Society, 19*(12), 1453–1456. https://doi.org/10.1002/mds.20220

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., Olanow, C. W., & Movement Disorder Society UPDRS Revision Task Force. (2008). Movement disorder society-sponsored revision of the unified parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Movement disorders: Official journal of the Movement Disorder Society, 23*(15), 2129–2170. https://doi.org/10.1002/mds.22340

Hanna-Pladdy, B., Pahwa, R., & Lyons, K. E. (2015). Paradoxical effect of dopamine medication on cognition in Parkinson's disease: relationship to side of motor onset. *J Int Neuropsychol Soc., 21*(4), 259–270. https://doi.org/10.1017/S1355617715000181

Hasan, H., Athauda, D. S., Foltynie, T., & Noyce, A. J. (2017). Technologies Assessing Limb Bradykinesia in Parkinson's Disease. *Journal of Parkinson's disease, 7*(1), 65–77. https://doi.org/10.3233/JPD-160878

Herb, J. N., Rane, S., Isaacs, D. A., Van Wouwe, N., Roman, O. C., Landman, B. A., Dawant, B. M., Hedera, P., Zald, D. H., Neimat, J. S., Wylie, S. A., Donahue, M. J., & Claassen, D. O. (2016). Cortical implications of advancing age and disease duration in parkinson's disease patients with postural instability and gait dysfunction. *Journal of Parkinson's Disease, 6*(2), 441–451. https://doi.org/10.3233/JPD-150753

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology, 17*(5), 427–442. https://doi.org/10.1212/wnl.17.5.427

Horváth, K., Aschermann, Z., Ács, P., Deli, G., Janszky, J., Komoly, S., Balázs, É., Takács, K., Karádi, K., & Kovács, N. (2015). Minimal clinically important difference on the Motor Examination part of MDS-UPDRS. *Parkinsonism & related disorders, 21*(12), 1421–1426. https://doi.org/10.1016/j.parkreldis.2015.10.006

Huang, S. L., Hsieh, C. L., Wu, R. M., Tai, C. H., Lin, C. H., & Lu, W. S. (2011). Minimal detectable change of the timed "up & go" test and the dynamic gait index in people with Parkinson disease. *Physical Therapy, 91*(1), 114–121. https://doi.org/10.2522/ptj.20090126

Iansek, R., & Huxham, F. (2006). McGinley, J, The sequence effect and gait festination in Parkinson disease: contributors to freezing of gait? *Mov Disord., 21*(9), 1419–1424. https://doi.org/10.1002/mds.20998

Jiao, S. R., Song, J., & Liu, B. (2020). A review of decision tree classification algorithms for continuous variables. In Journal of Physics: Conference Series (Vol. 1651, No. 1, p. 012083). IOP Publishing. doi: 10.1088/1742-6596/1651/1/012083.

Kim, Y., Suescun, J., Schiess, M. C., & Jiang, X. (2021). Computational medication regimen for Parkinson's disease using reinforcement learning. *Scientific Reports, 11*(9313). https://doi.org/10.1038/s41598-021-88619-4

Kishore, A., Espay, A. J., Marras, C., Al-Khairalla, T., Arenovich, T., Asante, A., Miyasaki, J., & Lang, A. E. (2007). Unilateral versus bilateral tasks in early asymmetric Parkinson's disease: differential effects on bradykinesia. *Movement disorders: Official journal of the Movement Disorder Society, 22*(3), 328–333. https://doi.org/10.1002/mds.21238

Kleinholdermann, U., Wullstein, M., & Pedrosa, D. (2021). Prediction of motor unified parkinson's disease rating scale scores in patients with parkinson's disease using surface electromyography. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 132*(7), 1708–1713. https://doi.org/10.1016/j.clinph.2021.01.031

Lan, B. L., & Yeo, J. (2019). Comparison of computer-key-hold-time and alternating-finger-tapping tests for early-stage Parkinson's disease. *PloS one, 14*(6), e0219114.

Lanciego, J. L., Luquin, N., & Obeso, J. A. (2012). Functional neuroanatomy of the basal ganglia. *Cold Spring Harb Perspect Med, 2*(12), Article a009621. https://doi.org/10.1101/cshperspect.a009621

Li, J., Zhu, H., Pan, Y., Wang, H., Cen, Z., Yang, D., & Luo, W. (2020). Three-Dimensional Pattern Features in Finger Tapping Test for Patients with Parkinson's disease. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference*, *2020*, 3676–3679. https://doi.org/10.1109/EMBC44109.2020.9176652.

Merola, A., Sturchio, A., Hacker, S., Serna, S., Vizcarra, J. A., Marsili, L., Fasano, A., & Espay, A. J. (2018). Technology-based assessment of motor and nonmotor phenomena in Parkinson disease. *Expert Review of Neurotherapeutics, 18*(11), 825–845. https://doi.org/10.1080/14737175.2018.1530593

Monje, M., Domínguez, S., Vera-Olmos, J., Antonini, A., Mestre, T. A., Malpica, N., & Sánchez-Ferro, Á. (2021). Remote evaluation of parkinson's disease using a conventional webcam and artificial intelligence. *Frontiers in neurology, 12*, Article 742654. https://doi.org/10.3389/fneur.2021.742654

Mukaka, M. M. (2012). Statistics corner: A guide to appropriate use of correlation coefficient in medical research. *Malawi Medical Journal: The journal of Medical Association of Malawi, 24*(3), 69–71.

Myers, T. L., Tarolli, C. G., Adams, J. L., Barbano, R., Cristina Gil-Díaz, M., Spear, K. L., Lowell, J., Daeschler, M., Riley, L., Amondikar, N., Auinger, P., Marras, C., Tanner, C. M., Ray Dorsey, E., & Schneider, R. B. (2021). Video-based parkinson's disease assessments in a nationwide cohort of fox insight participants. *Clinical parkinsonism & related disorders, 4*, Article 100094. https://doi.org/10.1016/j.prdoa.2021.100094

Opara, J., Małecki, A., Małecka, E., & Socha, T. (2017). Motor assessment in Parkinson's disease. *Annals of agricultural and environmental medicine: AAEM, 24*(3), 411–415. https://doi.org/10.5604/12321966.1232774

Pickerill, M. L., & Harter, R. A. (2011). Validity and reliability of limits-of-stability testing: a comparison of 2 postural stability evaluation devices. *Journal of Athletic Training, 46*(6), 600–606. https://doi.org/10.4085/1062-6050-46.6.600

Podsiadlo, D., & Richardson, S. (1991). The timed 'up & go': a test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society, 39*(2), 142–148.

Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkmann, J., Schrag, A. E., & Lang, A. E. (2017). Parkinson disease. *Nature Reviews. Disease Primers, 3*, 17013. https://doi.org/10.1038/nrdp.2017.13

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society, 30*(12), 1591–1601. https://doi.org/10.1002/mds.26424

Roalf, D. R., Rupert, P., Mechanic-Hamilton, D., Brennan, L., Duda, J. E., Weintraub, D., Trojanowski, J. Q., Wolk, D., & Moberg, P. J. (2018). Quantitative assessment of finger tapping characteristics in mild cognitive impairment, Alzheimer's disease, and Parkinson's disease. *Journal of Neurology, 265*(6), 1365–1375. https://doi.org/10.1007/s00415-018-8841-8

Rovini, E., Maremmani, C., & Cavallo, F. (2017). How wearable sensors can support parkinson's disease diagnosis and treatment: a systematic review. *Frontiers in Neuroscience, 11*, 555. https://doi.org/10.3389/fnins.2017.00555

Sánchez-Ferro, Á., Matarazzo, M., Martínez-Martín, P., Martínez-Ávila, J. C., Gómez de la Cámara, A., Giancardo, L., Arroyo Gallego, T., Montero, P., Puertas-Martín, V., Obeso, I., Butterworth, I., Mendoza, C. S., Catalán, M. J., Molina, J. A., Bermejo-Pareja, F., Martínez-Castrillo, J. C., López-Manzanares, L., Alonso-Cánovas, A., Herreros Rodríguez, J., & Gray, M. (2018). Minimal clinically important difference for UPDRS-III in daily practice. *Movement Disorders Clinical Practice, 5*(4), 448–450. https://doi.org/10.1002/mdc3.12632

Shimoyama, I., Ninchoji, T., & Uemura, K. (1990). The finger-tapping test. A quantitative analysis. *Archives of Neurology, 47*(6), 681–684. https://doi.org/10.1001/archneur.1990.00530060095025

Shulman, L. M., Gruber-Baldini, A. L., Anderson, K. E., Fishman, P. S., Reich, S. G., & Weiner, W. J. (2010). The clinically important difference on the unified parkinson's disease rating scale. *Archives of Neurology, 67*(1), 64–70. https://doi.org/10.1001/archneurol.2009.295

Sibley, K. G., Girges, C., Hoque, E., & Foltynie, T. (2021). Video-based analyses of parkinson's disease severity: a brief review. *Journal of Parkinson's disease, 11*(s1), S83–S93. https://doi.org/10.3233/JPD-202402

Specht, D. F. (191). A general regression neural network. *IEEE Transactions on Neural Networks, 2*(6): 568-576. doi: 10.1109/72.97934.

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary* (3rd ed.). Oxford: Oxford University Press.

Tavares, A. L., Jefferis, G. S., Koop, M., Hill, B. C., Hastie, T., Heit, G., & Bronte-Stewart, H. M. (2005). 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. *Movement disorders: official journal of the Movement Disorder Society, 20*(10), 1286–1298. https://doi.org/10.1002/mds.20556

Trager, M. H., Velisar, A., Koop, M. M., Shreve, L., Quinn, E., & Bronte-Stewart, H. (2015). Arrhythmokinesis is evident during unimanual not bimanual finger tapping in Parkinson's disease. *Journal of Clinical Movement Disorders, 2*, 8. https://doi.org/10.1186/s40734-015-0019-2

Trager, M. H., Wilkins, K. B., Koop, M. M., & Bronte-Stewart, H. (2020). A validated measure of rigidity in Parkinson's disease using alternating finger tapping on an engineered keyboard. *Parkinsonism & Related Disorders, 81*, 161–164. https://doi.org/10.1016/j.parkreldis.2020.10.047

Williams, S., Relton, S. D., Fang, H., Alty, J., Qahwaji, R., Graham, C. D., & Wong, D. C. (2020a). Supervised classification of bradykinesia in Parkinson's disease from smartphone videos. *Artificial Intelligence in Medicine, 110*, Article 101966. https://doi.org/10.1016/j.artmed.2020.101966

Williams, S., Zhao, Z., Hafeez, A., Wong, D. C., Relton, S. D., Fang, H., & Alty, J. E. (2020b). The discerning eye of computer vision: Can it measure Parkinson's finger tap bradykinesia? *Journal of the Neurological Sciences, 416*, Article 117003. https://doi.org/10.1016/j.jns.2020.117003