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Evaluation of a sensor algorithm for motor state rating in Parkinson's disease

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ABSTRACT

Introduction: A treatment response objective index (TRIS) was previously developed based on sensor data from pronation-supination tests. This study aimed to examine the performance of TRIS for medication effects in a new population sample with Parkinson's disease (PD) and its usefulness for constructing individual dose-response models.

Methods: Twenty-five patients with PD performed a series of tasks throughout a levodopa challenge while wearing sensors. TRIS was used to determine motor changes in pronation-supination tests following a single levodopa dose, and was compared to clinical ratings including the Treatment Response Scale (TRS) and six sub-items of the UPDRS part III.

Results: As expected, correlations between TRIS and clinical ratings were lower in the new population than in the initial study. TRIS was still significantly correlated to TRS (r_s = 0.23, $P < 0.001$) with a root mean square error (RMSE) of 1.33. For the patients (n = 17) with a good levodopa response and clear motor fluctuations, a stronger correlation was found (r_s = 0.38, RMSE = 1.29, $P < 0.001$). The mean TRIS increased significantly when patients went from the practically defined *off* to their *best on* state (P = 0.024). Individual dose-response models could be fitted for more participants when TRIS was used for modelling than when TRS ratings were used.

Conclusion: The objective sensor index shows promise for constructing individual dose-response models, but further evaluations and retraining of the TRIS algorithm are desirable to improve its performance and to ensure its clinical effectiveness.

1. Introduction

Due to progressively reduced duration of levodopa effects as well as fluctuations in bioavailability of levodopa in Parkinson's disease (PD), wearing-off episodes and levodopa induced dyskinesia may occur related to the narrowing therapeutic window [1,2]. Wearing-off episodes are also caused by reduced dopamine storage capacity as well as dyskinesia due to the change in sensitivity for levodopa treatment. It is important to individualize the magnitude of the response to the levodopa dose to achieve stable treatment effects. The advance of wearable sensors can be utilized to develop ambulatory monitoring systems that can quantify movement characteristics during multiple time points and settings which are difficult to achieve in standard clinical practice. The use of wearable sensors to monitor changes in PD motor states can provide sensitive estimations of dose duration and can make individualized treatments feasible.

We have previously developed a sensor-based dosing system [3–5] that can assess individual treatment effects in term of levodopa dose

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efficacy and duration of effect based on physician observed and rated response as well as quantitative objective assessments of levodopa motor response. The signal evaluation is performed in three steps: during a first step, a sensor-based algorithm automatically recognizes different features of the motor response to levodopa based on repeated hand pronation-supination tests and produces a continuous index as an output [5]. The treatment response index from sensors (TRIS) is used as an input for modelling individual dose response patterns as a second step of the signal evaluation and the models are used to produce dosing suggestions in a final step.

The measurement properties of TRIS were examined with regard to levodopa plasma levels and pharmacodynamic effects in previous studies [5,6]. TRIS had a good correlation to clinical assessments of motor state, not only the Treatment Response Scale (TRS) which it was mapped on [5], but also to selected items of the unified Parkinson's disease rating scale (UPDRS) part III. TRIS was also effective for detecting different motor states over the time course of a single levodopa dose [6]. An independent evaluation of the TRIS is essential for determining if the TRIS results can be generalized to other populations of PD patients and provides reliable information for constructing individual dose-response models.

The aim of this study was to examine TRIS for the use in automated quantification of motor responses to a single levodopa dose in an independent patient population. To proceed to the third step in an automated signal analysis it is necessary to be able to create individual dose models based on TRIS. Therefore we also compared the fitting of individual dose models built between TRIS and TRS ratings.

2. Methods

2.1. Study population and design

This study population was recruited from the Neurology Department at Sahlgrenska University Hospital, Sweden. The population was recruited between August 2016 and February 2017. Eligible participants were aged > 18 and had a diagnosis of idiopathic Parkinson's disease. Full inclusion and exclusion criteria as well as study design have previously been reported in detail [7]. This study protocol was approved by The Regional ethical review board in Gothenburg, Sweden and written informed consent was obtained from all participants, in agreement with the declaration of Helsinki.

2.2. Treatment-response index from sensor, TRIS

The TRIS algorithm was previously trained on an independent study population of 19 participants (referred to as study I) [5]. The developed algorithm was a support vectors machine model (SVM), using six selected principal components as predictors, that had been derived from 88 spatiotemporal features of the wrist sensor signals [5]. The SVM was mapped on the mean TRS ratings from three movement disorder specialists. Details of signal processing and the selected features have been described earlier [5].

2.3. Wearable sensors

Throughout this validation study (referred to as study II) the participants wore four small and lightweight sensors (51 × 34 × 14 mm; 28 g; Shimmer3 IMU units, Ireland) on the dorsum of each wrist and the lateral aspect of each ankle. Only the wrist sensor signals (six signals from three-axis acceleration and three-axis rotation) were used to produce TRIS values by applying the SVM model from study I.

2.4. Levodopa challenge test

The purpose of the levodopa challenge test was to measure the individual response to levodopa intake from a practically defined *off* state (baseline) to best mobility and/or evoked dyskinesia and back to *off* state. Participants performed a series of tasks including hand pronation-supination movements, finger and foot tapping, standing up from sitting, walking across the room and reading a text. The tasks were first performed in the morning when the participants had been off levodopa medication for at least 12 h (the practically defined *off* state). The tasks were repeated at predetermined time points (prior to dosing, dose administration at time 0, and thereafter at 20, 40, 60, 80, 110, 140, 170, 200 and 230 min after dose administration) [6], before and after receiving a single levodopa dose (120% of their regular levodopa derived levodopa equivalent morning dose[2]).

2.5. Video ratings

Video recordings of all participants of study I and II were rated by experienced movement disorder specialists using the TRS, six items of the UPDRS and the Dyskinesia rating scale, from practically defined *off* state (baseline) to 4 h levodopa administration [7]. In study I raters rated independently and mean ratings were used to train the algorithm. In the current study (study II), the raters discussed to reach a consensus rating. The TRS is an ordinal scale with seven levels for assessing global clinical motor response to Parkinson medication. TRS ranges from −3 (severe Parkinsonism) to +3 (severe choreatic dyskinesia), where 0 indicates “on” without any dyskinesias, the interval −1 to +1 as functional “on”, the interval −3 to −2 indicates severe to moderate Parkinsonism and interval +2 to +3 is “on” with moderate to severe dyskinesia [6]. The six items of the UPDRS were finger tapping (item 23), rapid alternating movement of hands (item 25), leg agility (item 26), arising from chair (item 27), gait (item 29) and body bradykinesia and hypokinesia (item 31). The selected six sub-items were considered to be the most relevant and convenient to assess the motor dynamics within a levodopa challenge test, in line with previous studies [6,8]. Dyskinesia was rated on the observed activities using the definitions of the Dyskinesia Rating Scale [9]. The two raters in this study had previously showed a good interrater reliability ($\kappa = 0.68$) and 91% agreement on TRS rating as well as UPDRS part III [8].

2.6. Individual dose-response models

The individual dose-response model is a system of mathematical equations that describes dose effects following levodopa intake [10], which is based on a pharmacokinetic-pharmacodynamics population model (PKPD) and can be created by altering selected parameter values of a population model [3]. The parameter values were selected based on sensitivity analysis and the individual dose-response models are built algorithmically through least squares optimization of the differences between the population PKPD and individual patients’ TRS ratings [3,11]. The selected parameter values are altered to minimize the distance between individual observations and mean PKPD behaviour. The method was first applied on data from 31 patients who were treated with levodopa-carbidopa intestinal gel [3]. When creating individual models TRIS can be used instead of TRS, since the scores are reported in the same range (−3 to +3). Individual dose-response models based on a single dose test can only be constructed if the TRS/TRIS values increase from baseline and then decrease towards baseline again. The behaviour of the TRS/TRIS values was evaluated based on the ability to fit individual dose-response models, which reflects the ability to produce individual parameter values for PKPD models. Because the UPDRS scale does not range from −3 to +3 and only rates aspects of bradykinesia, not dyskinesia, it is not easily mapped on the TRS scale. For that reason UPDRS ratings were not used to create mathematical individual models, but were evaluated visually for the presence of the

[2] Dopamine agonists and MAOB-inhibitors were not included in the calculation and were administered as usual.

above mentioned criteria for fitting an individual dose-response model.

2.7. Assessment of motor fluctuations

The presence of clear motor fluctuations in daily life was determined by two blinded independent movement disorder specialists based on a six-day objective free-living motor symptom accelerometry measurement (Parkinson Kinetigraphs, PKG, Global Kinetics Corporation, Australia) that was conducted prior to the data collection [7]. The objective measurements provide visual graphs of average bradykinesia and dyskinesia scores over the past week [12]. Discrepancies between the blinded evaluations from the two specialists were resolved with a final evaluation and decision by the responsible physician.

2.8. Data analysis and statistics

The motor response to levodopa was evaluated based on changes in TRS ratings over time. Levodopa response was considered positive if TRS improved by at least 1 score during the levodopa challenge test. The practically defined *off* state was the first assessments during the levodopa test (when the patient had been off medication for > 12 h). *Best on*, as "wanted" response, was defined as the maximum TRS value in the range −3 to +1 (as TRS -1 to +1 interval describes functional "on" [8]).

The participants who completed the levodopa challenge test were divided into two subgroups: participants with positive response to levodopa and unequivocal motor fluctuations (abbreviated as LR + MF), and participants without acute response in the levodopa challenge or without apparent motor fluctuations (abbreviated as non-LR/MF).

Spearman rank-order correlations were calculated between TRIS and the clinical ratings. The Spearman correlation coefficient was considered as small if r_s = 0.1 to 0.29, medium if r_s = 0.3 to 0.49, and large if r_s = 0.5 to 1.0 [13]. Changes in clinical ratings and TRIS, from practically defined *off* to *best on* state in the LR + MR group, were compared using parametric paired *t*-test and nonparametric Wilcoxon signed-rank test. The participants who were categorized as non-LR/MF were analyzed as a whole group due to the small number of subjects. Statistical analysis was conducted using SAS version 9.4 and the algorithm performance validation was analyzed in R version 3.3. The significance level was defined as $P < 0.05$.

3. Results

Twenty-five participants with PD (median age 68 years, range 58–82 years, 15 male [60%], Table 1) completed the levodopa challenge test producing a total of 239 assessment time points. The mean (SD) pre-study levodopa equivalent dose for the morning dose was 141 (70) mg and the mean levodopa test dose used in the study (120% of the morning dose) was 176 (79) mg. Individual normalized values of TRS and TRIS are presented in Supplementary Fig. 2. In three participants (participants 5, 8 and 21) TRS remained unaltered throughout the levodopa challenge test. Another five participants (participants 9, 10, 18, 20 and 23) displayed no clear motor fluctuations according to the blinded evaluations of a six-day free-living objective accelerometry measurements using PKG. The remaining 17 participants responded positively to levodopa and had unequivocal objective motor fluctuations (LR + MF).

3.1. Clinical ratings versus TRIS in study II

A stronger correlation with a lower root mean square error (RMSE) was found between TRIS and TRS in the LR + MF group compared to the total population sample (total r_s = 0.23 [small], $P < 0.001$, RMSE = 1.33; LR + MF group r_s = 0.38 [medium], $P < 0.001$, RMSE = 1.29). TRIS was significantly correlated with UPDRS III sum scores and each of 5 sub-items of UPDRS III except for the item of body bradykinesia and hypokinesia (Fig. 1). Out of the six examined UPDRS items gait and leg agility correlated most strongly with TRIS. The dyskinesia ratings were significantly correlated with both TRS and TRIS (Fig. 1).

3.2. Levodopa-induced changes in ratings and TRIS in study II

There was a significant change in clinical ratings and TRIS from practically defined *off* to *best on* state. The mean TRIS was −0.9 in practically defined *off* and −0.5 in *best on* (n = 17, mean diff = 0.32, $t = -2.515$, $P = 0.024$, range of changes −1.29 to 0.47). TRS increased from a median of −2 in practically defined *off* to +1 in *best on* (n = 17, a change of 3 scores, range of changes 0 to 4, $z = -3.45$, $P = 0.001$). A median improvement from practically defined *off* to *best on* of 3 points (n = 17, range of changes −1 to +12 points, $z = -3.24$, $P = 0.001$) was found in the UPDRS sum scores of the six sub-items. Individual changes in TRIS, UPDRS sum scores and TRS and the average spline are shown in Fig. 2.

No participants had dyskinesia in the practically defined *off* state and 3 participants (participants 7, 15 and 16) exhibited dyskinesia 20 min after the levodopa test dose was administered.

3.3. TRIS performance: study I versus study II

A medium correlation of 0.49 with RMSE of 1.14 was reported between TRS and TRIS in study I, using a leave one patient out cross validation setting [5]. In study II, TRIS had a lower correlation to TRS and higher RMSE, but in the LR + MF group the correlation between TRIS and TRS remained medium strength. There are no significant differences in gender, age and years since diagnosis between the two studies. The density functions of the TRS distributions of the two studies are given in Fig. 3. In comparison with study I, the present study had a higher percentage of TRS observations that were lower than or equal to −2 (10% in study I versus 34% in study II, Supplementary Fig. 1).

3.4. Individual dose-response models

Individual dose-response models could be fitted for 19 out of 25 participants (76%) when TRIS was used for modelling (Supplementary Fig. 2). Using TRS, the individual models could be only fitted for 11 out of 25 participants (44%). For those participants, the individual models could also be fitted using the algorithm-based TRIS. The effect of removing outlier data points was also evaluated for TRS and UPDRS. Outliers were identified as scores that either dropped suddenly after the onset of effect, or that suddenly spiked after wearing-off had been established. However, the PKPD model cannot account for these sudden motor fluctuations and that is why in the modelling part these are outliers, whether in clinical terms they are not. After removing such outliers, visual inspection demonstrated that individual dose-response models could be constructed from the UPDRS scores in 20 of the 25 patients (80%) (Supplementary Fig. 3).

4. Discussion

The TRIS could objectively describe motor symptom features that are responsive to levodopa also in a new independent population, and TRIS performed better in patients with positive clinical levodopa tests and obvious motor fluctuations on week-long accelerometry evaluations.

The raters were instructed to incorporate all present symptoms during the entire test sequences to score on the TRS. In contrast, TRIS were built based solely on movement characteristics of the pronation-supination tests. The raters can have difficulty to visually assess minute changes in amplitude and frequency of movements during a single levodopa dose due to the limitations of the human eye and limited

Table 1
Demographics and clinical characteristics of the study population.

Characteristic	All participants (n = 25)	LR + MF (n = 17)	Non-LR/MF (n = 8)
Male, n (%)	15 (60)	10 (59)	5 (63)
Age, median (range), years	68 (58–82)	68 (58–82)	67 (58–78)
Weight, mean (SD), kg	75 (15)	74 (16)	77 (15)
Body mass index, mean (SD), kg/m2	25 (4)	25 (4)	26 (5)
Years since diagnosis, median (range)	10 (4–30)	14 (4–30)	7.5 (5–10)
Symptom fluctuation duration, median (range), years	4 (1–20)	6 (1–20)	2.5 (1–7)
LED, mean (SD),mg/day	1110 (544)	1148 (504)	1030 (652)
Levodopa derived from LED, mean (SD), mg/day	749 (328)	806 (363)	629 (211)
Number of doses/day, mean (SD)	7 (5)	7 (6)	5 (1)
Morning dose, mean (SD), mg	141 (70)	147 (74)	127 (60)
Test dose, mean (SD), mg	176 (79)	178 (87)	173 (62)
MDS-UDPRS, median (range)			
part I	9 (1–22)	6 (3–22)	12.5 (1–20)
part II	18 (1–36)	18 (1–36)	17.5 (2–25)
part III	36 (15–55)	36 (15–55)	42.5 (25–50)
part IV	7 (3–13)	7 (3–13)	7 (4–9)
H& Y stage, n (%)			
2	20 (80)	13 (76)	7 (87)
3	4 (16)	3 (18)	1 (13)
4	1 (4)	1 (6)	0 (0)

LR + MF: levodopa responsive and with motor fluctuation; Non-LR/MF: without demonstrated levodopa response or without evident motor fluctuations; SD: standard deviation; LED: levodopa equivalent daily dose; MDS-UPDRS: Movement Disorder Society's version of the Unified Parkinson's Disease Rating Scale; H&Y: Hoehn and Yahr stage.

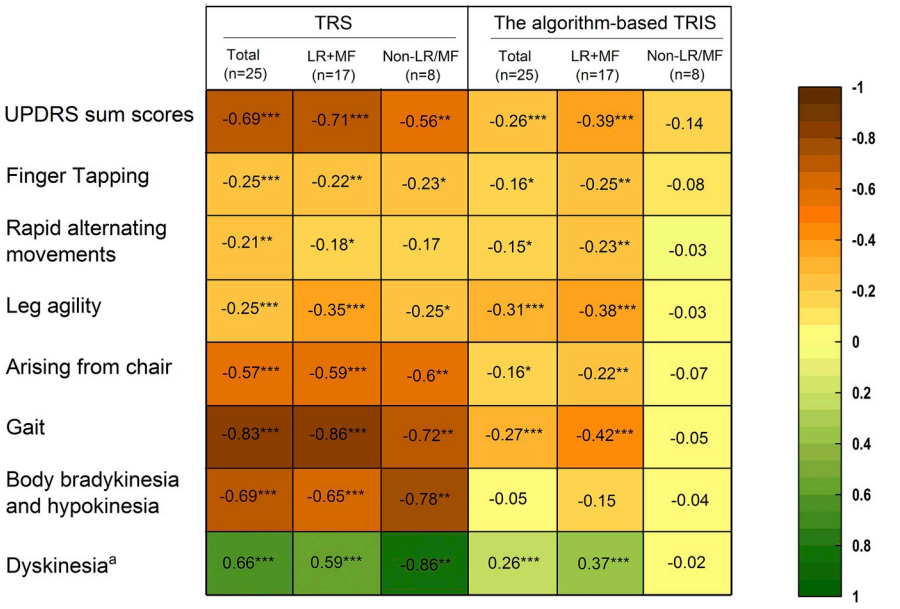

Fig. 1. Spearman correlations between UPDRS sub-items, TRS and TRIS for study II. [a] Dyskinesia was rated using the definitions of the Dyskinesia Rating Scale [9]; Significant level $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. UPDRS: Unified Parkinson's Disease Rating Scale; TRS: Treatment Response Scale; TRIS: Treatment Response Index from Sensors; LR + MF: levodopa responsive and with motor fluctuations; Non-LR/MF: without demonstrated levodopa response or without evident motor fluctuations.

attention. This is suggested by a stronger association between TRS and UPDRS III items that are relatively easy to assess visually (e.g. arising from chair, gait and body bradykinesia and hypokinesia) than the sub-items where rapid and smaller movements are involved (e.g. finger tapping, rapid alternating movements and leg agility, Fig. 1). The medium strength correlation between clinical ordinal scores and continuous measures is therefore somewhat expected. However, the purpose of developing the objective sensor index is to provide clinically relevant features of movement characteristics for constructing individual dose-response models, with a more sensitive measure, rather than to generate a sensor-based version of existing clinical rating scales.

It is common that correlations are weaker when an algorithm was trained on a limited population sample and tested in an independent population and a possible reason can be over- or undertraining of the algorithm. In line with this, the correlations between TRIS and clinical ratings were found to be generally lower in this study, compared to the initial study [5]. The performance of TRIS was robust in the sense that levodopa responses were detected and that the algorithm output TRIS resulted in a similar frequency of individual dose fitting as the more time consuming UPDRS III subset rating. Despite a high variability in both populations, the predictive algorithm was shown to be useful in a new independent population using a different test dose. In this study, a large proportion of the observations was at the −3 (severe Parkinsonism) of the TRS scale (Fig. 3) and there were also more observations at the TRS +2 to +3 level ("on" with moderate to severe dyskinesia) compared to in study I. As discussed previously, the initial training data set (study I) was dominated by TRS -2 to +1 values [5]. The algorithm cannot make accurate predictions in the extremes of the TRS, since only a few observations were present when the algorithm was trained. Therefore the algorithm consistently over-predicts when TRS values are lower or equal to −2 (i.e. Parkinsonism is underestimated). The current results are heavily influenced by the large errors in the predictions at very bradykinetic states, as they consist of one third of the total observations (Fig. 3). Retraining the model from study I with different

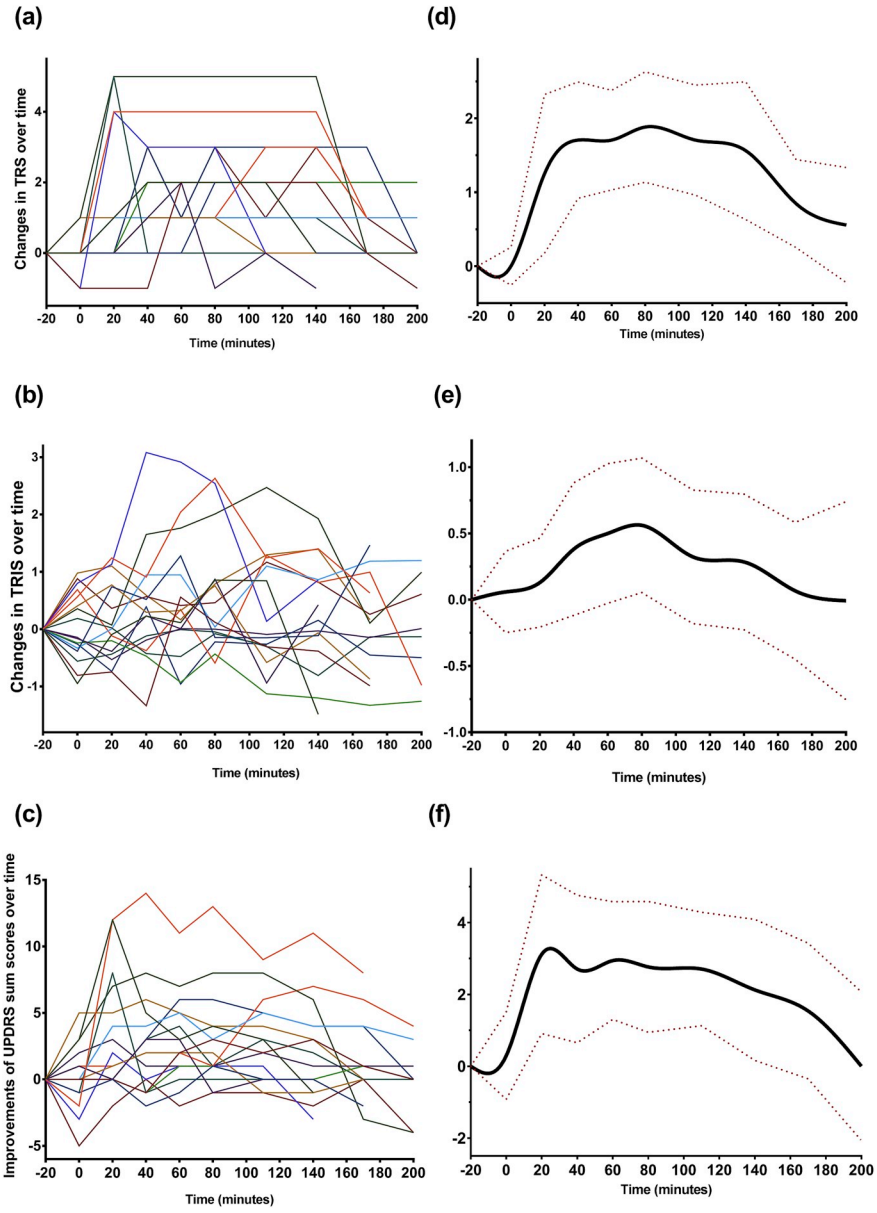

Fig. 2. Spaghetti plots of individual changes in TRS **(a)**, the accelerometry derived TRIS **(b)**, and UPDRS sum scores **(c)** are shown on the left panel. The cubic spline of the average changes with 95% confidence interval (red dots) are shown on the right panel: TRS **(d)**, the accelerometry derived TRIS **(e)** and UPDRS sum scores **(f)**. The maximum change in both TRS and TRIS was found at 80 min and the maximum change in UPDRS sum scores was observed at 20 min, even though these is uncertainty about these estimates, as seen by the confidence interval in the figure. UPDRS: Unified Parkinson's Disease Rating Scale; TRS: Treatment Response Scale; TRIS: Treatment Response Index from Sensors. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

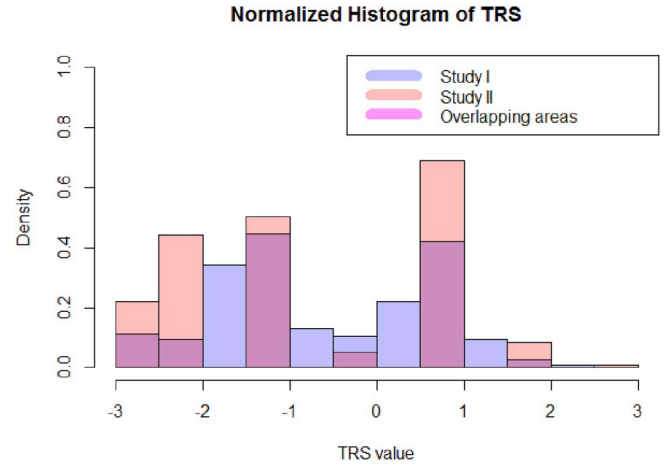

Fig. 3. The histogram of the TRS values for the two studies. It is seen in the plot that for values −3 and −2 study II had about 3 times more observations than study I. TRS, Treatment Response Scale.

feature selection methods did not meaningfully improve its predictive performance [14]. Retraining the TRIS algorithm on data with a higher prevalence of severe Parkinsonism and severe dyskinesia would, however, be useful to improve performance.

It was possible to fit more individual models using TRIS than when TRS was used for modelling. TRS is a seven-level discrete ordinal scale which may not be sensitive enough to capture changes of individual motor response during a single levodopa dose. The continuous TRIS indexes performed comparable well compared to when UPDRS sum scores were used to create individual models, and UPDRS sum scores have a maximum of 24 categorical levels. Although the UPDRS scale is well-validated and widely used to assess PD symptoms, it has some drawbacks compared to TRIS such as the required resources and time to conduct the assessments and of the need of experienced and trained professionals to assign ratings. The algorithm-based TRIS appears to assess motor symptoms and follow treatment effects at an individual level with a similar performance in the context of detecting a single dose dose-response.

The ability to fit individual dose-response models is essential for using dosing algorithms. In this study sample population, the 19 individual dose-response models that were fitted with TRIS produced

maintenance and morning dosing suggestions through dosing algorithms. These dosing suggestions were strongly correlated with dose adjustments made by a supervising neurologist based on information provided from a week-long objective assessment combined with patient interviews (maintenance dosing suggestions $r_p = 0.8$, the mean relative error of the prediction 21%; morning dosing suggestions $r_p = 0.95$, the mean relative error 12.5%) [11]. The weeklong objective assessment aided adjustments improved PD symptoms and disease related quality of life short term [7].

A sensor-based individual dosing suggestion system is a natural progression from objective instrumental tests [12,15]. Automated objective interpretation of sensor-based measurements and dose suggestions could in the long run improve care, and outcomes, by better individualization of levodopa dosing schedules. If integrated with web-based applications, it could also facilitate long distance assessments when patients are in their home environment [16].

The strengths of the present evaluation are that the developed algorithm was tested in a new population and the results were overall in line with the initial study. The TRIS is therefore potentially useful for modelling individual levodopa dose-responses. It can also be considered a strength that the algorithm performed best in patients with motor fluctuation and positive response to levodopa as it supports the clinical usefulness of applying this method on patients with undeniable levodopa response and short effect duration. Limitations include that the sample size was relatively small, which limits the generalization of the results. Furthermore, the consensus rating between the two raters in this study could affect the correlation between TRS and TRIS as a more limited set of integer outcome values was produced. Some of the mismatch could tentatively be addressed by retraining the TRIS algorithm on patients with more extreme TRS values. Further studies are necessary to clarify validity, reliability, responsiveness and clinical utility of the objective index.

In conclusion, correlations between the objective sensor index and clinical ratings were lower in the new population, and the predictive algorithm performed best in patients with a positive response to levodopa and clear motor fluctuations. Although the objective sensor index shows promise for constructing individual dose-response models, further improvement of TRIS is desirable to ensure its performance as well as its clinical effectiveness. Future evaluations will be based on a TRIS algorithm trained on a population sample pooled from study I and II.

Conflicts of interest

The private company Sensidose AB filed a patent application based on the results and the authors IT, MM and JW are listed as inventors in this application.

Author JS is an employee of Sensidose AB.

Author FO is an employee of RISE Research Institutes of Sweden AB.

Author DN served as a consultant to Sensidose AB until 2013.

Author AE was an employee of RISE Acreo AB at the time of his contribution.

The remaining authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.03.022.

References

[1] J.E. Ahlskog, M.D. Muenter, Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature, Mov. Disord. 16 (3) (2001) 448–458.
[2] C.D. McColl, K.A. Reardon, M. Shiff, P.A. Kempster, Motor response to levodopa and the evolution of motor fluctuations in the first decade of treatment of Parkinson's disease, Mov. Disord. 17 (6) (2002) 1227–1234.
[3] I. Thomas, M. Alam, D. Nyholm, M. Senek, J. Westin, Individual dose-response models for levodopa infusion dose optimization, Int. J. Med. Inform. 112 (2018) 137–142.
[4] I. Thomas, F. Bergquist, D. Johansson, D. Nyholm, M. Memedi, J. Westin, Automated dosing schemes for administration of microtablets of levodopa for Parkinson's disease, using wearable sensors, Mov. Disord. 32 (S2) (2017) 532.
[5] I. Thomas, J. Westin, M. Alam, F. Bergquist, D. Nyholm, M. Senek, et al., A treatment-response index from wearable sensors for quantifying Parkinson's disease motor states, IEEE J. Biomed. Health Inform. (99) (2017) 1-1.
[6] M. Senek, S.M. Aquilonius, H. Askmark, F. Bergquist, R. Constantinescu, A. Ericsson, et al., Levodopa/carbidopa microtablets in Parkinson's disease: a study of pharmacokinetics and blinded motor assessment, Eur. J. Clin. Pharmacol. 73 (5) (2017) 563–571.
[7] D. Johansson, A. Ericsson, A. Johansson, A. Medvedev, D. Nyholm, F. Ohlsson, et al., Individualization of levodopa treatment using a microtablet dispenser and ambulatory accelerometry, CNS Neurosci. Ther. 24 (5) (2018) 439–447.
[8] D. Nyholm, A.I. Nilsson Remahl, N. Dizdar, R. Constantinescu, B. Holmberg, R. Jansson, et al., Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease, Neurology 64 (2) (2005) 216–223.
[9] C.G. Goetz, G.T. Stebbins, H.M. Shale, A.E. Lang, D.A. Chernik, T.A. Chmura, et al., Utility of an objective dyskinesia rating scale for Parkinson's disease: inter- and intrarater reliability assessment, Mov. Disord. 9 (4) (1994) 390–394.
[10] J. Westin, D. Nyholm, S. Palhagen, T. Willows, T. Groth, M. Dougherty, et al., A pharmacokinetic-pharmacodynamic model for duodenal levodopa infusion, Clin. Neuropharmacol. 34 (2) (2011) 61–65.
[11] I. Thomas, M. Alam, F. Bergquist, D. Johansson, M. Memedi, D. Nyholm, et al., Sensor-based algorithmic dosing suggestions for oral administration of levodopa/carbidopa microtablets for Parkinson's disease: a first experience, J. Neurol. 266 (3) (2019) 651–658.
[12] R.I. Griffiths, K. Kotschet, S. Arfon, Z.M. Xu, W. Johnson, J. Drago, et al., Automated assessment of bradykinesia and dyskinesia in Parkinson's disease, J. Parkinson's Dis. 2 (1) (2012) 47–55.
[13] J. Cohen, CHAPTER 3 - the significance of a product moment rs, in: J. Cohen (Ed.), Statistical Power Analysis for the Behavioral Sciences, Academic Press, 1977, pp. 75–107.
[14] F. Javed, I. Thomas, M. Memedi, A comparison of feature selection methods when using motion sensors data: a case study in Parkinson's disease, Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society, IEEE Engineering in Medicine and Biology Society. Annual Conference, 2018, pp. 5426–5429 2018.
[15] D.A. Heldman, A.J. Espay, P.A. LeWitt, J.P. Giuffrida, Clinician versus machine: reliability and responsiveness of motor endpoints in Parkinson's disease, Park. Relat. Disord. 20 (6) (2014) 590–595.
[16] M. Memedi, J. Westin, D. Nyholm, M. Dougherty, T. Groth, A web application for follow-up of results from a mobile device test battery for Parkinson's disease patients, Comput. Methods Progr. Biomed. 104 (2) (2011) 219–226.