A mobile-based system can assess Parkinson's disease symptoms from ***home environments of patients***

Treatment of Parkinson's disease (PD) patients involves major challenges like the large within- and between-patient variability in symptom profiles and the emergence of motor complications. As PD progresses, the symptoms develop slowly and they represent a significant source of disability in advanced patients. During evaluation of treatments and symptoms, both the physician- and patient-oriented outcomes offer complementary information. In addition, quantitative assessments of symptoms using sensing technologies can potentially complement and enhance both patient and clinician perspectives. At Högskolan Dalarna, the Lecturer **Mevludin Memedi** has developed a telemetry system that assesses symptoms via analysis of self-assessments and motor tests to objectively measure disease-related outcomes and to improve the management of PD.

PD is a neurodegenerative disorder of the central nervous system that is associated with a number of motor and non-motor symptoms. The major motor symptoms of the disease include bradykinesia (slowness of initiating voluntary movements), rigidity (increased muscle tone), tremor (a 3–5 Hz tremor at rest) and impaired postural stability. A challenge for the clinical management of the disease is the large within- and between-patient variability in symptom profiles. Furthermore, PD patients experience fluctuations in symptoms during both under- and over-medications. When under-medicated patients experience common PD symptoms whereas when over-medicated they experience abrupt, involuntary movements also known as dyskinesias.

The most common way for assessing PD motor symptoms is during clinical visits by using clinical rating scales like the Unified Parkinson' Disease Rating Scale (UPDRS) and the 39-item PD questionnaire (PDQ-39). Although these in-clinic rating scales have proved to be useful in quantifying the severity of the symptoms, their main limitation is related to the low resolution of assessments by providing a momentary snapshot of the clinical condition of the patients. In addition, the clinical visit is experimental and may not accurately represent the activities of patients in their home environments.

Telemedicine methods for collecting, summarizing and visualizing symptom data can be useful in this context. In contrast to the in-clinic scales, these methods are useful for detecting subtle symptom changes as well as for providing objective (observer-independent) measures that can be repeated at multiple time points. This article presents the development and evaluation of computer-based methods for automatic and remote monitoring of PD symptoms, using data collected by means of a telemetry touch screen device. A summary of different studies and results can be found below. The summary was published in entirety as part of the doctoral thesis entitled "Mobile systems for monitoring Parkinson's disease" at the School of Science and Technology, Örebro University[1].

PATIENTS AND METHODS

The results presented in this article are based on data from two clinical studies, both of which were approved by the relevant agencies and written informed consent was given. In total, 95 patients in different clinical stages of PD and 10 healthy elderly (HE) subjects were assessed (Table 1). Sixty-five patients with advanced PD were recruited in an open longitudinal 36-months study at nine

THE TELEMETRY TEST BATTERY

Figure 1. A photograph of the telemetry test battery. The test battery consisted of a patient diary section for collecting self-assessments of symptoms and a motor test section (tapping and spirography) for collecting objective measures of upper limb motor function.

clinics around Sweden[2]. On inclusion, 35 of the patients were treated with levodopa-carbidopa intestinal gel (LCIG, hereafter denoted as LCIG-non-naïve) and 30 patients were candidates for switching from oral treatment to LCIG (hereafter denoted as LCIG-naïve). Thirty patients in Milan, Italy, who had a clinical diagnosis of idiopathic PD participated in a second study[3].

Both patients and HE subjects performed repeated, time-stamped and remote assessments of their subjective and objective health indicators using a telemetry test battery implemented on a touch screen handheld device[4]. On each test occasion, patients were first asked to answer seven PD-related questions and then to perform a set of upper limb motor tests including tapping and tracing spirals on the screen of the device (Figure 1). The subjects were instructed to place the device on a table, be seated in a chair and use an ergonomic stylus to perform the tests. Measurements with the test battery were performed four times per day during week-long test periods in the homes of patients.

One aim of the work was to develop methods for quantifying the severity of PD-related impairments during alternating tapping and spirography tests[5,6]. Initially, the digitized movement data, consisting of stylus position and timestamps, were processed using time series analysis techniques. This step was essential for deriving a number of quantitative measures, useful for representing relevant symptom information. Numerous measures comprising spatial displacements and time-dependent effects of movements were calculated including low- and high-frequency components, statistical moments, trend components, irregularity components and similarity measures. The tapping data was summarized into scores for speed, accuracy, fatigue, arrhythmia and a global tapping severity. Secondly, different machine learning methods were used to map the quantitative measures to clinician-based measures, which were derived through visual inspection of tapping graphs and images of static spirals. Va-

CHARACTERISTICS OF THE PARTICIPANTS IN THE TWO CLINICAL STUDIES

	Swedish study	Italian study (F group)	Italian study (S group)	Healthy elderly
Patients (n, gender)	65 (43m; 22f)	15 (13m; 2f)	15 (13m; 2f)	10 (5m; 5f)
Age (years)	65 ± 11	65 ± 6	65 ± 6	61 ± 7
Years with levodopa	13 ± 7	7 ± 8.5	5.5 ± 6	NA
Hoehn and Yahr stage at present	2.5 ± 1*	2 ± 0**	2 ± 0.5	NA
Total UPDRS	**49 ± 20.5***	**33.5 ± 11.8****	**26 ± 16.5**	**NA**

Table 1. Characteristics of PD patients and of healthy elderly participants, presented as median ± interquartile range.
* Assessments performed in the afternoon. ** Assessments performed in the On state. Abbreviation: NA, not applicable.

lidity of the methods was measured as the correlation/agreement between visual and computed scores. Reliability was measured as the internal consistency of the computed scores and as the test-retest reliability of the scores over time. The objective measures of motor function were then analyzed with respect to self-assessed motor conditions[7].

Another aim of the work was to develop a method for providing comparable information content as the UPDRS scale by combining self-assessments of symptoms and motor test results into composite scores[8, 9]. The scores represented six symptom dimensions including walking, satisfaction, dyskinesia, off, tapping and spiral, and an 'overall test score' (OTS) for reflecting the global health condition of the patients during week-long test periods. The OTS was defined as a linear combination of the six dimensions and their respective coefficients, which were estimated by a least squares multiple linear regression model with total UPDRS as a dependent variable. In addition, a web-based system for providing a visual representation of symptom scores over time was developed, allowing clinicians to remotely monitor the symptom profiles of their patients[8].

The evaluation of the system was done in two stages: first presenting and demonstrating its functionalities to an advisory board consisting of neurologists and to nurses who had experience using the telemetry device during the Swedish clinical study period. A second evaluation determined the level to which nurses were satisfied with the usability of the system by administering a standard questionnaire.

"Methods for assessing the severity of symptoms and treatment-related complications are crucial for effective clinical management of PD."

RESULTS

The method for scoring the drawing impairment in spirals correlated well with the visual ratings of spirals given by two neurologists with a Spearman rank correlation coefficient of 0.89 ($p<0.001$)[5]. In addition, the method had good test-retest reliability indicating a good stability of its scores over time. The method for automatic assessment of alternating tapping performance of patients had good validity, internal consistency and sensitivity to treatment changes[6]. In addition, the method was able to discriminate between patients in different stages of PD and HE subjects and its scores significantly differed among categories of the UPDRS motor scale measuring upper limb motor performance (Figure 2).

The objective measures of upper limb motor function could discriminate between motor conditions among patients; tapping speed was related to Off symptoms whereas spatial irregularity during spirography was related to dyskinesias[7].

The six symptom dimensions of the test battery had a good internal consistency with a Cronbach's alpha coefficient of 0.81. The OTS correlated well with total UPDRS and total PDQ-39 scores with a coefficient of 0.59 ($p<0.001$)[9]. In the case of LCIG-naïve patients, the mean OTS improved to the first test period on LCIG treatment and this improvement remained significant until month 24 (Figure 3). The maximum improvement was seen at month 3 with 0.15 units (32%, $p<0.001$) higher than at baseline.

In the case of evaluation of the web-based system, eleven of the 14 neurologists had a positive impression, 1 had a neutral impression and 2 had a negative impression. The responses of the nurses can be summarized in a qualitative manner as follows: the web-based system is very useful, the results during the test periods showed agreement with qualitative observations of the patient e.g. "one patient was in a bad condition at baseline, he improved after starting LCIG, then he became better again, 24-h infusion started and the patient became better again; we can clearly follow this change in the system, comparisons between patients are possible, that is one patient is in better/worse condition than another". Responses to the questionnaire were mixed; a majority of the nurses were quite satisfied with the usability although a sizeable minority was not.

TAPPING RESULTS VERSUS UPDRS MOTOR SCALE

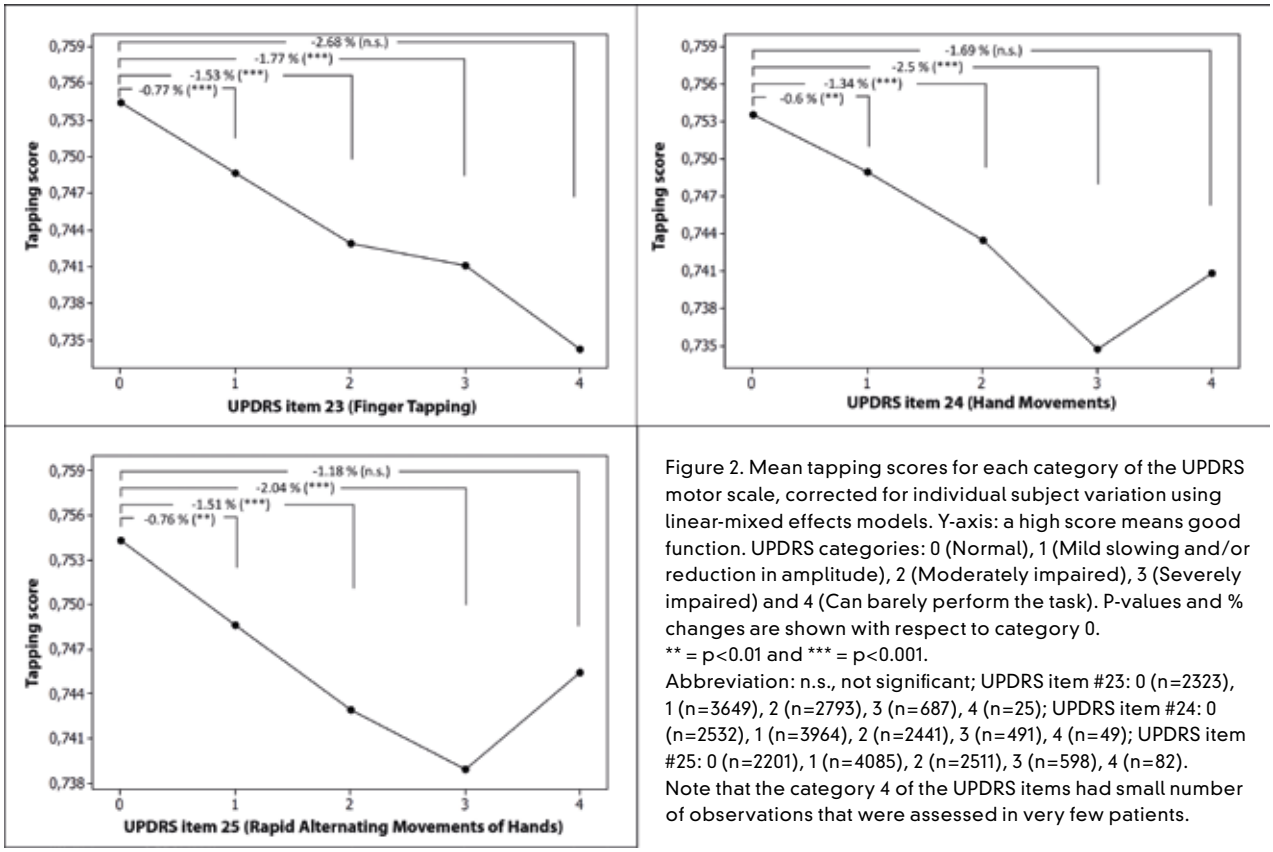

Figure 2. Mean tapping scores for each category of the UPDRS motor scale, corrected for individual subject variation using linear-mixed effects models. Y-axis: a high score means good function. UPDRS categories: 0 (Normal), 1 (Mild slowing and/or reduction in amplitude), 2 (Moderately impaired), 3 (Severely impaired) and 4 (Can barely perform the task). P-values and % changes are shown with respect to category 0.
** = p<0.01 and *** = p<0.001.
Abbreviation: n.s., not significant; UPDRS item #23: 0 (n=2323), 1 (n=3649), 2 (n=2793), 3 (n=687), 4 (n=25); UPDRS item #24: 0 (n=2532), 1 (n=3964), 2 (n=2441), 3 (n=491), 4 (n=49); UPDRS item #25: 0 (n=2201), 1 (n=4085), 2 (n=2511), 3 (n=598), 4 (n=82).
Note that the category 4 of the UPDRS items had small number of observations that were assessed in very few patients.

OVERALL TEST SCORES OF LCIG-NAÏVE AND LCIG-NON-NAÏVE PATIENTS

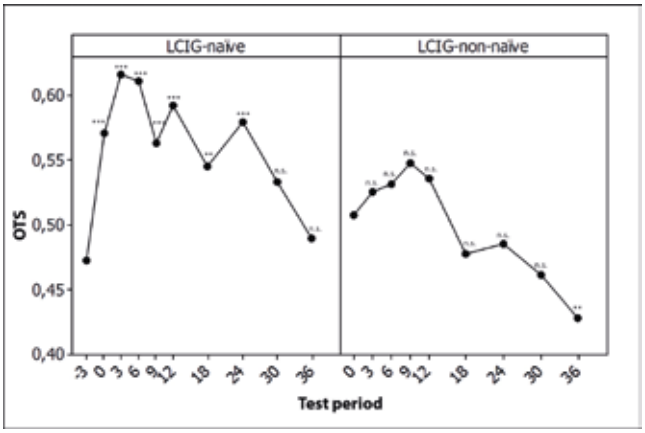

Figure 3. Trends of mean OTS scores of LCIG-naïve and LCIG-non-naïve patients over the 36 month study period, corrected for individual subject variation using linear-mixed effects models. A high OTS score means good function.
P-values are shown with respect to initial test periods.
* = p<0.05; ** = p<0.01; *** = p<0.001.
Abbreviation: LCIG = levodopa-carbidopa intestinal gel; n.s. = not significant;
Test period (LCIG-naïve): -3, baseline (n=20); 0 (n=19); 3 (n=19); 6 (n=16); 9 (n=16); 12 (n=16); 18 (n=15); 24 (n=13); 30 (n=9); 36 (n=4);
Test period (LCIG-non-naïve): 0 (n=35); 3 (n=32); 6 (n=30); 9 (n=26); 12 (n=25); 18 (n=24); 24 (n=20); 30 (n=14); 36 (n=16).
Note that the last two periods, that is month 30 and month 36, had small number of reports making conclusions from these periods difficult to interpret.

DISCUSSION

Methods for assessing the severity of symptoms and treatment-related complications are crucial for effective clinical management of PD. Relevant telemedicine approaches to remote monitoring of PD motor symptoms and complications include e-diaries, wearable inertia sensor systems, various testing tools and video-based monitoring systems. The objective methods for quantifying the symptom severity can potentially complement and enhance both clinician and patient perspectives. Objective assessments may better help to capture symptom severity and fluctuations as compared to using conventional clinical rating scales which are subject to clinical judgment and bias. In this article the use of IT-based methods was explored in order to develop a system architecture, consisting of computer-based methods for quantitative assessment of symptoms and the software around this platform, for providing an effective alternative to management of PD.

The methods for assessing the severity of upper limb motor impairments during alternating tapping and spirography were evaluated as being feasible approaches for quantitative and objective assessment of symptoms. The methods were designed and tailored for long-term telemetering of symptoms as well as had good level of clinical interpretability. Both the methods provided

means for deriving objective measures of symptom severity, which in turn can be used as valid outcomes in clinical trials for remote evaluation of upper limb motor function of patients.

The OTS and the six symptom dimensions of the test battery were evaluated as being feasible outcome measures for long-term and remote monitoring of PD symptoms. The internal consistency among the dimensions was good indicating that they measure the same construct of symptom severity. In addition, the OTS correlated well with total UPDRS and total PDQ-39 scores as well as was sensitive to treatment changes and could reflect the natural PD progression over time in advanced Swedish patients. In general, using an OTS may facilitate the patient screening process and help avoiding sub-optimization of treatments. The OTS could also be beneficial for deciding if a treatment change leads to an improvement of a patient's general condition or not.

The results from the usability evaluation of the web-based system showed that the information presented was comparable to qualitative clinical observations of the nurses who had experience using the telemetry device during the Swedish study. In addition, from the demonstration of its functionalities to the neurologists it was concluded that using the system assists in identifying patients who are not doing well and facilitates follow-up optimization of an individual patient's treatment. The system was seen as most important for fluctuating patients and for regional patients i.e. patients living in regions far away from a clinic and can be considered as a tool that will assist in the management of patients.

Although the methods presented in this article were good at reflecting the severity of symptoms, they could not detect and measure symptoms which are typical for movement patterns exhibited during under- and over-medicated motor conditions that is Off and dyskinesia, respectively. In order to accomplish this, future research may be directed towards collecting simultaneous and multidimensional movement data using wearable sensors, tapping and spirography tests, and eye movement sensors and then to map their quantitative measures to a Treatment Response Scale[10] which ranges from -3 (very off) to +3 (very dyskinetic). Having such kind of objective measures would be beneficial for both patients and health care providers; patients would be able to self-control their symptoms and treatments whereas health care providers would be able to use them as decision support during individualized evaluation of treatments so that their patients can avoid unwanted symptoms which occur during under- and over-medications. Another interesting issue that may be investigated is how dosing information will be related to the symptoms and how to develop a method for an individualized optimal dosing.

In summary, despite the efficacy of the currently available telemedicine systems, their effectiveness in routine clinical practice has yet to be established and should be widely adopted[11]. Many aspects including validity, reliability, security and privacy, usability and acceptability must be considered before they can be applied in routine clinical care.

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