



Clinical feasibility of a wearable, conformable sensor patch to monitor motor symptoms in Parkinson's disease[☆]



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ABSTRACT

Introduction: Clinical assessment of motor symptoms in Parkinson's disease (PD) is subjective and may not reflect patient real-world experience. This two-part pilot study evaluated the accuracy of the NIMBLE wearable bio-sensor patch (containing an accelerometer and electromyography sensor) to record body movements in clinic and home environments versus clinical measurement of motor symptoms.

Methods: Patients (Hoehn & Yahr 2–3) had motor symptom fluctuations and were on a stable levodopa dose. Part 1 investigated different sensor body locations (six patients). In Part 2, 21 patients wore four sensors (chest, and most affected side of shin, forearm and back-of-hand) during a 2-day clinic- and 1-day home-based evaluation. Patients underwent Unified Parkinson's Disease Rating Scale assessments on days 1–2, and performed pre-defined motor activities at home on day 3. An algorithm estimated motor-symptom severity (predicted scores) using patch data (in-clinic); this was compared with in-clinic motor symptom assessments (observed scores).

Results: The overall correlation coefficient between in-clinic observed and sensor algorithm-predicted scores was 0.471 ($p = 0.031$). Predicted and observed scores were identical 45% of the time, with a predicted score within a ± 1 range 91% of the time. Exact accuracy for each activity varied, ranging from 32% (pronation/supination) to 67% (rest-tremor-amplitude). Patients rated the patch easy-to-use and as providing valuable data for managing PD symptoms. Overall patch-adhesion success was 97.2%. The patch was safe and generally well tolerated.

Conclusions: This study showed a correlation between sensor algorithm-predicted and clinician-observed motor-symptom scores. Algorithm refinement using patient populations with greater symptom-severity range may potentially improve the correlation.

1. Introduction

Parkinson's disease (PD) is a highly debilitating neurodegenerative

disease that affects approximately 1 million individuals in the United States and approximately 2.3 million people in the European Union [1,2]. The cardinal symptoms are tremor, rigidity, akinesia (or bradykinesia),

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and postural instability [3]. However, differences in symptoms across patient populations and variant therapeutic options can complicate treatment [4]. Moreover, motor function and disability worsen with time [5], leading to substantial impairment in quality of life (QOL) [6,7]. Periodic assessment of changes in symptom severity thus plays an important role in tailoring PD treatment and tracking patient QOL.

In current clinical practice, assessment of motor symptoms in PD patients involves capture of patient history, use of patient diaries, and neurological evaluations. Patient diaries are susceptible to poor compliance [8], reporting bias, and inaccuracies [9]. The Unified Parkinson's Disease Rating Scale (UPDRS) [10], the most commonly used scale in clinical assessment of PD, is time-consuming to administer and performed by a trained clinician, as is the updated Movement Disorders Society instrument (MDS-UPDRS) [11]. This type of evaluation is subjective as subsequent assessments may be influenced by earlier reports and/or by inter-rater variability [12], and the brevity of routine in-clinic examinations may not accurately reflect motor impairments and fluctuations experienced in everyday life [13,14].

Tools are needed that provide objective, quantitative, continuous, and real-world assessment of PD. Such measures may help patients log medication use (and provide reminders when the next dose is due) and monitor the effects of therapeutics on their symptoms. In addition, there is potential for clinicians to obtain real-time data not otherwise available between clinic visits, such as symptom frequency, variation, and severity, which would allow them to customize treatment to the needs of individual PD patients.

Recently, body-integrated sensors, smartphones, and wrist-worn devices have begun to enable long-term continuous monitoring of motor symptoms of individuals with PD in the clinic and home environments [13]. Although much of the early work occurred in controlled clinical environments, later efforts have focused on home and community-based monitoring of PD motor symptoms [15–17]. The NIMBLE biosensor patch (MC10, Inc., Lexington, MA, USA) can be attached to different body parts, and was developed to record accelerometry and electromyograph (EMG) data in PD patients. This two-part exploratory pilot study assessed the accuracy of the patch in continuous measurement of motor symptoms in PD patients.

2. Materials and methods

2.1. Study population

Participants had PD (defined by bradykinesia, plus tremor at rest, rigidity, or impairment of postural reflexes) at Hoehn and Yahr (HY) stage 2–3 in the “on” state during screening, with troublesome motor fluctuations (e.g. tremor, gait, and dyskinesia including early morning motor impairment), and on a stable levodopa dose of ≥ 200 mg for ≥ 4 weeks before enrollment. Exclusion criteria included body mass index ≥ 30 kg/m², electronic implants, clinically relevant skin disease or sensitivities, or atypical PD symptoms resulting from drugs, metabolic neurogenetic disorders, encephalitis, or cerebrovascular or degenerative diseases. The study protocol was approved by an institutional review board (Aspire IRB, Santee, CA) and conducted in accordance with the principles of the Declaration of Helsinki; informed consent was obtained from all enrolled participants.

2.2. Device

The NIMBLE patch contains an accelerometer and an EMG embedded into a flexible, conformable patch that attaches to skin via an adhesive sticker (Supplemental Fig. 1). It measures and records patterns in movement and muscle activity and wirelessly transmits this information to a smartphone/tablet and to the cloud server. Additional technical details are available in Supplemental text. An administrator software application on a smartphone/tablet was used to configure and control the patch (Supplemental Fig. 2). This included wirelessly setting operating parameters to verify the device's functionality, and, in Part 2 of the study, to transfer data to a cloud server environment for analysis.

A participant-facing application (“diary app”) on a smartphone/tablet allowed wireless transmission of participant-reported data in Part 2.

2.3. Study design and procedures

This two-part study was conducted from December 2014 to February 2015 (Part 1) and from November 2015 to July 2016 (Part 2).

2.3.1. Part 1

During a 2-day, in-clinic, evaluation period, up to 10 patches were placed on various body locations (right and left forearms, right and left shins, chest, and back of tremor-dominant hand). Patches on the flexor digitorum (forearm) and tibialis anterior (shin) muscle groups recorded accelerometer and EMG data streams; patches on the back of the hand and chest recorded only accelerometer data. A device with similar sensor configuration recently demonstrated performance in tracking gait and step count (although simpler tasks to measure than those in the current study) comparable with commercially available devices [18].

Participants underwent a full MDS-UPDRS [11] assessment on day 1; and on day 2 participants underwent multiple MDS-UPDRS Part III assessments and completed the Parkinson's Disease Sleep Scale-2 (PDSS-2) [19] and a Hauser paper diary for PD [20]. Patches were then removed and participants were discharged. Raw data from the patch and clinician-provided MDS-UPDRS-III scores were used to establish algorithms, which were applied to motor assessment datasets in the clinic in Part 2 (feature extraction and model selection details in Supplemental text).

2.3.2. Part 2

On day 1 of a 3-day observation period (2 days in clinic), patches were applied to the chest, and the shin, forearm, and back of hand on the side of the body most affected by motor symptoms. Participants used the diary app (instead of paper diary) to document medicine intake, sleep, and PD symptoms, and to conduct and record a series of motor tasks (Supplemental Table 1). On the morning of day 2, new patches were applied to the shin and forearm (and other sites if needed), and a subset of UPDRS-III motor tasks were completed 60 and 30 min before levodopa intake and then repeated every 30 min after levodopa intake for seven or more sets. At least 1 h after the motor assessments were complete, patches were removed, new patches applied, and participants were discharged with the patches attached and the diary app containing device. On day 3, participants at home performed one set of motor tasks following instructions on the diary app in the morning before levodopa intake and at least two sets of motor tasks (30 min apart) after levodopa intake. Participants were instructed to complete additional motor activities when symptoms changed from “on” to “off”, or vice versa.

2.4. Outcomes

The primary outcome of the study was to translate the NIMBLE patch accelerometer and EMG output data into patterns of PD motor symptoms. For this, algorithms were developed to translate accelerometry and EMG output into motor symptom parameters.

Primary variables were:

- Recognizable patterns in motor symptoms obtained from patch output that could be:
 - o translated via algorithms into measures of PD symptoms (tremor and postural instability)
 - o during sleep, translated via algorithms into measures of sleep quality.
- UPDRS scores obtained in clinic in relation to patch output.

During data collection, sections of data were tagged via a timestamp (to indicate which motor task was occurring) and then underwent

numerous transformations. Pre-processing (filtering, segmentation) of data from the two sensors (accelerometer and EMG) derived several features (feature extraction: e.g. signal entropy, dominant frequency ratio, line length, spectral entropy) for each patient, patch location, and UPDRS motor task. The features were then passed to a machine learning model to determine the importance of each feature for predicting the severity of each UPDRS task. Processing steps and feature extraction are explained further in [Supplemental text](#), [Supplemental Figs. 3–4](#), and [Supplemental Tables 2–3](#).

Safety assessments included device-emergent adverse events (DEAEs) at the application site, device deficiencies, and skin tolerability. All participants had a safety follow-up approximately 3 days after patch removal.

Other variables are described in [Supplemental text](#).

2.5. Statistical analyses

Although no formal power analysis was performed, a sample size of 26 participants was anticipated to be appropriate for a pilot study [21].

Multiple algorithms were developed to translate raw patch output into data relating to PD motor symptom severity that could be analyzed (i.e. predicted scores).

Variables were analyzed using data from the full analysis set (FAS; all participants for whom at least one patch was applied for ≥ 4 h continuously in Part 1; a total of ≥ 24 h in Part 2). Safety was assessed in the safety set (SS; all participants for whom at least one patch was applied for any time period).

All analyses were descriptive and exploratory. A post hoc analysis was performed on observed (i.e. clinician-determined via UPDRS) and predicted scores (from Parts 1 and 2 algorithms) for each motor activity in the in-clinic assessments of Part 2. Pearson correlation coefficients between observed and predicted mean scores (computed for each participant) were calculated for each motor activity and globally, and reported together with their *p*-value.

3. Results

3.1. Participant disposition and characteristics

Twenty-five participants were included in the FAS and SS: six in Part 1 and 21 in Part 2 (two participants from Part 1 were also enrolled in Part 2). All six participants in Part 1 and 19 (90.5%) in Part 2 completed the study, with two lost to follow-up (therefore, these two patients did not complete the Patient Data Presentation Questionnaire). The majority were male and white ([Supplemental Table 4](#)). Participants had mild-to-moderate disease severity (HY stages 2/3, Part 1: 50%/50%, Part 2: 67%/33%).

3.2. Part 1 outcomes

Fifty-four NIMBLE patches were utilized in six participants. Assessment of data generated with the participants identified the forearm, shin, and back of tremor-dominant hand as the body locations that captured the preponderance of motor symptoms associated with PD, while minimizing the number of patches that must be worn ([Fig. 1](#)). Patch accelerometer data were most valuable for tasks that resulted in a large range of motion of the body segment to which the patch was attached (e.g. alternating hand movement [pronation/supination] and leg agility). When the range of motion was small (e.g. finger tapping, hand movements, and toe tapping), patch accelerometer data added less value.

The patch attached to the chest was deemed feasible to track sleep disturbances through capturing movement during sleep and had the potential to identify some motor symptoms and broadly monitor “on”/“off” fluctuations.

3.3. Part 2 outcomes

A total of 221 patches were applied to 21 participants on the forearm, back of the hand, shin (all on the more affected side), and chest. Algorithms were established as described in [Supplemental text](#). The algorithm models used the same identified data streams (accelerometry or EMG) collected at the established anatomical locations in Part 1.

3.3.1. Accuracy of Part 2 algorithm from in-clinic assessments

Error was defined as the difference between the observed (neurological assessment/clinical) and the predicted (biosensor data) scores, and ranged from -4 to $+4$ with the value 0 corresponding to an exact match (exact accuracy) between these two scores. The exact accuracy of Part 2 clinical algorithms as applied to overall Part 2 data, i.e. predicted vs observed scores, was 45%, and the overall predicted score was within a ± 1 range (error rate, -1 to 1) 91% of the time ([Fig. 2](#)). The exact accuracy of each individual activity varied, ranging from 32% (pronation/supination) to 67% (rest tremor amplitude). All assessments other than rest tremor amplitude (67%) and gait (58%) had $< 50\%$ exact accuracy. The algorithm accuracy with an error rate of ± 1 was greatest for postural tremor (98%). Algorithms for kinetic tremor, rest tremor amplitude, toe tapping, gait, and postural tremor also had scores of $\geq 90\%$ (90%, 94%, 95%, 97%, and 98%, respectively). Only accuracy of leg agility and pronation/supination was $< 90\%$ (83% and 86%, respectively).

The match between Part 2 algorithm-predicted scores and the scores observed by the neurologist for participants' PD symptoms during the in-clinic assessments ($n = 1117$) was evaluated with confusion matrices. Results showed that an observed overall score of 1 was most common (in 406 samples), and that 60% of these assessments were predicted by the algorithm to have the same score (i.e. a score of 1), indicating a 60% accuracy for this predicted score (additional data in [Supplemental text](#) and [Supplemental Fig. 5](#)).

A post hoc analysis showed the average correlation coefficient between observed and predicted scores in-clinic was 0.471. Among the individual activities, rest tremor amplitude and toe tapping algorithms had the highest correlations (0.746 and 0.709 respectively) ([Fig. 3](#)).

Individual participant mean absolute errors (MAE) between observed and Part 2 algorithm-predicted mean motor assessment scores (aggregate calculated from individual predicted scores from each activity) ranged from 0.161 to 0.857 (average value, 0.390; [Supplemental Table 5](#)).

The mean in-clinic predicted (from Part 1 and 2 algorithms) and observed scores were similar before and after levodopa intake ([Fig. 4](#)). Additional findings on motor assessment scores and timing of levodopa administration are in [Supplemental text](#) and [Supplemental Tables 5 and 6](#).

3.3.2. Adhesiveness

Adhesion scores were recorded for 213 of 221 patches in Part 2. Overall adhesion success (score, 0 or 1) was 97.2%, and six (2.8%) patches failed (score, 2–4) including full detachment (score, 4) in three (1.4%) patches.

3.3.3. Sleep quality

The quality of sleep was evaluated using participants' responses to sleep-related questions on the diary app.

Descriptors used included “fall asleep,” “stay asleep,” “night immobility,” “night cramps,” and “tremor on waking,” with each scored from 0 (no problems) to 4 (severe problems).

Sleep actigraphy data from patches showed the total mean (standard deviation (SD)) times lying down in clinic and at home were similar for the 21 participants (7 h 8 min (1 h 40 min); 7 h 10 min (1 h 19 min), respectively). More posture changes were observed in in-clinic (67.4 (34.6)) than at home (60.0 (28.0)).

MDS-UPDRS items	Sensor locations						Sensor type	
	RFA	RBH/LBH	LFA	RLS	LLS	CHS	ACC	EMG
Speech								
Facial expression								
Rigidity								
Postural stability								
Hoehn and Yahr stage								
Pronation/supination								
Toe tapping								
Leg agility								
Gait								
Postural tremor								
Kinetic tremor								
Rest tremor								
Finger tapping								
Hand movements								
Arising from chair								
Freezing of gait								
Posture								
Bradykinesia								
Constancy of rest tremor								

Yes
 No
 Unconfirmed

Fig. 1. Feasibility matrix. A matrix showing the feasibility of utilizing data from the NIMBLE patch at different locations on the body to characterize individual items of the MDS-UPDRS III.

Dark gray indicates positive confirmation of feasibility and light gray indicates negative confirmation of feasibility (partly based on the Davies-Bouldin index [DBI]). DBI is a measure of distance between objective classes (in this case, UPDRS scores 0–4) in the feature space. Patch locations where classes were well separated in the feature space, as demonstrated by the DBI, were considered feasible.

Black indicates unconfirmed feasibility because of lack of data. Data are from participants in Part 1. Abbreviations: MDS-UPDRS = Movement Disorders Society-Unified Parkinson’s Disease Rating Scale. For location: RFA/LFA = right/left forearm, RBH/LBH = right/left back of hand, RLS/LLS = right/left shin, CHS = chest. For sensor type: ACC = accelerometer, EMG = electromyography.

No discernible relationship was identified between the total amounts of motor activity, or total time lying down (both recorded by the patch) during sleep and the quality of the sleep pattern descriptors reported by participants via the diary app (Supplemental Fig. 6).

3.3.4. Participant feedback

Participants found the patch easy to use, not painful to detach, felt that it did not appreciably interfere with daily activities or sleep, or cause embarrassment in public, and were very satisfied with the usage training provided (Supplemental Table 7). In addition, most participants reported the information gathered from the patch (per the example shown on Supplemental Fig. 7), to be helpful, and considered the diary app an easy to use tool (Supplemental Table 8).

3.4. Safety

In Part 1, the mean (SD) total device application duration (from first patch application to last patch removal) was 18.14 (0.96) h. Four participants reported DEAEs of erythema; all were associated with the device upon its removal, were of minimal or mild intensity, and resolved within 24 h. No serious DEAEs or discontinuations because of DEAEs were reported.

In Part 2, the mean (SD) total device application duration was 43.55 (1.97) h. One participant (4.8%) reported application site irritation (moderate intensity) and application site pain (mild intensity); both were associated with the patch.

Mean vital signs (blood pressure (systolic and diastolic), pulse, and body temperature) were in the normal ranges in Parts 1 and 2.

Clinically significant physical and neurologic examination abnormalities observed at screening were all either PD or considered related to diagnosis of PD.

4. Discussion

Results of this pilot study support the potential usefulness of the NIMBLE patch in providing accurate, objective, and continuous measurement of motor symptoms in PD patients. In Part 1, the positions where body segment movement was recorded most accurately were the forearm, back of the hand, and shin (all on the more affected side); these body locations, together with the chest (for measurement of sleep and positional actigraphy) were used in Part 2. Results indicated that the patch was able to record motor activity associated with PD symptoms and the algorithms could transform the recorded data into meaningful symptom severity scores. Part 1 results also indicated that NIMBLE accelerometry data were most valuable for tasks that resulted in a significant range of motion of the body segment to which the patch was attached. When the range of motion was limited (e.g., hand movements, toe tapping), measuring accelerometry was not feasible due to sensor placement; in those instances EMG-data were more valuable. The overall accuracy of the patch (per algorithm accuracy data) as evaluated with the Part 2 algorithm was 45%, ranging from 32% (pronation/supination) to 67% (rest tremor amplitude) for an exact

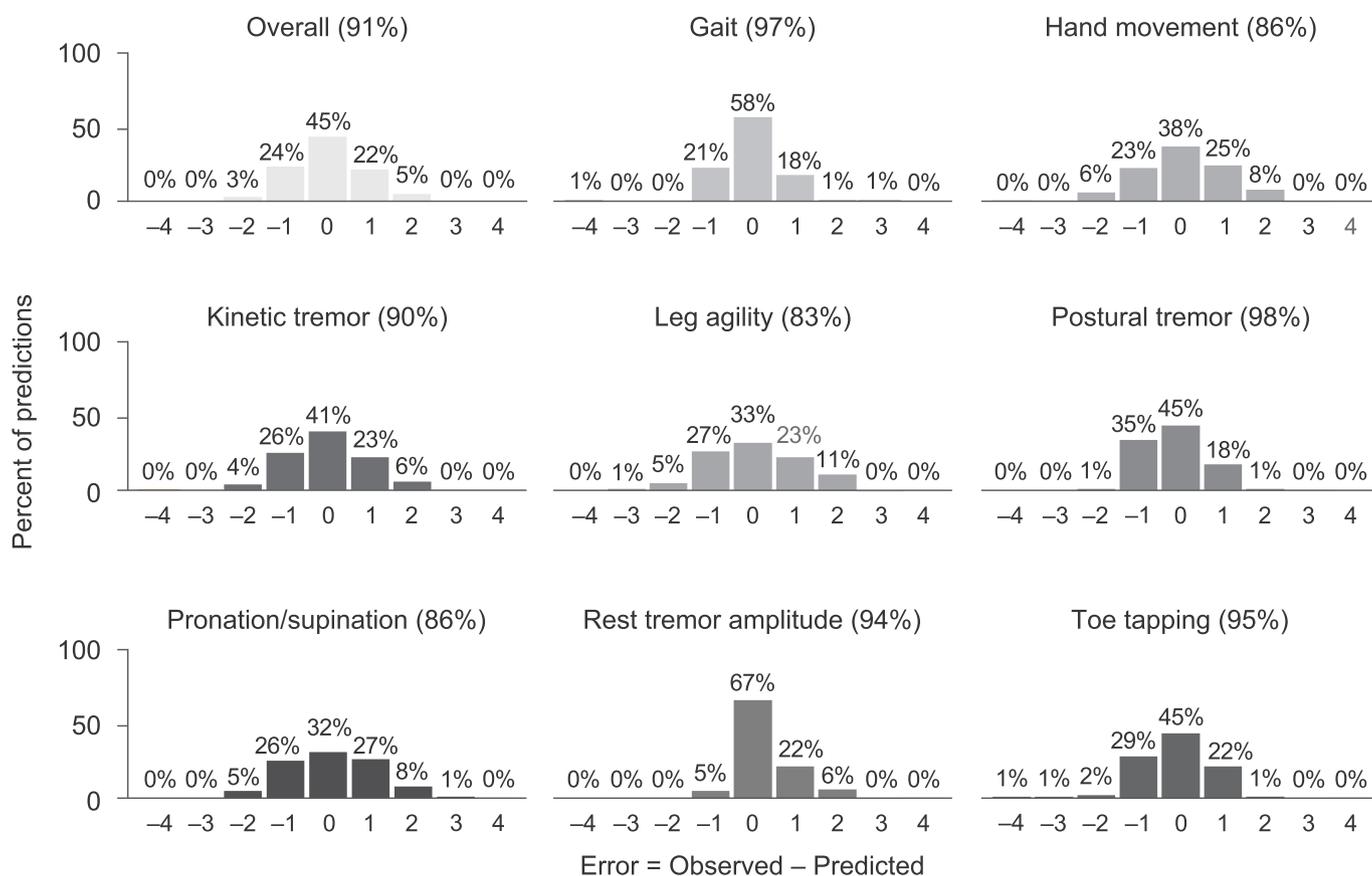


Fig. 2. Error distribution of Part 2 algorithm across UPDRS III subset activities performed in-clinic (FAS). The error was defined as the difference between the observed (neurological assessment) and the predicted (Part 2 algorithms leveraging patch data) scores, and ranged from -4 to +4 with the value 0 corresponding to an exact match between these two scores. Data above figures show the percentage of predicted scores within a ± 1 range of the observed score. Abbreviations: FAS = full analysis set, UPDRS = Unified Parkinson's Disease Rating Scale.

Activity	n	Number of assessments	Correlation coefficient	p value ¹	Clinician score distribution and algorithm prediction accuracy ²
Rest tremor amplitude	20	143	0.746	0.0002	0 1 2 3
Toe tapping	20	139	0.709	0.0005	0 1 2 3 4
Postural tremor	20	141	0.477	0.034	0 1 2 3
Kinetic tremor	20	137	0.437	0.054	0 1 2 3
Leg agility	19	133	0.320	0.182	0 1 2 3 4
Hand movements	21	146	0.291	0.201	0 1 2 3
Pronation-supination	20	140	0.213	0.367	0 1 2 3 4
Gait	20	138	0.164	0.489	0 1 3 4
Average (all activities)	21	140	0.471	0.031	0 1 2 3 4

Accuracy

Fig. 3. Correlation between in-clinic predicted and observed motor symptom severity scores across UPDRS III subset activities in Part 2 (post hoc exploratory analysis; FAS).

¹Test of significance by Pearson coefficient correlation.

²Data represent the relative representation of clinician scores for each activity (0–4 UPDRS score) in Part 2, colored by the accuracy of predicting that score (displayed below graphic). Algorithms were more accurate for scores with more assessments. No scores of 4 were observed for hand movement, kinetic tremor, postural tremor, and rest tremor amplitude, and no scores of 2 were observed for gait. Abbreviations: FAS, full analysis set, UPDRS = Unified Parkinson's Disease Rating Scale.

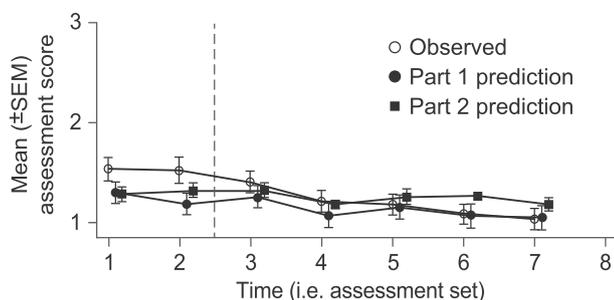


Fig. 4. In-clinic mean motor assessment scores over time for the average of eight MDS-UPDRS III (Part 1) or UPDRS III (Part 2) subset activities for all participants in Part 2 (FAS).

Dashed line indicates levodopa intake.

Abbreviations: FAS = full analysis set, MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale, SEM = standard error of the mean.

The mean motor assessment score was an aggregate score calculated from the individual predicted scores from each activity (gait, hand movement, kinetic tremor, leg agility, postural tremor, pronation-supination, rest tremor amplitude, and toe tapping).

match (error rate of 0) to the observed score of the participant's PD motor symptoms. The accuracy was within a ± 1 range (error rate of -1 to 1) 91% of the time. The correlation coefficient between the observed and predicted scores of the participant's mean motor symptoms of all activities based on the Part 2 algorithm was 0.471 ($N = 21$ participants). High correlation coefficients were observed for hand movements and rest tremor amplitude, suggesting movement was most accurately measured at these sites, and driving the overall correlation. The patch adhesion success was 97.2%. The patch was safe to use and generally well tolerated.

Participants found the patch easy to use and the information gathered, including symptom changes follow medication administration and postural changes during sleep, to be valuable in the management of their PD symptoms. Moreover, $> 75\%$ indicated they used the diary app to record and display information on their symptoms, and $> 40\%$ indicated the medication log and reminder feature was their favorite characteristic of the diary app.

This exploratory study had several limitations. All patients were in HY stage 2 or 3, representing a limited range of symptom severity, although reflective of clinical practice. The number of participants, per protocol, was small which may have led to sub-optimized sensor locations and sensing modes and to algorithms biased to the specific symptom types and severity levels of this participant set. However, the correlation between predicted and observed PD motor symptom severity will likely improve with algorithm refinement with larger studies in participants with greater ranges of symptom severity. Another limitation was the reliance on patient self-reporting for home-based data, which may be mitigated with continued use and greater acceptance of such remote tracking approaches.

No relationship between total motor activity during sleep or total time lying (as detected by the patch data and participant-reported sleep pattern) was discerned. This may be because of the use of measures of sleep quality (i.e. sleep pattern descriptor scores) which were not validated or granular enough, and is in accordance with other studies showing lack of correlation between objective and subjective sleep measures [22].

Further study limitations are described in [Supplemental text](#).

Despite these limitations, the NIMBLE patch showed potential as an objective, quantitative, and continuous measure of motor symptoms, sleep disorders, and symptoms that manifest during sleep in patients with PD. Monitoring of sleep disorders is of particular interest as up to 98% of PD patients may experience night-time sleep disruption [23].

Additionally, there may be value in future EMG-based studies for symptoms that are harder to diagnose via sensors or even cameras (e.g. rigidity) as well as value in a combined approach where EMG combined with accelerometry data may provide more accuracy or insights than using one modality alone.

These wearability and usability results highlight the utility of wearable sensors in clinic and home settings. In the future, this type of real-time tracking of motor symptoms could lead to the development of closed-loop systems [24], which utilize sensing capabilities to optimize drug dosing or provide wireless feedback to a deep brain stimulation device [25]. Furthermore, the tools presented here, including the patient-facing diary app, could increase patient engagement, facilitate improved communication between patients and physicians, and through improving the acceptability of clinically valid remote symptom monitoring, improve patient QOL and treatment satisfaction [26]. In conclusion, given the observed correlation seen between predicted and observed symptom scores (Fig. 3) and that this correlation can be further improved with algorithm refinement, the NIMBLE patch technology offers potential for measuring the severity of some PD motor symptoms.

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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.2018.11.024>.

Author contributions

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Declaration of interest

Babak Boroojerdi, Michael Markowitz, Katie Melton, Christian Otoul, Oliver Stumpp, Daljit Tatla, and Kasper Claes are employees of UCB Pharma. Michael Markowitz and Christian Otoul receive UCB stock units from their employment. Ellora Sen-Gupta and John A. Wright Jr. are employees of MC10, Inc. Ellora Sen-Gupta and John A. Wright, Jr. receive MC10, Inc. stock options from their employment. Shyamal Patel, Jake Phillips, Nirav Sheth, Roozbeh Ghaffari, Nikhil Mahadevan, and Briana Morey are former employees of MC10, Inc. Dolores Terricabras is a former employee of UCB Pharma.

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employed by UCB Pharma were involved in conduct of the research; in study design; in the collection, analysis, and interpretation of data; in writing the report; and preparation of the article and the decision to submit the article for publication.

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