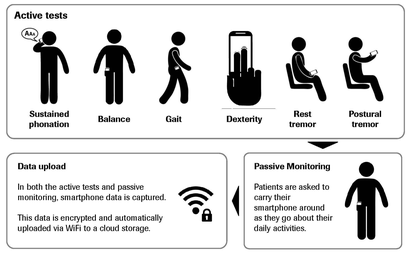
Successful passive monitoring of early-stage Parkinson's disease patient mobility in a Phase I RG7935/PRX002 clinical trial with smartphone sensors

Authors: Florian Lipsmeier[1], Ignacio Fernandez Garcia[1], Detlef Wolf[1], Timothy Kilchenmann[1], Alf Scotland[1], Jens Schjodt-Eriksen[1], Wei-Yi Cheng[1], Juliane Siebourg-Polster[1], Liping Jin[1], Jay Soto[2], Lynne Verselis[1], Meret Martin Facklam[1], Frank Boess[1], Martin Koller[2], Michael Grundman[2,3], Max A. Little[4,5], Andreas U. Monsch[6], Ron Postuma[7], Anirvan Ghosh[1*], Thomas Kremer[1], Kirsten I. Taylor[1], Christian Czech[1], Christian Gossens[1], Michael Lindemann[1]

[1] Roche Pharma Research and Early Development, pRED Informatics, Pharmaceutical Sciences, Clinical Pharmacology, and Neuroscience, Ophthalmology, and Rare Diseases Discovery and Translational Area, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, 4070 Basel, Switzerland; [2] Prothena Biosciences Inc, South San Francisco, U.S.A. [3] Global R&D Partners, LLC, San Diego, California, U.S.A.; [4] School of Mathematics, Aston University, Birmingham, United Kingdom; [5] Oxford Parkinson's Disease Centre, University of Oxford, UK; [6] Felix Platter Hospital, University Center for Medicine of Aging, Memory Clinic, Basel, Switzerland; University of Basel, Faculty of Psychology, Switzerland; [7] Department of Neurology, McGill University, Montreal General Hospital, Montreal, Canada; *current address: Biogen, Cambridge, U.S.A.

1. Rationale - Objectives

This investigation determined the feasibility and preliminary validity of passive-based measures of motor symptoms and mobility in early-stage Parkinson's disease (PD) patients.



2. Methods and clinical setting

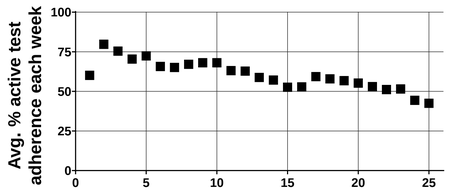
PD patients (n=44) from cohorts 4-6 of the Phase I PRX002/RG7935 Multiple Ascending Dose clinical trial performed smartphone-based assessments for 24 weeks at home. The study included three in-clinic MDS-UPDRS assessments. In a healthy control (HC) study (n=35), age and gender-matched participants performed the identical assessments for 6 weeks. Both cohorts were instructed to perform six active tests daily targeting postural tremor, rest tremor, sustained phonation, balance, gait, and dexterity. In addition, subjects carried the smartphone in their pocket as part of their daily routine (passive monitoring).

Parameter	PD patients in PhI RG7935/PRX002	Healthy Control Study
Study duration (days)	169 + screening	45
N	44	35
Age (y)	58.5 ± 8.5	56.2 ± 7.1
Gender (% male)	82	77
Hoehn & Yahr stage	1.9 ± 0.5	0 ± 0
Total MDS-UPDRS score	42.4 ± 17.4	3.2 ± 2.6

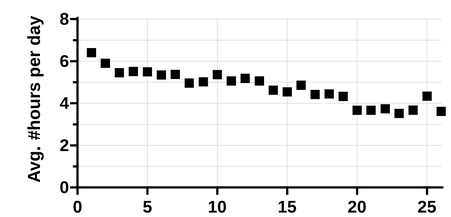
3. Robust workflow and excellent adherence in PD patients

Smartphones were distributed to 8 sites within the US and 1 HC site in Switzerland for disbursement after screening visits. Subjects were instructed to conduct the suite of active tests daily in the morning, to carry the phones with them during their day for passive monitoring recording, and to recharge their devices over night. During the study, subjects uploaded the data live to a secure server by connecting their devices to any WiFi network. At the last study visit, the subjects returned the phones to the sites, who delivered the devices back to Roche. All remaining data was then uploaded.

3A Active test adherence



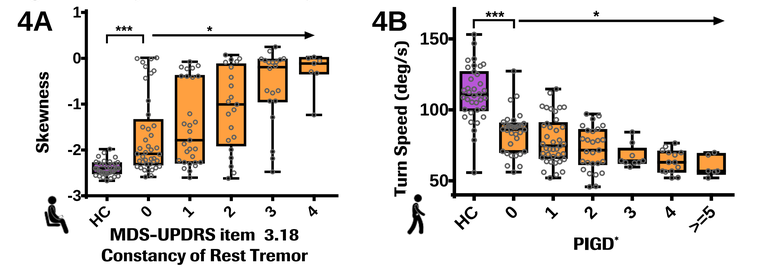
3B Passive monitoring adherence



Active test adherence was strong (61%), with patients performing the active tests on average at least three times a week for the duration of the study (Fig. 3A).

Passive monitoring adherence was likewise strong throughout the trial (Fig. 3B), dropping from ca. 6 to 4 hours per day with an approximate smartphone battery life of 7h. In total 24,104 hours of passive monitoring data were recorded. Passive monitoring data classified as times when the smartphone was not carried by the subjects (22%) was removed from subsequent analyses.

4. High validity and sensitivity of active tests



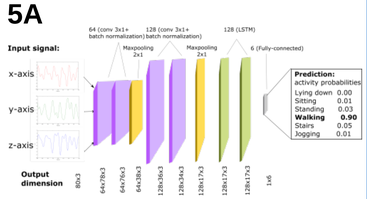
Figures 4A and 4B exemplify that features extracted from the active test data agree with physicians' scores on corresponding MDS-UPDRS items, demonstrating the validity of the remote monitoring approach. Moreover, active test features for HC were often significantly different from PD patients whose motor symptom were scored as '0' (i.e. absent), suggesting that active test data collected in the two weeks before and after a clinical visit may augment the clinical picture obtained at site visits. Please see [1] and table below for further details.

Active test	Feature	MDS-UPDRS item(s)*	HC vs. PD rated as '0' (p-value)[a]	Association between active test feature and MDS-UPDRS item score (p-value)[b]
Rest Tremor	Skewness [2]	3.13	<0.001	0.04
Postural Tremor	Power [2]	2.10	n.s.	0.01
Voice	MFCC2 [3]	3.1	<0.001	n.s.
Dexterity	Tap variability [4]	2.5	<0.001	0.04
Balance	Mean velocity [5]	3.13	0.005	<0.001
Gait	Turn speed [6]	PIGD	0.04	<0.001

5. High agreement between passive and active gait features

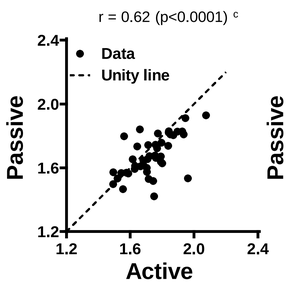
A human activity recognition model (HAR) based on a 9-layer neural network (Fig. 5A) trained on public data to classify six activities (walking, stairs, jogging, sitting, standing and lying down) [7], then used to classify our passive monitoring data. 96.6% of all active gait tests and 99.5% of all active balance tests were correctly classified. In all identified gait segments steps were detected for further analyses [8].

5A

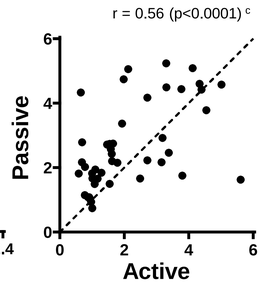


Figures 5B to 5D illustrate the relationships between the *same* gait features extracted from passive monitoring (y-axes) and the active gait test (x-axes) in patients. While notable differences exist – i.e. greater step power during passive monitoring, and faster turning speed during active tests – all correlate strongly (r from 0.56 – 0.82), validating the utility of HAR-derived passive gait features.

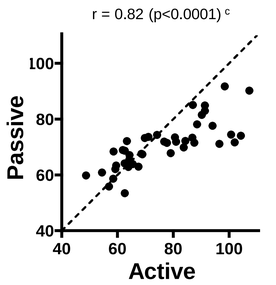
5B Avg. step frequency



5C Avg. step power



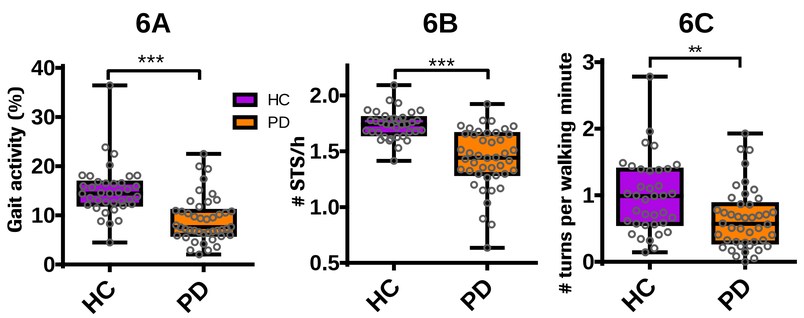
5D Avg. Turn speed



6. Passive monitoring data reveal impact of PD on everyday motor behavior

HAR-profiled mobility measurements revealed significant differences between HC and PD motor behavior:

Figure 6A: PD patients had a significantly lower gait activity (-36%) (Mann-Whitney U = 278, p<0.001), reflecting **reduced mobility** in PD compared to HC subjects.
Figure 6B: PD subject had significantly fewer (-17%) **standing up/sitting down (STS) transitions** per hour than HC subjects (Mann-Whitney U = 218, p<0.001).
Figure 6C: PD patients turned significantly less frequently while walking (-38% **fewer walking turns** per hour) than HCs (Mann-Whitney U = 503, p=0.003).



7. Conclusions

- It is **feasible** to **continuously and remotely monitor motor symptoms** in PD patients using smartphone-based assessments and sensors in a clinical trial setting.
- Patient **adherence** was strong for over six months.
- **Human activities can be robustly recognized** from large scale passive monitoring data using Deep Learning
- Features extracted from passive monitoring agree with clinically validated active test features providing **preliminary validation.**
- **Passive monitoring offers the unique opportunity to easily measure PD motor symptoms and their impact on patients' everyday lives.**

8. Bibliography & Footnotes

a Mann-Whitney test, b Linear mixed effects model with repeated measures, c Spearman correlation

* MDS-UPDRS items: 3.13 Constancy of Rest Tremor, 2.10 Tremor, 3.1 Speech, 2.5 Dressing, 3.13 Posture, PIGD - Postural Instability / Gait Difficulties (2.12, 2.13, 3.10, 3.11 & 3.12)

[1] Lipsmeier, F. (2017), et al., Neurodegenerative Diseases, suppl. 1 17: 568
[2] Timmer, J., et al. (1993)., Biological Cybernetics 70(1): 75-80.
[3] Khan, T., Westin, J., & Dougherty, M. (2014). Biocybernetics and Biomedical Engineering, 34(1), 25-34.
[4] Taylor Tavares, A. L., et al. (2005). Mov Disord 20(10): 1286-1298.
[5] Mancini, M., et al. (2012). Journal of NeuroEngineering and Rehabilitation 9(1): 1
[6]Salarian, A., et al. (2009). In Engineering in Medicine and Biology Society, 2009. EMBC 2009. Annual International Conference of the IEEE (pp. 224-227).
[7] Ordóñez, F. J., & Roggen, D. (2016). Sensors, 16(1), 115.
[8] Lee, H. H., Choi, S., & Lee, M. J. (2015). Sensors, 15(10), 27230-27250.