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Research Article

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Objective Identification of Pharmacological Interference in Parkinsonian Gait Using Continuous Digital Phenotyping

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Abstract

Building upon our previous demonstration that Apple HealthKit enables longitudinal monitoring of Parkinsonian gait [1], this study evaluates its utility for short-term pharmacological assessment. Using a self-controlled longitudinal design, gait performance was quantified across four pharmacological phases: pre-medication, on-medication, withdrawal day, and post-withdrawal recovery. Objective gait parameters—including coefficient of variation (CV), walking speed, asymmetry, and step length—were derived from real-world walking data. Rotigotine administration resulted in marked deterioration in gait stability, characterized by a substantial increase in CV and worsening asymmetry, accompanied by reduced step length. These abnormalities were further exacerbated on the withdrawal day and were rapidly reversible following discontinuation, with CV decreasing to below baseline levels. These findings demonstrate that continuous digital phenotyping enables objective identification of pharmacological interference and supports data-driven, individualized treatment strategies in Parkinson's disease.

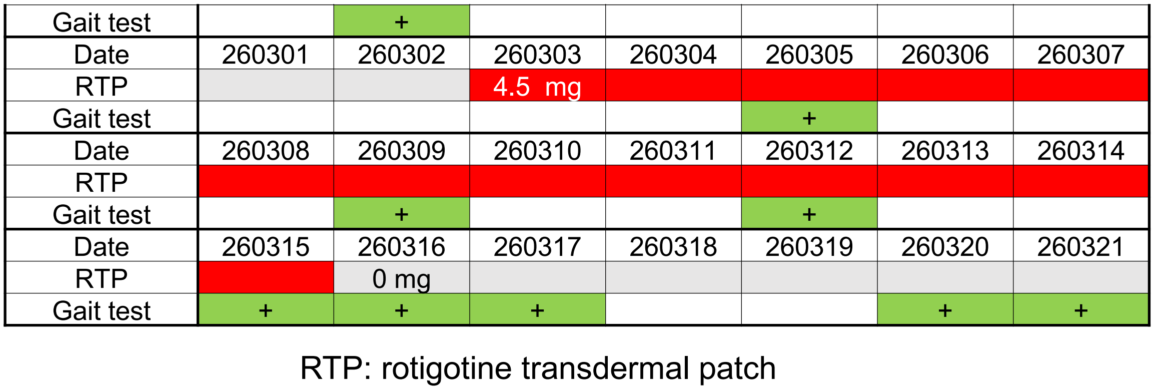
1. Introduction

Gait impairment is a major determinant of disability in Parkinson's disease (PD), yet its evaluation remains largely dependent on subjective clinical assessment [2,3]. Conventional tools such as MDS-UPDRS provide only episodic and coarse evaluation, limiting their ability to capture temporal variability and real-world motor fluctuations [2,3]. Recent advances in wearable technology have enabled continuous and objective measurement of gait. In our previous study, we demonstrated that Apple Health Kit-derived metrics can quantify long-term disease progression [1]. However, whether this framework can be applied to short-term pharmacological evaluation remains unclear. The present study addresses this gap by introducing the concept of "pharmacological interference," in which medication destabilizes motor control rather than improving it. Using a self-controlled longitudinal design, we evaluate gait changes across four pharmacological phases with emphasis on variability (CV) as a marker of motor noise.

2. Case Presentation

The subject was a 77-year-old male with Parkinson's disease. Gait assessments were maily conducted on a standardized outdoor route (~800 m round trip), ensuring consistency and safety. The study consisted of four phases:(1) pre-medication,(2) on-medication,(3) withdrawal day, (4) post-withdrawal recovery. The experimental timeline and gait test schedule are summarized in Table

	Sun	Mon	Tue	Wed	Thur	Fri	Sat
Date	260208	260209	260210	260211	260212	260213	260214
RTP	4.5mg	0 mg					
Gait test							
Date	260215	260216	260217	260218	260219	260220	260221
RTP							
Gait test			+			+	
Date	260222	260223	260224	260225	260226	260227	260228
RTP							



Gait test		+					
Date	260301	260302	260303	260304	260305	260306	260307
RTP			🟥 4.5 mg	🟥	🟥	🟥	🟥
Gait test					+		
Date	260308	260309	260310	260311	260312	260313	260314
RTP	🟥	🟥	🟥	🟥	🟥	🟥	🟥
Gait test		+			+		
Date	260315	260316	260317	260318	260319	260320	260321
RTP	🟥	0 mg					
Gait test	+	+	+			+	+

RTP: rotigotine transdermal patch

Table 1: Study Timeline Showing Pharmacological Status and Walking Test Schedule

3. Methods

3.1. Study Design

A longitudinal, single-subject design was employed, structured into four pharmacological phases (Table 1).

3.2. Data Acquisition

Gait data were collected using Apple Watch and iPhone-based applications. Walking speed curves were obtained via GPS tracking, and gait parameters were extracted from HealthKit.

3.3. Outcome Measures

Primary outcome:

- Coefficient of variation (CV) of walking speed

Secondary outcomes:

- Walking speed
- Gait asymmetry
- Step length

3.4. Statistical Analysis

Comparisons across phases were performed using one-way ANOVA. Given the repeated-measures design, emphasis was placed on consistency across parameters and effect magnitude.

4. Results

4.1. Quantitative Analysis (Table 2)

Significant differences were observed across all gait parameters among the four phases ($p < 0.001$).

During the on-medication phase (2), CV increased markedly compared to pre-medication (1), indicating substantial deterioration in gait stability. This was accompanied by increased asymmetry and reduced step length. On the withdrawal day (3), these abnormalities were further exacerbated, with CV reaching its highest value. In contrast, during the post-withdrawal recovery phase (4), all parameters improved significantly. Notably, CV decreased to below baseline levels, indicating restoration of motor stability. These results are summarized in **Table 2.**

Phase	N (days)	CV (%)	Walking speed (km/h)	Asymmetry (%)	Step Length (cm)
(1) Pre-medication	3	8.8 ± 1.4	3.52 ± 0.12	0.8 ± 0.2	40.5 ± 1.4
(2) On-medication	4	28.6 ± 6.2*	2.84 ± 0.18	3.5 ± 0.6*	33.2 ± 1.9*
(3) Withdrawal Day	1	35.9	2.45	4.2	31.5
(4) Post-withdrawal Recovery	3	6.1 ± 0.3†	3.98 ± 0.12†	0.3 ± 0.1†	44.5 ± 1.1†

Table 2: Quantitative Comparison of Gait Parameters Across Pharmacological Phases

*Significant impairment compared to (1) ($p < 0.01$).

†Significant improvement compared to (2) ($p < 0.01$).

4.2. Temporal Gait Dynamics (Figure 1)

Representative walking speed curves are shown in **Figure 1A–D.** During pre-medication (A), walking speed remained relatively stable. In contrast, during on-medication (B) and withdrawal day (C), pronounced irregular fluctuations were observed throughout the walking period. Following drug discontinuation (D), speed profiles became markedly smoother, indicating recovery of stable gait rhythm. Spatial mapping of the walking route (**Figure 1E**) demonstrated that localized speed reductions corresponded to predictable environmental factors (e.g., intersections), whereas irregular fluctuations observed during phases (2) and (3) were distributed across the entire route, supporting intrinsic motor instability.

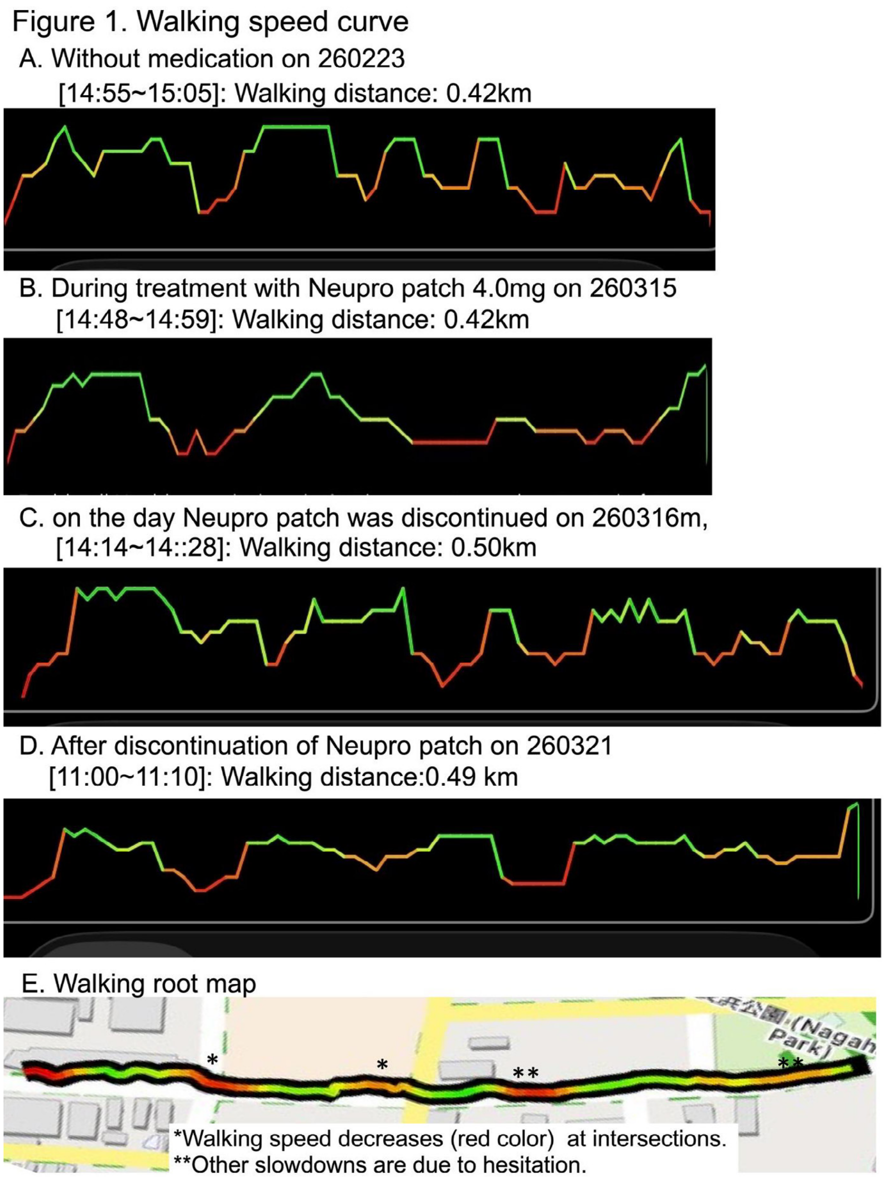


Figure 1. Walking speed curve

A. Without medication on 260223
[14:55~15:05]: Walking distance: 0.42km

B. During treatment with Neupro patch 4.0mg on 260315
[14:48~14:59]: Walking distance: 0.42km

C. on the day Neupro patch was discontinued on 260316m,
[14:14~14::28]: Walking distance: 0.50km

D. After discontinuation of Neupro patch on 260321
[11:00~11:10]: Walking distance:0.49 km

E. Walking root map

*Walking speed decreases (red color) at intersections.
**Other slowdowns are due to hesitation.

Figure 1: Temporal and Spatial Characteristics of Walking Speed Across Pharmacological Phases

(A) Pre-medication (260223). Walking distance: 0.42 km (14:55–15:05).(B) On-medication with rotigotine patch (260315). Walking distance: 0.42 km (14:48–14:59) and 0.50 km (14:14–14:28).(C) Withdrawal day (260316). (D) Post-withdrawal recovery (260321). Walking distance: 0.49 km (11:00–11:10). (E) Corresponding walking route map with color-coded speed. Red segments indicate localized reductions in speed at intersections, while other irregular slowdowns reflect hesitation during gait.

4.3. Integrated Parameter Visualization (Figure 2)

Quantitative changes in gait parameters are visualized in **Figure 2A–D.** CV (Figure 2A) showed the most prominent change, with a substantial increase during the on-medication phase and peak elevation on the withdrawal day, followed by marked reduction during recovery. Walking speed (Figure 2B) decreased during medication and withdrawal phases, while asymmetry (Figure 2C) increased in parallel with CV. Step length (Figure 2D) decreased during instability and recovered after discontinuation. Together, these results demonstrate a consistent pattern of motor deterioration during medication and recovery after discontinuation.

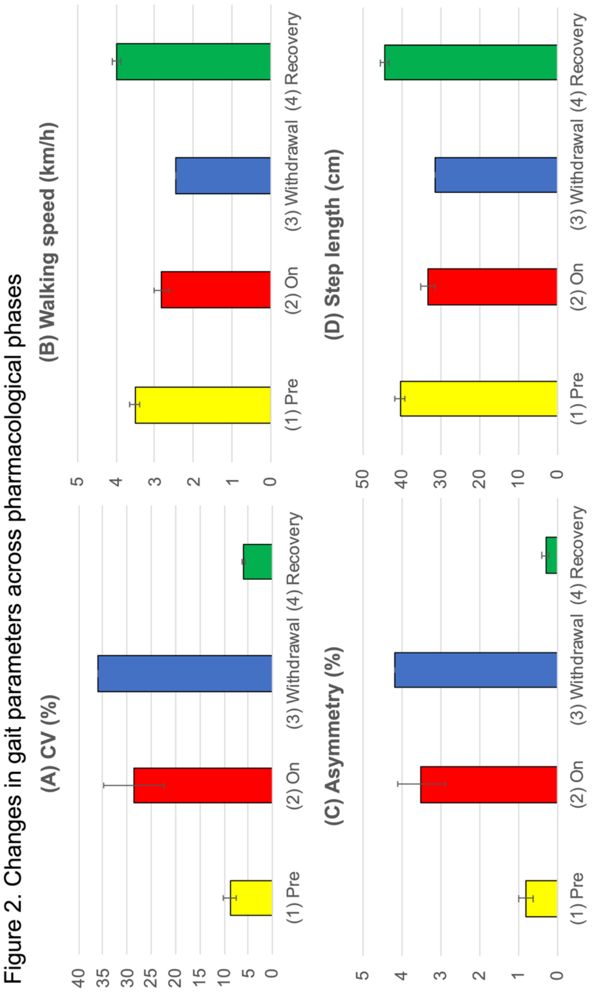


Figure 2: Quantitative Comparison of Gait Parameters Across Pharmacological Phases

Bar graphs show mean values (± SD) of gait parameters across four pharmacological conditions: (1) pre-medication, (2) on-medication, (3) withdrawal day, and (4) post-withdrawal recovery. (A) Coefficient of variation (CV), representing gait variability (motor noise) (B) Walking speed (C) Gait asymmetry (D) Step length. CV increased markedly during the on-medication phase and reached its highest value on the withdrawal day, indicating severe deterioration in gait stability. In contrast, all parameters improved after discontinuation, with CV decreasing to below baseline levels, demonstrating recovery of motor stability.

5. Discussion

This study demonstrates that continuous digital phenotyping enables objective identification of pharmacological interference in Parkinsonian gait. In this patient, administration of rotigotine resulted in a marked increase in gait variability, as reflected by CV, accompanied by increased asymmetry and reduced step length. These findings indicate disruption of motor stability rather than improvement.

Importantly, these changes were reversible. Following discontinuation, gait parameters returned to baseline and further stabilized, supporting a causal relationship between medication and motor deterioration.

The results suggest that, in certain PD phenotypes, the primary deficit lies not in reduced motor output but in instability of motor execution. In this context, dopaminergic stimulation may exacerbate motor noise, leading to impaired coordination. A major strength of this study is its real-world, continuous assessment framework. Unlike clinic-based evaluations, this approach enables gait assessment anytime and anywhere, independent of walking distance, allowing detection of clinically relevant phenomena that would otherwise remain unrecognized. This study extends our previous work by demonstrating that digital gait metrics can be used not only for disease monitoring but also for pharmacological evaluation [1]. Parkinson's disease is highly heterogeneous, both in clinical presentation and pharmacological response [3]. The present findings support a paradigm shift toward objective, withinsubject evaluation using continuous digital phenotyping. Future studies adopting similar approaches may enable truly personalized, data-driven treatment strategies.

6. Conclusion

Continuous digital phenotyping enables objective, real-world evaluation of pharmacological effects in Parkinsonian gait. This approach allows identification of both therapeutic benefit and drug-induced deterioration, supporting individualized treatment strategies [5-8].

Author Contributions:

Wrote the manuscript and Conceptualization: K.Y.
Data curation, Formal analysis: Z.L.
Investigation: Z.L., K.Y.
Writing – original draft: K.Y.
Writing – review & editing: Z.L.
All authors approved the final manuscript.

Ethics Statement

This study is a self-observational single-subject study. No identifiable personal data are included.

Consent

The participant provided informed consent.

Competing Interests

The authors declare no competing interests.

Funding

This study received no external funding.

Data Availability

Data are available from the corresponding author upon reasonable request.

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