

Long-term monitoring of gait in Parkinson's disease

Steven T. Moore^{a,*}, Hamish G. MacDougall^a, Jean-Michel Gracies^a,
Helen S. Cohen^b, William G. Ondo^c

^a Department of Neurology, Mount Sinai School of Medicine, New York, NY 10029, USA

^b Bobby R. Alford Department of Otolaryngology—Head and Neck Surgery, Baylor College of Medicine, Houston, TX, USA

^c Department of Neurology, Baylor College of Medicine, Houston, TX, USA

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Abstract

A new system for long-term monitoring of gait in Parkinson's disease (PD) has been developed and validated. The characteristics of every stride taken over 10-h epochs were acquired using a lightweight ankle-mounted sensor array that transmitted data wirelessly to a small pocket PC at a rate of 100 Hz. Stride was calculated from the vertical linear acceleration and pitch angular velocity of the leg with an accuracy of 5 cm. Results from PD patients (5) demonstrate the effectiveness of long-term monitoring of gait in a natural environment. The small, variable stride length characteristic of Parkinsonian gait, and fluctuations of efficacy associated with levodopa therapy, such as delayed onset, wearing off, and the 'off/on' effect, could reliably be detected from long-term changes in stride length.

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1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder reflecting a progressive loss of dopaminergic and other sub-cortical neurons [1]. Levodopa, the metabolic precursor to dopamine, has commonly been used to manage the motor symptoms of PD for over 40 years by regenerating depleted dopamine at the striatum. Although initially effective, as the disease advances the duration of each dose shortens (the 'wearing off' effect), necessitating more frequent levodopa administration. In addition, the development of dyskinesias (involuntary movements) and the 'off/on' phenomenon (abrupt and unpredictable locomotor responses to individual doses of levodopa) can limit mobility and complicate dosing [2].

Typically, clinical evaluation involves brief observation during simple motor tasks, such as getting up out of a chair and walking a short distance. Assessment of long-term

medication response usually takes the form of a patient diary, where the Parkinsonian state is noted as 'on' (i.e., effectively medicated), 'off' or 'on with dyskinesias' [3,4]. However, self-reporting can be unreliable [5]. The Unified Parkinson's Disease Rating Scale (UPDRS) [6], although widely utilized in research studies [7], has significant limitations. Analysis of gait is limited to assigning a single value between 0 (normal) and 4 (unable to walk, even with assistance) from brief clinical observation. Given the complexity of determining the optimal levodopa dosing schedule, a more objective means of assessing gait over longer periods during normal daily life may significantly improve management of locomotor dysfunction in PD.

Wrist or belt mounted accelerometers (activity monitors) have been used for long-term monitoring of motor fluctuations in PD [8–11], although 'on' and 'off' phases cannot be reliably determined in individual subjects. A more 'brute-force' approach to accelerometry (six tri-axial accelerometers; mounted on both upper arms, both upper legs, the sternum and one wrist) could distinguish 'on' and 'off' phases [12], as well as dyskinesias from voluntary movements [13]. However, the complexity and intrusive

* Corresponding author at: Mount Sinai School of Medicine, Department of Neurology, Box 1135, 1 E 100th Street, New York, NY 10029, USA. Tel.: +1 212 241 9306; fax: +1 212 831 1610.

E-mail address: steven.moore@mssm.edu (S.T. Moore).

nature of multiple body-segment accelerometry limits its use outside of the research environment.

Although gross body acceleration data can provide an objective alternative to periodic self reporting of motor state, it does not indicate the functional locomotor capacity of the individual; i.e., how well the patient is walking. One of the cardinal features of PD is locomotor dysfunction; shortened stride length, increased variability of stride [14–16], shuffling gait, and freezing [17]. To characterize pathological gait in the PD patient it is necessary to accurately monitor stride length over extended periods. A number of ambulatory systems have employed gyroscopes to measure the angular velocity of the thigh and/or shank, and integrated these waveforms to obtain the angular extent of leg swing, which when scaled by subject height yields an estimate of stride length [18,19]. Stride length estimates were relatively inaccurate, with an error of 15% [18]. A more recent realization utilizing gyroscopes on the shank of both legs and a third gyroscope on the right thigh improved stride length accuracy to 7 cm, and was capable of logging for up to 2.5 h [20,21]. However, cables used to relay data from leg-mounted gyroscopes to a central logging unit create an unacceptable trip hazard and interfere with patients' normal daily activity, limiting their use in the community.

In this paper, we describe a novel ambulatory system for accurate measurement of every stride taken over extended periods (up to 10 h). Clinical features of PD, such as small, variable stride length and fluctuations in motor performance with levodopa administration, were well correlated with data obtained from the stride monitor. Long-term stride monitoring may significantly improve pharmacological management of PD symptoms, particularly in the advanced stages of the disease where abrupt and unpredictable responses to levodopa complicate dosing.

2. Methods

2.1. Research participants

Ten healthy participants (five males and five females), with no history of gait abnormalities, provided calibration and validation of the stride monitor. Age ranged from 30 to 55

years [38 (S.D. 7.7)], and height from 153 to 183 cm [167 (S.D. 12.2)]. Seven participants diagnosed with idiopathic Parkinson's disease (three males and four females) were enrolled to verify measurement accuracy (2) and obtain pilot data (5) on the efficacy of long-term stride monitoring. Age ranged from 65 to 85 years [72.0 (S.D. 7.4)], age at onset of PD from 40 to 79 years [57.7 (S.D. 13.3)], and height from 160 to 193 cm [172.1 (S.D. 11.8)]. The study was approved by the Institutional Review Boards at the Mount Sinai School of Medicine and Baylor College of Medicine and Affiliated Hospitals, and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. Participants gave informed consent prior to their inclusion in the study.

2.2. Hardware

The stride monitor consisted of two subsystems. A small Inertial Measurement Unit (IMU: 28 mm × 38 mm × 54 mm; MT9, Xsens, Enschede, The Netherlands), with a 9 V battery and Bluetooth serial transmitter (BL-819, RS232 Bluetooth Converter, Brainboxes Ltd., Liverpool, United Kingdom), was mounted around the shank (just above the ankle) using an elasticized strap and Velcro. The IMU transduced 3D linear acceleration and angular velocity of the lower limb at a sample rate of 100 Hz. In addition, a Pocket PC (iPAQ 2200, Hewlett Packard, Palo Alto, CA), worn in a small pouch around the waist, acquired the leg movement data wirelessly (via Bluetooth) from the IMU within an effective range of 100 m, and stored data files on a secure digital (SD) flash memory card. The shank-mounted components (IMU, battery and Bluetooth transmitter) weighed less than 130 g, or less than 2% of the mass of the shank and foot [22], which should not significantly affect movement of the lower limb. The PC weighed 146 g, and was slightly larger than a cell phone (119 mm × 77 mm × 16 mm). The stride monitor was unobtrusive and did not interfere with the participant's normal activities.

2.3. Data processing

Vertical linear acceleration and pitch angular velocity (sagittal plane) of the shank were used to assess gait (Fig. 1). During upright stance there was a DC offset of 9.8 m/s² in

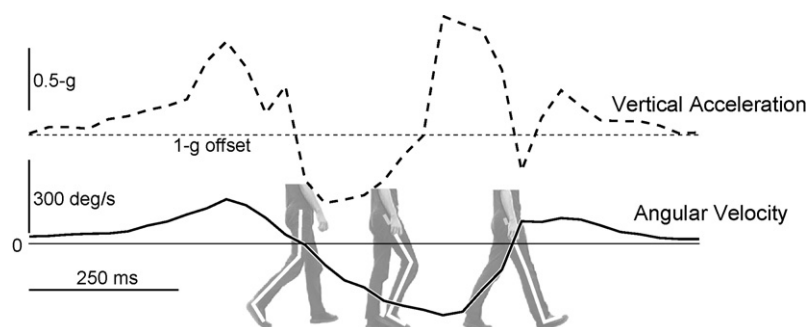


Fig. 1. Vertical linear acceleration (dashed trace) and pitch angular velocity (solid trace) from the stride monitor during locomotion. The negative portion of the angular velocity trace corresponds to forward rotation of the leg during the swing phase.

the vertical acceleration, and changes in this value were used to distinguish periods where the participant was supine (see Fig. 5A). A ‘moving’ RMS trace of the vertical acceleration waveform was calculated using a sliding window of 2 s width [23]. Locomotor activity was defined as periods where the RMS acceleration was greater than 0.4 m/s^2 above baseline [23]. According to the right-hand rule, negative pitch angular velocity corresponded to the forward rotation of the leg during the swing phase of locomotion (Fig. 1). An initial stride length estimate (SL_i) was calculated as follows:

$$SL_i = 2l \sin\left(\frac{\alpha}{2}\right) \quad (1)$$

where l is the length of the leg from the trochanter (hip joint) to the ground, and α is the angular extent of the swing phase (determined from integration of the angular velocity trace). Determining stride length from leg swing alone is reasonably accurate for small stride lengths ($<1 \text{ m}$). However, this technique underestimates larger strides due to the considerable forward motion of the body over the stance foot in addition to the component generated by leg swing. It was therefore necessary to provide a calibration algorithm based on the initial stride estimate to correct for longer strides.

Changes in stride length following levodopa administration in participants with Parkinson’s disease were assessed by fitting an exponential function to binned mean stride data (each bin comprising 60 sequential strides) using the Levenberg–Marquardt algorithm [24,25]. The time constant of the exponential rise or decay of stride length was estimated from the best fit (see Figs. 4B and 5B).

2.4. Calibration

The stride monitor was primarily calibrated using a direct measure of stride length obtained from 10 healthy participants walking along a 30-m hallway. Healthy controls were utilized as it was necessary to acquire angular velocity data over a wide range of stride lengths ($\sim 0.2\text{--}1.5 \text{ m}$) to determine the calibration algorithm; varying stride length on demand is beyond the capabilities of most PD patients, particularly in the ‘off’ state. An aluminum tube was taped to the heel of the left shoe and a whiteboard marker inserted such that the tip left a single dot on the floor during each foot placement. Simultaneous estimates of stride length were obtained from the stride monitor, also attached to the left leg. Actual stride length was determined from measurement of the distance between successive dots on the floor. Participants were instructed to walk at a natural pace but to vary gait according to verbal commands to produce a range of stride lengths, including small shuffling steps typical of Parkinson’s disease. The pen technique was chosen as it allowed calibration of the stride monitor over a wide range, was relatively accurate ($\sim 5 \text{ mm}$ error), and facilitated calibration outside of the laboratory. Accuracy of the device to monitor pathological (Parkinsonian) gait was

evaluated by two different techniques; (1) the pen technique described above, and (2) comparing stride monitor measures with those obtained from a video motion analysis system tracking horizontal foot movement with an accuracy of 5 mm (Optitrack, NaturalPoint, Corvallis, OR).

2.5. Stride monitoring of PD patients

Long-term stride monitoring (left leg) was performed on five PD patients at the Baylor College of Medicine Movement Disorders Clinic, Houston, TX. Stride length data was collected in two participants over a period of 75 min in the clinic. For the other three participants, the stride monitor was activated at the clinic prior to patient’s departure and collected from their home after 6 h of data acquisition during normal daily activity. They were also asked to keep a simple diary of activities and PD-related medication administration at approximately 30-min intervals.

3. Results

3.1. Calibration

Ten healthy controls travelled 27.9 m (S.D. 1.8) over 27 strides (S.D. 3.6) while traversing the 30-m corridor. Plotting height-normalized true-versus-estimated stride lengths from the 10 controls revealed a non-linear but consistent relationship, such that it was possible to generalize a calibration algorithm applicable to all participants (Fig. 2). To correct for underestimation of large ($>1 \text{ m}$) strides due to forward motion of the body over the stance foot, a least-squares fit (Labview Advanced Analysis Package, National Instruments, Austin, TX) was applied to the height-normalized initial stride length estimates (SL_{ni}) (Fig. 2, solid black circles) of the form:

$$SL_{nc} = a_0 + a_1 \sin(SL_{ni}^2) + a_2 \cos(SL_{ni}) + \frac{a_3}{SL_{ni} + 1} + a_4 SL_{ni}^4 \quad (2)$$

where SL_{nc} is the height-normalized corrected stride length (Fig. 2, solid grey circles), and the coefficients a_i were ($-43.3, 21.9, 14.9, -1.4, 2.3$). The resultant corrected stride length measures exhibited a highly linear relationship to true stride length ($r = 0.98$) (Fig. 2, dashed black line). The mean error was 2.8% (CI 1.1) of participant height (maximum error 9%), or 5 cm for the average participant height of 167 cm. The error per stride was also estimated by comparing the total distance traveled down the hallway (cumulative stride length of the true and corrected values) and dividing by the number of strides taken for each participant. Mean error was similar to that calculated from the height-normalized data at 4.8 cm (CI 1.1), with a maximum error of 8 cm.

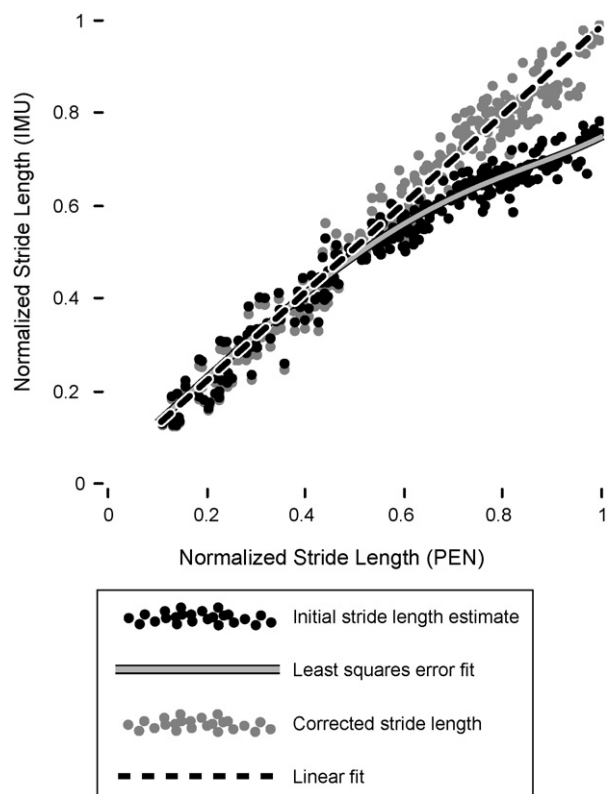


Fig. 2. True (pen) versus estimated (stride monitor) stride length from 10 healthy controls, normalized by height (filled black circles). A general least-square error fit (grey trace) to these data was used to derive a calibration algorithm that produced a highly linear relationship with actual stride values (black dashed line).

Stride data obtained from two PD participants in the ‘off’ state (no dopaminergic medication in the previous 12 h) demonstrated similar measurement accuracy. A participant with a relatively mild form of PD (69-year-old female, age at onset 59 years, height 173 cm) walked a distance of 4.5 m (five strides) and simultaneous pen and stride monitor measures of stride length (left leg) were obtained. Average stride length was 90.1 cm (pen) and 89.2 cm (stride monitor). Mean difference was 3.3 cm (maximum error 8 cm). A second participant (68-year-old male, age at onset 52 years, height 168 cm) with severe locomotor impairment traversed a distance of 89 cm utilizing small shuffling steps (seven strides). Stride length (left leg) was measured using the stride monitor, and from a *post hoc* video motion analysis of the horizontal displacement of the left foot. Average stride length was 12.7 cm (video analysis) and 10.4 cm (stride monitor); mean difference was 2.5 cm (maximum 4.7 cm). Thus, at two extremes of locomotor impairment in the PD ‘off’ state, the accuracy of the stride monitor was within that established in the 10 healthy controls.

3.2. Monitoring of gait in Parkinson’s disease

Fig. 3 illustrates the differences between healthy and Parkinsonian gait over extended periods. Over 4 h a healthy

participant (37-year-old male) covered a total of 3.9 km with 3071 strides, including two 1.5-km walks in an urban environment (Manhattan) at the start and end of the epoch (Fig. 3A, upper trace). In the intervening period the participant walked periodically while working in a laboratory. Stride length was stable at 1.5 m, as indicated by the stride histogram, consistent with the typical value for adult males [26]. This is clearly seen in the 4 min of stride data while walking home (Fig. 3A, lower trace). In contrast, 4 h of data from a PD patient (85-year-old female, age at onset 79 years) during normal daily activities outside of the clinic demonstrates the cardinal features of Parkinsonian gait; namely a small (~ 0.5 m), highly variable stride length (Fig. 3B, upper trace and histogram), covering a distance of 492 m with 923 strides. Note that this particular patient was not prescribed levodopa at the time of testing. Stride data from a well-managed PD patient (65-year-old female, age at onset 51 years) in the ‘on’ phase approximately 2 h after levodopa administration (levodopa 150 mg, pramipexole 1.5 mg) demonstrates the effectiveness of dopamine-replacement therapy (Fig. 3C). Over a 75-min period in the clinic stride length was relatively stable at ~ 1 m as observed in a 4-min interval (Fig. 3C, lower trace) as the participant walked along a corridor (although still less than the mean value of 1.3 m for adult females [27]).

A standard dose of levodopa typically becomes effective 20–40 min after drug ingestion [28], although onset can be considerably delayed and inconsistent in patients with advanced PD. The effect of levodopa on stride length was monitored in the clinic (during intermittent 30-m walks along a corridor) in an advanced PD patient (66-year-old male, age at onset 40 years). Over a period of 75 min post-administration (levodopa 100 mg, pramipexole 0.5 mg) stride length increased (and variability decreased) from 24 cm (S.D. 9) to 45 cm (S.D. 6) (Fig. 4A). Freezing occurred up to 30 min post-medication, but had ceased by 50 min. The time constant of levodopa onset (28 min) was estimated from an exponential fit to the mean stride data (Fig. 4B).

The levodopa cycle, characterized by changes in stride length, was also assessed from long-term monitoring in the community. A participant with advanced PD (79-year-old female, age at onset 69 years) wore the stride monitor for 6 h following a morning clinic visit. Stride length was decreasing at the clinic as the patient came off a morning dose of levodopa (levodopa 100 mg, ropinirole 2 mg). The patient went to bed shortly after being driven home (Fig. 5A). Approximately 10 min prior to getting out of bed the participant took a second dose of levodopa (levodopa 100 mg, ropinirole 2 mg) then walked to a local shopping mall. Stride length increased steadily over 60 min following levodopa administration, and then declined as the participant walked home (Fig. 5A). The time constants of the onset and decay of levodopa (Fig. 5B) were estimated at 24 and 23 min, respectively, using an exponential fit to the mean binned stride data (each bin comprising 60 sequential strides).

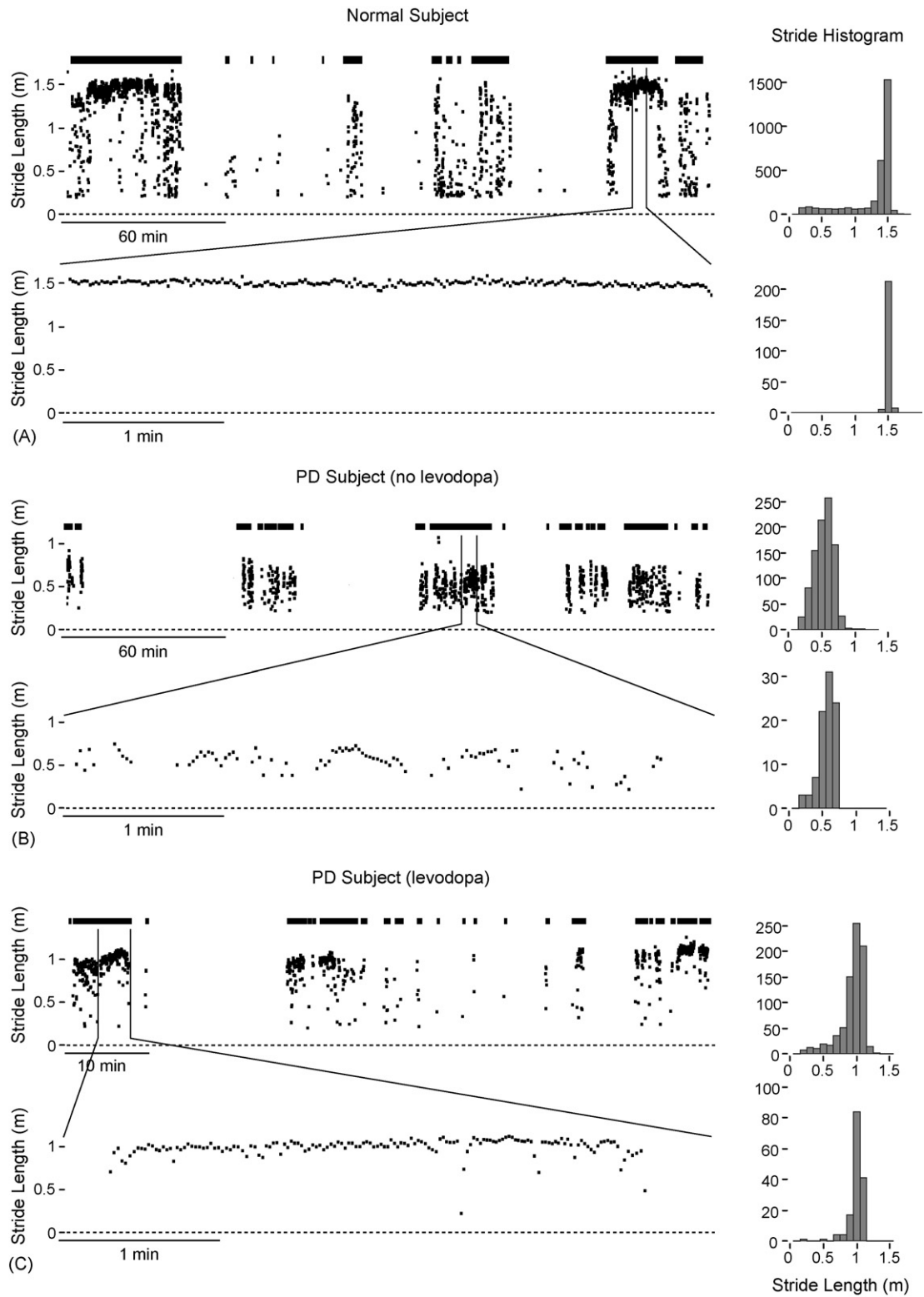
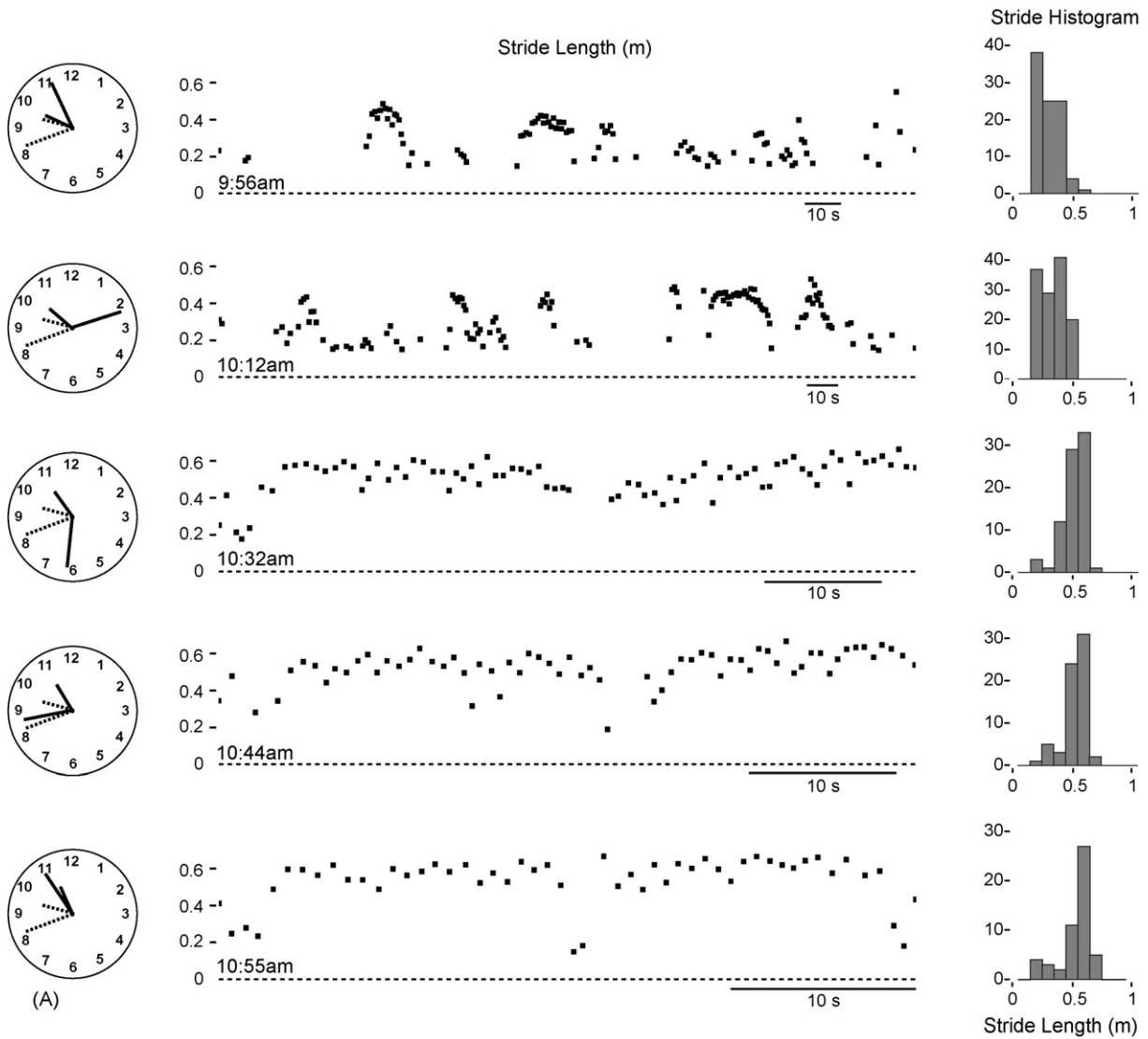
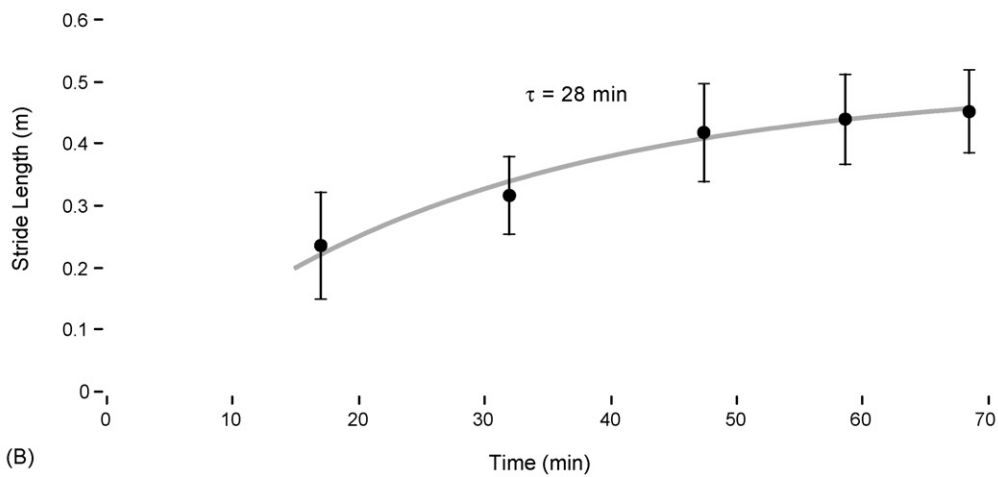


Fig. 3. (A) Four hours of stride data from a healthy participant. (B) Four hours of stride data from an unmedicated (i.e., no levodopa) PD patient during natural daily activity outside of the clinic. (C) Stride data (75 min of intermittent walking around the clinic) from a well-managed PD patient in the 'on' phase approximately 2 h post levodopa administration.



(A)



(B)

Fig. 4. The transition from ‘off’ to ‘on’ following levodopa administration was assessed in the clinic in a participant with advanced PD. (A) Stride data from periodic walking along a corridor of length 15 m (up and back) following levodopa administration at 9:41 a.m. (B) The time constant (τ) of the onset of levodopa was estimated at 28 min using an exponential fit to the mean stride data.

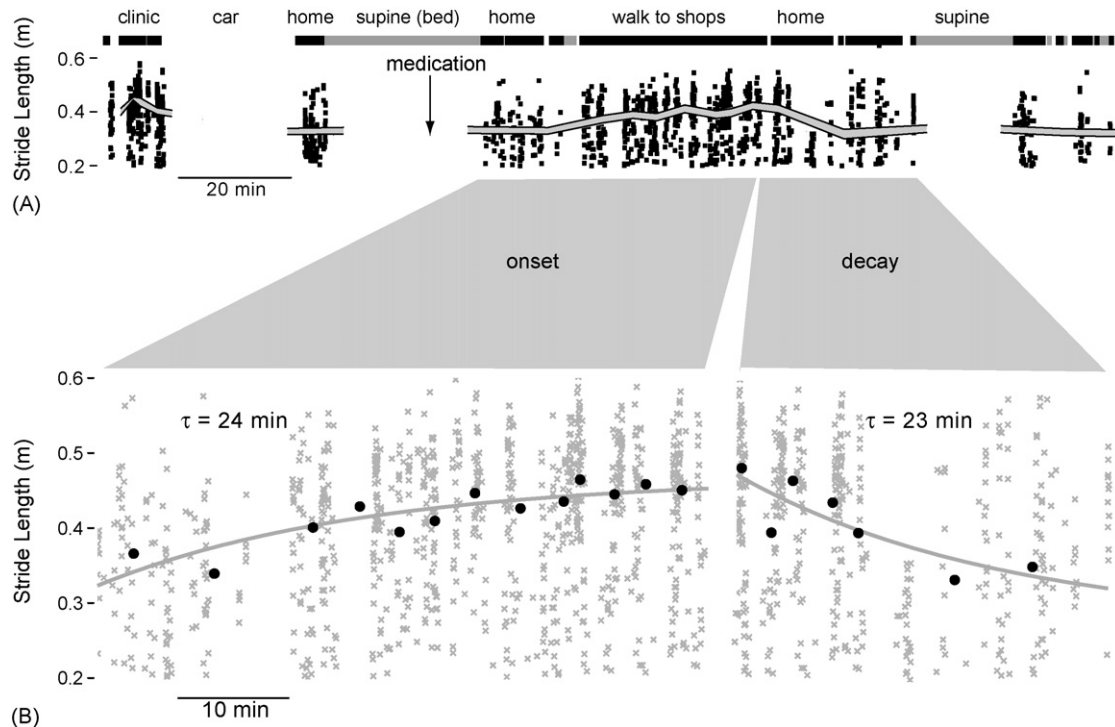


Fig. 5. The effect of levodopa administration during natural daily activities outside of the clinic. (A) Three hours of activity (mean and 90%CI of stride length, plus individual values); thick black lines above the stride data indicate locomotion; thick grey lines show periods where the participant was supine. (B) An exponential fit to binned mean stride length was used to estimate the time constant of onset (24 min) and decay (23 min) of levodopa.

4. Discussion

The results of this study demonstrate the feasibility of accurate stride length measurement using a single shank-mounted stride monitor, and the applicability of this technique to long-term monitoring of gait in Parkinson's disease. Improved accuracy (mean error 5 cm), relative to previous techniques utilizing both single (15% error) [18] and multiple (7 cm error) gyroscopes [20], was obtained using a combined accelerometer/gyroscope sensor array and a calibration algorithm to account for the forward motion of the body over the stance foot. The stride monitor is small and unobtrusive, and did not interfere with natural daily activities during extended monitoring of gait outside of the clinic.

Stride data obtained from PD patients demonstrated many facets of Parkinsonian gait, such as small stride length and larger stride-to-stride variability. Fluctuations of efficacy associated with levodopa therapy, such as delayed onset, wearing off, and the 'off/on' effect, could also be detected from long-term changes in stride length. The time constants of onset and decay of levodopa were estimated from stride length data acquired both at the clinic and in the real world. In contrast, a previous laboratory study [29] periodically assessed gait on a fixed 7-m walkway over the levodopa cycle and found no consistent changes in stride length, likely due to the contrived nature of the laboratory walking task that can temporarily enhance performance in PD patients [30]. Long-term gait assessment in a community

setting eliminates this confound and exhibits greater sensitivity to the dynamic effects of dopamine replacement therapy on stride length.

Locomotor impairment is one of the cardinal features of PD but certainly not the only one. Many other PD symptoms, such as rigidity, difficulty swallowing, stooped posture, olfactory dysfunction, and upper-body tremor and dyskinesias, cannot be detected with the stride monitor; however, no objective measures of these indicators are routinely used in the clinic. Tremor can readily be measured with an accelerometer but provides limited sensitivity to motor complications in PD patients [11]. The complexity of identifying 'off' and 'on' states and upper-body dyskinesias (requiring six triaxial accelerometers [13]) effectively curtails its use outside of the research environment. Despite these recent attempts at objectivity, the essentially subjective UPDRS remains the current standard of PD assessment.

Clinicians typically see a 'snapshot' of the patient's motor state and management of PD often involves a trial and error approach, relying heavily on the patient's subjective feedback to optimize the levodopa dosage regime. Objective long-term data obtained from stride monitoring may provide a faster and more valid end-point.

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References

- [1] Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res* 2004;318:121–34.
- [2] Ondo W. Investigational pharmacological treatments for Parkinson's disease. In: Pahwa R, Lyons K, Koller W, editors. *Handbook of Parkinson's disease*. New York: Marcel Dekker; 2003.
- [3] Brown RG, MacCarthy B, Jahanshahi M, Marsden CD. Accuracy of self-reported disability in patients with parkinsonism. *Arch Neurol* 1989;46:955–9.
- [4] Golbe LI, Pae J. Validity of a mailed epidemiological questionnaire and physical self-assessment in Parkinson's disease. *Mov Disord* 1988;3:245–54.
- [5] Goetz CG, Stebbins GT, Blasucci LM, Grobman MS. Efficacy of a patient-training videotape on motor fluctuations for on-off diaries in Parkinson's disease. *Mov Disord* 1997;12:1039–41.
- [6] Fahn S, Elton RL. Members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. *Unified Parkinson's Disease Rating Scale. Recent Developments in Parkinson's disease*. Florham Park: Macmillan Healthcare Information; 1987. p. 153–63, 293–304.
- [7] Mitchell SL, Harper DW, Lau A, Bhalla R. Patterns of outcome measurement in Parkinson's disease clinical trials. *Neuroepidemiology* 2000;19:100–8.
- [8] van Hilten JJ, Middelkoop HA, Kerkhof GA, Roos RA. A new approach in the assessment of motor activity in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1991;54:976–9.
- [9] Saito N, Yamamoto T, Sugiura Y, Shimizu S, Shimizu M. Lifecorder: a new device for the long-term monitoring of motor activities for Parkinson's disease. *Intern Med* 2004;43:685–92.
- [10] Hoff JJ, van den Plas AA, Wagemans EA, van Hilten JJ. Accelerometric assessment of levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 2001;16:58–61.
- [11] Hoff JJ, van der Meer V, van Hilten JJ. Accuracy of objective ambulatory accelerometry in detecting motor complications in patients with Parkinson's disease. *Clin Neuropharmacol* 2004;27:53–7.
- [12] Keijsers NL, Horstink MW, Gielen SC. Ambulatory motor assessment in Parkinson's disease. *Mov Disord* 2006;21:34–44.
- [13] Keijsers NL, Horstink MW, Gielen SC. Automatic assessment of levodopa-induced dyskinesias in daily life by neural networks. *Mov Disord* 2003;18:70–80.
- [14] Schaafsma JD, Giladi N, Balash Y, Bartels AL, Gurevich T, Hausdorff JM. Gait dynamics in Parkinson's disease: relationship to Parkinsonian features, falls and response to levodopa. *J Neurol Sci* 2003;212:47–53.
- [15] Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N. Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. *Exp Brain Res* 2003;149:187–94.
- [16] Hausdorff JM, Cudkovicz ME, Firtion R, Wei JY, Goldberger AL. Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease. *Mov Disord* 1998;13:428–37.
- [17] Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Mov Disord* 2004;19:871–84.
- [18] Miyazaki S. Long-term unrestrained measurement of stride length and walking velocity utilizing a piezoelectric gyroscope. *IEEE Trans Biomed Eng* 1997;44:753–9.
- [19] Tong K, Granat MH. A practical gait analysis system using gyroscopes. *Med Eng Phys* 1999;21:87–94.
- [20] Aminian K, Najafi B, Bula C, Leyvraz PF, Robert P. Spatio-temporal parameters of gait measured by an ambulatory system using miniature gyroscopes. *J Biomech* 2002;35:689–99.
- [21] Salarian A, Russmann H, Vingerhoets FJ, Dehollain C, Blanc Y, Burkhard PR, et al. Gait assessment in Parkinson's disease: toward an ambulatory system for long-term monitoring. *IEEE Trans Biomed Eng* 2004;51:1434–43.
- [22] US Navy. *Anthropometry and mass distribution for human analogues*. New Orleans: Naval Biodynamics Laboratory; 1988.
- [23] MacDougall HG, Moore ST. Marching to the beat of the same drummer: the spontaneous tempo of human locomotion. *J Appl Physiol* 2005;99:1164–73.
- [24] Levenberg K. A Method for the solution of certain problems in least squares. *Quart Appl Math* 1944;2:164–8.
- [25] Marquardt D. An algorithm for least-squares estimation of nonlinear parameters. *SIAM J Appl Math* 1963;11:431–41.
- [26] Murray MP, Drought AB, Kory RC. Walking patterns of normal men. *J Bone Joint Surg* 1964;46A:335–60.
- [27] Murray MP, Kory RC, Sepic SB. Walking patterns of normal women. *Arch Phys Med Rehabil* 1970;51:637–50.
- [28] Chana P, Kuntsmann C, Reyes-Parada M, Saez-Briones P. Delayed early morning turn "ON" in response to a single dose of levodopa in advanced Parkinson's disease: pharmacokinetics should be considered. *J Neurol Neurosurg Psychiatry* 2004;75:1782–3.
- [29] MacKay-Lyons M. Variability in spatiotemporal gait characteristics over the course of the L-dopa cycle in people with advanced Parkinson's disease. *Phys Ther* 1998;78:1083–94.
- [30] Yekutieli MP. Patients fall records as an aid in designing and assessing therapy in Parkinsonism. *Disabil Rehabil* 1993;15:189–93.