Courtesy of Prof. Gassert Roger. The figure is from the article entitled « Control strategies for active lower extremity prosthetics and orthotics : a review »[1]

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The temporal organization of stride duration variability for assessing gait stability

Clinical application to Parkinson's disease

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Contents

Résumé

Le mouvement humain est intrinsèquement dynamique et complexe. Une locomotion efficace, stable et adaptée requiert à la fois l'intégration continue d'afférences sensorielles multiples et la coordination des sorties motrices. Le caractère fluctuant de la marche humaine (autocorrélations à long-terme, LRA) relève tant de perturbations externes (e.g., environnement) et/ou internes (e.g., pathologie) que des réponses neuromécaniques à celles-ci. Bien que l'origine de cette propriété soit largement débattue, l'analyse des LRA fournirait d'importantes informations sur le contrôle de la marche et pourrait constituer un marqueur de dysfonctionnement. L'influence des facteurs externes et internes sur la locomotion humaine a été étudiée, permettant d'approfondir l'étude de possibles origines neuromécaniques des LRA et de leur utilité clinique potentielle. La récente considération des LRA donne lieu à une nouvelle façon de penser la variabilité, l'adaptabilité, la santé et la rééducation motrice.

Mots-clés : Variabilité, Autocorrélations à long-terme, Dynamique non-linéaire, Marche, Locomotion, Troubles de marche, Rééducation, Contrôle moteur

Summary

Human movement is intrinsically dynamic and complex. Continuous integration of multiple sensory inputs and coordination of motor outputs are needed to achieve efficient, stable and adaptable locomotion. Both externally (e.g. environment) and/or internally (e.g. pathology) generated perturbations and the neuromechanical responses to them contribute to the fluctuating dynamics of human gait (assessed by long-range autocorrelations; LRA). Although the origin of this property is largely debated, LRA may provide important information about neuromechanical control of gait and potentially constitute a powerful marker of dysfunction. Influence of external and internal factors on human locomotion was investigated, which allowed further investigation on both possible neuromechanical origin of LRA and their potential clinical utility. The recent consideration of LRA gives rise to new way of thinking about variability, adaptability, health and motor rehabilitation.

Keywords: Variability, Long-range autocorrelations, Nonlinear dynamics, Gait, Locomotion, Gait disorders, Rehabilitation, Motor control

General introduction

GENERAL INTRODUCTION

Self-organization, complexity and variability

Stock market prices, meteorological phenomena, social conflicts, swarm of bees, ants colony, school of fish, human movement, ... The observation of nature or of social phenomena offers us fascinating examples of self organized systems.[2–5] One of the most illustrative phenomena is school of fish displacements which aim to allow to feed as well as to avoid predators in a coordinated fashion (Figure 1). Of erratic appearance, such complex phenomena are governed by dynamic strain between order and disorder. This behavior is based on continuous interactions among elements that compose the system.[2–5] School of fish or ants colony consists of a large number of individual elements, interacting only with other elements located in their immediate vicinity and having only partial information available to them.[3,5,6] However, these non-hierarchical systems are capable of producing orderly structures on a large scale, over distances far beyond the perception of agents as food or predator. For example, schools of mackerel may extend for several kilometers, far beyond the perception zone of the individuals making them. Self-organization processes allow fishes to develop a form of collective

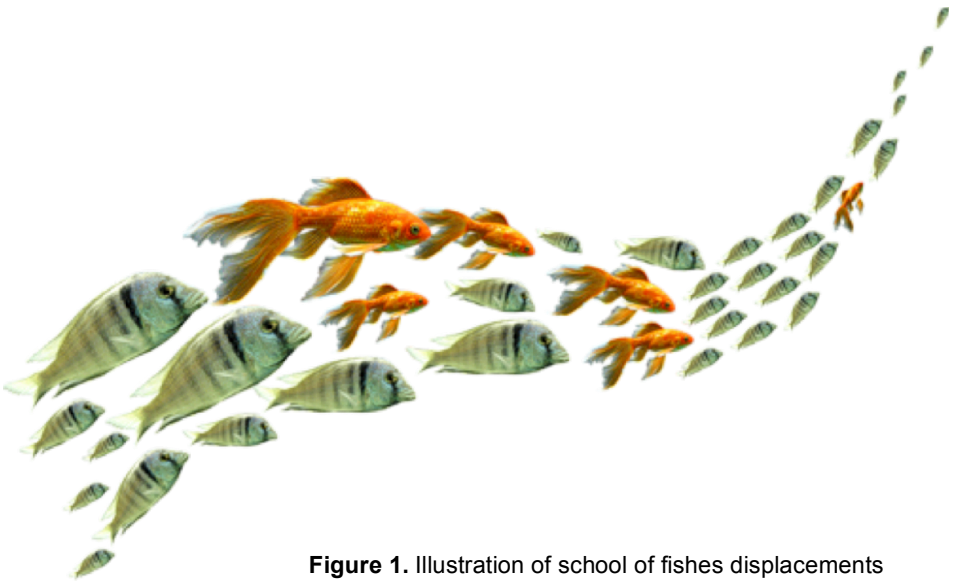

Figure 1. Illustration of school of fishes displacements

intelligence. Importantly, the information exchanged between individuals allows the group to perform much better than a single individual can achieve.[2,3].

Self-organization refers to the spontaneous (self-; i.e. without the need for a conductor) and dynamic emergence of a spatial organization, a rhythm or a spatiotemporal structure under the effect of interactions at work between the sub-components of the system under consideration. Together examples outline that self organization is not the prerogative of living beings or societies as well as this notion appears to be observed at both macroscopic and microscopic levels (e.g. migration of cells during embryogenesis). These non hierarchical systems illustrate how order may appear spontaneously within an apparent disorder. As Henri Atlan explains, after the discovery of the existence of genes in the 1960s, it was thought that the development of the cell was the result of a program coded in DNA. [7] The biologist proposes another, far more explicative view: any organized system, from crystal to social networks, via viruses, cells, insect societies, neural networks, develops and becomes more complex through interactions between its sub-components.[7] In line with Atlan's proposition, self-organization could be defined as an internally caused rise in complexity.[6,8]

Interactions are of prior importance in the definition of complexity. This feature distinguishes complexity from complication.[9] A system could be indeed complicated without being complex. The presence of infinitely entangled components characterizes complex systems while complication only refers to the significant number of elements. The number of constituents that make up a machine can suggest its complicated feature, without being necessarily complex. Conversely, a machine made up of few constituents can be complex because of a multitude of interactions that animates it.

Constant interaction between perception and action is needed to live in a complex and multisensory environment.[10] Our ability to merge information coming from several senses is crucial to produce and regulate our body movements. Similarly to school of fishes or ants colony, human movement is thus intrinsically dynamic and complex. Continuous integration of multiple sensory inputs and coordination of motor outputs are

needed to achieve efficient, stable, and adaptable physiological system as locomotion. Coordination among the multiple components and at multiple levels within the system reveals the complexity of physiological signals.[6,9] As such, human locomotion emerges from a wide set of interdependent elementary components, self-organized in coherent units and not dictated by a specific component within the system.[6,9]

Human movement variability: detrimental or beneficial?

Human movement variability stems inherently from multiple interrelated loops. Fluctuating dynamics of human movement does not simply result from perturbations within the system, but expresses its inherent complexity (Figure 2).[9] While initially perceived as an unmeaning noise, increasing evidence demonstrated that human movement variability contains hidden temporal organization that may provide insight into the neurophysiological organization of locomotion and into the regulation of the interacting subsystems, constituting the locomotor system.[11] According to different perspectives, human movement variability could be perceived both as detrimental (i.e. increased risk of falling), as well as beneficial (i.e. reflecting exploration of multiple task solutions).[12] These two different points of view could be greatly explained by the methodology applied.[11,13] Traditionally, standard linear metrics, such as the coefficient of variation describe the amount of variability, ignoring the temporal ordering of variations.[11,14] However, human movement variability contains hidden complex temporal organization displaying the temporal ordering of variations (i.e. the presence of long-range autocorrelations; LRA). LRA can be highlighted by the use of non-linear mathematical methods (e.g. rescaled-range analysis, detrended fluctuations analysis or entropy).[11,14–18] LRA result from the "memory" of the preceding values in the series, highlighting the existence of a complex temporal structure in human locomotion.[16,17,19,20] By applying both linear and non-linear methods, human movement variability is thus depicted in a complementary way.[13,21]

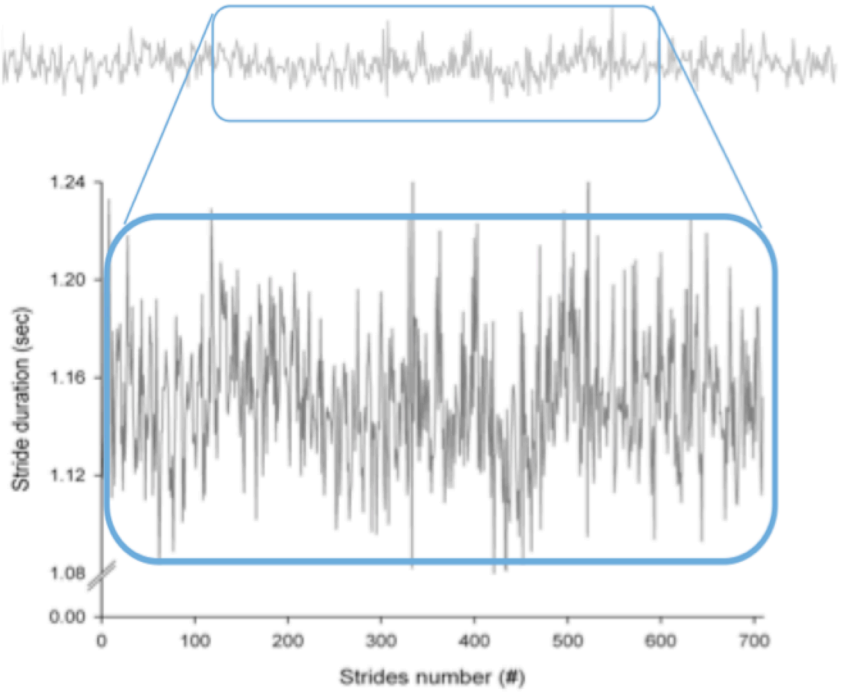

Figure 2. Typical traces of stride duration variability of a healthy youg adult walking at a self-selected speed

Origin and control of LRA in human locomotion

Although the presence of the LRA is largely demonstrated in human movement, their origin and control mechanism remain nevertheless elusive. Description of human walking dynamics and hypotheses with respect to the mechanisms of control are essentially based on both experimental observations and models.

Growing body of clinical and experimental observations suggest that LRA would reflect a centrally controlled process. Independently of age and walking speed, they are affected in patients presenting with central nervous diseases (e.g., Huntington's, Parkinson's, amyotrophic lateral sclerosis),

[22,23] whereas their characteristics are unaltered in diabetic patients suffering from severe peripheral neuropathy.[24]. As recently demonstrated for cycling variability[18], the involvement of supraspinal centers was also experimentally suggested by the breakdown of LRA during metronomically paced walking.[25] The role specialized spinal located neural networks, called central pattern generators (CPGs) has also been documented by some authors [19].

Based on these experimental results, previous modeling efforts were focused on properties of complex neural control mechanisms [19,26,27]. Originally, Hausdorff et al.[19], and extended by Ashkenazy et al. [28], proposed a correlated stochastic version of a CPG to describe the fluctuating dynamics of human walking. Later West and Scafetta[26] proposed a super central pattern generator (SCPG) based on the assumptions that human locomotion is regulated by both the supra- and intraspinal nervous system.

While these models appear promising, they do not exclude other, possibly simpler explanations.[27] In particular, the development of passive dynamic bipedal walking models suggested that LRA could simply result from the biomechanical structure of the system, without requiring the intervention of central neural networks [27,29,30]. Interestingly, Kurz and Stergiou demonstrated that a passive dynamic walking model can walk with a chaotic locomotive pattern when hip actuations are provided by a torsional spring connected between the swing and the stance legs.[31]

Thus, no simple answer to the question of origin and mechanisms of control of LRA can be firmly formulated because both the biomechanical properties of the body and the nervous system are entangled and both can contribute to the fluctuating gait pattern observed in human locomotion.

LRA as a pathological index: A clinical tool?

Of particular interest is the potential use of LRA to distinguish between healthy and pathological conditions in a number of diseases.[22,32–35] In human locomotion, the temporal organization of movement variability is the signature of an adaptive locomotor system characterized by a stable movement pattern with adaptive variation.[11,36] From a theoretical point of view, such adaptability is permitted by a structured optimal level of

variability, which provides a wide variety of responses to any perturbations (motor redundancy).[11] As a corollary, deviations from an optimal level of variability in either the direction of randomness or the over-regularity indicate the loss of the adaptive capabilities of the system.[11]

By extension, the loss of complexity with pathology was associated with dynamic instability in locomotion.[11,37] Here, the notion of stability is thought in a clinical perspective. Gait stability has been defined as "the ability to maintain functional locomotion despite the presence of external disturbances or internal control errors"[38], and a higher fall risk has typically been associated with a lack of adaptive gait control in the presence of sensorimotor variability or external disturbances.[39]

Falls are of prior importance among community dwelling older people. Evidence shows that, older people over 64 years of age, 28-35% fall each year. Gait disorders constitute important contributor of most of falls. With a prevalence estimated at approximately 35%, gait disorders are highly frequent in adults aged 65 years and older and reach higher percentage in neurological conditions.[40–42] Gait impairments and subsequent falls are indeed the most common and debilitating manifestation in neurological disorder and particularly in Parkinson's disease (PD). About two-thirds of PD patients report at least one fall, with about 39% reporting recurrent falls.[40] This puts a high burden on patient quality of life and independence. Consequences are devastating for affected individuals, often leading to injuries, secondary immobility, falls and institutionalization.[43] Mobility impairments and other PD-related disorders are also an important source of caregiver stress.[44] Finally, survival appears to be reduced once falls have occurred.[45] In addition to the individual physical, psychological and financial costs, falls and fall-related injuries induce important costs for the public health system and society more broadly. The detection of specific markers of gait instability appears thus to be critical for preventing falls and their consequences. However, there is no accepted quantitative way to assess gait stability.[46]

Interestingly, stride duration variability has been mentioned as a good candidate from which to derive markers of gait instability, as it is tightly linked to rhythm control, which is particularly impaired in basal ganglia disorders.[47] In addition to reduced gait speed, shorter stride length,

stooped posture, and reduced arm swing, the inability to produce a steady gait rhythm is indeed one of the primary temporal gait disorders in PD, which result in a more random gait pattern.[47–49] Perturbations of the temporal organization of gait variability have been suggested as a marker of gait disorder and fall risk among patients with central nervous diseases such as Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis.[13,22,34,50,51]

What about Parkinson's disease?

Parkinson's disease is one of the most frequent neurodegenerative disorders, affecting close to one percent of the population over the age of 60 years.[47] It currently affects 7 to 10 million people worldwide but could double by 2030.[52]. The clinical identification and the therapeutic management constitute one of the most important worldwide challenge in PD.

By resulting from the progressive degeneration of the nigro-striatal pathway, the symptoms are dominated by motor disorders that appear progressively during the course of the disease: bradykinesia, hypokinesia, tremor, rigidity, and postural disorders.[48,53–55] These neurological deficiencies reduce patients' ability to walk, their independence in carrying out activities of daily living, and their quality of life. Therefore, improving locomotor function is one of the main objectives of therapeutic management [56]. Also, any intervention that would promote the decrease of fall incidence in PD patients would have a direct benefit for the patient, caregiver, and society.

Currently, treatments for PD include medication via dopamine supplementation as well as neurosurgical treatments. However, the typical gait disorders as well as the postural instability are partially responsive to such approaches.[55,57,58] Thus, there is a pressing need to consider alternative approaches. In this context, recent guidelines also underline the importance of rehabilitation treatments in the management of PD patients[59], including treadmill based walking training[60]. Indeed, the regular practice of physical exercises demonstrated its effectiveness on gait disorders and postural instability as well as both in the preservation of locomotor capacities and in the prevention of complications (such as cardiovascular

disorders, osteoporosis, etc.).[59,61] It further slows the progression of the disease down and reduces the risk of falling.[59,62]

Series length influence for an adequate assessment of LRA in clinical context

Although the assessment of the temporal organization of gait variability may provide an easy and effective tool to quantify gait stability, one limitation of such approach is that physiological time series are unavoidably finite, whereas the presence of LRA is an asymptotic property, making the assessment of long-range dependency inherently based on approximations.[16] Thus, it is crucial to determine a good balance between the series length, which in the context of clinical application is limited by patients' ability to perform a task for a long time, and the minimum number of cycles necessary to obtain a reliable assessment of the series autocorrelation function.

Aims and content of the thesis

This thesis aims to investigate the potential clinical utility of gait variability as an objective and quantitative assessment of gait stability in PD and, secondarily, as a clinical tool for evaluating the therapeutic efficacy of rehabilitation approaches in a population of patients suffering from PD. Based on the definition of gait stability, influence of external and internal factors on human locomotion was investigated, which could allow to further investigate the possible origin of LRA (Figure 3). Prior to be studied in PD population, backward walking and dual task paradigm were used as external factors that could perturb the gait stability of healthy young adults (**Chapter 1**). Also, similarly to the influence of isochronic metronome observed on healthy gait pattern[37,63–65], investigation of an imposed cadence was performed during pedaling task in healthy population (**Chapter 1**).

Internal factors' influence on human locomotion was investigated using the pathological model of Parkinson's disease (**Chapter 2**). The impaired scaling and timing control in PD result from the defective activity among interacting subcomponents (e.g. basal ganglia). Considering the higher fall risk and temporal gait disorders in PD, we hypothesized that

stride duration variability will be less structured (i.e. more random) in PD and will be correlated with their functional assessment.

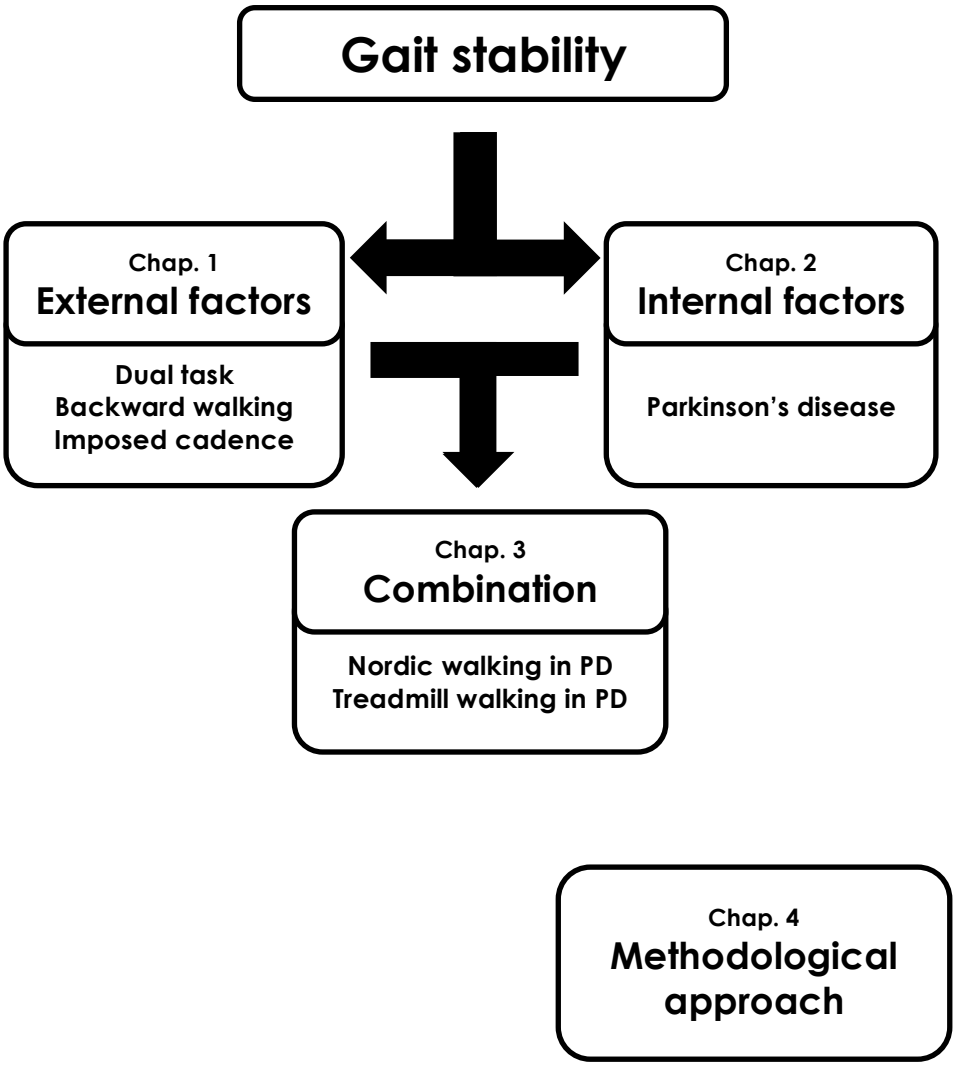

Figure 3. Thesis' flowchart

Compensating or restoring interactions among multiple components involved in healthy gait pattern is a key factor in restoring adaptability and flexibility of locomotion. In addition to studying the potential usefulness of LRA assessment as a clinical tool for assessing the risk of falls in PD, the project also aims to investigate the modulation of LRA to rehabilitative approaches as an objective and quantitative clinical measure of therapeutic efficacy. Among multiple rehabilitative approaches, treadmill and Nordic walking hold a special place allowing compensation for the impaired scaling and timing control in PD (**Chapter 3**). The treadmill belt or the use of Nordic poles may act as an external cue, triggering intact circuits and bypassing the defective basal ganglia—supplementary motor area loop. This chapter aims to investigate PD gait pattern in the presence of external factor, potentially compensating the internal defective control.

Finally, the perspective to extend the use of LRA assessment as a marker of gait stability applicable to a broad range of locomotor disorders lead us to consider methodological efforts made to reduce the acquisition time which constitute the most important limitation for an application to the largest disease spectrum (**Chapter 4**).

Chapter 1

External factors: Backward walking & Dual tasking

Variability of Human Gait: Effect of Backward Walking and Dual-Tasking on the Presence of Long Range Autocorrelations

Dynamics of Revolution Time Variability in Cycling Pattern: Voluntary Intent Can Alter the Long-Range Autocorrelations

CHAPTER 1 – Article 1

Variability of Human Gait: Effect of Backward Walking and Dual-Tasking on the Presence of Long Range Autocorrelations

Information from the central and peripheral nervous systems is continuously integrated to produce a stable gait pattern. However, stride duration fluctuates in a complex manner in healthy subjects, exhibiting long-range autocorrelations that can span over hundreds of consecutive strides. The present study was conducted to explore the mechanisms controlling the long-term fluctuation dynamics of gait. In the first part of the study, stride duration variability was evaluated on a treadmill during forward (FW) and backward walking (BW). Despite the modification of the biomechanical constraints imposed on the locomotor system, the characteristics of the long-range autocorrelations remained unchanged in both modes of locomotion (FW: H = 0.79 ± 0.04 and α = 0.58 ± 0.13; BW: H = 0.79 ± 0.11 and α = 0.53 ± 0.25). In the second part of the study, stride duration variability was assessed while the subjects were performing a dual-task paradigm that combined gait and mental calculation. The long-term variability of stride duration was similar during usual walking (H = 0.80 ± 0.06 and α = 0.57 ± 0.13) and in dual-tasking (H = 0.77 ± 0.06 and α = 0.52 ± 0.16), whereas walking altered the performance of the cognitive task. Hence, the biomechanical and cognitive interferences imposed in the present study were not sufficient to induce a modification of the long-range autocorrelations highlighted in walking variability. These observations underline the robustness of the long-range autocorrelations.

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INTRODUCTION

Human walking is a complex motor task that depends on multi-level mechanisms of neural control. Despite its automatic nature, gait requires the continuous integration of information from the central and peripheral nervous systems to produce a stable pattern. The magnitude of fluctuations between strides is low in young healthy subjects walking at a spontaneous speed, as demonstrated using classical mathematical methods (e.g., standard deviation, coefficient of variation).[21,66] However, it is known that gait fluctuates in a complex manner over the long term, and this variability is characteristic of healthy organisms.[22,34] Consecutive strides are indeed characterized by long range autocorrelations that can span over hundreds of consecutive strides.[23] The assessment of such fluctuation dynamics between strides necessitates the use of complex mathematical methods.

A wealth of studies have reported that time series of stride durations exhibit long-range autocorrelations.[17,19,23] However, the precise neurophysiological origin of such gait fluctuations remains unclear. The development of passive dynamic bipedal walking models suggested that these variations could simply result from the biomechanical structure of the system, without requiring the intervention of central neural networks.[27,29,31] The role of central pattern generators (CPGs) located at the spinal level has also been documented by some authors.[19] However, several clinical observations suggest that long range autocorrelations would reflect a centrally controlled process. They are affected in patients presenting with central nervous diseases (e.g., Huntington's, Parkinson's, amyotrophic lateral sclerosis),[22,23] whereas their characteristics are unaltered in diabetic patients suffering from severe peripheral neuropathy.[24] Long-range autocorrelations remain similar from 5 to 75 years of age in healthy subjects, appearing largely before the slow development of anthropometric parameters in children and persisting despite the appearance of peripheral modifications in the elderly.[21] As recently demonstrated for cycling variability,[18] the involvement of supraspinal centers was also experimentally suggested by the breakdown of long-range autocorrelations during metronomically paced walking.[23] However, this observation was later questioned in a reassessment of the data.[14] The present study was conducted to further experimentally investigate the mechanisms controlling the long-term fluctuation dynamics of human locomotion by exploring

backward walking (BW) and dual-tasking.

On one hand, gait belongs to the category of reversible movements for which the plantigrade-digitigrade sequence during the stance phase is inverted when walking backward. Stance begins with the heel strike and ends at toe-off during forward walking (FW), whereas it starts with the contact of the toes on the floor and finishes when heel is lifted off during BW.[67] Therefore, BW induces a particular modification of the biomechanical constraints and may help to get an insight into the control of human locomotion. A number of biomechanical constraints could be selected to explore the locomotor system, but BW is largely studied in the literature. FW and BW have already been compared on many aspects, including kinematics,[67–70] kinetics,[68,70] elevation angles,[67] or muscle activity.[67–70] An increase in stride duration magnitude of variability has also been shown during BW,[71] whereas modifications of the structure of kinematics variability have been highlighted after gait reversal in healthy subjects[71] and in patients with unilateral anterior cruciate ligament deficiency.[72]

On the other hand, there is growing evidence that gait is not merely an automatic task, but that it requires the intervention of cognitive functions.[73] In particular, the executive function is defined as a variety of cognitive processes that use information from the cortical sensory systems to produce a defined behavior.[74] Divided attention, a particular example of executive function, refers to the ability to allocate attentional resources between at least two tasks performed at the same time. It plays an important role in daily life while walking in multi-task conditions. Dual-task paradigms are usually used to test divided attention.[73] They consist of the simultaneous achievement of a primary ‘‘attentional’’ task and a secondary ‘‘motor’’ task, i.e., gait. Such paradigms are based on the hypothesis that two tasks performed simultaneously interfere with each other if they use similar cerebral areas, resulting in structural interferences between both tasks (bottleneck theory) or overwhelming the capacity of the processing resources (capacity sharing theory).[74,75] The interferences between both tasks are estimated by alteration of the performances of one or both. In particular, mental calculation could be used as an attention-demanding task to interfere with gait. The neural substrate of numerical processing is essentially located in the parietal, prefrontal and cingulate areas,[76] whereas frontal and parietal activity has also been shown using positron emission

tomography during imagination of locomotor-related tasks.[77]

A dual-task paradigm could be useful to investigate the neurophysiological origin of long-range autocorrelations, complementary way to BW. Using the Detrended Fluctuation Analysis, Decker et al.[78] recently failed to find an effect of a cognitive task on the persistent fluctuations of stride duration in young healthy adults. However, Lamoth et al.[79] showed in older adults that dual-tasking decreased the walking speed and cadence, increased the magnitude of stride duration variability and affected the stability and regularity of lateral trunk accelerations, including the characteristics of long-range autocorrelations. These changes were significantly more important in cognitively impaired subjects.

The objective of this study was to explore the mechanisms controlling the long-range autocorrelations highlighted in gait variability by (i) comparing FW and BW and (ii) using a dual-task paradigm. The first part of the study was conducted to explore the influence of the biomechanical constraints imposed on the locomotor system, whereas the role played by supraspinal networks was investigated in the second part of the study. The analysis of fluctuation dynamics was completed by the assessment of fluctuation magnitude (coefficients of variation) to obtain a more complete characterization of the gait pattern variability.

MATERIALS AND METHODS

Subjects

Part 1: Forward vs. Backward Walking

Twelve young subjects (six men, six women) with no history of neuromuscular or orthopedic disorders took part in the first part of the study. Their mean age was 23.0 ± 2.9 years, their mean height was 1.75 ± 0.10 m and their mean weight was 64.1 ± 8.3 kg.

Part 2: Dual-Tasking

For the second part of the study, 20 young and healthy males were recruited from the scientific community of our University. This sample comprised a different set of subjects from those who participated in the BW experiment, but their clinical characteristics were similar. Their mean age was 23.3 ± 1.2 years, their mean height was 1.80 ± 0.07 m and their mean weight was 72.3 ± 7.2 kg. They were also free of dyscalculia and any sight problems.

The study protocol was approved by the local ethics committee and each subject signed an informed written consent before participating.

Apparatus

The walking tests were performed on a 0.5 m-wide and 1.5 m-long treadmill. A unidimensional accelerometer was taped on the right lateral malleolus of each subject. The antero-posterior accelerations of the right lower limb were continuously measured with a high sampling rate (512 Hz). The stride duration was automatically calculated as the time elapsed between two successive acceleration peaks, which allowed for the determination of the fluctuations during the complete trial.

Tasks and Procedures

Part 1: Forward vs. Backward Walking

The subjects were first allowed to become accustomed with the treadmill by spending a few minutes walking forward and backward on the equipment. They were then instructed to perform two consecutive walking trials, the first in FW and the other in BW. Each test lasted 15 min and was preceded by a few minutes of warm-up. The sequence of acquisitions was randomly assigned to the subjects, and the sessions were separated by several minutes of rest to avoid fatigue. The gait speed was similar during both trials, and it was determined as the self-selected comfortable BW speed (mean: 0.88 ± 0.04 m s^{-1}).

Part 2: Dual-Tasking

Motor Task

The subjects had to walk on the treadmill at a constant speed of 1.11 m s^{-1} for 15 min. Recording started after a few minutes of warm-up during each trial.

Cognitive Task

The participants had to perform 85 arithmetical tasks (additions, subtractions, multiplications, divisions of two digit numbers; for example: 54x6, 81–49, etc.). The stimuli were visually presented to the subjects in a random order. Each calculation was presented for a duration of 2 s, which was followed by 10 s of thought each time. The participants were instructed to answer each calculation orally to the best of their ability, and not necessarily as quickly as possible. The percentage of correct responses was listed for each subject.

Organization of the Sessions

The experimental protocol was organized into three sessions. During the first session, the subjects were simply asked to walk on the treadmill (‘‘usual walking’’ session). During the second session, they had to perform calculations while walking on the treadmill (‘‘dual-tasking’’ session). The calculations were presented on a screen placed at a distance of 4 m from the treadmill, and priority was explicitly given to the cognitive task. During the third session, the participants had to perform the arithmetical task while sitting before a computer (‘‘cognitive task’’ session). The sequence of acquisition was randomized for each subject, and the trials were separated by periods of rest to avoid fatigue.

Data Analysis

Fluctuation Dynamics

The presence of long-range autocorrelations was evaluated using the integrated approach proposed by Rangarajan and Ding[80] and validated

by Crevecoeur et al.[16] in the context of physiological time series. These methods are described in greater details elsewhere. Briefly, the Hurst exponent (*H*) was calculated using the rescaled range analysis (RRA)[17,21] and the α exponent was evaluated using the power spectral density (PSD) of the time series.[17,21] For each time series, both methods were applied to sequences of 512 consecutive gait strides (1–512, 2–513, 3–514, etc.). In addition, we further considered that *H* and α had to satisfy the asymptotic relationship $d = H - \left[\frac{(1+\alpha)}{2}\right]$, which allowed to reject some false positive cases resulting from the application of the RRA and the PSD alone.[16,17,21] The sequence of 512 consecutive gait cycles presenting with the lower value of *d* was selected for each time series.

The presence of long-range autocorrelations can be determined with a good level of confidence when $H > 0.5$, α is significantly different from 0 ($p < 0.05$) and lower than 1, and $d \leq 0.10$.[16] Conversely, values of $H = 0.5$ and $\alpha = 0$ indicates the presence of a white noise, whereby the process is a collection of independent and identically distributed random variables. A value of $H = 0.5$ may also indicate the presence of short-range correlations, whereas an $H < 0.5$ indicates the presence of anti-correlations (i.e., an increase of the variable tends to be followed by a decrease and vice versa). These methods were applied under the assumption that the initial process generating the gait time series was stationary during treadmill walking.[21] The methods were selected above other more general ones[14,81] that are critical to identify the process under investigation (stationary vs. diffusion processes).

Fluctuation Magnitude

Mean stride duration and coefficient of variation (CV = [SD/mean] X 100) were calculated for the 512 consecutive strides that were previously selected for each time series.

Statistics

The paired *t*-test was used for all statistical comparisons: FW vs. BW, usual walking vs. dual-tasking, cognitive task vs. dual-tasking (percentage of correct responses). The results were considered significant

if $p < 0.05$. Sigmastat 3.5 software was used for all statistical analyses.

RESULTS

The time series of one subject walking forward (a) and backward (b) and of another participant during usual walking (c) and in dual-tasking (d) are presented in Figure 1 to illustrate the results obtained for all of the subjects presented hereafter.

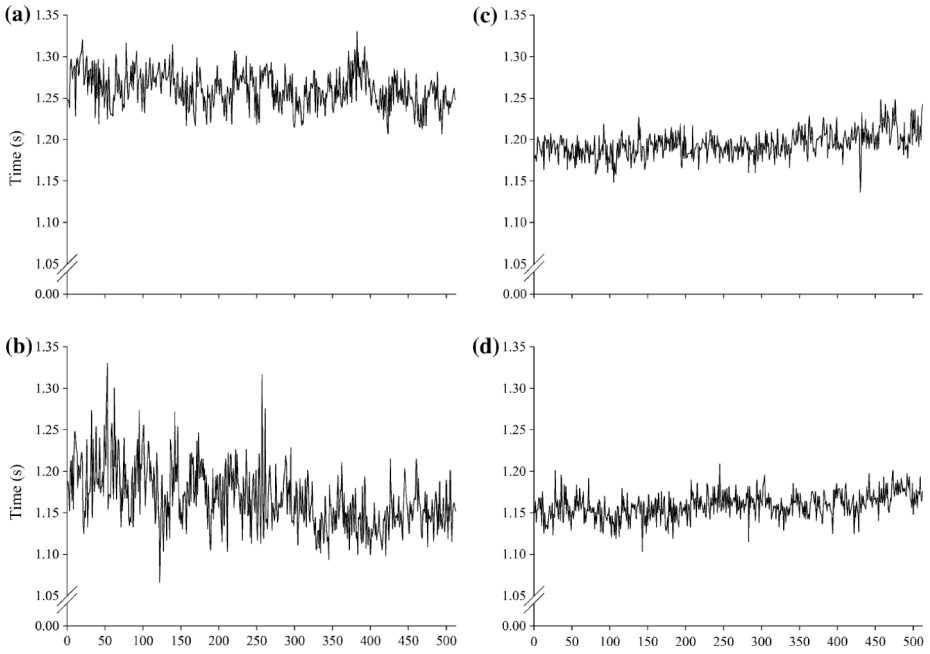

Figure 1. Several selected time series of 512 consecutive strides. In the left column, both time series were obtained from one participant during forward (a) and backward (b) walking. In the right column, both time series were obtained from one subject during usual walking (c) and during dual-tasking (d).

Part 1: Forward vs. Backward Walking

The integrated approach suggested the presence of long-range autocorrelations in FW and in BW in all the subjects. All values of the Hurst exponent were greater than 0.5, the α exponent was always significantly different from 0, and all values of *d* were far below 0.10, except for the Subject #8 during FW. The mean values of *H* , α and *d* were similar in both conditions, and the results of the statistical analyses confirmed that the characteristics of the long-range autocorrelations were not affected by the walking direction (Figure 2). Regarding the stride duration fluctuation magnitude, the values of CV were statistically smaller during FW than during BW (Figure 2), and the mean stride duration was statistically greater while walking forward. This result indicated that the walking cadence and magnitude of fluctuations increased when the subjects were walking backward.

Part 2: Dual-Tasking

The value of the Hurst exponent was superior to 0.5, the α exponent was significantly different from 0, and the value of *d* was far below 0.10 in all the time series. Hence, the presence of long-range autocorrelations was suggested in all participants during usual walking as well as in dual-tasking. Moreover, the mean results were similar in both conditions, showing that the characteristics of the long-range autocorrelations were not influenced by the cognitive task (Figure 3). The results were similar regarding the mean stride duration and CV with values that were statistically similar during usual walking and during dual-tasking (Figure 3). This result indicates that magnitude of fluctuations is not altered by dual-tasking. Conversely, the percentage of correct responses to mental calculations was lower during dual-tasking for all but two subjects. This result was statistically significant for the complete group of participants (Figure 3), which indicates that walking perturbs the cognitive task.

DISCUSSION

The present study shows that the fluctuation dynamics of stride duration is not affected by modifying the biomechanical constraints or

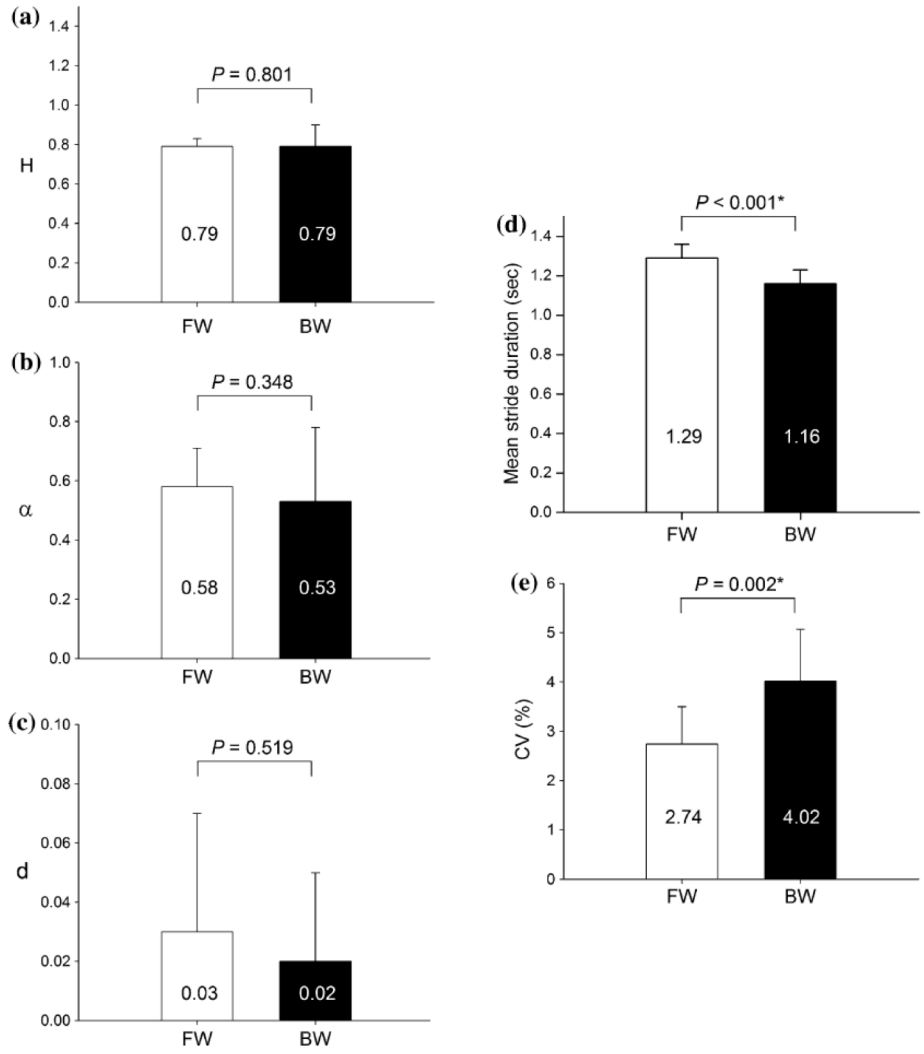

Figure 2. Comparison of mean (±SD) values of *H* exponent (a), α exponent (b), relation *d* (c), mean stride duration (d) and CV of stride duration (e) for the 12 subjects during FW (white) and BW (black). *Statistically significant.

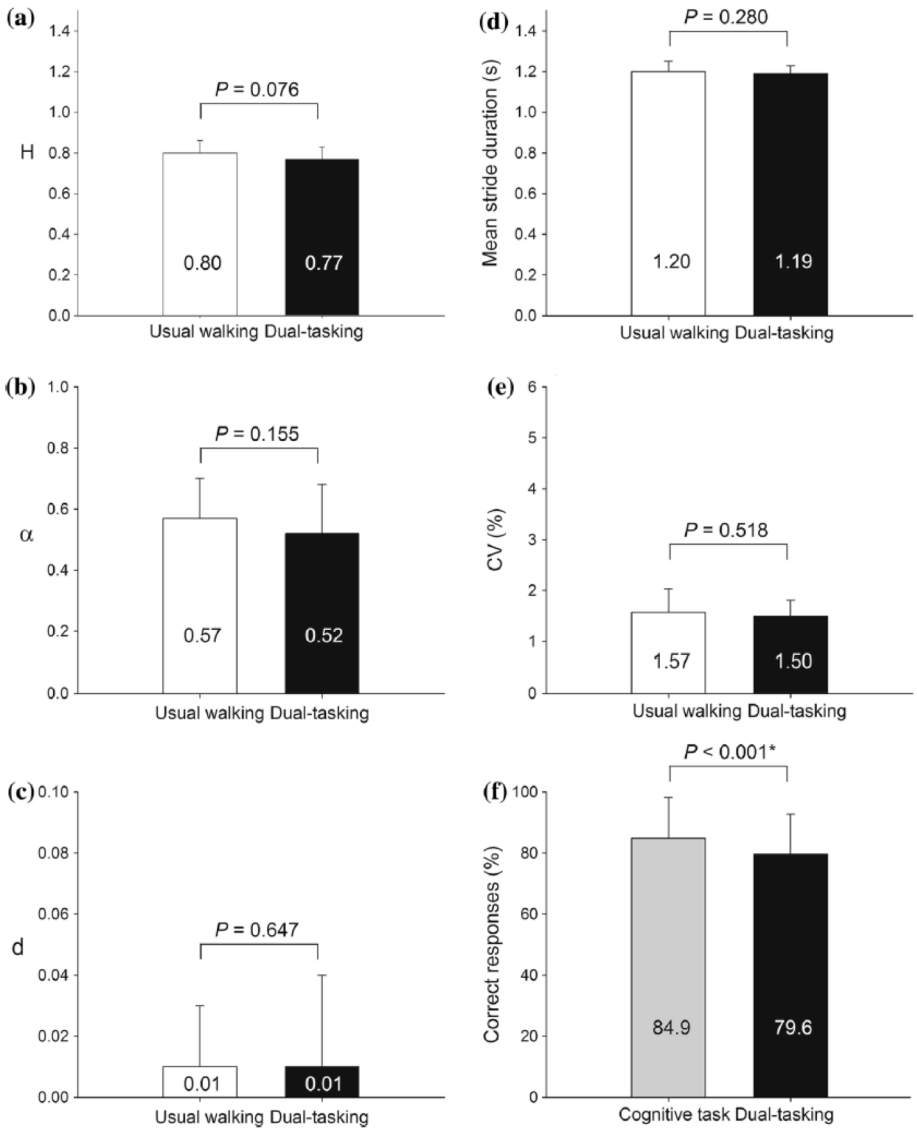

Figure 3. Comparison of mean (±SD) values of *H* exponent (a), α exponent (b), relation *d* (c), mean stride duration (d) and CV of stride duration (e) for the 20 subjects during usual walking (white) and dual-tasking (black). Graph (f) represents the percentage of correct responses to mental calculation during the cognitive task (grey) and dual-tasking (black). *Statistically significant.

cognitive constraints (dual-tasking). Indeed, the characteristics of long-range autocorrelations remained unchanged in both conditions.

It is established that BW induces large modifications of the biomechanical constraints imposed on the locomotor system. On the one hand, some BW variables are completely time-reversed copies of those of FW. This result was demonstrated for hip joint movements,[68–70] elevation angles of the lower limb segments,[67] some joint moment and power patterns[68,70] and the contribution of most lower limb muscles to the horizontal and vertical accelerations of the center of body mass.[68] On the other hand, FW and BW are not simply mirror images in other gait variables, including ankle and knee movements,[70] patterns of ground reaction forces,[67] knee joint torques[67,70] and the timing of activity of many muscles.[67–69] The present study also showed that BW induced significantly higher mean cadences and a greater magnitude of stride duration fluctuations, which confirms the results of previous studies.[67,70,71]

There is considerable evidence for supporting the presence of CPGs in animals and in humans, as well as for their roles in the generation of different motor patterns, including FW and BW. CPGs are spinal located neural networks that are believed to control limb coordination during gait. They would be able to work independently, but peripheral information and supraspinal pathways would also influence their functioning, making them able to adapt and to work differently in function of the context. Compared with FW, planar covariation of the elevation angles[67] and the trajectory of the fifth metatarsal[69] are maintained during backward locomotion, whereas the two walking modes differ considerably in terms of energy expenditure,[82] mechanics[67,70] and electromyographic activity.[67–69] Those unexpected observations led to the assumption that most gait variables were controlled in a subordinate manner with the respect to the conservation of the geometric shape, which would necessitate additional supraspinal inputs.[67,69] Similarly to the planar covariation of elevation angles and the trajectory of the fifth metatarsal, the characteristics of the long-range autocorrelations remained unchanged during FW and BW in the present study. This observation is consistent with the results of a previous study assessing the structure of stride duration variability through the approximate entropy.[72] This could suggest the role played by spinal and

supraspinal networks in the control of long-range autocorrelations.

However, the involvement of central mechanisms could not be confirmed by a dual-task paradigm combining gait and mental calculation, because the values of *H*, α and *d* were not affected by the additional cognitive task. Gait results from central and peripheral mechanisms that permanently interact with each other. The control of long-term walking variability was consecutively attributed to the biomechanical structure of the system,[27,29,31] CPGs[19] and supraspinal centers.[21–24] The persistence of similar long-range autocorrelations during BW and dual-tasking could suggest that they result from multi-level mechanisms of control, which would necessitate further investigations.

The interferences highlighted in dual-task paradigms rely on two main neuropsychological theories.[74,75] The bottleneck theory posits that two attentional tasks processed by the same networks induce structural interferences if they are performed simultaneously, resulting in reduced gait speed and in delayed performance of the cognitive task. The capacity sharing theory proposes that processing resources are limited in capacity. Simultaneous competing attention demands induced by dual-tasking lead to capacity sharing interferences and cause impairment of the performance in at least one of the tasks.

In the present study, we believe that the cognitive task used to induce capacity sharing interferences was adequate. This task was highly attention-demanding compared with classical cognitive tasks described in previous studies, which consisted, for example, of naming as many words as possible starting with a predefined letter[79,83] or counting backward.[84] The difficulty of the calculations was adapted to the intellectual level of the subjects, and the loading of attention remained constant throughout the assessment.[73] Moreover, the performance of the mental calculation was impaired during dual-tasking, which confirmed that both tasks interfered with each other. This observation is consistent with the results of a previous study showing that dual-tasking may alter the performance of the cognitive task without modifying the dynamical structure of gait variability.[85]

It has been shown that both young and older adults spontaneously prioritize walking stability over the cognitive task when no specific order of

importance is defined.[86] When priority is given to the cognitive task, quantitative gait parameters are more largely affected by dual-tasking than in the non-priority condition.[74,87] Similarly, sex differences have been highlighted for the prioritization effect, with gait being more largely altered in men than in women in the cognitive priority condition.[83] Hence, only men were recruited in the second part of the present study, and the participants were explicitly instructed to prioritize mental calculation over walking.

Walking speed was similar for all the subjects in usual walking and during dual-tasking (1.11 $m.s^{-1}$). Similarly, gait speed was selected as the self-selected comfortable BW speed in the first part of the study, which resulted in slow gait speed during FW (0.88 ± 0.04 $m.s^{-1}$). However, we recently suggested that walking velocity was not a confounder in the assessment of stride duration fluctuation dynamics.[21]

It can be hypothesized that the capacity of attentional resources was too large in young healthy subjects to be overloaded by the cognitive task and to result in impairment of gait performances. The same protocol could be used in older adults or in cognitively impaired subjects to increase the probability of inducing capacity sharing interferences, as previously proposed.[73,79,83,84,88,89] Changes in long-range autocorrelations characteristics had recently been suggested in older adults during dual-tasking, but this observation was based on the results of the Detrended Fluctuation Analysis applied exclusively.[79] Similarly, it can be suggested that the treadmill gave automatic priority to gait because the subjects were unable to stop or even to slow down. This could have resulted in decreased performance in mental calculation and in unchanged gait variability, which might have been different during level-ground walking. Finally, we only correlated particular variables of gait with selected features of the executive function. The inclusion of a broader range of assessments could help to identify disturbances in walking and to reveal the interdependence between gait and the executive function.

In conclusion, the present study highlights the robustness of the long-range autocorrelations characterizing the stride duration variability of human gait. Their persistence during BW likely indicates the role played by supraspinal networks in their mechanisms of control, whereas the steadiness of their characteristics during dual-tasking merely suggests that

they stem from low-level processes of the central nervous system.[78] However, the mechanisms of gait control are not limited to the cerebral areas involved in mental calculation. Many elements (e.g., the motor cortex, the basal ganglia, the cerebellum, the cortico-spinal tract, the peripheral nerves, the muscles, the osteo-articular structures, etc.) work together and permanently interact to produce the gait pattern. It can be postulated that the long-term dynamics of walking variability would emerge from peripheral and central constraints. The interferences imposed at a precise level could be compensated by other components of the system to maintain similar long-range autocorrelations. It seems difficult to affect their characteristics by punctual interferences, as imposed during BW or dual-tasking.

More complex paradigms should be designed to markedly interfere at one or several levels of the locomotor system, without forgetting that the subjects must be able to walk hundreds of strides to allow for a valid study of stride duration fluctuation dynamics.

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CHAPTER 1 – Article 2

Dynamics of Revolution Time Variability in Cycling Pattern: Voluntary Intent Can Alter the Long-Range Autocorrelations

Long-range dependency has been found in most rhythmic motor signals. The origin of this property is unknown and largely debated. There is a controversy on the influence of voluntary control induced by requiring a predetermined pace such as asking subjects to step to a metronome. We studied the cycle duration variability of 15 men pedaling on an ergometer at free pace and at an imposed pace (60 rpm). Revolution time was determined based on accelerometer signals (sample frequency 512 Hz). Revolution time variability was assessed by coefficient of variation (CV). The presence of long-range autocorrelations was based on scaling properties of the series variability (Hurst exponent) and the shape of the power spectral density (α exponent). Mean revolution time was significantly lower at freely chosen cadence, while values of CV were similar between both sessions. Long-range autocorrelations were highlighted in all series of cycling patterns. However, Hurst and α exponents were significantly lower at imposed cadence. This study demonstrates the presence of long-range autocorrelations during cycling and that voluntary intent can modulate the interdependency between consecutive cycles. Therefore, cycling may constitute a powerful paradigm to investigate the influence of central control mechanisms on the long range interdependency characterizing rhythmic motor tasks.

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INTRODUCTION

In humans, many periodic physiological signals such as gait, heartbeat, respiratory, and neuronal activities are characterized by their temporal complexity.[32,37,90,91] Indeed, most of their features continuously fluctuate in a complex manner over time.[32,91] Although fluctuations between cycles could appear to vary randomly, without apparent correlations between cycles, healthy systems possess the memory of preceding values of the series displaying a complex temporal structure.[11,37,90]

Variability is an intrinsic property within all biological systems and could provide insight into the neurophysiological organization and into the regulation of these systems.[11] Recent studies claimed that these fluctuations would represent the underlying physiologic capability to make flexible adaptations to everyday stresses placed on the human body.[11] Therefore, the presence of such temporal dynamics is thought to be a critical marker of health and their breakdown as an index of pathological condition.[11,37,90] In the human heart rate for instance, deviations from an optimal level of variability in either the direction of randomness (e.g., atrial fibrillation) or the over-regularity (e.g., congestive heart failure) indicate the loss of the adaptative capabilities of the system.[11,92]

In order to assess variability in physiological time series, several mathematical methods can be used. On one hand, classical mathematical methods, usually applied on shorter time series (tens of data points), quantify the fluctuation magnitude in a set of values independently of their order in the distribution, by computing the standard deviation (SD) and the coefficient of variation (CV). On the other hand, more complex mathematical methods can be used to assess the fluctuation dynamics over time.[21] These latter methods have demonstrated that variability of numerous physiological signals (e.g., cardiac and respiratory rhythm or locomotor activities) exhibit long-range autocorrelations, whereby the statistical inter-dependency between cycles spans of a very large number of cycles.[19]

In human locomotion, long-range autocorrelations have been well demonstrated only for stride duration and their study have until now received little attention in other rhythmic motor tasks, such as cycling.[19] Similarly to the stride duration, the cycling variable is naturally defined as the revolution time. This parameter is of particular interest as it represents one output of the locomotor system.[21] Cycling and walking result from complex dynamic sensorimotor interactions that constantly adapt locomotion to the environment. While these two rhythmic motor tasks have been shown to be generated by a similar central network, there remain differences in control of the two tasks. In comparison with walking, cycling is constrained to a circular trajectory with fixed biomechanical parameters (for instance cycle length corresponding to pedal length), and less movement amplitude. Cycling is also characterized by minimal need for trunk balance with no requirement of balancing on a single leg during any phase of pedaling and much less anticipatory adjustments. [61] Furthermore, in the particular case of stationary cycling, small amounts of body center of mass motion greatly reduce the contribution of visual or vestibular inputs in comparison with walking.

The origin of long-range autocorrelation remains unknown. One hypothesis is that the long-range interdependency results from the central control mechanism.[23–26,32,93] An alternative hypothesis suggests that these autocorrelations simply result from the effect of the biomechanical plant that filters noisy control input signals.[27,31] To the best of our knowledge, previous experiments based on gait have not succeeded in tackling this question. Indeed, the autocorrelation function seems to remain invariant on level ground walking and on a treadmill,[17] as well as across different walking speed.[21] One difficulty encountered in the context of gait analysis is that the work of gravity on the lower limb and the mechanical interaction with the environment may induce complex dynamics with possible long-range dependency.[94] In contrast, cycling reduces the contribution of gravity on the motor cycles because all phases must be actively controlled. This aspect of cycling task is potentially a strong asset to magnify the influence of centrally generated control signals on the series autocorrelation function. Furthermore, evidence that the long-range autocorrelation function can be altered by an explicit instruction, such as following an external pace imposed by a metronome or by the treadmill,[95] remains elusive. In this

study, we investigated this issue by using a cycling task, presenting the advantage to generate cyclic motor patterns while altering the biomechanical properties of the task as well as the underlying neural control process.

Therefore, the present study had two aims. The first one was to investigate the presence of long-range autocorrelations in the cycling pattern and the second one was to test the influence of a volitional control of a pre-determined cadence on the long-range interdependency characterizing rhythmic motor tasks.

MATERIALS AND METHODS

Subjects

Fifteen healthy young regular sportspersons participated in our study. In order to avoid any gender difference, we recruited only men. Their mean age was 23.8 (± 2.6) years, their mean weight was 74.2 (± 8.8) kg, and their mean height was 1.80 (± 0.07) m. None of them took medications or suff ered from any muscular, neurological, or orthopedic pathologies that could alter cycling performance. The study was approved by the local ethics committee, and each subject provided informed written consent before participating.

Materials

A friction-loaded Monark cycle ergometer (Varberg, Sweden, Model 828E) was used for the experiment. All subjects wore their own sport shoes that were fixed with straps to the pedals. To give optimal comfort, the saddle height was adjusted at 100% of the greater trochanter height (inducing a knee flexion of 25°–30° when the pedal was in lowest possible position).[96] Subjects were also asked to pedal in a seated position—keeping hands on top of the upper handlebars—which induced an elbow angle between 160° and 180°.[97] Leg accelerations were measured with a high sampling rate (512 Hz) using a unidimensional accelerometer taped in the anteroposterior direction on the head of the right fibula. During each test, data of acceleration were recorded (Figure 1) using the Vitaport 3

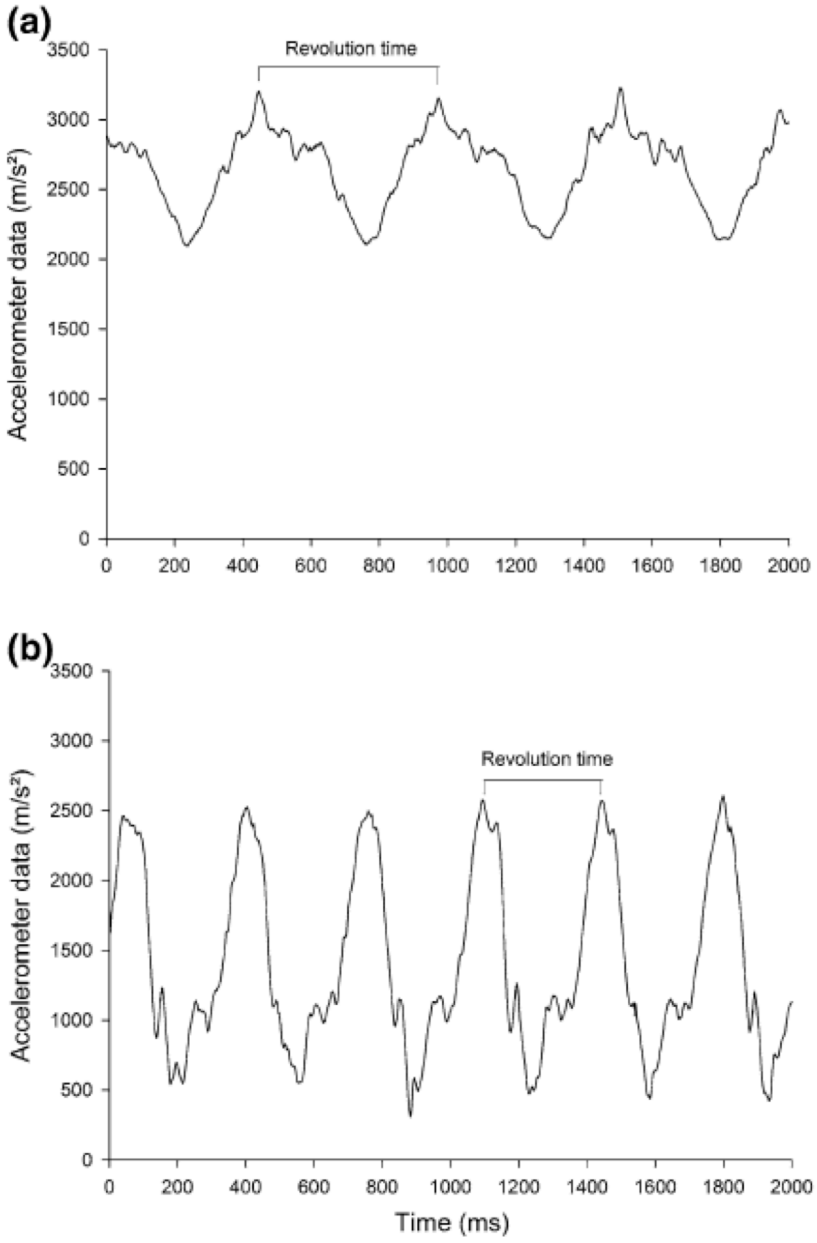

Figure 1. Example of accelerometer data over time obtained for the same subject at imposed (60 revolutions per minute) (a) and freely-chosen cadence (b).

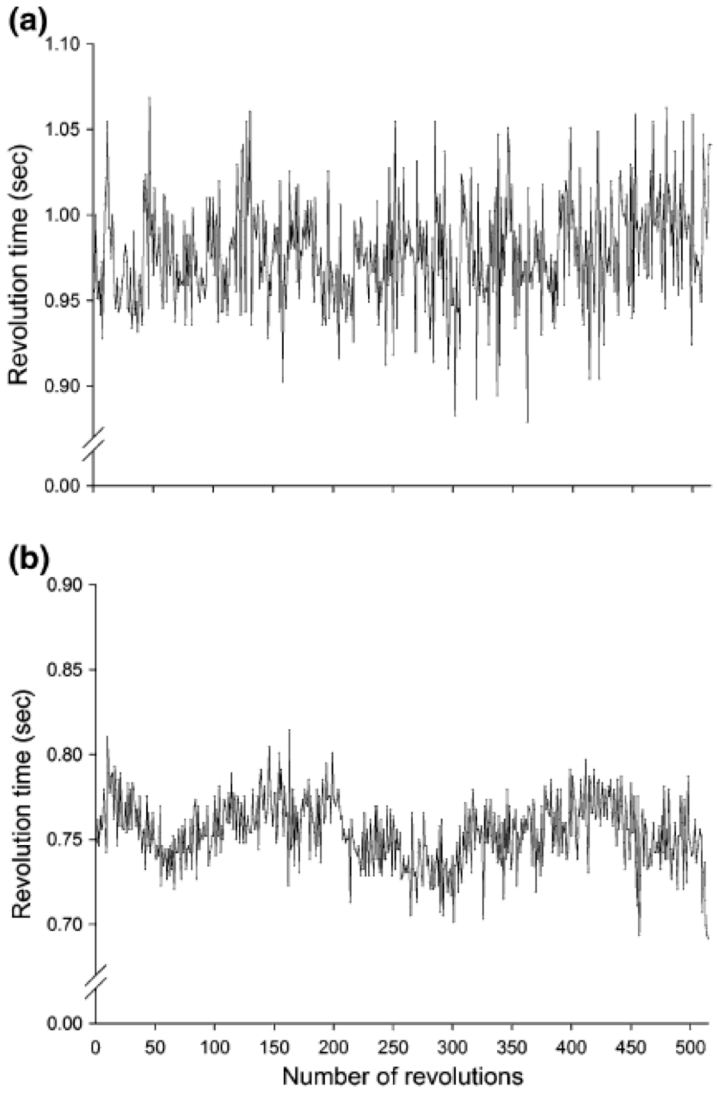

Figure 2. Typical traces of revolution time over 512 revolutions for the same subject at imposed (60 revolutions per minute) (a) and freely-chosen cadence (b).

(Temec Instruments B.V., Kerkrade, The Netherlands) ambulatory recorder, and next transferred to a computer. The cycle duration was determined from the peak of acceleration detected by a software and confirmed visually (Figure 2). A pilot study helped us to determine the ideal placement of the accelerometer. The accelerometer was initially placed on the lateral malleolus as for walking studies. However, we realized that this placement was not ideal as the wire tended to wind around the pedal. Furthermore, we also found that the peaks acceleration measured when the accelerometer were replaced on the right fibula tended to be more pronounced, which facilitated the extraction of the cycle duration.

Experimental Procedures

After a 2 min warm-up, subjects were requested to perform two successive 10 min sessions of cycling at a constant resistance of 10 N (or 1 Kp). During one session, cadence was freely chosen by the subjects. During the other session, subjects were invited to voluntarily (voluntary intent) maintain a cadence that was fixed at 60 revolutions per minute (rpm) for each participant and was controlled by a visual feedback. When subjects pedaled, the number of rpm was indicated in real time on a screen placed in front of the subjects. The order of sessions was randomly attributed to the subjects. To minimize the influence of fatigue, sessions were separated by at least 5 min rest. The second trial started only when heart rate had approached resting values (± 10%). After each cycling session, all subjects were asked to evaluate their perception of effort and indirectly their fatigue using the Borg RPE (Ratings of Perceived Exertion) and the Borg CR10 (Category Ratio) scales.[98,99]

Analysis of Revolution Time Variability

Revolution time variability was appreciated by classical and complex mathematical methods. Each method was applied to the same series of 512 consecutive revolutions. Classical mathematical methods (standard deviation, coefficient of variation) allow for evaluating the fluctuation magnitude, while complex mathematical methods (long-range autocorrelations) assess the dynamics of fluctuations over time.[21]

Fluctuation Magnitude

The mean revolution time and the mean cadence were calculated for the 512 consecutive revolutions that were previously selected for each time series. The standard deviation (SD_{RT}) and coefficient of variation of revolution time (CV_{RT} = [SD/Mean] X 100), were calculated on the same revolutions.

Assessment of Long-Range Autocorrelations

A process generating a time series contains long-range autocorrelations when the covariance of two distinct samples decreases slowly as the elapsed time between the two samples increases. Namely, if Xi denotes the duration of the ith cycle, a time series presenting long range autocorrelations is typically characterized by[17]:

$$E(X_i X_{i+n}) \sim n^{-\beta};$$

where $0 < \beta < 1$ and E(.) denotes the expected value of the argument.[80] Different mathematical methods, including rescaled range analysis (RRA) and power spectral density (PSD), are described in the literature to highlight the presence of long-range autocorrelations in time series. However, Rangarajan and Ding[80] demonstrated that both methods used separately presented drawback in their analysis. They presented an integrated approach combining RRA and PSD to cross-validate the results of each method, allowing rejection of some false positive results obtained from each method used independently. Recently, Crevecoeur et al.[16] validated this integrated approach in the context of physiological time series. Following his recommendations, each method was applied to a series of 512 consecutive revolution times.[16] The RRA, a random walk method, allows for the estimation of Hurst exponent.[16] The original time series of size *N* is first integrated. Then, the integrated series is divided in subsets of size s in which the local trend computed from linear regression is subtracted from the integrated series. The rescaled range of a given subseries of size s is defined as the range of the detrended subset (*R*) normalized to the standard deviation of the corresponding portion of the

original series (*S*). This procedure is applied to subseries of increasing size from τ = 10 to τ = N/2 and averaged across subsets of equal size. The slope of the relation between log(*R/S*) and log(τ) estimates the Hurst exponent (*H*) (Figure 3), which is asymptotically related to the autocorrelation function by the relation[17]:

$$H = \frac{2-\beta}{2} \qquad (1)$$

When 0.5< *H* <1, the time series typically presents long-range autocorrelations. If the process is a collection of independent and identically distributed random variables (i.e., a white noise, assuming a Gaussian distribution), then *H* = 0.5. An *H* < 0.5 indicates the presence of antipersistence, whereby an increase of the variable tends to be followed by a decrease and vice versa.[17,80,100] The shape of the series power spectral density (PSD) of the time series is calculated using Fourier transform analysis.[17,19,24] Long-range autocorrelated processes have a power spectral density that scales as $f^{-\alpha}$, where f is the frequency and α is related to the autocorrelation function by the relation

$$a = 1 - \beta \qquad (2)$$

The slope of the linear regression line computed by the logarithm of the power vs. the logarithm of the frequency determines the exponent a (Figure 3). An exponent a that is significantly greater than 0 indicates the presence of long-range autocorrelations, and an exponent a that is not significantly different from 0 is the signature of flat power spectrum corresponding to a white noise and short term correlated processes.[17] Equations (1) and (2) indicate that the scaling exponents *H* and a are theoretically related by the relation $H = \frac{1+\alpha}{2}$ [80] The integrated approach suggested by Rangarajan and Ding consists in computing *H* and a , and verifying that these two parameters are consistent through the equation *d* . $d = H - \left[\frac{(1+\alpha)}{2}\right] = 0$. A value of *d* ≤ 0.10 was considered acceptable since the asymptotic parameters are evaluated on finite time series.[17]

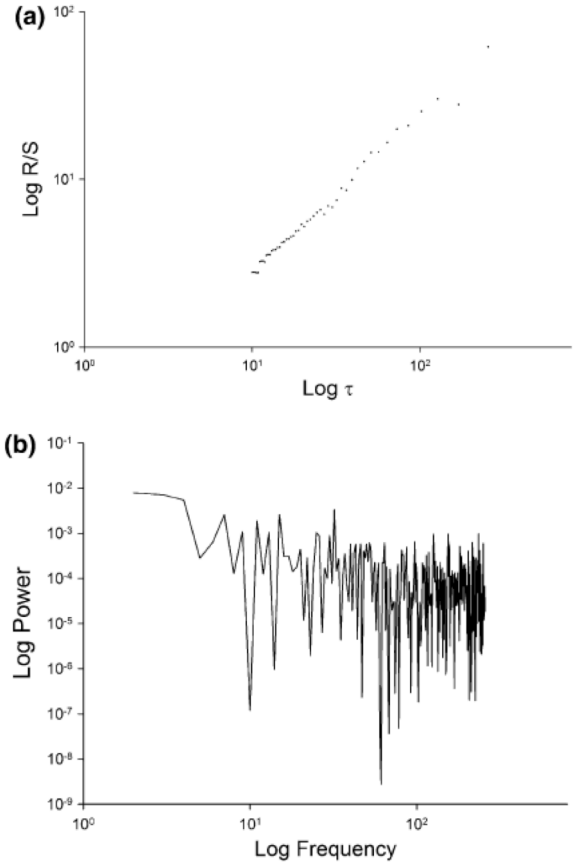

Figure 3. Graphical representation of Hurst and α exponents. A linear regression line is performed to each (log-log) data. The slope of this line is typically used to determine the Hurst exponent for rescaled range analysis (a) and the scaling exponent α for power spectral analysis (b).

In summary, the following three conditions must be satisfied to conclude for the presence of long-range auto-correlation[21] :

$H > 0.5$
α is significantly different from 0 and lower than 1
$d \leq 0.10$

Further analysis is strongly encouraged when inconsistencies appear between *H* and α. In the present study, we used the randomly shuffled surrogate data test, described by Theiler et al.[101] For each time series, 100 new series are generated from a random permutation of the original data. The only difference between the surrogate data sets and the original series is the sequential ordering of the data. *H* and α are then calculated for each new series and the mean and SD of these 100 new scaling exponents are computed and compared with the exponents of the original time series. The number of standard deviation between the original scaling exponent and the mean scaling exponent of the surrogate data sets (σ) is computed. If $\sigma \geq 2$, then the difference between the original data set and the surrogate data set is considered statistically different. It does not prove the presence of long-range autocorrelations in the original time series but it can reject the null hypothesis that the series under investigation has no temporal structure (i.e., uncorrelated random process).[17]

Statistical Analyses

Comparisons between conditions (imposed vs. freely chosen cadence) were made using paired t -tests. Level of statistical significance was set at a *p*-value < 0.05. For all statistical analyses, SigmaStat 3.5 software (Systat, Richmond, CA, USA) was used.

RESULTS

Using the Borg RPE scale and the Borg CR10 scale, the median values of perceived effort were respectively 11 (range: 8–17) and 3 (range: 1–7) at freely chosen cadence, which corresponded to a fairly light or moderate exercise. At an imposed cadence of 60 rpm, values were respectively 10 (range: 7–13) and 1 (range: 0.5–4), indicating a very light effort.

Fluctuation Magnitude

Mean revolution time, mean cadence, CV_{RT} and SD_{RT} for the 15 subjects in both conditions are presented in Table 1. Freely chosen

cadences were significantly greater than the imposed ones for the 15 subjects ($p < 0.001$). Conversely, results of statistical analyses revealed that CV_{RT} and SD_{RT} were similar in both conditions.

	Cadence		
Parameters	60 rpm	Freely chosen	*p* value (paired *t* test)
Mean cadence	60	82.043	**<0.001**
$Mean_{RT}$ (s)	0.99 (±0.01)	0.74 (±0.07)	**<0.001**
H exponent	0.68 (±0.07)	0.81 (±0.07)	**<0.001**
α exponent	0.24 (±0.18)	0.53 (±0.21)	**<0.001**
SD_{RT} (s)	0.03 (±0.01)	0.03 (±0.02)	0.730
CV_{RT} (%)	32.70 (±0.01)	44.80 (±0.03)	0.140

Table 1. Mean values of cadence, revolution time, Hurst exponent, α exponent, relation *d*, standard deviation, and coefficient of variation for young healthy adults pedaling at 60 revolutions per minute and at a freely-chosen cadence.

Bold values indicate statistical significance

Long-Range Autocorrelations

At freely chosen cadence, *H* exponent had a value between 0.5 and 1, and α exponent was significantly different from 0 for all subjects. The value of the relation *d* was also lower than the pre-specified limit of 0.10, excepted for three participants (Figure 4). According to the methods previously described by Crevecoeur et al.,[16] we can conclude that the majority of temporal series acquired at freely chosen cadence are long-term autocorrelated processes. For the three time series exhibiting a value of $d > 0.10$, randomly shuffled surrogate data tests revealed values of σ superior to 2 for *H* and for α, indicating that these time series could be statistically

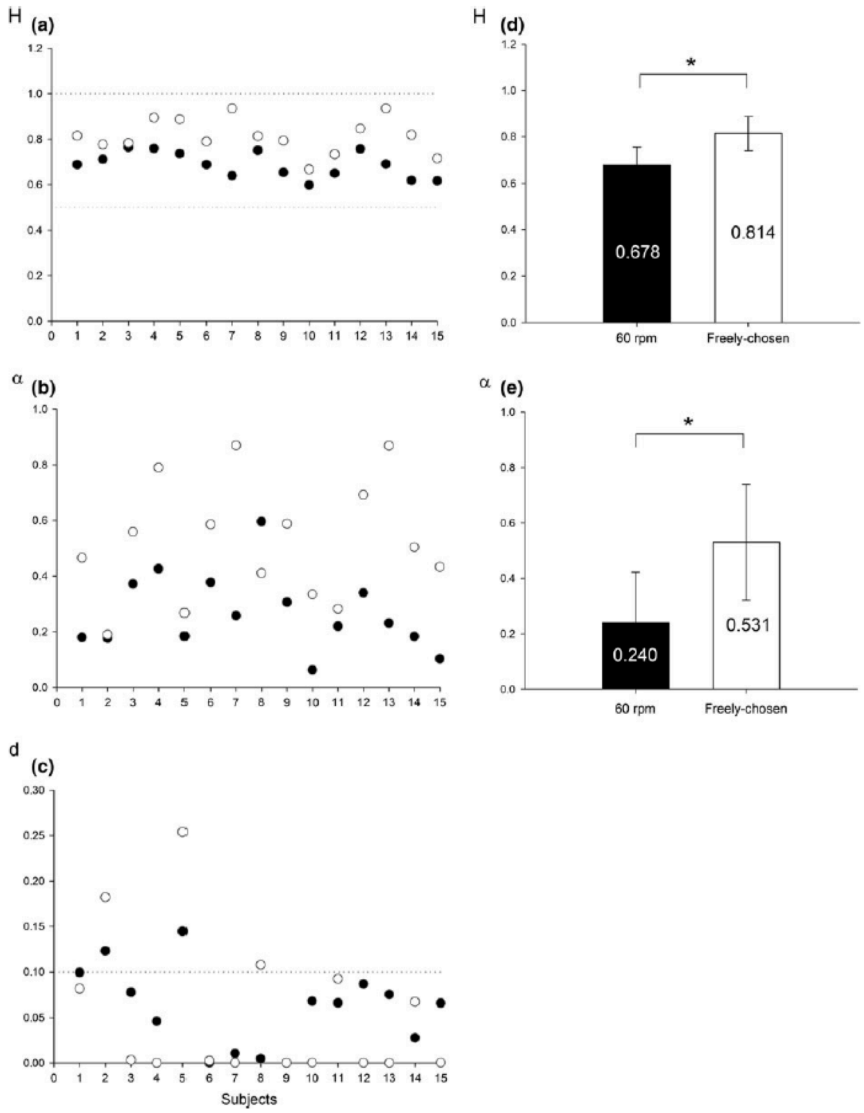

Figure 4. Individual results of rescaled range analysis (a), power spectrum analysis (b), relation *d* (c), mean and standard deviation of Hurst (d), and α exponents (e) at freely-chosen (white) and imposed cadence (60 revolutions per minute; black). Subjects were classified from 1 to 15 according to the power developed at freely-chosen cadence (by linear regression p=0.566 and p=0.691, respectively for Hurst's and α exponents). For Hurst exponent (a), horizontal lines correspond to limits of expected long-range autocorrelations. For relation *d* (c), horizontal line indicates the limit of acceptance. *p<0.001.

distinguished from white noise. Individual results were increasingly classified in Figure 4 according to power developed by subjects at freely chosen cadence. This classification showed that values of scaling exponents were not influenced by the mechanical power. At an imposed cadence of 60 rpm, *H* had a value superior to 0.5 and α was significantly different from 0 for all participants. Relation *d* exceeded the acceptable limit of 0.10 in only 2 of the 15 subjects (Figure 4). Presence of long-range autocorrelations was thus highlighted for 13 of the 15 time series. For the two remaining series, the randomly shuffled surrogate data tests revealed values of σ > 2 for *H* and α, indicating the presence of a temporal structure of the data (i.e., correlated process). RRA and PSD show that revolution time fluctuations exhibit long-range autocorrelations at freely chosen and imposed cadences. However, the mean values of *H* and α obtained in both conditions were different (Table 1; Figure 4). Individual results of Hurst exponent were always higher at freely chosen cadence, while 14 of the 15 subjects showed a higher value of α exponent in that condition. Using paired *t*-test, the decrease in scaling exponents observed at imposed cadence was statistically significant compared to the values obtained at freely chosen cadence (Table 1 ; Figure 4).

DISCUSSION

The present study demonstrates the presence of long-range autocorrelations in the cycling patterns of young healthy subjects by application of an integrated approach combining Hurst and α exponents. This observation agrees with the preliminary result of Padulo et al.[97] using only Lyapunov exponent. Additionally, in the present study, values of Hurst and α exponents were significantly different at freely chosen cadence compared with imposed cadence, showing that long-range autocorrelations can be altered by voluntary intent resulting from the task instructions.

In an effort to understand the meaning of the human movement variability, some authors make the link between the concepts of motor variability and motor redundancy.[11,93,102] Motor redundancy refers to having an infinite number of alternatives to perform a given motor task and allowing the motor control to modulate the variability of essential parameters for achieving a given task.[11,93,102] Indeed, some authors have

suggested that the neuromotor control of locomotion could be organized around a specified task goal.[93] In this context, humans have been brought to regulate only the variables that are directly linked to the task. Furthermore, Ranganathan and Newell[103] have proposed a dynamical degrees of freedom framework that could represent the adaptative capabilities of the system. According to this idea, it seems that motor control restricts (less freedom) the variability of parameters which are necessary to perform the desired task and, as a corollary, allows a higher variability (more freedom) to non-essential parameters. In this context, it appears that when the locomotor system adopt a fluctuating regime, it provides a wide range of potential behaviors to the healthy locomotor system that are adaptable and flexible in an unpredictable and ever-changing environment.[11] However, evidence supports the necessity of an optimal state of variability for health and functional movement, and deviation from this state can lead to the system that is either rigid, inflexible and highly predictable or on the contrary random, unfocused and unpredictable. Both situations are related to less adaptative capabilities and with a lack of health.[11]

While some studies failed to modulate the interdependency between consecutive cycles in walking,[14] cycling could represent a suitable tool to better characterize locomotor mechanisms in humans. Indeed, because cycling is a rhythmic task with less movement amplitude than walking and because many biomechanical parameters are fixed (for instance cycle length corresponding to pedal length), cycle ergometer pedaling could have fewer degrees of freedom than walking and thus it could be easier to alter the generation of long-range autocorrelations in cycling pattern.[104] This observation could explain why a breakdown of long-range autocorrelations was more pronounced during the constrained cycling task than when walking with a metronome. Indeed, a recent study conducted on gait have shown that when constraints were added (treadmill vs. treadmill and metronome), the long-range autocorrelations were altered behind a reduction of the adaptive capabilities of the system (less redundancy).[102]

To further our understanding of fluctuation dynamics in locomotor patterns, several studies have been conducted, especially in gait, showing that simple stochastic models are able to produce a healthy human-like

walking pattern.[93,94] This feature suggests that the long-range dependency between successive cycles might be due to the inherent biomechanical system and could not require any control of central nervous system.[94] However, many authors suggested that the complex temporal organization (long-range autocorrelations) highlighted in physiological signals could result from a centrally mediated process.[24–26,30,32,34,93] Additionally, an efficient, stable and adaptable locomotor pattern requires complex dynamic sensorimotor interactions depending on highly complex processes including efferent-type (from the motor cortex, the cerebellum, the basal ganglia and central pattern generator) and afferent-type information coming from different peripheral feedbacks.[19,37,105,106] Specific supraspinal mechanisms have been indeed suspected to provide appropriate cycle duration producing the most efficient locomotor pattern.[105] For instance, the importance of basal ganglia, prefrontal cortex, and supplementary motor area has been highlighted for their role in timing.[102]

Cycling and walking are strongly correlated neuronal and biomechanical processes that may be influenced by an external stress such as the constraint of following an imposed cadence (e.g., metronome).[107] Indeed, when cycling cadence is voluntarily forced by imposing a precise cadence, cycling movements appear more chopped, while they seem more natural and smoother at freely chosen cadence (Figure 1). At a freely chosen cadence, subjects could choose an infinite combination of biomechanical parameters owing to redundancy between parameters. On the contrary, when revolution time is tightly regulated and because cycling seems to have fewer degrees of freedom than walking, there is not enough remaining redundancy between biomechanical parameters to maintain statistical persistence (long-range autocorrelations) in revolution time. In the context of motor redundancy, pedaling at an imposed cadence could increase the constraint of the task by reducing the dynamical degrees of freedom of biomechanical parameters (i.e., revolution time, in this case) related to the task.

As presented above, in order to adapt its pattern healthy locomotor system modulate the variability of the essential parameters using a wide range of potential behavior (motor redundancy). The presence of long-range autocorrelations in cycling and walking patterns despite the absence

of passive component during cycling suggest that they are not specific to the biomechanics of gait and could reinforce the influence of an active central control of locomotion on the generation of long-range autocorrelations. Moreover, by the biomechanical constraints of pedaling, cycling has fewer degrees of freedom than walking. In this context, redundancy is more reduced in cycling than in walking. Therefore, cycling could be more sensitive than walking to perturbations placed on the locomotor system.

By the breakdown of long-range autocorrelations during constrained condition, the present study could also suggest a supraspinal influence on the modulation of the long-range interdependency characterizing rhythmic motor tasks, such as cycling. Specific supraspinal mechanisms have indeed been suspected to play a major role in initiating and adapting the locomotor pattern to internal and external conditions.[105] Because the two conditions use the same peripheral pathways (lower motoneurons, effectors and feedback loops) the voluntary supraspinal influence is therefore the only difference between both situations which could explain the perturbation of long-range autocorrelations under the constrained condition.[23] In other words, a psychophysical control, like that induced by an imposed cadence, could perturb long-range autocorrelations and generate a more random and unpredictable (less adaptable) cycling pattern. This hypothesis could provide additional argument to an integrated coordination of spinal mechanisms and supraspinal centers, requiring an intact brain stem. Brain stem and particularly mesencephalic locomotor region, traditionally considered as a convergence region receiving integrate inputs coming from supraspinal centers and producing excitation outputs, have been suggested as involved in the pathogenesis of freezing of gait in Parkinson's disease (PD).[61] Moreover, neurodegenerative disorders such as PD can disturb the intrinsic complexity of human walking.[25,32,34,108] However, in the particular case of cycling, it has been recently reported that parkinsonian patient's (with longstanding PD) abilities to initiate and ride a bicycle were remarkably preserved. [61]

Given this surprising phenomenon and the biomechanical differences between walking and cycling, it could be interesting to study the evolution of the revolution time variability in cycling among central nervous

system's disorders and particularly in parkinsonian patients. Indeed, specific mechanisms involved in generating and adapting the fluctuation dynamics of rhythmic tasks remain still unclear. Future studies may provide insight into the specific mechanisms involved within central nervous system, the practical utility of long-range autocorrelations and in the quantitative assessment of therapeutic intervention. It could also be interesting to compare the long-range autocorrelations obtained on a stationary cycloergometer and on a bicycle freely moving overground.

In conclusion, this study confirms with a high level of evidence the presence of long-range autocorrelations among the revolution time variability in cycling pattern of young healthy men, which suggests that this property is not specific to the biomechanics of walking. In a similar way to ''metronomic effect'' observed in walking variability, differences highlighted in long-range autocorrelations during constrained condition suggest that they can be altered by a centrally mediated process. Future studies including patients presenting with neurodegenerative pathologies could improve our comprehension of the neurophysiological origin and clinical implications of such dynamics.

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CONFLICT OF INTEREST

None of the authors of this manuscript have a conflict of interest to declare

Chapter 2

Internal factors: Parkinson's disease

Temporal organization of stride duration variability as a marker of gait instability in Parkinson's disease

CHAPTER 2

Temporal organization of stride duration variability as a marker of gait instability in Parkinson's disease

Objective Gait instability and fall risk are major concerns in Parkinson's Disease (PD). This study shows that the temporal organization of gait variability can represent a marker of gait instability that complement standard assessment of motor deficits in PD.

Methods Temporal organization (Long Range Autocorrelation, LRA) of stride duration variability, collected from twenty parkinsonian patients walking overground at a comfortable speed, was studied. The presence of LRA was based on the scaling properties of the series variability and the shape of the power spectral density. Simultaneously, measures of neurological impairment (MDS-UPDRS) and balance (BESTest, ABC-Scale) were collected. To precisely identify the relationship between LRA and functional measures, correlation coefficients were applied.

Results Degradation of LRA was strongly correlated with other clinical scores, in such a way that, the temporal organization of gait variability was more random for patients presenting with greater motor impairments. Importantly, these measures were relatively independent of the age, and of gait speed, which allows applying them to a wide clinical population.

Conclusion Our findings emphasize that the temporal organization of gait variability is related to degree of functional impairment in PD. LRA can then be possibly regarded as an objective and quantitative measure of gait stability for both clinical practice and research.

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INTRODUCTION

In addition to reduced gait speed, shorter stride length, stooped posture, and reduced arm swing, typical gait disorders in Parkinson's disease (PD) are characterized by postural and gait instability, which can lead to an increased fall risk [49]. Thus, detection of specific markers of gait instability appears critical for preventing falls and their consequences.

Gait stability has been defined as "the ability to maintain functional locomotion despite the presence of external disturbances or internal control errors" [38], and a higher fall risk has typically been associated with a lack of adaptive gait control in the presence of sensorimotor variability or external disturbances [39].

While falls generally occur during locomotion, gait variables from standard three-dimensional quantified walking analyses would not constitute adequate predictors of falls [109]. In addition, there is no accepted quantitative way to assess the gait stability [46]. However, stride duration variability has been mentioned as a good candidate from which to derive markers of gait instability as it is tightly linked to rhythm control, which is particularly impaired in PD [47]. Increasing number of studies have indeed shown that human movement variability is not simply the signature of random noise but contains hidden temporal organization that may provide insight into the neurophysiological organization of locomotion and into the regulation of the interacting subsystems, constituting the locomotor system [110].

Stride duration variability can be investigated either in terms of magnitude, using standard metrics such as sample mean, standard deviation (SD) and coefficient of variation (CV), or in terms of its organization, which provides complementary information about how stride duration evolves with time across consecutive strides. Temporal organization of variability can be quantified using non-linear analysis to determine the evolution of a behaviour over time. Indeed, stride duration fluctuates in a structured, complex manner over the long term, displaying the presence of long-range autocorrelations (LRA) that can span hundreds of consecutive strides [17,19]. LRA result from the "memory" of the preceding values in the series, highlighting the existence of a complex temporal

structure in human locomotion that is maintained across distinct tasks and even effectors (e.g., locomotion, cycling, eye-movements or upper-limb rhythmic movements) [16–18,20].

Interestingly, previous studies claimed that LRA would represent the signature of adaptive abilities of healthy systems and their breakdown an index of pathological condition [11,33,111]. From a theoretical point of view, Stergiou et al. proposed that deviations from an optimal level of variability in either the direction of randomness or the over-regularity indicate the loss of the adaptive capabilities of the system and are associated with poor health [11,111]. Such adaptability is permitted by a structured optimal level of variability, which provides a wide variety of responses to any perturbations (motor redundancy) [11,111]. A tight link between LRA and the capability of physiologic systems to make flexible adaptations to everyday stresses placed on the human body is thus suggested [11].

By extension, the degradation of LRA with pathology was associated to dynamic instability in locomotion [50]. In the specific context of basal ganglia disorders, strong correlation between the temporal organization of the stride duration variability and the Huntington's disease severity was demonstrated by Hausdorff et al. [34]. In addition, Ota et al. studied the interaction between neural rhythm generation disorders and physical abilities in PD, respectively assessed by the stride duration variability and the pull test [50]. However, this study presents some specific methodological limitations. On the one hand, Ota et al. collected a mean number of stride intervals of 154±23 strides which appears too short to draw reliable conclusions [50]. Indeed, series length of 256 gait cycles, or preferably of 512, is needed to appropriately assess LRA characteristics [16,112]. On the other hand, the pull test permits to assess only one aspect of the balance disorders spectrum. Therefore, to our knowledge, no studies have included the sound analysis of LRA in an extensive functional assessment of PD.

Considering gait instability and temporal gait disorders in PD, we hypothesised that stride duration variability will be less structured (i.e. more random) in PD and will be correlated with their functional assessment. More precisely, a poorer level of balance (BESTest) and a more pronounced

disease severity (H&Y scale) is hypothesized to be associated with a more random gait pattern (i.e. lower LRA exponents). Complementary to the standard, validated battery of clinical tests, LRA is finally hypothesized as an objective and quantitative measure of the gait stability of PD patients.

METHODS

Participants

Twenty patients (eleven males/nine females) with PD, aged 45–82 years (65.3 ± 9.6) participated in the study (see Table 1). The diagnosis of PD was made by an experienced neurologist (AJ) according to the UK PD society Brain Bank criteria [113]. Medication was stable for the four weeks preceding the study, and was maintained throughout the study. All patients were able to walk for 10 minutes without the use of walking aids. A minimum of 24/30 on the MMSE was a prerequisite to be included [114], and patients had to be free from any muscular, neurological (other than PD), or orthopaedic pathologies that could alter gait performance. The study was approved by the local ethics committee (Clinical Trial registration: NCT02419768). Participants were informed about the experimental protocol and provided written consent prior to data collection.

Apparatus and Procedure

A unidimensional accelerometer was taped in the antero-posterior direction on the lateral malleolus of the most affected side. Data of acceleration were recorded at 512 Hz using the Vitaport 3 ambulatory recorder (Temec Instruments B.V., Kerkrade, The Netherlands), and were later transferred to a computer. The stride duration was determined from the peak of acceleration, which was detected by software and confirmed visually (Figure 1). Accelerometer data were collected during a walking session of 10 minutes that consisted of walking overground at a self-selected speed around a 42m oval indoor track. The walking session was performed in a quiet environment and without any additional task in order to not increase the attentional cost of walking. To familiarise themselves with the track and the maintenance of a self-selected speed, subjects completed a single-lap warm-up immediately before data acquisition. Speed

Table 1

Characteristics of the study population (n=20)

Age (years)	65.3±9.6
Gender	11 (male) and 9 (female)
Height (cm)	170.3±9.7
Weight (kg)	74.0±17.1
Time since the diagnosis (years)	5.4±5.3
MMSE score	28.7±1.6
H&Y scale	
1 (n=):	3
1,5 (n=):	3
2 (n=):	5
2,5 (n=):	6
3 (n=):	3
Median [range]	2 [1-3]
MDS-UPDRS total (/260)	51 [18-133]
MDS-UPDRS III (/132)	26.2 [9-66]
BESTest total (%)	77.8±10.5
ABC-Scale (%)	78.7±12.2
Number of falls	0.4 ±1.0
Walking speed (m/s)	1.15±0.16
H exponent	0.70±0.09
α exponent	0.46±0.15
d	0.03±0.03
CV stride duration (%)	2.75±1.28

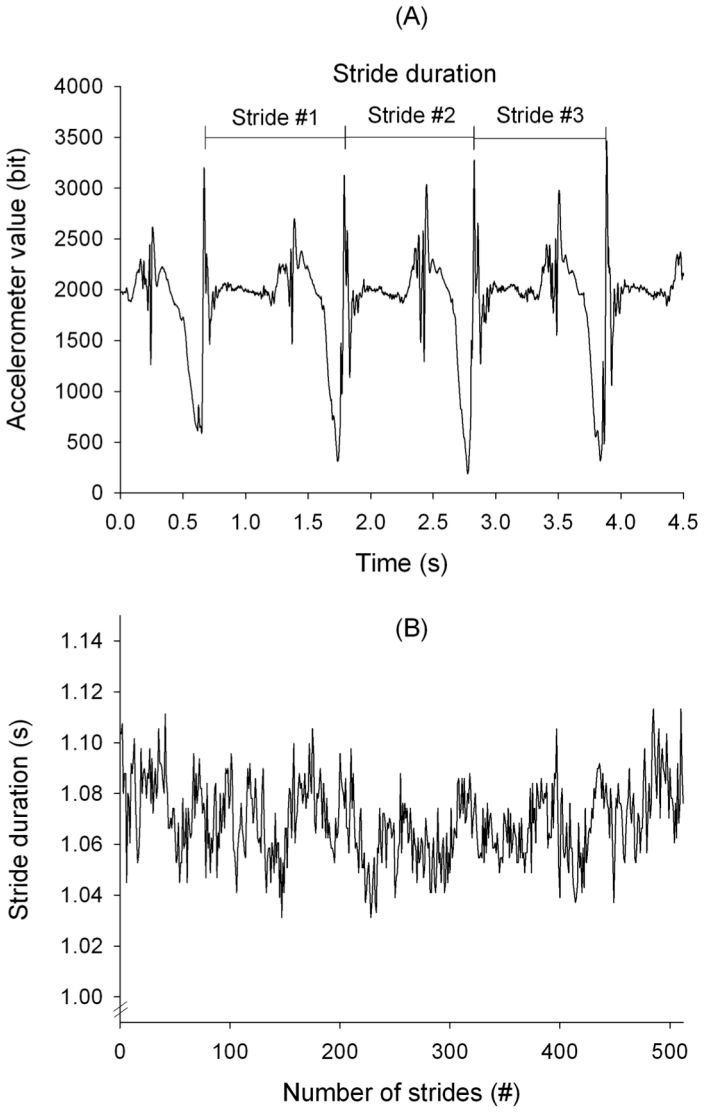

Figure 1. Stride duration determination
Example of accelerometer data over time (A) and typical trace of stride duration over 512 strides (B). The stride duration, corresponding to the time between each acceleration peak, is automatically computed to determine the stride duration fluctuations over the whole walking trial.

steadiness was verified using a stopwatch (Polar® RCX3), which was worn by the evaluator to avoid any visual feedback to the subject and an accelerometer (Polar® S3) placed on the shoelaces of the subject's most affected side. To avoid any perturbations, instructions to maintain walking speed were delivered only when the walking speed shifted by 10% or more of its mean value. All patients took at least five hundred and twelve consecutive strides without the use of walking aids. Such a series length is required to adequately apply the LRA mathematical methods described below [16].

All patients were tested in the ON phase, 60–120 min after their last medication intake. For all subjects, the same medical doctor (TW) assessed the severity of PD (modified Hoehn & Yahr scale), the patient's functional status (MDS-UPDRS), and the subjects' performance on a balance test (BESTest) [115]; administered the Activities Balance Confidence questionnaire (ABC-Scale) [116], assessing the fear of falling; and asked the subjects how many times they had fallen in the previous 6 months. Note that a value of 69% on the ABC-Scale and the BESTest is suggested as a cut-off score to discriminate fallers from non-fallers [115,116].

Assessment of temporal organization of stride duration variability (LRA)

The presence of LRA was assessed using the integrated approach proposed by Rangarajan and Ding, validated in the context of a physiological time series and described in details by Crevecoeur et al. [16,80] The method consists of estimating two parameters related to the autocorrelation function of the series under investigation: the Hurst exponent (*H*), using the Rescaled Range Analysis (RRA), and the slope of the power spectral density (PSD), plotted on a logarithmic scale (α).

In theory, the exponents *H* and *α* are asymptotically related by the equation:

$$H = \frac{1+\alpha}{2} \qquad (1)$$

Therefore, the integrated approach consists of separately computing *H* and *α* and using Eqn. (1) to verify that these two parameters are in agreement with each other. The inconsistency associated with Eqn. (1) can be defined as $d = H - \left[\frac{(1+\alpha)}{2}\right]$. Our previous reports indicated that a value of $d \leq 0.10$ can be considered acceptable because the asymptotic parameters are evaluated on a finite time series [16].

In summary, the following three conditions must be satisfied to conclude the presence of LRA:

- $H > 0.5$
- α significantly different from 0 and lower than 1
- $d \leq 0.10$

Assessment of magnitude of stride duration variability (CV stride duration)

For each subject's time series, the average stride duration (± SD) and the stride duration coefficient of variation (CV, 100 x SD/mean) were calculated on a series of 512 consecutive strides.

Statistical analysis

A sample size estimation was performed based on the previous results of Hausdorff et al. collected from a similar study conducted on Huntington's patients [34]. By hypothesizing a significant correlation with a minimal correlation coefficient (*r*) of 0.6 and a two sided α of 0.05, a sample size of n = 20 was needed to obtain a power of 80%. To address the relationship between stride duration variability and functional assessment in depth, the strength and direction of that relationship were assessed using Spearman's correlation coefficients. Correlation coefficient values of .00-.25 indicate little to no relationship; .25-.50, fair correlation; .50-.75, moderate correlation and .75-1.00, high correlation [115]. In a descriptive way, additional analyses were performed using a Principal Component Analysis (see Appendix). Level of statistical significance was set at a p value < 0.05. For all statistical analyses, SigmaStat 3.5 software (Systat, Richmond, CA, USA) was used.

RESULTS

Patient characteristics

Table 1 summarizes the anthropometric and clinical characteristics of the study population. Patients were moderately impaired with a median H&Y stage of 2 (range: 1-3), confirming that they were physically independent, and a median MDS-UPDRS of 51 (range: 18-133). ABC-Scale and BESTest scores were higher than the cut-off score of 69%, indicating that "non-fallers" patients essentially constitute our population. Two patients suffered from motor complications (one from freezing of gait (FOG) and one from dyskinesia of the upper limb). However, none of them presented such complications during the walking trial.

LRA and CV of stride duration in PD gait

Typical time series of PD and their modulation with disease severity, CV stride duration and LRA are shown in Figure 2. Table 2 shows a slow decrease of *H* and α exponents and a trend towards an increase of CV stride duration with disease progression.

Table 2

Progression of gait variability measures with disease severity

H&Y	Gait variability measures		
	H exponent	**α exponent**	**CV (%)**
1	0.84 (±0.06)	0.70 (±0.12)	2.0 (±0.5)
1.5	0.72 (±0.05)	0.56 (±0.09)	2.5 (±1.4)
2	0.70 (±0.05)	0.47 (±0.05)	2.3 (±0.5)
2.5	0.67 (±0.05)	0.36 (±0.09)	2.9 (±0.8)
3	0.58 (±0.03)	0.29 (±0.10)	4.2 (±2.4)

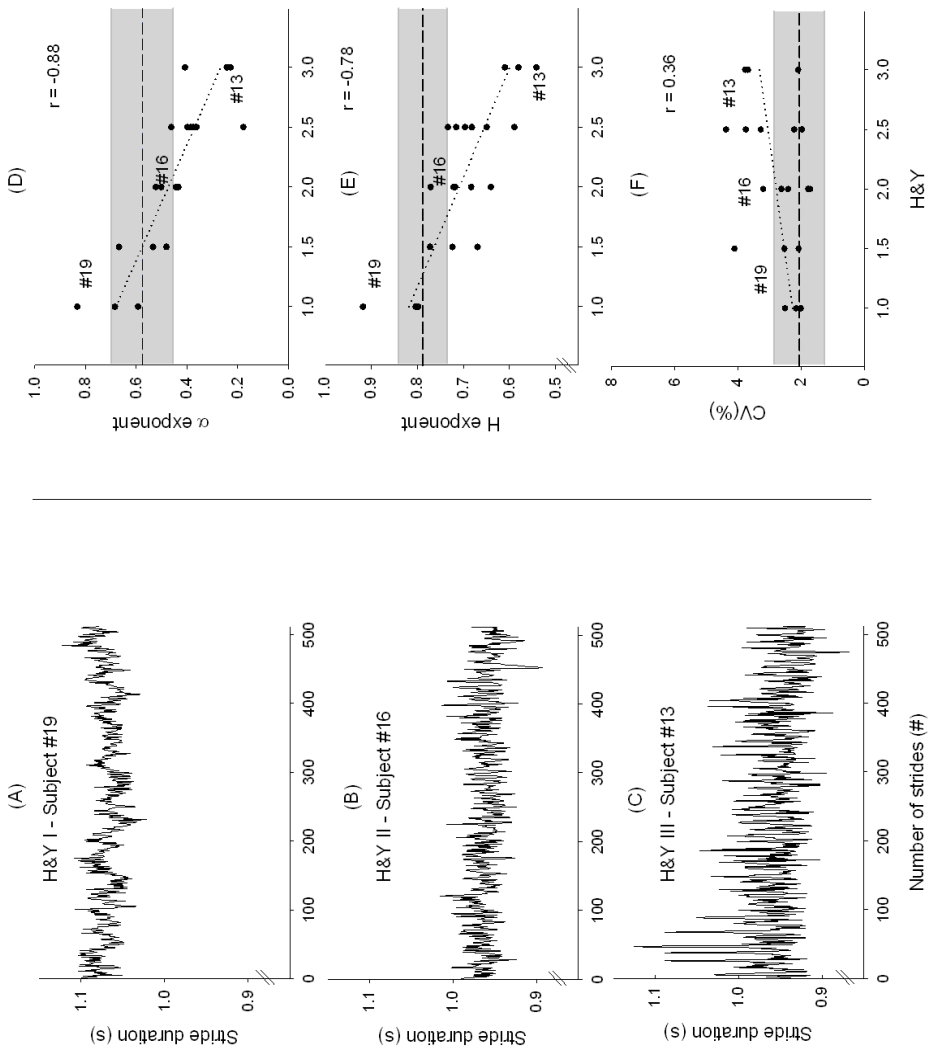

Figure 2. Typical traces
Selected typical traces of stride duration variability of PD patients according to disease severity (H&Y scale) (Fig 2. A-C). On the right side, the evolution of individual values of the α and Hurst exponents (Fig 2. D – Fig 2. E) and CV of stride duration (Fig 2. F) with disease severity. Grey areas indicate values from normative data set of healthy subjects. *r* =Spearman's correlation coefficient.

For all patients, the H exponent had a value between 0.5 and 1 (0.70 ± 0.09), the α exponent was significantly different from 0 (0.46 ± 0.15) and the value of *d* was also lower than the pre-specified limit of 0.10 for all patients (0.03 ± 0.03). These results clearly support the presence of LRA in all time series [16]. However, the LRA characteristics are modulated by the disease severity and balance status.

Concerning standard metrics, the CV of stride duration for the 20 patients were 2.75% (±1.28).

Study of stride duration variability correlations with disease severity and balance status

To explore relationships among stride duration variability, balance and functional status in more detail, the Spearman's correlation coefficients are used and presented in Figure 2 and Table 3. The α exponent was highly correlated with the Hurst exponent, the H&Y scale, and the BESTest, moderately correlated with the MDS-UPDRS III and fairly correlated with the ABC-Scale. The Hurst exponent was highly correlated with the H&Y scale and moderately correlated with the BESTest and the MDS-UPDRS III. Concerning the magnitude of stride duration variability, the CV of stride duration variability was moderately correlated with the gait speed and the ABC-Scale.

DISCUSSION

The present study is the first to assess long-range autocorrelations (LRA) in relation to the functional assessment of patients suffering from Parkinson's disease (PD). Our main findings are (1) highlighting the strong correlations of LRA with clinical measures of the patient's balance and functional status, (2) determining the absence of age and walking speed influence on parkinsonian gait autocorrelation, and (3) determining the relationship between usual measures of variability (CV) and the subjective fear of falling.

Table 3

Correlations study between stride duration variability, disease severity, balance status, gait speed and age

	CV	α exponent	H exponent	ABC-Scale	BESTest	MDS-UPDRS III	H&Y scale	Gait speed	Age
Age	-0.185	-0.005	0.067	0.029	-0.050	-0.307	0.026	-0.170	1.000
Gait speed	**-0.504***	0.232	0.132	0.378	0.403	-0.343	-0.377	1.000	
H&Y scale	0.363	**-0.883*****	**-0.779*****	**-0.639****	**-0.899*****	**0.821*****	1.000		
MDS-UPDRS III	0.436	**-0.581****	**-0.573***	**-0.630****	**-0.732*****	1.000			
BESTest	-0.383	**0.886*****	**0.692*****	**0.638****	1.000				
ABC-Scale	**-0.542***	**0.490***	0.379	1.000					
H exponent	-0.435	**0.894*****	1.000						
α exponent	-0.320	1.000							
CV	1.000								

***: p≤0.001 ; **: p≤0.01 ; *:p≤0.05

The usefulness of clinical tests and questionnaires has been demonstrated in the assessment of fall risk [117]. However, gait and balance impairments are sometimes quite subtle and their evaluation can be impaired by personal interpretation. By contrast, parameters collected from instrumented gait analysis provide complementary quantitative and objective information. In this way, inertia-based motion analysis (e.g., accelerometers) is a new outcome assessment tool that can produce objective movement parameters while being fast, economical and easy to use [118].

Devoid of any subjectivity, LRA could thus yield not only an objective and quantitative insight about the temporal complexity of the gait but also a clinical measure of the gait stability in PD patients. The original finding of the present study was indeed highlighting the strong relationships among LRA, balance and functional status. Indeed, following the results of correlation coefficients, the Hurst and α exponents were positively correlated with the BESTest and negatively correlated with disease severity (H&Y scale) and the motor part of the MDS-UPDRS. In such a way, a poorer level of balance (BESTest), a more pronounced disease severity (H&Y scale) are associated with lower Hurst and α exponents, indicative of a more random (less structured) walking pattern. Indeed, the closer the Hurst exponent is to 0.5 and the α exponent to 0, the more random the walking pattern where the stride duration at one moment is completely uncorrelated with any previous strides.

The increased randomness of parkinsonian gait pattern with disease severity contrasts with the structured gait pattern of healthy adults (Mean H exponent=0.79 and mean α exponent=0.58 computed in previous studies [15,17]; Figure 2) and could result from the defective activity among interacting subcomponents (e.g. basal ganglia). LRA are indeed thought as the result of subtle and complex interactions between subcomponents constituting dynamical systems.

In the specific context of basal ganglia disorders, Hausdorff et al. have already highlighted, in a similar way, such a breakdown of LRA and their strong correlations with neurological impairments in patients suffering from Huntington's disease [34]. In PD, Ota et al. suggested that patients

would firstly progress according to an increase of CV stride duration, and secondarily to a decrease of LRA [50]. However, this latter study presents some methodological issue regarding the number of gait cycles collected. Indeed, the mean number of stride intervals of 154±23 strides collected in this study appears too low to generate reliable conclusions concerning the temporal organization of the stride duration variability [14,119].

In accordance with recent studies, strong correlations between the balance test (BESTest), disease severity (H&Y) and functional status (MDS-UPDRS) have also been demonstrated [115,117]. Thus, at more advanced stages of PD, functional impairment is higher and balance performance is lower. Evidence suggests that, with disease severity, PD patients present less adaptive abilities and thus could be more prone to falls [120].

In contrast to balance and functional status, LRA were relatively independent of the age and walking speed. This finding extends, to Parkinson's disease, an observation that was already demonstrated in healthy adults, in the elderly and in the specific context of basal ganglia dysfunction with the Huntington disease [21,34]. Often perceived as a cautious walking strategy, reduced gait speed is usually associated with an increase in SD and CV stride duration [121,122].

Gait speed was indeed related with such standard metrics. Evidence suggests that the influence of gait speed on CV stride duration depends on the level of gait speed [21,122]. However, a significant association with high CV stride duration was demonstrated at low speeds (i.e., 0.2 to 0.6 $m.s^{-1}$) compared with speeds ranging from 0.8 to 1.4 $m.s^{-1}$ [122]. In addition, a gait speed of 1.15 $m.s^{-1}$ reported in our study population is close to the walking speed of 1.1 $m.s^{-1}$ required to safely cross the street within the time limit of traffic signals in a community [122]. This confirms the functional abilities of the studied population but the attentional load required while walking could explain such relationship.

Although CV stride duration in PD were not associated with LRA, functional status, balance performance, CV stride duration were inversely correlated with the patient's fear of falling as quantified by the ABC-Scale.

In terms of motor control, lower CV values reflect the reliability of lower limb movements and the automated regular rhythmic feature of gait [123]. Such automatic processes requires minimal attention, whereas higher variability is related to major attention involvement [122]. In addition, evidence suggests that automatic gait control is reduced in PD patients and more conscious attention is required [124,125]. Thus, complementary to LRA, the correlation between the subjective fear of falling and CV stride duration variability may be a marker of the impairment of higher levels of gait control.

Taken together with standard clinical tests, magnitude (CV) and organization (LRA) of stride duration variability allow for a comprehensive description of the balance control during walking with the ability to describe specific deficits. LRA could be considered as a reflection of gait stability and CV stride duration as marker of the degree of automaticity of gait, reflected by the attentional load required while walking. However, poor balance control may occur when one or more components are compromised, such as the loss of flexibility or an increased fear of falling. Balance control is usually conceived as a complex system with many elements (e.g., motor cortex, basal ganglia, cerebellum, cortico-spinal tract, peripheral nerves, muscles, osteo-articular structures…) that interact permanently to produce a stable gait pattern and prevent falls [19].

Balance is indeed multifactorial and depends on both physical (balance, flexibility, strength) and psychological (fear of falling, cognitive disorders) features. Based on the BESTest and ABC-Scale, predictive values of falls might be made to discriminate fallers from non-fallers in PD [117]. Although a fall is the ultimate marker of a higher fall risk, it is clearly desirable to prevent falls and, therefore, derive markers of gait instability prior to actual falls. To this end, LRA is a good candidate to derive an objective and quantitative gait stability assessment in the mild to moderately impaired PD population.

Furthermore, using accelerometers, LRA could be routinely assessed in clinical practice simultaneously with spatiotemporal parameters, such as gait speed, cadence or step length. Equipped with an accelerometer, the current smartphones are, in principle, able to perform such assessments as well as to detect freezing of gait (FOG) epochs and

release suitable cues every time FOG occurs during the patient's daily activities [118,126,127].

Some limitations to this study should be noticed. Instructions used to maintain the time series stationarity could alter the stride duration dynamics [18,37,128]. However, only one patient had to receive such specific instruction during the walking session. In addition, the explicit instructions used in the previous studies were delivered continuously during the whole walking session while our instruction was delivered once a time and on a limited period of several second. In the same vein, it is now clearly established that gait represents an attention-demanding task in PD. A specific attention was paid on the walking session to reduce the attentional cost of gait and ensure neutral condition. The walking session was thus performed in a quiet and wide environment without any additional task.

Although the resulting findings will be important for future hypothesis generation, it would be interesting to confirm the study with a larger population. Also, the strong correlations highlighted in mildly to moderately impaired PD patients should be carefully extended to the most impaired PD patients (i.e. beyond H&Y III). Indeed, LRA assessment typically requires a large number of cycles to generate reliable results, which may be difficult to obtain from the most impaired PD patients [16,112]. However, to be useful in fall risk assessment, LRA should be assessed when the gait instability is not yet clinically evident and the patient is still functionally independent. Hence, a collection of 512 gait cycles should be not a major constraint in future prospective and longitudinal studies. Moreover, owing to the specific advantages of inertia-based motion devices, LRA could easily be assessed in the daily clinical practice and collected to constitute a significant database.

In conclusion, the present study demonstrated that, using a wearable and inexpensive device, the analysis of both the magnitude and organization of stride duration variability could provide an objective and quantitative clinical measure of gait stability in PD patients for clinical practice and clinical research.

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CONFLICT OF INTEREST STATEMENT

We declare that we have no proprietary, financial, professional, or other personal competing interests of any nature or kind.

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Appendix

Principal component analysis (PCA): Potential relationships between LRA, measures of neurological impairement (MDS-UPDRS) and balance (BESTest, ABC-Scale).

APPENDIX

Additional analyses were performed in the article untitled “Temporal organization of stride duration variability as a marker of gait instability in Parkinson’s disease” to potentially identify relationships between LRA, measures of neurological impairment (MDS-UPDRS) and balance (BESTest, ABC-Scale).

In a descriptive way, the relationships among LRA, CV and SD stride duration, balance and functional status were studied using Principal Component Analysis (*PCA*) (Stat View for Windows; SAS Institute Inc., Cary, NC, USA). This technique was performed on 10 variables: CV and SD of stride duration, Hurst and α exponents, modified Hoehn & Yahr scale, PIGD, BESTest total, ABC Scale, age and walking speed. Only the first three principal components (*PCs*) were retained as important factors after orthogonal rotation (Varimax). Finally, we defined each of the three first *PCs*, and each *PC* was labelled. To determine what each *PC* measures, only those variables having the highest correlation with each *PC* (factor loadings with a threshold value of 0.6 or higher) were considered [129].

The orthogonal solution of the *PCA* and eigenvalues of each *PC* greater than 1 allowed the determination of three *PCs* [130]. The total variance accounted for by all three *PCs* was 83.2%. Figure 3 presents the relationship of each parameter to each *PC*; the highest relation indicates which parameters load most heavily onto each *PC* (factor loading). The first *PC*, labelled *“LRA, Balance & Functional Status”*, described LRA assessed by the Hurst and α exponents, disease severity assessed by the H&Y scale, functional status assessed by the PIGD, and balance status assessed by the BESTest total. When the Hurst exponent, α exponent and BESTest increased together, the H&Y scale and PIGD decreased. Therefore, higher LRA values indicate higher balance status and less functional impairment. This first *PC* explained 56.1% of the variance in the data set. Orthogonally to the first *PC*, age and walking speed were loaded on the second *PC,* labelled *“Age & Walking Speed”*. No other variables loaded strongly onto this *PC*. Age and walking speed loaded negatively, indicating that they tend to evolve in opposite directions and, therefore, that age is related to reduced walking speed independent of other variables.

This second *PC* explained 14.8% of the variance. Finally, traditional measures of variability (CV and SD stride duration) and the ABC Scale loaded negatively on the third *PC*, labelled “CV, SD Stride Duration & Fear of Falling”. Therefore, as linear measures of variability increased together, the ABC Scale decreased, as shown in Figure 3. This last *PC* accounted for 12.3% of variance.

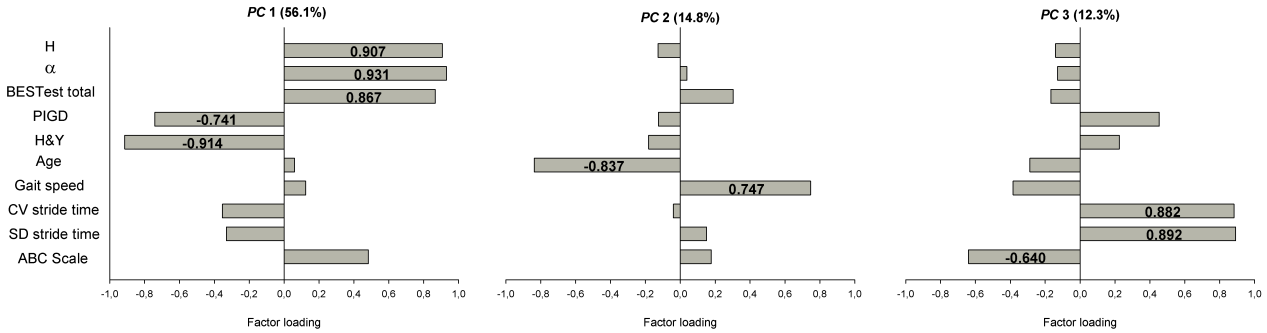

Figure 3. Principal component analysis
Orthogonal solutions in the principal component analysis of the selected variables allowed for the identification of three principal components. This figure presents the factor loading of each variable for the three components. Rectangles indicate the factor loading (between -1 and 1) of the variable with the component. The variables significantly related (factor loading > 0.6) to the component are indicated in grey.

Chapter 3

Combination of external and internal factors

Does Nordic Walking restore the temporal organization of gait variability in Parkinson's disease?

Gait complexity and regularity are differently modulated by treadmill walking in Parkinson's disease and healthy population

CHAPTER 3 – Article 1

Does Nordic Walking restore the temporal organization of gait variability in Parkinson's disease?

Background Gait disorders of Parkinson's disease (PD) are characterized by the breakdown of the temporal organization of stride duration variability that was tightly associated to dynamic instability in PD. Activating the upper body during walking, Nordic Walking (NW) may be used as an external cueing to improve spatiotemporal parameters of gait, such as stride length or gait variability, in PD. The aim of this study was to evaluate the beneficial effects of NW on temporal organization of gait variability and spatiotemporal gait variables in PD.

Methods Fourteen mild to moderate PD participants and ten age-matched healthy subjects performed 2×12min overground walking sessions (with and without pole in a randomized order) at a comfortable speed. Gait speed, cadence, step length and temporal organization (i.e. long-range autocorrelations; LRA) of stride duration variability were studied on 512 consecutive gait cycles using a unidimensional accelerometer placed on the malleola of the most affected side in PD patients and of the dominant side in healthy controls. The presence of LRA was determined using the Rescaled Range Analysis (Hurst exponent) and the power spectral density (α exponent). To assess NW and disease influences on gait, paired *t*-tests, Z-score and a two-way (pathological condition x walking condition) ANOVA repeated measure were used.

Results Leading to significant improvement of LRA, NW enhances step length and reduces gait cadence without any change in gait speed in PD. Interestingly, LRA and step length collected from the NW session are similar to that of the healthy population.

Conclusion This cross-sectional controlled study demonstrates that NW may constitute a powerful way to struggle against the randomness of PD gait and the typical gait hypokinesia. Involving a voluntary intersegmental coordination, such improvement could also be due to the upper body rhythmic movements acting as rhythmical external cue to bypass their defective basal ganglia circuitries.

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BACKGROUND

Scaling and timing internal control required for automatic and rhythmical movements are impaired and archetypally linked to the basal ganglia dysfunction in Parkinson's disease (PD). As a result of such impairment, a reduced gait speed, shorter stride length, reduced arm swing and a random walking pattern (i.e. increased gait variability) are typical features of PD gait [37,54,131–133]. From the specific temporal point of view, the inability to produce a steady gait rhythm, which result in more random stride-to-stride variability, is one of the primary temporal gait disorders and can indicate a sensitive marker of a higher fall risk in PD [37,134].

Interestingly, the randomness of PD gait was recently emphasized by subtle deterioration of the temporal organization of gait variability, using the long-range autocorrelations (LRA) assessment [134]. In addition, close correlations with disease severity and balance status were demonstrated in PD [134]. In a more theoretical framework, LRA have indeed been suggested as an indicator of adaptive abilities characterizing healthy systems [11,37,90,92]. As a corollary, deviations from an optimal level of variability in either the direction of randomness or the over-regularity are thought to reflect the loss of the adaptive capabilities of the system[11].

Consequently, interventions that improve LRA might be beneficial in PD gait, which is characterized by less efficient adaptive resources. Among numerous rehabilitative approaches, Nordic Walking (NW) holds a special place in PD as an emerging and promising strategy to stimulate an active lifestyle [135]. Using specially designed poles, NW involves an intentional coordination between upper and lower limbs and could constitute an interesting option to enhance the stride length and the gait speed [136–138]. Furthermore, the use of Nordic poles may act as an external cue, triggering intact circuits and bypassing the defective basal ganglia – SMA loop. This permits compensating for the impaired scaling and timing control in PD [137].

However, it remains unknown whether Nordic Walking, without any long-term training, can influence real-time spatial and temporal gait variables in Parkinson's disease, and especially long-range autocorrelations. Therefore, this study is aimed primarily at assessing LRA,

as well as spatiotemporal gait variables, by means of comparison between NW and Usual Walking (UW) in PD. Considering NW may act as an external cue to restore control movement [137], our primary hypothesis is that gait variability would become less random and spatiotemporal gait variables would improve with such a rehabilitative approach. Secondarily, the study is aimed at comparing long-range autocorrelations and gait variables in the PD population to healthy adults while usual and Nordic walking.

METHODS

Participants

Fourteen PD participants were enrolled from the Neurology Department of the Cliniques universitaires Saint-Luc, Brussels (AJ) and from the "Association Parkinson", Namur (Table 1). Note that several participants were directly recruited from another previous study which presented the same eligibility criteria [6]. This previous study aimed to investigate the potential usefulness of LRA assessment as a marker of gait instability in PD. A minimum of 6 months has been respected between the two studies. Eligibility criteria included: (1) fulfillment of the United Kingdom Parkinson's Disease Society Brain Bank (UKBB) criteria for idiopathic PD [113] and (2) ability to perform 512 consecutive strides without the need for walking aids. Such series length is required to adequately apply mathematical methods described below[16]. Exclusion criteria comprised of history of other neurologic disorders or orthopaedic pathologies known to impair gait performance. Ten age-matched healthy control participants (Table 1) were recruited as a control group.

Ethics, consent and permissions

Testing took place at the Cliniques universitaires Saint-Luc, Brussels from September 2015 till November 2016. This study was conducted according to the declaration of Helsinki and had ethical approval from the Comité d'Ethique Hospitalo-Facultaire de l'Université catholique de Louvain (B403201318916 / Clinical Trial registration: NCT02419768). Participants gave written informed consent prior to data collection.

Table 1

Characteristics of the study populations

	PD (n=14)	Healthy (n=10)	*p*-value
Age (years)	62.2±6.9	60.3±4.8	0.525
Gender (male/female)	9/5	3/7	
Height (cm)	171.8±10.3	170.3±7.6	0.813
Weight (kg)	74.7±15.9	67.8±10.7	0.186
Time since the diagnosis (years)	4.5±2.7	-	
MMSE score (/30)	29.5 [27-30]	30 [29-30]	0.049
H&Y scale	2 [1-3]	-	
1 (n=):	2	-	
1,5 (n=):	2	-	
2 (n=):	5	-	
2,5 (n=):	3	-	
3 (n=):	2	-	
MDS-UPDRS III (/132)	26.9 [10-46]	-	
MDS-UPDRS total (/260)	52.3 [18-94]	-	
BESTest total (%)	77.4 [69-92]	87.7 [85.2-96]	≤0.001
ABC Scale (%)	79.0 [54-100]	95.0 [72-100]	0.014

Mean (±SD) are expressed for quantitative variables normally distributed while median [range] are expressed for both ordinal and non-normally distributed variables

Procedure

During UW and NW sessions, a unidimensional accelerometer was taped, in the antero-posterior direction, on to the lateral malleolus of the side most affected by motor symptoms of PD and of the dominant side for healthy participants. Acceleration data was recorded at 512 Hz using the Vitaport 3 ambulatory recorder (Temec Instruments B.V., Kerkrade, The Netherlands), and transferred to a computer. The stride duration was determined from the peak of acceleration (i.e. peak detection method[128,139]; Figure 1) detected by the software internally developed and confirmed visually. Validated against ground reaction forces, this method assumes that each acceleration peak corresponds to successive foot contact. The peak detection method was designed to minimize the risk of false step detection making it the most accurate compared with other techniques (e.g. zero-crossing method)[128,139]. Accelerometer data was collected during a walking session of 12 minutes that consisted of walking overground at a self-selected speed around a 42 m oval indoor track with and without Nordic poles (usual and Nordic walking sessions). The two walking sessions were performed in a quiet environment to avoid all external perturbations that could increase the attentional cost of walking. Concerning NW, each PD and healthy participant received 3 one-hour sessions to learn the walking technique (ALFA method). Note that all PD and healthy participants were naive with NW technique prior to the study. The training sessions were delivered one week before the experimental sessions. The number of training sessions was limited to three to allow enough time to learn the basic walking technique but not to induce motor learning [135]. Experimental sessions were spread over two consecutive days and at the same part of the day in order to, respectively, reduce the fatigue and medication influences on gait in PD participants[49,140]. Also, the order of the two walking sessions was randomly allocated in order to avoid any gait rehabilitation benefits. Before the NW session, the walking technique of each patient was verified (MBL). Although the technique learning and familiarization period was respected, no specific instructions on gait pattern were delivered.

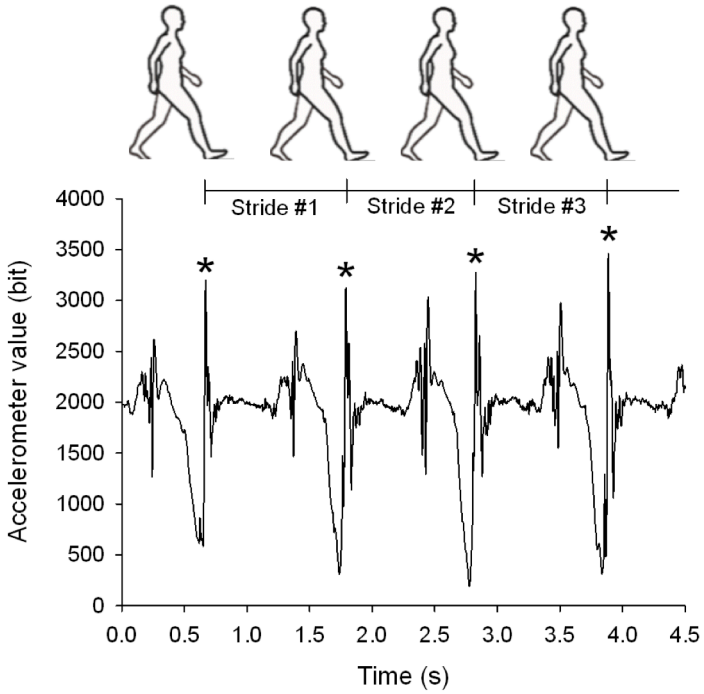

Figure 1. Stride duration determination – Peak detection method
Heel strikes correspond to each positive acceleration peak (* ; peak detection method). The time between successive heel contacts corresponds to the stride duration.

Each participant underwent a comprehensive assessment when medication provided significant functional improvement (ON phase), 60–120 min after their last medication intake.. The severity of PD (modified H&Y scale), the patient's functional status (Movement Disorder Society - Unified Parkinson´s Disease Rating Scale (MDS-UPDRS)), and the subjects' performance on a balance test (BESTest) were assessed and the Activities Balance Confidence questionnaire (Activities-specific Balance Confidence (ABC-Scale)) was administered.

Gait assessment

Stride duration variability

Stride duration variability can be investigated either in terms of magnitude, using standard metrics such as sample mean, standard deviation (SD) and coefficient of variation (CV), or in terms of its organization (i.e. LRA), which provides complementary information on how stride duration evolves with time across consecutive strides [21,141].

Temporal organization of the stride duration variability (LRA)

The presence of LRA was evaluated, using an integrated approach that combines the results of rescaled range analysis (*H* exponent) and power spectral analysis (α exponent). For each time series, both methods were applied to sequences of 512 consecutive gait strides [16]. To increase the level of confidence in the results, the consistency of *H* and α exponents was verified using the asymptotic relationship $d = H - \left[\frac{(1+\alpha)}{2}\right]$ [16]. Following this integrated approach, the following three criteria must be met to conclude the presence of LRA:

- $H > 0.5$
- α significantly different from 0 and lower than 1
- $d \leq 0.10$

For further details, these methods are described elsewhere [16].

Magnitude of the stride duration variability (CV)

Recently suggested as reflecting the attentional load allocated to the motor task [122], the magnitude of stride duration variability was assessed using the coefficient of variation (CV = [SD/mean] * 100) which was calculated for the 512 consecutive stride previously selected for each time series.

Spatiotemporal gait variables

Lap times and the number of laps were measured. The total distance was determined from the number of laps of 42m performed by the participants. Following the relationship between total walking distance and acquisition duration, mean gait speed, mean gait cadence and mean step length was independently assessed as follow:

$$Gait\ speed\ (m.s^{-1}) = \frac{Total\ walking\ distance\ (m)}{Acquisition\ duration\ (s)};$$

$$Gait\ cadence\ (\#steps.min^{-1}) = \frac{Total\ number\ of\ steps\ (\#)}{Acquisition\ duration\ (\mathrm{min})};\ \text{and}$$

$$Step\ length\ (m) = \frac{Gait\ speed}{Gait\ cadence}.$$

Note that stride duration variability and spatiotemporal gait variables were extracted from 512 consecutive gait strides. This large data number is required to measure gait variability, in particular to draw adequate conclusions about the temporal organization of the stride duration variability[16].

Transformation of gait data into Z-score

As age and walking speed were shown to influence gait variables[142,143], individual participant values were normalized to Z-score to identify PD-caused gait alterations as opposed to changes arising solely from the age of subjects or from different walking speeds. Normative data of spatiotemporal gait variables were extracted from the Andriacchi et al. and Winter's reference works[142,143]. Given that no normative values for *H* and α exponents are currently established and that no influence of age and gait speed were demonstrated, values from our healthy control population

were used as a reference point. Whereas the influence of gait speed on the CV of stride duration was highlighted at low speeds (i.e. 0.2 to 0.6 $m.s^{-1}$), people with PD with mild and moderate motor symptoms usually walk at a gait speed above 1 $m.s^{-1}$ [21,122,134,144–146]. Thus, considering this aspect and the absence of normative data for the CV of stride duration, healthy control values were also used as a reference point.

Statistical analysis

Sample size calculation was performed for the Hurst exponent as the main outcome. A sample size of 14 participants (power = 0.8, alpha = 0.05) was required to detect similar differences as the study of Hove et al. that investigated the influence of the rhythmic auditory stimulation on the temporal organization of the stride duration variability in PD [147].

Anthropometric and clinical characteristics were analysed with independent samples *t*-tests. A paired *t*-test and a two-way ANOVA (Walking condition x Pathological condition) repeated measure were applied to examine the influence of walking condition, as well as one of the pathological condition on LRA exponents, CV of stride duration and spatiotemporal gait variables. Holm-Sidak post hoc tests were performed and the effect size (partial eta squared; η^2_p) was measured. One-sample *t*-test or Wilcoxon signed-rank test (non-normally distributed variables) against zero was used to compare subjects Z-transformed gait variables with normal values (corresponding to Z score = 0). The results were considered statistically different for *p*-values < 0.05.

RESULTS

Anthropometric and clinical characteristics of the fourteen PD participants and the ten healthy controls are summarized in Table 1. PD participants presented mild to moderate motor symptoms, corresponding to stage 1 to 3 on the modified Hoehn & Yahr scale. Two patients suffered from motor fluctuations. However, none of them presented such fluctuations during the two walking sessions. The two groups were matched for age and height. PD participants reached significantly lower scores in balance performance and confidence compared to healthy controls.

Stride duration variability

The temporal organization and the magnitude of the stride duration variability are presented in Figures 2-4 and in Table 2.

Temporal organization of the stride duration variability (LRA)

The integrated approach showed the presence of LRA in both UW and NW in all the subjects (Figure 2 and Table 2). All values of the *H* exponent were greater than 0.5, the α exponent was always significantly different to 0, and all values of d were far below 0.10 (0.02 ±0.03 and 0.02±0.03 for UW and NW, respectively).

However, in PD participants, highly statistically significant differences were observed between the two walking conditions ($p \leq 0.001$ and $p=0.003$ for *H* and α exponents, respectively; Figure 2), *H* and α exponents being lower in UW compared to NW (i.e. closer to 0.5 and 0 for *H* and α exponents, respectively). Conversely, the walking conditions had no effect on *H* and α exponents among healthy controls. Importantly, a significant (Walking condition x Pathological condition) interaction ($F=7.421$; $p=0.012$ for *H* exponent, and $F=11.643$; $p=0.002$ for α exponent) was demonstrated, as illustrated in Figure 3 and reported in Table 2. Post-hoc comparisons confirmed that the use of Nordic poles influenced exclusively the PD participants' gait (Figure 3). LRA exponents values collected from UW were significantly lower than that of healthy adults ($p \leq 0.001$ for both exponents; Figures 2-3 and Table 3), while they did not differ during the NW session, which suggest an improvement in the temporal organization of the gait pattern with the use of Nordic poles compared to the more randomness variability observed in UW.

Magnitude of the stride duration variability (CV)

Regarding the stride duration fluctuation magnitude, the values of CV were statistically higher during NW than during UW for both populations ($p=0.002$ and $p=0.045$ for PD and healthy participants, respectively) (Figure 4 and Table 2). Importantly, no significant (Walking condition x Pathological

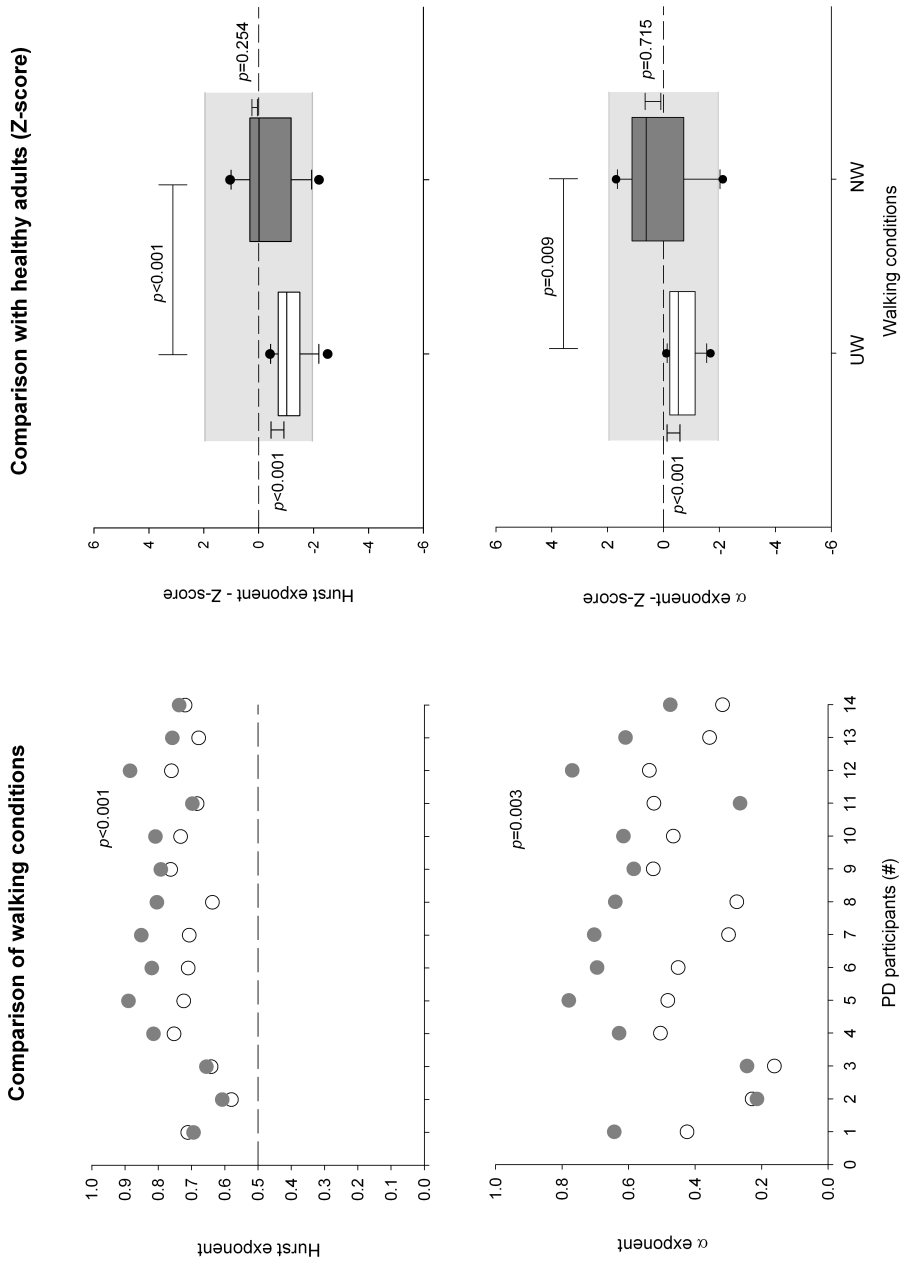

Figure 2. Temporal organization of stride duration variability
Comparison of Hurst and α exponents on usual walking (UW; white) and Nordic walking (NW; grey) in PD and comparison with healthy adults (Z-score).

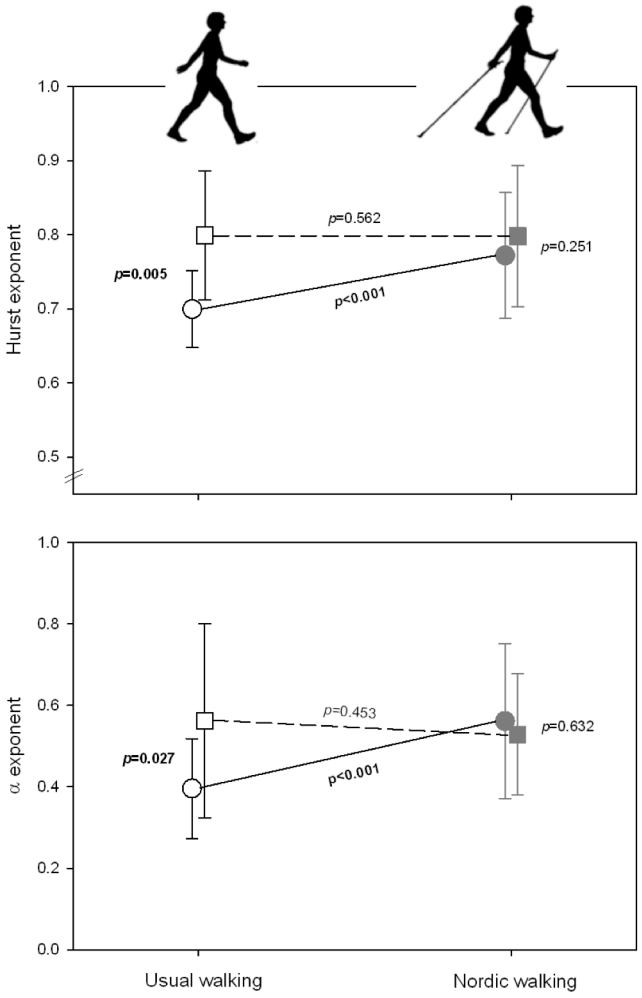

Figure 3. Influence of pathological and walking conditions on Hurst and α exponents in PD and healthy participants. Post-hoc analysis for the (pathological x walking) interaction for LRA exponents in PD (white and grey circles for usual and Nordic walking sessions, respectively; black solid line) and healthy controls (white and grey squares for usual and Nordic walking sessions, respectively; black dashed line).

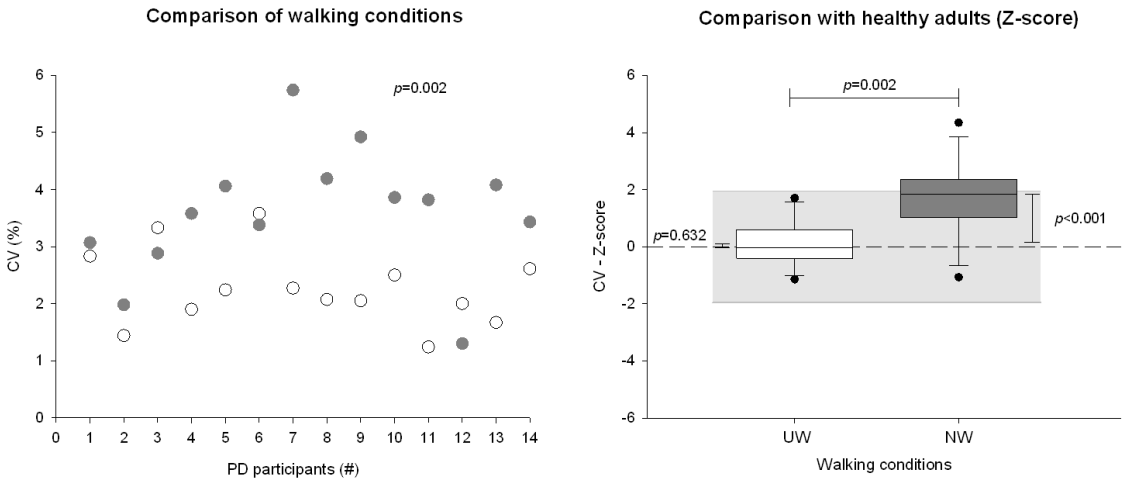

Figure 4. Magnitude of stride duration variability Comparison of coefficient of variation of stride duration variability (CV) on usual walking (UW; white) and Nordic walking (NW; grey) in PD and comparison with healthy adults (Z-score).

Table 2

Absolute mean values of the stride duration variability and spatiotemporal gait variables for the comparison between the usual walking (UW) and the Nordic walking (NW) sessions in Parkinson's disease and healthy controls and analysis of the (pathological x walking conditions) interaction for the stride duration variability and spatiotemporal gait variables.

	Parkinson's disease		Healthy controls		Interaction	
	UW	NW	UW	NW	*p*-value	η^2_p
Stride duration variability						
Temporal organization						
H exponent	0.70 (±0.05)	0.77 (±0.08)***	0.80 (±0.09)§§	0.81 (±0.08)	**0.012**	0.252
α exponent	0.39 (±0.12)	0.56 (±0.19)**	0.56 (±0.22)§	0.52 (±0.14)	**0.002**	0.346
Magnitude						
CV (%)	2.26 (±0.66)	3.59 (±1.11)**	2.17 (±0.82)	2.92 (±0.91)*	0.255	0.058
Spatiotemporal gait variables						
Gait speed (m/s)	1.18 (±0.19)	1.26 (±0.24)	1.47 (±0.17)	1.59(±0.14)**	0.468	0.025
Gait cadence (#steps/min)	112.90 (±9.48)	102.83 (±13.16)**	119.22 (±4.55)	117.15 (±5.47)*	0.063	0.155
Step length (m)	0.63 (±0.09)	0.73 (±0.09)***	0.74 (±0.09)	0.81 (±0.08)**	0.370	0.038

Absolute value is expressed as mean (± SD)
***: $p \leq 0.001$; ** $p \leq 0.01$; * $p \leq 0.05$ for the comparison between UW and NW (paired *t*-test)
§§§: $p \leq 0.001$; §§ $p \leq 0.01$; § $p \leq 0.05$ for the comparison of walking conditions between PD and healthy controls (independent *t*-test)
Bold data indicates if (pathological x walking condition) interaction was significant ($p<0.05$)
η^2_p: partial eta squared.

Table 3

Mean values of the normalized stride duration variability and spatiotemporal gait variables (Z-score) for the comparison between the usual walking (UW) and the Nordic walking (NW) sessions in Parkinson's disease.

	Z-score			
	UW	***p*-value**	**NW**	***p*-value**
Stride duration variability				
Temporal organization				
H exponent	-1.14 (±0.60)	**≤0.001**	-0.31 (±0.97)	0.254
α exponent	-0.70 (±0.51)	**≤0.001**	0.49 [-0.59;0.56]	0.715
Magnitude				
CV (%)	0.11 (±0.81)	0.632	1.72 (±1.35)	**≤0.001**
Spatiotemporal gait variables				
Gait speed (m/s)	-1.51 (±1.33)	**≤0.001**	-0.97 (±1.67)	**0.049**
Gait cadence (#steps/min)	-0.94 (±1.71)	0.059	-2.99 [-3.51;-0.13]	**≤0.001**
Step length (m)	-0.65 (±0.38)	**≤0.001**	0.09 (±0.43)	0.406

Z-score is expressed as mean (± SD) (one-sample t-test) or median [range] (one-sample Wilcoxon signed-rank test).
Bold data indicates if the Z-score significantly differed from 0 ($p < 0.05$): One-sample t-test (normally distributed values) or one-sample Wilcoxon signed-rank test (non-normally distributed values).

condition) interaction was observed (F=1.366; p=0.255), confirming that the use of Nordic poles influenced similarly the CV of both PD and healthy participants. In comparison to the healthy population, CV is higher with the use of Nordic poles ($p \leq 0.001$) while CV was similar to the healthy population without Nordic poles (Table 3), which can suggest a more attention-challenging task for PD participants.

Spatiotemporal gait variables

Mean absolute and Z-score values for gait speed, cadence and step length are summarized in Figure 5 and Tables 2 and 3.

While the gait speed remained similar between the two walking conditions (p=0.146), the use of Nordic poles significantly improved the step length ($p \leq 0.001$) and significantly reduced the gait cadence ($p \leq 0.001$) in comparison to the UW session (Table 2 and Figure 5). No significant (Walking condition x Pathological condition) interaction was observed (F= 0.547; p=0.468, F=3.854; p=0.063, F=0.839; p=0.370 for gait speed, cadence and step length, respectively), suggesting a similar influence of NW on spatiotemporal gait variables for both PD and healthy participants. Compared to the healthy population, PD participants demonstrated a statistically significant reduction in gait speed ($p \leq 0.001$) during UW as well as a reduced step length ($p \leq 0.001$), while gait cadence remained similar to healthy adults. During NW, the gait speed was slightly reduced (p=0.049) as well as the gait cadence ($p \leq 0.001$) whereas the step length was significantly improved.

DISCUSSION

In this study, we aimed to gain more insight into the immediate effect of Nordic walking on the temporal organization of gait variability (i.e. LRA) as well as on spatiotemporal gait variables in PD participants. Actively involving rhythmic movements of the upper body, Nordic walking (NW) leads to significant improvement of LRA compared to the more random gait pattern highlighted during the usual walking session (UW). Additionally, NW enhances step length without any change in gait speed. Interestingly, LRA and step length collected from the NW session are similar to that of the

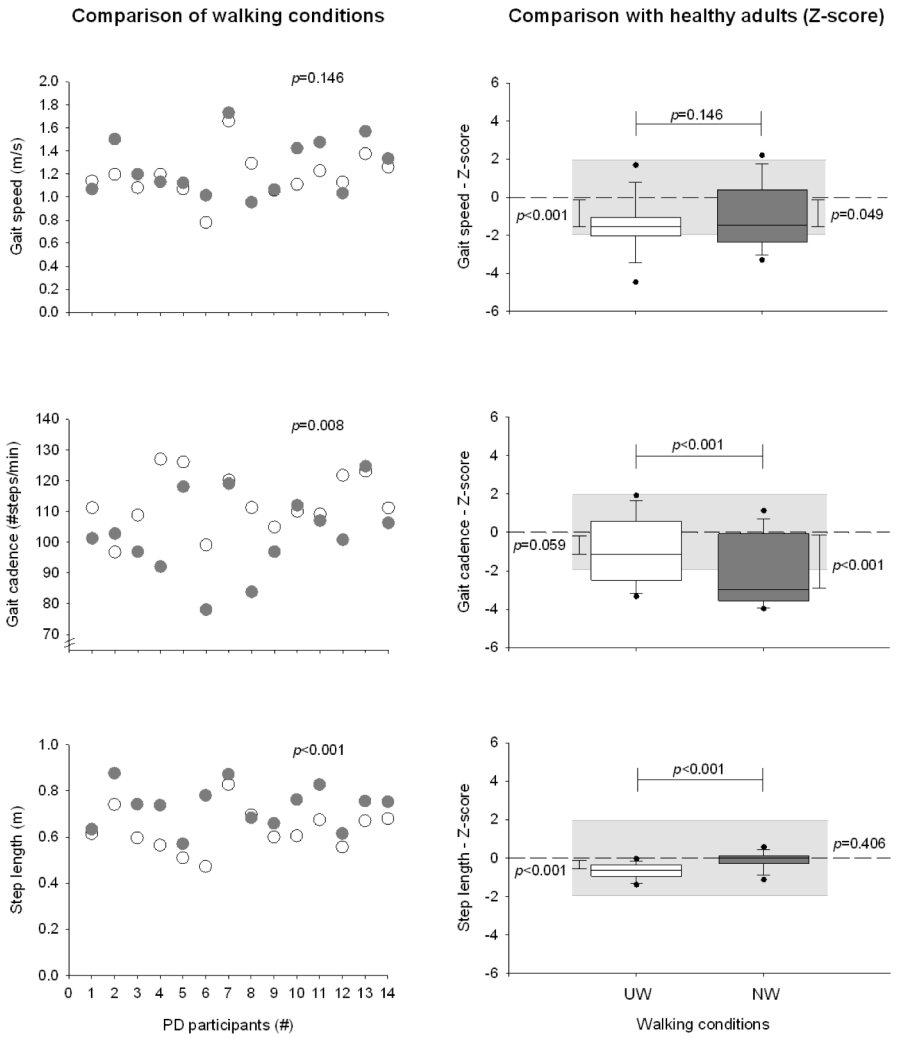

Figure 5. Spatiotemporal gait parameters Comparison of gait variables on usual walking (UW; white) and Nordic walking (NW; grey) in PD and comparison with healthy adults (Z-score).

healthy population. Those findings strongly support resorting to the use of Nordic poles in the struggle against the randomness of PD gait and the typical gait hypokinesia.

The randomness of PD gait pattern on UW contrasts with the structured gait pattern of age-matched healthy adults. Indeed, stride duration variability on UW appears less structured in PD (i.e. lower LRA exponent values). LRA, highlighted in gait and other rhythmic physiological signals, are thought of as the signature of subtle and complex interactions between subcomponents constituting dynamical systems [92,148]. Locomotor systems ranks among those systems that need to continuously adapt their pattern to constraints imposed by daily living activities [11]. The randomness of PD gait pattern could thus result from the defective activity among interacting subcomponents (e.g. basal ganglia). Furthermore, the breakdown of LRA highlighted in the specific context of basal ganglia disorders (e.g. Parkinson's and Huntington's diseases) was strongly associated with balance and functional status, and was suggested as a quantitative clinical measure of dynamic instability [34,134].

Compensating or restoring interactions among multiple components involved in healthy gait pattern is a key factor in restoring adaptability and flexibility of locomotion. Interestingly, NW can restore some temporal organization in PD gait pattern (Figure 3). LRA exponents were indeed significantly higher with Nordic poles than with usual walking in PD participants and similar to that of the healthy population, characterized by functional and adaptive locomotion (Tables 2-3 and Figures 2-3). The use of Nordic poles allows a more temporally organized behaviour than with UW, which suggest a more effective and powerful coordination of sub-components constituting the locomotor system [11,92,148].

Modulation of spatio-temporal gait parameters also seems different for people with PD walking with and without the Nordic poles (Tables 2-3 and Figure 5). Although the gait speed in UW and in NW remained slower than in healthy adults, the overall modulation of spatio-temporal gait parameters with the Nordic poles was similar to healthy adults. While the reduced gait speed during UW was largely attributed to hypokinesia

(significant reduction of step length), the gait speed in NW is modulated by both a significant improvement in step length and a reduction in gait cadence, which is particularly interesting in PD gait disorders management. Although the reduction of gait cadence could be perceived as dramatic, it should be noted that such decrease is usually observed with attentional strategies that specifically focus on step length criterion [144,149].

Decreased gait speed in PD is indeed largely attributed to difficulties in generating appropriate stride length while cadence control, used as a compensatory mechanism, remains intact [54,131–133]. However, Morris et al. demonstrated that the ability to generate a normal stepping pattern is not lost in PD [132]. Normal movement amplitude could be indeed elicited in PD given the appropriate conditions such as the use of attentional resources or external cues [132,144]. Both strategies appear to share the same mechanism of focusing attention on the stride length criterion[132].

Attention involvement in gait control on NW could be highlighted by a higher magnitude of gait variability (i.e. CV of stride duration variability; Figure 4), as recently suggested by Ayoubi et al. in their meta-analysis [122]. Attentional strategies are indeed often used to compensate for the impaired automaticity and could be involved in NW [132,150]. People with PD need to continuously think about their movement, sequencing the whole movement into sub-movement and the use of the frontal cortex facilitates movement size and timing regulation[150]. During NW, both PD and healthy participants were implicitly focused on walking and their attention was directed to the desired movement patterns[137]. The higher magnitude of the stride duration variability observed in all participants could be the signature of the attention involved in the task being performed, which could be observed with novice participants[151]. In addition, walking with Nordic poles involves the intentional action to move upper limbs in a coordinated fashion with legs, improving the movement of the most affected side in PD.

Therefore, NW appears to be an interesting rehabilitative option as arm swing is reduced in PD [152]. Recent studies agree wholeheartedly with the usefulness of arm swing on the stability of gait, especially in the elderly [152,153]. Moreover, gait seems to be more stable when the arm swing is amplified and could normalize the gait speed and the step length in this

population [152]. As already highlighted by Punt et al., this finding is important as the fall risk is already high for the elderly, and even more so in PD [153,154]. From this point of view, including arm swing in rehabilitation programmes, it seems to be an interesting strategy to normalize the PD gait pattern [152,155]. In particular, it has been suggested that normalizing coordination between limbs could improve gait in people with PD [152].

Arm swing is integrated into locomotion via tight neuronal interlimb coordination using specialized neural circuits in the spinal cord (central pattern generators, CPGs) [156]. Although such neuronal networks are able to produce coordinated motor patterns independently, the CPG output can be modulated by afferent feedback (i.e. cutaneous, joint and muscle input) and/or supraspinal input (i.e. cortical control). [155–159]. Interestingly, it has been demonstrated that cutaneous stimulation of the hand evoked significant changes in lower limb kinematics in healthy adults, with an increase in dorsiflexion at the stance-swing transition [160].

In addition, to help focus attention on walking, the use of Nordic poles could also act as an external sensory cue providing the necessary trigger in PD to bypass the defective pallidocortical circuit [137]. Among multiple cueing modalities, auditory and visual cues are the most studied [57,161]. However, tactile and proprioceptive cues have also demonstrated their usefulness in the struggle against the impaired gait automaticity, despite suggestions of impaired somatosensory function in PD [133].

From a biomechanical point of view, the use of Nordic poles implies a mechanically different movement pattern than UW [162–164]. By increasing the base of support, the use of poles helps to preserve gait stability after an unpredictable perturbation [165]. Nordic poles could serve as walking aids that are commonly prescribed to maintain balance in people with PD. However, the propulsive use of poles could reduce any alteration of the gait pattern classically observed with usual walking aids [162,166,167]. Also, higher impulse values and higher knee and ankle moments in the sagittal plane compared to UW could indicate a more dynamic movement in NW [163,164].

Although the use of Nordic poles seems to be effective in PD, our results should be carefully extended to the whole disease severity

spectrum. As recently highlighted, people with PD with only slight and mild gait impairment benefit most from NW [168]. The coordination between limbs during gait seems to be compromised of both bradykinesia and rigidity, which increase with the pathological progression, while the adaptive abilities of arm-leg coordination is preserved in people with PD in the early stage of the disease [169]. Also, people with PD often resort to cognitive strategies to compensate for a lack of gait automacity[170]. However, such compensatory strategies are useful as long as the cognitive resources are preserved [136,170]. The attentional involvement on gait induced by the use of Nordic poles could, as a result, be thus compromised in people with PD in the latest stages of the disease.

Some limitations of this study should be addressed. Motor complications, such as freezing of gait or dyskinesia, could alter the gait dynamics. However, only two patients suffered from such complications (one from freezing of gait and one from dyskinesia of the upper limb) and none of them presented such complications during the walking trial. Also, note that participants were probably the most motivated since they already participated in a previous study. Thus, our results should be interpreted in light of this specific aspect.

While several clinical trials were recently conducted to study the influence of NW on both motor and non-motor symptoms in PD[135–137], none assessed the beneficial effects of NW program on LRA, as a gait stability index. This study can constitute a pilot study offering new perspective to better characterize the sensitivity of the temporal organization of gait variability to rehabilitation approaches. Thus, it would be interesting to investigate the effectiveness of a tailored NW program on gait stability, concurrently assessed with clinical balance measures in a randomized control clinical trial.

CONCLUSION

In addition to the improvement of the typical gait hypokinesia, this study demonstrates in PD that the temporal organization of gait variability, which is considered as a marker of healthy locomotion, could be restored throughout the use the Nordic poles. Involving a voluntary intersegmental

coordination, such improvement could also be due to the upper body rhythmic movements acting as a rhythmic external cue to bypass the defective basal ganglia circuitries of PD. Therefore, Nordic walking may constitute a powerful way to manage gait disorders in PD, while being an accessible and affordable physical activity which offers the advantage that the activity can be performed by everybody, everywhere and at almost any time.

COMPETING INTERESTS

The authors declare that they have no proprietary, financial, professional, or other personal competing interests of any nature or kind.

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CHAPTER 3 – Article 2

Gait complexity and regularity are differently modulated by treadmill walking in Parkinson's disease and healthy population

Variability raises considerable interest as a promising and sensitive marker of dysfunction in physiology, in particular in neurosciences. Both internally (e.g. pathology) and/or externally (e.g. environment) generated perturbations and the neuro-mechanical responses to them contribute to the fluctuating dynamics of locomotion. Defective internal gait control in Parkinson's disease (PD), resulting in typical timing gait disorders, is characterized by the breakdown of the temporal organization of stride duration variability. Influence of external cue on gait pattern could be detrimental or advantageous depending on situations (healthy or pathological gait pattern, respectively). As well as being an interesting rehabilitative approach in PD, treadmills are usually implemented in laboratory settings to perform instrumented gait analysis including gait variability assessment. However, possibly acting as an external pacemaker, treadmill could modulate the temporal organization of gait variability of PD patients which could invalidate any gait variability assessment. This study aimed to investigate the immediate influence of treadmill walking (TW) on the temporal organization of stride duration variability in PD and healthy population. Here, we analyzed the gait pattern of 20 PD patients and 15 healthy age-matched subjects walking on overground and on a motorized-treadmill (randomized order) at a self-selected speed. The temporal organization and regularity of time series of walking were assessed on 512 consecutive strides and assessed by the application of non-linear mathematical methods (i.e. the rescaled range analysis and power spectral density; and sample entropy, for the temporal organization and regularity of gait variability, respectively). A more temporally organized and regular gait pattern seems to emerge from TW in PD while no influence was observed on healthy gait pattern. Treadmill could afford the necessary framework to regulate gait rhythmicity in PD. Overall, the results support the hypothesis of a greater dependence to regulatory inputs as an explanatory factor of treadmill influence observed in PD. Also, the present findings underline that gait analysis using treadmill devices should be carefully considered in PD and especially for gait variability assessment.

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INTRODUCTION

Human movement is intrinsically dynamic and complex. Continuous integration of multiple sensory inputs and coordination of motor outputs are needed to achieve efficient, stable, and adaptable locomotion [93]. Coordination among the multiple components and at multiple levels within the system reveals the complexity of physiological signals [9]. As such, human locomotion emerges from a wide set of interdependent elementary components, self-organized in coherent units and not dictated by a specific component within the system [9,11].

Beyond this theoretical approach, complexity and adaptability appears tightly linked. Archetypally linked to the defective activity among interacting subcomponents (e.g. basal ganglia), the randomness of gait pattern observed in neurodegenerative diseases such as Parkinson's or Huntington's disease compromises adaptive gait control [13,34]. Both externally (e.g. environment) and/or internally (e.g. pathology) generated perturbations and the neuro-mechanical responses to them contribute to the fluctuating dynamics of gait [12]. Adaptability stems from a wide range of potential behaviors that is allowed by adopting coordinated fluctuating regimen [11].

Deviations from a structured optimal level of variability in either the direction of randomness (i.e. weak coordination level) or the over-regularity (i.e. strong coordination level) indicate the loss of the adaptive capabilities of the system [11]. In human locomotion, perturbations of the temporal organization of gait variability have been suggested as a marker of gait disorder and fall risk among patients with central nervous diseases such as Parkinson's disease (PD) or Huntington's disease [13,22,34].

Interestingly, the use of assistive devices can modulate the temporal organization of gait variability in PD [171]. Beneficial effects of external sensory inputs from various natures (auditory, visual, tactile,…) were demonstrated to compensate or restore interactions among multiple components involved in healthy gait pattern [64,65,172,173]. By providing the necessary trigger, external sensory cues allow to bypass the defective

pallidocortical circuit in PD [55,133,144].

Treadmill training, recognized as a task-oriented approach for gait rehabilitation in the PD population, could act as an external pacemaker [174,175]. Improving stride length and gait speed, treadmill walking (TW) was suggested as a more optimal condition for the PD patients to generate a normal gait pattern compared to overground walking. [175]. In addition, as well as being an interesting rehabilitative approach in PD, treadmills are usually implemented in laboratory settings to perform instrumented gait analysis [17,176]. Although no treadmill effect was demonstrated in healthy population walking at a confortable speed and individually determined [17,176], potential treadmill effect during gait assessment needs thus to be considered in the specific context of PD.

Despite the frequent use of treadmill in research and rehabilitation fields, the influence of such type of locomotion on gait variability was poorly investigated in the specific context of Parkinson's disease. Only one study has compared the temporal organization of gait variability on treadmill and overground walking in PD while the treadmill walking influence on gait variability was the main focus of numerous studies conducted on healthy adults [174]. In 2005, Frenkel-Toledo et al. suggested that TW could act as an external cue to enhance gait rhythmicity and reduce gait variability. However, both the temporal organization and magnitude of gait variability (i.e. the coefficient of variation of gait variability) were assessed on walking session of 2 minutes, while both gait variability approaches are data-hungry techniques [14,16,119]. Gait variability measures should be respectively assessed on 512 and 127 consecutive gait cycles to draw adequate conclusions [177]. Hence, the practical challenge of capturing long-time series in pathological population is not trivial. Furthermore, the TW influence on severely affected patients and the role of fear of falling remains to be determined.

Therefore, considering the widespread attention paid on treadmill in the last decade in both rehabilitation and gait analysis and the necessity to reliably assess gait variability, we investigate whether TW influences the fluctuation dynamics of locomotion in PD. Given that treadmill ranks among rehabilitation approaches in PD [60], we put forward the hypothesis that the

temporal organization of variability would be more structured by external inputs from treadmill. On the contrary, the magnitude would be more pronounced on the moving surface of treadmill, potentially reflecting fear of falling. Since the gait automaticity and balance performance tend to decrease with the disease progression, the third hypothesis is that patient severely affected could benefit the most from TW.

MATERIALS AND METHODS

Subjects

Twenty participants suffering from idiopathic PD, diagnosed according to the UK Brain Bank Criteria [113], and fifteen healthy age-matched controls were recruited from the local community and local Parkinson's disease Association. A mandatory requirement for inclusion in the study was the ability to perform 512 consecutive strides without walking aids or assistance. Such series length is required to adequately apply mathematical methods described below [16]. PD patients were excluded if they had a past history of any neurological condition other than PD, orthopedic, or visual disturbance that affected walking ability. The study was approved by the local ethics committee (Comité d'Ethique Hospitalo-Facultaire de l'Université catholique de Louvain). Prior to data collection, all participants were informed about the experimental protocol and gave written consent in accordance with the Declaration of Helsinki.

Procedure

Prior to walking tests, each participant underwent a complete functional assessment including the subjects' performance on a balance test (BESTest) and the fear of falling (ABC-Scale). For PD participants, the disease severity (modified Hoehn & Yahr scale) and the patient's functional status (MDS-UPDRS) were also determined. All assessments were carried out during the ON state.

Each participant performed two walking sessions of 10 minutes that consisted of walking at a self-selected speed around a 42 m oval indoor track (overground walking (OW)) and on a motor-driven treadmill (treadmill

walking (TW); Mercury LT med, HP Cosmos, Germany). All participants were naïve to the treadmill walking. In order to avoid fatigue and any gait rehabilitation benefits, the two walking conditions were spread over two days and the order of sessions was randomly allocated. With respect to the treadmill walking session, each patient was instructed to walk on the treadmill at a comfortable walking speed without holding the handrails. The treadmill speed was adjusted to match each participant's comfortable speed [173,178]. This comfortable speed was determined following procedures used by Bayat et al. with patients suffering from stroke and Chien et al. with elderly individuals [173,178]. A gradual increase by increments of 0.10 m/s, initiated at 0.15 m/s, was executed until the subject indicated that the speed was too fast. In that case, the speed was decreased by 0.10 m/s, determining the comfortable gait speed. Once the patient reached his own comfortable speed, a familiarization period of 5 minutes was respected. Participants were then asked to continue further for 10 minutes. In order to ensure patient security, a safety harness was used (LiteGait ®, Mobility Research, Inc.). However, the system was adjusted to not support the subject (0% body weight support) in order to not influence patient's stride time dynamics [179].

In each of the two walking conditions, a unidimensional accelerometer was taped in the antero-posterior direction on the lateral malleolus of the most affected side in PD participants and the dominant side in healthy controls. Acceleration data were recorded at 512 Hz using the Vitaport 3 ambulatory recorder (Temec Instruments B.V., Kerkrade, The Netherlands), and next transferred to a computer. Heel strike was detected in the raw acceleration signal with a peak detection method designed to minimize the risk of false step detection [128,180]. Validated against ground reaction forces, this method assumes that each acceleration peak corresponds to successive foot contact [181]. The stride duration was determined from time elapsed between successive acceleration peaks, easily and accurately revealed by the use of a high sampling rate.

The stride duration variability was the primary outcome of our study and was investigated both in terms of magnitude, using standard metrics such as sample mean, standard deviation (SD) and coefficient of variation (CV), and in terms of its organization, which provides complementary

information about how stride duration evolves with time across consecutive strides [11,13,15]. In human locomotion, stride duration fluctuates in a structured, complex manner over the long term, displaying the presence of long-range autocorrelations (LRA) that can span hundreds of consecutive strides. For each time series, the magnitude and the temporal organization of stride duration variability were applied to sequences of 512 consecutive gait strides. The presence of LRA was evaluated, using an integrated approach that combines the results of distinct non-linear mathematical methods. The Detrended Fluctuation Analysis (DFA) and the Power Spectral Analysis (PSD) were applied to compute the Hurst exponent and the α exponent, respectively. Those methods were preferred given their relevance on both stationary and non-stationary processes [14]. To increase the level of confidence in the results, the consistency of H and α exponents was verify through the asymptotic relationship: $d = H - \left[\frac{(1+\alpha)}{2}\right]$.

Following such integrated approach, the three following criteria must be met to conclude the presence of LRA:

- $0.5 < H \leq 1$
- α significantly different from 0 and lower than 1
- $d \leq 0.10$

Further analyses were applied when *H* and *α* violate their asymptotic relationship under the hypothesis of a long-range auto-correlated process. In the present study, we used the randomly shuffled surrogate data test, described by Theiler et al. [101]. For each time series, 100 new series are generated from a random permutation of the original data. The only difference between the surrogate data sets and the original series is the sequential ordering of the data. *H* and *α* are then calculated for each new series and the mean and SD of these 100 new scaling exponents are computed and compared with the exponents of the original time series. The number of standard deviation between the original scaling exponent and the mean scaling exponent of the surrogate data sets (σ) is computed. If $\sigma > 2$, then the difference between the original data set and the surrogate data set is considered statistically different. It does not prove the presence of long-range autocorrelations in the original time series but it can reject the null hypothesis that the series under investigation has no temporal structure

(i.e., uncorrelated random process).

Sample Entropy (SampEn) was also calculated on 512 consecutive strides to assess the regularity or predictability of the lower-limb movement. Smaller value is associated with the greater regularity whereas a system with high SampEn appears less predictable; generating more non-redundant information over time. Since SampEn values were influenced depending on input parameter, *m* (i.e. length of the data segment being compared) and *r* (similarity criterion) were set according to the recommendations of Yentes et al. Values of 2 and 0.2 were respectively used for *m* and *r* [182].

For further details, these methods are described elsewhere [14,16,80,101,182].

Classical spatio-temporal gait parameters, assessed during both overground and treadmill walking sessions, constitute the secondary outcomes. During the treadmill walking session, the mean gait speed is known and the gait cadence is extracted from the accelerometer data. By identifying heel strikes (peak detection method), the total number of steps can be determined from the raw acceleration signals. The step length was assessed following the relationship between the gait speed and gait cadence. During overground walking, lap times, laps number and the total distance were measured. Following the relationship between total walking distance and acquisition duration, mean gait speed, mean gait cadence and mean step length were assessed as follow:

$$Gait\ speed\ (m.s^{-1}) = \frac{Total\ walking\ distance\ (m)}{Acquisition\ duration\ (s)};$$

$$Gait\ cadence\ (\#steps.min^{-1}) = \frac{Total\ number\ of\ steps\ (\#)}{Acquisition\ duration\ (\mathrm{min})};\ \text{and}$$

$$Step\ length\ (m) = \frac{Gait\ speed}{Gait\ cadence}.$$

Statistical analysis

Data were analyzed with the Sigmaplot 13.0 software (Systat, Richmond, CA, USA). Standard measures of statistical dispersion (mean (±standard deviation) and median (interquartile range) for normally and non-normally distributed data sets, respectively) were computed to describe

the study populations. Normality of data distribution was verified (using the Shapiro-Wilk test) for all variables, except for the gait cadence and the CV of stride duration that required the use of a log-transformation. A one-way ANOVA (PD vs Healthy), one-way repeated measures ANOVA (OW vs TW) and a two-way repeated measures ANOVA (Walking condition x Pathological condition) were applied to examine the influence of walking condition, as well as one of the pathological condition on LRA exponents, CV of stride duration and spatiotemporal gait variables. The effect size of TW as compared to OW was expressed in standardized terms (Hedge's *g*). Most of gait variables are speed- and/or age-dependent. Thus, to further identify the walking condition-caused gait modulations as opposed to changes arising solely from the age of subjects or from different walking speeds, all gait variables were age- and speed-normalized using a Z-score transformation. Andriacchi et al. and Winter's reference works provided normative data of spatiotemporal gait variables [142,183]. Given that no normative values for LRA exponents are currently established and that no influence of age and gait speed were demonstrated, values from our healthy control population were used as a reference point. Whereas the influence of gait speed on the CV of stride duration was highlighted at low speeds (i.e. 0.2 to 0.6 $m.s^{-1}$), most of our PD participants walked at a gait speed above 0.6 $m.s^{-1}$. Thus, considering this aspect and the absence of normative data for the CV of stride duration, healthy control values were also used as a reference point. Subjects Z-transformed gait variables were compared with normative reference values (corresponding to Z score = 0) using one-sample *t*-test or Wilcoxon signed-rank test (non-normally distributed variables) against zero. The treadmill influence in PD was also further investigated with respect to clinical factors such as disease severity, balance performance or fear of falling using Spearman's correlation coefficients. The results were considered statistically different for $p < 0.05$.

RESULTS

Anthropometric and clinical characteristics of the PD and healthy control groups are summarized in Table 1. Both groups were similar with respect to age, gender, height, and weight. Significantly lower scores were reached in balance performance, balance confidence and cognitive function among PD participants in comparison with the healthy age- and gender-

matched controls. Three PD patients suffered from motor complications in their daily-life (one from freezing of gait and two from dyskinesia (trunk or upper limb). However, none of such complications hindered the two walking acquisition of those patients.

Table 1

Characteristics of the study populations

	Parkinson's disease (n=20)	**Healthy** (n=15)	**p-value**
Age (years)	65.3±9.6	60.1±13.3	0.166
Gender	11 (male) and 9 (female)	9 (male) and 6 (female)	
Height (cm)	170.3±9.7	171.8±5.4	0.600
Weight (kg)	74.0±17.1	67.0±10.0	0.168
Time since the diagnosis (years)	4.5±2.7	-	
MMSE score	29.0 [24-30]	30.0 [29-30]	0.014
H&Y scale	2 [1-3]	-	
Most affected/dominant side	13 (left) and 7 (right)	2 (left) and 13 (right)	
MDS-UPDRS III (/132)	24.0 [9-66]	-	
MDS-UPDRS total (/260)	49.0 [15-133]	-	
BESTest total (%)	78.0 [49-92]	88.0 [82-90]	0.005
ABC Scale (%)	78.0 [54-100]	95.0 [76-98]	0.001

Mean (±SD) are expressed for quantitative variables normally distributed while median [range] are expressed for both ordinal and non-normally distributed variables

Treadmill effect on PD and healthy gait pattern

Absolute and normalized values of stride duration variability measures and spatio-temporal gait variables are summarized in Tables 2-3 and Figures 1-2. The standardized effect-size (Hedge's *g*) is depicted for the PD participants and healthy controls in Figure 3.

The PD gait pattern was greatly influenced by TW while measures of gait variability and classical spatio-temporal gait variables remained similar in healthy controls (Table 2 and Figures 1-2). In PD participants, TW was on averaged performed at lower gait speed than on OW, associated with a decrease of both gait cadence and step length (Table 2 and Figure 2). In comparison to the more unpredictable and random gait pattern observed on overground in PD, a more regular and temporally organized (i.e. decrease of SampEn and increase of *H* and α exponent, respectively) gait pattern seemed to emerge from TW (Table 2 and Figure 1). While values of *H* lower than 0.5 were highlighted for five PD participants on OW, values of *H* and α exponents closer to 1 or even higher than 1 for some participants were reached on TW. Values of *d* were below 0.10 in healthy population and both walking conditions (0.06 ± 0.02 and 0.07 ± 0.08 for OW and TW, respectively) while it reached values higher than 0.10 in PD population (0.12 ± 0.10 and 0.11 ± 0.10 for OW and TW, respectively). Using the surrogate data tests, the presence of a specific temporal structure in original time series can still be suggested for time series that did not verify the *H*, *α* and/or *d* criteria. Across all conditions, the number of standard deviations between the original scaling exponent and the scaling exponent of the surrogate series (σ_H and σ_α) were on average clearly superior to 2 for both populations. Higher magnitude of stride duration variability (i.e. increase of CV stride duration) was also induced by the TW. Importantly, significant (Walking condition x Pathological condition) interactions were demonstrated for LRA exponents, and the gait speed and step length confirming that TW influenced differently the gait pattern of PD and healthy participants (Table 2).

Table 2

Absolute mean values of the stride duration variability and spatiotemporal gait variables for the comparison between the overground walking (OW) and the treadmill walking (TW) sessions in Parkinson's disease and healthy subjects and analysis of the (pathological x walking conditions) interaction for the stride duration variability and spatiotemporal gait variables.

	Parkinson's disease		Healthy controls		Interaction	
	OW	TW	OW	TW	F	*p*-value
Stride duration variability						
H exponent	0.66 (±0.17)	0.89 (±0.14)***	0.78 (±0.07)§§	0.82 (±0.12)	8.303	**0.007**
α exponent	0.46 (±0.16)	0.81 (±0.27)***	0.54 (±0.14)	0.56 (±0.20)§	10.921	**0.002**
Sample Entropy	1.89 (±0.24)	1.71 (±0.27)*	1.94 (±0.19)	1.93 (±0.13)§§	3.088	0.088
CV (%)	2.45 [1.97-3.73]	3.68 [2.10-7.09]*	1.78 [1.42-2.31]§	1.77 [1.34-2.66]§§	3.698	0.063
Spatiotemporal gait variables						
Gait speed (m/s)	1.15 (±0.16)	0.74 (±0.27)***	1.34 (±0.16)§§	1.23(±0.16)§§§	23.055	**≤0.001**
Gait cadence (#steps/min)	111.85 (±8.12)	102.78 (±6.46)***	113.83 (±10.13)	109.80 (±8.83)*§	3.160	0.085
Step length (m)	0.61 (±0.09)	0.41 (±0.14)***	0.70 (±0.07)§§	0.67 (±0.07)§§§	29.263	**≤0.001**

Absolute value is expressed as mean (± SD) or median [range]
***: p≤0.001; ** p≤0.01; * p≤0.05 for the comparison between UW and NW (paired t-test)
§§§: p≤0.001; §§ p≤0.01; § p≤0.05 for the comparison of walking conditions between PD and healthy controls (independent t-test)
Bold data indicates if (pathological x walking condition) interaction was significant (p<0.05)

Table 3

Mean values of the normalized stride duration variability and spatiotemporal gait variables (Z-score) for the comparison between the overground walking (OW) and the treadmill walking (TW) sessions in Parkinson's disease.

	Z-score				Paired *t*-test
	OW	*p*-value	TW	*p*-value	*p*-value
Stride duration variability					
H exponent	-1.71 (±2.48)	**0.006**	0.46 (±1.02)	0.058	**≤0.001**
α exponent	-0.58 (±1.13)	**0.033**	0.98 [0.36-1.86]	**≤0.001**	**≤0.001**
Sample Entropy	-0.38 (±1.26)	0.259	-1.60 (±1.90)	**0.001**	**0.009**
CV (%)	1.00 [0.18-3.36]	**0.002**	1.20 [-0.06-3.93]	**0.007**	0.888
Spatiotemporal gait variables					
Gait speed (m/s)	-1.72 (±1.13)	**≤0.001**	-4.71 (±1.95)	**≤0.001**	**≤0.001**
Gait cadence (#steps/min)	-0.19 (±1.42)	0.568	1.15 (±1.84)	**0.014**	**≤0.001**
Step length (m)	-0.53 (±0.52)	**≤0.001**	-1.05 (±0.42)	**≤0.001**	**≤0.001**

Z-score is expressed as mean (± SD) (one-sample t-test) or median [range] (one-sample Wilcoxon signed-rank test).
Bold data indicates if the Z-score significantly differed from 0 ($p < 0.05$): One-sample t-test (normally distributed values) or one-sample Wilcoxon signed-rank test (non-normally distributed values).

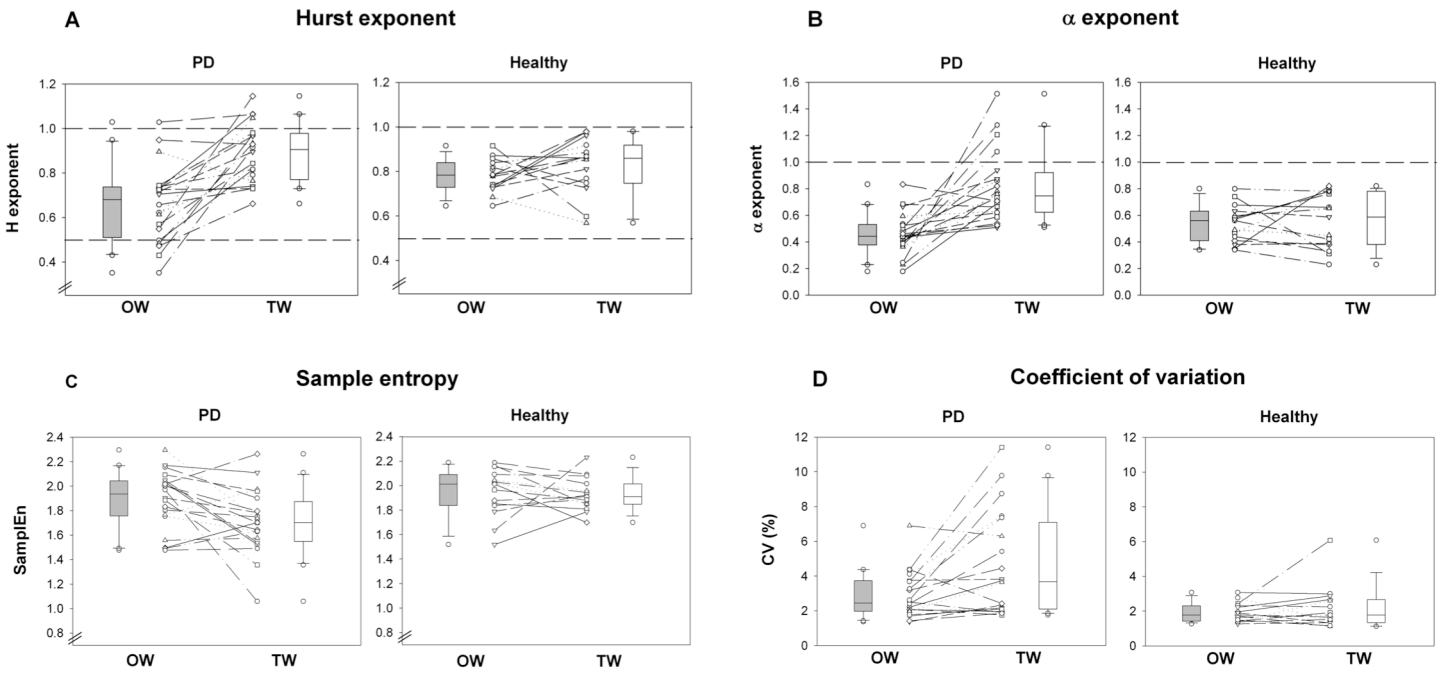

Figure 1. Stride duration variability. (A) shows individual changes of Hurst exponent for overground walking (OW) and treadmill walking (TW) in PD and healthy populations. **(B)** shows individual changes of α exponent between walking conditions and study populations. **(C)** shows individual changes of sample entropy between walking conditions and study populations. **(D)** shows individual changes of the coefficient of variation of the stride duration variability between walking conditions and study populations. Boxplots represent the median and the quartiles.

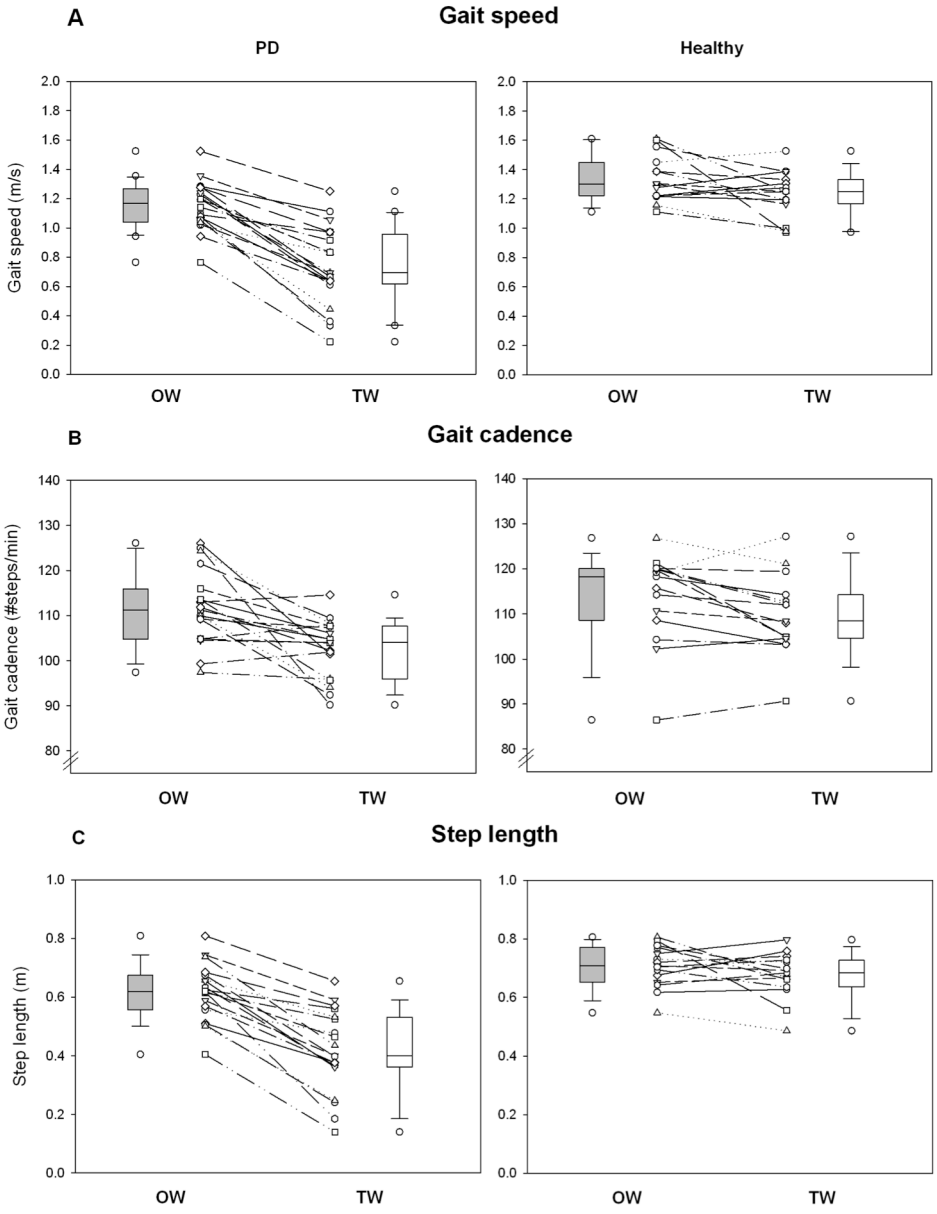

Figure 2. **Spatiotemporal gait variables. (A)** shows individual changes of gait speed for overground walking (OW) and treadmill walking (TW) in PD and healthy populations. **(B)** shows individual changes of gait cadence between walking conditions and study populations. **(C)** shows individual changes of step length between walking conditions and study populations. Boxplots represent the median and the quartiles.

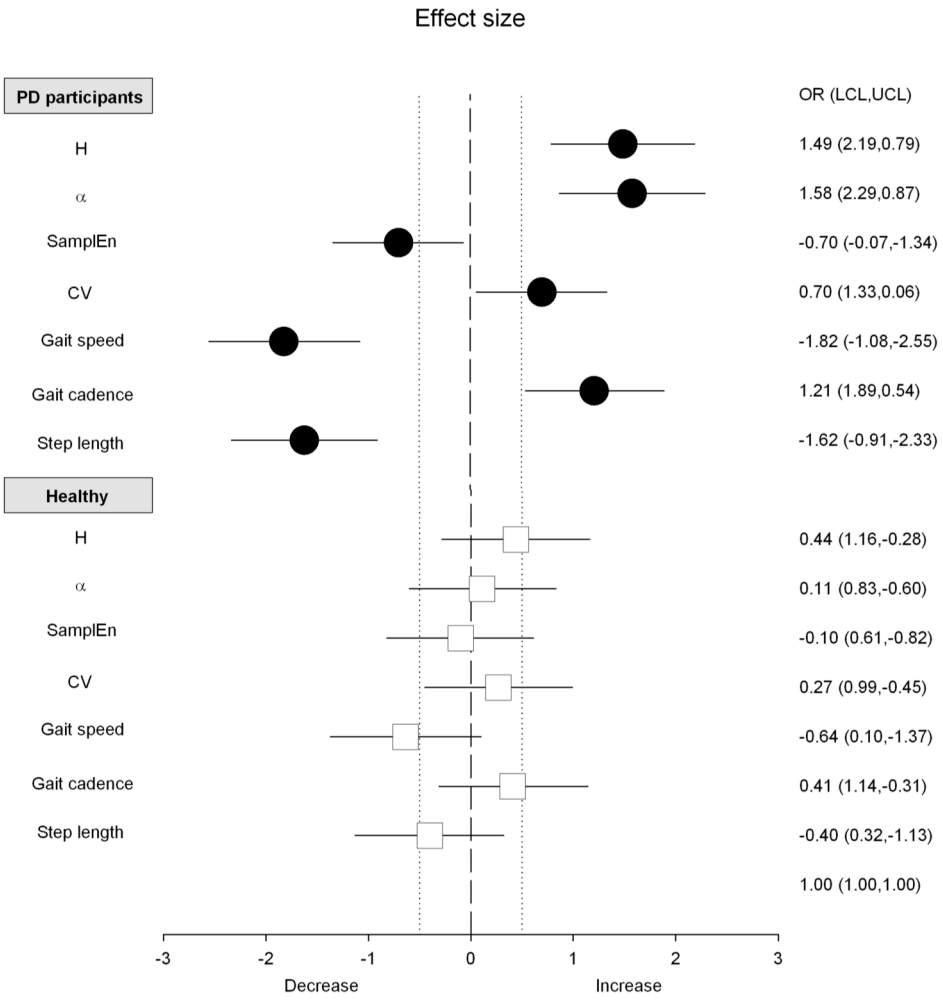

Figure 3. Effect size and confidence intervals for the differences between overground and treadmill walking. Black circles (PD patients) and white squares (Healthy controls) are the standardized effect size (Hedge's g). Horizontal lines are the 95% confidence intervals. Vertical dotted lines, arbitrarily fixed at 0.5 and -0.5, correspond to a medium effect as defined by Cohen.

As PD walked at their own comfortable speed that differed on OW and TW, normalized values (Z-score) were used to refine previous observations and draw adequate conclusions by taking into account gait speed differences observed between the two walking sessions (Table 3). Interestingly, the statistical difference based on absolute values highlighted for the CV stride duration became non-significant using normalized values while all other comparisons led to the same conclusions (Table 3). Adequate comparisons with healthy controls were also allowed by the use of normalized values. In comparison to the healthy population, the reduced gait-speed and step length and the increased CV highlighted on OW were intensified on TW. On the contrary, the random gait pattern observed on OW tended to be performed at a higher gait cadence and tended to be more regular and organized on TW than healthy controls.

Clinical status influence on walking behavior

As depicted on Figures 1-2, some PD participants tended to be highly influenced by the treadmill while no influence was observed for others. To further investigate potential factors that could explain such distinct behaviors, Spearman's correlation coefficients were calculated between gait changes induced by the treadmill and the patients' clinical status (Table 4). The temporal organization appeared highly related to the patient's functional status, and in particular its balance performance, while the magnitude of the stride duration variability was related to the gait speed changes. Similarly, the step length was correlated to both balance performance and confidence. The balance status could be thus the explanatory factor of the important changes observed between the two walking sessions in some patients.

DISCUSSION

The aim of the present study was to investigate the immediate influence of treadmill walking compared to overground ambulation on both gait variability and spatiotemporal gait variables in Parkinson's disease and healthy controls. Firstly, our study demonstrated a more regular and temporally organized gait pattern in PD participants while healthy controls remained insensitive. A second observation was the highlighting of a

Table 4

Correlations study between the changes of both stride duration variability and gait parameters with clinical parameters in Parkinson's disease. The change expresses the difference between the two walking conditions (OW and TW).

	Changes between overground and treadmill walking sessions (OW-TW)						
	Stride duration variability				Gait parameters		
	Temporal organization		Regularity	Magnitude			
	H	α	SamplEn	CV	Gait speed	Gait cadence	Step length
Clinical parameters							
Age	-0.28	-0.08	-0.11	0.18	-0.05	-0.06	-0.18
Disease duration	0.38	0.43	0.13	0.04	-0.29	0.16	-0.39
H&Y scale	**0.60****	**0.75*****	-0.18	0.09	-0.35	0.20	-0.39
MDS-UPDRS III	**0.56***	**0.58****	-0.27	0.09	-0.32	0.22	**-0.52***
BESTest	**-0.51***	**-0.64****	0.20	-0.19	**0.55***	-0.11	**0.73*****
ABC-Scale	-0.22	**-0.52***	-0.15	-0.20	**0.63****	-0.13	**0.66****
Gait speed change	0.14	-0.35	-0.05	**-0.51***	-	0.42	**0.96*****

***: p≤0.001; ** p≤0.01; * p≤0.05

reduced gait speed and a concomitant decreased step length, suggesting a cautious gait pattern adopted by PD participants walking on a treadmill. Finally, greater influence of TW was demonstrated among instable patients.

Complexity and regularity of stride time signals may reveal insight into the neurophysiological organization of locomotion and into the regulation of the interacting subsystems, constituting the locomotor system [9,184]. Interestingly, the PD gait pattern was more temporally organized on treadmill, indicating strong coordination among the multiple sub-systems [9,11]. LRA exponents indeed yielded values close to 1 in PD, and were significantly higher than healthy age-matched controls where the temporal organization of gait variability was insensitive to TW (Tables 2-3). Also, a more constrained and predictable locomotion is induced (i.e. reduction in SampEn) in PD patients walking on a treadmill while the healthy gait pattern remained indifferent to TW (Tables 2-3). Therefore, although less complex gait dynamics would emerge from such constrained system, constraints induced by the treadmill belt could afford the necessary framework to regulate gait rhythmicity in PD while allowing some adaptations and not a completely rigid gait control.

Although some similarities are shared between overground and treadmill ambulation, TW has sources of constraint that are not present for OW [184]. Gait regulation could be modulated by physical constraints that reduce the number of available degrees of freedom. The intrinsic dynamics emerge from the multiplicative interactions that constitute the entire system including the locomotor system, the environment and their mutual history [92]. The coupling of the participant and environment modulates gait dynamics. Motor behavior emerges to satisfy the intrinsic and extrinsic constraints of the task at hand. Additionally, the strength of the coupling determines the quality of coordination within the organism–environment system [92]. The greater complexity and regularity of PD gait pattern on TW could be thus explained by a greater dependence on environmental conditions. Treadmill walking implies specific physical and environmental constraints.

Mechanisms potentially involved in the therapeutic effect of the treadmill were identified by Bello and Fernandez-Del-Olmo who reviewed 10 years of investigation of treadmill training in PD [175]. Although the mechanisms implicated in the treadmill effect on PD gait pattern remain elusive, PD patients could take advantage of the hip extension, the constant gait speed or the absence of visual flow on the treadmill [175]. However, based on our experimental protocol, some mechanisms such as hand support or motor learning did not seem to explain the treadmill effect on PD gait pattern.

Adequate sensory inputs from TW may stimulate the spinal locomotor circuitry (i.e. Central Patterns Generators; CPG). Descendent supraspinal signals and afferent input of the limbs are suggested to regulate the CPG activity. In this way, lower limbs that are rhythmically moved backwards and behind the trunk can constitute a regulatory input from the environment that could restore some interaction within the locomotor system. Efficient, stable and adaptable locomotor pattern requires complex dynamic sensorimotor interactions depending on highly complex processes including efferent-type (from the motor cortex, the cerebellum, the basal ganglia and central pattern generator) and afferent-type information coming from different peripheral feedbacks.

The use of regulatory inputs from the environment appears crucial to overcome the defective internal rhythm of the basal ganglia disorders [55,133,144]. Greater propensity to be entrained by regulatory inputs characterizes PD gait control in comparison to healthy adults. Sensory inputs from TW could provide the necessary trigger to maintain some gait rhythmicity in the same way as external cues. From various nature (auditory, visual or proprioceptive and tactile), their usefulness in the struggle against the impaired gait automaticity was demonstrated in PD by bypassing the defective pallidocortical circuit [63,133,173]. In this way, TW could act as an external pacemaker and the fixed timing of leg movements could reduce the regulatory load on defective cortical areas allowing relative adaptations of gait parameters [61,174]. Such adaptation was indeed highlighted on a 0.5-meterwide and 1.5-meter-long treadmill [15].

Similarly, the constant gait speed could also modulate the free regulation of walking in PD[128], to such an extent that some authors postulated that the treadmill could function like a metronome [185]. Although isochronic auditory stimulations are indeed suggested to afford the necessary framework to maintain gait rhythmicity in PD, evidence agrees that isochronic metronome breaks the complexity of both PD and healthy gait patterns [63]. Our results demonstrated TW influence only for PD population. Across existing literature, the influence of TW on the intrinsic gait dynamics appears indeed more equivocal for healthy population [17,128,176]. The gait speed determination could be the key explicative factor. In our study, comfortable speed individually determined was preferred to an imposed speed applied for all subjects. Influence of TW in healthy population was indeed highlighted in studies where the gait speed was not individually determined which could have induced higher constraints on gait control [128].

The damaged automaticity in PD gait pattern can also be overcome by the use of attentional strategies [144,171]. Among the environmental constraints of TW, the absence of optical flow could reduce distraction and allow the patients to allocate attentional resources on the task at hand [175]. Attentional allocation could be highlighted by the higher magnitude of the stride duration variability observed in PD participants, which could be particularly increased given the newness of the task and the fear of falling expressed by some patients. However, the gait speed seems to be a better candidate to explain such an increase (Table 4). Walking on a treadmill does not seem to require greater involvement of attentional resources in both groups since the magnitude of gait variability became not significantly higher on TW than OW when parameters were normalized for gait speed (Table 3). Also, a previous study highlighted that PD gait pattern seems to be more dependent on sensory inputs generated by the belt movement than on attentional resources [186]. Thus, in accordance with the existing literature, this study extends previous observations that gait speed is tightly linked to the magnitude of gait variability [21].

Gait pattern modifications could also be induced by the newness of task despite a familiarization period. Treadmill walking modulated classical spatiotemporal gait parameters in PD population. Compared to overground

ambulation, gait speed and step length were clearly decreased in PD participants walking on treadmill while only slight changes were observed in healthy controls. In parallel, cadence of PD gait pattern increased, acting as a compensatory mechanism. Reduced gait speed and step length ranks among other gait parameters modifications that characterize precautious gait pattern highlighted in frailty patients [51,187]. Indeed, PD patients presented lower balance performance and higher level of fear of falling than healthy age-matched controls (Table 1).

Gait pattern seems indeed to be the most influenced by TW in patients with the most precarious balance status (Figure 1 and Table 4). The temporal organization of gait variability was recently suggested as a gait stability index [13,47]. Indeed, the more random the walking pattern (i.e. Hurst and α exponents close to 0.5 and to 0, respectively), the greater influence of TW is observed. The most important improvement of gait dynamics was thus observed in patients with the greater instability. As largely reported in literature [51,187], balance status also greatly explains the cautious gait pattern adopted by the most instable patients.

Importantly, all of those modifications observed in PD population walking on a treadmill arise the question of adequate gait assessment including gait variability on TW in PD participants. This study highlights the necessity to carefully consider the use of motorized-treadmill in gait variability assessment as well as classical spatio-temporal gait parameters in gait analysis and usual clinical practice. Hence, gait disorders resulting from the insufficiency of internal rhythm generation is the most accurately depicted on OW given the higher propensity of PD population to be influenced by external rhythmical inputs.

The present study has some limitations that should be addressed. A safety harness was used to ensure the patient's security while some studies have highlighted influences of TW on vertical trunk acceleration and lower limb kinematics [188,189]. Influences are particularly evident with body weight support and even more with static body weight support [188,190]. However, the body weight support was set at 0% in our study since, when interval variables are the primary interest, the emergence of natural gait dynamics did not seem to be disrupted by the non-weight support harness

[179]. Similarly to backpack or hydrotherapy treatments, the safety harness could also provide the necessary sensory trick to struggle against postural instability in PD [191,192]. Familiarization period can also constitute a limitation of the present study. Actually, no guidelines were edited with respect to the duration of the familiarization period [193–195]. A familiarization period of 5 minutes was determined based on a previous study conducted on stroke patients to allow adaptation to TW and avoid any fatigue [178]. As suggested by our observations, PD gait dynamics could be modulated by the rhythmical inputs generated by the motorized treadmill. Therefore, it could be interesting to investigate the influence of non-motorized treadmill to better elucidate the participation of the motor-driven part of the TW compared to the common parts shared with the overground ambulation.

In conclusion, the present study highlights that the treadmill could afford the necessary framework to regulate gait rhythmicity in PD while precautious gait pattern seems to be adopted with such type of walking. A more temporally organized and more regular gait pattern emerges from treadmill walking in PD while no influence was observed in healthy gait pattern. Those observations support the hypothesis of a greater dependence to regulatory inputs as an explanatory factor of treadmill influence observed in PD. Our results may form a further step towards a better understanding of the effect of treadmill on PD gait. Also, the present findings underline that gait analysis using treadmill devices should be carefully considered in PD and especially for gait variability assessment.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Chapter 4

Methodological approach

Impact of series length on statistical precision and sensitivity of autocorrelation assessment in human locomotion

CHAPTER 4

Impact of series length on statistical precision and sensitivity of autocorrelation assessment in human locomotion

Long-range autocorrelations (LRA) are a robust feature of rhythmic movements, which may provide important information about neural control and potentially constitute a powerful marker of dysfunction. A clear difficulty associated with the assessment of LRA is that it requires a large number of cycles to generate reliable results. Here we investigate how series length impacts the reliability of LRA assessment. A total of 94 time series extracted from walking or cycling tasks were re-assessed with series length varying from 64 to 512 data points. LRA were assessed using an approach combining the rescaled range analysis or the detrended fluctuation analysis (Hurst exponent, *H*), along with the shape of the power spectral density (α exponent). The statistical precision was defined as the ability to obtain estimates for *H* and α that are consistent with their theoretical relationship, irrespective of the series length. The sensitivity consisted of testing whether significant differences between experimental conditions found in the original studies when considering 512 data points persisted with shorter series. We also investigate the use of evenly-spaced diffusion plots as a methodological improvement of original version of methods for short series. Our results show that the reliable assessment of LRA requires 512 data points, or no shorter than 256 data points provided that more robust methods are considered such as the evenly-spaced algorithms. Such series can be reasonably obtained in clinical populations with moderate, or even more severe, gait impairments and open the perspective to extend the use of LRA assessment as a marker of gait stability applicable to a broad range of locomotor disorders.

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INTRODUCTION

Temporal complexity is a hallmark of physiological systems, including the generation of rhythmic motor patterns such as gait or in the spontaneous activity of the heart [90] or firing patterns of neurons [196] under resting conditions. Indeed, recent studies have highlighted that most physiological signals continuously fluctuate over time in a complex manner, such that consecutive cycles exhibit an interdependency spanning over long time intervals [11,16,17,32,90,112].

Of particular interest is the potential use of long-range autocorrelations (LRA) to distinguish between healthy and pathological conditions in a number of diseases [11,32]. In human locomotion, perturbations of LRA have been suggested as a marker of gait disorder and fall risk among patients with central nervous diseases such as Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis [13,22,34].

One limitation of such approach is that physiological time series are unavoidably finite, whereas the presence of LRA is an asymptotic property, making the assessment of long-range dependency inherently based on approximations [16]. Thus, it is crucial to determine a good balance between the series length, which in the context of clinical application is limited by patients' ability to perform a task for a long time, and the minimum number of cycles necessary to obtain a reliable assessment of the series autocorrelation function.

The issue of series length on its own has been considered previously. Although series of 512 data points have been usually considered in both synthetic [112] and physiological time series [16], methodological efforts are continuously made to improve the performance of the usual algorithms with even shorter series [119,197,198]. Recently, the use of evenly spaced methods, which partially correct for the distortion of the data when transformed into logarithmic scale, yielded substantial improvement of the DFA with relatively short generated time series (i.e. 256 data points) [197]. In human locomotion, such improvement could extend the LRA assessment to a broader range of locomotor disorders, especially for the most impaired patients for whom series of 512 cycles remain challenging to perform. We thus investigated the benefits of the evenly-

spaced method on physiological series.

Given that the assessment of long-range correlations may provide an easy and effective tool to quantify gait stability [11,13,34], we investigated whether statistical precision and the sensitivity of the scaling parameters associated with the autocorrelation function could be preserved across series of shorter lengths. Our results suggest that reliable series as short as ~128 data points do not capture well the underlying scaling properties found in the same series when longer intervals are considered. Furthermore, we found that reliable results could be obtained with series no shorter than 256 data points, provided that robust techniques such as evenly-spaced regressions are used to mitigate the impact of the rather short series length. Gait stability assessment could be thus extended to population suffering from moderate or even more locomotor impairments, which are still able to perform a ~5 min continuous walking trial.

MATERIALS AND METHODS

Participants

We re-analysed the original time series (in walking or cycling conditions) collected from previous studies including a total of 47 healthy young adults [15,18]. Their mean age was 23.2 (±2.0) years, their mean weight was 69.2 (±8.5) kg and their mean height was 178.3 (±8.5) cm. Participants were free of any muscular, neurological, or orthopaedic pathology that could alter their locomotor performance. Each participant provided informed written consent and the procedures were approved by the local ethics committee at the host institution.

Procedure

Among the 47 participants, 32 were instructed to perform two different walking trials on a treadmill at their self-selected speed [15]: 20 were instructed to walk while performing or not a cognitive task (dual task or single task) and the 12 other participants were instructed to walk in backward and forward directions. The remaining 15 participants performed two cycling sessions on a friction-loaded cycle-ergometer at spontaneous and imposed (60 RPM) cadences [18]. Details on each protocol are provided

in these original references. A total of 94 time series were re-evaluated in the present paper.

Data were recorded from the peak of the anteroposterior leg accelerations using a unidimensional accelerometer taped on the right malleolus for walking conditions and on the head of the right fibula for pedaling conditions (512 Hz). The extracted data were the stride or cycle duration for the gait or cycling conditions, respectively.

Reliability assessment of LRA estimates

The reliability of LRA estimates as a function of series length and algorithm used was assessed using statistical precision and sensitivity measures.

Statistical precision was defined as the ability to obtain similar LRA estimates, computed on original series of 512 data points, using a shorter series. In each condition (i.e., single and dual task, walking forward and backward, cycling at spontaneous and imposed cadence), mean exponent estimates (±SD) were calculated for the global number of participants for each series length and for both algorithms. To assess the statistical precision of the scaling exponent of interest, the standard deviation of those measures were calculated for each series length and algorithms. By highlighting a reduced standard deviation, a more precise estimate of the scaling exponent could be suggested.

Sensitivity was defined as the ability to reproduce the properties of the original series of 512 data points across testing conditions with varying series lengths and algorithms. Paired *t*-tests were used to verify whether conclusions edited from original comparisons persisted with shorter series.

To investigate the impacts of series length and of the algorithm considered on the assessment of LRA, each time series was re-analyzed with various numbers of data points. Series length of 64, 128, 256 and 512 data points were considered. It should be noted that using a series of length equal to a power of 2 was preferred to optimize the numerical conditioning of the Fourier transform analysis. In addition, the shorter series length were not deliberately selected but spread over the whole data set.

For instance, multiple series of 64 consecutive data points were analyzed from the first series of 64 points (1 to 64, 2 to 65, 3 to 66, etc).

Assessment of LRA

A process generates a time series contains LRA when the covariance of two distinct samples decreases slowly as the elapsed time between the two samples increases. Namely, if X_i denotes a parameter associated with the i^{th} cycle (e.g., inter-stride time interval), a time series presenting LRA is typically characterized by:

$$E(X_i X_{i+n}) \sim n^{-\beta}, \qquad (1)$$

where $0 < \beta < 1$ and $E(.)$ denotes the expected value of the argument. The "slow" decay of the auto-correlation function refers to the fact that the integral of Eqn. 1, also called the process memory, is infinite when $0 < \beta \leq 1$, while it becomes finite for values of β greater than 1, as observed for short-range auto-correlated processes. The presence of LRA was assessed using the integrated approach proposed by Rangarajan and Ding (2000), and validated in the context of a physiological time series [16]. Briefly, the combination of two methods described below consists of verifying that the estimates of the scaling exponents (the Hurst exponent and the shape of the power spectral density which we call α) from both methods are consistent with each other. Although this technique does not provide a definite answer to the question of whether the series contains a long-range autocorrelation [112], it reduces the rate of false-positive results that follows the application of each method independently [80].

Original algorithms

The Hurst exponent was computed using the Rescaled Range Analysis (RRA) and the Detrended Fluctuation Analysis (DFA) [16,80,90,112]. RRA, a random walk method, allows for the estimation of the Hurst exponent. The original time series of size N is first integrated. Then, the integrated series is divided into subsets of size τ in which the local trend computed from linear regression is subtracted. The rescaled range of a given subset of size τ is defined as the range of the detrended subset (R) normalized to the standard deviation of the original time series computed

on the corresponding subset (*S*). The rescaled range is computed on subsets of distinct size from $\tau = 10$ to $\tau = N/2$, where *N* is the number of data points limited to 64, 128, 256 or 512 according to the series length under investigation, and averaged across subsets of equal size. The slope of the relation between log(*R/S*) and log(*τ*) determines the Hurst exponent (*H*).

An alternative technique is based on Detrended Fluctuation Analysis (DFA), in which the range attained by the random walk used for RRA is replaced by the standard deviation of the series [90,112]. DFA and RRA are similar in the sense that both algorithms estimate the Hurst exponent. Observe that in theory, DFA can be applied to both stationary and non-stationary processes whereas RRA is restricted to stationary processes [112].

It can be demonstrated that *H* is asymptotically related to the autocorrelation function by the relation [80,199]:

$$H = \frac{(2-\beta)}{2} \qquad (2)$$

When $0.5 < H < 1$, the time series typically presents LRA. If the process is a collection of independent and identically distributed random variables (i.e., a white noise, assuming a Gaussian distribution), then $H = 0.5$. An $H < 0.5$ indicates the presence of anti-correlations, whereby an increase of the variable tends to be followed by a decrease, and vice-versa [16,80,112].

The Power Spectral Density (PSD), also usually reported as the power spectrum, was used to estimate the *α* exponent. The PSD of the time series is calculated using Fourier transform analysis [16,19,24]. Long-range autocorrelated processes have a power spectral density that scales as $f^{-\alpha}$, where *f* is the frequency and *α* is related to the autocorrelation function by the relation:

$$\alpha = 1-\beta. \qquad (3)$$

The slope of the linear regression line computed by the logarithm of the power spectral density versus the logarithm of the frequency determines the *α* exponent. An *α* exponent that is significantly greater than

0 indicates the presence of LRA, and an exponent *α* that is not significantly different from 0 is the signature of a flat power spectrum, at least at low frequencies, corresponding to a white noise or to a series with a short-range autocorrelation function [80].

Note that a combination of preprocessing operations is proposed to improve the computation of PSD [112,200]. However, the original version of PSD was preferred since such version is better for comparisons across groups, as investigated in our study [112].

Evenly spaced algorithm

The logarithmic transformation used in the RRA, DFA or PSD results in an unbalanced density of points along the abscissa axis, which increases with interval length [197]. Such uneven distribution of data can clearly impact the estimate of regression parameters for each method. To overcome this issue, the method of evenly-spaced diffusion was initially introduced by Peng et al. [90] and recently used, among other, by Damouras et al. [119] and Almurad and Delignières [197]. This method consists in selecting the data used for the regressions as follows:

$$\begin{cases} n_1 = n_{min} \\ n_i = \left[n_{i-1} 10^{\frac{log_{10}(n_{max}) - log_{10}(n_{min})}{k-1}} \right] \end{cases}$$

where k represents the number of points to include in the diffusion plot, the k interval lengths are noted $(n_i (i = 1,2, \dots, k)$ and n_{max} and n_{min} correspond to the maximum and the minimum interval lengths. We used $n_{min} = 10$, $n_{max} = N/2$ and $k = 18$ to follow the study by Almurad and Delignières [197]. After selecting evenly spaced data points, the linear regressions can be performed on these selected points (evenly spaced), or on the average data across the data points that are between selected points (evenly spaced averaged). We use these techniques to show the merits of evenly-spaced methods for assessing LRA on short physiological time series.

Proof-Checking the Exponents' Asymptotic Relationship

Plugging Eqn. 3 into Eqn. 2 indicates that, in theory, the exponents *H* and *α* are asymptotically related by the relation $H = \frac{1+\alpha}{2}$ [80]. Hence, the integrated approach consists of separately computing *H* and *α* and verifying that these two parameters are consistent through the equation $d := H - \frac{1+\alpha}{2} = 0$. A value of | *d* | ≤ 0.10 was considered acceptable because the asymptotic parameters are evaluated on a finite time series [16]. In summary, the following three conditions must be satisfied to conclude the presence of LRA with a high level of confidence [16]:

- 0.5<*H*<1
- *α* is significantly different from 0 and lower than 1
- | *d* | ≤ 0.10

Randomly shuffled surrogate data test

Further analyses are applied when *H* and *α* violate their asymptotic relationship under the hypothesis of a long-range auto-correlated process. In the present study, we used the randomly shuffled surrogate data test [101]. For each time series, 100 new series were generated from a random permutation of the original data. The only difference between the surrogate data sets and the original series is the sequential ordering of the data, while the first and second statistical moments remain identical (series mean and variance). *H* and *α* are then calculated for each new series, and the mean and *SD* of these 100 new scaling exponents are computed and compared with the exponents of the original time series. Note that normality of both original and newly generated time series was checked using a Kolmogorov-Smirnov test, which allowed to apply parametric statistics in our study. The number of standard deviations (*σ*) between the original scaling exponent and the mean scaling exponent of the surrogate data sets is computed (σ_H for the Hurst exponent and σ_α for the α exponent). If *σ* ≥ 2, then the difference between the original and surrogate series is considered statistically significant at the level *P*<0.05, which suggest the presence of a specific temporal structure in original time series. It is important to observe that this method does not prove the presence of LRA in the original time series. Instead, it is used to reject the null hypothesis that the series under

investigation has no temporal structure, thereby proving the presence of a non-zero autocorrelation function in the process [16].

Model selection

The linear relationship of the log-log representation of the data is interpreted as the signature of scaling properties in the series [201] . However it is important to keep in mind that although the linear regression may be significant, these models may not always be the best ones for describing the nature of the underlying phenomenon. Model selection can be considered to address whether the assumption of scaling properties in the data is relevant, or at least parsimonious given the sample under investigation. Model selection consists in comparing the performance of distinct models, and selecting the model that achieves the best compromise between accuracy (through the likelihood function) and parsimony by penalizing the number of parameters in the model [201]. Bayesian Information Criteria (BIC) a commonly used information criteria which is defined as:

$$\mathrm{BIC} = -2\ln\mathcal{L}_{\max} + K\ln M$$

where K represents the number of parameters of the model under study, M the size of data, and $\mathcal{L}_{\max}$ denotes the maximum value of the likelihood function $\mathcal{L}$, which quantifies the goodness-of-fit [201]. This method approximates the density function of the mean squared fluctuations per interval to estimate the maximum likelihood function rather than averaging these mean squared fluctuations over consecutive intervals like in DFA [201]. In our study, the selection was performed following the description of Ton and Daffertshofer [201]. Following this reference, the linear model was first compared to polynomials up to third order, to piecewise linear models, and to stochastic processes known to generate series with long-range autocorrelations. See the original work by Ton and Daffertshofer for more details about these models [201].

Statistical analysis

The effect of the series length on *H* and *α* exponents, as well as the algorithm (original and evenly-spaced) influence on the same parameters, was examined using one-way analyses of variance (ANOVA). Specifically,

Kruskal-Wallis one-way ANOVAs were performed given that normal distribution (Shapiro-Wilk test) and/or homogeneity of variance (Brown-Forsythe test) was not respected. To further investigate the series length influence and potential benefits of the use of evenly spaced methods on LRA assessement, pairwise multiple comparisons (Tukey Test) were used. Regarding the sensitivity, a paired *t*-test was performed for each comparison between conditions, for each number of data points and for each algorithm to determine if the initial observations persisted with a shorter series. The level of statistical significance was set at a *p*-value ≤ 0.05. For all statistical analyses, SigmaStat 3.5 software was used.

RESULTS

We first present the influence of the series length and algorithm on the statistical precision of the estimates of the scaling exponents. The following section then presents the results of the sensitivity analysis performed across experimental conditions. Finally we end the section by presenting the results of the model selection criterion applied to all time series.

Statistical precision

We computed the Hurst and α exponents for each series length and for every algorithm. A significant effect of the series length was found for the values of *H* and α while a significant effect of the algorithms was highlighted only for the *H* exponent, computed from both RRA and DFA (Figure 1 and Tables 1-2). An overall slight decrease of the exponents' values was observed with the shortening of the series length. However, the *H* exponents (from both RRA and DFA) yielded higher values than the theoretical upper bound of 1 with the application of the original algorithms on series length of 256 data points. Interestingly, such increase seems to be avoided with the use of evenly spaced algorithms (Figure 1).

Also, variability of estimates increased (i.e. higher SD values) as series length decreased to yield values higher than 0.1 for the shortest series (i.e. 128 and 64 data points; Figure 2), regardless of the algorithm considered. However, a similar level of variability was maintained by the use of the evenly spaced DFA on series length of 512 and 256 data points

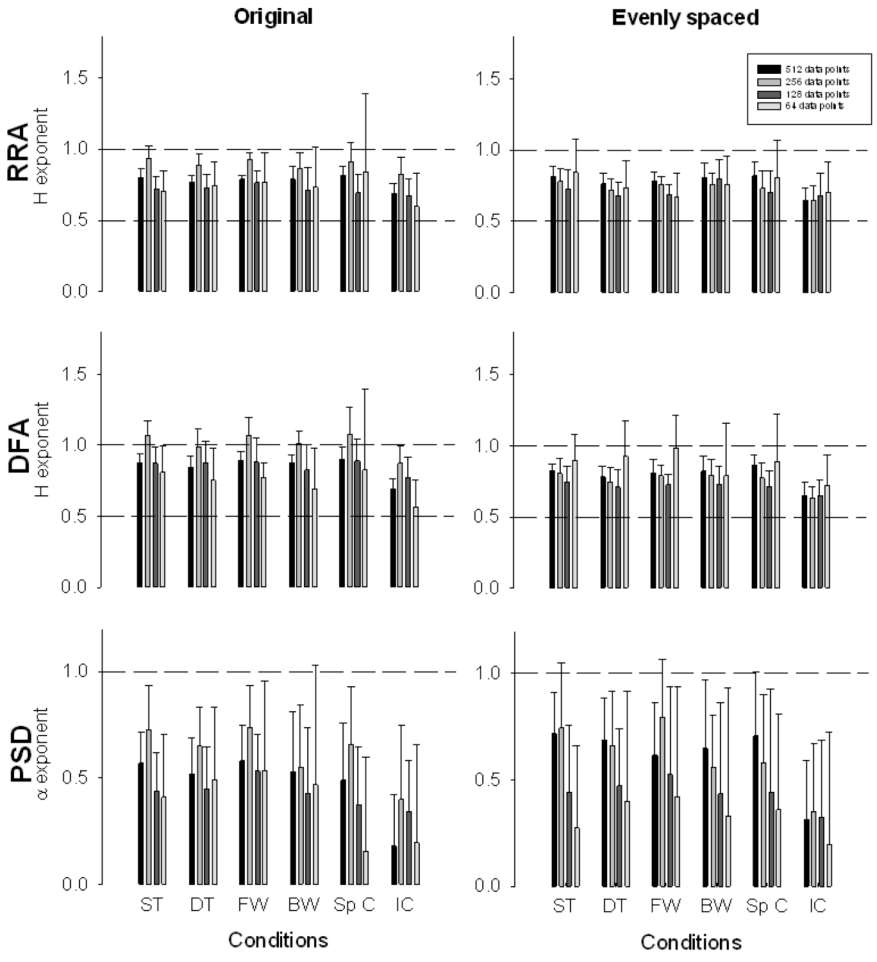

Figure 1. Mean and SD of Hurst exponent (computed from RRA and DFA) and α exponent for each condition, each number of data points and both algorithms. Dashed lines represent the reference values of all parameters.

Table 1. Descriptive statistics

N=94	Algorithm	Series length							
		512		256		128		64	
		Median	IQR	Median	IQR	Median	IQR	Median	IQR
RRA (H)	O	0.81	0.76-0.87	0.90	0.82-0.95	0.71	0.65-0.77	0.72	0.56-0.85
	E	0.79	0.70-0.84	0.72	0.66-0.81	0.71	0.62-0.80	0.76	0.59-0.88
DFA (H)	O	0.85	0.79-0.91	1.01	0.91-1.12	0.84	0.73-0.96	0.78	0.56-0.91
	E	0.80	0.73-0.86	0.75	0.68-0.83	0.71	0.63-0.78	0.90	0.69-1.03
PSD (α)	O	0.55	0.39-0.70	0.63	0.46-0.80	0.41	0.30-0.54	0.72	0.56-0.85
	E	0.64	0.45-0.80	0.62	0.43-0.81	0.46	0.18-0.64	0.35	0.01-0.62
d (H from RRA)	O	0.02	0.00-0.08	0.07	0.00-0.13	0.01	0.00-0.01	0.01	0.00-0.01
	E	0.08	0.04-0.12	0.12	0.07-0.19	0.10	0.04-0.17	0.18	0.07-0.31
d (H from DFA)	O	0.06	0.00-0.14	0.22	0.11-0.29	0.01	0.00-0.05	0.01	0.00-0.01
	E	0.12	0.05-0.17	0.17	0.09-0.26	0.17	0.11-0.26	0.24	0.13-0.38
σH (RRA)	O	4.51	3.19-5.90	2.08	1.09-3.13	7.21	6.41-8.30	9.41	8.71-9.78
	E	4.95	3.04-6.13	2.60	1.47-3.70	1.76	0.87-2.91	0.57	0.30-1.01
σH (DFA)	O	5.47	4.35-6.86	3.11	1.57-4.79	5.88	5.12-7.05	7.73	7.46-8.31
	E	5.58	4.04-6.71	3.75	2.89-5.00	2.58	1.82-3.27	1.15	0.59-1.67
σα (PSD)	O	9.51	6.76-12.23	7.20	4.54-9.57	2.36	1.45-3.66	1.86	0.72-2.69
	E	4.06	2.43-5.61	3.06	1.75-4.34	1.46	0.84-2.29	1.21	0.59-1.83

RRA=Rescaled Range Analysis ; DFA=Detrended Fluctuation Analysis ; PSD=Power Spectral Density ; O=Original algorithm ; E=Evenly-spaced algorithm ; IQR Interquartile range

Table 2. Statistical results

	K-W One-Way ANOVA						Multiple comparison		
	Algorithm effect			Series length effect			512 O – 512 E	512 O – 256 O	512 E – 256 E
	X^2	df	*p*	X^2	df	*p*			
RRA	18.34	1	**≤0.001**	66.34	3	**≤0.001**	*p=0.*408	***p*=0.002**	*p*=0.312
DFA	56.81	1	**≤0.001**	31.70	3	**≤0.001**	*p*=0.114	***p*<0.001**	*p*=0.739
PSD	0.613	1	0.434	74.28	3	**≤0.001**	*p*=0.444	*p*=0.488	*p*=1.000

RRA=Rescaled Range Analysis ; DFA=Detrended Fluctuation Analysis ; PSD=Power Spectral Density ; X^2=Chi-squared test ; df =degree of freedom ; O=Original algorithm ; E=Evenly-spaced algorithm

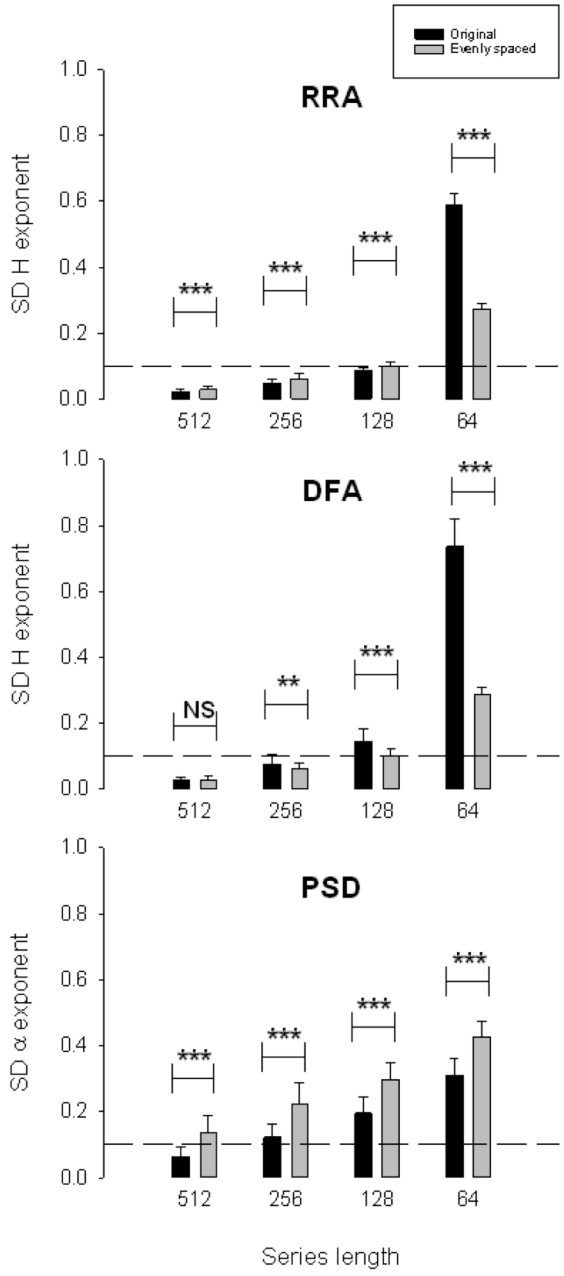

Figure 2. Variability over all conditions in estimation of scaling exponents for each series length and for both algorithms. Dashed lines represent the upper limit. ** p<0.01; *** p<0.001; ns: non significant difference.

while the variability was significantly higher with the evenly spaced RRA and PSD algorithms. Taking all of these results into account, it seems that the precision was not preserved with series of 128 data points or shorter.

Pairwise multiple comparisons (Tukey Test) were performed to gain better insight into the influence and potential benefits of the use of evenly spaced methods. Only comparisons between 512 and 256 data points are displayed in Table 2 since the statistical precision seems unacceptable for the shortest series length. No significant difference was observed between the original and evenly spaced methods in series length of 512 data points while the influence of the series length differ between both algorithms. By applying evenly spaced methods, statistical precision was preserved in series of 256 data points.

We then analysed whether the values of *H* and *α* were consistent with each other through the value of the parameter *d* (see Methods). The average values of *d* computed across all conditions with series lengths of 256 and 512 data points and both algorithms are summarized in Table 1 and presented in Figure 3 A-B. Observe that this parameter appeared more variable with a series length of 256 data points than with 512 data points (Figure 3), showing that values of *d* were consistently closer to 0 for longer series (≥512 data points). By influencing differently the *H* and *α* exponents estimates, the evenly spaced method leads to an even more variable relation *d*, yielding to value higher than 0.1.

The randomly shuffled surrogate data test was applied to all time series with 256 and 512 data points (Table 1 and Figure 3C-E). Interestingly, this test revealed that only the time series of 512 data points assessed with both algorithms could be statistically distinguished from white noise. Across all conditions, the number of standard deviations between the original scaling exponent and the scaling exponent of the surrogate series (σ_H and σ_α) were on average clearly superior to 2 when a series of 512 data points was considered (Table 1), thus significantly distinct from the distribution of estimates obtained with the series having the same mean and standard deviation, but no temporal structure.

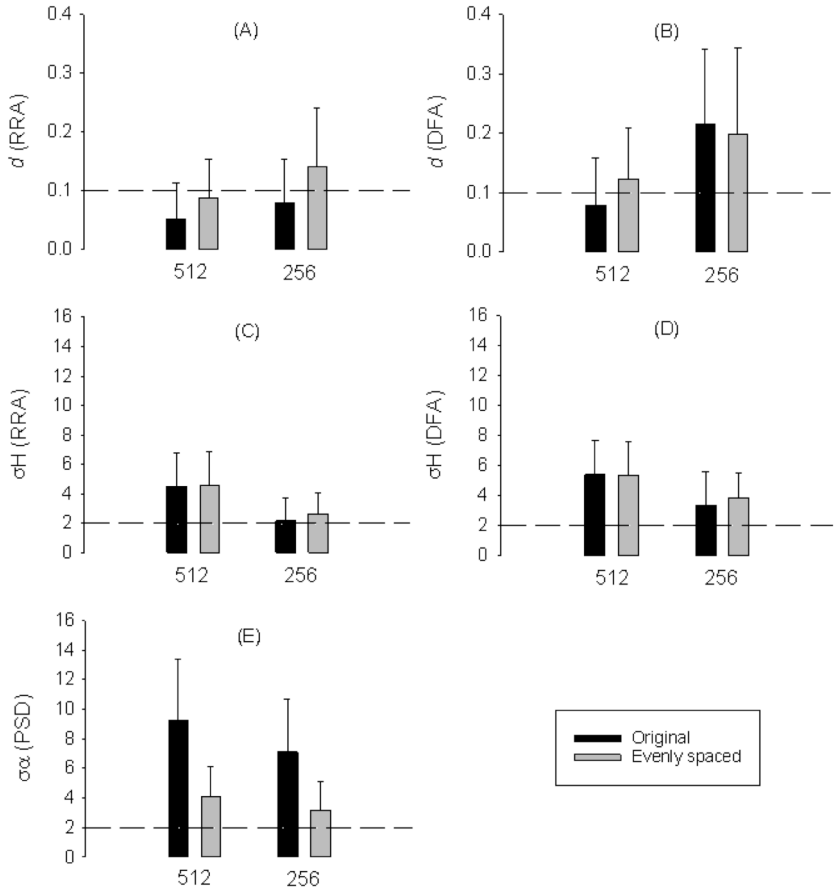

Figure 3. Mean and SD of *d*, *σ*H and *σ*α for each algorithm for series length of 256 and 512 data points. Value of d refers to the cross-validation method between H and α exponents (i.e. $d := H - \frac{1+\alpha}{2} < 0.1$) *σ*H and *σ*α are required when H, α or *d* criteria are not satisfied. *σ* refers to the number of deviation standard between original scaling exponent and the mean scaling exponent of the surrogate data sets. A value of *σ* ≥ 2 suggests the presence of a specific temporal structure in the original time series. Dashed lines represent the reference values of all parameters.

In contrast, the value of σ_H and σ_α when computed with 256 data points decreased to such extent that series of length 256 became more difficult to distinguish from white noise, in particular based on the Hurst exponent (H). Indeed we observed that ~50% and ~70% of the series did not exceed 2*σ* for *H* (respectively assessed with RRA and DFA), while ~90% exceeded 2*σ* for the α exponent (Figure 3) With the evenly spaced methods, σ_H remained similar to the original algorithm while the value of σ_α clearly decreased (~70%) with the evenly spaced method compared to the original algorithm.

Finally we investigated the impact of averaging the data between the evenly spaced points to assess whether this technique could improve the results (evenly spaced averaged, Almurad & Delignières [197]). Note that Almurad and Delignières reported that this technique had limited impact on the estimates of the scaling exponents. We tested this result in the context of the present paper on 20 randomly selected gait time series. Consistent with the results of Almurad and Delignières, we found that the values of H and α were statistically similar with or without averaging (direct comparisons of the slopes were performed with paired t-tests on series of 512 data points: $t_{(19)}<1.02$, $p>0.2$). In contrast, we observed that the confidence interval around the estimated slope decreased significantly with averaging (comparisons of confidence intervals: $t_{(19)}>2.7$, $p<0.015$). Thus, although the estimated exponents were stable, averaging may be preferred in cases where the conditioning of the fit must be improved.

Sensitivity

Mean *H* (±SD), mean α (±SD) and *p*-values for each comparison and for each number of data points assessed with both original and evenly spaced algorithms were reported in Table 3. The original comparison between spontaneous and imposed cadences in the cycling condition showed that the *H* and α exponents calculated with 512 data points presented with statistically significant differences. Such a difference could only be reproduced with 128 data points when the Hurst exponent was computed based on DFA. Regarding the comparison between forward and backward walking, as well as for the comparison between single and dual task, no significant differences were highlighted in the original studies using 512 data points. With a decreasing number of data points, the conclusions

Table 3. Mean and SD of Hurst and α exponents and *p*-values for each comparison for each number of data points and for both algorithms. Bold values indicate statistical significance.

Original algorithm

# data	Method	Backward vs Forward Walking				Simple Task vs Dual Task				Self-selected vs Imposed Cadence			
		FW	BW	p-value	Power	ST	DT	p-value	Power	SC	IC	p-value	Power
512	RRA	0,79 (±0,03)	0,79 (±0,09)	**0,801**	0,061	0,80 (±0,06)	0,77 (±0,05)	**0,076**	0,722	0,82 (±0,06)	0,69 (±0,07)	**≤0,001**	0,984
	DFA	0,89 (±0,06)	0,87 (±0,06)	**0,412**	0,200	0,88 (±0,06)	0,84 (±0,08)	**0,100**	0,376	0,90 (±0,08)	0,69 (±0,07)	**≤0,001**	1,000
	PSD	0,58 (±0,17)	0,53 (±0,28)	**0,348**	0,575	0,57 (±0,14)	0,52 (±0,17)	**0,155**	0,054	0,49 (±0,27)	0,18 (±0,24)	**≤0,001**	0,606
256	RRA	0,93 (±0,05)	0,87 (±0,11)	**0,065**	0,464	0, 94 (±0,08)	0,89 (±0,07)	**0,058**	0,483	0,91 (±0,13)	0,83 (±0,11)	**0,054**	0,498
	DFA	1,06 (±0,12)	1,01 (±0,08)	**0,122**	0,333	1,07 (±0,09)	0,99 (±0,12)	**0,022**	0,655	1,07 (±0,19)	0.87 (±0,12)	**0,002**	0,939
	PSD	0,73 (±0,20)	0,55 (±0,29)	**0,045**	0,542	0,72 (±0,20)	0,65 (±0,18)	**0,128**	0,328	0,65 (±0,27)	0,40 (±0,35)	**0,050**	0,512
128	RRA	0,76 (±0,08)	0,71 (±0,15)	**0,289**	0,175	0,72 (±0,09)	0 ,72 (±0,10)	**0,850**	0,054	0,70 (±0,08)	0,70 (±0,07)	**0,978**	0,050
	DFA	0,88 (±0,17)	0,82 (±0,18)	**0,324**	0,157	0,87 (±0,11)	0,87 (±0,15)	**0,973**	0,050	1,08 (±0,15)	0,90 (±0,08)	**≤0,001**	0,974
	PSD	0,53 (±0,17)	0,43 (±0,31)	**0,290**	0,174	0,44 (±0,18)	0,45 (±0,20)	**0,854**	0,054	0,49 (±0,31)	0,28 (±0,33)	**0,163**	0,278
64	RRA	0.77 (±0,21)	0.73 (±0,28)	**0.692**	0.066	0.70 (±0,14)	0.75 (±0,17)	**0.476**	0.106	0.84 (±0,55)	0.60 (±0,23)	**0.139**	0.309
	DFA	0.77 (±0,10)	0.69 (±0,28)	**0.301**	0.168	0.81 (±0,19)	0.75 (±0,23)	**0.346**	0.151	0.83 (±0,56)	0.57 (±0,20)	**0.148**	0.297
	PSD	0.54 (±0,42)	0.47 (±0,56)	**0.714**	0.064	0.41 (±0,29)	0.49 (±0,34)	**0.482**	0.105	0.16 (±0,44)	0.19 (±0,46)	**0.837**	0.054

Evenly spaced algorithm

# data	Method	Backward vs Forward Walking				Simple Task vs Dual Task				Self-selected vs Imposed Cadence			
		FW	BW	p-value	Power	ST	DT	p-value	Power	SC	IC	p-value	Power
512	RRA	0,79 (±0,06)	0,81 (±0,10)	**0,461**	0,108	0,81 (±0,07)	0,76 (±0,07)	**0,015**	0,723	0,80 (±0,13)	0,65 (±0,17)	**≤0,001**	0,951
	DFA	0,81 (±0,10)	0,82 (±0,10)	**0,414**	0,122	0,82 (±0,05)	0,78 (±0,07)	**0,025**	0,638	0,82 (±0,12)	0,65 (±0,17)	**≤0,001**	0,996
	PSD	0,62 (±0,24)	0,65 (±0,32)	**0,811**	0,056	0,72 (±0,19)	0,69 (±0,20)	**0,623**	0,076	0,71 (±0,27)	0,40 (±0,32)	**≤0,001**	0,964
256	RRA	0,76 (±0,06)	0,76 (±0,07)	**0,948**	0,050	0,78 (±0,08)	0,72 (±0,08)	**0,015**	0,720	0,73 (±0,13)	0,65 (±0,18)	**0,061**	0,473
	DFA	0,79 (±0,08)	0,79 (±0,11)	**0,863**	0,053	0,80 (±0,08)	0,74 (±0,07)	**0,042**	0,545	0,76 (±0,12)	0,64 (±0,17)	**0,002**	0,937
	PSD	0,79 (±0,27)	0,56 (±0,25)	**0,040**	0,564	0,74 (±0,30)	0,66 (±0,25)	**0,214**	0,231	0,61 (±0,29)	0,45 (±0,34)	**0,023**	0,648
128	RRA	0,69 (±0,07)	0,68 (±0,09)	**0,022**	0,683	0,72 (±0,14)	0,68 (±0,10)	**0,258**	0,302	0,71 (±0,15)	0,67 (±0,21)	**0,305**	0,170
	DFA	0,72 (±0,07)	0,68 (±0,03)	**0,921**	0,061	0,75 (±0,11)	0,71 (±0,12)	**0,339**	0,154	0,71 (±0,12)	0,65 (±0,18)	**0,097**	0,381
	PSD	0,52 (±0,41)	0,43 (±0,42)	**0,566**	0,138	0,44 (±0,31)	0,47 (±0,27)	**0,757**	0,060	0,51 (±0,44)	0,41 (±0,38)	**0,310**	0,168
64	RRA	0,67 (±0,16)	0,76 (±0,20)	**0,204**	0,353	0,84 (±0,23)	0,74 (±0,19)	**0,033**	0,588	0,78 (±0,24)	0,69 (±0,24)	**0,121**	0,338
	DFA	0,98 (±0,23)	0,79 (±0,37)	**0,102**	0,370	0,90 (±0,18)	0,92 (±0,25)	**0,704**	0,065	0,84 (±0,31)	0,71 (±0,24)	**0,041**	0,550
	PSD	0,42 (±0,51)	0,33 (±0,60)	**0,696**	0,066	0,27 (±0,38)	0,40 (±0,51)	**0,408**	0,127	0,45 (±0,42)	0,31 (±0,52)	**0,375**	0,139

remained similar as series length decreased. Interestingly, the use of evenly spaced algorithm led to similar conclusions but also revealed significant differences between single and dual tasks that were only suggested with the original algorithms (Table 3).

Model selection

Finally, we address whether the assumption of scaling properties was justified in light of the performance of alternative models, and using the Bayesian Information Criterion to select the best of several candidate models. The first four model candidates (i.e. the first, second and third order polynomials) were selected as describing the data regardless of series length. The linear model was selected for a majority of series (~50% of the total number of time series) series while the remaining 50% was spread over other models (with a maximum of 25% per model). Specifically, the second model was selected with a decreased frequency along with the series length (i.e. 26.6% with series length of 512 data points to 4% with series length of 64 data points). Conversely, the fourth model was increasingly selected with the series length (i.e. 23.4% to 44.7% for series length of 512 and 64 data points, respectively).

Altogether, our results highlight that statistical precision and sensitivity of LRA assessment need series length of 512 data points assessed using an integrated approach combining original algorithms or 256 data points when the DFA evenly-spaced algorithm is individually applied. Finally, the scaling model (i.e. linear regression on a logarithmic scale) was selected for most of the time series, regardless of the series length, showing that the assumption of scaling properties in the processes explained more variance at minimum cost in the sense of degrees of freedom in the model than other candidate models.

DISCUSSION

Assessing the presence of long-range autocorrelation is a potentially important tool for characterizing series such as gait in fundamental or applied research. An important question is to determine how long the time series experimentally acquired should be to estimate the series autocorrelation function reliably. Our results emphasize a clear effect

of the series length on the statistical precision and the sensitivity of scaling exponents associated with the presence of long-range autocorrelation (H and α). By considering distinct methods for assessing the presence of LRA (RRA, DFA or PSD), and using robust conditioning based on evenly spaced technique, we found that some but not all properties extracted from series of 512 data points were preserved with series of 256 points. More precisely, the use of evenly spaced regressions appeared necessary to compensate for the loss of accuracy associated with series of 256 points, yielding overall similar conclusions as the original analysis. Finally, although there probably cannot be a firm lower bound on the series length, it seems that series shorter or equal to 128 data points in length do not allow a reliable extraction of scaling exponents that characterize long-range auto-correlation functions. Observe that we adopted a conservative approach, as the series shorter than 512 were averaged across the distinct subseries (2 series of 256, 4 series of 128, etc). Indeed, by averaging N sessions of length 512/N, we reduced the variability of these shorter series and the reduction in precision or accuracy is thus more difficult to highlight (by an increased type II risk of error) in comparison with a random selection of subseries from the original series.

Besides the series length, we also addressed whether the statistical model based on a regression of the data in logarithmic scale was a good model based on Bayesian Information Criterion. We found that this model was indeed selected in a majority of cases, which support its use for assessing scaling properties. Intuitively, BIC favors models that explain the data well (through the log-likelihood term), and penalize those that use too many parameters. Clearly, polynomial models may do a better job at explaining the data, however these models typically use more parameters (up to 4 for polynomials of the 3rd order), while the linear regression only uses 2 (slope and intercept). Thus the selection of the linear model indicates that it does a very good job considering that it explains much of the variance with parsimony.

The series length significantly affects the statistical precision and the sensitivity of scaling exponents, such that the approach based on cross-validating the Hurst exponent and the power spectral density seems not applicable with series lengths of 64 and 128 data points. Intuitively, the reason is that such series are too short to be statistically distinct from short-

range correlated processes ($\beta > 1$ in Eqn. 1). This was further observed when the estimates of *H* and α exponents computed on randomly shuffled surrogates were not statistically distinct from those of the original series.

With the application of the original algorithms on series length of 256 data points, the *H* exponent, computed from both RRA and DFA, yielded higher values than the upper value of 1 while the α exponent remained inferior to 1. However, the *H* exponent cannot theoretically be greater than 1, so our observation that the value of *H* becomes greater than 1 (see Figure 1) may reflect the fact that such series tend to violate the hypothesis of a stationary underlying process [112].

Interestingly, such increase seems to be avoided with the use of evenly-spaced algorithms, showing the importance of this approach when working with relatively short series (~256 in length). So, evenly spaced methods seem able to reduce the series length effect on scaling estimates in physiological time series as recently demonstrated by Almurad and Delignières on generated time series [197]. Also, statistical and non-statistical differences initially observed with original algorithms persisted with series length of 256 data points when evenly spaced DFA is individually applied.

However, since misleading conclusions related to the investigation of long memory processes cannot be avoided by the individual application of such methods, integrated approaches should be thus considered [16,80]. Agreement between the *H* and α exponents (i.e., low values of $|d|$) was verified at 512 data points while $|d|$ was consistently higher when the series contained 256 data points, especially with the evenly spaced algorithms (Table 1).

Considering this apparent inconsistency between the *H* and α exponents with 256 data points, an additional analysis was strongly encouraged to confirm (or reject) the presence of a specific temporal structure. Following the randomly shuffled surrogate data tests, no temporal organization could be highlighted with 256 data points, with the exception of the evenly-spaced DFA algorithm. When series of 256 data points are considered, *H* exponents computed on randomly shuffled surrogates were statistically distinct ($\sigma_H > 2$) from those of the original series only with the evenly-spaced DFA method, in comparison with the RRA (Figure 3). The

DFA evenly-spaced algorithm individually applied could thus constitute an alternative when short series length is necessary (~256 data points), with the precaution needed regarding individual application of mathematical methods. Otherwise, the use of series length of 512 data points in locomotion constitutes a good compromise between the requirements of mathematical analyses and experimental constraints. Note that our study does not aim to investigate absolute accuracy but the reproduction of results obtained with series length of 512 data points, for which we have the best precision in principle. Thus, our study does not conclude anything about the accuracy of LRA estimates assessed with 512 data points.

The physiological time series analysed in the present study extend previous conclusions arisen from generated time series [16,112]. Unlike generated time series have fully known statistical properties, experimental series have unknown autocorrelation function and may also be contaminated by noise. Choosing the best method to accurately and reliably assess the presence of LRA is not an easy question. The strengths and weaknesses of each methods, and the experimental context of the research must be carefully considered [16,112]. For instance, the stationarity or the non-stationarity of the time series and specific experimental goals (e.g. means comparisons of experimental groups or accurate estimation of the scaling exponents) will guided the choice [112,202–204].

Our study is clearly motivated by the potential benefits of assessing pathological walking patterns based on their autocorrelation function. We recently demonstrated that LRA are related to degree of functional impairment in Parkinson's disease, suggesting that LRA may be regarded as an objective and quantitative measure of gait stability in people with Parkinson's disease for both clinical practice and research (Warlop et al., 2016). Importantly our previous study showed that the decay of scaling parameters (*H* and α exponents) with the clinical assessment was not redundant with other metrics such as age or walking speed [13,21]. It thus seems to capture fundamental structure in the gait pattern that constitutes a complementary assessment tool. Ideally, LRA should be assessed in the earliest stages of a locomotor disorder, when the balance disorder is not yet clinically evident and the patient is still functionally independent, in order to efficiently monitor fall risk in these populations [13]. Observe that 512 gait cycles can be collected in approximately 10 minutes of walking in healthy

adults. Thus it is easily applicable to patients with moderate impairments and we expect that future work further investigate whether LRA can constitute a precautious marker of impaired locomotion. As well, robust conditioning of the data based on evenly-spaced regressions may render LRA also applicable to series of 256 data points, which extends their applicability to patients having more severe gait disorders, and potentially evaluate the therapeutic efficacy of interventions initiated in this population where the fall risk is already present.

In conclusion, the present study suggests that the robust assessment of LRA requires 512 data points to derive reliable estimates of the scaling exponents but series length of 256 data points could be used as an alternative, provided that robust conditioning such as evenly spaced regressions are used. We expect that these results provide an important guideline for future research, and in particular for developing complementary assessment of clinical gait as a marker of dysfunction in the nervous system.

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General discussion

GENERAL DISCUSSION

Metrics capturing the nature of gait variability, through long-range autocorrelations (LRA) assessment, formed the core analysis of this thesis. Going beyond metrics of steady-state performance, LRA captures the temporal organization of gait variability, reflects the physiological state, and possibly constitutes a gait stability index. Considering the definition of gait stability as the ability to maintain functional locomotion despite the presence of external disturbances (e.g. environment) or internal control errors (e.g. pathology), this thesis aimed to investigate the possible origin of LRA by influencing the gait complexity with internal and/or external factors disrupting LRA. Additionally, this thesis aimed to investigate the potential clinical utility of gait variability as an objective and quantitative assessment of gait stability in Parkinson's disease (PD) and, secondarily, as a clinical tool for evaluating the therapeutic efficacy of rehabilitation approaches in a population of patients suffering from PD.

Although the presence of LRA has been demonstrated in a variety of human motor behavior including stride time durations in walking or running, their neurophysiological origin remains still elusive [17,37,205]. Biomechanically or centrally mediated processes were proposed [24,47,107]. However, the important question of which aspects of bipedal locomotion are passively controlled by biomechanical properties of the body and which aspects are actively controlled by the nervous system remains still open.

The development of passive dynamic bipedal models suggested that variations could simply result from the biomechanical structure of the system, without requiring the intervention of central neural networks [27,29,31]. In this perspective, the nervous system takes advantage the motor redundancy to select a desired locomotive pattern from among the infinite number of behaviors naturally present in the locomotor system. The role of spinal located neural networks, commonly known as Central Pattern Generator (CPG), has also reported as independently ensuring the limb coordination during gait [19]. However, efficient, stable and adaptable locomotor pattern requires complex dynamic sensorimotor interactions depending on highly complex processes including efferent-type (from the motor cortex, the cerebellum, the basal ganglia and central pattern

generator) and afferent-type information coming from different peripheral feedbacks [105,106].

Rather than the involvement of a single structure, LRA could arise as an emergent property from interactions between the subsystems composing the complex locomotor system [206]. In this way, such specific neural network can be considered as a chain where each link treats the information in a specific way in order to produce a coordinated and adapted locomotor behavior. Therefore, external and internal factors interfering with one of these links could influence the emergence of LRA.

Thesis' main findings

To better elucidate the possible origin of LRA, the influence of external and/or internal factors of various natures on gait dynamics were investigated in the present thesis. Biomechanical and cognitive constraints respectively induced by backward walking and dual tasking did not affect the fluctuation dynamics of stride duration of healthy adults [15]. The robustness of LRA during backward walking likely indicates the role played by supraspinal networks in their mechanisms of control, whereas the steadiness of their characteristics during dual-tasking merely suggests that they stem from low-level processes of the central nervous system [15,78]. The persistence of similar LRA during backward walking and dual-tasking could thus suggest that they result from multi-level mechanisms of control, which would necessitate further investigation.

While our first study and other studies failed to modulate the LRA in walking, further investigation on the LRA control mechanisms was conducted on cycle ergometer. Because cycling is a rhythmic task with less movement amplitude and gravitational constraints than walking and because many biomechanical parameters are fixed (for example, cycle length corresponds to the pedal length), cycle ergometer pedaling was thought as a suitable tool to better characterize any alteration in the control mechanisms of LRA in the cycling pattern of healthy adults. A supraspinal influence on the modulation of LRA could be suggested by the breakdown of LRA highlighted during the constrained condition (i.e. imposed pedaling cadence) while the presence of LRA in cycling suggested that they are not specific to the biomechanics of cycling or gait [18]. Because the two pedaling

conditions (i.e. self-selected and imposed cadences) use the same peripheral pathways (lower motoneurons, effectors and feedback loops), the voluntary supraspinal influence appears indeed as the only one difference between both situations. Such finding provides additional argument to an integrated coordination of spinal mechanisms and supraspinal centers.

Specific supraspinal neural networks such as basal ganglia, prefrontal cortex or supplementary motor area are of prior importance for their role in timing, as well as in initiating and adapting the locomotor pattern to internal and external conditions [102,105]. Scaling and timing internal control required for automatic and rhythmical movements are impaired and archetypally linked to the basal ganglia dysfunction in Parkinson's disease (PD) [37,132]. Influence of internal factors on LRA generation was thus explored in patients suffering from PD.

From the specific temporal of view, the inability to produce a steady gait rhythm in PD was highlighted by the breakdown of LRA that could result from the defective activity among interacting subcomponents (e.g. basal ganglia) [13]. Interestingly, such a breakdown was also strongly correlated to the disease severity, in a similar way that was previously demonstrated by Hausdorff et al in people with Huntington's disease [34]. But, the most original finding was the demonstration of strong relationships among LRA, balance and functional status. Devoid of any subjectivity, LRA could thus yield not only an objective and quantitative insight about the temporal complexity of the gait, but also a clinical measure of gait stability in people with PD for clinical practice and research [13].

By potentially compensating the internal defective control in PD, the use of external simulations could act as an external cue, triggering intact circuits and bypassing the defective pallidocortical circuit [55,133,144]. External cues can facilitate the emergence and the maintenance of motor behavior in neurological conditions whereas it could perturb the gait complexity of healthy adults. Auditory and visual cues are the most studied among multiple cueing modalities [55,57,207]. However, tactile and proprioceptive cues have also demonstrated their usefulness in the struggle against the impaired gait automaticity in PD [133,137]. Using specially designed poles, Nordic Walking constitutes an emerging and promising rehabilitative

approach involving an intentional coordination between upper and lower limbs. In addition to help focus attention on walking, the use of Nordic poles indeed allows a more temporally organized behavior than with usual walking (i.e. without Nordic poles), which suggests a more effective and powerful coordination of subcomponents constituting the locomotor system [171].

Also, recognized as a task-oriented approach for gait rehabilitation in the PD population, treadmill training could act as an external pacemaker [174,175]. Treadmill seems indeed to afford the necessary framework to regulate gait rhythmicity in PD by inducing a more temporally organized and more regular gait pattern (Warlop et al., 2017 (in preparation)). Those observations support the hypothesis of a greater dependence to regulatory inputs as an explanatory factor of treadmill influence observed in PD. In addition, modulation of the temporal organization of gait variability with the two rehabilitative approaches could suggest some compensation or restoration of the interactions among multiple components altered in pathological conditions and involved in healthy gait pattern.

Reflexion about potential mechanisms of control

The healthy temporally organized gait pattern could result from both passive and active control by biomechanical properties of the body and the nervous system, respectively. From the biomechanical perspective, hip joint actuations could be one of the key explanative factors of our results [31]. Our studies conducted on treadmill did not highlight any differences in the temporal organization of the gait pattern of healthy young adults. Hip angle during backward walking is the time-reversed mirror images of the forward walking and the walking direction was the same between the simple and dual-task conditions [68,69]. Through stretch facilitation of hip flexors at the end of the stance phase, the belt of the treadmill induces hip extension during forward walking which may stimulate the spinal locomotor circuitry (CPG) [186,208,209]. Similarly to the hip torsional spring used in biomechanical models, hip joint actuations could be thus similar across the different walking conditions explaining alike regulation of the temporal organization of gait variability in healthy subjects.

Although an active control is suggested during dual-tasking and backward walking, the range of motor alternatives seems to remain sufficiently wide to allow the persistence of LRA despite external constraints imposed on the locomotor system. Pedaling conditions also required an active motor control. However, the selection of potential motor behavior was restricted by the biomechanical constraints of pedaling and even more when the pedaling cadence is imposed by the experimental instructions. The limited repertoire of motor behaviors resulting from both the biomechanical constraint of pedaling and the instructions could thus explain the easier alteration of LRA during cycling than in walking conditions.

Contrary to healthy population, Parkinson's disease is characterized by an internal defective pallidocortical circuitry. Neural system seems to be less effective to select a desired locomotor pattern from among the infinite number of behaviors naturally present in the locomotor system. In addition, rigidity of hip flexors is usually observed in PD patients. Those features could explain the randomness observed in the PD gait pattern. Conversely, the modulation of LRA during treadmill and Nordic walking could be allowed by a higher hip extension that possibly acting as an adequate sensory input to externally regulate the impaired gait pattern from a low-level process.

The entanglement of the biomechanical properties of the body and the nervous system reveals the complexity of the locomotor system in which the central nervous system constitutes one of the interacting elements without dictating one motor behavior. In this perspective, supraspinal structures are suggested to modulate the elementary motor behavior emerging from low-level structures.

Methodological considerations

Some methodological issues were also raised regarding the diverse protocols adopted. All changes observed in PD population walking on a treadmill arisen the first issue concerning adequate gait assessment in PD participants (Warlop et al., 2017 (in preparation)). As well as being an interesting rehabilitative approach in PD, treadmills are indeed usually implemented in laboratory settings to perform instrumented gait analysis.

Although no treadmill effect was demonstrated in healthy population walking at a confortable speed and individually determined [17,176], careful consideration of motorized-treadmill in gait variability assessment as well as spatio-temporal gait parameters (cadence and step length) should be recommended in gait analysis and usual clinical practice. Gait disorders resulting from the insufficiency of internal rhythm generation should be the most accurately depicted on overground given the higher propensity of PD population to be influenced by external rhythmical inputs.

The second issue concerned the determination of an adequate balance between the series length, which in the context of clinical application is limited by patients' ability to perform a task for a long time, and the minimum number of cycles necessary to obtain a reliable assessment of the series autocorrelation function. The issue of series length on its own continues to constitute a matter of debate. Series of 512 data points have been usually considered in both synthetic [112] and physiological time series [16]. However, methodological efforts are continuously made to improve the performance of the usual algorithms with even shorter series [119,197,198]. Recently, the use of evenly spaced methods yielded substantial improvement of non-linear mathematical method, such as the Detrended Fluctuation Analysis (DFA), with relatively short generated time series (i.e. 256 data points) [197]. On physiological signals, the same statement can be done. Reliable assessment of LRA should require 512 data points, or no shorter than 256 data points provided that more robust methods are considered such as the evenly-spaced algorithms. Interestingly, such series can be reasonably obtained in clinical populations with moderate, or even more severe, gait impairments and open the perspective to extend the use of LRA assessment as a marker of gait stability applicable to a broad range of locomotor disorders.

Finally, the integrated approach adopted in this thesis suggests a cross-validation between the RRA/DFA and the PSD to increase the level of confidence in our results. The firm determination of the LRA' presence in the time series analyzed requires that $0.5< H <1.0$ and $0< \alpha <1.0$. However, the optimal value remains to be determined. If, theoretically, an H value of 1.0 would be expected for healthy signals,[92] it is less well established for the α exponent. In experimental settings, however, H and α exponents yield a mean value of ~0.80 and ~0.5, respectively. According to the theoretical

model of optimal movement variability, *H* and *α* exponents should be indeed in the intermediate region between excessive order and excessive disorder to be flexible to the constraints imposed on the system [11].

Perspectives

As outlined in this study, the origin and mechanisms of control of LRA remain a matter of debate without any firm answer. Further investigations including biomechanical modifications should be performed. Adding weight to the legs or walking on a split-belt treadmill would provide additional observational about some biomechanical origin on LRA. Supraspinal influence on LRA generation could also be studied in cognitively impaired population while performing a pedaling task that inherently restrict the motor behavior alternatives present in the locomotor system.

The growing interest of gait variability in neurological disorders (Parkinson's disease, Huntington's disease, multiple sclerosis or Alzheimer disease) was recently synthesized by Moon et al. [210]. Importantly, this meta-analysis emphasized the ability of gait variability measures to discriminate the pathological conditions from healthy controls, as well as the distinctive neurological conditions among each other [210].

Assessments of gait stability and intervention's therapeutic efficacy could constitute a potential application of the present findings. Using a wearable and inexpensive device (e.g. accelerometer or inertial measurement unit), both the magnitude and the temporal organization of gait variability could be routinely assessed simultaneously with spatiotemporal parameters (e.g. gait speed, cadence or step length) and provide an objective and quantitative clinical measure of gait stability for clinical practice and research.

Interestingly, in addition to such assessments, the current smartphones are also able to detect gait disorders, such as freezing of gait epochs, and to release suitable cues to overcome those events [118,127,211]. Although some studies investigating the influence of different cues on gait dynamics were recently conducted, the type of cues and the specific

parameters to set remains to be determined.

Although LRA assessment seems to be a promising tool to quantify the gait stability, their clinical utility remains to determine. Our results do not seem to constitute an early biomarker of the emergence of Parkinson's disease. Slightly impaired PD patients did not seem to present a significantly different temporal organization of their gait pattern compared to healthy age-matched population. However, longitudinal studies conducted on large population and screened over the long-term should be performed to better determine its utility as diagnostic tool. In addition, their ability to discriminate patients who are prone to fall should be also further studied. Maybe as a provocative test, more challenging studies (e.g. walking on a slippery surface, or moving surfaces) could also be conducted in the future. The study of center of pressure displacements in upright position and constrained by fall-prone paradigm could also be performed possibly allowing assessment of an even wider disease spectrum.

However, observational studies of this thesis offer reasonable basis to conduct a randomized controlled trial to fully appreciate the ability of gait variability assessment in evaluating the therapeutic efficacy of a specific intervention. We are currently performing a pilot RCT on 30 PD patients. This study consists of a randomized, controlled, single-blind study evaluating the effects of a 3 months physical activity program. The control group did not modify their usual physical activity level while the intervention group benefited from the exercise program. Medication was optimized before the study and remained unchanged during the study for both groups. Randomization was performed to obtain similar groups for disease severity (Hoehn & Yahr scale). The evaluator was not informed of the patient's allocation and was thus blind. The exercise program consists of 25 sessions of 60 minutes over three months. The major aim of the study is to conduct a randomized, controlled, single-blind clinical trial to assess the effect of exercise programs on gait variability measures and to further investigate possible relationships with neurological and gait improvements. We hypothesize that the gait variability assessment could be a clinical tool for assessing the therapeutic efficacy of exercise in a population of patients suffering from Parkinson's disease. The originality of the study lies on the clinical potential of gait variability as an objective and quantitative measure of gait stability.

In a broader view, variability measures were also recently suggested as an objective measure of the structural changes in artworks over an artist's lifetime. And more interestingly, painters suffering from neurodegenerative diseases such as Parkinson's (e.g. Dali or Morrisseau) and Alzheimer's disease (e.g. de Kooning or Brooks) could be diagnosed with their brush strokes. Forsythe et al. indeed demonstrated that the fractal dimension of the paintings could differentiate artists who suffered from neurological deterioration from those of healthy aging controls (e.g. Picasso, Monet or Chagall) [212]. Similarly to the writing of authors or the speeches of politicians (e.g. Ronald Reagan), this study highlights the potential of changes in the structure of paintings as an early indicator of neurological disease, years before the diagnosis. Together with our results, such finding open new vistas of application of nonlinear analysis of variability and maybe as a marker of disease progression.

Le visage de la guerre ;

Salvador Dali (1940)

Conclusion

In sum, the complexity of human walking refers to the multi-level mechanisms of control needed to safely and adaptively walk. Despite its automatic nature, gait requires the continuous integration of information from the central and peripheral nervous systems to produce a stable pattern. Gait stability is indeed allowed by an optimal level of gait variability emerging from such dynamic sensorimotor interactions that are coordinated into a self-organized motor behavior [9,11]. This thesis strongly contributes to

support the entanglement of both biomechanical properties of the human body and the nervous system in LRA generation as well as their potential utility in both clinical research and practice. While this thesis provide additional argument for an integrated coordination of spinal mechanisms and supraspinal centers, further investigation are needed to better determine the LRA's clinical usefulness in rehabilitation and in the wider human body perspective. The recent consideration of non-linear analysis of variability gives rise to new way of thinking about variability, adaptability, health and motor rehabilitation.

Long-range autocorrelations express the subtle compromise between ordered and disordered behavior needed to be both stable and adaptive…

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