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Full Length Article

Benefits of nonlinear analysis indices of walking stride interval in the evaluation of neurodegenerative diseases

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ABSTRACT

Indices characterising the long-range temporal structure of walking stride interval (SI) variability such as Hurst exponent (H) and fractal dimension (D) may be used in addition to indices measuring the amount of variability like the coefficient of variation (CV). We assess the added value of the former indices in a clinical neurological context. Our aim is to demonstrate that they provide a clinical significance in aging and in frequent neurodegenerative diseases such as Parkinson's disease, Huntington, and amyotrophic lateral sclerosis.

Indices assessing the temporal structure of variability are mainly dependent on SI time series length and algorithms used, making quantitative comparisons between different studies difficult or even impossible. Here, we recompute these indices from available SI time series, either from our lab or from online databases. More precisely, we recompute CV, H, and D in a unified way. The average SI is also added to the measured parameters.

We confirm that variability indices are relevant indicators of aging process and neurodegenerative diseases. While CV is sensitive to aging process and pathology, it does not discriminate between specific neurodegenerative diseases. H, which measures predictability of SI, significantly decreases with age but increases in patients suffering from amyotrophic lateral sclerosis. D, catching complexity of SI, is correlated with total functional capacity in patients with Huntington's disease.

We conclude that the computation of H complements the clinical diagnosis of walking in patients with neurodegenerative diseases and we recommend it as a relevant supplement to classical CV or averaged SI. Since H and D indices did not lead to the same observations, suggesting the multi-fractal nature of SI dynamics, we recommend to open clinical gait analysis to the evaluation of more parameters.

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1. Introduction

Since the seminal work of Graham Brown (1911) on how rhythmic locomotor behaviors are controlled in mammals, research along this line has continued to expand and is now a priority topic in disciplines as diverse as physiology, neurosciences and biomechanics. Natural – even automatic – processes are always accompanied with some randomness. More recently, the investigation of the variability of those behaviors has revealed, on the one hand, significant highlights suggestive of underlying mechanisms of control and, on the other hand, general lessons on motor variability: "More variable does not mean more random, and more controllable does not mean more deterministic" (Riley & Turvey, 2002).

Walking is an harmoniously coordinated behavior that relies mainly on the neuro-musculoskeletal system. For Bernstein (1967), this system plays a key role in imposing degrees of constraint to organize the many degrees of freedom that affect locomotor task performance. Reducing the degrees of freedom is crucial to favor locomotor behavior that is context-appropriate (Van Orden, 2010). For more than 20 years, researchers have been interested in the long-term structure of human walking, and more particularly in the variability of stride interval (SI). Though human walking is highly stereotyped, the SI fluctuates from one stride to the next around an average value with a peculiar statistical variability. It appears that the long-term SI pattern, during a walk for about ten minutes, is auto-correlated: the temporal characteristics of a step are strongly dependent on the temporal characteristics of the previous steps (Hausdorff et al., 1997; Hausdorff, Peng, Ladin, Wei, & Goldberger, 1995).

During the 1990s, Hausdorff and his collaborators (Hausdorff et al., 1995; Hausdorff et al., 1997) proposed a framework for analyzing temporal dynamics of walking SI over a consistent number of strides (above 500) which has since been successfully used in different physiological contexts such as performing a dual task during walking (Bollens, Crevecoeur, Detrembleur, Warlop, & Lejeune, 2014; Dierick, Buisseret, Renson, & Luta, 2020) or or studying aging process during walking (Goldberger et al., 2002; Hausdorff et al., 1997; Hausdorff, Zemany, Peng, & Goldberger, 1999). A decade later, from centre of pressure excursion measures of two case studies in sitting (child with cerebral palsy) and standing (adult with cerebral concussion) postures, Stergiou, Harbourne, and Cavanaugh (2006) proposed the theory of optimal movement variability to explain variability from its complexity and predictability. The main strength of this theory is that it can be used in a clinical context because movement variability can be directly related to abnormal motor development or unhealthy states. More recently, this theory was generalized into a theory of complex adaptive behavior that expects to reveal behavioral robustness (periodicity) and flexibility (adaptability) of system organization (Harrison & Stergiou, 2015).

In clinical gait analysis, information about the variability of SI is easily provided by tools that quantify the amount of SI variability like the coefficient of variation (CV). Nonlinear analysis methods go one step beyond by assessing its temporal organization in terms of complexity and predictability (Dierick, Nivard, White, & Buisseret, 2017; Stergiou et al., 2006). It is challenging to diagnose neurodegeneration at an early stage. Yet, it is also critical since the sooner an impairment is identified, the larger the likelihood of efficient intervention. In view of the existing evidences and that the presence of long-range temporal correlations in walking SI reflect optimal variability (Stergiou & Decker, 2011) and optimal coordination of degrees of freedom across the individual and the task environment (Van Orden, 2010), we believe that the assessment of these complementary nonlinear variability indices of SI could reveal as powerful metric candidates for use in clinical practice (Cavanaugh, Kelty-Stephen, & Stergiou, 2017).

The mathematical tools preferably used to assess the long-range temporal structure of a time series' variability belong to nonlinear analysis (Kantz & Schreiber, 1997), of which fractal analysis is a part. The factor that has been mostly used up to now is the Hurst's exponent (H or α), originally developed in the field of hydrology (Hurst, 1951). This index, usually obtained by a detrended fluctuation analysis (DFA), assesses the predictability of SI time series. Put differently, it assesses whether its dynamics is autocorrelated or random. In neurodegenerative diseases, DFA has been applied mainly in Parkinson's disease (Bartsch et al., 2007; Dotov et al., 2017; Frenkel-Toledo et al., 2005; Hausdorff, 2009; Marmelat, Reynolds, & Hellman, 2018; Ota, Uchitomi, Ichiro Ogawa, Orimo, & Miyake, Y., 2014; Warlop et al., 2016; Warlop, Detrembleur, Stoquart, Lejeune, & Jeanjean, 2018), and to a very limited extent in Huntington's disease (Hausdorff et al., 1997) and amyotrophic lateral sclerosis (Hausdorff et al., 2000).

The computation of the Minkowski's fractal dimension (D) has also been applied to SI time series and proved to be a reliable estimator of complexity over time, see *e.g.* Dierick et al. (2017). Where do the autocorrelations find its origins in the walking cycle? What are the hidden physiological mechanisms that drive behaviors? Clues or answers to these fundamental questions could be provided by genuine analyses of indices such as H or D. However, the calculation methods used in the aforementioned studies lack homogeneity mainly in terms of the different algorithms used, which can lead to biases in their interpretation, and making quantitative comparisons between different studies unreliable.

There is therefore a necessity to process and analyse all available data recorded in different studies by adopting a unified protocol. Our aim is to assess the influence of aging in healthy subjects and of common neurodegenerative diseases – Parkinson's and Huntington's diseases and amyotrophic lateral sclerosis – on SI variability indices uniform throughout measurements, using either time series recorded in our lab, available in online databases or provided by the authors of previous research. The two main questions that will be addressed in this research work are the following. First, are walking SI variability indices able to differentiate healthy subjects from patients, or even better provide information about the neurodegenerative disease involved and its progress? The current literature already suggests an affirmative answer to this question in the case of Parkinson's (Hausdorff, 2009; Warlop et al., 2016) and Huntington's (Hausdorff et al., 1997) diseases but only for the computation of H. However, D of SI time series still needs to be explored in these neurodegenerative diseases. Concomitant analysis of CV, H, and D is now required in different neurodegenerative pathologies and healthy subjects in order to understand the clinical significance of the variability indices, assessing either the amount or the temporal structure of SI variabilty. Second, is a clinical use of the walking SI variability indices possible, specifically in terms of complexity and predictability of movement variability? It has already been suggested that "healthy" biological systems are characterized by an optimal variability, observable through physiological signals, be it electrocardiogram (Goldberger et al., 2002) or more

generic time series coming from motion analysis (Stergiou & Decker, 2011). Along the lines of that framework we focus on the peculiar case of SI time series, with the hypothesis that any departure from an optimal variability defined by the behavior of healthy individuals may reveal a possible dysfunction to be identified.

Our present work goes along the lines of Ravi et al. (2020). This very recent systematic review coupled with a meta-analysis, proposes guidelines for a relevant measure of SI and optimal thresholds for Hurst's exponent. It is found that 0.86 [0.76, 0.96] and 0.82 [0.72, 0.92] discriminate age- and Parkinson's disease-related influences on SI's variability (Ravi et al., 2020). The bounds of the intervals correspond to ±2 standard deviations. We provide further evidences of the clinical relevance of indices assessing temporal structure of SI variability: Not only H but also D are computed. Also, we study other pathologies than Parkinson's disease: amyotrophic lateral sclerosis and Huntington's disease are included too. Finally, we correlate the indices with clinical disability scales in Parkinson's and Huntington's diseases.

2. Methods

2.1. Time series and variability assessment

SI time series of lengths between 116 and 957 gait cycles (Table 1) were measured in individuals walking at self-selected pace. Table 1 presents a summary of the data we have gathered. We refer the interested reader to the cited references for more details about the experiments in which these time series were first obtained. Fig. 1 depicts typical SI time series. One can readily observe that each time series fluctuates around an average value, and that the dynamics of these fluctuations is nontrivial. These dynamics are assessed by resorting to the methodology developed in Dierick et al. (2017), that we summarize below.

Our data set consists in SI time series, denoted as $\boldsymbol{T}$ and containing the durations T_i of the successive cycles. The time series gathered are of variable length, in particular because of the small walking speed of patients suffering from neurodegenerative diseases. As shown in Warlop et al. (2017), the computed value of variability indices may significantly differ from their exact, asymptotic, value when time series are shorter than 256 points. We therefore choose to truncate time series longer than 256 SI to their last 256 points and to keep unchanged the shorter time series in order to reduce lengths biases.

We first computed the average value $E(\boldsymbol{T})$ and named it SI in the rest of this work. Then we computed three variability indicators: (1) the coefficient of variation, CV=$SD(\boldsymbol{T})$/SI, which yields the relative amplitude of the SI fluctuations around the mean value – the amount of variability. It is worth noting that CV does not provide any information on the temporal structure itself of these variations. Instead, these are quantified by the two independent indices D and H. (2) The Minkowski fractal dimension, D, is computed with the box-counting method: if $N(\varepsilon)$ is the number of square boxes of size ε needed to cover the plot of $\boldsymbol{T}$, then $N(\varepsilon \to 0) \propto \varepsilon^{-\mathrm{D}}$. D ranges from 1 to 2: The closer D is to 2, the more important the SI relative fluctuations from one cycle to another. Intuitively, D measures the "apparent roughness" of $\boldsymbol{T}$, that we also call complexity. The box-counting algorithm was successfully used in a previous study (Dierick

Table 1
Summary of the different groups analysed in the present work. Data come from our own laboratory (Dewamme, 2017; Dierick et al., 2017), from the free online Gait and balance PhysioNet Databases (Goldberger et al., 2000), or were provided by the first author of Warlop et al. (2016). For each group we display the number of time series available, the age of participants/ patients under the form mean±SD, and give the minimal and maximal ages between brackets. The minimal and maximal time series length in each group are given between brackets in the sixth column. The last column gives the device used to record the raw data from which SI time series are obtained, with the corresponding sampling frequency. We also summarize results from disability scales under the form median [Q1–Q3] when applicable. Healthy groups: Young Children (YC), Middle Children (MC), Old Children (OC), Adults (AD), Old Adults (OAD). Pathological groups: Parkinson's disease (PD), Huntington's disease (HUNT), amyotrophic lateral sclerosis (ALS). Disability scales: Modified Hoehn & Yahr (H&Y) for PD, Total Functional Capacity (TFC) for HUNT, number of months since first diagnosis (Onset in months) for ALS.

Group	N	Age (years)	Scale	From	Length	Measurement device (sampling frequency)
YC	11	4.2±0.4 [3.3,4.8]		(Hausdorff et al., 1999)	[459–550]	Force sensor inside subect's right shoe (300 Hz)
MC	20	7.2±0.4 [6.6,7.8]		(Hausdorff et al., 1999)	[439–529]	Force sensor inside subect's right shoe (300 Hz)
OC	12	12.0±0.8 [11,14]		(Hausdorff et al., 1999)	[400–495]	Force sensor inside subect's right shoe (300 Hz)
AD	68	25.0±6.7 [18,52]		(Dierick et al., 2017)	[512–936]	Force sensor within instrumented treadmill (500 Hz)
				(Dewamme, 2017)		Force sensor within instrumented treadmill (500 Hz)
OAD	5	70.4±7.0 [57,77]		(Hausdorff et al., 1997)	[709–892]	Force sensor inside subect's right shoe (300 Hz)
PD	35	66.0±9.9 [44,80]	2.5 [2−3]	(Hausdorff, 2009)	[219–957]	Force sensor inside subect's right shoe (300 Hz)
				(Warlop et al., 2016)		Accelerometer taped on the lateral malleolus of the subject's most affected side (512 Hz)
HUNT	20	46.7±12.3 [29,71]	8 [3−10]	(Hausdorff et al., 1997)	[167–310]	Force sensor inside subect's right shoe (300 Hz)
ALS	13	55.6±12.3 [36,70]	18.3±17.1	(Hausdorff et al., 2000)	[116–246]	Force sensor inside subect's right shoe (300 Hz)

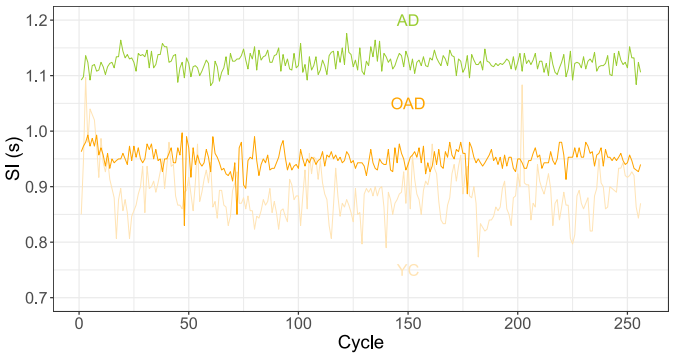

Fig. 1. Typical SI time series for three healthy subjects of different ages: a young child (YC), an adult (AD) and an old adult (OAD)

et al., 2017) to compute SI fractal dimension and may provide additional information to the Hurst exponent (Croce, Quercia, Costa, & Zappasodi, 2018; Phinyomark, Larracy, & Scheme, 2020). (3) The Hurst exponent H is computed by using the Detrended Fluctuation Analysis with a linear detrending (higher-order polynomial detrending is sometimes used in other similar studies). Computational details may be found in Kantz and Schreiber (2004), but the main steps are as follows. The cumulated time series $\boldsymbol{Z}$ computed from $\boldsymbol{T}$ are divided into windows of length l. A local least squares linear fit is performed for each window and the fluctuation function $F(l)$ is computed. The asymptotic relation $F(l \to \infty) \propto l^{\mathrm{H}}$ leads to H. A random process is close to $\mathrm{H} = 0.5$, while long-range autocorrelated processes are such that $0.5 < \mathrm{H} \leq 1$ ($\mathrm{H} > 1$ for unstable processes) in which an increase in SI is likely to be followed by another increase in SI at long range, and similarly for a decrease. Time series with $0 < \mathrm{H} < 0.5$ are anticorrelated; this case is typically not encountered in SI time series. H is regarded as a predictability index. Strongly autocorrelated dynamics are such that the time series value at a given time is strongly dependent on its previous values, hence predictable.

Computation of SI, CV, H and D has been performed with R software (v.3.4.2) – packages *dfa* and *fractaldim*.

2.2. Data analysis

We have first compared adults (AD), Parkinson's disease (PD), Huntington's disease (HUNT) and amyotrophic lateral sclerosis (ALS) groups through a one-way ANOVA with significance level set at $p = 0.05$. In case of significant group effect, a Holm-Sidak *post-hoc* was used for comparison of the pathological groups (PD, HUNT, ALS) to the AD group seen as a control condition. Kruskal-Wallis test with Dunn's method was used if normality test failed. ANOVAs were performed with SigmaPlot software (v.11.0, Systat Software, San Jose, CA). Comparisons were made regarding SI, the amount of variability CV, and the temporal structure of variability H and D.

Then we have computed Spearman's correlation coefficients, ρ, between the different parameters and subject's ages for all groups: young children (YC), middle children (MC), old children (OC), adults (AD) and old adults (OAD). For this analysis, all healthy subjects have been gathered into the Healthy group. Within the Healthy group, ρ has been computed between the parameters themselves. In the pathological groups (PD, HUNT, ALS), ρ has been computed between the different parameters and disability scores. We consider a correlation as significant if $|\rho| > 0.3$ and $p < 0.05$ following Guilford lines (Guilford & Fruchter, 1973). Correlation between parameters have been further assessed by performing separated Principal Component Analysis (PCA) for healthy and pathological groups.

Finally, we have compared the Healthy and pathological groups *via* a nonparametric ANCOVA (Young & Bowman, 1995) in order to "remove" the (nonlinear) age-dependence of parameters from the comparison. Significance level was set to $p = 0.05$. Spearman's correlation coefficients computations, PCA and nonparametric ANCOVAs have been performed with R software (v.3.4.2) – packages *corrplot*, *FactoMineR* and *sm* respectively.

Table 2
Results from the one-way ANOVA applied to SI, CV, H, and D. Means±SD are given for all groups, or medians [Q1-Q3] if normality test failed. The p−value showing group influence and *post-hoc* comparisons are shown in the last lines; significant results are written in bold font.

Group	SI (s)	CV	H	D
AD	1.112 [1.080–1.159]	0.015 [0.010–0.023]	0.739±0.145	1.624±0.150
PD	1.082 [1.026–1.150]	0.034 [0.019–0.056]	0.685±0.185	1.576±0.138
HUNT	1.102 [1.045–1.203]	0.072 [0.048–0.096]	0.669±0.155	1.544±0.155
ALS	1.268 [1.204–1.543]	0.061 [0.051–0.066]	0.842±0.176	1.596±0.102
p	<**0.001**	<**0.001**	<**0.001**	0.513
AD *vs* PD	NS	<**0.001**	0.661	
AD *vs* HUNT	NS	<**0.001**	0.616	
AD *vs* ALS	**0.015**	<**0.001**	0.371	

3. Results

SI and CV. One-way ANOVA showed significant group-dependence for SI and CV. Mean and median results are displayed in Table 2, as well as *post-hoc* results. These "standard" indices are significantly correlated with age in healthy subjects; detailed values are given in Table 3 and a graphical illustration is given in Fig. 2. No correlation with age is observed in pathological subjects but CV is correlated with the disability scales in PD and HUNT groups. The nonparametric ANCOVA indicates that the behavior of SI *versus* age is different between Healthy and HUNT groups. Healthy and ALS show parallel SI trends with age, shifted by 0.214 s upwards in ALS group. In other words, SI of ALS patients are significantly longer than Healthy individuals of the same age. Moreover, behaviors of CV *versus* age are different between Healthy and HUNT and between Healthy and ALS groups.

H and D. One-way ANOVA showed significant group-dependence for H. Mean and median results for these indices assessing temporal structure of variability are displayed in Table 2, as well as *post-hoc* results. H is significantly correlated with age in healthy subjects; detailed values are given in Table 3. D is correlated with TFC in HUNT group. Besides correlations showed in Table 3 we notice a significant correlation between CV and D in all groups but ALS: Healthy $\rho = -0.422$ ($p = 0.001$), PD $\rho = -0.400$ ($p = 0.018$), HUNT $\rho = 0.486$ ($p = 0.019$). Correlation is positive in HUNT and negative in Healthy and PD groups.

Global results. The PCA displayed in Fig. 3 shows that the set of computed parameters (SI, CV, D, H) accounts for 70.1% of the total variability of Healthy group only including the first two dimensions. Moreover the "standard" indices (SI and CV) and the "fractal" ones (D and H) are rather uncorrelated, showing the relevance of including both kinds of indices in a characterization of SI time series. Similar conclusions can be drawn from the PCA in the pathological group. We note that CV and SI are negatively (positively) correlated in the Healthy (pathological) group. Our results are graphically summarized in Fig. 4. Individual results are shown in the pathological groups while a smoothed trend is shown for Healthy group. The most obvious observation is that any pathology tends to increase CV from its healthy value. ALS subjects have a higher SI and H, as confirmed by the nonparametric ANCOVA.

4. Discussion

The objective of this study was to recompute linear and nonlinear variability indices in a uniform way from raw SI time series collected previously in healthy subjects and three common neurodegenerative diseases. In addition to variability indices computed from SI, the patient's level of disability was also correlated with these indices. Measures of variability in general are more and more frequently considered in gait analysis in patients with neurodegenerative diseases. Finding new ways to improve the sensitivity of these methods is therefore highly relevant if one aims at highlighting their clinical relevance. Here we focus on the Hurst exponent and the Minkowski fractal dimension in an attempt to provide a more accurate description of temporal structure of patients' SI variability. Our findings show that these indices indeed probe other features of SI time series (see Fig. 3) than usual SI average value and coefficient of variation. Moreover several variability indices were significantly correlated with the disability scores. Since predictability (H) and complexity (D) indices did not lead to the same observations, we conclude that variability of SI cannot be entirely described by a single scaling exponent. A similar observation has been done for brain electrical activity (Croce et al., 2018). As for brain dynamics, our results suggest a multi-fractal nature of SI dynamics, *i.e.* a dynamics whose accurate characterization needs several variability indices.

In healthy subjects, the average SI is an increasing function of age from birth to approximately 20 years and eventually reaches a plateau. This observation could be partly explained by a mechanical effect of growth: in any pendular model of walk for example, SI $\sim\sqrt{L}$ is expected, with L the lower limb's length. Our observations are compatible with well-known results about changes in gait patterns of growing children, see Beck, Andriacchi, Kuo, Fermier, and Galante (1981). While growing, children also learn to control their gait, and the magnitude of SI fluctuations decreases: CV reaches a minimal value of 0.015 [0.010 − 0.023] in AD group. This value is compatible with the meta-analysis conducted by Moon, Sung, An, Hernandez, and Sosnoff (2016) reporting an average value of 0.024 ± 0.005 for CV in healthy adults. Healthy adults thus reach an optimal control of their walk; any deviation from this optimal state will result in an increase of CV. Hurst exponent is found to be equal to 0.739 ± 0.145 in AD group. Our value is very close to that of 0.75 found in the one-central pattern generator (CPG) model proposed by Hausdorff et al. (1995). In contrast, the fractal dimension does not significantly vary with age. As detailed in a previous study of our group (Dierick et al., 2017), we interpret this parameter as a complexity index of the SI time series, see Goldberger et al. (2002) for a discussion of this parameter in the case of electrocardiographic time series. According to the maximal complexity model (Stergiou & Decker, 2011), D should be maximal in healthy subjects, as an indicator of optimal adaptability to external environment. Here, we observe no significant variation of D with aging, but we point out

Table 3
Spearman correlation coefficients between the parameters SI, CV, H, and D and subject's ages for all groups, and between the different parameters and disability scores for PD (H&Y) and HUNT (TFC) groups, and months since first diagnosis (Onset) for ALS. The $p-$values are given between parenthesis and significant correlations are displayed in bold font.

Group	*vs*	SI	CV	H	D
Healthy	Age	**0.499 (0.002)**	**−0.429 (0.002)**	**−0.354 (<0.001)**	−0.040 (0.336)
PD	Age	0.120 (0.484)	−0.069 (0.668)	−0.029 (0.842)	−0.145 (0.342)
	H&Y	0.240 (0.054)	**0.551 (<0.001)**	−0.196 (0.727)	0.019 (0.848)
HUNT	Age	0.246 (0.285)	0.354 (0.350)	−0.117 (0.393)	0.146 (0.615)
	TFC	−0.282 (0.236)	**−0.667 (0.011)**	0.297 (0.149)	**−0.457 (0.019)**
ALS	Age	0.371 (0.224)	0.604 (0.187)	0.264 (0.530)	0.094 (0.736)
	Onset	0.325 (0.237)	0.179 (0.305)	−0.099 (0.584)	−0.157 (0.210)

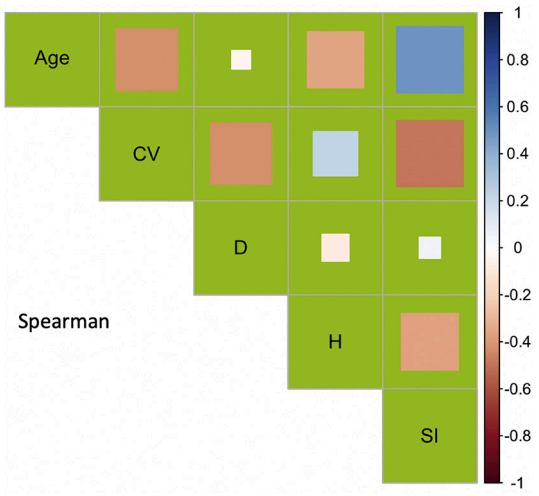

Fig. 2. Correlation plot of the Healthy subject's parameters. Each square has an area proportional to $|\rho|$, the full square being of unit area

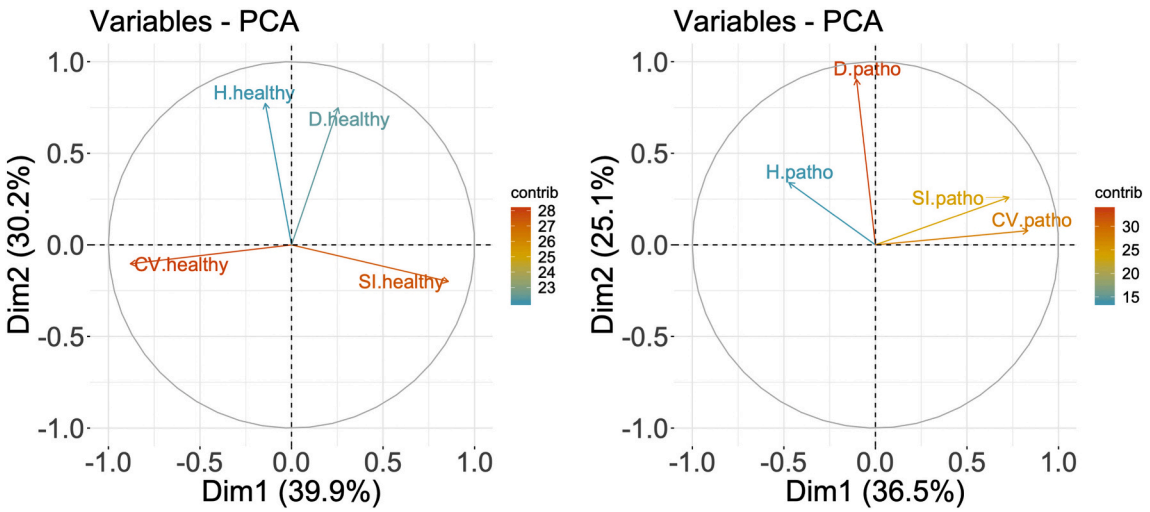

Fig. 3. PCA performed on the computed parameters for the Healthy (left panel) and pathological (right panel) groups. The correlation circles for dimensions 1 and 2 are shown. The contribution of each variable to the principal axes (contrib) are coded in colors, with cold colors (turquoise blue) showing low contribution and warm colors (orange) high contribution. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the negative correlation obtained between D and CV: healthy adults reach minimal CV which corresponds to large values of D, in-line with the optimal complexity framework.

The value of H we find in the AD group is typical of chaotic dynamics. As shown in Kurz, Stergiou, Heidel, and Foster (2005), chaotic walking dynamics naturally emerges from a passive dynamic double pendulum walking model. Moreover, hip actuation plays a key role in allowing transitions between locomotive patterns available in the chaotic attractor and increases stability (Kurz & Stergiou, 2005, 2007). The biomechanical model of Gates, Su, and Dingwell (2007) goes along the lines of the previous references. They use a pendular model of walk, with initial condition updated at each new step, *i.e.* at each heel strike. Sensory and motor noise, regulated by a simple proportional feedback controller, were incorporated in the model to vary the push-off forces generated by the trailing leg from step to step. Large H values can be obtained for large values of feedback control which makes sense since children's walk are more consciously controlled. CV and H tend to increase and decrease respectively in healthy old adults compared to the adult condition. This may simply be related to physiological aging (sarcopenia, joint stiffness, *etc.*), leading to a less efficient control (higher CV) and a general disorganization of long-range walking variability (smaller H). Our findings are inline with the previous study of Kurz and Stergiou (2003), where it has been observed that range of motion entropy during 8 min of walk increases in elderly for ankle, knee and hip angle. This increase may be caused by an altered neuromuscular memory of prior joint behaviors (Kurz & Stergiou, 2006). Similarly in Gates et al. (2007), an increase in motor noise (a random noise added to the feedback controller) leads to the behaviors we

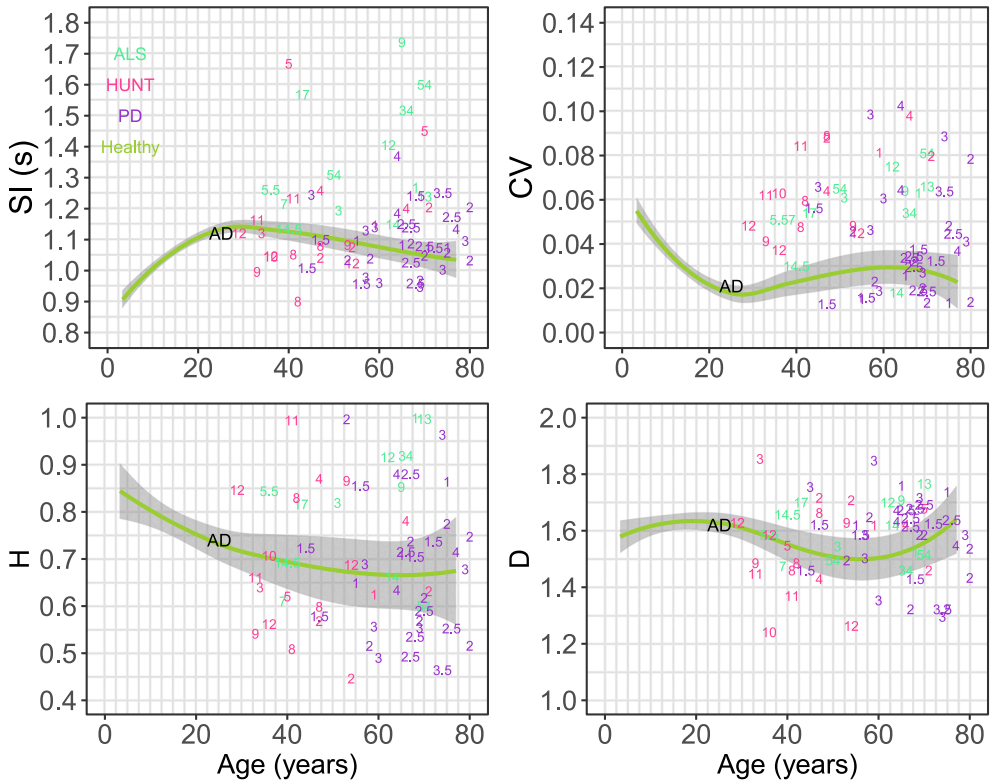

Fig. 4. Comparison of pathological subjects (each subject is labelled by the associated disability scores for PD and HUNT, and months since onset of disease for ALS) and Healthy subjects (green solid lines +95% grey confidence intervals) concerning the evolution of the computed parameters SI, CV, H, and D *versus* subject's age. A label AD is located at the average position of AD group. The Healthy group trends have been obtained by a second-order polynomial smoothing of individual data (*sm* package in R). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

observe in old adults.

Parkinson's and Huntington's diseases both lead to an alteration of the basal ganglia, and the degeneration of the central grey nuclei leads to an alteration in the transmission of information to the CPG *via* the mesencephalon (Takakusaki, 2017). Such perturbation necessarily increases the amount of gait variability and CV with respect to an healthy adult, as confirmed by the nonparametric ANCOVA (Table 4) in Huntington's case and by the *post-hoc* results in all pathological cases (Table 2). However, Parkinson's and Huntington's diseases have an opposite clinical manifestation: Parkinsonian, lacking of dopamine neurons, suffer from hypokinesia while the patient suffering from Huntington's disease suffer from hyperkinesia due to a decrease in striatum activating neurons. The averaged H exponent is indeed significantly lower in the HUNT group compared to other pathological groups: hyperkinesia induces random perturbation of the SI, *i.e.* reduces the temporal predictability of the lower limb movements. Consequently, from a clinical perspective, H reflects a lower ability of patients to plan their walk at long term which expose them to increased risks of falls as observed in patients with Huntington's disease (Busse, Wiles, & Rosser, 2008). Lyapunov exponents may assess similar features of walking kinematics (Dingwell & Cusumano, 2000). A detailed graphical inspection of our findings revealed that, for patients with Parkinson's disease with low H&Y scores (1 and 1.5), H is higher than in healthy subjects of the same age. It underlines a more predictable or stereotyped walk. In contrast, H is globally lower in patients with Parkinson's disease with higher H&Y scores than in healthy subjects of comparable age. As for Huntington's patients, walk becomes more random. From a clinical perspective, since low H&Y scores are mainly observed at early stages of the disease, an increase of H value for SI could help in the early diagnosis of Parkinson's disease, at a time when it is precisely difficult to diagnose because it is based solely on observable symptoms. Though non significant, we find a negative correlation between modified H&Y score and Hurst exponent as reported in Warlop et al. (2018).

In Huntington's disease, CV is negatively correlated with TFC: the smaller TFC (the more serious the disability), the larger the CV. A correlation between H and TFC was found too in Hausdorff et al. (1997) but not confirmed by our computations. Note, however, that we calculate H by using another algorithm. We find a negative correlation between D and TFC in Huntington's disease: The latter disease introduces an extra complexity in SI time series that is related to pathology. Our results confirm that an alteration of SI variability is linked to a loss of functional ability in patients suffering from neurodegenerative pathologies. Would a treatment aiming at improving a patient's variability, assessed by CV, H and D, lead to an improvement of his/her functional ability? This question is, to our knowledge, still to be addressed.

ALS, also known as Lou Gehrig's disease, is a fatal disorder characterized by a progressive degeneration of upper (cerebral cortex)

Table 4
Results of nonparametric ANCOVA comparing the Healthy group *versus* pathological groups. The null hypothesis of equal behaviors of parameters *versus* time is tested in the first line (Equal). The null hypothesis of parallel behaviors of parameters *versus* time is tested in the second line (Parallel). In case this last hypothesis is not rejected, the shift between both groups is given in the third line (Shift). Significant differences are written in bold font.

	SI			CV			H		
Healthy *vs*	PD	HUNT	ALS	PD	HUNT	ALS	PD	HUNT	ALS
Equal	0.208	<**0.001**	<**0.001**	0.095	<**0.001**	<**0.001**	0.936	0.663	**0.004**
Parallel	–	<**0.001**	0.324	–	0.132	**0.063**	–	–	0.303
Shift			0.214 s		0.065				0.117

and lower motor neurons (brainstem and spinal cord) (Cleveland & Rothstein, 2001; Kiernan et al., 2011). In addition to altering the cortical-spinal pathway, the motoneurons disconnect from their target muscles, which will create a weakening or even a paralysis of these muscles (Martineau, Di Polo, Vande Velde, & Robitaille, 2018). A lack of "peripheral" muscle control logically leads to a higher value of CV, and the muscle paralysis is associated to a significantly higher value of SI in ALS group. Patients suffering from ALS also show a higher value of H, exhibiting a more predictable gait pattern.

It is also worth noting that, in a statistically non-significant way, D was decreased in all three neurodegenerative diseases. This decrease indicates a loss in the complexity of SI time series, making them more repeatable and regular. In the optimal movement variability and complex adaptive behavior theories (Harrison & Stergiou, 2015; Stergiou et al., 2006), they are representative of a loss of flexibility (adaptability) of the neuro-musculoskeletal system with less available degrees of freedom.

Some limitations of our study should be mentioned. First, the length of available time series were variable which is known to induce potential biases in the estimation of indexes such as Hurst exponents. To limit the risk of artefacts, we have decided to truncate time series to 256 points (or close to), which may be a minimal length to compute accurate variability indices (Warlop et al., 2017). Even if the duration of a walking session – around 8 min for all time series of our data set – is a natural parameter, a more rigorous analysis scheme will be reached by standardizing the number of steps in future studies. We think that the different measurement systems used do not introduce an extra experimental uncertainty since the sampling frequency, which is the actual limitation on SI duration's accuracy, is always larger than or equal to 300 Hz: It is beyond the recommended 120 Hz of the recent meta-analysis (Ravi et al., 2020). Second, no disability score was available for ALS patients and no correlation could be calculated with the nonlinear variability indices. Third, Hurst exponents were only computed by using the Detrended Fluctuation Analysis for the sake of homogeneity. However, Rescaled Range Analysis has also been used previously (Warlop et al., 2017) and may have been included too.

Other nonlinear analysis tools such as the largest Lyapunov exponent (Kaipust, Huisinga, Filipi, & Stergiou, 2012) or Higuchi fractal dimension (Higuchi, 1988) could have been computed in order to evidence modulation of SI regularity and complexity in neurodegenerative diseases. The largest Lyapunov exponent of lower-limb kinematic parameters times series during treadmill walking appears to be significantly modified by aging (Buzzi, Stergiou, Kurz, Hageman, & Heidel, 2003). As shown very recently (Phinyomark et al., 2020), the complexity measured using the Higuchi dimension seems to lead to different results than those obtained by that of Minkowski. It is worth noting that "complexity" is a rather subjective concept. Different mathematical candidates aiming at assessing it may give different results. Finding the most convenient (or intuitive) measure of complexity from a clinical point of view amongst the numerous variability indicators is, in our opinion, an important direction of research in the field.

Nowadays, SI fluctuations during walking can be easily computed on large data series in neurological patients. These fluctuations must not be considered by clinicians as "noise" but rather as an informative signal of human locomotor performance that can be revealed by the computation of variability indices assessing not only the amount of variability but also the temporal structure of this variability. We recommend that these moment-to-moment variations in movement must be progressively but surely introduced in clinical practice in order to aid clinical assessment, track disease progression, optimize pharmacological treatment and rehabilitation follow-up in neurological patients. Guidelines for an optimal measurement of Hurst's exponent may be found in recent study of Ravi et al. (2020), which confirms from a systematical review and a meta-analysis that modifications in Hurst's exponent may be considered as a relevant indicator of aging or Parkinson's disease.

5. Conclusions

We have confirmed that healthy adults reach an optimal variability state, here assessed by CV (minimal), D and H (typical of chaotic systems (Stergiou & Decker, 2011)). Any deviation from this optimal state, either through aging or pathology, will cause at least CV to increase. Hence, CV is a linear relevant index but has to be complemented with nonlinear indices. D is expected to be lower in pathological cases and has been shown to be negatively correlated to CV in healthy adults and patients suffering from Parkinson's diseases. A surprising result is however that Huntington's patients show both larger CV and D values than a healthy adult: a too large D is therefore not optimal and correlated with a poor TFC. Finally, H tends to decrease with the H&Y scale in Parkinson's disease and in patients suffering from Huntington's disease but increases in patients suffering from ALS.

Declaration of Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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