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Gait Variability Measures Reveal Differences between Multiple Sclerosis Patients and Healthy Controls

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Gait Variability Measures Reveal Differences Between Multiple Sclerosis Patients and Healthy Controls

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The purpose of this study was to determine the differences in gait variability between patients with multiple sclerosis (MS) and healthy controls during walking at a self-selected pace. Methods: Kinematics were collected during three minutes of treadmill walking for 10 patients with MS and 10 healthy controls. The Coefficient of Variation (CoV), the Approximate Entropy (ApEn) and the Detrended Fluctuation Analysis (DFA) were used to investigate the fluctuations present in stride length and step width from continuous strides. Results: ApEn revealed that patients with MS had significantly lower values than healthy controls for stride length ($p < .001$) and step width ($p < .001$). Conclusions: ApEn results revealed that the natural fluctuations present during gait in the stride length and step width time series are more regular and repeatable in patients with MS. These changes implied that patients with MS may exhibit reduced capacity to adapt and respond to perturbations during gait.

Keywords: Multiple Sclerosis, gait variability, nonlinear dynamics, stride length, step width.

Multiple sclerosis (MS) is a demyelinating inflammatory disease of the central nervous system with subsequent destruction of myelin, oligodendrocytes and axons (Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000). The functional impairments that result from the demyelination include abnormal gait, poor balance, muscle weakness and fatigue. These abnormalities typically result from the axonal degeneration and conduction block (White & Dressendorfer, 2004). These functional impairments contribute to fatigue, reduced daily activity and increase the risk of secondary diseases (Freeman, 2001). Specific examination of walking mechanics in patients with MS has been limited to temporal and spatial parameters. These measures have revealed that patients with MS walk slower with shorter stride lengths and prolonged double support phases compared with healthy controls (Benedetti et

al., 1999; Gehlsen et al., 1986; Morris, Cantwell, Vowels, & Dodd, 2002; Rodgers et al., 1999). While the determination of these deficits is important, spatial and temporal classifications do not provide any information regarding the changes in motor control that precipitate these deficits. Investigating gait variability, however, can provide an important understanding of the motor control strategies employed by patients with MS while walking at self-selected pace and may help to determine specific rehabilitation recommendations for patients with MS to improve functional abilities and walking mechanics. Such insights have been possible in several other pathological conditions that are associated with gait disability (e.g., elderly fallers, Parkinson's disease, and stroke) (Brach, Berlin, VanSwearingen, Newman, & Studenski, 2005; Brach et al., 2010; Buzzi, Stergiou, Kurz, Hageman, & Heidel, 2003b; Hausdorff, Edelberg, Mitchell, Goldberger, & Wei, 1997a; Hausdorff et al., 2007; Herman, Giladi, Gruendlinger, & Hausdorff, 2007).

Gait variability is defined as the normal variations that occur across multiple strides (Stergiou, Buzzi, Kurz, & Heidel, 2004). Several factors (environmental, biomechanical, morphological, and task-related constraints) contribute to the variability in the gait pattern (Stergiou et al., 2004). In addition to gait, variability is also inherent within other biological phenomena such as the heartbeat and respiration (Babloyantz & Destexhe, 1986; Buchman, Cobb, Lapedes, & Kepler, 2001; Goldberger & West, 1987; Goldberger, Rigney, Mietus, Antman, & Greenwald, 1988; Lanza et al., 1998; Skarda & Freeman, 1987; Slutzky, Cvitanovic, & Mogul, 2001; Toweill & Goldstein, 1998; Wagner, Nafz, & Persson, 1996). It has been hypothesized that in biological systems there is an "optimal" state of variability that is associated with health (Stergiou, Harbourne, & Cavanaugh, 2006). Changes in this optimal state of variability are generally associated with disease. This variability can be attributed to several physiologic factors such as neural control and muscle function (Stergiou et al., 2006). According to this hypothesis a decrease from the optimal state of variability makes the system more predictable and inflexible, which is referred to as a periodic state (i.e., walking more like a robot), while an increase makes the system unstable and noisy which is referred to as a random state (i.e., walking more like a frail elder or even a drunken sailor) (Stergiou et al., 2006). Support for this hypothesis has been provided by several studies. For example, elderly individuals with extreme step width variability (either low or high step width variability) were more likely to report a fall in the past year than those with moderate step width variability (Brach et al., 2005; Buzzi, Stergiou, Kurz, Hageman, & Heidel, 2003a; Hausdorff, Edelberg, Cudkowicz, Singh, & Wei, 1997a; Hausdorff, Edelberg, Mitchell et al., 1997b; Kurz & Stergiou, 2003; Maki, 1997). In another study Rocchi, Chiari, & Horak (2002) demonstrated that variability of postural sway was larger than normal in patients with Parkinson's disease without the effects of drugs and even larger with levodopa (Rocchi, Chiari, & Horak, 2002). However, when receiving deep brain stimulation, these patients exhibited smaller than normal variability of postural sway. The normal healthy control behavior was found to be between all these conditions, suggesting that too much or too little is not optimal. In anterior cruciate ligament (ACL) deficient patients, it has been found that while walking the ACL-deficient knee is less adaptable and inflexible when compared with the noninjured knee, while the ACL-reconstructed is more noisy and unstable (Georgoulis, Moraiti, Ristanis, & Stergiou, 2006; Moraiti, Stergiou, Ristanis, & Georgoulis, 2007; Moraiti et al., 2009; Moraiti, Stergiou, Vasiliadis,

Motsis, & Georgoulis, 2010). On the other hand, Myers et al. (2009) found more unstable and noisy gait patterns in patients with Peripheral Arterial Disease (PAD) suggestive of multilevel neuromuscular deterioration in the locomotor system (Myers et al., 2009). Similar results have been found in Parkinson's and Huntington's disease patients. These pathological populations have been associated with increased risks of falling and decrease in activities of daily living (Buzzi, Stergiou, Kurz, Hageman, & Heidel, 2003a; Hausdorff, Cudkowicz, Firtion, Wei, & Goldberger, 1998; Maki, 1997). Therefore, restoration of healthy or normal movement patterns should ideally involve recovering the optimal state of variability, which exists in the continuum of being between random and periodic (Stergiou et al., 2006). This state is characterized by high levels of motor adaptability and flexibility and consequently, with increased ability to respond to perturbations successfully.

The analysis of gait variability can be performed using linear and nonlinear tools. Linear tools provide information on the magnitude of variability within the system and are typically reported using the range, standard deviation, and coefficient of variation of the time series. Changes in the coefficient of variation are indicative of increases or decreases in the amount of variability. Nonlinear tools, however, focus on understanding how variations in the gait pattern change over time (Stergiou et al., 2004) and provide information on the temporal structure of the time series allowing explorations of the above-described optimal state of variability. Several investigators have studied how aging and disease affects the variability of gait parameters from a nonlinear perspective and found that the elderly display increased randomness during walking as evidenced by higher values for the nonlinear tool of Approximate Entropy (ApEn; Buzzi, Stergiou, Kurz, Hageman, & Heidel, 2003b; Kurz & Stergiou, 2003; Kurz, Markopoulou, & Stergiou, 2010). In addition to elderly, nonlinear tools have been used to study Parkinson's disease patients where patients showed increased randomness in the variability of joint movement patterns (ankle, knee and hip) compared with elderly controls (Kurz et al., 2010). Gait patterns in PAD patients also displayed increased randomness compared with healthy age matched controls (Myers et al., 2009). Finally, Hausdorff et al. (1997a) used another nonlinear tool, the Detrended Fluctuation Analysis (DFA), to study gait variability in Huntington's disease patients, healthy elderly, and healthy young. The authors found that Huntington's disease patients and healthy elderly display a more random and less correlated gait pattern compared with young healthy individuals (Hausdorff et al., 1997a).

While gait variability has been examined in the neurological disease populations, very few studies have examined gait variability in patients with MS. During the disease process the myelin sheath surrounding nerve fibers in patients with MS is destroyed. This affects the ability of the muscle to generate forces at an appropriate rate and timing during complex motor tasks (Lambert, Archer, & Evans, 2001). Walking mechanics in patients with MS are therefore likely affected by this disease characteristic, yet the motor control strategies that are employed by patients with MS to compensate for loss of neural signal conduction during walking are unknown. This study seeks to explore the fundamental differences in gait variability between patients with MS and healthy controls. Therefore, the purpose of this study was to examine the gait variability present in patients with MS compared with controls by evaluating the step width and stride length time series during self-selected walking. From these gait parameters it may be possible to determine whether patients

with MS gait are similar to those affected by other neurological conditions, or if the disease effects are unique. Previously mentioned studies which examined kinematic variability (Burnfield, Josephson, Powers, & Rubenstein, 2000; Buzzi, 2001; Buzzi, Stergiou, Kurz, Hageman, & Heidel, 2003b; Kurz & Stergiou, 2003) in Parkinson's disease and elderly patients reported increased values of ApEn and DFA that revealed a more random gait pattern compared with healthy controls. Hausdorff et al. (1997a) reported increased randomness in stride length time in Huntington's disease patients when compared with healthy controls (Hausdorff et al., 1997a). Like patients with Huntington's disease, a neurological disorder, we hypothesized that patients with MS would also show increased amount of variability in the evaluated spatiotemporal parameters. This will be indicated by linear measures where both standard deviation and coefficient of variation (CoV) would be increased in the MS group. In addition, we expected an altered temporal structure of gait variability, as indicated by the nonlinear measures of ApEn and DFA. It was anticipated that when compared with controls, patients with MS would display higher ApEn values and a decreased DFA scaling exponent.

Methods

Subject Inclusion and Exclusion Criteria

A total of ten MS subjects and ten healthy controls participated in this study (Table 1). Patients provided informed consent and all procedures were approved by the University's Medical Center Institutional Review Board. Specific inclusion criteria were: 1) cognitive competency to give informed consent which entailed an understanding of the procedures that were taking place and why they were performed, as determined by a clinician specializing in MS care (author MF), 2) age ranging from 19 years to 65 years, and 3) an EDSS score of 1.0–6.0. All physical and neurological examinations for the patients with MS were found to be "clinically acceptable", where evidence is required that the MS patient's physical and neurological condition would not place the patient in undue risk by participating or interfere with

Table 1   Baseline Characteristics of Controls and Patients With MS. Values Are Presented as Means ± *SD*.

Characteristics	Control (*n* = 10)	MS (*n* = 10)	P
Age (years)	35.30 ± 9.78	35.40 ± 9.02	.981
Gender	8 Female	8 Female	
	2 Male	2 Male	
Height (cm)	167.64 ± 13.36	167.84 ± 10.62	.985
Mass (kg)	72.49 ± 15.19	79.77 ± 17.42	.332
Self-Selected Pace (m/s)	1.08 ± 0.21	0.67 ± 0.25	.001*
EDSS Score Extended Disability Status Scale		3.95 ± 1.48	

*Significant difference between groups, p < 0.05.

outcome measures of the study. Exclusion criteria for the study included: 1) any other neurological or vestibular disorder, 2) pregnancy, breastfeeding, or within three months post partum at the initiation of the study, and 3) any other comorbid conditions which would make participation unsafe.

Experimental Procedure and Data Collection

For all data collections, participants wore a form-fitting outfit while reflective markers were placed bilaterally according to anatomical position and a modified Helen Hayes marker set (Houck, Yack, & Cuddeford, 2004). Once the markers were placed, participants walked on the treadmill to find a self-selected speed. The treadmill started at 0.045 m/s and the speed was increased by investigators until participants reported that a comfortable walking speed was found. Participants then walked for three minutes on the treadmill at their self-selected speed. Three-dimensional kinematics were acquired with an eight camera, high-speed, real-time camera system sampling at 60 Hz (EvaRT 5.0 software, Motion Analysis Corp, Santa Rosa, CA). The amount of time sampling took place falls between the ranges collected by Hausdorff et al., who analyzed two to six minutes of overground walking (Hausdorff, 2007). In addition, patients with MS were divided into mild (EDSS < 4.0) and moderate (EDSS ≥ 4.0) severity groups according to their EDSS score.

Data Analysis

Treadmill data from the three-dimensional marker trajectories were exported and processed in custom software using MATLAB software (MathWorks Inc., Natick, MA). This software was used to calculate the stride length and step width from the time series. From each time series, the mean, the standard deviation, and the coefficient of variation (CoV; Equation 1) for the stride length and the step width were calculated for each participant. These linear measures characterize the amount of variability present in the data (Harbourne & Stergiou, 2003; Harbourne & Stergiou, 2009; Stergiou et al., 2006). The CoV presented here is expressed as a percentage of the mean.

$$CoV = \left(\frac{standard\ deviation}{mean} \right) * 100 \qquad \text{Equation 1}$$

Approximate Entropy (ApEn; Equation 3) and Detrended Fluctuation Analysis (DFA; Equation 5) were also used with the time series. Rather than quantifying the amount of variability as the linear measures do (Harbourne & Stergiou, 2003; Harbourne & Stergiou, 2009; Stergiou et al., 2006), these nonlinear tools are sensitive to patterns in the data. ApEn quantifies the repeatability or regularity of a time series (Pincus & Goldberger, 1994; Ryan, Goldberger, Pincus, Mietus, & Lipsitz, 1994). ApEn was calculated using algorithms written by Pincus (Pincus, 1991; Pincus & Goldberger, 1994) and implemented in MATLAB (m= 2; $r = .2*SD$). The ApEn values typically range from 0 to 2. Values close to 0 are consistent with high regularity and repeatability (i.e., a sine wave). Conversely, values close to 2 represent high irregularity (i.e., white noise). A time series with a more regular and repeatable (i.e., periodic) pattern of data points results in lower ApEn values. Functionally, this translates to a system that is less capable of responding to a

perturbation. A time series with irregular and nonrepeatable (i.e., random) pattern of data points results in higher ApEn values. Functionally, this is a sign of diminished motor control and poor neuromuscular health (Hausdorff, 2009). In brief, to define ApEn we start with our N input data points $u(1)$, $u(2)$. . . ., $u(N)$ and also incorporate two input parameters, m and r. The input parameter m is length of compared runs, and r is a tolerance. First we form vector sequences $x(1)$ through $x(N\text{-}m\text{-}1)$ from $\{u(i)\}$, defined by $x(i)= [u(i),. . . ,u(i+m-1)]$. These vectors are m consecutive u values beginning with the ith point. The next step is to define the distance $d[x(i),x(j)]$ between vectors $x(i)$ and $x(j)$ as the largest difference in their respective scalar components. The third step is to use the vector sequences $x(1)$ through $x(N\text{-}m\text{-}1)$ to create (for each $i \text{ \# } N\text{-}m+1$) (equation 2).

$$C_i^m(r) = \frac{\text{number of } x(j) \text{such that } d\left[x(i),x(j)\right] \text{\#} r}{\left(N-m+1\right)} \qquad \text{Equation 2}$$

The $C_i^m(r)$ values measure (within tolerance r) the regularity of patterns similar to a given pattern of window length m. The final step is to define $\Phi^m(r)$ as the average value of ln $C_i^m(r)$, where ln is the natural logarithm. Finally, approximate entropy is defined as

$$ApEn(m,r,N) = \Phi^m(r) - \Phi^{m+1}(r) \qquad \text{Equation 3}$$

DFA evaluates the presence of long-range, power-law correlations as part of multifractal cascades that exist over a wide range of time scales. This method first forms an accumulated sum of the time series, sectioning it into windows, and then the log of the average size of fluctuation for a given window size is plotted against the log of the window size (Peng, Havlin, Stanley, & Goldberger, 1995). In brief, if $B(i)$ is the ith interval and B_{ave} is the average interval then:

$$y(k) = \sum_{i=1}^{k} \left[B(i) - B_{ave}\right] \qquad \text{Equation 4}$$

Thus, the time series is divided into boxes of equal length, n. In each box of length n, a least-squares line is fit to the data. The y coordinate of the straight-line segments is denoted by $y_n(k)$. The time series is detrended, $y(k)$, by subtracting the local trend, $y_n(k)$, in each box and then the root mean square fluctuation of this integrated and detrended time series is calculated by equation 5. This calculation is repeated across the entire times series to provide a relationship between $F(n)$, the average fluctuation as a function of box size, and the box size n. A linear relationship on a double log graph indicates the presence of scaling. The fluctuations can be characterized by the scaling exponent α, the slope of the line relating log $F(n)$ to log n (Peng et al., 1995).

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^{N} \left[y(k) - y_{n(k)}\right]^2} ^2 \qquad \text{Equation 5}$$

The DFA algorithm was also implemented in MATLAB according to the methods used by Peng (Peng et al., 1993; Peng et al., 1995). An α-value less than 0.5 indicates a time series that is nonpersistent; α of 0.5 indicates a time series that has no correlation; α greater than 0.5 and less than 1 indicate persistent long-range correlations; and α greater than 1 and less than 1.5 indicates Brown noise. With regards to variability, aging and disease have been associated with either random

noise or brown noise, and long-range correlations are present in physiological variability from a healthy person (Goldberger, Peng, & Lipsitz, 2002; Iyengar, Peng, Morin, Goldberger, & Lipsitz, 1996). Each time series is self-similar if the fluctuations at different observation windows ($F(n)$) scale as a power-law with the window size n. $F(n)$ will increase with the window size (Hausdorff et al., 1997a).

Statistical Analysis

Group means were calculated for the standard deviation, CoV, ApEn, and α-values for the stride length and step width time series for patients with MS and healthy controls. Patients with MS and healthy controls were compared using independent *t* tests. The severity groups were compared with each other and to healthy controls using independent *t* tests. Statistical comparisons were performed using SPSS 15.0 software (SPSS Inc., Chicago, IL). The level of significance was set at 0.05.

Results

Group means for age, height, and mass did not differ between the patients with MS and controls. This verifies that the two groups were well matched. Self-selected walking velocity was significantly faster ($p = .001$) in the control group (1.08 ± 0.21 m/s) as compared with the patients with MS (0.67 ± 0.25 m/s) (Table 1).

Linear Measures

Mean stride length was 1.14 m in the control group and was 0.94 m in patients with MS ($p = .070$). Mean step width was 0.09 m in the control group and was 0.11 m in patients with MS ($p = .421$) (Table 2). The stride length standard deviation was 0.01 for controls and 0.02 in patients with MS (Table 3). Standard deviation for step width was 0.01 in the control group and 0.01 in patients with MS. There were no differences in the standard deviation between groups for stride length ($p = .134$) or step width ($p = .842$). CoV values (expressed as a percentage) for stride length were 2.81 and 4.10 for controls and patients with MS, respectively. The CoV for step width was 20.73 for controls and 12.90 for patients with MS. There were no differences in CoV between groups for stride length ($p = .123$) or step width ($p = .172$).

Table 2   Stride Length Values for Controls and Patients with MS. Values Are Presented as Means ± *SD*.

	Control (*n* = 10)	MS (combined) (*n* = 10)	MS Mild (*n* = 5)	MS Moderate (*n* = 5)
Mean (meters)	1.14 ± 0.27	0.94 ± 0.17	1.04 ± 0.19	0.85 ± 0.09*
Standard Deviation	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.01
COV (%)	2.81 ± 1.51	4.10 ± 2.00	3.23 ± 1.37	4.96 ± 2.30*
ApEn	0.70 ± 0.07	0.55 ± 0.07*	0.57 ± 0.06*	0.54 ± 0.08*
DFA	0.79 ± 0.23	0.69 ± 0.22	0.74 ± 0.23	0.64 ± 0.17

*Significant difference compared with controls, p < 0.05.

Table 3   Step Width Values for Controls and Patients with MS. Values Are Presented as Means ± *SD*.

	Control (*n* = 10)	MS (combined) (*n* = 10)	MS Mild (*n* = 5)	MS Moderate (*n* = 5)
Mean (meters)	0.09 ± 0.05	0.11 ± 0.05	0.11 ± 0.03	0.12 ± 0.07
Standard Deviation	0.01 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
COV (%)	20.73 ± 17.1	12.90 ± 3.16	12.16 ± 2.81	13.64 ± 3.64
ApEn	0.68 ± 0.06	0.51 ± 0.05*	0.52 ± 0.05*	0.51 ± 0.06*
DFA	0.56 ± 0.21	0.70 ± 0.20	0.76 ± 0.12	0.64 ± 0.26

*Significant difference between groups, $p < 0.05$.

Comparisons between patients with MS based on EDSS scores did not reveal significant differences in stride length between the mild and moderate severity patients for stride length mean ($p = .078$), stride length standard deviation ($p = .283$), or stride length coefficient of variation ($p = .185$). No significant differences were present for step width between patients with MS for step width mean ($p = .848$), step width standard deviation ($p = .817$), or step width CoV ($p = .492$). When compared with the healthy controls, the moderate severity group had a significantly lower stride length mean ($p = .038$) and a significantly higher stride length CoV ($p = .047$). The stride length standard deviation between the moderate severity group and healthy controls was not significant ($p = .061$). The mild severity group did not have significant differences in the stride length mean ($p = .474$), stride length standard deviation ($p = .516$), or stride length CoV ($p = .612$). The difference of step width between the moderate severity group and healthy controls was not significant for step width mean ($p = .491$), step width standard deviation ($p = .984$), or step width CoV ($p = .384$). The mild severity group did not show significant differences in step width compared with healthy controls for step width mean ($p = .539$), step width standard deviation ($p = .765$), or step width CoV ($p = .294$).

Nonlinear Measures

ApEn values were significantly lower for the patients with MS compared with controls for the stride length ($p = .001$) and for the step width ($p = .001$) (Figure 1). Between MS severity groups there was no significant difference in stride length for ApEn ($p = .599$) or for DFA exponent ($p = .494$). DFA values showed no significant differences between patients with MS and healthy controls for stride length ($p = .258$) or step width ($p = .142$) (Figure 2). Compared with healthy controls, ApEn for stride length was significantly lower ($p = .003$) in the moderate severity group and was significantly lower ($p = .001$) in the mild severity group. Compared with healthy controls, there were no significant differences for the stride length for the DFA exponent in the moderate severity ($p = .157$) or the mild severity ($p = .630$) groups. Between MS severity groups there was no significant difference in step width for ApEn ($p = .642$) or for the DFA exponent ($p = .380$). Compared with healthy controls, step width for ApEn was significantly lower ($p = .001$) in the
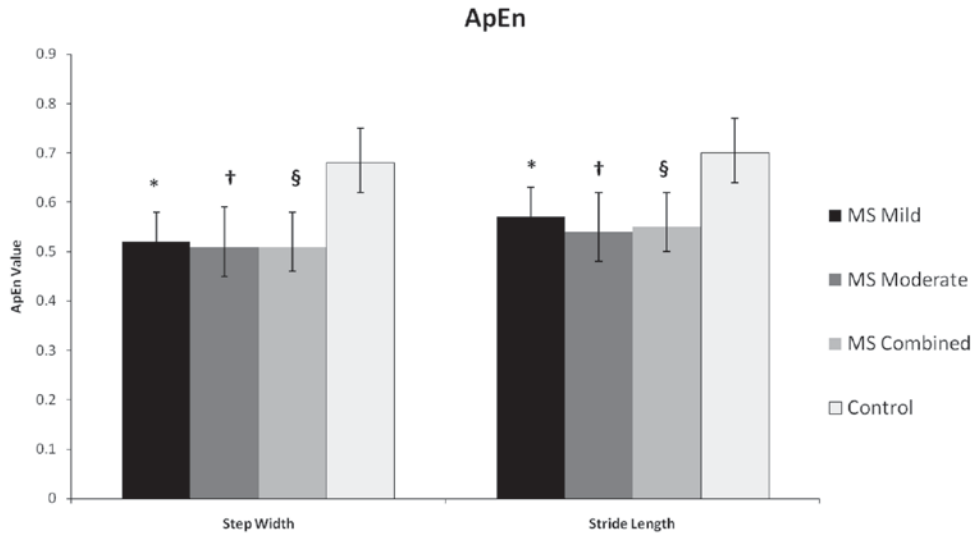
Figure 1 — ApEn values for step width and stride length (means ± *SD*). Significant differences were found between patients with MS and controls for both variables. ApEn = Approximate Entropy. *Significant difference MS mild compared with controls, ($p < .05$). † Significant difference MS moderate compared with controls, ($p < .05$). § Significant difference MS combined compared with controls, ($p < .05$).

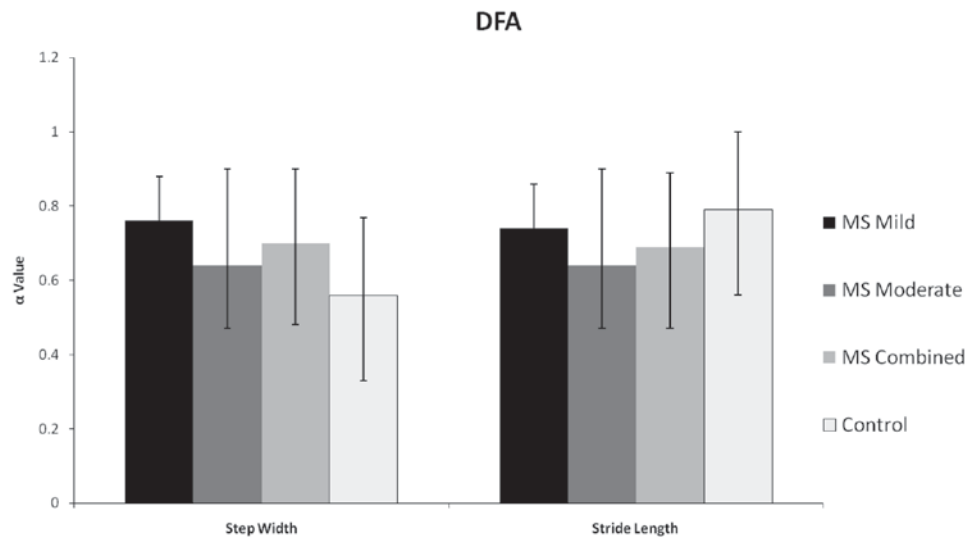**Figure 2** — DFA values for step width and stride length (means ± *SD*). No significant differences were found between patients with MS and controls for both variables. DFA = Detrended Fluctuation Analysis; α = scaling exponent calculated by DFA.

moderate severity group and was significantly lower ($p = .001$) in the mild severity group. Compared with healthy controls, step width for the DFA exponent was not different for the moderate severity group ($p = .519$) or the mild severity group ($p = .074$).

Discussion

The purpose of this study was to examine the gait variability present in patients with MS compared with controls by evaluating the step width and stride length time series during walking at a self-selected speed. To our knowledge this is the first study to investigate gait variability from continuous strides in patients with MS. We hypothesized that patients with MS would also show increased amount of variability in the evaluated spatiotemporal parameters. This will be indicated by linear measures where both standard deviation and CoV would be increased in the MS group. In addition, we expected an altered temporal structure of gait variability, as indicated by nonlinear measures of ApEn and DFA. It was anticipated that when compared with controls, patients with MS would display higher ApEn values and a decreased DFA scaling exponent.

Both standard deviation and CoV for stride length and step width showed no differences in the amount of variability between MS and healthy controls. The lack of differences does not support the original hypothesis that patients with MS would have higher amounts (linear measures) of variability. Stride length variability has previously been investigated in other neurological and aging populations. When examining stride length CoV in patients with Parkinson's disease, Rosano et al. (2007) found a stride length CoV of 6.3% from four continuous strides over a four-meter walkway. The stride length CoV of those patients was higher than the stride length CoV found in our study for patients with MS (4.3%), however their data had a much lower number of strides. From their data, Rosano et al. (2007) concluded that a greater amount of stride-to-stride variability can be a sign of the presence of a neurological disorder (Rosano, Brach, Studenski, Longstreth, & Newman, 2007). Hausdorff et al. (2007) also examined stride to stride variability using CoV of stride time in Parkinson's disease patients over 100 m. The authors found that compared with controls, such patients had significantly higher stride time variability but when an auditory stimulus was added, the Parkinson's patients reduced their stride-to-stride variability. It was suggested that the reductions in the amount of stride-to-stride variability indicate improved rhythmicity and stability (Hausdorff et al., 2007). Our patients with MS, while walking on a treadmill, displayed a similar amount of stride-to-stride variability compared with controls. These results taken independent of the nonlinear variability measures indicate that patients with MS already have stride length variability with sufficient rhythmicity and stability. Importantly, these results are different from the above-mentioned literature. It is possible that this is due to methodological issues since we used many more strides to fully explore gait variability. However, it is also possible that the effect of MS is quite different than of the other mentioned pathologies in terms of amount of variability measures.

ApEn for stride length and step width were lower in patients with MS compared with healthy controls. The lower ApEn values indicate that for patients with MS, the gait pattern is more predictable and less adaptable than healthy controls.

The results do not support our original hypothesis, which stated that patients with MS would have increased ApEn values as compared with healthy controls. The decreased ApEn values indicate that in patients with MS, the fluctuations present in the stride length and step width time series are more repeatable and regular. Therefore, they are indicative of a system that is inflexible and has less available degrees of freedom. Fewer degrees of freedom have been associated with reduced capability to alter gait patterns. Cavanaugh et al. (2005) found that "this reduced capability of adapting indicates that a system cannot optimally respond to or produce a proper physiological response to a particular task or perturbation which will usually result in a near fall or fall" (Cavanaugh, Guskiewicz, & Stergiou, 2005). Currently there are no established normative values for ApEn measure during walking in patients with MS. This is why it is critical to refer to healthy control values to establish a reference point (Buzzi, 2001; Stergiou et al., 2004). The step widths reported in the studies performed on healthy elderly subjects by Brach et al. (2010) across a four-meter walkway and Callisaya et al. (2010) across a four-meter walkway fall into a range from 0.08 to 0.12 m (Brach et al., 2010; Callisaya, Blizzard, Schmidt, McGinley, & Srikanth, 2010). We know that the elderly are associated with a higher risk for falling; the patients with MS are also believed to have a similar risk because of imposed limitations due to the disease progression. Other studies investigating stride length in patients with MS (Martin et al., 2006) have reported values ranging from 0.89 to 1.2 m for the stride length (Benedetti et al., 1999; Givon, Zeilig, & Achiron, 2009). When comparing our values with those in the literature for patients with MS, our stride length for the patients with MS was within this range (0.945 m). Values for step width reported by Gutierrez et al. (2005) in patients with MS were 0.19 m and in our study we found values of 0.11 m (Gutierrez et al., 2005). However, it was found by Owings et al. (2004) that variability of step width while walking on a treadmill decreases, so this could explain our deviation from the literature (Gutierrez et al., 2005; Owings & Grabiner, 2004). These data for stride length and step width reflect that the patients with MS display similar values to those of the elderly. However, the average age of the patients with MS was only 35.4 years.

The decrease in the ApEn measures in patients with MS is in contrast with the change seen in other neurological disease groups when compared with healthy controls. Specifically Parkinson's and Huntington's disease both show an increase in ApEn compared with healthy controls. Both of these conditions are the result of basal ganglia dysfunction, while MS affects nerve conduction in the brain, spinal cord, and peripheral nerves (Noseworthy et al., 2000). We speculate that the increase in regularity of step width and stride length in patients with MS may be the result of this wide spread demyelination where both spinal nerves and supraspinal nerves are affected. Because the spinal cord and supraspinal structures can no longer send and receive signals appropriately, the supraspinal control of walking is decreased in patients with MS. This results in an increased reliance on spinal generated signals to control walking and the increase in reliance on rhythmic stepping patterns. This proposed mechanism would explain the decrease in ApEn values for both step width and stride length, which indicates increased regularity of movement. In addition, MS patients are reported to have large, but delayed automatic postural response latencies, which correlated, with the latencies of their spinal somatosensory evoked potentials (Cameron, Horak, Herndon, & Bourdette, 2008). Because

of these response latencies, it is possible that patients with MS require increased regularity of movement to avoid excess perturbations during walking. While the purpose of this paper is not to compare across pathologies it is worth mentioning that the epidemiology of specific disease processes appears to affect gait variability differently across groups.

To verify that disease severity, according to EDSS, was not a confounding factor in our results, post hoc independent *t* tests were run between the two defined severity groups within the patients with MS. The mean stride length was significantly lower in the moderate severity group compared with the healthy controls while the mild severity group did not have a lower stride length compared with controls. This difference indicates that more severe patients with MS (according to EDSS) have a shorter stride length, which could reflect a strategy employed by the moderate severity group to maintain stability during walking. Examination of treadmill walking speed in two severity groups showed that the moderate severity group walked slower (0.58 m/s), though not significantly, than the mild severity group (0.76 m/s). A slower walking speed on a treadmill would facilitate a shorter step length. If the moderate severity group walked at a faster treadmill speed they would likely have increased stride length to maintain the pace. Overall, there were no differences between the mild and moderate severity groups in any of the variability measures. This lack of differences indicates that grouping all patients with MS, regardless of disease severity, was appropriate. Though the groups did not show statistically different treadmill walking patterns, there is a clinical difference between the mild and moderate patients. The patients were separated based on an EDSS score of greater or less than 4.0. According to the Kurtzke scale (Kurtzke, 1983), MS patients with a score below 4.0 are fully ambulatory without aid. Patients with scores above 4.0 start to have ambulatory problems and may require assistance when walking distances of 200 m. As patient's ambulatory ability worsens, including intermittent or constant aid in the form of a cane or walker, the EDSS score increases (Kurtzke, 1983).

In summary, this study is the first to investigate gait variability of patients with MS. The nonlinear measure of ApEn showed that patients with MS have a more periodic walking pattern with respect to their stride length and step width. This periodic pattern is not the type of variability associated with healthy gait patterns (Harbourne & Stergiou, 2003; Stergiou et al., 2006). Some limitations of the study need to be addressed. First, many of the patients with MS were not familiar with walking on a treadmill. However, the treadmill is essential to examine the variability of the gait pattern over multiple continuous strides. To address this issue, we had the patients with MS walk at their preferred self-selected pace. We also allowed them to hold onto the handrails of the treadmill. Utilizing the handrails can also be a limitation of the study. Chang et al. (2009) found that holding onto a front handrail while walking on a treadmill can produce a significantly higher α value than not holding onto the handrail (Chang, Shaikh, & Chau, 2009). Our α-values were not significantly different from the healthy controls, so this cannot be stated as a reason for difference. In dealing with a neurological population we also wanted to ensure safety while walking on the treadmill so patients without treadmill walking experience were allowed to use the handrails.

To the authors' knowledge, this is the first paper to investigate the differences in gait variability between patients with MS and healthy controls by examining

data with nonlinear variability tools. This study found that patients with MS have a more repeatable and less adaptable pattern of walking. A gait pattern that is inflexible does not allow the patients with MS to properly adjust their gait to meet the demands of the environment and the task. Results should be considered when assessing severity of patients with MS gait disability and when evaluating the effects of pharmaceutical or exercise interventions for the MS population. Both of these interventions should be focused on restoring the system to the optimal healthy status. Such a change may be indicative of learning and a reorganization of the available degrees of freedom (Vaillancourt & Newell, 2000). With this reorganization of the degrees of freedom, patients with MS will demonstrate a more flexible gait pattern and increase their ability to properly respond to a specific task or perturbation.

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