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Dynamic markers of altered gait rhythm in amyotrophic lateral sclerosis

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Hausdorff, Jeffrey M., Apinya Lertratanakul, Merit E. Cudkowicz, Amie L. Peterson, David Kaliton, and Ary L. Goldberger. Dynamic markers of altered gait rhythm in amyotrophic lateral sclerosis. *J Appl Physiol* 88: 2045–2053, 2000.—Amyotrophic lateral sclerosis (ALS) is a disorder marked by loss of motoneurons. We hypothesized that subjects with ALS would have an altered gait rhythm, with an increase in both the magnitude of the stride-to-stride fluctuations and perturbations in the fluctuation dynamics. To test for this locomotor instability, we quantitatively compared the gait rhythm of subjects with ALS with that of normal controls and with that of subjects with Parkinson's disease (PD) and Huntington's disease (HD), pathologies of the basal ganglia. Subjects walked for 5 min at their usual pace wearing an ankle-worn recorder that enabled determination of the duration of each stride and of stride-to-stride fluctuations. We found that the gait of patients with ALS is less steady and more temporally disorganized compared with that of healthy controls. In addition, advanced ALS, HD, and PD were associated with certain common, as well as apparently distinct, features of altered stride dynamics. Thus stride-to-stride control of gait rhythm is apparently compromised with ALS. Moreover, a matrix of markers based on gait dynamics may be useful in characterizing certain pathologies of motor control and, possibly, in quantitatively monitoring disease progression and evaluating therapeutic interventions.

nervous system diseases; Huntington's disease; Parkinson's disease; motor control; nonlinear dynamics

AMYOTROPHIC LATERAL SCLEROSIS (ALS) is a disorder primarily affecting the motoneurons of the cerebral cortex, brain stem, and spinal cord (11, 21). Gait typically becomes abnormal during the course of the disease. A decreased (average) walking velocity has been documented in ALS (14). However, it is unknown whether the loss of motoneurons also perturbs the stability and stride-to-stride dynamics of gait. Such knowledge would enhance the understanding of motor control and might also prove beneficial in monitoring disease progression and in assessing potential therapeutic interventions (6).

In healthy adults, the gait cycle duration, also referred to as the stride time (or interval), fluctuates from one stride to the next in a complex manner (18, 28). These fluctuations can be described both with respect to the fluctuation magnitude (e.g., the variance or SD) and the fluctuation dynamics (how the stride time changes from one stride to the next, independent of the variance). In adults with intact neural control, the fluctuation magnitude is relatively small (~2%) (17, 35). Furthermore, although these fluctuations appear to vary randomly, quantitative analysis demonstrates that they are not random (i.e., uncorrelated noise). Instead, recent evidence indicates that the healthy adult locomotor system actually possesses "memory" such that the change from one stride to the next displays a subtle, "hidden" temporal structure (18, 19, 35). Remarkably, analyses based on statistical physics and nonlinear dynamics reveal that these healthy stride time dynamics have a fractal (self-similar) organization (7, 13): the stride-to-stride variations over small time scales (e.g., a few strides) are statistically similar to those over larger and larger time scales (hundreds and even thousands of strides).

With certain types of neurological disease, the fluctuation magnitude is increased, and the fluctuation dynamics, including those related to the temporal (fractal) organization, are also altered (8, 9, 15, 17, 24). For example, in both Parkinson's disease (PD) and Huntington's disease (HD), two neurodegenerative disorders of the basal ganglia, the ability to maintain a steady walk with small stride-to-stride fluctuations is dramatically impaired. With HD, the temporal organization of these fluctuations is also dramatically altered. In advanced HD, the fluctuation dynamics lose their fractal characteristics, and the stride-to-stride fluctuations become almost completely random (17). Although the effects of basal ganglia disease on the fluctuations in gait rhythm have been studied, the mechanisms that contribute to the magnitude and dynamics of stride-to-stride fluctuations remain largely unknown. In contrast to HD and PD, basal ganglia function is intact with ALS. However, given the loss of motoneurons and the potential degradation of fine motor control in ALS, we hypothesized that ALS would also alter gait rhythm, producing both an increase in the fluctuation magnitude and perturbations in the fluctuation dynamics. To test this hypoth-

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esis and to characterize and quantify the effects of ALS on the motor control of gait, we used a recently developed foot-switch system (16) that enables relatively "long-term," continuous monitoring of stride-to-stride dynamics and analysis methods based on nonlinear dynamics. In particular, we quantified how the gait rhythm in ALS differs from that of pathology-free healthy controls and determined which features of altered gait rhythm are associated both with basal ganglia (i.e., PD and HD) and motoneuron (i.e., ALS) pathology and which are different among these three patient groups.

METHODS

Subjects. Subjects with ALS were recruited from the Neurology Outpatient Clinic at Massachusetts General Hospital. Subjects who were likely to be able to walk independently for 5 min, who did not usually use a wheelchair or assistive device for mobility, and who were free from other pathologies likely to affect gait were asked to participate. Eleven subjects (8 men and 3 women) with ALS participated in the study. The mean age of the subjects was 54.9 ± 13.4 (SD) yr (range 36–70 yr). The number of months since the diagnosis of ALS ranged from 5.5 to 54 with a mean of 21.3. Two subjects had familial ALS. Medication usage was not altered. All subjects provided informed, written consent. The study was approved by the Massachusetts General Hospital Institutional Review Board.

The measures obtained in the subjects with ALS were compared with those previously obtained in HD ($n = 20$), PD ($n = 15$), and healthy control ($n = 16$) subjects as they walked under identical conditions (15). The mean age of the control, HD, and PD subjects was 39 (range 20–74), 47 (range 29–71), and 67 (range 44–80) yr, respectively. The subjects with ALS and PD were, on average, older than both other groups ($P < 0.05$ vs. controls). Control and HD subjects were predominantly women (14 of 16 controls and 14 of 20 HD), whereas subjects with PD were predominantly men (10 of 15). Height of the ALS, HD, PD, and control subjects was 1.73 ± 0.03 (SE) m, 1.83 ± 0.02, 1.87 ± 0.04, and 1.83 ± 0.02 m, respectively. Weight of the ALS, HD, PD, and control subjects was 73.3 ± 6.5, 72.1 ± 3.8 kg, 75.1 ± 4.4, and 66.8 ± 2.8 kg, respectively. Heights and weights of the subjects in the four groups were not significantly different (and height and weight were not significantly correlated with any of the measures of gait dynamics). The presence or absence of clinical symptoms that might affect gait dynamics (e.g., lower extremity weakness) was determined by physical examination and chart review and was coded without knowledge of the measures of gait dynamics.

Assessment of gait dynamics. The protocol was identical to that used previously to study HD and PD subjects (15). Briefly, subjects were instructed to walk at their normal pace along a 77-m-long hallway for 5 min. To measure the gait rhythm and the timing of the gait cycle, force-sensitive insoles (16) were placed in the subject's shoe. These inserts produce a measure of the force applied to the ground during ambulation. A small, lightweight (5.5 × 2 × 9-cm; 0.1-kg) recorder was worn on the ankle and held in place using an ankle wallet. An on-board analog-to-digital converter (12 bit) sampled the output of the foot switches at 300 Hz and stored the data. Subsequently, the digitized data were transferred to a UNIX workstation for analysis by using software that extracts the initial contact time of each stride (16). With this information,[1] the stride time or duration of the gait cycle (time from initial contact of 1 foot to subsequent contact of same foot) was determined for each stride. Each subject's mean gait speed was also determined by dividing the total distance walked by the duration of the walk time. [Mean gait speed of the control subjects was similar to previously reported normal values (2, 27), but measures of gait speed may have been slightly lower than "usual" walking speed because of the additional time required for subjects to turn around at the end of the hallway.] As summarized in the next two sections, several measures were used to quantitatively assess different aspects of the stride time dynamics (17, 20).

Fluctuation magnitude. To study the intrinsic dynamics of the gait rhythm, the time series of the stride time was analyzed as follows (15, 17). The first 20 s of the recorded data were excluded to minimize start-up effects, and a median filter was applied to remove data points that were 3 SDs greater than or less than the median value. These outliers were largely due to the turns at the end of the hallway. The average stride time was determined, and two measures of stride-to-stride variability (fluctuation magnitude) were calculated: *1*) the coefficient of variation (variability normalized to mean value; CV = 100 × SD/mean) and *2*) the SD of the detrended time series ($SD_{detrended}$). Detrending was performed by taking the first difference of the time series. This measure of the magnitude of the stride-to-stride fluctuations minimizes the effects of local changes in the mean by calculating successive stride-to-stride changes (i.e., the difference between the value at 1 stride and the previous stride) of the stride time. (Similar results were also obtained if the SD of the original time series was used.) All calculations were derived by using the right foot.

Fluctuation dynamics. We calculated three measures of the fluctuation dynamics to probe the temporal "structure" of each time series (independent of the overall variance). First, we applied detrended fluctuation analysis (DFA) (18) to each time series. DFA is a modified random walk analysis that can be used to quantify the long-range, fractal properties of a relatively long time series, or, in the case of shorter time series (i.e., the present study), it can be used to measure how correlation properties change over different time scales or observation windows (17). Methodological details have been provided elsewhere (17–19, 23). Briefly, the root-mean-square fluctuation of the integrated and detrended time series is calculated at different time scales, and the slope of the relationship between the fluctuation and the time scale determines a fractal scaling index (α). For a process in which the value at one step is completely uncorrelated with any previous values (i.e., white noise), α equals 0.5. To determine the degree and nature of stride time correlations, we used previously validated methods (17) and calculated α over the region $10 \leq n \leq 20$ (where n is the number of strides in the window of observation). This region was chosen because it has been shown to provide a statistically robust estimate of stride time correlation properties that are most independent of finite size effects (length of data) (17, 29).

As a second, complementary method for analyzing the temporal structure of gait dynamics, we analyzed the autocorrelation of the stride time series. The autocorrelation function estimates how a time series is correlated with itself over different time lags and provides another measure of the

[1] The gait data on which our subsequent analyses are made will be available at http://www.physionet.org, the National Institutes of Health-sponsored *Research Resource for Complex Physiologic Signals*.

memory in the system, specifically for up to how many strides the present value of the stride time is correlated with past values. For an aperiodic signal, the autocorrelation is largest at zero time lag and typically decreases as the time lag increases. Each time series was detrended (subtraction of best-fit line). Then, after direct calculation of the autocorrelation function in the time domain, we quantified how the autocorrelation function decays as a function of time lag: the autocorrelation decay time, defined as the number of strides for the autocorrelation to fall to 63% ($1 - 1/e$) of its initial value. Although both α and the autocorrelation decay time reflect the memory of the system, α and the autocorrelation decay time correspond to relatively long- and short-term effects, respectively. One might speculate that both the autocorrelation decay time and α would be decreased with ALS.

A third measure of the fluctuation dynamics, a normalized nonstationarity index (NSI), was used to evaluate how the local average changes with time, independent of the fluctuation magnitude. To minimize the effects of differences in data length, mean, or variance, the first 100 points of each time series were normalized with respect to the mean SD, yielding new time series each with mean = 0 and SD = 1 but with different dynamic properties depending on how the local values change with time. This normalized time series was then divided into 20 segments, and, in each segment, the (local) average was computed. The NSI, defined as the SD of these 20 means, was then calculated to estimate the dispersion of these normalized, local means. (We note that similar results were obtained if the local averages were calculated over different time scales. Note, too, that for stationary, "long" time series, the NSI metric is related to low-frequency spectral power.) Thus the NSI metric provides a measure of the consistency of the local average values, independent of the overall variance (the fluctuation magnitude) of the original time series. Higher NSI values indicate more inconsistent local averages.

Statistical analysis. For continuous data, the Kruskal-Wallis test was used to test for statistical differences between the four groups. If this test showed significant group differences, multiple Wilcoxon rank-sum tests were performed to compare two groups at a time. These nonparametric tests were used because they make no assumptions about the underlying distribution of the data. A P value ≤ 0.05 was considered statistically significant. Correlations between variables were evaluated by using Spearman's correlation coefficient. Statistical analysis was performed by using SAS software release 6.12 (Cary, NC). Group results are reported as means ± SE.

RESULTS

A representative example of the effects of ALS on gait rhythm and stride time dynamics is shown in Fig. 1. Two features are visually apparent. First, the average stride time, the gait cycle duration, is much longer for this subject with ALS compared with that of the control subject. Second, the stride time varies from one stride to the next to a much larger extent in the ALS subject.

The changes in gait rhythm dynamics shown in Fig. 1 were characteristic of the ALS group as a whole (Table 1). The average stride time was significantly longer in subjects with ALS compared with that of the control subjects and also compared with that of subjects with HD and PD. Walking speed of subjects with ALS was lower than that of controls and similar to that of

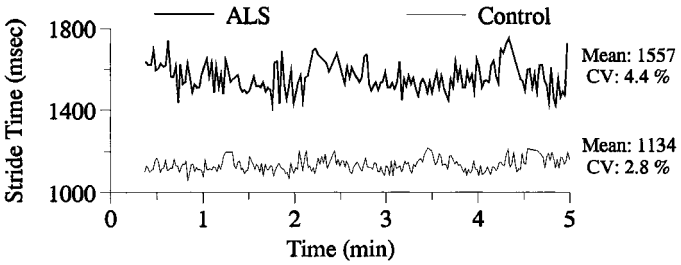

Fig. 1. Representative time series of a 43-yr-old man with amyotrophic lateral sclerosis (ALS; disease duration of 17 mo) and a healthy 74-yr-old male control subject. Average stride time and magnitude of stride-to-stride fluctuations are much larger for the subject with ALS. CV, coefficient of variation.

subjects with HD and PD. In addition, all measures of the magnitude of the stride-to-stride fluctuations were significantly increased in subjects with ALS compared with those of controls. These measures of stride variability were about twice as large in the ALS subjects compared with those of controls. This increased variability is similar to that observed in PD but was much lower than that seen in subjects with HD (see Table 1).

Two measures of the temporal structure of the fluctuation dynamics, α and the autocorrelation decay time, tended to be lower in the subjects with ALS compared with the controls (Table 1). The NSI of the subjects with ALS was similar to that observed in controls and significantly higher compared with that of subjects with HD.

To determine whether the stride characteristics of subjects with ALS were simply related to muscle fatigue during this 5-min walk, we recalculated measures of the stride dynamics (except for those pertaining to the fluctuation dynamics which require longer data sets) using only the first 60 strides of each subject's time series. The results are similar to those shown in Table 1. Compared with control subjects, the subjects with ALS walked with a longer stride time and increased stride-to-stride variability, even when only the first 60 strides are examined.

To further study the relationship between ALS and gait disturbances and to begin to examine how differences in ALS symptoms affect gait dynamics, we stratified the subjects with ALS on the basis of symptoms and the site of symptom onset. All subjects with ALS had symptoms of weakness, 8 had cramps, and 10 had fasciculations. In addition, seven had speech-related, five had swallowing-related, and four had breathing-related symptoms. The disease was heralded by lower extremity symptoms in three subjects, upper extremity symptoms in five subjects, and bulbar region symptoms in three subjects. Pyramidal signs were observed in all subjects, increased lower extremity tone was observed in five subjects, and cerebellar signs were not observed in any subjects. When comparing the ALS subjects with or without these symptoms, we found few differences in gait dynamics among any of the subgroups (e.g., a comparison of limb vs. bulbar onset). Changes in temporal structure of the fluctuation dynamics (specifically, stride time NSI) were lower in the ALS patients with breathing difficulties compared with patients without

Table 1. *Gait rhythm dynamics*

	ALS	HD	PD	CO
Average values				
Stride time, ms	1,370 ± 61	1,138 ± 38†	1,118 ± 30†	1,091 ± 23§
Speed, m/s	1.02 ± 0.07	1.15 ± 0.08	1.00 ± 0.05	1.35 ± 0.04‡
Fluctuation magnitude				
Stride time CV, (%)	4.5 ± 0.6	7.6 ± 1.2	4.4 ± 0.6	2.3 ± 0.1†
Stride time $SD_{detrended}$, ms	65 ± 10	120 ± 25	52 ± 6	27 ± 2‡
Fluctuation dynamics				
α	0.74 ± 0.07	0.60 ± 0.04	0.82 ± 0.06	0.91 ± 0.05
Autocorrelation decay time	4.2 ± 0.6	3.2 ± 0.5	7.2 ± 1.6	5.9 ± 0.4*
Nonstationarity index	0.69 ± 0.05	0.54 ± 0.03*	0.64 ± 0.03	0.67 ± 0.02

Values are means ± SE. CV, coefficient of variation; α, fractal scaling index; ALS, amyotrophic lateral sclerosis; CO, controls; HD, Huntington's disease; PD, Parkinson's disease; $SD_{detrended}$, SD of the detrended time series. Gait speed was not measured in 2 ALS subjects. Compared with controls, gait speed and fluctuation magnitude measures were different in HD and PD subjects, but stride time was similar in these groups. Measures of fluctuation dynamics were also different in HD compared to CO subjects. Gait speed and stride time were similar in the subjects with HD and PD, but all measures of the fluctuation magnitude and dynamics were significantly different in these 2 groups. Kruskal-Wallis tests detected significant differences among the 4 groups for all measures. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$, §$P < 0.0001$ compared with subjects with ALS.

($P < 0.05$) and tended to be lower in ALS patients with difficulty with speech compared with those without ($P = 0.07$). Other measures, including mean age, gait speed, stride time, and stride time CV, were similar in those with and without breathing or speech difficulties.

The medication most frequently used by the ALS patients was riluzole (a presynaptic glutamate-release inhibitor). Stride time CV tended to be lower in those taking riluzole ($n = 7$) compared with those not ($n = 4$; $P = 0.07$). Three patients were taking procsysteine and two neurontin, and the gait of patients taking these agents did not appear to differ from the gait of other subjects with ALS. However, with relatively small numbers in these subgroups, there may be insufficient statistical power to detect subtle differences.

Among all neurological patients, pyramidal symptoms were present in all subjects with ALS and were absent in all but one subject with HD and one subject with PD. Extrapyramidal signs were present in all subjects with HD and PD and in two subjects with ALS. Cerebellar signs were evident only in one subject with PD. Lower extremity weakness was evident in all but one subject with ALS and none of the subjects with HD or PD. Increased lower extremity tone was evident in five subjects with HD, nine subjects with PD, and five subjects with ALS. Thus the presence or absence of symptoms of weakness, pyramidal, or extrapyramidal signs was largely determined by the presence or absence of basal ganglia disease (vs. ALS). In contrast, increased lower extremity tone was not uncommon in HD, PD, and ALS, although the prevalence was group dependent ($P < 0.04$). Multivariate logistic regression analysis showed that, compared with HD and PD subjects, an increased stride time remained characteristic of subjects with ALS ($P < 0.05$), even after controlling for lower extremity tone. Similarly, the difference in the NSI of subjects with ALS and HD (Table 1) persisted after adjustment for increased lower extremity tone.

Among subjects with HD, the number of rapid finger taps achieved in 5 s was also assessed. The number of taps may reflect the severity of upper extremity dysfunction and may help clarify the clinical profile of the HD patients, because rapid tapping requires smooth motor unit recruitment and discharge frequency modulation (25). All measures of gait dynamics were significantly associated with tapping ability, whereas average stride time and gait speed were not. Measures of the fluctuation magnitude were inversely associated with tapping ability (e.g., $r = -0.63$ and $P = 0.004$ for stride time $SD_{detrended}$). The three measures of fluctuation dynamics were also associated with tapping ability (e.g., $r = 0.53$, $P = 0.02$; and $r = 0.50$, $P = 0.03$ for α and NSI, respectively).

Effects of degree of functional impairment . The three patient groups consisted of subjects with varying degrees of impairment. To further study the effects of pathophysiology on gait dynamics and to examine whether measures on the basis of gait dynamics might be useful in augmenting clinical assessment, we compared the different patient groups with the controls after stratifying the neurological patients into two groups: mild lower extremity functional impairment (gait speed greater than or equal to the median value of all patients; 1.05 m/s) and more advanced functional impairment (gait speed less than the median value). Gait speed was used because it is often employed as a simple marker of lower extremity function (3, 30).

On the basis of this division, only four subjects with ALS were considered mildly impaired. Even in this small subgroup, an increased stride time ($P < 0.01$) and a decreased autocorrelation decay time ($P < 0.04$) were evident compared with the healthy control subjects. Among HD subjects with relatively mild impairment, all measures of the fluctuation magnitude and fluctuation dynamics were significantly different compared with those of the control subjects, except for the NSI for which the difference was marginal ($P = 0.1$). Among PD subjects with relatively mild impairment, measures of the fluctuation magnitude were significantly increased compared with those of controls. Gait speed was not significantly different from that of the controls in any of the three patient groups with only mild impairment.

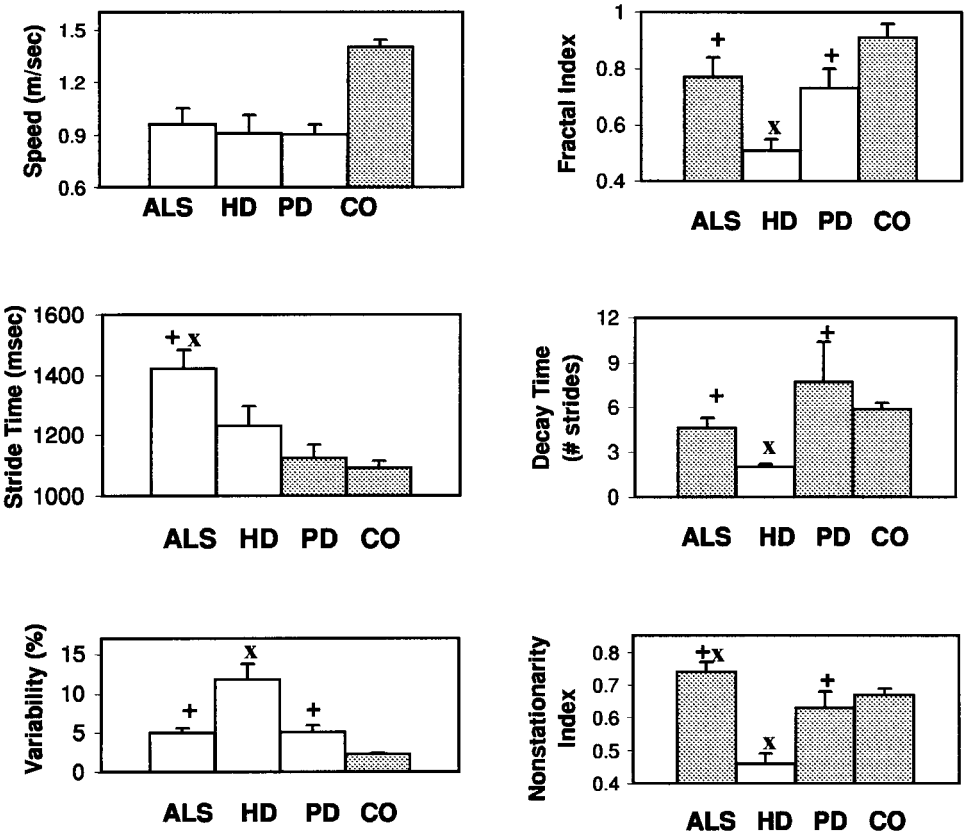

Fig. 2. Comparison of effects of advanced ALS, Huntington's disease (HD), and Parkinson's disease (PD) on stride dynamics. Values are mean ± SE for subjects with more severe impairment (Hoehn and Yahr score ≥3 for PD subjects, $n = 9$; total functional capacity score ≤5 for HD subjects, $n = 9$; and stride time >1.2 s for ALS subjects, $n = 9$). In this subset of patients, average age and gait speed were very similar in all 3 patient groups. Note that certain alterations in dynamic measures of gait rhythm were disease specific. Stippled bars, values of control (CO) group and group values not significantly different from CO group; open bars, values statistically different from CO group. $^{+}P < 0.05$ compared with HD subjects; $^{x}P < 0.05$ compared with PD subjects (except that difference between ALS and PD was $P = 0.06$ for the nonstationarity index and was $P < 0.07$ for the fractal scaling in a comparison of HD with PD, and HD with ALS). Variability measure shown here is the CV, but similar results were obtained with both measures of stride time fluctuation magnitude. Note, too, that, although there are some distinctions, similar group differences are obtained if subjects are not stratified on the basis of disease severity (see Table 1).

Among subjects with more advanced functional impairment, the fluctuation magnitude was significantly increased and gait speed was significantly reduced in subjects with ALS, HD, and PD, compared with the controls. Stride time was significantly increased in ALS and HD but not in PD. The three measures of the fluctuation dynamics were also significantly different in HD and controls.

Comparison of gait dynamics in ALS, PD, and HD. As noted above and in Table 1, there appear to be differences among the three patient groups, perhaps reflecting differences in neuropathology. To further evaluate the effects of the different neurological impairments on gait and any specificity of the changes in gait rhythm, we compared subjects with more severe levels of functional impairment to each other (i.e., gait speed less than the median value). Among these subjects, stride time was increased in subjects with ALS compared with subjects with HD and PD ($P < 0.04$). The magnitude of the stride time fluctuations was increased in subjects with HD compared with subjects with PD and ALS ($P < 0.05$). The three measures of fluctuation dynamics were lower among subjects with HD compared with subjects with PD ($P < 0.05$). The NSI was also lower in subjects with HD compared with subjects with ALS (and PD; $P < 0.05$) and tended to be increased in subjects with ALS compared with PD subjects ($P = 0.1$).

Another way of characterizing impairment is to use functional scales. HD patients with total functional capacity (33) scores ≤5 and PD patients with Hoehn and Yahr scores ≥3 were compared with ALS subjects with more advanced alterations in gait (15). A specific measure of disease severity was not available for the subjects with ALS. However, it appears that increased stride time may be characteristic of ALS (see Table 1) and may serve as a surrogate for disease severity in these patients. Thus ALS subjects with increased stride time (>1.2 s; among all subjects, a stride time above 1.2 s corresponds to the upper quartile) were identified as having advanced disease. As shown in Fig. 2, average gait speed is comparably reduced in all three patient groups with advanced disease compared with that of controls. In contrast, average stride time is significantly increased in subjects with ALS compared with HD and PD, whereas measures of the fluctuation magnitude are similar in PD and ALS and significantly increased in subjects with HD. As summarized in Table 2, all group differences are similar to those observed when gait speed is used as the marker of level of impairment.

In the subjects with advanced disease, α tended to be lower in ALS and PD compared with controls. In subjects with advanced HD, all measures of the temporal organization were significantly altered with respect to controls, reflecting shorter memory and more randomness in the stride dynamics of HD (Table 2). The autocorrelation decay time was significantly reduced in HD compared with ALS, PD, and the controls. The NSI was different in all three patient groups, providing complete separation between the ALS and HD patients. These group differences are very similar to those ob-

Table 2. *Gait rhythm in advanced disease*

	ALS	HD	PD
↓ Average speed	*	*	*
↑ Average stride time	*†	*	
↑ Stride variability (CV)	*	*†	*
↓ Autocorrelation decay time		*†	
↓ Fractal scaling (α)		*†	*
↑ Nonstationarity index	†		
↓ Nonstationarity index		*†	

↓, Decrease; ↑, increase. *Measures that are significantly different ($P < 0.05$) from normal control values. †Apparently distinguishing feature ($P < 0.05$) of one of these three specific neurological syndromes among subjects with advanced disease (see Fig. 2).

tained when subjects were classified on the basis of gait speed.

To identify those gait parameters that specifically characterize the three different disease states, we compared the subjects with advanced ALS with the other subject groups having advanced disease. This process was repeated for subjects with HD and PD. The results (Table 2) indicate that a longer stride time and an increased NSI are prominent features of advanced ALS. Increased fluctuation magnitude, decreased memory (as evidenced both by α and decay time), and decreased NSI are markers of advanced HD. When viewed as a single group, all measures of gait rhythm except the NSI were significantly altered with respect to control values among all subjects with advanced neurological disease. Multiple logistic regression indicated that a lower α and a reduced gait speed are the two independent features of altered gait dynamics of these subjects with advanced neurodegenerative disease. Similar results were obtained if *1*) the definition of "advanced disease" was based on gait speed or *2*) subjects within each group were ranked by each gait measure and those subjects who were not in the quartile closest to the values observed in the controls were studied.

Comparison of dynamic markers of gait rhythm. To evaluate whether average stride time, fluctuation magnitude, and fluctuation dynamics are independent, we studied the relationships among these different qualities of gait rhythm. These findings (Table 3) indicate the following. *1*) Gait speed, average stride time, and stride time variability (fluctuation magnitude) are highly correlated with each other. However, much of the variance in each measure is not explained by the association with the other (i.e., $r < 1.0$). *2*) Similarly, the three measures of fluctuation dynamics are significantly correlated with each other, although these three measures are not redundant. As illustrated in Fig. 2, NSI and α show different behavior among subjects with more advanced disease. *3*) The three measures of fluctuation dynamics are independent of gait speed and stride time.

DISCUSSION

This study demonstrates that, compared with healthy subjects, the gait rhythm of patients with ALS is altered in several ways: *1*) average stride time is significantly longer and average walking speed is significantly slower, 2) measures of the magnitude of stride-to-stride variability are significantly increased, and 3) the fluctuation dynamics are perturbed (Table 1). The decreased average gait speed and increased stride time are similar to those previously reported (14). Here we extend those findings by quantitatively demonstrating, for the first time, that gait stability and the stride-to-stride control of walking are also affected in ALS. In addition to walking more slowly and with more time spent in each stride, patients with ALS have a gait that is less steady and more temporally disorganized compared with that of healthy controls. Furthermore, we find that new measures of gait dynamics provide information about the regulation of locomotor function that is independent of conventional measures of walking, namely average gait speed and stride time (Table 3), and that these measures may be altered even before changes in gait speed are evident.

Potential mechanisms of gait alterations in ALS. ALS is marked by muscle weakness, decreased endurance, and muscle fatigability (31, 32). These factors may result in a reduced walking speed and an increased stride time (14). An earlier study (14) showed that gait speed was correlated with muscle weakness in ALS. However, muscle weakness by itself would not necessarily be expected to alter gait rhythm and the stride-to-stride control of walking. Indeed, an increased stride time and alterations in gait dynamics were observed even among the ALS subjects with relatively intact gait speed. In addition, among all ALS subjects, increased stride time and stride-to-stride variability were apparent even during the initial 60 strides of the walk, when muscle fatigue is less likely to play a role and the need for long-term endurance is minimized. Lower extremity tone did not appear to be responsible for these changes.

Table 3. *Correlations among measures of gait rhythm*

	Speed	Stride Time	Variability	Decay Time	Fractal scaling (α)
Average speed					
Average stride time	−0.51 (0.0001)				
Stride variability (CV)	−0.58 (0.0001)	0.35 (0.006)			
Autocorrelation decay time	NS	NS	−0.33 (0.009)		
Fractal scaling (α)	NS	NS	−0.38 (0.003)	0.71 (0.0001)	
Nonstationarity index	NS	NS	NS	0.69 (0.0001)	0.64 (0.0001)

Spearman correlation coefficients are shown with the associated *P* values in parentheses when different gait parameters among all subjects are compared. Similar results were obtained by using the Pearson correlation coefficient. NS, not significant (in these instances $P > 0.20$). The 2 measures of fluctuation magnitude (stride time CV and stride time $SD_{detrended}$) were highly correlated ($r = 0.95$; $P < 0.0001$).

The role of weakness, tone, and decreased muscle endurance in the alterations of gait dynamics in ALS requires further study; however, it seems possible that the observed changes in gait stability may be due to other mechanisms as well.

In addition to loss of motoneurons, other neuromuscular properties are also affected with ALS (22, 26, 36). For example, the motor cortex is hyperexcitable, muscle fiber conduction velocity decreases, mechanical efficiency is reduced, and muscle activation distal to the muscle membrane may be impaired (4, 5, 31, 32, 34, 36). Whereas healthy subjects generate a reproducible motoneuronal response to magnetic stimulation, the motor units of patients with ALS exhibit marked variability in their response (4, 5). Such pathological changes could potentially contribute to the observed unstable alterations in the stride-to-stride control of gait rhythm in ALS.

Gait rhythm in ALS compared with basal ganglia diseases. Among patients with ALS, HD and PD, neurological impairment is associated with certain common features of altered stride dynamics as well as with those that appear to be more dependent on the specific disease. One common feature is reduced gait speed (Tables 1 and 2, Fig. 2). Although this feature may be a general marker of neurodegenerative disease, it is not a distinguishing feature among these disorders.

Stride-to-stride variability is also increased in all three groups. However, with HD the increase is almost twice as large as in PD and ALS. With HD, multiple aspects of stride-to-stride control are significantly impaired, with respect to both normal subjects and subjects with ALS and PD. In contrast, with PD and ALS, changes are seen only in a subset of gait parameters (Fig. 2). A key distinguishing feature of gait in ALS is the markedly increased stride time. Compared with HD and PD, the time spent in each gait cycle is much larger, perhaps reflecting differences in neuropathology.

Certain changes in fluctuation dynamics also appear to be different among subjects with ALS, PD, and HD (Table 2). Comparison of the NSI among those with more advanced neurodegenerative disease is interesting for a number of reasons (Fig. 2): *1*) this index was different in all three patient groups; *2*) there was no overlap when the values obtained in ALS and HD subjects were compared; *3*) in contrast to other measures of gait dynamics, in which differences among the three patient groups were due to effect size (e.g., fluctuation magnitude was increased in both PD and ALS compared with normals but increased further in HD), the effects of ALS and HD on this nonstationarity measure were in opposite directions; and *4*) whereas measures of stride-to-stride variability were much larger in HD than in ALS, the NSI was significantly smaller in HD, indicating markedly different dynamics and changes in the underlying control system. The mechanisms underlying these differences are unknown, and it remains to be determined whether these distinctions are specific to the groups studied or whether they also occur in other disorders that share common pathology and symptomatology. Nonetheless, future attempts to understand and model locomotor control under healthy and pathological conditions will need to account for these observed qualitative and quantitative differences in both fluctuation magnitude and dynamics.

Limitations and potential implications. This study has a number of limitations. *1*) The groups were not matched with respect to age and gender. However, previous studies of healthy subjects have found no gender effects on the study of gait variability during usual walking (12), and it seems likely that any effects of gender would be small compared with the large effects that we observed. Earlier studies also reported no age effect on gait variability of healthy subjects (12, 17), but the effect of age on fluctuation dynamics of stride is more complex (17). Evidence suggests that the effects of neurodegenerative disease are much more pronounced than those due to physiological aging (12, 15, 17). Figure 1 illustrates that the gait dynamics of a 43-yr-old man with ALS are markedly abnormal compared with a much older, healthy 74-yr-old man. Although additional studies are needed to further examine the effects of gender and age on gait rhythm dynamics, it seems likely that such effects are relatively small compared with the effects of disease (Fig. 2). *2*) Subjects were also not perfectly matched with respect to height. However, it is important to note that when the ALS and control subjects are compared, the mean difference in height is ~5%, whereas the difference in stride time is 26% and the difference in stride time CV is 96%. Thus any differences in height do not seem likely to have been responsible for the increased stride time or increased stride time fluctuation magnitude in ALS (compared with controls). *3*) Because of the relatively small number of subjects in each group, it is possible that we failed to detect more subtle distinctions among the groups, especially in any subgroup analysis ("type 2 error"). *4*) By recruiting subjects likely to be able to walk independently for 5 min, we may have focused our study on relatively less impaired patients. For some subjects, a 5-min walk may be a maximal challenge, but for others it may be a relatively simple task. However, as noted in RESULTS, we found similar results when analyzing only the first minute of walking. *5*) It may be helpful to see how the alterations in gait dynamic in ALS correspond to scores on the recently developed scale for assessing function in ALS (1) and to study the effects of early and advanced disease by using common and disease-specific measures of clinical function. *6*) Finally, the present study focused on gait rhythm as measured by the stride time by using a lightweight, portable foot-switch system (16) in an outpatient clinic. Additional information regarding the alterations of gait in ALS might be provided by studying other aspects of walking, including changes in kinematics and kinetics, and by obtaining stride-by-stride measures of stride length and gait speed.

Further understanding of the origin and mechanisms of these and other neurological disorders is essential to more completely characterize the underlying pathophysiologies, and to define both common and distinct

pathways that bring about alterations in specific aspects of gait and stride dynamics. For example, it will be important to determine whether the alterations in stride time dynamics observed in ALS, both increased fluctuation magnitude and altered fluctuation dynamics, are common to other patient groups with lower extremity weakness. Future study of a larger group of subjects with ALS may also help provide additional insight into the observed and other subtle distinctions in gait rhythm dynamics related to clinical symptomatology (e.g., respiratory function), medication usage, and genetic factors. Recent studies offer hope for the treatment of ALS and other neuropathologies (6) and further motivate the need for quantitative, clinically acceptable methods that objectively quantify disease state and progression in ALS and other neurodegenerative diseases and the effects of pharmacological agents on function (10). The present study provides the basis for future studies addressing these important questions. Even before changes are observed in gait speed, there appear to be marked alterations in gait dynamics in ALS, PD, and HD. Some of these perturbations are apparently group specific, perhaps reflecting the distinctions in neuropathology, and may assist in initial, early diagnosis. Our results suggest, that when combined with other clinical indexes, a matrix of measures (Table 2) based on gait rhythm dynamics may be useful for augmenting our ability to objectively track disease progression and, perhaps, for quantifying even subtle effects of potential therapeutic interventions.

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