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Gait Variability and Basal Ganglia Disorders: Stride-to-Stride Variations of Gait Cycle Timing in Parkinson's Disease and Huntington's Disease

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Summary: The basal ganglia are thought to play an important role in regulating motor programs involved in gait and in the fluidity and sequencing of movement. We postulated that the ability to maintain a steady gait, with low stride-to-stride variability of gait cycle timing and its subphases, would be diminished with both Parkinson's disease (PD) and Huntington's disease (HD). To test this hypothesis, we obtained quantitative measures of stride-to-stride variability of gait cycle timing in subjects with PD (n = 15), HD (n = 20), and disease-free controls (n = 16). All measures of gait variability were significantly increased in PD and HD. In subjects with PD and HD, gait variability measures were two and three times that observed in control subjects, respectively. The degree of gait variability correlated with disease severity. In contrast, gait speed was significantly lower in PD, but not in HD, and average gait cycle duration and the time spent in many subphases of the gait cycle were similar in control subjects, HD subjects, and PD subjects. These findings are consistent with a differential control of gait variability, speed, and average gait cycle timing that may have implications for understanding the role of the basal ganglia in locomotor control and for quantitatively assessing gait in clinical settings. **Key Words:** Gait analysis—Time series analysis—Motor control.

Disorders of the basal ganglia are associated with characteristic changes in gait. Patients with Huntington's disease (HD) often display an uncoordinated, lurching walk,[1,2] while the gait of subjects with Parkinson's disease (PD) is marked by slowness, postural instability, small shuffling steps, and difficulty in initiation.[3–7] We sought to determine whether the ability to accurately regulate variations in gait cycle timing is also impaired in these disorders. To this end, we evaluated the stride-to-stride variability of gait cycle timing in HD and PD.

Gait cycle duration, or cadence, and the ability to modulate gait cycle duration apparently are unaffected in PD.[5,8–10] Indeed, some authors observed that rhythmicity and the stepping pattern remain intact with PD.[8,10,11] However, there is some evidence that rhythmicity, as manifested in the stride-to-stride variations in gait cycle timing, does depend on basal ganglia function. Gabell and Nayak[12] speculated that increased variability of double support timing (when both feet are in contact with the ground) may be related to impaired balance control, while increased variability of gait cycle duration reflects a failure of the automatic stepping mechanisms. Because the basal ganglia are thought to play an important role in initiating and regulating motor programs involved in balance, gait, and the fluidity and sequencing of movement,[9,13] stride-to-stride regulation of double support and gait cycle duration may both be affected with basal ganglia disease. Moreover, during short walks, a significant increase in stride length variability in PD subjects was observed[14] and increased variability of the electromyogram of the gastrocnemius, a muscle critical to gait cycle timing, was also reported in PD.[15] Variable walking speed and variable step length have been observed in HD subjects.[1] However, these parameters have not been quantitatively measured. Furthermore, because different areas of the basal ganglia are

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involved with PD and HD and the associated gait disorders differ in these two pathologies, stride-to-stride variability measures may also be different in PD and HD.

To assess stride-to-stride variability, we used a recently developed method[16] to quantify relatively "long-term" (5 minutes) stride-to-stride variations of the gait cycle (stride time) and its subdivisions (for example, double support and swing time) in subjects with HD and PD. We hypothesized that (a) stride-to-stride variability of gait cycle timing and its subphases would be increased in both diseases, (b) gait variability would increase with disease severity, and (c) the differences in pathophysiology underlying HD and PD would produce distinct perturbations in the ability to regulate walking.

METHODS

Subjects

Subjects with HD and idiopathic PD were recruited from the Neurology Outpatient Clinic at Massachusetts General Hospital (MGH). Subjects were selected based on their ability to walk independently for 5 minutes. Twenty subjects with HD and 15 subjects with PD participated in the study. Medication use was not altered. Eleven of the PD subjects reported motor fluctuations; all were tested in the "on" phase and no episodes of "freezing" or dyskinesias were observed. Sixteen control subjects who were without neurologic illness and gait abnormalities were recruited from the general community. All subjects provided informed, written consent. The study was approved by the MGH Institutional Review Board.

HD subjects were assessed using the Unified HD Rating Scale[17] and the degree of neurologic impairment was evaluated using the Total Functional Capacity (TFC)[18] score (0 = most severe; 13 = healthiest). The TFC score correlates with positron emission tomography scan indices of caudate metabolism.[19] The Hoehn and Yahr (H & Y) scale (5 = most severe; 1 = healthiest) was used to assess degree of neurologic impairment in subjects with PD.[20] Subjects underwent a medical history and examination.

There was a wide range of neurologic impairment in both disease groups. Six HD subjects had TFC scores above 9, seven had TFC scores ranging from 5–9, and seven subjects had TFC scores less than 5. Chorea scores for each body segment of the HD subjects ranged from 0 (absent) to 4 (severe) and the average values were approximately 1.5 (slight/intermittent—moderate). Dystonia scores (the sum of 5 body segments) ranged from 0 (absent) to 9 with the mean (and median) near 3.5. Among the HD patients, signs of depression, confusion, and dementia were present in 7, 5, and 6 subjects, respectively. Antidepressants and neuroleptics were used by 9 and 6 subjects, respectively. HD subjects were free of other neurologic disease or comorbidities and were not taking other medications that might affect gait. Two PD patients had H & Y scores of 1 or 1.5, four had scores of 2 or 2.5, five had scores of 3, and four had scores of 3.5 or 4. Among PD subjects, coronary artery disease ($n = 1$), hypothyroidism ($n = 1$), and anxiety ($n = 1$) were comorbidities. All PD subjects were taking Sinemet (DuPont Pharmaceuticals, Wilmington, DE, U.S.A.).

The mean age of the control subjects, HD subjects, and PD subjects was 39 (range, 20–74), 47 (range, 29–71), and 67 (range, 44–80), respectively. The subjects with PD were, on average, significantly older than both other groups ($p < 0.0003$ versus control subjects). The age of the HD subjects was not significantly different from the control subjects. Control and HD subjects were predominantly female (14 of 16 control subjects and 14 of 20 HD subjects), while subjects with PD were predominantly male (10 of 15) ($p < 0.006$; PD subjects versus control subjects). Height and weight of the three groups were not significantly different.

Assessment of Gait Function

Subjects were instructed to walk at their normal pace up and down a 77 meter-long hallway for 5 minutes. A self-determined pace was chosen because in healthy subjects, walking variability is minimized at this rate.[21] To measure the temporal parameters of gait, force-sensitive insoles[16] were placed in the subject's shoes. These inserts produce a measure of the force applied to the ground during ambulation. The output was sampled continuously at 300 Hz, stored in an ankle-worn recorder, and analyzed in software that determined initial and end contact times of each stride. The following six gait parameters were calculated for each gait cycle: (1) stride time or duration of the gait cycle (time from initial contact of one foot to subsequent contact of same foot); (2) swing time (amount of time one foot is in the air), (3) percentage swing time (100 × swing time/stride time), (4) double stance time (time of bilateral foot contact), (5) percentage double stance time (100 × double stance time/stride time), and (6) step time (time from initial contact of one foot to initial contact of the other foot). Each subject's mean gait speed was also determined.

Each of the six gait parameters was analyzed as follows. The first 20 seconds were removed to minimize start-up effects and a median filter was applied to eliminate any outliers with respect to the median.[22] The outliers were largely the result of the turns at the end of the hallway and were filtered so that the intrinsic dynamics

of each time series could be analyzed. The average of each parameter was determined and three measures of stride-to-stride variability were calculated for each parameter: (1) the standard deviation (this reflects the dispersion about the average value); (2) the coefficient of variation (variability normalized to mean value) (CV = 100 × standard deviation/mean); and (3) the standard deviation of the first differenced time series (defined below).

The standard deviation and CV provide a measure of overall variations in the gait during the 5-minute walk, that is, how large are the fluctuations in the time series with respect to the mean. However, these measures may be influenced by trends in the data (for example, resulting from a change in speed) and can not distinguish between a walk with large changes from one stride to the next and one in which stride-to-stride variations are small and more global changes (for example, a change in average value) result in a large standard deviation. To minimize effects of local changes in the mean, we quantified the successive stride-to-stride changes (that is, the difference between the stride time of one stride and the previous stride) by determining the first difference of each of the six time series. The first difference, a discrete analog of the first derivative, is a widely used method for removing trends and is calculated by subtracting the previous value in the time series from the current value.

Unless stated otherwise, all calculations are derived using the right foot as a reference. Left and right foot timing is usually similar; however, there may be asymmetry in the presence of disease. To estimate asymmetry, we calculated the absolute value of the difference between the mean step times for left and right foot. To assess whether the results were dependent on any asymmetry, we compared all the results: (a) using the left foot as the reference; (b) using the right foot of the control subjects and "worst" foot as the reference for the HD and PD subjects; and (c) using the right foot for the control subjects and the "best" foot as the reference for the HD and PD subjects (best and worst are relative to control subjects).

Statistical Analysis

For continuous data, the Kruskal-Wallis test was used to test for statistical differences among the three groups. If this test showed significant group differences, multiple Wilcoxon Ranked 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. Because of the multiple comparisons, an alpha level of $p \leq 0.01$ was used as the level for statistical significance. For categorical data, Fisher's exact test was used to test for group differences. Correlations between disease severity and gait measures were evaluated using Spearman's correlation coefficient. Regression analysis using a stepwise procedure was performed to determine which variables were independently associated with disease severity and to identify which parameters were most characteristic ("predictive") of the patient populations. Statistical analysis was performed using SAS software release 6.09 (Cary, NC, U.S.A.). Group results are reported as mean ± standard deviation.

RESULTS

Timing of the Gait Cycle and Its Subdivisions

Figure 1 illustrates the stride time dynamics of PD, HD, and control subjects 64, 59, and 47 years old, respectively. For this PD subject, stride-to-stride fluctuations about the mean are even larger than that of the control subject. These fluctuations are larger in the HD subject. In contrast, the mean values of each time series are similar. In general (Table 1), stride time CV of subjects with PD was almost twice that observed in control subjects ($p < 0.0001$); it was more than three times larger in subjects with HD compared with control subjects ($p < 0.0001$). Values of average stride time were lowest in the control subjects, intermediate in the subjects with PD, and highest in subjects with HD; however, these differences were not statistically significant.

For all subphases of the gait cycle, stride-to-stride variability was lowest in the control subjects, significantly increased in subjects with PD, and further increased in subjects with HD (Table 1). Variability was often two times larger in PD subjects and three times larger in HD subjects compared with control subjects. The results of each Kruskal-Wallis test performed to determine if there was any group effect were identical for all measures of variability: $p < 0.0001$. Differences between HD and PD were generally marginally significant ($.01 < p < 0.1$) as a result, in part, to the wide range in disease severity.

In contrast to the variability measures, the average time spent in different phases of the gait cycle did not consistently distinguish the HD, PD, and control subjects (Table 2). Subjects with HD and PD tended to have longer gait cycles and spend more time with the feet in contact with the ground, both in absolute time and when normalized as a percentage of the gait cycle duration. This is reflected in increased double support times (and percentage) and lower swing times (and percentage). However, control subjects and the subjects with HD were not statistically different with respect to average gait tim-

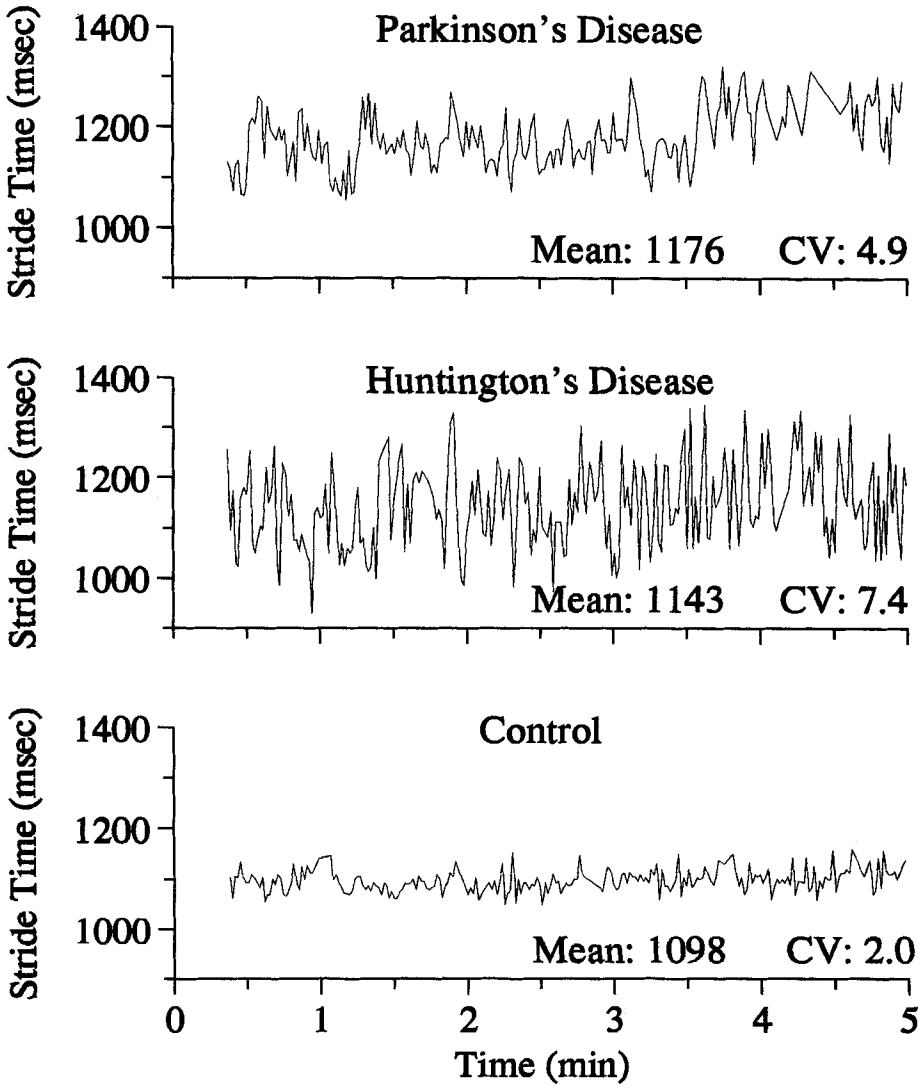

FIG. 1. Examples of stride time (gait cycle duration) in PD, HD, and control subjects. Mean values of stride time, averaged over the 5-minute walk, were similar in the three subjects. In contrast, the coefficient of variation (CV), a measure of stride-to-stride variability, was smallest in this control subject, larger in this PD subject, and larger still in this HD subject.

ing. In PD subjects, several parameters indicative of bradykinesia and more time spent with feet in contact with the ground (that is, walking speed, percentage swing time, double support time, and percentage double support time) were statistically different from that of the control group.

Other Measures of Variability

After detrending each time series by taking the first difference, there was still a significant increase in all measures of stride-to-stride variability, especially in subjects with HD (Table 3). To confirm that the large increase in stride-to-stride variations was not simply the result of changes in speed (perhaps resulting from fatigue during the walk), we calculated the average stride time and its variability using only the first and last 60 strides of the filtered time series. Similar findings were observed in these time segments as well. For example, during the first 60 strides, average stride time was 1091 ± 98, 1125 ± 100, and 1139 ± 167 msec in the control, PD, and HD subjects, respectively ($p > 0.4$, not significant). Stride time CV was 2.3 ± 0.5, 4.0 ± 1.3, and 7.0 ± 5.2 in the control, PD, and HD subjects, respectively ($p < 0.0001$). Thus, all analysis methods consistently showed a significant increase in variability measures in PD and a further increase in HD.

The left–right asymmetry measure was larger in both HD and PD subjects compared with control subjects, and

TABLE 1. *Gait timing: variability**

	Controls	Huntington's	Parkinson's	p values† CO vs. HD	p values† CO vs. PD
Stride time CV	2.3 ± 0.5	7.6 ± 5.6	4.4 ± 2.1	.0001	.0001
Swing time CV	3.4 ± 0.9	13.0 ± 10.7	7.7 ± 4.1	.0001	.0001
% swing time CV	2.6 ± 0.9	9.6 ± 8.1	5.7 ± 2.9	.0001	.0005
Double support time CV	5.8 ± 1.1	13.1 ± 6.8	8.5 ± 1.9	.0001	.0003
% double support time CV	4.8 ± 1.1	11.6 ± 5.6	8.1 ± 2.6	.0001	.0003
Step time CV	2.9 ± 0.6	9.7 ± 6.6	5.5 ± 2.4	.0001	.0001

* Values in the tables are the mean ± standard deviation of the group. n = 16 for controls, n = 20 for HD subjects, and n = 15 for PD subjects, except that for one HD subject, double support measures were not available. The coefficient of variation (CV) is a normalized measure of the variance of each time series. Similar differences were obtained when using the magnitude (unnormalized) of the variance (the standard deviation).

† p values are the results of Wilcoxon ranked sum tests comparing control subjects (CO) with Huntington's subjects (HD) and control subjects (CO) with Parkinson's subjects (PD). See also Tables 3, 4, and 5.

this effect reached statistical significance in HD subjects ($p < 0.01$). However, group differences were independent of which foot (right, left, "best" or "worst") was used to compare the groups. In all cases, the results were similar to those reported above.

Age, Speed, and Gait Variability

From among all gait variables, age, height, weight, and speed, multiple logistic regression selected double support time CV and walking speed as the best predictors of PD compared with control subjects (sensitivity: 94%, specificity: 87%, and number of subjects identified correctly: 90%; using a cut-point probability of 0.5). Age and the average gait cycle timing were not independent characteristics of PD. When comparing HD with control subjects using the same model variables, step time CV was the single best "predictor" of HD (sensitivity: 88%, specificity: 90%, and number of subjects identified correctly: 89%). Age, speed, and average gait cycle timing were not independently associated with HD.

Disease Severity and Gait

For HD and PD subjects, disease severity was significantly correlated with most measures of gait variability (Table 4). The greater the degree of neurologic impairment, the larger the gait variability. For example, a decrease of one on the TFC scale was associated with a 1% change in step time CV of subjects with HD. With severe HD (TFC $\leq$ 6), step time CV was almost three times greater than those with less severe impairment (severe: 14.3 ± 7.0%; not severe: 5.5 ± 1.9%; $p < 0.005$). With the exception of double support variability, the degree of association between variability and impairment was larger in the subjects with HD than in the subjects with PD. The only average measures of gait timing significantly associated with disease severity were swing time percentage (in HD subjects) and walking speed (in PD subjects).

With all gait variables (including speed) as potential independent variables and disease severity as the de-

TABLE 2. *Gait timing: average values**

	Controls	Huntington's	Parkinson's	p values† CO vs. HD	p values† CO vs. PD
Stride time (msec)	1091 ± 91	1138 ± 168	1118 ± 116	NS	NS
Swing time (msec)	396 ± 39	397 ± 64	375 ± 39	NS	NS
% swing time	36.3 ± 1.7	35.0 ± 3.6	33.5 ± 2.4	NS	.002
Double support time (msec)	305 ± 37	362 ± 90	376 ± 73	NS	.003
% double support time	28.0 ± 2.8	31.5 ± 6.1	33.6 ± 4.8	NS	.0008
Step time (msec)	543 ± 43	566 ± 71	560 ± 64	NS	NS
Speed (m/sec)	1.35 ± 0.16	1.15 ± 0.35	1.00 ± 0.20	NS	.0001

NS = not significant ($p > .01$).

* Values in the tables are the mean ± standard deviation of the group. Unless otherwise indicated, n = 16 for controls, n = 20 for HD subjects, and n = 15 for PD subjects. For one HD subject, double support and speed measures were not available.

† p values are the results of Wilcoxon ranked sum tests comparing control subjects (CO) with Huntington's subjects (HD) and control subjects with Parkinson's subjects (PD).

TABLE 3. *Variability after detrending**

	Controls	Huntington's	Parkinson's	p values† CO vs. HD	p values† CO vs. PD
Stride time (msec)	27 ± 7	119 ± 113	52 ± 24	.0001	.0001
Swing time (msec)	16 ± 4	73 ± 71	34 ± 18	.0001	.0001
% swing time (%)	1.2 ± 0.3	4.4 ± 3.6	2.3 ± 1.1	.0001	.0003
Double support time (msec)	19 ± 5	64 ± 51	37 ± 13	.0001	.0001
% double support time (%)	1.5 ± 0.4	5.0 ± 2.9	3.3 ± 1.2	.0001	.0001
Step time (msec)	18 ± 4	77 ± 64	36 ± 15	.0001	.0001

* Values shown are the standard deviation of each subject's time series after detrending (by taking the first difference, see *Methods*) averaged in each group.

† For each Kruskal-Wallis test performed to determine if there was any group effect, $p < 0.0001$. Differences between Huntington's disease (HD) and Parkinson's disease (PD) were generally marginally significant ($.01 < p < 0.1$), resulting, in part, to the wide range in disease severity. See also Tables 4 and 5.

pendent, outcome measure, percentage swing time CV was the only independent predictor of HD severity. For PD, double support standard deviation was selected. Walking speed and all measures of average gait cycle timing were not independent predictors of disease severity in either group.

Stride Variability and Other Potential Confounders

To estimate the effect of other clinical variables on gait variability, stride time CV was compared after HD subjects were stratified based on medication use, cognition, and depression. Compared with the other HD subjects, stride time CV was not increased in those HD subjects with signs of depression (or in those taking antidepressants). This measure was slightly (not significantly) larger in subjects with signs of confusion and dementia and in the subjects taking neuroleptics. Nevertheless, even in those HD patients without signs of dementia or confusion (n = 13) and in HD subjects not taking neuroleptics (n = 14), stride time variability was significantly larger than in controls. Stride time CV was not associated with the amount of chorea (of any body segment or with the sum of all segments) nor was it larger in HD subjects with greater amounts of chorea.

TABLE 4. *Association of gait measures with disease severity**

	Huntington's	Parkinson's
Stride time (msec)		
Variability	.75 (.0001)	.63 (.01)
Swing time (msec)		
Variability	.75 (.0001)	NS
% swing time (msec)	−.63 (.003)	NS
Variability	.78 (.0001)	.65 (.008)
Double support time		
Variability	.56 (.01)	.71 (.003)
% double support time		
Variability	.63 (.004)	NS
Step time (msec)		
Variability	.73 (.0003)	.64 (.01)
Speed (m/sec)	NS	−.67 (.006)

NS = not significant ($p > .01$).

* Disease severity measured using the Hoehn and Yahr scale for PD and the total functional capacity (TFC) scale for HD. Numbers are the Spearman's Correlation coefficient and, in parentheses, the associated p value. For consistency, the signs have been inverted in the HD values so that for both HD and PD increases in disease severity correspond to increases in variability. Values are selected from among the three measures of variability (standard deviation [SD], coefficient of variation [CV], and first difference) and the one with the largest degree of association is listed.

Comparison of Parkinson's Disease and Huntington's Disease

Measures of gait variability of subjects with HD and PD appear to be different (Table 1). However, because both groups are made up of subjects with varying degrees of impairment, it may be misleading to compare one entire cohort with the other. To better evaluate the effects of the different basal ganglia impairments, we compared subjects who had severe levels of impairment with each other (TFC ≤ 5 or H & Y ≥ 3). Variability was much larger in subjects with HD and these differences were significant for all parameters except swing time (Table 5). This increased variability occurred with only small (not statistically significant) differences in the average values of gait cycle timing (Table 6). Average walking speed was similar in the HD and PD subjects with severe impairment.

DISCUSSION

We demonstrated that quantitative measures of stride-to-stride variability of gait timing are significantly increased in subjects with HD and PD. In subjects with PD, measures of the variability of gait cycle duration were, on average, twice that of control subjects; in subjects with HD, these measures were more than three times those of control subjects. Similar results were observed for all of the subphases of the gait cycle. The degree of gait variability increased significantly with disease severity in both HD and PD subjects. The increase in

TABLE 5. *Gait timing: variability in severe* Parkinson's disease and Huntington's disease*

	Huntington's (n = 9)	Parkinson's (n = 9)	p value
Stride time CV	11.8 ± 5.9	5.1 ± 2.5	.008
Swing time CV	21.4 ± 10.6	9.3 ± 4.5	NS
% swing time CV	16.0 ± 8.3	6.8 ± 3.1	.008
Double support time CV	16.8 ± 8.0	9.1 ± 1.7	.01
% double support time CV	14.9 ± 5.7	9.1 ± 2.5	.01
Step time CV	14.3 ± 7.0	6.4 ± 2.7	.006

NS = not significant ($p > .01$).

* Data are from subjects with total functional capacity (TFC) values ≤5 and Hoehn and Yahn scores ≥3.

stride-to-stride variability was not simply the result of fatigue or changing of speed during the 5-minute walk. Instead, diminished capacity to control gait timing from one stride to the next appears to be intrinsic to HD and PD locomotor function.

In contrast, *average* gait cycle duration (stride time) was not significantly altered in HD and PD subjects. This is consistent with previous findings of little or no differences in stride duration or cadence in subjects with PD.[5,8,9] Because of the normal cadence in PD subjects, some have concluded that the "stepping mechanism," the neural process that produces sequential contraction and relaxation of muscle groups necessary for walking,[12] remains largely intact with PD.[8,9,11] The present results indicate that *average* gait cycle timing is, to some degree, distinct from the control of *stride-to-stride variability* of gait timing. Apparently, with both HD and PD, the mechanisms responsible for average gait timing remain fairly unaltered while accurate stride-to-stride regulation is severely compromised.

The apparent dichotomy in walking ability is not unique to stride-to-stride regulation of gait cycle timing. Although duration of the gait cycle was close to normal values, gait speed was significantly lower in subjects with PD. This reduced gait speed is consistent with previous findings and the general description of bradykinesia in PD.[1–7] HD subjects did not walk significantly slower than control subjects. Thus, there appears to be a differential control of gait variability, on the one hand, and speed and average cycle timing on the other. This may have implications for improving our understanding of the role of basal ganglia in locomotor control.

Origins of Stride-to-Stride Variability

A priori, one possible explanation for increased gait variability, at least in PD subjects, is that it is a byproduct of lower gait speed. Indeed, many of the gait changes associated with PD are related to diminished ability to generate normal stride length and velocity.[8–10] While future study may more directly test this question, there is, however, ample evidence suggesting that walking speed and stride-to-stride variability are independent. No significant increase in stride-to-stride variability was observed in healthy elderly subjects although they walked significantly slower than young controls.[12,23] Maki demonstrated that among the elderly, walking speed was significantly reduced in those with a fear of falling, while gait variability was not related to fear of falling.[24] Blin and colleagues[25] found that in response to L-dopa administration, PD subjects significantly increased gait speed without affecting variability of stride duration. After rhythmic training of PD subjects, Miller et al.[15] observed a significant increase in gait speed, but no significant changes in variability measures.

Our findings are also not consistent with the hypothesis that speed alone is responsible for the increased gait variability observed in PD and HD subjects. If this hypothesis were correct, one would have predicted that PD subjects, who walked the slowest of any group, would exhibit the greatest variability. However, HD subjects walked with the most variability of the three groups, tended to walk faster than PD subjects, and did not walk significantly slower than control subjects. Even among the HD subjects, multivariate analysis showed that a measure of variability (swing time CV) was an indepen-

TABLE 6. *Gait timing: average values in severe* Parkinson's disease and Huntington's disease*

	Huntington's (n = 9)	Parkinson's (n = 9)
Stride time (msec)	1231 ± 201	1122 ± 132
Swing time (msec)	405 ± 95	365 ± 41
% swing time	32.8 ± 4.2	32.6 ± 2.3
Double support time (msec)	421 ± 70	390 ± 74
% double support time	34.8 ± 5.8	34.8 ± 4.6
Step time (msec)	603 ± 81	563 ± 76
Speed (m/sec)	0.91 ± 0.29	0.90 ± 0.18

* Data are from subjects with total functional capacity (TFC) values ≤5 and Hoehn and Yahr scores ≥3.

dent predictor of HD severity, but speed was not. Average walking speed of the more severely impaired HD and PD subjects was essentially identical, yet variability measures were much higher in these HD subjects than in these PD subjects (Tables 5 and 6). Therefore, the increased gait variability in HD and PD subjects is probably not the result of reduced walking speed.

The reason for the inability of subjects with HD and PD to accurately regulate gait timing on a stride-to-stride basis is unknown. Our findings show that it is not simply the result of comorbidities, medication use, or chorea (in HD subjects). The increased variability may reflect a disjointedness in the gait so that walking becomes a sequence of disconnected strides rather than a single continuous motion. This may be the result of impairment in anticipatory reflexes, the disruption in the normal internal cueing required to string together submovements, or the diminished capacity to perform automatic sequential movements.[9,11] Conversely, this irregular rhythm may be related to an inability to generate muscle forces at a constant level rather than to a deficit in timing per se.[25–27] Alternatively, the increased gait variability may be more directly related to the impaired reflexes responsible for the postural instability characteristic of PD. Finally, changes in the basal ganglia's effectiveness in integrating sensory stimuli[28] may also be involved.

HD patients exhibited significantly more gait variability than PD subjects (Table 5). This may reflect the impairment of different neural pathways involved in stride-to-stride regulation,[28] consistent with numerous differences in the gait of PD and HD subjects. Alternatively, the origin of the increased variability may be the same in PD and HD and the differences merely a matter of degree. Although the underlying pathology of each disease involves different portions of the basal ganglia, both diseases share some common sequelae (for example, postural instability) that may be the primary reason for the impairment in regulation of gait timing.

Future studies may be able to address the origin(s) of this increased gait variability by examining the effects of different pharmacologic agents or therapies[15,29–33] on stride-to-stride variability. Interestingly, several studies have shown that when cued properly, PD subjects can modulate both their cadence and stride length to achieve gait speeds near to control values.[8,11,29,32] In contrast, gait variability, at least as measured during short walks, is apparently dopa-resistant and not amenable to change, despite increases in walking speed.[15,25] Perhaps these differences in L-dopa responsiveness also relate to a differential control of gait variability, speed, and average cycle timing. Dopaminergic pathways appear to regulate speed[15,25] but not gait variability. At the same time, gait variability and average gait cycle duration also apparently rely on somewhat different systems; variability, but not duration is different from control values in HD and PD. A complete explanation of the mechanisms behind the increased gait variability of gait cycle timing should account for these phenomena as well as the differences found between HD and PD.

Stride-to-Stride Variability and Falls

The apparent dichotomy in walking ability is not unique to HD and PD. Regulation of stride-to-stride variability is also diminished in elderly persons prone to falling (for no apparent reason), while average gait cycle duration and speed may remain largely unchanged in this group.[22,24] HD and PD subjects are also prone to falls[34–36] and it is interesting to consider the common behavior of these three groups. The origins of increased stride-to-stride variability have not been extensively studied in the elderly persons who fall. However, some have speculated that it too is a manifestation of impaired motor control.[12,24] Like HD and PD, aging has been associated with alteration of basal ganglia function.[37–39] Perhaps these subclinical, age-related changes in basal ganglia function are exacerbated further in some elderly persons who fall. Subjects with HD and PD and elderly persons prone to falling also share increased postural instability. The relationship between postural instability and stride-to-stride variability, however, is as yet not established. Regulation of stride-to-stride variability may be compromised even if (static) balance mechanisms are intact. Indeed, the challenges of standing and walking are different, and function in one area is not always indicative of the other.[40–45] Either way, it appears that the modulating effects that are provided by normal basal ganglia function on motor control are necessary both for regulating stride-to-stride variability and minimizing the likelihood of falls.

Study Limitations

All of the PD subjects were receiving L-dopa therapy that may have affected some or all of the gait measures. In particular, walking speed and stride length often improve with L-dopa, and the possible side effects of L-dopa therapy include dyskinesias which may have affected gait variability. The role of L-dopa in the increased PD gait variability deserves future investigation. However, L-dopa probably did not have a major effect on our observed results because dyskinesias were not observed during any of the testing; two studies have found that the temporal parameters of gait related to rhythm and variability (like those that we used) did not change with administration of L-dopa therapy[10,25]; and, while L-dopa improves stride length and velocity, the change is rela-

tively small[10,46] and these measures remain significantly altered compared with healthy controls,[10] as we observed. Therefore, it is likely that our measures of gait and gait variability in PD predominantly reflect the underlying pathophysiology and not medication response or side effects.

The study groups were not similar with respect to age and gender. However, Gabell and Nayak[12] found no gender effects in their study of gait variability. It seems likely that any effects of gender would be small compared with the large effects that we observed. It is also likely that the slight increase in age of the HD subjects relative to controls did not play a significant role. The age difference was small and not significantly different and age was not independently associated with HD.

PD subjects were significantly older than control subjects. Although future studies will more directly address this issue, several facts suggest that the changes seen in the PD subjects are the result of pathology and not age. In the present study, many older PD subjects had relatively low variability measures, while some younger subjects had high variability. For example, the three PD subjects with lowest stride time variability were 68, 76, and 79 years old, while the PD subject with the largest variability was 57 years old. Among the entire cohort, the subject with the highest stride time variability was a 40 year old with HD. No significant age-related increases in any measures of gait variability (including stride time CV and double support CV) were found in a group of 32 healthy elderly subjects.[12] Consistent with these findings, we previously observed no change in stride time variability (CV) in a healthy elderly cohort (average age, 75.7 ± 3.2 yrs) compared with healthy young adults (24.6 ± 1.9 yrs) even when studied in a walk of extended duration (6 minutes).[23] In addition, our findings of increased variability in subjects with PD are generally consistent with those of previous findings.[14,15,25] This evidence fully supports the view[12] "that any increase in variability occurring in an old person is not normal but is due to some pathological cause."

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