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Levodopa influences the regularity of the ankle joint kinematics in individuals with Parkinson's disease

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Abstract The aim of the investigation was to explore the influence of levodopa therapy on the regularity of the structural variations present in the lower extremity joints of individuals with Parkinson's disease (PD). Ten participants with PD walked on a treadmill during the states of "off" and "on" levodopa. Approximate entropy was used to quantify the regularity of the structural variations present in the joint kinematics. Additionally, a pseudo-periodic surrogation analysis was used to evaluate if changes in the regularity of the joint's movement were associated with a noisy or deterministic motor process. This investigation provided two key findings. The first was that the structural variations present in ankle joint were more regular with levodopa therapy. The second was that changes in the structural variations were related to a deterministic motor process. This indicated that the variations present in the walking patterns of individuals with PD most likely arose from higher-order neural couplings rather than noise in the motor process. Monitoring the regularity of the structural variations present in gait may help improve the management of PD.

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1 Introduction

Healthy physiological biorhythms demonstrate subtle structural variations that are a result of interacting regulatory processes that are operating over multiple time scales (Lipsitz and Goldberger 1992; Vaillancourt and Newell 2002). The influential work of Lipsitz and Goldberger (1992) provided the initial framework for the hypothesis that the human body was less adaptive to stress and disease if these variations had a more regular pattern. Since the original conception of this hypothesis, it has been supported by a plethora of scientific data from a variety of human biorhythms (Goldberger et al. 1998; Kaplan et al. 1991; Lehnerts and Elger 1998; Pikkujamsa et al. 1999; Vaillancourt and Newell 2000, 2002). For example, heart rhythms with a more regular structural variations are associated with disease states and sudden death (Goldberger et al. 1998). Alternatively, a heart rhythm that has subtle, but less predictable structural variations, is associated with health. Similar changes in the structural variations present in other biorhythms of diseased and healthy physiological systems have been reported for encephalic waves, tremors, and systolic blood pressure (Lehnerts and Elger 1998; Pikkujamsa et al. 1999; Vaillancourt and Newell 2000).

The loss of complexity hypothesis appears to extend to the parkinsonian motor system during standing posture and isometric force tasks that are performed with the fingers. The variations in the postural sway and finger force profiles are more regular for individuals with PD (Schmit et al. 2006; Vaillancourt and Newell 2003; Vaillancourt et al. 2002). However, recent experimental work using a rhythmical finger force task has resulted in contradictory evidence that has challenged the hypothesis that a more

regular physiological signal is a signature of disease. The structure of the variations become less regular when the aged perform a finger force task that has a rhythmical pattern (Vaillancourt and Newell 2003). The noted loss of regularity in the rhythmical finger force pattern is supported by experiments that have evaluated the structural variations found in human gait, and rodent models of PD that have evaluated the temporal components of the walking pattern (Amende et al. 2005; Hausdorff 2007, 2009; Kurz et al. 2007; Pothakos et al. 2009). These results imply that changes in the regularity of physiological signals from diseased systems may be task dependent. Furthermore, they highlight the fact that greater irregularities in the structural variations of a rhythmical task, such as gait, are associated with a lack of motor control and a diminished neuromuscular health (Amende et al. 2005; Hausdorff 2007, 2009; Kurz et al. 2007; Pothakos et al. 2009; Vaillancourt and Newell 2003)

Traditionally, irregularities found in the structural variations present in the performance of the motor system have been viewed as a result of noisy neural processes (Faisal et al. 2008; Riley and Turvey 2002). Based on this viewpoint, the major challenge of the motor command is to overcome the noise to achieve the desired goal. An alternative perspective is what appears to be noise is actually a deterministic process that arises from the higher-order couplings in the nervous system. As such, changes in the regularity of the structural variations present in gait may represent changes in the coordinative output of the excitatory and inhibitory neural oscillators that govern the motor command. Currently, it is unknown if variations present in the walking pattern of PD patients is related to a noisy or deterministic motor processes.

Levodopa is a metabolic precursor for dopamine, which works on the striatal-nigra system to improve the motor symptoms in PD; including freezing gait. Previously, it has been demonstrated that levodopa could reduce the magnitude of the variations in the stride time interval dynamics (Moore et al. 2008; Schaafsma et al. 2003). Most likely these changes resided in an improved regulation of the lower extremity joint kinematics. However, the influence of levodopa on the regularity of the structural variations in the joint kinematics is not clear. Furthermore, it is unknown if the improved regulation of the walking pattern is a result of a reduction in noise in the motor system or an improvement in the higher-order neural couplings which control the walking pattern.

In this study, we explored the influence of levodopa on the regularity of the lower extremity joint patterns of PD patients. Specifically, our experiment addressed the following questions: (1) Does levodopa improve the regularity of the structural variations found in the lower extremity joint kinematics?, (2) Are the changes in the structural variations found in the joint kinematics of individuals with PD a deterministic or noisy motor process?

2 Materials and methods

A total of ten individuals diagnosed with PD participated in this investigation (Table 1). The inclusion criteria were (a) diagnosis of idiopathic PD by a neurologist specialized in movement disorders, (b) on a stable regimen of anti-Parkinsonian medications, and (c) early or moderate PD with the ability of independent walking—stage 2 or 3 of the Hoehn and Yahr stage (Hoehn and Yahr 1967). This study conformed to all the regulations of University of Houston and Baylor College of Medicine pertaining to research on human subjects. It was approved by the Committees for the Protection of Human Subjects of University of Houston and the Institutional Research Board of Baylor College of Medicine. All procedures were carried out with the adequate understanding and written consent of the subjects involved.

All participants were initially assessed in the morning during the "off" state, that is, without taking their first dose of levodopa for at least eight hours from the previous night. Initially, the participants walked on the treadmill and selected a walking speed. The participant was instructed to select a speed that was representative of their walking pace when performing community-based activities. The participant explored the range of speeds by speeding up and slowing down the treadmill until they found a comfortable walking pace that could be maintained for a long duration. The selected walking speed was used for both the "on" and "off" levodopa conditions. Immediately after walking on the treadmill during the "off" state of levodopa, the participants took their morning dose of levodopa. We waited 45 min for the levodopa to be turned "on" before having the participant repeat the walking bout.

During the three-minutes of walking on the treadmill, a high-speed (120 Hz) motion capture system (Vicon, Centennial, CO) collected the three dimensional positions of reflective markers that were placed on the hip, knee, ankle, heel and toe of the leg (Fig. 1). The positions of

Table 1 Participants' characteristics

Age (years)	76±6
Height (meters)	1.7±0.1
Mass (kg)	71.9±12
Walking Speed (m/s)	0.62±0.4
UPDRS III Score[a]	28.6±4.6
Hoehn & Yahr Stage	2.8±0.7

[a] Assessed while on levodopa

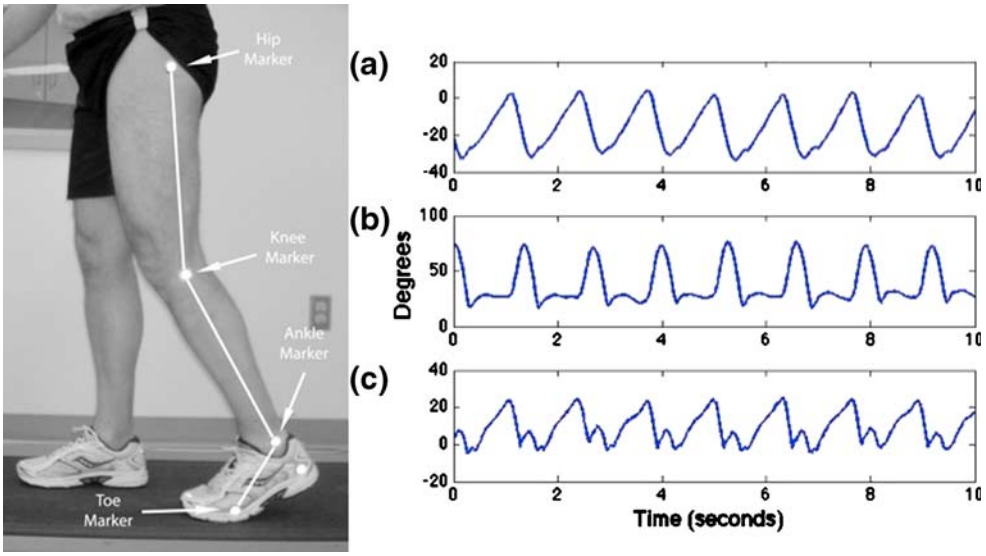

Fig. 1 Placement of reflective markers that were used to calculate the hip (**a**), knee (**b**) and ankle (**c**) sagittal plane joint angles

these markers were used to calculate the sagittal plane hip, knee and ankle joint angles. The respective continuous joint angle time series were analyzed unfiltered in order to get a more accurate representation of the variability within the joint's pattern (Mees and Judd 1993).

The regularity of the structural variations present in the joint angles was evaluated using Approximate Entropy (ApEn) (Pincus 1991; Stergiou 2004; Vaillancourt and Newell 2003). ApEn calculates the regularity of occurrence of self-similar structures within a time series. The calculation yields a score in range of 0 to 2, where the score of 0 reflects a highly repeatable and regular signal, and the score of 2 indicates a random signal. Highly regular signals are very predictable and have a high likelihood of reoccurrence of similar patterns. Irregular, random signals have low predictability and have less likelihood of reoccurrence of self-similar patterns. Calculation of ApEn was performed using Eq. (1):

$$ApEn(m,r) = \ln\left[\frac{C_m(r)}{C_{m+1}(r)}\right] \quad (1)$$

where N was the number of measurements in the time series (*i.e.,* number of completed leg swings), m was the number of points compared, r is radius of acceptance or a similarity criterion between compared points in a time series, C is the number of self similar vectors defined by m points based on the r criterion. Similar to previous investigations of the structural variability present in a physiological time series, m was 2, and r was 20% of the standard deviation of the time series (Pincus 1991; Vaillancourt and Newell 2000, 2003). A lower ApEn value indicated greater regularity in the structural variations seen in the joint pattern. We used a 2 X 3 repeated measures ANOVA (drug x joint) with a Tukey HSD post-hoc to evaluate the effect of levodopa on the regularity of the structural variations present in the joint kinematics. All statistical tests were performed at a 0.05 alpha level.

We used a pseudo periodic surrogation (PPS) algorithm to determine if the calculated ApEn values were related to a deterministic or noisy process. Complete details of the algorithm are found in Small & Tse (Small and Tse 2002) and Miller et al. (Miller et al. 2006). The PPS algorithm generates a surrogate of the original time series that preserves the inherent periodic components while destroying the nonlinear structure. The structure of the surrogate follows the same vector field as the original joint angle time series, but was contaminated with noise. If fluctuations in the original time series had deterministic structural variations, these features were destroyed in the surrogate. Alternatively, if the structural variations in the time series are a result of a noisy motor process, the surrogate will be no different from the original time series. The surrogation analysis only informed us if the kinematic variations are from a deterministic or stochastic source. The surrogation analysis did not provide information as to the amount of noise present in the joint's movement pattern. Dependent t-test was used to determine if the ApEn values for the original joint angle time series of the while "on" and "off" levodopa was statistically different from the ApEn values from the surrogate time series. The structural variations were considered to be deterministic if ApEN of the original data was statistically different from the surrogate at a 0.05 alpha level.

We also evaluated if there were changes in the mean range of motion of the lower extremity joints during the states of "off" and "on" levodopa. The maximal horizontal position of the heel marker was used to identify the heel contacts. These heel contact events were used to partition the continuous joint angle time series into the respective strides. Each stride was time normalized to 101 points, and a mean ensemble curve

was constructed for each of the respective joints. The total range of motion of the joint was calculated by subtracting the local maximum from the local minimum of the mean ensemble curve. A 2 X 3 (drug X joint) repeated measures ANOVA was used to determine if there were any statistical differences in the average range of motion of the joint during states of "off" and "on" levodopa.

3 Results

Our analysis revealed that there was a significant joint-drug interactive effect for the structural variations present in the joints while being "off" and "on" levodopa (p=0.009; Fig. 2). Our post-hoc analysis indicated that the structural variations present in the ankle joint kinematics were more regular during the "on" state (p<0.0001). No significant differences in the regularity of the structural variations were found in the knee (p>0.05) and hip (p>0.05) joints' kinematics.

There was a significant difference (p<0.0001) between the ApEn of the original data (ApEn=0.12±0.04) and the surrogates (ApEn=0.59±0.4). Hence, indicating that the structural variations found in the joint kinematics had a deterministic pattern.

There was no significant difference in the mean range of motion between the respective joints during the "on" and "off" states (Table 2). This indicated that levodopa therapy did not alter the functional range of motion of the joint.

Table 2 Lower extremity mean (± SD) joint range of motions during the states of "off" and "on" levodopa. No significant differences (p> 0.05) were found between the respective conditions

Condition	Ankle	Knee	Hip
"Off" levodopa	23.0±5.7	48.9±5.7	32.2±5.0
"On" levodopa	22.4±5.9	49.3±7.3	33.9±7.1

4 Discussion

Several human and rodent models have shown that the structural variations that are present in the gait kinematics of individuals with Parkinson's disease are less regular than healthy age matched controls (Bartsch et al. 2007; Hausdorff 2009; Hausdorff et al. 2000; Kurz et al. 2007; Pothakos et al. 2009). Impairments in the regulation of these structural variations is considered to be a sign of diminished motor control and poor neuromuscular health (Hausdorff 2009). Although these concepts have begun to become more widely accepted in the clinical literature as a characteristic of Parkinson's disease, modalities that can be used to improve the regularity of the structural gait variations are lacking. Our results are the first to show that levodopa improves the regularity of the structural variations that are present in the rhythmical pattern of the ankle joint kinematics for walking. These results are promising and further support the notion that dopamine therapy is beneficial for individuals with Parkinson's disease. We suggest that the improved regularity is most likely related to the ankle joint's ability to control a consistent muscular performance. This notion is supported by a previous investigation that demonstrated that individuals with Parkinson's disease have a decreased amount of ankle power at push-off if not taking levodopa (Morris et al. 1999). Alternatively, we suggest that the improved regularity of the structural variations present in the ankle joint's kinematics may be related to a reduced amount of interference of the spinal central pattern generator by the higher dopamine-mediated networks in the brain. We speculate that this may have allowed for the walking pattern to become more of a continuous motion, rather than a series of disconnected strides. Conversely, the more regular ankle joint structural variations may represent changes in the basal ganglia's ability to integrate sensory stimuli for the maintenance of the time dependent changes that are occurring in the gait pattern (Maschke et al. 2003).

The perceived resistance of the knee and hip joints to levodopa may be related to the fact that our investigation was conducted on a treadmill. Potentially, the treadmill may have acted as an external cueing device that assisted in the regulation of the structural variations present in the knee and hip joint kinematics. This notion is partially supported by an investigation that found that the magnitude of the stride-time interval variations is reduced when individuals with Parkinson's disease walk on a treadmill (Frenkel-Toledo et al. 2005). It is alternatively possible that the

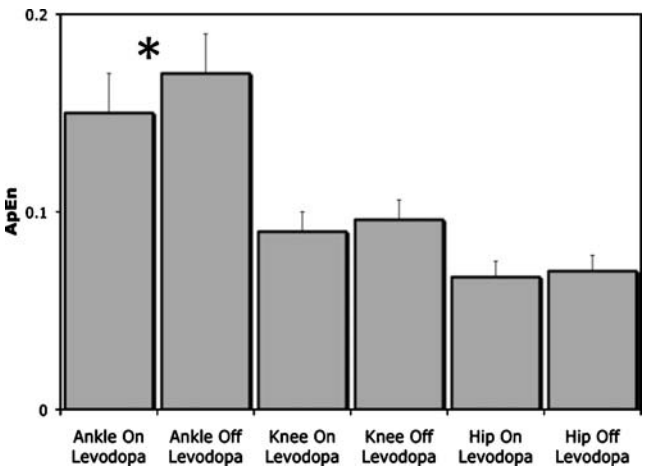

Fig. 2 ApEn values (Mean ± SD) for the respective joints while "on" and "off" levodopa. A higher ApEn value indicates less regularity in the structural variations present in the joint. * significant difference at the 0.05 alpha level

results from the knee and hip joints may be related to the severity of the disease in our participants. Possibly changes in the regularity of the structural variations of the knee and hip may be present in patients that are in later stages of the disease.

The surrogation analysis indicated that differences in the structural variations present in the joint angles were deterministic and were most likely not a result of a noisy motor process. These results support the concept that the structural variations that are present in the motor performance are a result of how inhibitory and excitatory neural oscillators cooperate for an effective motor command (Vaillancourt and Newell 2002). Furthermore, they imply that the movement disorders seen in the walking pattern of individuals with Parkinson's disease may be a result of faulty computation by the nervous system of relevant movement parameters. Our surrogation analysis also implied that levodopa therapy may not influence the noise in the motor system, but rather it appears to improve the cooperation of neural oscillators in the basal ganglia and related structures that are involved in the generation of the deterministic portion of the motor command. Further exploration of the deterministic and noisy motor processes may provide better insight on the nature of the variations seen in the movement patterns of individuals with Parkinson's disease.

Changes in the joint's mean range of motion were not effective in discerning differences in the motor performance while on and off levodopa. This result was most likely due to the fact that the statistical mean provides a general picture, and does not provide insight on the time evolving changes present in the performance of the motor system. The results presented here indicate that the time evolving changes in the structural kinematic variations may be important for discerning the influence of levodopa on the performance of the Parkinsonian motor system. We suggest that further exploration of the regularity of the structural variations will provide further insight on the influence of Parkinson's disease on the performance of the motor system.

Part III of the Unified Parkinson's Disease Ration Scale (UPDRS) is the most widely used clinical measure used to quantify the influence of levodopa on the motor function of individuals with Parkinson's disease (Fahn and Elton 1987; Miyasaki et al. 2002). The general consensus is that the UPDRS motor scores improve with levodopa therapy (Fahn 2005; Miyasaki et al. 2002). The results presented here provide further support for an improvement in motor function with levodopa therapy, and suggest that these improvements may reside in the ability to regulate the motor command for each step of the walking pattern. A limitation of this investigation is that we did not measure the subject's UPDRS scores while on and off levodopa. This information would provide a stronger foundation for clarifying if changes in the regularity of the joint's pattern are associated with noticeable clinical improvements. Further exploration of the utility of using the structural variations in the gait pattern for augmenting clinical decisions are warranted.

Long-term use of levodopa is associated with a tendency to induce dyskinesia (Fahn 2005). As such, it is possible that dyskinesia may influence the regularity of the structural variations present in the joint's movement pattern during gait. A limitation of this investigation is that we did not measure the amount of dyskinesia present in the subjects while they were on levodopa. We suggest that future investigations should consider dyskinesia as a possible factor when assessing why there are changes in regularity of the joint kinematics while on and off levodopa. This will provide further guidance for the use of the regularity of the structural variations in the gait kinematics as a clinical tool for the management of Parkinson's disease.

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References

Amende, I., Kale, A., McCue, S., Glazier, S., Morgan, J. P., & Hampton, T. G. (2005). Gait dynamics in mouse models of Parkinson's disease and Huntington's disease. *Journal of Neuroengineering and Rehabilitation, 2*, 20.

Bartsch, R., Plotnik, M., Kantelhardt, J. W., Havlin, S., Giladi, N., & Hausdorff, J. M. (2007). Fluctuation and synchronization of gait intervals and gait force profiles distinguish stages of Parkinson's disease. *Physica A, 383*(2), 455–465.

Fahn, S. (2005). Does levodopa slow or hasten the rate of progression of Parkinson's disease? *Journal of Neurology, 252*(Suppl 4), IV37–IV42.

Fahn, S., & Elton, R. L. (1987). Unified Parkinson's disease rating scale. In S. Fahn, C. D. Marsden, D. B. Calne & M. Goldstein (Eds.), *Recent developments in Parkinson's disease, Vol. 2* (pp. 153–164). Florham Park: Macmillan Health Care Information.

Faisal, A. A., Selen, L. P., & Wolpert, D. M. (2008). Noise in the nervous system. *Nature Reviews Neuroscience, 9*(4), 292–303.

Frenkel-Toledo, S., Giladi, N., Peretz, C., Herman, T., Gruendlinger, L., & Hausdorff, J. M. (2005). Treadmill walking as an external pacemaker to improve gait rhythm and stability in Parkinson's disease. *Movement Disorders, 20*(9), 1109–1114.

Goldberger, A. L., Rigney, D. R., Mietus, J., Antman, E. M., & Greenwald, S. (1998). Nonlinear dynamics in sudden cardiac death syndrome heart oscillations and bifurcations. *Experimentia, 44*, 983–987.

Hausdorff, J. M. (2007). Gait dynamics, fractals and falls: finding meaning in the stride-to-stride fluctuations of human walking. *Human Movement Science, 26*(4), 555–589.

Hausdorff, J. M. (2009). Gait dynamics in Parkinson's disease: common and distinct behavior among stride length, gait variability, and fractal-like scaling. *Chaos, 19*(2), 026113.

Hausdorff, J. M., Lertratanakul, A., Cudkowicz, M. E., Peterson, A. L., Kaliton, D., & Goldberger, A. L. (2000). Dynamic markers of

altered gait rhythm in amyotrophic lateral sclerosis. *Journal of Applied Physiology, 88*(6), 2045–2053.

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology, 17*(5), 427–442.

Kaplan, D. T., Furman, M. I., Pincus, S. M., Ryan, S. M., Lipsitz, L. A., & Goldberger, A. L. (1991). Aging and the complexity of cardiovascular dynamics. *Biophysical Journal, 59*(4), 945–949.

Kurz, M. J., Pothakos, K., Jamaluddin, S., Scott-Pandorf, M., Arellano, C., & Lau, Y. S. (2007). A chronic mouse model of Parkinson's disease has a reduced gait pattern certainty. *Neuroscience Letters, 429*(1), 39–42.

Lehnerts, K., & Elger, C. E. (1998). Can epileptic seizures be predicted? Evidence from nonlinear time series analysis of brain electrical activity. *Physical Review Letters, 80*, 5019–5022.

Lipsitz, L. A., & Goldberger, A. L. (1992). Loss of 'complexity' and aging. Potential applications of fractals and chaos theory to senescence. *Jama, 267*(13), 1806–1809.

Maschke, M., Gomez, C. M., Tuite, P. J., & Konczak, J. (2003). Dysfunction of the basal ganglia, but not the cerebellum, impairs kinaesthesia. *Brain, 126*(Pt 10), 2312–2322.

Mees, A. I., & Judd, K. (1993). Dangers of geometric filtering. *Physicia D Nonlinear Phenomena, 68*, 427–436.

Miller, D. J., Stergiou, N., & Kurz, M. J. (2006). An improved surrogate method for detecting the presence of chaos in gait. *Journal of Biomechanics, 39*(15), 2873–2876.

Miyasaki, J. M., Martin, W., Suchowersky, O., Weiner, W. J., & Lang, A. E. (2002). Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology, 58*(1), 11–17.

Moore, S. T., MacDougall, H. G., Gracies, J. M., & Ondo, W. G. (2008). Locomotor response to levodopa in fluctuating Parkinson's disease. *Experimental Brain Research, 184*(4), 469–478.

Morris, M. E., McGinley, J., Huxham, F., Collier, J., & Iansek, R. (1999). Constraints on the kinetic, kinematic and spatotemporal paramters of gait in Parkinson's disease. *Human Movement Science, 18*, 461–483.

Pikkujamsa, S. M., Makikallio, T. H., Sourander, L. B., Raiha, I. J., Puukka, P., Skytta, J., et al. (1999). Cardiac interbeat interval dynamics from childhood to senescence: comparison of conventional and new measures based on fractals and chaos theory. *Circulation, 100*(4), 393–399.

Pincus, S. M. (1991). Approximate entropy as a measure of system complexity. *Proceedings of the National Academy of Sciences of the United States of America, 88*(6), 2297–2301.

Pothakos, K., Kurz, M. J., & Lau, Y. S. (2009). Restorative effect of endurance exercise on behavioral deficits in the chronic mouse model of Parkinson's disease with severe neurodegeneration. *BMC Neuroscience, 10*(1), 6.

Riley, M. A., & Turvey, M. T. (2002). Variability of determinism in motor behavior. *Journal of Motor Behavior, 34*(2), 99–125.

Schaafsma, J. D., Giladi, N., Balash, Y., Bartels, A. L., Gurevich, T., & Hausdorff, J. M. (2003). Gait dynamics in Parkinson's disease: relationship to Parkinsonian features, falls and response to levodopa. *Journal of the Neurological Sciences, 212*(1–2), 47–53.

Schmit, J. M., Riley, M. A., Dalvi, A., Sahay, A., Shear, P. K., Shockley, K. D., et al. (2006). Deterministic center of pressure patterns characterize postural instability in Parkinson's disease. *Experimental Brain Research, 168*(3), 357–367.

Small, M., & Tse, C. (2002). Applying the method of surrogate data to cyclic time series. *Physica D, 164*, 187–201.

Stergiou, N. (2004). *Innovative analysis of human movement*. Champaign: Human Kinetics.

Vaillancourt, D. E., & Newell, K. M. (2000). The dynamics of resting and postural tremor in Parkinson's disease. *Clinical Neurophysiology, 111*(11), 2046–2056.

Vaillancourt, D. E., & Newell, K. M. (2002). Changing complexity in human behavior and physiology through aging and disease. *Neurobiol Aging, 23*(1), 1–11.

Vaillancourt, D. E., & Newell, K. M. (2003). Aging and the time and frequency structure of force output variability. *Journal of Applied Physiology, 94*(3), 903–912.

Vaillancourt, D. E., Slifkin, A. B., & Newell, K. M. (2002). Inter-digit individuation and force variability in the precision grip of young, elderly, and Parkinson's disease participants. *Motor Control, 6*(2), 113–128.