

Rhythmic auditory stimulation modulates gait variability in Parkinson's disease

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Abstract

Patients with Parkinson's disease (PD) walk with a shortened stride length and high stride-to-stride variability, a measure associated with fall risk. Rhythmic auditory stimulation (RAS) improves stride length but the effects on stride-to-stride variability, a marker of fall risk, are unknown. The effects of RAS on stride time variability, swing time variability and spatial-temporal measures were examined during 100-m walks with the RAS beat set to 100 and 110% of each subject's usual cadence in 29 patients with idiopathic PD and 26 healthy age-matched controls. Carryover effects were also evaluated. During usual walking, variability was significantly higher (worse) in the patients with PD compared with the controls ($P < 0.01$). For the patients with PD, RAS at 100% improved gait speed, stride length and swing time ($P < 0.02$) but did not significantly affect variability. With RAS at 110%, reductions in variability were also observed ($P < 0.03$) and these effects persisted 2 and 15 min later. In the control subjects, the positive effects of RAS were not observed. For example, RAS increased stride time variability at 100 and 110%. These results demonstrate that RAS enables more automatic movement and reduces stride-to-stride variability in patients with PD. Further, these improvements are not simply a by-product of changes in speed or stride length. After walking with RAS, there also appears to be a carryover effect that supports the possibility of motor plasticity in the networks controlling rhythmicity in PD and the potential for using RAS as an intervention to improve mobility and reduce fall risk.

Introduction

Previous studies have shown that rhythmic auditory stimulation (RAS) can improve the spatiotemporal features of gait in patients with Parkinson's disease (PD) (Rubenstein *et al.*, 2002; Lim *et al.*, 2005). When using RAS, administered in the form of a metronome, gait speed and stride length improved in PD patients in both 'on' and 'off' states (McIntosh *et al.*, 1997). When RAS was administered at a rate either equal to the patient's baseline step rate or 10% higher, it reduced the double support time and increased stride length (Freedland *et al.*, 2002). Similarly, gait speed increased when RAS was set higher than the usual step rate (Howe *et al.*, 2003; Willems *et al.*, 2006). The effects of RAS may also carry over to no-RAS walking; an increase in gait speed and stride length were observed after administration of RAS to PD patients for 3 weeks (Thaut *et al.*, 1996).

Although there is evidence indicating that RAS improves stride length and other spatiotemporal features of gait in PD, the effects of RAS on stride-to-stride variability and the consistency or rhythmicity of the gait pattern are largely unknown. *A priori*, one could argue that if key features of gait in PD, such as stride length and gait speed, improve then rhythmicity would also improve with RAS. Further, one could suggest that because RAS sets the pace, it can act like an external rhythm generator and help restore rhythmicity, thereby reducing stride-to-stride variability. Conversely, in PD, gait rhythmic-

ity often behaves differently from stride length, gait speed and other parkinsonian features (Blin *et al.*, 1991; Hausdorff *et al.*, 1998; Schaafsma *et al.*, 2003; Frenkel-Toledo *et al.*, 2005a; Hausdorff, 2005). Thus, one could suggest that damage to the circuits that regulate rhythmicity may prevent these patients from walking with a consistent pattern, even in the presence of RAS.

Given the association between stride-to-stride variability and falls (Nakamura *et al.*, 1996; Hausdorff *et al.*, 2001; Schaafsma *et al.*, 2003; Hausdorff, 2005) and the importance of learning more about the motor control of PD and the potential clinical utility of RAS, the primary objective of the present study was to test the hypothesis that RAS reduces stride-to-stride variability in patients with PD. Following the example of previous investigations, which demonstrated that improvements in gait speed and stride length may be rate dependent (Freedland *et al.*, 2002; Howe *et al.*, 2003; Willems *et al.*, 2006), we studied the effects of RAS when it was set to 100 and 110% of the usual step rate. We also examined possible carryover effects, compared the effects in PD with those of a group of healthy controls and studied the effects of RAS on spatiotemporal parameters.

Materials and methods

Subjects

Twenty-nine patients with PD and 26 age- and sex-matched healthy controls volunteered to participate in the study. Potential participants were identified from the registry of the Movement Disorders Unit at

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the Tel Aviv Sourasky Medical Center. Patients were recruited if they were on a stable antiparkinsonian medication regimen, were free of motor response fluctuations, had mild to moderate disease severity, i.e. Hoehn & Yahr stage II–III (Hoehn & Yahr, 1967) and were able to ambulate independently for at least 100 m. Subjects were excluded if they had other neurological or orthopedic conditions, if their hearing was impaired (as determined using a 124-cp tuning fork) or if they had dementia, as determined by a Mini-Mental State Exam score (Folstein *et al.*, 1975) less than 24. Subjects of similar age who were reported as being free of neurological, visual, vestibular and gait disturbances were recruited from the community to form the control group. The study was approved by the local human studies committee of the Tel Aviv Sourasky Medical Center and informed written consent was obtained from all participants before they entered the study, according to the Declaration of Helsinki.

Subject characteristics

General demographic data and fall history (number of falls in the previous year) were obtained. Cognitive function was assessed using the Mini-Mental State Exam and functional mobility was evaluated using the Timed Up and Go test (Podsiadlo & Richardson, 1991). Patients were evaluated with respect to the Hoehn & Yahr staging (Goetz *et al.*, 2004) (a measure of PD disease severity) and PD severity was evaluated using the Unified PD Rating Scale (Fahn *et al.*, 1987). The total Unified PD Rating Scale and its motor subscale (part III) were obtained.

Assessment of gait

After completing the assessment of subject characteristics, the effects of RAS on gait were examined under six conditions in the following order: (i) baseline (walking at a usual walking, comfortable pace without RAS); (ii) walking with RAS matched to the baseline cadence (RAS = 100% of the baseline step rate); (iii) walking at a comfortable pace without RAS (to examine any immediate carryover effect); (iv) walking with RAS at 110% of the baseline step rate; (v) walking at a comfortable pace without RAS (to examine any immediate carryover effect) and (vi) walking at a comfortable pace without RAS after a 15-min rest (to examine any delayed carryover effect). For each RAS condition, a metronome (Quark Metronome, Qwik Time™) was set to the desired step rate (based upon each subject's usual walking step rate). Subjects listened to the beat of the metronome and were told to try to match their walking (foot contact of each step) with the RAS. The walking distance for each condition was 100 m (i.e. four times along a 25-m level corridor); subjects were instructed to keep walking in time to the metronome when they turned at the end of the corridor. There was a 2-min break between each condition except between the fifth and sixth conditions, where there was a 15-min break to allow for evaluation of longer-term carryover effects. Before the first and second conditions, the participants underwent training in order to familiarize them with the walking environment and test equipment, and to allow them to practice walking with the RAS apparatus. Approximately 2 weeks later, 15 patients participated in a second session that followed the same protocol as detailed above but without the RAS intervention, in order to examine any possible within-session training effects.

A previously described computerized force-sensitive system was used to quantify gait rhythm, timing of the gait cycle (i.e. the stride time), swing time and stride-to-stride variability (Bazner *et al.*, 2000; Frenkel-Toledo *et al.*, 2005b; Yogev *et al.*, 2005). The system

measures the forces underneath the foot as a function of time. It consists of a pair of shoes and a recording unit. Each shoe contains eight pressure-sensitive sensors that cover the surface of the sole and measure the vertical forces under the foot. The recording unit (19 × 14 × 4.5 cm; 1.5 kg) is carried on the waist. Plantar pressures under each foot are recorded at a rate of 100 Hz. Measurements are stored in a memory card during the walk and, after the walk, are transferred to a personal computer for further analysis. The following gait parameters were determined from the force record using previously described methods that filter out outliers, like those caused by turns, before further processing (Hausdorff *et al.*, 2001; Schaafsma *et al.*, 2003; Frenkel-Toledo *et al.*, 2005b): average stride time (and cadence), average swing time (as percentage of gait cycle), stride time variability and swing time variability. The measure of cadence (as determined from each subject's average stride time) during the first test was used to define RAS in subsequent tests. Variability measures were quantified using the coefficient of variation, e.g. stride time variability = 100 × (SD of stride time/average stride time). These measures were obtained for the left and right foot but, as they were highly correlated with one another, here we report values based only on the right foot (i.e. Pearson's correlation coefficients indicated moderate to strong correlations for all measures in all test conditions, based on the World Health Organization classification scheme). The average gait speed was determined by measuring the time that the subject took to walk the middle 8 m of the walkway and then averaging over all transversals. Each subject's average stride length was determined by multiplying the average gait speed by the average stride time. Although the portion of the walk in which average gait speed and average stride length were calculated was not identical to the steps in which the other measures were determined, all calculations were designed to reflect steady-state walking.

Statistical analysis

Descriptive statistics are reported as mean ± SD. We used the Student's *t* and chi-square tests to compare the PD and control subjects with respect to different background characteristics (e.g. age and gender). In order to estimate the effect of RAS, we applied mixed-effect models for repeated measures to evaluate within-group and between-group differences. For each gait variable, we applied a separate model where the dependent variable was the gait measure (a continuous one) and the independent variables were categorical, i.e. the group (PD patients or controls), walking condition (e.g. no RAS or RAS at 100%) and group × walking condition interaction term. The fixed factors in these models were group and walking condition, whereas the subject was the random factor. In each model, for the walking condition, the no-RAS baseline walk was considered as the reference category, inherent in the modeling procedure. Mixed-effect models were also applied in order to assess any possible training effect on each gait parameter (here the independent variable was the order of the walking condition). *P*-values reported are based on two-sided comparison. A *P*-value of 0.05 was considered statistically significant. All statistical analyses were performed using SAS 8.2 (Proc Mixed).

Results

Subject characteristics

The PD patients and the controls were similar with respect to age, gender, weight and height (Table 1). There was a significant difference between the groups for the Timed Up and Go test, fall history and Mini-Mental State Exam scores. Patients with PD took significantly

TABLE 1. Characteristics of the study participants: patients with Parkinson's disease and control subjects

	<i>P</i> -value	Controls (<i>n</i> = 26)	Patients (<i>n</i> = 29)
Age (years)	NS	64.6 ± 6.8	67.2 ± 9.1
Height (cm)	NS	168.69 ± 8.59	166.44 ± 7.64
Weight (kg)	NS	71.5 ± 11.1	70.3 ± 8.4
Gender (male% : female%)	NS	47 : 53	55 : 45
Timed Up and Go test (s)	< 0.001	9.3 ± 1.7	11.9 ± 3.4
Mini Mental State Exam	< 0.001	29.6 ± 0.8	28.3 ± 1.5
No. of falls in previous year	< 0.001	0.0 ± 0.0	1.2 ± 2.1

Data are presented as mean ± SD. For fall history, significant group differences are found by using a one-sample Kolmogorov-Smirnov test, a one sample *t*-test (i.e. comparing with 0.0) or transforming the data and comparing fall status (yes/no) between the two groups using chi-square analysis or Fischer's exact test (*P* < 0.002). NS, non significant.

longer to perform the Timed Up and Go test, reported more falls in the previous year and performed slightly worse on the Mini-Mental State Exam. In the patient group, the mean Hoehn & Yahr stage was 2.4 ± 0.4 and Unified PD Rating Scale total and motor scores were 24.9 ± 8.5 and 15.8 ± 4.5, respectively, indicating mild to moderate disease severity.

As shown in Table 2, under usual walking conditions (without any RAS), the average stride time was similar in the two subject groups. Gait speed, stride length and swing time were, however, significantly reduced in the subjects with PD (*P* < 0.001). Without RAS, subjects with PD also walked with greater stride-to-stride variability, as reflected by significantly higher (i.e. worse) stride time variability and swing time variability compared with the control group.

Immediate effects of rhythmic auditory stimulation

Table 2 summarizes the effects of RAS on the gait of the two subject groups. When RAS was set to each subject's most comfortable walking step rate (i.e. with RAS equal to 100% of the non-RAS step rate, 111 steps/min, on average), mean stride times were unchanged relative to the no-RAS condition in both groups, as expected. For the

subjects with PD, gait speed, stride length and swing time significantly increased with RAS. There were, however, no significant effects on the two measures of variability. For the control subjects, gait speed, stride length and swing time were unchanged with RAS at 100%. Surprisingly, stride time variability of the control subjects increased (became worse) compared with the no-RAS condition.

When RAS was set to 110% of the usual walking step rate (e.g. 122 instead of 111 steps/min), the average stride time was significantly reduced in both subject groups (see Table 2). For both groups, at this faster RAS, gait speed significantly increased compared with the no-RAS condition (*P* < 0.001). Stride length and swing time significantly increased in the patients with PD (*P* = 0.02) but were unchanged in the controls. Compared with the no-RAS condition, the two variability measures were significantly reduced (improved) in the patients with PD when walking with RAS at 110% of the most comfortable stepping rate. An example of the effect of RAS on stride time variability is shown in Fig. 1 for one patient with PD. In contrast, in the control subjects at 110% RAS, stride time variability was increased (worse) compared with the no-RAS condition, whereas swing time variability was unchanged.

Carryover effects

Table 3 summarizes the carryover effects of RAS. After walking with RAS set to 100% of the step rate, there was an immediate carryover effect for three parameters in the PD group; the increase in gait speed, stride length and swing time persisted even when RAS was removed. Consistent with the absence of any effect observed while walking with RAS set to 100% of the step rate, there was, however, no significant change in either measure of variability shortly after RAS was switched off. For the control group, carryover effects after walking with RAS set to 100% of their step rate were also similar to the effects observed when walking with RAS set to this step rate. There were no significant effects on stride time, swing time, stride length or gait speed but there was a small but significant increase in stride time variability compared with the usual walking, no-RAS condition.

After walking with RAS set to 110% of the step rate, carryover effects were also observed, both immediately and 15 min later (see Table 3). For the subjects with PD, all of the improvements observed while walking with RAS set to 110% were also observed 15 min later. This included a

TABLE 2. Effects of rhythmic auditory stimulation (RAS) at 100% and 110% of each subject's usual walking cadence (No RAS)

	Control subjects			Patients with PD		
	No RAS	RAS at 100%	RAS at 110%	No RAS	RAS at 100%	RAS at 110%
Stride time (s)	1.08 ± 0.09	1.09 ± 0.10 (NS)	1.01 ± 0.09 (0.001)	1.08 ± 0.13 (NS)	1.08 ± 0.13 (NS)	1.03 ± 0.15 (0.001)
Gait speed (m/s)	1.24 ± 0.14	1.24 ± 0.17 (NS)	1.33 ± 0.21 (0.001)	1.00 ± 0.21 (0.001)	1.04 ± 0.22 (0.02)	1.09 ± 0.25 (0.001)
Stride length (m)	1.35 ± 0.19	1.37 ± 0.23 (NS)	1.37 ± 0.25 (NS)	1.06 ± 0.21 (0.001)	1.10 ± 0.23 (0.02)	1.10 ± 0.25 (0.05)
Swing time (%)	36.3 ± 1.4	36.1 ± 1.8 (NS)	36.0 ± 1.9 (NS)	33.8 ± 3.3 (0.001)	34.3 ± 3.1 (0.006)	34.3 ± 3.2 (0.02)
Stride time variability (%)	1.8 ± 0.6	2.2 ± 0.8 (0.01)	2.2 ± 1.3 (0.03)	2.6 ± 1.0 (0.003)	2.4 ± 1.1 (NS)	2.2 ± 0.9 (0.004)
Swing time variability (%)	2.9 ± 1.3	2.8 ± 1.2 (NS)	3.1 ± 1.7 (NS)	4.7 ± 3.2 (0.01)	4.5 ± 3.4 (NS)	4.1 ± 3.1 (0.03)

Data are presented as mean ± SD; numbers in parentheses are *P*-values based on within-group comparisons to usual walking (i.e. without RAS), except for the usual walking for the Parkinson's disease (PD) group, where the *P*-values are with respect to the usual walking (no RAS) values of the control subjects. Note that, in response to RAS at 110% of usual walking cadence, significant effects in stride time variability were seen in both the patient and controls but the effects were in opposite directions. NS, non significant.

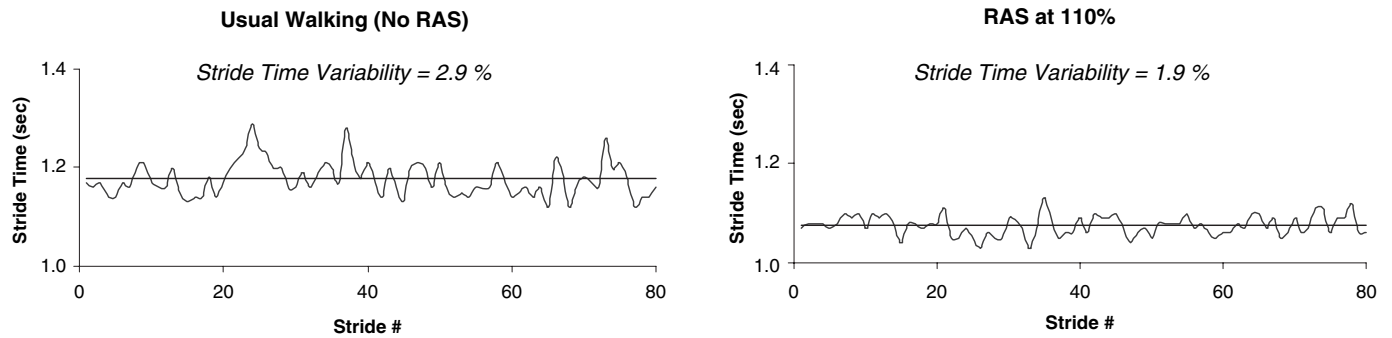


FIG. 1. Example of the effect of rhythmic auditory stimulation (RAS) (at 110% of the usual cadence) on the stride-to-stride variability of the stride time in one patient with Parkinson's disease. Note how the stride time fluctuates to a much lower degree with RAS (right, stride time variability 1.9%) compared with usual walking (left, stride time variability 2.9%). The horizontal lines are the average stride time for each condition.

TABLE 3. Carryover effects after walking with rhythmic auditory stimulation (RAS) set to 100 and 110% of each subject's usual walking cadence

	Control subjects			Patients with PD		
	15-min carryover after 110%	Immediate carryover effect at 110%	Immediate carryover effect at 100%	15-min carryover after 110%	Immediate carryover effect at 110%	Immediate carryover effect at 100%
Stride time (s)	1.05 ± 0.08 (0.003)	1.06 ± 0.09 (0.03)	1.07 ± 0.09 (NS)	1.03 ± 0.09 (0.001)	1.03 ± 0.09 (0.001)	1.06 ± 0.13 (NS)
Gait speed (m/s)	1.30 ± 0.16 (0.001)	1.29 ± 0.16 (NS)	1.27 ± 0.16 (NS)	1.11 ± 0.20 (0.001)	1.12 ± 0.19 (0.001)	1.06 ± 0.24 (0.001)
Stride length (m)	1.38 ± 0.20 (NS)	1.37 ± 0.20 (NS)	1.37 ± 0.20 (NS)	1.12 ± 0.20 (0.002)	1.14 ± 0.20 (0.001)	1.10 ± 0.23 (0.02)
Swing time (%)	36.1 ± 2.5 (NS)	36.0 ± 2.0 (NS)	35.9 ± 2.3 (NS)	34.9 ± 2.9 (0.001)	34.9 ± 2.5 (0.001)	34.4 ± 3.2 (0.009)
Stride time variability (%)	1.9 ± 0.5 (NS)	1.9 ± 0.5 (NS)	2.0 ± 0.7 (0.03) [†]	2.2 ± 1.0 (0.03)	2.4 ± 0.9 (NS)	2.5 ± 1.2 (NS)
Swing time variability (%)	2.9 ± 2.2 (NS)	2.6 ± 1.1 (NS)	2.8 ± 2.3 (NS)	3.5 ± 1.4 (0.003)	3.4 ± 1.8 (0.003)	4.2 ± 2.9 (NS)

Data are presented as mean ± SD; numbers in parentheses are *P*-values based on within-group comparisons to usual walking values (i.e. without RAS) shown in Table 2 (left-most column for each group). [†]Although RAS tended to reduce stride time variability in the subjects with Parkinson's disease (PD), it produced an increased stride time variability in the control subjects. NS, non significant.

significant reduction in both the stride time variability and swing time variability compared with pre-RAS walking. For the control subjects, the only changes that persisted 15 min after walking with RAS were the significant reduction in the average stride time and significant increase in the average gait speed. Significant carryover effects were not observed for either of the measures of variability in the control subjects.

As can be seen in Tables 2 and 3, the effects of RAS were similar in the two groups for certain gait measures but the effects were different in each group for others. Thus, for example, the effects of RAS on stride time and gait speed in the subjects with PD paralleled the effects observed in the control subjects (*P* = NS for the group × intervention interactions). However, the effects on swing time and stride time variability were clearly different (*P* ≤ 0.01 for the group × intervention interaction effects, e.g. RAS tended to reduce stride time variability in subjects with PD but to increase it in the control subjects).

Training effects

To test whether the observed effects of RAS may have been due to training, practice or familiarization with the surroundings, a subset of patients with PD (*n* = 15, arbitrarily selected) were asked to walk six

100-m bouts, similar to the RAS protocol but without any RAS. Compared with the first 100-m trial, there was a small but significant increase in gait speed and average stride time over time (*P* < 0.0001). In contrast, these repeated trials had no significant effects on either measure of variability (e.g. *P* = 0.97 for stride time variability).

Discussion

Consistent with previous reports (Blin *et al.*, 1990; Morris *et al.*, 1994; Hausdorff *et al.*, 1998; Ebersbach *et al.*, 1999a; Schaafsma *et al.*, 2003; Giladi *et al.*, 2005; Sofuwa *et al.*, 2005; Baltadjieva *et al.*, 2006), the patients with PD in this study walked with a reduced gait speed and swing time compared with an age-matched control group and with an increased stride-to-stride variability under the usual walking (no-RAS) condition. The effects of RAS on average gait speed, stride length and swing time were also generally similar to those reported earlier (McIntosh *et al.*, 1997; Freedland *et al.*, 2002; Rubenstein *et al.*, 2002; Howe *et al.*, 2003; Lim *et al.*, 2005; Willems *et al.*, 2006). For the patients with PD, RAS increased gait speed, stride length and swing time, both when RAS was set to the usual step rate and when it was 10% higher. The present investigation both

concur with and extends previous findings. The results are consistent with the reports that showed that RAS affects stride length and gait speed. Here we extend those studies by demonstrating that RAS also affects rhythmicity and stride-to-stride variability when it is set to a rate that is greater than the subject's usual cadence, that an intriguing carryover effect exists and that the effects of RAS on variability are apparently independent of those on stride length.

In the Introduction, we presented two possibilities about the effects of RAS on stride-to-stride variability; in brief, either it would reduce stride-to-stride variability or it would not. The results suggest that the answer is not a simple yes or no and that the stated arguments were not completely correct. Among the patients with PD, with RAS set to the usual walking step rate, both measures of stride-to-stride variability were not significantly different from those obtained while walking without RAS. Conversely, while walking at the higher step rate (110%), both measures of stride-to-stride variability were reduced (indicating improved rhythmicity and stability), moving closer to the control values. RAS seems to enhance rhythmicity in patients with PD but the effect may be rate dependent. In addition, the present findings demonstrate that the positive effects of RAS on variability are group specific and, interestingly, that the effects apparently endure even when RAS is removed.

How should the observed effects of the external cueing on stride-to-stride variability be interpreted? First, it is clear that, with appropriate cueing, patients with PD are capable of walking with a relatively reduced stride-to-stride variability and more 'normal' rhythmicity. Second, the differential effects of RAS on gait speed, stride length and variability in the subjects with PD (Table 2) suggest that the observed effects on stride-to-stride variability are not simply a by-product of changes in gait speed or stride length. At the lower RAS rate, gait speed and stride length of the patients with PD became larger than those of the no-RAS, usual walking condition. There was no effect on variability until RAS was increased to 110%, even though stride length remained unchanged compared with the value observed with RAS at 100%. Thus, the effects of RAS on variability are somewhat independent of the effects of RAS on stride length and gait speed.

Careful examination of the response of the control subjects and the effects of the repeated walks on gait speed but not on variability in PD also supports the idea that the RAS influence on variability differs from that of its impact on gait speed and stride length. Apparently, gait speed alone is not the single driver of variability, consistent with previous reports that observed a dissociation between stride length and variability (Frenkel-Toledo *et al.*, 2005a; Grabiner *et al.*, 2001; Hausdorff, 2004, 2005). Thus, the present results indicate that RAS apparently affects rhythmicity somewhat independently of speed and stride length. Although stride length and gait speed clearly play a critical role in many of the gait changes common in PD (Morris *et al.*, 1994, 1996), the present findings suggest that stride length does not fully determine rhythmicity, that RAS affects stride length and variability differently, and that the diminished stride length in PD is probably not the only source of the increased stride-to-stride variability in the presence of impaired basal ganglia function.

The effects of RAS on variability could be explained in several ways. Perhaps the most straightforward explanation for the observed effects of RAS on stride-to-stride variability is that, in patients with PD, RAS acts like a pacemaker and provides an external rhythm that is able to stabilize the defective internal rhythm of the basal ganglia (McIntosh *et al.*, 1997; Brotchie *et al.*, 1991; Thaut, 2003; Jantzen *et al.*, 2005; Zelaznik *et al.*, 2005; Nagy *et al.*, 2006). RAS may circumvent the pallidal-supplementary motor area pathway, possibly via the premotor cortex, and provide external cues to guide movement (Mushiake *et al.*, 1991; Halsband *et al.*, 1993; Hanakawa *et al.*, 1999a; Elsinger *et al.*,

2003). Increased activation of the lateral premotor cortex in PD patients during cueing lends support to this view (Hanakawa *et al.*, 1999b).

This explanation, that RAS works simply by acting as an external time-keeper, is rather intuitive but the rate-dependent nature of the effect of RAS on variability, the group-specific response and observed carryover effects present difficulties to this theory. If RAS acts as a pacemaker, it is not readily apparent why RAS increased stride-to-stride variability in the healthy control subjects, rendering their gait rhythm more 'abnormal' and why the effect should be rate dependent in PD. Indeed, further support for the rate-dependent nature of RAS comes from previous studies that showed that RAS at 80% of the normal cadence and similarly RAS at 60 beats/min increased stride time variability in patients with PD (Ebersbach *et al.*, 1999b; Almeida *et al.*, 2007). The carryover effects of RAS on variability (Table 3) pose the greatest challenge to the idea that RAS enhances rhythmicity simply by supplying an external cue. It is difficult to understand why the effects of RAS persist in the absence of the external cueing. Instead, the enduring effects suggest that neural time-keeping circuitry is apparently influenced by RAS.

Other explanations of the observed effects of RAS revolve around its influence on the neural circuitry regulating gait. The rate-dependent and enduring effects could be achieved by affecting striatal activation (Brown *et al.*, 2006) or via an effect on the cerebellum (Eckert *et al.*, 2005; Brown *et al.*, 2006; Del Olmo *et al.*, 2006). Indeed, extensive training of speech in PD has demonstrated evidence for striatal plasticity, changes in the cerebellum and long-term carryover effects that persist well beyond the training period (Liotti *et al.*, 2003), effects that may also be achievable with gait.

Just as extensive speech training has long-term benefits that have brought this approach into the clinic (Ramig *et al.*, 2001; Liotti *et al.*, 2003), the observed carryover effects raise the possibility that RAS might be used as a non-pharmacological intervention to complement standard pharmacological treatment in patients with PD. Indeed, RAS may have the potential to retrain some of the very basic and early abnormalities in PD, i.e. locomotion dysrhythmicity (Morris *et al.*, 1994; Ashburn *et al.*, 2001; Bloem *et al.*, 2004; Baltadjieva *et al.*, 2006), consistent with recent animal and human studies that support the idea that basal ganglia and related circuits manifest plasticity, even in the presence of PD (Liotti *et al.*, 2003; Fisher *et al.*, 2004; Wu & Hallett, 2005; Steiner *et al.*, 2006). The ability of RAS to restore rhythmicity and its previously demonstrated effect on gait speed and stride length (Thaut *et al.*, 1996; Howe *et al.*, 2003; Willems *et al.*, 2006) suggest that extensive use of RAS may have a profound, positive impact on mobility, fall risk and quality of life in PD (Morris *et al.*, 1994; Ashburn *et al.*, 2001; Bloem *et al.*, 2004). Important questions do, however, remain. The fact that improvement was observed even 15 min after walking with RAS was very encouraging and somewhat surprising. However, the carryover effects were acute and clinical significance remains to be proven. Nonetheless, the present findings combine with intriguing previous work (Thaut *et al.*, 1996; Howe *et al.*, 2003; Willems *et al.*, 2006) to argue for the plasticity of the neural control of gait rhythmicity in PD, independent of stride length, and for the use of RAS as an alternative therapeutic approach for the treatment of parkinsonian gait disturbances and, perhaps, for reducing fall risk.

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Abbreviations

PD, Parkinson's disease; RAS, rhythmic auditory stimulation.

References

- Almeida, Q.J., Frank, J.S., Roy, E.A., Patla, A.E. & Jog, M.S. (2007) Dopaminergic modulation of timing control and variability in the gait of Parkinson's disease. *Mov. Disord.*, [Epub ahead of print, DOI: 10.1002/mds.21603].
- Ashburn, A., Stack, E., Pickering, R.M. & Ward, C.D. (2001) A community-dwelling sample of people with Parkinson's disease: characteristics of fallers and non-fallers. *Age Ageing*, **30**, 47–52.
- Baltadjieva, R., Giladi, N., Gruendlinger, L., Peretz, C. & Hausdorff, J.M. (2006) Marked alterations in the gait timing and rhythmicity of patients with de novo Parkinson's disease. *Eur. J. Neurosci.*, **24**, 1815–1820.
- Bazner, H., Oster, M., Daffertshofer, M. & Hennerici, M. (2000) Assessment of gait in subcortical vascular encephalopathy by computerized analysis: a cross-sectional and longitudinal study. *J. Neurol.*, **247**, 841–849.
- Blin, O., Ferrandez, A.M. & Serratrice, G. (1990) Quantitative analysis of gait in Parkinson patients: increased variability of stride length. *J. Neurol. Sci.*, **98**, 91–97.
- Blin, O., Ferrandez, A.M., Pailhous, J. & Serratrice, G. (1991) Dopa-sensitive and dopa-resistant gait parameters in Parkinson's disease. *J. Neurol. Sci.*, **103**, 51–54.
- Bloem, B.R., Hausdorff, J.M., Visser, J.E. & Giladi, N. (2004) Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Mov. Disord.*, **19**, 871–884.
- Brotchie, P., Iansek, R. & Home, M.K. (1991) Motor function of the monkey globus pallidus. 1. Neuronal discharge and parameters of movement. *Brain*, **114**, 1667–1683.
- Brown, S., Martinez, M.J. & Parsons, L.M. (2006) The neural basis of human dance. *Cereb. Cortex*, **16**, 1157–1167.
- Del Olmo, M.F., Arias, P., Furio, M.C., Pozo, M.A. & Cudeiro, J. (2006) Evaluation of the effect of training using auditory stimulation on rhythmic movement in Parkinsonian patients – a combined motor and [18F]-FDG PET study. *Parkinson. Relat. Disord.*, **12**, 155–164.
- Ebersbach, G., Sojer, M., Valldeoriola, F., Wissel, J., Muller, J., Tolosa, E. & Poewe, W. (1999a) Comparative analysis of gait in Parkinson's disease, cerebellar ataxia and subcortical arteriosclerotic encephalopathy. *Brain*, **122**, 1349–1355.
- Ebersbach, G., Heijmenberg, M., Kindermann, L., Trottenberg, T., Wissel, J. & Poewe, W. (1999b) Interference of rhythmic constraint on gait in healthy subjects and patients with early Parkinson's disease: evidence for impaired locomotor pattern generation in early Parkinson's disease. *Mov. Disord.*, **14**, 619–625.
- Eckert, S., Barnes, A., Dhawan, V., Frucht, S., Gordon, M.F., Feigin, A.S. & Eidelberg, D. (2005) FDG PET in the differential diagnosis of parkinsonian disorders. *Neuroimage*, **26**, 912–921.
- Elsinger, C.L., Rao, S.M., Zimelman, J.L., Reynolds, N.C., Blindauer, K.A. & Hoffmann, R.G. (2003) Neural basis for impaired time reproduction in Parkinson's disease: an fMRI study. *J. Int. Neuropsychol. Soc.*, **9**, 1088–1098.
- Fahn, S., Elton, R. & members of the UPDRS development committee (1987) Unified Parkinson's disease rating scale. In Fahn, S., Marsden, C.D., Calne, D. & Goldstein, M. (Eds), *Recent Developments in Parkinson's Disease*. Macmillan Health Care Information, Florham Park, NJ, pp. 153–163.
- Fisher, B.E., Petzinger, G.M., Nixon, K., Hogg, E., Bremner, S., Meshul, C.K. & Jakowec, M.W. (2004) Exercise-induced behavioral recovery and neuroplasticity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse basal ganglia. *J. Neurosci. Res.*, **77**, 378–390.
- Folstein, M.F., Folstein, S.E. & McHugh, P.R. (1975) 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.*, **12**, 189–198.
- Freedland, R.L., Festa, C., Sealy, M., McBean, A., Elghazaly, P., Capan, A., Brozycki, L., Nelson, A.J. & Rothman, J. (2002) The effects of pulsed auditory stimulation on various gait measurements in persons with Parkinson's Disease. *Neurorehabilitation*, **17**, 81–87.
- Frenkel-Toledo, S., Giladi, N., Peretz, C., Herman, T., Gruendlinger, L. & Hausdorff, J.M. (2005a) Effect of gait speed on gait rhythmicity in Parkinson's disease: variability of stride time and swing time respond differently. *J. Neuroeng. Rehabil.*, **2**, 23.
- Frenkel-Toledo, S., Giladi, N., Peretz, C., Herman, T., Gruendlinger, L. & Hausdorff, J.M. (2005b) Treadmill walking as an external pacemaker to improve gait rhythm and stability in Parkinson's disease. *Mov. Disord.*, **20**, 1109–1114.
- Giladi, N., Hausdorff, J.M. & Balash, Y. (2005) Episodic and continuous gait disturbances in Parkinson's disease. In Galvez-Jimenez, N. (Ed.), *Scientific Basis for the Treatment of Parkinson's Disease*. Taylor & Francis, London, pp. 321–332.
- Goetz, C.G., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G.T., Counsell, C., Giladi, N., Holloway, R.G., Moore, C.G., Wenning, G.K., Yahr, M.D. & Seidl, L. (2004) Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: Status and recommendations The Movement Disorder Society Task Force on rating scales for Parkinson's disease. *Mov. Disord.*, **19**, 1020–1028.
- Grabner, P.C., Biswas, S.T. & Grabner, M.D. (2001) Age-related changes in spatial and temporal gait variables. *Arch. Phys. Med. Rehabil.*, **82**, 31–35.
- Halsband, U., Ito, N., Tanji, J. & Freund, H.J. (1993) The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. *Brain*, **116** (1), 243–266.
- Hanakawa, T., Fukuyama, H., Katsumi, Y., Honda, M. & Shibasaki, H. (1999a) Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. *Ann. Neurol.*, **45**, 329–336.
- Hanakawa, T., Katsumi, Y., Fukuyama, H., Honda, M., Hayashi, T., Kimura, J. & Shibasaki, H. (1999b) Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. *Brain*, **122** (7), 1271–1282.
- Hausdorff, J.M. (2004) Stride variability: beyond length and frequency. *Gait Posture*, **20**, 304.
- Hausdorff, J.M. (2007) Gait dynamics, fractals and falls: Finding meaning in the stride-to-stride fluctuations of human walking. *Hum. Mov. Sci.*, **26**, 555–589.
- Hausdorff, J.M., Cudkovicz, M.E., Firtion, R., Wei, J.Y. & Goldberger, A.L. (1998) Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease. *Mov. Disord.*, **13**, 428–437.
- Hausdorff, J.M., Rios, D. & Edelberg, H.K. (2001) Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Arch. Phys. Med. Rehabil.*, **82**, 1050–1056.
- Hoehn, M.M. & Yahr, M.D. (1967) Parkinsonism: onset, progression and mortality. *Neurology*, **17**, 427–442.
- Howe, T.E., Lovgreen, B., Cody, F.W., Ashton, V.J. & Oldham, J.A. (2003) Auditory cues can modify the gait of persons with early-stage Parkinson's disease: a method for enhancing parkinsonian walking performance? *Clin. Rehabil.*, **17**, 363–367.
- Jantzen, K.J., Steinberg, F.L. & Kelso, J.A. (2005) Functional MRI reveals the existence of modality and coordination-dependent timing networks. *Neuroimage*, **25**, 1031–1042.
- Lim, I., van Wegen, E., de Goede, C., Deutekom, M., Nieuwboer, A., Willems, A., Jones, D., Rochester, L. & Kwakkel, G. (2005) Effects of external rhythmical cueing on gait in patients with Parkinson's disease: a systematic review. *Clin. Rehabil.*, **19**, 695–713.
- Liotti, M., Ramig, L.O., Vogel, D., New, P., Cook, C.I., Ingham, R.J., Ingham, J.C. & Fox, P.T. (2003) Hypophonia in Parkinson's disease: neural correlates of voice treatment revealed by PET. *Neurology*, **60**, 432–440.
- McIntosh, G.C., Brown, S.H., Rice, R.R. & Thaut, M.H. (1997) Rhythmic auditory-motor facilitation of gait patterns in patients with Parkinson's disease. *J. Neurol. Neurosurg. Psychiatr.*, **62**, 22–26.
- Morris, M.E., Iansek, R., Matyas, T.A. & Summers, J.J. (1994) The pathogenesis of gait hypokinesia in Parkinson's disease. *Brain*, **117** (5), 1169–1181.
- Morris, M.E., Iansek, R., Matyas, T.A. & Summers, J.J. (1996) Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. *Brain*, **119** (2), 551–568.
- Mushiaki, H., Inase, M. & Tanji, J. (1991) Neuronal activity in the primate premotor, supplementary, and precentral motor cortex during visually guided and internally determined sequential movements. *J. Neurophysiol.*, **66**, 705–718.
- Nagy, A., Eordeghe, G., Paroczky, Z., Markus, Z. & Benedek, G. (2006) Multisensory integration in the basal ganglia. *Eur. J. Neurosci.*, **24**, 917–924.
- Nakamura, T., Meguro, K. & Sasaki, H. (1996) Relationship between falls and stride length variability in senile dementia of the Alzheimer type. *Gerontology*, **42**, 108–113.
- Podsiadlo, D. & Richardson, S. (1991) The timed 'Up & Go': a test of basic functional mobility for frail elderly persons. *J. Am. Geriatr. Soc.*, **39**, 142–148.

- Ramig, L.O., Sapis, S., Countryman, S., Pawlas, A.A., O'Brien, C., Hoehn, M. & Thompson, L.L. (2001) Intensive voice treatment (LSVT) for patients with Parkinson's disease: a 2 year follow up. *J. Neurol. Neurosurg. Psychiat.*, **71**, 493–498.
- Rubenstein, T.C., Giladi, N. & Hausdorff, J.M. (2002) The power of cueing to circumvent dopamine deficits: a review of physical therapy treatment of gait disturbances in Parkinson's disease. *Mov. Disord.*, **17**, 1148–1160.
- 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. *J. Neurol. Sci.*, **212**, 47–53.
- Sofuwa, O., Nieuwboer, A., Desloovere, K., Willems, A.M., Chavret, F. & Jonkers, I. (2005) Quantitative gait analysis in Parkinson's disease: comparison with a healthy control group. *Arch. Phys. Med. Rehabil.*, **86**, 1007–1013.
- Steiner, B., Winter, C., Hosman, K., Siebert, E., Kempermann, G., Petrus, D.S. & Kupsch, A. (2006) Enriched environment induces cellular plasticity in the adult substantia nigra and improves motor behavior function in the 6-OHDA rat model of Parkinson's disease. *Exp. Neurol.*, **199**, 291–300.
- Thaut, M.H. (2003) Neural basis of rhythmic timing networks in the human brain. *Ann. N.Y. Acad. Sci.*, **999**, 364–373.
- Thaut, M.H., McIntosh, G.C., Rice, R.R., Miller, R.A., Rathbun, J. & Brault, J.M. (1996) Rhythmic auditory stimulation in gait training for Parkinson's disease patients. *Mov. Disord.*, **11**, 193–200.
- Willems, A.M., Nieuwboer, A., Chavret, F., Desloovere, K., Dom, R., Rochester, L., Jones, D., Kwakkel, G. & Van Wegen, E. (2006) The use of rhythmic auditory cues to influence gait in patients with Parkinson's disease, the differential effect for freezers and non-freezers, an explorative study. *Disabil. Rehabil.*, **28**, 721–728.
- Wu, T. & Hallett, M. (2005) A functional MRI study of automatic movements in patients with Parkinson's disease. *Brain*, **128**, 2250–2259.
- Yogev, G., Giladi, N., Peretz, C., Springer, S., Simon, E.S. & Hausdorff, J.M. (2005) Dual tasking, gait rhythmicity, and Parkinson's disease: Which aspects of gait are attention demanding? *Eur. J. Neurosci.*, **22**, 1248–1256.
- Zelaznik, H.N., Spencer, R.M., Ivry, R.B., Baria, A., Bloom, M., Dolansky, L., Justice, S., Patterson, K. & Whetter, E. (2005) Timing variability in circle drawing and tapping: probing the relationship between event and emergent timing. *J. Mot. Behav.*, **37**, 395–403.