Interactive Rhythmic Auditory Stimulation reinstates natural 1/*f* structure in gait of Parkinson's patients

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Abstract

Parkinson's disease (PD) and basal ganglia dysfunction impair movement timing, which leads to gait instability and falls. Parkinsonian gait consists of random, disconnected stride times—rather than the 1/*f* structure observed in healthy gait—and this low fractal scaling of stride times is a strong predictor of falling. Walking with fixed-tempo Rhythmic Auditory Stimulation (RAS) improves many aspects of gait timing; however it requires attention and lowers fractal scaling away from healthy 1/f structure. In this experiment, PD patients and healthy participants walked with a) no auditory stimulation; b) fixed-tempo RAS; and c) an *interactive* rhythmic auditory stimulation system that used foot sensors and nonlinear oscillators to track and interact with the human's timing. Patients effortlessly synchronized with the interactive system, their gait felt more stable, and their fractal scaling returned to levels of healthy participants. With the fixed-tempo RAS, patients and healthy participants rarely synchronized, and when they did their fractal scaling declined away from healthy 1/*f* levels. After removing the interactive rhythmic stimulation, the PD patients' boost in fractal scaling persisted, indicating that the interaction stabilized the internal rhythm generating system and reintegrated timing networks. Interactive rhythmic auditory stimulation offers a flexible, portable, low-cost, non-invasive rehabilitation system that can improve the mobility, safety, and quality of life of Parkinson's Disease patients.

Keywords: Timing; Parkinson's Disease; Cognitive Technology; Nonlinear oscillators; 1/*f*; Scaling Laws.

Introduction

Human timing systems involve a distributed and interactive network that rely heavily on the basal ganglia (Buhusi & Meck, 2005). Impairments of the basal ganglia, such as in Parkinson's disease (PD) and Huntington's disease, lead to problems of movement timing and rhythm (Grahn & Brett, 2009; Graybiel, Aosaki, Flaherty, & Kimura, 1994; Schwartze, Keller, Patel, & Kotz, 2010). Among the most debilitating symptoms of PD are gait timing disturbances, for they can lead to falls, reduced independence, and the associated problems of isolation, cognitive decline, and increased mortality (Hausdorff, 2009). These gait disturbances are manifest in numerous ways including a slow shuffling gait, accelerating walking, or highly variable stride timing (Jankovic & Tolosa, 2006).

PD is treated with dopaminergic medication, deep brain stimulation, and behavioral techniques. Deficient internal rhythms can be compensated for with external Rhythmic Auditory Stimulation (RAS), as auditory rhythms are thought to entrain motor rhythms via the relatively close neural connections between auditory and motor areas (Thaut & Abiru, 2010; Thaut, et al., 1996). Extensive clinical studies have shown that fixed-tempo Rhythmic Auditory Stimulation improves many aspects of gait timing (for reviews see (Rubinstein, Giladi, & Hausdorff, 2002; Thaut & Abiru, 2010). Fixed-tempo RAS can increase gait tempo and stride length (McIntosh, Brown, Rice, & Thaut, 1997) and decrease the magnitude of stride-time variability (Arias & Cudeiro, 2008; Hausdorff, et al., 2007). Improvements in timing continue in the short-term after the auditory cues are removed, suggesting that the external rhythms can stabilize internal rhythm generating networks (Hausdorff, et al., 2007; McIntosh, et al., 1997).

Another important method for diagnosing gait impairment examines the fractal scaling of stride times, and how walking dynamics unfold over time (Hausdorff, 2009). In healthy adults the small timing fluctuations from stride-to-stride are not random (white noise); instead, a stride time is related to adjacent stride-times and to stride-times hundreds of strides later. The distribution of stride-times in a healthy walk has a 1/*f*-like structure (Hausdorff, 2009; Hausdorff, et al., 1996) similar to the fractal-like long-range correlations observed in many complex systems in nature (Gilden, Thornton, & Mallon, 1995; Newman, 2005). In 1/*f* relations, the fluctuations are self-similar across multiple time scales (scale-invariance), and log power is roughly proportional to log frequency. While many sources of 1/*f* have been proposed, a prominent idea is that 1/*f* structure emerges from the complex interactions between components in a self-organized system (Bak, Tang, & Wiesenfeld, 1997; Chen, Ding, & Kelso, 2001; Schmidt, Beek, Treffner, & Turvey, 1991; Torre & Wagenmakers, 2009).

In Parkinson's disease, the fractal scaling of stride times is considerably weaker; each stride time is relatively random and unrelated to other strides (Bartsch, et al., 2007; Hausdorff, 2009; Hausdorff, et al., 2000). Decreased fractal scaling is associated with pathology in gait and in cardiovascular activity (Goldberger, et al., 2002). The increased randomness and lack of 'memory' suggests defective activity among interacting subcomponents (e.g. basal ganglia). Elderly adults with low fractal scaling (i.e., high stride-to-stride randomness) are more likely to fall than

those with a high fractal-scaling, and this index is a better predictor of falling than other indices (Herman, Giladi, Gurevich, & Hausdorff, 2005).

Fixed-tempo RAS has proven very promising in gait rehabilitation, but has a few limitations. First, when synchronized with fixed-tempo RAS, the fractal scaling decreases away from healthy 1/*f* structure (Hausdorff, et al., 1996), as stride-time variability becomes organized around a single frequency rather than retaining fluctuations (Delignieres & Torre, 2009). Fixing on a single tempo can decrease adaptability by overtraining one tempo during rehabilitation. Additionally, fixed-tempo RAS requires that the human synchronizes to the external rhythms, but the ability to synchronize with auditory stimuli is impaired in patients with Parkinson's (O'Boyle, Freeman, & Cody, 1996) and basal ganglia lesions (Schwartze, et al., 2010). One possible method to increase gait stability and flexibility and concurrently circumvent Parkinson's patients' impaired synchronization capabilities is to offload some of the synchronization task to an *interactive* external timing system.

Here, we compare the effects of walking with fixed-tempo RAS and *interactive* rhythmic auditory stimulation generated by a computer system that can track and interact with a person's gait. The interactive "WalkMate" system developed by Miyake and colleagues generates rhythmic pacing sequences using nonlinear limit-cycle oscillators (Miyake, 2009; Miyake, Miyagawa, & Tamura, 2004; Miyake & Shimizu, 1994; Miyake & Tanaka, 1997). The system's intrinsic oscillators transmit auditory pacing signals and receive information about human step times from pressure sensors in the human's shoes (Fig. 1). The system calculates the relative phase difference, and in real time adjusts its frequency and phase to complement the human's step timing. This in turn affects the human's gait, thus creating reciprocal interaction (Miyake, 2009).

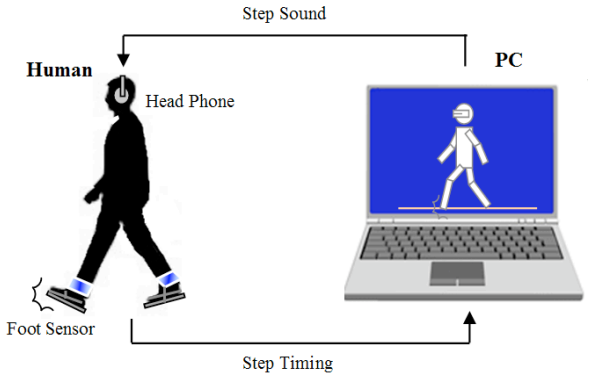

Figure 1: Depiction of interactive rhythmic auditory stimulation system.

In the experiment, Parkinson's patients and healthy participants walked around a long corridor with three rhythmic cueing conditions: interactive rhythmic cueing with frequency and relative phase adjustment ("WalkMate"); non-interactive fixed-tempo Rhythmic Auditory Stimulation set to the individual's spontaneous walking tempo ("RAS"); and a silent control condition ("Silent Control"). For the PD patients, each of these experimental conditions was followed by a lap without auditory stimulation to look for carry-over or memory effects. Data were analyzed using Detrended Fluctuation Analysis (DFA) (Goldberger, et al., 2002; Peng, Havlin, Stanley, & Goldberger, 1995); and the primary dependent measure of interest was the DFA fractal-scaling exponent as this is an indicative measure of healthy gait (Hausdorff, 2009) and a strong predictor of falling (Herman, et al., 2005).

Methods

Participants Twenty patients (12 women, 8 men) with idiopathic Parkinson's Disease participated in the experiment (mean age = 69.2 years; SD = 7.7). Patients' disease severity was Hoehn and Yahr Stage 2-3, and mean duration of disease was 3.6 years. All were tested while "on" dopaminergic medication. Eighteen healthy controls (16 men) also participated (mean age = 24.7 years; SD = 2.7). Informed consent was provided and participants were paid for participating. Experimental procedures were approved by the Kanto Central Hospital Ethics Committee.

Procedure and Equipment Participants were instructed to walk at a natural and comfortable pace around a long corridor. Rhythmic auditory stimuli (short sine tones at 523 and 700 Hz) were played over circumaural headphones. Three types of auditory stimulation were presented in separate, counter-balanced blocks: interactive rhythmic cueing with period and phase adjustment ("Walkmate"); fixed-tempo rhythmic auditory stimulation ("RAS"); and unassisted silent control condition ("Silent control"). For the PD patients, each block consisted of three separate laps: first, a pretest lap without auditory stimulation to establish baseline performance; second, a test lap with one of the three auditory stimulation conditions to establish the immediate efficacy of stimulation; and third, a post-test lap without auditory stimulation to examine potential carry-over effects. Laps within a block were separated by 5-minute breaks, and blocks were separated by 30-minute breaks. No baseline differences, nor order effects, were observed among the pretest laps. After each lap, patients reported their perceived movement stability and perceived speed on a 7 point Likert-scale. The healthy control experiment omitted the baseline and carry-over laps, and thus consisted of the three rhythmic cueing conditions counter-balanced in order. On average, each lap lasted 180 seconds and contained 320 footsteps.

Gait timing information was collected via pressure sensors attached to participants' shoes, was relayed to a laptop via radio frequency every 10 ms, and was processed in real time for the requisite auditory stimulation. In trials with auditory stimulation, the rhythmic auditory presentation started after 25 seconds of walking. The participant's walking tempo from this initial stage determined the stimulus start-tempo (based on the mean of 5

step-periods after excluding extreme values). In the fixed-tempo RAS condition, the stimulus tempo remained constant throughout the trial. In the interactive WalkMate condition, the stimulus tempo changed in response to the participant's gait timing. The computer algorithms controlling the stimulus tempo were run in Matlab on a Panasonic CF-W5 laptop.

The computer's timing system used nonlinear oscillators and was organized hierarchically in two modules. Module 1 mutually entrained the frequencies of the computer's auditory outputs and the participant's strides. Module 2 adjusted the relative phase difference between the computer and the participant to a target phase difference.

Module 1 utilized phase oscillators in its control law, as shown in equation (1). Here, θ_m represents the computer system's phase of its cycle, and ω_m designates its natural frequency. When θ_m in equation (1) attained an integer multiple of 2π, the system transmitted a tone to the participant. The input variable of this equation, θ_h, presents the phase of the participant's gait cycle, estimated from the discontinuous timing of the participant's heel strike. K_m (> 0) designates the coupling constant.

$$\dot{\theta}_m = \omega_m + K_m \sin(\theta_h - \theta_m) \quad (1)$$

Module 2 was responsible for adjusting the relative phase difference to a target value. The relative phase between the human's step time and the computer system's auditory output from Module 1 is $\Delta\theta_m = \theta_h - \theta_m$. The control law for Module 2 could then be presented as in equation (2), in which $\Delta\theta_m$, $\Delta\theta_d$, and μ denote the Module 1 phase difference, the target phase difference, and the control gain, respectively.

$$\dot{\omega}_m = -\mu \sin(\Delta\theta_d - \Delta\theta_m) \quad (2)$$

The above equations can be applied for both the right and left legs, with a phase shift of π. In this study, empirically derived values of 0.5, 0.32, and 0.2 rad were used for K_m, μ, $\Delta\theta_d$ respectively.

Data Analysis Temporal processes often show long-range correlations and fractal scaling. Long-range dependence, "long memory," power laws, and 1/f-like noise have been observed in time series from many domains (for a review see Kello, et al., 2010).

One can inspect the degree of scale-invariance by plotting the fluctuations at different temporal resolutions. We quantified the long-range correlations using detrended fluctuation analysis (DFA) (Goldberger et al. 2002; Peng et al., 1995; Hausdorff, 2009). This technique offers certain advantages over other methods (e.g., spectral or Hurst analyses) when dealing with non-stationary time series, for it "avoids spurious detection of apparent long-range correlations that are an artifact of non-stationarity" (Peng et al. 1995). We briefly describe the DFA algorithm following Peng et al. (1995) and Goldberger et al. (2002). First the human's gait-period time series is integrated, and then this integrated time series is split into equal boxes of size, n. In each box of length n, a least-squares line is fit to the data, which represents the trend in that box. The fluctuation $F(n)$ for each box is then calculated as the root-mean-square deviation between the integrated time-series and its local trend. This calculation is repeated for all time scales (box sizes). Typically, the fluctuation, $F(n)$, will increase with larger box sizes. A linear relationship on a log-log plot indicates self-similar scaling, in that fluctuations in the smaller boxes are related to the fluctuations in the larger boxes in a power-law relation. The slope of the line log $F(n)$ over log n is the scaling exponent α, and gives a measure of the "roughness" of the original gait time-series (see Fig 2). Using DFA, a scaling exponent $\alpha \approx 0.5$ corresponds to rough and unpredictable white noise; $\alpha \approx 1.0$ corresponds to 1/f-like noise and long-range correlations (Goldberger, et al., 2002). The first 30 seconds and last 10 strides of each trial were not analyzed.

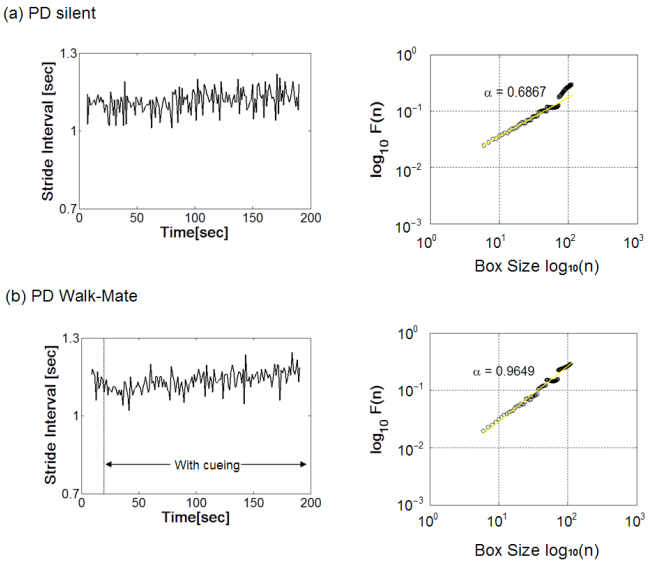

Figure 2: Examples of two trials. On the left, the stride times of one leg are plotted against trial time. On the right, the DFA technique plots the average fluctuation per box size. The mean and SD of stride-times are similar, but during the Silent condition (2a), the PD patient's strides are unpredictable akin to white noise, whereas during interactive rhythmic stimulation (2b), the stride fluctuations have a 1/f-like structure.

Results

Results indicate that during unassisted walking (Silent Control), the stride time DFA fractal-scaling exponent for Parkinson's patients (M = .90) is significantly lower than for healthy participants (M = 1.05), $t(36)$=3.38, p = .002 (Fig. 3). This reduced fractal scaling in PD away from healthy 1/f structure is indicative of impaired gait (e.g., (Bartsch, et al., 2007).

Rhythmic stimulation affected PD patients' fractal scaling, $F(2,38)$ = 4.44, p = .019. The interactive WalkMate auditory stimulation lead to significantly higher fractal scaling compared to unassisted Silent Control and fixed-

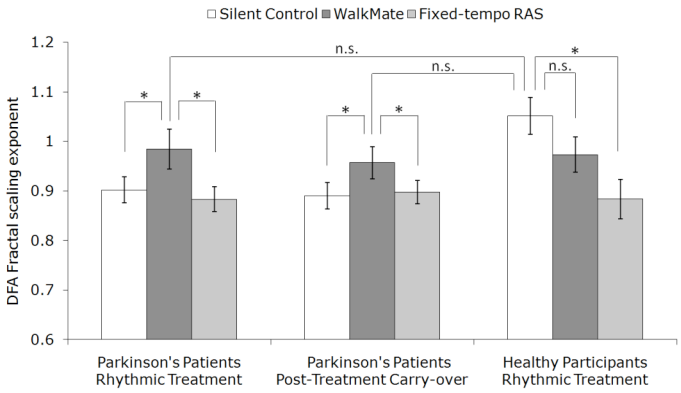

Figure 3. DFA fractal-scaling exponents (± SEM). *$p < .05$; n.s. = non-significant.

tempo RAS conditions (ps < .05); no difference was observed between Silent and fixed-tempo RAS ($p > .6$). The observed between Silent and fixed-tempo RAS ($p > .6$). The mean and standard deviation of stride times did not differ among the three conditions, nor did they correlate with fractal scaling; thus dynamic analyses can capture important signals in gait not revealed with more conventional analyses (Hausdorff, 2009). Importantly, fractal scaling for PD patients with WalkMate (M = 0.99) did not differ from healthy participants' normal walking (M = 1.05), $t(36)=1.2$, $p > .2$. This suggests that for Parkinson's patients, interacting with the WalkMate system can reinstate healthy gait dynamics.

For the *healthy* participants, rhythmic stimulation also affected fractal scaling, but differently than for PD patients, $F(2,34)=4.39$, $p = .02$. Unlike the PD patients, fractal scaling did not differ between WalkMate and silent baseline ($p > .1$), but fixed-tempo RAS drove fractal scaling lower than baseline ($p = .018$). WalkMate boosted fractal scaling only for PD patients. A reduction in fractal scaling with fixed-tempo RAS has been previously observed, as the variance becomes organized around the stimulus tempo (Delignieres & Torre, 2009; Hausdorff, et al., 1996).

Closer inspection of the step-to-tone phase differences showed that stable synchronization was uncommon for fixed-tempo RAS. Five of 18 healthy participants and only 2 of 20 PD patients had a unimodal distribution of step-to-tone phase differences (Rayleigh test of uniformity p-values <.01). Other studies show that PD patients *can* synchronize their steps to fixed-tempo RAS when instructed to synchronize (Rubinstein, et al., 2002; Thaut & Abiru, 2010); but our data indicate that if they are not explicitly instructed to synchronize, they often won't. Regardless, across groups the fractal scaling was lower when synchronized with fixed-tempo RAS (M = .79; n = 7) than when un-synchronized (M = .90, n= 31), $t(36) = 1.95$, p =.059.

With WalkMate, all PD patients and healthy participants exhibited stable synchronization between their footsteps and the auditory stimuli (Rayleigh test p-values < .01 for all trials). Even without explicit instruction, the PD patients and the WalkMate system effortlessly coupled in mutual interaction; and this manipulation of interaction increased fractal scaling. In addition to more stable step-to-tone coupling and higher fractal scaling with WalkMate compared to fixed-tempo RAS, patients also preferred WalkMate and reported that their body movements fluctuated less with WalkMate than with fixed-tempo RAS, $t(19)= 2.67$ p = .015.

Finally, potential carry-over effects from the rhythmic stimulation were examined. After each of trial, the PD patients rested for 5 minutes then walked another lap without sound. The carry-over fractal scaling differed between conditions, $F(2,38)=4.48$, p = .018. Trials without sound post-WalkMate retained higher fractal scaling (M=.96), compared to post-fixed-tempo RAS (M=.90) or post-Silent (M = .90) (ps < .05). This 'memory' effect indicates that the rhythmic stabilization induced by the interactive system carries-over into the short term.

Discussion

Without auditory stimulation, the PD patients' stride-times had lower fractal scaling (higher randomness) than healthy participants, and this low fractal scaling of stride times has been associated with impaired gait and basal ganglia dysfunction (Hausdorff, et al., 2000). In the fixed-tempo RAS condition, the fractal scaling decreased when steps and tones were synchronized, as previously observed (Hausdorff, et al., 1996), since the stride times become organized around the metronome rather than flexibly fluctuating. We did not explicitly instruct synchrony; somewhat surprisingly, the patients rarely synchronized with the fixed-tempo RAS, and hence their fractal scaling remained at the impaired level. Synchronization is not automatic. Fixed-tempo RAS effectively improves many gait impairments, but the attentional and/or volitional requirements diminish its applicability in rehabilitation. Additionally, a walking support device with a fixed tempo (or requiring manual adjustment) is impractical in a dynamic real-world environment.

Patients and healthy participants effortlessly coupled with the interactive WalkMate system. The computer system took over some of the synchronization task by correcting a portion of the relative phase difference and adjusting its frequency to complement the human's timing. The system's intrinsic oscillators were set to adapt yet persist, and hence served as a 'memory,' in that the output timing is partially based on previous beat period, which decreases temporal randomness and increases predictability. This stabilized the reciprocal interaction and allowed the system to support, rather than dictate, human gait timing. Previous work showed that healthy participants' finger-tapping was more synchronized with a slightly adaptive metronome (Repp & Keller, 2008; cf. Kelso, de Guzman, Reverley, & Tognoli, 2009); such adaptivity might importantly compensate for patients' impaired synchronization abilities.

When the internal and external rhythms integrate and interact, the patients' fractal-scaling index returned to levels

of the healthy participants. This reinstatement of 1/*f* structure is consistent with proposals that fractal scaling emerges from self-organized interactions among multiple components. In gait, many subcomponents interact in feedforward and feedback loops, including the neural-muscular periphery, the intraspinal nervous system, and central networks for motor control and timing that contain the basal ganglia (Scafetta, Marchi, & West, 2009). Disruptions of the basal ganglia, such as in Parkinson's and Huntington's diseases, lead to gait impairments; fractal scaling decreases and walking consists of more random disconnected strides (Hausdorff, et al., 2000). We argue that the WalkMate system essentially acts as an "external basal ganglia," in that it supplants some of the impaired functionality of generating rhythmic oscillations, integrating sensorimotor information, and relaying timing signals for the motor system.

The carry-over effect of higher fractal scaling after synchronizing with rhythmic stimulation (cf. McIntosh, et al., 1997), suggests that rhythmic auditory stimulation is not simply an external pace-maker driving motor systems, but that it influences the neural time-keeping circuitry (Hausdorff, et al., 2007). The basal ganglia-SMA circuit supports synchronizing internal oscillations with external events (Grahn & Rowe, 2009; Kotz, Schwartze, & Schmidt-Kassow, 2009), and these oscillations continue after removing the external stimulation. Internal rhythmicity can be reestablished in basal ganglia impairments (Kotz, et al., 2009), and a similar reestablishment of the basal ganglia oscillations likely occurs in the short-term after interactive rhythmic stimulation.

The 1/*f* structure is not merely an epiphenomenal by-product of healthy gait or reintegrated timing circuits, but it could serve to increase flexibility, predictability, and stability. The fractal scaling in healthy gait (as well as in healthy heart beat time-series) might benefit the system by avoiding "mode locking" to a single local tempo, thereby increasing flexibility and responsiveness to environmental demands (Goldberger, et al., 2002; Hausdorff, 2009). Additionally, the strong association between low fractal scaling and falling (Herman, et al., 2005) might relate to decreased predictability: Highly random stride times undermine the temporal predictability of an upcoming stride time, which in turn would hinder corrective movement, balance, and stability. In a 1/*f* time series, the upcoming stride-time is more predictable than in a random series, because a) short-range correlations have a more circumscribed set of temporal possibilities, and b) due to scale-invariance, the long-range correlations can be used to predict the short-range ones and vice-versa (similarly, fractal structure in music improves predictability of tempo changes, Rankin, Large, & Fink, 2009). This increased predictability might explain the patients' higher perceived movement stability.

The interactive rhythmic auditory system seamlessly integrates with the human; oscillation frequencies mutually entrain, fractal-scaling increases back to healthy 1/*f* levels, and patients' perceived stability improves. This human-machine interaction provides a good example of coupling internal and external systems (Miyake, et al., 2004; Miyake & Shimizu, 1994) and is a promising rehabilitation tool. Previous work showed that the interactive system can stabilize gait in hemiparetic stroke patients (Muto, Herzberger, Hermsdoerfer, Pöppel, & Miyake, 2007) and in Parkinson's patients with strongly accelerating gait (Miyake, 2009). Future work should investigate effectiveness in patients "off" or with reduced dopaminergic medication. Additionally the carry-over effect of improved rhythmicity post-WalkMate suggests potential in a long-term rehabilitation program. Interactive rhythmic auditory stimulation system offers a flexible, portable, low-cost, non-invasive therapeutic intervention that can improve the mobility and quality of life of Parkinson's Disease patients.

Acknowledgments

This research was supported by JSPS Grants to YM and a Fulbright Fellowship to MJH. We thank James Cutting, David Field and Peter Keller for insightful discussion.

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