Computer-Based Motor Training Activities Improve Function in Parkinson's Disease: a Pilot Study

Daniel M. Togasaki, M.D., Ph.D.

The Parkinson's Institute, 1170 Morse Avenue, Sunnyvale, CA 94089

Tel. (408) 734-2800

Fax (408) 734-9208

dtogasaki@att.net

This study was supported by a grant from Interactive Metronome

Abstract—*Objective:* This pilot study examined the effect of computer-based motor training activities upon the severity of signs and symptoms in patients with mild or moderate Parkinson's disease. *Methods:* Thirty-six subjects were randomly assigned to train using the Interactive Metronome (IM) device, which provides training for rhythmicity and timing, or to a control regimen consisting of motor activities directed by a rhythm or a computer (e.g., clapping or exercising to music or to a metronome tone or playing computer games). The severity of parkinsonism was compared before and after 20 hour-long training sessions as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) part 3 and, as secondary measures, the UPDRS part 2, the Hoehn and Yahr stage, a timed finger tapping test, and the timed "Up & Go" test. *Results:* Twelve subjects completed training with the IM device and nine completed the control regimen. Both groups improved in the scores on the UPDRS part 3 and the two timed tests. Those patients trained on the IM device showed slightly more improvement, but the difference between the two groups was not statistically significant. The IM-trained group improved in the UPDRS part 2 score, but the control group did not. Neither group changed in the Hoehn and Yahr stage. *Conclusions:* These results suggest that computer-based motor training regimens might be useful for improving or retaining motor function in Parkinson's disease.

Parkinson's disease is a neurodegenerative disorder that impairs motor function. There are a number of pharmacologic therapies that are effective in alleviating the symptoms, but these drugs all have side effects that can limit their use. Non-pharmacologic treatments can thus play an important and useful role in this disease. In fact, approaches of this type are frequently sought out by many patients who are looking for therapies that do not involve taking medications.

Exercise (as part of a regimen of physical therapy and otherwise) has often been recommended as a component of the overall treatment program for Parkinson's disease, and there are a number of studies suggesting that it can be beneficial (1-11). This improvement in parkinsonism does not appear to be related to a direct and immediate effect, insofar as single episodes of exercise do not appear to affect motor function (i.e., "limbering up") or influence levodopa pharmacokinetics (12-14). In those studies demonstrating improvement, the change was seen after multiple sessions. Various types of exercise regimens have been beneficial: resistance training can increase muscle strength (15, 16); both physical therapy (5-10) and music therapy (11) has been shown to provide beneficial effects; and exercise alone has been shown to improve motor function (1-3). More recently, animal studies have suggested that exercise might improve the neurochemical deficits in parkinsonism as well as the behavioral deficits (17-20), an intriguing possibility that suggests that motor training might induce plasticity changes in the brain that could partially correct the lesion in Parkinson's disease.

The Interactive Metronome (IM) device is a timing and rhythmicity training apparatus that is thought to improve the execution of motor programs (21). It employs a metronome beat to set a rhythm that the subject uses to time motor tasks. A computerized system provides auditory feedback to the subject to illustrate the accuracy of synchronization between his motor performance and the cueing beat. This device has been used by children with attention deficit

hyperactivity disorder (ADHD), with improvement in both motor and cognitive activities after finishing training (22).

To test its utility for treating Parkinson's disease, this study examined the effect of training with the IM device by comparing motor performance before and after training, as measured with Part 3 of the Unified Parkinson's Disease Rating Scale (UPDRS) and with other clinical and timed tests. Comparison was made with a control group that underwent a similar amount of computer-guided physical activity, but without the feedback provided by the IM device.

Methods. *Participants.* Participants were recruited from the patient population seen at The Parkinson's Institute and from support groups in the surrounding geographic area (south San Francisco Bay area). Close proximity to The Parkinson's Institute was necessary because of the number and frequency of the training sessions.

Patients were eligible for enrollment in the study if they had a diagnosis of idiopathic Parkinson's disease, were between 30 and 80 years old, and were Hoehn and Yahr stage 3 or less. They could not be receiving any other experimental therapy during the time of their participation in the study.

Patients were excluded from the study if they had cognitive dysfunction that impaired their ability to give informed consent, if they had a medical condition that would preclude their ability to properly participate in training (e.g., unable to hear, unable to tolerate physical activity) as judged by the enrolling neurologist, or if their clinical condition for parkinsonism was unstable such that it would likely require medication changes during the period that training would be given.

This study was conducted in accordance with Good Clinical Practice guidelines and the protocol and consent form were approved by an independent institutional review board (Western Institutional Review Board, Olympia, Washington). All patients signed written consent prior to participation.

Objectives and Outcome Variables. The primary objective of this study was to determine the effect of movement training using a computer-based device (the IM device) on the severity of the signs and symptoms of Parkinson's disease. The effect was measured by comparing the total scores before and after training for the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS part 3). Additional outcome variables that were examined included the following: the total score for the activities of daily living subsection of the UPDRS (part 2), a timed finger tapping test, the timed "Up & Go" test, and the Hoehn and Yahr stage. All clinical neurologic examinations were performed by a Movement Disorder Specialist. The examiner was blinded regarding the group assignment of the subject being evaluated, except for seven subjects enrolled as a separate open-label group.

Interventions. The IM device (Interactive Metronome, Weston, Florida) consists of a computer, a controller box, headphones, and a set of pressure-activated sensors (Fig. 1). The subject wears headphones that are connected to the controller box. A rhythmic tone sounds at a rate of 54 beats per minute. The subject performs motor tasks attempting to keep in synchrony with the tone. These tasks were performed according to a predetermined protocol and included clapping, toe tapping, thigh slapping, and other similar types of movements, which, at various times, involve each of the four limbs. In making each movement, a sensor is activated. For example, a button is affixed to the palm by a strap wrapped around the hand. With each clapping movement, the button is pressed. For leg movements, a footpad containing a built-in sensor was

used. The controller box detects each activation of the sensor and records the accuracy of the synchronization with the provided rhythmic tone. The time differences are stored on the computer. The controller box also provides an audio tone as feedback to the subject when the sensor is activated to indicate how accurately the movement coincides with the rhythmic tone. If the sensor is activated in close temporal proximity to the provided rhythmic tone, the feedback sound is a pleasant bell-like noise. As the accuracy of the movement decreases, and the time between the sensor activation and the rhythmic tone increases, the feedback sound morphs into a more unpleasant buzzing-like noise. This feedback allows the subject to become progressively more accurate in these motor tasks. Throughout each session, a trainer guides and assists the subject in a one-on-one interaction, providing suggestions and recommendations to increase accuracy.

The training protocol for the IM device used in this study was provided by the manufacturer based upon preliminary trials they did with several parkinsonian patients. In the course of that pilot project, they initially used their standard protocol for children affected with ADHD, which was then was modified (*i*) to take into account the decreased ability of these patients to tolerate the physical activity required and (*ii*) to allow additional time for the patients to achieve the level of expertise sufficient to be considered proficient in using the device. Generally, patients with Parkinson's disease fatigue more easily, so that the amount of activity possible during a single 1-hour training session had to be reduced. Accordingly, the total number of training sessions was increased from the 15 normally used in other subjects to 20 for these patients. That training protocol was supplied to The Parkinson's Institute and used to design this study.

The control group underwent a similar amount of training (20 sessions each lasting 1 hour). Their activities consisted mostly of motor activity, but without the auditory feedback. This was

accomplished by having them make movements (*i*) to music played through the computer (20 minutes), (*ii*) to the tone from the IM device without the sensors and thus without the feedback cues (15 minutes), and (*iii*) by playing computer arcade games (25 minutes). Each subject was guided through the control session by a trainer providing one-on-one assistance. The trainers for the control sessions also were trainers for the IM sessions.

Study Design. This was a single-blind, controlled, parallel-group study conducted at The Parkinson's Institute. Patients were randomly assigned to either the group receiving training with the IM device or to the control group (by coin flip). The participants in the control group were kept unaware that theirs was not the study group, as all subjects were told that this was a study of computer-based movement training. An open-label group of seven patients all received training with the IM device and were included in a separate analysis.

At baseline, each subject underwent neurologic examination to determine the UPDRS part 3 motor exam score and the Hoehn and Yahr stage. They also underwent evaluation for timed finger tapping (23) and the timed "Up & Go" test (24). Finger tapping was performed by having the subject alternately press a lever on one of two counters mounted 12 inches apart. The total number of taps completed in 60 seconds is recorded for the dominant hand and averaged over 3 trials. For the timed "Up & Go" test, the seated subject is timed for how long it takes for him to arise, walk ten feet, and return. The score from the activities of daily living section of the UPDRS (part 2) was determined from the answers recorded by the subject on a self-administered questionnaire (25). These evaluations were repeated following completion of the 20 training sessions.

Training Protocol. After enrollment into the study and initial evaluation, each patient underwent a series of training sessions. Each session lasted approximately 1 hour, but it was not

unusual for the sessions to last up to an additional 15 minutes to allow the subject extra rest time between tasks (due to fatigability). The schedule for the sessions differed among subjects because of individual circumstances, but the general guideline was training two or three times weekly without large gaps between sessions. Because the patients differed greatly in their stamina, and because of the difficulties scheduling the large number of sessions, there was a relatively wide range of times the subjects needed to complete training: the control group took from 39 to 119 days, except for a single outlier at 190 days, with an mean of 87 days; and the IM group took from 42 to 134 days with a mean of 93 days.

All subjects, both in the IM group and in the control group, were trained by persons who were Interactive Metronome certified providers.

Sample Size and Statistical Analysis. This study was designed as a pilot study, as there was no previous information for performing a power calculation to determine sample size. Our initial goal was to enroll 20 subjects in each group (40 total).

Baseline comparisons of the variables between the treatment groups were performed by *t*-tests or by chi-square analyses. The effect of each intervention was determined by *t*-tests on each of the variables. Statistical analyses were performed using StatView for Windows version 5.0.1 (SAS Institute Inc., Cary, North Carolina). For all analyses, $P < .05$ was considered statistically significant. All results are reported as mean (SEM) unless specified otherwise.

Results. *Study Population and Treatment Groups.* The subject flow is diagrammed in Fig. 2. Seventy-seven patients were screened for entry into this study. Two subjects were excluded and 39 declined to participate. The major problem causing subjects to decline participation was the logistical difficulty of having to attend 20 training sessions over approximately 2 months. The 36

subjects that entered the study were randomly assigned to one of the two groups. Nine patients in the IM group and six patients in the control group discontinued from the study. One patient in the control group withdrew after suffering a heart attack, which was deemed unrelated to his participation in this study. The remaining subjects completed their course of training. Subjects that did not complete the training were excluded from analysis. One of the control subjects that completed training was excluded from analysis of the UPDRS part 2 scores because of missing data and another was excluded from the timed "Up & Go" test analysis for the same reason. Two subjects from the IM group also had missing data, but both patients dropped out of the study and were thus excluded from any analyses. An additional seven subjects, all of whom completed their training, were assigned to the IM group in an open-label extension of the study and were included in a separate analysis.

The demographic and baseline disease characteristics for the study population are presented in Table 2. The first patient was enrolled in June 2003 and the last was enrolled in March 2004. The last evaluation was performed in July 2004.

Safety. A single subject in the IM group suffered a serious adverse event—a heart attack. This occurred at night while the subject was at home, and did not appear to be related to any activity associated with the study. He was treated with angioplasty and recovered without further incident. He was withdrawn from the study, although he expressed a strong desire to resume training. An additional subject in the IM group withdrew because of fatigue, i.e., being unable to tolerate the physical demands. Two subjects in the IM group and one subject in the control group withdrew because of needing adjustment of their antiparkinsonian medications.

Efficacy. Paired *t*-tests indicated that there was an improvement in the UPDRS part 3 scores for both of the groups (Fig. 3A). The IM group improved by 4.4 (1.9) points ($P = .0415$), and the

control group improved by 3.7 (1.2) points (P = .0166). Although the IM group scores improved slightly more, a direct comparison of the two groups indicated that there was no statistical difference between them (P = .7924).

The timed tests also improved for both groups (Fig. 3B,C). The number of finger taps increased by 24.6 (5.9) taps per minute for the IM group and by 13.2 (4.7) for the control group. The time required to perform the "Up & Go" test improved by 1.5 (0.4) seconds in the IM group and by 1.3 (0.3) in the control group. Again, although the IM group improved slightly more for both measures, there were no statistical differences between the groups (finger tapping, P = .1675; timed "Up & Go" test, P = .7100). The UPDRS part 2 scores improved in the IM group by 1.3 (0.6) points (P = .0412); the control group showed a slightly larger improvement of 2.2 (1.3) points, but this change did not achieve statistical significance (P = .1252). There were no statistical differences between the groups (P = .4528). The Hoehn and Yahr stages (Fig. 3E) did not change for the IM group (P = .7545) and the control group (P = .3466).

These analyses were repeated with the inclusion of the seven subjects that were assigned to the IM group in the open-label extension. Both sets of analyses had very similar outcomes, with only one difference: the change in the UPDRS part 2 scores for the IM group with the additional seven subjects did not show a statistically significant improvement when compared to baseline (P = .3512).

Discussion. In this controlled pilot study, computer-directed movement training, both with the IM device and with the control training activities, was found to improve the motor signs of parkinsonism, both on clinical examination (UPDRS part 3) and in objective timed tests (finger tapping and the timed "Up & Go" test). This is the first direct demonstration that these types of

exercises can improve parkinsonism, lending support for the phrase "use it or lose it" that is often quoted to patients. Non-pharmacologic interventions such as these are highly attractive to patients, and they help to foster a sense of higher personal control over the disease. The use of such interventions is generally embraced by patients with Parkinson's disease (sometimes with a little "irrational exuberance").

Seven additional subjects were enrolled in an open-label extension of the IM treatment group. A second set of analyses was carried out that included these seven subjects. The results of this second analysis were essentially the same as the first. The only difference was that the improvement in the UPDRS part 2 scores are found to lose statistical significance for the IM group, perhaps suggesting that less weight can be given to this being a true effect.

The motor subscore on the UPDRS (part 3) was prospectively chosen as the primary outcome measure in this study, as it is the standard measure of the severity of parkinsonism. It involves, however, subjective evaluation, so that the observation of improvement with this instrument was buttressed by the observation of improvement using the objective measures of the finger tapping test and the timed "Up & Go" test. That these additional tests confirm improvement provides a greater degree of comfort that the finding is valid. That there is a lack of change for both the ADL subscore of the UPDRS and the Hoehn and Yahr stage for the subjects does not detract from this result. This is especially true for the Hoehn and Yahr stages, as they are relatively broad categories, and were not expected to improve with this type of intervention. The use of a self-administered questionnaire for the UPDRS part 2 subscore, as opposed to an interviewer, is not expected to be a detracting factor, as (*i*) this instrument correlates well with live interviews, and (*ii*) it was used both before and after training, so that there should not have been any bias introduced.

These observed improvements in motor function were only in patients with mild and moderate Parkinson's disease, as more severely affected patients were excluded. The subjects had to have sufficient motor control and dexterity to perform the exercises needed in both treatment arms. Because of the nature of the tasks, patients with great difficulty with balance or with marked motor complications were self-selected out of the study. Furthermore, performance of these tasks required cognition to be relatively intact, and participation would be impossible with dementia. As such, these findings cannot be generalized to more severely affected patients, who, in any case, would not be candidates for this type of intervention. Given that the subjects in both treatment arms derived benefit, future studies would be important that examine the effects of motor training using simpler tasks that can be performed by patients with more severe parkinsonism or cognitive difficulties.

This study also was not designed to examine how long the benefits provided by training might last. The post-training evaluations generally occurred within a few days of the last training session. One previous study investigating the effect of an exercise regimen on parkinsonism found that the beneficial effects were still present 6 weeks later (1). Another study found that 6 months after finishing a course of physical therapy the beneficial effects had been lost, although this might have occurred because the patients had stopped their home exercises despite being instructed to continue with them (7). Another study found a loss of benefit from a course of physical therapy after 6 weeks, but that a second group following the same training regimen supplemented with sensory cues (visual, tactile, and auditory with a metronome) retained their gains (5). This suggests that sensory cues, and possibly feedback, might play an important role in retention of benefit. Determining whether there are long-term effects from these computer-based

training regimens would certainly be an area for further investigation in any study undertaken as a follow-up to this one.

The IM device is of great interest as a treatment because part of its effect is improvement in utilization of motor programs (21), which is an area thought to be deficient in patients with Parkinson's disease (26). Previously, this device has been shown to improve both motor and cognitive function in children with ADHD (22) and to improve performance accuracy in golf (27). As such, it seemed ideally suited as a treatment for parkinsonism. This study, however, did not find a difference between the two treatment arms. Parkinsonism did improve slightly more in the IM group, but the difference was not statistically significant. Both groups went through a substantial training regimen, although that for the IM group was more structured than for the control group. Of note, in neither group was the training aimed specifically at improving the movements tested with the UPRDS or at improving gait and balance. This suggests that participation in any physical activity regimen providing a concentrated degree of motor training might benefit parkinsonism. Alternatively (or additionally), the interaction between the subject and the trainer might play a role, although the theoretical basis for how this might improve motor function is less obvious.

The rhythmic nature of the exercises might contribute to or be a necessary part of their ability to improve motor function. There have been studies demonstrating that repetitive and rhythmic movements as rehabilitative therapies following a stroke can improve arm paresis (28), and might induce reorganization of motor networks within the central nervous system (29). The investigators used a technique called bilateral arm training with rhythmic auditory cueing (BATRAC). They suggest that important components of BATRAC include bilaterality, rhythmicity, and sensory feedback. If rhythmicity is a necessary component of this therapeutic

approach, it could explain the trend toward greater improvement with the IM regimen as a dose effect, since the subjects in this treatment arm received longer training with rhythmic activities.

Another advantage that was provided by the IM regimen over that of the control group was greater retention of subjects. A lower percentage of withdrawals occurred among the IM trainees (9/28 = 32%) than the control group (6/15 = 40%). This, surprisingly, might be related to the more regimented structure of the training. Anecdotally, the IM group experienced a higher sense of accomplishment, leading to a higher degree of motivation, as was evidenced by the subject who strongly desired to resume training even after suffering a heart attack. Interestingly, subjects in some prior studies of the effect of exercise and activity on parkinsonism reported improvement in a sense of mood and well-being, when such measures were collected (2, 3, 11), although this improvement was not universal (7).

A recent report indicated that whether negative or positive feedback is more effective for motor training in a patient with Parkinson's disease depends upon his or her treatment state (30). Patients learn better with positive feedback when their dopaminergic medications are working, but learn better with negative feedback when their medications have worn off. Because the IM device uses both positive and negative feedback, it might have an advantage as a training tool since it would be effective regardless of the medication state of the subject.

The logistics of attending frequent training sessions proved difficult, so that many potential subjects declined participation, and a portion of the enrolled subjects withdrew because of scheduling conflicts. In many cases, participation in this study required a considerable commitment of time over 2 or 3 months. Training exercises that could be performed at home would make it much easier for patients to complete the full number of sessions. Along these lines, Interactive Metronome has recently developed and released a version of their device that

can be used for self-training at home. Comparing the effect on motor function between two groups undergoing similar training regimens, one with a trainer and one self-directed, might also provide a way to separate the contribution of the physical activity and the contribution of the subject-trainer interaction.

In summary, this investigation demonstrated improvement in motor function in patients with mild and moderate parkinsonism with the use of computer-directed motor training. This training utilized music therapy, computer games, and the IM device. These types of therapeutic interventions are welcomed by patients and could provide a useful supplement to pharmacologic treatments for Parkinson's disease.

Acknowledgment

This trial was supported by Interactive Metronome (Weston, Florida). I would like to thank Sandy Gabrielli for designing the control group protocol and for training subjects. I would also like to thank Edward Jonathans, Janet Rios, William Whitney, and Sarah Forsblad for training subjects, and Rondalyn Varney Whitney and the Lighthouse Project for their assistance. Lee E. Jacokes, Richard T. Margo, and Randy Dayle provided much helpful advice. I would like to thank Caroline Tanner for her helpful comments on the manuscript. And, finally I would like to thank Stephanie Yang for her invaluable help in keeping things on track.

TABLE 1. *Study protocol and training session activities*

<table>
<tr><th>Control group</th><th>IM group</th></tr>
<tr><td colspan="2">Baseline evaluation (UPDRS 2 and 3, H&Y stage, timed tapping, timed Up & Go test)</td></tr>
<tr><td colspan="2">20 1-hour sessions</td></tr>
<tr><td>Movement to music (20 min)
Preselected songs</td><td rowspan="3">Movement to tone with feedback (60 min)
IM device with feedback</td></tr>
<tr><td>Movement to tone (15 min)
IM device without feedback</td></tr>
<tr><td>Computer arcade games (25 min)
Patient selects from a list</td></tr>
<tr><td colspan="2">Baseline evaluation (UPDRS 2 and 3, H&Y stage, timed tapping, timed Up & Go test)</td></tr>
</table>

Each subject underwent training for 20 1-hour sessions.

TABLE 2. *Subject demographics*

Characteristic	Control group n = 15	IM group		
		Randomized n = 21	Open label n = 7	All n = 28
Age	67.3 (7.4)	65.3 (8.2)	67.4 (8.4)	65.9 (8.2)
Male gender, n (%)	7 (47)	16 (76)	5 (71)	21 (75)
Caucasian race, n (%)	15 (100)	17 (81)	7 (100)	24 (86)
UPDRS Motor subscale (part 3)	12.0 (5.7)	13.6 (8.3)	18.9 (8.8)*	14.9 (8.6)
UPDRS ADL subscale (part 2)	10.2 (6.1)	10.0 (4.8)	14.1 (3.6)†	11.1 (4.8)
Hoehn and Yahr stage	1.9 (0.3)	1.8 (0.6)	2.0 (0.3)	1.8 (0.5)
Finger Taps per min	111.4 (25.0)	122.6 (27.2)	135.2 (26.2)	126.0 (27.0)
Timed “Up & Go” Test in sec	10.2 (2.3)	10.2 (3.8)	9.6 (2.5)	10.0 (3.5)

Data are mean (SD) unless otherwise indicated. UPDRS, Unified Parkinson’s Disease Rating Scale; ADL, activities of daily living. There were no statistically-significant differences between the control and IM-randomized groups. *Differs from control group, $P = .0384$. †Differs from IM-randomized group, $P = .0481$.

FIG. 1. The Interactive Metronome device.

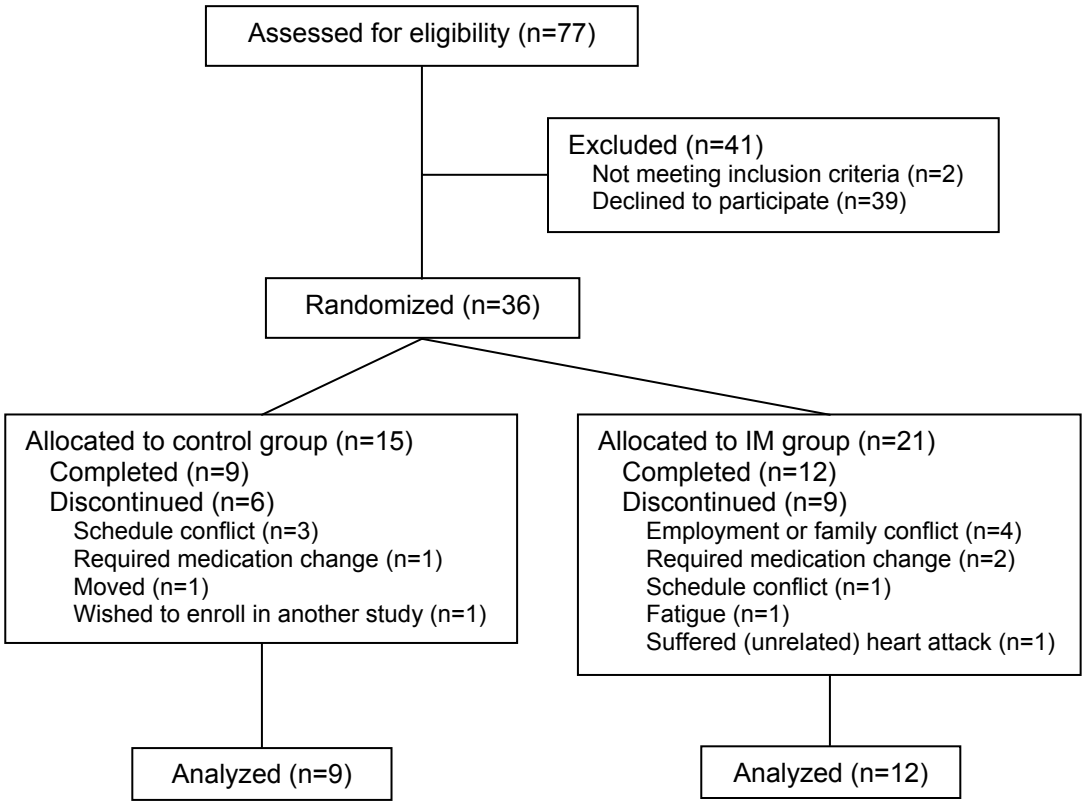

FIG. 2. Flow diagram of subject progression from screening to study completion.

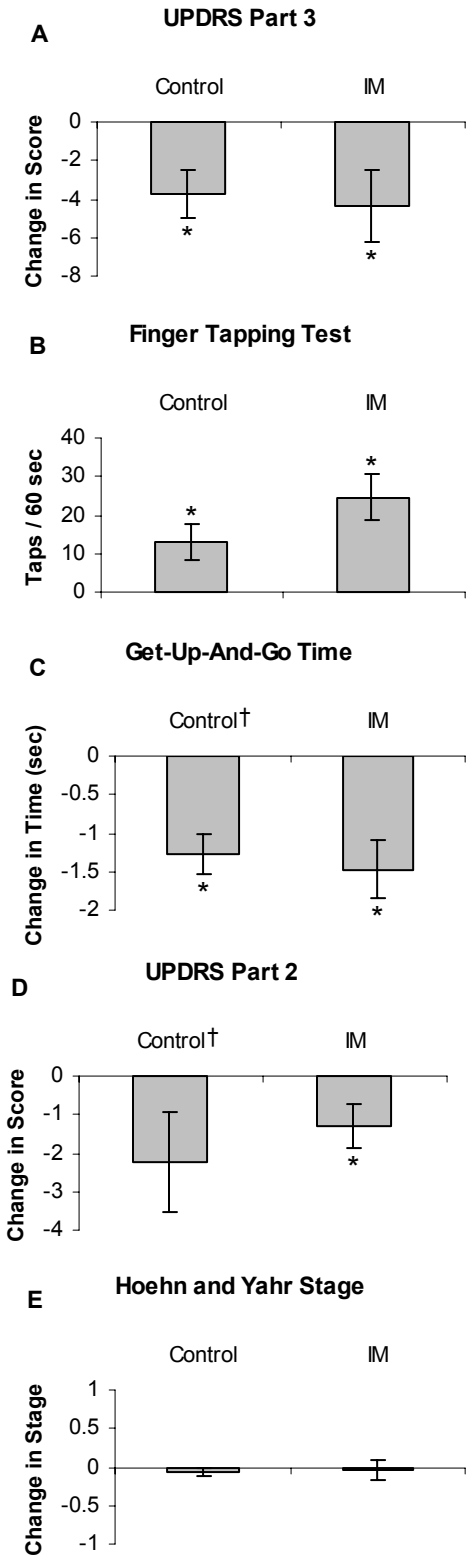

FIG. 3. Changes from baseline in measures of parkinsonism in subjects trained with the IM device (n = 12) or the non-feedback control regimen (n = 9, except †n = 8). Data expressed as mean ± SEM. *p < .05.

REFERENCES

1. Reuter I, Engelhardt M, Stecker K, Baas H. Therapeutic value of exercise training in Parkinson's disease. Med Sci Sports Exerc 1999;31(11):1544-1549.
2. Baatile J, Langbein WE, Weaver F, Maloney C, Jost MB. Effect of exercise on perceived quality of life of individuals with Parkinson's disease. J Rehabil Res Dev 2000;37(5):529-534.
3. Palmer SS, Mortimer JA, Webster DD, Bistevins R, Dickinson GL. Exercise therapy for Parkinson's disease. Arch Phys Med Rehabil 1986;67(10):741-745.
4. Kuroda K, Tatara K, Takatorige T, Shinsho F. Effect of physical exercise on mortality in patients with Parkinson's disease. Acta Neurol Scand 1992;86(1):55-59.
5. Marchese R, Diverio M, Zucchi F, Lentino C, Abbruzzese G. The role of sensory cues in the rehabilitation of parkinsonian patients: a comparison of two physical therapy protocols. Mov Disord 2000;15(5):879-883.
6. Szekely BC, Kosanovich NN, Sheppard W. Adjunctive treatment in Parkinson's disease: physical therapy and comprehensive group therapy. Rehabil Lit 1982;43(3-4):72-76.
7. Comella CL, Stebbins GT, Brown-Toms N, Goetz CG. Physical therapy and Parkinson's disease: a controlled clinical trial. Neurology 1994;44(3 Pt 1):376-378.
8. Knott M. Report of a case of parkinsonism treated with proprioceptive facilitation technics. Phys Ther Rev 1957;37(4):229.
9. Bilowit DS. Establishing physical objectives in the rehabilitation of patients with Parkinson's disease; gymnasium activities. Phys Ther Rev 1956;36(3):176-178.
10. de Goede CJ, Keus SH, Kwakkel G, Wagenaar RC. The effects of physical therapy in Parkinson's disease: a research synthesis. Arch Phys Med Rehabil 2001;82(4):509-515.
11. Pacchetti C, Mancini F, Aglieri R, Fundaro C, Martignoni E, Nappi G. Active music therapy in Parkinson's disease: an integrative method for motor and emotional rehabilitation. Psychosom Med 2000;62(3):386-393.
12. Goetz CG, Thelen JA, MacLeod CM, Carvey PM, Bartley EA, Stebbins GT. Blood levodopa levels and unified Parkinson's disease rating scale function: with and without exercise. Neurology 1993;43(5):1040-1042.
13. Mouradian MM, Juncos JL, Serrati C, Fabbrini G, Palmeri S, Chase TN. Exercise and the antiparkinsonian response to levodopa. Clin Neuropharmacol 1987;10(4):351-355.
14. Reuter I, Harder S, Engelhardt M, Baas H. The effect of exercise on pharmacokinetics and pharmacodynamics of levodopa. Mov Disord 2000;15(5):862-868.
15. Scandalis TA, Bosak A, Berliner JC, Helman LL, Wells MR. Resistance training and gait function in patients with Parkinson's disease. Am J Phys Med Rehabil 2001;80(1):38-43; quiz 44-36.
16. Hirsch MA, Toole T, Maitland CG, Rider RA. The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease. Arch Phys Med Rehabil 2003;84(8):1109-1117.
17. Tillerson JL, Cohen AD, Philhower J, Miller GW, Zigmond MJ, Schallert T. Forced limb-use effects on the behavioral and neurochemical effects of 6-hydroxydopamine. J Neurosci 2001;21(12):4427-4435.
18. Tillerson JL, Cohen AD, Caudle WM, Zigmond MJ, Schallert T, Miller GW. Forced nonuse in unilateral parkinsonian rats exacerbates injury. J Neurosci 2002;22(15):6790-6799.

19. Tillerson JL, Caudle WM, Reveron ME, Miller GW. Exercise induces behavioral recovery and attenuates neurochemical deficits in rodent models of Parkinson's disease. Neuroscience 2003;119(3):899-911.
20. Fisher BE, Petzinger GM, Nixon K, Hogg E, Bremmer S, Meshul CK, et al. Exercise-induced behavioral recovery and neuroplasticity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse basal ganglia. J Neurosci Res 2004;77(3):378-390.
21. Koomar J, Burpee JD, DeJean V, Frick S, Kawar MJ, Fischer DM. Theoretical and clinical perspectives on the Interactive Metronome: a view from occupational therapy practice. Am J Occup Ther 2001;55(2):163-166.
22. Shaffer RJ, Jacokes LE, Cassily JF, Greenspan SI, Tuchman RF, Stemmer PJ, Jr. Effect of interactive metronome training on children with ADHD. Am J Occup Ther 2001;55(2):155-162.
23. Nutt JG, Lea ES, Van Houten L, Schuff RA, Sexton GJ. Determinants of tapping speed in normal control subjects and subjects with Parkinson's disease: differing effects of brief and continued practice. Mov Disord 2000;15(5):843-849.
24. Morris S, Morris ME, Iansek R. Reliability of measurements obtained with the Timed "Up & Go" test in people with Parkinson disease. Phys Ther 2001;81(2):810-818.
25. Louis ED, Lynch T, Marder K, Fahn S. Reliability of patient completion of the historical section of the Unified Parkinson's Disease Rating Scale. Mov Disord 1996;11(2):185-192.
26. Marsden CD. The mysterious motor function of the basal ganglia: the Robert Wartenberg Lecture. Neurology 1982;32(5):514-539.
27. Libkuman TM, Otani H, Steger N. Training in timing improves accuracy in golf. J Gen Psychol 2002;129(1):77-96.
28. Whitall J, McCombe Waller S, Silver KH, Macko RF. Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. Stroke 2000;31(10):2390-2395.
29. Luft AR, McCombe-Waller S, Whitall J, Forrester LW, Macko R, Sorkin JD, et al. Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial. Jama 2004;292(15):1853-1861.
30. Frank MJ, Seeberger LC, O'Reilly R C. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science 2004;306(5703):1940-1943.