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Changes in Executive Function After Acute Bouts of Passive Cycling in Parkinson's Disease

Angela L. Ridgel, Chul-Ho Kim, Emily J. Fickes, Matthew D. Muller, and Jay L. Alberts

Individuals with Parkinson's disease (PD) often experience cognitive declines. Although pharmacologic therapies are helpful in treating motor deficits in PD, they do not appear to be effective for cognitive complications. Acute bouts of moderate aerobic exercise have been shown to improve cognitive function in healthy adults. However, individuals with PD often have difficulty with exercise. This study examined the effects of passive leg cycling on executive function in PD. Executive function was assessed with Trail-Making Test (TMT) A and B before and after passive leg cycling. Significant improvements on the TMT-B test occurred after passive leg cycling. Furthermore, the difference between times to complete the TMT-B and TMT-A significantly decreased from precycling to postcycling. Improved executive function after passive cycling may be a result of increases in cerebral blood flow. These findings suggest that passive exercise could be a concurrent therapy for cognitive decline in PD.

Keywords: exercise, rehabilitation, cognition, movement disorders

The Administration on Aging predicts that the U.S. population over 65 years of age will increase from 40 million in 2010 to 55 million in 2020 (Siegel, 2009). In anticipation of this trend, there is interest in lifestyle interventions that enhance cognitive ability and prevent age-related diseases such as Parkinson's and Alzheimer's (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Papp, Walsh, & Snyder, 2009). Parkinson's disease is a progressive neurological disorder that affects 1 in 100 individuals over the age of 60 (de Lau & Breteler, 2006). The cardinal motor symptoms of Parkinson's disease include resting tremor, slowness of movement, rigidity, gait problems, and postural instability. There are also nonmotor symptoms that accompany the disease, such as cognitive impairment, mood disorders, and sleep difficulties (Chaudhuri, Yates, & Martinez-Martin, 2005). In addition, individuals with Parkinson's disease show a six-fold increase in the probability of developing dementia compared with healthy controls (Aarsland et al., 2001; Janvin, Larsen, Aarsland, & Hugdahl, 2006).

Ridgel, Kim, Fickes, and Muller are with the Dept. of Exercise Physiology, Kent State University, Kent, OH. Alberts is with the Lerner Research Institute, Cleveland Clinic, Cleveland, OH.

Parkinson's disease develops when dopamine-producing cells in the midbrain degenerate and dopamine production decreases. Endogenous dopamine plays an important role in cognition (Braskie et al., 2008), motor activity (Garraux, Peigneux, Carson, & Hallett, 2007), motivation (Robbins, 2005), sleep (Volkow et al., 2008), mood (Badgaiyan, Fischman, & Alpert, 2009), attention (Gibbs, Naudts, Spencer, & David, 2007), and learning (Badgaiyan, Fischman, & Alpert, 2007). Current pharmacological approaches (dopamine-replacement therapy) to treating the symptoms of Parkinson's disease improve motor function, but cognitive effects of the medication are controversial. Dopamine can have positive, neutral, or negative effects on cognitive performance and attention (Cools, Barker, Sahakian, & Robbins, 2001a; Jubault, Monetta, Strafella, Lafontaine, & Monchi, 2009; Kulisevsky et al., 2000).

Individuals with Parkinson's disease often have difficulties in psychomotor speed, attention, and set shifting (ability to alter a response in the face of change) and visuospatial impairment (Molloy et al., 2006; Muslimovic, Post, Speelman, De Haan, & Schmand, 2009). The Trail-Making Test (TMT) examines set shifting, psychomotor speed, and visual attention (Gaudino, Geisler, & Squires, 1995; Reitan, 1958). It is sensitive to cognitive changes that occur with Parkinson's disease (Hietanen & Teravainen, 1986). The TMT test has two components: TMT-A and TMT-B. TMT-A requires individuals to connect 25 targets on a computer screen with numbers in sequential order, and TMT-B requires alternating between 25 lettered and numbered targets. The score on each of these tests represents the amount of time it takes to complete it (Tombaugh, 2004). TMT-A focuses on testing visual search and motor speed, whereas TMT-B tests visual search and set shifting (Crowe, 1998). Both of these tests have motor components, but TMT-B provides a better measure of cognitive flexibility because it requires participants to alternate between numbers and letters. Cognitive flexibility is a component of executive function in which an individual switches a behavioral response depending on the situational demands (Arbuthnott & Frank, 2000; Kortte, Horner, & Windham, 2002). Executive function allows for adaptation to changing situations and is necessary for goal-directed behavior (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). The difference in the total time between TMT-A and TMT-B is highly correlated with intelligence and severity of impairment (Corrigan & Hinkeldey, 1987). Specifically, the motor component of the response can be removed by subtracting the time to complete TMT-B from TMT-A (Dubois et al., 2007). In light of disease-related declines in cognitive function, concurrent therapies to limit cognitive decline, such as exercise, should be examined in this population. In a study by Lautenschlager et al. (2008), 24 weeks of physical activity resulted in modest improvement in cognitive abilities in older adults with memory impairment. Furthermore, a number of meta-analyses have described several cases of improved cognition with long-term exercise in older healthy adults, whereas others found no association (Angevaren et al., 2008; Colcombe & Kramer, 2003; van Uffelen, Chinapaw, Hopman-Rock, & van Mechelen, 2008). Tanaka et al. (2009) described significant benefits of a multimodal exercise program on executive function in Parkinson's disease. They used a 6-month intervention program of weight, balance, and coordination training. Therefore, it is difficult to determine the exact type of exercise that contributed to these improvements. Furthermore, we are not aware of any studies that have examined the acute effects of exercise on cognition in Parkinson's disease.

To examine the possible relationship between exercise intensity and cognitive improvement in Parkinson's disease, acute changes in executive function were measured after passive leg cycling on a motorized bicycle. Passive leg rotation was investigated in light of studies that have documented increased cerebral blood flow and blood pressure during passive cycling (Christensen et al., 2000; Nobrega, Williamson, Friedman, Araujo, & Mitchell, 1994).

Although passive cycling is not expected to promote improvements in executive function as much as active exercise, this type of therapy could be useful for Parkinson's patients who are unable to exercise in the recommended aerobic zones (60–80% of heart-rate reserve; American College of Sports Medicine, 2006) because of disease severity, cardiovascular disease, muscle weakness, or other disability.

Further work is needed to determine the relationship between exercise intensity and cognitive function in Parkinson's disease. The goals of this study were to examine the effects of passive leg cycling on performance on the TMT and to determine whether leg-rotation rate alters performance on the TMT in Parkinson's disease. Passive cycling may provide an alternative method of improving executive function in individuals who are unable to complete active or high-intensity exercise.

Methods

Participants

Nineteen individuals with mild to moderate idiopathic Parkinson's disease (12 men, 7 women) were recruited from community support groups (Table 1). All participants were 41–73 years old (63.2 ± 8.5). Disease duration was 5.1 ± 2.9 years, and Hoehn and Yahr (1967) stages ranged from I to III (1.9 ± 0.8). Participants maintained their preenrollment activity level and medication dosage during the study. Individuals were excluded if they had contraindications to exercise, such as cardiovascular disease or stroke. Written informed consent was obtained according to the guidelines of the Kent State University institutional review board.

Protocol

This study used a within-subject design wherein each individual served as his or her own control. Participants visited the laboratory for four sessions on the same day of the week, separated by 1 week. The first visit was a baseline fitness and measurement session while individuals were "on" anti-Parkinson's medication. Measurement of baseline fitness while on anti-Parkinson's medication minimized the chance that participants could not safely complete the test because of tremor or unstable posture. The next three visits included three passive cycling sessions on a motorized bicycle (Figure 1[A]; modified Motomed Viva 2, Reck Co., Betzenweiler, Germany) at rates of 60, 70, or 80 rpm in a counterbalanced order, while participants were off anti-Parkinson's medications for at least 10 hr. We asked participants to skip their morning dose of medication, and testing began at 9 or 10 a.m. We believe this is an appropriate washout period because the half-life of carbidopa-levodopa is 1.5 hr.

Table 1 Subject Demographics

Gender	Age (years)	H&Y	Duration of PD (years)	LEDD	BMI	VO_{2max} (estimated)
Male	65	1	5	0	23	48
Female	51	3	9	1,625	18	31
Male	62	1	7	201	27	32
Male	62	3	12	1,601	27	26
Female	57	1	5	67	24	26
Female	41	2	6	844	45	16
Male	66	2	2	0	29	18
Male	74	2	3	375	27	23
Male	67	1	5	1,143	24	29
Female	73	3	6	1,100	22	—
Female	54	2	3	175	22	24
Male	67	1	1.5	313	24	34
Male	57	1	0.5	0	25	31
Female	70	2	7	0	27	17
Male	68	3	5	250	24	24
Male	68	3	3	1,590	26	22
Male	56	2	2	675	26	35
Female	71	1	6	494	22	34
Male	71	2	9	670	29	35
M	63	1.9	5.1	1,625	26	28
SD	8.5	0.8	2.9	576	5	8

Note. H&Y = Hoehn and Yahr score; PD = Parkinson's disease; LEDD = levodopa equivalent daily dose; BMI = body-mass index (kg/m^2) = VO_{2max} = cardiovascular fitness ($ml \cdot kg^{-1} \cdot min^{-1}$).

Participants were asked to be passive, not resist, and let the motor rotate their legs. The 30-min passive cycling sets were preceded and concluded by a 5-min warm-up or cooldown at 40 rpm. Heart rate (HR) and Borg rating of perceived exertion (Borg, 1998) were continuously monitored.

Baseline Fitness Assessment

The YMCA submaximal cycle-ergometer test was used to estimate maximal oxygen uptake (VO_{2max}; Golding, 2000). Participants were on medication during this session. The test was completed on a Lode Excalibur cycle ergometer. Patients pedaled the ergometer for 6–9 min at 50 rpm (two or three 3-min stages). Each stage was 3 min in duration and progressed by 25 W after a 50-W first stage. HR was continuously measured via a Polar HR monitor (Accurex Plus, Lake Success, NY), and HR values were recorded every 30 s. Average HR during the last 30 s of each minute was plotted against workload for each stage to calculate VO_{2max}. Participants were allowed to stop the test at any time if they experienced discomfort.

Cognitive Testing

TMT-A and -B were administered using a tablet PC and a computer stylus (Figure 1[B]). The object of the TMT-A is for the individual to connect the numbered targets in order, beginning with 1 and ending with 25, in as little time as possible.

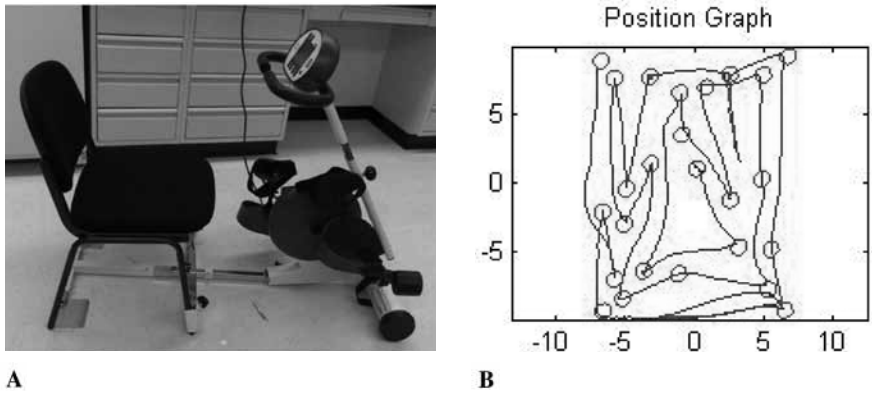

Figure 1 — (A) Participants sat in a chair, and their feet were secured to the Motomed Viva 2 using Velcro straps and stirrups. They rested their arms by their sides or on their thighs. (B) Sample trial (screen capture) from Trail-Making Test B. Each circle represents a target with either a letter or number. The line from each target represents the participant's trace with the stylus.

The TMT-B requires the participant to connect numbered and lettered targets in an alternating pattern (1-A-2-B-3-C, etc.) in as little time as possible. Participants were asked to move the computer stylus, using their dominant hand, from one target to another as quickly and accurately as possible. In the first session, participants were given a practice trial of each test before collecting the precycling trial to limit practice effects. One trial of each test was collected, immediately before and after each cycling session, in a darkened and quiet room so that participants were not distracted. The pattern of targets differed between TMT-A and TMT-B, but the same pattern was used in the precycling and postcycling trials.

Statistical Analysis

Using a crossover design, we assessed executive function before and after cycling at each of the three cycling rates. Dependent variables include dwell time (DT), the time spent within each target; intertarget time (IT), the elapsed time from exiting a target to entering the next; and total time (TT) to complete the task (TT = IT + DT). TMT B-A is the difference between the total times to complete TMT-B and TMT-A. First, correlation analysis was used to determine whether there were relationships between the dependent variables and potential confounding variables such as cardiovascular fitness, age, disease duration, body-mass index, and Hoehn and Yahr stage. For each dependent variable, a 2 (times, pre vs. post) × 3 (rates, 60, 70, 80 rpm) repeated-measures ANOVA examined potential interactions. If there was no main affect for pedaling rate, data were combined and comparisons were made by time only. To address possible learning effects, an ANOVA with session sequence (first, second, third) was performed on the delta (change from pretest to posttest) of the TT variable in the TMT-B. Significance was set at $p \leq .05$, and error values were reported as standard error of the mean.

Results

Passive Leg Cycling

There were no significant differences in HR during the warm-up (71 ± 1 beats/min), main set (73 ± 1 beats/min), or cooldown (73 ± 1 beats/min) among any of the pedaling rates. Furthermore, patients reported ratings of perceived exertion of 6–8 (on a scale 6–20) during the main set. These results show that they were mostly passive during the cycling sessions.

Trail-Making Tests

There was no correlation between changes in TMT scores from precycling to postcycling (baseline session), cardiovascular fitness ($r = –.117$, $p = .645$), age ($r = .012$, $p = .961$), disease duration ($r = –.212$, $p = .384$), body-mass index ($r = –.156$, $p = .523$), or Hoehn and Yahr stage ($r = .169$, $p = .489$). Therefore, none of these variables was used as a cofactor in the repeated-measures ANOVAs.

There was no main effect of time, $F(1, 18) = 1.71$, $p = .207$, $\eta^2 = .08$, or pedaling rate, $F(2, 17) = 0.57$, $p = .569$, $\eta^2 = .03$, and no time-by-trial interaction, $F(2, 17) = 0.59$, $p = .555$, $\eta^2 = .03$, in total time to TMT-A completion. There was no significant change in performance on the TMT-A between precycling (32.6 ± 1.4 s) and postcycling (31.4 ± 1.3 s). After the baseline testing session (Day 1), there was a significant decrease, $F(3, 16) = 3.78$, $p = .01$, $\eta^2 = .17$, in the total time to complete the TMT-B in the remaining precycling testing sessions. However, there was no significant difference, $F(2, 17) = 0.15$, $p = .86$, $\eta^2 = .08$, among the precycling values for the three experimental sessions. Furthermore, the change (delta) in precycling to postcycling TMT-B TT scores did not vary as a function of session sequence, $F(2, 17) = 0.964$, $p = .391$, $\eta^2 = .05$. A significant improvement was seen after passive cycling in TT of the TMT-B. There was a main effect for time, $F(1, 18) = 10.23$, $p = .005$, $\eta^2 = .36$, and a significant decrease in TT from precycling (70.3 ± 3.7 s) to postcycling (62.4 ± 2.6 s; Figure 2[A]). There was no main effect for pedaling rate, $F(2, 17) = 0.109$, $p = .897$, $\eta^2 = .006$, and no significant time-by-rate interaction, $F(2, 17) = 0.154$, $p = .858$, $\eta^2 = .008$. Further analysis of DT and IT indicates that improvements in TT were a result of changes in DT. DT analysis showed a main effect for time (Figure 2[B]), $F(1, 18) = 6.39$, $p = .021$, $\eta^2 = .26$, with a significant decrease from 44.1 ± 2.5 s in precycling trials to 38.2 ± 1.8 s in postcycling trials. There were no main effects for pedaling rate, $F(2, 17) = 0.377$, $p = .688$, $\eta^2 = .21$, and no significant time-by-rate interaction, $F(2, 17) = 0.581$, $p = .564$, $\eta^2 = .31$. In contrast, IT did not change after cycling at any of the pedaling rates, $t(56) = 1.56$, $p = .124$. Therefore, a decrease in DT after passive leg cycling was responsible for the change in total time for the TMT-B.

TMT B-A difference showed a main effect of time (Figure 2[C]), $F(1, 18) = 9.59$, $p = .006$, $\eta^2 = .34$, with a significant decrease from 37.6 ± 2.6 s in precycling trials to 31.0 ± 1.9 s after cycling. There was no effect by cycling rate, $F(2, 17) = 0.004$, $p = .996$, $\eta^2 = 0$, or time by rate, $F(2, 17) = 0.007$, $p = .993$, $\eta^2 = 0$, in the TMT B-A difference.

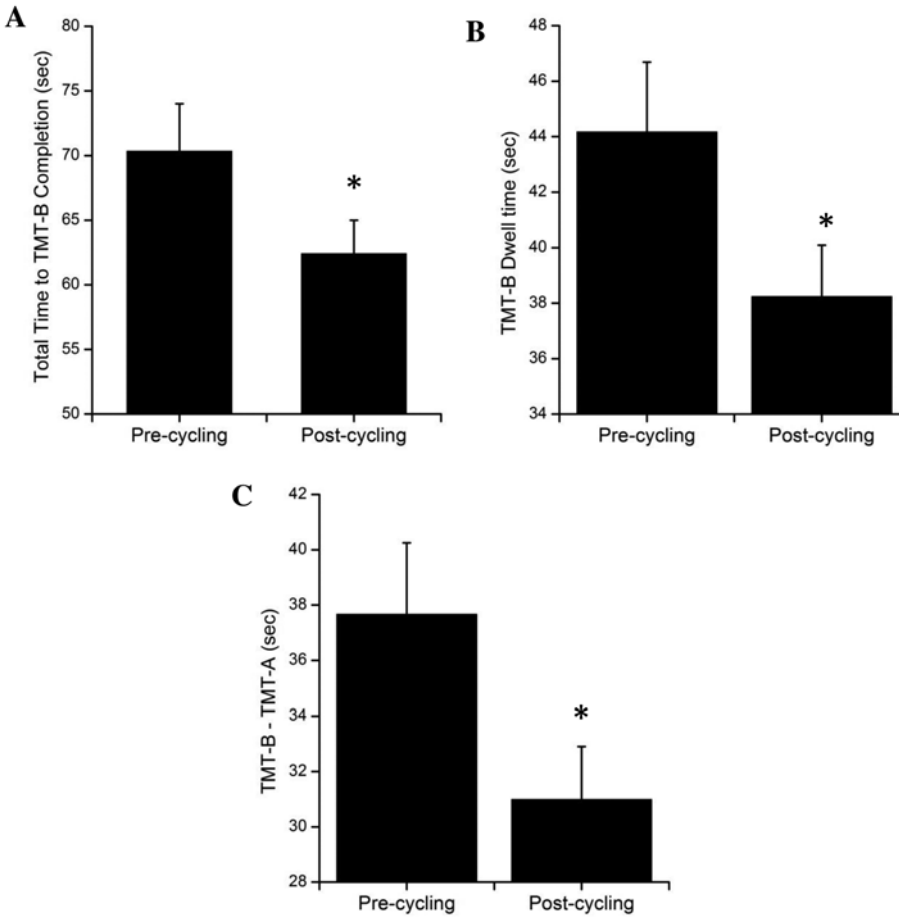

Figure 2 — (A) Trial time to complete the Trail-Making Test (TMT) B before and after passive leg cycling. (B) TMT-B dwell time before and after passive leg cycling. (C) TMT B-A difference before and after passive leg cycling. *$p < .05$. Error bars indicate standard error of the mean.

Cardiovascular Fitness

This population had low to moderate cardiovascular fitness, with a range of 16–48 ml · kg^{-1} · min^{-1} (M = 28 ± 2). There was no correlation between total time to completion of the TMT-B and baseline cardiovascular fitness ($r = –.117$, $p = .645$).

Discussion

This is the first study, to our knowledge, to show that acute passive cycling improves executive function in individuals with Parkinson's disease. If TMT scores were strictly a result of changes in motor function or movement initiation, we would

expect significant improvements in both TMT-A and -B. The lack of improvement in TMT-A suggests that visual search and motor speed did not improve after passive leg cycling. However, TMT-B did improve. Significant decreases in DT and TMT B-A difference further suggest that passive cycling can improve executive function, specifically set shifting, in individuals with Parkinson's. Slowness in motor speed often occurs in Parkinson's disease, so the improvement in TMT B-A difference score is especially interesting, because it minimizes the influence of motor speed and emphasizes set-shifting ability.

The processing of set shifting takes place in the frontal lobes (Owen et al., 1993), prefrontal cortex (Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000), and basal ganglia (Monchi, Petrides, Strafella, Worsley, & Doyon, 2006). Deficits in set-shifting tasks in Parkinson's disease are believed to be caused by disruptions in corticostriatal circuits or deficiencies in frontal dopamine as measured by fMRI (Cools, Barker, Sahakian, & Robbins, 2001b; Gotham, Brown, & Marsden, 1988; Monchi et al., 2004). Animal studies have documented increases in dopamine after exercise (Meeusen et al., 1997) and neuroprotection of dopaminergic neurons in Parkinson's animal models (Ahmad, Park, Stenho-Bittel, & Lau, 2009; Fisher et al., 2004; Tillerson, Caudle, Reveron, & Miller, 2003). No studies have directly shown that exercise is neuroprotective against Parkinson's disease in humans. Although exercise increases serum dopamine levels in healthy adults (Winter et al., 2007), serum dopamine levels are not pertinent to brain dopaminergic transmission in Parkinson's disease. It is not known whether passive cycling or other types of exercise increase brain dopamine levels in Parkinson's disease.

There are a number of physiological responses to passive exercise. Although some studies have documented increased cardiac output and stroke volume without a significant increase in HR (Muraki & Tsunawake, 2008; Nobrega et al., 1994), others have recorded increases in HR and cardiac output and decreases in vagal tone after passive cycling (Nurhayati & Boutcher, 1998). Although the mechanisms for cognitive improvement after passive cycling have not been measured, it is likely that these combined physiological responses to passive cycling could alter blood circulation and promote improvements in cognitive function in individuals with Parkinson's disease.

Acute bouts of intense exercise can improve cognitive functioning in healthy adults (Tomporowski, 2003). However, intense exercise would likely be difficult for Parkinson's patients with bradykinesia and fatigue (Elbers et al., 2009). An alternative to intense exercise could be assisted exercise with a motorized bicycle. Future work should build on these results by examining the effects of active assisted cycling at different intensities on cognitive function.

There were several limitations to this study. First, we did not control for participants' education level or intelligence. A number of studies have shown that education level affects the time to complete TMT-B (Hashimoto et al., 2006; Tombaugh, 2004). However, Hashimoto et al. suggested that the educational effects on the TMT-B disappeared when the results were adjusted to TMT-A (e.g., TMT-B – TMT-A). Furthermore, each subject served as his or her own control, so confounding variables are minimized. Second, it is possible that improvements are a result of learning effects. To limit these learning effects, the order of the cycling rates was randomized and counterbalanced between participants, and no association between the order of the sessions and the change in the TMT-B total time

was detected. In addition, there were no significant changes across the precycling experimental trials. This suggests that any possible learning effect was minimized after the first session. Learning effects could have been further minimized by serial testing without intervention between tests. In future studies, we will add a session without an intervention to further examine this trend.Although our results with the TMT are significant, it would be helpful to have additional measures of executive function, such as working memory, set activation, and maintenance (Dubois et al., 2007). A comprehensive assessment would yield further insight into the effects of active or passive leg cycling on cognition in Parkinson's disease. Second, this study focused on individuals without dementia, and it is possible that passive leg cycling may promote greater improvement in individuals with significant cognitive impairment. Future studies should examine the effects of this protocol in Parkinson's patients with significant deficits in executive function. Third, it would be interesting to investigate the time course of the cognitive improvements after single bouts of acute passive cycling. Finally, the ability of repeated bouts of passive cycling to stabilize cognitive improvements needs to be examined. This information would have clinical relevance for these individuals and would help determine how passive cycling could improve cognition over the long term.

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