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HIGH-FREQUENCY EXERCISE BENEFITS EXECUTIVE FUNCTION IN INDIVIDUALS WITH PARKINSON'S DISEASE

M. C. CĂCIULĂ[1] **M. HORVAT**[2]

Abstract: *The purpose of the present study was to identify the effects of different frequencies of chronic exercise training on aspects of executive function, specifically cognitive flexibility and working memory in individuals with Parkinson's disease (PD). Forty-three participants (M_{age} = 68.5 (SD = 11.3), 26 males), with idiopathic PD completed a category switching task and an* N*-back task at baseline and after 12 weeks of multimodal exercise training. The participants were divided into two training frequency groups: high-frequency: 4–5 times each week (N = 23) and low–frequency: 3 times or less each week (N = 20). Both frequency groups improved in executive function, showing improved global switch-cost accuracy (*F *(1, 41) =5.08,* $p<.05$, $\eta_p^2 = 0.11$) *and* N*-back accuracy (*F *(1, 41) =17.37,* $p<.001$, $\eta_p^2 = 0.29$). *The high-frequency group displayed significantly greater reductions in global switch costs (*F *(1, 41)=5.53,* $p<.05$., $\eta_p^2 = 0.09$), *and working memory response time (*$F(1,41)=14.96$, $p<.001$, $\eta_p^2 = 0.26$), *than the low-frequency group. A high frequency, multimodal exercise program involving aerobic, strength, and flexibility exercises may preserve executive functioning in PD.*

Key words: *Parkinson's disease, exercise frequency, executive function.*

1. Introduction

Parkinson's disease (PD) is identified as a movement disorder and is characterized by a progressive neurodegeneration of the basal ganglia which affects the motor control of planned and unplanned movements [1]. Cognitive impairments are increasingly recognized as associated features of PD. In this context, indices of executive function, especially working memory (WM), are among the risk factors for the progression of dementia in PD [11], [23], [26]. Other indicators of the impaired executive function may include poor performance in tasks involving planning, problem solving, set-elaboration, set shifting, and set maintenance [18].

The hallmark of WM is the ability to both maintain information in a transient

[1] School of Health and Kinesiology, Georgia Southern University, PO Box 8076, Statesboro, GA, USA. Email address: mbarna@georgiasouthern.edu
[2] Department of Kinesiology, University of Georgia, Ramsey Center 330 River Rd., Athens, Georgia 30602, USA. Email: mhorvat@uga.edu

short-term store of limited capacity and simultaneously manipulate and transform information. Alteration of WM could be partly responsible for the executive function impairments encountered in individuals with PD [3]. As the disease progresses WM tends to deteriorate in PD, interfering with mobility and functional ability decreasing their psychomotor speed [9].

Although the latest findings support the benefits of exercise for cognitive function in individuals with PD, lacking is information concerning the optimal frequency of exercise training need to promote cognitive benefits.

2. Objectives

This study examined the effects of frequency of multimodal exercise on selective aspects of executive function, including WM and cognitive flexibility, in individuals with idiopathic PD without dementia. We hypothesized changes of executive functioning in individuals with PD following exercise intervention, with high–frequency group 4-5 times/ week) displaying greater improvements than then a lower–frequency group (≤3x times/ week).

3. Material and Methods

3.1. Participants

Initially, 90 individuals with PD were screened; based on inclusion and exclusion criteria 43 individuals were recruited (n = 43; 26 males and 17 females) from the Atlanta Metropolitan area through the PD Support Group meetings. Individuals were included based on the following criteria: 1) a Montreal Cognitive Assessment (MoCA) scores ≥ 22 (a score lower than 21 indicates increased odds of dementia) [14]; 2) age between 50 yr. and 80 yr. and 3) medical clearance and absence of other health related problems that could interfere with safe participation in an exercise training program. Participants were excluded from the study if they were experiencing any neurological severe motoric impairment that impacted their mobility, had a cardiovascular disease or metabolic disorder, or had undergone deep brain stimulation surgery. A summary of the clinical and demographic features of the participants is presented in Table 1.

Table 1

Demographic and clinical features of 43 patients with Parkinson's disease (PD)

Variable	HF exercise	LF exercise	p
Number of patients	23	20	
Male/ Female	16/7	10/10	
	mean (SD)	mean (SD)	
Age (years)	68.6 (5.8)	67.65 (4.5)	0.55
Age of PD onset (years)	57.5 (12.9)	58 (13.5)	0.62
PD duration (years)	10.6 (5.2)	9.8 (4.9)	0.83
Hoehn and Yahr	2.3 (0.5)	2.5 (0.4)	0.27
Education (years)	18.3 (2.9)	17.9 (2.7)	0.81
Exercise habits (times/ week)	5.1 (1.1)	2.2 (0.6)	< 0.001*
MoCA score	25.5 (2.7)	25.4 (2.5)	0.88
UPDRS motor score	26.4 (4.3)	26.5 (5.0)	0.95

Legend: HF, high – frequency; LD, low – frequency; SD, standard deviation; MoCA, Montreal Cognitive Assessment; *significant difference (p< 0.05); UPDRS, Unified Parkinson's Disease Rating Scale.

3.2. Procedures

All participants were informed on the components of the study and signed the University of Georgia Institutional Review Board consent forms prior to beginning testing and exercising. Participants completed two testing sessions conducted one week apart prior to beginning the exercise intervention, and at the conclusion of 12 weeks of exercise training. The effects of levodopa and dopamine agonists on PD participants were diminished by assessing and exercising the participants at 2 hours after medicine ingestion, which is the approximate peak of the medication effect [17]. Medications prescribed for control of PD was not adjusted or withdrawn for any participants during the study. During the first session, participants completed a demographic and medical history questionnaire, took a screening test (MoCA), and were trained to perform two executive function (EF) tests: an auditory switch task and an auditory *N*-back task. Session two took place after approximately 5 days (± 2 days) and included retraining on the EF tasks followed by the baseline administration of the two EF tests, counterbalanced across participants, at 10 minutes after retraining. The learning effects on the cognitive tests were diminished by training participants to a performance criterion (< 5% errors for a block of trials). All training and testing trials were administered individually in a quiet room, and the assessors were blinded to the exercise groups. Participants sat in front of a laptop computer, wore headphones and pressed a regular size optical mouse. Participants were instructed to respond as quickly and accurately as possible.

Following session two, participants were assigned into one of two exercise–frequency groups, based on their self-selected exercise habits: a high–frequency group (exercise 4-5 times/ week, for 30–45 min. /bout), and a low–frequency exercise group (exercise dose ≤ 3 times/ week, 30–45 min. /bout). Following treatments, all participants completed a replication of session 2, performed with alternate versions of the switch task and the *N*- back, but maintaining the same structure of the baseline testing session.

Auditory Switch Test.

The auditory switch test is designed to measure cognitive flexibility [13], and shifting attention, an aspect of EF known to deteriorate in PD. In the switch test, computer-generated letters or numbers were presented binaurally via headphones via a commercial software program, Cedrus-SuperLab. The letters consisted of four vowels (A, E, I, and O) and four randomly selected consonants (B, D, L, and C). The numbers consisted four even numbers (2, 4, 6. and 8) and four odd numbers (1, 3, 5, and 7). The participant was required to respond to each stimulus by pressing a specified key on the mouse (even number-left key; odd number-right key; vowel letter-left key; consonant letter-right key). Each key press was followed 100 ms later by the presentation of the next stimulus. Two types of stimulus blocks of trials were used: in homogenous blocks, participants were instructed to respond to letters only or numbers only; in mixed, or heterogeneous blocks, participants were instructed to respond alternatively to letters and numbers. In mixed blocks, letters or numbers were presented in series lengths of two, three, or four stimuli. Global switch cost was calculated based on Response times (RT) for each trial and response. Accuracy was scored as the percentage of correct responses. This protocol has been utilized previously and is demonstrated to be reliable [6], [16].

N-back task.

The *N*-back task is a continuous performance task of working memory, and has been previously used in individuals with PD [3], [7]. Participants performed an *N*-back task based on the protocol developed by Perlstein and his colleagues [19]. In the 0-back condition, the target was any letter that matched a pre-specified letter (i.e., "c"), which was a condition that required sustained attention but no working memory demand. In the 1-back condition, the target was any letter identical to the letter immediately preceding it (i.e., the letter presented one trial back). In the 2-back condition, the target was any letter that was identical to the one presented two trials back. In the 3-back condition, the target was any letter that was identical to the one presented three trials back. Stimuli were random consonants presented binaurally to headphones via a commercial software program (Cedrus-SuperLab) [5] for a 500-ms duration with a 2500-ms inter-stimulus interval. Participants completed 12 blocks of trials (three blocks of each of the four conditions) with each block consisting of 25 trials. The first three trials of each block were never targets and of the remaining trials 30% were targets. The participant controlled the duration of a short break (5–20 s) provided between blocks. Response time and accuracy measures (% correct) were obtained for each trial.

3.3. Exercise Protocol

All participants engaged in group exercise classes organized under the auspice of American Parkinson's Disease Association (APDA). The activities were consistent at all five centers; they included aerobic activities such as walking, running, stationary bike, water aerobics; resistance exercises with bands and dumbbells, and movement activities such as Zumba and Tai Chi. Training was conducted by instructors who were certified by APDA. The exercise intervention was goal oriented and focused on aspects of functional ability specific to people with PD. The weekly exercise frequency, the types of exercises, the duration and perceived intensity were documented through individual daily exercise logs reported by each participant in the study. The intensity and type of the exercise intervention was match for all the participants in the study, and the frequency was varied by group: high-frequency group exercised 4-5 times/ week, and low frequency ≤3 times/ week. A paired sample t-test revealed that the high-frequency group (M=2.3, SD=0.92) and the low-frequency exercise group (M=2.15, SD=0.74) were not significantly different in exercise participation prior to the intervention, $t\ (19) = -0.64$, $p=0.527$.

3.4. Statistical Analyses

Separate switch-cost scores were calculated for tests composed for the numbers and letter as well as the mixed condition. Global switch cost scores were calculated using the procedure recommended by Wasylyshyn et al. [25]. For both the global switch cost scores and percentage accuracy scores an initial 2 (exercise frequency group: high-frequency, low-frequency) x 2 (time: pre-exercise, post-exercise) mixed measures factorial ANOVA, with time as the repeated factor was conducted to assess the effects of exercise frequency and training.

Means and standard errors of RTs for correct responses were computed for each *N*-back condition. RT greater or less than three standard deviations, calculated per participant, per condition were excluded from further analyses. Excluded trials accounted for only 2.4% of the total number of trials. N-back accuracy was calculated with the following algorithm: [1 - (number of commissions + number of omissions)/total possible correct)] × 100. Mixed measures factorial ANOVA were used to examine group, time, and load differences on these measures.

Analyses were conducted using SPSS 22 software [22]. The $p = 0.05$ rejection level was used in all analyses. Were appropriate, significant effects were decomposed through post-hoc t-tests.

4. Results and Discussions

Auditory Switch Task

Global switch costs. Means and standard errors for the auditory switch task are presented (Table 2). A mixed factorial ANOVA of the switch cost scores yielded a significant interaction between time and exercise frequency, F (1, 41) = 5.53, $p < .05$, $\eta_p^2 = 0.09$, indicating a greater improvement in the measure of cognitive flexibility for the high – frequency exercise group after the intervention. Post-hoc *t*-tests indicated that the two exercise frequency groups were not significantly different prior to the exercise intervention, $t = -0.04$, $p = 0.96$, but their performance was significantly different after the 12 weeks of training, $t = -2.11$, $p < .05$ with the high frequency group demonstrating greater improvements in global switch cost.

A mixed model factorial ANOVA revealed a significant main effect of time on the response accuracy, F (1, 41) = 5.08, $p < .05$, $\eta_p^2 = 0.11$, indicating that regardless of the frequency, exercise improves shifting accuracy in individuals with PD. The group by time interaction was non-significant F (1, 41) = 1.64, $p = .20$, $\eta_p^2 = 0.39$.

Table 2

Mean global switch cost scores (ms) (SE), and response accuracy (percent correct) by group and time for the Auditory Switch Task

Condition	High - frequency	Low - frequency
Pre-Exercise		
Switch-cost	139.48 (10.8)	140.15 (11.6)
Accuracy (% correct)	93.86	94.01
Post-Exercise		
Switch-cost	110.81 (10.6)	143.72 (11.3)
Accuracy (% correct)	94.93	94.33

N-back task

Response time (RT). Analysis of RTs revealed a significant interaction between time and group, F (1, 41) = 14.96, $p < .001$, $\eta_p^2 = 0.26$, indicating a greater improvement in working memory response time for the high – frequency exercise group after the intervention. Post-hoc *t*-tests revealed that regardless of the WM load there was no significant difference between the two groups prior to exercise, and after the exercise intervention. Also, analysis revealed a significant main effect of load, F (3, 123) = 468.94, $p < .001$, $\eta_p^2 = 0.92$. Post-hoc *t*-tests indicated that RTs for each load differed significantly from RTs for all other loads, both prior to exercise and at the end of the intervention.

Response Accuracy (% correct).

Analysis of response accuracy revealed a significant main effect of time, F (1, 41) = 17.37, $p < .001$, $\eta_p^2 = 0.29$, suggesting that both frequency groups improved accuracy in working memory after the exercise intervention. Also, analyses revealed a main effect of load, *F* (3, 123) = 613.96, $p < .001$, $\eta_p^2 = 0.93$. Post-hoc *t*-tests indicated that accuracy for each load differed significantly from accuracy for all other loads, both prior to exercise and at the end of the intervention.

The intent of our study was to determine the effects of exercise frequencies on select components of executive function in individuals with PD, after 12 weeks of multimodal exercise training. A paired sample t-test revealed that the high-frequency group (M=2.3, SD=0.92) and the low-frequency exercise group (M=2.15, SD=0.74) were not significantly different in exercise participation prior to the intervention, t (19) = -0.64, p=0.527. It was apparent that exercise benefitted executive function in all individuals with PD. More importantly the higher frequency exercise group attained greater benefits on cognitive flexibility and working memory than those individuals in the lower frequency exercise group.

Analyses of the global switch costs data revealed that higher frequency of exercise are more beneficial for cognitive flexibility for individuals with PD than lower frequency of exercise. The switch cost index reflects the changes in the attention-demanding mental processes required of participants to abandon one response set and to reconfigure a different response set [12], [21] Also, exercise, regardless of its frequency, had a positive impact on response accuracy. The lack of a differential effect of exercise frequency on accuracy could be limited by the ceiling effect, with most participants' response accuracy were between 90% and 100%. However, a speed–accuracy tradeoff between the switch cost scores and response accuracy that often occurs when individuals attempt to maintain or reduce RT but at the cost of increasing errors was not observed, which provides support for exercise interventions on the shifting aspects of executive function in individuals with PD.

Exercise also benefitted participants' working memory processes. For example, the *N*-back test, participants who exercised more frequently evidence more rapid response times than those who exercised less frequently. The lack of a speed-accuracy tradeoff for the *N*-back task provides verification of benefits of multimodal exercise on selective aspects of executive functions. The results obtained are similar to those of Tanaka et al. [20], Ahlskog [2], and Cruise et al. [8] and their conclusions that physical exercise benefits executive function in older individuals with PD, and that vigorous exercise and physical fitness may have a neuroprotective effect in PD. The improvements in cognitive function as a result of exercise may be due to enhanced neuroplasticity, exercise-related protection from dopaminergic neurotoxins, or increased neurotrophic factor expression Benjamin and his colleagues' findings [4] suggest that people with generally lower cognitive performances tend to benefit more from exercise interventions, and this might be the case of our participants since their MoCA screening scores were on the lower end of non-demented status. Similarly, our findings are in line with the work by Kramer et al [10], who propose that exercise has a selective influence on cognitive function during the aging process.

Previous clinical studies have shown that various types of exercise and more specifically, exercise that incorporate goal-based training and aerobic activity have the potential to improve both cognitive and automatic components of motor control in individuals with mild to moderate disease through experience-dependent neuro-plasticity [2], [24], [20]. In our study, all participants were exposed to group exercise classes specifically designed for people with PD, thus the exercise training was goal-based and helped the participants to learn through instructions, feedback (reinforcement), and encouragement to perform beyond self-perceived capability. Through practice and learning of new movements and skills, individuals with PD are thought to become more cognitively engaged, providing another potential explanation for the changes observed in selective aspects of executive function following multimodal exercise [15].

Although we have demonstrated the beneficial aspects of cognitive function in PD, this study was limited to a highly educated sample of participants, which may not represent the typical PD patient. In addition, all participants were tested during "on stages" of dopaminergic medication, which may alter task performance [7]. While the lack of a control group may be viewed as a limitation, the focus of the present study was to isolate the effects of exercise dose, measured in terms of frequency on cognitive outcomes. Besides, previous studies demonstrated beneficial effects in PD for the exercise group when compared to the non-exercise control group [15]. The results obtained in the present study argue for the need for randomized trials that can evaluate the role of such potential moderators as the social environment experienced by participants.

5. Conclusions

Noteworthy aspects of the present study suggest that multimodal exercises performed consistently, at least four times/ week at moderate to high intensities can benefit selective aspects of executive function, such as WM and set shifting, in individuals with PD without dementia. Because of the availability of services in a large metropolitan area, individuals were able to access programs designed specifically for PD. Although these services may not be available in less populated areas, the value of exercise in treatment of PD should become a primary factor in the treatment of PD. Additional intervention opportunities such as home – based programs that were used by Nocera and colleagues [15] should be encouraged to supplement our findings, and to help further identify the optimal delivery content of exercise for PD.

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