Functional Electrical Stimulation Cycling Exercise in People with Multiple Sclerosis

Secondary Effects on Cognition, Symptoms, and Quality of Life

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Background: Functional electrical stimulation (FES) cycling is an advanced rehabilitation modality that involves systematic mild electrical stimulation of focal muscle groups to produce leg cycling movement against an adjustable work rate. The present study reports on the efficacy of an assessor-blinded, pilot randomized controlled trial of supervised FES cycling exercise in people with multiple sclerosis (MS) on secondary trial outcomes, including cognition, fatigue, pain, and health-related quality of life.

Methods: Eleven adult participants with MS were randomized to receive FES cycling exercise (n = 6) or passive leg cycling (n = 5) for 24 weeks. Cognitive processing speed was assessed using the Symbol Digit Modalities Test. Symptoms of fatigue and pain were assessed using the Fatigue Severity Scale, the Modified Fatigue Impact Scale, and the short-form McGill Pain Questionnaire. Physical and psychological health-related quality of life were assessed using the 29-item Multiple Sclerosis Impact Scale.

Results: Eight participants (four, FES; four, passive leg cycling) completed the intervention and outcome assessments. The FES cycling exercise resulted in moderate-to-large improvements in cognitive processing speed (d = 0.53), fatigue severity (d = –0.92), fatigue impact (d = –0.45 to –0.68), and pain symptoms (d = –0.67). The effect of the intervention on cognitive performance resulted in a clinically meaningful change, based on established criteria.

Conclusions: We provide preliminary evidence for the benefits of FES cycling exercise on cognition and symptoms of fatigue and pain. Appropriately powered randomized controlled trials of FES cycling exercise are necessary to determine its efficacy for people with MS. *Int J MS Care*. 2019;21:258-264.

Exercise training has increasingly been recommended as a rehabilitation approach for the management of functional, symptomatic, and participatory outcomes in people with multiple sclerosis (MS).[1] This evidence, however, is derived primarily from samples with mild-to-moderate disability (ie, Expanded Disability Status Scale [EDSS] scores < 6.0). Conversely, the benefits of exercise training in people with MS with greater disability levels are far less clear.[2] Recent research suggests that there are limited, but promising, data regarding the benefits of exercise training in people with MS with EDSS scores of 6.0 or greater (ie, intermittent or unilateral constant assistance required to walk ~100 m with or without rest), and the need for additional trials of exercise training with this population has been highlighted.[2]

Rehabilitation approaches, including exercise training, might be particularly important for people with MS with higher disability levels. Current disease-modifying therapies are limited in their ability to prevent the progression of disability long-term and are often discontinued in later disease stages.[3] Particularly low levels of

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physical activity and fitness have been reported in people with MS with higher disability compared with those with mild-to-moderate MS,[4,5] and exercise training has been efficacious for improving physical fitness in people with MS overall.[6,7] Higher EDSS scores have been associated with greater cognitive impairment and symptoms, such as fatigue, as well as lower health-related quality of life (HRQOL).[8-10] Consequently, exercise training should be considered as an approach for managing disability burden and its secondary consequences in people with MS with higher disability levels.

The ability to effectively prescribe and provide exercise training for people with MS who have greater disability levels requires advanced rehabilitation strategies. We previously conducted an assessor-blinded, pilot randomized controlled trial (RCT) for examining the feasibility and preliminary efficacy of 24 weeks of supervised functional electrical stimulation (FES) cycling exercise in people with MS with mobility impairment.[11] The FES cycling exercise was compared with passive leg cycling as a placebo-control condition, and the primary efficacy outcomes of that trial were mobility and physiological fitness. We determined that FES cycling exercise was feasible (ie, good adherence rates, few adverse events, high participant satisfaction) and resulted in small improvements in mobility (Cohen's d = 0.40) and cardiorespiratory fitness (peak oxygen consumption [VO_{2peak}], d = 0.34) compared with passive leg cycling.[11] Herein we report on the efficacy of this intervention on secondary cognitive, symptomatic, and HRQOL outcomes. Such evidence is important to further characterize the potential benefits of FES cycling exercise with the goal of informing future trials.

Methods

Participants

The recruitment, screening, and enrollment strategy for this trial has been previously published.[11,12] In brief, participants were recruited through advertisements distributed through local media outlets, through local chapters of the National Multiple Sclerosis Society, and to individuals who were involved in previous studies with our research group and had expressed interest in future research opportunities. The inclusion criteria were 1) age 18 to 64 years; 2) physician-confirmed diagnosis of MS; 3) EDSS score of 5.5 to 6.5 based on Neurostatus-certified examination; 4) relapse free in the past 30 days; 5) engaging in <2 days per week of exercise; 6) no known cardiovascular, pulmonary, or metabolic disease or major signs or symptoms suggestive of these conditions based on the Physical Activity Readiness Questionnaire[13]; and 7) physician approval for exercise testing and training. Participants were excluded if they had any known contraindications to FES cycling (eg, epilepsy, unstable fractures, pregnancy).

Outcome Measures

Disability

Neurologic status was assessed through a clinically administered EDSS[14] examination performed by a Neurostatus-certified assessor. The EDSS scores were used to characterize the disability level of the sample.

Cognition

The oral response version of the Symbol Digit Modalities Test (SDMT)[14] was used to assess cognitive processing speed. The SDMT involves pairing nine abstract symbols with single-digit numbers based on a key presented at the top of a page. Below the key are rows that contain only symbols. The participant was asked to voice the correct numbers corresponding with the unpaired symbols as quickly as possible while the researcher recorded the responses. The number of correct responses provided in 90 seconds was recorded as the outcome measure.

Fatigue

Fatigue severity and impact were assessed using the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS), respectively.[15,16] The FSS is a nine-item scale that assesses the severity of MS-related fatigue. Each item is scored from 1 (strongly disagree) to 7 (strongly agree), and the overall score is computed as a mean of the nine items. Scores on the FSS range from 1 to 7, and higher scores indicate greater fatigue severity. The MFIS is a 21-item scale that assesses physical, cognitive, psychosocial, and total fatigue. Each item assesses the impact of fatigue on daily activities and is scored from 0 (never) to 4 (always). Physical subscale scores range from 0 to 36; cognitive subscale scores, from 0 to 40; and psychosocial subscale scores, from 0 to 8. The MFIS total score is computed by summing the responses on all 21 items and ranges from 0 to 84. Higher scores indicate greater impact of fatigue on daily activities.

Pain

Self-reported pain was assessed using the 15-item short-form McGill Pain Questionnaire.[17] Each item is scored from 0 (none) to 3 (severe), and the overall score is calculated by summing the responses from each item. Scores on this questionnaire range from 0 to 45, and higher scores indicate greater pain severity.

Health-Related Quality of Life

Physical and psychological HRQOL were assessed using the 29-item Multiple Sclerosis Impact Scale (MSIS-29).[18] The MSIS physical subscale contains 20 items and the MSIS psychological subscale contains nine items. Each item is scored from 1 (not at all) to 5 (extremely), and each subscale total is computed as the sum of the item scores. Scores on the physical and psychological subscales are converted to range from 0 to 100, with higher scores indicating a greater physical and psychological impact of MS on daily activities.

Intervention

The FES cycling exercise and passive leg cycling conditions were delivered using RT300 cycles (Restorative Therapies Inc, Baltimore, MD), as previously reported.[11,12] The RT300 cycle consists of an electrically powered motor and multichannel FES controlled by a microprocessor and custom software. Both conditions were delivered at the same cadence (50 rpm), frequency (three times per week), and duration over 24 weeks. The FES cycling condition was delivered using self-adhering surface electrodes (Pals Platinum, Fallbrook, CA) placed over the quadriceps, hamstrings, and gluteal muscle groups. The FES parameters were developed in consultation with Restorative Therapies Inc, and involved a biphasic symmetrical waveform, a phase duration of 250 µs, and a pulse rate of 50 pulses per second. Participants in the FES cycling condition actively pedaled with the goal of maintaining a target cadence and prescribed heart rate based on recommendations for aerobic exercise from the American College of Sports Medicine and MS-specific physical activity guidelines.[19,20] We previously reported that the intensity of this training protocol is consistent with guidelines for moderate-to-vigorous aerobic exercise.[21] Participants in the passive leg cycling condition did not receive any electrical stimulation, and leg movement was driven entirely by the cycle ergometer motor. The passive leg cycling condition was identical to the FES cycling exercise condition in that it included the same exposure with the training facility, the equipment (ie, RT300 cycles), and the research staff (ie, social contact and attention) but did not include stimulation and active pedaling. We note that the mean power output during training for passive leg cycling over 24 weeks was 0.8 W, suggesting that minimal active cycling was achieved by the passive group. Training data for both groups across the 24-week intervention are presented in the primary article.[11]

Procedures

The University of Illinois at Urbana-Champaign Institutional Review Board approved all the procedures, and all the participants provided written informed consent. Screening for inclusion was first conducted over the telephone using a checklist and screening questionnaires.[22,23] Confirmation of MS diagnosis and approval for exercise was then obtained by the prospective participants' physicians. After enrollment, participants underwent a neurologic examination and completed a battery of cognitive, symptomatic, and HRQOL outcomes, in addition to primary efficacy outcomes of mobility and physiological fitness. A member of the research team (R.W.M.) who was uninvolved with the collection of outcomes or the delivery of the intervention randomly allocated participants to receive FES cycling exercise or passive leg cycling for 24 weeks. The supervised training sessions took place at a university research laboratory and were delivered by personnel (T.E.) trained in FES cycling and exercise prescription for people with MS. Treatment-blinded assessors administered the same testing battery as baseline at 24 weeks. Participants received $50 remuneration per testing session.

Data Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp, Armonk, NY). Demographic and clinical characteristics of participants were summarized using descriptive statistics. Baseline characteristics and outcomes were compared between groups using independent-samples t tests and χ^2 tests. Mean absolute and percentage changes on cognitive, symptomatic, and HRQOL outcomes per group were calculated for comparative purposes with previous work and for making inferences on the meaningfulness of change based on established minimal clinically important difference values, when available. The efficacy of the intervention (ie, the difference between groups over time) on cognitive, symptomatic, and HRQOL outcomes was determined using effect sizes calculated as Cohen's d,[24] based on the purpose of the pilot trial to inform future work. The effect sizes were calculated as the mean change from before to after the intervention of the FES group minus the mean change in the passive leg cycling group per outcome, divided by the pooled baseline SD for each respective outcome.[25-27] The effect sizes were interpreted as small, moderate, and large based on criteria of 0.2, 0.5, and 0.8, respectively.[24]

Results

Participants

Eleven participants were enrolled in the trial, as previously reported.[11] Six participants were randomized to the FES cycling exercise group and five to the passive leg cycling group. Eight participants (four FES and four passive leg cycling) completed the intervention and outcome assessments at follow-up. Participant dropout in both groups (two FES and one passive leg cycling) was attributed to the time commitment involved with the study. Baseline characteristics of participants who completed the study are presented in Table 1. There were no significant differences (all $P > .05$) between groups at baseline on demographic and clinical variables. There were significant differences between groups at baseline on the physical ($P = .01$) and psychosocial ($P = .04$) fatigue subscales such that participants in the FES cycling group reported higher physical and psychosocial fatigue impact compared with those in the passive leg cycling group. There were no group differences on any other cognitive, symptomatic, or HRQOL outcomes.

Table 1. Demographic and clinical characteristics of study participants

Characteristic	Passive leg cycling group (n = 4)	FES group (n = 4)
Age, y	48.5 (7.7)	57.3 (6.0)
Sex, F/M	4/0	3/1
EDSS score	6.25 [0.5]	6.25 [0.875]
EDSS score distribution, 5.5/6.0/6.5	0/2/2	1/1/2
Time since diagnosis, y	20.8 (8.5)	22.3 (5.3)
MS type, relapsing/progressive	2/2	2/2
Employed/unemployed	0/4	1/3
Level of education		
High school or some college/university	2	1
College/university graduate	1	1
Postgraduate	1	2

Note: Values are given as mean (SD), number, or median [interquartile range].
Abbreviations: EDSS, Expanded Disability Status Scale; FES, functional electrical stimulation; MS, multiple sclerosis.

Outcomes

Cognition

There was a moderate positive effect ($d = 0.53$) of FES cycling exercise compared with passive leg cycling on cognitive processing speed after the intervention (Table 2). Importantly, participants in the FES cycling group demonstrated a 6-point increase on SDMT scores, surpassing the 3- to 4-point change that has been reported as the minimal clinically important difference.[28,29] A mean increase of 1.3 points on the SDMT was noted in the passive leg cycling group, which might reflect practice effects.

Fatigue

Moderate-to-large negative effects of FES cycling exercise were observed on fatigue severity ($d = –0.92$) and overall fatigue impact ($d = –0.60$) compared with passive leg cycling, indicating an overall decrease in fatigue symptoms in response to FES cycling exercise (Table 2). With respect to the fatigue impact subscales, the largest effect of FES cycling exercise was observed in the physical domain ($d = –0.68$); participants in the FES cycling group reported a decrease in physical fatigue, whereas participants in the passive leg cycling group reported an increase in physical fatigue after the intervention. Despite moderate-to-large improvements in fatigue symptoms, these effects did not meet the reported criteria for a minimal detectable change (MDC) on the FSS (MDC = 1.9 points) and the MFIS total (MDC = 20.2 points).[30]

Pain

There was a moderate negative effect of FES cycling exercise on pain symptoms ($d = –0.67$) after the intervention (Table 2). Participants in the FES cycling group reported a decrease in pain symptoms, whereas participants in the passive leg cycling group reported an increase; however, baseline pain levels were higher in the FES cycling group.

Health-Related Quality of Life

Both groups reported a decrease (ie, improvement) on the physical HRQOL subscale, although the overall effect favored the passive leg cycling group and was small in magnitude ($d = 0.33$) (Table 2). There was a small positive effect for passive leg cycling on the psychological HRQOL subscale after the trial ($d = 0.21$) (Table 2). Changes in HRQOL scores did not approach the criteria for MDC on the physical (MDC = 26.4 points) or psychological (MDC = 36.7 points) subscales.[31]

Table 2. Cognitive, symptomatic, and quality-of-life outcomes at baseline and after 24 weeks of passive leg cycling and FES cycling exercise in people with multiple sclerosis

	Passive leg cycling (n = 4)			FES (n = 4)			
Outcome	Baseline	24 wk	Δ (%)	Baseline	24 wk	Δ (%)	Cohen's *d*
Cognition							
SDMT score	42.8 (10.5)	44.0 (11.9)	1.3 (2.9)	41.5 (8.8)	47.5 (7.0)	6.0 (14.5)	0.53
Symptoms							
FSS score	5.3 (0.9)	5.5 (1.1)	0.3 (4.8)	6.1 (0.7)	5.6 (0.8)	–0.6 (–9.1)	–0.92
MFIS							
Total score	37.5 (16.4)	37.0 (9.6)	–0.5 (–1.3)	58.3 (14.0)	47.0 (5.7)	–11.3 (–19.3)	–0.60
Physical score	16.8 (5.4)	18.3 (3.8)	1.5 (9.0)	29.8 (5.1)[a]	25.5 (5.7)	–4.3 (–14.3)	–0.68
Cognitive score	16.5 (10.1)	15.3 (6.1)	–1.3 (–7.6)	21.8 (8.2)	16.5 (1.3)	–5.3 (–24.1)	–0.45
Psychosocial score	4.3 (1.7)	3.5 (1.0)	–0.8 (–17.7)	6.8 (1.0)[a]	5.0 (1.4)	–1.8 (–25.9)	–0.54
SF-MPQ score	4.0 (2.2)	6.5 (4.1)	2.5 (62.5)	14.8 (13.0)	10.3 (7.7)	–4.5 (–30.5)	–0.67
Quality of life							
MSIS-29 physical score	45.3 (25.1)	34.1 (13.5)	–11.3 (–24.8)	63.1 (21.0)	59.7 (19.2)	–3.4 (–5.5)	0.33
MSIS-29 psychological score	25.7 (18.8)	22.2 (13.8)	–3.5 (–13.5)	37.5 (28.6)	38.9 (36.0)	1.4 (3.7)	0.21

Note: Values are given as mean (SD), unless otherwise noted.
Abbreviations: FES, functional electrical stimulation; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MSIS-29, 29-item Multiple Sclerosis Impact Scale; SDMT, Symbol Digit Modalities Test; SF-MPQ, short-form McGill Pain Questionnaire.
[a]Denotes significant difference between groups at baseline ($P < .05$).

Discussion

To our knowledge, this study reports the first RCT results concerning the efficacy of FES cycling exercise on cognitive, symptomatic, and HRQOL outcomes in people with MS. Compared with passive leg cycling, FES cycling exercise resulted in moderate-to-large improvements in cognitive performance, as well as symptoms of fatigue and pain. Most notably, the effect of the intervention on cognitive performance resulted in a clinically meaningful change, based on established criteria. This pilot trial provides preliminary evidence for the modification of cognitive and symptomatic outcomes in response to supervised FES cycling exercise in people with MS with mobility disability. These findings warrant further exploration in the context of an appropriately powered RCT.

Few studies have examined FES cycling interventions in people with MS, and none have involved an RCT design. One trial of FES cycling (n = 5; EDSS score = 6.0-6.5) delivered in the home setting reported an 8.7% increase in cognitive performance, based on scores on the Paced Auditory Serial Addition Test, after 24 weeks (no statistical analyses).[32] Evidence for the effects of exercise training on cognitive performance in people with MS overall is inconclusive, primarily due to the low-quality evidence at this time.[33] These findings may be particularly relevant for people with MS with higher disability levels, as cognitive impairment has been reported to increase with increasing disability status,[10] and there is limited evidence for the modification of cognitive performance with exercise training in this population.[33]

Another trial involving 4 weeks of FES cycling (two to three sessions per week) in 16 participants with MS who were nonambulatory reported similar improvements in overall fatigue, as well as in the MFIS subscales (d = 0.31-0.74).[34] The largest change in that trial was reported on the psychosocial fatigue subscale (d = 0.74), whereas we reported the largest change on the physical fatigue subscale (d = –0.68), although we are cautious in this interpretation given the elevated baseline physical fatigue levels in the FES cycling group. The discrepancy between studies in effects on fatigue subscales might be related to differences in the training duration. It is possible that improvements in physiological fitness (ie, VO_{2peak}) observed in response to the 24-week intervention translated into greater efficacy in everyday tasks and movements and, consequently, lower reported symptoms of physical fatigue. Systematic reviews and meta-analyses of exercise training in people with MS with mild-to-moderate disability support a consistent, moderate effect on symptoms of fatigue.[25,35,36] The 4-week trial of FES cycling in nonambulatory participants similarly reported a moderate decrease (d = –0.55) in symptoms of pain based on the Medical Outcomes Study Pain Effects Scale; however, there was no change in quality of life (MS Quality of Life Inventory) observed after the trial.[34] There is limited evidence for the role of exercise training on symptoms of pain and mixed evidence for effects on HRQOL in MS samples overall.[1,37]

Considering the limited number of studies that have examined the efficacy of FES cycling on cognitive, symptomatic, and participatory outcomes in people with MS, the discrepancies between studies likely reflect differences in the training protocols, participant characteristics, delivery settings (ie, supervised/institution-based vs home-based), and measurement tools used to capture the various outcomes. Importantly, the present study builds on and extends existing work in this area through the use of an RCT design with a strong control condition that accounts for possible expectations and social interactions associated with supervised exercise interventions, and was matched for stimulus frequency and duration. The intervention further involved FES with active cycling with the goal of maximizing potential adaptations to the training stimulus. Importantly, a higher disability status in MS has been associated with increased prevalence and severity of impairments and symptoms,[8-10,38] highlighting the need for effective strategies to manage these outcomes, as well as disability and disease progression. Studies of exercise training in people with MS with higher disability levels (EDSS score ≥ 6.0) are limited, but current evidence supports a potential role for adapted exercise training, such as FES cycling, on symptomatic and participatory outcomes.[2] Additional research is needed to determine the efficacy of FES cycling exercise for people with MS with higher disability levels.

The results of this study are limited primarily by the small sample size and the EDSS score range of the participants included in this trial, which may limit the generalizability of the findings. The outcomes reported herein were not the primary outcomes of the trial, and therefore, participants were not selected for inclusion based on criteria related to these measures; however, scores on some of the outcomes reflect an elevated symptomology based on criterion values (eg, FSS score ≥ 4.0 indicates severe fatigue).[39] We note that participatory outcomes in this trial were limited to HRQOL measures. Future studies should examine other participatory measures, such as employment, recreation and leisure, and activities of daily living. The intervention was delivered in a supervised laboratory environment, and it is unclear whether similar results would be obtained in other clinical, community, or home-based settings. It will be important to examine the feasibility and efficacy of FES cycling for people with MS in other environments to determine the potential of FES cycling exercise as an advanced rehabilitation approach. We further highlight the importance of examining the timeline of adaptations and the potential for lasting effects of FES cycling exercise, particularly in this population.

In conclusion, FES cycling exercise might have beneficial effects on cognition and symptoms of fatigue and pain. Larger RCTs are needed to confirm these preliminary findings and establish the potential of this rehabilitation approach for people with MS with higher disability levels. Considering the limited evidence for exercise interventions overall, and FES cycling specifically, in people with MS with higher disability levels, the results of this pilot study are novel and promising. □

PRACTICE POINTS

- Advanced rehabilitation strategies are needed for managing disability accumulation in people with MS.
- We examined effects of 24 weeks of functional electrical stimulation cycling exercise in adults with MS with mobility disability.
- Functional electrical stimulation cycling might have beneficial effects on cognition and symptoms of fatigue and pain in people with MS with mobility disability.

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