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ORIGINAL ARTICLE

# Improved Physical Fitness Correlates With Improved Cognition in Multiple Sclerosis

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**Abstract**

**Objective:** To determine whether there is an association between improvements in objective measures of physical fitness and performance on cognitive tests in people with multiple sclerosis (MS).

**Design:** Post hoc correlational analysis in which people demonstrating physical improvement were compared with those not demonstrating physical improvement.

**Setting:** Individuals with MS residing in the community.

**Participants:** Adults with clinically confirmed MS (N=88) who participated in a controlled trial of a telephone-based health promotion intervention, chose to work on exercise, and completed the pre- and postintervention assessments.

**Interventions:** Participants were measured for strength (isokinetic dynamometer), aerobic fitness (bicycle ergometer), and cognition (Paced Auditory Serial Addition Test [PASAT], Trail Making Test [TMT]) at baseline and 12 weeks later. Change in fitness was calculated by subtracting each participant's baseline score from the outcome score, and then transforming the difference to a $z$ score. Individuals with a $z$ score $\geq 1$ on any fitness measure were placed in the physically improved group (n=25). All others were in the physically not improved group (n=57).

**Main Outcome Measures:** TMT, PASAT.

**Results:** After controlling for covariates (age, sex, ethnicity, education, disease activity, MS type), there was a significant group-by-time interaction, suggesting that cognitive functioning changed over time based on level of fitness. Participants in the physically improved group demonstrated improved performance on measures of executive functioning after 12 weeks of exercise.

**Conclusions:** The results of this study lend support to the hypothesis that change in fitness is associated with improved executive functioning in people with MS.

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Cognitive impairment is one of the most common and disabling features of multiple sclerosis (MS). Prevalence studies[1-3] have reported rates of cognitive impairment ranging from 22% to 60%, depending in large part on whether the data were acquired from community or hospitalized samples and also on the assessment tool used. The cognitive deficits seen in MS appear most often in 3 domains: (1) information processing speed and working memory, (2) new learning and episodic memory, and (3) executive functioning. MS-related cognitive dysfunction has a major impact on quality of life,[4,5] activities of daily living,[6,7] vocational functioning,[8,9] and rehabilitation outcomes.[10]

Medical and rehabilitation approaches to improving cognition are disappointing. Studies of donepezil,[11] psychostimulants,[12] aminopyridines,[13,14] ginkgo biloba,[15] and memantine[16] have not been consistently effective for improving cognition. Research on cognitive rehabilitation in MS suggests that learned strategies can improve cognitive performance; however, this area of investigation is in its infancy and largely focused on memory.[17-19]

Based on the older adult literature, exercise training represents a promising approach to improve cognitive functioning in MS.[20]

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Systematic reviews and meta-analyses demonstrate that both aerobic and strength training significantly improve cognitive functioning in older adults and people with mild cognitive impairment.[21-25] The most profound benefits of exercise training occurred in the domain of executive functioning,[22,26,27] and the improvements seemingly depend on changes in physical fitness (defined as health-related elements such as aerobic and muscular endurance, muscle strength, body composition, and flexibility[28]).

Much less is known about exercise training and cognition in MS. Correlational studies have reported a link between physical fitness and cognition in people with MS. For example, both higher cardiorespiratory endurance and greater muscle strength have been associated with better performance on tests of speed of information processing and working memory.[29,30] Furthermore, cardiorespiratory endurance is positively associated with functional magnetic resonance imaging indices of both white and gray matter integrity.[31] Nevertheless, 2 existing trials[32,33] have failed to demonstrate benefits of exercise training on cognition in MS. Those trials might have been ineffective because there was poor compliance and no documentation of change in fitness levels. This underscores the importance of future research that examines the possibility that improvements in physical fitness can contribute to improved cognition in people with MS.

We analyzed data from a previously published randomized controlled trial[34] examining the effects of telephone counseling on health promotion in people with MS. In that trial, a subgroup of 88 people chose to work on exercise and the subjects were randomly assigned to an intervention group or waitlist control condition. Unfortunately, there were no between-group differences on objective measures of leg muscle strength, aerobic endurance, or cognition. However, the availability of pre- and postintervention data on these measures provided an opportunity to examine the relationship between objective improvement in muscle strength or aerobic endurance and improvement in cognitive functioning within the study group as a whole. To do this we created a “physically improved” group (improvement in muscle strength, aerobic endurance, or both) and a “physically not improved” group. We compared changes in speed of information processing, psychomotor speed, and executive functioning between these 2 groups. Our primary hypothesis was that after controlling for demographic and disease-related variables, the physically improved group would demonstrate significantly greater improvement on measures of speed of information processing, psychomotor speed, and executive functioning compared with the physically not improved group.

# Methods

## Participants

Subjects were 88 community-dwelling individuals with clinically confirmed MS who wanted help with exercise as part of the previously published health promotion trial.[34] Participants were recruited from the University of Washington MS Center, MS newsletters, newspaper advertisements and articles, support groups in the Puget Sound region, and from flyers mailed to local neurology offices. Participants were also recruited from a large survey study[34] of persons with MS.

The inclusion criteria for participation were (1) age ≥18 years; (2) diagnosis of MS confirmed by a neurologist or physiatrist specializing in MS; (3) ability to walk 300ft (90m) without assistance, equating to an Expanded Disability Status Scale score of ≤5.5[35]; and (4) interest in receiving help to exercise more. All MS types (relapsing-remitting, secondary progressive, primary progressive, progressive-relapsing) were included. Participants were excluded if they (1) had a medical condition that contraindicated exercise, or (2) screened positive for depression on the Primary Care Evaluation of Mental Disorders.[36] The Primary Care Evaluation of Mental Disorders is a 26-item screener of “yes” or “no” questions for a variety of symptoms. The 2 depression questions ask about depressed mood and anhedonia. Six participants were excluded from the final analysis because of missing data. Two individuals were missing all fitness measures, and 4 were missing cognitive data. This resulted in 82 participants who were included in the final analysis.

*List of abbreviations:*

| | |
|---|---|
| **MS** | **multiple sclerosis** |
| **PASAT** | **Paced Auditory Serial Addition Test** |
| **rpm** | **revolutions per minute** |
| **TMT-A** | **Trail Making Test—Part A** |
| **TMT-B** | **Trail Making Test—Part B** |
| **TMT-BA** | **Trail Making Test—Part B minus Part A** |

## Procedures

The University of Washington Institutional Review Board approved the study protocol. Before data collection, all participants provided written informed consent. Participants meeting inclusion criteria during a telephone interview were invited to the study center for a baseline assessment. Trained research assistants, supervised by study investigators, conducted baseline assessments in dedicated laboratory space at the medical center. Afterward, participants chose a health promotion activity (exercise in the present analysis) for which they wanted help. Trained research assistants conducted in-person outcome assessments 12 weeks postrandomization. Baseline and outcome assessments were conducted in the same laboratory space with the temperature controlled between 19°C and 22°C.

## Measures

Self-reported demographic and medical variables such as age, ethnicity, marital status, educational level, date of diagnosis, and MS subtype[37] were collected during a telephone screen.

### Measure of disease activity

The Timed 25-Foot Walk[38] is a clinical tool used to measure the stability of MS disease. Research suggests this is a useful tool for detecting stability of disease and the presence of an exacerbation.[38] The 25-Foot Walk was measured at baseline and follow-up. The change score was used as a covariate for controlling for disease activity.

### Measures of strength and fitness

Right and left leg flexion and extension muscle strength were measured on a Cybex 6000 isokinetic dynamometer.[a] The Cybex was calibrated weekly using the manufacturer’s procedures. Each subject was given 5 submaximal trial repetitions before testing. To obtain peak torque output for knee flexion and extension, 10 maximal repetitions were performed by each leg at a rate of 60 per minute. Leg strength was defined as peak torque averaged over 10 repetitions for the right and left legs and for both extension and flexion.