Aerobic Fitness Is Associated with Inhibitory Control in Persons with Multiple Sclerosis

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Abstract

Cognitive impairment is highly prevalent, disabling, and poorly managed in persons with multiple sclerosis (MS). Aerobic fitness might be a target of exercise training interventions for improving cognition in this population. It is unknown if the well-established pattern of associations between higher aerobic fitness and better inhibitory control in the general population exists among persons with MS. The current cross-sectional study examined the effects of aerobic fitness (VO2peak) on inhibitory control, using a modified flanker task, in 28 persons with MS and 28 healthy controls matched by age, sex, and body mass index. This involved performing bivariate correlations and hierarchical linear regression analyses on measures of aerobic fitness and inhibitory control. Persons with MS demonstrated lower VO2peak (d = -0.45), slower (d = 0.62–0.84), and less accurate (d = -0.60 to 0.71) performance on the flanker task than controls. VO2peak was similarly associated with reaction time measures of inhibitory control in the MS and control samples (r = -0.40 to 0.54). VO2peak (p < .01), but not group (p ≥ .08) (MS vs. control), predicted reaction time on the flanker task, irrespective of age, sex, and education. This supports the development of aerobic exercise interventions for improving reaction time on tasks of inhibitory control in persons with MS, much like what has been successfully undertaken in the general population.

Keywords: Multiple sclerosis; Cognition; Fitness; Inhibition; Executive control; Exercise

Introduction

There is a wealth of evidence documenting associations between aerobic fitness and cognition across the lifespan (i.e., children, young adults, and older adults; Colcombe & Kramer, 2003; Etier, Nowell, Landers, & Sibley, 2006; Hillman, Erickson, & Kramer, 2008; Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011). The associations have been disproportionately larger for tasks involving greater amounts of executive function (i.e., planning, coordination, inhibitory control, mental flexibility, and working memory; Shallice, 1994) (Colcombe & Kramer, 2003). For example, studies have reported that higher aerobically fit pre-adolescent children demonstrate shorter reaction times and greater accuracy on a modified flanker task (i.e., a task of inhibitory control) relative to lower fit children (Hillman, Buck, Themanson, Pontifex, & Castelli, 2009; Pontifex et al., 2011). Higher aerobically fit younger adults (i.e., 18–25 years) demonstrated shorter reaction times, but not better accuracy, on a modified flanker task, regardless of congruency, than lower fit younger adults (Alderman & Olson, 2014). One seminal study reported that older adults (i.e., mean age of 66 years) with higher aerobic fitness demonstrated smaller costs of interfering stimuli on reaction time on a modified flanker task than older adults with worse aerobic fitness (Colcombe et al., 2004). Such research has set the stage for examinations of aerobic exercise training on executive control across the lifespan (Colcombe & Kramer, 2003; Hillman et al., 2014; Voss et al., 2011).

By comparison, there is markedly less research on aerobic fitness and executive control in persons with neurological disorders such as multiple sclerosis (MS). MS, in particular, is a non-traumatic, immune-mediated disease of the central nervous system that results in cognitive impairment. Cognitive impairment occurs in upwards of 50% of patients based on neuropsychological testing.
(Benedict & Zivadinov, 2011), primarily in domains of cognitive processing speed, learning and memory, and executive functioning (Benedict & Zivadinov, 2011; Prakash, Snook, Lewis, Motl, & Kramer, 2008). Cognitive impairment is highly disabling in MS (e.g., Benedict et al., 2005), and further is poorly managed by pharmacotherapy (i.e., disease-modifying therapies and symptomatic treatments) and cognitive rehabilitation (e.g., Amato et al., 2013). This underscores the importance of examining other factors associated with cognitive impairment in MS that might be targets for interventions, such as aerobic fitness and exercise training (Motl, Sandroff, & Benedict, 2011).

There have been four published studies of aerobic fitness and cognition in those with MS. Of note, those studies reported consistent, moderate-size correlations between aerobic fitness and cognitive processing speed, but not learning and memory, in persons with mild MS disability (Prakash, Snook, Motl, & Kramer, 2010; Sandroff & Motl, 2012; Sandroff, Pilutti, Benedict, & Motl, 2015). Recently, a longitudinal study in persons with MS reported that increases in aerobic or muscular fitness were associated with increases in Trail Making Test scores (i.e., a neuropsychological test of executive functioning) over a 12-week period (Beier, Bombardier, Haroonian, Motl, & Kraft, 2014). This suggests that improvements in physical fitness might too be associated with improvements in executive functioning in persons with MS, consistent with findings from the general population. However, the authors recognized that they did not include a gold-standard measurement of aerobic fitness (i.e., VO_{2\text{peak}} based on expired gas analysis), and grouped participants based on non-specific improvements in aerobic or muscular fitness, thus limiting the study’s ability to directly inform future exercise training interventions for improving executive functioning. Therefore, to better inform such potential exercise training interventions, it would be advantageous to examine the selective associations between VO_{2\text{peak}} and measures of inhibitory control (i.e., an executive function often associated with aerobic fitness in the general population) in persons with MS, using paradigms that are widely adopted in well-designed examinations of fitness, exercise, and cognition in the general population (e.g., measurement of expired gases for VO_{2\text{peak}} and computerized flanker tasks). This methodology could better elucidate if the pattern of associations between higher aerobic fitness and better inhibitory control in the general population can be extended amongst persons with MS. If so, such evidence could provide stronger support for the development of aerobic exercise training interventions for improving inhibitory control in persons with MS, much like what has been successfully undertaken in older adults (Colcombe & Kramer, 2003).

The current cross-sectional study examined the association between aerobic fitness, based on expired gas analysis, and measures of inhibitory control, based on flanker task performance, in persons with MS and healthy controls who were matched by age, sex, and body mass index (BMI). We hypothesized that persons with MS would have significantly poorer aerobic fitness and inhibitory control compared with healthy controls. This is based on previous reports that have described aerobic deconditioning (Motl & Fernhall, 2012) and executive dysfunction (Benedict & Zivadinov, 2011; Prakash et al., 2008) in persons with MS compared with the general population. We further hypothesized that aerobic fitness would be significantly associated with measures of inhibitory control in the MS subsample based on previous associations of aerobic fitness and cognition in persons with MS (Beier et al., 2014; Prakash et al., 2008; Sandroff & Motl, 2012; Sandroff et al., 2015). We expected that aerobic fitness would be associated with measures of inhibitory control in the matched control sample, based on previous research in the general population (e.g., Alderman & Olson, 2014; Colcombe et al., 2004; Zhu et al., 2014), and that the magnitudes of those associations would be comparable with those in the MS sample. This hypothesis is based on our previous research that describes similar correlations between measures of fitness and cognitive processing speed in persons with MS and matched controls (e.g., Sandroff & Motl, 2012). Given this potentially similar relationship, we finally hypothesized that aerobic fitness would explain a larger portion of variance in inhibitory control than group (i.e., MS vs. control) irrespective of demographic factors (i.e., age, sex, and education) that are typically associated with cognitive function (Heaton, Ryan, Grant, & Matthews, 1996). If our hypotheses are supported, the current cross-sectional study could provide critical information regarding the generalizability of the aerobic fitness–inhibitory control relationship among persons with MS and might support the design and implementation of longitudinal aerobic exercise training interventions that focus on inhibitory control processes as a primary outcome in this population.

**Methods**

**Participants**

The current examination represents a secondary analysis of data from an examination of the acute effects of different modalities of exercise on inhibitory control in persons with MS (Sandroff, Hillman, Benedict, & Motl, 2015). The overall sample included 28 persons with MS and 28 healthy controls who were matched by age, sex, and BMI (i.e., kg/m²). Prospective participants with MS were contacted using a database from previous studies conducted in our laboratory over the past 5 years and healthy controls were contacted via the provision of public e-mail postings, advertising a study of exercise and cognition. All participants were contacted via phone or e-mail and a researcher explained the basic protocol of the study. If the contacted individual was interested...
in the study, the researcher undertook screening for inclusion criteria. The inclusion criteria involved: first, definite diagnosis of MS based on physician’s confirmation of MS and its clinical course based on accepted criteria (Lublin & Reingold, 1996; McDonald et al., 2001; Poser et al., 1983); second, relapse free for the past 30 days (i.e., relative neurologic stability; not currently taking steroids); third, self-reported ability to read 14-point font; fourth, walk with or without minimal assistance (i.e., cane or crutch, but not a walker/bilateral support); fifth, age between 18 and 54 years; sixth, willingness and ability to complete the aerobic fitness and executive control assessments; and seventh, low risk for contraindications of maximal exercise testing based on a ‘no’ response to all items of the Physical Activity Readiness Questionnaire (Thomas, Reading, & Shephard, 1992), or a single “yes” response along with a physician’s approval. The same inclusion criteria were applied for the controls, with the exception of being relapse-free over past 30 days, and the controls had to match a person with MS on age (± 5 years), sex, and BMI (± 2.5 kg/m²).

We contacted 84 individuals with MS, and 36 remained interested after the initial telephone contact; those persons then underwent screening. Of those who underwent screening, one individual did not qualify based on being outside of the age range. Seven participants qualified, but declined to participate in the study citing lack of time. This resulted in a final sample of 28 persons with MS. Seventy-five healthy controls expressed interest in the study following e-mail contact. Of those 75, 28 were matched by age, sex, and BMI with persons who had MS; those persons were then screened, and upon fulfillment of inclusion criteria, were subsequently enrolled into the study.

Aerobic Fitness

Aerobic fitness was measured as peak oxygen consumption (VO₂peak; cardiorespiratory capacity) using an incremental exercise test performed to exhaustion on an electronically braked, computer-driven cycle ergometer (Lode BV, Groningen, The Netherlands) and a calibrated open-circuit spirometry system (TrueOne, Parvo Medics, Sandy, UT) for analyzing respiratory gases. All participants were initially fitted to the cycle ergometer and instrumented for the collection of expired gases. Participants underwent a 3-min warm-up at 0 W. The initial work rate for the incremental exercise test was 0 W, and the work rate continuously increased at a rate of 15 W/min until the participant terminated the test based on volitional fatigue (i.e., inability to continue exercising). This protocol is valid for evaluating aerobic fitness (i.e., VO₂peak) in persons with MS who have Expanded Disability Status Scale (EDSS) scores ranging from 0 to 6 (Motl & Fernhall, 2012). Oxygen consumption (VO₂), respiratory exchange ratio (RER), and work rate were measured continuously by the open-circuit spirometry system and expressed as 20-s averages. Heart rate (HR) was displayed using a Polar HR monitor (Polar Electro Oy, Finland), and HR and rating of perceived exertion (RPE; Borg, 1998) were recorded every minute. VO₂peak was expressed in milliliter per kilogram per minute based on highest recorded 20-s VO₂ value when two of four criteria were satisfied: first, VO₂ plateau with increasing work rate; second, RER ≏ 1.10; third, peak HR within 10 bpm of age-predicted maximum (i.e., ~1 SD); or fourth, peak RPE ≥ 17.

Inhibitory Control

The modified flanker task was included as a computerized measure of executive functioning (i.e., inhibitory control) (Eriksen & Eriksen, 1974). This task has been highly sensitive for capturing the effects of cardiorespiratory fitness on inhibitory control in the general population (e.g., Alderman & Olson, 2014; Colcombe et al., 2004; Hillman et al., 2009; Pontifex et al., 2011). The modified flanker task requires individuals to inhibit task-irrelevant information in order to correctly respond to a centrally presented target stimulus amid either congruent (< < < < <) or incongruent flanking stimuli (< < > < <). Participants are required to press a left button on a keyboard (i.e., the ‘z’ key) if the target stimulus is pointing to the left and a right button on a keyboard (i.e., the ‘m’ key) if the target stimulus is pointing to the right, regardless of congruency. The stimuli were 3 cm tall white arrows presented on a black background for a fixed 80 ms duration and jittered inter-trial interval of 1100, 1300, or 1500 ms, respectively. Participants completed 1 block of 200 stimuli (100 congruent/100 incongruent, occurring with equal probability in a randomized order). Outcomes from the flanker test included mean reaction time latency (ms) and percent accuracy for congruent and incongruent trials. We further computed an interference control score for reaction time and percent accuracy. This was calculated for reaction time as (incongruent trials − congruent trials) and for percent accuracy as (congruent trials − incongruent trials) to provide positive values for both measures. Interference control scores represent a measure of the cost of interfering (i.e., incongruent flanking) stimuli on aspects of cognitive performance.

Disability Status

Participants with MS underwent a neurological exam by a Neurostatus-certified examiner who generated Expanded Disability Status Scale (Kurtzke, 1983) scores for describing the disability status of the sample.
Protocol

All study procedures were approved by a University Institutional Review Board, and all participants provided written informed consent. The study protocol involved one session of testing in our laboratory. Participants initially completed a short demographics questionnaire, followed by administration of the modified flanker task in a quiet, sound-damped room. Participants first completed 20 practice trials to ensure that they understood the test instructions and were able to complete the task without problem. No participants (i.e., MS or control) reported difficulty viewing the stimuli on the modified flanker task during the practice trials. Participants then underwent the full version of the modified flanker task (i.e., 1 block of 200 stimuli). Immediately following the flanker task, the Neurostatus-certified assessor administered a neurological examination for generation of an EDSS score in persons with MS. All participants then underwent the incremental exercise test to exhaustion on a cycle ergometer for measurement of aerobic fitness. Participants were remunerated $20 following the completion of the testing session.

Data Analysis

Data were analyzed in SPSS version 21 (SPSS Inc., Chicago, IL). We first examined differences between MS and control groups in demographic and clinical characteristics using independent samples t-tests and $\chi^2$ difference tests. We performed additional independent samples t-tests to detect differences between MS and control groups in aerobic fitness and measures of inhibitory control. We further computed effect sizes for differences in aerobic fitness and executive control variables between groups as Cohen’s $d$ (i.e., difference in mean scores between groups divided by the pooled SD), with values of 0.2, 0.5, and 0.8 interpreted as small, moderate, and large, respectively (Cohen, 1988). We then performed bivariate Spearman rho ($\rho$) rank-order correlations between aerobic fitness and inhibitory control measures in the overall, MS, and matched control samples, separately, in case outliers or non-linearity were biasing the correlations (Rousselet & Pernet, 2012). Values for correlation coefficients of 0.1, 0.3, and 0.5 were interpreted as small, moderate, and large, respectively (Cohen, 1988). To examine whether the correlation coefficients were significantly different in magnitude between the MS and control samples, we applied Fisher’s $z$-test. Our final analysis involved performing hierarchical linear regressions to examine if aerobic fitness explained a larger portion of variance than group (i.e., MS versus control) in measures of inhibitory control irrespective of age, sex, and education. This was undertaken by separately regressing inhibitory control measures (i.e., measures that correlated with aerobic fitness overall) on age, sex, and education in Step 1 and then adding both group (i.e., MS vs. control) and aerobic fitness in Step 2. We compared the $\beta$-coefficients for group and aerobic fitness in Step 2 to examine if aerobic fitness was a stronger predictor of inhibitory control than group (i.e., an indicator of the generalizability of the potential fitness–inhibitory control association across the MS and control samples).

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the MS and matched control samples are presented in Table 1. Briefly, there were no differences in age ($t(54) = 0.45, p = .64$), BMI ($t(54) = 0.17, p = .86$), or self-reported aerobic exercise days per week ($t(54) = -1.39, p = .17$) between groups based on independent samples t-tests. There were no group differences in EDSS levels (median, range) 3.0 (2.0–6.0) in MS group and — in control group. Disease duration (years) was 10.0 (8.6) in MS group and — in control group.

Table 1. Demographic and clinical characteristics of 28 persons with MS and 28 healthy controls matched by age, sex, and body mass index

<table>
<thead>
<tr>
<th>Variable</th>
<th>MS (N = 28)</th>
<th>Control (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.0 (7.8)</td>
<td>42.9 (10.0)</td>
</tr>
<tr>
<td>Sex (n, % female)*</td>
<td>26/28 (92.9%)</td>
<td>26/28 (92.9%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.3 (9.6)</td>
<td>28.9 (7.6)</td>
</tr>
<tr>
<td>Exercise history (days/week)*</td>
<td>2.6 (1.8)</td>
<td>3.3 (1.8)</td>
</tr>
<tr>
<td>Education*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School Graduate</td>
<td>3/28 (10.7%)</td>
<td>2/28 (7.1%)</td>
</tr>
<tr>
<td>Some College</td>
<td>6/28 (21.4%)</td>
<td>6/28 (21.4%)</td>
</tr>
<tr>
<td>College/University Graduate</td>
<td>19/28 (67.9%)</td>
<td>20/28 (72.4%)</td>
</tr>
<tr>
<td>EDSS (median, range)</td>
<td>3.0 (2.0–6.0)</td>
<td>—</td>
</tr>
<tr>
<td>Disease Duration (years)</td>
<td>10.0 (8.6)</td>
<td>—</td>
</tr>
</tbody>
</table>

Notes: All data are presented as mean (SD) unless described otherwise. BMI = body mass index; EDSS = Expanded Disability Status Scale.

*Non-statistically significant difference between groups based on independent samples t-tests or $\chi^2$ difference tests (all $p > .17$).
education \( (\chi^2(df = 2) = 0.15, p = .93) \). There further was an identical sex distribution between groups (i.e., 26 females and 2 males). There were no significant group differences in ethnicity \( (\chi^2(df = 2) = 1.41, p = .49) \) or employment \( (\chi^2(df = 2) = 1.98, p = .16) \), as both the MS and control samples were mostly Caucasian (MS = 89.3%; control = 96.4%) and currently employed (MS = 85.7%; control = 96.4%). Regarding clinical characteristics, the MS sample had a median EDSS score of 3.0 (range 2.0–6.0) indicating relatively mild MS disability based on well-established disability benchmarks (Confavreux & Vukusic, 2006). Among those with MS, the median visual functional system (FS) score was 2.0 (range 0–3.0), indicating relatively mild visual impairment (i.e., corrected visual acuity better than 20/59). We did not collect EDSS data on matched controls. All 28 persons with MS had a relapsing-remitting clinical disease course, and the average disease duration was 10.0 \((SD = 8.6)\) years.

**Group Differences in Aerobic Fitness and Inhibitory Control**

Descriptive characteristics of aerobic fitness and inhibitory control measures for the overall, MS, and control samples are reported in Table 2. All 56 participants fulfilled at least two of the four criteria for determining VO2peak. Overall, persons with MS had moderately lower aerobic fitness than matched controls, though this difference did not reach statistical significance \( (t(54) = −1.71, p = .09, d = −0.45) \). Regarding the outcomes from the modified flanker task, there were statistically significant differences between groups in reaction time on congruent \( (t(54) = 2.41, p = .02, d = 0.62) \) and incongruent \( (t(54) = 2.34, p = .02, d = 0.84) \) trials, respectively. The effect sizes indicated moderately-to-largely longer reaction times on both congruent and incongruent trials of the modified flanker task for persons with MS relative to healthy controls. There were significant group differences in percent accuracy on both congruent \( (t(54) = −2.77, p < .01, d = −0.71) \) and incongruent \( (t(54) = −2.33, p = .02, d = −0.60) \) trials of the modified flanker task, respectively. The effect sizes indicated moderately-to-largely poorer accuracies on both congruent and incongruent trials of the modified flanker task for persons with MS relative to healthy controls. There further was a nearly statistically significant group difference in interference control scores (i.e., the cost of interfering stimuli on inhibitory control) for percent accuracy \( (t(54) = 1.91, p = .06, d = 0.50) \), and the effect size indicated a moderately greater cost of interfering stimuli on performance for persons with MS compared with healthy controls. There were not statistically significant group differences on interference control scores for reaction time \( (t(54) = 0.76, p = .44, d = 0.21) \).

**Correlations**

Correlations among variables in the overall sample are reported in Table 3, and the correlations between aerobic fitness and inhibitory control measures in the MS and matched control samples are presented in Table 4.

**Overall sample.** Aerobic fitness was moderately-to-strongly correlated with reaction time on both congruent \( (p = −0.49, p < .01) \) and incongruent \( (p = −0.48, p < .01) \) trials of the modified flanker task, such that those with higher aerobic fitness demonstrated significantly shorter reaction times on both congruent and incongruent trials of the modified flanker task. The association between aerobic fitness and reaction time did not depend on congruency (i.e., non-significant association between fitness and interference control of reaction time) \( (p = −0.16, p = .25) \). Aerobic fitness was not significantly associated with percent accuracy on congruent \( (p = 0.15, p = .26) \) trials, incongruent \( (p = 0.17, p = .20) \) trials, nor the cost of interfering stimuli on percent accuracy \( (p = −0.20, p = .14) \) on the modified flanker task in the overall sample.

**MS sample.** Aerobic fitness was moderately-to-strongly associated with reaction time on both congruent \( (p = −0.54, p < .01) \) and incongruent \( (p = −0.48, p < .01) \) trials of the modified flanker task, such that higher fit persons with MS demonstrated

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall ((N = 56))</th>
<th>MS ((N = 28))</th>
<th>Control ((N = 28))</th>
<th>(d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2peak ((\text{ml kg}^{-1} \text{min}^{-1}))</td>
<td>23.7 (8.4)</td>
<td>21.8 (8.8)</td>
<td>25.6 (7.7)</td>
<td>−0.45</td>
</tr>
<tr>
<td>Congruent-RT ((\text{ms}))</td>
<td>437.6 (53.0)</td>
<td>454.0 (58.3)</td>
<td>421.3 (41.9)</td>
<td>0.62*</td>
</tr>
<tr>
<td>Incongruent-RT ((\text{ms}))</td>
<td>504.6 (63.6)</td>
<td>523.8 (70.6)</td>
<td>485.4 (50.1)</td>
<td>0.84*</td>
</tr>
<tr>
<td>Interference control-RT ((\text{ms}))</td>
<td>67.0 (26.7)</td>
<td>69.7 (30.9)</td>
<td>64.2 (22.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Congruent-accuracy (%)</td>
<td>97.5 (3.8)</td>
<td>96.1 (4.7)</td>
<td>98.8 (1.8)</td>
<td>−0.71*</td>
</tr>
<tr>
<td>Incongruent-accuracy (%)</td>
<td>89.6 (10.9)</td>
<td>86.3 (13.7)</td>
<td>92.8 (5.6)</td>
<td>−0.60*</td>
</tr>
<tr>
<td>Interference control-accuracy (%)</td>
<td>7.9 (7.8)</td>
<td>9.9 (9.6)</td>
<td>6.0 (4.9)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Statistical significance at \( p < .05 \).
significantly shorter reaction times on both congruent and incongruent trials. The association between aerobic fitness and interference control of reaction time was not statistically significant ($r = 0.14, p = .48$). Aerobic fitness was not significantly associated with any accuracy outcome from the modified flanker task in the MS sample ($|r| = 0.10–0.22, p = .26$).

**Matched control sample.** Aerobic fitness was moderately-to-strongly associated with reaction time on both congruent ($r = −0.40, p = .04$) and incongruent ($r = −0.45, p = .02$) trials of the modified flanker task, such that higher fit healthy controls demonstrated significantly shorter reaction times on both congruent and incongruent trials. The association between aerobic fitness and interference control of reaction time was not significant ($r = −0.17, p = .39$). Further, in the healthy control sample, aerobic fitness was not significantly associated with accuracy outcomes from the modified flanker task ($|r| = 0.10–0.21, p > .29$).

**Comparison of correlation coefficients.** We applied Fisher’s $z$-test to compare the statistically significant correlations between aerobic fitness and both reaction time on congruent and incongruent trials between the MS and control samples. The magnitude of the correlations between aerobic fitness and reaction time on congruent trials of the modified flanker task was not significantly different between persons with MS and controls ($z = −0.64, p = .52$). Similarly, the magnitude of the correlations between aerobic fitness and reaction time on incongruent trials of the modified flanker task was not significantly different ($z = −0.14, p = .89$).

**Regression Analysis**

Results for the hierarchical linear regression analyses are presented in Tables 5 and 6. Given that aerobic fitness was associated with reaction time on both congruent (Table 5) and incongruent (Table 6) trials of the modified flanker task in the overall sample, we included each dependent variable in a separate regression analysis. In the first regression, age, sex, and education explained a non-statistically significant ($F(3,52) = 2.19, p = .10$) portion of variance in reaction time on congruent trials of the modified flanker task in Step 1 ($R^2 = 0.112$). In Step 2 of the model, aerobic fitness ($β = −0.47, p < .01$), but not group (i.e., MS vs. control) ($β = 0.21, p = .08$), was a significant predictor of reaction time on congruent trials of the modified flanker task, beyond age, sex, and education.
In the second regression, age, sex, and education explained a statistically significant ($F(3,52) = 3.63, p = .02$) portion of variance in reaction time on incongruent trials of the modified flanker task in Step 1 ($R^2 = 0.173$). Similarly, in Step 2 of the model, aerobic fitness ($b = 0.39, p = .01$), but not group (i.e., MS vs. control) ($b = 0.21, p = .09$), was a significant predictor of reaction time on incongruent trials of the modified flanker task, beyond age, sex, and education.

Post hoc Comparison of Reaction Time Based on Fitness Groups

We were interested in the potential differences in reaction time on congruent and incongruent trials of the modified flanker task between groups of persons with MS and matched controls who had high and low fitness levels. This was based on the possibility that an individual with MS might be able to improve reaction time within the context of an inhibitory control paradigm to that of a healthy control by improving aerobic fitness. To do this, we performed a post hoc analysis on reaction time of congruent and incongruent trials of the modified flanker task, separately, for extreme high ($n = 10, V_{O2peak} > 23.7 \text{ ml kg}^{-1} \text{ min}^{-1}$) and low aerobic fitness ($n = 9, V_{O2peak} < 15.3 \text{ ml kg}^{-1} \text{ min}^{-1}$) groups within the MS sample and extreme high ($n = 10, V_{O2peak} > 26.4 \text{ ml kg}^{-1} \text{ min}^{-1}$) and low aerobic fitness ($n = 10, V_{O2peak} < 21.1 \text{ ml kg}^{-1} \text{ min}^{-1}$) groups within the control sample, respectively. Fitness groups were formed based on the upper and lower $V_{O2peak}$ tertiles of the MS and control samples, separately. Plots of reaction times based on those groupings are presented in Figure 1 (i.e., congruent trials) and Figure 2 (i.e., incongruent trials). Interestingly, high-fit persons with MS demonstrated shorter reaction times on congruent and incongruent trials of the modified flanker task (429.4 (35.1) ms, 463.6 (45.5) ms, respectively) than low-fit controls (439.0 (42.0) ms, 510.8 (55.3) ms, respectively), but longer reaction times on congruent and incongruent trials of the modified flanker task than high-fit controls (398.1 (39.1) ms, 463.6 (45.5) ms, respectively).

Discussion

The current cross-sectional study examined the associations between aerobic fitness and inhibitory control in persons with MS and healthy controls matched by age, sex, and BMI. The primary novel results were that: first, persons with MS demonstrated lower
aerobic fitness and significantly slower, less accurate performance on the modified flanker task compared with matched controls; second, aerobic fitness was similarly associated with measures of reaction time, but not accuracy, regardless of congruency, within the context of an inhibitory control paradigm in the MS sample and the matched control sample, and those associations were moderate-to-strong in magnitude; and third, aerobic fitness, but not group, predicted reaction time on both congruent and incongruent trials of the modified flanker task, beyond potential demographic influences on cognitive performance. Collectively, this suggests that aerobic fitness might be an important correlate of reaction time aspects of inhibitory control in persons with MS and

Fig. 1. Plots of reaction time on congruent trials of a modified flanker task based on groups of high- and low-fit persons with MS and matched controls, respectively. 

Notes: Data are presented as mean reaction time (ms) along with standard error bars; MS = multiple sclerosis; RT = reaction time. Based on post hoc Bonferroni corrections: * p < .05 for low-fit persons with MS versus high-fit persons with MS; † p < .05 for low-fit persons with MS versus high-fit matched controls; no significant group differences (p > .07) for low-fit persons with MS versus low-fit matched controls, high-fit persons with MS versus low-fit healthy controls, and high-fit persons with MS versus high-fit matched controls.

Fig. 2. Plots of reaction time on incongruent trials of a modified flanker task based on groups of high- and low-fit persons with MS and matched controls, respectively. 

Notes: Data are presented as mean reaction time (ms) along with standard error bars; MS = multiple sclerosis; RT = reaction time; ms = milliseconds. Based on post hoc Bonferroni corrections: * p < .05 for low-fit persons with MS versus high-fit persons with MS; † p < .05 for low-fit persons with MS versus high-fit matched controls; no significant group differences (p > .14) for low-fit persons with MS versus low-fit matched controls, high-fit persons with MS versus low-fit healthy controls, and high-fit persons with MS versus high-fit matched controls.
provides stronger evidence to support the design and implementation of longitudinal aerobic exercise training interventions for improving reaction time measures on tasks of inhibitory control in this population. This is important given that cognitive impairment (e.g., poor inhibitory control) is highly prevalent, poorly managed, and disabling in persons with MS (Benedict & Zivadinov, 2011), and exercise training may represent an approach for managing cognitive dysfunction in this population (Motl et al., 2011).

The current results further indicate a generalized effect of fitness on reaction time within an inhibitory control paradigm such that the effects of VO2peak on modified flanker performance were similar in magnitude across groups. This is consistent with the line of fitness research continually undertaken in the general population that has been recently extended to persons with other neurological conditions (e.g., mild cognitive impairment, chronic stroke, and Parkinson’s disease) in the form of longitudinal aerobic exercise training interventions on inhibitory control (Baker et al., 2010; Kluding, Tseng, & Billinger, 2011; Uc et al., 2014).

The modified flanker task measures both speed- and accuracy-related aspects of cognitive performance (i.e., inhibitory control), and the present pattern of associations between aerobic fitness and inhibitory control outcomes are both general and selective for persons with MS. Aerobic fitness was selectively associated with speed-related outcomes of this task over accuracy outcomes in the MS sample. This pattern of results is consistent with that observed in the matched control sample and in previous studies of fitness and cognitive processing speed in persons with MS, whereby those with better aerobic fitness demonstrated faster cognitive processing speed (Sandroff & Motl, 2012; Sandroff et al., 2015). Indeed, aerobic fitness has been associated with reaction time, but not accuracy, on the modified flanker task in several other studies in healthy adults from the general population (e.g., Alderman & Olson, 2014; Colcombe et al., 2004). There further were general effects of aerobic fitness on reaction time on tasks that required variable amounts of inhibitory control in the current MS sample. This was reflected by significant associations between aerobic fitness and reaction time on both congruent and incongruent trials of the modified flanker task, coupled with a non-statistically significant association between aerobic fitness and interference control of reaction time on the modified flanker task. This indicates that persons with MS with higher aerobic fitness did not have differentially faster performance on the modified flanker task based on congruency (i.e., interference control scores). Additionally, this pattern of results was present in the matched control sample.

Those general effects of aerobic fitness on reaction time within the context of an inhibitory control paradigm are partially consistent with previous research on fitness and inhibitory control in the general population. For example, one seminal study reported that older adults with higher aerobic fitness demonstrated reductions in the cost of interfering stimuli (i.e., incongruent trials relative to congruent trials; a more ‘executive’ measure than reaction time on congruent and incongruent trials, respectively) compared with lower fit older adults (Colcombe et al., 2004). Conversely, other studies have reported general effects of aerobic fitness on flanker task reaction time that do not vary by condition (i.e., congruent vs. incongruent trials) in healthy adults (e.g., Alderman & Olson, 2014). This is in line with recent research that suggests that there is less of a selective benefit of aerobic fitness on executive functioning in the general population (e.g., Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Etnier et al., 2006) whereby improvements in aerobic fitness might result in smaller, more general benefits on cognitive speed or more global cognitive processes (Etnier et al., 2006). For example, a recent prospective study reported that better aerobic fitness was associated with better performance on tests of psychomotor speed, verbal learning and memory, and executive function (i.e., Stroop test scores) in younger adults (Zhu et al., 2014). Interestingly, that study measured cognitive performance 25 years later and reported that baseline aerobic fitness only predicted psychomotor speed (i.e., digit–symbol substitution test scores) in middle-aged adults (i.e., 43–55 years) (Zhu et al., 2014). As such, the current study extends this association among persons with MS and provides novel data on beneficial effects of aerobic fitness on reaction time within an inhibitory control paradigm in this population.

The current results extend previous studies of aerobic fitness and cognition in persons with MS. There have been consistent, moderate-sized cross-sectional associations of aerobic fitness and cognitive processing speed in persons with mild MS disability, largely based on performance on neuropsychological tests (Prakash et al., 2010; Sandroff & Motl, 2012; Sandroff et al., 2015). The present results extend this association into measures of reaction time on tasks requiring variable amounts of inhibitory control. This is further supported by a recent longitudinal study in persons with MS that reported that increases in aerobic or muscular fitness were associated with increases in Trail Making Test scores (Beier et al., 2014). The current cross-sectional results improve upon those from that previous study given the gold-standard measurement of aerobic fitness, and association between aerobic fitness, in particular, and measures of inhibitory control. Taken together, this pattern of results suggests that chronic aerobic exercise training might result in improvements of cognitive performance in persons with MS, particularly for reaction time aspects of cognitive tasks that involve perceptual interference and response inhibition. Importantly, there are no published studies examining the effects of aerobic exercise training on inhibitory control, using a modified flanker paradigm in persons with MS. Based on the similar associations between aerobic fitness and inhibitory control in the MS and control samples, future studies should carefully examine exercise training effects on inhibitory control in adults of the general population (Colcombe & Kramer, 2003; Voss et al., 2011) that might be applicable for designing similar interventions in persons with MS.

To examine the potential impact of such an intervention, we performed a post hoc analysis on cognitive performance based on groups of high and low-fit persons with MS and matched controls. This seemingly indicated that low-fit persons with MS might be
able to improve reaction time on congruent and incongruent trials of the modified flanker task to a level of a healthy control by increasing aerobic fitness. However, those results should be interpreted with caution, given that there may be several moderating factors beyond aerobic fitness that may result in improved cognitive performance (Etñier et al., 2006). For example, we recently hypothesized that certain modalities of aerobic exercise (i.e., treadmill walking) might require a greater cognitive demand (i.e., aspects of balance and coordination) than others, which might result in cognitive adaptations over time in persons with MS (Sandroff et al., 2015).

The current study is not without limitations. The primary limitation includes the cross-sectional design as it does not indicate causality between aerobic fitness and inhibitory control. Indeed, cognitive ability might influence participation in exercise training that increases aerobic fitness, as much as aerobic fitness influences inhibitory control. However, this laboratory-based cross-sectional study was necessary prior to investing considerable time, resources, and effort into a randomized, controlled trial of aerobic exercise training and inhibitory control outcomes in MS. Further, the current study involved a relatively small sample size, as it represents a secondary analysis of baseline data from a within-subjects study of the acute effects of different modalities of exercise on cognition in MS (Sandroff et al., 2015). Perhaps the small sample size contributed to demographic factors explaining a statistically significant portion of variance in reaction time on incongruent, but not congruent, trials of the modified flanker task. This was not expected given that age, sex, and education often influence performance on neurocognitive tasks in general (Heaton et al., 1996). It is possible that moderating factors beyond aerobic fitness might account for the association with cognition in persons with MS. Some potential moderating factors include white matter lesion volume, disease-modifying treatment use, fatigue, sleep quality, fluctuations in blood glucose/diabetes, anxiety, and depression. In the current study, we did not include those measures as potential confounding variables of the aerobic fitness—cognition relationship in persons with MS. Future research should consider the effects of those variables on both fitness and cognition in this population. An additional study limitation is that we did not collect EDSS data for healthy controls to examine whether neurological disability, rather than aerobic fitness, explains group differences in cognition, given that there is evidence of an association between EDSS scores and aerobic fitness in persons with MS (Motl & Goldman 2011). We do note that disability status and aerobic fitness are inter-related, but not iso-morphic constructs. Another limitation of the current study involves the lack of a valid neuropsychological measure of executive function (beyond inhibitory control processes) in MS as a potential moderator of the effects of aerobic fitness on cognition. Future studies should take this variable into consideration, given that it would be advantageous to develop an aerobic exercise training intervention for improving reaction time within an inhibitory control paradigm in persons with MS who have documented executive dysfunction. The entire MS sample presented with a relapsing-remitting clinical disease course, which limits the generalizability of the current results among individuals with other clinical courses of MS (i.e., progressive MS). A final limitation is that the study involved a convenience sample of persons with MS who had previously participated in our research. We acknowledge that this could have upwardly biased scores on the modified flanker task; however, we do not believe this to be the case, given that this is the first study in our laboratory that involved this test as a primary outcome measure.

Conclusions

The primary novel results from the current cross-sectional study of 28 persons with MS and 28 healthy controls matched by age, sex, and BMI were that first, persons with MS demonstrated worse aerobic fitness and significantly slower and less accurate performance on a modified flanker task compared with matched controls; second, aerobic fitness was similarly associated with measures of reaction time, but not accuracy, regardless of congruency, on the modified flanker task in the MS and matched control samples; and third, aerobic fitness, but not group, was a statistically significant predictor of reaction time across congruent and incongruent trials of the modified flanker task irrespective of potential demographic influences on cognitive performance. Collectively, the present results provide stronger support for the design and implementation of aerobic exercise training interventions, in particular, for improving reaction time measures within the context of an inhibitory control paradigm in persons with MS. This is important in that aerobic exercise represents a promising symptom management tool for potentially mitigating executive dysfunction in this population.

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Conflict of Interest

None declared.
References


