Systematically-Developed Pilot Randomized Controlled Trial of Exercise and Cognition in Persons with Multiple Sclerosis

Brian M. Sandroff\textsuperscript{1}, Curtis L. Johnson\textsuperscript{2}, Julia M. Balto\textsuperscript{2}, Rachel E. Klaren\textsuperscript{2}, Elizabeth A. Hubbard\textsuperscript{2}, Sarah M. Sommer\textsuperscript{2}, & Robert W. Motl\textsuperscript{2}

\textsuperscript{1}Kessler Foundation, West Orange, NJ
\textsuperscript{2}University of Illinois at Urbana-Champaign, Urbana, IL

Disclosures

- The authors report no conflicts of interest
- The work presented in this presentation was not funded by an external grant, but was completed in partial fulfillment of the first author’s graduate degree under the supervision of last author
Cognitive Impairment in MS

- Cognitive impairment is prevalent, disabling, and poorly-managed in multiple sclerosis (MS)
  - Upwards of 50% demonstrate cognitive impairment\(^1\)
  - Impairment in domains of CPS, learning/memory, EF\(^1,2\)
  - Associated with negative health outcomes\(^3\)
  - No FDA-approved treatment for cognitive impairment in MS (e.g., symptomatic or DMTs)\(^4\)
  - Studies involving cognitive rehabilitation have been conflicting\(^4\)

\(^1\) Chiaravalloti & DeLuca, 2008; \(^2\) Prakash et al., 2008; \(^3\) Benedict et al., 2005; \(^4\) Amato et al., 2013;

Exercise Training and Cognition in MS

- Inconsistent evidence from 5 RCTs of exercise training and cognition in MS:\(^5-9\)
  - Not in-line with literature from the general population on exercise and cognitive function\(^10\)
  - Methodological concerns of MS studies:
    - Unsupervised exercise
    - Importance of physical fitness\(^11\)
    - Cognition as non-primary outcome

\(^5\) Oken et al., 2004; \(^6\) Romberg et al., 2005; \(^7\) Briken et al., 2014; \(^8\) Carter et al., 2014; \(^9\) Hoang et al., 2016; \(^10\) Voss et al., 2011; \(^11\) Motl et al., 2013
**Optimal Exercise Intervention?**

- For optimally improving cognition in MS, recent evidence suggests:
  
  **Domain of exercise training?**
  - Aerobic exercise\(^{12,13}\)

  **What type (modality) and intensity of exercise?**
  - Light, moderate, and vigorous intensity treadmill walking exercise\(^{14,15}\)

  **Which domains of cognitive functioning?**
  - CPS/EF\(^{12,13,16}\)

  **What about disability status?**
  - Fully-ambulatory persons with MS\(^{13,17,18}\)

---

**Can This ‘Optimal’ Intervention Actually Work?**

- Not yet applied as a chronic exercise training intervention for improving CPS and EF

- Would provide preliminary proof-of-concept data for treadmill walking exercise training effects on cognition in MS

- Early phase RCT research important for developing better interventions
  - Reducing threats to internal validity
  - Promoting innovation
  - Reducing Type II error
  - Providing evidence against premature dismissal of a possibly beneficial intervention\(^{19}\)

---

\(^{12}\) Sandroff & Motl, 2012; \(^{13}\) Sandroff et al., 2015, Neurorehabil Neural Repair; \(^{14}\) Sandroff et al., 2015, J Clin Exp Neuropsychol; \(^{15}\) Sandroff et al., 2016; \(^{16}\) Sandroff et al., 2015, Arch Clin Neuropsychol; \(^{17}\) Sandroff et al., 2013; \(^{18}\) Sandroff et al., 2014

\(^{19}\) Mohr et al., 2009
**Purpose**

- Single-blind pilot RCT design
- Examine the effects of a systematically-developed, progressive treadmill walking exercise training intervention compared with a waitlist control condition on CPS, EF, and cardiorespiratory fitness outcomes among fully-ambulatory persons with MS
- Examined associations among changes in CPS, EF, and cardiorespiratory fitness outcomes
  - Potential mechanisms of intervention effects

**Participants**

- **N=10** fully-ambulatory persons with MS
  - EDSS ≤ 4.0
  - Low-risk for contraindications for exercise training
  - Relapse-free for 30 days

[Flowchart diagram showing the participant flow from eligible to included and participation status]
Primary Measures

- **Cognitive Processing Speed**
  - Symbol Digit Modalities Test (SDMT)\(^{20}\)
  - Modified Flanker Task\(^{21}\)

- **Executive Function**
  - Delis-Kaplan Executive Function System (DKEFS) Sorting Test\(^{22}\)
  - Modified Flanker Task\(^{21}\)

- **Cardiorespiratory Fitness**
  - Graded Exercise Test

\(^{20}\) Smith, 1982; \(^{21}\) Eriksen & Eriksen, 1974; \(^{22}\) Delis et al., 2001

---

SDMT

- Best-characterized measure of CPS in MS\(^{23}\)

- Pairing as many abstract symbols with single-digit numbers as possible in 90 seconds based on a key

- Primary outcome: raw score

\(^{23}\) Benedict & Zivadinov, 2011
DKEFS Sorting Test

- Neuropsychological measure of EF (i.e., conceptual reasoning/cognitive flexibility)
- Sorting 6 cards into 2 groups of 3 cards in as many ways as possible in 4 minutes
- Primary outcomes: total number of correct sorts and verbal description score across 2 trials

Modified Flanker Task

- Computerized measure of CPS and EF
- Particularly sensitive to aerobic exercise\textsuperscript{14,15,24}
- Requires participants to inhibit task-irrelevant information in order to correctly respond to centrally presented target stimulus
- Target stimulus presented amid congruent or incongruent flanking stimuli

\textsuperscript{24} Colcombe et al., 2004
Modified Flanker Task—Outcomes

• Mean reaction time (RT) collapsed across trials in ms
  – Complex CPS$^{25}$

• Interference control (IC) score:
  – Provides a measure of the cost of interfering stimuli on RT
  – EF/conflict resolution$^{25}$

Cardiorespiratory Fitness

• Peak oxygen consumption (VO$_{2peak}$)
  – Graded exercise test to exhaustion on motor-driven treadmill and a metabolic cart

  – Modified Balke protocol$^{26}$
    • Brisk, submaximal walking pace
    • Grade increases 2.0% every 2 minutes until volitional fatigue
Intervention Condition

- 3 days/week of progressive (duration and intensity) treadmill walking exercise training for 12-weeks
  - Based on pilot work and ACSM guidelines
- Initially consisted of 15-minutes of light-to-moderate intensity treadmill walking exercise (based on heart rate reserve)
- Eventually progressed to 40-minutes of vigorous intensity treadmill walking exercise by week 12
- Participants wore HR monitor and completed an exercise log for each session

<table>
<thead>
<tr>
<th>Week</th>
<th>Sessions</th>
<th>Exercise Intensity</th>
<th>Exercise Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-3</td>
<td>Light-to-Moderate</td>
<td>15-20 min</td>
</tr>
<tr>
<td>2</td>
<td>4-6</td>
<td>Light-to-Moderate</td>
<td>20-25 min</td>
</tr>
<tr>
<td>3</td>
<td>7-9</td>
<td>Moderate</td>
<td>20-25 min</td>
</tr>
<tr>
<td>4</td>
<td>10-12</td>
<td>Moderate</td>
<td>25-30 min</td>
</tr>
<tr>
<td>5-6</td>
<td>13-18</td>
<td>Moderate-to-Vigorous</td>
<td>25-30 min</td>
</tr>
<tr>
<td>7-8</td>
<td>19-24</td>
<td>Moderate-to-Vigorous</td>
<td>30-35 min</td>
</tr>
<tr>
<td>9-10</td>
<td>25-30</td>
<td>Vigorous</td>
<td>30-35 min</td>
</tr>
<tr>
<td>11-12</td>
<td>31-36</td>
<td>Vigorous</td>
<td>35-40 min</td>
</tr>
</tbody>
</table>

Control Condition

- Waitlist
- Participants received intervention following 12-week study period
- All participants encouraged not to undertake additional exercise (i.e., joining a new gym) outside of their normal routine
**Protocol**

**Baseline Testing:**
1. Informed Consent
2. SDMT
3. DKEFS Sorting Test
4. Modified Flanker Task
5. EDSS
6. Graded Exercise Test

**12-Weeks**
- **N=5**
- Treadmill Walking Exercise Training

**12-Weeks**
- **N=5**
- Waitlist

**Follow-Up Testing**
1. SDMT*
2. DKEFS Sorting Test*
3. Modified Flanker Task*
4. Graded Exercise Test

* = Alternate form used

---

**Data Analysis**

- Examined effects of the intervention on cognitive and fitness outcome measures using repeated-measures ANOVAs

- Given the small sample size, reaching significance was unlikely
  - Computed effect sizes for changes in cognitive and fitness outcomes between groups as Cohen’s $d^{28}$

- Bivariate correlations ($r$) for associations among changes in cognitive and fitness outcomes
  - Examination of possible mechanisms of intervention effects

---

27 Kurtzke, 1983
28 Cohen, 1988
Descriptive Characteristics of Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise (N=5)</th>
<th>Control (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.6 (11.5)</td>
<td>44.2 (6.6)</td>
</tr>
<tr>
<td>Sex (n, % female)</td>
<td>5/5 (100%)</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>Education (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some College</td>
<td>3/5 (60.0%)</td>
<td>2/5 (40.0%)</td>
</tr>
<tr>
<td>College/University Graduate</td>
<td>2/5 (40.0%)</td>
<td>3/5 (60.0%)</td>
</tr>
<tr>
<td>Employment (n, % employed)</td>
<td>3/5 (60.0%)</td>
<td>5/5 (100.0%)</td>
</tr>
<tr>
<td>Disease Duration (years)</td>
<td>11.4 (9.8)</td>
<td>12.2 (7.9)</td>
</tr>
<tr>
<td>EDSS (median, range)</td>
<td>3.0 (1.5-4.0)</td>
<td>2.5 (1.5-4.0)</td>
</tr>
<tr>
<td>Clinical Course (n, % RRMS)</td>
<td>5/5 (100%)</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>Compliance (% of sessions attended)</td>
<td>96.3% (6.5%)</td>
<td>--</td>
</tr>
</tbody>
</table>

Note: All data presented as mean (SD) unless otherwise noted; EDSS=Expanded Disability Status Scale

Cognitive and Fitness Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise (N=5)</th>
<th>Control (N=5)</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDMT (raw score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>55.0 (9.2)</td>
<td>65.2 (15.8)</td>
<td>0.95</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>58.2 (7.9)</td>
<td>61.8 (9.7)</td>
<td></td>
</tr>
<tr>
<td>DKEFS (correct sorts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>11.0 (2.2)</td>
<td>13.2 (2.2)</td>
<td>-0.59</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>10.0 (1.9)</td>
<td>13.0 (1.0)</td>
<td></td>
</tr>
<tr>
<td>DKEFS (description score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>40.4 (8.4)</td>
<td>51.0 (6.9)</td>
<td>-0.23</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>38.2 (7.1)</td>
<td>50.6 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Modified flanker RT (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>486.3 (98.5)</td>
<td>440.8 (12.5)</td>
<td>-0.43</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>476.2 (69.8)</td>
<td>441.8 (7.5)</td>
<td></td>
</tr>
<tr>
<td>IC-RT (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>45.0 (34.7)</td>
<td>49.4 (17.9)</td>
<td>0.37</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>43.3 (45.0)</td>
<td>44.9 (9.9)</td>
<td></td>
</tr>
<tr>
<td>VO₂peak (ml·kg⁻¹·min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>24.2 (6.0)</td>
<td>31.8 (4.1)</td>
<td>1.08</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>27.6 (5.7)</td>
<td>31.4 (2.4)</td>
<td></td>
</tr>
</tbody>
</table>

Note: All data presented as mean (SD); d calculated as change in exercise condition minus change in control condition divided by pooled SD of change.
Correlations

- In overall sample, change in VO2peak significantly associated with change in SDMT ($r = .60$, $p = .03$) only

What Might This Mean?

- Large intervention effects on CPS (i.e., SDMT performance) and cardiorespiratory fitness (i.e., VO2peak)
  - Change in VO2peak moderately-to-strongly associated with change in SDMT score

- Provides initial proof-of-concept data supporting progressive treadmill walking exercise training for possibly improving CPS and cardiorespiratory fitness in a larger sample of fully-ambulatory persons with MS

- Importance of CPS in MS\textsuperscript{29}

\textsuperscript{29} DeLuca et al., 2004
Next Steps?

- Intervention as a treatment for cognitive impairment
  - Inclusion of persons with MS-related CPS impairment

- Neuroimaging outcomes
  - Impaired CPS associated with thalamic atrophy\(^{30}\), thalamocortical disruption\(^{31,32}\) in persons with MS

30 Houtchens et al., 2007; 31 Tona et al., 2014; 32 Schoonheim et al., 2015

Strengths and Limitations

- Strengths:
  - Single-blind RCT design
  - Continuation of systematic approach for developing better RCTs of exercise and cognition in MS

- Limitations:
  - Small convenience sample; possibly underpowered
    - Preliminary results warrant further study
  - Apparent baseline differences in cognitive and fitness outcomes between groups
  - Sample not recruited as having impaired CPS or EF
    - 50% of participants had baseline SDMT scores > 1 SD below norm\(^{33}\)
  - Passive control condition

33 Parmenter et al., 2009
Acknowledgements

• Everyone in attendance
• CMSC
• ENRL Director: Prof. Rob Motl
• Senior VP for Research and Training at KF: Dr. John DeLuca
• Research staff of post-docs, grads, URAs, and project coordinators
• Research participants

Individual Changes in Outcomes

<table>
<thead>
<tr>
<th>Subject</th>
<th>SDMT</th>
<th>DKEFS-Correct Sorts</th>
<th>DKEFS-Description Score</th>
<th>Modified flanker RT (ms)</th>
<th>IC-RT (ms)</th>
<th>VO&lt;sub&gt;2peak&lt;/sub&gt; (ml·kg⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>−1</td>
<td>0</td>
<td>+2</td>
<td>+18.7</td>
<td>−13.4</td>
<td>+1.2</td>
</tr>
<tr>
<td>2</td>
<td>−1</td>
<td>+1</td>
<td>+4</td>
<td>+2.7</td>
<td>+11.4</td>
<td>+0.5</td>
</tr>
<tr>
<td>3</td>
<td>+5</td>
<td>−2</td>
<td>−9</td>
<td>−34.1</td>
<td>−11.7</td>
<td>+4.1</td>
</tr>
<tr>
<td>4</td>
<td>+4</td>
<td>−2</td>
<td>−2</td>
<td>−55.5</td>
<td>−6.7</td>
<td>+4.6</td>
</tr>
<tr>
<td>5</td>
<td>+9</td>
<td>−2</td>
<td>−6</td>
<td>+18.1</td>
<td>+11.7</td>
<td>+6.3</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>+8</td>
<td>0</td>
<td>0</td>
<td>+11.6</td>
<td>+8.2</td>
<td>+0.3</td>
</tr>
<tr>
<td>2</td>
<td>−8</td>
<td>+1</td>
<td>+5</td>
<td>−9.5</td>
<td>−9.1</td>
<td>−4.6</td>
</tr>
<tr>
<td>3</td>
<td>−13</td>
<td>−2</td>
<td>−3</td>
<td>+20.4</td>
<td>−4.6</td>
<td>−0.6</td>
</tr>
<tr>
<td>4</td>
<td>−1</td>
<td>−1</td>
<td>−4</td>
<td>−20.4</td>
<td>−1.9</td>
<td>−2.2</td>
</tr>
<tr>
<td>5</td>
<td>−3</td>
<td>+1</td>
<td>0</td>
<td>+2.8</td>
<td>−15.3</td>
<td>+5.0</td>
</tr>
</tbody>
</table>
Intervention Effects on SDMT Scores

![Graph showing SDMT scores over time for two groups: control and intervention.]

Intervention Effects on VO$_{2\text{peak}}$

![Graph showing VO$_{2\text{peak}}$ over time for two groups: control and intervention.]
Systematic Development of Exercise Interventions

- Systematic line of research indicated that perhaps aerobic exercise, in the form of treadmill walking exercise, represents the optimal exercise stimulus for improving CPS in fully-ambulatory persons with MS\textsuperscript{12-18}

- Results of current study suggest that CPS can actually be improved using such a stimulus

- Improvements in cardiorespiratory fitness might be a possible mechanism of improvements in CPS
  - Consistent with cross-sectional research in MS\textsuperscript{12,13,32,33}

\textsuperscript{32} Prakash et al., 2007; \textsuperscript{33} Prakash et al., 2010