Exercise, Walking, and Cognition in Multiple Sclerosis: A Lifespan Perspective

Robert W. Motl, PhD & Brian M. Sandroff, PhD
Department of Physical Therapy
University of Alabama at Birmingham
Disclosures

RWM: No conflicts of interest; received grant funding from the National Multiple Sclerosis Society, National Institutes of Health, Consortium of Multiple Sclerosis Centers, Teva Neuroscience, EMD Serono, Inc., Biogen Idec, Acorda Therapeutics, Sun Health, and MC-10; provided educational lectures for EMD Serono, Inc., Novartis, and MSCOC.

BMS: No conflicts of interest; received grant funding from the Consortium of Multiple Sclerosis Centers, EMD Serono, Inc., and the National Institutes of Health; provided educational lecture for the Consortium of Multiple Sclerosis Centers/National Multiple Sclerosis Society.
Outline

• MS Overview (RWM)
• Scope of the Presentation: Mobility, Cognition, and Exercise (RWM)
• Exercise, Mobility, and Brain in MS (RWM)
• Break
• Exercise, Cognition, and Brain in MS (BMS)
• Translation of Research into Clinical Practice (RWM)
• Questions (Audience)
Outline

• MS Overview (RWM)
• Scope of the Presentation: Mobility, Cognition, and Exercise (RWM)
• Exercise, Mobility, and Brain in MS (RWM)
• Break
• Exercise, Cognition, and Brain in MS (BMS)
• Translation of Research into Clinical Practice (RWM)
• Questions (Audience)
Multiple Sclerosis

- MS is a common neurological disease of the CNS\(^1\)
- Initially characterized by inflammatory processes\(^2\)
  - Eventually neurodegenerative disease process\(^2\)
    - Irreversible damage of grey and white matter in the brain\(^2\)
- Accumulation of physical and cognitive disability

\(^1\) Kingwell et al., 2013; \(^2\) Trapp & Nave, 2008
Multiple Sclerosis Phenotypes

Progressive-relapsing multiple sclerosis
Steady decline since onset with superimposed attacks.

Secondary progressive multiple sclerosis
Initial relapsing-remitting multiple sclerosis that suddenly begins to have decline without periods of remission.

Primary progressive multiple sclerosis
Steady increase in disability without attacks.

Relapsing-remitting multiple sclerosis
Unpredictable attacks which may or may not leave permanent deficits followed by periods of remission.

Compston & Coles, Lancet, 2008; 372:1502-1517
Major Consequences of Aging and MS

Differential effects of aging on motor and cognitive functioning in multiple sclerosis

Shumita Roy, Seth Fradak, Allison S Drake, Lauren Irwin, Robert Zivadinov, Bianca Weinstock-Guttman and Ralph HB Benedict

Abstract

Background: Multiple sclerosis (MS) patients are impaired in motor and cognitive performance, but the extent to which these deficits are magnified by aging is unknown. In one prior study, differences in cognitive processing speed between MS patients and healthy individuals were of similar magnitude across the lifespan. Here, we have improved on this work by expanding assessment to multiple cognitive domains and motor functioning.

Objective: To determine whether the degree of cognitive and motor dysfunction in MS is magnified with increasing age.

Methods: In all, 698 MS patients (aged 29–71 years) and 226 healthy controls (HCs; aged 18–72 years) completed neuropsychometric tests covering ambulation, upper extremity function, information processing speed, and memory.

Results: Linear regression models predicting cognitive and motor function revealed main effects of MS/HC diagnosis, age, and education across all measures. There was also an interaction between age and diagnosis on measures of motor function, but not on cognitive outcomes.

Conclusion: The progression of motor decline is amplified by aging in MS. However, the degree of cognitive impairment does not vary across the lifespan. Thus, evidence of accelerated cognitive impairment in older adults with MS may signal the presence of other age-related cognitive pathologies.
MS Across the Lifespan

Pediatric-Onset MS

Adults with MS

Aging with MS
The benefits of exercise training in multiple sclerosis

Robert W. Motl and Lara A. Pilutti

Abstract | Multiple sclerosis (MS) is an immune-mediated disease characterized by inflammatory demyelination and neurodegeneration within the CNS. This damage of CNS structures leads to deficits of body functions, which, in turn, affect patient activities, such as walking, and participation. The pathogenesis and resulting consequences of MS have been described as concepts within the International Classification of Functioning, Disability and Health (ICF) model—an international standard to describe and measure health and disability. Evidence suggests that exercise training in people with MS has the potential to target and improve many of the components outlined in the ICF model. Although the body of research examining the effects of exercise training on depression, cognition and participatory outcomes is not sufficiently developed, some preliminary evidence is promising. Exercise training is proposed to affect inflammation, neurodegeneration, and CNS structures, but current evidence is limited. In this review, we discuss evidence from clinical trials that suggests beneficial effects of exercise training on muscle strength, aerobic capacity and walking performance, and on fatigue, gait, balance and quality of life. Issues with current studies and areas of future research are highlighted.
Outline

• MS Overview (RWM)
• Scope of the Presentation: Mobility, Cognition, and Exercise (RWM)
• Exercise, Mobility, and Brain in MS (RWM)
• Break
• Exercise, Cognition, and Brain in MS (BMS)
• Translation of Research into Clinical Practice (RWM)
• Questions (Audience)
Walking Mobility in MS

• Loss of mobility highly prevalent and burdensome in MS\textsuperscript{3-5}

• Evidence for reduced performance in tests of walking speed, endurance, functional mobility\textsuperscript{6}; worse spatiotemporal gait parameters\textsuperscript{7} than healthy controls

• Walking difficulty associated with unemployment, worse physical function, quality of life, and reduced community participation\textsuperscript{4,8,9}

• Physiological deconditioning associated with worse walking mobility in MS\textsuperscript{10}

\textsuperscript{3} Motl & Learmonth, 2014; \textsuperscript{4} LaRocca, 2011; \textsuperscript{5} Heesen et al., 2008; \textsuperscript{6} Kieseier & Pozzilli, 2012; \textsuperscript{7} Cavanaugh et al., 2011; \textsuperscript{8} Motl, 2013; \textsuperscript{9} Motl et al., 2007; \textsuperscript{10} Sandroff et al., 2013
Cognitive Impairment in MS

• Upwards of 50% demonstrate cognitive impairment\(^\text{11}\)
• Impairment in domains of CPS, learning and memory, EF\(^\text{11}\)
• Associated with negative health outcomes\(^\text{12}\)
• No FDA-approved treatment for cognitive impairment in MS (e.g., symptomatic or DMTs)\(^\text{13}\)
• Studies involving cognitive rehabilitation have been conflicting\(^\text{13}\)

11 Chiaravalloti & DeLuca, 2008; 12 Benedict et al., 2005; 13 Amato et al., 2013;
Why Exercise for Mobility and Cognition in MS?

• Disease modifying therapies as first-line approach for modifying immune system and its effects on the CNS

• Efficacy of DMTs on disease progression and relapse rate

• Lack of efficacy of DMTs on functional outcomes (i.e., mobility and cognition)

• Exercise might be a behavioral approach/adjuvant therapy for improving functioning in MS
  • Robust evidence in older adults supporting exercise for improving mobility and cognition outcomes
## Important Definitions

<table>
<thead>
<tr>
<th>Construct</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>Physical activity that is planned, structured, and repetitive for the purpose of improving or maintaining one or more components of physical fitness</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>Bodily movement produced by contraction of skeletal muscle that increases energy expenditure above basal level</td>
</tr>
<tr>
<td>Physical Fitness</td>
<td>An attained set of attributes (e.g., cardiorespiratory capacity and endurance; flexibility; body composition; skeletal muscle strength and endurance) that relates to the ability to perform physical activity</td>
</tr>
</tbody>
</table>

14 Bouchard & Shepherd, 1994
Conceptual Model

Figure 1. Model for possible cognitive and exercise rehabilitation effects on cognition and walking in multiple sclerosis.

Motl, Sandroff, & DeLuca, 2016, *Neurorehabil Neural Repair*
Outline

• MS Overview (RWM)
• Scope of the Presentation: Mobility, Cognition, and Exercise (RWM)
• Exercise, Mobility, and Brain in MS (RWM)
• Break
• Exercise, Cognition, and Brain in MS (BMS)
• Translation of Research into Clinical Practice (RWM)
• Questions (Audience)
Meta-analysis I: Overview

Review Article

Effect of Exercise Training on Walking Mobility in Multiple Sclerosis: A Meta-Analysis

Erin M. Snook, MS, and Robert W. Motl, PhD

Objective. The study used meta-analytic procedures to examine the overall effect of exercise training interventions on walking mobility among individuals with multiple sclerosis. Methods. A search was conducted for published exercise training studies from 1960 to November 2007 using MEDLINE, PsychINFO, CINAHL, and Current Contents Plus. Studies were selected if they measured walking mobility, using instruments identified as acceptable walking mobility constructs and outcome measures for individuals with neurologic disorders, before and after an intervention that included exercise training. Results. Forty-two published articles were located and reviewed, and 22 provided enough data to compute effect sizes expressed as Cohen’s $d$. Sixty-six effect sizes were retrieved from the 22 publications with 600 multiple sclerosis participants and yielded a weighted mean effect size of $g = 0.19$ (95% confidence interval, 0.09-0.28). There were larger effects associated with supervised exercise training ($g = 0.32$), exercise programs that were less than 3 months in duration ($g = 0.28$), and mixed samples of relapsing-remitting and progressive multiple sclerosis ($g = 0.52$). Conclusions. The cumulative evidence supports that exercise training is associated with a small improvement in walking mobility among individuals with multiple sclerosis.
Meta-analysis I: Results

<table>
<thead>
<tr>
<th>Study name</th>
<th>Hedges's $g$</th>
<th>Standard error</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oken</td>
<td>-0.16</td>
<td>0.33</td>
<td>-0.81</td>
<td>0.50</td>
</tr>
<tr>
<td>Patti</td>
<td>-0.04</td>
<td>0.19</td>
<td>-0.41</td>
<td>0.33</td>
</tr>
<tr>
<td>Romberg_b</td>
<td>-0.04</td>
<td>0.21</td>
<td>-0.45</td>
<td>0.37</td>
</tr>
<tr>
<td>RasoVa</td>
<td>0.10</td>
<td>0.20</td>
<td>-0.30</td>
<td>0.50</td>
</tr>
<tr>
<td>Taylor</td>
<td>0.12</td>
<td>0.62</td>
<td>-1.08</td>
<td>1.33</td>
</tr>
<tr>
<td>Rampello</td>
<td>0.14</td>
<td>0.55</td>
<td>-0.95</td>
<td>1.22</td>
</tr>
<tr>
<td>AyanPerez</td>
<td>0.20</td>
<td>0.40</td>
<td>-0.57</td>
<td>0.98</td>
</tr>
<tr>
<td>Romberg_a</td>
<td>0.21</td>
<td>0.21</td>
<td>-0.20</td>
<td>0.62</td>
</tr>
<tr>
<td>Yates</td>
<td>0.24</td>
<td>0.65</td>
<td>-1.02</td>
<td>1.51</td>
</tr>
<tr>
<td>White</td>
<td>0.25</td>
<td>0.62</td>
<td>-0.96</td>
<td>1.46</td>
</tr>
<tr>
<td>vandenBerg</td>
<td>0.26</td>
<td>0.48</td>
<td>-0.67</td>
<td>1.20</td>
</tr>
<tr>
<td>Newman</td>
<td>0.30</td>
<td>0.48</td>
<td>-0.83</td>
<td>1.23</td>
</tr>
<tr>
<td>Kieff</td>
<td>0.32</td>
<td>0.66</td>
<td>-0.97</td>
<td>1.61</td>
</tr>
<tr>
<td>Rodgers</td>
<td>0.33</td>
<td>0.45</td>
<td>-0.55</td>
<td>1.22</td>
</tr>
<tr>
<td>Husted</td>
<td>0.34</td>
<td>0.44</td>
<td>-0.52</td>
<td>1.21</td>
</tr>
<tr>
<td>Gutierrez</td>
<td>0.36</td>
<td>0.62</td>
<td>-0.86</td>
<td>1.57</td>
</tr>
<tr>
<td>Petajan</td>
<td>0.38</td>
<td>0.29</td>
<td>-0.19</td>
<td>0.96</td>
</tr>
<tr>
<td>Schulz</td>
<td>0.42</td>
<td>0.32</td>
<td>-0.21</td>
<td>1.05</td>
</tr>
<tr>
<td>DeBolt</td>
<td>0.43</td>
<td>0.33</td>
<td>-0.22</td>
<td>1.08</td>
</tr>
<tr>
<td>Jones</td>
<td>0.47</td>
<td>0.61</td>
<td>-0.72</td>
<td>1.66</td>
</tr>
<tr>
<td>Bjarnadottir</td>
<td>0.62</td>
<td>0.50</td>
<td>-0.36</td>
<td>1.61</td>
</tr>
<tr>
<td>Freeman</td>
<td>0.73</td>
<td>0.59</td>
<td>-0.43</td>
<td>1.90</td>
</tr>
</tbody>
</table>

Figure 2
Funnel Plot of the 66 Effect Sizes from the 22 Published Studies Examining the Effects of Exercise Training on Walking Mobility
## Meta-analysis I: Results

<table>
<thead>
<tr>
<th>Categoric Moderator</th>
<th>Level of Moderator</th>
<th>Study References</th>
<th>Number of Effect Sizes</th>
<th>Average Effect Size (g)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>20, 27, 39</td>
<td>6</td>
<td>0.30</td>
<td>-0.20, 0.80</td>
</tr>
<tr>
<td></td>
<td>Male and female</td>
<td>10, 11, 20-26, 28-30, 32-38</td>
<td>57</td>
<td>0.19</td>
<td>0.09, 0.28</td>
</tr>
<tr>
<td>EDSS score</td>
<td>≤4.5</td>
<td>10, 11, 20-22, 24, 29, 30, 32-35, 38</td>
<td>33</td>
<td>0.18</td>
<td>0.05, 0.31</td>
</tr>
<tr>
<td></td>
<td>≥5.0</td>
<td>23, 29</td>
<td>4</td>
<td>0.04</td>
<td>-0.21, 0.29</td>
</tr>
<tr>
<td>MS duration</td>
<td>≤10 y</td>
<td>11, 20, 21, 25, 30, 33, 34, 36</td>
<td>18</td>
<td>0.17</td>
<td>0.02, 0.32</td>
</tr>
<tr>
<td></td>
<td>≥10 y</td>
<td>22, 23, 28, 29</td>
<td>16</td>
<td>0.18</td>
<td>0.00, 0.36</td>
</tr>
<tr>
<td>Type of MS</td>
<td>Relapsing-remitting</td>
<td>21, 24, 25</td>
<td>7</td>
<td>0.35</td>
<td>-0.09, 0.80</td>
</tr>
<tr>
<td></td>
<td>Progressive</td>
<td>10, 20, 29, 39</td>
<td>10</td>
<td>-0.04</td>
<td>-0.23, 0.15</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>22, 23, 26</td>
<td>4</td>
<td>0.52</td>
<td>0.08, 0.96</td>
</tr>
<tr>
<td>Walking aid</td>
<td>No aid used</td>
<td>21, 24, 33-36, 39</td>
<td>18</td>
<td>0.19</td>
<td>0.03, 0.35</td>
</tr>
<tr>
<td></td>
<td>All participants used aid</td>
<td>27</td>
<td>4</td>
<td>0.40</td>
<td>-0.26, 0.99</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>22, 25, 28, 32, 37</td>
<td>21</td>
<td>0.33</td>
<td>0.13, 0.54</td>
</tr>
<tr>
<td>Type of mobility measure</td>
<td>Quantitative</td>
<td>10, 20, 22-28, 30, 32, 34-39</td>
<td>50</td>
<td>0.24</td>
<td>0.12, 0.36</td>
</tr>
<tr>
<td></td>
<td>Functional</td>
<td>11, 21, 23, 27, 29, 31-33, 37, 38</td>
<td>16</td>
<td>0.11</td>
<td>-0.04, 0.25</td>
</tr>
<tr>
<td>Type of research design</td>
<td>Nonexperimental</td>
<td>20, 23, 24, 26-30, 32, 36-39</td>
<td>44</td>
<td>0.22</td>
<td>0.08, 0.36</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>10, 11, 21, 22, 25, 31, 33-35, 37</td>
<td>22</td>
<td>0.16</td>
<td>0.04, 0.29</td>
</tr>
<tr>
<td>Intervention setting</td>
<td>Home</td>
<td>22, 29</td>
<td>3</td>
<td>0.03</td>
<td>-0.22, 0.27</td>
</tr>
<tr>
<td></td>
<td>Exercise facility</td>
<td>11, 20, 21, 23-28, 30-32, 35-39</td>
<td>55</td>
<td>0.32</td>
<td>0.19, 0.44</td>
</tr>
<tr>
<td></td>
<td>Reth</td>
<td>10, 33, 34</td>
<td>8</td>
<td>0.02</td>
<td>-0.15, 0.29</td>
</tr>
<tr>
<td>Mode of exercise</td>
<td>Aerobic</td>
<td>10, 11, 27, 30-32, 35, 37</td>
<td>36</td>
<td>0.25</td>
<td>0.11, 0.39</td>
</tr>
<tr>
<td></td>
<td>Nonaerobic</td>
<td>10, 23, 26</td>
<td>5</td>
<td>0.27</td>
<td>-0.11, 0.64</td>
</tr>
<tr>
<td></td>
<td>Resistance</td>
<td>20, 22, 24, 25, 36, 38, 39</td>
<td>18</td>
<td>0.34</td>
<td>0.06, 0.62</td>
</tr>
<tr>
<td></td>
<td>Aerobic and resistance</td>
<td>21, 33, 34</td>
<td>5</td>
<td>0.09</td>
<td>-0.11, 0.29</td>
</tr>
<tr>
<td>Length of intervention</td>
<td>&lt;3 mon</td>
<td>20-26, 28, 30, 31, 35-38</td>
<td>45</td>
<td>0.28</td>
<td>0.15, 0.41</td>
</tr>
<tr>
<td></td>
<td>≥3 mon</td>
<td>10, 11, 27, 29, 32-34, 39</td>
<td>21</td>
<td>0.09</td>
<td>-0.03, 0.22</td>
</tr>
<tr>
<td>No. of sessions/week</td>
<td>&lt;3</td>
<td>23, 24, 26, 27, 31, 35, 36, 38, 39</td>
<td>25</td>
<td>0.28</td>
<td>0.11, 0.46</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>11, 20-22, 28, 30, 32-34, 37</td>
<td>34</td>
<td>0.23</td>
<td>0.10, 0.35</td>
</tr>
<tr>
<td>Minutes/session</td>
<td>0-30</td>
<td>22, 24, 27, 28, 31, 32, 35, 37, 38</td>
<td>37</td>
<td>0.32</td>
<td>0.17, 0.47</td>
</tr>
<tr>
<td></td>
<td>31-60</td>
<td>11, 20, 21, 23, 26, 30, 36</td>
<td>17</td>
<td>0.31</td>
<td>0.09, 0.52</td>
</tr>
<tr>
<td>Mode of aerobic exercise</td>
<td>Cycling</td>
<td>10, 11, 21, 27, 30-32, 35</td>
<td>21</td>
<td>0.22</td>
<td>0.05, 0.38</td>
</tr>
<tr>
<td></td>
<td>Treadmill</td>
<td>28, 37</td>
<td>16</td>
<td>0.31</td>
<td>0.06, 0.55</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale.
Meta-analysis II

Exercise as a Therapy for Improvement of Walking Ability in Adults With Multiple Sclerosis: A Meta-Analysis

Melissa Pearson, BSc Hons, Gudrun Dieberg, PhD, Neil Smart, PhD

From the University of New England, School of Science and Technology, Armidale, New South Wales, Australia.

Abstract
Objective: To quantify improvements in walking performance commonly observed in patients with multiple sclerosis (pwMS), a systematic literature search and meta-analysis were conducted quantifying the expected benefits of exercise on walking ability in pwMS.


Study Selection: Randomized controlled trials of exercise training in adult pwMS.

Data Extraction: Data on patient and study characteristics, walking ability, 10-m walk test (10mWT), timed 25-foot walk test (T25FW), 2-minute walk test (2MWT), 6-minute walk test (6MWT), and timed Up and Go (TUG) were extracted and archived.

Data Synthesis: Data from 13 studies were included. In pwMS who exercised, significant improvements were found in walking speed, measured by the 10mWT (mean difference [MD] reduction in walking time of −1.76 s; 95% confidence interval [CI], −2.47 to −1.06; P < .001), but no change in the T25FW (MD = −.59 s; 95% CI, −2.55 to 1.36; P = .55). In pwMS who exercised, significant improvements were found in walking endurance as measured by the 6MWT and 2MWT, with an increased walking distance of MD = 36.46 m (95% CI, 15.14−57.79; P < .001) and MD = 12.51 m (95% CI, 4.79−20.23; P = .001), respectively. No improvement was found for TUG (MD = −1.05 s; 95% CI, −2.19 to 0.09; P = .07).

Conclusions: Our meta-analysis suggests that exercise improves walking speed and endurance in pwMS.

Archives of Physical Medicine and Rehabilitation 2015;96:1339-48
Meta-analysis II: Study Selection

Records identified through database search (n = 659)

Additional records identified through other sources (n = 4)

Records after duplicates removed (n = 437)

Records screened (n = 437)

Full-text articles assessed for eligibility (n = 32)

Studies included in meta-analysis (n = 13)

Records excluded after reading Titles and Abstracts (n = 405)
Exclusions due to: reviews and analysis, Abstracts only, not an exercise intervention, not an RCT

Full-text articles excluded, with reasons (n = 19)
13 exclusions due to: outcome measures not meeting specified criteria, inappropriate mode of exercise sample size less than specified criteria, comparator studies with no “non-intervention” control
6 exclusion due to insufficient data to calculate effect size
## Meta-analysis II: Study Quality

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility Criteria Specified (No Point for This Criterion)</th>
<th>Random Allocation of Participants</th>
<th>Allocation Concealed</th>
<th>Groups Similar at Baseline</th>
<th>Assessors Blinded</th>
<th>Outcome Measures Assessed in 85% of Initially Allocated Participants</th>
<th>Intention-to-Treat Analysis</th>
<th>Reporting of Between-group Statistical Comparison</th>
<th>Point and Variability Measure Reported</th>
<th>Total Score Out of 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmadi et al., 2013</td>
<td>1</td>
<td>1</td>
<td>Unclear</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Cai et al., 2010</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Carter et al., 2014</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Dalgas et al., 2009</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>DeBolt et al., 2004</td>
<td>1</td>
<td>1</td>
<td>Unclear</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Dodd et al., 2011</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Geddes et al., 2009</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Larmoth et al., 2012</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Negahban et al., 2013</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Oken et al., 2004</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Romberg et al., 2004</td>
<td>1</td>
<td>1</td>
<td>Unclear</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Tarakci et al., 2013</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Van den Berg et al., 2006</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviation: PEDro, Physiotherapy Evidence Database.
Meta-analysis II: Results I

![Graph showing the mean difference in 10mWT (s) after exercise in pwMS. Abbreviations: A, aerobic; Comb, combined aerobic and resistance training; C-PRT, cycling and progressive resistance training; H, home exercise; IV, inverse variance; R, resistance training; Y, yoga.](image-url)
Meta-analysis II: Results II

**Fig 4**  Change in 6MWT (m) after exercise in pwMS. Abbreviations: A, aerobic; Comb, combined aerobic and resistance training; IV, inverse variance; R, resistance training.

**Fig 5**  Change in 2MWT (m) after exercise in pwMS. Abbreviations: A, aerobic; Comb, combined aerobic and resistance training; IV, inverse variance; R, resistance training; Y, yoga.
Is exercise working? YES

• But, can it work better? OF COURSE!
Better approach – Target sources, particularly in those who need it!

Stage 1

Multiple sclerosis → Physical inactivity → Physiological deconditioning

Stage 2

Physiological deconditioning → Mobility disability

Figure 1: The two-stage cycle of physical inactivity, physiological deconditioning, and walking impairment in persons with MS.
Physical Activity and Irreversible Disability in Multiple Sclerosis

Robert W. Motl
Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Urbana, IL

MOTL, R.W. Physical activity and irreversible disability in multiple sclerosis. Exerc. Sport Sci. Rev., Vol. 38, No. 4, pp. 186–191, 2010. Multiple sclerosis (MS) is a neurological disease that may result in the progressive worsening of disability. Recent research has identified physical activity as a behavioral correlate of disability in MS. The current review highlights that preclinical research has generally included samples with minimal disability and provides a rationale for considering physical activity as an influence of disability in the second stage of MS. Key Words: exercise, mobility, neurology, physiological function, walking

Figure 5. Multiple modes of exercise training and associated consequences for domains of physiological function and clinical outcomes.
Cross-sectional Data I

Relationships Among Physical Inactivity, Deconditioning, and Walking Impairment in Persons With Multiple Sclerosis

Brian M. Sandroff, MS, Rachel E. Klaren, BS, and Robert W. Motl, PhD

Figure 1. Cyclical model of physical inactivity, physiological deconditioning, and worsening of multiple sclerosis over time.
Cross-sectional Data II

Physical fitness, walking performance, and gait in multiple sclerosis

Brian M. Sandroff, Jacob J. Sosnoff, Robert W. Motl

University of Illinois at Urbana-Champaign, Department of Kinesiology and Community Health, United States

Abstract

Background: Walking impairment is a prevalent, life-altering feature of multiple sclerosis (MS). There has been recent speculation that physiological deconditioning (i.e., reductions in aerobic capacity, balance, and muscular strength) contributes to walking and gait impairments in MS.

Objective: This study examined the associations among aerobic capacity, balance, and lower-limb strength asymmetries, walking performance, and gait kinematics in 31 persons with MS and 31 matched controls.

Table 2

Correlations among fitness, walking, and gait variables for the overall (n = 62), MS (n = 31), and matched control (n = 31) samples.

<table>
<thead>
<tr>
<th>Variable</th>
<th>VO_{peak}</th>
<th>95% COP ellipse</th>
<th>KE asymmetry</th>
<th>KF asymmetry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall sample</td>
<td>MS</td>
<td>Controls</td>
<td>Overall sample</td>
</tr>
<tr>
<td>T25FW</td>
<td>-0.48*</td>
<td>-0.46*</td>
<td>-0.68*</td>
<td>.42*</td>
</tr>
<tr>
<td>6MW</td>
<td>.74*</td>
<td>.62*</td>
<td>.86*</td>
<td>-.44*</td>
</tr>
<tr>
<td>Velocity</td>
<td>.53*</td>
<td>.46*</td>
<td>.55*</td>
<td>-.32*</td>
</tr>
<tr>
<td>Cadence</td>
<td>.22*</td>
<td>.33*</td>
<td>-.01</td>
<td>-.23*</td>
</tr>
<tr>
<td>Step length</td>
<td>.60*</td>
<td>.49*</td>
<td>.61*</td>
<td>-.30*</td>
</tr>
<tr>
<td>Base of support</td>
<td>-.24*</td>
<td>-.33*</td>
<td>-.01</td>
<td>.30*</td>
</tr>
<tr>
<td>Double support</td>
<td>-.54*</td>
<td>-.56*</td>
<td>-.49*</td>
<td>.32*</td>
</tr>
</tbody>
</table>

Note: Pearson product-moment correlation coefficient (r).

VO_{peak} = peak aerobic capacity; COP = center of pressure; KE = knee extensor; KF = knee flexor; T25PW = timed 25-foot walk; 6MW = six minute walk.

* Denotes statistical significance at p < .05.
Cross-sectional Data II

a: T25FW performance

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>-1.082</td>
<td>0.391</td>
<td>-0.336*</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>-0.153</td>
<td>0.393</td>
<td>-0.047</td>
</tr>
<tr>
<td>VO₂peak</td>
<td>-0.064</td>
<td>0.023</td>
<td>-0.325*</td>
</tr>
<tr>
<td>Balance</td>
<td>0.111</td>
<td>0.060</td>
<td>0.224</td>
</tr>
<tr>
<td>KE asymmetry</td>
<td>0.037</td>
<td>0.014</td>
<td>0.284*</td>
</tr>
</tbody>
</table>

Note: $R^2 = .336$ for Step 1; $\Delta R^2 = .283$ for Step 2 ($p < .05$, two-tailed test).

*p < .05 with one-tailed test.

b: 6MW distance

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>450.097</td>
<td>92.542</td>
<td>0.532*</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>200.721</td>
<td>75.734</td>
<td>0.237*</td>
</tr>
<tr>
<td>VO₂peak</td>
<td>30.293</td>
<td>4.358</td>
<td>0.583*</td>
</tr>
<tr>
<td>Balance</td>
<td>-10.512</td>
<td>11.575</td>
<td>-0.081</td>
</tr>
<tr>
<td>KE asymmetry</td>
<td>-6.971</td>
<td>2.761</td>
<td>-0.201*</td>
</tr>
</tbody>
</table>

Note: $R^2 = .532$ for Step 1; $\Delta R^2 = .286$ for Step 2 ($p < .05$, two-tailed test).

*p < .05 with one-tailed test.

d: Step length

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Group</th>
<th>7.220</th>
<th>2.385</th>
<th>0.369*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>Group</td>
<td>2.879</td>
<td>2.272</td>
<td>0.147</td>
</tr>
<tr>
<td>VO₂peak</td>
<td>0.658</td>
<td>0.140</td>
<td>0.510*</td>
<td></td>
</tr>
<tr>
<td>Balance</td>
<td>-0.046</td>
<td>0.347</td>
<td>-0.015</td>
<td></td>
</tr>
<tr>
<td>KE asymmetry</td>
<td>-0.190</td>
<td>0.083</td>
<td>-0.238*</td>
<td></td>
</tr>
</tbody>
</table>

Note: $R^2 = .369$ for Step 1; $\Delta R^2 = .300$ for Step 2 ($p < .05$, two-tailed test).

*e < .05 with one-tailed test.

e: Base of support

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Group</th>
<th>-1.491</th>
<th>0.860</th>
<th>-0.222*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>Group</td>
<td>-0.454</td>
<td>0.985</td>
<td>-0.068</td>
</tr>
<tr>
<td>VO₂peak</td>
<td>-0.062</td>
<td>0.061</td>
<td>-0.141</td>
<td></td>
</tr>
<tr>
<td>Balance</td>
<td>0.222</td>
<td>0.151</td>
<td>0.217</td>
<td></td>
</tr>
<tr>
<td>KE asymmetry</td>
<td>0.011</td>
<td>0.036</td>
<td>0.040</td>
<td></td>
</tr>
</tbody>
</table>

Note: $R^2 = .222$ for Step 1; $\Delta R^2 = .124$ for Step 2 ($p < .05$, two-tailed test).

*f < .05 with one-tailed test.

f: Double support time

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Group</th>
<th>-1.994</th>
<th>1.051</th>
<th>-0.242*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>Group</td>
<td>0.069</td>
<td>1.050</td>
<td>0.008</td>
</tr>
<tr>
<td>VO₂peak</td>
<td>-0.255</td>
<td>0.065</td>
<td>-0.468*</td>
<td></td>
</tr>
<tr>
<td>Balance</td>
<td>0.172</td>
<td>0.160</td>
<td>0.137</td>
<td></td>
</tr>
<tr>
<td>KE asymmetry</td>
<td>0.056</td>
<td>0.038</td>
<td>0.166</td>
<td></td>
</tr>
</tbody>
</table>

Note: $R^2 = .242$ for Step 1; $\Delta R^2 = .339$ for Step 2 ($p < .05$, two-tailed test).

*g < .05 with one-tailed test.
Randomized Controlled Trial I

Resistance training improves muscle strength and functional capacity in multiple sclerosis

U. Dalén, PhD
E. Steenberg, MD
J. Jakobsen, MD
T. Petersen, MD
H.J. Hansen, MD
C. Knudsen, PT
K. Overgaard, PhD
T. Ingemann-Hansen, MD

ABSTRACT

Objective: To test the hypothesis that lower extremity progressive resistance training (PRT) can improve muscle strength and functional capacity in patients with multiple sclerosis (MS) and to show the effect of supervised PRT twice per week for 12 weeks.

Methods: Patients were randomized to either the exercise group (19 patients) or the control group (19 patients). The exercise group performed supervised PRT twice per week for 12 weeks, while the control group continued their usual activity. Muscle strength was measured using the knee extension/contraction (KE MVC) and functional capacity was measured using the Functional Scale (FS).

Results: The exercise group showed a significant improvement in muscle strength and functional capacity compared to the control group. The mean change in KE MVC was 15% in the exercise group and 2% in the control group (p < 0.05). The mean change in FS was 10 points in the exercise group and 2 points in the control group (p < 0.05).

Conclusion: Lower extremity progressive resistance training is an effective intervention to improve muscle strength and functional capacity in patients with multiple sclerosis.

Key words: Multiple sclerosis, Progressive resistance training, Muscle strength, Functional capacity

Figure 1: Flow chart showing patient inclusion

Figure 2: Effects of progressive resistance training on muscle strength and functional capacity

Data from the randomized trial including a post-1 patients with MS were 19. The exercise group afterward encouraged to intervention. Both groups

- Supervised PRT 2/wk over 12 wk
- Leg press, knee flex/ext, & hip flex/ext
Randomized Controlled Trial II

Multimodal exercise training in multiple sclerosis: A randomized controlled trial in persons with substantial mobility disability

Brian M. Sandroff\textsuperscript{a,1}, Rachel E. Bollaert\textsuperscript{b}, Lara A. Pilutti\textsuperscript{c}, Melissa L. Peterson\textsuperscript{d}, Tracy Baynard\textsuperscript{e}, Bo Fernhall\textsuperscript{f}, Edward McAuley\textsuperscript{b}, Robert W. Motl\textsuperscript{a,1,2}

\textsuperscript{a} University of Alabama at Birmingham, Department of Physical Therapy, United States
\textsuperscript{b} University of Illinois at Urbana-Champaign, Department of Kinesiology and Community Health, United States
\textsuperscript{c} University of Ottawa, Interdisciplinary School of Health Sciences, Canada
\textsuperscript{d} Bradley University, Department of Physical Therapy and Health Science, United States
\textsuperscript{e} University of Illinois at Chicago, Integrative Physiology Laboratory, Department of Kinesiology & Nutrition, United States

Table 1
Baseline demographic and clinical characteristics of 83 persons with multiple sclerosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention (N = 43)</th>
<th>Control (N = 40)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.8 (8.5)</td>
<td>51.2 (8.7)</td>
<td>0.47</td>
</tr>
<tr>
<td>Sex (n, % female)</td>
<td>36/43 (83.7%)</td>
<td>35/40 (87.5%)</td>
<td>0.63</td>
</tr>
<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>29.2 (10.1)</td>
<td>31.2 (7.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>PDDS (median, IQR)</td>
<td>4.0 (2.0)</td>
<td>3.0 (2.0)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Note: All data presented as mean (SD) unless otherwise noted; BMI = body mass index; PDDS = Patient-determined disease steps.

Fig. 1. CONSORT diagram for multimodal exercise training intervention.
## Randomized Controlled Trial II

Table 3

Mobility, gait, physical fitness, and cognitive processing speed outcomes in 62 persons with multiple sclerosis (per protocol analysis).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention (N = 32)</th>
<th>Control (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Mid-point</td>
</tr>
<tr>
<td>6MW (ft)</td>
<td>1057.6 (554.6)</td>
<td>1143.4 (591.4)</td>
</tr>
<tr>
<td>T25FW (ft/s)</td>
<td>3.6 (1.9)</td>
<td>3.8 (1.9)</td>
</tr>
<tr>
<td>MSWS-12</td>
<td>62.9 (26.0)</td>
<td>53.1 (23.5)</td>
</tr>
<tr>
<td>Gait</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAP</td>
<td>80.3 (19.6)</td>
<td>84.1 (19.1)</td>
</tr>
<tr>
<td>Velocity (cm/s)</td>
<td>89.3 (38.0)</td>
<td>92.9 (38.5)</td>
</tr>
<tr>
<td>Cadence (steps/min)</td>
<td>95.4 (19.2)</td>
<td>96.2 (21.5)</td>
</tr>
<tr>
<td>Step time (s)</td>
<td>0.66 (0.16)</td>
<td>0.66 (0.17)</td>
</tr>
<tr>
<td>Step length (cm)</td>
<td>54.4 (15.9)</td>
<td>55.9 (15.6)</td>
</tr>
<tr>
<td>Physical fitness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO$_{2\text{peak}}$ (ml/kg/min)</td>
<td>17.4 (6.7)</td>
<td>17.3 (5.7)</td>
</tr>
<tr>
<td>Peak power (W)</td>
<td>84.3 (40.1)</td>
<td>97.8 (41.8)</td>
</tr>
<tr>
<td>KE peak torque (Nm)</td>
<td>125.8 (43.3)</td>
<td>138.0 (46.9)</td>
</tr>
<tr>
<td>KF peak torque (Nm)</td>
<td>52.3 (18.8)</td>
<td>56.9 (21.4)</td>
</tr>
<tr>
<td>Cognitive processing speed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDMT (raw score)</td>
<td>45.8 (11.3)</td>
<td>47.5 (9.6)</td>
</tr>
<tr>
<td>3’ PASAT (raw score)</td>
<td>43.0 (11.2)</td>
<td>45.0 (11.4)</td>
</tr>
</tbody>
</table>

Note: all data presented as mean (SD); 6MW = six-minute walk; T25FW = timed 25-foot walk; MSWS-12 = Multiple Sclerosis Walking Scale-12; FAP = Functional Ambulation Profile; VO$_{2\text{peak}}$ = peak oxygen consumption; KE = knee extensor; KF = knee flexor; SDMT = Symbol Digit Modalities Test; PASAT = Paced Auditory Serial Addition Test.
MRI and Mobility

Pallidal and caudate volumes correlate with walking function in multiple sclerosis


1 Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, USA
2 Department of Biomechanics, University of Illinois at Urbana-Champaign, USA
3 Department of Neurology, University at Buffalo, State University of NY, School of Medicine and Biomedical Sciences, USA

Table 1
Bivariate correlations among walking performance and MRI outcomes in 61 patients with multiple sclerosis.

<table>
<thead>
<tr>
<th></th>
<th>6 MW</th>
<th>T25FW</th>
<th>Thalamus</th>
<th>Caudate</th>
<th>Pallidum</th>
<th>Putamen</th>
<th>Whole-brain WM</th>
<th>Whole-brain GM</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 MW</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T25FW</td>
<td>.936**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>.382**</td>
<td>.383**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate</td>
<td>.388**</td>
<td>.416**</td>
<td>.753**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pallidum</td>
<td>.457**</td>
<td>.457**</td>
<td>.822**</td>
<td>.856**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>.258*</td>
<td>.293*</td>
<td>.757**</td>
<td>.789**</td>
<td>.769**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-brain WM</td>
<td>.371**</td>
<td>.378**</td>
<td>.823**</td>
<td>.633**</td>
<td>.765**</td>
<td>.680**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-brain GM</td>
<td>.260*</td>
<td>.219</td>
<td>.677**</td>
<td>.602**</td>
<td>.638**</td>
<td>.504**</td>
<td>.702**</td>
<td></td>
</tr>
</tbody>
</table>

Note. 6 MW = six-minute walk; T25FW = timed 25-foot walk test; WM = white matter; and GM = gray matter.
* p < .05.
** p < .01.

Table 2
Partial correlations among walking performance and deep gray matter MRI outcomes in 61 patients with multiple sclerosis.

<table>
<thead>
<tr>
<th></th>
<th>6 MW</th>
<th>T25FW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>.108</td>
<td>.128</td>
</tr>
<tr>
<td>Caudate</td>
<td>.243**</td>
<td>.312**</td>
</tr>
<tr>
<td>Pallidum</td>
<td>.321**</td>
<td>.345**</td>
</tr>
<tr>
<td>Putamen</td>
<td>.034</td>
<td>.096</td>
</tr>
</tbody>
</table>

Note. Analysis controlled for age, MS clinical course, and whole-brain white and gray matter volumes. 6 MW = six-minute walk; and T25FW = timed 25-foot walk test.
* p < .05.
** p < .01.
MRI and Fitness Domains

Cardiorespiratory fitness and its association with thalamic, hippocampal, and basal ganglia volumes in multiple sclerosis

Robert W. Motl\textsuperscript{a}\textsuperscript{*}, Lara A. Pilutti\textsuperscript{a}, Elizabeth A. Hubbard\textsuperscript{a}, Nathan C. Wetter\textsuperscript{b}, Jacob J. Sosnow\textsuperscript{a}, Bradley P. Sutton\textsuperscript{b}

\textsuperscript{a}Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, IL, USA
\textsuperscript{b}Department of Bioengineering, University of Illinois at Urbana-Champaign, IL, USA

Table 1
Descriptive statistics for cardiorespiratory fitness (ml/kg/min) and scaled composite volumes (mm\textsuperscript{3}) of the thalamus, hippocampus, and basal ganglia in 35 people with multiple sclerosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall sample (n = 35)</th>
<th>MS clinical course</th>
<th>Disability status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RRMS (n = 26)</td>
<td>Progressive MS (n = 9)</td>
</tr>
<tr>
<td>VO\textsubscript{2peak}</td>
<td>17.6 (6.8)</td>
<td>18.2 (7.3)</td>
<td>15.8 (4.9)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>8581 (1216)</td>
<td>8574 (1253)</td>
<td>8600 (1181)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>4339 (702)</td>
<td>4251 (714)</td>
<td>4583 (641)</td>
</tr>
<tr>
<td>Caudate</td>
<td>3898 (740)</td>
<td>3866 (806)</td>
<td>3986 (545)</td>
</tr>
<tr>
<td>Pallidum</td>
<td>1829 (315)</td>
<td>1828 (348)</td>
<td>1832 (214)</td>
</tr>
<tr>
<td>Putamen</td>
<td>5181 (920)</td>
<td>5157 (945)</td>
<td>5249 (897)</td>
</tr>
</tbody>
</table>

Note. Values are mean (standard deviation). MS = multiple sclerosis; RRMS = relapsing–remitting MS; EDSS = Expanded Disability Status Scale; VO\textsubscript{2peak} = peak oxygen consumption.
MRI and Fitness Domains
Pulling it ALL Together

**Figure 1.** Model for possible cognitive and exercise rehabilitation effects on cognition and walking in multiple sclerosis.
Outline

• MS Overview (RWM)
• Scope of the Presentation: Mobility, Cognition, and Exercise (RWM)
• Exercise, Mobility, and Brain in MS (RWM)
• Break
• Exercise, Cognition, and Brain in MS (BMS)
• Translation of Research into Clinical Practice (RWM)
• Questions (Audience)
Outline

• MS Overview (RWM)
• Scope of the Presentation: Mobility, Cognition, and Exercise (RWM)
• Exercise, Mobility, and Brain in MS (RWM)
• Break
• Exercise, Cognition, and Brain in MS (BMS)
• Translation of Research into Clinical Practice (RWM)
• Questions (Audience)
Why Exercise and Cognition in MS?

• “Cells-to-society” approach:
  • Animal work
  • Children, healthy adults, older adults
  • Neurological populations (e.g., schizophrenia)\(^1\)

• Early data on exercise effects on the brain in neurological populations:
  • Cognitive and motor domains are interrelated whereby targeted interventions may improve both domains of function\(^2\)
  • Effects of exercise on cognitive functioning in persons with MS

\(^1\) Pajonk et al., 2011; \(^2\) Benedict et al., 2011;
Exercise and Cognition in MS

- Systematic Review: Exercise, physical activity (PA), and physical fitness effects on cognition in MS

- Purpose: To accurately describe current status of the field, offer recommendations for clinicians, and identify study-specific and participant-specific characteristics for providing future direction for ongoing MS research

- Performed open-dated search of Medline, PsycInfo, and CINAHL in December 2015

- Final analysis included 26 studies of exercise training, acute exercise, PA, physical fitness and neuropsychological test outcomes in persons with MS

---

3 Sandroff et al., 2016, *Neuropsychol Rev*

- N=9 studies\(^{4-12}\)
- 5/9 RCTs

### Table 6

<table>
<thead>
<tr>
<th>Study</th>
<th>Fitness Results</th>
<th>Cognition Results</th>
<th>Fitness/Cognition Association</th>
<th>AAM Classification of Evidence</th>
<th>PEDro Scale Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olken et al. 2004</td>
<td>NA</td>
<td>NS intervention effects on any cognitive outcome (all (p &gt; .05)), ES NR</td>
<td>NA</td>
<td>I</td>
<td>7/10</td>
</tr>
<tr>
<td>Kernberg et al. 2006</td>
<td>NA</td>
<td>NS intervention effects on PASAT z-score ((p = .09), \text{ES NR})</td>
<td>NA</td>
<td>I</td>
<td>5/10</td>
</tr>
<tr>
<td>Velikonja et al. 2010</td>
<td>NA</td>
<td>NS intervention effects context of ATT and EF (all (p &gt; .10)); NS intervention effects on EF ((p &gt; .05)) Between-group analysis; NR; ES NR</td>
<td>NA</td>
<td>III</td>
<td>NA</td>
</tr>
<tr>
<td>Pilutti et al. 2011</td>
<td>NA</td>
<td>NS intervention effects on PASAT z-score ((p = 64, d = 0.12))</td>
<td>NA</td>
<td>IV</td>
<td>NA</td>
</tr>
<tr>
<td>Carter et al. 2013</td>
<td>NA</td>
<td>NS intervention effects on PASAT at 12 weeks ((p = .03)) and 6 months ((p = .10)); ES NR</td>
<td>NA</td>
<td>II</td>
<td>5/10</td>
</tr>
<tr>
<td>Sjogren et al. 2013</td>
<td>NA</td>
<td>NS effects of either acute aerobic EX or resistance EX on PASAT; ES between-group differences in EX and BASC</td>
<td>NA</td>
<td>IV</td>
<td>NA</td>
</tr>
<tr>
<td>Biken et al. 2014</td>
<td>Significance improvements in (V_{O2,peak}) for cycle ergometer group only ((p &lt; .01)), ES NR</td>
<td>Significant improvements in all 3 EX groups compared with CON ((p &lt; .01)), ES NR; Test Battery of ATT performance significantly improved in cycle ergometer group only compared with CON ((p &lt; .01)), ES NR</td>
<td>Significant, mild-to-moderate associations between improvement in (V_{O2,peak}) and Vertical LM Test performance; ES NR</td>
<td>III</td>
<td>7/10</td>
</tr>
<tr>
<td>Leavitt et al. 2014</td>
<td>EX participant demonstrated 10% increase in (V_{O2,peak}), ES NR</td>
<td>EX participant demonstrated 55% increase in CVLT-II scores, 51% increase in DMT-R score; no changes for CON; ES NR</td>
<td>NA</td>
<td>IV</td>
<td>NA</td>
</tr>
<tr>
<td>Hoang et al. 2016</td>
<td>NA</td>
<td>NS intervention effects on TMT ((d = 0.13, p = .20)), TMT ((d = 0.14, p = .60))</td>
<td>NA</td>
<td>II</td>
<td>R/10</td>
</tr>
<tr>
<td>Sandhoff et al. 2015a</td>
<td>NA</td>
<td>Largely significant pre-to-post improvements in PS based on modified flanker task performance for all 3 EX conditions relative to CON ((\text{ES} = .34, p &lt; .01))</td>
<td>NA</td>
<td>II</td>
<td>NA</td>
</tr>
<tr>
<td>Sandhoff et al. 2015b</td>
<td>NA</td>
<td>No significant pre-to-post improvements in EF based on modified flanker task performance for TM walking only relative to CON ((\text{ES} = .34, p &lt; .01))</td>
<td>NA</td>
<td>II</td>
<td>NA</td>
</tr>
<tr>
<td>Sandhoff et al. 2016</td>
<td>NA</td>
<td>Large, significant pre-to-post improvements in FS and EF based on modified flanker task performance for all 3 TM conditions ((\text{ES} = .34, p &lt; .01))</td>
<td>NA</td>
<td>II</td>
<td>NA</td>
</tr>
</tbody>
</table>

\(^{4}\) Oken et al., 2004; \(^{5}\) Romberg et al., 2005; \(^{6}\) Velikonja et al., 2010; \(^{7}\) Pilutti et al., 2011; \(^{8}\) Carter et al., 2013; \(^{9}\) Briken et al., 2014; \(^{10}\) Leavitt et al., 2014; \(^{11}\) Hoang et al., 2015; \(^{12}\) Sangelaji et al., 2015;
First RCT of Exercise on Cognition in MS

• 26-weeks of aerobic exercise vs. yoga vs. waitlist control condition on cognition in 57 persons with MS

• Aerobic exercise stimulus:
  • 1x/wk, 90-min/session of partially supervised cycle ergometry at very light intensity + optional Swiss ball exercise; home exercise encouraged

• Iyengar yoga:
  • 1x/wk, 90-min/session; home exercise encouraged

• Primary outcome measures:
  • Neuropsychological measures of attention, executive function, learning and memory, and cognitive processing speed
First RCT of Exercise on Cognition in MS⁴

• **Primary results:**
  • Non-significant intervention effects for any cognitive measure

• **Observations:**
  • Unsupervised exercise
  • Lack of fitness outcome assessments
  • Low intensity exercise stimulus
  • Exercise program not selectively developed for improving cognition
  • Did not recruit cognitively-impaired persons with MS *a priori*
Exemplar RCTs with Cognition as Non-Primary Outcome

• Romberg et al., 2005\(^5\):
  • 26-weeks of home-based combined aerobic and resistance exercise training vs. waitlist control on functional outcomes in 91 persons with MS

  • Exercise stimulus:
    • 5 resistance training sessions and 5 aerobic exercise training sessions over the first 3-weeks of the trial

    • Home-based exercise prescription (designed to take place 3-4x/wk) for next 23 weeks

  • Primary outcome measures:
    • “Function” based on MSFC (i.e., T25FW; 9HPT; 3-second PASAT)

  • **Primary results:** Non-significant intervention effects on PASAT
Exemplar RCTs with Cognition as Non-Primary Outcome

• Carter et al., 2013\textsuperscript{8}:
  • 12-weeks of ‘pragmatic’ exercise program vs. usual care control condition on general health related outcomes in 120 persons with MS

  • Exercise stimulus:
    • Weeks 1-6: 2x/week, 60-min/session supervised, combined aerobic and resistance exercise (RPE of 12-14), with additional prescription of 1x/week home-based exercise
    • Weeks 7-12: 1x/week, 60-min/session supervised exercise, with additional prescription of 2x/week home-based exercise

  • Primary outcome measures:
    • Self-reported exercise behavior based on GLTEQ; PASAT from MSFC as secondary outcome

  • Primary results: Non-significant intervention effects on PASAT
Exemplar RCTs with Cognition as Non-Primary Outcome

- Observations across both studies:
  - Cognition not primary outcome — PASAT as ‘general’ test of processing speed as part of MSFC
  - Largely unsupervised exercise
  - No manipulation check of fitness
  - Not designed for specifically improving cognition
  - Did not recruit cognitively-impaired participants \textit{a priori}
Focused RCT of Exercise and Cognition in MS

• Briken et al., 2014\textsuperscript{9}
  • 8-10 weeks of supervised aerobic exercise training versus waitlist control condition on cardiorespiratory fitness and cognitive outcomes in 42 persons with progressive MS

• Exercise stimuli:
  • Arm ergometry, rowing, cycle ergometry groups
    • 2-3x/week, 15-45 mins/session at a moderate intensity

• Primary outcome measures:
  • Cardiorespiratory fitness based on VO$_{\text{2peak}}$
  • Cognition was \textit{a priori} secondary outcome:
    • Neuropsychological tests of attention, executive function, learning and memory, cognitive processing speed, and verbal fluency
Focused RCT of Exercise and Cognition in MS

• Primary results:
  • Verbal memory improved for all 3 exercise groups relative to control ($p=.01$)
  • Alertness improved only for cycle ergometry and rowing groups relative to control
  • Cardiorespiratory fitness improvements for cycle ergometry only
  • Change in cardietorespiratory fitness explained 16% of variance in verbal memory and alertness for cycle ergometry group
Focused RCT of Exercise and Cognition in MS

• Observed strengths:
  • Cognition *a priori* secondary outcome
  • Larger neuropsychological battery
  • Supervised exercise training
  • Fitness manipulation check
  • Progressive MS

• Observed limitations:
  • Small samples per group (underpowered?)
  • Did not recruit cognitively-impaired participants *a priori*
  • Exercise stimulus issues?
    • Prescription based on aerobic threshold
    • Variable intervention duration
    • 2/3 intervention arms did not improve cardiorespiratory fitness
Other Exercise Training Studies on Cognition in MS

- Effects of sports climbing vs. yoga on cognition\textsuperscript{6}:
  - Yoga-related improvements in selective attention; primary study outcomes unclear

- Effects of body-weight supported treadmill training on functional outcomes in progressive MS\textsuperscript{7}:
  - No effects on PASAT; no control condition

- Effects of combined aerobic, balance, and flexibility exercise on cognition in MS\textsuperscript{12}:
  - Apparent effects on long-term memory; magnitude of effects unclear

- Limited experimental designs, non-cognitively impaired samples, no fitness manipulation check, unclear effects of interventions, limited neurocognitive batteries
Exercise Training and Cognition in MS

- Collectively, conflicting evidence for exercise training effects on cognition in MS

- At this time, cannot provide recommendations for clinical practice
  - 4/9 studies support exercise training for improving cognition
  - 5/9 studies do not support exercise training for improving cognition

- Emerging themes across studies:
  - Cognition as non-primary outcome
  - No *a priori* recruitment of cognitively-impaired persons with MS
  - Heterogeneous interventions/exercise stimuli
  - Heterogeneous neuropsychological outcome measures
  - Poor experimental designs
Acute Exercise and Cognition in MS (2014-2016)

- N=3 studies\textsuperscript{13-15}; all involved within-subjects, repeated-measures designs

- Acute effects of cycling exercise and upper/lower extremity resistance exercise on core body temperature and symptom intensity\textsuperscript{13}
  - No acute exercise-related changes in PASAT for either condition

- Acute effects of different modalities\textsuperscript{14} and intensities\textsuperscript{15} of exercise on cognition

\textsuperscript{13} Skjerbaek et al., 2014; \textsuperscript{14} Sandroff et al., 2015, \textit{J Clin Exp Neuropsychol}; \textsuperscript{15} Sandroff et al., 2016, \textit{Physiol Behav}
Acute Exercise and Cognition in MS

• Collectively, conflicting evidence for acute exercise effects on cognition in MS

• At this time, cannot provide recommendations for Clinical Practice
  • 2/3 studies support acute exercise for improving cognition
  • 1/3 studies does not support acute exercise for improving cognition

• Emerging themes across studies:
  • Limited neurocognitive batteries*
  • Did not recruit cognitively impaired samples a priori
Physical Activity and Cognition in MS (2011-2014)

- N=6 studies\(^{16-21}\)
- 1/6 RCT

### Table 4: Summary table of study characteristics for reviewed evidence of physical activity effects on cognition in persons with MS

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>CON Condition</th>
<th>PA</th>
<th>Study Duration</th>
<th>Cognitive Domains/Tests</th>
<th>Cognition Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motl et al. 2011(^{a})</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>Accelerometer-measured, free-living PA, over a 7-day period (average steps/day)</td>
<td>1 time point</td>
<td>LTM: SRT, BV/TER, PS, PASAT, SDMT: Episode Memory: Item and Relational Memory Task</td>
<td>No</td>
</tr>
<tr>
<td>Prakash et al. 2011</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>Accelerometer-measured, free-living PA over a 7-day period (average activity counts/day)</td>
<td>1 time point</td>
<td>ATE: MUSC, Long-Term Memory: MUSC NP battery PS, PASAT, oral SDMT, written SDMT</td>
<td>No</td>
</tr>
<tr>
<td>Waschbisch et al. 2012</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>Self-reported PA based on Baseline questionnaire</td>
<td>1 time point</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sandroff et al. 2013*</td>
<td>Pre-Post</td>
<td>N/A</td>
<td>Accelerometer-measured, free-living PA over a 7-day period (average steps/day) at baseline and 26 weeks later, without intervention</td>
<td>26 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sandroff et al. 2014a</td>
<td>Cross-sectional</td>
<td>N/A</td>
<td>Accelerometer-measured, free-living PA over a 7-day period (average steps/day)</td>
<td>1 time point</td>
<td>PS: PASAT, SDMT</td>
<td>Yes</td>
</tr>
<tr>
<td>Sandroff et al. 2014b*</td>
<td>RCT</td>
<td>Waitlist</td>
<td>SCT-based, internet-delivered behavioral intervention for increasing ambulatory PA (measured using self-report [IPAQ] and pedometer [steps/day])</td>
<td>24 weeks</td>
<td>PS: SDMT</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Denotes different analyses from the same dataset.

\(^{16}\) Motl et al., 2011; \(^{17}\) Prakash et al., 2011; \(^{18}\) Waschbisch et al., 2012; \(^{19}\) Sandroff et al., 2013, *Ment Health Phys Act*; \(^{20}\) Sandroff et al., 2014a, *Mult Scler Relat Disord*; \(^{21}\) Sandroff et al., 2014b, *J Neurol*;
RCT of Physical Activity and Cognition in MS\textsuperscript{21}

• 26 weeks of an Internet-based behavioral physical activity intervention vs. a waitlist control condition on cognitive processing speed and walking endurance outcomes in 76 persons with MS

• Intervention condition:
  • Visiting a study website based on SCT, wearing a pedometer, completing a logbook, using computerized software for guiding goal-setting and attainment, participating in 1-on-1 video chats with behavior-change coaches
RCT of Physical Activity and Cognition in MS\textsuperscript{21}

- **Primary results:**
  - Statistically significant improvements in processing speed based on SDMT scores for persons with mild, but not moderate MS ambulatory disability for intervention versus control condition
  - Changes in objectively-measured PA associated with changes in SDMT

- **Observations:**
  - Intervention designed \textit{a priori} for improving PA behavior
  - Lack of comprehensive neurocognitive battery
  - Passive control condition
  - Non-cognitively impaired sample

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig2.png}
\caption{SDMT scores based on condition and disability in 76 persons with multiple sclerosis}
\end{figure}
Other Studies of Physical Activity and Cognition in MS

• Cross-sectional studies \(^\text{16-18,20}\)  
  • Physical activity associated with processing speed, but not learning and memory in persons with MS

• Prospective, longitudinal study\(^\text{19}\)  
  • Baseline physical activity associated with cognitive processing speed 6 months later in persons with mild, but not moderate MS ambulatory disability

• Noteworthy observations:
  • Not interventional studies
  • PA measured objectively with accelerometers, and subjectively with self-report
  • No comprehensive neuropsychological batteries
  • Lack of cognitively-impaired samples
Physical Activity and Cognition in MS

• Collectively, preliminary support for beneficial physical activity effects on cognition in MS

• At this time, insufficient evidence to definitively support clinical utility of physical activity for selectively improving cognition in MS
  • Lack of a Class I RCT
  • 4/6 studies support PA for improving cognition
  • 2/6 studies do not support PA for improving cognition

• Overall observations:
  • Most studies included cognition as a primary outcome
  • Only 1 interventional study
  • No studies measured executive function outcomes

- N=8 studies
- N=3 Cross-sectional, comparative studies
- N=4 Cross-sectional studies in MS only
- N=1 Retrospective, longitudinal study in MS only

Based on definition of physical fitness, no RCTs

Cross-Sectional Comparative Studies\textsuperscript{23,25,29} 

- Associations between domains of physical fitness and cognition in MS compared with healthy controls:
  
  - Overall, significant group differences in cardiorespiratory fitness\textsuperscript{23,25,29}, lower extremity muscular strength\textsuperscript{25}, balance\textsuperscript{25}, cognitive processing speed\textsuperscript{23,25,29}, and inhibitory control\textsuperscript{29}

  - Within MS samples:
    - Better fitness significantly associated with faster processing speed ($|r| = .39-.52$)\textsuperscript{23,25,29}, but not learning and memory\textsuperscript{23}, verbal fluency\textsuperscript{23}, or executive function\textsuperscript{23,29}

  - Better fitness explained group differences in processing speed ($R^2=.39$)\textsuperscript{29}
Cross-Sectional Studies\textsuperscript{22,24,27,28}

- Associations between domains of physical fitness and cognition in MS only:
  - Higher cardiorespiratory fitness\textsuperscript{22,27} and better lower-extremity muscular strength\textsuperscript{27} significantly associated with faster cognitive processing speed in persons with mild MS ambulatory disability ($r = .35-.42$)
  - Non-significant associations between cardiorespiratory\textsuperscript{22,27} and muscular\textsuperscript{27} fitness and learning and memory\textsuperscript{22,27}, verbal fluency\textsuperscript{22}, or executive function\textsuperscript{22} overall or in persons with substantial MS disability\textsuperscript{27}

- Conflicting evidence for association between body composition and cognition
  - 1 study reported significant associations between bone mineral density (DEXA) and learning and memory\textsuperscript{24}, whereas another\textsuperscript{28} did not
Physical Fitness and Cognition in MS

• Collectively, preliminary support for beneficial physical fitness effects on cognition in MS
  • Primarily based on associations between cardiorespiratory fitness and cognitive processing speed

• At this time, not enough high-level evidence to definitively support clinical utility of physical fitness for selectively improving cognition in MS
  • Implications for exercise training studies on cognition in MS
    • 7/8 studies report significant associations between fitness and cognition
    • 1/8 studies report no significant fitness/cognition associations

• Observations:
  • All fitness studies included cognition as primary outcome
  • Lack of cognitively-impaired samples
Overall Summary of Systematic Review

• Field is in its infancy, data on effects of exercise, PA, and fitness on cognition in MS are promising

• However, such behavioral approaches are not ready for clinical application (yet)

• Overarching limitations of the field:
  • Cognition often not examined as primary outcome (56% of the time for exercise training!)
  • Inclusion of non-cognitively impaired samples
  • Few high-level RCTs
  • Lack of fitness outcomes as a manipulation check
  • Poorly-designed interventions
Systematic Review: Cognition as a Primary Outcome

Summary of exercise, physical activity, and physical fitness effects on cognition in persons with MS based on inclusion of cognition as a primary or non-primary outcome.
Systematic Review: Classes of Evidence

Summary of exercise, physical activity, and physical fitness effects on cognition in persons with MS based on class of evidence

<table>
<thead>
<tr>
<th>Class of Evidence</th>
<th>Exercise</th>
<th>Physical Activity</th>
<th>Physical Fitness</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Positive</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
What About the Brain?

• Importance of examining neuroimaging outcomes in addition to cognitive outcomes

• N=7 studies\textsuperscript{10,17,22,23,30-32} examining the effects of exercise, PA, or physical fitness on brain neuroimaging outcomes in persons with MS
  • N=4 exercise training
  • N=1 physical activity
  • N=2 physical fitness

\textsuperscript{30} Feys et al., 2017; \textsuperscript{31} Sandroff et al., 2017, \textit{Neuroradiology}; \textsuperscript{32} Sandroff et al., 2018, \textit{Mult Scler Exp Trans Clin}
Exercise, Cognition, and Brain in MS

• Hippocampus:

  • Aerobic exercise related improvements in learning and memory\textsuperscript{10,30,31}, hippocampal volume, resting-state functional connectivity\textsuperscript{10}, and viscoelastic properties\textsuperscript{31}

  • Change in learning and memory associated with change in hippocampal neuroimaging outcomes\textsuperscript{31}
Exercise, Cognition, and Brain in MS

• Thalamus:
  
  • Aerobic exercise-related improvements in cognitive processing speed and resting-state functional connectivity between the thalamus and frontal lobe regions (i.e., superior frontal gyrus, medial frontal gyrus)\(^32\)
  
  • Changes in brain function associated with change in processing speed\(^32\)
Physical Activity, Cognition, and Brain in MS

• Hippocampus:
  • Objectively-measured physical activity associated with increased resting state functional connectivity between hippocampus and posterior medial cortex
  • No association between PA and relational memory in this study

Fig. 1. Presents the right and left hippocampal masks segmented for a representative subject using FIRST. For each participant, the center of gravity in these masks was calculated to create a 10-mm sphere around it. This 10-mm sphere, presented here in white, was used as the seed of interest in the functional connectivity analyses. All images are presented in radiological orientation: R = L, L = R.
Physical Fitness, Cognition, and Brain in MS

- **Brain Structure**
  - Higher cardiorespiratory fitness associated with faster cognitive processing speed, greater grey matter volume in midline brain structures, and better white matter integrity in midbrain structures

- **Brain Function**
  - Higher cardiorespiratory fitness associated with faster cognitive processing speed and increased activation of right inferior frontal gyrus/medial frontal gyrus and decreased activation of anterior cingulate cortex during executive function task

- No associations between fitness, other cognitive domains, and brain structure/function
Since the Systematic Review...

- N=12 studies on exercise, physical activity, physical fitness, cognition in MS

<table>
<thead>
<tr>
<th>Construct</th>
<th>Study</th>
<th>Primary Outcome</th>
<th>Cognitively-Impaired Sample</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise Training</td>
<td>Kueuk et al., 2016</td>
<td>-</td>
<td>-</td>
<td>Mixed</td>
</tr>
<tr>
<td></td>
<td>Kierkegaard et al., 2016</td>
<td>-</td>
<td>-</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Sandroff et al., 2016</td>
<td>X</td>
<td>-</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Feys et al., 2017</td>
<td>-</td>
<td>-</td>
<td>Mixed</td>
</tr>
<tr>
<td></td>
<td>Gonzalez et al., 2017</td>
<td>-</td>
<td>-</td>
<td>Mixed</td>
</tr>
<tr>
<td></td>
<td>Sandroff et al., 2017a</td>
<td>X</td>
<td>-</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Sandroff et al., 2017b</td>
<td></td>
<td>-</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Zimmer et al., 2017</td>
<td>-</td>
<td>-</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Sandroff et al., 2018</td>
<td>X</td>
<td>X</td>
<td>Positive</td>
</tr>
<tr>
<td>Acute Exercise</td>
<td>Sandroff et al., 2015</td>
<td>X</td>
<td>-</td>
<td>Positive</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>Coote et al., 2017</td>
<td>-</td>
<td>-</td>
<td>Negative</td>
</tr>
<tr>
<td>Physical Fitness</td>
<td>Sandroff et al., 2017</td>
<td>X</td>
<td>X</td>
<td>Positive</td>
</tr>
</tbody>
</table>

33 Kueuk et al., 2016; 34 Kierkegaard et al., 2016; 35 Sandroff et al., 2016, Neurocase; 36 Gonzalez et al., 2017; 37 Sandroff et al., 2017b, Contemp Clin Trials; 38 Zimmer et al., 2017; 39 Sandroff et al., 2015, Neurodegen Dis Manag; 40 Coote et al., 2017; 41 Sandroff et al., 2017, Med Sci Sports Exerc;
Future Directions

• Exercise, PA, fitness, cognition, and the brain: is there something there?

• If so, how do we take this to the next level?

• Systematically-developed interventions!\(^{42}\)

---

\(^{42}\) Sandroff, 2015, *Neurosci Biobehav Rev*
Optimal Exercise Intervention?

• **Domain of exercise training?**
  • Aerobic exercise$^{25,27,29,41}$

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

• **Which domains of cognitive functioning?**
  • Cognitive processing speed$^{25,27,29,35,41}$

• **What about disability status?**
  • Fully-ambulatory persons with MS$^{25,27,29,41}$ with objective cognitive processing speed impairment$^{41}$

• **What about the brain?**
  • Thalamocortical resting-state functional connectivity$^{32}$
So What Now?

- **Upcoming Larger Phase I/II RCT (NIH: 1 R01 HD091155-01A1)**
  - (N=88) of treadmill walking versus active control condition on CPS, cardiorespiratory fitness, and brain function (thalamocortical RSFC) in fully-ambulatory persons with MS with impaired CPS
Exercise, Mobility, Cognition, and Brain in MS:

- Researchers have often asked “how” the brain adapts with exercise, but often overlook *why* the brain adapts with exercise.

- PRIMERS Framework and Model\(^ {43}\):

\(^ {43}\) Sandroff, Motl, Reed, Barbey, Benedict, & DeLuca, *under review*
Outline

• MS Overview (RWM)
• Scope of the Presentation: Mobility, Cognition, and Exercise (RWM)
• Exercise, Mobility, and Brain in MS (RWM)
• Break
• Exercise, Cognition, and Brain in MS (BMS)
• Translation of Research into Clinical Practice (RWM)
• Questions (Audience)
The benefits of exercise training in multiple sclerosis

Robert W. Motl and Lara A. Pilutti

Abstract | Multiple sclerosis (MS) is an immune-mediated disease characterized by inflammatory demyelination and neurodegeneration within the CNS. This damage of CNS structures leads to deficits of body functions, which, in turn, affect patient activities, such as walking, and participation. The pathogenesis and resulting consequences of MS have been described as concepts within the International Classification of Functioning, Disability and Health (ICF) model—an international standard to describe and measure health and disability. Evidence suggests that exercise training in people with MS has the potential to target and improve many of the components outlined in the ICF model. Although the body of research examining the effects of exercise training on depression, cognition and participatory outcomes is not sufficiently developed, some preliminary evidence is promising. Exercise training is proposed to affect inflammation, neurodegeneration, and CNS structures, but current evidence is limited. In this Review, we discuss evidence from clinical trials that suggests beneficial effects of exercise training on muscle strength, aerobic capacity and walking performance, and on fatigue, gait, balance and quality of life. Issues with current studies and areas of future research are highlighted.

The Solution? Overcome Major Limitations

1. Inadequate quality and scope of evidence
2. Incomplete understanding of mechanisms
3. Absence of a conceptual framework and toolkit for translating into clinical practice
The Patient-Provider Interaction I

Multiple sclerosis patients need and want information on exercise promotion from healthcare providers: a qualitative study

Yvonne C. Leamonth PhD, 1  |  Brynn C. Adamson MSc, 1  |  Julia M. Balto BSc, 1  
Chung-yi Chiu PhD, 1  |  Isabel Molina-Guzman PhD, 2  |  Marcia Finlayson PhD, 3  
Barry J. Riskin MD, 1  |  Robert W. Motl PhD, 1  

1Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Urbana, IL, USA
2Department of Kinesiology, University of Illinois at Urbana-Champaign, Urbana, IL, USA
3School of Rehabilitation Therapy, Queen’s University, Kingston, ON, Canada

Correspondence
Robert W. Motl, Exercise Neuroscience Laboratory, Department of Kinesiology & Community Health, University of Illinois, Urbana, IL, USA.
Email: rwmotl@illinois.edu

Abstract
Background: There is growing recognition of the benefits and safety of physical activity in the comprehensive care of persons with multiple sclerosis. However, uptake is low.

Objective: To explore the needs and wants of patients with MS regarding exercise promotion through healthcare providers.

Setting and participants: Participants were adults with MS who had mild to moderate disability and a range of exercise levels. All participants lived in the USA.

Methods: Fifty semi-structured interviews were conducted and analyzed using thematic analysis. Two themes emerged: (1) interactions between patients and providers, and (2) wishes for healthcare promotion.

Results: Analysis of participants’ accounts illustrate that current exercise promotion strategies do not meet patient needs. Patients with MS frequently interact with healthcare providers and are generally unsatisfied with the amount of information and knowledge on exercise promotion. Healthcare providers can address the low uptake of exercise among patients by acting upon the identified unmet needs involving materials, knowledge, and change strategies for exercise.

Keywords: exercise promotion, healthcare communication, multiple sclerosis, qualitative

FIGURE 2 Key components of exercise promotion in MS through healthcare providers care.
The Patient-Provider Interaction II

Investigating the needs and wants of healthcare providers for promoting exercise in persons with multiple sclerosis: a qualitative study

Yvonne C. Learmonth*, Brynn C. Adamson*, Julia M. Balto*, Chung-Yi Chiu*, Isabel M. Molina-Guzman*, Marcia Finlayson*, Elizabeth A. Barstow† and Robert W. Moff†

*Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Champaign, IL, USA; †Departments of Latino/Latina studies, Media & Cinema Studies, University of Illinois at Urbana-Champaign, Champaign, IL, USA; ‡School of Rehabilitation Therapy, Queen’s University, Kingston, Canada; §Department of Occupational Therapy, University of Alabama at Birmingham, Birmingham, AL, USA

ABSTRACT
Purpose: We undertook a qualitative study that explored the needs of healthcare providers for promoting exercise among persons with mild or moderate multiple sclerosis (MS).
Methods: We used interpretive description methodology, and conducted semi-structured interviews (n = 13); occupational therapists (n = 10), physical therapists (n = 11), and interviews were analysed using thematic analysis.
Results: We identified three themes with multiple subthemes regarding exercise promotion by healthcare providers. The first theme was “opportunities for exercise promotion” through the healthcare team, and clinical appointment. The second theme was “healthcare provider strategies,” including professional training, training among healthcare providers, and clear and defined protocols. The third theme was “patient tools/strategies” that should be delivered with MS as part of the exercise prescription.
Conclusions: Providers in MS healthcare consider the patient-provider interaction system, healthcare team, and clinical appointment as a novel opportunity for exercise promotion. Exercise opportunity requires education of healthcare providers and provision of tools for promotion among persons with MS.

Figure 2. Summary of thematic findings.
The Patient-Provider Interaction III Conceptual Model

Promotion of Exercise in Multiple Sclerosis Through Health Care Providers

Robert W. Motl,1 Elizabeth A. Barstow,2 Sarah Blaylock,3 Emma Richardson,3
Yvonne C. Learmonth,4 and Matthew Floor6
Departments of 1Physical Therapy and 2Occupational Therapy, University of Alabama at Birmingham, School of Physical Therapy, and 3Department of Health Care Management, University of Alabama at Birmingham, AL.

Motl, R.W., E.A. BARSTOW, S. BLAYLOCK, E. RICHARDSON, Y.C. LEARMONTH, and M. Floor. Promotion of exercise in multiple sclerosis through health care providers. Exerc. Sport Sci. Rev., Vol. 46, No. 2, pp. 50–50, 2018. Participation in exercise among individuals with multiple sclerosis (MS) is widespread; however, many individuals report barriers to exercise that can be addressed through education and support. This paper reviews the literature on exercise in MS and discusses strategies for promoting exercise among individuals with MS.

Figure 1. Conceptual model describing the patient-provider interaction for exercise behavior change in people with multiple sclerosis.
The Patient-Provider Interaction III Conceptual Model

This Will Require a Decision Support System
Summary/Future Directions

• Exercise can benefit mobility and cognition in MS, but studies tend to include participants who don’t have the actual problem being studied!

• Importance of including brain neuroimaging outcome measures

• Translating knowledge from the laboratory into clinical practice
Thank You!

• Questions? Prospective PhD students?
  • robmotl@uab.edu
  • sandroff@uab.edu