Physical Fitness and Cognitive Function in Multiple Sclerosis: Does Disability Status Matter?
Brian M. Sandroff, Lara A. Pilutti
Ralph H.B. Benedict, Robert W. Motl

Cognitive Impairment in MS

- Cognitive impairment is prevalent, disabling, and poorly-managed in MS
  - Upwards of 50% demonstrate cognitive impairment¹
  - Impairment in domains of CPS, learning and memory, etc.²
  - No FDA-approved treatment for cognitive impairment in MS (e.g., symptomatic or DMTs)³
  - Studies involving cognitive rehabilitation have been conflicting³

¹ Benedict & Zivadinov, 2011; ² Prakash et al., 2008; ³ Amato et al., 2013;
Exercise Training and Cognition in MS

• There is equivocal evidence from 3 RCTs of exercise training and cognition in MS\(^4-6\)

• First 2 RCTs: Unsupervised exercise in mild MS disability\(^4,5\)
  • No significant intervention effects on cognition
  • Methodological concerns; importance of physical fitness\(^7\)

\(^4\) Oken et al., 2004; \(^5\) Romberg et al., 2005; \(^6\) Briken et al., 2013; \(^7\) Motl, Sandroff, & Benedict, 2011

Exercise Training and Cognition in MS

• Recent RCT: Supervised aerobic exercise on fitness and cognition in moderate MS disability\(^6\)
  • Significant effects for cycle ergometer training on fitness and verbal memory and alertness, but not CPS
  • Not consistent with results from previous cross-sectional studies of fitness and cognition in MS\(^8,9\)

\(^8\) Prakash et al., 2010; \(^9\) Sandroff & Motl, 2012
Fitness and Cognition in MS

• Aerobic capacity:
  • Moderate correlations between aerobic fitness and CPS ($pr = .46; r = .44$)$^8,9$, but not learning and memory, in persons with mild MS disability

• Muscular strength:
  • Moderate correlations between muscular strength and CPS ($r = .39$) in persons with mild MS disability$^9$

Fitness and Cognition in MS

• Two observations to clarify previous research on fitness and cognition in MS
  • Multiple domains of fitness might be associated with multiple domains of cognition
  • Disability status might moderate the associations of fitness and cognition
    • Physical activity and CPS in MS$^{10,11}$

$^8$ Sandroff et al., 2013; $^9$ Sandroff et al., 2014; $^{10}$ Sandroff et al., 2013; $^{11}$ Sandroff et al., 2014
Purpose

• Current study examined multiple domains of physical fitness and cognitive dysfunction in persons with mild, moderate, and severe MS disability
  
  – To better inform exercise training interventions for improving specific cognitive functions in MS, depending on disability status

Hypotheses

• Multiple domains of physical fitness would be associated with CPS and learning and memory
  
  – Better fitness would be associated with better cognitive performance

• Disability status would moderate the associations between fitness and cognition
  
  – Fitness would be significantly associated with cognitive function in persons with mild, but not moderate or severe MS disability
Participants

- 62 persons with neurologist-confirmed MS diagnosis (age 18-64)
- Ambulatory with or without assistive device
- No more than one “Yes” response on the Physical Activity Readiness Questionnaire (PAR-Q)\textsuperscript{12}
- Relapse-free for 30 days

\begin{tabular}{|c|c|c|}
\hline
\textbf{PAR-Q} & \textbf{YES} & \textbf{NO} \\
\hline
1 & Has your Doctor ever said that you have a heart condition and that you should only do physical activity recommended by a Doctor? & \\
\hline
2 & Do you feel pain in your chest when you do physical activity? & \\
\hline
3 & In the past month, have you had chest pain when you were not doing physical activity? & \\
\hline
4 & Do you lose your balance because of dizziness or do you ever lose consciousness? & \\
\hline
5 & Do you have a bone or joint problem that could be made worse by a change in your physical activity? & \\
\hline
6 & Is your doctor currently prescribing drugs for your blood pressure or heart condition? & \\
\hline
7 & Do you have any other reason why you should not do physical activity? & \\
\hline
\end{tabular}

\textsuperscript{12} Thomas, Reading, & Shephard, 1992

Primary Measures

- Fitness Measures:
  - Aerobic capacity (VO\textsubscript{2peak})
    - Incremental exercise test to exhaustion on recumbent stepper
  - Muscular strength
    - Peak isometric torque of knee extensors (KE), knee flexors (KF), KE and KF asymmetry scores
    - Isokinetic dynamometer
Primary Measures

• Cognitive Measures:
  – BICAMS Neuropsychological Battery\textsuperscript{13}
    - Symbol Digit Modalities Test (SDMT)\textsuperscript{14}
    - California Verbal Learning Test-2 (CVLT-2)\textsuperscript{15}
    - Brief Visuospatial Memory Test-Revised (BVMT-R)\textsuperscript{16}

13 Langdon et al., 2012; 14 Smith, 1982; 15 Delis et al., 2000; 16 Benedict, 1997

Primary Measures

• Disability Status:
  – EDSS, performed by Neurostatus-certified assessors
    - Mild Disability (N=20; EDSS 0-3.5)
    - Moderate Disability (N=21; EDSS 4.0-5.5)
    - Severe Disability (N=21; EDSS 6.0-6.5)

  – Consistent with benchmarks of disability accumulation in MS\textsuperscript{17}

17 Confavreux & Vukusic, 2006
Procedure

• Study was approved by University IRB and all participants provided written informed consent

• 2 separate sessions, separated by 7 days
  – This was done to minimize fatigue during and across sessions
  – 2 different orders counter-balanced across participants

• Testing Order 1:
  – Session 1: EDSS, questionnaires, muscle strength
  – Session 2: BICAMS, aerobic capacity

• Testing Order 2:
  – Session 1: EDSS, BICAMS, aerobic capacity
  – Session 2: Questionnaires, muscle strength

Data Analysis

• Data were analyzed in SPSS v.21
  – Examined EDSS group differences in fitness and cognition using one-way ANOVA
    • Post-hoc Bonferroni corrections
  – Computed z-scores for SDMT, CVLT-2, BVMT-R
  – Bivariate correlations in overall sample
  – Bivariate correlations in EDSS groups, separately
  – Post-hoc stepwise linear regression to detect which domains of fitness explain variance in cognitive domains
# Demographic/Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n=62)</th>
<th>Mild (EDSS 0 – 3.5) (n=20)</th>
<th>Moderate (EDSS 4.0 – 5.5) (n=21)</th>
<th>Severe (EDSS 6.0 – 6.5) (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.39 (7.27)</td>
<td>50.24 (9.44)</td>
<td>51.57 (7.10)</td>
<td>54.10 (6.93)</td>
</tr>
<tr>
<td>Sex (n, % female)</td>
<td>45/62 (72.6%)</td>
<td>13/20 (65.0%)</td>
<td>15/21 (71.4%)</td>
<td>17/21 (81.0%)</td>
</tr>
<tr>
<td>Education (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School</td>
<td>9/62 (14.5%)</td>
<td>3/20 (15.0%)</td>
<td>4/21 (19.0%)</td>
<td>2/21 (9.5%)</td>
</tr>
<tr>
<td>Some College</td>
<td>21/62 (33.9%)</td>
<td>2/20 (10.0%)</td>
<td>11/21 (52.4%)</td>
<td>8/21 (38.1%)</td>
</tr>
<tr>
<td>College Grad</td>
<td>32/62 (51.6%)</td>
<td>15/20 (75.0%)</td>
<td>6/21 (28.6%)</td>
<td>11/21 (52.4%)</td>
</tr>
<tr>
<td>Disease Duration (years)</td>
<td>14.4 (9.2)</td>
<td>10.9 (7.4)</td>
<td>16.0 (9.8)</td>
<td>16.0 (9.5)</td>
</tr>
<tr>
<td>DMT Use (n, %)</td>
<td>49/62 (79.0%)</td>
<td>18/20 (90.0%)</td>
<td>15/21 (71.4%)</td>
<td>16/21 (76.2%)</td>
</tr>
<tr>
<td>MS Type (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsing</td>
<td>48/61 (77.4%)</td>
<td>19/20 (95.0%)</td>
<td>18/21 (85.7%)</td>
<td>11/21 (52.4%)</td>
</tr>
<tr>
<td>Progressive</td>
<td>13/61 (21.0%)</td>
<td>0/20 (0.0%)</td>
<td>3/21 (14.3%)</td>
<td>10/21 (47.6%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1/61 (1.6%)</td>
<td>1/20 (5.0%)</td>
<td>0/21 (0.0%)</td>
<td>0/21 (0.0%)</td>
</tr>
</tbody>
</table>

Note: Data presented as mean (SD) unless otherwise noted.

---

# Fitness Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n=62)</th>
<th>Mild (EDSS 0 – 3.5) (n=20)</th>
<th>Moderate (EDSS 4.0 – 5.5) (n=21)</th>
<th>Severe (EDSS 6.0 – 6.5) (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2peak (ml/kg/min)</td>
<td>19.26 (7.25)</td>
<td>24.11 (6.60)</td>
<td>19.01 (6.84)</td>
<td>14.67 (3.64)</td>
</tr>
<tr>
<td>KE peak torque (N-m)</td>
<td>149.15 (52.41)</td>
<td>180.34 (52.02)</td>
<td>153.72 (39.83)</td>
<td>114.89 (44.65)</td>
</tr>
<tr>
<td>KF peak torque (N-m)</td>
<td>57.50 (24.75)</td>
<td>71.07 (29.68)</td>
<td>60.17 (13.67)</td>
<td>41.92 (19.94)</td>
</tr>
<tr>
<td>KE asymmetry score</td>
<td>19.87 (17.32)</td>
<td>8.93 (5.65)</td>
<td>14.40 (12.62)</td>
<td>35.75 (17.59)</td>
</tr>
<tr>
<td>KF asymmetry score</td>
<td>21.47 (19.53)</td>
<td>14.26 (15.20)</td>
<td>16.82 (12.74)</td>
<td>32.99 (23.81)</td>
</tr>
</tbody>
</table>

Note: Data presented as mean (SD) unless otherwise noted.
Cognitive Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n=62)</th>
<th>Mild (EDSS 0 – 3.5) (n=20)</th>
<th>Moderate (EDSS 4.0 – 5.5) (n=21)</th>
<th>Severe (EDSS 6.0 – 6.5) (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDMT (raw score)</td>
<td>50.44 (12.75)</td>
<td>58.25 (8.14)</td>
<td>51.81 (13.72)</td>
<td>41.62 (10.00)</td>
</tr>
<tr>
<td>SDMT (z-score)</td>
<td>−1.18</td>
<td>−0.34</td>
<td>−1.03</td>
<td>−2.12</td>
</tr>
<tr>
<td>CVLT-2 (raw score)</td>
<td>54.77 (12.79)</td>
<td>61.05 (11.24)</td>
<td>53.76 (14.16)</td>
<td>49.81 (10.60)</td>
</tr>
<tr>
<td>CVLT-2 (z-score)</td>
<td>−0.11</td>
<td>0.56</td>
<td>−0.22</td>
<td>−0.64</td>
</tr>
<tr>
<td>BVMT-R (raw score)</td>
<td>21.37 (7.04)</td>
<td>23.90 (6.11)</td>
<td>19.48 (6.98)</td>
<td>20.86 (7.51)</td>
</tr>
<tr>
<td>BVMT-R (z-score)</td>
<td>−0.96</td>
<td>−0.50</td>
<td>−1.30</td>
<td>−1.05</td>
</tr>
</tbody>
</table>

Note: Data presented as mean (SD) unless otherwise noted

Covariate Analysis

- Examined age, sex, education, DMT use as potential covariates
  - **Age:** VO$_{2peak}$, KE$_{max}$, KF$_{max}$, KE$_a$, but not KF$_{ar}$, SDMT, CVLT-2, BVMT-R
  - **Sex:** VO$_{2peak}$, KE$_{max}$, KF$_{max}$, but not KE$_a$, KF$_{ar}$, SDMT, CVLT-2, BVMT-R
  - **Education:** No associations with any fitness or cognitive outcome
  - **DMT use:** SDMT, but no other fitness or cognitive outcome

Note: DMT=disease modifying treatment; VO$_{2peak}$ = peak aerobic capacity, KE$_{max}$=peak torque of knee extensors, KF$_{max}$=peak torque of knee flexors, KE$_a$=knee extensor asymmetry score; KF$_{ar}$=knee flexor asymmetry score
Hypothesis 1: Correlations-Overall Sample (N=62)

<table>
<thead>
<tr>
<th>Variable</th>
<th>VO_{peak}</th>
<th>KE_{max}</th>
<th>KF_{max}</th>
<th>KE_a</th>
<th>KF_a</th>
<th>SDMT</th>
<th>CVLT-2</th>
<th>BVMT-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO_{peak}</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KE_{max}</td>
<td>.622*</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KF_{max}</td>
<td>.686*</td>
<td>.842*</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KE_a</td>
<td>-.390*</td>
<td>-.346*</td>
<td>-.445*</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KF_a</td>
<td>-.120</td>
<td>-.157</td>
<td>-.245*</td>
<td>.581*</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDMT</td>
<td>-.410*</td>
<td>.352*</td>
<td>.393*</td>
<td>-.353*</td>
<td>-.061</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT-2</td>
<td>-.193</td>
<td>.067</td>
<td>.132</td>
<td>-.194</td>
<td>-.091</td>
<td>.505*</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>BVMT-R</td>
<td>.184</td>
<td>.090</td>
<td>.075</td>
<td>-.141</td>
<td>-.038</td>
<td>.319*</td>
<td>.640*</td>
<td>--</td>
</tr>
</tbody>
</table>

Note: * denotes statistical significance at $p < 0.05$, based on a 1-tailed test;

Scatter Plots-Overall Sample (N=62)
Hypothesis 2: Correlations Based on EDSS Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>SDMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (n=20)</td>
<td>VO₂peak</td>
<td>.42*</td>
</tr>
<tr>
<td></td>
<td>KEₘₐₓ</td>
<td>.20</td>
</tr>
<tr>
<td></td>
<td>KFₘₐₓ</td>
<td>.39*</td>
</tr>
<tr>
<td></td>
<td>KEₐ</td>
<td>-.53*</td>
</tr>
<tr>
<td>Moderate (n=21)</td>
<td>VO₂peak</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>KEₘₐₓ</td>
<td>.06</td>
</tr>
<tr>
<td></td>
<td>KFₘₐₓ</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>KEₐ</td>
<td>.37</td>
</tr>
<tr>
<td>Severe (n=21)</td>
<td>VO₂peak</td>
<td>.14</td>
</tr>
<tr>
<td></td>
<td>KEₘₐₓ</td>
<td>.08</td>
</tr>
<tr>
<td></td>
<td>KFₘₐₓ</td>
<td>.13</td>
</tr>
<tr>
<td></td>
<td>KEₐ</td>
<td>-.21</td>
</tr>
</tbody>
</table>

Note: * denotes statistical significance at p < 0.05, based on a 1-tailed test; Mild = EDSS of 1.5-3.5; Moderate = EDSS of 4.0-5.5; Severe = EDSS of 6.0-6.5;

Post-hoc Regression Analysis

- Stepwise Linear Regression in overall sample
- DV = SDMT score
  - Predictors = VO₂peak, KF peak torque, KE asymmetry score
- VO₂peak entered into the equation alone
  - (B = .75, SE B = .22, β = .41)
- Aerobic capacity independently explained a statistically significant amount of variance in CPS in the overall sample (R² = .17)
Primary Results

• Hypothesis 1: Aerobic capacity and muscle strength associated with CPS, but not learning and memory in overall sample

• Hypothesis 2: Disability was a moderator of fitness and cognition
  – Association of fitness and CPS in mild, but not moderate or severe MS

• Post-hoc regression: Aerobic capacity, but not muscle strength, independently explained variance in CPS in overall sample

• Favors aerobic exercise training intervention for improving CPS particularly among persons with mild MS disability

Clarifying Previous Research...

• Provides direct, preliminary evidence to explain previously reported pattern of results
  – Fitness associated with CPS in mild MS
  – VO$_{2\text{peak}}$ not associated with CPS in moderate MS
  – Physical activity and CPS moderated by disability status

• VO$_{2\text{peak}}$ not associated with learning/memory
  – Memory impairment

19 Leavitt et al., 2013
Potential Explanations?

• EDSS ≥ 4.0 indicative of irreversible disability\textsuperscript{17}
  – Existing MS therapies largely ineffectual
  – Perhaps at this stage, MS disease process overwhelms the capacity for aerobic exercise to affect brain regions important for CPS

• EDSS < 4.0
  – Results might reflect widely-reported associations of aerobic fitness and cognitive functioning in general population, across the lifespan

Implications for Future Research

• Aerobic exercise training interventions for improving CPS, particularly among persons with mild MS disability

• Optimal modality and intensity of aerobic exercise unknown for selectively improving CPS in persons with mild MS

• Need for additional work on fitness and cognition in persons with moderate-to-severe MS disability
Strengths and Limitations

• Strengths:
  – Objective measurement of physical fitness
  – Valid neuropsychological tests
  – Large overall sample size

• Limitations:
  – Cross-sectional investigation
  – Small sample size within disability groups
  – Lack of comparison group of healthy matched controls

Acknowledgements

• Everyone in attendance
• ENRL Director: Prof. Rob Motl
• Research staff of post-docs, grads, URAs, and project coordinators
• This study was funded by a grant from the National Multiple Sclerosis Society (IL 0003)