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

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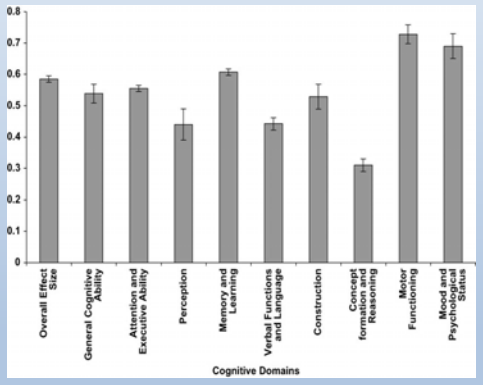
Cognitive Impairment in MS

- **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:**
  - **<u>Domain of exercise training?</u>**
    - **Aerobic exercise[12,13]**
  - **<u>What type (modality) and intensity of exercise?</u>**
    - **Light, moderate, and vigorous intensity treadmill walking exercise[14,15]**
  - **<u>Which domains of cognitive functioning?</u>**
    - **CPS/EF[12,13,16]**
  - **<u>What about disability status?</u>**
    - **Fully-ambulatory persons with MS[13,17,18]**

[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

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]**

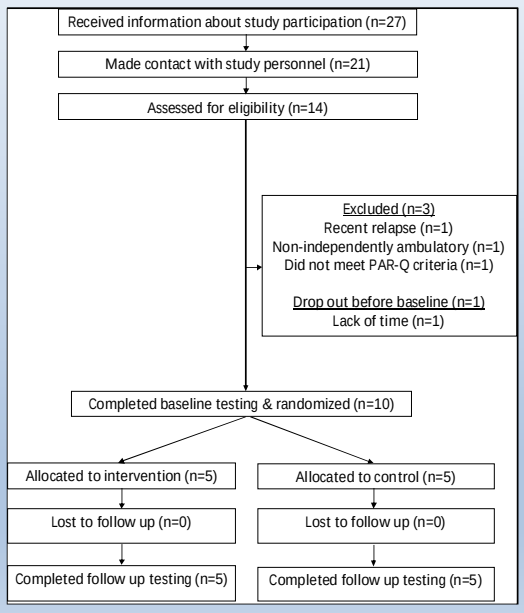
[19] Mohr et al., 2009

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**



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

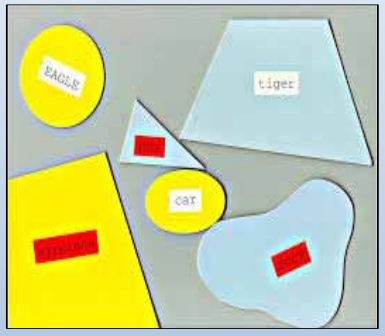
SDMT

- 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

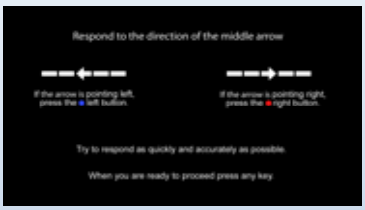
DKEFS Sorting Test

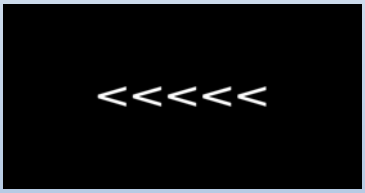
- **Neuropsychological measure of EF (i.e., conceptual reasoning/cognitive flexibility)**
- **Sorting 6 cards into 2 groups of 3 cards in as many ways as possible in 4 minutes**
- **Primary outcomes: total number of correct sorts and verbal description score across 2 trials**

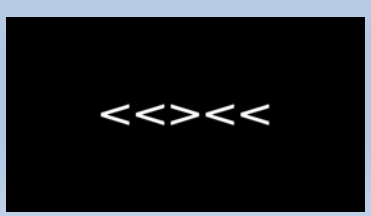


Modified Flanker Task

- **Computerized measure of CPS and EF**
- **Particularly sensitive to aerobic exercise[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**



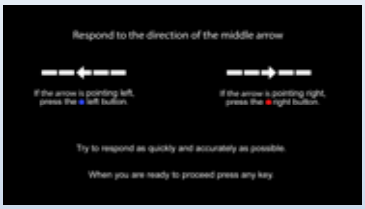


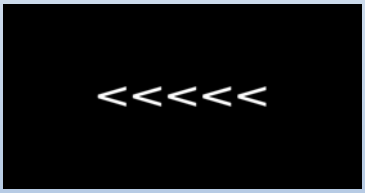


[24] Colcombe et al., 2004

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]**





[25] Holtzer et al., 2014

Cardiorespiratory Fitness

- **Peak oxygen consumption (VO_{2peak})**
  - **Graded exercise test to exhaustion on motor-driven treadmill and a metabolic cart**
  - **<u>Modified Balke protocol</u>[26]**
    - **Brisk, submaximal walking pace**
    - **Grade increases 2.0% every 2 minutes until volitional fatigue**

[26] American College of Sports Medicine, 2013

Intervention Condition

- 3 days/week of progressive (duration and intensity) treadmill walking exercise training for 12-weeks
  - Based on pilot work and ACSM guidelines[26]
- 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

Week	Sessions	Exercise Intensity	Exercise Duration
1	1-3	Light-to-Moderate	15-20 min
2	4-6	Light-to-Moderate	20-25 min
3	7-9	Moderate	20-25 min
4	10-12	Moderate	25-30 min
5-6	13-18	Moderate-to-Vigorous	25-30 min
7-8	19-24	Moderate-to-Vigorous	30-35 min
9-10	25-30	Vigorous	30-35 min
11-12	31-36	Vigorous	35-40 min

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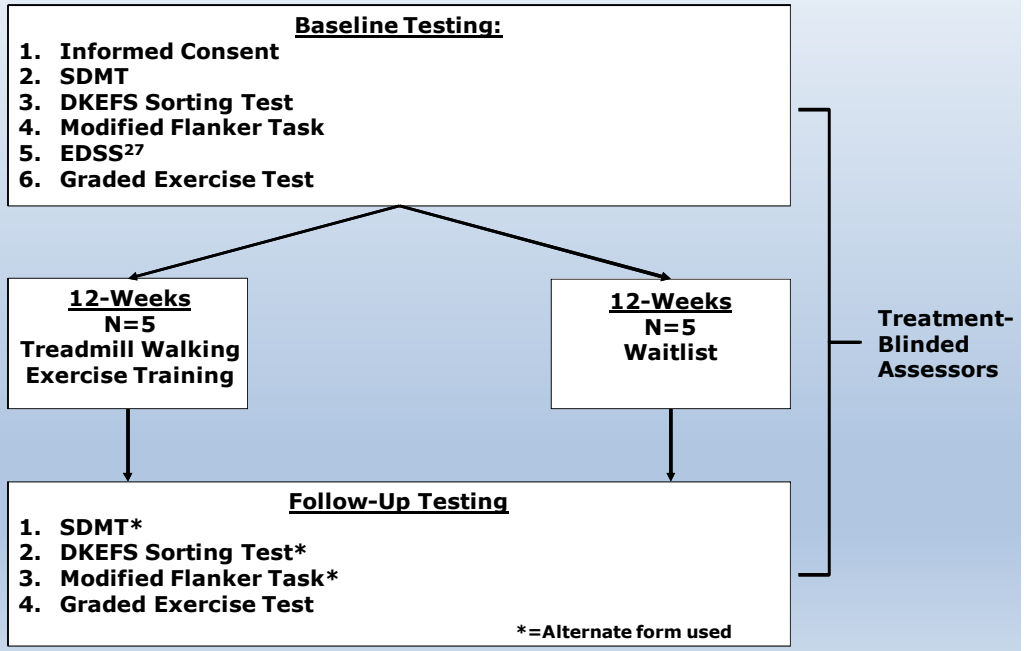
Control Condition

- 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



[27] Kurtzke, 1983

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

[28] Cohen, 1988

Descriptive Characteristics of Sample

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

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

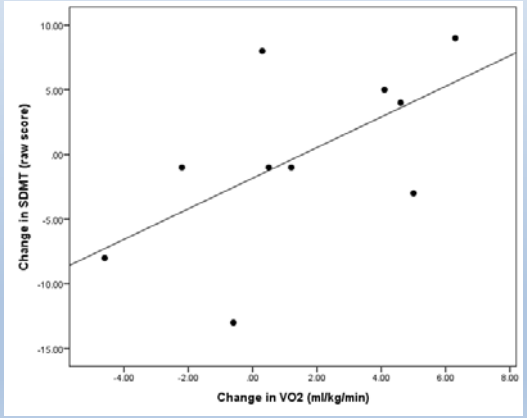
Cognitive and Fitness Outcomes

	Exercise (N=5)		Control (N=5)		
Variable	Baseline	Follow-Up	Baseline	Follow-Up	*d*
SDMT (raw score)	55.0 (9.2)	58.2 (7.9)	65.2 (15.8)	61.8 (9.7)	0.95
DKEFS (correct sorts)	11.0 (2.2)	10.0 (1.9)	13.2 (2.2)	13.0 (1.0)	−0.59
DKEFS (description score)	40.4 (8.4)	38.2 (7.1)	51.0 (6.9)	50.6 (3.7)	−0.23
Modified flanker RT (ms)	486.3 (98.5)	476.2 (69.8)	440.8 (12.5)	441.8 (7.5)	−0.43
IC-RT (ms)	45.0 (34.7)	43.3 (45.0)	49.4 (17.9)	44.9 (9.9)	0.37
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	24.2 (6.0)	27.6 (5.7)	31.8 (4.1)	31.4 (2.4)	1.08

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 VO_{2peak} significantly associated with change in SDMT (r=.60, p=.03) only**



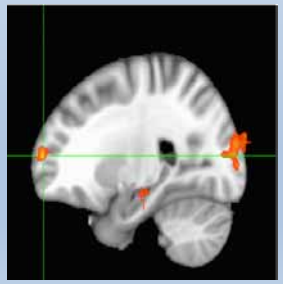
What Might This Mean?

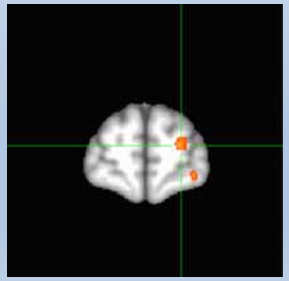
- **Large intervention effects on CPS (i.e., SDMT performance) and cardiorespiratory fitness (i.e., VO_{2peak})**
  - **Change in VO_{2peak} moderately-to-strongly associated with change in SDMT score**
- **Provides initial proof-of-concept data supporting progressive treadmill walking exercise training for possibly improving CPS and cardiorespiratory fitness in a larger sample of fully-ambulatory persons with MS**
- **Importance of CPS in MS[29]**

[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

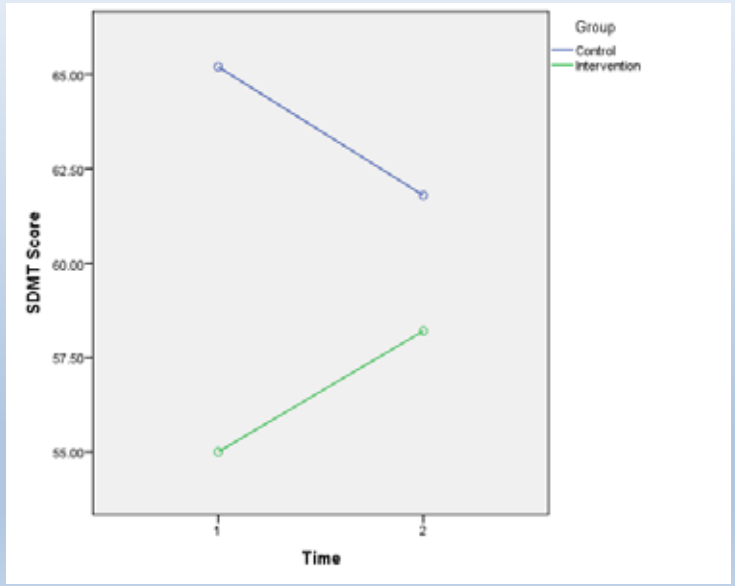
Acknowledgements

- 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

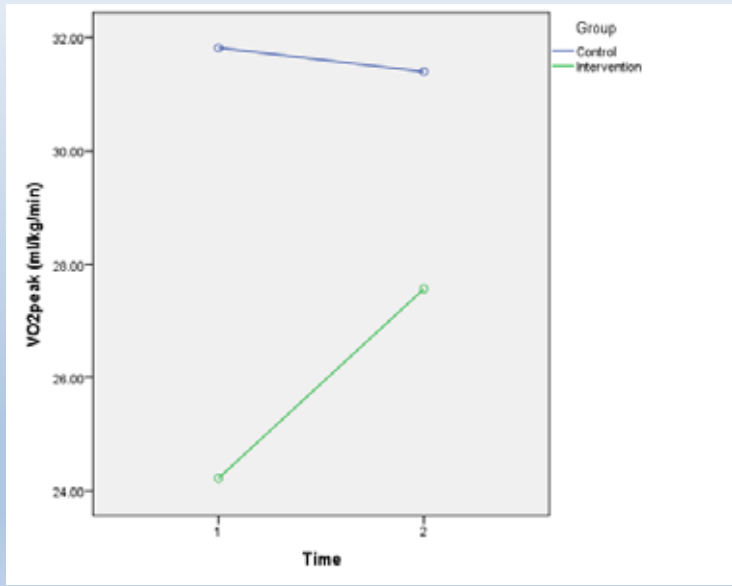
Individual Changes in Outcomes

Subject	SDMT	DKEFS-Correct Sorts	DKEFS-Description Score	Modified flanker RT (ms)	IC-RT (ms)	VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)
Exercise						
1	−1	0	+2	+18.7	−13.4	+1.2
2	−1	+1	+4	+2.7	+11.4	+0.5
3	+5	−2	−9	−34.1	−11.7	+4.1
4	+4	−2	−2	−55.5	−6.7	+4.6
5	+9	−2	−6	+18.1	+11.7	+6.3
Control						
1	+8	0	0	+11.6	+8.2	+0.3
2	−8	+1	+5	−9.5	−9.1	−4.6
3	−13	−2	−3	+20.4	−4.6	−0.6
4	−1	−1	−4	−20.4	−1.9	−2.2
5	−3	+1	0	+2.8	−15.3	+5.0

Intervention Effects on SDMT Scores



Intervention Effects on VO_{2peak}



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[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[12,13,32,33]**

[32] Prakash et al., 2007; [33] Prakash et al., 2010