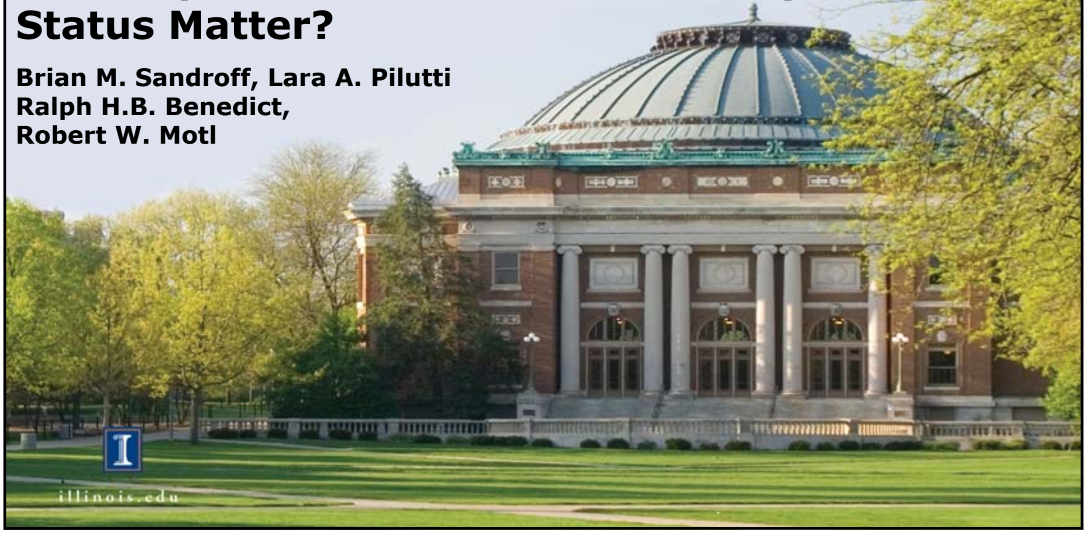
UNIVERSITY OF ILLINOIS
AT URBANA-CHAMPAIGN

Physical Fitness and Cognitive Function in Multiple Sclerosis: Does Disability Status Matter?

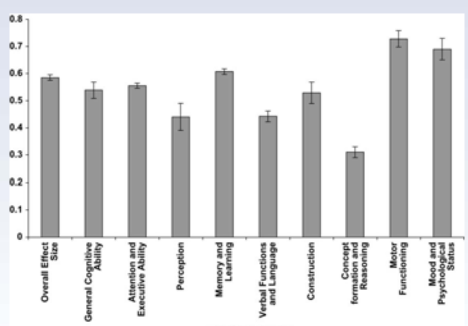
Brian M. Sandroff, Lara A. Pilutti
Ralph H.B. Benedict,
Robert W. Motl



illinois.edu

Cognitive Impairment in MS

- **Cognitive impairment is prevalent, disabling, and poorly-managed in MS**
  - **Upwards of 50% demonstrate cognitive impairment[1]**
  - **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 conflicting[3]**



illinois.edu

[1] Benedict & Zivadinov, 2011; [2] Prakash et al., 2008; [3] Amato et al., 2013;

Exercise Training and Cognition in MS

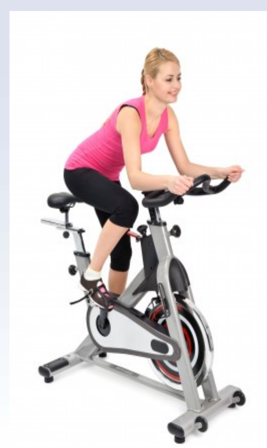
- There is equivocal evidence from 3 RCTs of exercise training and cognition in MS[4-6]
- First 2 RCTs: Unsupervised exercise in mild MS disability[4,5]
  - No significant intervention effects on cognition
  - Methodological concerns; importance of physical fitness[7]

illinois.edu

[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]



illinois.edu

[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]**

illinois.edu

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]**

illinois.edu

[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

illinois.edu

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

illinois.edu

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)[12]
- Relapse-free for 30 days

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

illinois.edu

[12] Thomas, Reading, & Shephard, 1992

Primary Measures

- Fitness Measures:
  - Aerobic capacity (VO_{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

illinois.edu

Primary Measures

- **Cognitive Measures:**
  - **BICAMS Neuropsychological Battery[13]**
    - **Symbol Digit Modalities Test (SDMT)[14]**
    - **California Verbal Learning Test-2 (CVLT-2)[15]**
    - **Brief Visuospatial Memory Test-Revised (BVMT-R)[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[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

illinois.edu

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

illinois.edu

Demographic/Clinical Characteristics

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

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

illinois.edu

Fitness Characteristics

Variable	Overall (n=62)	Mild (EDSS 0 – 3.5) (n=20)	Moderate (EDSS 4.0 – 5.5) (n=21)	Severe (EDSS 6.0 – 6.5) (n=21)
VO_{2peak} (ml/kg/min)	19.26 (7.25)	24.11 (6.60)	19.01 (6.84)	14.67 (3.64)
KE peak torque (N·m)	149.15 (52.41)	180.34 (52.02)	153.72 (39.83)	114.89 (44.65)
KF peak torque (N·m)	57.50 (24.75)	71.07 (29.68)	60.17 (13.67)	41.92 (19.94)
KE asymmetry score	19.87 (17.32)	8.93 (5.65)	14.40 (12.62)	35.75 (17.59)
KF asymmetry score	21.47 (19.53)	14.26 (15.20)	16.82 (12.74)	32.99 (23.81)

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

illinois.edu

Cognitive Characteristics

Variable	Overall (n=62)	Mild (EDSS 0 – 3.5) (n=20)	Moderate (EDSS 4.0 – 5.5) (n=21)	Severe (EDSS 6.0 – 6.5) (n=21)
SDMT (raw score)	50.44 (12.75)	58.25 (8.14)	51.81 (13.72)	41.62 (10.00)
SDMT (*z*-score)[18]	−1.18	−0.34	−1.03	−2.12
CVLT-2 (raw score)	54.77 (12.79)	61.05 (11.24)	53.76 (14.16)	49.81 (10.60)
CVLT-2 (*z*-score)[18]	−0.11	0.56	−0.22	−0.64
BVMT-R (raw score)	21.37 (7.04)	23.90 (6.11)	19.48 (6.98)	20.86 (7.51)
BVMT-R (*z*-score)[18]	−0.96	−0.50	−1.30	−1.05

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

illinois.edu

[18] Parmenter et al., 2009

Covariate Analysis

- Examined age, sex, education, DMT use as potential covariates
  - **Age**: VO_{2peak}, KE_{max}, KF_{max}, KE_{a}, but not KF_{a}, SDMT, CVLT-2, BVMT-R
  - **Sex**: VO_{2peak}, KE_{max}, KF_{max}, but not KE_{a}, KF_{a}, 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_{a}=knee flexor asymmetry score

illinois.edu

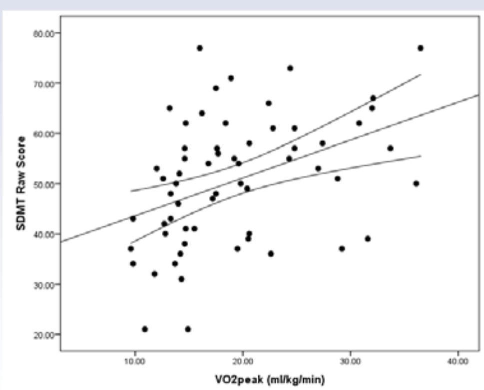
Hypothesis 1: Correlations-Overall Sample (N=62)

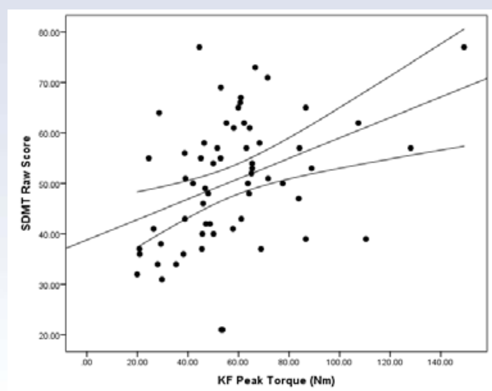
Variable	VO_{2peak}	KE_{max}	KF_{max}	KE_a	KF_a	SDMT	CVLT-2	BVMT-R
VO_{2peak}	–							
KE_{max}	.622*	–						
KF_{max}	.686*	.842*	–					
KE_a	−.390*	−.346*	−.445*	–				
KF_a	−.120	−.157	−.245*	.581*	–			
SDMT	.410*	.352*	.393*	−.353*	−.061	–		
CVLT-2	.193	.067	.132	−.194	−.091	.505*	–	
BVMT-R	.184	.090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

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

illinois.edu

Scatter Plots-Overall Sample (N=62)





illinois.edu

Hypothesis 2:
Correlations Based on EDSS Groups

Group	Variable	SDMT	
Mild (n=20)		*r*	*p*
	VO_{2peak}	.42*	.03
	KE_{max}	.20	.20
	KF_{max}	.39*	.04
	KE_a	−.53*	.01
Moderate (n=21)			
	VO_{2peak}	.05	.41
	KE_{max}	.06	.40
	KF_{max}	.04	.44
	KE_a	.37	.06
Severe (n=21)			
	VO_{2peak}	.14	.27
	KE_{max}	.08	.36
	KF_{max}	.13	.28
	KE_a	−.21	.18

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;

illinois.edu

Post-hoc Regression Analysis

- **Stepwise Linear Regression in overall sample**
- **DV = SDMT score**
  - **Predictors = VO_{2peak}, KF peak torque, KE asymmetry score**
- **VO_{2peak} 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 (R^2 = .17)**

illinois.edu

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**

illinois.edu

Clarifying Previous Research…

- **Provides direct, preliminary evidence to explain previously reported pattern of results**
  - **Fitness associated with CPS in mild MS[8,9]**
  - **VO_{2peak} not associated with CPS in moderate MS[6]**
  - **Physical activity and CPS moderated by disability status[10,11]**
- **VO_{2peak} not associated with learning/memory**
  - **Memory impairment?[6,19]**

illinois.edu

[19] Leavitt et al., 2013

Potential Explanations?

- **EDSS ≥ 4.0 indicative of irreversible disability[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**

illinois.edu

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**

illinois.edu

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**

illinois.edu

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)**

EXERCISE NEUROSCIENCE LABORATORY

ILLINOIS
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

illinois.edu