Check for updates

MSJ Experimental Translational Clinical

Short Report

Treadmill walking exercise training and brain function in multiple sclerosis: Preliminary evidence setting the stage for a network-based approach to rehabilitation

Multiple Sclerosis Journal — Experimental, Translational and Clinical

January-March 2018, 1–5

DOI: 10.1177/2055217318760641

© The Author(s), 2018.
Reprints and permissions:
http://www.sagepub.co.uk/journalsPermissions.nav

Brian M Sandroff, Glenn R Wylie, Brad P Sutton, Curtis L Johnson, John DeLuca and Robert W Motl

Abstract

Exercise training has been identified as a highly promising approach for managing the cognitive consequences of multiple sclerosis (MS). This study represents a secondary analysis of resting-state functional connectivity (RSFC) magnetic resonance imaging data from a pilot treadmill walking exercise training intervention for improving cognitive processing speed (CPS) in MS. There were large intervention effects on RSFC between the thalamus and right superior frontal gyrus ($d = 1.92$) and left medial frontal gyrus ($d = 1.70$). There further were moderate-to-large intervention effects on CPS ($d = 0.72$). Such preliminary data highlight FC within thalamocortical circuitry as a potential target for rehabilitation interventions for improving CPS in cognitively impaired individuals with MS.

Keywords: Exercise, cognition, neuroimaging, multiple sclerosis, rehabilitation, functional connectivity

Date received: 31 October 2017; revised 6 December 2017; accepted: 26 January 2018

Introduction

Exercise training has been identified as a highly promising approach for managing the pervasive and burdensome cognitive consequences of multiple sclerosis (MS).[1] However, little is known about its effects on central nervous system (CNS) structure and function in MS. This is inconsistent with burgeoning evidence for aerobic exercise training-induced neuroplasticity based on changes in neuroimaging outcomes that explain cognitive improvements across the lifespan in the general population.[2]

We have recently completed a successful, systematically developed, pilot, randomized controlled trial (RCT) demonstrating that progressive (i.e. both intensity and duration) treadmill walking exercise (TMWX) training improved cognitive processing speed (CPS) among fully ambulatory patients with MS.[3] However, no published RCTs of exercise training and cognition in MS have included neuroimaging approaches for measuring changes in brain function in networks important for CPS (i.e. thalamocortical network).[4] Such an investigation would provide preliminary but critical proof-of-concept data for TMWX training as an approach for potentially inducing neuroplastic changes in functional connectivity within a select neural network associated with CPS in MS. To that end, the present pilot RCT examined the effect of progressive TMWX training on thalamocortical resting-state functional connectivity (RSFC) neuroimaging outcomes for explaining changes in CPS among eight fully ambulatory females with MS.

Methods

Participants

The current study represents a secondary analysis of functional magnetic resonance imaging data from a systematically developed pilot TMWX training

Correspondence to:
Brian M Sandroff,
University of Alabama at Birmingham, Department of Physical Therapy, SHP 389, 1720 2nd Ave. S., Birmingham, AL 35294, USA.
sandroff@uab.edu

Brian M Sandroff, University of Alabama at Birmingham, USA

Glenn R Wylie, Kessler Foundation, USA

Brad P Sutton, University of Illinois at Urbana-Champaign, USA

Curtis L Johnson, University of Delaware, USA

John DeLuca, Kessler Foundation, USA

Robert W Motl, University of Alabama at Birmingham, USA

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

intervention for improving cognition in eight fully ambulatory females with MS.[3]

Outcome measures

Thalamocortical RSFC. Thalamocortical RSFC was measured using a 10-minute resting-state scan on a United States Food and Drug-approved Siemens 3T MRI scanner. Seed-based RSFC was derived using Analysis of Functional NeuroImages (AFNI) software (http://afni.nimh.nih.gov/afni). We believe that the seed-based, targeted approach is advantageous over performing an independent-components analysis given our a priori hypothesis that TMWX training would influence thalamic/frontal RSFC based on task-dependent neuroplasticity[5] in networks previously linked with MS-related CPS impairment.[4] The data were checked for excessive motion (a shift of more than 3.5 mm, or one degree of angular motion) and for spikes (using the root mean squared error (RMSE) of each volume relative to a reference volume that was the volume half-way through the acquisition run). Data acquisition runs with excessive motion were discarded. Individual acquisitions with an RMSE amplitude that exceeded the 75th percentile plus the value of 150% of the interquartile range of RMSE for all volumes in a given run were excluded from further analysis using the "censorTR" function in 3dDeconvolve. The motion parameters from the realignment step were used as regressors of no interest in the deconvolution, and the residuals from the deconvolution were saved. Using a seed-based analytical approach in AFNI, a seed (3 mm radius) was centered in the bilateral thalamus (i.e. bilateral ventroposterior lateral nuclei). As we were interested in RSFC between the thalamus and frontal regions (i.e. superior, middle, inferior frontal gyri, respectively; medial frontal gyrus; anterior cingulate cortex; posterior cingulate cortex) a priori, we used those regions of interest (ROIs) to guide the voxel-wise analyses performed. Time series from the thalamic seed was correlated with the time series from every voxel in the aforementioned frontal ROIs. We then z-transformed the correlation coefficients (Fisher's z), and the resulting statistical maps were used in the group-level analyses. We used the Montreal Neurological Institute (MNI) atlas to create a mask that was applied to each participant's data after it had been warped into standard MNI space.

CPS. We included the Symbol Digit Modalities Test (SDMT[6]) as a CPS measure for examining the impact of potential exercise-related changes on thalamocortical RSFC.

Cardiorespiratory fitness. We included a cardiorespiratory fitness measure (VO_{2peak}) as a manipulation check for documenting the success of the intervention.[3]

Intervention/Control conditions

Details of the present supervised, 12-week TMWX training intervention and waitlist control conditions are reported elsewhere.[3]

Data analysis

We performed two-way repeated-measures analyses-of-variance (ANOVAs) on the outcome measures. Given the small sample size, reaching statistical significance for SDMT scores and VO_{2peak} using ANOVA was unlikely. Thus, we computed effect sizes for changes in those outcomes per group as Cohen's d.[7] We report Spearman's (ρ) correlations for associations among changes in cardiorespiratory fitness (i.e. a surrogate for TMWX training), thalamocortical RSFC, and CPS. Effect sizes were interpreted based on established criteria.[7]

Results

Baseline demographic and clinical characteristics based on condition are provided in Table 1.

There was a statistically significant group-by-time interaction on thalamic/right superior frontal gyrus (SFG) RSFC ($F(1,6) = 411.38$, $p < 0.01$, $d = 1.92$; Figure 1); those who underwent TMWX training demonstrated increased RSFC compared with decreased RSFC in the control condition. There further was a statistically significant group-by-time interaction on thalamic/left medial frontal gyrus (MFG) RSFC ($F(1,6) = 411.38$, $p < 0.01$, $d = 1.70$; Figure 1); those who underwent TMWX training demonstrated small increases in RSFC compared with decreased RSFC in the control condition.

There were further moderate-to-large effects on SDMT scores ($d = 0.72$; Table 1), and large intervention effects on VO_{2peak} ($d = 0.88$; Table 1) based on differential mean changes between groups. Of note, all participants who were randomly assigned to the TMWX training condition demonstrated improvements in VO_{2peak} (range = 0.5–6.3 ml/kg/min improvement).

The change in VO_{2peak} was moderately associated with change in thalamic/right MFG RSFC ($\rho = 0.43$)

Table 1. Descriptive characteristics, cognitive performance, and cardiorespiratory fitness of eight females with relapsing–remitting multiple sclerosis.

Variable	Exercise ($N = 5$)		Control ($N = 3$)	
Age (years)	41.6 (11.5)		46.7 (11.6)	
Education (*n*, %)				
Some college	3/5 (60.0%)		2/3 (66.7%)	
College/University graduate	2/5 (40.0%)		1/3 (33.3%)	
Employment (*n*, % employed)	3/5 (60.0%)		3/3 (100.0%)	
Disease duration (years)	11.4 (9.8)		13.7 (9.6)	
EDSS (median, range)	3.0 (1.5–4.0)		3.5 (2.5–4.0)	
Adherence (% of sessions attended)	96.3% (6.5%)		–	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
SDMT	55.0 (9.2)	58.2 (7.9)	64.0 (18.7)	63.0 (12.2)
VO_{2peak}	24.2 (6.0)	27.6 (5.7)	30.8 (5.4)	31.0 (3.1)

All data are presented as mean (SD) unless otherwise noted. EDSS: Expanded Disability Status Scale; SDMT: Symbol Digit Modalities Test; VO_{2peak}: peak oxygen consumption.

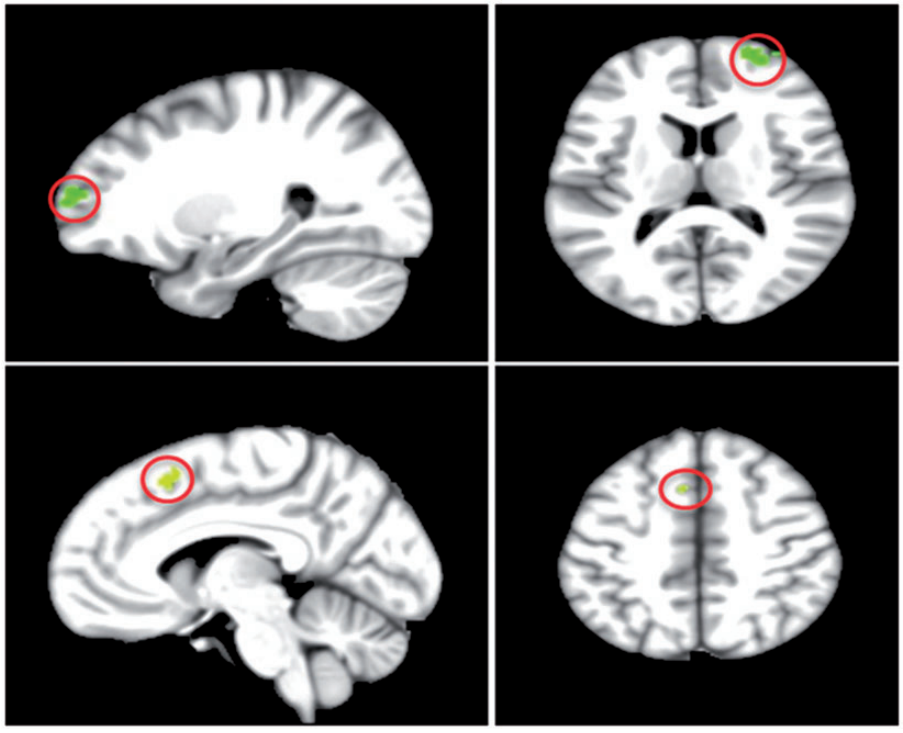

Figure 1. Cortical regions in which resting-state functional connectivity with the thalamus significantly increased following treadmill walking exercise training compared with waitlist control.
Top row: right superior frontal gyrus; bottom row: left medial frontal gyrus.

and thalamic/left SFG RSFC ($\rho = 0.43$). The change in thalamic/right SFG RSFC was moderately associated with change in SDMT ($\rho = 0.59$) scores. The change in thalamic/left MFG RSFC was moderately associated with change in SDMT ($\rho = 0.63$) scores. Lastly, the change in VO_{2peak} was moderately associated with change in SDMT ($\rho = 0.37$) performance. Collectively, this indicates interrelations among changes in VO_{2peak} (i.e. as a TMWX training adaptation), thalamocortical RSFC, and CPS.

Discussion

This pilot RCT in MS provides preliminary efficacy data that 12 weeks of TMWX training resulted in large, statistically significant increases in thalamocortical RSFC and moderate-to-large, albeit nonsignificant, improvements in SDMT performance compared with the control condition. The increases in thalamocortical RSFC were moderately associated with CPS improvements. Overall, this pattern of preliminary results supports a potential adaptive compensatory mechanism whereby progressive TMWX training improves CPS through increased thalamocortical RSFC in fully ambulatory individuals with MS. These preliminary data provide an exciting springboard for examining exercise training as a rehabilitative approach for inducing beneficial changes (i.e. neuroplasticity) in neural networks that are particularly relevant for MS.

TMWX is a complex behavior with continuously changing multisensorial environmental demands. Successfully and rapidly adapting to such challenges requires enhanced communication between the thalamus and frontal cortex.[5] This especially might be the case for patients with MS, who might be particularly challenged by the complex task demands of TMWX.[2,8] Indeed, engaging in chronic TMWX might repeatedly activate this network, resulting in increased thalamocortical RSFC over time (i.e. task-dependent neuroplasticity). The present results are consistent with this hypothesis as 12 weeks of supervised, progressive TMWX training resulted in increased thalamocortical RSFC and improved CPS in patients with MS. This extends previous results wherein single bouts of TMWX resulted in improved cognitive functions dependent on thalamic and frontal circuitry in MS.[9,10] The present TMWX training-related increases in thalamocortical RSFC might suggest that putative neural benefits of single bouts of TMWX might accumulate over time and result in meaningful improvements in brain function and CPS in individuals with MS. The inclusion of functional neuroimaging outcomes during the resting state provides a neural substrate for generalized TMWX-related adaptations (i.e. core neuroplastic changes) resulting in improved CPS in this population.

There are study limitations. This study represents a secondary analysis of neuroimaging data from a pilot RCT on TMWX effects on cognition in fully ambulatory individuals with MS.[3] This study involved a small sample, and the results of this RCT are preliminary and require further examination and confirmation in larger MS samples. We did not recruit participants a priori based on having impaired CPS. Accordingly, we are unable to consider TMWX training as a possible treatment of MS-related CPS dysfunction since not all participants had objective CPS impairment at baseline. There were possible clinically meaningful baseline differences between groups in thalamocortical RSFC, CPS, and cardiorespiratory fitness outcomes, whereby the intervention condition demonstrated lower baseline RSFC, CPS, and cardiorespiratory fitness compared with the control condition. The pattern of preliminary results indicated improvements in those outcomes for the intervention condition compared with slight decrements for the control condition. As such, it is possible that the changes represent regression to the mean rather than intervention effects per se. Unfortunately, the small sample size did not permit significance testing using analysis of covariance models, given the subsequent reduction in degrees of freedom when including baseline outcomes as covariates as well as the untenable assumption of homogeneity of regression slopes between groups. This limits the internal validity of the present pilot RCT, and the differential effects of the intervention versus the waitlist control condition on the primary outcomes should be interpreted with caution. Future RCTs of TMWX training on cognitive and neuroimaging outcomes in patients with MS might consider adopting a block randomization scheme, matching participants on baseline SDMT score. Lastly, though decreased RSFC in the control condition was unexpected, we speculate that a lack of physical activity engagement for those persons over the study period might explain such an observation.

Conclusions

This small pilot RCT provides preliminary proof-of-concept data supporting progressive TMWX training for potentially inducing selective neuroplastic changes in thalamocortical RSFC, and possibly explaining CPS improvements in MS patients. Such preliminary data highlight functional connectivity within thalamocortical circuitry as a potential target for rehabilitation interventions for improving CPS in larger samples of cognitively impaired individuals with MS.

Acknowledgment

This study was carried out, in part, at the Biomedical Imaging Center at the Beckman Institute for Advanced Science and Technology at the University of Illinois.

Conflicts of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Motl RW, Sandroff BM and Benedict RH. Cognitive dysfunction and multiple sclerosis: Developing a rationale for considering the efficacy of exercise training. *Mult Scler* 2011; 17: 1034–1040.
2. Stillman CM, Cohen J, Lehman ME, et al. Mediators of physical activity on neurocognitive function: A review at multiple levels of analysis. *Front Hum Neurosci* 2016; 10: 1–17.
3. Sandroff BM, Balto JM, Klaren RE, et al. Systematically-developed pilot randomized controlled trial of exercise and cognition in persons with multiple sclerosis. *Neurocase* 2016; 22: 443–450.
4. Houchens MK, Benedict RH, Killiany R, et al. Thalamic atrophy and cognition in multiple sclerosis. *Neurology* 2007; 69: 1213–1223.
5. Jensen SK and Yong VW. Activity-dependent and experience-driven myelination provide new directions for the management of multiple sclerosis. *Trends Neurosci* 2016; 39: 356–365.
6. Smith A. *Symbol digit modalities test: Manual*. Los Angeles, CA: Western Psychological Services, 1982.
7. Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd ed. Hillsdale NJ: Lawrence Erlbaum Associates, 1988.
8. Carey JR, Bhatt E and Nagpal A. Neuroplasticity promoted by task complexity. *Exerc Sport Sci Rev* 2005; 33: 24–31.
9. Sandroff BM, Hillman CH, Benedict RH, et al. Acute effects of walking, cycling, and yoga exercise on cognition in persons with relapsing–remitting multiple sclerosis without impaired cognitive processing speed. *J Clin Exp Neuropsychol* 2015; 37: 209–219.
10. Sandroff BM, Hillman CH, Benedict RH, et al. Acute effects of varying intensities of treadmill walking exercise on inhibitory control in persons with multiple sclerosis: A pilot investigation. *Physiol Behav* 2016; 154: 20–27.