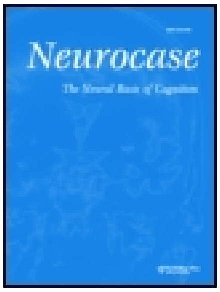

Neurocase: The Neural Basis of Cognition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/nncs20

Aerobic exercise increases hippocampal volume and improves memory in multiple sclerosis: Preliminary findings

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Published online: 04 Oct 2013.

Neurocase, 2013
http://dx.doi.org/10.1080/13554794.2013.841951

Aerobic exercise increases hippocampal volume and improves memory in multiple sclerosis: Preliminary findings

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Multiple sclerosis leads to prominent hippocampal atrophy, which is linked to memory deficits. Indeed, 50% of multiple sclerosis patients suffer memory impairment, with negative consequences for quality of life. There are currently no effective memory treatments for multiple sclerosis either pharmacological or behavioral. Aerobic exercise improves memory and promotes hippocampal neurogenesis in nonhuman animals. Here, we investigate the benefits of aerobic exercise in memory-impaired multiple sclerosis patients. Pilot data were collected from two ambulatory, memory-impaired multiple sclerosis participants randomized to non-aerobic (stretching) and aerobic (stationary cycling) conditions. The following baseline/follow-up measurements were taken: high-resolution MRI (neuroanatomical volumes), fMRI (functional connectivity), and memory assessment. Intervention was 30-minute sessions 3 times per week for 3 months. Aerobic exercise resulted in 16.5% increase in hippocampal volume and 53.7% increase in memory, as well as increased hippocampal resting-state functional connectivity. Improvements were specific, with no comparable changes in overall cerebral gray matter (+2.4%), non-hippocampal deep gray matter structures (thalamus, caudate: −4.0%), or in non-memory cognitive functioning (executive functions, processing speed, working memory: changes ranged from −11% to +4%). Non-aerobic exercise resulted in relatively no change in hippocampal volume (2.8%) or memory (0.0%), and no changes in hippocampal functional connectivity. This is the first evidence for aerobic exercise to increase hippocampal volume and connectivity and improve memory in multiple sclerosis. Aerobic exercise represents a cost-effective, widely available, natural, and self-administered treatment with no adverse side effects that may be the first effective memory treatment for multiple sclerosis patients.

Keywords: Multiple sclerosis; Aerobic; Memory; Functional connectivity; Hippocampus.

Aerobic exercise stimulates hippocampal neurogenesis and improves memory in nonhuman animals (van Praag, Christie, Sejnowski, & Gage, 1999). To date, only two randomized controlled trials (RCTs) have investigated the impact of aerobic exercise on hippocampal volume in human samples characterized by memory decline (healthy elders (Erickson, Voss, & Prakash, 2011) and schizophrenia patients (Pajonk, Wobrock, & Gruber, 2010)). While both studies linked aerobic exercise to increased hippocampal volume, only one investigated episodic memory, showing a concomitant improvement in memory (Pajonk et al., 2010). Here, we present preliminary evidence for aerobic exercise as a treatment to increase hippocampal volume and improve memory in a memory-impaired neurologic sample: multiple sclerosis (MS). Approximately 50% of MS

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patients suffer memory impairment (Thornton & Raz, 1997), even early in the disease course, with negative consequences for quality of life. Memory impairment in MS has been linked to prominent hippocampal atrophy (Sicotte, Kern, & Giesser, 2008), with about 10% hippocampal volume reduction in relapsing-remitting MS (RRMS) patients within 5 years of diagnosis (Sicotte et al., 2008). There are currently no effective memory treatments for MS, either pharmacological or behavioral (das Nair, Ferguson, Stark, & Lincoln, 2012). Promising findings for aerobic exercise as an effective method to increase hippocampal volume and improve memory in nonhuman animals and two RCTs in non-neurologic populations motivated the current investigation in MS patients. Of note, this is the first study to investigate benefits on three levels: neuroanatomical (hippocampal volume), neurophysiological (hippocampal functional connectivity), and behavioral (memory).

METHODS

In this pilot study, two ambulatory, memory-impaired female RRMS patients were randomized to one of two exercise training conditions, non-aerobic (Patient 1: age 33, 15 months since MS diagnosis) and aerobic exercise (Patient 2: age 44, 14 months since MS diagnosis). Both subjects were memory-impaired as determined by the selected reminding test (Patient 1: $z = -1.64$, 5‰, Patient 2: $z = -3.07$, <1‰).

Baseline and follow-up measurements. High-resolution MRI was collected for each participant on a 3T Siemens scanner (Erlangen, Germany). Structural volumes for hippocampus, caudate, thalamus, and overall cerebral gray matter were calculated using Freesurfer software (http://surfer.nmr.mgh.harvard.edu). Functional MR images were acquired during rest. Seed-based functional connectivity was derived using AFNI software (Cow, 1996). Correlations were calculated between a 3-mm-radius seed centered in left hippocampus (LHIPP) and every brain voxel. Cognitive impairment in MS patients is characterized primarily by memory impairment and cognitive inefficiency. Memory was assessed with verbal and nonverbal tasks (California Verbal Learning Test-second edition (CVLT-II), Brief Visual Memory Test-revised (BVMT-R)).Cognitive efficiency was assessed with tests of processing speed (Symbol Digit Modality Test (SDMT), Paced Auditory Serial Addition Test (PASAT), executive function (Stroop), and working memory (Digit Span). Patients underwent $VO_{2\,peak}$ testing to measure aerobic fitness.

Treatment. Intervention was 30-minute sessions, 3 times per week for 12 weeks, consistent with methods of a prior study conducted in schizophrenia patients (Pajonk et al., 2010). The aerobic condition consisted of stationery cycling using an individualized program of graduated resistance developed by an exercise physiologist (CC) informed by baseline aerobic fitness testing. The non-aerobic condition consisted of a program of stretching specifically developed for MS patients.

RESULTS

Aerobic exercise resulted in a 16.5% increase in hippocampal volume (baseline = 5958 mm^3, follow-up = 6942 mm^3), a 55.9% increase in verbal memory (CVLT Total Learning baseline = 31, follow-up = 48; CVLT Long Delay Free Recall baseline = 7, follow-up = 11), and 51.3% increase in nonverbal memory (BVMT Total Learning baseline = 18, follow-up = 23; BVMT Delayed Recall baseline = 4, follow-up = 7). Additionally, a large increase in hippocampal resting-state functional connectivity was shown (see Figure 1, bottom panel). $VO_{2\,peak}$ increased by 10% (baseline = 20.2 ml/kg/min, follow-up = 22.3 ml/kg/min). Non-aerobic exercise resulted in relatively no change in hippocampal volume (+2.8%), no change in verbal and nonverbal memory (0.0%), no changes in hippocampal resting-state functional connectivity (see Figure 1, top panel), and no increase in $VO_{2\,peak}$. Furthermore, and consistent with our a priori hypotheses, effects of aerobic exercise were specific to the hippocampus and memory, as there were no comparable changes in overall cerebral gray matter (+2.4%) or in non-hippocampal deep gray matter structures (thalamus, caudate: –4.0%), nor were there any changes in non-memory cognitive functioning (executive functions, processing speed, working memory: change ranged from −11% to +4%).

DISCUSSION

These are the first data supporting the benefits of aerobic exercise to increase hippocampal volume, improve memory, and increase hippocampal functional connectivity in MS. These improvements

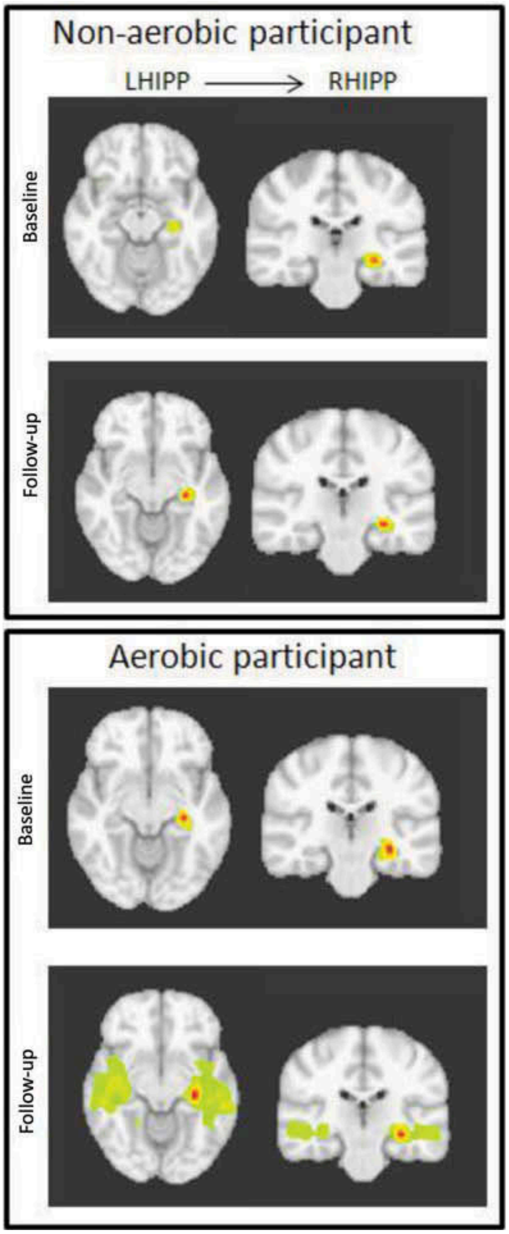

Figure 1. Displayed are r-maps for each participant revealing cortical regions showing functional connectivity to the LHIPP seed at baseline and follow-up in each participant. [To view this figure in color, please visit the online version of this Journal.]

were shown after only 12-weeks of aerobic exercise training. Although based on only two cases, the strength of this interventional case report is bolstered by the specificity of our findings. That is, the positive effects of exercise on hippocampal volume/functional connectivity and memory, were specific to the aerobic exercise condition. The results for the aerobic patient also showed specificity to our stated hypotheses: increased hippocampal volume/functional connectivity and memory, but not non-hippocampal volume or non-memory cognition. Furthermore, an increase in hippocampal volume of this magnitude (+16.5%) over 3 months in the absence of an outside influence is unlikely to occur by chance alone. There is currently no effective approved treatment for memory impairment in MS. Aerobic exercise represents an inexpensive, widely available, natural, and self-administered treatment with no adverse side effects that may be the first effective memory treatment for MS patients. Future large-scale RCTs to test aerobic exercise as a treatment for memory decline in MS are clearly warranted, particularly to highlight the specific benefit of aerobic exercise for memory function that is supported by these pilot data, and not cognitive function more generally (e.g., executive functioning, processing speed).

Original manuscript received 4 March 2013
Revised manuscript received 22 July 2013
Revised manuscript accepted 28 August 2013
First published online 27 September 2013

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