NeuroImage xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Entorhinal volume, aerobic fitness, and recognition memory in healthy young adults: A voxel-based morphometry study

Andrew S. Whiteman [a,b], Daniel E. Young [c], Andrew E. Budson [d,g], Chantal E. Stern [a,b], Karin Schon [a,b,e,f,*]

[a] Dept. of Psychological and Brain Sciences, Boston Univ., 2 Cummington Mall, Boston, MA 02215, USA
[b] Center for Memory and Brain, Boston Univ., 2 Cummington Mall, Boston, MA 02215, USA
[c] College of Nursing and Health Sciences, Exercise and Health Sciences Program, Univ. of Massachusetts Boston, 100 Morrissey Blvd, Boston, MA 02125, USA
[d] Dept. of Neurology, Boston Univ. School of Medicine, Boston, MA, USA
[e] Dept. of Anatomy and Neurobiology, Boston Univ. School of Medicine, 72 East Concord St., Boston, MA, USA
[f] Center for Biomedical Imaging, Boston Univ. School of Medicine, 72 East Concord St., Boston, MA, USA
[g] VA Boston Healthcare System, 150 South Huntington St., Boston, MA 02130, USA

ARTICLE INFO

Article history:
Received 14 July 2015
Accepted 20 November 2015
Available online xxxx

Keywords:
Medial temporal lobes
Hippocampus
Recognition memory
Cardiovascular fitness
Neurotrophins

ABSTRACT

Converging evidence supports the hypothesis effects of aerobic exercise and environmental enrichment are beneficial for cognition, in particular for hippocampus-supported learning and memory. Recent work in humans suggests that exercise training induces changes in hippocampal volume, but it is not known if aerobic exercise and fitness also impact the entorhinal cortex. In animal models, aerobic exercise increases expression of growth factors, including brain derived neurotrophic factor (BDNF). This exercise-enhanced expression of growth hormones may boost synaptic plasticity, and neuronal survival and differentiation, potentially supporting function and structure in brain areas including but not limited to the hippocampus. Here, using voxel based morphometry and a standard graded treadmill test to determine cardio-respiratory fitness (Bruce protocol; VO_2 max), we examined if entorhinal and hippocampal volumes were associated with cardio-respiratory fitness in healthy young adults ($N = 33$). In addition, we examined if volumes were modulated by recognition memory performance and by serum BDNF, a putative marker of synaptic plasticity. Our results show a positive association between volume in right entorhinal cortex and cardio-respiratory fitness. In addition, average gray matter volume in the entorhinal cortex, bilaterally, was positively associated with memory performance. These data extend prior work on the cerebral effects of aerobic exercise and fitness to the entorhinal cortex in healthy young adults thus providing compelling evidence for a relationship between aerobic fitness and structure of the medial temporal lobe memory system.

Introduction

The beneficial effects of cardio-respiratory fitness, aerobic exercise, and environmental enrichment on brain health and cognition are well documented (e.g. see van Praag et al., 2000; Cotman and Berchtold, 2002; Cotman et al., 2007 for reviews). For example, aerobic exercise and environmental enrichment are thought to improve learning and memory and to induce changes in the morphology of many brain structures, notably the hippocampus, through a variety of mechanisms. Most of this knowledge, however, is inferred from rodent models, which have focused eminently on effects in the dentate gyrus (DG), a sub-region of the hippocampus. Comparatively fewer direct observations have been made in humans. We therefore take a translational approach considering putative physical and neural correlates of exercise adaptation cross-sectionally in healthy young adults.

In rodents, both exercise and environmental enrichment have been shown to upregulate birth and survival rates of adult born neuronal and glial cells in the DG of the hippocampus, as well as improve performance on hippocampal dependent memory tasks (Creer et al., 2010; Falls et al., 2010; Fordyce and Farrar, 1991; Kempermann et al., 1997; O'Callaghan et al., 2007; Uda et al., 2006; Van Praag et al., 1999, 2005). More generally, environmental enrichment has also been linked to increased cortical thickness across the brain, most notably in posterior regions and the entorhinal cortex (EC) (Diamond et al., 1976, 1987; Greer

Abbreviations: ACSM, American College of Sports Medicine; BDNF, brain-derived neurotrophic factor; BMI, Body Mass Index; CBV, cerebral blood volume; DMS, delayed matching-to-sample; EC, entorhinal cortex; ELISA, Enzyme-Linked Immunosorbent Assay; MTLs, medial temporal lobes; RER, respiratory exchange ratio; RER_{max}, maximum observed respiratory exchange ratio; SMT, subsequent memory test; VEGF, vascular endothelial growth factor; VBM, voxel-based morphometry; VO_2 max, rate of maximal oxygen consumption in ml per kg of body weight per min; VO_2 peak, peak rate of oxygen consumption in ml per kg of body weight per min, measured during test.

* Corresponding author at: Dept. of Anatomy and Neurobiology, Boston University School of Medicine, 72 East Concord St., L-1004, Boston, MA, USA. Fax: +1 617 638 4216.

E-mail addresses: asw221@bu.edu (A.S. Whiteman), daniel.young@umb.edu (D.E. Young), abudson@bu.edu (A.E. Budson), chantal@bu.edu (C.E. Stern), kschon@bu.edu (K. Schon).

http://dx.doi.org/10.1016/j.neuroimage.2015.11.049
1053-8119/© 2015 Published by Elsevier Inc.

et al., 1982a, 1982b; reviewed in Mohammed et al., 2002). Exercise-induced brain plasticity is thought to be regulated in part by the complex, pleiotropic actions of different neurotrophins, namely brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1). These neurotrophins are associated with synaptic plasticity, neuronal survival, and differentiation (Kang and Schuman, 1995; McAllister et al., 1999; Trejo et al., 2001; see Cotman et al., 2007 for a review). In animal models BDNF mRNA expression, while highest in the hippocampus, is also high in EC and perirhinal cortex (Conner et al., 1997; Okuno et al., 1999).

Owing to the adult neurogenesis hypothesis, animal models have primarily targeted the DG and the hippocampal memory system. Exercise not only affects the DG, however, but also other regions of the medial temporal lobes (MTLs), especially hippocampal subfield CA1 and the EC (Neeper et al., 1996; Stranahan et al., 2007). Specifically, structural changes have been observed in these regions in the form of increased dendritic spine density in basal dendrites of pyramidal neurons in entorhinal layer III and in basal and apical CA1 neurons after two months of voluntary wheel running (Stranahan et al., 2007). These findings stand on their own, but also integrate well with the literature on neurogenesis, given that the EC has direct projections to the DG and CA1 via layers II and III, respectively (Steward and Scoville, 1976; Van Hoesen and Pandya, 1975; Witter et al., 1988, 1989), and entorhinal input may be needed to integrate newborn DG neurons into existing functional networks (Vivar et al., 2012). In addition, angiogenesis could also affect hippocampal and/or entorhinal structure following exercise training. Angiogenesis and neurogenesis are upregulated cooperatively (Palmer et al., 2000), resulting in enhanced formation of new blood vessels that support newborn neurons. Together, these findings suggest that aerobic exercise and cardio-respiratory fitness may directly alter the structure of the MTL more broadly.

It is plausible that angiogenesis, adult neurogenesis, and neurotrophin-mediated plasticity may underlie aerobic exercise-related changes in MTL function and structure in humans. Although these hypotheses cannot be assessed directly in living individuals, evidence for adult neurogenesis has been observed in postmortem human tissue (Eriksson et al., 1998). In addition, increased cerebral blood volume (CBV) in the DG (and somewhat in the EC) has been linked to exercise, providing a possible correlate of exercise-induced neurogenesis in mice and by extension, perhaps in humans (Pereira et al., 2007). In support of these ideas, recent human studies indicate that aerobic exercise training and cardio-respiratory fitness may be positively correlated with hippocampal volume (Erickson et al., 2009, 2011b) and hippocampal cerebral blood flow in healthy older adults (Maass et al., 2015b). In turn, changes in hippocampal volume following the exercise intervention were correlated with changes in serum BDNF (Erickson et al., 2011b). Previous work from our lab suggests that effects of aerobic fitness and serum BDNF interact to support episodic recognition memory (Whiteman et al., 2014) in a task we have shown to recruit the hippocampus and perirhinal/EC (Schon et al., 2004, 2005). Additionally, increased cardio-respiratory fitness is associated with greater volume of the parahippocampal gyrus in Alzheimer's disease patients (Honea et al., 2009), and aerobic exercise consistently appears as one of the most effective interventions to attenuate cognitive decline in geriatric populations (Barnes & Yaffe, 2011; Burns et al., 2008). In younger cohorts, exercise-induced gains in cardio-respiratory fitness have been linked to better relational memory in children (Chaddock et al., 2010), and better learning of a virtual Morris Water Maze task in adolescents (Herting and Nagel, 2012).

Given this background, it is likely that entorhinal-dependent memory is associated with cardio-respiratory fitness and related mechanisms, but a direct link has not yet been established with entorhinal structure in humans. Establishing such a connection is of interest given that the EC provides the primary input to the hippocampus during episodic memory encoding. The present study reports on a subsample of participants from Whiteman et al. (2014) that participated in a magnetic resonance imaging (MRI) study to examine associations between aerobic capacity and volumes of structures in the medial temporal lobe (MTL) memory system. Healthy young participants underwent a standard graded treadmill test to measure cardiorespiratory fitness (Bruce et al., 1963; Thompson et al., 2010), provided blood samples to assay serum BDNF concentration, and performed an episodic recognition memory task (Schon et al., 2004; Whiteman et al., 2014). We used region-of-interest (ROI) based voxel-based morphometry (VBM; Ashburner and Friston, 2000) to analyze regional gray matter volume in the EC and hippocampus in an unbiased manner. We predicted that volume in these structures would be positively associated with cardiorespiratory fitness. In addition, based on our previous work (Whiteman et al., 2014), we hypothesized that serum BDNF would also predict MTL volumes. Here, we report evidence for a relationship between aerobic fitness and gray matter volume in the EC. We also report that performance on our recognition memory task was correlated with average volume in both the hippocampus and EC; we did not find relationships between gray matter volume and serum BDNF.

Materials and methods

Participants

One hundred and fourteen healthy young participants were recruited from the Boston University student community. A random subsample of this cohort (sixty-one individuals) was recruited to participate in an MRI study; the full sample is described in Whiteman et al. (2014). Of this sub-sample, 16 did not meet inclusion/exclusion criteria, and forty-five participants were enrolled. Ten participants voluntarily withdrew or were lost to contact, and two were excluded due to equipment malfunction, leaving a final sample size of $N = 33$ participants (20 female, 13 male).

All participants were native English speakers or bilingual, all had normal or corrected to normal vision, and all gave signed, informed consent prior to the start of any study procedures. All protocols were approved by the Boston University Charles River Campus Institutional Review Board. Subject characteristics are described in Table 1.

Procedure

For each participant, the experiment consisted of three visits: (i) informed consent and screening; (ii) VO_2 max aerobic capacity and body composition testing; and (iii) blood draw and MRI (including functional MRI and cognitive testing). For each participant, all visits were performed approximately within one month, and visit three (MRI and blood draw) took place no later than one week after visit two (aerobic fitness testing).

Table 1
Participant demographics. Data are presented as mean ± sd. Asterisks in the $Mean_{male}$ column indicate differences in the gender group means.

$N = 33$ (20 female)	Range	Mean	$Mean_{female}$	$Mean_{male}$
Age (yrs)	18.0–30.0	21.1 ± 2.8	20.9 ± 2.8	21.6 ± 2.9
Education (yrs)	12.0–22.0	15.3 ± 2.2	14.9 ± 1.6	15.7 ± 2.9
Fitness percentile	17.9–100.0	65.3 ± 27.0	55.9 ± 23.7	78.7 ± 26.4*
Memory accuracy (%)	26.3–68.2	46.6 ± 9.8	46.8 ± 11.5	46.4 ± 7.4
BDNF ($ng \cdot ml^{-1}$)	4.6–30.5	18.0 ± 6.4	17.7 ± 6.1	18.5 ± 7.1
VO_2 peak ($ml \cdot kg^{-1}$)	31.3–66.5	45.5 ± 10.3	39.8 ± 6.9	53.6 ± 8.7***
RER_{max}	1.0–1.6	1.3 ± 0.2	1.2 ± 0.1	1.3 ± 0.2
Intra-cranial volume (l)	1.2–1.8	1.5 ± 0.1	1.4 ± 0.1	1.6 ± 0.1**
BMI	19.2–28.9	23.4 ± 2.8	23.2 ± 3.0	23.7 ± 2.4
Body fat (%)	5.0–29.2	18.7 ± 8.3	24.5 ± 3.9	10.3 ± 5.2***
Height (m)	1.5–1.9	1.7 ± 0.1	1.6 ± 0.1	1.7 ± 0.1***
Weight (kg)	49.2–86.1	66.2 ± 11.4	61.4 ± 10.5	73.0 ± 9.1**
Waist circumference (cm)	62.0–93.4	74.9 ± 7.5	72.5 ± 6.6	78.4 ± 7.6*
Hip circumference (cm)	81.0–112.5	93.4 ± 8.2	93.2 ± 9.0	93.7 ± 7.2

Please cite this article as: Whiteman, A.S., et al., Entorhinal volume, aerobic fitness, and recognition memory in healthy young adults: A voxel-based morphometry study, NeuroImage (2015), http://dx.doi.org/10.1016/j.neuroimage.2015.11.049