Brain, Behavior, and Immunity 28 (2013) 90–99

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

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

Neurobiological markers of exercise-related brain plasticity in older adults

Michelle W. Voss [a,*], Kirk I. Erickson [d], Ruchika Shaurya Prakash [e], Laura Chaddock [b], Jennifer S. Kim [b], Heloisa Alves [b], Amanda Szabo [c], Siobhan M. Phillips [c], Thomas R. Wójcicki [c], Emily L. Mailey [c], Erin A. Olson [c], Neha Gothe [c], Victoria J. Vieira-Potter [c], Stephen A. Martin [c], Brandt D. Pence [c], Marc D. Cook [c], Jeffrey A. Woods [c], Edward McAuley [c], Arthur F. Kramer [b]

[a] The University of Iowa, Department of Psychology, IA, United States
[b] Beckman Institute & Department of Psychology, IA, United States
[c] Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, IL, United States
[d] Department of Psychology, University of Pittsburgh, PA, United States
[e] Department of Psychology, The Ohio State University, OH, USA

ARTICLE INFO

Article history:
Received 20 June 2012
Received in revised form 24 October 2012
Accepted 24 October 2012
Available online 2 November 2012

Keywords:
Exercise
Aging
Functional connectivity
fMRI
Default mode network
Aerobic fitness
Growth factors

ABSTRACT

The current study examined how a randomized one-year aerobic exercise program for healthy older adults would affect serum levels of brain-derived neurotrophic factor (BDNF), insulin-like growth factor type 1 (IGF-1), and vascular endothelial growth factor (VEGF) – putative markers of exercise-induced benefits on brain function. The study also examined whether (a) change in the concentration of these growth factors was associated with alterations in functional connectivity following exercise, and (b) the extent to which pre-intervention growth factor levels were associated with training-related changes in functional connectivity. In 65 participants (mean age = 66.4), we found that although there were no group-level changes in growth factors as a function of the intervention, increased temporal lobe connectivity between the bilateral parahippocampus and the bilateral middle temporal gyrus was associated with increased BDNF, IGF-1, and VEGF for an aerobic walking group but not for a non-aerobic control group, and greater pre-intervention VEGF was associated with greater training-related increases in this functional connection. Results are consistent with animal models of exercise and the brain, but are the first to show in humans that exercise-induced increases in temporal lobe functional connectivity are associated with changes in growth factors and may be augmented by greater baseline VEGF.

1. Introduction

Aerobic exercise is beneficial for brain function in older adults (Colcombe et al., 2004; Rosano et al., 2010; Voss et al., 2010b). However, the neurobiological mechanisms for these benefits are not fully understood. Whereas animal models have identified several neurochemicals that mediate downstream effects of exercise on the brain and cognition, including brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) (Cotman et al., 2007), the role of these molecules in exercise-induced changes in human brain function is unknown. We have previously found that exercise training benefits functional connectivity in several brain networks (Voss et al., 2010b) that are relevant for understanding cognition and human behavior, including the default mode network (DMN) and two brain networks involved in cognitive control (Fronto-parietal and Fronto-executive, also referred to as the Cingulo-opercular network) (Voss et al., 2010a). The goal of this study was to investigate the relationship between serum BDNF, IGF-1, and VEGF, and functional connectivity in healthy elderly adults following one year of exercise training.

The DMN includes the posterior cingulate, ventral and superior frontal medial cortices, and bilateral lateral occipital, middle frontal, hippocampal and parahippocampal, and middle temporal cortices, with the posterior cingulate and temporal cortex portions being most adversely affected by age and mild cognitive impairment MCI status (Buckner et al., 2008; Fox et al., 2005; Greicius et al., 2004). The DMN shows greater activity during autobiographical memory and theory of mind processes, and is less metabolically active when attention is engaged exogenously (Buckner et al., 2008). However, the extent to which different regions in the DMN co-activate at rest has also been associated with individual differences in cognitive performance, progression from MCI to Alzheimer's Disease, and other psychiatric disorders (Andrews-Hanna et al., 2007; Khamsi, 2012; Voss et al., 2010a). We have

* Corresponding author. Address: The University of Iowa, Department of Psychology, 300 Iowa Avenue Iowa City, IA 52242, United States. Tel.: +1 319 335 2057; fax: +1 217 335 0191.
E-mail address: michelle-voss@uiowa.edu (M.W. Voss).

0889-1591/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bbi.2012.10.021

previously reported that one year of moderate intensity aerobic exercise (walking) increases task-independent functional coactivation of the hippocampus with the middle temporal gyrus and the lateral parieto-occipital cortex, as well as the middle temporal gyrus with the left middle frontal gyrus (Voss et al., 2010b). Given the links between the DMN, cognitive aging, and progression of MCI to AD, in conjunction with links between exercise and reduced risk of MCI and AD (Larson et al., 2006), these results suggest one pathway for the benefits of exercise is through improved DMN function. However the neurobiological mechanisms for improved DMN function remain unknown.

The fronto-executive network includes the anterior prefrontal cortex, insular and frontal operculum cortices, the temporo-parietal junction, and the dorsal posterior and anterior cingulate gyri and is involved in sustained task-set maintenance and error feedback for tuning top-down control (Dosenbach et al., 2006; Rushworth et al., 2004). Of all the regions in this network, aerobic exercise training was associated with increased task-independent functional connectivity of the left and right anterior prefrontal cortices in this network (Voss et al., 2010b). The fronto-parietal network includes the inferior parietal cortices, the supplementary motor and primary cortices, the frontal eye-fields, primary and extrastriate visual cortices, the inferior frontal cortex, and some overlapping portions of the temporo-parietal junction with the fronto-executive network, and is involved in rapid engagement and tuning of goal-directed attention (Dosenbach et al., 2006). In our previous study we found that a stretching and toning intervention benefited this network after 6 months of training (Voss et al., 2010b). These results are exciting in that moderate aerobic exercise can benefit functional brain networks in regions that typically degrade with aging and onset of disease. However, the mechanisms for how aerobic exercise confers such benefits in humans are relatively unknown. The present study seeks to further examine the potential mechanisms through which exercise exerts it benefits on functional brain connectivity in late life.

BDNF, IGF-1, and VEGF likely play complementary roles in explaining how exercise impacts brain networks. Central BDNF, and its receptor tyrosine kinase (TrkB), are highly concentrated in the hippocampus, but are also distributed throughout the brain (Murer et al., 1999), and mediate the effects of exercise on synaptogenesis, synaptic plasticity, and enhanced learning and memory (Christie et al., 2008). Consistent with this, in humans, circulating levels of BDNF have been linked to greater hippocampal volume and spatial memory performance (Erickson et al., 2010), and exercise-induced change in hippocampal volume (Erickson et al., 2012). Decreased BDNF plasma and serum levels have also been associated with behavioral and cognitive symptoms of clinical depression, Alzheimer's disease, and psychiatric disorders such as schizophrenia and autism (for reviews, see Erickson et al., 2012; Sen et al., 2008). These studies suggest that plasma and serum BDNF may in part reflect BDNF released from the brain and may be viable biomarkers for age- and clinically-relevant brain dysfunction.

However, BDNF is also produced by a number of organs and tissues in the peripheral nervous system, including the heart and lungs (Scarisbrick et al., 1993; Timmusk et al., 1993), and is stored and released from blood platelets and immune cells (Yamamoto and Gurney, 1990; Gielen et al., 2003; Kerschensteiner et al., 1999). Thus an important area of future research is to improve the understanding of the relationship between human peripheral and brain BDNF. This area of future research is challenging however, if not impossible, given the inherent limitations in acquiring brain biopsies from living humans. A promising alternative approach is to conduct longitudinal studies that manipulate a variable expected to modulate growth factor levels in the brain, such as exercise, and examine the covariance of individual differences in serum BDNF and brain-related biomarkers hypothesized to be functionally related to BDNF expression. A cross-sectional study with a similar approach found that serum BDNF was positively associated with a marker of neuronal integrity and metabolism in the neocortex (Lang et al., 2007), which parallels an animal study finding high correlation between peripheral and cortical BDNF (Karege et al., 2002). Previous studies have found support for the idea that aerobic exercise training increases serum BDNF, however findings are mixed overall with some studies not finding reliable increases in BDNF post exercise (for review, see Coelho et al., 2012; Erickson et al., 2012; Knaepen et al., 2010). Though, many of these (human) studies do not look at how individual differences in change in BDNF relate to other brain-based outcomes known to be associated with aerobic training, such as structural and functional integrity of the hippocampus, which may have better sensitivity to shared variance between brain-derived BDNF in the periphery and direct effects of BDNF in the brain. The current study examined both mean-level change in serum BDNF following chronic aerobic training, and covariance of individual differences in fitness gains with a measure of functional network integrity (functional connectivity) that has previously been related to increased availability of central BDNF based on genetic variation of the val66-met polymorphism (Thomason et al., 2009).

More consistent findings have shown that training-induced neuroprotective effects of IGF-1 may stem from increased brain uptake of peripheral (primarily liver-derived) IGF-1 during exercise, particularly in the hippocampus (Carro et al., 2000). Peripheral IGF-1 is produced primarily in the liver from growth hormone stimulation (Yakar et al., 1999). Animal studies have found that IGF-1 mediates exercise-induced angiogenesis, stimulates increased central BDNF and VEGF production (Ding et al., 2006; Lopez-Lopez et al., 2004), and is necessary for exercise-induced neurogenesis (Carro et al., 2000; Trejo et al., 2001). Related to aging, studies have shown late life is accompanied by reduction in both serum IGF-1 and density of IGF-1 receptors in the hippocampus and throughout the brain (for review, see Sonntag et al., 2005). Similar to IGF-1, animal studies have found that peripheral VEGF increases during aerobic exercise and in part mediates exercise-induced angiogenesis and neurogenesis (Lopez-Lopez et al., 2004). Sources of circulating VEGF include blood platelets (Möhle et al., 1997) and skeletal muscle contractions (Kraus et al., 2004). Through peripheral-central receptor pathways, circulating VEGF may promote neurogenesis and synaptic plasticity by stimulating neural stem cell proliferation and differentiation and increases central endothelial cell and astrocytic production of VEGF, BDNF, and IGF-1 (Zacchigna et al., 2008; de Almodovar et al., 2009). Together with some evidence that VEGF expression in the hippocampus declines with age (Shetty et al., 2005), exercise-associated increases in VEGF may play an important role in the therapeutic effects of exercise on the brain.

Given the evidence for their interdependence, we hypothesized that BDNF, IGF-1, and VEGF would increase following the aerobic exercise intervention, and that each would be associated with increased functional connectivity in the temporal and frontal cortices, where BDNF is highly concentrated and age-related brain dysfunction is greatest.

2. Materials and methods

2.1. Participants

Participants were recruited from the local community of Urbana-Champaign, Illinois. Eligible participants had to (1) demonstrate strong right handedness (since brain organization can vary based on handedness), with a 75% or above on the Edinburgh Handedness