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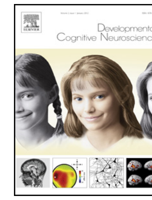

Aerobic fitness is associated with greater hippocampal cerebral blood flow in children

Laura Chaddock-Heyman[a,*], Kirk I. Erickson[b], Michael A. Chappell[c], Curtis L. Johnson[a], Caitlin Kienzler[a], Anya Knecht[a], Eric S. Drollette[d], Lauren B. Raine[d], Mark R. Scudder[d], Shih-Chun Kao[d], Charles H. Hillman[a,d], Arthur F. Kramer[a]

[a] Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, IL, USA
[b] Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA
[c] Institute of Biomedical Engineering and Oxford Centre for Functional MRI of the Brain, University of Oxford, Oxford, United Kingdom
[d] Department of Kinesiology & Community Health, University of Illinois at Urbana-Champaign, Urbana, IL, USA

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ABSTRACT

The present study is the first to investigate whether cerebral blood flow in the hippocampus relates to aerobic fitness in children. In particular, we used arterial spin labeling (ASL) perfusion MRI to provide a quantitative measure of blood flow in the hippocampus in 73 7- to 9-year-old preadolescent children. Indeed, aerobic fitness was found to relate to greater perfusion in the hippocampus, independent of age, sex, and hippocampal volume. Such results suggest improved microcirculation and cerebral vasculature in preadolescent children with higher levels of aerobic fitness. Further, aerobic fitness may influence how the brain regulates its metabolic demands via blood flow in a region of the brain important for learning and memory. To add specificity to the relationship of fitness to the hippocampus, we demonstrate no significant association between aerobic fitness and cerebral blood flow in the brainstem. Our results reinforce the importance of aerobic fitness during a critical period of child development.

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1. Introduction

Participation in physical activity and higher levels of aerobic fitness are associated with superior scholastic achievement, cognitive control, and memory in children (Buck et al., 2008; Castelli et al., 2007; Chaddock et al., 2010a,b, 2011; Chomitz et al., 2009; Hillman et al., 2009; Pontifex et al., 2011; Voss et al., 2011). Still, little is known about the neural mechanisms by which aerobic fitness influences the developing brain during childhood. Volumetric and functional magnetic resonance imaging (MRI) techniques provide some clues, such that higher fit children show larger brain volumes in the hippocampus and basal ganglia (Chaddock et al., 2010a,b), as well as differences in blood oxygenation level dependent (BOLD) fMRI brain activation in areas of frontal and parietal cortex (Chaddock et al., 2012; Voss et al., 2011), relative to their lower fit peers. Non-human animal work raises the possibility that, mechanistically, children with higher levels of aerobic fitness may have increased growth and expansion of neural tissue and/or increased vasculature (see Voss et al., 2013 for a review).

The present study is the first to investigate whether increased cerebral blood flow (CBF) in the hippocampus is associated with aerobic fitness during childhood. This hypothesis cannot be directly tested with traditional BOLD techniques, given that BOLD can change depending on a number of factors related to local metabolism and neural function, including blood volume, perfusion, blood velocity, and cerebral metabolic rate of oxygen (Hoge et al., 1999). Hence, here we use arterial spin labeling (ASL) perfusion MRI to provide a quantitative measure of blood flow and a more direct link to local neuronal activity (Alsop and Detre, 1996). Specifically, an ASL signal arises from the delivery of magnetically tagged arterial water into an imaging slice of interest, where the blood water exchanges in the tissue. The output measure of CBF, or the blood supply to a brain area in a given time (mL/100 g/min), is known to provide information regarding how the brain meets and regulates its metabolic demands via the delivery of metabolites, oxygen and nutrients to activated neurons (Hales et al., 2014; Sokoloff et al., 1977) (see ASL Scan Acquisition section in the Method for more information about ASL).

* Corresponding author at: Department of Psychology, The Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, 405 North Mathews Avenue, Urbana, IL 61801, USA.
E-mail address: lchaddo2@illinois.edu (L. Chaddock-Heyman).

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We specifically focused on CBF in the hippocampus, in view of converging evidence that demonstrates positive physical activity-related brain changes in the hippocampus in rodents and humans across the lifespan (Bugg and Head, 2011; Burdette et al., 2010; Chaddock et al., 2010a; Erickson et al., 2009, 2011; Honea et al., 2009; Pereira et al., 2007; van Praag et al., 1999b). For example, voluntary wheel running in rodents has been found to enhance learning and memory (van Praag et al., 2005) as well as induce angiogenesis and increased vascular density (Black et al., 1990; Clark et al., 2009; Kleim et al., 2002; Rhyu et al., 2010), and the growth of new neurons in the hippocampus (van Praag et al., 1999a). In humans, physical activity and aerobic fitness are associated with a greater number of small-caliber vessels (Bullitt et al., 2009), increased cerebral blood volume in the hippocampus in middle-aged adults (Pereira et al., 2007; age 21–45) and increased hippocampal blood flow in older adults (Burdette et al., 2010). Cognitively, increased hippocampal CBF has been linked to higher task performance on a spatial memory task in middle-aged and older adults (Heo et al., 2010; Pereira et al., 2007). It is possible that these findings extend to children, such that aerobic fitness relates to greater perfusion in the hippocampus, which may suggest improved microcirculation, cerebral vasculature, and function.

We hypothesized that aerobic fitness in 7- to 9-year-old preadolescent children would be associated with increased resting CBF in the hippocampus. We explored anterior and posterior subsections of the hippocampus to examine whether aerobic fitness had selective effects on hippocampal blood flow, and to investigate distinct contributions of different anatomical regions within the hippocampus given that functional distinctions have been described along the anterior/posterior axis of the hippocampus (i.e., spatial versus relational processing) (Giovanello et al., 2009; Sperling et al., 2003). To provide additional specificity to a fitness-CBF relationship, we also measured CBF in the brainstem as a control region. Like the hippocampus, the brainstem is a subcortical structure in the midbrain included in our ASL slice acquisition, yet this region has not been found to relate to aerobic fitness. Thus, we did not predict an association between aerobic fitness and brainstem CBF. Given these hypotheses, the present study will provide insight into a potential cerebrovascular mechanism by which aerobic fitness enhances brain health in children.

2. Method

2.1. Participants

Children were recruited from schools in East-Central Illinois. Eligible children were required to (1) report an absence of school-related learning disabilities (i.e., individual education plan related to learning), adverse health conditions, physical incapacities, or neurological disorders, (2) qualify as prepubescent (Tanner pubertal timing score ≤ 2; Taylor et al., 2001), (3) report no use of medications that influence central nervous system function, (4) demonstrate right handedness (as measured by the Edinburgh Handedness Questionnaire; Oldfield, 1971), (5) complete a mock MRI session successfully to screen for claustrophobia in an MRI machine, and (6) sign an informed assent approved by the University of Illinois at Urbana-Champaign. A legal guardian also provided written informed consent in accordance with the Institutional Review Board of the University of Illinois at Urbana-Champaign. The guardian was asked to provide information regarding participants' socioeconomic status, as determined by: (1) participation in free or reduced-price lunch program at school, (2) the highest level of education obtained by the mother and father, and (3) number of parents who worked full-time (Birnbaum et al., 2002).

Ninety-one children were eligible for the study. Eighteen children were excluded from the analysis due to excessive head motion during the ASL scan. Seventy-three children (41 girls, 32 boys), ages 7–9 years (M = 8.63 years, SD = 0.54) were included in the ASL analysis.

2.2. Aerobic fitness testing

Children completed a VO_{2max} test to assess aerobic fitness. The aerobic fitness of each child was measured as maximal oxygen consumption (VO_2max) during a graded exercise test (GXT). The GXT employed a modified Balke Protocol and was administered on a LifeFitness 92T motor-driven treadmill (LifeFitness, Schiller Park, IL) with expired gases analyzed using a TrueOne2400 Metabolic Measurement System (ParMedics, Sandy, Utah). Children walked and/or ran on a treadmill at a constant speed with increasing grade increments of 2.5% every 2 min until volitional exhaustion occurred.

Oxygen consumption was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400) with averages for VO_2 and respiratory exchange ratio (RER) assessed every 20 s. A polar heart rate (HR) monitor (Polar WearLink+ 31; Polar Electro, Finland) was used to measure HR throughout the test, and ratings of perceived exertion (RPE) were assessed every 2 min using the children's OMNI scale (Utter et al., 2002). Maximal oxygen consumption was expressed in mL/100 g/min and VO_2max was based upon maximal effort as evidenced by (1) a plateau in oxygen consumption corresponding to an increase of less than 2 mL/kg/min despite an increase in workload; (2) a peak HR $\geq$ 185 beats per minute (American College of Sports Medicine, 2014) and an HR plateau (Freedson and Goodman, 1993); (3) RER $\geq$ 1.0 (Bar-Or, 1983); and/or (4) a score on the children's OMNI ratings of perceived exertion (RPE) scale $\geq$ 8 (Utter et al., 2002). Our sample consisted of relatively lower fit children (average VO_2max percentile = 33.5%).

2.3. Arterial spin labeling (ASL) scan acquisition

Quantitative resting CBF in the child sample was measured using multi-slice pseudo-continuous arterial spin labeling (pCASL) (Wu et al., 2007). A number of studies have reported successful use of the ASL technique in children (Helton et al., 2009; Thomason et al., 2009; van den Tweel et al., 2009; Wang et al., 2003). In general, during an ASL scan, one or more radiofrequency (RF) pulses excite water molecules in arterial blood water in upstream blood (i.e., below the slice or region of interest), thus "labeling" or "tagging" the blood. Following a period of time, the labeled blood enters the imaging plane and alters the signal in the image, which is referred to as the "tag image." Then, this acquisition is repeated, without the RF labeling, and a "control image" is created without the added signal contribution from tagged arterial blood. The difference between the tag image and the control image is the perfusion image, which reflects only blood flow, or CBF. Therefore, the perfusion image quantifies the amount of arterial blood delivered to each voxel in the slice within the post-label delay. This is affected by the arterial transit time (ATT), which is the time it takes for blood to travel from labeling plane to image voxel.

During the pCASL scan, the slices were oriented axially, perpendicular to the vertebral arteries. The top slice was positioned superior to the corpus callosum so that the slices covered the temporal lobes of the brain, including the hippocampus. Prior to acquisition, shimming was performed over a region that extended from the imaging slices to the tagging plane. The acquisition parameters included: multi-slice, gradient-echo echo-planar imaging (EPI) sequence, repetition time (TR) = 4000 ms, echo time (TE) = 19 ms, field-of-view (FOV) = 220 mm × 220 mm, matrix = 64 × 64, in-plane resolution = 3.4 mm, 16 slices, slice

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