A NEUROIMAGING INVESTIGATION OF THE ASSOCIATION BETWEEN AEROBIC FITNESS, HIPPOCAMPAL VOLUME AND MEMORY PERFORMANCE IN PREADOLESCENT CHILDREN

BY

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Abstract

Because children are becoming increasingly overweight, unhealthy and unfit, understanding the neurocognitive benefits of an active lifestyle in childhood has important public health and educational implications. Animal research has indicated that aerobic exercise is related to increased cell proliferation and survival in the hippocampus as well as enhanced hippocampal-dependent learning and memory. Recent evidence extends this relationship to elderly humans by suggesting that high aerobic fitness levels in older adults are associated with increased hippocampal volume and superior memory performance. The present study aimed to further extend the link between fitness, hippocampal volume, and memory to a sample of preadolescent children. To this end, magnetic resonance imaging was employed to investigate whether high- and low-fit 9- and 10-year-old children showed differences in hippocampal volume and if the differences were related to performance on an item and relational memory task. Relational but not item memory is primarily supported by the hippocampus. Consistent with predictions, high-fit children showed greater bilateral hippocampal volumes. Furthermore, hippocampal volume was positively associated with performance on the relational but not the item memory task. The findings are the first to suggest that aerobic fitness can impact the structure and function of the developing human brain.

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Introduction

Children in today's industrial and technological society are becoming increasingly sedentary and unfit, leading to an increase in the incidence of obesity and illness (Olshansky et al. 2005; Baker et al. 2007; Ludwig 2007). A sedentary lifestyle also influences neurocognitive function and academic performance. For example, children with low physical activity levels show poorer academic achievement scores, diminished neuroelectric activity, and inferior cognitive performance compared to physically fit children (Sibley and Etnier 2003; Hillman et al. 2005, 2009; Castelli et al. 2007; Buck et al. 2008; Chomitz et al. 2009). This evidence is consonant with a growing research initiative in older adults which indicates that increased aerobic fitness can be neuroprotective and can enhance brain structure and function (Kramer et al. 1999; Colcombe and Kramer 2003; Colcombe et al. 2004, 2006; Heyn et al. 2004; Etnier et al. 2006; Pereira et al. 2007; Erickson et al. 2009). In one recent study, aerobically fit older adults had larger hippocampal volumes than less fit older adults, and this was associated with superior spatial memory performance (Erickson et al. 2009). The present study applies these findings to a youth population by exploring the association between aerobic fitness, hippocampal volume and memory function in preadolescent 9- and 10-year-old children.

Rodent and human studies provide a number of reasons to explore the link between aerobic fitness levels and hippocampal structure and function. To begin, rodent models have unequivocally demonstrated that voluntary aerobic exercise positively affects the hippocampus. Specifically, wheel-running (1) increases cell proliferation and survival in the dentate gyrus of the hippocampus in young adulthood through old age (van Praag et al. 1999, 2005; Eadie et al. 2005), (2) enhances hippocampal-dependent learning and memory processes (Fordyce and Wehner

1993; Vaynman et al. 2004; van Praag et al. 2005), and (3) increases hippocampal levels of brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF), and vascular endothelial-derived growth factor (VEGF), molecules involved in neuronal survival, synaptic development, learning, and angiogenesis (Barde 1994; Neeper et al. 1995; Lu and Chow 1999; Cotman and Berchtold 2002; Lopez-Lopez et al. 2004; Vaynman et al. 2004; Berchtold et al. 2005). Although the histological, cellular, and chemical basis for exercise-induced changes in the human brain is unknown, the broad hippocampal effects observed with exercise training in rodent populations suggest that greater aerobic fitness level may be associated with increased hippocampal volume during development.

Furthermore, exercise has been shown to impact memory function across the human lifespan (Pereira et al. 2007; Hillman et al. 2008; Erickson et al. 2009). During development, high levels of aerobic fitness have been associated with superior response accuracy on a relational memory behavioral task in 9- and 10-year-old children, a finding which suggests that physically fit children exhibit stronger executive control abilities and flexible use of memory via prefrontal-hippocampal interactions (Hillman et al. 2008). No preadolescent fitness effects were found for items studied non-relationally. This conclusion highlights the role of the hippocampus in the formation of new relational memories and in the “relational binding” process involved in successful retrieval while memory for single objects or items (i.e., item memory which requires little relational binding) is said to depend on the perirhinal cortex of the middle temporal lobe, prefrontal regions or parahippocampal circuits (Cohen and Eichenbaum 1993; Henke et al. 1997; Maguire et al. 1997; Cohen et al. 1999; Rombouts et al. 1999; Eichenbaum and Cohen 2001; Brassen et al. 2006). The current study extends Hillman et al.’s (2008) behavioral results by using a task more suitable for studying hippocampal function and by employing magnetic resonance imaging (MRI) techniques to examine the relationship between aerobic fitness, memory performance and hippocampal volume.

Most imaging investigations of the developing brain focus on the structural development of the cortex rather than subcortical regions (Giedd et al. 1999; Gogtay et al. 2004). However, medial temporal lobe gray matter structures, including the hippocampus, are said to increase in volume during childhood and adolescence (Durston et al. 2001; Toga et al. 2006). In terms of memory performance, most developmental neuroscientists have explored how changes in dorsolateral prefrontal cortex and parietal regions map onto working memory abilities (Bunge and Wright 2007) rather than the link between the developing hippocampus and memory abilities. The present investigation extends previous neurocognitive investigations by specifically exploring the development of hippocampal structure and function.

Given (1) the positive impact of physical activity and aerobic fitness on cognition in children, (2) the link between aerobic exercise, memory, and the hippocampus in rodent and human populations, and (3) the maturational trajectory of hippocampal development, the present study hypothesizes that children with high aerobic fitness levels will show larger bilateral hippocampal volumes and superior relational memory performance compared to low-fit children.

Method

Participants

Preadolescent 9- and 10-year-old children were recruited from East-Central Illinois. Children were screened for several factors that influence physical activity participation or cognitive function. To begin, the Kaufman Brief Intelligence Test (K-BIT; Kaufman and Kaufman 1990) was administered to each child to obtain a composite intelligence quotient (IQ) score including both crystallized and fluid intelligence measures. Subjects were excluded if their scores were more than 1 standard deviation below the mean (85%). Next, a guardian of the child completed the ADHD Rating Scale IV (DuPaul et al. 1998) to screen for the presence of attentional disorders. Participants were excluded if they scored above the 85th percentile. Pubertal timing was also assessed using a modified Tanner Staging System (Tanner 1962; Taylor et al. 2001) with all included prepubescent participants at or below a score of 2 on a 5-point scale of developmental stages. In addition, socioeconomic status was determined by creating a trichotomous index based on three variables: participation in a free or reduced-price lunch program at school, the highest level of education obtained by the mother and father, and the number of parents who worked full-time (Birnbaum et al. 2002).

Furthermore, eligible participants were required to (1) qualify as high-fit or low-fit (see Aerobic Fitness Assessment section), (2) demonstrate right handedness (as measured by the Edinburgh Handedness Questionnaire) (Oldfield 1971), (3) report no adverse health conditions, physical incapacities or neurological disorders, (4) report no use of medications that influenced central nervous system function, (5) have a corrected visual acuity of 20/20 and no color-blindness, (6) successfully perform a “mock MRI” session to test for body size compatibility with an MRI machine and to screen for claustrophobia, and (7) 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. Subjects were compensated for participation.

Fifty-nine subjects were initially eligible for the present study (after exclusions due to K-BIT scores, ADHD, pubertal timing, VO_2 max criteria, etc). Additional subjects were excluded due to poor scan quality because of excessive motion (n=4), hippocampal volume outliers (n=1), and less than chance memory performance (less than 30% accuracy on either the item or relational memory task) (n=5). Analyses were conducted on a total of 49 subjects, including 21 high-fit children (10 boys, 11 girls) with an average age of 10.0 years (SD=0.6; range 9-10) and 28 low-fit children (10 boys, 18 girls) with an average age of 10.0 years (SD=0.6; range 9-10). No statistically reliable differences in age, gender, socioeconomic status, or Kaufman Brief Intelligence Test (KBIT) scores existed between the fitness groups. Table 1 provides a list of demographic and fitness information for the final sample.

Aerobic Fitness Assessment

The aerobic fitness level of each child was determined by measuring maximal oxygen consumption (VO_2 max) using a computerized indirect calorimetry system (ParvoMedics True Max 2400) during a modified Balke protocol (American College of Sports Medicine 2006). Specifically, participants ran on a motor-driven treadmill at a constant speed with increases in grade increments of 2.5% every two minutes until volitional exhaustion. Averages for oxygen uptake (VO_2) and respiratory exchange ratio (RER) (the ratio between carbon dioxide and oxygen percentage) were assessed every 30 seconds. In addition, heart rate was measured throughout the fitness test (using a Polar heart rate monitor [Polar WearLink®+ 31, Polar Electro, Finland]), and ratings of perceived exertion (RPE) were assessed every two minutes using the children's OMNI scale (Utter et al. 2002).

VO_2 max was defined when oxygen consumption remained at a steady state despite an increase in workload. Relative peak oxygen consumption was based upon maximal effort as evidenced by (1) a peak heart rate greater than 185 beats per minute (American College of Sports Medicine 2006) accompanied by a heart rate plateau (i.e., an increase in work rate with no concomitant increase in heart rate) (Freedson and Goodman 1993), (2) RER greater than 1.0 **(**Bar-Or 1983), and/or (3) ratings on the children's OMNI scale of perceived exertion greater than 8 (Utter et al. 2002). Relative peak oxygen consumption was expressed in mL/kg/min.

Fitness group assignments (i.e., high-fit and low-fit) were based on whether a child's VO_2 max value fell above the 70th percentile or below the 30th percentile according to normative data provided by Shvartz and Reibold (1990). Children who did not qualify as high-fit or low-fit were excluded from participation.

MR Imaging Protocol and Image Processing

For all participants, high resolution (1.3 mm x 1.3 mm x 1.3 mm) T1-weighted structural brain images were acquired using a 3D MPRAGE (Magnetization Prepared Rapid Gradient Echo Imaging) protocol with 144 contiguous axial slices, collected in ascending fashion parallel to the anterior and posterior commissures (echo time (TE)=3.87 ms, repetition time (TR)=1800 ms, field of view (FOV)=256 mm, acquisition matrix 192 mm x 192 mm, slice thickness=1.3 mm, and flip angle=8º). All images were collected on a 3T head-only Siemens Allegra MRI scanner.

Segmentation and volumetric analysis of the left and right hippocampus was performed using a semi-automated, model-based subcortical tool (FMRIB's Integrated Registration and Segmentation Tool) in FMRIB's Software Library (FSL) version 4.1.4 (Patenaude 2007; Patenaude et al. 2007a; Patenaude et al. 2007b). To begin, a two-stage affine registration to a standard space template (MNI space) with 1 mm resolution using 12-degrees of freedom and a subcortical mask to exclude voxels outside the subcortical regions was performed on each subject's MPRAGE.

Next, the left and right hippocampus was segmented with 30 modes of variation. To achieve accurate segmentation, the FIRST methodology models 317 manually segmented and labeled T1-brain images from normal children, adults, and pathological populations (obtained from the Center for Morphometric Analysis, Massachusetts General Hospital, Boston) as a point distribution model with the geometry and variation of the shape of each structure submitted as priors. Volumetric labels are parameterized by a 3D deformation of a surface model based on multivariate Gaussian assumptions. FIRST searches through linear combinations of shape modes of variation for the most probable shape (i.e., brain structure) given the intensity distribution in the T1-weighted image, and specific brain regions are extracted (see Patenaude et al. 2007a,b for further description of the method). Modes of variation are optimized based on leave-one-out cross-validation on the training set, and they increase the robustness and reliability of the results (Patenaude et al. 2007b).

The hippocampus included the dentate gyrus, the ammonic subfields (CA1–4), the prosubiculum, and the subiculum and did not include the fimbria / fornix behind the posterior commissure. Hippocampal segmentations were visually checked for errors, and no errors were noted. Finally, boundary correction was run, a process which classifies boundary voxels as belonging to the structure (or not) based on a statistical probability (z-score >3.00; $p < 0.001$). The volume of each participant's left and right hippocampus was measured in mm^3, and these values were used in all subsequent analyses. See Figure 1 for a sample FIRST segmentation of the left and right hippocampus.

Item and Relational Memory Paradigm

The paradigm examined memory in successive encoding-then-recognition phases. Each block included an encoding phase followed by a recognition phase. Six blocks were included in the paradigm in the following order for all participants: "item (encoding and recognition)," "relational (encoding and recognition)," "relational," "item," "item," "relational." The stimuli were novel visual objects (created using Bryce software; used in Konkel et al. 2008) to ensure that participants had no prior exposure to the images or previous representations of the stimuli. See Figure 2 for an illustration of the stimuli and task.

During encoding, each participant was presented with a series of trials consisting of "scrambled stimuli" (to serve as a baseline) or "encoding stimuli" (to be recognized later). The scrambled stimuli in each block were created using the same pixels as the encoding stimuli displayed during the block. Stimuli were presented sequentially during "item encoding" (i.e., no fixation cross between stimuli) and in triplets (separated into groups of 3 via a 1000 milliseconds [ms] fixation cross) during "relational encoding." Specifically, participants viewed 18 scrambled stimuli followed by 18 encoding stimuli. Each image was presented for 2000 ms, and the scrambled sequence and encoding sequence were separated by a 2000 ms fixation cross. The identical sequence of scrambled and encoding item images was presented twice.

"Relational encoding" blocks were distinguished from "item encoding" blocks in two ways. Firstly, in terms of subject instructions, for item blocks, subjects were instructed to "remember as many shapes as possible," while for relational blocks, participants were instructed to "remember which shapes were in each group of 3." Secondly, in terms of stimulus presentation, item stimuli were presented sequentially and individually, without intermixed fixation crosses, whereas an additional 1000 ms fixation cross separated the relational scrambled and encoding stimuli into triplets (i.e., 3 stimuli were presented individually and sequentially, then a fixation cross appeared for 1000 ms, followed by 3 new stimuli presented individually and sequentially).

During recognition, memory was probed for either individual test items ("item recognition") or associative relations of stimuli within a triplet ("relational recognition"). For both item and relational recognition, 3 test items were displayed simultaneously during the probe period, and participants were given 4 seconds to respond. Each trial was separated by a fixation cross presented for 1 second. Six recognition trials (i.e., 6 groups of 3) were presented.

Specifically, during "item recognition," participants read the following instructions: "You will see 3 shapes appear at the same time. If all 3 shapes were seen in the previous block of shapes, press your right index finger. If any of the 3 shapes was not seen in the previous block, press your left index finger." Right index finger responses (i.e., all 3 shapes were seen during item encoding) contained 3 studied stimuli (i.e., stimuli that had occurred in the 18 stimuli presented during encoding) while left index finger responses (i.e., all 3 shapes were not seen during item encoding) contained two never-studied stimuli and one studied stimulus.

During "relational recognition," participants read the following instructions: "You will see 3 shapes appear at the same time. If all 3 shapes are from the same group, press your right index finger. If any of the shapes do not belong in the group, press your left index finger." Right index finger responses (i.e., the 3 shapes were in the same triplet) contained 3 stimuli that had occurred as a triplet (i.e., enclosed with 2 fixation crosses) during encoding while left index finger responses (i.e., if any of the 3 shapes were not seen together as a triplet) contained stimuli that had occurred in the 18 stimuli presented during encoding but were not presented as a sequential triplet. Each recognition condition was designed to probe one type of memory or form of representation (i.e., item memory or relational memory), unconfounded by the other.

Results

Participant Demographics

Participant demographic and fitness data are provided in Table 1. Demographic variables (i.e., age, IQ, SES, ADHD) did not differ between fitness groups. Furthermore, fitness comparisons using independent t-tests indicated that high-fit participants (*M*=51.51 mL/kg/min, *SD*=4.31 mL/kg/min) had higher VO_2 max scores than low-fit children (*M*=36.40 mL/kg/min, *SD*=4.03 mL/kg/min) ($t\ (47) = 12.61, p < 0.001$) which confirmed the aerobic fitness groupings.

Aerobic Fitness and Hippocampal Volume

The results support the hypothesis that aerobic fitness influences hippocampal volume. The hypothesis was examined by conducting two univariate ANCOVAs to compare left and right hippocampal volumes as a function of fitness group, with total intracranial gray matter volume (mm^3) as a covariate to control for variation in head size. High-fit children (*M*=3821.04 mm^3, *SD*=554.07 mm^3) showed greater left hippocampal volume compared to low-fit children (*M*=3388.91 mm^3, *SD*=765.43 mm^3) ($F\ (1, 46) = 4.97, p{=}0.031$). Similarly, high-fit children (*M*=3951.56 mm^3, *SD*=536.92 mm^3) showed greater right hippocampal volume compared to low-fit children (*M*=3465.18 mm^3, *SD*=850.34 mm^3) ($F\ (1, 46) = 5.62, p{=}0.022$) (See Figure 3).

Hippocampal Volume and Memory Performance

The results support the predicted dissociation between item and relational memory performance with regard to hippocampal volume. Left hippocampal volume was positively correlated with accuracy (percent correct) on the relational memory task ($r{=}\ 0.432, p{=}0.003$). Right hippocampal volume showed a similar trend ($r{=}\ 0.244, p{=}0.1$). However, there were no significant correlations between hippocampal volume and item memory accuracy (left hippocampus, *r*= -0.036, p=0.811; right hippocampus, *r*= -0.014, *p*=0.927). There were also no significant correlations between hippocampal volume and response speed for either the item or relational memory condition (all *r* < -0.195, *p*>0.2).

Aerobic Fitness and Memory Performance

The results of an independent t-test revealed a trend such that high-fit children showed superior accuracy (*M*=61.1%; *SD*=0.14) on the relational memory task compared to low-fit children (*M*=54.0%; *SD*=0.12) (*t* (44) = 1.86, *p*=0.06). There were no fitness-based differences in accuracy on the item memory task (*t* (44) = 0.40, *p*=0.69), and there were no fitness-based differences in response speed for either the relational memory (*t* (44) = 0.47, *p*=0.64) or item memory (*t* (44) = 0.37, *p*=0.71) task.

Discussion

Prior research has demonstrated that elderly adults with higher aerobic fitness levels have larger hippocampal volumes compared to older adults with lower fitness levels (Erickson et al. 2009). The results from the present study demonstrate that children with high aerobic fitness levels also have larger hippocampal volumes compared to low-fit children. Furthermore, left hippocampal volume was positively correlated with accuracy rates on the relational memory task, and right hippocampal volume showed a similar trend. No association between hippocampal volume and item memory performance was observed, a finding consistent with the hypothesized specificity of the hippocampal-memory relationship (Cohen and Eichenbaum 1993; Eichenbaum and Cohen 2001). Finally, a trend indicated that high-fit children showed superior accuracy on the relational memory paradigm, and no fitness differences were reported for the item memory task. Together, the structural imaging and behavioral results suggest that high-fit and low-fit children may exhibit differential hippocampal maturational trajectories which may impact relational memory function. The results are important because they provide a starting point for a greater understanding of the neural underpinnings of cognitive enhancement through physical activity in preadolescent children as well as a potential neural correlate of the fitness-memory performance link in children (Hillman et al. 2008).

The results are consistent with animal models that indicate aerobic activity positively impacts hippocampal structure and function (e.g., Cotman and Berchtold 2002). Given that many of the neurochemical processes involved in hippocampal changes with exercise in rodents are also involved in human brain development and organization, it seems possible that aerobic fitness may impact the developing brain. For example, changes in gray and white matter during brain development are said to reflect the interplay among changes in cell proliferation / apoptosis, dendritic branching / pruning, synaptic formation / elimination, growth factors (e.g., BDNF, IGF) and myelination (Giedd et al. 1996; Giedd et al. 1999; Anderson 2003; Gogtay et al. 2004). These cellular underpinnings parallel exercise-induced neural effects including changes in cell number, dendritic complexity, synaptic plasticity, and growth factors (e.g., Cotman and Berchtold 2002). The current study provides initial evidence for the impact of exercise on the developing brain by revealing that greater aerobic fitness level in preadolescents is related to greater hippocampal volume. Importantly, the results also partially suggest that the hippocampal volume differences are associated with cognitive ability, and in particular relational memory.

Future Directions and Conclusions

The results provide a foundation for future developmental research by suggesting that physical activity influences the development of the brain and cognition. While the present cross-sectional study provides a first step in understanding the relationship between fitness and developing neurocognition, a cross-sectional design raises the possibility that the observed behavioral and structural fitness-related differences were caused by another factor (e.g., motivation, genes, personality characteristics, nutrition). Thus, randomized clinical trials are necessary to account for potential selection bias and to establish a direct relationship between aerobic fitness and hippocampal structure and function in children. Future research should explore how a physical activity intervention relates to hippocampal structure and memory performance over time to gain a deeper understanding of cognitive development, neural organization and techniques which impact developing neurocognitive function.

The current study focused on a 9- and 10-year-old preadolescent population, given that this age range is undergoing a critical phase of brain growth when brain circuitry is being fine-tuned to support the operations of the adult brain (Caviness et al. 1996). Future explorations should examine the effects of fitness at different ages across development as well as track changes in cognition and brain patterns in the same individuals across time. Given the evidence that physical activity is positively associated with preadolescent neurocognition, it is possible that high levels of fitness may affect adolescent brain development as well as the number of suboptimal, impulsive behaviors associated with this developmental stage (e.g., violence, drug abuse, unprotected sexual activity) (Casey et al. 2008). Furthermore, given that the present study recruited healthy children without learning disabilities or ADHD, it is important to examine the impact of fitness on children with cognitive and social disorders.

Finally, while the investigation by Hillman et al. (2008) reported that high-fit children demonstrate significant performance benefits on a relational memory challenge compared to low-fit children, the current study indicates a marginally significant trend for the fitness-relational memory relationship. It is possible that task difficulty influenced the present results given the relatively low task accuracy rates for all preadolescent participants. Across all subjects, average item memory accuracy was 75% (*SD*=0.18) while average relational memory accuracy was 57% (*SD*=0.13). Future investigators should employ a task with graded levels of performance to gain a stronger understanding of the link between aerobic fitness and memory abilities.

In conclusion, the present investigation is the first to employ MRI methodology to examine the link between aerobic fitness, brain structure, and cognition in preadolescent children. For the first time, a study has shown that aerobic fitness may influence the structural and functional maturational patterns of developing children. The results extend previous research which has mainly focused on how fitness impacts the brain and cognition in elderly adults. Not only does fitness protect against age-related brain tissue loss (Colcombe et al. 2006), it also seems to affect brain development and cognitive abilities. According to Tomporowski, exercise may have a more long-lasting effect on brains that are still developing (Davis et al. 2007). To strengthen this claim, the effect size of Sibley and Etnier's (2003) children-fitness-cognition meta-analysis (*ES*=0.32) was slightly larger than the effect size of a meta-analysis of the effects of physical activity on cognition across the lifespan (6-90 years) (*ES*=0.25) (Etnier et al. 1997), a finding which suggests that physical activity may be especially beneficial for children. Thus, although physical activity seems to be beneficial at all stages of life, early intervention might be important for the improvement and/or maintenance of cognitive health and function throughout the adult lifespan (Sibley and Etnier 2003). Moreover, it is plausible that developing a love of sport and exercise as a child will encourage an active lifestyle during adulthood and old age.

The findings carry significant educational and public health implications. Educators are under increased pressure to improve the standardized test scores of their pupils. This pressure, coupled with the popular belief that physical education is of less educational value than academic work, has led to the elimination of physical education classes and recess in favor of "core academic subjects." However, as children are becoming increasingly sedentary, overweight, and unfit, recent estimates have indicated that younger generations may live less healthy and shorter lives than their parents (Olshansky et al. 2005). Furthermore, inactivity during childhood can increase the prevalence of obesity as well as a number of diseases and disorders throughout the lifespan (e.g., depression, anxiety, cardiovascular disease, colon cancer, type-2 diabetes)

(Olshansky et al. 2005; Baker et al. 2007; Ludwig 2007).

The present results suggest that physical fitness programs should be integrated into educational curriculums not only for obesity and public health purposes, but because exercise seems to benefit brain structure and function. It is possible that physical activity during childhood encourages optimal cortical development and results in long-term changes in brain structure and function. Hopefully, the present findings will encourage modifications of educational and health care policies which emphasize the importance of physical activity on physical and cognitive health.

Table 1

Participant mean demographic and fitness data (SD) by fitness group.

Variable	Low-Fit	High-Fit
n	28 (10 male)	21 (10 male)
Age (years)	10.0 (0.6)	10.0 (0.6)
VO_2 max (mL/kg/min)	36.4 (4.0) *	51.5 (4.3) *
K-BIT[a] Composite Score (IQ)	115.0 (15.1)	114.4 (6.9)
K-BIT[a] Crystallized Score (Vocabulary)	111.0 (11.9)	108.5 (6.0)
K-BIT[a] Fluid Score (Matrices)	115.8 (17.8)	117.4 (8.9)
SES[b] (median)	2.8 (0.6)	2.6 (0.7)
ADHD[c]	5.9 (3.9)	6.7 (4.2)

[a] Kaufman Brief Intelligence Test (Kaufman & Kaufman 1990).

[b] Socioeconomic Status. SES was determined by the creation of a trichotomous index based on three variables: child participation in a free or reduced-price lunch program at school, the highest level of education obtained by the child's mother and father, and the number of parents who worked full-time (Birnbaum et al. 2002).

[c] Scores on the *ADHD Rating Scale V* (DuPaul et al. 1998).

*Significantly different at $p < 0.001$.

Figures

Figure 1. FIRST segmentation of the left (red) and right (blue) hippocampus on a structural brain reconstruction.

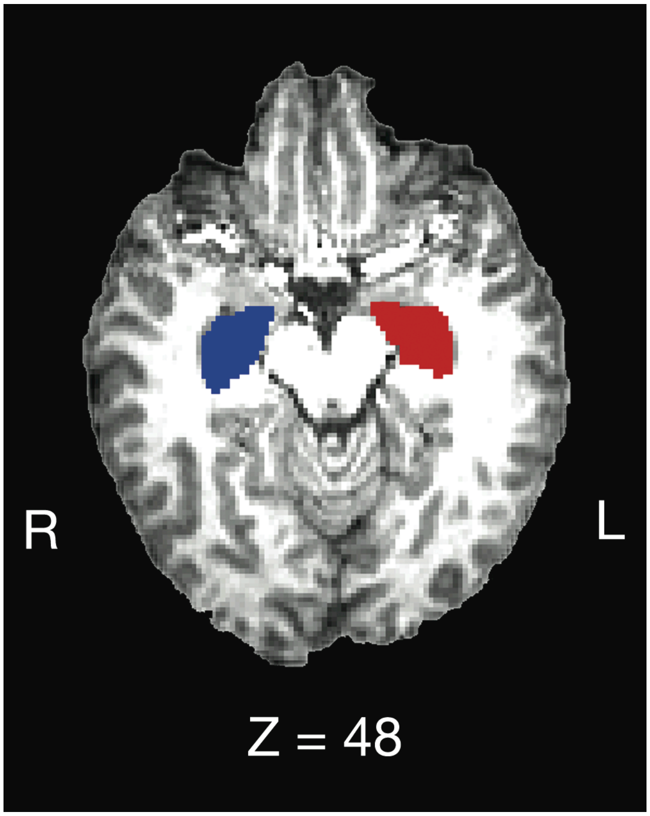


Figure 2. Sample scrambled stimuli are presented on the left, and sample encoding stimuli are presented on the right. A fixation cross only separated scrambled and encoding triplets during relational memory encoding trials. Each image was presented individually and sequentially during encoding trials, and three images were presented simultaneously during item and relational recognition trials (see example at bottom of figure).

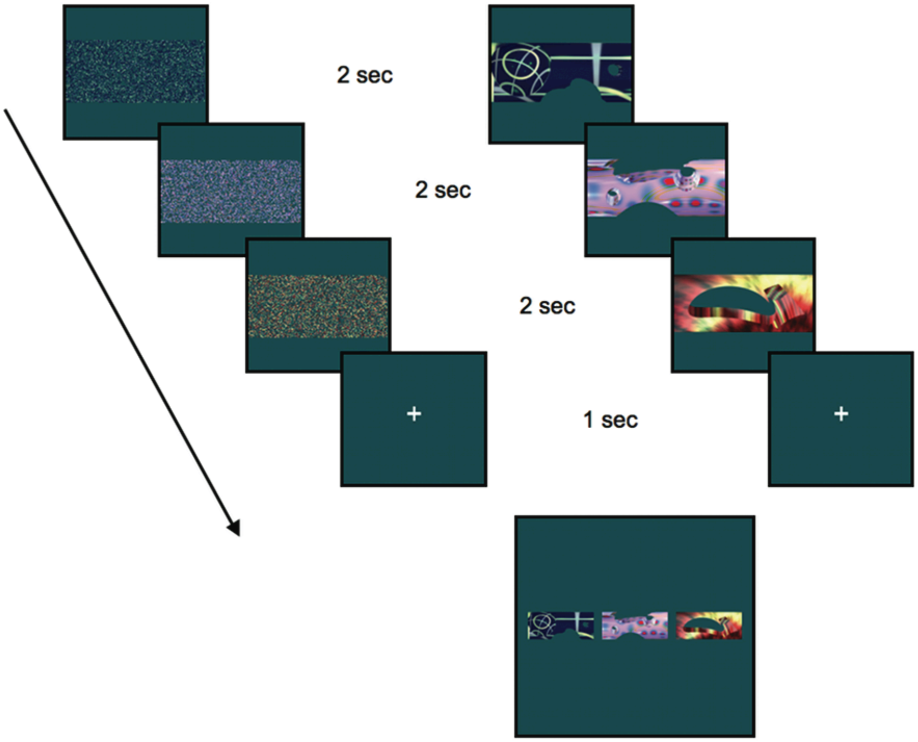
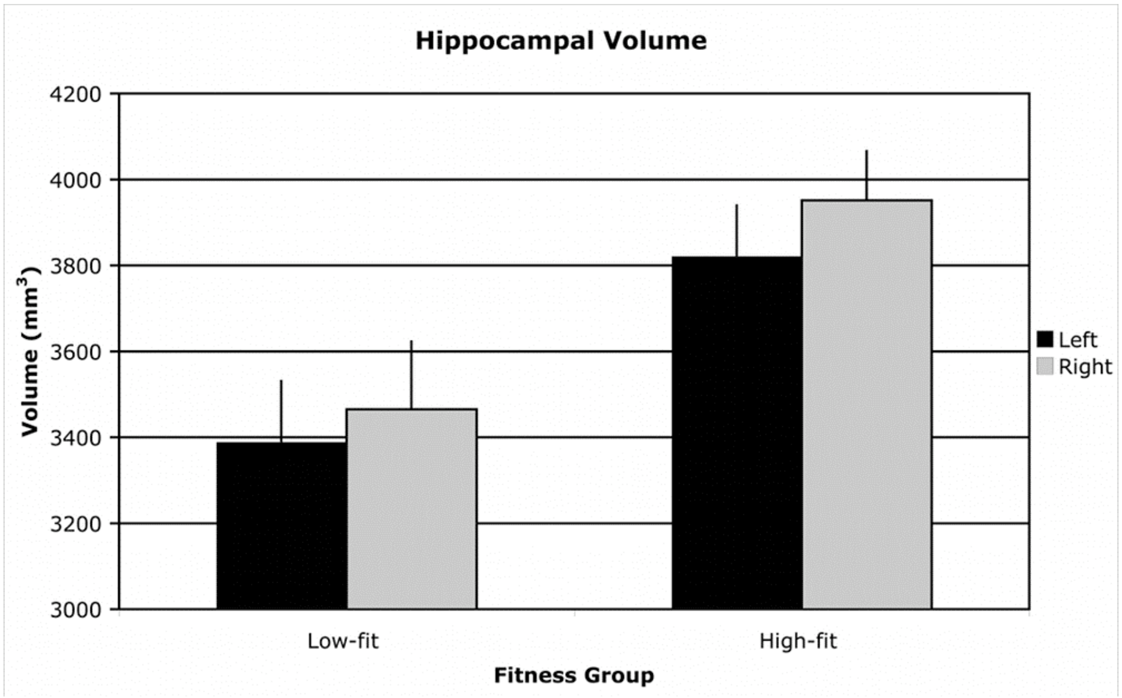


Figure 3. Left and right hippocampal volume as a function of fitness group. Error bars represent standard error.



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