Brain Behavior and Immunity xxx (xxxx) xxx-xxx

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: http://ees.elsevier.com

# Physical fitness, hippocampal functional connectivity and academic performance in children with overweight/obesity: The ActiveBrains project

Irene Esteban-Cornejo[a,*], Chelsea M. Stillman[b], Maria Rodriguez-Ayllon[a], Arthur F. Kramer[c,d], Charles H. Hillman[d,e], Andrés Catena[f], Kirk I. Erickson[g], Francisco B. Ortega[a]

[a] PROFITH "PROmoting FITness and Health through Physical Activity" Research Group, Sport and Health University Research Institute (iMUDS), Department of Physical Education and Sports, Faculty of Sport Sciences, University of Granada, Granada, Spain
[b] Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA
[c] Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, IL, USA
[d] Center for Cognitive and Brain Health, Department of Psychology, Northeastern University, Boston, MA, USA
[e] Department of Physical Therapy, Movement, & Rehabilitation Sciences, Northeastern University, Boston, MA, USA
[f] Department of Experimental Psychology, Mind, Brain and Behavior Research Center (CIMCYC), University of Granada, Granada, Spain
[g] Brain Aging & Cognitive Health Lab, Department of Psychology, University of Pittsburgh, 3601 Sennot Square, Pittsburgh, PA, USA

ARTICLE INFO

*Keywords*
Physical fitness
Functional connectivity
Hippocampus
Brain
fMRI
Behavior
Academic performance
Obesity
Childhood

ABSTRACT

*Objectives:* Physical fitness is a modifiable factor associated with enhanced brain health during childhood. To our knowledge, the present study is the first to examine: (i) whether physical fitness components (i.e., cardiorespiratory, motor and muscular fitness) are associated with resting state functional connectivity of hippocampal seeds to different cortical regions in children with overweight/obesity, and (ii) whether resting state hippocampal functional connectivity is coupled with better academic performance.
*Patients and methods:* In this cross-sectional study, a total of 99 children with overweight/obesity aged 8–11 years were recruited from Granada, Spain (November 2014 to February 2016). The physical fitness components were assessed following the ALPHA health-related fitness test battery. T1-weighted and resting-state fMRI images were acquired with a 3.0 Tesla Siemens Magnetom Tim Trio system. Academic performance was assessed by the Woodcock-Muñoz standardized test. Hippocampal seed-based procedures with post-hoc regression analyses were performed.
*Results:* In the fully adjusted models, cardiorespiratory fitness was independently associated with greater hippocampal connectivity between anterior hippocampus and frontal regions (β ranging from 0.423 to 0.424, $p < 0.001$). Motor fitness was independently associated with diminished hippocampal connectivity between posterior hippocampus and frontal regions (β ranging from −0.583 to −0.694, $p < 0.001$). However, muscular fitness was not independently associated with hippocampal functional connectivity. Positive resting state hippocampal functional connectivity was related to better written expression (β ranging from 0.209 to 0.245; $p < 0.05$).
*Conclusions:* Physical fitness components may associate with functional connectivity between hippocampal subregions and frontal regions, independent of hippocampal volume, in children with overweight/obesity. Particularly, cardiorespiratory fitness may enhance anterior hippocampal functional connectivity and motor fitness may diminish posterior hippocampal functional connectivity. In addition, resting state hippocampal functional connectivity may relate to better written expression.

## 1. Introduction

The hippocampus is a subcortical region of the human brain known for its neuroplasticity throughout the lifespan and important role in learning and memory (Raz et al., 1991; Erickson et al., 2011). Childhood is a critical period of neurodevelopment in which maturation of the hippocampus, as well as increased levels of hippocampal neurogenesis, are observed (Hueston et al., 2017). Hippocampal volume is sensitive to numerous neurologic and psychiatric conditions (e.g., depression, schizophrenia, Alzheimer's disease) (Huijbers et al.,

*Abbreviations*: ALPHA, Assessing Levels of Physical fitness and Health in Adolescents; BET, brain extraction tool; BOLD, blood-oxygen-level-dependent; FIRST, FMRIB's Integrated Registration and Segmentation Tool; FOV, field of view; FSL, FMRIB's Software Library; MNI, Montreal Neurological Institute; MRI, Magnetic Resonance Imaging; MPRAGE, magnetization-prepared rapid gradient-echo; PHV, peak height velocity; rsfMRI, resting-state fMRI; TE, echo time; TI, inversion time; TR, repetition time.

* Corresponding author.
*E-mail address:* ireneesteban@ugr.es (I. Esteban-Cornejo)

https://doi.org/10.1016/j.bbi.2020.10.006
Received 28 April 2020; Received in revised form 5 October 2020; Accepted 6 October 2020
Available online xxx
0889-1591/

2015; Voss et al., 2013; Liu et al., 2017; Nakahara et al., 2018), as well as metabolic diseases (e.g., obesity) (Mestre et al., 2005). For example, children who are overweight or obese have reduced hippocampal volume, which is associated with poorer academic performance, compared to normal-weight children (Mestre et al., 2005; Kamijo et al., 2012). In contrast, physical fitness is a modifiable factor that has been associated with enhanced brain health during childhood (Donnelly et al., 2016). Specifically, volumetric studies in children suggest that higher cardiorespiratory fitness and motor fitness, but not muscular fitness, are associated with greater gray matter volume in distinct subcortical regions, including the hippocampus (Esteban-Cornejo et al., 2017; Chaddock et al., 2010a, 2010b); and in turn, greater hippocampal volume is associated with better relational memory and academic performance (Esteban-Cornejo et al., 2017; Chaddock et al., 2010). However, it is unknown whether different physical fitness components (i.e., cardiorespiratory, motor, and muscular fitness) measured in children differentially associate with hippocampal function as well as the behaviors that it supports.

Animal studies provide the foundation for the hypothesis that cardiorespiratory fitness may promote the integration of new neurons into existing brain networks through system-wide mechanisms that enhance neuronal growth and survivability (Voss et al., 2013; Cotman et al., 2007). Indeed, the hippocampus, a primary site for exercise-induced neuroplasticity, has widespread connections with association cortices, including strong connections with the frontal and temporal cortex, and projections to the parietal and lateral occipital cortex through cingulate pathways (Miller, 1991). Two studies, both in young adults, have examined associations between cardiorespiratory fitness and resting state hippocampal functional connectivity (Stillman et al., 2018; Kronman et al., 2019). Stillman et al. found that higher cardiorespiratory fitness was associated with more positive resting state functional connectivity of the anterior hippocampus to several regions including the prefrontal cortex (Stillman et al., 2018). Kronman et al., in a small sample of 25 participants aged 20 to 33 years, showed that cardiorespiratory fitness predicted causal influence from the hippocampus to other regions of the default mode network and vice versa (Kronman et al., 2019). Among children, while two studies on cardiorespiratory fitness and task-evoked activation patterns showed variations in brain circuits involved in executive function (Voss et al., 2011; Chaddock et al., 2012), there are no studies examining how physical fitness may relate to variation in resting state hippocampal functional connectivity and its coupled relation to academic performance. Importantly, regionally-specific functional activation in the brain does not occur in isolation and may indirectly affect the functioning of other brain regions; as such resting state functional connectivity could shed light on the intrinsic communication patterns between physically disparate brain regions. Understanding how these patterns are modulated by physical fitness performance would help develop public health and educational strategies, since exercise programs improve physical fitness levels, which in turn, may positively influence brain functioning (Stillman et al., 2019). This is particularly relevant in the context of childhood obesity, since overweight and obese children have poorer executive function and academic performance, and disrupted brain network organization compared to normal-weight children (Kamijo et al., 2012, 1991; Augustijn et al., 2005).

To our knowledge, the present study is the first to investigate in children whether individual variability in hippocampal functional connectivity is explained by variation in physical fitness. We examined: (i) whether physical fitness components (i.e., cardiorespiratory, motor and muscular fitness) are associated with resting state functional connectivity of the hippocampus to different cortical regions in children with overweight/obesity, and (ii) whether resting state hippocampal functional connectivity is coupled with better academic performance. We conducted these analyses using anterior and posterior hippocampal seeds separately since a previous study in healthy young adults reported stronger associations between cardiorespiratory fitness and anterior regions of the hippocampus than posterior regions (Stillman et al., 2018). We hypothesized that physical fitness components will be differently correlated with connectivity of the hippocampus and that the associations might be particularly salient for anterior hippocampal resting state functional connectivity, since several studies in adults showed stronger associations between cardiorespiratory fitness and anterior regions of the hippocampus than posterior regions (Erickson et al., 2011, 2009; Stillman et al., 2018). Finally, we also hypothesized that resting state hippocampal functional connectivity would be coupled with better academic performance in children with overweight/obesity, since brain structure and function have been previously shown to be associated with academic performance in children (Esteban-Cornejo et al., 2017, 2019; Chaddock-Heyman et al., 2018).

## 2. Methods and materials

### 2.1. Study design

For the present cross-sectional study, we used baseline data, which were collected prior to randomizing children to treatment group (i.e., exercise, control). Data were obtained from the ActiveBrains project (http://profith.ugr.es/activebrains). Detailed information about the study method is available elsewhere (Cadenas-Sanchez et al., 2016). In brief, the ActiveBrains project is a randomized controlled trial designed to examine the effects of an exercise program on brain, cognition and academic performance, as well as on selected physical and mental health outcomes in children with overweight/obesity.

### 2.2. Participants

Participants were recruited from Granada, Spain. A total of 110 children aged 8–11 participated in the project. Baseline data were collected from November 2014 to February 2016. There were 99 children with overweight/obesity (10.0 ± 1.1 years; 40% girls) with complete baseline data on physical fitness, brain outcomes and academic performance. For each participant, all assessments were performed in a 4-days window. Parents or legal guardians were informed of the purpose of the study and written informed parental consents were obtained. The ActiveBrains project was approved by the Human Research Ethics Committee of the University of Granada, and was registered in ClinicalTrials.gov (identifier: NCT02295072).

### 2.3. Physical fitness

Physical fitness was assessed following the ALPHA (Assessing Levels of Physical fitness and Health in Adolescents) health-related fitness test battery for youth, which is a valid, reliable, feasible, and safe assessment of health-related physical fitness in this age group (Ruiz et al., 2011; Castro-Pinero et al., 2010; Ortega et al., 2005). The physical fitness components assessed were cardiorespiratory, motor and muscular fitness, which have been extensively used in previous studies (Esteban-Cornejo et al., 2017, 2019, 2014; Cadenas-Sanchez et al., 2020; Mora-Gonzalez et al., 2019a, 2019b; Muntaner-Mas et al., 2018). All tests were performed in a single session assessed by trained researchers in a familiar environment and warm-up was not required.

*Cardiorespiratory fitness* was assessed by the 20-m shuttle-run test. The test was performed once and always at the end of the fitness testing session. Participants were required to run between two lines 20-m apart, while keeping pace with a pre-recorded audio CD. The initial speed was 8.5 km/h, which was increased by 0.5 km/h each minute (1 min = 1 stage). The last stage completed was recorded and transformed to maximal oxygen consumption ($VO_2$max, mL/kg/min) using the Léger equation (Leger et al., 1988).

*Motor fitness* was assessed with the 4 × 10-m shuttle-run test of speed-of-movement, agility and coordination. The test was performed twice and the fastest time was recorded in seconds (Vicente-Rodriguez et al., 2011). Participants were required to run back and forth twice between two lines 10-m apart. Since a longer time indicates poorer performance (i.e., the person is slower and less agile and coordinated), the variable expressed in seconds was inverted by multiplying by −1, so that a higher score indicates better performance.

*Muscular fitness* was assessed using maximum handgrip strength and the standing long jump tests (Artero et al., 2012). A hand dynamometer with an adjustable grip was used (TKK 5101 Grip D, Takey, Tokyo Japan) for the handgrip strength test. The participant squeezed the dynamometer continuously for at least 2-s, alternatively with right and left hand, with the elbow in full extension (Espana-Romero et al., 2010). The test was performed twice and the maximum score for each hand was recorded in kilograms (kg). The average score of the left and right hands was calculated in kg as an absolute measurement of upper body muscular fitness (Espana-Romero et al., 2010; 2008). Standing long jump test was performed from a starting position behind a line, standing with feet approximately shoulder width apart (Castro-Pinero et al., 2010). The test was performed three times. The longest distance was recorded in centimeters, and subsequently multiplied by body weight in order to obtain an absolute measurement of lower body muscular fitness. A single muscular fitness score was computed from the two muscular tests. The individual score of each test was standardized as follows: Z-standardized value = (value – the sample mean)/SD. The muscular fitness score was calculated as the mean of the two standardized scores.

### 2.4. Magnetic resonance imaging (MRI)

Structural and functional images were collected on a 3.0 Tesla Siemens Magnetom Tim Trio system (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. High-resolution T1-weighted images were acquired using a 3D magnetization-prepared rapid gradient-echo (MPRAGE) protocol. The parameters were as follows: repetition time (TR) = 2300 ms, echo time (TE) = 3.1 ms, inversion time (TI) = 900 ms, flip angle = 9°, field of view (FOV) = 256 × 256, acquisition matrix = 320 × 320, 208 slices, resolution = 0.8 × 0.8 × 0.8 mm, and scan duration of 6 min and 34 s (Esteban-Cornejo et al., 2017; 2019). The resting-state fMRI (rsfMRI) data consisted of a series of 160 scans acquired using a Gradient Echo Pulse Sequence while participants rested with eyes closed. The parameters were as follows: TR = 1000 ms, TE = 25 ms, flip angle = 80°, FOV = 240 mm, acquisition matrix = 240 × 240, 35 slices, resolution = 3.5 × 3.5 × 3.5 mm, and scan duration of 5 min and 25 s.

### 2.5. Academic performance

Academic performance was assessed by the Spanish version of the Woodcock-Johnson III (i.e., the Bateria III Woodcock-Muñoz Tests of Achievement). This battery is a well validated measure of academic performance (McGrew and Woodcock-Johnson, 2001). All the tests were individually administered by a trained evaluator in one session of 100–120 min. The data collected for each participant was independently checked by two trained evaluators. The main dependent measures in this study were the standard scores of 5 academic indicators: mathematics, reading, writing, written expression and total achievement.

### 2.6. Covariates

Sex and peak height velocity (PHV) were included as covariates in the main analyses. PHV is a common indicator of maturity in children and adolescents (Malina et al., 2015). PHV was obtained from anthropometric variables (weight, height and/or seated height) using Moore's equations (Sharkey et al., 2015). Anthropometric measurements were performed twice (weight using an electronic SECA 861 scale and height using a SECA 225 stadiometer) with participants having bare feet and wearing underclothes, and averages were used. Years from PHV were calculated by subtracting the age of PHV from the chronological age. The difference in years was defined as a value of maturity offset. Hippocampal seed volume was included as covariate in post-hoc analyses, which allowed us to determine the unique effects of fitness on hippocampal functional connectivity, independent of volume.

### 2.7. Statistical analysis steps

#### 2.7.1. Preprocessing analysis

Preprocessing steps were carried out in FMRIB's Software Library (FSL) version 5.0.7. The following steps were applied via custom scripts: (i) skull-stripping using brain extraction tool (BET), (ii) spatial normalization of structural image to Montreal Neurological Institute (MNI) space, (iii) alignment of all rsfMRI frames to correct for head motion during the scan, (iv) co-registration to each participant's structural image and spatial normalization to MNI space, as well as visual check to ensure registration quality, (v) the rsfMRI time courses were then band-pass filtered (0.1–0.01 Hz) to attenuate respiration and other physiological noise and to focus on signal frequencies associated with intrinsic connectivity, (vi) six affine transformation parameters from the alignment process, as well as the mean time courses from the brain parenchyma including white matter tissue and ventricles were included as covariates to further account for motion and physiological noise. We visually checked each individual image (n = 100) for acquisition artifacts, and one child was excluded due to visual image corruption, resulting in a total of 99 participants. In addition, we calculated framewise displacement (M + SD = 0.20 mm ± 0.3), and only two subjects had a framewise displacement higher than 1.0 mm; when excluding these two subjects (M + SD framewise displacement = 0.16 mm ± 0.10), results did not change, and therefore all subjects were included in the analyses. Lastly, in order to achieve normality, we converted the residualized parameter estimate maps to z scores (via Fishers r to z transformation) and entered it into higher level analyses.

#### 2.7.2. Seed creation

For functional connectivity of the hippocampus seeds, we used FMRIB's Integrated Registration and Segmentation Tool (FIRST) in FSL 5.0.7. FIRST, a semi-automated model based subcortical segmentation tool, uses a Bayesian framework from shape and appearance models obtained from manually segmented images from the Center for Morphometric Analysis, Massachusetts General Hospital, Boston, MA, USA (Patenaude et al., 2011). In brief, we performed the following steps: (i) a two-stage affine registration to a standard MNI space with 1 mm resolution using 12 degrees of freedom was run and a subcortical mask was used to exclude voxels outside the hippocampus; (ii) the hippocampus is separately segmented for each hemisphere. Manual volumetric region labels are parameterized as surface meshes and modeled as a point distribution model; (iii) then, the left and right hippocampi were split based on the center of gravity of the region into anterior and posterior sub-regions using custom scripts. Previous studies showed differences as a function of cardiorespiratory fitness and exercise when using this procedure for dividing the hippocampus in adults (Erickson et al., 2011, 2009; Stillman et al., 2018). The final segmentations of the hippocampus seeds were visually inspected for quality, and no additional adjustments were needed. The gray matter volume of each seed region was obtained from FIRST in $mm^3$. Fig. 1 shows the masks for the hippocampal seeds on a representative participant's MPRAGE and Fig. S1 on a standard template.

#### 2.7.3. First and second level statistical analyses

Descriptive statistics are presented as means (SD) or percentages using IBM SPSS Statistics (version 18.0 for Windows; P set at < 0.05).

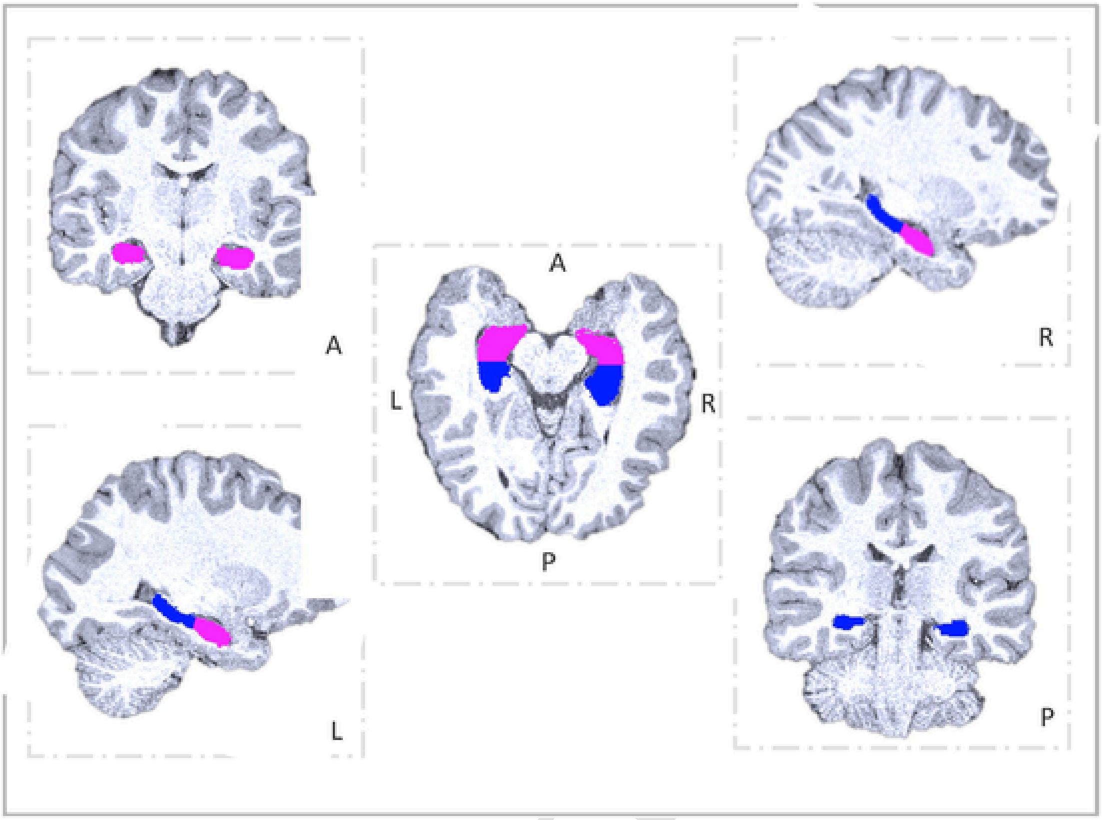


**Fig. 1.** Location of the hippocampal seed regions in each hemisphere derived from FIRST segmentation. The seed masks are presented on a representative subject's MPRAGE. The colors represent the hippocampal seeds: pink: anterior hippocampus; blue: posterior hippocampus. A, anterior; L, left; P, posterior; R, right. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

For the statistical analyses of imaging data, voxel-wise functional connectivity network maps were constructed for each seed, for each participant using the pre-processed rsfMRI data. These first-level seed maps were then entered into three separate group-level linear regressions to identify regions where connectivity with the seed was associated with cardiorespiratory fitness, motor fitness or muscular fitness. Sex and PHV were included as covariates in the group-level analyses of functional connectivity. All variables were mean centered prior to being entered into group-level models. The clusters in the cerebellum extending to brain stem regions were discarded in the analyses. Results were corrected for multiple comparisons at $p < 0.05$ using FSL's automatic FEAT cluster-based thresholding, which is a method of Family-Wise Error correction based on Gaussian Random Field Theory.

In addition, we extracted the blood-oxygen-level-dependent (BOLD) signals for each significant region to perform post-hoc analyses (IBM SPSS Statistics). First, we visually detected overlapping between physical fitness associated clusters for each seed. Second, we averaged the overlapped extracted signals (i.e., separately for positive and negative connectivity) for each region. Third, we conducted multiple regression analyses including the statistically significant physical fitness components simultaneously as independent variables for each significant cluster to examine which physical fitness component was driving the associations. Finally, we examined the associations between functional connectivity-related physical fitness components and academic performance adjusted for multiple comparisons separately for positive and negative connectivity using the Benjamini and Hochberg method (IBM SPSS Statistics; P set at $< 0.05$).

## 3. Results

### 3.1. Background characteristics

Table 1 shows the characteristics of the study sample. Overall, 26% of children had overweight and 74% had obesity (43% obesity grade I, 20% obesity grade II and 11% obesity grade III). The average age of the sample was 10.0 ± 1.1, and 40% were female.

### 3.2. Positive hippocampal functional connectivity correlates of physical fitness components

#### 3.2.1. Left and right anterior hippocampus

Greater cardiorespiratory fitness was associated with greater connectivity between the left anterior hippocampus to a cluster in the left superior frontal gyrus that extended to the paracingulate gyrus ($k = 413$, $z = 3.87$). In addition, greater cardiorespiratory fitness was associated with greater connectivity between the right anterior hippocampus to a cluster in the right supplementary motor area ($k = 384$, $z = 3.70$). Similarly, greater muscular fitness was associated with greater connectivity between the left anterior hippocampal seed to a cluster in the left superior frontal gyrus that extended to the paracingulate gyrus ($k = 260$, $z = 3.51$), and with greater connectivity between the right anterior hippocampus to a cluster in the right supplementary motor area ($k = 257$, $z = 3.78$). No positive motor fitness – connectivity relationships survived correction for the left and right anterior hippocampal seeds (Table 2). Fig. 2 shows the overlap between cardiorespiratory and muscular fitness clusters. Cardiorespiratory fitness, and not muscular fitness, was the only component significantly associated with greater connectivity between the left anterior hippocampal seed to a cluster in the left superior frontal gyrus that extended to the

**Table 1**
Characteristics of study sample.

| | *All* | *Boys* | *Girls* |
|---|---|---|---|
| *n* | 99 | 60 | 39 |
| Physical characteristics | | | |
| Age (years) | 10.0 ± 1.1 | 10.2 ± 1.1 | 9.8 ± 1.1 |
| Peak height velocity (years) | −2.3 ± 1.0 | −2.7 ± 0.8 | −1.8 ± 1.0 |
| Weight (kg) | 55.8 ± 11.1 | 56.7 ± 10.7 | 54.4 ± 11.7 |
| Height (cm) | 143.9 ± 8.3 | 144.7 ± 7.4 | 142.7 ± 9.5 |
| Body mass index (kg/m $^2$) | 26.7 ± 3.7 | 27.0 ± 3.8 | 26.5 ± 3.4 |
| Body mass index category (%) | | | |
| Overweight | 26 | 26 | 26 |
| Obesity grade I | 43 | 45 | 38 |
| Obesity grade II | 20 | 17 | 26 |
| Obesity grade III | 11 | 12 | 10 |
| Physical fitness components | | | |
| Cardiorespiratory fitness (mL/kg/min)* | 40.8 ± 2.8 | 40.8 ± 2.8 | 40.7 ± 2.8 |
| Motor fitness (s) † | 15.1 ± 1.6 | 14.9 ± 1.6 | 15.4 ± 1.5 |
| Muscular fitness (z-score) ‡ | 0.0 ± 0.9 | 0.0 ± 0.9 | 0.0 ± 1.0 |

Values are mean ± SD or percentages. *Measured by the 20-m shuttle run test, Lèger equation for transforming stage to VO2max (mL/kg/min): [predicted VO2-max = 31.025 + (3.238 × (8 + 0.5 × last stage completed)) – (3.248 × age) + (0.1536 × (8 + 0.5 × last stage completed) × age)]. †Measured by the 4 × 10-m shuttle run test; values were multiplied by −1 before analyses so that higher values indicate better performance. ‡z-score computed from handgrip strength (kg) and standing long jump (cm*kg) tests.

**Table 2**
Brain regions in which hippocampal connectivity is positively associated with the physical fitness components *(n = 99).*

| *Seed* | *Cluster location* | *X* | *Y* | *Z* | *Cluster size* | *Peak z* |
|---|---|---|---|---|---|---|
| *Cardiorespiratory fitness(mL/kg/min)* | | | | | | |
| L Anterior H | L superior frontal gyrus to paracingulate gyrus | −2 | 16 | 38 | 413 | 3.87 |
| R Anterior H | R supplementary motor area | 10 | −2 | 60 | 384 | 3.70 |
| L Posterior H | – | – | – | – | – | – |
| R Posterior H | – | – | – | – | – | – |
| *Motor fitness (s $^{-1}$)* | | | | | | |
| L Anterior H | – | – | – | – | – | – |
| R Anterior H | – | – | – | – | – | – |
| L Posterior H | – | – | – | – | – | – |
| R Posterior H | – | – | – | – | – | – |
| *Muscular fitness (z-score)** | | | | | | |
| L Anterior H | L superior frontal gyrus to paracingulate gyrus | −4 | 18 | 46 | 260 | 3.51 |
| R Anterior H | R supplementary motor area | 8 | 2 | 62 | 257 | 3.78 |
| L Posterior H | – | – | – | – | – | – |
| R Posterior H | – | – | – | – | – | – |

Analyses were adjusted by sex and peak high velocity (years). Each physical fitness component was introduced in separate models. All variables were mean-centered prior to being entered into group-level models. Analyses were corrected for multiple comparisons at p < 0.05 using FSL' automatic FEAT cluster-based thresholding, which is a method of Family-Wise Error correction based on Gaussian Random Field Theory. Anatomical coordinates (X,Y,Z) are given in Montreal Neurological Institute (MNI) Atlas space.
L, left; R, right.
* Z-score computed from handgrip strength (kg) and standing broad Jump (cm*kg) test.
H, hippocampus;

paracingulate gyrus (β = 0.423, p < 0.001 for cardiorespiratory fitness and β = 0.158, p = 0.257 for muscular fitness), and between the right anterior hippocampus to a cluster in the right supplementary motor area (β = 0.424, p < 0.001 for cardiorespiratory fitness and β = 0.159, p = 0.265 for muscular fitness). Results did not change when hippocampal volume or framewise displacement were included in the model (data not shown).

#### 3.2.2. Left and right posterior hippocampus

Consistent with prior work in adults (Stillman et al., 2018), no positive fitness – connectivity relationships survived correction for the left and right posterior hippocampal seeds for any of the physical fitness components (i.e., cardiorespiratory, motor and muscular fitness).

### 3.3. Negative hippocampal functional connectivity correlates of physical fitness components

#### 3.3.1. Left and right anterior hippocampus

Greater motor fitness was associated with less connectivity between the right anterior hippocampus to clusters located in the left and right orbitofrontal cortex (k ranging from 285 to 370, z ranging from 3.63 to 3.89). Greater muscular fitness was associated with less connectivity between the right anterior hippocampus to a cluster located in the right orbitofrontal cortex (k = 326, z = 3.67) No negative cardiorespiratory fitness – connectivity relationships survived correction for the left and right anterior hippocampal seeds (Table 3).

#### 3.3.2. Left and right posterior hippocampus

Greater cardiorespiratory fitness was associated with less connectivity between the left posterior hippocampus to a cluster in the left precentral gyrus extended to the right precuneous (k = 514, z = 3.62). Further, greater motor fitness was associated with less connectivity between the left posterior hippocampus to a cluster located in the left and right precentral gyrus extended to the right anterior cingulate cortex (k = 4523, z = 4.10); and, greater motor fitness was associated with less connectivity between the right posterior hippocampus to clusters located in the right frontal pole, the left and right precentral gyrus extended to the left and right anterior cingulate cortex and the left lateral occipital cortex extended to the left lingual gyrus (k ranging from 286 to 6490, z ranging from 3.41 to 4.28).

Lastly, greater muscular fitness was associated with less connectivity between the left posterior hippocampus to clusters located in the left superior frontal gyrus and the right precentral gyrus extended to right anterior cingulate cortex (k ranging from 242 to 775, z ranging from 3.16 to 3.78); and, greater muscular fitness was associated with less connectivity between the right posterior hippocampus to clusters located in the right anterior cingulate cortex and the right precentral gyrus (k ranging from 409 to 577, z ranging from 3.25 to 3.79) (Table 3). Fig. 3 shows the overlap between motor and muscular fitness clusters. Motor fitness, but not muscular fitness, was significantly associated with less connectivity between the left posterior hippocampus seed to a cluster in the right and left precentral gyrus extended to right and left anterior cingulate cortex (β = −0.583, p < 0.001 for motor

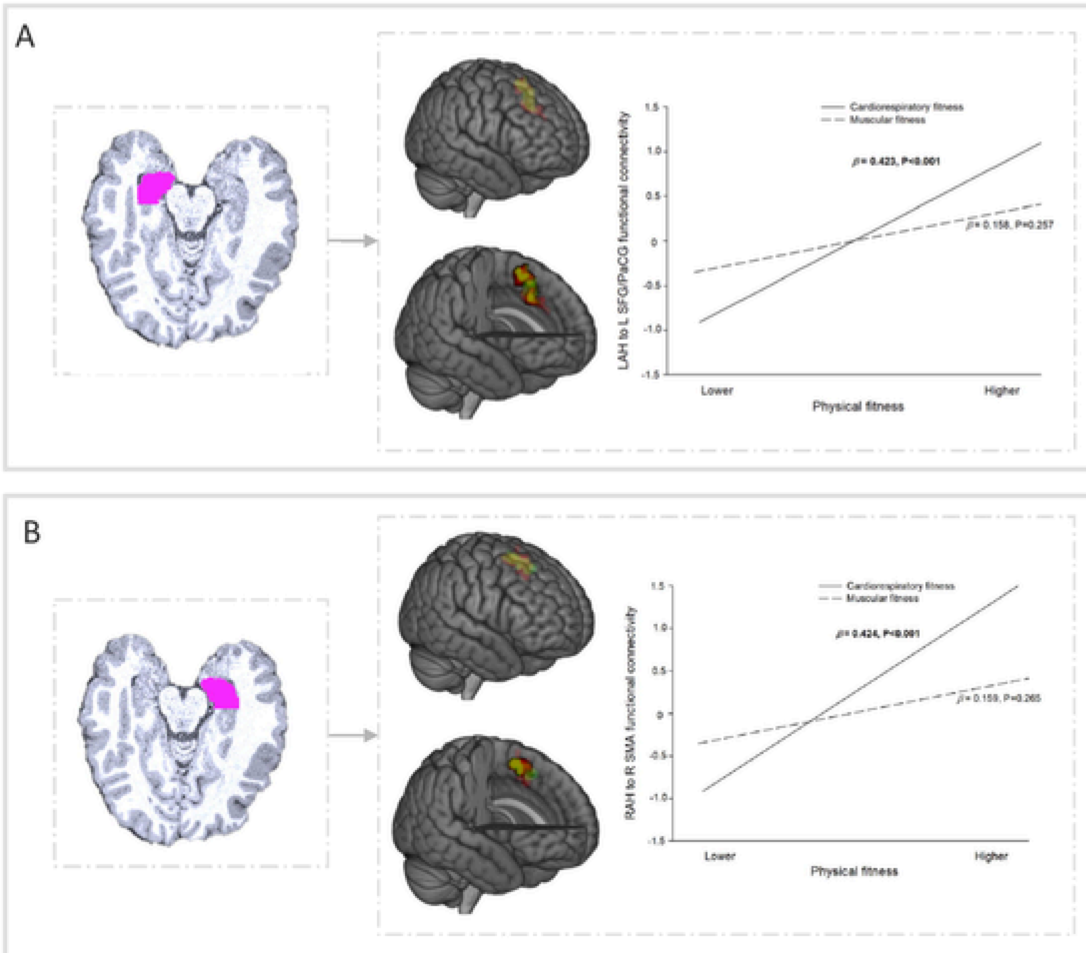


**Fig. 2.** Overlapped brain regions in which left (A) and right (B) anterior hippocampal connectivity is positively associated with both cardiorespiratory and muscular fitness. L, left; R, right; LAH, left anterior hippocampus; RAH, right anterior hippocampus; SFG, superior frontal gyrus; PacG, paracingulate gyrus; SMA, supplementary motor area. The colors represent the regions: pink: anterior hippocampal seed (A, left; B, right); red: associated cardiorespiratory fitness regions; green: associated muscular fitness regions; yellow: overlapped regions between cardiorespiratory and muscular fitness. Scatter plots depict post-hoc regression analyses between the averaged extracted signals for each overlapped region as the dependent variable and the physical fitness components simultaneously (i.e., cardiorespiratory and muscular fitness) as independent variables adjusted for sex and peak high velocity (years). β values are standardized. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

fitness, and $\beta = 0.139$, $p = 0.297$ for muscular fitness), between the right posterior hippocampus to a cluster in the right and left precentral gyrus extended to right and left anterior cingulate cortex ($\beta = -0.694$, $p < 0.001$ for motor fitness and $\beta = -0.027$, $p = 0.827$ for muscular fitness) and between the right anterior hippocampus to a cluster in the right orbitofrontal cortex ($\beta = -0.573$, $p < 0.001$ for motor fitness and $\beta = 0.062$, $p = 0.645$ for muscular fitness). Results did not change when hippocampal volume or framewise displacement were included in the model (data not shown).

### *3.4. Association between functional connectivity and academic performance*

Tables S1 and S2 display the relationship between fitness-related associations in hippocampal functional connectivity and academic performance adjusting for sex and PHV, after controlling for multiple comparisons using the Benjamini and Hochberg method. Positive hippocampal functional connectivity was positively associated with higher written expression ($\beta$ = ranging from 0.209 to 0.245; p ranging from 0.016 to 0.036) (Table S1). There were no significant relationships between negative fitness-related associations in hippocampal functional connectivity and academic performance indicators (Table S2). Results did not change when both body mass index and chronological age (instead of PHV) were additionally included as covariates.

## 4. Discussion

The main findings of the present study were consistent with our initial hypothesis showing that different physical fitness components were selectively associated with functional connectivity between hippocampal subregions and frontal regions in children with overweight/obesity. Mainly, cardiorespiratory fitness was associated with greater hippocampal connectivity between anterior hippocampus and frontal regions, while motor fitness was associated with diminished hippocampal connectivity between posterior hippocampus and frontal regions. In addition, physical fitness appeared to account for unique portion of variance in the functional connectivity between hippocampal subregions and frontal regions, above and beyond hippocampal volume. Lastly, positive resting state hippocampal functional connectivity was related to better written expression.

The study of hippocampal functional connectivity in humans has gained attention in the last decades (Voss et al., 2019). Cardiorespiratory fitness is known to deliver global beneficial effects that shape the functional connectivity of multiple brain networks (Stillman et al., 2018; Kronman et al., 2019; Talukdar et al., 1991; Voss et al., 2010; Ikuta and Loprinzi, 2019). Surprisingly, there are only two previous human studies focused on cardiorespiratory fitness and hippocampal functional connectivity (Stillman et al., 2018; Kronman et al., 2019). Using a Granger causality analytical approach, Kronman

**Table 3**
Brain regions in which hippocampal connectivity is negatively associated with the physical fitness components *(n = 99)*.

| *Seed* | *Cluster location* | *X* | *Y* | *Z* | *Cluster size* | *Peak z* |
|---|---|---|---|---|---|---|
| *Cardiorespiratory fitness (mL/kg/min)* | | | | | | |
| L Anterior H | – | – | – | – | – | – |
| R Anterior H | – | – | – | – | – | – |
| L Posterior H | L precentral gyrus to R precuneous | −2 | −34 | 54 | 514 | 3.62 |
| R Posterior H | – | – | – | – | – | – |
| *Motor fitness ($s^{-1}$)* | | | | | | |
| L Anterior | – | – | – | – | – | – |
| R Anterior H | R orbitofrontal cortex | 52 | 38 | −8 | 370 | 3.89 |
| | L orbitofrontal cortex | −32 | 14 | −32 | 285 | 3.63 |
| L Posterior H | L & R precentral gyrus to L ACC | 4 | 8 | 30 | 4523 | 4.10 |
| R Posterior H | R frontal pole | 22 | 44 | 26 | 286 | 4.04 |
| | L & R precentral gyrus to L& R ACC | 8 | −8 | 32 | 6490 | 4.28 |
| | L lateral occipital cortex to L lingual gyrus | −26 | −88 | 0 | 417 | 3.41 |
| *Muscular fitness (z-score)** | | | | | | |
| L Anterior H | – | – | – | – | – | – |
| R Anterior H | R orbitofrontal cortex | 52 | 38 | −8 | 326 | 3.67 |
| L Posterior H | L superior frontal gyrus | −20 | −12 | 42 | 242 | 3.16 |
| | R precentral gyrus to R ACC | 22 | −12 | 48 | 775 | 3.78 |
| R Posterior H | R anterior cingulate cortex | 8 | −8 | 32 | 409 | 3.79 |
| | R precentral gyrus | 22 | 4 | 38 | 577 | 3.25 |

Analyses were adjusted by sex and peak high velocity (years). Each physical fitness component was introduced in separate models. All variables were mean-centered prior to being entered into group-level models. Analyses were corrected for multiple comparisons at $p < 0.05$ using FSL' automatic FEAT cluster-based thresholding, which is a method of Family-Wise Error correction based on Gaussian Random Field Theory. Anatomical coordinates (X,Y,Z) are given in Montreal Neurological Institute (MNI) Atlas space. *Z-score computed from handgrip strength (kg) and standing broad Jump (cm*kg) test. ACC, anterior cingulate cortex; H, hippocampus; L, left; R, right.

et al. showed that cardiorespiratory fitness predicted the causal connectivity between the hippocampus to other regions of the default mode network (i.e., ventromedial prefrontal cortex, posterior cingulate cortex, and lateral temporal cortex) and vice versa (from the dorsomedial prefrontal cortex to the hippocampus) in a small sample of 25 participants aged 20 to 33 years (Kronman et al., 2019). Stillman et al. used hippocampal subregions as seeds, instead of the whole hippocampus, and mainly observed that higher cardiorespiratory fitness was associated with greater functional connectivity of the anterior hippocampus to the frontal pole, middle frontal gyrus, and parahippocampus in a sample of 50 adults aged 18 to 38 years (Stillman et al., 2018). The present findings confirm and extend these previous studies performed in young healthy adults, showing for the first time how different components of physical fitness may relate to hippocampal functional connectivity in children with overweight or obesity.

In particular, we found that greater cardiorespiratory and muscular fitness were individually associated with greater connectivity between the anterior hippocampus and common frontal regions. However, neither cardiorespiratory nor muscular fitness enhanced connectivity between posterior hippocampal seeds and any region in the brain. Further, there was no association between motor fitness and greater hippocampal functional connectivity for anterior or posterior seeds. Thus, cardiorespiratory and muscular fitness may both have overlapping influences on hippocampal functional connectivity, and these associations are selective for the anterior hippocampus. Specifically, cardiorespiratory and muscular fitness were associated with greater connectivity between the left anterior hippocampus to a cluster in the left superior frontal gyrus, which extended to paracingulate gyrus and between the right anterior hippocampus to a cluster in the right supplementary motor area. These regions are often implicated in supporting working memory, attentional switching and language processing (Leonard et al., 2009; Hertrich et al., 2016; du Boisgueheneuc et al., 2006; Beaty et al., 2015), suggesting that both cardiorespiratory and muscular fitness may benefit tonic intrinsic communication in specific executive function networks. Remarkably, in the analyses of overlapping and independent influence, when we included both cardiorespiratory and muscular fitness as predictors in the same model, we found that only cardiorespiratory fitness, and not muscular fitness, was associated with enhanced connectivity between the anterior hippocampus and those frontal regions. This further highlights the specificity of cardiorespiratory fitness to enhance functional connectivity between the anterior hippocampus and frontal regions.

Another interesting and somewhat unexpected finding was that physical fitness components were also associated with weakened hippocampal functional connectivity in children who were overweight or obese. For cardiorespiratory fitness, we found a single association of greater cardiorespiratory fitness with less connectivity between the left posterior hippocampus to a cluster in the left precentral gyrus extended to the right precuneous. Similarly, Stillman et al. found that higher cardiorespiratory fitness was associated with less functional connectivity between the right anterior hippocampus and the superior frontal gyrus (Stillman et al., 2018). The present study provides novel data on how other components of physical fitness may diminish hippocampal functional connectivity; namely, greater motor and muscular fitness were related to less functional connectivity between posterior hippocampus and other individual and not overlapped brain regions. For example, greater motor fitness may relate to diminished connectivity between the right posterior hippocampus to frontal (i.e., right frontal pole) and occipital (i.e., the left lateral occipital cortex extended to the left lingual gyrus) regions, and greater muscular fitness was associated with less connectivity between the left posterior hippocampus and left superior frontal gyrus. As previously indicated, our findings are speculative in the context of shifting allocation of resources or attentional focus, since decreased connectivity may be beneficial for behavior and long term goals (Stillman et al., 2018).

Regarding the overlapping associations of motor and muscular fitness, we observed that greater motor and muscular fitness were individually associated with less connectivity between the posterior hippocampus and common frontal regions (i.e., between left posterior hippocampus to a cluster located in the left and right precentral gyrus extended to the right anterior cingulate cortex, and between the right posterior hippocampus to a cluster located in the left and right precentral gyrus extended to the left and right anterior cingulate cortex). Yet, when both motor and muscular fitness were included in the same model, only motor fitness, and not muscular fitness, was associated with diminished connectivity between the posterior hippocampus and those frontal regions. Therefore, this may point to the specificity of motor fitness to lessen hippocampal functional connectivity, and further suggests that this association may be selective for the posterior hippocampus, with the exception of an independent association of greater motor fitness with less connectivity between the right anterior hippocampus to the orbitofrontal cortex.

There are several potential reasons underlying the regional specificity of cardiorespiratory fitness being selectively associated with ante-

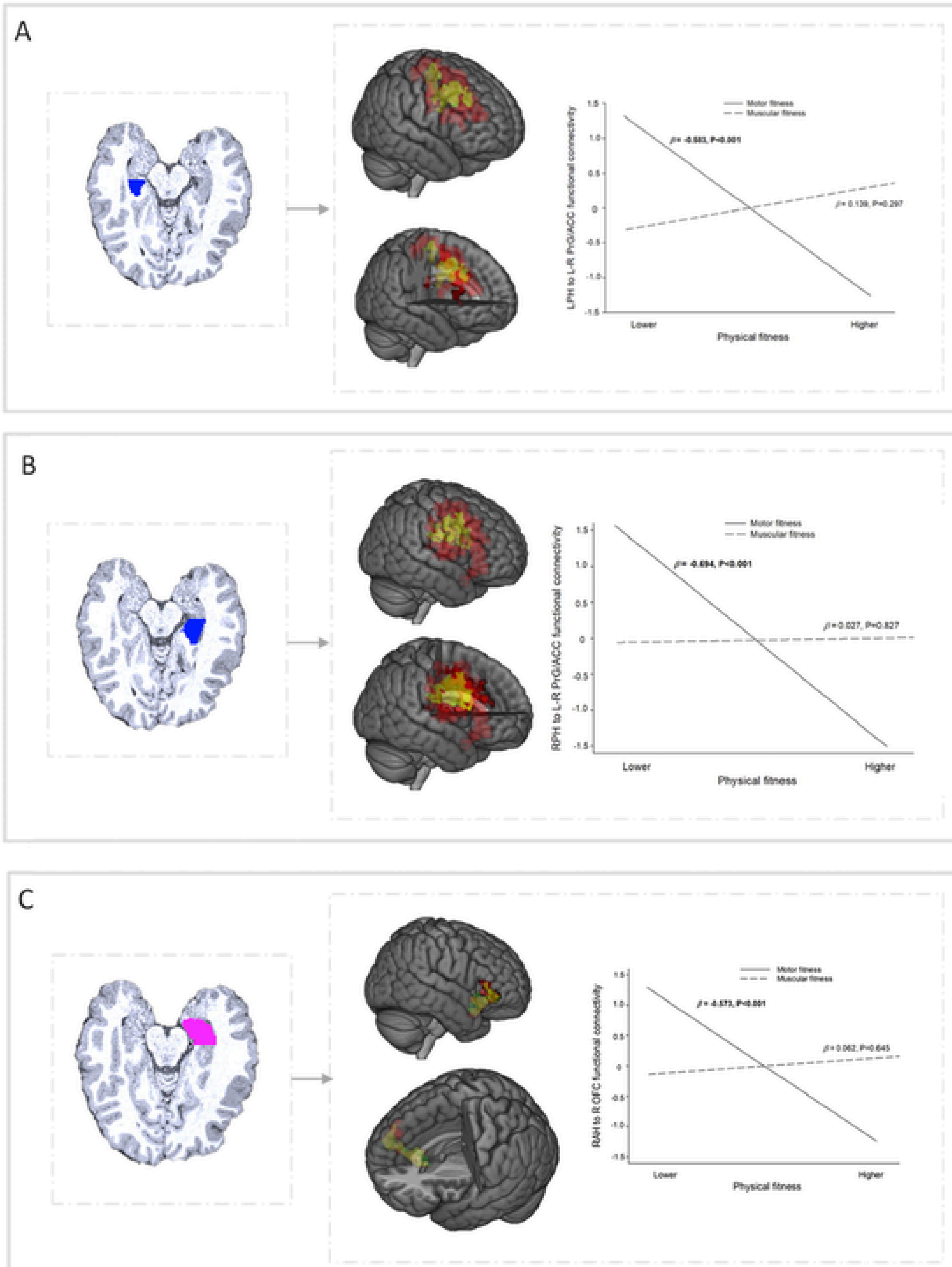


**Fig. 3.** Overlapped brain regions in which left (A) and right (B) posterior and right anterior (C) hippocampal connectivity is negatively associated with both motor and muscular fitness. L, left; R, right; LPH, left posterior hippocampus; RPH, right posterior hippocampus; RAH, right anterior hippocampus; PrCG, precentral gyrus; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex. The colors represent the regions: blue: posterior hippocampal seed (A, left; B, right); pink: right anterior hippocampal seed (C); red: associated motor fitness regions; green: associated muscular fitness regions; yellow: overlapped regions between motor and muscular fitness. Scatter plots depict post-hoc regression analyses between the averaged extracted signals for each overlapped region as dependent variable and the physical fitness components simultaneously (i.e., motor and muscular fitness) as independent variables adjusted for sex and peak high velocity (years). β values are standardized. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

rior hippocampal functional connectivity, and motor fitness with posterior hippocampal functional connectivity. The hippocampus differs in structure and function along its longitudinal axis (Poppenk et al., 2013). The anterior hippocampus, which includes the dentate gyrus, is where most cell proliferation and survival occur. Experimental evidence in rodent models supports the role of cardiorespiratory exercise on neurogenesis in the dentate gyrus (van Praag et al., 1999; 2005). In addition, previous volumetric studies in humans showed stronger associations between cardiorespiratory fitness, but not motor or muscular fitness, with hippocampus, and specifically with the anterior hippocampus (Erickson et al., 2011; Esteban-Cornejo et al., 2017; Stillman et al., 2018; Chaddock-Heyman et al., 2015; Killgore et al., 2013). Conversely, complementary research in rodents indicates that motor learning and activity (major determinants of motor fitness) increase synaptic activity and the density of blood vessels in cerebellar cortex, respectively (Black et al., 1990). As such, it is a reasonable to speculate that the role of motor fitness on synaptogenesis and angiogenesis may spread to the posterior hippocampus. Beyond physiological implications, other mechanisms related to the functional organization of the hippocampal longitudinal axis can be hypothesized. For example, evidence in rodents has shown a functional gradient along the hippocampal axis for spatial processing. The posterior hippocampus processes small-scale spatial information, which may be comparable with the characteristics of the motor fitness tests which imply shorter-distance (10 m). Further, the anterior hippocampus subserves similar spatial processing function at a lager spatial scale, which may be comparable with the longer-distance used in the cardiorespiratory fitness tests (20 m) (Strange et al., 2014). However, future experimental studies should test the effect of aerobic and motor training on hippocampal sub-regions to further support the selective associations of cardiorespiratory fitness with anterior hippocampus and motor fitness with posterior hippocampus.

In addition to the regional specificity, functional connectivity of the anterior and posterior hippocampus may be differentially affected by several factors (Damoiseaux et al., 2016) (e.g., age, physical fitness, body mass). For example, some studies showed lower functional connectivity of the posterior hippocampus for older individuals (Damoiseaux et al., 2016; Andrews-Hanna et al., 2007), and either no age-related differences (Damoiseaux et al., 2016; Koch et al., 2010) or an increase in connectivity with age (Salami et al., 2014) for the anterior hippocampus. Furthermore, we found that functional connectivity patterns were modulated in a selective and reversed fashion by physical fitness components, with enhancement in (anterior) hippocampal connectivity due to cardiorespiratory fitness and reduced (posterior) hippocampal connectivity due to motor fitness. Importantly, one of the key functions of the hippocampus is memory consolidation, which occurs when the brain is in a resting state (Strange et al., 2014). It is possible that to achieve this process, the anterior hippocampus needs to enhance connectivity and the posterior hippocampus needs to decrease connectivity with frontal regions; and in turn, this may be modified as a function of physical fitness.

Importantly, we also showed that physical fitness, namely cardiorespiratory and motor fitness, accounted for unique portions of variance in the functional connectivity between hippocampal subregions and frontal regions beyond hippocampal volume, suggesting a unique contribution of cardiorespiratory fitness and motor fitness to hippocampal functional connectivity. Thus, combining neuroimaging techniques into a single analytic approach may improve our understanding of the associations between physical fitness and hippocampal volume and function. Lastly, our results may also have implications for academic performance (Cadenas-Sanchez et al., 2020). We found that greater fitness-related associations in anterior hippocampal functional connectivity were associated with higher academic performance, and specifically with higher written expression. However, there were no significant relationships between negative fitness-related associations in hippocampal functional connectivity and academic performance indicators. One explanation that could partially account for the specificity of the anterior hippocampal functional connectivity on written expression may be that tasks requiring semantic processing, such as written expression, engage the anterior hippocampus. Semantic processing implies encoding the meaning of a word and relating it to similar words, which in turn, is needed for meaningful written expression and sentence writing fluency (Chua et al., 2007). As such, higher cardiorespiratory fitness may play a protective role in enhancing neural connections that are keys to memory and other cognitive functions, which in turn, may improve academic performance in children with overweight/obesity. Previous interventional studies have shown that exercise may have the potential to influence brain networks and task-evoked activation patterns, but if and how these brain changes reflect long-term developmental trajectories remains unknown (Krafft et al., 2014a, 2014b; Chaddock-Heyman et al., 2013; Davis et al., 2011). Future studies are needed to address these gaps in the literature and anchor the patterns to behavioral outcomes to determine their importance.

Limitations of this study include its cross-sectional design, which precludes our ability to draw causal interpretations. In addition, our focus on children with overweight/obesity limits the generalizability of our findings to normal weight youth. However, since obesity has been associated with detectable structural differences in the brain compared to the brains of normal-weight individuals already during childhood and adolescence (Reinert et al., 2013), and children with overweight/obesity have poorer cognitive control and academic performance compared to normal-weight children (Kamijo et al., 2012; 1991), it is relevant to focus on children with overweight/obesity. Indeed, given the growing percentage of children with overweight/obesity, our results have public health significance for a large portion of the population. Moreover, while we expanded previous studies by including structural (volume) and functional (rsfMRI) measures of hippocampal integrity, more comprehensive multimodal techniques including additional hippocampal measures (e.g., white matter integrity, viscoelasticity, vascularization) are required. Finally, the seed-based approach for analyzing functional connectivity does not allow us to examine connectivity between other brain regions. Future studies could use graph-based network analysis of rsfMRI to expand our understanding of the brain as a complex network. However, this approach is based on a well-established theoretically-driven hypothesis focusing on the hippocampus and its subregions, which facilitates the interpretation of findings. The study has several strengths, including the relatively large sample with MRI, the complete and standardized assessment of the physical fitness components, the theoretical focus on the hippocampus based on previous studies across the lifespan (Firth et al., 2018) and the use of hippocampal segmentation for analyzing the hippocampal functional connectivity for each sub-region.

In conclusion, an integrative perspective of the current findings posits that different physical fitness components may relate to functional connectivity between hippocampal subregions and frontal regions, independently of hippocampal volume. Specifically, while cardiorespiratory fitness may enhance anterior hippocampal functional connectivity, motor fitness may diminish posterior hippocampal functional connectivity. In addition, resting state hippocampal functional connectivity may be coupled with better written expression in children with overweight/obesity.

**Acknowledgments**

The authors gratefully acknowledge the children and parents who participated in this study.

**Financial support and conflict of interest disclosure**

This study was supported by the Spanish Ministry of Economy and Competitiveness (DEP2013-47540, BES-2014-068829, DEP2016-79512-R & PSI2012-3929, DEP2017-91544-EXP, RTI2018-095284-J-100), the Alicia Koplowitz Foundation and for the Spanish Ministry of Science and Innovation (RYC-2011-09011 & IJCI-2017-33642). This study takes place thanks to the additional funding from the University of Granada, Plan Propio de Investigación 2016, Excellence actions: Units of Excellence; Unit of Excellence on Exercise and Health (UCEES), the Junta de Andalucía, Consejería de Conocimiento, Investigación y Universidades and European Regional Development Fund (ERDF, SOMM17/6107/UGR). Additional funding from the EXERNET Research Network on Exercise and Health in Special Populations (DEP2005-00046/ACTI, the SAMID III network, RETICS, funded by the PN I + D + I 2017-2021

(Spain), ISCIII- Sub-Directorate General for Research Assessment and Promotion and the European Regional Development Fund (ERDF) (Ref. RD16/0022, SOMM17/6107/UGR). The present study was awarded *"Premios Nacionales de Investigación en Medicina del.*

*Deporte Liberbank, año 2019. Escuela de Medicina del Deporte. Universidad de Oviedo"*. The authors declare no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.10.006.

## References

Andrews-Hanna, J.R., Snyder, A.Z., Vincent, J.L., Lustig, C., Head, D., Raichle, M.E., et al., 2007. Disruption of large-scale brain systems in advanced aging. Neuron 56 (5), 924–935 PubMed PMID: 18054866. Pubmed Central PMCID: PMC2709284. Epub 2007/12/07. eng..

Artero, E.G., Espana-Romero, V., Castro-Pinero, J., Ruiz, J., Jimenez-Pavon, D., Aparicio, V., et al., 2012. Criterion-related validity of field-based muscular fitness tests in youth. J. Sports Med. Phys. Fitness 52 (3), 263–272 PubMed PMID: 22648464. Epub 2012/06/01. eng.

Augustijn, M., Di Biase, M.A., Zalesky, A., Van Acker, L., De Guchtenaere, A., D'Hondt, E., et al., 2005. Structural connectivity and weight loss in children with obesity: a study of the "connectobese". Int. J. Obesity 2019 PubMed PMID: 31350442. Epub 2019/07/28. eng.

Beaty, R.E., Benedek, M., Kaufman, S.B., Silvia, P.J., 2015. Default and executive network coupling supports creative idea production. Sci. Rep. 5, 10964 PubMed PMID: 26084037. Pubmed Central PMCID: PMC4472024. Epub 2015/06/18. eng.

Black, J.E., Isaacs, K.R., Anderson, B.J., Alcantara, A.A., Greenough, W.T., 1990. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proc. Natl. Acad. Sci. U.S.A. 87 (14), 5568–5572 PubMed PMID: 1695380. Pubmed Central PMCID: PMC54366. Epub 1990/07/01. eng.

Cadenas-Sanchez, C., Mora-Gonzalez, J., Migueles, J.H., Martin-Matillas, M., Gomez-Vida, J., Escolano-Margarit, M.V., et al., 2016. An exercise-based randomized controlled trial on brain, cognition, physical health and mental health in overweight/obese children (ActiveBrains project): rationale, design and methods. Contemporary Clin. Trials 47, 315–324 PubMed PMID: 26924671. Epub 2016/03/01. eng.

Cadenas-Sanchez, C., Migueles, J.H., Esteban-Cornejo, I., Mora-Gonzalez, J., Henriksson, P., Rodriguez-Ayllon, M., et al., 2020. Fitness, physical activity and academic achievement in overweight/obese children. J. Sports Sci. 38 (7), 731–740 PubMed PMID: 32091309. Epub 2020/02/25. eng.

Castro-Pinero, J., Artero, E.G., Espana-Romero, V., Ortega, F.B., Sjostrom, M., Suni, J., et al., 2010. Criterion-related validity of field-based fitness tests in youth: a systematic review. Br. J. Sports Med. 44 (13), 934–943 PubMed PMID: 19364756. Epub 2009/04/15. eng.

Castro-Pinero, J., Ortega, F.B., Artero, E.G., Girela-Rejon, M.J., Mora, J., Sjostrom, M., et al., 2010. Assessing muscular strength in youth: usefulness of standing long jump as a general index of muscular fitness. J. Strength Conditioning Res./National Strength & Conditioning Association 24 (7), 1810–1817 PubMed PMID: 20555277. Epub 2010/06/18. eng.

Chaddock, L., Erickson, K.I., Prakash, R.S., VanPatter, M., Voss, M.W., Pontifex, M.B., et al., 2010. Basal ganglia volume is associated with aerobic fitness in preadolescent children. Dev. Neurosci. 32 (3), 249–256 PubMed PMID: 20693803. Pubmed Central PMCID: PMC3696376. Epub 2010/08/10. eng.

Chaddock, L., Erickson, K.I., Prakash, R.S., Kim, J.S., Voss, M.W., Vanpatter, M., et al., 2010. A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. Brain Res. 1358, 172–183 PubMed PMID: 20735996. Pubmed Central PMCID: PMC3953557. Epub 2010/08/26. eng.

Chaddock, L., Erickson, K.I., Prakash, R.S., Voss, M.W., VanPatter, M., Pontifex, M.B., et al., 2012. A functional MRI investigation of the association between childhood aerobic fitness and neurocognitive control. Biol. Psychol. 89 (1), 260–268 PubMed PMID: 22061423. Epub 2011/11/09. eng.

Chaddock-Heyman, L., Erickson, K.I., Voss, M.W., Knecht, A.M., Pontifex, M.B., Castelli, D.M., et al., 2013. The effects of physical activity on functional MRI activation associated with cognitive control in children: a randomized controlled intervention. Front. Hum. Neurosci. 7, 72 PubMed PMID: 23487583. Pubmed Central PMCID: PMC3594762. Epub 2013/03/15. eng..

Chaddock-Heyman, L., Mackenzie, M.J., Zuniga, K., Cooke, G.E., Awick, E., Roberts, S., et al., 2015. Higher cardiorespiratory fitness levels are associated with greater hippocampal volume in breast cancer survivors. Front. Hum. Neurosci. 9, 465 PubMed PMID: 26379528. Pubmed Central PMCID: PMC4549568. Epub 2015/09/18. eng.

Chaddock-Heyman, L., Weng, T.B., Kienzler, C., Erickson, K.I., Voss, M.W., Drollette, E.S., et al., 2018. Scholastic performance and functional connectivity of brain networks in children. PLoS One 13 (1) PubMed PMID: 29364911. Pubmed Central PMCID: PMC5783351. Epub 2018/01/eng.

Chua, E.F., Schacter, D.L., Rand-Giovannetti, E., Sperling, R.A., 2007. Evidence for a specific role of the anterior hippocampal region in successful associative encoding. Hippocampus 17 (11), 1071–1080 PubMed PMID: 17604351. Epub 2007/07/03. eng.

Cotman, C.W., Berchtold, N.C., Christie, L.A., 2007. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci. 30 (9), 464–472 PubMed PMID: 17765329. Epub 2007/09/04. eng.

Damoiseaux, J.S., Viviano, R.P., Yuan, P., Raz, N., 2016. Differential effect of age on posterior and anterior hippocampal functional connectivity. NeuroImage 133, 468–476 PubMed PMID: 27034025. Pubmed Central PMCID: PMC4889536. Epub 2016/04/02. eng.

Davis, C.L., Tomporowski, P.D., McDowell, J.E., Austin, B.P., Miller, P.H., Yanasak, N.E., et al., 2011. Exercise improves executive function and achievement and alters brain activation in overweight children: a randomized, controlled trial. Health Psychol. 30 (1), 91–98 PubMed PMID: 21299297. Pubmed Central PMCID: Pmc3057917. Epub 2011/02/09. eng.

Donnelly, J.E., Hillman, C.H., Castelli, D., Etnier, J.L., Lee, S., Tomporowski, P., et al., 2016. Physical activity, fitness, cognitive function, and academic achievement in children: a systematic review. Med. Sci. Sports Exercise 48 (6), 1197–1222 PubMed PMID: 27182986. Pubmed Central PMCID: PMC4874515. Epub 2016/05/18. eng.

du Boisgueheneuc, F., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., et al., 2006. Functions of the left superior frontal gyrus in humans: a lesion study. Brain 129 (Pt 12), 3315–3328 PubMed PMID: 16984899. Epub 2006/09/21. eng..

Erickson, K.I., Prakash, R.S., Voss, M.W., Chaddock, L., Hu, L., Morris, K.S., et al., 2009. Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus 19 (10), 1030–1039 PubMed PMID: 19123237. Pubmed Central PMCID: PMC3072565. Epub 2009/01/06. eng.

Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., et al., 2011. Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. U.S.A. 108 (7), 3017–3022 PubMed PMID: 21282661. Pubmed Central PMCID: PMC3041121. Epub 2011/02/0eng.

Espana-Romero, V., Artero, E.G., Santaliestra-Pasias, A.M., Gutierrez, A., Castillo, M.J., Ruiz, J.R., 2008. Hand span influences optimal grip span in boys and girls aged 6 to 12 years. J. Hand Surg. 33 (3), 378–384 PubMed PMID: 18343294. Epub 2008/03/18. eng.

Espana-Romero, V., Ortega, F.B., Vicente-Rodriguez, G., Artero, E.G., Rey, J.P., Ruiz, J.R., 2010. Elbow position affects handgrip strength in adolescents: validity and reliability of Jamar, DynEx, and TKK dynamometers. J. Strength Conditioning Res./National Strength & Conditioning Association 24 (1), 272–277 PubMed PMID: 19966590. Epub 2009/12/08. eng.

Esteban-Cornejo, I., Tejero-Gonzalez, C.M., Martinez-Gomez, D., del-Campo, J., Gonzalez-Galo, A., Padilla-Moledo, C., et al., 2014. Independent and combined influence of the components of physical fitness on academic performance in youth. J. Pediatrics 165 (2) 306-12 e2. PubMed PMID: 24952710. Epub 2014/06/24. eng.

Esteban-Cornejo, I., Cadenas-Sanchez, C., Contreras-Rodriguez, O., Verdejo-Roman, J., Mora-Gonzalez, J., Migueles, J.H., et al., 2017. A whole brain volumetric approach in overweight/obese children: Examining the association with different physical fitness components and academic performance. The ActiveBrains project. NeuroImage 159, 346–354 PubMed PMID: 28789992. Epub 2017/08/10. eng.

Esteban-Cornejo, I., Mora-Gonzalez, J., Cadenas-Sanchez, C., Contreras-Rodriguez, O., Verdejo-Roman, J., Henriksson, P., et al., 2019. Fitness, cortical thickness and surface area in overweight/obese children: the mediating role of body composition and relationship with intelligence. NeuroImage 186, 771–781 PubMed PMID: 30500426. Epub 2018/12/01. eng.

Esteban-Cornejo, I., Rodriguez-Ayllon, M., Verdejo-Roman, J., Cadenas-Sanchez, C., Mora-Gonzalez, J., Chaddock-Heyman, L., et al., 2019. Physical fitness, white matter volume and academic performance in children: findings from the ActiveBrains and FITKids2 Projects. Front. Psychol. 10, 208 PubMed PMID: 30809168. Pubmed Central PMCID: PMC6379335. Epub 2019/02/28. eng.

Firth, J., Stubbs, B., Vancampfort, D., Schuch, F., Lagopoulos, J., Rosenbaum, S., et al., 2018. Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis. NeuroImage 166, 230–238 PubMed PMID: 29113943. Epub 2017/11/09. eng.

Hertrich, I., Dietrich, S., Ackermann, H., 2016. The role of the supplementary motor area for speech and language processing. Neurosci. Biobehav. Rev. 68, 602–610 PubMed PMID: 27343998. Epub 2016/06/28. eng.

Hueston, C.M., Cryan, J.F., Nolan, Y.M., 2017. Stress and adolescent hippocampal neurogenesis: diet and exercise as cognitive modulators. Transl. Psychiatry 7 (4), e1081 PubMed PMID: 28375209. Pubmed Central PMCID: PMC5416690. Epub 2017/04/05. eng.

Huijbers, W., Mormino, E.C., Schultz, A.P., Wigman, S., Ward, A.M., Larvie, M., et al., 2015. Amyloid-beta deposition in mild cognitive impairment is associated with increased hippocampal activity, atrophy and clinical progression. Brain 138 (Pt 4), 1023–1035 PubMed PMID: 25678559. Pubmed Central PMCID: PMC4438387. Epub 2015/02/1eng.

Ikuta, T., Loprinzi, P.D., 2019. Association of cardiorespiratory fitness on interhemispheric hippocampal and parahippocampal functional connectivity. Eur. J. Neurosci. 50 (2), 1871–1877 PubMed PMID: 30719776. Epub 2019/02/06. eng.

Kamijo, K., Pontifex, M.B., Khan, N.A., Raine, L.B., Scudder, M.R., Drollette, E.S., et al., 2014. The negative association of childhood obesity to cognitive control of action monitoring. Cerebral cortex (New York, NY: 1991) 24 (3), 654–662 PubMed PMID: 23146965. Pubmed Central PMCID: PMC3920765. Epub 2012/11/14. eng.

Kamijo, K., Khan, N.A., Pontifex, M.B., Scudder, M.R., Drollette, E.S., Raine, L.B., et al., 2012. The relation of adiposity to cognitive control and scholastic achievement in preadolescent children. Obesity (Silver Spring, Md) 20 (12), 2406–2411 PubMed PMID: 22546743. Pubmed Central PMCID: PMC3414677. Epub 2012/05/02. eng.

Killgore, W.D., Olson, E.A., Weber, M., 2013. Physical exercise habits correlate with gray matter volume of the hippocampus in healthy adult humans. Sci. Rep. 3, 3457 PubMed PMID: 24336512. Pubmed Central PMCID: PMC3860009. Epub 2013/12/18. eng.

Koch, W., Teipel, S., Mueller, S., Buerger, K., Bokde, A.L.W., Hampel, H., et al., 2010. Effects of aging on default mode network activity in resting state fMRI: does the method of analysis matter? NeuroImage 51 (1), 280–287.
Krafft, C.E., Pierce, J.E., Schwarz, N.F., Chi, L., Weinberger, A.L., Schaeffer, D.J., et al., 2014. An eight month randomized controlled exercise intervention alters resting state synchrony in overweight children. Neuroscience 256, 445–455 PubMed PMID: 24096138. Pubmed Central PMCID: PMC3995346. Epub 2013/10/08. eng.
Krafft, C.E., Schwarz, N.F., Chi, L., Weinberger, A.L., Schaeffer, D.J., Pierce, J.E., et al., 2014. An 8-month randomized controlled exercise trial alters brain activation during cognitive tasks in overweight children. Obesity (Silver Spring, Md). 22 (1), 232–242 PubMed PMID: 23788510. Pubmed Central PMCID: PMC4077546. Epub 2013/06/22. eng.
Kronman, C.A., Kern, K.L., Nauer, R.K., Dunne, M.F., Storer, T.W., Schon, K., 2019. Cardiorespiratory fitness predicts effective connectivity between the hippocampus and default mode network nodes in young adults. Hippocampus PubMed PMID: 31647603. Epub 2019/10/28. eng.
Leger, L.A., Mercier, D., Gadoury, C., Lambert, J., 1988. The multistage 20 metre shuttle run test for aerobic fitness. J. Sports Sci. 6 (2), 93–101 PubMed PMID: 3184250. Epub 1988/01/01. eng.
Leonard, C.M., Towler, S., Welcome, S., Chiarello, C., 2009. Paracingulate asymmetry in anterior and midcingulate cortex: sex differences and the effect of measurement technique. Brain Struct Function 213 (6), 553–569 PubMed PMID: 19636589. Epub 2009/07/29. eng.
Liu, W., Ge, T., Leng, Y., Pan, Z., Fan, J., Yang, W., et al., 2017. The role of neural plasticity in depression: from hippocampus to prefrontal cortex. Neural Plasticity 6871089 PubMed PMID: 28246558. Pubmed Central PMCID: PMC5299163. Epub 2017/03/02. eng.
Malina, R.M., Rogol, A.D., Cumming, S.P., Coelho e Silva, M.J., Figueiredo, A.J., 2015. Biological maturation of youth athletes: assessment and implications. Br. J. Sports Med. 49 (13), 852–859.
McGrew, K., Woodcock-Johnson III, W.R., 2001. Technical Manual. Riverside Publishing Company, Itasca, IL.
Mestre, Z.L., Bischoff-Grethe, A., Eichen, D.M., Wierenga, C.E., Strong, D., Boutelle, K.N., 2017. Hippocampal atrophy and altered brain responses to pleasant tastes among obese compared with healthy weight children. Int. J. Obesity 41 (10), 1496–1502 PubMed PMID: 2857258Pubmed Central PMCID: PMC5626610. Epub 2017/06/03. eng.
Miller, R., 1991. Cortico-Hippocampal Interplay and the Representation of Contexts in the Brain.
Mora-Gonzalez, J., Esteban-Cornejo, I., Cadenas-Sanchez, C., Migueles, J.H., Molina-Garcia, P., Rodriguez-Ayllon, M., et al., 2019. Physical fitness, physical activity, and the executive function in children with overweight and obesity. J. Pediatrics 208 (50–6), e1 PubMed PMID: 30902422. Epub 2019/03/25. eng.
Mora-Gonzalez, J., Esteban-Cornejo, I., Cadenas-Sanchez, C., Migueles, J.H., Rodriguez-Ayllon, M., Molina-Garcia, P., et al., 2019. Fitness, physical activity, working memory, and neuroelectric activity in children with overweight/obesity. Scand. J. Med. Sci. Sports 29 (9), 1352–1363 PubMed PMID: 31058358. Epub 2019/05/07. eng.
Muntaner-Mas, A., Palou, P., Vidal-Conti, J., Esteban-Cornejo, I., 2018. A mediation analysis on the relationship of physical fitness components, obesity, and academic performance in children. J. Pediatrics 198 90-7 e4. PubMed PMID: 29685619. Epub 2018/04/25. eng.
Nakahara, S., Matsumoto, M., Van Erp, T.G.M., 2018. Hippocampal subregion abnormalities in schizophrenia: a systematic review of structural and physiological imaging studies. Neuropsychopharmacol. Rep. 38 (4), 156–166 PubMed PMID: 30255629. Epub 2018/09/2eng.
Ortega, F.B., Artero, E.G., Ruiz, J.R., Vicente-Rodriguez, G., Bergman, P., Hagstromer, M., et al., 2008. Reliability of health-related physical fitness tests in European adolescents. The HELENA Study. Int. J. Obesity 2005 (32 Suppl 5), S49–S57 PubMed PMID: 19011654. Epub 2008/11/26. eng.
Patenaude, B., Smith, S.M., Kennedy, D.N., Jenkinson, M., 2011. A Bayesian model of shape and appearance for subcortical brain segmentation. NeuroImage 56 (3), 907–922 PubMed PMID: 21352927. Pubmed Central PMCID: PMC3417233. Epub 2011/03/01. eng.
Poppenk, J., Evensmoen, H.R., Moscovitch, M., Nadel, L., 2013. Long-axis specialization of the human hippocampus. Trends Cognitive Sci. 17 (5), 230–240 PubMed PMID: 23597720. Epub 2013/04/20. eng.
Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., et al., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cerebral Cortex (New York, NY: 1991) 15 (11), 1676–1689 PubMed PMID: 15703252. Epub 2005/02/1eng.
Reinert, K.R., Po'e, E.K., Barkin, S.L., 2013. The relationship between executive function and obesity in children and adolescents: a systematic literature review. J. Obes. 2013, 820956 PubMed PMID: 23533726. Pubmed Central PMCID: PMC35956Epub 2013/03/28. eng.
Ruiz, J.R., Castro-Pinero, J., Espana-Romero, V., Artero, E.G., Ortega, F.B., Cuenca, M.M., et al., 2011. Field-based fitness assessment in young people: the ALPHA health-related fitness test battery for children and adolescents. Br. J. Sports Med. 45 (6), 518–524 PubMed PMID: 20961915. Epub 2010/10/22. eng.
Salami, A., Pudas, S., Nyberg, L., 2014. Elevated hippocampal resting-state connectivity underlies deficient neurocognitive function in aging. Proc. Natl. Acad. Sci. 111 (49), 17654–17659.
Sharkey, R.J., Karama, S., Dagher, A., 2015. Overweight is not associated with cortical thickness alterations in children. Front. Neurosci. 9, 24 PubMed PMID: 25698918. Pubmed Central PMCID: PMC4316697. Epub 2015/02/24. eng.
Stillman, C.M., Uyar, F., Huang, H., Grove, G.A., Watt, J.C., Wollam, M.E., et al., 2018. Cardiorespiratory fitness is associated with enhanced hippocampal functional connectivity in healthy young adults. Hippocampus 28 (3), 239–247 PubMed PMID: 29341303. Pubmed Central PMCID: PMC5820159. Epub 2018/01/18. eng.
Stillman, C.M., Donofry, S.D., Erickson, K.I., 2019. Exercise, fitness and the aging brain: a review of functional connectivity in aging. Arch. Psychol. 3 (4).
Strange, B.A., Witter, M.P., Lein, E.S., Moser, E.I., 2014. Functional organization of the hippocampal longitudinal axis. Nature Rev. Neurosci. 15 (10), 655–669 PubMed PMID: 25234264. Epub 2014/09/23. eng.
Talukdar, T., Nikolaidis, A., Zwilling, C.E., Paul, E.J., Hillman, C.H., Cohen, N.J., et al., 2018. Aerobic fitness explains individual differences in the functional brain connectome of healthy young adults. Cerebral Cortex (New York, NY: 1991) 28 (10), 3600–3609.
van Praag, H., Christie, B.R., Sejnowski, T.J., Gage, F.H., 1999. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc. Natl. Acad. Sci. U.S.A. 96 (23), 13427–13431 PubMed PMID: 10557337. Pubmed Central PMCID: PMC23964. Epub 1999/11/11. eng..
van Praag, H., Shubert, T., Zhao, C., Gage, F.H., 2005. Exercise enhances learning and hippocampal neurogenesis in aged mice. J. Neurosci. 25 (38), 8680–8685 PubMed PMID: 16177036. Pubmed Central PMCID: PMC1360197. Epub 2005/09/24. eng.
Vicente-Rodriguez, G., Rey-Lopez, J.P., Ruiz, J.R., Jimenez-Pavon, D., Bergman, P., Ciarapica, D., et al., 2011. Interrater reliability and time measurement validity of speed-agility field tests in adolescents. J. Strength Conditioning Res./National Strength & Conditioning Association 25 (72059) PubMed PMID: 214991Epub 2011/04/19. eng.
Voss, M.W., Erickson, K.I., Prakash, R.S., Chaddock, L., Malkowski, E., Alves, H., et al., 2010. Functional connectivity: a source of variance in the association between cardiorespiratory fitness and cognition? Neuropsychologia. 48 (5), 1394–1406 PubMed PMID: 20079755. Pubmed Central PMCID: PMC3708614. Epub 2010/01/19. eng.
Voss, M.W., Chaddock, L., Kim, J.S., Vanpatter, M., Pontifex, M.B., Raine, L.B., et al., 2011. Aerobic fitness is associated with greater efficiency of the network underlying cognitive control in preadolescent children. Neuroscience 199, 166–176 PubMed PMID: 22027235. Pubmed Central PMCID: PMC3237764. Epub 2011/10/27. eng.
Voss, M.W., Vivar, C., Kramer, A.F., van Praag, H., 2013. Bridging animal and human models of exercise-induced brain plasticity. Trends Cognitive Sci. 17 (10), 525–544 PubMed PMID: 24029446. Pubmed Central PMCID: PMC4565723. Epub 2013/09/14. eng.
Voss, M.W., Soto, C., Yoo, S., Sodoma, M., Vivar, C., van Praag, H., 2019. Exercise and hippocampal memory systems. Trends Cognitive Sci. 23 (4), 318–333 PubMed PMID: 30777641. Pubmed Central PMCID: PMC6422697. Epub 2019/02/20. en.