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A whole brain volumetric approach in overweight/obese children: Examining the association with different physical fitness components and academic performance. The ActiveBrains project

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ABSTRACT

Obesity, as compared to normal weight, is associated with detectable structural differences in the brain. To the best of our knowledge, no previous study has examined the association of physical fitness with gray matter volume in overweight/obese children using whole brain analyses. Thus, the aim of this study was to examine the association between the key components of physical fitness (i.e. cardiorespiratory fitness, speed-agility and muscular fitness) and brain structural volume, and to assess whether fitness-related changes in brain volumes are related to academic performance in overweight/obese children. A total of 101 overweight/obese children aged 8–11 years were recruited from Granada, Spain. The physical fitness components were assessed following the ALPHA health-related fitness test battery. T1-weighted images were acquired with a 3.0 T S Magnetom Tim Trio system. Gray matter tissue was calculated using Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL). Academic performance was assessed by the Batería III Woodcock-Muñoz Tests of Achievement. All analyses were controlled for sex, peak high velocity offset, parent education, body mass index and total brain volume. The statistical threshold was calculated with AlphaSim and further Hayasaka adjusted to account for the non-isotropic smoothness of structural images. The main results showed that higher cardiorespiratory fitness was related to greater gray matter volumes ($P < 0.001$, $k = 64$) in 7 clusters with β ranging from 0.493 to 0.575; specifically in frontal regions (i.e. premotor cortex and supplementary motor cortex), subcortical regions (i.e. hippocampus and caudate), temporal regions (i.e. inferior temporal gyrus and parahippocampal gyrus) and calcarine cortex. Three of these regions (i.e. premotor cortex, supplementary motor cortex and hippocampus) were related to better academic performance (β ranging from 0.211 to 0.352; all $P < 0.05$). Higher speed-agility was associated with greater gray matter volumes ($P < 0.001$, $k = 57$) in 2 clusters (i.e. the inferior frontal gyrus and the superior temporal gyrus) with β ranging from 0.564 to 0.611. Both clusters were related to better academic performance (β ranging from 0.217 to 0.296; both $P < 0.05$). Muscular fitness was not independently associated with greater gray matter volume in any brain region. Furthermore, there were no statistically significant negative association between any component of physical fitness and gray matter volume in any region of the brain. In conclusion, cardiorespiratory fitness and speed-agility, but not muscular fitness, may independently be associated with greater volume of numerous cortical and subcortical brain structures; besides, some of these brain structures may be related to better academic performance. Importantly, the identified associations of fitness and gray matter volume were different for each fitness component. These findings suggest that increases in cardiorespiratory fitness and speed-agility may positively influence the development of distinctive brain regions and academic indicators, and thus counteract the harmful effect of overweight and obesity on brain structure during childhood.

Abbreviations: ALPHA, Assessing Levels of Physical fitness and Health in Adolescents; Bas, Brodmann areas; BDNF, Brain-derived neurotrophic factor; BMI, Body mass index; DARTEL, Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra; PHV, Peak height velocity; TVB, Total brain volume.

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1. Introduction

Physical fitness is a major determinant of health throughout the lifespan. The main components of physical fitness with documented benefits on health are cardiorespiratory fitness, speed-agility and muscular fitness (Ortega et al., 2008b; Ruiz et al., 2009). While the benefits of fitness on physical health are well established (Ortega et al., 2008b; Ruiz et al., 2015), there is emerging evidence on the potential impact of physical fitness on cognitive and brain health (Donnelly et al., 2016). During childhood and adolescence, high levels of cardiorespiratory fitness have been positively associated with academic performance and cognition, as well as brain functioning and structure (Hillman et al., 2008; Chaddock et al., 2011; Esteban-Cornejo et al., 2014; Ortega et al., 2017). In contrast, individuals with lower cardiorespiratory fitness are at greater risk of having cognitive deficits and developing neurodegenerative disorders later in life (Newson and Kemps, 2006; Defina et al., 2013; Nyberg et al., 2014).

Particularly, recent evidence has shown that the brain's volumetric structure of individuals with overweight and obesity is 10 years older compared to that of lean peers, and this accelerated brain aging is evident from young adulthood onwards (Ronan et al., 2016). Indeed, obesity has been associated with detectable structural differences in the brain as compared to the brains of normal-weight individuals already during childhood and adolescence (Reinert et al., 2013). For instance, body mass index (BMI) has been negatively associated with gray matter volume in a dose-dependent manner (Maayan et al., 2011; Ou et al., 2015). In addition, overweight and obese children have worse cognitive control and academic performance compared to normal-weight children (Kamijo et al., 2012, 2014). These findings highlight the importance of examining the potential benefits of physical fitness for brain health in the context of overweight and obesity during early stages of life. It is indeed plausible that physical fitness has a positive impact on brain health, resulting in better academic performance, and may thus attenuate the negative effect of overweight and obesity on brain structure during childhood.

Despite the marked relevance of fitness for brain health in overweight/obese children (Maayan et al., 2011; Reinert et al., 2013; Ou et al., 2015), no previous volumetric study has focused on populations with excess body weight, and only two studies have been performed in normal weight children (Chaddock et al., 2010a, 2010c). These studies showed that higher cardiorespiratory fitness was associated with greater volume of the hippocampus and the dorsal striatum of the basal ganglia; and in turn, hippocampal volume was related to relational memory and dorsal striatum volume with better cognitive control and response resolution. However, there is a number of research questions that still need to be addressed (Donnelly et al., 2016). Firstly, previous studies focused on the two fitness extremes, i.e. children with a very high fitness vs. a very low fitness, leaving out from the analyses the rest of children with a middle fitness level, which it has been considered in a recent position stand as a limitation of existing evidence (Donnelly et al., 2016). Secondly, different dimensions of fitness may have different effects on the brain. For example, cardiorespiratory fitness is related to angiogenesis, whereas speed-agility and muscular fitness are associated with synaptogenesis in animals (Adkins et al., 2006). Thirdly, brain changes may translate into improved academic performance. Therefore, to have a complete picture of fitness-brain-academic performance relationships, there is a need for studies that examines all different components of fitness and their associations with gray matter volume on a whole brain level, rather than at the region-of-interest level, as well as whether these gray matter volume changes are related to academic performance.

Understanding the association of different physical fitness components with brain measures and how those brain changes relate to academic performance would help develop public health and educational strategies, since exercise programs improve physical fitness levels, which in turn, may positively influence physical and cognitive health (Voelcker-Rehage and Niemann, 2013). To the best of our knowledge, no previous study has examined the association of physical fitness with gray matter volume of all known brain structures in overweight/obese children or its links to academic performance.

Therefore, the aim of this study was twofold: (i) to examine the association between the key components of physical fitness (i.e. cardiorespiratory fitness, speed-agility and muscular fitness) and brain volume, and (ii) to examine whether fitness-related changes in brain volumes are related to academic performance in relatively large sample of overweight/obese children. To achieve this aim, firstly, we used multiple regression analyses including the three components of fitness as predictors (separately and independently), while controlling for relevant confounders using a whole-brain analytical approach; and secondly, we extracted the eigenvalues from each significant brain cluster to include them as predictors of academic performance.

2. Materials and methods

2.1. Participants

Participants in this study were enrolled in the ActiveBrains project (http://profith.ugr.es/activebrains). ActiveBrains is a randomized controlled trial designed to examine the effects of an exercise program on brain, cognitive and academic performance, as well as on selected physical and mental health outcomes in overweight/obese children (Cadenas-Sanchez et al., 2016). A total of 110 overweight/obese children aged 8–11 years were recruited from Granada (south of Spain). All participants met the defined inclusion criteria: 1) to be overweight or obese based on World Obesity Federation cut-off points 2) to be 8 to 11 years-old, 3) not to have any physical disabilities or neurological disorder that affects their physical performance and 4) in the case of girls, not to have started the menstruation at the moment of the assessments (Cadenas-Sanchez et al., 2016). Data were collected from November 2014 to February 2016. The present cross-sectional analyses were completed on baseline assessment data prior to randomizing children and included 101 overweight/obese children (10.0 ± 1.1 years; 60.4% boys) with complete baseline data on physical fitness and brain variables.

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).

2.2. Physical fitness

The different components of physical fitness were assessed following the ALPHA (Assessing Levels of Physical fitness and Health in Adolescents) health-related fitness test battery for youth. Detailed information about the ALPHA battery is available elsewhere (Ortega et al., 2008a; Castro-Pinero et al., 2010a; Ruiz et al., 2011). In brief, 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. The last stage completed was recorded and transformed to maximal oxygen consumption (VO_2max, ml/kg/min) using the Léger equation (Leger et al., 1988).

Speed-agility 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). In this test, a longer time indicates poorer performance (i.e., the person is slower and less agile). 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 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 was performed from a starting position behind a line, standing with feet approximately shoulder width apart (Castro-Pinero et al., 2010b). 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 then calculated as the sum of the two standardized scores.

2.3. Magnetic Resonance Imaging (MRI) procedure

2.3.1. Data acquisition

All images were acquired with a 3.0 T S Magnetom Tim Trio system (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. Three-dimensional, high-resolution, T1-weighted images were collected using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence. The parameters were as follows: repetition time (TR) = 2300 ms, echo time (TE) = 3.58 ms, inversion time (TI) = 900 ms, flip angle = 10°, acquisition matrix = 256 × 240, 160 slices, resolution = 1 × 1 × 1.1 mm, and scan duration of 7 min and 31 s.

2.3.2. Structural image processing

Structural imaging data were pre-processed using Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (The MathWorks, Inc, Natick, MA). Before tissue classification we checked each individual image for acquisition artifacts and alignment along the horizontal anterior commissure and posterior commissure plane.

Pre-processing steps are shown in Fig. 1. First, using the latest segmentation algorithm implemented in SPM12, we segmented T1-weighted structural images of each participant into gray matter tissue, white matter tissue, and cerebrospinal fluid (Ashburner and Friston, 2005). Second, segmented gray matter/white matter tissues for all participants were used to create a customized template using Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) (Ashburner, 2007). DARTEL estimates a best set of smooth deformations from every participant's tissue to their common average and reiterates the process until convergence. The resultant images were spatially normalized to Montreal Neurological Institute (MNI) space with affine transformation to create the DARTEL template. Subsequently, each participant's segmented images were normalized to the DARTEL template via nonlinear transformation. To perform a volume change correction, the normalized gray matter images were modulated with Jacobian determinants derived from the spatial normalization (Ashburner and Friston, 2000). Finally, the volumetric images were smoothed by convolving them with an isotropic Gaussian kernel of 8 mm full-width at half-maximum (FWHM).

2.4. 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), which is a well validated measure of academic achievement (McGrew and Woodcock, 2001). We applied 12 tests: 11 from the standard battery (i.e. 3 tests of reading, 3 tests of mathematics, 2 tests of oral language and 3 tests of written language) and one from the extended battery (i.e. a test based on science, social science and humanities). 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. All the data were processed in the Compuscore and profile software version 3.1 (Riverside

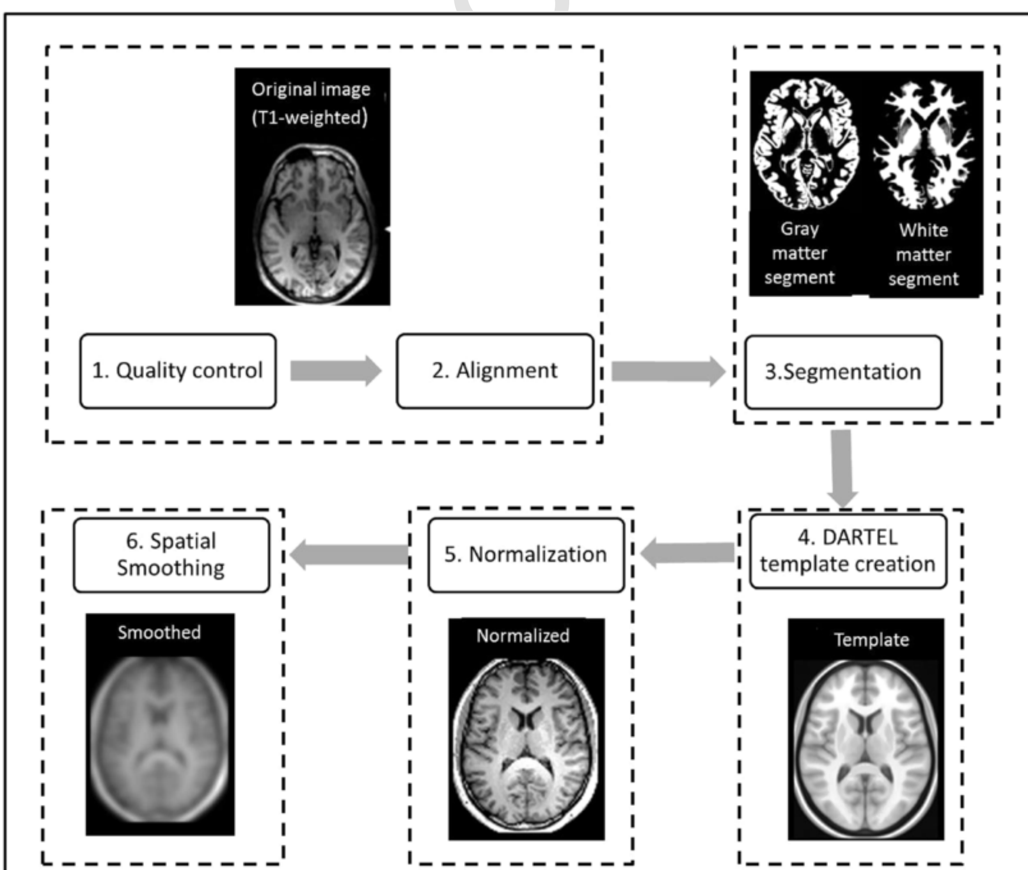

Fig. 1. Data preprocessing steps. GM, gray matter tissue; WM, white matter tissue; CSF, cerebrospinal fluid.

Publishing Company, Itasca, IL, USA). The main dependent measures were the standard scores of the 12 academic indicators: oral language, reading, writing, written expression, mathematics, mathematics calculation skills, science, academic skills, academic fluency, academic applications and total achievement (Davis et al., 2011).

2.5. Covariates

2.5.1. Total brain volume (TBV)

TBV was calculated by adding the volumes of gray and white matters derived from non-normalized segmented images.

2.5.2. BMI

Body weight was measured with an electronic scale (SECA 861, Hamburg, Germany) and height (cm) with a stadiometer (SECA 225, Hamburg, Germany). Both measurements were performed twice with participants having bare feet and wearing underclothes, and averages were used. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). BMI categories were defined (i.e. overweight, obesity grade I, II, III) according to Cole and Lobstein (2012).

2.5.3. Biological maturation

Peak height velocity (PHV) is the most commonly used indicator of maturity in studies of children and adolescents (Malina et al., 2015). PHV was obtained from anthropometric variables (weight, height and seated height) using Mirwald's equations (Mirwald et al., 2002). 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.

2.5.4. Parental education level

Socioeconomic status was assessed by the educational level of mother and father reported as no elementary school, elementary school, middle school, high school and university completed. Parent responses were combined as: none of the parents had a university degree, one of the parents had a university degree and both parents had a university degree (Huppertz et al., 2016).

2.6. Statistical analysis

The characteristics of study sample are presented as means (SD) or percentages. All variables were checked for normality. Differences between sexes were determined by t-tests and chi-squared tests for continuous and categorical variables, respectively, using IBM SPSS Statistics (version 18.0 for Windows; P set at < 0.05).

Statistical analyses of imaging data were performed using the GLM approach implemented in SPM12. The association between each component of physical fitness (i.e. cardiorespiratory fitness, speed-agility and muscular fitness) and gray matter volume was analyzed using three whole-brain voxel-wise multiple regression models (one model for each fitness component), adjusted for sex, PHV offset, parental education, BMI and TBV. To account for the common variance among the three physical fitness components, we examined the association between physical fitness components (i.e. cardiorespiratory fitness, speed-agility and muscular fitness) and gray matter volume simultaneously in one whole-brain voxel-wise multiple regression, adjusted for sex, PHV offset, parental education, BMI and TBV.

Additionally, we extracted the eigenvalues from the peak coordinates of each significant cluster. To estimate the amount of explained variance, we used those eigenvalues to perform linear regressions in SPSS with the physical fitness components as predictor variables and the extracted mean gray matter volumes as outcomes, adjusted for the set of covariates mentioned above. The associations of the extracted mean gray matter volumes as predictor variables and academic performance indicators as outcomes, adjusted for sex, PHV offset, parental education and BMI were examined by linear regressions in SPSS.

The statistical threshold in the imaging analyses was calculated with AlphaSim, as implemented in Resting-State fMRI Data Analysis Toolkit toolbox (RESTplus) (Song et al., 2011). Parameters were defined as follows: cluster connection radius (rmm) = 5 mm and the actual smoothness of the data after model estimation, incorporating a gray mask volume of 128190 voxels. The voxel-level alpha significance (threshold, $p < 0.001$ uncorrected) along with the appropriate cluster size for controlling for multiple comparisons in each analysis were indicated in the results. The resulting cluster extents were further adjusted to account for the non-isotropic smoothness of structural images, in accordance with Hayasaka et al. (2004).

3. Results

3.1. Background characteristics

Table 1 shows the sociodemographic, body composition and physical fitness characteristics of the study sample. Overall, boys had similar average BMI to that of girls (27.0 vs. 26.5 kg/m^2; $P > 0.05$) and 25% of the participants were overweight and 75% were obese (42% obesity grade I, 21% obesity grade II and 12% obesity grade III). Boys had on average higher TBV than girls ($P < 0.001$).

3.2. Gray matter correlates of individual physical fitness components

Table 2 presents the brain regions showing positive associations between each physical fitness component and gray matter volume after adjustment for potential confounders.

Cardiorespiratory fitness was associated with greater gray matter volumes ($P < 0.001$, $k = 75$) in 10 clusters with β ranging from 0.391 to 0.506; specifically, in frontal regions (i.e. orbitofrontal cortex and premotor cortex), parietal region (posterior cingulate cortex), subcortical nuclei (i.e. hippocampus), temporal regions (i.e. superior temporal gyrus, parahippocampal gyrus and fusiform gyrus), calcarine cortex and cerebellum VI.

Speed-agility was related to greater gray matter volumes ($P < 0.001$, $k = 62$) in 5 clusters with β ranging from 0.398 to 0.472; specifically, in frontal regions (i.e. middle and inferior frontal gyri), temporal regions (i.e. superior temporal gyrus and fusiform gyrus) and cerebellum (i.e. cerebellum VIII).

Muscular fitness was associated with greater gray matter volumes ($P < 0.001$, $k = 47$) in two clusters of the cerebellum, crus I ($\beta = 0.362$) and crus II ($\beta = 0.568$). No brain region showed a statistically significant negative association between any physical fitness component and gray matter volume.

3.3. Gray matter correlates of the independent physical fitness components

Table 3 (also Fig. 2) presents the clusters showing independent positive associations of cardiorespiratory fitness and speed-agility with gray matter volume, after controlling for potential confounders and mutually fitness adjustment (all physical fitness components were introduced in the same model).

Cardiorespiratory fitness was related to greater gray matter volumes ($P < 0.001$, $k = 64$) in 7 clusters with β ranging from 0.493 to 0.575. Speed-agility was associated with greater gray matter volumes ($P < 0.001$, $k = 57$) in 2 clusters with β ranging from 0.564 to 0.611. Muscular fitness was not independently associated with greater gray matter volume in any brain regions ($P < 0.001$, $k = 53$). Furthermore, there were no statistically significant negative association between any component of physical fitness and gray matter volume in any region of the brain.

Fig. 2 illustrates the brain areas showing independent positive associations of cardiorespiratory fitness and speed-agility with gray matter volume. Cardiorespiratory fitness was related to greater gray matter volume in frontal regions (i.e. premotor cortex and medial primary motor cortex), subcortical nuclei (i.e. hippocampus and caudate), temporal regions (i.e. inferior temporal gyrus and parahippocampal gyrus) and calcarine cortex (Fig. 2A). Speed-agility was associated with higher volume of gray matter of the inferior frontal gyrus and the superior temporal gyrus (Fig. 2B). Muscular fitness was not independently associated with

Table 1
Characteristics of study sample.

n	All	Boys	Girls	P for sex
	101	61	40	
Physical characteristics				
Age (years)	10.0 ± 1.1	10.1 ± 1.1	9.8 ± 1.1	0.166
Peak height velocity offset (years)	−2.0 ± 1.0	−2.5 ± 0.7	−1.1 ± 0.8	< **0.001**
Weight (kg)	55.9 ± 11.0	56.8 ± 10.7	54.4 ± 11.5	0.297
Height (cm)	144.0 ± 8.2	144.7 ± 7.3	142.8 ± 9.4	0.247
Body mass index (kg/m^2)	26.8 ± 3.6	27.0 ± 3.8	26.5 ± 3.4	0.511
Body mass index category (%)				0.826
Overweight	25	26	23	
Obesity grade I	42	43	43	
Obesity grade II	21	18	25	
Obesity grade III	12	13	10	
Parental education university level (%)				0.245
Neither parent	66	72	58	
One parent	18	16	20	
Both parents	16	11	23	
Physical fitness components				
Cardiorespiratory fitness (stage)[a]	1.7 ± 1.0	1.8 ± 1.0	1.5 ± 0.9	0.151
Cardiorespiratory fitness (mL/kg/min)[a]	40.8 ± 2.8	40.8 ± 2.7	40.7 ± 2.8	0.855
Speed-agility (s) [b]	15.1 ± 1.6	14.9 ± 1.6	15.4 ± 1.5	0.163
Muscular fitness (z-score) [c]	0.0 ± 1.9	0.3 ± 1.9	−0.4 ± 1.8	0.094
Total brain volume (cm^3)	1199.5 ± 106.5	1244.3 ± 89.7	1131.2 ± 93.7	< **0.001**
Academic performance[d]				
Oral language	89.8 ± 13.4	89.8 ± 12.8	89.9 ± 14.3	0.994
Reading	107.7 ± 13.5	107.6 ± 12.2	107.9 ± 15.5	0.922
Writing	113.2 ± 12.9	111.9 ± 12.3	115.1 ± 13.8	0.237
Written expression	103.2 ± 8.8	102.7 ± 8.8	104.1 ± 8.9	0.446
Mathematics	101.4 ± 10.7	101.8 ± 11.5	100.8 ± 9.6	0.641
Math calculation skills	102.9 ± 12	101.9 ± 12.9	104.2 ± 10.5	0.358
Science	96.4 ± 11.7	96.3 ± 10.8	96.6 ± 13.1	0.914
Academic skills	117.8 ± 16.5	116.3 ± 15.5	120 ± 17.8	0.283
Academic fluency	103.2 ± 12.2	103.5 ± 11.5	102.7 ± 13.3	0.751
Academic applications	99.4 ± 9	99.9 ± 9.1	98.7 ± 9.0	0.532
Total achievement	108.7 ± 12.2	108.3 ± 11.5	109.3 ± 13.4	0.685

Values are mean ± SD or percentages.

[a] Measured by the 20-m shuttle run test, Lèger equation for transforming stage to VO2max (mL/kg/min): [predicted VO2max = 31.025 + (3.238 × (8 + 0.5 × last stage completed)) - (3.248 × age) + (0.1536 × (8 + 0.5 × last stage completed) × age)].

[b] Measured by the 4 × 10-m shuttle run test; values were multiplied by −1 before analyses so that higher values indicate better performance.

[c] z-score computed from handgrip strength (kg) and standing long jump (cm*kg) tests.

[d] Measured by the Bateria III Woodcock-Muñoz Tests of Achievement.

Table 2
Brain regions showing separately positive associations of the components of physical fitness with gray matter volume in overweight/obese children (n = 101).

Brain Regions (mm^3)	X	Y	Z	Peak t	Cluster size	Hem	B (95% CI)	β	Brodmann area
Cardiorespiratory fitness (mL/kg/min)									
Orbitofrontal cortex	−35	38	−12	3.8	95	L	0.012 (0.006,0.018)	0.454	11/47
Premotor cortex	48	3	29	4.2	176	R	0.010 (0.005,0.015)	0.506	6/9
	−51	5	20	4.2	371	L	0.015 (0.008,0.021)	0.480	44/45
Posterior cingulate cortex	18	−57	20	3.6	255	R	0.022 (0.010,0.034)	0.440	31
Hippocampus	−33	−14	−17	3.8	109	L	0.006 (0.003,0.008)	0.447	–
Superior temporal gyrus	47	9	−12	3.4	125	R	0.008 (0.003,0.012)	0.391	38
Parahippocampal gyrus	23	−53	−11	3.6	238	R	0.010 (0.004,0.015)	0.451	19
Fusiform gyrus	−32	−62	−18	3.5	154	L	0.013 (0.006,0.020)	0.445	37
Calcarine cortex	9	−84	11	3.7	385	R	0.013 (0.006,0.021)	0.454	17/18
Cerebellum VI	14	−69	−30	3.8	165	R	0.007 (0.004,0.011)	0.436	–
Speed-agility (s^{-1})[a]									
Middle frontal gyrus	−41	47	26	3.8	341	L	0.014 (0.007,0.021)	0.552	10/46
Inferior frontal gyrus	−48	12	15	3.8	526	L	0.021 (0.010,0.031)	0.457	44
Superior temporal gyrus	59	−41	15	4.1	688	R	0.022 (0.011,0.032)	0.472	22
Fusiform gyrus	−39	−54	−12	3.7	457	L	0.021 (0.010,0.032)	0.436	37
Cerebellum VIII	−12	−69	−42	3.4	187	L	0.012	0.398	–

Table 3
Brain regions showing positive independent associations of cardiorespiratory and speed-agility with gray matter volume in overweight/obese children (n = 101).

Brain regions (mm^3)	X	Y	Z	Peak t	Cluster size	Hem	B(95% CI)	β	Brodmann area
Cardiorespiratory fitness (mL/kg/min)									
Premotor cortex	48	3	30	3.9	184	R	0.011 (0.005,0.017)	0.511	6/9
Supplementary motor cortex	2	−17	68	3.8	103	R	0.008 (0.004,0.013)	0.505	6
Hippocampus	−32	−14	−17	3.7	64	L	0.007 (0.003,0.011)	0.493	–
Caudate[a]	−15	3	24	3.3	67	L	0.005 (0.002,0.008)	0.494	–
Inferior temporal gyrus	−35	−14	−44	4.0	803	L	0.011 (0.005,0.016)	0.545	20
Parahippocampal gyrus	23	−53	−8	3.9	145	R	0.012 (0.006,0.018)	0.558	19
Calcarine cortex	11	−84	12	4.2	624	R	0.015 (0.008,0.022)	0.575	17/18
Speed-agility(s^{-1})[b]									
Inferior frontal gyrus	−44	12	27	3.7	94	L	0.032 (0.015,0.049)	0.564	44
Superior temporal gyrus	68	−47	19	4.3	534	R	0.010 (0.006,0.015)	0.611	22
Muscular fitness (z-score)[c]									
Non-significant associations	–	–	–	–	–	–	–	–	–

Analyses were adjusted by sex, peak height velocity offset (years), parent education university level (neither/one/both), body mass index (kg/m^2) and total brain volume (cm^3). All physical fitness components (cardiorespiratory fitness, speed-agility and muscular fitness) were introduced in the same model and the contrasts were independently tested. All contrasts were thresholded using AlphaSim at $P < 0.001$ with $k = 64$ voxels for cardiorespiratory fitness, k = 57 for speed-agility and k = 53 for muscular fitness (non-significant associations), and surpassed Hayasaka correction. Anatomical coordinates (X, Y, Z) are given in Montreal Neurological Institute (MNI) Atlas space. Hem, hemisphere; R, right, L, left.

[a] This cluster extent did not reach statistical significance after Hayasaka correction.

[b] The original score of the speed-agility test expressed in seconds was multiplied by −1 to invert the variable, so that a higher score indicates higher fitness performance.

[c] z-score computed from handgrip strength and standing long jump tests. .

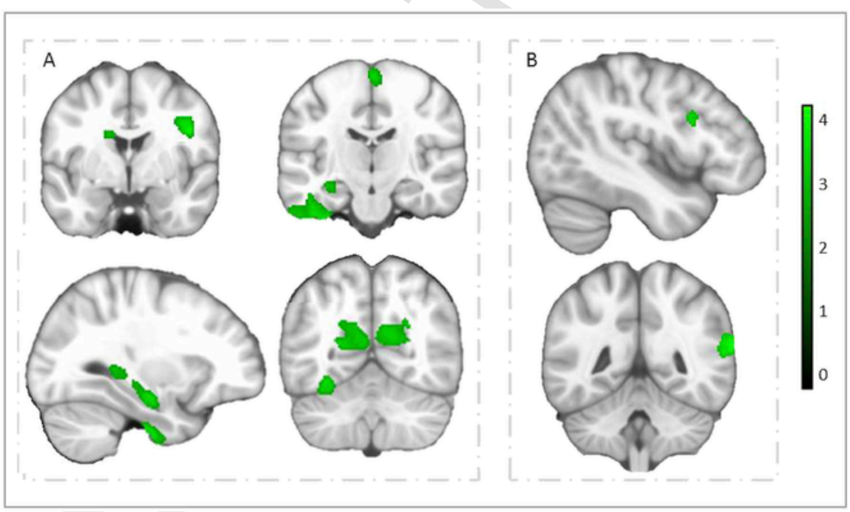

Fig. 2. Brain regions showing positive independent associations of (A) cardiorespiratory and (B) speed-agility with gray matter volume in overweight/obese children (n = 101). Analyses were adjusted by sex, peak height velocity offset (years), parent education university level (neither/one/both), body mass index (kg/m^2) and total brain volume (mm^3). All physical fitness components (cardiorespiratory fitness, speed-agility and muscular fitness) were introduced in the same model and the contrasts were independently tested. Maps were thresholded using AlphaSim at $P < 0.001$ with $k = 64$ voxels for cardiorespiratory fitness, $k = 57$ for speed-agility and $k = 53$ for muscular fitness (non-significant associations), and surpassed Hayasaka correction (see Table 3). The color bar represents T-values, with lighter green colour indicating higher significant association. Images are displayed in neurological convention, therefore the right hemisphere corresponds to the right side in coronal displays. Sagittal planes show the left hemisphere. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4. Associations between gray matter volumes and academic performance

Table 4 displays the associations between fitness-related changes in gray matter volume and academic performance assessed by the Bateria III Woodcock-Muñoz Tests of Achievement, after controlling for potential confounders.

Regarding the brain regions previously associated with cardiorespiratory fitness, 6 of 7 regions were related or borderline related with any academic indicator. Premotor cortex was positively related to writing (β=0.228, P = 0.027) and borderline related to written expression and total achievement (both P = 0.080). Supplementary motor cortex was positively associated with mathematics and academic applica-

Regarding the brain regions previously associated with speed-agility, inferior frontal gyrus was positively associated with reading, academic fluency and total achievement (β ranging from 0.217 to 0.234, $p < 0.05$) and borderline associated with writing and academic skills (both P = 0.072); superior temporal gyrus was positively related to reading, science, academic fluency, academic applications and total achievement (β ranging from 0.240 to 0.296, $p < 0.05$) and borderline related to written expression, mathematics and academic skills (all P = 0.080).

4. Discussion

The main finding of the present study was that physical fitness com-

Table 4
Associations between fitness-related changes in gray matter volume and academic performance assessed by the Bateria III Woodcock-Muñoz Tests of Achievement in overweight/obese children (n = 101).

Fitness-related component	Cardiorespiratory fitness (mL/kg/min)														Speed-agility(s^{-1})*	
Brain regions (mm^3)	Premotor cortex		Supplementary motor cortex		Hippocampus		Caudate		Inferior temporal gyrus		Parahippocampal gyrus		Calcarine cortex		Inferior frontal gyrus	
	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P
Oral language	−0.097	0.373	−0.048	0.674	0.163	0.151	−0.306	0.760	0.175	0.112	−0.169	0.103	−0.097	0.374	−0.041	0.70
Reading	0.125	0.224	0.119	0.272	**0.352**	**0.001**	0.111	0.270	0.135	0.199	0.051	0.611	0.096	0.356	**0.234**	**0.01**
Writing	**0.228**	**0.027**	0.135	0.217	0.169	0.122	0.039	0.705	0.048	0.654	0.006	0.953	0.076	0.473	0.182	0.07
Written expression	0.182	0.080	0.203	0.064	0.207	0.058	0.007	0.943	0.158	0.138	0.143	0.157	0.138	0.190	0.106	0.29
Mathematics	0.121	0.233	**0.228**	**0.031**	**0.211**	**0.046**	0.147	0.136	0.146	0.157	−0.037	0.707	0.143	0.161	0.137	0.16
Math calculation skills	0.105	0.300	0.167	0.118	0.178	0.094	0.011	0.914	0.088	0.397	−0.099	0.312	0.088	0.388	0.119	0.22
Science	0.003	0.977	0.064	0.564	**0.248**	**0.024**	0.081	0.433	0.054	0.617	−0.069	0.501	0.102	0.340	0.058	0.57
Academic skills	0.159	0.111	0.098	0.352	**0.253**	**0.015**	0.094	0.337	0.032	0.755	−0.056	0.562	0.037	0.712	0.178	0.06
Academic fluency	0.171	0.111	0.148	0.188	**0.291**	**0.009**	0.024	0.818	0.206	0.058	0.144	0.163	0.209	0.052	**0.230**	**0.02**
Academic applications	0.091	0.364	**0.229**	**0.028**	0.196	0.061	0.171	0.079	0.173	0.090	0.024	0.807	0.106	0.297	0.129	0.18
Total achievement	0.179	0.074	0.182	0.084	**0.300**	**0.004**	0.117	0.234	0.132	0.196	0.011	0.907	0.117	0.246	**0.217**	**0.02**

Values are standardized regression coefficients (β).Analyses were adjusted by sex, peak height velocity offset (years), parent education university level (neither/one/both) and body mass index (kg/m^2). Statistically significant values are shown in bold ($p < 0.05$), and borderline significant values are shown in italics ($p < 0.1$).

rior temporal gyrus) were related to better academic performance. In contrast, muscular fitness was not associated with cortical and subcortical brain volumes independently of the other two physical fitness components. These results suggest that cardiorespiratory fitness and speed-agility might be the two health-related physical fitness components with the potential to improve brain development resulting in higher academic performance, with cardiorespiratory fitness clearly being the component associated with more regions in the brain.

There are only two previous comparable studies with volumetric analysis in children and these studies have solely examined the cardiorespiratory component in relation to isolated subcortical brain structures (Chaddock et al., 2010a, 2010c). Our findings are important in four dimensions: firstly, cardiorespiratory fitness was assessed along with other physical fitness components, such as speed-agility and muscular fitness; secondly, this study covered the whole fitness range of the targeted population (i.e. not only the children with the highest and lowest fitness as in previous studies). In fact, even if only overweight-obese participants were included in this study (by inclusion criteria), we found a fairly wide variation in fitness level, which for example ranged from percentile 1st to 60th compared to specific international normative values in normal-weight children (Tomkinson et al., 2016). Thirdly, by using a whole brain volumetric approach rather than an isolated brain regions approach as well as examining the association between brain volumes and academic performance; and finally, this study examined more than one hundred children which is, to the best of our knowledge, the largest study thus far. The previous two studies (N = 49 and 55) found that higher fit children showed greater volume of the hippocampus and the basal ganglia components, specifically of the dorsal striatum (i.e. caudate, putamen, and globus pallidus), than lower fit children, but not of the nucleus accumbens of the ventral striatum. Moreover, they found hippocampal volume was associated with relational memory and dorsal striatum volume with better cognitive control and response resolution (Chaddock et al., 2010a, 2010c). Our findings concur with the above-mentioned studies suggesting that, cardiorespiratory fitness was independently related to greater volume of hippocampus and dorsal striatum (i.e., caudate) and in turn hippocampus volume was associated with most of the academic indicators in overweight/obese children.

Complementing previous studies, we found that cardiorespiratory fitness was related to the volume of several cortical brain structures (i.e. premotor cortex and supplementary motor cortex, inferior temporal gyrus, parahippocampal gyrus, and calcarine cortex) and some of these brain structures were also related to academic performance. Experimental evidence in rodent models supports that brain development is highly susceptible to environmental factors such as engagement in aerobic exercise (Hillman et al., 2008), a major determinant of cardiorespiratory fitness. For example, aerobic exercise increases cell proliferation and survival in the dentate gyrus of the hippocampus (Cotman et al., 2007), increases hippocampal and striatal levels of brain-derived neurotrophic factor (BDNF), and specifically hippocampal levels of insulin-like growth factor 1 (IGF-1) and vascular endothelial-derived growth factor (Cotman et al., 2007; Aguiar et al., 2008; Marais et al., 2009). These growth factors are shown to be involved in neuronal survival and synaptic development (Cotman et al., 2007). Aerobic exercise also increases presynaptic proteins and postsynaptic GluA1 and GluA2/3 receptors in the motor cortex, which lead to increased synaptic efficiency (Real et al., 2015). Besides, cardiorespiratory fitness is associated with angiogenesis in the motor cortex and increases blood flow (Adkins et al., 2006). Thus, based on this animal evidence, the positive associations between physical fitness and gray matter found in children with overweight and obesity are biologically plausible.

Evidence regarding speed-agility and muscular fitness in relation to brain structure is nonexistent, which hampers comparisons with other studies. This study provides novel data on the positive association of speed-agility with gray matter volume in the inferior frontal gyrus and the superior temporal gyrus, and in turn, these regions were related to better academic performance in overweight/obese children. Basically, the speed-agility test used involves coordinative abilities, short sprints and motor skills (change of directions, take/leave objects in movement). Interestingly, motor skills induce syntaptogenesis, increases in BDNF and tyrosine kinase receptors, and reorganization of movement representations within the motor cortex (Adkins et al., 2006). This set of coordinated neuronal changes related to speed-agility could contribute to explanation of our present findings. Furthermore, we found that the relationship between muscular fitness and cerebellum disappeared after controlling for cardiorespiratory fitness and speed-agility. This suggests that the cardiorespiratory fitness and speed-agility may be more important to brain structure than muscular fitness, yet more studies are needed to examine the influence of different components of physical fitness on brain development during childhood.

Cardiorespiratory fitness was associated with higher volume of more subcortical and cortical brain structures (i.e.7 regions) than speed-agility (i.e. 2 regions). Conversely, the influence of speed-agility on those brain structures seems to be slightly higher (β ranging from 0.564 to 0.611) than that from cardiorespiratory fitness (β ranging from 0.493 to 0.575). These results suggest that, although cardiorespiratory fitness is linked to a broader set of brain structures, speed-agility may have a slightly stronger relationship with specific brain structures (i.e. superior temporal gyrus). However, although there are differences in the specificity linking these two fitness components with the brain, both sets of regions associated with them significantly predicted better academic performance in overweight/obese children. Consequently, combining physical exercises that improve cardiorespiratory fitness with exercises that improve speed, agility and diverse motor skills may be an effective approach to stimulate brain development and academic performance in overweight/obese children. Intervention studies are needed to confirm or contrast these results.

There are several potential reasons why cardiorespiratory fitness and speed-agility may be associated with different parts of the brain. For instance, while cardiorespiratory fitness has been shown to be implicated in cortical and subcortical structures related to executive function and learning, motor and visual processes (Chaddock et al., 2010b, 2010c); speed-agility has been related to cortical structures basically involved in reading and language processing (Friederici et al., 2000; Uchiyama et al., 2008). Another explanation that could partially account for the specificity of speed-agility on brain structures related to verbal processes may be the relevance of fine motor skills in some language–related abilities, for example in reading or writing (Pangelinan et al., 2011). In agreement with that, we found that speed-agility-related changes in the inferior frontal gyrus (Broca area, BA 44) and the superior temporal gyrus (Wernicke area, BA 22) were related to better reading skills in overweight/obese children, consistently with their roles in language and processing of speech. However, more studies combining structural imaging and behavioral data are necessary to examine the potential pathways through which volumetric brain changes, associated with improved physical fitness, may impact diverse behavioral processes.

The study has several strengths including the relatively large sample of overweight/obese children, the complete and standardized assessment of the 3 physical fitness components, the inclusion of a wide spectrum of fitness (instead of only comparing two extremes, as in many previous studies) and the focus on analyzing the entire brain rather than pre-specified regions of interest. Nonetheless, results should also be appraised in the context of limitations including its cross-sectional nature, which does not allow us to draw causal associations. Furthermore, the study only investigated overweight and obese children, which limits the generalizability of our findings to the whole range of the BMI distribution.

5. Conclusion

Our results support that cardiorespiratory fitness and speed-agility, but not muscular fitness, might independently be associated with greater gray matter volume of numerous cortical and subcortical brain structures. In addition, some of these brain structures (i.e. hippocampus, premotor cortex, supplementary motor cortex, inferior frontal gyrus and superior temporal gyrus) were related to better academic performance. Importantly, the identified associations of fitness and gray matter volume were different for each fitness component, suggesting that the development of cardiorespiratory fitness and speed-agility may influence the development of distinctive brain regions. This research may have important implications since levels of physical activity are creasing (Ortega et al., 2013), while the number of unfit and overweight/obese children is drastically increasing (CDC, 2009). From a public health perspective, promoting physical activity that enhances cardiorespiratory fitness and speed-agility, may be important not only for the physical health, but also for the development of brain and academic skills in overweight/obese children. However, further longitudinal and experimental studies are needed to shed light on the importance of physical activity and fitness for brain development.

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