The Differential Effects of Adiposity and Fitness on Functional Connectivity in Preadolescent Children

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ABSTRACT

LOGAN, N. E., D. R. WESTFALL, L. B. RAINE, S. A. ANTERAPER, L. CHADDOCK-HEYMAN, S. WHITFIELD-GABRIELI, A. F. KRAMER, and C. H. HILLMAN. The Differential Effects of Adiposity and Fitness on Functional Connectivity in Preadolescent Children. *Med. Sci. Sports Exerc.*, Vol. 54, No. 10, pp. 1702–1713, 2022. **Purpose:** Childhood obesity is a global health concern, with >340 million youth considered overweight or obese. In addition to contributing greatly to health care costs, excess adiposity associated with obesity is considered a major risk factor for premature mortality from cardiovascular and metabolic diseases and is also negatively associated with cognitive and brain health. A complementary line of research highlights the importance of cardiorespiratory fitness, a by-product of engaging in physical activity, on an abundance of health factors, including cognitive and brain health. **Methods:** This study investigated the relationship among excess adiposity (visceral adipose tissue [VAT], subcutaneous abdominal adipose tissue), total abdominal adipose tissue, whole-body percent fat [WB%FAT], body mass index (BMI), and fat-free cardiorespiratory fitness (FF-$\dot{V}O_{2max}$) on resting-state functional connectivity (RSFC) in 121 (f = 68) children (7–11 yr) using a data-driven whole-brain multivoxel pattern analysis. **Results:** Multivoxel pattern analysis revealed brain regions that were significantly associated with VAT, BMI, WB%FAT, and FF-$\dot{V}O_2$ measures. Yeo's (2011) RSFC-based seven-network cerebral cortical parcellation was used for labeling the results. *Post hoc* seed-to-voxel analyses found robust negative correlations of VAT and BMI with areas involved in the visual, somatosensory, dorsal attention, ventral attention, limbic, frontoparietal, and default mode networks. Further, positive correlations of FF-$\dot{V}O_2$ were observed with areas involved in the ventral attention and frontoparietal networks. These novel findings indicate that negative health factors in childhood may be selectively and negatively associated with the 7 Yeo-defined functional networks, yet positive health factors (FF-$\dot{V}O_2$) may be positively associated with these networks. **Conclusions:** These novel results extend the current literature to suggest that BMI and adiposity are negatively associated with, and cardiorespiratory fitness (corrected for fat-free mass) is positively associated with, RSFC networks in children. **Key Words:** RESTING STATE, FMRI, BRAIN FUNCTION, CHILDHOOD OBESITY, CARDIORESPIRATORY FITNESS

Childhood obesity is a global health concern. Around the world, over 340 million children and adolescents 5–19 yr old, and 38 million children under the age of 5 yr, are considered overweight or obese (1). Obesity has become the focus of many public health efforts in the United States because of increasing prevalence over the last few decades. In addition to contributing greatly to health care costs (2), excess adiposity associated with obesity is considered a heritable neurobehavioral disorder that is highly sensitive to environmental conditions (3), a major risk factor for premature mortality from cardiovascular and metabolic diseases (4), and has recently been associated with negative cognitive (5–7) and brain (8–13) health outcomes. Notably, children with obesity commonly become adults with obesity, with 52% of adults over the age of 18 yr considered overweight (1.9 billion adults) or obese (650 million adults) (1). As such, considerable efforts have been taken to reduce the negative health outcomes associated with childhood obesity, as assessed via body mass index (BMI). Previous research has highlighted the importance of cardiorespiratory fitness, a by-product of engaging in physical activity, on an abundance of physical health outcomes throughout the life span, including the prevention of obesity (14) and the promotion of cognitive and brain health (15,16). Therefore, investigations into the relationship between excess adiposity and cardiorespiratory fitness are necessary to understand the effects on brain health.

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Given that a hallmark of obesity is excess adiposity, distinguishing between amount and type of adipose tissue within the body is of further importance. Dual-energy x-ray absorptiometry (DXA) is used as the gold standard method of characterizing adipose tissue within the body, such as the distinction between subcutaneous and visceral adipose tissues (VAT). Whole-body percent fat (WB%FAT), derived from the DXA scan, represents the total mass of fat divided by total body mass (17). Subcutaneous abdominal adipose tissue (SAAT) lies beneath the skin and on top of the abdominal musculature. In adults, approximately 80% of total fat is stored at SAAT. VAT is located in the body cavity beneath the abdominal muscles, surrounding the liver, pancreas, and intestines. VAT accounts for 20% of total fat in men and 5%–8% in women (18), and preadolescent boys tend to accumulate more VAT than girls (19). Consequently, VAT is considered a more dangerous type of adipose tissue when accumulated in excess. As such, VAT is also a strong predictor of age-related cognitive impairment in humans (20) and has been related to impaired cognitive function in children (5–7). Here, we define total abdominal adipose tissue (TAAT) as the total adipose tissue within these regions (SAAT and VAT).

Functional connectivity and childhood obesity. Cognitive functions during childhood are sensitive to obesity and the health complications associated with obesity (5). Further, childhood obesity has been associated with magnetic resonance imaging (MRI) studies of brain structure (10–12) and function (fMRI) (8,9,13). Individual differences, such as adiposity and obesity, have been associated with variance in brain structures among children and adolescents. For example, early life factors such as birth weight, birth height, and breast feeding have been associated with gray matter volumes in regions related to higher-order cognition and emotion regulation (12), and lean mass index was positively associated with white matter volumes in tracts that subserve executive function, memory, and attention (10). Similarly, different types of adipose tissue are selectively associated with cognitive and brain functions. Specifically, better performance on tasks of intellectual abilities and cognitive efficiency were associated with less VAT in children with normal weight (7). However, worse performance on tasks of intellectual abilities and cognitive efficiency were associated with greater VAT in children with obesity (7). Additionally, in children with obesity, VAT has been selectively associated with poorer neuroelectric indices of executive function compared with SAAT (21), and VAT has also been associated with poorer cognitive abilities in children compared with SAAT and WB%FAT (7). Further, fMRI studies have identified differences in resting-state functional connectivity (RSFC) associated with obesity across the life span. In adults, obesity has been associated with alterations in salience network connectivity (9) and specific reductions in activity in brain regions associated with memory (hippocampus, angular gyrus, dorsolateral prefrontal cortex) compared with their normal weight counterparts during tasks of episodic memory (8). Collectively, cognitive and brain studies demonstrate robust evidence for negative associations among children and adults with obesity.

Functional connectivity and cardiovascular fitness in children. A complimentary line of research has continually demonstrated a beneficial influence of fitness on cognitive and brain function in children (22–25) and adult populations (16). Of specific focus, children with greater fitness demonstrate positive associations with neuroelectric indices of cognitive function (24,25), greater hippocampal volume (as measured using MRI) coupled with better relational memory task performance (23), and greater efficiency of brain networks underlying cognitive function (22). Additionally, in a sample of healthy young adults using a connectome-wide association approach, positive brain–fitness (cardiovascular fitness and RSFC) relationships were present (16). Notably understudied, however, is the influence of cardiorespiratory fitness on RSFC in preadolescent children.

Few studies have investigated the differential relationships of underlying brain network correlates with excess adiposity and fitness in preadolescent children. Notably, greater cardiorespiratory fitness in children with overweight/obesity has been related to greater gray matter volumes in premotor cortex, supplementary motor cortex, and hippocampus, which were also related to better academic performance (26). Differences in brain structure among weight status and physical activity or fitness have also been supported elsewhere (27,28). Additionally, sedentary behaviors and overweight/obesity in childhood have been negatively associated with gray matter volume (28), and white matter microstructure (27) in children.

Current study. Consequently, research continues to demonstrate that fitness has a beneficial effect on childhood brain health. However, risk factors associated with obesity, including excess adiposity and risk for developing metabolic syndrome, appear to dampen various aspects of this trajectory. As such, the primary objective of the current study was to decompose the brain–fitness–adiposity relationship in children by using an unbiased data-driven approach with multivoxel patten analysis. The aim of multivoxel pattern analysis is to derive seeds based on the data before performing a *post hoc* analysis on the seeds to analyze brain connectivity patterns (29). Multivoxel pattern analysis is a well-suited method for uncovering subtle representational differences in a precise manner, especially when these representations are hypothesized to be distributed (30). The current analysis also used a preprocessing technique, aCompCor, which allows for the interpretation of anticorrelations between different cortical networks (31). We investigated the relationship between different types of adipose tissue and cardiorespiratory fitness on RSFC networks in preadolescent children. We predicted that functional connectivity would be differentially and selectively associated with adiposity and BMI compared with cardiorespiratory fitness. We predicted that VAT and BMI would be negatively associated with functional connectivity. We further predicted that WB%FAT, TAAT, and SAAT would be positively associated with functional connectivity, as previous studies suggest a positive relationship between these measures of adiposity and cognition in children with normal weight (7). Lastly, we predicted that fat-free cardiorespiratory fitness (FF-$\dot{V}O_2$) would be positively associated with functional connectivity. VAT is considered to

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be the more metabolically dangerous type of adipose tissue when accumulated in excess compared with SAAT, TAAT, and WB%FAT. Finally, an abundance of previous research demonstrates the positive influence of cardiorespiratory fitness on brain health, which provides a basis for our predication of a positive association between these variables.

METHODS

Participants. The present study includes 121 participants that were used in the final analysis. This sample size originates from combined imaging data from a subset of the 283 children between 7- and 11-yr-olds who were recruited to participate in the FITKids2 trial (n = 192, baseline data only) (ClinicalTrials.gov identifier numbers: NCT01334359) and the FLEX study (n = 91). All participants provided written assent, and their legal guardians provided written informed consent in accordance with the Institutional Review Board of the University of Illinois at Urbana–Champaign. Participants were administered the Kaufman Brief Intelligence Test or the Woodcock Johnson (III) to assess IQ, a Tanner Staging System (32) questionnaire to assess pubertal status, and the Physical Activity Readiness Questionnaire to screen for health issues exacerbated by physical exercise. Socioeconomic status (SES) was determined using a trichotomous index based on participation in free or reduced-price meal program at school, the highest level of education obtained by parents, and the number of parents who worked full time (33). Legal guardians completed health history and demographics questionnaires. Based on these questionnaires, participants included in this analysis did not receive special educational services from their school, were right-handed, reported no use of medications that influenced central nervous system function, qualified as prepubescent, and had normal or corrected-to-normal vision. Participants were excluded if there was 1) a presence of neurological disorders and physical disabilities, and other factors that precluded participation in the physical aspects of the study, such as not completing: 2) the mock MRI session to successfully screen for claustrophobia; 3) the aerobic fitness test; or the 4) DXA scan to assess body composition. Participants were further excluded from data analyses if 5) they did not complete the MRI/fMRI scans (n = 133), 6) did not complete both resting-state scans or had missing brain slices in the field of view (n = 16), or 7) they had excessive removal of data after scrubbing resulting in less than 5 min (34) of useable data (n = 13; see "fMRI Preprocessing" for criteria). Data from 121 participants were used for final analysis (Table 1). There were no significant differences between participants who were included or excluded from analysis based on age, sex, SES, pubertal timing, or IQ (all Ps > 0.05). Although the removal of 13 participants due to data scrubbing-related issues that resulted in scans with less than 5 min of useable data is quite large, previous papers have found a 30%–50% scan attrition rate due to motion in preadolescent children using even less stringent movement criteria (compared with 19% herein) (35). Further, increased scanning motion has been associated

TABLE 1. Participant demographics and body composition.

Measure	Mean ± SD
n	121 (68 females)
Age (yr)	9.3 ± 1.1 (range, 7.6–12.5)
Pubertal timing	1.44 ± 0.5
IQ	111.2 ± 13.3
SES	2.1 ± 0.8
FF-$\dot{V}O_2$ (mL·$kg^{-1}_{(lean)}$·min^{-1})	62.7 ± 7.8 (range, 46.91–93.92)
BMI	19.0 ± 4.2 (range, 13.07–35.64)
SAAT (g)	797.6 ± 540.3 (range, 135.57–2758.82)
TAAT (g)	984.7 ± 627.4 (range, 245.16–3435.58)
VAT (g)	187.1 ± 114.2 (range, 30.77–676.76)
WBFAT (%)	31.1 ± 6.9 (range, 17.44–48.59)

with obesity (36,37), and head motion artifacts have also been found to influence intrinsic functional connectivity measurements (38). Consequently, care was taken to sufficiently remove scans with motion. Because of the initial sample size, head motion–related artifacts, as well as the high amounts of motion in a preadolescent and obese populations, stringent quality control methods (see "fMRI Preprocessing") were used in the data analysis pipeline.

Weight status and adiposity assessment. Standing height and weight measurements were completed with participants wearing light-weight clothing and no shoes. Height and weight were measured using a stadiometer (Seca; model 240) and a Tanita WB-300 Plus digital scale (Tanita, Tokyo, Japan), respectively. Weight status was determined with BMI, calculated by dividing body mass (kg) by height (m) squared (kg·m^{-2}). The Centers for Disease Control and Prevention growth charts (39) were used to determine individual BMI and BMI percentiles for age and sex values. Children from the current sample were categorized into the following BMI classes: underweight (n = 4, 3.3% of sample), normal weight (n = 72, 59.5%), overweight (n = 22, 18.2%), and obese (n = 23, 19%). Adiposity measurements included VAT, SAAT, TAAT, and WB%FAT. Whole-body and regional soft tissue were measured by DXA using a Hologic QDR 4500A Discovery bone densitometer (software version 13.4.2; Hologic, Bedford, MA) as an accurate and valid measure of body composition in the pediatric population (40). Central adiposity (i.e., VAT, SAAT, and TAAT) and WB%FAT were estimated using an algorithm that models SAAT at the fourth lumbar vertebra and subtracts it from the regional abdominal region fat (6).

Cardiorespiratory fitness testing. Maximal oxygen consumption was measured on a treadmill using a graded $\dot{V}O_{2max}$ exercise test, with a computerized indirect calorimetry system (ParvoMedics true Max 2400). A modified Balke protocol was used, whereby participants walked or ran at a constant speed with increasing grade increments of 2.5% every 2 min until volitional exhaustion, with time interval averages of $\dot{V}O_2$ and RER assessed every 20 s. The protocol was administered on a LifeFitness 92 T motor-driven treadmill (LifeFitness, Schiller Park, IL) with expired gases analyzed using a ParvoMedics TrueOne2400 Metabolic Measurement System (ParvoMedics, Sandy, UT). Heart rate was assessed throughout the test with a Polar Heart Rate Monitor. The children's OMNI scale (41) was used to assess ratings of

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perceived exertion every 2 min. $\dot{V}O_{2max}$ qualification was based on achieving at least three of the following four criteria: (i) a peak heart rate ≥185 bpm and a heart rate plateau, (ii) RER ≥ 1.0, (iii) an OMNI rating of perceived exhaustion ≥8, and/or (iv) a plateau in oxygen consumption corresponding to an increase of less than 2 $mL \cdot kg^{-1} \cdot min^{-1}$ despite an increase in intensity (41). Fat-Free $\dot{V}O_{2max}$ (FF-$\dot{V}O_2$; $mL \cdot kg^{-1} \cdot min^{-1}$ lean mass) was calculated using absolute $\dot{V}O_{2max}$ ($L \cdot min^{-1}$) and lean mass (g) as the primary measure of fitness. Total lean mass (g) was derived from the DXA scanner and was entered into the following equation: FF-$\dot{V}O_2$ = (absolute $\dot{V}O_{2max}$ [$L \cdot min^{-1}$]/total lean mass [g]) × 1000. This measure has previously been shown to be the primary contributor to aerobic capacity in children of varying body mass (40) and has been used in previous research when assessing adiposity, fitness, cognitive, or brain outcomes (7,21,42,43).

MRI data acquisition. Imaging data were collected on a 3 T Siemens Magnetom Trio whole-body scanner with 12-channel radiofrequency head coil (Siemens Healthcare, Erlangen, Germany). High-resolution structural data were acquired using a T1-weighted MPRAGE sequence with 0.9 mm isotropic resolution (repetition time = 1900 ms, echo time = 2.32 ms, inversion time = 900 ms) over 4 min 26 s. Resting scans were collected for 8–11 min using a T2*-weighted EPI sequence (repetition time = 2000 ms, echo time = 25 ms, flip angle = 90°, GRAPPA acceleration factor = 2, 92 × 92 matrix resolution, voxel size = 2.6 × 2.6 × 3 mm^3).

fMRI preprocessing. Data were preprocessed using the default analysis pipeline in CONN toolbox (44), which includes realignment, slice timing correction, outlier detection, segmentation, normalization with respect to MNI template, and smoothing (6-mm FWHM kernel). The Artifact Detection Toolbox (ART) (http://www.nitrc.org/projects/artifact_detect) was used to flag scans with mean signal intensity outside 3 SD from global mean and/or 0.5 mm scan-to-scan motion. To assure scan quality, these "invalid scans" were then regressed out. After data scrubbing, a minimum of 5-min scan time was required to include a participant in the analysis (34). Band-pass filtering was executed at 0.008–0.1 Hz. A component-based noise correction method (aCompCor) was used for denoising (45) as implemented in the CONN toolbox, as this method allows for the interpretation of anticorrelations. The combination of aCompCor and ART toolboxes allows for an optimized preprocessing approach for the analysis of functional connectivity data.

Multivoxel pattern analysis. Whole-brain connectome-wide multivoxel pattern analysis was used as an agnostic, data-driven approach to identify seed regions for standard seed-to-voxel analysis of resting-state data using CONN toolbox (44,46). Principal components analysis (PCA) was used to reduce the dimensionality of the resultant data. First, 64 PCA components were retained for each participant's voxel-to-voxel correlation structure. A second PCA was run across all participants, and the first six components were retained to maintain a conservative 20:1 participant-to-component ratio (46). An *F*-test was performed on all six multivoxel pattern analysis components. Physiological measures for adiposity, body composition, and fitness (BMI, SAAT, TAAT, VAT, WB%FAT, and FF-$\dot{V}O_2$) were entered separately in the multivoxel pattern analysis to determine patterns of functional connectivity associated with each of these measures, for a total of six separate analyses (body composition: BMI; adiposity: SAAT, TAAT, VAT, and WB%FAT; and fitness: FF-$\dot{V}O_2$). Age, IQ, SES, and pubertal timing were entered as covariates in second-level analyses as they correlated with physiological measures. In addition, mean motion did not correlate with IQ, SES, or pubertal timing measures (all Ps > 0.05). A height-level statistical threshold of $P < 0.001$, a cluster threshold of $P < 0.005$ false discovery rate (FDR) corrected, and $k > 50$ were used to determine significant clusters. These clusters were then used as seeds for seed-to-voxel *post hoc* RSFC analyses to explore patterns of Yeo's seven-network parcellation (2011) (47) functional connectivity differences between these seed time courses and those with the rest of the brain, which were associated with adiposity and body composition. *Post hoc* analyses used a height threshold of whole-brain $P < 0.001$ and FDR-corrected cluster threshold of $P < 0.005$ with nonparametric statistics to reduce type 1 error due to multiple comparisons (48). An additional *post hoc* analysis was conducted by adding mean motion as a covariate and the patterns of connectivity did not change.

Supplementary statistical analysis. Pearson product–moment correlations were conducted between aerobic fitness (FF-$\dot{V}O_2$) and adiposity measures (BMI, VAT, SAAT, TAAT, and WB%FAT). Next, mediation analyses using the R mediation process package (49) were performed to assess (i) whether fitness (FF-$\dot{V}O_2$) mediated the associations between adiposity (BMI and VAT) and adiposity-associated RSFC outcomes and (ii) whether adiposity factors (BMI and VAT) mediated associations between FF-$\dot{V}O_2$ and fitness-associated RSFC outcomes. The total effects (effect of X [predictor variable] on Y [outcome variable]), direct effects (effect of X on Y accounting for M [mediator] [average direct effect]), and indirect effects (the mediation effect) are reported. The presence of statistical mediation was determined through nonparametric bootstrap confidence intervals via 5000 bootstrap resamples of the estimated indirect effect. The estimated indirect effect (mediation effect) corresponds to the reduction in the independent variable effect on the dependent variable when adjusted for the mediator. Multiple comparisons were corrected using Benjamini and Hochberg's FDR, at a q value of 0.05, after pooling the P values from the mediation analyses for each predictor model.

RESULTS

Statistically significant seed regions from the multivoxel pattern analysis are displayed in Figure 1 and in Table 2. A whole-brain threshold of $P < 0.001$ and an FDR-corrected cluster threshold of $P < 0.005$ were used to determine significant clusters.

Results from the multivoxel pattern analysis-derived clusters can be seen in Figure 2 and Table 2. A height threshold of whole-brain $P < 0.001$, an FDR-corrected cluster threshold of $P < 0.005$, and a $K \geq 50$ cluster-level threshold were used for parametric *post hoc* characterization.

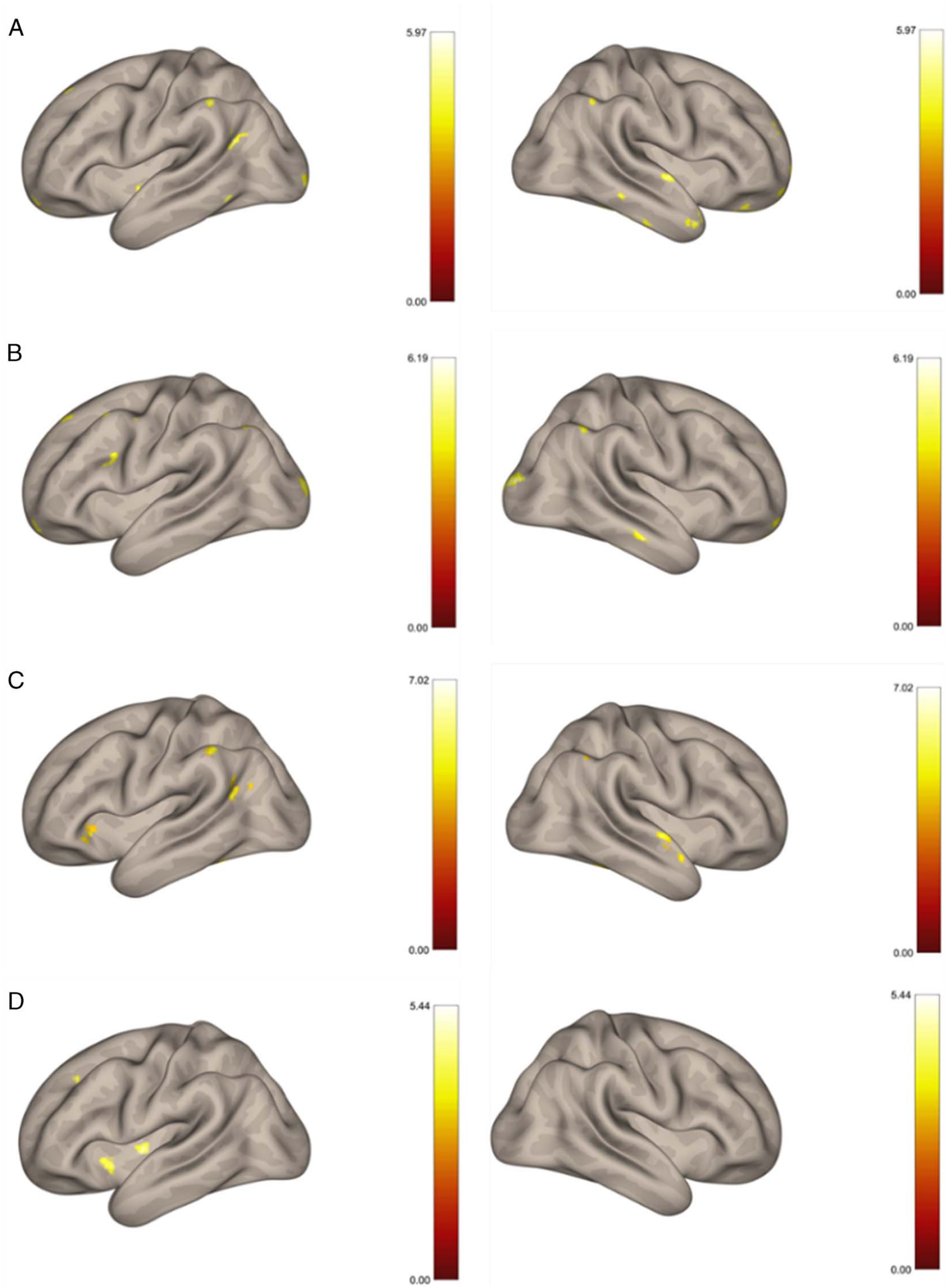

FIGURE 1—Whole-brain multivoxel pattern analysis results depicting the connectivity patterns significantly associated with BMI (A), visceral adipose tissue (VAT, B), whole-body percent fat (WB%FAT; C), and FF-$\dot{V}O_2$ (D).

Results from the correlation analysis between physiological variables are shown in Table 3 and Figure 3. As expected, adiposity variables (BMI, SAAT, TAAT, VAAT, and WB%FAT) were highly and significantly correlated with each other. FF-$\dot{V}O_2$ was significantly negatively correlated with SAAT (r = −0.259, $P \le 0.05$), TAAT (r = −0.231, $P \le 0.05$), and WB%FAT (r = −0.186, $P \le 0.05$) but was not correlated with BMI (r = −0.174, $P > 0.05$) or VAT (r = −0.04, $P > 0.05$).

BMI

Multivoxel pattern analysis results. Analyses revealed six significant clusters associated with BMI located in the right parahippocampal gyrus (cluster a, Fig. 1A).

***Post hoc* seed-to-voxel characterization of multivoxel pattern analysis-derived clusters of interest.** The seed region located in the right parahippocampal gyrus (cluster a) was found to be negatively correlated with the visual, somatosensory,

TABLE 2. Body composition, adiposity and fitness associated resting state functional connectivity.

Model		FC Region	Peak Coordinate (MNI)			Peak Coordinate	BA	Voxels per Cluster (k)											
			x	y	z	(Brain Region)		Visual	Somatosensory	Dorsal Attention	Ventral Attention	Limbic	Frontoparietal	Default Mode	Not Labeled	Total K	F	t	P_{FDR}
BMI	Seed	MVPA (a)	24	58	28	Parahippocampal_R	Right amygdala (53)						10	63		73	5.18		0.0003*
	Voxels	Cluster a1	−52	2	−18	Temporal_Mid_L	Left-BA38	553	738	186	223	99	63	1804	411	4077		−8.36	0.0000*
		Cluster a2	58	−12	0	Temporal_Sup_R	Right-PrimAuditory (41)	585	762	297	102	19	1	563	312	2641		−8.17	0.0000*
		Cluster a3	28	−74	−20	Cerebelum_6_R	Right-BA19	845							375	1220		−5.51	0.0000*
		Cluster a4	−38	−48	−20	Fusiform_L	Left-Fusiform (37)	356		247			30		70	703		−5.81	0.0000*
		Cluster a5	38	−36	−20	Fusiform_R	Right-Fusiform (37)	415		79		36			26	415		−5.56	0.0000*
		Cluster a6	−20	60	−14	Frontal_Sup_Orb_L	Left-BA11					192	3	117	52	364		−6.28	0.0000*
VAT	Seed	MVPA (b)	−30	34	50	Frontal_Mid_L	Left-BA8				9		21	86	41	157	6.44		0.0000*
	Voxels	Cluster b1	−56	−10	−10	Temporal_Mid_L	Left-BA22	53	224	108	151	491	24	2445	471	3697		−8.75	0.0000*
		Cluster b2	56	−6	−16	Temporal_Mid_R	Right-BA22	148	193	217	221	489	7	1599	494	3368		−8.35	0.0000*
		Cluster b3	−42	−56	−16	Fusiform_L	Left-Fusiform (37)	461		220		61			57	799		−6.15	0.0000*
		Cluster b4	44	−50	−20	Fusiform_R	Right-Fusiform (37)	294		64					72	430		−4.86	0.0000*
		Cluster b5	−2	50	−18	Rectus_L	Left-BA11					184		129	41	354		−5.62	0.0000*
WB%FAT	Seed	MVPA (c)	−52	−60	22	Temporal_Mid_L	Left-BA39							74	16	90	6.35		0.0000*
	Voxels	Cluster c1	16	56	−26	Frontal_Sup_Orb_R	Right-BA11					27	19		94	140		−6.32	0.0066
		Cluster c2	−30	−88	−20	Cerebelum_Crus1_L	Left-VisualAssoc (18)	87							20	107		−5.38	0.0143
		Cluster c3	−20	50	−18	Frontal_Mid_Orb_L	Left-BA11					62	3		23	88		−5.03	0.0238
FF-VO_2	Seed	MVPA (d)	−12	−88	18	Cuneus_L	Left-VisualAssoc (18)	51							20	71	5.03		0.0004*
	Voxels	Cluster d1	−2	14	36	Cingulum_Mid_L	Left-BA32		2		569		69		114	754		6.44	0.0000*
		Cluster d2	−42	14	−2	Insula_L	Left-Insula (13)		1		420	1	25	20	130	597		8.06	0.0000*
		Cluster d3	−32	52	28	Frontal_Mid_L	Left-BA10				216		48	6	15	285		6.10	0.0000*
		Cluster d4	42	12	2	Insula_R	Right-BA44				253				19	272		5.97	0.0000*
SAAT	Seed	MVPA	−2	38	38	Frontal_Sup_Medial_L	Left-BA8						1	52	5		4.61		0.0228
	Voxels	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		–	–
TAAT	Seed	MVPA	−4	40	38	Frontal_Sup_Medial_L	Left–BA9						1	58	4		4.53		0.0125
	Voxels	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		–	–

*Significance at the PFDR ≤ 0.005 level and $K \geq 50$ (cluster-level threshold).

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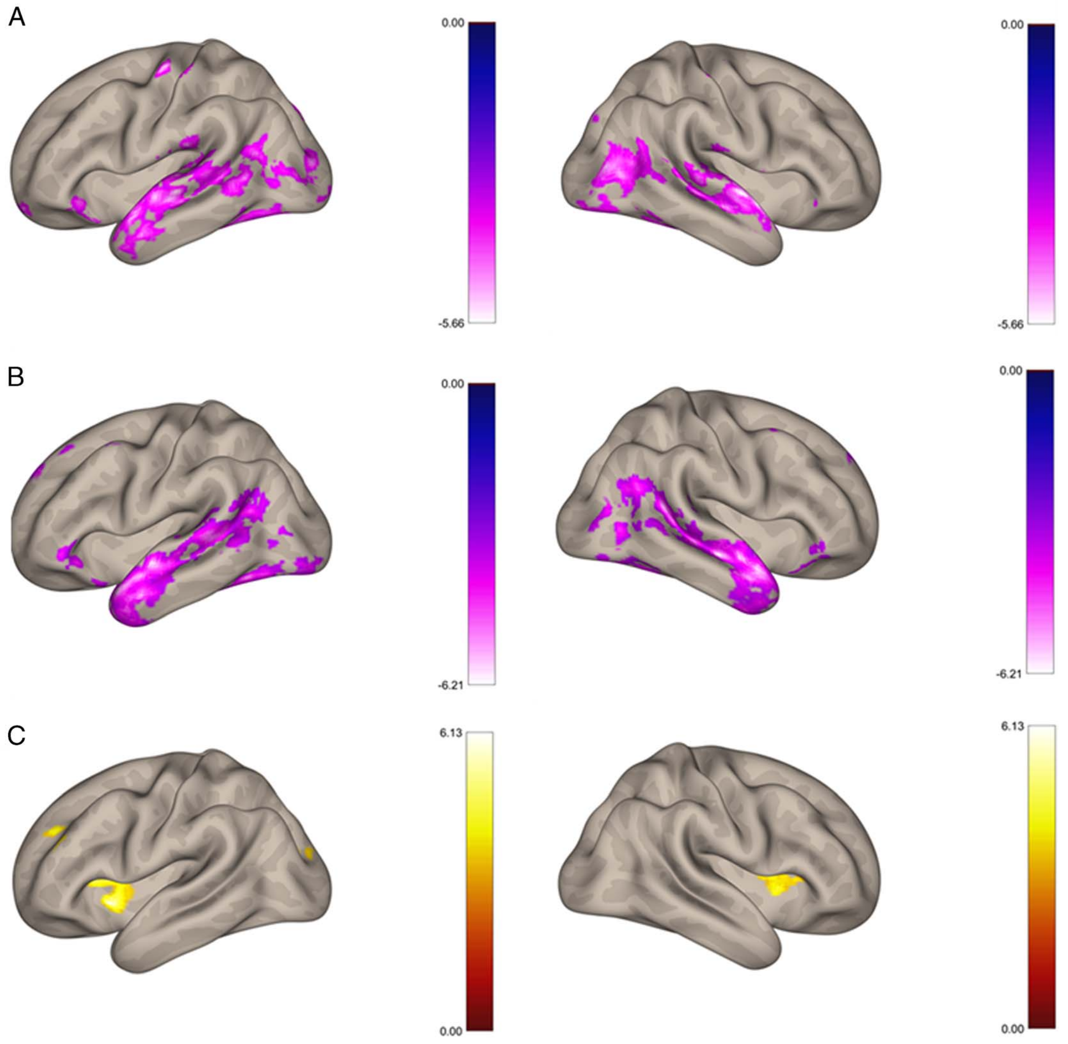

FIGURE 2—Results from the second-level seed-to-voxel RSFC analysis for multivoxel pattern analysis clusters associated with BMI (A, clusters a1–a6), VAT (B, clusters b1–b5), and FF-$\dot{V}O_2$ (C, clusters d1–d4).

dorsal attention, ventral attention, limbic, frontoparietal, and default mode networks, as a function of BMI (Fig. 2A).

VAT

Multivoxel pattern analysis results. Analyses revealed nine significant clusters associated with VAT located in the left middle frontal lobe (cluster b, Fig. 1B).

***Post hoc* seed-to-voxel characterization of multivoxel pattern analysis-derived clusters of interest.** The seed region located in left middle frontal lobe (cluster b) was found to be negatively correlated with visual, somatosensory, dorsal attention, ventral attention, limbic, and default mode networks, as a function of VAT (Fig. 2B).

WB%FAT

Multivoxel pattern analysis results. Analyses revealed six significant clusters associated with WB%FAT, located in the left middle temporal gyrus (cluster c, Fig. 1C).

***Post hoc* seed-to-voxel characterization of multivoxel pattern analysis-derived clusters of interest.** The seed region located in the left middle temporal gyrus (cluster c) was not significantly correlated with any of the 7 Yeo-defined functional networks, as a function of WB%FAT (Fig. 2C).

SAAT

Multivoxel pattern analysis results. There were no significant clusters associated with SAAT.

TAAT

Multivoxel pattern analysis results. There were no significant clusters associated with TAAT.

FF-$\dot{V}O_2$

Multivoxel pattern analysis results. Analyses revealed three significant cluster associated with FF-$\dot{V}O_2$, located in the left cuneus (cluster d, Fig. 1D).

***Post hoc* seed-to-voxel characterization of multivoxel pattern analysis-derived clusters of interest.** The seed

TABLE 3. Correlation table between physiological variables (adiposity: WBPFAT, TAAT, SAAT, VAT; BMI; and FF-$\dot{V}O_2$).

		BMI	VAT (g)	WBFAT (%)	TAAT (g)	SAAT (g)	$\dot{V}O_2$_FF (mL·kg$^{-1}_{(lean)}$·min^{-1})
BMI	*r*	–	0.870**	0.811**	0.902**	0.863**	–0.174
	p	–	0	0	0	0	0.056
VAT (g)	*r*	0.870**	–	0.693**	0.801**	0.719**	–0.04
	p	0	–	0	0	0	0.663
WBFAT (%)	*r*	0.811**	0.693**	–	0.891**	0.889**	–0.186*
	p	0	0	–	0	0	0.041
TAAT (g)	*r*	0.902**	0.801**	0.891**	–	0.992**	–0.231*
	p	0	0	0	–	0	0.011
SAAT (g)	*r*	0.863**	0.719**	0.889**	0.992**	–	–0.259**
	p	0	0	0	0	–	0.004
FF-$\dot{V}O_2$ (mL·kg$^{-1}_{(lean)}$·min^{-1})	*r*	–0.174	–0.04	–0.186*	–0.231*	–0.259**	–
	p	0.056	0.663	0.041	0.011	0.004	–

**Correlation is significant at the 0.01 level (two-tailed).
*Correlation is significant at the 0.05 level (two-tailed).

region located in the left cuneus (cluster d) was significantly correlated with ventral attention, and frontoparietal networks, as a function of FF-$\dot{V}O_2$.

Mediation Results

Given that adiposity and fitness measures were differentially associated with RSFC outcomes, we asked whether (i) fitness mediated the relationship between adiposity on adiposity-associated RSFC outcomes (see Supplemental Table S1, Supplemental Digital Content, http://links.lww.com/MSS/C622) and (ii) whether adiposity mediated the relationship between fitness on fitness-associated RSFC outcomes (see Supplemental Table S2 and Table S3, Supplemental Digital Content, http://links.lww.com/MSS/C622). Supplemental Table S1 (see Supplemental Digital Content, http://links.lww.com/MSS/C622) displays the results of the first mediation analyses, whereby FF-$\dot{V}O_2$ did not mediate the relationship between VAT (g) or BMI and RSFC outcomes. Supplemental Tables S2 and S3 (see Supplemental Digital Content, http://links.lww.com/MSS/C622) display the results of the second mediation analyses, whereby adiposity (BMI: Supplemental Table S2; VAT: Supplemental Table S3; see Supplemental Digital Content, http://links.lww.com/MSS/C622)

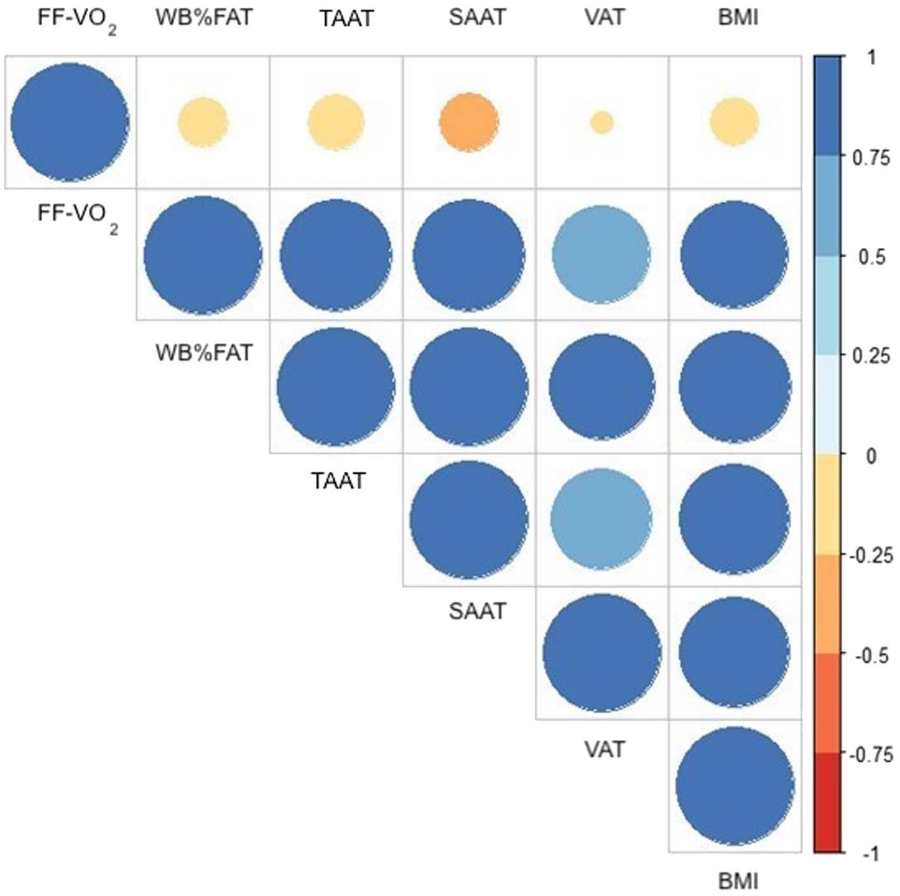

FIGURE 3—Correlation plot between physiological variables (adiposity: WBPFAT, TAAT, SAAT, and VAT; BMI; and FF-$\dot{V}O_2$).

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did not mediate the relationship between FF-$\dot{V}O_2$ and RSFC outcomes.

DISCUSSION

This study used an agnostic, connectome-wide multivoxel pattern analysis approach to identify whole-brain RSFC associations with adiposity, body composition, and cardiorespiratory fitness in preadolescent children. We found that a number of network connectivity patterns were differentially associated with negative health factors (VAT and BMI) compared with positive health factors (FF-$\dot{V}O_2$). Specifically, BMI was negatively correlated with RSFC in the visual, somatosensory, dorsal attention, ventral attention, limbic, frontoparietal, and default mode networks. Additionally, VAT was negatively correlated with RSFC in the visual, somatosensory, dorsal attention, ventral attention, limbic, and default mode networks, which confirmed our *a priori* prediction. Alternatively, FF-$\dot{V}O_2$ was correlated with ventral attention and frontoparietal networks, which also confirmed our *a priori* prediction. Notably, WB%FAT, TAAT, and SAAT were unrelated to any of the functional networks, failing to confirm our prediction. Together, the data described herein provide novel support for a differential adiposity–fitness–brain relationship in preadolescent children. Overall, there was a negative effect of adiposity-related patterns and a positive effect of fitness-related patterns on whole-brain functional connectivity in preadolescent children.

Additionally, mediation analyses revealed that FF-$\dot{V}O_2$ did not mediate the relationship between adiposity (BMI and VAT) and RSFC, and that adiposity (BMI and VAT) did not mediation the relationship between FF-$\dot{V}O_2$ and RSFC. Notably, FF-$\dot{V}O_2$ was not correlated with either BMI or VAT. As such, the negative effects of adiposity-related RSFC patterns and the positive effect of fitness-related RSFC patterns suggest that these relationships are independent from each other. These results indicate that positive health factors (such as increased fitness), alongside negative health factors (such as obesity), act differentially and independently from each other on RSFC networks.

The original results presented herein advance our understanding of the underlying functional networks associated with physiological health factors in children, which is important to consider given the global health concerns associated with childhood obesity. As such, considerable efforts should be taken to reduce the negative health outcomes associated with childhood obesity, such as with the promotion of cardiovascular fitness through physical activities. Accordingly, previous investigations into the relationship between aerobic fitness, obesity, and cognitive and brain function within the FITKids2 sample have found that 9 months of physical activity prevents the decline of obesity-associated neuroelectric function during preadolescent development (21).

The patterns identified in the current study are similar to patterns identified in previous research in children. For example, adolescents with obesity showed reduced global functional connectivity in the insula, middle temporal cortex, and DLPFC compared with normal weight participants (50), indicating negative associations between negative health factors (childhood obesity) and RSFC. Additionally, physical activity in preadolescent children was recently found to be positively associated with resting-state network connectivity in parietal cortices, supplementary motor cortex, putamen, and right primary motor cortex (51), indicating positive associations between positive health behaviors (physical activity) and RSFC.

The negative associations found with VAT are of particular interest because excess VAT has been linked to poorer intellectual and cognitive abilities among children with obesity (7). However, VAT is also positively associated with intellectual abilities and cognitive efficiency among normal weight children (7). Adiposity and cognition research thus demonstrates a negative association between excess VAT and cognitive function only in children with obesity. Neuroimaging studies further suggest negative associations between VAT and brain structure (10–12) and function (8,9,13). This relationship is particularly concerning considering the dangerous metabolic nature of VAT, such that increased VAT is related to a higher risk of metabolic diseases, has a greater lipid turnover and a higher fat uptake (52), and contributes to insulin resistance (18) due to the production of inflammatory cytokines and hormones (52). Consequently, VAT is considered to be the more dangerous type of adipose tissue when accumulated in excess, compared with SAAT and TAAT, and has been related to impaired cognitive function in children (5–7). Following previous research, no associations were found between SAAT, TAAT, and RSFC in the current study. This extends the current literature, which demonstrates a selective relationship for adiposity measures, such that VAT is negatively and uniquely associated with cognitive and brain outcomes (7). The selective adiposity associations observed in the current study are important to consider when evaluating the effect of VAT on Yeo's (47) functional connectivity networks, as these networks have been associated with cognitive function in humans.

The concept of functional connectivity alludes to the notion that the purpose of neural populations is to collectively interact within the brain to produce sensorimotor and cognitive abilities (53). Additionally, the structural organization of the human cerebral cortex is suggested to derive from intrinsic functional connectivity, further indicating that information processing in the brain involves interactions among distributed areas of neural populations (47). As such, associations with physiological measures, including findings from the current study, on the spontaneous fluctuations in the BOLD signal via fMRI may elucidate the neural representation of individual differences in functional architecture, which may also be associated with cognitive processes. As excess VAT in childhood has been negatively implicated with cognitive abilities (7), the results from the current study suggest a negative relationship between adiposity and functional brain networks.

The agnostically derived positive associations with cardiorespiratory fitness and RSFC in the current study contribute to the strong breadth of literature in this area across the life span. However, the results herein are the first to demonstrate positive associations between FF-$\dot{V}O_2$ and whole-brain RSFC in preadolescent children, as previous work has focused on associations with physical activity (54), hippocampal connectivity (55), or young adult (16) populations. Further, the current study is also the first to differentiate between positive (fitness) and negative (BMI and VAT) health factors on RSFC patterns. Subsequently, we have demonstrated that data-driven RSFC methodologies are a strong candidate for investigating neuroimaging markers of the beneficial effect of fitness on brain function and how obesity negatively influences this trajectory in preadolescent children. As such, our findings provide 1) novel support for a differential adiposity–fitness–brain relationship in preadolescent children, such that adiposity-related patterns showed negative correlations and fitness-related patterns showed positive correlations within the Yeo networks; 2) support for the use of multivoxel pattern analysis methodologies in future neuroimaging studies, which assess the influence of functional brain imaging; and 3) support for the use of multivoxel pattern analysis results from the current study as seeds in seed-to-voxel analyses when investigating relationships between brain and fitness and/or obesity in children.

LIMITATIONS

These findings should be interpreted in light of several limitations. The data were cross-sectional in nature, and as such, causal associations between adiposity, BMI, and fitness cannot be inferred. Similarly, because RSFC was assessed at one time point, this study is unable to account for fluctuations of resting-state focus, which may occur over longer periods of time. Additionally, the current study did not directly assess cognitive function, and as such, assumptions of RSFC networks and their associations with cognitive function should be taken lightly. Further, the current study used a data-driven approach to identify RSFC networks. Future studies could benefit from using a hypothesis-based approach to seed selection, based on the data-driven seeds identified herein, as well as previously identified areas associated with adult populations and fitness (i.e., default mode, dorsal and ventral attention, and frontoparietal networks) and adiposity (i.e., prefrontal cortex, hippocampus, angular gyrus, and salience network). The comparison between adult- and child-identified RSFC networks could provide evidence toward changes during brain development over the life span. Lastly, as previously discussed, child populations and individuals with obesity are two populations within the current sample associated with greater amounts of motion artifact. As such, the aggregation of the two populations resulted in a high amount of movement that occurred during data collection, resulting in the loss of a number of participants who did not meet the required criteria of at least 5 min of clean scanning data. However, the stringent motion artifact criteria are also a strength of the current study, as previous research has found that movement causes issues with the integrity of RSFC measures (37). Further, the sample of 121 participants is also a strength of the current study, as this is relatively larger than previous RSFC studies in children.

CONCLUSIONS

To the best of our knowledge, this is the first data-driven analysis investigating the association of positive and negative health factors on RSFC outcomes in preadolescent children. Using connectome-wide multivoxel pattern analysis, we report robust negative associations between BMI, VAT, and RSFC patterns with areas involved with the visual, somatosensory, dorsal attention, ventral attention, limbic, frontoparietal, and default mode networks. Further, we report robust positive associations between fitness and RSFC patterns with areas involved in the ventral attention and frontoparietal networks. Of particular interest is the differential nature of these relationships to VAT, BMI, and fitness. Overall, these novel findings advance our understanding of the underlying RSFC networks associated with physiological health factors in children and augment support for the utility of whole-brain data-driven methodologies. Childhood obesity is a global health concern, which contributes greatly to healthcare costs and is a major risk factor for premature mortality from cardiovascular and metabolic diseases. As such, considerable efforts should be taken to reduce the negative health factors associated with childhood obesity, such as with the promotion of cardiovascular fitness through physical activity.

The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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C. Hillman and A. Kramer conceived the study and provided statistical, research, and manuscript expertise. L. Raine and L. Chaddock-Heyman conducted the data collection. N. Logan conducted the data analyses. D. Westfall provided research expertise. S. Whitfield-Gabrieli and S. Anteraper provided neuroimaging expertise. N. Logan wrote the manuscript, and all authors approved the final version for submission.

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request because of the need for a formal data sharing agreement.

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The authors of this document report no conflicts of interested associated with the collection, dissemination, or interpretation of this research. No patents, copyrights, or royalties are involved or included in this work. The results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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