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ORIGINAL ARTICLE

Widespread Positive Direct and Indirect Effects of Regular Physical Activity on the Developing Functional Connectome in Early Adolescence

Skylar J. Brooks[1], Sean M. Parks[1] and Catherine Stamoulis[1,2]

[1]Boston Children's Hospital, Department of Pediatrics, Division of Adolescent Medicine, Boston, MA 02115, USA and [2]Harvard Medical School, Boston, MA 02115, USA

Address correspondence to Catherine Stamoulis, Department of Pediatrics, Harvard Medical School/Boston Children's Hospital, Department of Pediatrics, Division of Adolescent Medicine, 300 Longwood Avenue, Boston, MA 02115, USA. Email: caterina.stamoulis@childrens.harvard.edu

Abstract

Adolescence is a period of profound but incompletely understood changes in the brain's neural circuitry (the connectome), which is vulnerable to risk factors such as unhealthy weight, but may be protected by positive factors such as regular physical activity. In 5955 children (median age = 120 months; 50.86% females) from the Adolescent Brain Cognitive Development (ABCD) cohort, we investigated direct and indirect (through impact on body mass index [BMI]) effects of physical activity on resting-state networks, the backbone of the functional connectome that ubiquitously affects cognitive function. We estimated significant positive effects of regular physical activity on network connectivity, efficiency, robustness and stability ($P \leq 0.01$), and on local topologies of attention, somatomotor, frontoparietal, limbic, and default-mode networks ($P < 0.05$), which support extensive processes, from memory and executive control to emotional processing. In contrast, we estimated widespread negative BMI effects in the same network properties and brain regions ($P < 0.05$). Additional mediation analyses suggested that physical activity could also modulate network topologies leading to better control of food intake, appetite and satiety, and ultimately lower BMI. Thus, regular physical activity may have extensive positive effects on the development of the functional connectome, and may be critical for improving the detrimental effects of unhealthy weight on cognitive health.

Key words: adolescence, BMI, brain networks, functional connectome, physical activity

Introduction

In a period of just a few decades, childhood obesity in the United States of America has grown into a serious public health problem that currently affects 14 million children (CDC), including >20% of all adolescents (Hales et al. 2020). These highly alarming statistics highlight an urgent need for intervention to address the obesity epidemic, given serious detrimental short- and long-term effects of unhealthy weight on physical and mental health (Reeves et al. 2008; Dockray et al. 2009; Arseneault et al. 2010; Esposito et al. 2014; Sahoo et al. 2015; Quek et al. 2017; Lindberg et al. 2020). Beyond its potential lifelong effects on the individual, obesity has an enormous negative economic impact on society. Yearly direct medical care costs are ~$150 billion and indirect costs due to loss of productivity, higher insurance premiums, and lower household income are a staggering ~$3–6 billion (Colditz and Wang 2008; Trogdon et al. 2008). In children, the direct costs of obesity are over $14 billion (Cawley 2010).

Extensive adverse structural, cognitive, and biochemical effects of unhealthy weight on the brain have been identified in a wide range of studies (Wang et al. 2001; Schwartz and Porte 2005; Raji et al. 2010; Shefer and Stern 2013). In the developing brain, these effects may have important long-term implications for cognitive heath. Recent studies involving 9–10-year-old children from the Adolescent Brain Cognitive Development (ABCD) study (Casey et al. 2018) have shown that higher body mass index (BMI) is associated with lower

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prefrontal cortical thickness and decreased executive function and control (Laurent et al. 2019; Ronan et al. 2020), and have linked differences in waist circumference to cellular density in the nucleus accumbens (Rapuano et al. 2020). Earlier studies in smaller cohorts have also reported distributed structural differences, for example, in white matter volume, between overweight children and adults compared to those with normal BMI (Wang et al. 2001; Raji et al. 2010). Unhealthy weight in adolescence may have specific detrimental effects on brain regions and associated neural circuitry related to executive control, which is still developing during this period (Kamijo et al. 2014). Although there is a genetic predisposition to unhealthy weight (Choquet and Meyre 2011), poor diet and lack of physical activity are also significant contributors. Nutrition plays a critical role in neural maturation (Georgieff 2007; Prado and Dewey 2014; Cusick and Georgieff 2016) and poor diet may lead to neuroinflammation and brain changes that reinforce unhealthy eating habits and ultimately weight gain (Freeman et al. 2014).

Physical activity has been shown to play an important role in supporting neural maturation and cognitive health (Khan and Hillman 2014; Donnelly et al. 2016; Bidzan-Bluma and Lipowska 2018; Di Liegro et al. 2019). Intense and/or regular cardiovascular exercise and increased fitness may positively affect the basal ganglia and the hippocampus, enhance gray matter volume, and protect white matter integrity, particularly in regions associated with executive function (e.g., prefrontal and parietal regions), leading to improved short- and long-term memory processes, cognitive control, and academic performance (Colcombe et al. 2003; Di Martino et al. 2008; Draganski et al. 2008; Aron et al. 2009; Stroth et al. 2009; Chaddock et al. 2010; Davis et al. 2011; Erickson et al. 2011; Pontifex et al. 2011; Ruscheweyh et al. 2011; Roig et al. 2013; Voss et al. 2013; Chaddock-Heyman et al. 2014; Donnelly et al. 2016; Firth et al. 2018).

The impact of physical activity on the brain may depend on its intensity level. In adults, low-intensity exercise, for example, walking, may increase connectivity in regions involved in attention and executive processes (e.g., the frontoparietal network), whereas high-intensity exercise, for example, running, may increase connectivity in regions supporting emotional processing and the affective and reward networks (Weng et al. 2017; Schmitt et al. 2019). Long-term aerobic activity may increase resting-state connectivity between regions of the default-mode network (DMN; Voss et al. 2010) and decrease connectivity in task-irrelevant networks during selective attention (Wengaard et al. 2017; Peven et al. 2019). In contrast, a sedentary life may lead to lower global and local efficiency of the dorsal attention network and suboptimal performance in decision-making tasks (Pindus et al. 2020). In children, lack of physical activity may adversely affect functional connectivity across brain networks (Voss et al. 2011).

Despite encouraging findings on the positive impact of physical activity on the brain, related large-scale studies, particularly in children, are limited. During development, the topology of the human connectome progressively changes from a localized (anatomically clustered) to an increasingly distributed organization of functional networks (Fair et al. 2007, 2009). In addition, the DMN is only sparsely connected in early school-age children (Fair et al. 2008) but becomes progressively robust by adulthood (Greicius et al. 2003). To date, the impact of physical activity on the topological organization of the heterogeneous and vulnerable developing connectome remains elusive. As functional networks maturate and become increasingly specialized during almost 2 decades of development, they progressively assume topological properties that maximize the efficiency of information processing, facilitate learning and adaptation and optimize the brain's response to cognitive demands (Bullmore and Sporns 2009; Pessoa 2014). In addition to optimal functional connectivity across spatial scales, these properties include network efficiency, a distance metric between nodes that reflects how rapidly information can propagate through the network (Martinez et al. 2018) and modularity, which reflects the ability to partition the network into modules (or communities) that support localized computation (Newman 2006; Bullmore and Sporns 2009, 2012; Meunier et al. 2009). Both properties emerge during development, as redundant neural connections are progressively eliminated and selective sparse connections are strengthened, leading to networks in adulthood that optimally integrate and coordinate local information (computed at the module level) and transmit it across the brain via long-range connections (Chen and Deem 2015). A related topological property is small-worldness (Watts and Strogatz 1998; Bassett and Bullmore 2006), which is characteristic of optimally organized networks and combines high clustering and shortest node distance (average path length), thus minimizing computational cost and maximizing processing efficiency through the network. Given the complexity of inputs the brain receives and the extensive repertoire of human behaviors, these properties are paramount to cognitive function. In addition, small-worldness and modularity are also critical to network stability, robustness and resilience (Babaei et al. 2011; Gilarranz et al. 2017). A modular network organization may increase "fault tolerance," that is, the network's ability to remain functional despite individual module failure. To date, the impact of positive factors such as physical activity and negative factors such as unhealthy weight on these critical properties during development (particularly in adolescence), remain only partially understood (Huang et al. 2015).

To address this gap in knowledge and leverage ongoing large studies on brain development, this study investigated the direct and indirect (through impact on BMI) effects of physical activity on resting-state networks. A cohort of 5955 children from the ABCD study were analyzed and resting-state functional magnetic resonance imaging (rs-fMRI) was used to estimate task-independent networks and their properties, which may be relatively homogeneous in healthy adult populations (Greicius et al. 2003; Mantini et al. 2007; Fox et al. 2009; Van den Heuvel and Sporns 2013) but highly heterogeneous in developing children (Fransson et al. 2007; Menon 2013) and vulnerable to the adverse effects of unhealthy weight and/or lack of exercise. Multiple measures quantified each participant's level and pattern of physical activity. Statistical analyses examined the direct impact of physical activity on the connectome and its properties as well as indirect effects through BMI. Although there is a clear association between exercise and BMI, there is relatively limited prior work on the impact of BMI on the resting connectome's topology and properties, particularly in children. Given the heterogeneity of the typically developing connectome, these associations need to be assessed in large samples. The ABCD dataset provides a unique opportunity for this purpose.

Materials and Methods

Participants

Rs-fMRI, clinical assessments, behavioral, and demographic data, collected at entry in the ABCD study (a longitudinal

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investigation of >11 000 children, starting at age 9–10 years), were analyzed. These data are available through the National Institute of Mental Health Data Archive (NDA). At the time of this study, data from release 2.0.1 were available. Children imaged only with a GE or Siemens scanners were identified ($n = 9304$). Per the ABCD consortium guidelines, those imaged with a Philips scanner needed to be excluded due to preprocessing issues and reprocessed data were not available at the time of this analysis. Following exclusion based on imaging data quality, clinical findings in structural MRI ($n = 344$) or history of bipolar disorder ($n = 184$), $n = 5955$ children (median age = 120.0 months, interquartile range [IQR] = 13.0) with rs-fMRI of adequate quality for analysis were included ($n = 4489$ [75.38%] were measured with a Siemens scanner).

fMRI Resting-State Data Processing

Data Preprocessing

Analyzed neuroimaging data had been minimally preprocessed by the dedicated Data Analysis, Informatics & Resource Center (DAIRC) of the ABCD study (Hagler et al. 2019) and were further processed in this study using the Next Generation Neural Data Analysis (NGNDA) pipeline. Each participant had data from up to 4 rs-fMRI (5-min long) runs. Motion, artifacts, and other nonbiological signal contaminants were suppressed following structural segmentation, initial fMRI frame removal, coregistration to structural MRI, slice-time correction, and normalization to MNI152 space. Denoised signals from runs with < 10% of motion-censored frames were further analyzed. The data processing steps using NGNDA are described in detail in Supporting Information (S1). For each participant, only one rs-fMRI run was selected for estimating resting network properties. Assuming that functional connectivity at rest is relatively low even at this age (with the exception of predominantly the DMN), and to minimize the likelihood of spuriously increased connectivity associated with residual motion artifacts, the rs-fMRI run with the lowest median connectivity was selected for further analysis. This run typically corresponded to the one with the lowest number of censored frames. Following these imposed constraints, median percent of motion-censored frames across the sample was 1.87% (IQR = 4.8%). Given this overall low number, analyses were predominantly conducted without including this parameter in statistical models. However, in additional analyses percent of censored frames for each participant was included as an additional adjustment in models.

Analysis of fMRI Signals

Connectivity was estimated as the peak cross-correlation between pairs of regional time-series, resulting in a 1088 × 1088 symmetric matrix (based on the resolution of the parcellation). Other methods (e.g., mutual information) yielded overall similar connectivity patterns. For each participant, one rs-fMRI run was selected for estimating network properties, based on the approach described in Supporting Information (S2). Estimated network properties included mean and median connectivity, modularity, local and global clustering coefficients, node degree, global efficiency, eigenvector centrality, small-worldness (Bassett and Bullmore 2017), natural connectivity, and the largest eigenvalue of the adjacency matrix, used as a proxy for network stability to perturbations (Restrepo et al. 2007). The brain connectivity toolbox (Rubinov and Sporns 2010) as well as custom codes (for network modularity, robustness, and stability), all available in (NGNDA), were used for these estimations.

Analyses of network properties were performed both at the level of the global topology (the entire brain) as well as local topology (individual brain regions/parcels assumed as the network nodes). Several network measures analyzed in this study are described in Rubinov and Sporns (2010). Local (node-specific) clustering coefficient was calculated as the ratio of a node's neighbors that were neighbors themselves and global clustering was estimated as the mean of these local coefficients. Modularity measured the degree to which the network could be divided into nonoverlapping communities (modules). Degree was the number of nonzero connections for each node. Global efficiency was calculated as the average inverse shortest path length between pairs of nodes and quantified the efficiency of distant information transfer (Stanley et al. 2015). Eigenvector centrality measured node importance in the network. Small-worldness was calculated as the ratio of normalized global clustering to normalized characteristic path length, using the approach in Bassett and Bullmore (2006, 2017), using 20 random graphs generated from binary adjacency matrices (Anderson and Cohen 2013). The topological organization of the network as a combination of highly connected node clusters (modules) communicating via sparse long-range connections was measured by the network's small-worldness (Watts and Strogatz 1998; Telesford et al. 2011). Natural connectivity, measuring network robustness, was estimated as the average eigenvalue of the binary adjacency matrix (Wu et al. 2009).

Measures of Physical Activity, Clinical Assessments, and Demographic Data

Age, sex, race, ethnicity, weeks born prematurely, pubertal stage data, height, weight, sleep duration, and screen time were collected from relevant questionnaires (NDA). At the time of this investigation, neuroimaging site information was not available. BMI was calculated from measured height (in inches) and weight (in pounds), by multiplying weight by 703 and dividing by height squared. Age- and sex-specific growth curves were also used for reference (CDC-1). Number of hours of sleep per night was coded (by the ABCD) as 1 = 9–11 h, 2 = 8–9 h, 3 = 7–8 h, 4 = 5–7 h, and 5 = < 5 h. Screen time included time spent watching television, playing games, texting, and visiting social network sites, but not time spent on school-related work. Average time spent per weekday and weekend days was combined to obtain total weekly screen time in minutes.

Physical activity measures, extracted from the Youth Risk Behavior survey, included days/week being physically active for ≥60 min/day, days/week spent strengthening/toning muscles and days/week of PE class. The Parent Sports and Activities Involvement Questionnaire was used to calculate the total number of sports/activities a child was involved in (out of 23 activities that included individual and group sports, e.g., running, soccer, and ballet/dance).

Statistical Analysis

Statistical analyses were performed using the software MATLAB (R2019a, Mathworks, Inc.). Figures were created using the software MRICroGL (NITRC.org). Ordinary linear regression models assessed the associations between connectome properties and physical activity, BMI and covariates and potential confounders. Across variables analyzed in this study, it is reasonable

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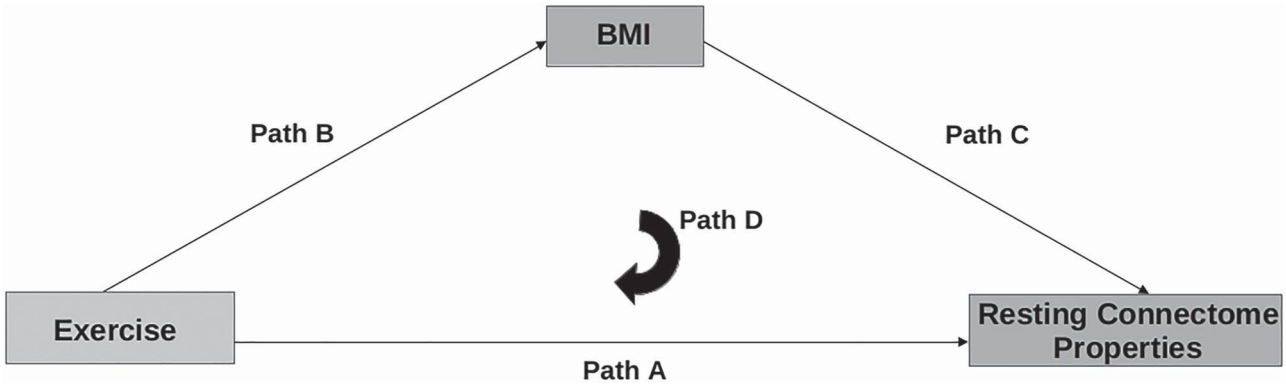

Figure 1. Statistical (mediation) model assessing the direct (path A) and indirect (mediated by BMI improvement; paths B and C) effects of physical activity on connectome properties. Path D represents the full model.

to assume that nonavailable data were missing at random. Overall, for most variables, a small number of participants were missing data (age: 0, sex: 1 [0.02%]; race: 78 [1.31%]; ethnicity: 68 [1.14%]; BMI: 1 [0.02%]; physical activity: 6 (0.10%); family income: 437 [7.34%], number of sports: 0, sleep duration: 0, screen time: 4 [0.07%]; and weeks born prematurely: 62 [1.04%]). Pubertal stage information was missing for a more substantial number of participants ($n = 1090$ [18.30%]) but models were run with and without this adjustment. In models excluding pubertal stage but including demographics, BMI and/or physical activity, $n = 5396$ (90.61%) had complete data. Results based on these models were compared with those obtained from the entire sample, using imputation for missing data. Results from the 2 sets of models were statistically identical.

Significance level was set at $\alpha = 0.05$. Given a large number of developed models, regression coefficient *P*-values were adjusted for false discovery using well-established methods (Benjamini and Hochberg 1995). All analyses were based on the model in Figure 1, used to assess both direct effects of physical activity on connectome properties (path A) and indirect effects through its impact on BMI (path D). The latter's effects were also separately assessed (path C). Mediation analyses followed the approach in Baron and Kenny (1986) and the Sobel test (Sobel 1982) was used to assess the level and significance of mediation.

Models were adjusted for age, sex and accounted for propensity weights (recommended by the ABCD consortium to account for sampling differences between sites). Race was modeled as a dichotomous variable (white vs., non-white). Given the highly skewed racial distribution of the ABCD cohort, only this representation led to consistent model convergence. Ethnicity was modeled as a binary variable (Hispanic = 1; non-Hispanic = 0). For family income, the ABCD ordinal scale was used: 1 = <$5000, 2 = $5000–$11 999, 3 = $12 000–$15 999, 4 = $16 000–$24 999, 5 = $25 000–$34 999, 6 = $35 000–$49 999, 7 = $50 000–$74 999, 8 = $75 000–$99 999, 9 = $100 000–$199 999, and 10 ≥ $200 000. Models were also adjusted for gestation age (calculated as 40 minus the number of weeks born prematurely) and several sets of models for pubertal stage (using the ABCD ordinal scale: 1 = prepuberty, 2 = early puberty, 3 = mid-puberty, 4 = late puberty, and 5 = postpuberty).

Univariate ordinary linear regression models were first used to identify independent variables significantly associated with network properties. A forward selection approach was then used to build multivariate models. Collinearity between independent variables was also assessed. The order of parameter inclusion was shuffled to minimize the final model's dependence on it (Hurvich and Tsai 1990; Chatfield 1995). Models with a fixed set of parameters were also tested. The results for the primary predictor varied nonsignificantly between modeling approaches. Each model was evaluated for overall fit using the adjusted R^2 and AIC values. The scatter index (SI; Zambresky 1988), calculated as the root-mean-squared error (RMSE) of each model normalized by the mean of the corresponding observations, was also estimated as another measure of model fit. Given the large sample and relatively small parameter space, the model selection steps were appropriate (Harrell 2001). Model parameters reported in Tables 1 and 2 include both raw and standardized regression coefficients to facilitate comparisons between measures. Cohen's f^2 was also used to assess the effect size of the primary predictors (physical activity, number of sports, and BMI) in various models. Finally, in addition to using the entire cohort to develop explanatory statistical models, an out-of-sample approach was also used for validation. The cohort was split into 2 sub-cohorts, with 75% of participants randomly selected and used to develop models and the remaining 25% used to validate them. The process was repeated 100 times. In addition to the AIC, the coefficient of variation of the root-mean-squared error (CV[RMSE] between predicted and measured validation data) was used as the measure of the model's predictive power.

Results

Multimodal data from 2925 (49.12%) males and 3029 (50.86%) females were analyzed. This sample reflected the overall race distribution of the ABCD cohort (which is predominantly white), and included 3995 (67.09%) white, 1182 (31.60%) non-white, and 1150 (19.31%) Hispanic children. Median family income was $75 000–$99 999 and $n = 1772$ (29.81%) of families had income $100 000—$199 999.

Median gestation age was 40 weeks (IQR = 0; 12.86% had gestation < 37 weeks). $N = 4865$ participants (81.70%) had pubertal stage data. On average, participants were in early puberty, slept 8–9 h/day and spent > 1000 min/week on an electronic device (median = 1065.00 min, IQR = 840.00). Median BMI was 17.37 kg/m^2 (IQR = 4.28), with 798 children (13.40%) above the 95th BMI percentile for their age. Girls had significantly higher BMI than boys ($P = 0.03$, Wald statistic = 4.57). Participants were physically active for ≥60 min on average 3 days/week (IQR = 3 days), attended PE class 2 days/week (IQR = 2 days),

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Table 1 Summary of statistics for the mediation model with whole-brain network properties as outcomes (paths A, C, D) or BMI (path B)

Mediation model path	Outcome	Standardized regression coefficient	Raw regression coefficient (beta)	Standard error (SE)	Beta confidence intervals (CI)	P-value	Wald statistic
Path A (direct path)	**Model statistics for exercise as predictor of resting network properties**						
	Efficiency	0.040	0.002	0.001	[0.001, 0. 003]	0.008	8.542
	Global clustering	0.040	0.001	<0.001	[<0.001, 0.002]	0.008	8.178
	Median connectivity	0.032	<0.001	<0.001	[<0.001, < 0.001]	0.026	5.140
	Modularity	−0.037	−0.002	0.001	[−0.004, −0.001]	0.010	7.359
	Robustness	0.047	2.950	0.873	[1.239, 4.661]	0.002	11.421
	Stability	0.048	2.171	0.630	[0.936, 3.405]	0.002	11.884
Path B	**Model statistics for exercise as predictor of BMI**						
	BMI	−0.028	−0.047	0.022	[−0.091, 0.003]	0.038	4.317
Path C	**Model statistics for BMI as predictor of resting brain network properties**						
	Efficiency	−0.052	−0.001	<0.001	[−0.002, −0.001]	0.001	13.407
	Global clustering	−0.058	−0.001	<0.001	[−0.001, < 0.000]	0.001	16.273
	Median connectivity	−0.040	−0.001	<0.001	[−0.001, < 0.000]	0.008	7.531
	Modularity	0.042	0.002	0.001	[0.001, 0.003]	0.006	8.614
	Robustness	−0.043	−1.581	0.527	[−2.614, −0.549]	0.006	9.021
	Small-worldness	0.031	0.010	0.004	[0.001, 0.018]	0.030	4.739
	Stability	−0.043	−1.146	0.380	[−1.831, −0.437]	0.006	9.112
Path D (full model)	**Model statistics for weekly physical activity (E) and BMI (B) as predictors of resting brain network properties**						
	Efficiency	E: 0.039	E: 0.002	0.001	[<0.001, 0.003]	0.011	7.966
		B: −0.051	B: −0.001	<0.001	[−0.002, −0.001]	0.001	13.049
	Global clustering	E: 0.038	E: 0.001	<0.001	[<0.001, 0.002]	0.011	7.563
		B: −0.057	B: −0.001	<0.001	[−0.001, < 0.000]	0.001	15.780
	Median connectivity	E: 0.031	E: < 0.001	<0.001	[<0.001, < 0.001]	0.032	4.804
		B: −0.039	B: <−0.000	<0.001	[<0.000, < 0.000]	0.009	7.189
	Modularity	E: −0.036	E: −0.002	0.001	[−0.004, −0.001]	0.013	6.924
		B: 0.041	B: 0.001	0.001	[<0.001, 0.003]	0.007	8.407
	Robustness	E: 0.046	E: 2.878	0.873	[1.167, 4.588]	0.003	10.873
		B: −0.042	B: −1.545	0.527	[−2.578, −0.513]	0.007	8.613
	Small-worldness	E: −0.010	E: −0.005	0.007	[−0.020, 0.009]	0.468	0.526
		B: 0.031	B: 0.010	0.004	[0.001, 0.018]	0.033	4.748
	Stability	E: 0.047	E: 2.118	0.629	[0.884, 3.352]	0.003	11.324
		B: −0.042	B: −1.119	0.380	[−1.864, −0.375]	0.007	8.684

Note: All P-values have been adjusted for FDR. Standardized beta coefficients were estimated from raw coefficients before rounding.

Table 2 Summary of statistics for models with total number of sports as the predictor and whole-brain network properties as individual outcomes

	Model statistics for total number of sports as predictor of resting brain network properties					
Outcome	Standardized regression coefficient	Raw regression coefficient (Beta)	Standard error (SE)	Beta confidence intervals (CI)	P-value	Wald statistic
Efficiency	0.038	0.002	0.001	[0.001, 0.003]	0.022	7.994
Global clustering	0.038	0.001	<0.001	[<0.001, 0.002]	0.022	7.895
Mean connectivity	0.034	0.001	0.001	[<0.001, 0.002]	0.028	6.278
Robustness	0.033	2.358	0.963	[0.471, 4.245]	0.028	5.999
Stability	0.033	1.676	0.693	[0.318, 3.035]	0.028	5.850

Note: All P-values have been adjusted for FDR. Standardized beta coefficients were estimated from raw coefficients before rounding.

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3136 (52.66%) were involved in ≤2 sports, and 845 (14.19%) were not involved in any sport.

Impact of Physical Activity on Whole-Brain Network Properties

The results of models in Figure 1 are summarized in Table 1a. The number of physically active days was positively associated with network efficiency, global clustering, median (and mean) connectivity, robustness, and stability but negatively associated with modularity (path A: $P < 0.01$, Wald statistic > 6.00). Similar associations were estimated for number of sports, with the exception of modularity (Table 1b). Increased physical activity was also significantly associated with longer sleep duration and shorter screen time ($P < 0.01$, Wald statistic = 15.28, and 33.10, respectively). Being white and from a higher income family were positively associated with connectivity, network efficiency, global clustering and stability (individually and in combination; $P < 0.01$, Wald statistic >5.90). Being at a more advanced pubertal stage was negatively associated with connectivity ($P \leq 0.01$, Wald statistic ≥6.0) and positively associated with modularity (individually and in combination with race and family income; $P < 0.02$, Wald statistic > 5.20). As the brain assumes an increasingly efficient topological configuration, modularity is expected to increase with pubertal stage (Chen and Deem 2015). In addition, the adult brain at rest is overall weakly connected (with the exception of strong connections between elements of default-mode network), a configuration and connectivity state that are presumably optimized throughout development. Thus, as neural connections are pruned and only selected (and relatively sparse) connections are strengthened, overall (brain-wide) connectivity in the brain at rest is expected to decrease as a function of pubertal stage. Finally, ethnicity had no significant impact on network properties ($P \geq 0.66$). Similarly, when included in models as additional independent variables, the percent of censored frames, although significant as a parameter ($P < 0.01$) did not alter the significance of the association between network properties and physical activity and/or BMI. All remaining independent variables were nonsignificant across models ($P \geq 0.32$).

A negative association between number of physically active days (but not number of sports) and BMI was estimated (Path B: $P = 0.04$, Wald statistic = 4.32). BMI had a significant negative effect on most network properties (Path C: $P < 0.01$, Wald statistic > 9.4) except modularity and small-worldness, possibly a pubertal stage effect (since the 2 were collinear). Finally, in the model testing the indirect impact of physical activity through its effect on BMI (path D), both physical activity and BMI had opposite significant effects on most network properties, with smaller negative effects of BMI than in path C, suggesting partial mediation of the relationship between physical activity and connectome properties through lower BMI (Table 1). Only in the case of small-worldness, BMI, but not physical activity, was positively associated with it ($P = 0.05$, Wald statistic = 3.95), possibly an age effect since BMI is collinear with age/pubertal stage, and small-worldness increases with neural maturation (Tomasi and Volkow 2014; Bassett and Bullmore 2017).

In additional analyses, the direction of mediation was reversed, in order to test 2 paths: 1) physical activity → network properties (mediator) → BMI outcomes and 2) BMI outcomes → network properties (mediator) → physical activity, that is, mediation of the relationship between physical activity and BMI by the brain. One set of models included both physical activity and network properties (a separate model for each property) as independent variables and BMI as the dependent variable. Physical activity became marginally significant ($P = 0.05$) in all models, whereas network properties remained significant ($P < 0.01$), suggesting almost complete mediation. Similar results were obtained for the second path. BMI became marginally significant in all models ($P < 0.06$), whereas network properties remained significant. This indicates almost complete mediation of the relationship between BMI and physical activity by the brain.

Overall, estimated effects were relatively small (effect size ≤0.10) but of comparable size for physical activity, BMI, and sports. In addition, models for median connectivity, global clustering, and modularity had good predictive power (CV[RMSE] < 0.20). The SI for all models was < 0.85 but for some fit was better than others (with SI < 0.31 for modularity and efficiency and SI ≤ 0.01 for median connectivity).

Impact of Physical Activity on Region (Node)-Specific Network Properties

The direct and indirect effects of physical activity on network node properties (centrality, clustering and degree) were also assessed. Individual models were tested for each node and property and results were adjusted for false discovery. No significant associations were found between node centrality and physical activity, sports involvement or BMI. Significant, spatially distributed positive effects of physical activity (path A) and even more extensive negative effects of BMI (path C) on node clustering were estimated in bilateral areas of the ventral/salience and dorsal attention (Fox et al. 2006), DMN (Greicius et al. 2003), somatomotor (pre and postcentral gyri and supplementary motor areas), limbic, and partially the frontoparietal control networks. BMI was also negatively associated with node clustering in the cerebellum and posterior visual areas. These effects are shown in Figure 2. In the model testing the indirect effect of physical activity on the brain through its impact on BMI (path D), both physical activity and BMI had significant opposite effects (i.e., increased physical activity was associated with lower BMI) with the exception of bilateral temporoparietal areas in which physical activity was no longer significant. This is also reflected in smaller BMI effects on network properties than those estimated in path C (testing the direct effect of BMI on the brain). Similar results were obtained for node degree, with additional positive effects of exercise in the basal ganglia (particularly the dorsal striatum) and the thalamus ($P \leq 0.03$) and consistent negative effects of BMI in similar structures. The top 20% of effects (based on the regression coefficients) on node degree are shown in Figure 3.

Finally, sports involvement also had distributed positive small effects on both node clustering and degree but, similarly to whole-brain properties, no significant effect on BMI (so the path D model in Fig. 1 was no longer relevant). Impacted areas partially overlapped with those positively affected by physical activity, particularly somatomotor areas and elements of the dorsal and ventral attention and DM networks as well as the thalamus. An additional significant positive effect on node degree in the cerebellum was estimated ($P = 0.047$). Effect sizes for sports were overall smaller than those of physical activity. The results for node degree are shown in Figure 4.

Discussion

In a large cohort of almost 6000 children age 9–10 years, this first of its kind study has investigated the direct and indirect (through BMI) effects of regular physical activity on the developing, task-independent (resting-state) functional connectome,

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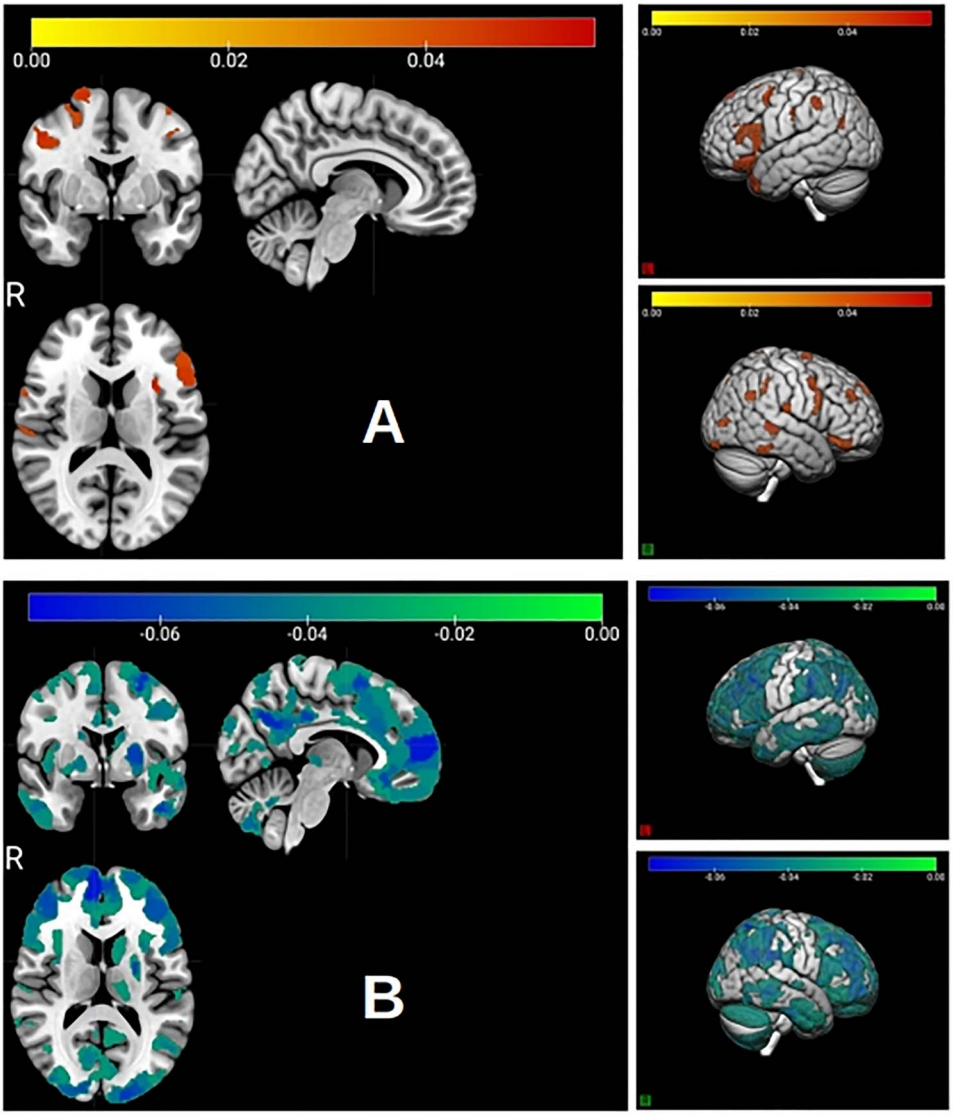

Figure 2. Top panels (*A*): Significant positive effects of physical activity (shown in orange) across the brain on node clustering. Bottom panels (*B*): Significant negative effects of BMI (shown in green) across the brain. In both sets, the colorbar shows the range of the standardized regression coefficient values in respective models. Two- and 3-dimensional views of both hemispheres are shown.

which plays a critical role in the brain's flexibility, response to cognitive demands and learning (Biswal et al. 1995; Greicius et al. 2003; Dosenbach et al. 2007; Chen et al. 2019). During development, the resting connectome is vulnerable to negative/risk factors, stressors, and adverse experiences (Greenough et al. 1987; Tierney and Nelson 2009; Di Martino et al. 2014; Stamoulis et al. 2015, 2017; Cao et al. 2017; Quinlan et al. 2018; Taylor et al. 2020), but may also significantly benefit by positive factors and enriching experiences, including physical activity (Dawson et al. 2000; Shonkoff and Phillips 2000; Spear 2000; Grossman et al. 2003; Houston et al. 2014; Whittle et al. 2014; Kaiser 2017; Minh et al. 2017). In adolescence, these experiences may have long-term effects on neural circuits that continue to maturate during this period, for example, those supporting executive control and decision-making (Vasa et al. 2020), and may affect cognitive function across the lifespan. Physical activity during this period may improve cognitive performance across domains and the structural and functional neural circuitry that supports it (Raichlen et al. 2016; Herting and Chu 2017).

This study has identified extensive, spatially distributed positive effects of physical activity and sports involvement on brain-wide and local network properties that may play a critical role in neural information processing and cognitive performance. These included connectivity, efficiency, robustness, and topological stability. Recent work has shown that diet and metabolic processes (also stimulated by physical activity) may have a significant impact on brain network stability (Coyle 2000; Mujica-Parodi et al. 2020). Throughout development, the brain's functional circuitry progressively assumes an optimal configuration that maximizes its efficiency. Distant networks are increasingly integrated through selective strengthening of sparse long-range connections, while maintaining local highly-connected networks that perform segregated computations. Physical activity was associated with increased global connectivity and

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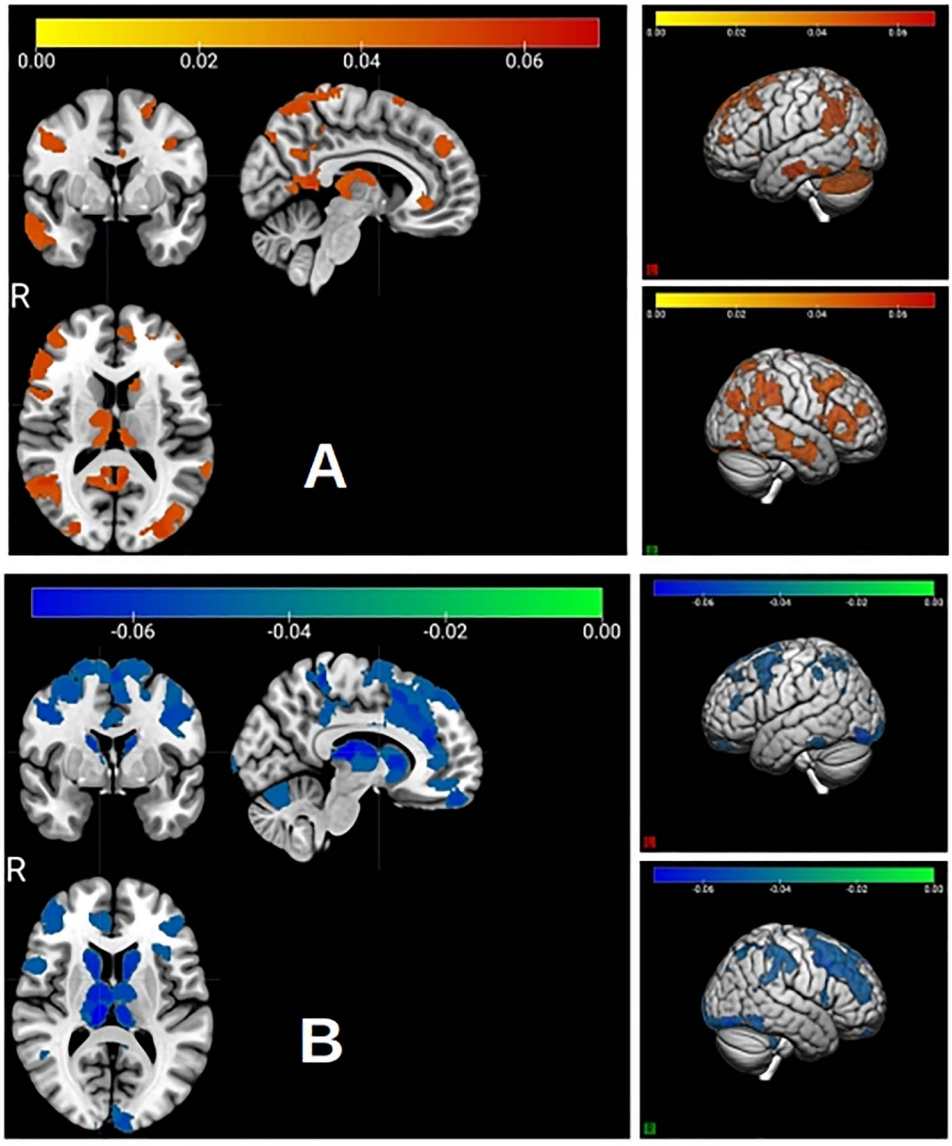

Figure 3. Top panels (*A*): Top 20% significant positive effects of physical activity (shown in red/orange) across the brain on node degree. Bottom panels (*B*): Top 20% significant negative effects of BMI (shown in blue) across the brain. In both sets, the colorbar shows the range of the standardized regression coefficient values in respective models. Two- and 3-dimensional views of both hemispheres are shown.

lower ability for further network segregation, both hallmarks of neural maturation (Fair et al. 2007). In contrast, BMI was negatively associated with multiple whole-brain network properties as well as physical activity, which partially modulated these adverse effects.

When the direction of mediation was reversed and connectome properties were assumed as the mediator, the indirect effect of physical activity on BMI became marginally significant, suggesting almost total mediation by the brain. Although regular physical activity has ubiquitous positive effects across organs and systems that support healthy weight, prior work has shown that consistent physical activity may specifically modulate metabolic and biochemical processes in the brain that improve hemodynamic activity and support neuroplasticity (Cotman and Berchtold 2002; Cotman and Engesser-Cesar 2002; Sutoo and Akiyama 2003; Kramer and Erickson 2007; Camandola and Mattson 2017; Matura et al. 2017). In turn, these modulations may lead to changes in functional network organization and topological configurations that facilitate cognitive flexibility and efficient information processing but also support better control of food intake, appetite and satiety, which may in turn result in lower BMI (Berthoud 2007; Ahima and Antwi 2009). Prior work has also associated changes in large-scale functional brain networks with eating behaviors and unhealthy weight (Broberger 2005; Park et al. 2016; Noble et al. 2019).

Similar negative BMI effects and positive effects of physical activity and sports involvement were estimated in local network properties (node clustering and degree). Extensive negative effects of BMI were estimated in the sensorimotor, frontoparietal, temporoparietal, limbic, cerebellum, and DM networks. Node clustering and degree may reflect both the efficiency of within-network computations (facilitated through

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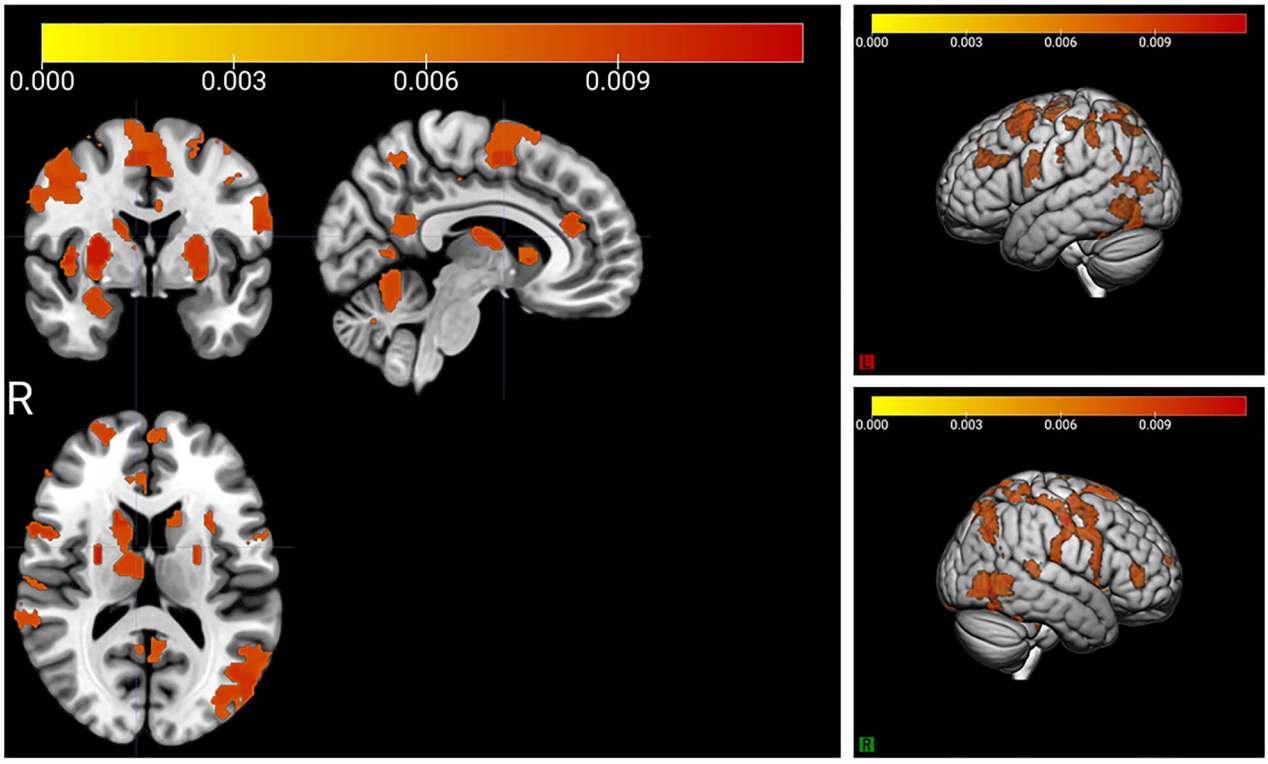

Figure 4. Significant positive effects of sports involvement (number of sports) on node degree. The colorbar shows the range of the standardized regression coefficient values. Two- and 3-dimensional views of both hemispheres are shown.

highly synchronized local neural communication) and the presence of hubs (sparse but highly connected nodes that are critical to multidomain processing, e.g., elements of the DMN). Negative associations between these properties and BMI suggested potentially impaired local computation, less connected network hubs and deficits in long-range communication. These findings have important implications for cognition and behavior across domains and suggest that unhealthy weight may have detrimental effects on motor function, executive control, memory processes, attention, overall flexibility of the brain, and emotional processing (Reinert et al. 2013; Marek and Dosenbach 2018). Notably, deficits in these networks, including aberrant connectivity and maturation of the DMN, have also been associated with neurodevelopmental and neuropsychiatric disorders (Supekar et al. 2010; Washington et al. 2014; Yerys et al. 2015).

Extensive positive effects of physical activity and sports involvement on local network topologies, including node degree and clustering, were also estimated (separately), including in critical structures such as the thalamus, striatum and cerebellum as well as premotor areas. Both had a direct impact (instead of just indirect effects through lower BMI) on distributed nodes, including those in the DMN, frontoparietal, and limbic networks. Overall, physical activity also partially modulated the negative effects of unhealthy BMI, including in somatomotor areas which has been previously shown to be significantly affected by adiposity (Rapuano et al. 2016). In turn, this suggests that regular physical activity may play a critical neuroprotective role and support neural maturation in fundamental networks that are still developing in adolescence (Fair et al. 2008), which support higher-level processes such as executive control, emotional processes, and the social brain (Mars et al. 2012). Finally, specific positive effects of physical activity on the limbic network may have important implications for a wide range of processes, including motor control and learning (further supported by a positive effect of sports involvement on the cerebellum and of physical activity on the sensorimotor network), memory, and response to stressors (Shonkoff and Phillips 2000; Mars et al. 2012; Catani et al. 2013).

Despite its strengths, including a large sample that may capture the connectome's topological heterogeneity in pre-/early adolescence, the study has some limitations. First, other factors (e.g., environmental and/or genetic) may moderate the relationship between physical activity and brain network properties and have not been considered in this study or measured by the ABCD. However, these likely contribute to the heterogeneity of analyzed networks and, despite such variability, significant positive effects of physical activity have been consistently identified using models with good predictive power and fit. In addition, method dependence and the choice of fMRI data need to be considered in connectivity studies. However, similar spatial connectivity patterns were estimated using both a cross-correlation and an information theoretic approach, leading to statistically similar network property estimates. Also, assuming that networks are weakly coordinated at rest (with the exception of the DMN), for each brain the rs-fMRI run with the lowest connectivity (in most cases coinciding with the run with the lowest number of motion-censored frames) was chosen. Differences between parameter estimates from multiple rs-fMRI runs were not estimated but are expected to be relatively small based

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on the conservative cutoff of < 10% censored frames. Furthermore, all reported effects were estimated in task-independent networks. Nevertheless, positive and negative modulations of the resting-state connectome topology have ubiquitous implications for cognitive function across domains (Chen et al. 2019). Finally, in regard to assessments of physical activity, another limitation is that all data analyzed in this study were from self and/or parent reports and not from direct measurements of physical activity. The ABCD study includes actigraphy data from a subset of participants (<50% of the entire cohort of ~12 000 participants and thus potentially less than half of the children in our cohort). Here, we chose physical activity and sports questionnaires since they were available for > 99.8% of participants. However, the impact of physical activity measured more precisely via actigraphy on brain networks and their properties is a planned direction of this ongoing work.

This study makes a significant scientific contribution in showing that regular physical activity in general, independently of specific sports or PE class, may have a widespread positive impact on brain development and the progressive topological optimization of functional circuits, whereas a sedentary life and unhealthy weight may have detrimental effects on these circuits (including fundamental default mode, thalamus and limbic networks) and their topologies and ultimately cognitive health. These results complement earlier findings from the ABCD and other pediatric cohorts on the impact of unhealthy BMI on brain structure and function (Wang et al. 2001; Raji et al. 2010; Rapuano et al. 2016, 2020; Laurent et al. 2019) and cognitive benefits of exercise (Voss et al. 2011; Wengaard et al. 2017; Peven et al. 2019; Pindus et al. 2020).

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

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