

## ARTICLE



Pediatrics

# Excess BMI in early adolescence adversely impacts maturing functional circuits supporting high-level cognition and their structural correlates

Skylar J. Brooks<sup>1,2,4</sup>, Calli Smith<sup>1,4</sup> and Catherine Stamoulis<sup>1,3</sup>

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**BACKGROUND/OBJECTIVES:** Adverse effects of excess BMI (affecting 1 in 5 children in the US) on brain circuits during neurodevelopmentally vulnerable periods are incompletely understood. This study investigated BMI-related alterations in maturing functional networks and their underlying brain structures, and high-level cognition in early adolescence.

**SUBJECTS/METHODS:** Cross-sectional resting-state fMRI, structural sMRI, neurocognitive task scores, and BMI from 4922 youth [median (IQR) age = 120.0 (13.0) months, 2572 females (52.25%)] from the Adolescent Brain Cognitive Development (ABCD) cohort were analyzed. Comprehensive topological and morphometric network properties were estimated from fMRI and sMRI, respectively. Cross-validated linear regression models assessed correlations with BMI. Results were reproduced across multiple fMRI datasets.

**RESULTS:** Almost 30% of youth had excess BMI, including 736 (15.0%) with overweight and 672 (13.7%) with obesity, and statistically more Black and Hispanic compared to white, Asian and non-Hispanic youth ( $p < 0.01$ ). Those with obesity or overweight were less physically active, slept less than recommended, snored more frequently, and spent more time using an electronic device ( $p < 0.01$ ). They also had lower topological efficiency, resilience, connectivity, connectedness and clustering in Default-Mode, dorsal attention, salience, control, limbic, and reward networks ( $p \leq 0.04$ , Cohen's  $d$ : 0.07–0.39). Lower cortico-thalamic efficiency and connectivity were estimated only in youth with obesity ( $p < 0.01$ , Cohen's  $d$ : 0.09–0.19). Both groups had lower cortical thickness, volume and white matter intensity in these networks' constituent structures, particularly anterior cingulate, entorhinal, prefrontal, and lateral occipital cortices ( $p < 0.01$ , Cohen's  $d$ : 0.12–0.30), which also mediated inverse relationships between BMI and regional functional topologies. Youth with obesity or overweight had lower scores in a task measuring fluid reasoning - a core aspect of cognitive function, which were partially correlated with topological changes ( $p \leq 0.04$ ).

**CONCLUSIONS:** Excess BMI in early adolescence may be associated with profound aberrant topological alterations in maturing functional circuits and underdeveloped brain structures that adversely impact core aspects of cognitive function.

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## INTRODUCTION

Childhood obesity has grown into an epidemic in the US, currently affecting over 15 million youth, including >20% of adolescents [1], and is associated with profound physical, mental and cognitive health problems. These include cardiovascular disease, disordered sleep, diabetes [2–10], suicide ideation and increased risk of suicide [8, 11–19], impaired attention, social skills, executive function, visuospatial processing, and verbal skills [20–25].

Almost 60% of children ages 2–19 years are projected to become adults with obesity [26]. In addition to profound effects on the individual, obesity carries staggering socioeconomic costs that include ~\$260 billion annual healthcare costs mostly covered by third-party payers, including public health insurance [27]. As

the rate of obesity rises, it will likely lead to unprecedented losses that call for urgent action, to understand the underlying causes of this epidemic and heterogeneity of the condition, i.e., obesities rather than obesity, and to develop individualized approaches to address it.

Unhealthy excess BMI in the first two decades of life can have life-long detrimental health effects, including an increased risk of morbidity and mortality [28, 29]. Its effect on the developing brain, and associated mental and cognitive health problems remain incompletely understood [21, 30, 31]. Complex negative relationships between BMI and cognitive function have been reported as early as preschool ages [20, 25, 32–38]. Lower academic performance, visuospatial organization, impaired visual memory

<sup>1</sup>Boston Children's Hospital, Department of Pediatrics, Division of Adolescent Medicine, Boston, MA, USA. <sup>2</sup>University of California Berkeley, Helen Wills Neuroscience Institute, Berkeley, CA, USA. <sup>3</sup>Harvard Medical School, Department of Pediatrics, Boston, MA, USA. <sup>4</sup>These authors contributed equally: Skylar J. Brooks, Calli Smith. ✉email: [caterina.stamoulis@childrens.harvard.edu](mailto:caterina.stamoulis@childrens.harvard.edu)

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and executive function (including inhibitory control) and higher impulsivity have been reported in preschool- and school-age children and adolescents with obesity [34, 39–50].

Adult studies have reported detrimental effects of obesity on the integrity of the brain's white matter tracts and their connections [51–55], and associated deficits in executive function [56]. Pediatric studies have reported reduced cortical thickness (particularly in prefrontal areas) and hippocampal volume in children with obesity or overweight [57, 58]. Childhood obesity has also been linked to altered organization and properties of reward and motor networks, including lower community structure (modularity) – a property that is critical to the efficiency of domain-specific computations in the brain and information processing [59]. Functional neuroimaging studies have linked obesity to aberrant connectivity specifically in circuits that support executive function and eating behaviors, including salience, reward and Default Mode (DM) networks [60–71]. A few studies have reported other obesity-related topological changes as well, such as reduced efficiency and small-worldness, across cortical and subcortical functional networks [72–74]. There are limited (if any) investigations on the impact of excess BMI on the organization of developing functional networks, particularly during periods of heightened neural maturation, such as adolescence [75], a vulnerable period during which stressors, risk factors and unhealthy behaviors can lead to miswiring of neural circuits and long-term cognitive and mental health issues.

The typically developing brain is inherently heterogeneous. Thus, the effects of excess BMI need to be studied in large cohorts, for findings to be generalizable and drive fundamental policy changes to combat the obesity epidemic. A few studies have used neuroimaging data from the historically large ABCD study [76] to assess the impact of excess BMI on the developing brain's structure. They have linked high BMI to decreased cortical thickness of regions involved in executive function, increased inflammation in reward structures, and changes in total brain volume [58, 77–79]. One study has also reported negative associations between BMI and functional connectivity [80], but did not investigate other topological properties or cognitive measures. To the best of our knowledge, no study has extensively investigated the effects of excess BMI on the topological organization of maturing functional networks in early adolescence, associated changes in the morphology of brain structures that form these networks, and their cognitive correlates.

To address this significant gap in knowledge, using fMRI and structural MRI from 4922 youth from the ABCD cohort, this study investigated the relationship between excess BMI and the topological organization of large-scale resting-state functional brain networks that play a fundamental role in cognitive function, and their structural substrates, in early adolescence. It hypothesized that having obesity is associated with consistent, widespread alterations in these networks' local and global topologies. These include changes that adversely impact the brain's ability to efficiently process information, perform domain-specific local computations and integrate the latter's output in highly connected network hubs in response to cognitive demands. These alterations are accompanied by morphological changes in underlying brain structures. The study also hypothesized that functional network alterations are measurable in youth with overweight as well. In turn, these changes adversely impact high-level cognitive processes. These hypotheses were tested through multiscale network-level analyses of resting-state (rs)-fMRI, structural MRI, and neurocognitive data. Analyses compared well-defined resting-state networks [81], including reward, social and thalamic networks, in normal BMI, with overweight and obese youth, and their structural and cognitive correlates. Results were reproduced across several datasets to ensure reliability of significant findings.

## METHODS

### Participants

Multimodal data from  $n = 4922$  typically developing children were analyzed [median age = 120.0 months, interquartile range (IQR) = 13.0 months; range = 107.0–132.0 months; 2349 males (47.72%), 2572 females (52.25%), 1 missing sex information]. Participants were excluded based on a combination of factors that could independently impact the brain's topological organization, or the study focus. These included a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD;  $n = 389$ ), Autism Spectrum Disorder (ASD;  $n = 51$ ) or history of bipolar disorder ( $n = 184$ ) [82–86], clinical findings in their anatomical MRI ( $n = 344$ ), poor-quality fMRI data ( $n = 315$ ), or BMI below the 5th percentile for sex and age ( $n = 278$ ). A small number of participants had a history of other conditions that could potentially impact the relationship between adiposity and brain structural and functional networks, including Traumatic Brain Injury (TBI;  $n = 54$ ) and diabetes ( $n = 19$ ). In addition,  $n = 382$  had a history of depression. Participants with TBI, diabetes, or depression were not excluded from the main analyses, by models were adjusted for these conditions as additional covariates. Additional secondary models were also tested, excluding these participants. Neither model adjustments nor exclusion of these participants led to any change in the findings. The study sample reflected the race and ethnicity distribution of the ABCD cohort, and included 3266 (66.35%) white and 3876 (78.75%) non-Hispanic youth. Given small numbers of participants in some racial groups, nonwhite participants were categorized as Black [933 (18.96%)], Asian [297 (6.03%)], or Other [356 (7.23%)].

### Body mass index (BMI)

BMI, BMI z-score (for the entire cohort and stratified for sex), and percent median BMI (%mBMI) were calculated from each participant's weight and height (see Table 1). Cutoffs for overweight (BMI  $\geq 85^{\text{th}}$  but  $< 95^{\text{th}}$  percentile), and obesity (BMI  $\geq 95^{\text{th}}$  percentile), respectively, were estimated from age- and sex-specific growth charts [1, 87]. Given the age distribution of the sample and discretization in the charts, five ranges were used:  $\leq 9.0$ ,  $> 9.0$  to  $\leq 9.5$ ,  $> 9.5$  to  $\leq 10.0$ ,  $> 10.0$  to  $\leq 10.5$ , and  $> 10.5$  to  $\leq 11.0$  years. Corresponding median BMI and 85th and 95th percentiles are summarized in supplemental Table S1. All primary and most of secondary analyses and comparisons were conducted as a function of BMI status (normal – the reference group in most analyses, with overweight, with obesity). The study sample had over 95% statistical power to detect at least small differences between BMI groups (Cohen's  $d \geq 0.10$ ).

### Additional variables

BMI may be correlated with physical activity, sleep, and screen time [35–38]. Physical activity was estimated from the Youth Risk Behavior survey as the number of days/week spent being physically active for  $\geq 60$  min [88]. Sleep quantity and quality (in the past 6 months) were measured via the Sleep Disturbance Scale for Children (SDSC) [89]. Total (combined average weekday plus weekend) screen time was calculated from the Parent Screen Time Survey as time spent using a phone or computer for any reason other than schoolwork [90]. Past/present anxiety and depressive symptoms and self-worth tied to weight were extracted from the Parent Diagnostic Interview for DSM-5 Full (KSADS-5) and Child Behavior Checklist (CBCL). Finally, the neurocognitive battery of the ABCD study, based on the NIH Toolbox [91], includes extensive tasks that assess cognitive function across domains [92]. This study hypothesized that adiposity-related changes in functional circuits adversely impact performance on tasks reflecting high-level cognition. However, a comprehensive analysis of performance across tasks in the neurocognitive battery was also conducted, as a function of BMI status.

### fMRI data and topological network properties

Resting-state rs-fMRI [from releases 2.0.1 (R2.0.1) and 4.0 (R4.0)], minimally preprocessed by the Data Analysis, Informatics & Resource Center (DAIRC) of the ABCD study [93] were analyzed using the Next-Generation-Neural-Data-Analysis-NGNDA platform [88, 94]. Minimal fMRI preprocessing by the DAIRC included multiple corrections, for head motion correction, B0 distortions, and distortions due to gradient nonlinearities. Further processing steps by the NGNDA included co-registration to each participant's structural MRI, normalization to MNI152 space, time-series denoising, and spatial downsampling from voxel- to parcel-level resolution (1088 parcels), using cortical, subcortical, and cerebellar atlases [88].

**Table 1.** Demographic and anthropometric data, sleep duration, physical activity and screen time as a function of BMI status.

	<b>Total N = 4922</b>	<b>Normal BMI (N = 3514)</b>	<b>With overweight (N = 736)</b>	<b>With obesity (N = 672)</b>
<b>Sex</b>				
Male	2349 (47.72%)	1690 (48.09%)	335 (45.52%)	324 (48.21%)
Female	2572 (52.26%)	1824 (51.91%)	401 (54.48%)	347 (51.64%)
Missing	1 (0.02%)	0	0	1 (0.15%)
<b>Race</b>				
White	3266 (66.36%)	2498 (71.09%)	428 (58.15%)	340 (50.60%)
Nonwhite	1586 (32.22%)	982 (27.94%)	293 (39.81%)	311 (46.28%)
• Black	933 (18.96%)	536 (15.25%)	175 (3.78%)	222 (3.04%)
• Asian	297 (6.03%)	233 (6.63%)	39 (5.30%)	25 (3.72%)
• Other	356 (7.23%)	213 (6.06%)	79 (10.73%)	64 (9.52%)
Missing	70 (1.42%)	34 (0.97%)	15 (2.04%)	21 (3.12%)
<b>Ethnicity</b>				
Hispanic	992 (20.15%)	590 (16.79%)	205 (27.85%)	
Non-Hispanic	3876 (78.75%)	2887 (82.16%)	524 (71.20%)	
Missing	54 (1.10%)	37 (1.05%)	7 (0.95%)	
<b>Family income</b>				
Median	\$75,000–\$99,999	\$75,000–\$99,999	\$50,000–\$74,999	\$50,000–\$74,999
<b>Parent Highest Level of Education</b>				
Median	Bachelor's Degree	Bachelor's Degree	Associate Degree (Academic)	Associate Degree (Occupational)
<b>BMI</b>				
Median (IQR)	17.61 (4.32)	16.68 (2.24)	21.06 (1.56)	25.33 (3.81)
<b>%mBMI</b>				
Median (IQR)	104.86 (25.42)	99.38 (13.16)	125.74 (8.91)	150.25 (21.57)
<b>BMI z-score</b>				
Median (IQR)	-0.22 (1.10)	-0.46 (0.57)	0.66 (0.40)	1.75 (0.97)
<b>BMI z-score stratified by sex</b>				
Male (Median (IQR))	-0.23 (1.06)	-0.46 (0.56)	0.66 (0.39)	1.77 (1.02)
Female (Median (IQR))	-0.20 (1.13)	-0.45 (0.59)	0.69 (0.38)	1.74 (0.97)
<b>Pubertal stage</b>				
Median	Early puberty	Early puberty	Early puberty	Early puberty
Pre-puberty	1086 (22.06%)	859 (24.44%)	122 (16.58%)	105 (15.62%)
Early Puberty	1524 (30.96%)	1110 (31.59%)	222 (30.16%)	192 (28.57%)
Mid-puberty or later	1411 (28.67%)	925 (26.32%)	240 (32.61%)	246 (36.61%)
Missing	901 (18.31%)	620 (17.65%)	152 (20.65%)	129 (19.20%)
<b>Phys. Activity- # days ≥ 60 min</b>				
Median (IQR)	3 (3)	4 (3)	3 (3)	3 (4)
<b>Number of Sports</b>				
Median (IQR)	2 (3)	2 (3)	2 (2)	2 (2)
<b>Sleep Duration (h)</b>				
Median (IQR)	8–9 (1–2)	9–11 (1–2)	8–9 (1–2)	8–9 (1–2)
<b>Snoring</b>				
More than twice/week	285 (5.79%)	153 (4.35%)	49 (6.66%)	83 (12.35%)
<b>Difficulty Falling Asleep</b>				
More than twice/week	305 (6.20%)	226 (6.43%)	41 (5.57%)	38 (5.65%)
<b>Waking Up at Night</b>				
More than twice/week	46 (0.68%)	37 (1.05%)	5 (0.68%)	4 (0.60%)
<b>Screen time (min/week)</b>				
Median (IQR)	1080 (840.0)	960 (780.0)	1140 (930.0)	1230 (1037.5)

Frames with displacement (an estimate of overall head motion)  $>0.3$  mm were censored, and rs-fMRI runs with  $>10\%$  of frames censored for motion were excluded from further analysis. Analyzed participants had at least one 5-min rs-fMRI run that met all quality criteria, and a subset had 2 or more runs. Each run represents a 'snapshot' of spontaneous, task-independent blood-oxygen-level-dependent (BOLD) activity in the brain.

Differential preprocessing and the inherent temporal variability of fMRI can lead to inconsistent results. To confirm reliability and reproducibility of findings, four fMRI datasets were analyzed: (a) best-quality run ( $n = 4922$ ; based on two data quality criteria, minimum number of frames censored for motion and lowest median resting-state connectivity) from R2.0.1; (b) averaged data across all runs with  $<10\%$  censored frames, also from R2.0.1; (c) second best-quality run ( $n = 3821$ ; 77.63% of 4922), which, based on the same quality criteria, typically coincided with the run with the second lowest number of frames censored for motion; (d) best-quality run from the recommended dataset in R4.0 ( $n = 3896$ , only partially overlapping with those from R2.0.1). Neuroimaging data in R2.0.1 had been collected in a Siemens or a GE scanner [95]. R4.0 data had been preprocessed slightly differently [95], and also included participants imaged in a Philips scanner. Scanner effects were assessed and data were harmonized through normalization during preprocessing in the NGNDA platform. Topological properties estimated from multiple runs were moderately correlated (Spearman's  $\rho \geq 0.41$ ). Results reproduced across all datasets are reported, except those of secondary analyses, which are based on the best-quality run (R2.0.1). The purpose of estimating network properties and correlations with BMI status across partially overlapping datasets from different releases was also to assess the reliability of the results as a function of differential preprocessing between releases.

Topological network properties were estimated at the scale of individual regions (nodes), large-scale networks [81], including the reward [96] and social networks [97], and the whole-brain connectome, as described in detail in Brooks et al. [88, 90]. They included median connectivity (two measures, one for connectivity within each network, and the other for connectivity between networks), modularity (the degree to which the connectome can be subdivided into distinct communities), global clustering (a measure of the brain's ability to perform local/domain-specific computations in specialized regions), topological efficiency (which reflects efficiency of information processing and functional integration), small-worldness (which measures how close the network's topology is to an optimally organized network that combines locally connected segregated communities with strong (but relative sparse) connections between them), network robustness (a measure of topological resilience to external perturbations) [98], topological stability [99], node centrality, which reflects the importance of a node (region) in the network, local clustering, and degree (number of node connections) [100]. Together, these properties comprehensively describe the organization of the connectome, including its ability to compute information locally in domain-specific networks, process information efficiently and integrate it in highly-connected (hub), as well as its resilience to internal (e.g., BMI-related) and external (e.g., environmental) stressors.

### Structural MRI data

Structural MRI data already preprocessed by the ABCD study [93] were analyzed. Morphometric and intensity measures included cortical thickness and volume, and averaged white-matter intensity (reflecting myelin content and axonal density). These parameters were estimated for each brain structure based on the Destrieux [101] and Desikan-Killiany [102] parcellations used by the ABCD study. Statistical correlations with BMI status were estimated separately for each morphological and intensity parameter and each set of parcels. To compare and assess reproducibility of findings, the 74 structures identified via the Destrieux parcellation were mapped onto the 34 regions identified via the Desikan-Killiany parcellation, using anatomical descriptions of the two sets of parcels, and visual inspection (to confirm overlap) using MRICroGL [103]. Only results that were consistent across parcellations and their joint mapping are reported. Finally, in order to correlate BMI-related structural and functional changes, the 1088 nodes of functional networks were mapped onto the 34 Desikan-Killiany-based structures, and node-level network properties (centrality, local clustering, and node degree) were averaged in each structure. Median (across nodes within each structure) functional properties were then compared to morphological parameters in each structure.

### Statistical analysis

Primary analyses examined associations between BMI status (normal, with overweight, with obesity), network properties, morphological measures, and cognitive task scores in the entire cohort, and race/ethnicity-based and sleep-based subcohorts [ $\geq 9$  h (recommended sleep for age) versus  $<9$  h per night]. Secondary analyses assessed correlations between connectome properties and continuous BMI, BMI z-score and %BMI. Ordinary linear regression models were developed with continuous BMI or status as the primary predictor (modeled as contrast variables, with normal BMI as the reference), and each network property, morphological parameter or task score as the dependent variable. An additional set of separate models compared those with obesity to overweight youth. Mediation models were also developed to test the hypothesis that BMI impacts the topological organization of functional networks both directly and indirectly, through its effects on the morphological properties of the underlying brain regions.

Propensity weights, provided by the ABCD, were used to adjust all analyses for sampling effects at different ABCD study sites. Adjustments for confounding effects of age, sex, ethnicity (1 = Hispanic, 0 = non-Hispanic), family income, physical activity, sleep duration, screen time, and race were included in all models. Depending on the model, race was either dichotomized [white (= 0) vs nonwhite (= 1)] or included as indicator variables for white, Black, Asian, or other race (a category that included all smaller racial groups). In models involving brain networks, the percent of frames censored for motion was also included as a covariate [88].

The adjusted  $R^2$  and Akaike Information Criterion (AIC) estimators were used to assess model fit, and predictive power was assessed using split-sample cross-validation, with a 75:25% split. At each of 100 draws, 75% of the sample from R2.0.1 was randomly selected for development, and a non-overlapping sample from R4.0 (i.e., an independent sample that was also processed slightly differently than the model development sample), corresponding to 25% of the study cohort, was used for validation. The coefficient of variation of the root mean squared error (CV-RMSE) between observed and predicted values was calculated, and the 95% confidence intervals (CI) for median CV-RMSE were estimated. All reported results are based on models with acceptable predictive power (CV-RMSE  $< 0.25$  [104]). The significance level was set at  $\alpha = 0.05$ , and all p-values were adjusted for the False Discovery Rate (FDR [105]). At the level of the whole-brain connectome and individual networks, FDR corrections were done across topological properties. At the node level, FDR corrections were done across nodes within individual networks. Only results that met significance after FDR correction are reported. Missing data were assumed to be missing at random. With the exception of pubertal stage,  $<5\%$  of participants were missing other variables. Statistical models included participants with complete data. Analyses were conducted using the software MATLAB (R2021a, Mathworks, Inc), and figures were generated with MRICroGL and BrainNet Viewer [103].

## RESULTS

### Cohort characteristics as a function of BMI status

A total of 3514 (71.39%) participants had normal BMI, 736 (14.95%) had overweight, and 672 (13.65%) had obesity. Corresponding median BMIs were 16.68, 21.06, and 25.33 kg/m<sup>2</sup>. Sample demographics are summarized in Table 1. Participants were predominantly in pre- and early puberty ( $n = 1086$ ; 22.06%, and  $n = 1524$ ; 30.96%, respectively). More females had obesity or overweight than males (54.48% of those with overweight and 51.64% of those with obesity). Almost 20% of Black and over 22% of youth in the 'Other' racial category had overweight, and  $\sim 25\%$  and  $\sim 18\%$ , respectively, had obesity. In contrast,  $<15\%$  of white and  $\sim 13\%$  of Asian youth had overweight, and 10% and  $\sim 9\%$ , respectively, had obesity. Over 20% of Hispanic participants had overweight and almost 20% had obesity, whereas  $\sim 13\%$  of non-Hispanics had overweight and  $\sim 12\%$  had obesity. Thus, proportionally more Black, Hispanic or those in the 'Other' racial group youth had excess BMI compared to white, Asian or non-Hispanic youth ( $p < 0.01$ ). Families of youth with obesity or obesity had lower median income (\$50,000–\$74,000) than those with normal BMI (\$75,000–\$99,000), and lower parental education [Associate degree in these BMI groups compared Bachelor's degree in the entire cohort and those with normal BMI].

**Table 2.** Parameters of models testing associations between BMI status (comparing youth with obesity vs normal BMI, with overweight vs normal BMI and with obesity vs with overweight) and individual network properties.

Network	Parameter	Efficiency	Global Clustering	Med. Conn. (in)	Med. Conn. (out)	Modularity	Topological Robustness	Topological Stability
<b>A1. WITH OBESITY vs NORMAL BMI COHORTS: LEFT HEMISPHERE</b>								
Dorsal Attention	Beta for BMI status contrast	-0.069 to -0.045	-0.073 to -0.050	-0.096 to -0.049	-0.074 to -0.046	0.032-0.050	-0.062 to -0.041	-0.075 to -0.048
	P value	≤0.011	≤0.009	≤0.009	≤0.009	≤0.032	≤0.009	≤0.009
	Effect size	0.178 to 0.275	0.183 to 0.279	0.173 to 0.298	0.165 to 0.204	0.156 to 0.231	0.187 to 0.273	0.187 to 0.284
Salience/Ventral Attention	Beta for BMI status contrast	-0.081 to -0.070	-0.087 to -0.065	-0.078 to -0.062	-0.085 to -0.069	0.052-0.068	-0.078 to -0.058	-0.082 to -0.067
	P value	<0.001	<0.001	<0.001	<0.001	≤0.004	≤0.002	<0.001
	Cohen's d	0.152 to 0.261	0.137 to 0.245	0.100 to 0.177	0.071 to 0.156	0.136 to 0.241	0.143 to 0.202	0.142 to 0.251
Limbic	Beta for BMI status contrast	-0.079 to -0.054	-0.090 to -0.046					
	P value	≤0.016	≤0.029					
	Cohen's d	0.097 to 0.193	0.042 to 0.186					
Control	Beta for BMI status contrast	-0.086 to -0.070	-0.101 to -0.083	-0.115 to -0.085	-0.091 to -0.068	0.062-0.077	-0.088 to -0.065	-0.094 to -0.078
	P value	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001
	Cohen's d	0.210 to 0.309	0.243 to 0.332	0.248 to 0.358	0.145 to 0.205	0.178 to 0.257	0.216 to 0.296	0.228 to 0.311
Default	Beta for BMI status contrast	-0.078 to -0.053	-0.087 to -0.063	-0.096 to -0.074	-0.082 to -0.056	0.046 - 0.069	-0.081 to -0.051	-0.086 to -0.061
	P value	≤0.004	≤0.001	<0.001	≤0.002	≤0.009	≤0.004	≤0.001
	Cohen's d	0.176 to 0.311	0.205 to 0.329	0.241 to 0.336	0.108 to 0.197	0.135 to 0.283	0.164 to 0.329	0.185 to 0.336
Reward	Beta for BMI status contrast	-0.087 to -0.074	-0.095 to -0.075	-0.092 to -0.062	-0.094 to -0.074	0.045-0.059	-0.081 to -0.058	-0.082 to -0.065
	P value	<0.001	<0.001	≤0.001	<0.001	≤0.012	≤0.001	<0.001
	Cohen's d	0.172-0.270	0.167-0.258	0.119-0.228	0.132-0.219	0.085-0.165	0.122-0.237	0.144-0.234
Social	Beta for BMI status contrast	-0.084 to -0.065	-0.111 to -0.093	-0.106 to -0.087	-0.090 to -0.065			-0.090 to -0.061
	P value	<0.001	<0.001	<0.001	<0.001			≤0.001
	Cohen's d	0.149-0.273	0.227-0.323	0.181-0.288	0.171-0.249			0.148-0.238
<b>A2. WITH OBESITY vs NORMAL BMI COHORTS: RIGHT HEMISPHERE</b>								
Somatomotor	Beta for BMI status contrast	-0.058 to -0.047	-0.058 to -0.042	-0.050 to -0.034	-0.049 to -0.044		-0.051 to -0.038	-0.054 to -0.044
	P value	≤0.022	≤0.029	≤0.032	≤0.022		≤0.032	≤0.022
	Cohen's d	0.072 to 0.118	0.026 to 0.073	0.025 to 0.058	<0.001 to 0.035		0.025 to 0.073	0.022 to 0.061
Dorsal Attention	Beta for BMI status contrast	-0.070 to -0.046	-0.076 to -0.050	-0.077 to -0.051	-0.072 to -0.048		-0.059 to -0.036	-0.067 to -0.037
	P value	≤0.011	≤0.009	≤0.009	≤0.009		≤0.042	≤0.042
	Cohen's d	0.183 to 0.265	0.176 to 0.286	0.185 to 0.281	0.175 to 0.198		0.180 to 0.284	0.176 to 0.289
Salience/Ventral Attention	Beta for BMI status contrast	-0.101 to -0.078	-0.095 to -0.072	-0.077 to -0.060	-0.080 to -0.066	0.055-0.083	-0.095 to -0.067	-0.093 to -0.073
	P value	≤0.011	≤0.009	≤0.009	≤0.009		≤0.042	≤0.042
	Cohen's d	0.183 to 0.265	0.176 to 0.286	0.185 to 0.281	0.175 to 0.198		0.180 to 0.284	0.176 to 0.289



Table 2. continued

Network	Parameter	Efficiency	Global Clustering	Med. Conn. (in)	Med. Conn. (out)	Modularity	Topological Robustness	Topological Stability
Limbic	P value	<0.001	<0.001	≤0.001	<0.001	≤0.003	<0.001	<0.001
	Cohen's d	0.209 to 0.348	0.185 to 0.309	0.094 to 0.200	0.049 to 0.133	0.182 to 0.303	0.190 to 0.318	0.201 to 0.314
	Beta for BMI status contrast	-0.080 to -0.058	-0.082 to -0.064	-0.058 to -0.040				-0.072 to -0.059
Control	P value	≤0.002	≤0.002	≤0.030				≤0.002
	Cohen's d	0.090 to 0.183	0.063 to 0.157	0.037 to 0.104				0.052 to 0.122
	Beta for BMI status contrast	-0.110 to -0.063	-0.114 to -0.082	-0.109 to -0.080	-0.096 to -0.072	0.060-0.080	-0.095 to -0.070	-0.108 to -0.072
Default	P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Cohen's d	0.210 to 0.352	0.227 to 0.341	0.224 to 0.319	0.163 to 0.213	0.163 to 0.279	0.208 to 0.321	0.206 to 0.339
	Beta for BMI status contrast	-0.088 to -0.048	-0.091 to -0.068	-0.102 to -0.076	-0.075 to -0.054	0.039-0.080	-0.087 to -0.045	-0.090 to -0.054
Reward	P value	≤0.008	<0.001	<0.001	≤0.002	≤0.025	≤0.011	≤0.004
	Cohen's d	0.142 to 0.302	0.174 to 0.312	0.176 to 0.298	0.063 to 0.153	0.103 to 0.278	0.129 to 0.309	0.142 to 0.316
	Beta for BMI status contrast	-0.107 to -0.085	-0.109 to -0.095	-0.070 to -0.054	-0.083 to -0.069	0.044-0.073	-0.092 to -0.064	-0.091 to -0.070
Social	P value	<0.001	<0.001	≤0.002	<0.001	≤0.009	<0.001	<0.001
	Cohen's d	0.206 to 0.335	0.231 to 0.318	0.093 to 0.173	0.098 to 0.191	0.067 to 0.174	0.117 to 0.251	0.142 to 0.245
	Beta for BMI status contrast	-0.097 to -0.070	-0.115 to -0.096	-0.104 to -0.070	-0.074 to -0.064	0.054-0.073	-0.085 to -0.051	-0.092 to -0.080
Thalamic network	P value	<0.001	<0.001	<0.001	<0.001	≤0.002	≤0.004	<0.001
	Cohen's d	0.205 to 0.323	0.264 to 0.369	0.145 to 0.274	0.100 to 0.181	0.116-0.210	0.063 to 0.232	0.190 to 0.276
	Beta for BMI status contrast	-0.064 to -0.048	-0.056 to -0.051		-0.077 to -0.062			-0.066 to -0.048
SomatoMotor	P value	≤0.006	≤0.007	≤0.002	≤0.002			≤0.006
	Cohen's d	0.102-0.161	0.069-0.119		0.089-0.193			0.085-0.130
	Beta for BMI status contrast			-0.060 to -0.050	-0.054 to -0.042			
Dorsal Attention	P value			≤0.009	≤0.037			
	Cohen's d			0.054 to 0.095	0.045 to 0.059			
	Beta for BMI status contrast			-0.053 to -0.040	-0.063 to -0.049			
Saliency/Ventral Attention	P value			≤0.028	≤0.023			
	Cohen's d			0.085 to 0.117	0.106 to 0.135			
	Beta for BMI status contrast			-0.071 to -0.054	-0.076 to -0.058			
Control	P value	≤0.013	≤0.003	<0.001	<0.001		≤0.023	≤0.013
	Cohen's d	0.084 to 0.165	0.107 to 0.157	0.092 to 0.172	0.084 to 0.154		0.079 to 0.120	0.097 to 0.180
	Beta for BMI status contrast	-0.046 to -0.041	-0.068 to -0.051	-0.084 to -0.062	-0.077 to -0.061	0.041-0.052	-0.059 to -0.045	-0.063 to -0.053

Table 2. continued

Network	Parameter	Efficiency	Global Clustering	Med. Conn. (in)	Med. Conn. (out)	Modularity	Topological Robustness	Topological Stability
	Beta for BMI status contrast							
	P value	≤0.015	≤0.007	≤0.002	≤0.002	≤0.018	≤0.015	≤0.006
	Cohen's d	0.101 to 0.124	0.115 to 0.158	0.126 to 0.183	0.102 to 0.131	0.113–0.145	0.126 to 0.171	0.127 to 0.164
Default	Beta for BMI status contrast							
	P value	≤0.034	≤0.034	≤0.011	≤0.011	≤0.040	≤0.040	≤0.015
	Cohen's d	0.114 to 0.130	0.114 to 0.130	0.130 to 0.178	0.104 to 0.137	0.113 to 0.149	0.113 to 0.149	0.128 to 0.146
Reward	Beta for BMI status contrast							
	P value	≤0.017	≤0.005	≤0.005	≤0.002	≤0.048	≤0.012	≤0.008
	Cohen's d	0.090 to 0.132	0.105 to 0.171	0.133 to 0.182	0.143 to 0.185	0.067–0.095	0.111 to 0.130	0.107 to 0.134
Social	Beta for BMI status contrast							
	P value	≤0.049	≤0.004	≤0.002	≤0.004	≤0.034	≤0.034	≤0.020
	Cohen's d	0.074 to 0.120	0.091 to 0.178	0.118 to 0.181	0.120 to 0.154	0.057 to 0.143	0.057 to 0.143	0.099 to 0.132
B2. WITH OVERWEIGHT vs NORMAL BMI COHORTS: RIGHT HEMISPHERE								
Somatomotor	Beta for BMI status contrast							
	P value			–0.049 to –0.045	–0.057 to –0.051			
	Cohen's d			0.023	≤0.020			
Dorsal Attention	Beta for BMI status contrast							
	P value			0.023 to 0.054	0.061 to 0.080			
	Cohen's d			–0.065 to –0.050	–0.065 to –0.050			
Saliency/Ventral Attention	Beta for BMI status contrast							
	P value	≤0.003	≤0.001	≤0.001	<0.001	≤0.042	≤0.007	≤0.003
	Cohen's d	–0.062 to –0.056	–0.066 to –0.060	–0.072 to –0.059	–0.079 to –0.063	0.036–0.054	–0.063 to –0.049	–0.064 to –0.054
Limbic	Beta for BMI status contrast							
	P value	0.111 to 0.159	0.137 to 0.174	0.141 to 0.206	0.113 to 0.173	0.105 to 0.160	0.112–0.178	0.129 to 0.179
	Cohen's d	–0.058 to –0.043	–0.058 to –0.043					
Control	Beta for BMI status contrast							
	P value	≤0.019	≤0.003	≤0.001	≤0.001	≤0.019	≤0.033	≤0.008
	Cohen's d	–0.062 to –0.034	–0.082 to –0.061	–0.091 to –0.069	–0.094 to –0.068	0.044–0.055	–0.065 to –0.048	–0.073 to –0.051
Default	Beta for BMI status contrast							
	P value	≤0.017	<0.001	<0.001	<0.001	<0.004	≤0.002	≤0.001
	Cohen's d	0.086 to 0.145	0.140 to 0.189	0.152 to 0.224	0.127 to 0.204	0.104–0.138	0.121 to 0.165	0.121 to 0.170
	Cohen's d	–0.051 to –0.040	–0.061 to –0.053	–0.085 to –0.069	–0.076 to –0.061	0.038–0.053	–0.054 to –0.037	–0.057 to –0.049
	P value	≤0.019	≤0.003	≤0.001	≤0.001	≤0.019	≤0.033	≤0.008

Table 2. continued

Network	Parameter	Efficiency	Global Clustering	Med. Conn. (in)	Med. Conn. (out)	Modularity	Topological Robustness	Topological Stability
Reward	Cohen's d	0.097 to 0.132	0.126 to 0.164	0.174 to 0.204	0.142 to 0.170	0.092 to 0.130	0.102 to 0.147	0.113 to 0.145
	Beta for BMI status contrast	-0.071 to -0.057	-0.091 to -0.068	-0.079 to -0.054	-0.080 to -0.068	0.040-0.052	-0.071 to -0.055	-0.075 to -0.057
	P value	≤0.002	<0.001	≤0.002	<0.001	≤0.021	≤0.002	≤0.002
Social	Cohen's d	0.124 to 0.180	0.138 to 0.222	0.138 to 0.209	0.168 to 0.204	0.069-0.142	0.103 to 0.183	0.116 to 0.196
	Beta for BMI status contrast	-0.063 to -0.052	-0.077 to -0.064	-0.085 to -0.057	-0.081 to -0.064	0.047 - 0.059	-0.058 to -0.036	-0.078 to -0.063
	P value	≤0.002	<0.001	<0.001	<0.001	≤0.004	≤0.018	<0.001
C1. WITH OBESITY vs WITH OVERWEIGHT BMI COHORTS: LEFT HEMISPHERE	Cohen's d	0.125 to 0.175	0.107 to 0.192	0.112 to 0.200	0.151 to 0.186	0.099 to 0.161	0.057 to 0.143	0.131 to 0.202
	Beta for BMI status contrast	-0.048 to -0.038	-0.054 to -0.040				-0.045 to -0.037	-0.049 to -0.041
	P value	≤0.021	≤0.029				≤0.042	≤0.019
Central Visual	Cohen's d	0.133-0.177	0.135-0.192				0.134 to 0.178	0.164 to 0.187

All reported p values have been adjusted for the False Discovery Rate. Results are based on all 4 analyzed datasets, and thus ranges of statistics are provided. Effect sizes were estimated using Cohen's d.

Participants with obesity or overweight were on average less physically active (3 days/week), had longer weekly screen time (median = 1170.0 (IQR = 930.0) min/week, and 1230.0 (IQR = 1020.0) min/week, respectively) and slept less (median = 8-9 h, IQR = 1-2 h) compared to those with normal BMI, who were on average active 4 days/week (IQR = 3 days), had shorter screen time (median = 960.0 (IQR = 810.0) min/week), and slept on average 9-11 hours/night (IQR = 1-2 h),  $p < 0.01$ . Also, proportionally, more youth with obesity snored more than twice/week (12.35%). Depression and anxiety have been associated with excess BMI in youth [13, 19, 106], but their prevalence did not differ significantly between BMI groups (7.31% of those normal BMI, 8.97% of those with overweight, and 8.78% of those with obesity reported current/past depression,  $p \geq 0.12$ ; 30.65%, 27.58% and 29.46% reported anxiety,  $p \geq 0.10$ ). However, statistically more youth with overweight (3.67%) and obesity (8.04%) reported lower self-worth tied to weight (1.22%;  $p < 0.01$ ).

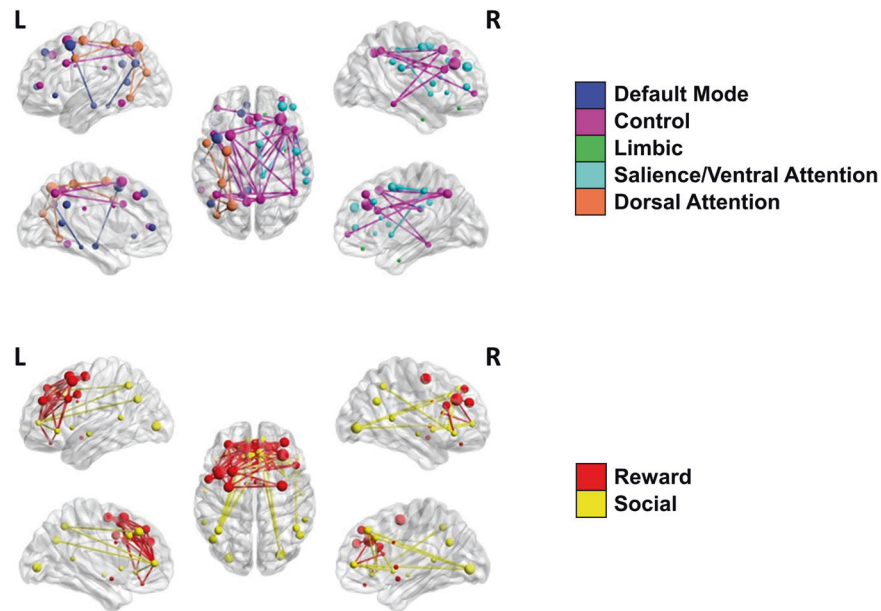
**Associations between BMI status and functional network properties**

*Whole-brain connectome.* Youth with obesity had significantly lower connectome efficiency, clustering, median connectivity, topological robustness and stability ( $p < 0.01$ , Wald Statistic  $\geq 8.18$ ), compared to those with normal BMI. Obesity was also associated with increased modularity ( $p \leq 0.01$ , Wald Statistic  $\geq 7.22$ ), potentially a developmentally aberrant rather than BMI effect [88]. These inverse associations were moderated by sleep duration and race. Similar topological differences were estimated in youth with overweight ( $p < 0.02$ ), although the effects were smaller and the association with modularity was nonsignificant. These results are summarized in Table S2. There were no statistical connectome differences between youth with overweight versus those with obesity ( $p > 0.1$ ).

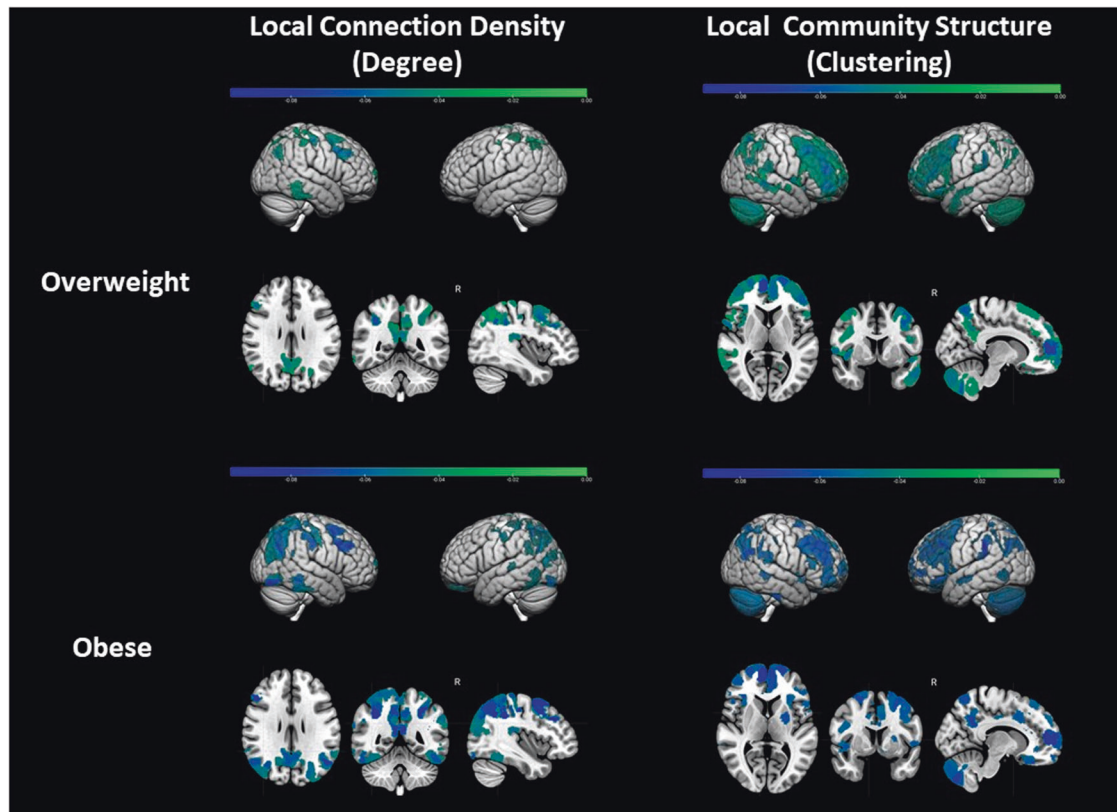
Within racial groups, white youth with obesity had lower connectome efficiency and global clustering compared to white youth with normal BMI ( $p \leq 0.01$ , Wald statistic  $\geq 8.43$ ). Nonwhite youth with obesity had more extensive connectome changes compared to those with normal BMI (in efficiency, global clustering, modularity, topological robustness and stability;  $p \leq 0.03$ , Wald statistic  $\geq 4.95$ ). Similarly, within the group that obtained the recommended amount of sleep, those with obesity have lower connectome efficiency and global clustering ( $p \leq 0.03$ , Wald statistic  $\geq 6.92$ ) compared to those with normal BMI. Within the group that obtained less than recommended sleep, those with obesity had more extensive connectome alterations than those with normal BMI (in efficiency, global clustering, modularity, topological robustness and stability;  $p < 0.01$ , Wald statistic  $\geq 7.41$ ). The effects of obesity on functional network properties in these separate groups were overall small (Cohen's  $d = 0.13 - 0.21$ ). Furthermore, being Black statistically moderated the relationship between obesity and topological changes, but the effects were overall small (Cohen's  $d < 0.10$ ). These results are summarized in Table S3. The impact of ethnicity was nonsignificant ( $p > 0.05$ ). In youth with overweight, similar but less extensive topological changes were estimated, which were, however, independent of race and ethnicity ( $p > 0.1$ ). No statistical differences were found between youth with overweight vs obesity across all 4 datasets. Lower connectome efficiency in those with obesity vs overweight was estimated in 3 of 4 datasets ( $p < 0.05$ , Wald statistic = 7.34). Finally, significant negative relationships between BMI as a continuous variable and whole-brain connectome properties were also estimated, and were consistent across representations of BMI (actual, %BMI, z-score and z-score stratified by sex). These results are summarized in Table S4.

*Individual resting-state networks.* Extensive topological differences, including lower efficiency, clustering, connectivity and robustness, were estimated between youth with obesity and those





**Fig. 1 Network plots showing regions and connections that are correlated with excess BMI (with overweight or obesity) relative to normal BMI.** Plots show the differential median (across the cohort) connectedness of affected network regions (indicated by the size of the circles/network nodes), as well as consistent edges across participants, corresponding to the strongest inter-region connections (based on a conservative connectivity threshold). The top panel shows associations in the Default Mode, frontoparietal control, limbic, salience/ventral, and dorsal attention networks. The bottom panel shows associations in the social (yellow) and reward (red) networks.



**Fig. 2 Significant negative correlations between BMI status (with overweight—top plot, with obesity—bottom plot), relative to normal BMI, and regional node properties, including node degree and clustering.** Color bars represent the range of standardized regression coefficient values in statistical models used to assess these correlations. Three-dimensional views of both hemispheres, and two-dimensional coronal, horizontal, and sagittal slices are shown.

**Table 3.** Parameters of models testing associations between BMI status and cortical thickness, cortical volume and white matter intensity.

Brain region	Standardized Regression coefficient (beta)	Cohen's d	SE	Wald	P Value
WITH OBESITY vs NORMAL BMI COHORTS					
Cortical Thickness: Left Hemisphere					
Entorhinal cortex/parahippocampal gyrus	-0.043	0.164	0.006	6.093	0.034
Lateral orbitofrontal cortex	-0.066	0.203	0.004	14.429	0.001
Pars orbitalis	-0.054	0.169	0.004	9.235	0.009
Rostral middle frontal gyrus	-0.053	0.165	0.003	8.866	0.009
Superior frontal gyrus	-0.054	0.149	0.003	9.499	0.006
Superior temporal gyrus	-0.059	0.194	0.005	11.214	0.004
Frontal pole	-0.065	0.136	0.006	13.763	0.001
Temporal pole	-0.058	0.151	0.006	10.772	0.002
Cortical Thickness: Right Hemisphere					
Caudal anterior cingulate	-0.089	0.282	0.003	26.192	<0.001
Lateral orbitofrontal cortex	-0.091	0.206	0.004	26.536	<0.001
Lingual gyrus	-0.050	0.264	0.003	8.532	0.011
Medial orbitofrontal cortex	-0.074	0.172	0.003	17.383	<0.001
Pars orbitalis	-0.065	0.206	0.004	14.009	0.001
Rostral middle frontal gyrus	-0.105	0.296	0.003	35.954	<0.001
Superior frontal gyrus	-0.073	0.182	0.003	17.007	<0.001
Frontal pole	-0.091	0.288	0.004	26.536	<0.001
Cortical Volume: Left Hemisphere					
None					
Cortical Volume: Right Hemisphere					
Isthmus division of cingulate cortex	0.052	0.052	0.006	9.123	0.036
White Matter Intensity: Left Hemisphere					
Lateral occipital cortex	-0.109	0.302	0.045	39.122	<0.001
White Matter Intensity: Right Hemisphere					
Lateral occipital cortex	-0.052	0.184	0.044	8.895	0.023
Frontal pole	0.056	0.183	0.055	10.330	0.015
WITH OVERWEIGHT vs NORMAL BMI COHORTS					
Cortical Thickness: Left Hemisphere					
Entorhinal cortex /parahippocampal gyrus	-0.053	0.200	0.005	9.195	0.023
Lateral orbitofrontal cortex	-0.067	0.207	0.003	14.992	<0.001
Rostral middle frontal gyrus	-0.063	0.209	0.002	12.825	0.001
Frontal pole	-0.070	0.154	0.004	16.175	<0.001
Temporal pole	-0.047	0.139	0.006	7.133	0.010
Cortical Thickness: Right Hemisphere					
Caudal anterior cingulate	-0.063	0.180	0.003	13.121	0.001
Entorhinal cortex /parahippocampal gyrus	-0.057	0.218	0.007	10.639	0.008
Inferior temporal gyrus	-0.047	0.162	0.004	7.395	0.018
Lateral orbitofrontal cortex	-0.067	0.174	0.004	14.614	<0.001
Pars orbitalis	-0.062	0.148	0.004	12.898	0.002
Rostral middle frontal gyrus	-0.089	0.225	0.002	25.882	<0.001
Superior frontal gyrus	-0.058	0.141	0.003	11.047	0.003
Cortical Volume: Left Hemisphere					
Isthmus division of cingulate cortex	0.052	0.117	0.006	10.086	0.023
Cortical Volume: Right Hemisphere					
None					
White Matter Intensity: Left Hemisphere					
Lateral occipital cortex	-0.098	0.221	0.043	31.91	<0.001
Right Hemisphere					
Lateral occipital cortex	-0.062	0.189	0.042	12.599	0.003

**Table 3.** continued

Brain region	Standardized Regression coefficient (beta)	Cohen's d	SE	Wald	P Value
WITH OBESITY vs WITH OVERWEIGHT COHORTS					
Cortical Thickness: Left and Right Hemisphere					
None					
Cortical Volume: Left Hemisphere					
None					
Cortical Volume: Right Hemisphere					
Paracentral lobule	-0.051	0.197	0.003	9.330	0.011
White Matter Intensity: Left and Right Hemispheres					
None					

Multiple structures from the higher-resolution Destrieux parcellation were mapped onto the the larger regions of the Desikan-Killiany parcellation. All *p* values have been adjusted for FDR. Since models were tested separately for brain regions parcellated based on the Destrieux atlas, and several of these parcels (regions) were mapped onto the larger brain areas in the Desikan-Killiany atlas, the statistics reported in the table are for the brain region-specific model with the largest absolute standardized regression coefficient for BMI status. All effect sizes were estimated using Cohen's *d*.

with normal BMI, in bilateral dorsal and ventral attention, control, DM, reward, and social networks ( $p \leq 0.04$ ). Lower efficiency and clustering was estimated bilaterally also in the limbic network and the thalamic network (thalamus and hypothalamus;  $p \leq 0.03$ ), and lower median connectivity between the thalamic network and the rest of the brain ( $p < 0.01$ ). Topological differences were also estimated in the right somatomotor network ( $p \leq 0.03$ ). The effects of obesity were overall small to medium (Cohen's  $d \leq 0.37$ ).

Similar differences were estimated between youth with overweight and those with normal BMI in most of the same networks. The extent of altered properties was, however, more limited. No topological differences in the thalamic network were estimated. The effects of overweight were overall small (Cohen's  $d \leq 0.22$ ). When youth with overweight were compared to those with obesity, the only statistical difference was estimated in the left visual network ( $p \leq 0.04$ ). The effects of obesity relative to overweight were small (Cohen's  $d \leq 0.19$ ). All network results are summarized in Table 2 and Fig. 1, which shows functional networks and regions that differed topologically in youth with obesity or overweight relative to those with normal BMI. Associations between BMI status and individual network properties were also examined in race-, ethnicity- and sleep-based subcohorts. Similar differences to those identified in the entire cohort were estimated in these subcohorts ( $p < 0.05$ ).

**Individual brain regions.** Spatially distributed differences in local topological properties were estimated both in youth with obesity and overweight. Lower local clustering and connectedness (node degree) were estimated bilaterally in prefrontal (and orbitofrontal) cortex, elements of the DMN, frontoparietal control, dorsal attention, limbic network and salience networks, and the cerebellum. Several of these regions also overlapped with elements of the social and reward networks. Local connectedness differences were more extensive in youth with obesity, and the negative effects of excess BMI on both regional clustering and connectedness were on average twice as large in this group compared to youth with overweight. These results are summarized in Fig. 2. Model regression coefficients for regional properties that were correlated with BMI status are shown separately for those with obesity and overweight.

#### Associations between BMI status and structural brain properties

Distributed morphological differences across the parietal, temporal, frontal and cingulate cortices were estimated between participants with excess BMI and those with normal BMI. Having obesity was associated with lower cortical thickness in left entorhinal cortex/parahippocampal gyrus,

bilaterally in lateral orbitofrontal cortex, middle and superior frontal gyrus and frontal pole, right medial orbitofrontal cortex, right lingual gyrus, left pars orbitalis, left superior temporal gyrus, and left temporal pole ( $p < 0.04$ , Cohen's  $d < 0.30$ ). Higher cortical volume in youth with obesity compared to those with normal BMI was estimated in the right isthmus division of the cingulate cortex ( $p = 0.05$ , Cohen's  $d = 0.05$ ), lower white matter intensity was estimated bilaterally in lateral occipital cortex ( $p \leq 0.02$ , Cohen's  $d \leq 0.30$ ), and higher white matter intensity was estimated in right frontal pole ( $p = 0.01$ , Cohen's  $d = 0.18$ ). Similar morphological differences were identified between youth with overweight (but not obesity) compared to those with normal BMI, in almost all the same brain structures, with the exception of lateral (only right hemisphere) differences in cortical thickness of pars orbitalis and superior frontal gyrus, no difference in left superior temporal gyrus, right medial orbitofrontal cortex or lingual gyrus, but additional differences in right entorhinal cortex/parahippocampal gyrus and right inferior temporal gyrus ( $p \leq 0.02$ , Cohen's  $d \leq 0.23$ ). Similarly to those with obesity, youth with overweight had higher cortical volume in the isthmus division of the cingulate cortex (however in the left instead of the right hemisphere), and lower white matter intensity bilaterally in lateral occipital cortex ( $p \leq 0.02$ , Cohen's  $d \leq 0.22$ ). When youth with obesity were compared to overweight, the only significant difference was lower cortical volume of the paracentral lobule (the posterior extent of the superior frontal gyrus) in the frontal lobe ( $p = 0.01$ , Cohen's  $d = 0.20$ ). Model statistics for these analyses are summarized in Table 3.

#### Associations between BMI, brain structure and local functional network properties

Relationships between continuous measures of BMI (raw, z-score and %mBMI), morphometric properties of individual brain regions and local functional network properties in these regions (centrality, node degree and local clustering) were also investigated, and potential mediating effects of structural alterations on the relationship between BMI and functional network properties were assessed. Statistically similar results were obtained for all BMI measures. Changes in cortical thickness of left lateral orbitofrontal cortical cortex mediated the negative relationship between BMI and node centrality in this region ( $p < 0.01$ , Sobel's test statistic = 2.86), and bilateral changes in white matter intensity of lateral occipital cortex mediated the negative relationship between BMI and local clustering in this region ( $p < 0.02$ , Sobel's test statistic  $\geq 2.38$ ). Changes in white matter intensity of right lateral occipital cortex also mediated the negative relationship between BMI and node degree in this region ( $p < 0.04$ , Sobel's test statistic = 2.02).

**Table 4.** Statistics of models testing associations between BMI status and cognitive task performance.

Cognitive task	Standardized regression coefficient ( $\beta$ )	Cohen's <i>d</i>	Standard error (SE)	<i>P</i> value	Wald statistic
With Overweight vs Normal BMI (excluding youth with obese): <i>N</i> = 4250					
Matrix reasoning task	-0.042	0.253	0.122	0.041	6.791
With Obesity vs Normal BMI (excluding youth with overweight): <i>N</i> = 4186					
Matrix reasoning tas	-0.062	0.355	0.128	0.001	14.28

### Associations between BMI status and cognitive task performance

Cognitive performance across tasks was compared between BMI groups, in both the cohorts in R2 and R4 data releases. When youth with overweight or normal BMI were compared (i.e., excluding those with obesity), and similarly for those with obesity versus normal BMI (i.e., excluding those with overweight), participants with excess BMI (with overweight or obesity) had lower scores in the Matrix Reasoning Task, which measures nonverbal/fluid reasoning, visuospatial ability and attention, and perceptual organization ( $p \leq 0.04$ , Wald statistic  $\geq 6.79$ ). No statistical differences in task performance were identified between youth with obesity and overweight ( $p > 0.05$ ). These results are summarized in Table 4. For the Martix Reasoning Task, associations between performance and topological network properties were also examined. There were significant positive associations between task performance and within-network connectivity and clustering in the right frontoparietal control (for the entire cohort;  $p = 0.04$ ), and similarly in the left temporoparietal network (when comparing overweight to normal BMI;  $p = 0.03$ ).

### DISCUSSION

In a historically large sample of almost 5000 early adolescents, using advanced computational techniques and multimodal data, this study investigated the relationship between excess BMI, the topological organization of developing resting-state networks, related alterations in these networks' constituent brain structures, and their cognitive correlates. Statistically more Hispanic participants and those from racial minority groups (with the exception of Asian) had overweight or obesity compared to white, Asian and non-Hispanic youth, in agreement with prior reports on racial and ethnic BMI disparities in children [107, 108]. Youth with overweight or obesity were less physically active, obtained less than recommended sleep for their age, snored more frequently, and spent more time using an electronic device. Similar correlations between screen time, sleep disturbances, lack of physical activity and BMI have been previously reported [58, 88, 90, 109–112]. Also, statistically more participants with excess BMI had lower-self worth tied to weight, in agreement with prior reports on BMI-related body image and self-worth issues [11, 16, 31].

A significant finding of this study is that across scales of spatial organization in the brain, youth with obesity and overweight had similar alterations in topological network properties, compared to those with normal BMI. In youth with overweight they were, however, more limited in spatial extent and number of affected properties, but were nonetheless significant in both groups even after adjusting for sleep quantity, physical activity, and screen time. These alterations were confirmed across datasets. They included lower network efficiency, which adversely impacts how rapidly information is processed through the brain, lower global and local clustering and connectedness, which adversely affect the brain's ability to perform computations in functionally specialized regions, and lower topological robustness, thus higher vulnerability to the negative effects stressors and risk factors. Prior studies have suggested that adiposity-related metabolic dysfunction and aberrant signaling may adversely impact the brain's vulnerability [113]. Metabolic and neuroinflammatory effects of

excess BMI may partly explain the estimated connectome-wide (and thus cognitive domain-independent) topological changes [114]. The implications of the identified effects on the entire developing connectome suggest that excess BMI may have global effects on the developing brain. Lower brain-wide efficiency of information processing and communication between brain regions, and impaired ability to perform domain-specific computations in locally connected networks may have ubiquitous adverse effects across cognitive domains and processes. In addition, increased topological vulnerability in the developing brain is also associated with increased likelihood of miswiring of incompletely matured circuits, leading to both cognitive deficits and mental health issues across the lifespan.

Extensive topological differences were also estimated in domain-specific functional networks, including attention, cognitive control, limbic, salience, reward, social and DM networks in youth with obesity and overweight relative to those normal BMI. Prior work has specifically identified obesity-related aberrant structural and functional connectivity, including in salience and reward networks [54, 55, 61, 62, 67, 68]. Prior diffusion MRI studies have also reported changes in structural network properties, such as lower clustering coefficient, in youth with obesity [59]. Results from the present large study provide important new insights into similar functional topological changes not only in youth with obesity but also in those with overweight. In addition, multiple morphological BMI-related alterations were identified in structures that are part of the reward network, including lower cortical thickness in entorhinal, anterior cingulate and prefrontal cortices. Aberrant modulations of the topological properties of large-scale networks, particularly the DM, may adversely impact cognitive processing across domains, since the DM plays a ubiquitous role in cognitive function [115, 116]. Aberrant changes in limbic, reward and salience networks in adolescence may have implications for addictive food behaviors, food reward processing and impaired control of food intake, not only in this period but also in adulthood [63, 67, 117–119].

Regional BMI-related modulations of functional network properties were also identified. Lower posterior regional connectedness and lower local community structure were estimated in extensive frontoparietal (including prefrontal and orbitofrontal) regions. Inverse correlations between BMI status and regional topologies were higher in youth with obesity compared to overweight. A prior study on the ABCD cohort has also associated high BMI with lower cortical thickness in prefrontal areas [120], which may, in turn, explain the identified functional network differences in these areas. In the present study' cohort, widespread morphological differences were identified between youth with obesity or overweight compared to those with normal BMI, including lower cortical thickness in multiple frontal structures bilaterally, including lateral orbitofrontal cortex, frontal pole, superior frontal gyrus, the rostral part of the middle frontal gyrus, and pars orbitalis. In addition, lower white matter intensity was estimated bilaterally in lateral occipital cortex, which may be correlated with aberrant connectedness in these areas, and is also coupled to both the DM and frontoparietal control networks in perception. Finally, higher white matter intensity was estimated in the right anterior prefrontal cortex of participants with obesity but not overweight. Prior work in adults has also linked obesity with white matter



hyperintensities in frontal regions (particularly orbitofrontal cortex) [121]. Their occurrence in pre/early adolescents is of significant concern, given that frontal areas undergo extensive reorganization throughout adolescence to support complex high-level function, including executive control, social function and decision-making.

Mediation analyses identified statistical relationships between BMI, structural changes and alterations in local functional network properties as well. Specifically, lower cortical thickness of left lateral orbitofrontal cortex mediated the negative association between BMI and local regional importance (average node centrality). Also, bilateral lower white matter intensity of lateral occipital cortex mediated the negative relationship between BMI and local clustering in this region. Changes in white matter intensity of right lateral occipital cortex also mediated the negative relationship between BMI and local connectedness (node degree) in this region. These results suggest that BMI also indirectly impacts functional network architecture, through its negative impact on morphological properties of underlying structures.

An inverse association between obesity (but not overweight) and cortico-thalamic (thalamus and hypothalamus) connectivity was also estimated. The hypothalamus plays a critical role in regulating body weight, and changes in this structure, including decreased connections with cortical regions have been reported in obese adults and children [122–124]. Prior neuroimaging studies (including in the ABCD cohort) have suggested neuroinflammation in these structures in children with or at risk of obesity as another mechanism through which excess BMI could impact cognitive function [124].

A substantial body of work has linked obesity to cognitive deficits across domains [21–24, 32, 35, 39, 44, 47, 48, 50, 125], which could be in part explained by the extent of identified functional network changes in this study. Associations between BMI and cognitive task performance were also examined. Relative to those with normal BMI, youth with overweight or obesity performed worse in the Matrix Reasoning Task, which measures fluid reasoning and visuospatial ability and attention [126]. Fluid reasoning is a core aspect of cognitive function, and its development serves as the foundation for the acquisition of other cognitive skills and academic achievement [127, 128]. Given negative associations between topological efficiency and community organization (clustering), both across the entire brain and in networks playing a critical role in cognition across domains (such as the DMN), these results are not surprising and are in agreement with those of prior work in the ABCD cohort [120].

Despite its many strengths, the study also has some limitations. First, nutrition, genetic information and family history of excess BMI were not available at the baseline assessment of the ABCD study. These data could provide valuable insights into causal factors impacting BMI as well as developing brain circuits. Second, the study focused on resting-state rather than task-activated networks, and neurocognitive data were collected independently of neuroimaging. However, the investigated networks represent fundamental neural circuitry that supports cognitive function across domains. Thus, their organization at rest provides valuable information on their baseline topology. A future study could examine correlations between BMI-impacted circuits, such as the reward network, and task performance assessing reward processing and related (e.g. monetary) decision-making.

This study makes a significant novel contribution to the field's incomplete understanding of the effects of excess BMI on the brain's developing circuits. Its primary finding, which has significant clinical implications, is that not only obesity but also overweight may have similar widespread detrimental effects on developing neural circuits, the morphology of their underlying brain structures, and the cognitive processes they support. A second major finding is that aberrant anatomical and

topological alterations associated with excess BMI in youth with obesity or overweight occur across spatial scales of organization in the developing brain, from the entire connectome to individual large-scale networks involved in multiple aspects of cognition, to local changes in individual structures and circuits that may affect domain-specific information processing. In turn, these alterations may disrupt normal neural maturation, with potentially serious negative implications for long-term cognitive health. Finally, a third important finding is that youth with obesity or overweight performed worse than those with normal BMI in a task measuring fluid reasoning, a core aspect of cognitive function that affects other high-level cognitive processes, which continue to develop during adolescence. These differences in performance may reflect the identified large-scale negative effects of excess BMI on the brain's circuitry, i.e., across the entire connectome and networks such as the DMN, which play a ubiquitous role in cognitive function. These findings are based on a large sample that captures the heterogeneity of typical brain development and were reproduced across datasets. They provide strong evidence of detrimental effects of unhealthy excess BMI on brain development, which could be leveraged to raise societal awareness and implement critical new policies to combat the childhood weight epidemic in the US.

#### DATA AVAILABILITY

All analyzed data are publicly available through the National Institute of Mental Health Data Archive (NDA) <https://nda.nih.gov/>. All computer codes associated with neuroimaging data analyses are part of the publicly shared Next-Generation Neural Data Analysis-NGNDA <https://github.com/cstamoulis1/Next-Generation-Neural-Data-Analysis-NGNDA> platform. Codes associated with statistical analyses are available in: <https://github.com/cstamoulis1/Brain-BMI-Analyses.git>.

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### AUTHOR CONTRIBUTIONS

CS<sub>t</sub> conceived and designed the study. SB and CS<sub>m</sub> conducted the data analyses. All three authors wrote, reviewed and approved the manuscript.

### COMPETING INTERESTS

The authors declare no competing interests.

### ADDITIONAL INFORMATION

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**Correspondence** and requests for materials should be addressed to Catherine Stamoulis.

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