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Original Article

Obesity is associated with decreased gray matter volume in children: a longitudinal study

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Childhood obesity has become a global health problem. Previous studies showed that childhood obesity is associated with brain structural differences relative to controls. However, few studies have been performed with longitudinal evaluations of brain structural developmental trajectories in childhood obesity. We employed voxel-based morphometry (VBM) analysis to assess gray matter (GM) volume at baseline and 2-year follow-up in 258 obese children (OB) and 265 normal weight children (NW), recruited as part of the National Institutes of Health Adolescent Brain and Cognitive Development study. Significant group × time effects on GM volume were observed in the prefrontal lobe, thalamus, right precentral gyrus, caudate, and parahippocampal gyrus/amygdala. OB compared with NW had greater reductions in GM volume in these regions over the 2-year period. Body mass index (BMI) was negatively correlated with GM volume in prefrontal lobe and with matrix reasoning ability at baseline and 2-year follow-up. In OB, Picture Test was positively correlated with GM volume in the left orbital region of the inferior frontal gyrus (OFCinf_L) at baseline and was negatively correlated with reductions in OFCinf_L volume (2-year follow-up vs. baseline). These findings indicate that childhood obesity is associated with GM volume reduction in regions involved with reward evaluation, executive function, and cognitive performance.

Key words: ABCD; childhood obesity; executive function; gray matter volume; prefrontal lobe.

Introduction

Overweight and obesity in children and adolescents has become a serious global health problem (Gonzalez-Alvarez et al. 2020). The World Health Organization (WHO) reported that over 340 million children and adolescents aged 5–19 were overweight or obese in 2016 (WHO Obesity and Overweight 2021, https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight). Childhood obesity not only leads to musculoskeletal, respiratory, and digestive diseases, but also results in psychological problems such as depression, social marginalization, and lack of self-confidence (Pont et al. 2017; Sarokhani et al. 2020). Thus, mental and physical health problems associated with childhood obesity continue into adulthood, increasing the risk of ill health throughout the lifespan (Singh et al. 2008).

A number of studies reported that childhood obesity is associated with executive dysfunction (Maayan et al. 2011; Reinert et al. 2013; Liang et al. 2014; Yau et al. 2014; Laurent et al. 2020; Ronan et al. 2020), including inhibitory-control, attention, working memory, and reward sensitivity. Children with higher BMI had poorer cognitive performance than their lean counterparts (Liang et al. 2014; Laurent et al. 2020; Ronan et al. 2020), which had a large impact on food-intake, decision-making, response inhibition, and reward evaluation (Gluck et al. 2017). Functional magnetic resonance imaging studies demonstrated differences in activation in the dorsolateral prefrontal cortex in both adults and children with obesity (Le et al. 2006; Davids et al. 2010; Reinert et al. 2013). The orbitofrontal cortex (OFC) is also closely linked to obesity, and its activity was involved in decision making and emotional modulation (Rudebeck and Rich 2018). Differences in OFC activation during food cue exposure were observed between children/adolescents with obesity and normal weight (Batterink et al. 2010; Bruce et al. 2010; Stice et al. 2010).

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Recently, a growing number of structural magnetic resonance imaging (sMRI) studies showed structural alterations in regions involved in executive function in obese children (Maayan et al. 2011; Saute et al. 2018; Laurent et al. 2020; Ronan et al. 2020). However, differences in sample size, statistical testing, sample population characteristics, and MRI metrics have led to mixed results. sMRI studies reported that obese children performed worse in working memory tasks than lean children and had lower cortical volume (Maayan et al. 2011) and cortical thickness (Saute et al. 2018) in the OFC, which was associated with BMI and visceral fat, respectively. Several recent studies based on the Adolescent Brain and Cognitive Development (ABCD) dataset reported that higher BMI was associated with lower prefrontal cortical thickness and executive function (Laurent et al. 2020; Ronan et al. 2020), and the decreased cortical thickness mediated the relationship between childhood obesity and impaired executive function. BMI also partially mediated the relationship between area deprivation index (ADI) and both cortical volume and executive function (Dennis et al. 2022). An increasing number of studies have highlighted the important role of the reward system including nucleus accumbens, caudate, putamen, and thalamus and emotion system including amygdala and hippocampus in weight regulation (Holsen et al. 2005; Holsen et al. 2006; Stoeckel et al. 2008; Stoeckel et al. 2009; Orsi et al. 2011). Other studies have demonstrated that higher BMI was associated with lower gray matter (GM) volume in the hippocampus, amygdala, caudate, and thalamus compared with normal weight controls (Orsi et al. 2011; Kirouac 2015). However, these studies were conducted cross-sectionally; few studies have been performed longitudinal evaluations of brain developmental trajectories in obese children.

The current study aimed to explore brain structural changes in obese children longitudinally by using the ABCD dataset, which includes sMRI data of both baseline and 2-year follow-up. Voxel-based morphometry (VBM) analysis was employed to assess differences in GM volume between 258 obese children (OB) and 265 normal weight children (NW). We hypothesized that the development of childhood obesity would be associated with differential developmental trajectories of GM volume in regions involved with executive function and reward processing.

Materials and methods

Participants

The current longitudinal study used data from the ABCD study (release 3.0; https://abcdstudy.org/), which was designed to prospectively examine the impact of childhood experiences on brain development and evaluate how these experiences are associated with social, emotional, and physical health and the development of risky behaviors and substance use. More than eleven thousand 9–10 years old children were recruited at 21 US sites and will be followed over the course of 10 years (Jernigan et al. 2018). Children are extensively assessed with measures of mental health, cognitive function, and social, cultural, and physical environments (Laurent et al. 2020). The assessments included structural and functional MRI using a standardized multi-site protocol (Casey et al. 2018). Analyses were conducted on data from the ABCD study (release 3.0), which included 11 787 children at baseline, 11 158 children at 1-year follow-up and 6546 children at 2-year follow-up (Supplementary Fig. 1). We excluded children with a current or past diagnosis of attention deficit/hyperactivity disorder, type 1 or type 2 diabetes, lead exposure, muscular dystrophy, history of traumatic brain injury, gestational age younger than 28 weeks and a BMI <10 or >45. The BMI percentiles for age and sex were used to classify individuals as underweight (i.e. < 5%), within acceptable limits (i.e. 5–85%), overweight (i.e. 85–95%), and obese (i.e. ≥95%) (CDC Growth Charts 2018, https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm). Subjects who were obese at both baseline and 2-year follow-up were included in the OB group ($n = 258$, female 48.4%). Similarly, age-, gender-, race/ethnicity-, parental education-, household income-, site-matched NW subjects were included ($n = 265$, female 47.2%, Table 1).

MRI acquisition

Subjects received an MRI scan at baseline, and an identical MRI scan was conducted at the 2-year follow-up. sMRI data were acquired using a protocol optimized for 3 T scanners (including Siemens, General Electric, and Philips). Whole-brain coverage was achieved using isotropic voxel resolution of $1 \times 1 \times 1$ mm^3, 256×256 matrix, repetition time of 2400–2500 ms, echo time of 2–2.9 ms, flip angle of 8°, inversion time of 1060 ms, 176–225 sections, field of view of 256×240 to 256, field of view phase of 93.75–100%, and parallel imaging of 1.5×2.2. Due to different parameters, the total acquisition time ranged from 5 min 38 s to 7 min 12 s (Casey et al. 2018).

Executive functions

All subjects were required to complete the National Institutes of Health (NIH) toolbox Cognitive measures (including baseline and 2-year follow-up) (Luciana et al. 2018), Cash Choice Task (CCT, including baseline) (Wulfert et al. 2002), Game of Dice Task (GDT, including 2-year follow-up) (Brand et al. 2005), and Matrix Reasoning Task (including baseline). Flanker Inhibitory-control and Attention (Flanker), Pattern Comparison Processing Speed (Pattern), Picture Sequence Memory (Picture), Oral Reading Recognition (Reading), Picture Vocabulary (Picvocab) and Crystallized Composite (Cryst) NIH toolbox Cognitive measures were included in the analysis. The raw scores were corrected for age to yield a final age-corrected score.

Table 1. Demographic and clinical information of obese (OB) and normal weight (NW) participants.

	OB, $N = 258$ (mean ± SE)			NW, $n = 265$ (mean ± SE)			OB_1 vs. NW_1	OB_2 vs. NW_2	Time × Group effect
	Baseline	2-Year	*P* value	Baseline	2-Year	*P* value	*P* value	*P* value	*P* value
Age (months)	119.5 ± 0.5	143.2 ± 0.5	<0.001	119.1 ± 0.4	142.8 ± 0.4	<0.001	0.456	0.501	0.819
Gender (F/M)	125/133	125/133	N/A	125/140	125/140	N/A	0.770[a]	0.770[a]	N/A
BMI (kg/m^2)	26.5 ± 0.2	30.0 ± 0.3	<0.001	16.8 ± 0.1	18.1 ± 0.1	<0.001	<0.001	<0.001	<0.001
ICV (cm^3)	1495.0 ± 10.3	1521.1 ± 10.4	<0.001	1483.1 ± 9.1	1513.7 ± 9.3	<0.001	0.387	0.594	0.148
Race/Ethnicity									
White	39.1%	39.1%	N/A	38.9%	38.9%	N/A	0.809[a]	0.809[a]	N/A
Black	15.5%	15.5%		19.2%	19.2%				
Hispanic	32.2%	32.2%		29.8%	29.8%				
Asian	3.5%	3.5%		3.8%	3.8%				
Other	9.7%	9.7%		8.3%	8.3%				
Household income, $									
<50 K	47.7%	47.7%	N/A	45.7%	45.7%	N/A	0.511[a]	0.511[a]	N/A
50 K–100 K	48.4%	48.4%		48.3%	48.3%				
>100 K	3.9%	3.9%		6.0%	6.0%				
Parental education									
<GED	24.8%	18.2%	N/A	23.8%	23.8%	N/A	0.880[a]	0.880[a]	N/A
college	39.9%	39.9%		38.1%	38.1%				
Bachelor	24.4%	24.4%		24.9%	24.9%				
Postgraduate	10.9%	10.9%		13.2%	13.2%				
ADI	99.33	N/A	N/A	95.66	N/A	N/A	0.056	N/A	N/A
Site	N/A	N/A	N/A	N/A	N/A	N/A	0.803[a]	0.803[a]	N/A

Note: [a]: χ^2 test. OB_1, OB_Baseline; NW_1, NW_Baseline; OB_2, OB_2-Year; NW_2, NW_2-Year.

Voxel-based morphometry

T1 structural images were analyzed with Matlab 2012a (MathWorks Inc., Natick, MA) using VBM toolbox (http://dbm.neuro.uni-jena.de/vbm/download/) and Statistical Parametric Mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/). In the current longitudinal study, preprocessing steps containing realignment, bias-correction, tissue classification, and spatial normalization were performed for imaging data of the two time points simultaneously. The GM images were smoothed by convolution with an isotropic Gaussian kernel (Full width at half maximum [FWHM] = 8 mm).

In addition, image quality check was performed visually (option "Display slices") and quantitatively (option "Check sample homogeneity") with tools available in the VBM toolbox. A total of 22 subjects (including 12 NW subjects and 10 OB subjects) were removed from the group analyses.

Statistical parametric mapping

SPM12 was used to perform voxel-wise analysis on GM images. Repeated-measures analysis of variance (ANOVA) was employed to assess time × group effects on GM volume while regressing out ADI. Clusters showing significant differences in GM volume after whole-brain false discovery rate (FDR) corrected $P < 0.05$ at the minimum cluster size of 20 voxel level were identified as regions of interest.

Time effects on GM volume were corrected for multiple comparisons using family wise error (FWE) corrections at the voxel level ($P_{FWE} < 0.001$) with a minimum cluster size of 100 voxels. Group effects on GM volume were corrected for multiple comparisons using FWE corrections at the voxel level ($P_{FWE} < 0.01$) with a minimum cluster size of 100 voxels.

Statistical analysis

Demographic information and executive function were analyzed by using SPSS (Statistical Package for Social Sciences, Release 22.0, IBM). Chi-square test was employed to evaluate differences in gender, race/ethnicity (including White, Black, Hispanic, Asian, and other), household income (including < $50 K, $50 K–$100 K and >$100 K), parental education (including <general educational development [GED], college, Bachelor, and postgraduate) and research site. Two-sample *t*-test was employed to examine differences in BMI, age (in months), intracranial volume (ICV), ADI, and executive function between OB and NW. Paired *t*-test was employed to examine differences in BMI, age, and ICV between baseline and 2-year follow-up. Repeated-measures ANOVA was employed to calculate interaction effects on age, BMI, ICV, and cognitive measures.

Associations between BMI, executive function, and GM volume

Partial correlations were performed to examine associations between GM volume, BMI, and executive function while controlling for ADI. Bonferroni corrections for multiple comparisons were set at $P < 0.00177$ (0.05/30) to control for 10 regions (Table 3), 2 cognitive measures (Picture Sequence Memory test and Matrix Reasoning total scaled score), and BMI.

Table 2. Executive function of OB and NW group.

		OB, N = 258 (Mean ± SE)	NW, N = 265 (Mean ± SE)	Group effect		Time × Group effect	
				T value	P value	F value	P value
NIH toolbox cognitive measurement age-corrected							
Flanker Test	Baseline	93.87 ± 0.83	94.68 ± 0.86	−0.682	0.496	0.109	0.742
	2-Year	94.96 ± 0.88	95.33 ± 0.80	−0.311	0.756		
Pattern Test	Baseline	90.34 ± 1.37	91.94 ± 1.35	−0.837	0.403	0.109	0.741
	2-Year	104.21 ± 1.25	106.44 ± 1.22	−1.277	0.202		
Picture Test	Baseline	98.21 ± 0.952	100.97 ± 0.93	−2.074	0.039	0.660	0.417
	2-Year	102.10 ± 0.99	106.01 ± 0.90	−2.932	0.004		
Reading Test	Baseline	98.47 ± 1.03	99.49 ± 0.97	−0.724	0.469	1.228	0.268
	2-Year	97.77 ± 0.97	99.96 ± 0.93	−1.631	0.103		
Picvocab Test	Baseline	104.35 ± 1.06	103.90 ± 0.95	0.318	0.750	1.214	0.271
	2-Year	99.78 ± 0.89	100.53 ± 0.93	−0.581	0.562		
Cryst Test	Baseline	101.77 ± 1.05	102.11 ± 0.97	−0.236	0.813	2.052	0.153
	2-Year	98.78 ± 0.97	100.47 ± 0.94	−1.246	0.213		
CCT	Baseline	1.63 ± 0.03	1.62 ± 0.03	0.179[a]	0.914[a]	N/A	N/A
GDT	2-Year	8.36 ± 0.33	8.12 ± 0.30	0.539	0.590	N/A	N/A
Matrix Reasoning Total Scaled Score	Baseline	9.19 ± 0.17	9.87 ± 0.18	−2.800	0.005	N/A	N/A

Note: [a]: χ^2 test. **Abbreviation:** OB, obese children; NW, normal-weight children; Flanker, Flanker inhibitory control and attention; Pattern, pattern comparison processing speed; Picture, picture sequence memory; Reading, oral reading recognition; Picvocab, picture vocabulary; Cryst, crystallized composite.

Results

Demographic characteristics

There were no significant group differences in gender, age, ICV, race/ethnicity, household income, highest educational level of caregiver, ADI, and research site between OB and NW ($P > 0.05$, Table 1), as expected. There were no time × group effects on age, ICV (Table 1), or cognitive measures (Table 2). There was a significant interaction effect on BMI ($P < 0.001$, Table 1), such that the OB group had significantly greater BMI increases than NW at 2-year follow-up compared with baseline. There were significant group effects on the Picture Sequence Memory test (at baseline and 2-year follow-up) and in the Matrix Reasoning total scaled score (at baseline), such that OB relative to NW had significantly lower scores on both tests (Table 2). There were no significant group differences in other cognitive tasks ($P > 0.05$, Table 2).

Alterations in GM volume

Significant group × time interaction effects on GM volume were observed in the right inferior parietal lobule (IPL_R), superior medial frontal gyrus (SFGmed), superior dorsolateral frontal gyrus (SFGdor), orbital part of superior and middle frontal gyrus (OFCsup/mid), OFCinf_L, THA, PreCG_R, CAU_R, and PHG/AMYG_R ($P_{FDR} < 0.05$, Fig. 1A). Post hoc tests showed that compared with NW, OB had significantly greater decreases in GM volume in the IPL_R, SFGmed, SFGdor, OFCsup/mid, OFCinf_L, THA, PreCG_R, CAU_R, and PHG/AMYG_R at 2-year follow-up compared with baseline (Fig. 1B, Table 3).

Significant time effects on GM volume were observed across the whole brain ($P_{FWE} < 0.001$). Compared with baseline, children had significantly lower whole brain GM volume at 2-year follow-up (Supplementary Fig. 2).

Significant group effects on GM volume were observed in the superior temporal gyrus (STG), middle cingulate cortex (MCC), right insula (INS_R), OFCinf_R, THA, left triangular part of inferior frontal gyrus (IFGtri_L), AMYG_R, right supplementary motor area (SMA_R), left precuneus (PCUN_L), and calcarine fissure (CAL) ($P_{FWE} < 0.01$). Compared with NW, OB had significantly lower GM volume in the STG, MCC, INS_R, OFCinf_R, THA, IFGtri_L, AMYG_R, SMA_R, PCUN_L, and CAL (Supplementary Fig. 3, Supplementary Table 1).

Correlation between BMI, executive function, and GM volume

Across individuals in the OB group, BMI was negatively correlated with GM volume in THA_R ($r = -0.2151$, $P = 0.0005$) at baseline, and with GM volume in the THA_R ($r = -0.2802$, $P < 0.0001$) and THA_L ($r = -0.2186$, $P = 0.0004$; Fig. 2) at the 2-year follow-up, which all survived the correction for multiple comparisons ($P < 0.00177$).

In OB, there was a negative correlation between GM volume in the prefrontal lobe (OFCsup/mid_R, SFGmed_R, SFGdor/med_L, OFCsup/mid_L, OFCinf_L), CAU_R, and PHG/AMYG_R with BMI (Supplementary Figs. 4 and 5). GM volume in OFCinf_L was positively correlated with the Picture Sequence Memory test score at baseline ($r = 0.137$, $P = 0.028$, Supplementary Fig. 4), and the reduction in GM volume in OFCinf_L (2-year follow-up vs. baseline) was negatively correlated with Picture Sequence Memory Test score (at baseline, $r = -0.133$, $P = 0.032$, Supplementary Fig. 4) in OB. Matrix reasoning total scaled score (at baseline) was positively correlated with GM volume in OFCsup/mid_R at 2-year follow-up ($r = 0.130$, $P = 0.046$, Supplementary Fig. 4) and negatively correlated with BMI in OB at baseline ($r = -0.162$,

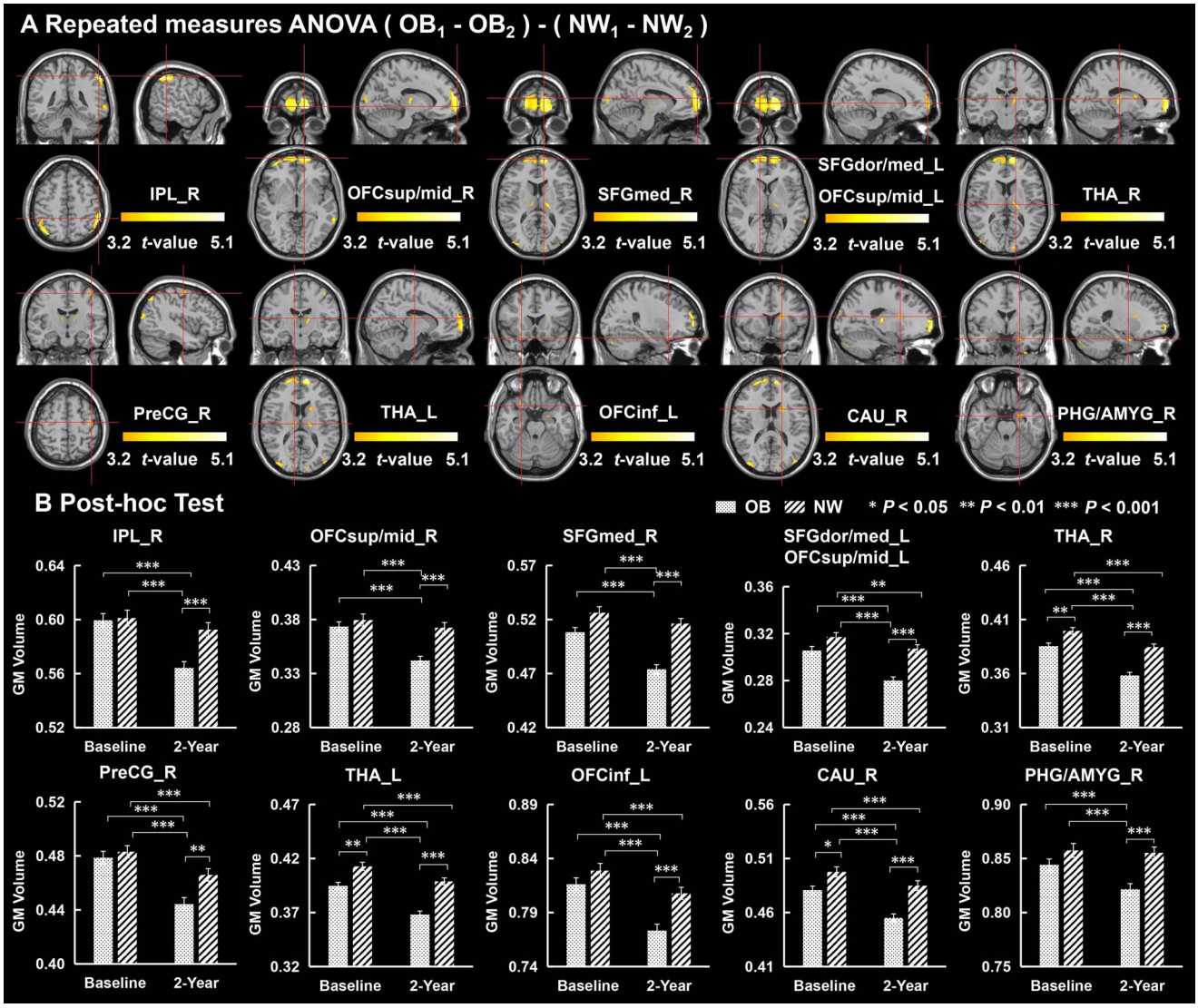

Fig. 1. Repeated measures ANOVA analysis for GM volume at baseline and 2-year follow-up between OB and NW group (voxel level-corrected, $P_{FDR} < 0.05$). (A) Compared with NW, there were significant decreases in GM volume in the IPL_R, OFCsup/mid, SFGmed, SFGdor_L, PreCG_R, OFCinf_L THA, CAU_R and PHG/AMYG_R at 2-year follow-up compared with baseline in OB group. ADI was regressed out as a covariate. (B) Post-hoc tests for GM volume. IPL_R, right inferior parietal lobule; OFCsup/mid_R, right orbital part of superior and middle frontal gyrus; SFGmed_R, right superior medial frontal gyrus; SFGdor/med_L, left superior medial and dorsolateral frontal gyrus; OFCsup/mid_L, left orbital part of superior and middle frontal gyrus; THA_R, right thalamus; PreCG_R, right precentral gyrus; THA_L, left thalamus; OFCinf_L, left orbital part of inferior frontal gyrus; CAU_R, right caudate; PHG/AMYG_R, right Parahippocampal gyrus/amygdala.

$P = 0.012$) and at 2-year follow-up ($r = -0.133$, $P = 0.041$, Supplementary Fig. 5). However, these correlations did not survive correction for multiple comparisons.

Discussion

The current study compared changes in GM volume at baseline and 2-year follow-up between OB and NW children using the ABCD study dataset and explored their associations with BMI and executive functions. Results showed significant group × time effects on GM volume in IPL, OFC, SFG, CAU, PHG, AMYG, and THA. Compared with NW, OB had significantly decreased GM volume in IPL, OFC, SFG, CAU, PHG, AMYG, and THA at 2-year follow-up compared with baseline. BMI was negatively correlated with GM volume in THA_R at both time points and with GM volume in THA_L at 2-year follow-up. These findings highlight that childhood obesity is associated with GM volume reductions in regions involved with reward evaluation, executive function, and emotion, and that high BMI negatively affects brain development.

A number of studies showed decreases in GM volume across cortical regions in healthy adolescents throughout adolescence, with the largest decreases occurring in the prefrontal and parietal cortices (Tamnes et al. 2017), which are important components of the executive-control network and whose dysfunctions are closely related to obesity (Krafft et al. 2014; Kim et al. 2019; Ding et al. 2020), food preferences, eating disorders (Park et al. 2018; Lee et al. 2020), and cognitive functions (Seeley et al. 2007). Our data showed that OB compared with NW had significantly greater decreases in GM volume in the

Table 3. Repeated measures ANOVA analysis on GM volumes between OB and NW group at baseline and 2-year follow-up. (voxel level-corrected, $P_{FDR} < 0.05$).

Region	Cluster size	MNI			Peak T-value	OB_1 vs. OB_2		NW_1 vs. NW_2		OB_1 vs. NW_1		OB_2 vs. NW_2	
		X	Y	Z		T	P	T	P	T	P	T	P
IPL_R	976	56	−42	52	4.99	9.324	<0.001	1.896	0.059	−0.215	0.830	−4.044	<0.001
OFCsup/mid_R	2922	15	69	−3	4.89	8.126	<0.001	1.561	0.120	−0.879	0.380	−5.197	<0.001
SFGmed_R		9	65	12	4.52	8.864	<0.001	2.137	0.033	−2.537	0.011	−6.669	<0.001
SFGdor/med_L OFCsup/mid_L		−22	66	3	4.51	9.696	<0.001	3.211	0.001	−2.274	0.023	−5.973	<0.001
THA_R	158	15	−16	9	4.29	10.878	<0.001	5.981	<0.001	−3.376	<0.001	−6.464	<0.001
PreCG_R	79	41	−12	58	3.58	9.619	<0.001	4.929	<0.001	−0.683	0.495	−3.241	0.001
THA_L	31	−14	−16	13	3.53	9.541	<0.001	4.541	<0.001	−3.634	<0.001	−6.827	<0.001
OFCinf_L	20	−26	18	−23	3.47	10.297	<0.001	3.912	<0.001	−1.417	0.157	−4.257	<0.001
CAU_R	124	18	12	16	3.37	11.780	<0.001	4.808	<0.001	−2.831	0.005	−5.082	<0.001
PHG/AMYG_R	82	21	0	−24	3.36	5.311	<0.001	0.453	0.651	−1.588	0.113	−4.435	<0.001

Abbreviation: IPL_R, Right Inferior parietal lobule; OFCsup/mid_R, Right Orbital part of superior and middle frontal gyrus; SFGmed_R, Right Superior medial frontal gyrus; SFGdor/med_L, Left Superior medial and dorsolateral frontal gyrus; OFCsup/mid_L, Left Orbital part of superior and middle frontal gyrus; THA_R, Right Thalamus; PreCG_R, Right Precentral gyrus; THA_L, Left Thalamus; OFCinf_L, Left Orbital part of inferior frontal gyrus; CAU_R, Right Caudate; PHG/AMYG_R, Right Parahippocampal gyrus/Amygdala.

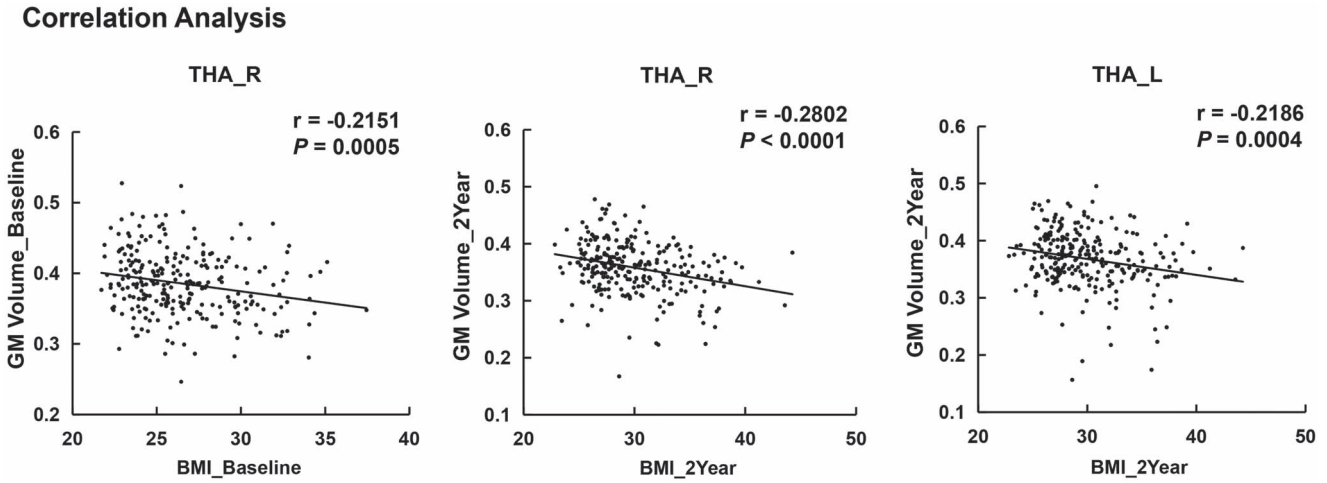

Fig. 2. Correlation analysis between BMI and GM volume in the THA_R at baseline and 2-year follow-up, and correlation analysis between BMI and GM volume in the THA_L at 2-year follow-up in OB. THA_R, right thalamus; THA_L, left thalamus.

prefrontal lobe (OFCsup/mid_R, SFGmed_R, SFGdor/med_L, OFCsup/mid_L, OFCinf_L) and IPL_R at 2-year follow-up compared with baseline. Obesity is associated with accelerated reduction in GM volume in the IPL_R and prefrontal lobe (2-year follow-up vs. baseline), regions that are known to contribute to dysfunction of inhibitory-control and eating disorders. A functional magnetic resonance imaging (fMRI) study reported that children with higher BMI had less activation in the prefrontal cortex in response to unhealthy food (van Meer et al. 2016). Continuous changes in GM volume in these brain regions may reflect the children's eating habits. Our data documented a negative correlation between GM volume in the prefrontal lobe and BMI, which suggests detrimental structural changes in the prefrontal cortex (PFC) may lead to ensuing behavioral changes such as impairments in self-regulation that exacerbate weight gain. The GM volume in OFCinf_L was positively correlated with scores in the Picture Sequence Memory Test score at baseline, whereas volume reductions at 2-year follow-up (compared with baseline) were negatively correlated with the scores in Picture Sequence Memory Test at baseline. An fMRI study reported that obese compared with lean children had greater activation in the OFC when exposed to food cues (Bruce et al. 2010). The Picture Sequence Memory Test assess episodic memory, which plays an important role in food intake and weight regulation. High BMI was associated with worse episodic memory (Higgs and Spetter 2018). Several sMRI studies demonstrated that obese children had worse working memory performance than normal weight children and had lower cortical volume and cortical thickness in the OFC (Maayan et al. 2011; Saute et al. 2018; Laurent et al. 2020; Ronan et al. 2020). Cortical thickness in the OFC mediated the association between BMI and working memory (Laurent et al. 2020; Ronan et al. 2020). Episodic memory and working memory impairments contribute to problems with appetite control and weight gain (Higgs and Spetter 2018). The relationship between GM volume in the OFC and Picture Sequence Memory Test

suggests obesity may affect GM volume development in children and impair episodic memory and working memory, which may further contribute to overeating and weight gain. We also found that Matrix Reasoning total scaled score (at baseline) was positively correlated with GM volume in OFCsup/mid_R at 2-year follow-up and negatively correlated with BMI in OB at baseline. Previous studies also reported a positive correlation between GM volume in the OFC and matrix reasoning ability in adolescents and young adults (Laurent et al. 2020; Ronan et al. 2020). The OFC is an important component of reward processing, which may regulate motivational pathways for food approach. The link between decreased GM volume in the OFC and reduced Matrix Reasoning ability in obese children suggests that lower reasoning ability might contribute to increased BMI by affecting food choices (Freidl et al. 2013). Although we did not observe the correlation between GM volume in SFG and executive function in the current study, prior studies found that GM volume in SFG was positively correlated with cognitive function, especially working memory and inhibitory control (du Boisgueheneuc et al. 2006; Taylor et al. 2020). In summary, we speculate that obesity leads to accelerated reductions in GM volume in IPL_R, SFG and OFC, which may account for the dysfunction of executive-control, episodic memory, and working memory.

The brain structures related to reward processing, particularly the amygdala (Kim, Luo, et al. 2020b), hippocampus, caudate, thalamus, play an important role in food intake control and body weight regulation (Areias and Prada 2015; Kirouac 2015; Kim, Shim, et al. 2020a). Previous sMRI studies revealed that obese individuals had reduced GM volume in the hippocampus, amygdala, caudate, and thalamus compared with normal weight individuals (Shott et al. 2015; Nouwen et al. 2017). Obese individuals have abnormal structural connectivity and lower fiber integrity of the reward network (including amygdala, caudate), which are associated with increased food intake (Marques-Iturria et al. 2015). In the present study OB showed significantly lower GM volume in THA_L/R, CAU_R, and PHG/AMYG_R at baseline and 2-year follow-up, compared with NW. These group differences GM volumes increased over the 2-year period, which was not reported in previous studies. Obese children with higher BMI had lower GM volume in the THA. These findings indicated that persistently reduced GM volume in these regions may contribute to weight gain in children. Since these regions have known roles in control of food intake and reward processing, we speculate that children who are obese for a long time may lead to dysfunction of the reward system. In addition, BMI (at 2-year follow-up) was negatively correlated with GM volume in PHG/AMYG_R (at 2-year follow-up), and with reduced GM volume in the CAU_R (2-year follow-up vs. baseline). Hippocampal-dependent learning and memory mechanisms involve food intake and body weight regulation (Kanoski and Grill 2017). The AMYG is an important region for food intake regulation and emotions such as anxiety and fear (Areias and Prada 2015). The CAU is an important component of reward system, including food-related reward processing. Previous studies reported that OB had reduced GM volume in these regions (Shott et al. 2015; Nouwen et al. 2017; Huang et al. 2019). In obese individuals, hippocampus and amygdala showed greater activation than normal weight individuals when exposed to food cues and greater resting-state activity (Li et al. 2021). In addition, the hippocampus and amygdala are also involved in emotional processing. Damage to the hippocampus and amygdala contribute to overeating. Previous studies showed that the hippocampus and amygdala are strongly involved in emotional eating in obese individuals, such as using overeating to counteract negative emotions (Wang et al. 2006; Konttinen 2020). However, due to the lack of eating behavior measurements, in the current study we could not determine the relationship between structural changes and motivation toward obtaining food rewards.

Limitations

There are some limitations of the current study. Firstly, at the time of this study, the ABCD dataset (release 3.0) has released only imaging data at 2-year follow-up for 6546 children. Due to the strict matching of children's gender, age, race/ethnicity, household income, parental education, sites distribution and ICV, the sample size is relatively small, which limits the generalizability of our findings. Secondly, we evaluated obese children at two time points but longer follow-up studies are needed to determine how childhood obesity influences brain structural developmental trajectories throughout adolescence. Finally, our findings are currently limited to sMRI studies. In the future, we will conduct multimodal MRI to evaluate brain developmental trajectories in obese children.

Conclusion

The current study revealed that compared with NW, OB had sustained reductions in GM volume in the prefrontal lobe, THA, PreCG_R, CAU_R, and PHG/AMYG_R at 2-year follow-up compared with baseline, which are regions involved in food intake control, reward processing, executive-control, episodic memory, and working memory. The findings indicate the impact of obesity on brain structural developmental trajectories in children.

Author contribution

Conceptualization: Gene-Jack Wang, Yi Zhang; Data acquisition, Fukun Jiang, Weibin Ji, Feifei Wu, Yaqi Zhang, Wenchao Zhang; Data analysis: Fukun Jiang, Guanya Li, Yang Hu; Writing-Original Draft: Fukun Jiang, Yi Zhang, Gene-Jack Wang; Writing-Review and Editing: XinBo Gao, Peter Manza, Dardo Tomasi, and Nora D. Volkow.

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Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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