

ARTICLE



Pediatrics

Altered effective connectivity between the prefrontal cortex and caudate in children with overweight and obesity

Haiyan Xin^{1,2,6}, Ximei Chen^{1,2,6}✉, Wei Li^{1,2}, Mingyue Xiao^{1,2}, Shiqing Song³, Yong Liu^{1,2}, Xiao Gao^{1,2}, Cheng Guo^{1,2} and Hong Chen^{1,2,4,5}✉

© The Author(s), under exclusive licence to Springer Nature Limited 2025

OBJECTIVE: This study aimed to examine the interaction patterns between the reward and inhibitory control systems in children with overweight and obesity.

METHODS: Resting-state fMRI data were collected at baseline from 38 children with overweight and obesity (OW/OB) and 68 children with normal weight (NW). We first examined the differences in seed-based functional connectivity (FC) between the two groups, focusing on eight predefined regions of interest in the reward and inhibitory control systems. Based on the FC results, we further applied the spectral dynamic causal modeling technique to assess the between-group differences in effective connectivity (EC). Finally, we employed a machine learning approach to determine whether these baseline core connections could predict eating behaviors at the one-year follow-up.

RESULTS: Compared with the NW group, the FC between the left superior frontal gyrus (SFG) and left caudate was stronger while the FC between left SFG and right ventromedial prefrontal cortex (vmPFC) was weaker in the OW/OB group after controlling for age, sex, and head motion. After Bayesian contrasts, the OW/OB group exhibited stronger negative EC from the left caudate to left SFG, weaker negative EC from the left SFG to right vmPFC, and weaker positive EC from the right vmPFC to left SFG than NW group. The results indicated that the baseline caudate→caudate and vmPFC→SFG connectivity could predict changes in children's eating behaviors one year later.

CONCLUSION: The current study provides novel evidence for the neural hierarchical basis of childhood obesity (especially the caudate→SFG, SFG→vmPFC and vmPFC→SFG connectivity), suggesting that interventions targeting reward processing and inhibition control may have important implications for childhood obesity.

International Journal of Obesity; <https://doi.org/10.1038/s41366-025-01973-5>

INTRODUCTION

Obesity is a chronic metabolic condition where energy intake surpasses energy expenditure, resulting in an excessive accumulation of body fat that poses significant health risks [1]. Recent research indicates that over 1 billion people worldwide suffer from obesity in 2022, including 160 million children and adolescents aged 5–19 years [2]. In China, the prevalence of overweight and obesity among children and adolescents aged 6–17 is as high as 19%, and over 10% of children under 6 years old are affected [3]. Childhood obesity is strongly associated with a range of negative physical and psychological consequences, including cardiovascular disease, sleep disorders, diabetes, an increased risk of suicide, and impaired cognitive function [4–7]. As such, it is crucial to identify the underlying neural substrates of obesity during this critical developmental period.

At a theoretical level, the human brain's regulation of eating involves multiple systems, including the endocrine system, attention system, emotion and memory system, cognitive control system, and reward system [8]. Notably, recent studies have emphasized the critical role of the reward and inhibitory control circuits in obesity [9–11]. These neural circuits interact to regulate an individual's energy intake and expenditure. The reward system primarily consists of dopaminergic neuronal projections that involve the ventral tegmental area, substantia nigra, orbitofrontal cortex, striatum, and ventromedial prefrontal cortex, particularly the nucleus accumbens [8, 12–14]. Conversely, inhibitory control is closely linked to the prefrontal cortex, including areas such as the cingulate cortex, inferior frontal cortex, pre-supplementary motor area, and dorsolateral prefrontal cortex [8, 15, 16]. The reward overload theory suggests that those at risk of obesity have a heightened reward circuitry response to high-calorie foods,

¹Key Laboratory of Cognition and Personality, Ministry of Education, Faculty of Psychology, Southwest University, Chongqing, China. ²Faculty of Psychology, Southwest University, Chongqing, China. ³School of Psychology, Shaanxi Normal University, Xi'an, China. ⁴Research Center of Psychology and Social Development, Faculty of Psychology, Southwest University, Chongqing, China. ⁵Collaborative Innovation Team for Children and Adolescent Mental Health, Southwest University, Chongqing, China. ⁶These authors contributed equally: Haiyan Xin, Ximei Chen. ✉email: ximeichen@swu.edu.cn; chenhg@swu.edu.cn

Received: 19 February 2025 Revised: 31 October 2025 Accepted: 17 November 2025

Published online: 13 May 2026

leading to increased consumption of such foods [17]. In addition, the inhibitory control deficit theory states that individuals with poor inhibitory control and reduced activity in relevant brain regions are more sensitive to food cues and more likely to overeat appetizing foods [18].

Empirically, neuroimaging studies have shown that children with overweight and obesity exhibited altered connectivity between regions involved in reward processing and cognitive control. Specifically, a higher body mass index (BMI) has been correlated with weaker connectivity between the ventral striatum and orbitofrontal cortex [13]. Evidence from resting-state functional network connectivity studies also found that BMI was inversely associated with functional connectivity (FC) in reward and control networks [4, 19]. These findings suggested that dysfunction in reward and inhibitory control systems plays a key role in pediatric obesity. More importantly, identifying the interactive relationships among multiple relevant systems (especially the reward and inhibitory control systems) will yield more accurate predictions regarding which children are most prone to developing dysfunctional eating habits and obesity [20]. Relevant studies have revealed that children with obesity exhibited greater resting-state FC than healthy weight controls between the left middle frontal gyrus (MFG) and reward-related regions (i.e., the left ventromedial prefrontal cortex [vmPFC] and the left lateral orbitofrontal cortex) [21]. Higher BMI was found to be associated with decreased intra-network and inter-network FC, including the salience and cingulo-opercular networks [19]. Existing evidence has demonstrated that the functional imbalance between the reward and control circuits may play a significant role in childhood obesity. However, the precise dual-system interaction patterns (e.g., directional influences) remain insufficiently defined during this developmental period, which hinders our understanding of the neuromarkers associated with pediatric obesity.

Furthermore, prior research on childhood obesity has primarily focused on undirected synchronizations through FC analyses, which do not determine the direction of connectivity between brain regions. Effective connectivity (EC) analyses could address this limitation by clarifying the impact of interactions among key regions. Among the diverse array of alternative metrics, spectral dynamic causal modeling (spDCM) stands out as a well-established Bayesian inference technique that utilizes resting-state functional magnetic resonance imaging (rs-fMRI) time-series data to model directional relationships between distinct brain regions [22]. One adult study found that the information flow between the lateral hypothalamus and medial hypothalamus at rest was correlated with body weight and energy homeostasis when using spDCM [23]. A recent study also applied the spDCM method in patients with type 2 diabetes and reported that BMI was positively associated with increased EC from the lateral prefrontal cortex to the left anterior insula [24]. However, examinations of obesity-related neurofunctional abnormalities using spDCM have rarely involved children.

Longitudinally, baseline FCs between the right hippocampus with right lingual gyrus, right paracingulate gyrus, and frontal pole have been found to positively predict changes in emotional eating [25]. A recent study reported that children with excess weight displayed abnormal bidirectional inhibitory effects between the right hippocampus and left postcentral gyrus, which could further predict BMI and food approach behavior one year later [26]. These results imply that altered dual-system connections may be key predictors of eating behaviors and childhood obesity. However, existing evidence examining whether and how reward-inhibition dual-system connectivity predicts future eating behaviors remains limited. The current study will explore obesity-related dual-system interaction patterns and identify which connections can further predict children's future eating behaviors.

By and large, this study employed the spDCM technique to investigate the EC profiles based on resting-state fMRI data,

aiming to reveal abnormal connectivity patterns within the reward-inhibition dual system in children with overweight and obesity. Specifically, we investigated alterations in functional and effective connections between the dual systems in children with overweight and obesity. In addition, this study employed a machine learning approach to determine whether the core connections exhibiting significant between-group differences within the reward-inhibition dual system could predict future eating behaviors. The present study will enhance our understanding of the neural hierarchy mechanisms underlying childhood obesity and it reveals that interventions targeting reward function and inhibition control may have important implications for childhood obesity.

METHODS

Participants

A total of 130 healthy primary school students participated in this study. All participants were recruited from two primary schools in Chongqing (south of China). Participants were recruited via posters and flyers (the research assistant briefed children and their parents on the purpose of the study). Participants fulfilled the following inclusion criteria, which were assessed via parental self-report: right-handed; no history of psychiatric or neurological illnesses; no use of psychoactive medications (binary variables indicating the presence or absence of particular disorders); and Chinese as the primary language. Twenty-four participants were excluded from analysis since the cephalic motion index greater than 0.5 mm, resulting in a sample of 106 participants (females, 53; males, 53). The 106 participants were grouped using the screening criteria for overweight and obesity among school-aged children and adolescents from Chinese Center for Disease Control and Prevention (2018) (see Table S1), resulting in 38 children with overweight and obesity (OW/OB) and 68 children with normal weight (NW). All participants received a set of stationery as compensation for participation in this study. Baseline measurements of participants' demographic information, eating behaviors, and resting-state fMRI data were collected, followed by a 1-year follow-up assessment of their BMI and eating behaviors. Measurements were performed from April 2018 to October 2019.

Ethics approval and consent to participate

This research was reviewed for compliance with the standards for the ethical treatment of human participants and approved by the Ethical Committee of the Southwest University (IRB No. H22003). All participants and their parents signed an informed consent document prior to the study.

Measures

Demographics. Prior to the MRI scanning session, the children's height and weight were measured at the Brain Imaging Center. To ensure accuracy, the measurements were taken with the children wearing light clothing and bare feet. Trained research assistants carried out standardized anthropometric measurement procedures using a portable stadiometer to measure height and a digital scale to measure weight. Each measurement was conducted twice to ensure reliability. The BMI was calculated using the mean recorded values of height and weight, applying the formula kg/m^2 .

Children's Eating Behaviour Questionnaire. The Children's Eating Behaviour Questionnaire is a 35-item measure that assesses children's eating behaviors (e.g., "My child has a good appetite") [27]. The questionnaire contains eight dimensions of food response, food enjoyment, satiety response, slow food performance, emotional overeating, emotional under-eating, desire to drink water, and picky and partial eating. All items are scored on a 5-point scale ranging from 1 (never) to 5 (always). To obtain the score for this scale, we reverse-scored the negatively worded items (items 3, 4, 10, 16, 32) and then summed the ratings of all items, with higher total scores indicating more pronounced eating behaviors. The scale was administered at two time points: baseline (Time 1) and the one-year follow-up (Time 2).

Neuroimaging data acquisition and preprocessing

For each child, an approximately 8-min (486 s) resting-state functional MRI scan was performed in a 3T Trio scanner (Siemens Medical, Erlangen,

Germany). Prior to the formal scan, all participants underwent a 5-min simulated scan to adapt to the scanning environment. During the formal resting-state scanning session, the children were given specific instructions to ensure optimal data acquisition. They were instructed to remain still and motionless, relax with their eyes closed, and avoid falling asleep. Furthermore, they were instructed not to engage in any thoughts or mental activities during the scan. To enhance the quality of the scanning procedure, foam pads were utilized to minimize head motion, while earplugs were provided to mitigate the impact of scanning noise. To capture the resting-state functional MRI image, we employed a gradient echo planar imaging sequence. The scanning parameters are as follows: TE = 30 ms, TR = 2000 ms, FA = 90°, FOV = 224 × 224 mm², matrix size = 64 × 64, slice = 33, thickness = 3.5 mm, distance between slice = 1 mm, voxel size = 3.5 mm × 3.5 mm × 3.5 mm. A total of 180 consecutive images is obtained at 180 time points.

Data preprocessing was carried out using the Data Processing Assistant for Resting-State fMRI (DPARSF) toolbox in MATLAB (The Math Works, Inc., Natick, MA, USA) platform [28]. Preprocessing was conducted with the following steps: (1) the first 10 time points were removed to minimize the instability of initial MRI signals; (2) the remaining 170 volumes were slice-time corrected and head-motion realigned; (3) each participant's functional MRI images were registered to their segmented high-resolution T1-weighted anatomical images; (4) regressing nuisance variables included six head motion parameters, white matter signal, and cerebral spinal fluid signal; (5) functional MRI images were normalized to the standard Montreal Neurological Institute (MNI) template with a resolution voxel size of 3 × 3 × 3 mm³ and smoothing with a 6-mm full width at half maximum of Gaussian kernel; and (6) linear detrending and band-pass filtering (0.01–0.1 Hz) to discard physiological noise, drift from scanner instabilities and head motion. Moreover, the frame-wise displacement (FD) was calculated as a measure of head motion and was treated as a covariate in subsequent data analyses.

Considering that our sample consisted of children, this study also normalized the data using a pediatric template during preprocessing [29],

and other preprocessing steps remain unchanged. The results are presented in the Supplementary Material (Table S2).

Seed-based functional connectivity

We first examined the differences in seed-based FC between children with OW/OB and healthy controls. The seed regions of the reward and inhibitory control systems (e.g., the caudate, nucleus accumbens, and superior frontal gyrus) were defined based on prior obesity literature [11, 13, 21, 30–32]. Each spherical region of interest (ROI) was created with radius 5 mm centered on the MNI coordinates (Table 1 and Fig. 1), as in previous studies [26]. The mean BOLD signal time series from each ROI was extracted and correlated with the time series of all other ROIs to create Pearson's correlation coefficient maps. Fisher's *r*-to-*z* transformation was then applied in these maps to improve the normality of the correlation coefficients.

Effective connectivity

Based on the FC results, we assessed the between-group differences in EC using the spDCM to further reveal the abnormal directional interactions between reward and inhibitory control nodes in children with OW/OB.

ROI selection and time series extraction. BOLD time series (the first eigenvectors) was extracted from preprocessed (slice timing, realigned, normalized, and smoothed) rs-fMRI data. For the significant clusters in the FC analysis, time series were extracted from a sphere of 8 mm radius centered on the peak coordinates, as in previous studies [26, 33, 34]. The choice of different radii for FC and EC analyses is based on the theoretical considerations of the need for precise localization for functional connections and high signal-to-noise ratio for effective connections. We corrected nuisance regressors including six head-motion parameters, cerebrospinal fluid, and white matter. Low-frequency signal drifts were filtered using a 128-high-pass filter.

First-level analysis: specification and inversion of DCM. The spectral DCM analyses were conducted using DCM12 implemented in SPM12 (revision 7771, www.fil.ion.ucl.ac.uk/spm). We build a DCM for each significant FC at the subject level, generating a total of six models, which fits the complex cross spectral density using a power-law model of endogenous neuronal fluctuations. We then estimated each participant's DCM with Bayesian model inversion, finding the posterior density over parameters [22].

Second-level analysis: parametric empirical bayes. Second-level analysis with the Parametric Empirical Bayes (PEB) framework examined the between-group differences in EC. The PEB framework specifies a hierarchical statistical model of connectivity parameters. We built a PEB model to partition the variability in connectivity parameters across subjects into hypothesized group-level effects and uninteresting between-subject variability. Three covariates were specified (overall group mean, between-group difference and sex) in the design matrix. Then we used the standard two-level variational Laplace procedure to estimate the parameters of the PEB model. The reduced models are searched automatically using Bayesian model reduction [35]. Bayesian model averaging was performed on the second-level PEB model to investigate which direction of connectivity best explains the differences between groups (OW/OB vs NW). According to the PEB framework, the parameters best describing between-group effects were reported in terms of posterior probability (PP) rather than p-value [36].

Table 1. Names and MNI coordinates of the regions of interest.

| Region name | Coordinates (in mm) |
|--|---------------------|
| Reward system | |
| Right ventromedial prefrontal cortex (vmPFC.R) | 3, 49, -14 |
| Left caudate (CAU.L) | -13, 15, 9 |
| Right caudate (CAU.R) | 13, 15, 9 |
| Left nucleus accumbens (NAc.L) | -9, 9, -8 |
| Right nucleus accumbens (NAc.R) | 9, 9, -8 |
| Inhibitory control system | |
| Left inferior frontal gyrus (IFG.L) | -44, 10, 14 |
| Left superior parietal gyrus (SPG.L) | -29, -65, 52 |
| Left superior frontal gyrus (SFG.L) | -21, 57, 30 |

Note: The last letter in region name abbreviations (if available) indicates left or right hemisphere.

MNI Montreal Neurological Institute.

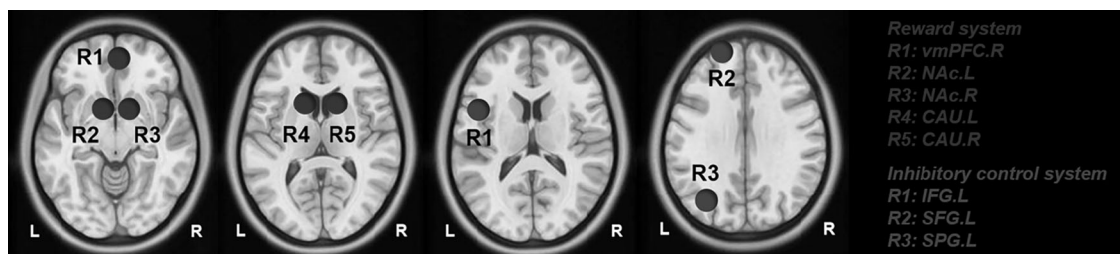


Fig. 1 Illustration of the ROIs within the reward and inhibitory control systems. Here we show the spatial locations of eight ROIs on standard MNI coordinates. Images are displayed according to neurological convention; therefore, the right hemisphere corresponds to the right side in axial displays. ROI region of interest, MNI Montreal Neurological Institute, vmPFC ventromedial prefrontal cortex, CAU caudate, NAc nucleus accumbens, IFG inferior frontal gyrus, SPG superior parietal gyrus, SFG superior frontal gyrus, L left, R right.

Table 2. Demographic characteristics of the samples.

| Variables | NW (<i>n</i> = 68) | OW/OB (<i>n</i> = 38) | Statistics | | |
|------------------------|---------------------|------------------------|-----------------|-----------|-----------------|
| | Mean ± SD | Mean ± SD | <i>t</i> -value | <i>df</i> | <i>p</i> -value |
| Sex, female/male | 27/41 | 26/12 | | | |
| Age, years | 10.33 ± 0.85 | 10.54 ± 0.86 | −1.23 | 104 | 0.22 |
| BMI, kg/m ² | 16.34 ± 1.60 | 22.64 ± 2.44 | −14.30 | 104 | <0.001*** |
| Head motion, mm | 0.17 ± 0.10 | 0.15 ± 0.09 | 0.83 | 104 | 0.41 |
| SES | 21.13 ± 3.67 | 20.76 ± 3.51 | 0.51 | 104 | 0.615 |

OW/OB overweight/obesity, NW normal weight, SD standard deviation, BMI body mass index, SES socioeconomic status. Significance is indicated by the asterisks (***p* < 0.001).

Table 3. Altered resting-state FCs between the two groups.

| Significant connections | NW (<i>n</i> = 68) | OW/OB (<i>n</i> = 38) | <i>t</i> -value | <i>p</i> -value |
|-------------------------|---------------------|------------------------|-----------------|-----------------|
| | Mean ± SD | Mean ± SD | | |
| SFG.L - CAU.L | 0.10 ± 0.22 | 0.07 ± 0.20 | 3.05 | 0.013* |
| SFG.L - vmPFC.R | 0.13 ± 0.24 | 0.22 ± 0.25 | −2.98 | 0.013* |

Note: Statistical significance was set at a cluster-size threshold of *p* < 0.05 false discovery rate corrected. Covariates included sex, age, and head motion. FC functional connectivity, SFG superior frontal gyrus, CAU caudate, vmPFC ventromedial prefrontal cortex, L left, R right, SD standard deviation, OW/OB overweight/obesity, NW normal weight. Results are two-sided. Significance is indicated by the asterisks (**p* < 0.05).

In this study, ECs with PP greater than 0.95 were considered to best describe the differences between groups ("strong evidence").

Statistical analyses

An independent sample *t*-test was used to test the between-group difference in demographic characteristics.

A generalized linear model was used to examine the differences in seed-based FC values based on their *z*-maps across two groups, which was implemented in the CONN toolbox (<https://web.conn-toolbox.org>). The random field theory was used for multiple comparisons correction (a voxel height threshold of *p* < 0.001, and the false discovery rate (FDR)-corrected cluster-size threshold of *p* < 0.05), which could appropriately control the family-wise error rate and improve the reliability of results [37]. To reduce the effects of potential confounding factors, we controlled for age, sex, and head motion.

Based on the FC results, we used spDCM approach to further examine the directionality of FC, with statistical significance set at PP values > 0.95. The EC analysis was performed in the SPM12 (revision 7771, www.fil.ion.ucl.ac.uk/spm).

Predictive analyses

To test the robustness of the brain-behavior relationship, this study performed a machine-learning method named linear support vector regression (SVR) and leave one out cross-validation procedure [38]. First, eating behaviors at Time 2 were taken as the dependent variable, while significant connections at Time 1 (i.e., SFG-caudate, SFG-vmPFC, caudate→SFG, caudate→caudate, SFG→SFG, SFG→vmPFC, and vmPFC→SFG connectivity) served as independent variables in the linear regression algorithm. Furthermore, we added baseline eating behaviors as a covariate, and here the effective sample size was 80, consisting of 30 children in the OW/OB group and 50 children in the NW group. Finally, the changes in eating behaviors (calculated as eating behaviors at Time 2 minus baseline eating behaviors) were taken as the dependent variable, and baseline eating behaviors were taken as a covariate. The $r_{(\text{predicted, observed})}$ was estimated by leave one out cross-validation, and represent the prediction accuracy of the independent variable [39]. The 1000 Pearson's correlations between observed and predicted scores composed null distributions of *r*

values. The number of null *r* values was greater than or equal to the $r_{(\text{predicted, observed})}$ value and was then divided by 1000, providing an estimated p_{permu} value.

RESULTS

Demographics

Demographic characteristics and results of behavioral tasks are presented in Table 2. No group differences were observed in age ($t = -1.23$, $p = 0.22$) and head motion ($t = 0.83$, $p = 0.41$). The OW/OB group had significantly higher BMI than the NW group ($t = -14.30$, $p < 0.001$). We included age, sex and head motion as covariates in subsequent analysis to ensure that our results were not confounded by participants' age, sex, or head motion.

Altered functional connectivity in children with overweight and obesity

Significant between-group differences in the FCs were observed (Table 3). Relative to NW, the FC between left superior frontal gyrus (SFG) and left caudate was stronger in the OW/OB group ($p\text{FDR} < 0.05$). In addition, the FC between left SFG and right vmPFC was weaker in the OW/OB group ($p\text{FDR} < 0.05$) (Fig. 2).

Altered effective connectivity in children with overweight and obesity

After Bayesian contrasts, significant between-group differences in the ECs were observed. Compared with NW, the OW/OB group showed: (1) stronger negative EC from the left caudate to left SFG (averaged connectivity values: OW/OB = −0.714, NW = −0.405, PP = 0.987), which indicates that the caudate is inhibiting the SFG to a greater degree in the OW/OB group during rest, relative to the NW group. (2) weaker negative EC from the left SFG to the vmPFC (averaged connectivity values: OW/OB = 0.032, NW = −0.211, PP = 0.990), which indicates that the SFG is inhibiting the vmPFC to a lesser degree in the OW/OB group during rest, relative to the NW group. (3) weaker positive EC from the right vmPFC to left SFG (averaged connectivity values: OW/OB = −0.040, NW = 0.210, PP = 1.000), which indicates that the vmPFC has a weak excitatory effect on SFG in the OW/OB group during rest, relative to the NW group (Fig. 3). All PP values of average connectivity are greater than 0.95.

Prediction of future eating behavior

The regression model was applied to investigate whether these sensitive connections at baseline could further predict future eating behaviors. First, the intrinsic caudate→caudate connectivity significantly predicted food response ($r_{(\text{predicted, observed})} = 0.207$, $p = 0.003$) and desire to drink water ($r_{(\text{predicted, observed})} = 0.177$, $p = 0.021$) one year later. The vmPFC→SFG connectivity significantly predicted food enjoyment one year later ($r_{(\text{predicted, observed})} = 0.257$, $p = 0.005$, see Fig. 4(a-c)). After controlling for eating behaviors at baseline, only the vmPFC→SFG connectivity

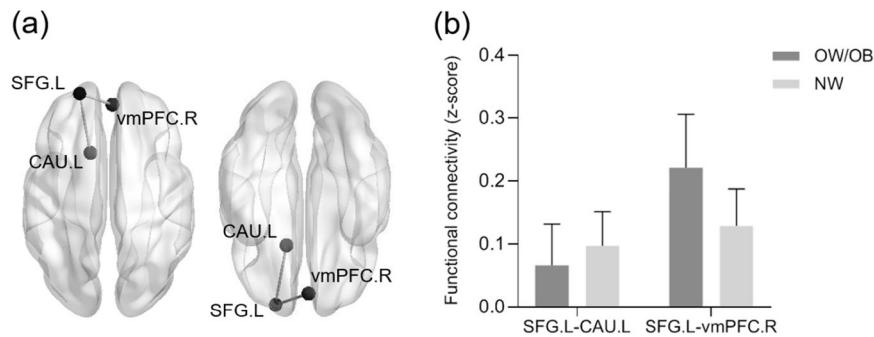


Fig. 2 Comparison of seed-based FCs between the OW/OB ($n = 38$) and NW ($n = 68$) groups. **a** The OW/OB group exhibited stronger FC between the left SFG and left caudate but lesser FC between left SFG and right vmPFC after adjusting for age, sex, and head motion (false discovery rate-corrected $p < 0.05$). **b** Bar graph illustrates significant between-group differences in means and 95% confidence intervals of seed-based FCs. FC functional connectivity, OW/OB overweight/obesity, NW normal weight, CAU caudate, SFG superior frontal gyrus, vmPFC ventromedial prefrontal cortex, L left, R right.

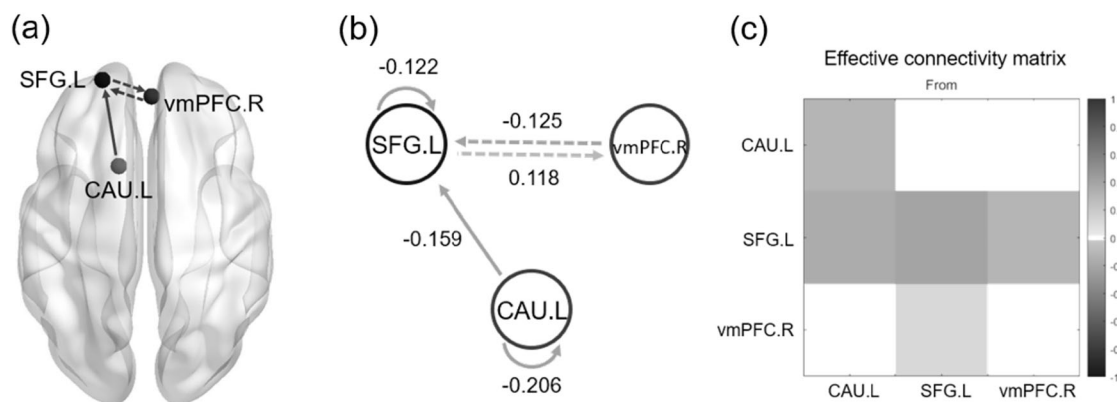


Fig. 3 Comparison of ECs between the OW/OB ($n = 38$) and NW ($n = 68$) groups. **a** Red and blue lines represent the excitatory (positive) and inhibitory (negative) effects, respectively. Solid/dotted line represents a stronger/weaker effect in the OW/OB group, compared with NW group. **b** Schema summarizing group differences in EC within and between each region. The numbers represent the average difference in effective connectivity. The yellow dotted line represents a decreased excitatory effect, and the cyan solid/dotted line represents an increased/decreased inhibitory effect in the OW/OB group compared with NW group. All posterior probability values of each surviving connection are greater than 0.95. **c** Group differences in the EC matrix of the three brain regions after Bayesian model reduction. Connections were retained after pruning any parameters that did not contribute to the free energy (i.e., posterior probabilities with v. without were $> 95\%$). Colors show the connection parameters (in Hz) obtained by Bayesian model averaging. EC effective connectivity, OW/OB overweight/obesity, NW normal weight, CAU caudate, SFG superior frontal gyrus, vmPFC ventromedial prefrontal cortex, L left; R right.

significantly predicted food enjoyment one year later ($r_{(\text{predicted}, \text{observed})} = 0.130$, $p = 0.026$, see Fig. 4(d)). Notably, the results indicated a close relationship between changes in eating behaviors and baseline connections. Specifically, the intrinsic caudate→caudate connectivity significantly predicted changes in desire to drink water ($r_{(\text{predicted}, \text{observed})} = 0.267$, $p = 0.038$) one year later. Similarly, the vmPFC→SFG connectivity significantly predicted changes in food enjoyment one year later ($r_{(\text{predicted}, \text{observed})} = 0.173$, $p = 0.016$, see Fig. 4(e-f)).

DISCUSSION

The present study employed the spDCM technique to investigate the EC profiles based on resting-state fMRI data, aiming to examine abnormal connectivity patterns in the reward-inhibition dual-system in children with OW/OB. We found that the OW/OB group showed stronger FC between the left SFG and left caudate but weaker FC between the left SFG and right vmPFC. In addition, the negative EC from the left caudate to left SFG was stronger, while the negative EC from the left SFG to right vmPFC and the positive EC from the right vmPFC to left SFG were significantly weaker in the OW/OB group. Altered FCs between the reward and inhibitory control systems may reflect a reduced ability to

maintain a balance between reward reactivity and inhibitory control in the OW/OB group, and abnormal ECs further reveal the directionality of dysfunctional communication between the dual systems. This study is the first to reveal abnormal EC patterns between the dual systems in children with OW/OB, which will deepen our understanding of the neural mechanisms underlying childhood obesity. These findings reveal that interventions targeting reward function and inhibition control may have important implications for childhood obesity.

Altered functional connectivity in childhood obesity

Enhanced functional connectivity in children with overweight and obesity. We observed that the FC between the left SFG and left caudate was stronger in the OW/OB group, relative to the NW group. However, one study involving children aged 9 to 10 years reported that higher BMI was associated with decreased intra-network and inter-network FC, including the salience and cingulo-opercular networks [19]. This difference may be due to differences in the extent of functional networks and regions of interest. Additionally, these findings varied depending on the sample sizes of participants (i.e., $n = 4576$ or $n = 106$). The SFG has been consistently associated with inhibitory control and top-down cognitive regulation of eating [11, 40, 41]. The caudate nucleus is a

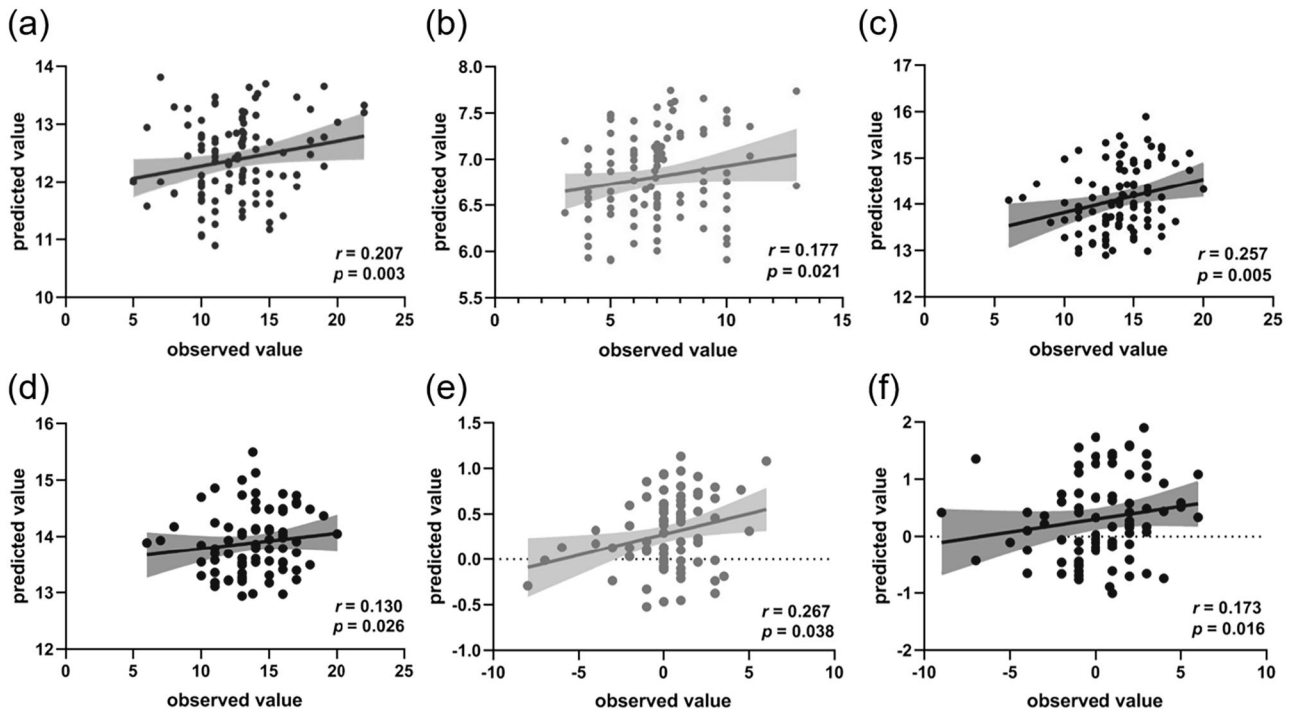


Fig. 4 The correlation between the observed and predicted EB values. *P* values were based on 1000 permutation tests. **a** The CAU → CAU connectivity-FD predictive model. **b** The CAU → CAU connectivity-DDW predictive model. **c** The vmPFC → SFG connectivity-FE predictive model. **d** The vmPFC → SFG connectivity-FE predictive model after controlling for baseline eating behaviors. **e** Predictive model of the CAU → CAU connectivity-changes in DDW. **f** Predictive model of the vmPFC → SFG connectivity-changes in FE. EB eating behaviors, CAU caudate, SFG superior frontal gyrus, vmPFC ventromedial prefrontal cortex, FD food response, DDW desire to drink water, FE food enjoyment. In (a–c), $n = 106$, and in (d–f), $n = 80$.

crucial region for reward processing, including reward anticipation, reactivity, and sensitivity [42–44]. Given that pediatric obesity has been linked to altered resting-state connectivity between cognitive control and reward processing networks [45], our findings may suggest an impaired ability to maintain a balance between reward reactivity and inhibitory control in children with OW/OB.

Weakened functional connectivity in children with overweight and obesity. The finding that the OW/OB group showed weaker FC between the left SFG and vmPFC compared to the NW group aligns with recent rs-fMRI studies. These have reported an inverse association between BMI and functional synchronization within the reward and control networks [4, 19]. The vmPFC and its related networks are involved in the rewarding aspects of eating, which could predispose individuals toward overconsuming unhealthy high-calorie foods) and contribute to impulsive responses and binge eating behaviors [46, 47]. In the present study, the reduced FC between the left SFG and right vmPFC in the OW/OB group suggests that children with excess weight may have decreased communication between brain regions involved in food reward and self-control.

After applying the pediatric template and controlling for sex, age, and head motion, we did not obtain identical FC results with two-sided tests. Significant findings were only observed under uncorrected conditions with one-sided tests. The partial consistency of FC results when using a pediatric MNI template warrants careful interpretation. While the uncorrected similar results may reflect the potential biological relevance, the absence of statistical significance after false discovery rate (FDR) correction may reflect neuroanatomical variations between the American-sourced template and the current Chinese pediatric data. Existing studies have demonstrated that populations of different ethnic groups exhibit significant

differences in brain structure and function [48, 49]. These discrepancies could attenuate template-based normalization accuracy, particularly for spatially sensitive connectivity metrics (e.g., vmPFC-SFG pathways). Thus, while the conceptually similar findings are retained, population-specific pediatric templates are critical for future validation in Chinese populations. In addition, the differences between the original results and those obtained using the pediatric template highlight the importance of adopting age-appropriate templates in future studies to minimize spatial distortions during preprocessing and improve the reliability of developmental neuroimaging findings.

Altered effective connectivity in childhood obesity

Enhanced effective connectivity in children with overweight and obesity. We further identified a stronger negative EC from the left caudate to SFG in children with OW/OB, which is in line with our results of enhanced FC between the left SFG and caudate. The negative effect means that brain activity in the left caudate might decrease the rate of change in activity in the left SFG [33, 50]. Although no studies have explored the directional interaction between reward and inhibitory control systems at rest in children, some evidence suggests the crucial role of resting-state FC in children's eating behaviors and childhood obesity (e.g., the left MFG–vmPFC connectivity) [4, 19, 21]. One possible explanation for this finding is that increased interference from the left caudate to SFG at rest, as indicated by the enhanced negative effect, may be linked to dysfunctional communication between the reward and inhibitory control systems in children with OW/OB.

Weakened effective connectivity in children with overweight and obesity. The most prominent finding was the significantly weaker negative effect from the SFG to vmPFC in the OW/OB group. A recent study reported that BMI was positively associated with increased EC from the lateral prefrontal cortex

to the left anterior insula in patients with type 2 diabetes mellitus, suggesting that the EC from inhibitory control to reward regions is stronger in adults at higher weight [24]. The discrepancy may largely stem from differences in the samples. Specifically, children's brains are still developing, while adults' brains are fully developed, which could result in inherent differences in spontaneous brain activity during rest [51]. Regarding our results, the negative effect from the inhibitory control region to reward region might reflect the underlying information exchange, in which inhibitory control information in the SFG suppresses the conversion of reward sensitivity information in the vmPFC, thereby exerting executive function. Hence, the reduced SFG→vmPFC connectivity strength of children with OW/OB might suggest a diminished capacity for such information exchange.

Interestingly, the positive effect from the vmPFC to SFG was also decreased in the OW/OB group. The positive effect means that brain activity in the vmPFC might increase the rate of change in activity in the SFG. Accordingly, the weaker positive EC from the vmPFC to SFG reflects a weaker weak excitatory of the inhibitory control region, suggesting that children with OW/OB may have a diminished capacity to balance behavioral control and reward reactivity. More importantly, both bidirectional ECs between the SFG and vmPFC were significantly attenuated, indicating a poor overall synergy between the inhibitory control region (SFG) and the reward-related brain region (ventromedial prefrontal cortex (vmPFC)) in children with OW/OB. Taken together, the EC results expand prior studies by revealing the directionality of information flow between the core nodes at rest, and again support complex interactions between inhibitory control and reward systems in childhood obesity.

Baseline connections predict future eating behaviors

Our analyses revealed distinct predictive patterns within reward and valuation circuits regarding eating behaviors. In the initial model, baseline intrinsic caudate→caudate connectivity predicted future food response and desire to drink water, while the vmPFC→SFG connectivity predicted food enjoyment. After controlling for baseline eating behaviors, however, only the vmPFC→SFG connectivity significantly predicted food enjoyment one year later. Critically, the results revealed that intrinsic caudate→caudate connectivity predicted the changes in desire to drink water and the vmPFC→SFG connectivity predicted the changes in food enjoyment, independent of baseline behaviors. Previous studies found that baseline FC or EC in dual-system (e.g., FC of the hippocampus and frontoparietal network, EC of the right hippocampus and left postcentral gyrus) could predict eating behaviors one year later [25, 26]. Our findings provide additional evidence for the association between dual-system connectivity and children's eating behaviors.

The caudate, a hub of the striatal reward system, shows altered dopaminergic regulation in obesity [43]. Its intrinsic connectivity may reflect neuroplastic changes in dopamine receptor availability, where obesity-related downregulation enhances reward-seeking behaviors across consummatory domains [43, 52]. Conversely, the vmPFC→SFG pathway may integrate subjective food valuation (vmPFC) and control (SFG). Weakened top-down regulation in obesity permits progressive hedonic adaptation, where baseline connectivity strength influences future trajectories of food enjoyment [26, 51]. Mechanistically, these processes may involve synaptic efficacy changes in glutamatergic projections or neuroinflammatory pathways exacerbated by high-fat diets [45, 53]. Importantly, these neural indexes predicted behavioral changes independent of baseline status, suggesting that they may capture latent neuroplastic vulnerability preceding observable symptom shifts. Future studies should investigate whether these predictive signatures are generalizable across diverse weight trajectories.

Limitations and future directions

This study has several potential limitations. Our sample included a wide age range (from 8 to 13 years old), and the sample size was relatively small ($n = 106$), which may affect the generalizability of the findings. Large-scale cohort studies of children are needed to further validate the stability of the results. Given that pubertal status has been recognized as an important factor associated with brain function and structure [54], it is essential for future research to validate our findings by incorporating pubertal status (e.g., utilizing the Pubertal Development Scale) as covariates of no interest [55]. In addition, the present study employed a cross-sectional design, which cannot infer a causal relationship between neural interactions and childhood obesity; therefore, prospective longitudinal studies are necessary to further investigate this issue. Lastly, the hypothesis-driven DCM technique relies on a priori assumption on which brain regions to include in the model space, thus limiting the number of regions that can be evaluated [50]. Future studies could utilize a causal search algorithm (e.g., GIMME), which can incorporate more regions than DCM, thereby supporting more complex model explanations of neurological activity in children at higher weight.

CONCLUSION

This study represents the first attempt to combine the FC and EC indices to identify the underlying neural interaction patterns in children with OW/OB at rest, from the perspective of a reward-inhibition dual-system interaction. Children with OW/OB exhibited abnormal functional synchrony between the reward and inhibitory control systems (i.e., stronger SFG-caudate connectivity and weaker SFG-vmPFC connectivity). Furthermore, the altered directional connections among the caudate, SFG and vmPFC (i.e., stronger caudate→SFG connectivity, weaker SFG→vmPFC and weaker vmPFC→SFG connectivity) may act as crucial neuromarkers of childhood obesity. Importantly, these core obesity-related connections could be generalized to predict future eating behaviors. The current study provides novel evidence on the neural hierarchical basis of childhood obesity, suggesting that interventions targeting reward processing and inhibition control may have important implications for childhood obesity.

DATA AVAILABILITY

Data will be made available on request.

REFERENCES

- Ji CY, Cheng TO. Epidemic increase in overweight and obesity in Chinese children from 1985 to 2005. *Int J Cardiol.* 2009;132:1–10.
- Key facts: Obesity and overweight. <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>. 2022.
- Yuan X, Jiang H, Wei Y, Wang H, Wang Z, Zhang B, et al. Relationship between macronutrients intake and overweight/obesity among Chinese children and adolescents aged 6–17 years in 2018. *Acta Nutrimenta Sin.* 2024;46:215–9+227.
- Brooks SJ, Smith C, Stamoulis C. Excess BMI in early adolescence adversely impacts maturing functional circuits supporting high-level cognition and their structural correlates. *Int J Obes.* 2023;47:590–605.
- Salama M, Balagopal B, Fennoy I, Kumar S. Childhood Obesity, Diabetes, and Cardiovascular Disease Risk. *J Clin Endocrinol Metab.* 2023;108:3051–66.
- Cui J, Li G, Zhang M, Xu J, Qi H, Ji W, et al. Associations between body mass index, sleep-disordered breathing, brain structure, and behavior in healthy children. *Cereb Cortex.* 2023;33:10087–97.
- Lindberg L, Hagman E, Danielsson P, Marcus C, Persson M. Anxiety and depression in children and adolescents with obesity: a nationwide study in Sweden. *BMC Med.* 2020;18:30.
- Farr OM, Li CshanR, Mantzoros CS. Central nervous system regulation of eating: Insights from human brain imaging. *Metab-Clin Exp.* 2016;65:699–713.
- Yokum S, Stice E. Relation of Overweight/Obesity to Reward Region Response to Food Reward and the Moderating Effects of Parental History of Eating Pathology in Adolescent Females. *Nutrients.* 2023;15:2558.

10. Guo Y, Xia Y, Chen K. The body mass index is associated with increased temporal variability of functional connectivity in brain reward system. *Front Nutr.* 2023;10:1210726.
11. Liu X, Turel O, Xiao Z, Lv C, He Q. Neural differences of food-specific inhibitory control in people with healthy vs higher BMI. *Appetite.* 2023;188:106759.
12. Murray SB, Alba C, Duval CJ, Nagata JM, Cabeen RP, Lee DJ, et al. Aberrant functional connectivity between reward and inhibitory control networks in pre-adolescent binge eating disorder. *Psychol Med.* 2023;53:3869–78.
13. Pujol J, Blanco-Hinojo L, Martinez-Vilavella G, Deus J, Perez-Sola V, Sunyer J. Dysfunctional brain reward system in child obesity. *Cereb Cortex.* 2021;31:4376–85.
14. Assari S, Boyce S, Bazargan M. Nucleus accumbens functional connectivity with the frontoparietal network predicts subsequent change in body mass index for American Children. *Brain Sci.* 2020;10:703.
15. Carnell S, Benson L, Chang KY (Virginia), Wang Z, Huo Y, Geliebter A, et al. Neural correlates of familial obesity risk and overweight in adolescence. *NeuroImage.* 2017;159:236–47.
16. Ronan L, Alexander-Bloch A, Fletcher PC. Childhood obesity, cortical structure, and executive function in healthy children. *Cereb Cortex.* 2020;30:2519–28.
17. Stice E, Burger K. Neural vulnerability factors for obesity. *Clin Psychol Rev.* 2019;68:38–53.
18. Nederkoorn C, Braet C, Van Eijs Y, Tanghe A, Jansen A. Why obese children cannot resist food: the role of impulsivity. *Eat Behav.* 2006;7:315–22.
19. Kaltenhauser S, Weber CF, Lin H, Mozayan A, Malhotra A, Constable RT, et al. Association of Body Mass Index and Waist Circumference with imaging metrics of brain integrity and functional connectivity in children aged 9 to 10 years in the US, 2016–8. *JAMA Netw Open.* 2023;6:e2314193.
20. Smith KE, Luo S, Mason TB. A systematic review of neural correlates of dysregulated eating associated with obesity risk in youth. *Neurosci Biobehav Rev.* 2021;124:245–66.
21. Black WR, Lepping RJ, Bruce AS, Powell JN, Bruce JM, Martin LE, et al. Tonic hyperconnectivity of reward neurocircuitry in obese children. *Obesity.* 2014;22:1590–3.
22. Friston KJ, Kahan J, Biswal B, Razi A. A DCM for resting state fMRI. *NeuroImage.* 2014;94:396–407.
23. Voigt K, Andrews ZB, Harding IH, Razi A, Verdejo-Garcia A. Hypothalamic effective connectivity at rest is associated with body weight and energy homeostasis. *Netw Neurosci.* 2022;6:1316–33.
24. Zhang Y, Yin X, Chen YC, Chen H, Jin M, Ma Y, et al. Aberrant brain triple-network effective connectivity patterns in type 2 diabetes mellitus. *Diab Ther.* 2024;15:1215–29.
25. Cerit H, Davidson P, Hye T, Moondra P, Haimovici F, Sogg S, et al. Resting-state brain connectivity predicts weight loss and cognitive control of eating behavior after vertical sleeve gastrectomy. *Obesity.* 2019;27:1846–55.
26. Li W, Chen X, Gao X, Pang Q, Guo C, Song S, et al. Altered hippocampal effective connectivity predicts BMI and food approach behavior in children with obesity. *Int J Clin Health Psychol.* 2025;25:100541.
27. Wardle J, Guthrie C, Sanderson S, Rapoport L. Development of the children's eating behaviour questionnaire. *J Child Psychol Psychiatry.* 2001;42:963–70.
28. Yan CG, Cheung B, Kelly C, Colcombe S, Craddock RC, Di Martino A, et al. A comprehensive assessment of regional variation in the impact of head micro-movements on functional connectomics. *NeuroImage.* 2013;76:183–201.
29. Fonov V, Evans AC, Botteron K, Almlri CR, McKinstry RC, Collins DL. Unbiased average age-appropriate atlases for pediatric studies. *NeuroImage.* 2011;54:313–27.
30. Bhutani S, Christian IR, Palumbo D, Wiggins JL. Reward-related neural correlates in adolescents with excess body weight. *NeuroImage: Clin.* 2021;30:102618.
31. Jiang F, Li G, Ji W, Zhang Y, Wu F, Hu Y, et al. Obesity is associated with decreased gray matter volume in children: a longitudinal study. *Cereb Cortex.* 2023;33:3674–82.
32. Nakamura Y, Ozawa S, Koike S. Caudate functional connectivity associated with weight change in adolescents. *Front Hum Neurosci.* 2020;14:587763.
33. Chen X, Li W, Liu Y, Xiao M, Chen H. Altered effective connectivity between reward and inhibitory control networks in people with binge eating episodes: A spectral dynamic causal modeling study. *Appetite.* 2023;188:106763.
34. Bajaj S, Killgore WDS. Association between emotional intelligence and effective brain connectome: a large-scale spectral DCM study. *NeuroImage.* 2021;229:117750.
35. Friston KJ, Litvak V, Oswal A, Razi A, Stephan KE, van Wijk BCM, et al. Bayesian model reduction and empirical Bayes for group (DCM) studies. *NeuroImage.* 2016;128:413–31.
36. Zeidman P, Jafarian A, Seghier ML, Litvak V, Cagnan H, Price CJ, et al. A guide to group effective connectivity analysis, part 2: Second level analysis with PEB. *NeuroImage.* 2019;200:12–25.
37. Worsley K, Marrett S, Neelin P, Vandal A, Friston K, Evans A. A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp.* 1996;4:58–73.
38. Mao Y, Zuo XN, Ding C, Qiu J. OFC and its connectivity with amygdala as predictors for future social anxiety in adolescents. *Dev Cogn Neurosci.* 2020;44:100804.
39. Shapiro ALB, Johnson SL, Sutton B, Legget KT, Dabelea D, Tregellas JR. Eating in the absence of hunger in young children is related to brain reward network hyperactivity and reduced functional connectivity in executive control networks. *Pediatr Obes.* 2019;14:e12502.
40. Haynos AF, Camchong J, Pearson CM, Lavender JM, Mueller BA, Peterson CB, et al. Resting state hypoconnectivity of reward networks in binge eating disorder. *Cereb Cortex.* 2021;31:2494–504.
41. Tuulari JJ, Karlsson HK, Hirvonen J, Salminen P, Nuutila P, Nummenmaa L. Neural circuits for cognitive appetite control in healthy and obese individuals: an fMRI study. *PLoS One.* 2015;10:e0116640.
42. Balleine BW, Delgado MR, Hikosaka O. The role of the dorsal striatum in reward and decision-making. *J Neurosci.* 2007;27:8161–5.
43. Nummenmaa L, Hirvonen J, Hannukainen JC, Immonen H, Lindroos MM, Salminen P, et al. Dorsal striatum and its limbic connectivity mediate abnormal anticipatory reward processing in obesity. *PLoS One.* 2012;7:e0031089.
44. Zhang Y, Ji W, Jiang F, Wu F, Li G, Hu Y, et al. Associations among body mass index, working memory performance, gray matter volume, and brain activation in healthy children. *Cereb Cortex.* 2023;33:6335–44.
45. Sadler JR, Thapaliya G, Ranganath K, Gabay A, Chen L, Smith KR, et al. Paediatric obesity and metabolic syndrome associations with cognition and the brain in youth: Current evidence and future directions. *Pediatr Obes.* 2023;18:e13042.
46. Balodis IM, Molina ND, Kober H, Worhunsky PD, White MA, Sinha R, et al. Divergent neural substrates of inhibitory control in binge eating disorder relative to other manifestations of obesity. *Obesity.* 2013;21:367–77.
47. Vainik U, Garcia-Garcia I, Dagher A. Uncontrolled eating: a unifying heritable trait linked with obesity, overeating, personality and the brain. *Eur J Neurosci.* 2019;50:2430–45.
48. Rao NP, Jeelani H, Achalia R, Achalia G, Jacob A, Bharath RD, et al. Population differences in brain morphology: Need for population specific brain template. *Psychiatry Res: Neuroimaging.* 2017;265:1–8.
49. Cao G, Zhang S, He Z, Wang Z, Guo L, Yan Z, et al. Gyrus peak variations between HCP and CHCP: functional and structural implications. *Brain Struct Funct.* 2025;230:37.
50. Maturana-Quijada P, Steward T, Vilarrasa N, Miranda-Olivos R, Jimenez-Murcia S, Carey HJ, et al. Dynamic fronto-amygdalar interactions underlying emotion-regulation deficits in women at higher weight. *Obesity.* 2023;31:2283–93.
51. Lowe CJ, Morton JB, Reichelt AC. Adolescent obesity and dietary decision making—a brain-health perspective. *Lancet Child Adolesc Health.* 2020;4:388–96.
52. Volkow ND, Wang GJ, Telang F, Fowler JS, Thanos PK, Logan J, et al. Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: Possible contributing factors. *NeuroImage.* 2008;42:1537–43.
53. Ribeiro R, Silva EG, Moreira FC, Gomes GF, Cussat GR, Silva BSR, et al. Chronic hyperpalatable diet induces impairment of hippocampal-dependent memories and alters glutamatergic and fractalkine axis signaling. *Sci Rep.* 2023;13:16358.
54. Murray SB, Duval CJ, Balkchyan AA, Cabeen RP, Nagata JM, Toga AW, et al. Regional gray matter abnormalities in pre-adolescent binge eating disorder: a voxel-based morphometry study. *Psychiatry Res.* 2022;310:114473.
55. Chen X, Li W, Qin J, Gao X, Liu Y, Song S, et al. Gray matter volume and functional connectivity underlying binge eating in healthy children. *Eat Weight Disord-Stud Anorex Bulim Obes.* 2022;27:3469–78.

ACKNOWLEDGEMENTS

This study was funded by National Natural Science Foundation of China (Nos. 32271087; 32500937), National Social Science Foundation of China (No. 22&ZD184), Philosophy and Social Science Collaborative Innovation Team in Chongqing Universities (No. 7110200530), and the Fundamental Research Funds for the Central Universities (No. SWU2509739). The authors would like to express their gratitude to all associated research assistants for their help with participant recruitment and data collection and thank all participants for their time and cooperation.

FUNDING

This study was funded by the National Natural Science Foundation of China (No. 32271087; 32500937), the National Social Science Foundation of China (No. 22&ZD184), Philosophy and Social Science Collaborative Innovation Team in Chongqing Universities (No. 7110200530), and Fundamental Research Funds for the Central Universities (No. SWU2509739).

AUTHOR CONTRIBUTIONS

Hong Chen, Haiyan Xin, and Ximei Chen were responsible for conceiving experiments. Haiyan Xin and Ximei Chen analyzed the data, interpreted the results, conducted literature searches, generated figures, and wrote the original article. Wei Li and Mingyue Xiao searched the literature and interpreted the data. Shiqing Song and Yong Liu contributed to organizing the data and executing the experiments. Hong Chen, Xiao Gao, and Cheng Guo managed the project and provided feedback on the manuscript. All authors were involved in writing the paper and gave their final approval for both the submitted and published versions.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41366-025-01973-5>.

Correspondence and requests for materials should be addressed to Ximei Chen or Hong Chen.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.