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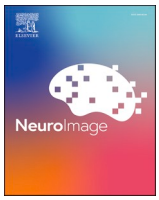

Influence of insulin sensitivity on food cue evoked functional brain connectivity in children

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ABSTRACT

Objective: Insulin resistance during childhood is a risk factor for developing type 2 diabetes and other health problems later in life. Studies in adults have shown that insulin resistance affects regional and network activity in the brain which are vital for behavior, including ingestion and metabolic control. To date, no study has investigated how brain connections during exposure to food cues are association with peripheral insulin sensitivity in children.

Methods: We included 53 children (36 girls) between the age of 7–11 years, who underwent an oral Glucose Tolerance Test (oGTT) to estimate peripheral insulin sensitivity (ISI). Brain responses were measured using functional magnetic resonance imaging (fMRI) before and after glucose ingestion. We compared food-cue task-based activity and functional connectivity (FC) between children with lower and higher ISI, adjusted for age and BMIz.

Results: Independent of prandial state (i.e., glucose ingestion), children with lower ISI showed higher FC between the anterior insula and caudate and lower FC between the posterior insula and mid temporal cortex than children with higher ISI. Sex differences were found based on prandial state and peripheral insulin sensitivity in the insular FC. No differences were found on mean brain responses to food cues.

Conclusions: In response to food cues, children with lower peripheral insulin sensitivity exhibited distinctive patterns of neural connectivity, notably in the insula's functional connections, when contrasted with their counterparts with higher peripheral insulin sensitivity. These differences might influence eating behavior and future risk of developing diabetes.

1. Introduction

The prevalence of overweight and obesity among the global population is increasing worldwide, with 43 % of adults living with these conditions [World Health Organization (WHO), 2024].Unfortunately, this upward trend impacts children as well, with 18 % of European children between 2 and 7 years old having overweight/obesity (Garrido-Miguel et al., 2019). In several European countries, the number

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of children with overweight/obesity peaks at around 50 % in those aged 6–9 years old (Buoncristiano et al., 2021), a trend similar to that observed in the American population (Fryar et al., 2018). Overweight and obesity in childhood are risk factors for obesity and type 2 diabetes mellitus (T2DM) in adulthood (Barton, 2012), and they have adverse effects on psychological health, cognition, brain structure and function (Brooks et al., 2023; Wang et al., 2019). Peripheral insulin resistance, which is a condition where insulin is not able to adequately promote glucose uptake by peripheral tissues, is considered a risk factor for the future development of obesity, type 2 diabetes and cardiovascular diseases (Kahn et al., 2006).

Exposure to high-calorie food in the environment may promote overconsumption of unhealthy meals through stimulation of brain areas associated with reward and motivation (Pujol et al., 2021; Stice et al., 2013). These areas include the amygdala, anterior cingulate cortex, hippocampus, hypothalamus, dorsal and ventral striatum, insula, and prefrontal cortex (Yang et al., 2021). Supporting this theory, increased neural activation in response to pictures of high-caloric foods has been observed in individuals with obesity, compared to their lean counterparts, among adults, adolescents, and children (Li et al., 2023). Of note, neural reactivity to food cues is predictive of future weight gain and linked to food craving, which may contribute to obesity onset in both children and adults (Boswell and Kober, 2016; Stice et al., 2010). Functional connectivity (FC) between areas of the reward network during the presentation of food cues is also enhanced in adults with obesity, increasing the motivational value of food (Stoeckel et al., 2009) and food intake (Carnell et al., 2014), and decreasing self-regulation (Donofry et al., 2020a, b).

The current state of satiety and postprandial hormonal responses modulates regional brain activity and functional connectivity in areas essential for ingestive behaviour (Capucho and Conde, 2023). For example, the increase in insulin after glucose ingestion is associated with a reduction in food cue reactivity in the insula, striatum and orbitofrontal cortex in adults (Heni et al., 2014; Kroemer et al., 2013). Overall, the brain responses to glucose ingestion are more pronounced in children compared to adults, and they are related to overweight and obesity (Ge et al., 2021). In adults, insulin resistance is associated with heightened activation to food cues in the insula and cingulate cortex (Drummen et al., 2019). Moreover, it is linked to stronger reward network connectivity post-meal, potentially increasing the risk for overeating and obesity (Ryan et al., 2018). Additionally, insulin resistance in adolescents also correlates with lower activation to food cues in brain areas related to inhibitory control (Mucellini et al., 2022).

Even though glucose uptake in the brain is mostly independent of insulin, proper insulin signalling is essential for maintaining energy homeostasis and cognitive functions (Kullmann et al., 2020). Insulin receptors are expressed throughout the brain, including the hypothalamus, striatum, amygdala, hippocampus, insula cortex, and PFC [for a review, see Kullmann et al. (2020)]. In adults, central insulin action, measured by the neural response to intranasal insulin, has been found to modulate regional activity and FC of brain networks underlying food behaviour and reward (Kullmann et al., 2017, 2018; Tiedemann et al., 2017), attributed to regulating hunger, food craving and food choice differentially in adults with normal weight or obesity. First evidence points to the development of central insulin resistance in utero, as fetal brain responses to oral glucose were found to be slower in the offspring of mothers with gestational diabetes mellitus [GDM, Linder et al. (2015)]. Similarly, children exposed to GDM before the 26th week of gestation fail to inhibit hypothalamic activity following glucose consumption (Page et al., 2019). In the same cohort, hippocampal FC following food cues was also influenced by GDM exposure (Zhao et al., 2024). These differences in glucose-induced brain responses are interpreted as a possible risk factor for the development of obesity.

However, little is known about the impact of peripheral insulin sensitivity on the brain during childhood. To this end, the present study aims to explore the relationship between peripheral insulin sensitivity index (ISI) and both reactivity and whole-brain functional connectivity (FC) during a food cue task, before and after glucose ingestion, in children aged 7–11 years old. The analysis was conducted in the BrainChild Cohort on the effects of early-life exposures on brain and metabolic health (Page et al., 2019). Prior findings in this cohort have shown greater food-cue reactivity in brain areas involved in reward and motivation (i.e., orbitofrontal cortex, amygdala, striatum, insula) among children in the fasted state (Luo et al., 2019). In addition, prior reports in the BrainChild cohort have shown that prenatal exposure to maternal obesity or GDM is associated with alterations in the structural development of the hippocampus (Alves et al., 2020; Lynch et al., 2021), as well as greater food cue reactivity in brain reward regions and greater caloric intake (Luo et al., 2021). In the current study, we hypothesize that, in contrast to children with higher peripheral insulin sensitivity, those with lower insulin sensitivity will display increased whole brain activation and enhanced functional connectivity (FC) in response to food cues compared to non-food cues. We expected such effects in insulin-sensitive brain areas related to reward and motivation such as bilateral hypothalamus, nucleus accumbens, caudate nucleus, putamen, pallidum, hippocampus, amygdala, insula, and PFC (Kullmann et al., 2020). Additionally, in the same areas, we expect a reduction in both neural activation and functional connectivity in response to food cues post-glucose ingestion in children with higher insulin sensitivity.

2. Methods

2.1. Participants

The current study includes 53 healthy children aged 7 to 11 years old from the BrainChild study (Page et al., 2019), which examines risks for diabetes and obesity in children exposed to maternal gestational diabetes during pregnancy. Therefore, children were exposed to different levels of maternal gestational diabetes, obesity, or normal glycemic control during pregnancy. The children were recruited from Kaiser Permanente Southern California (KPSC). To be included, children had to be healthy, right-handed, with no neurological, psychological, or significant medical disorders, not taking medications affecting metabolism, and with normal or corrected vision. The analyses included here required functional MRI (fMRI) data before and after glucose consumption.

2.2. Procedure

Prior to data collection, parental consent and child assent were obtained. The Institutional Review Board of the University of Southern California and KPSC approved all procedures. The baseline study visits are comprised of two separate visits conducted on different days. During the first visit, anthropometric data were collected and an oral Glucose Tolerance Test (oGTT) was performed. The second visit involved the fMRI based food cue task conducted before and after glucose ingestion. For details see Luo et al. (2019).

The first measurements were conducted at the Clinical Research Unit of the USC Diabetes and Obesity Research Institute in the morning after a 12 h overnight fast. Child's anthropometric measures were collected as previously described (Page et al., 2019). BMIz (standardized BMI, specific for age and sex standard deviation) scores were computed for children based on the Center for Disease Control (CDC) normative data (2000 CDC Growth Charts for the United States: Methods and Development, 2002). Finally, a 3 h oGTT was performed, and children's peripheral insulin sensitivity (ISI) was estimated using the Matsuda index (Matsuda and DeFronzo, 1999).

During the second visit, which took place at the USC Dana and David Dornsife Neuroimaging Center, children underwent MRI measurements after being trained on a mock scanner. Here, children were familiarized with the environment, sounds, and the importance of staying still. They were provided with earplugs, noise-canceling headphones, and foam

cushions for stability before the scan began. The MRI protocol consisted of a food cue task before (fasted state) and ~15 min after the glucose drink. MRI scans were conducted in the morning between 8 and 10 AM, after a 12 h overnight fast. The food cue task is described in detail in Luo et al. (2019). In a randomized order, the participants were presented with 12 pictures of high-caloric food (F, high-caloric food such as french fries or pancakes) and 12 pictures of non-food pictures (NF, such as books and rulers) and were asked to attentively watch these pictures. Each block consisted of three pictures from one of the two stimulus types (F vs. NF), which were presented in a random order. The pictures were chosen based on pilot testing, which was conducted in studies with children of the same age group. Only food images previously rated as 'appealing' and 'familiar' and non-food images rated as 'familiar' were included. These images were selected from the International Affective Picture System (Lang, 2005) and from various internet sources, such as food blogs. All stimuli had a resolution of 1024 × 768 pixels but the food and non-food images were not matched for visual properties like color or shape. Each image was displayed for 4 s and followed by a 1 s inter-stimulus interval. The total duration of the task was 196 s. After the first MRI measurement, participants consumed a glucose drink (1.75 g/kg of body weight, max 75g) to match the design of the oGTT test performed on the first study visit. About 15 min after the glucose ingestion, participants underwent a second food cue task using the same procedure as before. Glucose ingestion was used to match the oGTT done in the previous visit. The picture set in the two food cue tasks was the same, with the order of the images randomized both within and between blocks. Overall, the task was optimized to detect differential effects (food vs. non-food) using a short stimulus onset asynchrony, rather than to assess common task effects or task effects relative to the implicit baseline. *Fig. 1* illustrates the study protocol.

2.3. MRI data acquisition

The imaging was conducted using a Siemens MAGNETOM Prismafit 3-Tesla scanner equipped with a 20-channel phased array coil. The children were positioned supine on the scanner bed and presented with food cue stimuli through a mirror attached to the head coil. Blood-oxygen-level-dependent (BOLD) functional scans were obtained using a single-shot gradient echo planar imaging sequence with these parameters: repetition time (TR) of 2000 milliseconds (ms), echo time (TE) of 25 ms, bandwidth of 2520 Hz/pixel, flip angle of 85°, field of view of 220 × 220 mm, matrix size of 64 × 64, voxel size 3 × 3 × 2.5, and a slice thickness of 4 mm, resulting in 32 slices covering the entire brain. A 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence was also collected as a structural template for multi-subject registration. Here, parameters were: repetition time of 1950 ms, echo time of 2.26 ms, flip angle of 9°, inversion time of 900 ms, matrix size of 256 × 256 × 224, a voxel resolution of 1 × 1 × 1 mm^3, acquired in interleaved order. The functional scan lasted for 196 s, and the structural scan for 4 min and 14 s.

2.4. Image preprocessing

The whole analysis (preprocessing, first-level, second-level, functional connectivity) of the fMRI data was conducted using Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12) software, which is implemented in Matlab (MathWorks, Natick, MA, USA). Prior to analysis, the functional images underwent slice time correction and realignment. The anatomical images were then co-registered to the mean functional image and segmented using unified segmentation, which allowed for normalization of the structural image to the standard adult Montreal Neurological Institute (MNI) space. The resulting transformation matrix was then used to normalize the

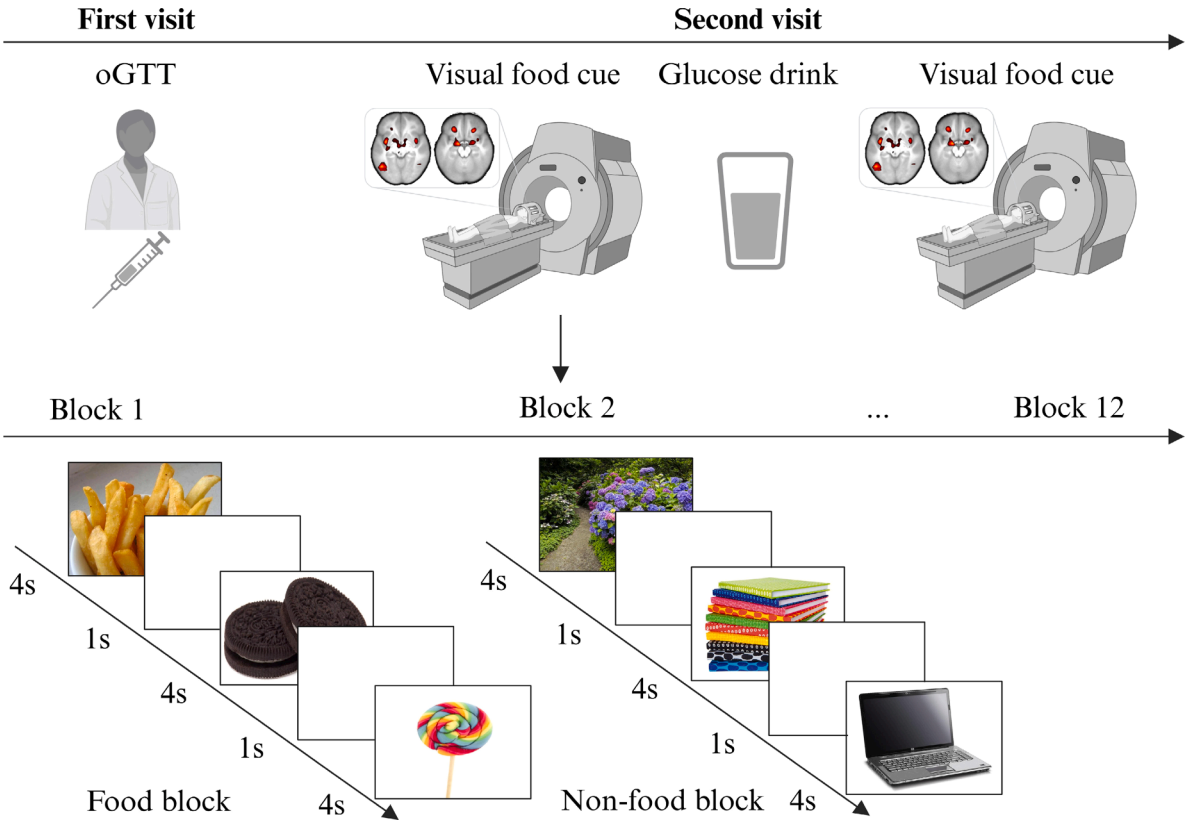

Fig. 1. Experimental protocol. During the first visit, children undergo an oGTT to assess their insulin sensitivity. During the second visit, children undergo food-cue task in an fMRI scanner before and after glucose ingestion. The food-cue task consists of 12 blocks of either food or non-food images. The figure was created with the help of Biorender.com.

realigned functional images. Prior studies in children used a standard adult MNI template for transformation (Bohon, 2017; Boutelle et al., 2015; Luo et al., 2019). Finally, the functional images were smoothed with an 8 mm FWHM Gaussian kernel. For noise correction, white matter and cerebrospinal fluid (CSF) signals were extracted from the normalized functional images using the PhysIO toolbox (Kasper et al., 2017). Analysis was confined to participants with complete datasets, encompassing pre- and post-glucose ingestion fMRI scans and separate oGTT results. Exclusion criteria included excessive motion during scans, defined as exceeding a threshold of 2 mm or 2° in any direction, in line with Luo et al. (2019). Visual inspections were also performed to detect artefacts. Of the 112 participants originally recruited, 51 were excluded due to excessive motion or acquisition artefacts — one due to a metallic interference and another due to detectable brain lesions. An additional eight participants were excluded for incomplete oGTTs. Consequently, 53 participants met the inclusion criteria for all analyses.

2.5. Neural food cue reactivity

For the first-level analyses, brain responses to stimuli were modelled for each participant as blocks convolved with a canonical hemodynamic response function using the general linear model. Two regressors representing high-caloric food images (F) and non-food images (NF) were included, respectively. To account for head motion, the six realignment parameters were included as confounds. The PCA based extracted white matter and CSF signals were also added as confounds. The data were high-pass filtered with a cut-off of 128 s and separate contrast images between F versus NF were calculated before and after glucose drink for each individual. In the second-level analysis, the F-NF images obtained from the first-level analysis were used in a full-factorial model (described below, see 2.7).

2.6. Functional connectivity. Generalized Psychophysiological Interaction (gPPI)

To investigate FC during the food cue task, a generalized psychophysiological interaction (gPPI) analysis was employed (McLaren et al., 2012, https://www.nitrc.org/projects/gppi, version 13.1), which is a well-established method for FC analysis in task-based fMRI. Nine seeds were defined based on significant neural food cue reactivity (F-NF contrast), using a spherical ROI with 6 mm ($p < 0.05$, FWE-cluster level; see *Table 2*). Functional brain connectivity was then calculated for each of these seed regions. The gPPI contrast images of F vs. NF for each seed region (and visit) were included in a second-level full-factorial model (described below, see 2.7).

2.7. Second level statistics

In the second-level analysis, the F-NF images (neural food cue reactivity and gPPI) obtained from the first-level analysis were used in a full-factorial model with ISI and sex as between-subject factors, and before vs. after glucose ingestion as a within-subject factor (time-point). The assignment of children with higher or lower ISI was based on median split (ISI-Matsuda range: 0.94–26.57, median split at 8.96). Age and BMIz were included as adjusted covariates. In addition, we tested whether body fat (%) and waist-hip ratio as alternative covariates to BMI in our analyses, given their association with metabolic disorders. Finally, we conducted an additional model including exposure to GDM as covariate to assess its potential impact on our findings.

The primary aim of the analysis was to evaluate the main effect of ISI (low vs high) and before and after glucose ingestion (time-point) on neural food-cue reactivity and functional connectivity. In exploratory analyses, interactions between sex and ISI and time-point were evaluated. Statistical significance was determined using a primary threshold of $p < 0.001$ uncorrected and a secondary threshold of $p < 0.05$ family wise error corrected for multiple comparisons at the cluster level (cFWE). We used the SPM Cluster Threshold toolbox (https://github.com/CyclotronResearchCentre/SPM_ClusterSizeThreshold) to calculate the minimum number of voxels which determine a significant cluster for a corrected p-value of 0.05. The resulting threshold for cluster significance was 65 voxels. In addition, small volume correction (svc) was performed for insulin-sensitive brain regions-of-interest (ROI's) including the bilateral hypothalamus, nucleus accumbens, caudate nucleus, putamen, pallidum, hippocampus, amygdala, insula, and PFC (Kullmann et al., 2020). These regions were combined in one single mask. The masks were based on the AAL atlas 3 (https://www.oxcns.org) and wfu_PickAtlas (https://www.nitrc.org/projects/wfu_pickatlas/). For our post-hoc testing, p-values were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) method (Benjamini and Hochberg, 1995).

3. Results

3.1. Participants

The 53 children included 29 girls and 24 boys, with a mean and standard deviation (SD) age of 8.59±0.99 years. The median ISI based Matsuda index was 8.96. *Table 1* presents the comparison of sex, exposure to GDM during pregnancy, age, adiposity measures, HOMA IR and ISI-Matsuda for the lower ISI vs. higher ISI group. Boys and girls are similarly distributed across the groups. As expected, high ISI is associated with lower adiposity and insulin resistance. *Supplementary Tables 1* and *2* provide additional information on the general characteristics of the included and excluded participants. In addition, *Supplementary Table 3* offers an overview of the participants' characteristics stratified by sex, showing no differences between boys and girls.

3.2. Neural food cue reactivity

In the whole brain analysis, we observed several regions that were more activated during visual presentation of high-caloric food images compared to non-food images (F-NF contrast, *Fig. 2*, *Table 2*). This corresponds to findings of previous studies investigating neural food cue responsivity (Luo et al., 2019). The coordinates reported in *Table 2* correspond to the centre of the 9 peak coordinates extracted and used as seed regions for the gPPI analysis (6 mm spherical ROIs). No significant main effects of time-point (before and after glucose ingestion), sex, or ISI were found. No significant 2-way interactions were found. Comparable results were obtained using body fat (%) or waist-hip ratio as alternative covariates to BMI in our analyses (data not shown).

Table 1
Participants' characteristics.

Variable	Lower ISI (N = 27)	Higher ISI (N = 26)	p-value
Sex	14 Girls / 13 Boys	15 Girls / 11 Boys	0.78
GDM exposure	12 GDM / 15 NGT	19 GDM / 7 NGT	0.051
	Mean ± SD	Mean ± SD	
Age (years)	8.88±1.07	8.28±0.82	0.026
BMI (kg/m^2)	21.09±4.85	16.99±2.27	<0.001
BMI percentile	80.86±23.09	59.07±27.10	0.002
BMI z-score	1.13±1.01	0.31±0.90	<0.001
Body fat (%)	28.94±9.93	21.00±5.94	<0.001
Waist-hip ratio	0.90±0.06	0.86±0.05	0.04
HOMA-IR	1.88±1.51	0.48±0.20	<0.001
ISI-Matsuda	5.43±2.58	16.16±4.66	<0.001
Fasting glucose (mg/dL)	88.70±10.65	82.16±8.68	0.02
2-hour glucose (mg/dL)	122.98±17.37	106.51±22.10	0.004

Abbreviations: ISI = insulin sensitivity index, SD = standard deviation, BMI = body mass index, HOMA-IR = homeostatic model assessment for insulin resistance, GDM = gestational diabetes mellitus, NGT = normal glucose tolerance. ISI-Matsuda range (0.94–26.57, median split at 8.96). Statistical comparisons were performed using Fisher's exact test for count variables and two-sample *t*-tests for continuous variables.

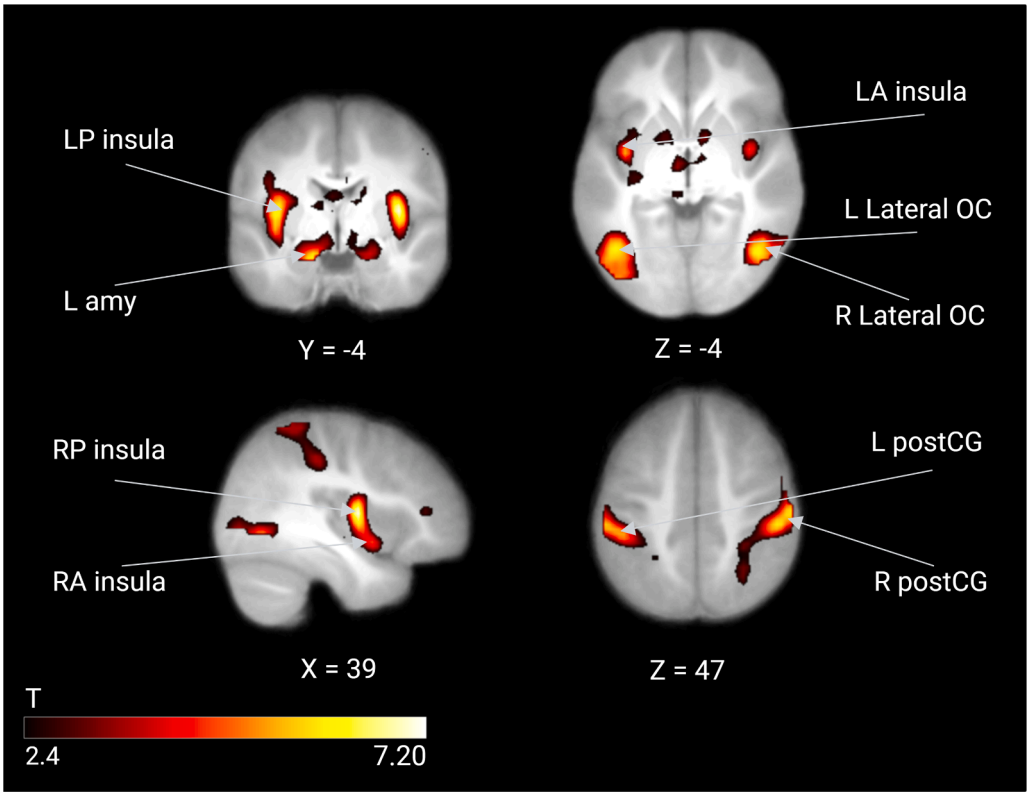

Fig. 2. Neural food cue reactivity. Figure shows food cue responsive brain areas based on the F-NF contrast. These regions were used as seeds for gPPI functional connectivity analysis. Color map corresponds to T values ($P < 0.001$ uncorrected for display) overlaid on the average normalized T1 weighted image of the children. R = right; L = left; P = posterior; A = anterior; amy = amygdala; postCG = postcentral gyrus; OC, occipital cortex.

Table 2
Brain food cue response (Food > non food).

Brain region	Peak MNI coordinates (X,Y,Z)	Peak t	p (cFWE)	Cluster size
R posterior Insula	39, −4, 8	7.19	0.012	116
R anterior Insula	36, 5, −13	5.20		
L posterior Insula	−39, −7, 8	7.12	<0.001	237
L anterior Insula	−36, 2, −10	5.58		
R Lateral occipital cortex	45, −64, −4	6.21	0.018	104
L Lateral occipital cortex	−45, −64, 4	6.16	<0.001	241
R Postcentral gyrus	60, −19, 41	6.13	<0.001	462
L Postcentral gyrus	−57, −28, 47	5.67	<0.001	349
L Amygdala	−15, −4, −22	6.07	0.031	89

Table presents areas in which activation was higher following presentation of high-caloric food compared to non-food pictures, before and after glucose ingestion, adjusted for age and BMI z-score. Labels from the SPM Neuromorphometrics atlas, adapted for children. Abbreviations: L = Left, R = Right, cFWE = family wise error corrected for multiple comparisons at the cluster level.

3.3. Task-based functional connectivity analysis

We investigated functional connectivity in response to food cues before and after glucose ingestion (time-point) in children with high and low peripheral insulin sensitivity. There was a significant main effect based on ISI group such that FC was higher between the left anterior insula and the right nucleus caudate in the lower ISI compared to the higher ISI group (Cohen's d = 1.25, *Fig. 3*, *Table 3*). In addition, we found lower FC between the left posterior insula and the right middle temporal gyrus (MTG) in the lower ISI compared to the higher ISI group (Cohen's d = −1.14, *Fig. 4*, *Table 3*).

We found an interaction between time-point × sex in FC between the left postcentral gyrus and the left anterior insula (*Fig. 5*, *Table 3*). FC in boys increased from before to after glucose ingestion, while it decreased in girls (Post hoc tests: Boys before < Boys after: t(46) = −2.60, p_{FDR} = 0.01, Cohen's d = −0.75; Girls before > Girls after: t(56) = 4.05, p_{FDR} = 0.0004, Cohen's d = 1.05; Boys before < Girls before: t(51) = −2.70, p_{FDR} = 0.004, Cohen's d = −0.84; Boys after > Girls after: t(51) = 3.61, p_{FDR} = 0.001, Cohen's d = 0.96).

We found an interaction between ISI × sex in FC between the right anterior insula and the left precentral gyrus (*Fig. 6*, *Table 3*). Boys with low ISI and girls with high ISI showed the strongest FC (Post hoc test: Boys lower ISI > Boys higher ISI: t(46) = 4.28, p_{FDR} = 0.001, Cohen's d = 1.01; Girls lower ISI < Girls higher ISI: t(56) = −3.61, p_{FDR} = 0.0004, Cohen's d = −1.16; Boys lower ISI > Girls lower ISI: t(52) = 3.70, p_{FDR} = 0.0004, Cohen's d = 1.22; Boys higher ISI < Girls higher ISI: t(50) = −4.34, p_{FDR} = 0.001, Cohen's d = −0.91).

No main effects of sex or of time-point were found. No other interactions were detected. Similarly to what was observed for food-cue reactivity, similar results on FC were obtained using body fat (%) or waist-hip ratio as alternative covariates to BMI in our analyses (data not shown).

After including exposure to GDM as an additional covariate (see *supplementary Table 4* and *supplementary figures 1–4*), the main effect of ISI on FC between the left anterior insula and the right nucleus caudate was no longer significant (p^{svc} = 0.14). The remaining findings stay largely unchanged. With a sample size of N = 53 children and a mean effect size of Cohen's d = 1.20 for the main effect (higher ISI vs. lower ISI), we achieved a statistical power of 0.99 at an alpha level of 0.05. For our interactions effects, with average Cohen's d = 0.99, the achieved power ranged between 64 and 72.

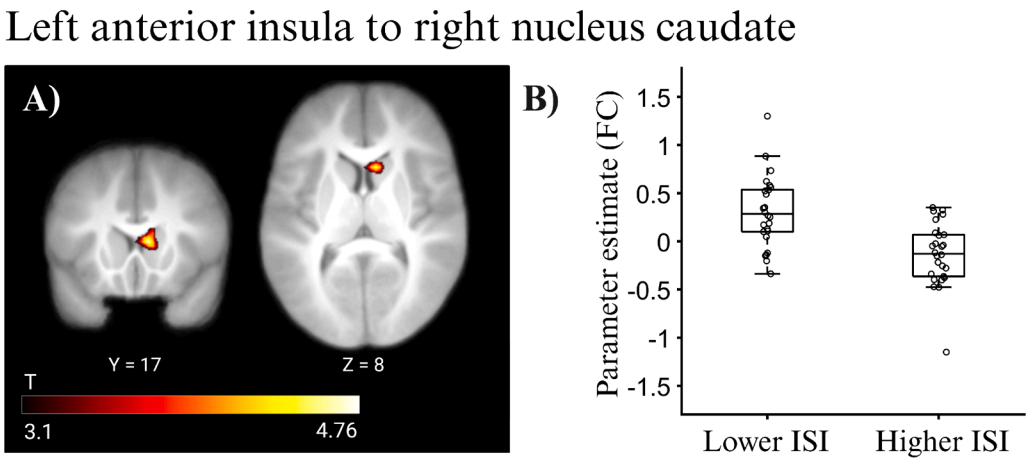

Fig. 3. Higher food-cue induced functional connectivity in lower ISI compared to higher ISI children. A) Shown is the cluster of the right nucleus caudate, revealing higher FC with the anterior insula in children with lower peripheral insulin sensitivity. Color map corresponds to T values ($P < 0.001$ uncorrected for display) overlaid on the average normalized T1 weighted image of the children. B) Box plots show the left anterior insula FC to the right nucleus caudate in children with lower and higher peripheral insulin sensitivity (lower ISI and higher ISI, respectively). Displayed the mean FC between before and after glucose ingestion. Whiskers indicate 1.5 interquartile range. ISI = Insulin Sensitivity Index. Data are adjusted for age and BMI z-score.

Table 3
Food-cue induced functional connectivity (food vs. non-food).

Seed region	Target region	MNI coordinates of target region (X Y Z)			Peak T	Cluster size	p FWE
Lower ISI > Higher ISI							
L anterior insula	R Nucleus caudate	9	17	8	4.76	23	0.007[svc]
Lower ISI < Higher ISI							
L posterior insula	R Middle temporal gyrus	51	−28	−4	4.95	111	0.006*
Time-point (before vs. after glucose ingestion) × sex							
L postcentral gyrus	L anterior insula	−45	5	−10	5.10	189	<0.001*
ISI (Lower vs. Higher) × sex							
R anterior insula	L Precentral gyrus	−33	−13	50	4.50	189	<0.001*

R = right; L = left, FWE = family wise error corrected for multiple comparisons. Data are adjusted for age and BMI z-score.
* indicates significance at the cluster level.
svc indicates significance after small volume correction. For the svc, we used the mask as specified in section 2.7.

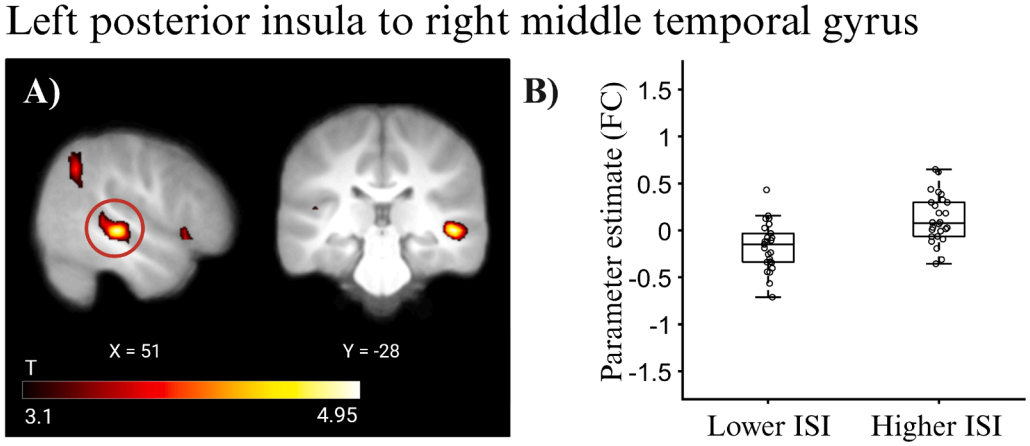

Fig. 4. Lower food-cue induced functional connectivity in lower ISI compared to higher ISI children. A) Shown is the cluster in the middle temporal gyrus, revealing lower FC with the left posterior insula in children with lower peripheral insulin sensitivity. Color maps on the left correspond to T values ($P < 0.001$ uncorrected for display) overlaid on the average normalized T1 weighted image of the children. B) Box plots show the left posterior insula FC to the right middle temporal gyrus in children with lower and higher peripheral insulin sensitivity (lower ISI and higher ISI, respectively). Displayed the mean FC between before and after glucose ingestion. Whiskers indicate 1.5 interquartile range. ISI = Insulin Sensitivity Index. Data are adjusted for age and BMI z-score.

4. Discussion

The aim of this study was to examine the relationship between peripheral insulin sensitivity and neural food-cue induced activity and functional connectivity (FC) both before and after glucose ingestion in children aged between 7 and 11 years from the BrainChild Cohort (Alves et al., 2020; Luo et al., 2019; 2021; Lynch et al., 2021). Neural food cue reactivity reported in the current study corresponds to previous works in the BrainChild study (Luo et al., 2019), with higher activity to food compared to non-food in the bilateral posterior and anterior insula,

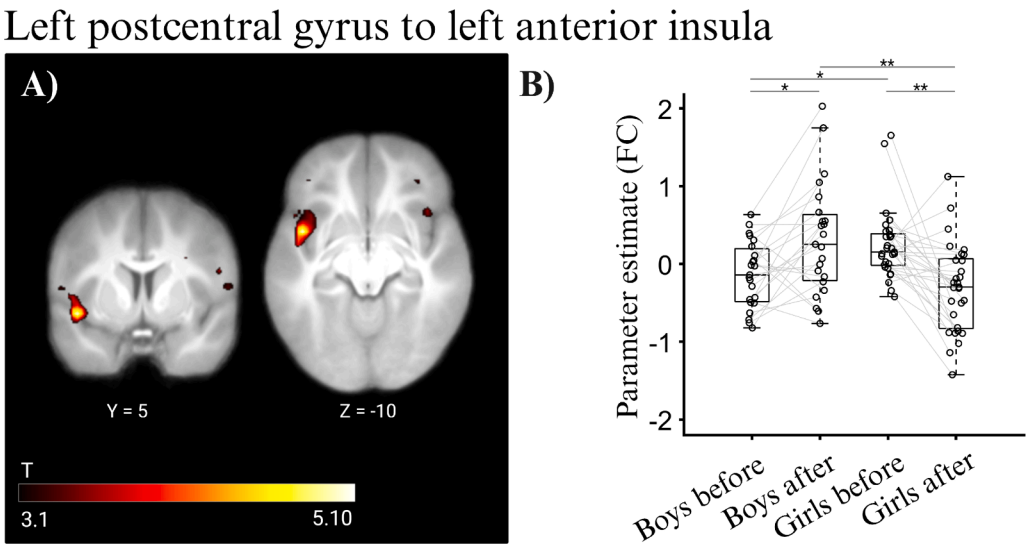

Fig. 5. Interaction between time-point (before and after glucose ingestion) and sex on functional connectivity in children. A) Shown are the clusters of the left postcentral gyrus network, revealing an interaction between sex and time-point (before and after glucose ingestion). Color maps on the left correspond to T values ($P < 0.001$ uncorrected for display) overlaid on the average normalized T1 weighted image of the children. B) Box plots showing the left postcentral gyrus FC to the left anterior insula in boys and girls before and after glucose ingestion. Whiskers indicate 1.5 interquartile range. * indicates $p_{FDR} \leq 0.01$, ** $p_{FDR} \leq 0.001$.

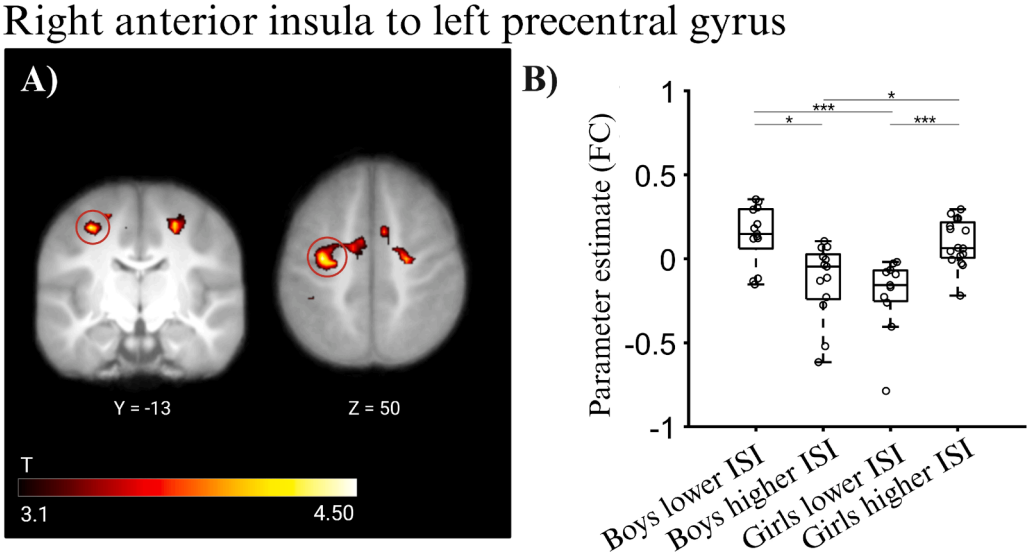

Fig. 6. Interaction between peripheral insulin sensitivity and sex on functional connectivity in children. A) Shown are the clusters of the right anterior insula network, revealing an interaction between sex and peripheral insulin sensitivity. Color maps on the left correspond to T values ($P < 0.001$ uncorrected for display) overlaid on the average normalized T1 weighted image of the children. B) Box plots showing the right anterior insula FC to the left precentral gyrus in boys and girls with lower and higher peripheral insulin sensitivity (lower ISI and higher ISI, respectively). Displayed the mean FC between before and after glucose ingestion. Whiskers indicate 1.5 interquartile range. * indicates $p_{FDR} \leq 0.01$, *** $p_{FDR} \leq 0.0001$. ISI = Insulin Sensitivity Index.

lateral occipital cortex, postcentral gyrus, and left amygdala to food compared to non-food visual cues. We found no significant effects of peripheral insulin sensitivity on whole-brain food cue reactivity. However, we observed that children's FC patterns in response to high-calorie food cues vary depending on their insulin sensitivity. Specifically, our findings indicate that children with lower insulin sensitivity exhibited altered insular functional connectivity to regions implicated in food processing (e.g. Li et al., 2023; Stice et al., 2008). These differences in FC patterns, particularly within the insular region, were evident both when children were fasting and after glucose ingestion, and might suggest an altered processing of homeostatic regulation of hunger (Parsons et al., 2022). Moreover, explorative analysis revealed sex differences in functional connectivity responses to food cues. Our results suggest that children with lower peripheral insulin sensitivity, independent of body mass index, have alterations in FC between food-cue responsive brain regions regardless of prandial state. In addition, we obtained similar results considering body mass index, body fat (%) or waist-hip ratio as covariates, suggesting that the choice of adiposity measure does not significantly alter the observed relationship between insulin sensitivity and food-cue evoked FC.

4.1. *Insular functional connectivity during food cues is associated with ISI*

While we found differences in FC during the food cue task with respect to peripheral insulin sensitivity, we did not observe differences in whole brain reactivity to food images. This corresponds to a recent meta-analysis showing that there is little evidence for obesity related differences on whole brain food cue reactivity in children and adults

suggesting that there are other mediating factors that may not have been considered thus far (Morys et al., 2020). Our results show, however, distinct patterns of insular FC during the viewing of food-cues in children based on their peripheral insulin sensitivity. Generally, reduced insulin responsiveness in the insula cortex has been observed in adults with peripheral insulin resistance and poor cognitive control (Wagner et al., 2022, 2023). Post hoc computation of achieved power revealed that our sample size was adequate to detect a main effect of insulin sensitivity of FC.

In our work, we found differences in connectivity independent of prandial state in two regions of the insula, an anterior and a posterior region that are known to underlie brain responses to taste and visual presentation of food (Avery et al., 2020; J.A. 2021). However, these two insular regions also present functional differences. While the dorsal, posterior region is associated with cognitive and attentional processing, the anterior ventral insula is primarily involved in social and emotional functions (Avery et al., 2021; Kurth et al., 2010). Connections of the two insular regions are also different. Specifically, the posterior section is mainly connected with frontoparietal regions, while the anterior ventral region is connected with emotional regions in the limbic system (Avery et al., 2021; Kurth et al., 2010). In agreement with our hypothesis, we observed higher FC between areas responsive to high-caloric food images in children with lower ISI vs. higher ISI, with higher FC between the left anterior insula and the right caudate (*Fig. 3*). The insula and caudate play a crucial role in associating food cues with rewards, in wanting and craving, and attributing subjective value to palatable food (Kahathuduwa et al., 2016). Hyper- or hypoactivations in neural activity along these areas are associated with alterations in reward processing, inhibitory control, and body weight regulation (Li et al., 2023) and may lead to overeating due to increased sensitivity to food cues (Meng et al., 2020; Rothemund et al., 2007). Prior studies have shown that adults with obesity (Stoeckel et al., 2009; Wijngaarden et al., 2015) and lean adolescents at high risk of developing obesity (Sadler et al., 2023) have higher FC between reward-related areas, which is thought to contribute to the elevated motivational value of food in this population. Specifically, heightened connectivity between the anterior insula and caudate was previously interpreted as one factor that may lead to overeating by impairing self-awareness, increasing arousal in response to food cues, and reducing responsiveness to a post-prandial state (Donofry et al., 2020b; Geha et al., 2017; Nummenmaa et al., 2012). In light of these previous reports, the observed heightened functional connectivity between the anterior insula and caudate in children with lower peripheral insulin sensitivity might serve as an early marker of insulin resistance and an increased susceptibility to obesity in youth. Notably, the ISI-based difference in FC to the caudate was no longer significant after adjusting for GDM exposure. This reflects current evidence suggesting that brain insulin sensitivity may mediate the effects of early life adversities, including GDM, on brain development, including striatal regions (Alberry and Silveira, 2023; Batra et al., 2021; Zhao et al., 2024).

In addition, we found that children with lower insulin sensitivity have lower FC between the left posterior insula and the right MTG (*Fig. 4*). The MTG is involved in emotional memory and processing of food odors (Dolcos et al., 2005; Han et al., 2021; Kohn et al., 2014). Adults with obesity exhibit reduced intrinsic activity in the MTG following intermittent energy restriction (Li et al., 2023). The authors attributed this reduction to a potential decrease in cognitive functions and neural processing of sensory information, which could in turn impact eating behavior. The role of MTG in obesity is found also in earlier life stages. For example, a lower FC in the MTG was found in adolescents with overweight and obesity (Moreno-Lopez et al., 2016). Furthermore, in children aged 7 to 9 with obesity, there was a lower brain response in the MTG when exposed to high-energy food pictures (Masterson et al., 2019). These results are consistent with the idea that metabolic conditions like overweight, obesity, and insulin resistance may have an effect not only on the brain networks responsible for metabolic control and reward, but also on more complex cognitive functions (Moreno-Lopez et al., 2016; Verdejo-García et al., 2010).

4.2. Sex differences on food cue induced FC

In our exploratory analysis, no overall sex differences were found on food-cue reactivity and FC. However, sex differences in FC were found depending on prandial state and on peripheral insulin sensitivity. Specifically, FC between the left postcentral gyrus and the left anterior insula increased after glucose ingestion in boys, and decreased in girls (*Fig. 5*). In addition, when comparing children with different ISI levels, we observed that boys with lower ISI had higher FC, whereas this trend was reversed in girls (*Fig. 6*). However, our power analysis revealed that a larger sample size would be required to achieve sufficient power for interaction effects. In the current analysis, interactions with sex were intended as exploratory, and while they provide valuable insight on food-cue processing in children, their significance should be interpreted with caution and have to be confirmed in future studies.

Generally, sex effects on insula and sensorimotor regions functional connectivity have been reported before in the context of obesity and metabolic research. However, the outcomes of these studies do not yet show a clear pattern. For example, there is some indication that males (vs. females) with obesity had higher FC in response to food cues with the amygdala in supplementary and primary motor areas (Atalayer et al., 2014; Kilpatrick et al., 2023). In addition, males showed a more prominent decrease in postprandial insular resting-state connectivity with sensorimotor and prefrontal cortex (Kilpatrick et al., 2020). Based on these results, the authors have suggested an increased vulnerability of males to obesity-related alterations in the precentral gyrus and occipital cortex (Gupta et al., 2017; Kilpatrick et al., 2023). In general, however, alterations in somatosensory regions in children with overweight and obesity might indicate an expanded somatosensory and motor cortical representation of the body as a function of body mass (Pujol et al., 2021). In their work, the authors found that higher body mass was associated with higher integration of the sensorimotor cortex to superior parietal regions that underlie body awareness. Possible sex differences might also be attributed to the differential distribution of subcutaneous and visceral adipose depots observed between males and females, which is implicated in insulin resistance (Machann et al., 2005).

5. Limitations

In the current analysis we recognize some limitations. The cross-sectional nature of the analysis precludes inference about the directionality between children's peripheral insulin sensitivity and the differences in brain functional connectivity. Moreover, since the majority of children in our study were peripherally insulin sensitive (ISI-Matsuda > 5) and the ISI distribution was skewed, the median split we applied represents an arbitrary threshold rather than a meaningful indicator of insulin resistance. Therefore, the group of lower ISI is partly insulin sensitive. In addition, GDM exposure may partially influence the observed brain connectivity patterns. Further research is needed to evaluate whether, and to what extent, children with obesity, insulin resistance and exposure to GDM show similar alterations to those observed the current study. Perinatal and birth variables are also not included in our sample. In addition, the ~15 min interval between the two food cues tasks (before and after glucose ingestion) may not capture neural food cue processing when circulating insulin levels are at their peak. Moreover, presenting the same set of food cues before and after glucose ingestion may introduce familiarity or habituation effects. Additionally, while our study was well powered to detect main effects of insulin sensitivity on FC, a larger sample size is needed to validate the interaction effects. Finally, in our analysis we focused on task-related FC during a food cue task. Analysis of resting-state connectivity is also useful to study brain network changes at a young age (Brooks et al., 2023).

6. Conclusion

The study investigated the relationship between peripheral insulin sensitivity and neural responses, encompassing both neural reactivity and whole brain FC in children during the processing of high-caloric food cues. Our findings showed no relationship between peripheral insulin sensitivity and whole-brain food reactivity. However, our data revealed a significant association between low peripheral insulin sensitivity and increased functional connectivity to the insula, specifically from neural circuits involved in food processing such as the caudate nucleus and the middle temporal gyrus. In addition, our exploratory analysis identified sex-specific patterns of functional connectivity that were dependent upon peripheral insulin sensitivity and the prandial state, whether fasted or post-glucose ingestion. However, future studies with larger sample sizes are needed to further validate these interactions. Overall, the results support the premise that lower insulin sensitivity, independent of body mass index, contributes to the modulation of neural communication within circuits governing food processing, reward, regulation of food intake, and emotional regulation in a pediatric population. These findings not only corroborate existing literature on obesity but also extend our understanding by delineating the congruent neural correlates of obesity and insulin resistance in children. The implications of this study are that metabolic dysregulations, including overweight, obesity, and lower insulin sensitivity, exert tangible effects on the brain networks implicated in metabolic control and cognitive operations, with these influences manifesting during the critical developmental stages of childhood.

Data availability

The data supporting the conclusions of this study are available and stored online on the Open Science Framework (OSF) website and they can be found using the following link: https://osf.io/4r6n9/. DOI number: 10.17605/OSF.IO/4R6N9.

CRediT authorship contribution statement

Lorenzo Semeia: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. **Ralf Veit:** Writing – review & editing, Supervision, Formal analysis. **Sixiu Zhao:** Writing – review & editing, Formal analysis. **Shan Luo:** Writing – review & editing, Investigation, Conceptualization. **Brendan Angelo:** Writing – review & editing, Data curation. **Andreas L. Birkenfeld:** Writing – review & editing, Supervision. **Hubert Preissl:** Writing – review & editing, Supervision. **Anny H. Xiang:** Writing – review & editing, Data curation, Conceptualization. **Stephanie Kullmann:** Writing – review & editing, Supervision. **Kathleen A. Page:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare no conflict of interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2025.121154.

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