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Imbalance in resting state functional connectivity is associated with eating behaviors and adiposity in children

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Abstract

Background and Hypothesis: Over the past 30 years, childhood obesity in the US has nearly doubled, while obesity has tripled among adolescents. Non-homeostatic eating, influenced by impulsivity and inhibition, may undermine successful long-term weight loss. We hypothesized that unhealthy eating habits and adiposity among children are associated with functional connectivity between brain regions associated with impulsivity, response inhibition, and reward.

Methods: We analyzed resting state functional magnetic resonance images from 38 children, ages 8–13. Using seed-based resting state functional connectivity, we quantified connectivity between brain regions associated with response inhibition (inferior parietal lobe [IPL]), impulsivity (frontal pole), and reward (nucleus accumbens [NAc]). We assessed the relationship of resting state functional

connectivity with adiposity, quantified by BMI z-score, and eating behaviors, as measured by the Child Eating Behaviour Questionnaire (CEBQ). We computed an imbalance measure—the difference between [FRONTAL POLE:NAC] and [IPL:NAC] functional connectivity—and investigated the relationship of this imbalance with eating behaviors and adiposity.

Results: As functional connectivity imbalance is increasingly biased toward impulsivity, adiposity increases. Similarly, as impulsivity-biased imbalance increases, food approach behaviors increase and food avoidance behaviors decrease. Increased adiposity is associated with increased food approach behaviors and decreased food avoidance behaviors.

Conclusions: In the absence of any explicit eating-related stimuli, the developing brain is primed toward food approach and away from food avoidance behavior with increasing adiposity. Imbalance in resting state functional connectivity that is associated with non-homeostatic eating develops during childhood, as early as 8–13 years of age. Our results indicate the importance of identifying children at risk for obesity for earlier intervention. In addition to changing eating habits and physical activity, strategies that normalize neural functional connectivity imbalance are needed to maintain healthy weight. Mindfulness may be one such approach as it is associated with increased response inhibition and decreased impulsivity.

Keywords: Methods in neuroscience, Magnetic resonance imaging, Neural circuits, Obesity, Methods to study human brain function, Neuroscience

1. Introduction

Childhood obesity in the US has nearly doubled over the past 30 years; among adolescents obesity has tripled [1]. Children who are overweight or obese have a higher risk of metabolic syndrome [2], type 2 diabetes [3], hypertension [4], hyperlipidemia [5], musculoskeletal disorders [6], and nonalcoholic fatty liver disease [7]. Additionally, the most prevalent, and perhaps most disruptive, co-morbidities are psychosocial. Self-reported quality-of-life for children who are obese is comparable to children receiving chemotherapy [8]. The stigma of obesity can create feelings of low self-esteem [9], social isolation [10], and victimization [11]. Adolescents who are obese are 80% more likely to have thoughts of suicide compared to healthy weight adolescents [12].

The efficacy of long-term weight loss among adults is poor [13], with up to 90% returning to baseline weight within 3 years after behavioral treatment [14,15]. Returning to baseline weight is due to, in part, homeostatic compensatory mechanisms [16]. Homeostatic regulation of food intake is coordinated by neuroendocrine feedback loops involving nutrient and hormonal signals indicating energy store levels to the hypothalamus and hindbrain [17].

Additionally, maintenance of long-term weight loss may be untenable due to non-homeostatic neural mechanisms [17]. Non-homeostatic eating can be initiated via complex neural systems [17]. Brain regions associated with response inhibition, impulsivity, and reward, are increasingly recognized as potent modulators of eating habits [18, 19]. Therefore, to address the lack of efficacious, long-term obesity treatment, an understanding of the neurobiological underpinnings of childhood obesity, involving the interplay among response inhibition, impulsivity, and reward, is needed to address the root cause. Response inhibition is the ability to override a planned or already initiated response [20, 21]. Impulsivity is a poorly conceived, risky, or inappropriate action, often resulting in undesirable consequences [22].

Neuroimaging studies among adults have contributed tremendous insight into obesity; for review see Carnell *et al.*, 2012 [23]. However, as brain structure and function change throughout development [24, 25], our understanding of neural pathophysiology in adults may not apply to children. Indeed, neurological maturation continues into early adulthood [25, 26], with the prefrontal cortex, a brain area associated with executive control, maturing later than the limbic system, associated with drive and reward [26]. The most common behaviors associated with the immature adolescent brain are impulsive behaviors.

There are many foundational activation studies elucidating the neural underpinnings of childhood obesity by identifying discrete brain region. For a review, see Bruce *et al.*, 2011 [27]; for more recent studies, see Batterink, *et al.*, 2010; Bruce, *et al.*, 2013; and Yokum *et al.*, 2011 [28, 29, 30]; and for studies examining neural response to actual food intake, see Stice *et al.*, 2008; Stice *et al.*, 2010; and Stice *et al.*, 2011 [31, 32, 33]. Taken together, these studies have identified differences between children who are obese and healthy weight within discrete brain regions associated with response inhibition, impulsivity, and reward.

However, the brain functions as a network. Functional connectivity analyses generate inferences about brain networks thus providing new insight into the communication and organization of the brain [34]. There are many functional connectivity studies comparing adults who are obese with healthy weight adults [35, 36, 37, 38, 39, 40, 41, 42, 43]. However, there are only a few functional connectivity studies in childhood obesity. Olde Dubbelink, *et al.*, examined resting state functional connectivity in girls, ages 9–12 years, using magnetoencephalography (MEG) [44]. They reported increased synchronization in the delta and beta frequency bands among girls who were severely obese compared to healthy weight girls. Zhang *et al.*, examined resting state functional connectivity using fMRI among children with Prader-Willi syndrome compared to their healthy weight siblings [45]. They reported decreased functional connectivity in the default mode network and the motor sensory network, and

both increased and decreased functional connectivity in the prefrontal cortex network. Black *et al.*, examined resting state functional connectivity using fMRI among children who are severely obese compared to healthy weight children [46]. They reported increased functional connectivity among regions associated with cognitive control and reward anticipation.

The aim of this study was to better understand resting state functional connectivity between regions in the brain associated with non-homeostatic eating among children across a continuous range of weights. We therefore defined a neural model comprised of three *a priori*-defined regions (Fig. 1): (1) inferior parietal lobe (IPL), associated with response inhibition; (2) frontal pole (fPole), associated with impulsivity; and (3) the nucleus accumbens (NAc), associated with reward and reward-motivated behaviors. We also investigated the associations of resting state functional connectivity with eating behaviors. Insight into these relationships will provide a better understanding of the mechanisms and potential efficacy of novel treatments for weight loss and maintenance among children.

Response inhibition is the ability to override a planned or already initiated response [20, 21]. Neuroimaging studies show that decreased response inhibition is associated with increased body mass index (BMI) [47, 48, 49, 50]. Increased neural activity in the inferior parietal lobe (IPL) has been consistently associated with increased response inhibition [21, 51, 52, 53]; when comparing lean adults to obese adults [54]; and among patients with restricting type anorexia compared to

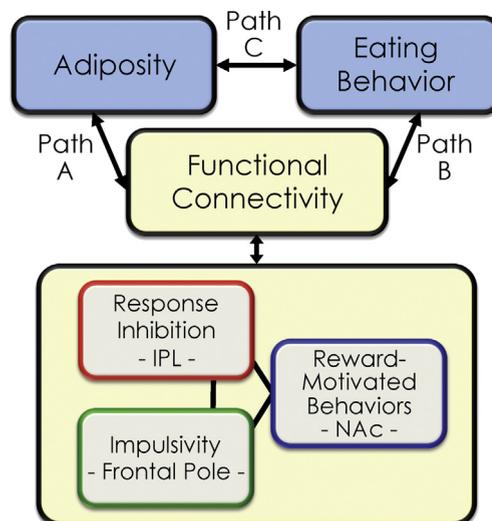


Fig. 1. Hypotheses and functional brain model. *Upper:* We hypothesized that resting state functional connectivity is associated with adiposity (Path A) and eating behaviors (Path B). We also hypothesized that adiposity is associated with eating behaviors (Path C). *Lower:* The neural model is comprised of three brain regions: (1) inferior parietal lobe (IPL), associated with response inhibition; (2) frontal pole, associated with impulsivity; and (3) nucleus accumbens (NAc), associated with reward-motivated behaviors.

patients with binge eating/purging eating disorders and to healthy controls [55]. Taken together, this evidence suggests that decreased response inhibition is associated with increased BMI, as well as decreased neural response in the IPL.

Impulsivity is a poorly conceived, risky, or inappropriate action, often resulting in undesirable consequences [22]. Increased impulsivity is associated with obesity among adults and children and decreased weight loss during treatment [18, 28, 47, 48, 56, 57]. The frontal pole, the most anterior part of Brodmann area 10 (BA 10), is associated with impulsivity. Decreased neural response in the frontal pole among healthy adults was associated with increased impulsivity during a delayed discounting task [58]. Compared to healthy controls, adults with impulsive aggression had decreased neural response in the frontal pole when viewing images of angry faces [59]. Decreased neural activity in the frontal pole was associated with poorer weight management in women one year after a 12-week diet [60]. Taken together, this evidence suggests that increased impulsivity is associated with increased BMI, as well as decreased neural response in the frontal pole.

The nucleus accumbens (NAc) is associated with reward, food-related reward, and reward-motivated behaviors [61, 62, 63] (for a comprehensive discussion of its functions, see Floresco *et al.*, 2015 [64]). Cauda *et al.*, reported resting state functional connectivity and structure-based meta-analytic connectivity between NAc and IPL [65]. Choi *et al.*, reported resting state functional connectivity between NAc and the frontal pole [66]. Using diffusion tensor images (DTI) acquired from humans, Zhang *et al.*, identified distinct anatomical connectivity patterns in the posteromedial cortex (PMC), a critical region associated with the default mode network [67]. One anatomical connectivity pattern within the PMC suggests functional connectivity between IPL and the frontal pole.

We will refer to response inhibition-associated resting state functional connectivity between IPL and NAc as [IPL:NAc] resting state functional connectivity (rsFC). Similarly, we will refer to impulsivity-associated resting state functional connectivity between frontal pole and NAc as [FPOLE:NAc] rsFC. And we will refer to resting state functional connectivity between frontal pole and IPL as [FPOLE:IPL] rsFC. Given the three paths depicted in our neural model (Fig. 1), we have a three-pronged, interdependent hypothesis. Our hypothesis is built on the premise that increased functional connectivity reflects increased functional integration [68], and that decreased response inhibition and increased impulsivity are associated with increased adiposity. We hypothesized that decreased response inhibition-associated [IPL:NAc] rsFC and increased impulsivity-associated [FPOLE:NAc] rsFC will be associated with: increased adiposity (Fig. 1, Path A); increased food approach behaviors; and decreased food avoidance behaviors (Fig. 1, Path B). Additionally, as increased

food approach behaviors and decreased food avoidance behaviors are associated with increased BMI among children ages 7–12 years [69] (Fig. 1, Path C), we hypothesized a similar association in this study.

2. Materials and methods

2.1. Participants

Data were acquired from the Enhanced Nathan Kline Institute Rockland Sample (NKI-RS) [70] from children 8–13 years old. The NKI-RS was designed as a large dataset with broad and deep phenotypic measures and state-of-the-art neuroimaging data, in an open neuroscience model where all data are shared prospectively [70]. A strength of the NKI-RS study is its controlled recruitment from across all of Rockland County, NY, which is representative of the US population as described by the 2010 US census [71]. All participants were screened for psychiatric, neurological, and chronic medical illnesses, and for MRI safety considerations. Participants were encouraged to eat breakfast before arriving and were provided lunch. Institutional Review Board (IRB) approval was obtained at NKI and Montclair State University. Participants and their legal guardians provided written informed consent. Data were de-identified prior to receipt.

2.2. Adiposity

Among adults, BMI is a convenient proxy measure for adiposity. However, because body composition changes throughout childhood, a measure of adiposity that accounts for changes in body composition during childhood is needed. Age- and sex-specific BMI percentile is one such measure. While BMI percentiles are easier to use in the clinical setting, they are not ideal for statistical analyses. For example, percentiles at the extremes, *e.g.*, $\geq 99\%$, are non-linear as this category can include a wide range of weights. Instead, BMI *z*-scores are a continuous measure and therefore not subject to the non-linearity problem seen with BMI percentiles. Therefore BMI *z*-scores are better suited for statistical analyses [72]. However, BMI *z*-scores can be more difficult to explain to the public. While BMI *z*-scores are not a direct measure of adiposity, they are more strongly associated with percentage of body fat, as measured by dual-energy X-ray absorptiometry, than BMI percentiles [73]. We therefore used BMI *z*-scores as a proxy measure for childhood adiposity. In all statistical analyses, we used continuous BMI *z*-scores. However, when reporting summary statistics, children were classified as healthy weight for ($-1.64 \leq \text{BMI } z\text{-scores} < 1.04$); overweight for ($1.04 \leq \text{BMI } z\text{-scores} < 1.64$); and obese for ($\text{BMI } z\text{-scores} \geq 1.64$) [72]. We calculated an age- and sex-specific BMI *z*-score for each child using LMS transformation parameters *lambda*, *mu*, and *sigma* [74, 75].

2.3. Eating behaviors

The Child Eating Behaviour Questionnaire (CEBQ) is a validated 35-item questionnaire that measures eight aspects of eating behavior [76]:

1. **DD:** Desire to Drink indicates frequent drinking.
2. **EF:** Enjoyment of Food indicates an overall interest in food.
3. **EO:** Emotional Overeating indicates increased eating under negative emotions.
4. **EU:** Emotional Undereating indicates decreased eating under negative emotions.
5. **FF:** Food Fussiness indicates rejection of both new and familiar foods.
6. **FR:** Food Responsiveness assesses eating in response to food cues.
7. **SE:** Slowness in Eating assesses reduced eating due to low interest and/or enjoyment of food; and
8. **SR:** Satiety Responsiveness assesses how well a child controls the amount he/she eats in response to eating recently.

Each item is rated on a Likert scale from 1 (never) to 5 (always). “Food approach” behavior is indicated by increasing DD, EF, EOE, and FR scores, whereas “food avoidance” behavior is indicated by increasing EUE, FF, SE, and SR scores [76]. Food approach behaviors have been associated with increased weight among children and food avoidance behaviors have been associated with decreased weight [69, 77, 78, 79, 80]. The NKI-RS study was designed such that the CEBQ was administered only to children younger than 12 years old.

The NKI-RS study did not acquire food recall surveys. However, the CEBQ was developed to measure eating styles among children through parental-reporting [76]. Reported behavioral measures are preferable to retrospective food recall as recalls often result in an underestimate of food consumption due to, in part, memory bias and social expectations and pressure [81]. While a 24-hour recall may be more accurate compared to a retrospective recall, food consumption can vary greatly from day to day such that a single day may not be representative [82]. Self-report instruments, such as the CEBQ, identify eating habits rather than actual food intake. The CEBQ has good factorial validity and external validity [76, 83, 84, 85, 86].

2.4. Neural model

We defined an *a priori* model with three brain regions: (1) response inhibition; (2) impulsivity; and (3) reward-motivated behaviors (Fig. 1). The specific determination of these three regions is discussed below. Because we are interested in the functional organization of the brain, we defined regions based

on functionality rather than anatomy, particularly as anatomically-defined regions may encompass functionally heterogeneous areas. To this end, we used Neurosynth (<http://neurosynth.org>) [88], which identifies functionally related brain regions via meta-analytic methods across more than 11,000 neuroimaging studies. We identified functional regions using Neurosynth's reverse inference maps. The forward inference map defines regional co-activations from a psychological term, whereas the more selective reverse inference map defines a psychological term from regional co-activations (<http://neurosynth.org/faq/#q15>).

To investigate the possibility that our results were due to global, brain-wide phenomena, we defined a second model as a negative control. We selected *a priori* brain regions not typically associated with response inhibition or impulsivity, auditory and foot motor cortex, while retaining the same reward region, NAc.

Of note, Neurosynth does not allow for additional filters in the specification of its meta-analyses, such as limiting its analyses to “children-only” studies. However, its resulting inference maps are in Montreal Neurological Institute (MNI)-space. We spatially normalized our participants' brain scans to a child-specific template [89, 90], also in MNI-space, thereby allowing the transformation of Neurosynth results to our cohort of children. As noted previously, our understanding of adult neurofunctionality may not apply to children. However, using functional regions identified by Neurosynth is one way to contribute to the limited study of childhood obesity by objectively building upon the vast corpus of neuroimaging research.

2.4.1. Inferior parietal lobe (IPL) / response inhibition

Because the IPL is associated with response inhibition, we used Neurosynth to identify an *a priori* region in the IPL via a meta-analysis using the term “response inhibition.” Using the resulting reverse inference map from 176 neuroimaging studies, we identified the IPL and noted its most statistically significant voxel. We then created a spherical ROI with radius 5 mm (volume = 648 mm³ [81 voxels]) centered on the peak *z*-score of 6.6 at (38, -54, 44) in MNI-space (Fig. 2).

2.4.2. Frontal pole / impulsivity

Because the frontal pole is associated with impulsivity, we used Neurosynth to identify an *a priori* region in the frontal pole via a meta-analysis using the term “impulsivity.” Using the resulting reverse inference map from 76 neuroimaging studies, we identified the frontal pole and selected its most statistically significant voxel. We created a spherical ROI with radius 5 mm (volume = 648 mm³ [81 voxels]) centered on a peak *z*-score of 5.4 at (-32, 62, -6) (Fig. 2).

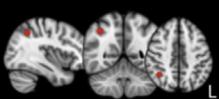
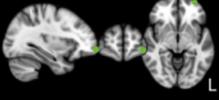
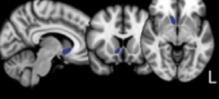
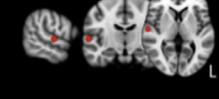
	Region	Association	Region in MNI-space	MNI coordinates / Atlas	Volume mm ³ (voxels)	
Functional Model	Inferior parietal lobe (IPL; right)	Response inhibition		38, -54, 44	648 (81)	Negative Control Model
	Frontal pole (left)	Self-control		-32, 62, -6	648 (81)	
	Nucleus accumbens (NAc; right)	Reward		Harvard-Oxford subcortical atlas	472 (59)	
Auditory cortex (right)	Negative control		60, -14, 4	648 (81)		
Foot motor cortex (left)	Negative control		-6, -20, 54	648 (81)		

Fig. 2. Brain regions in a functional model associated with non-homeostatic eating and in a negative control model. MNI = Montreal Neurological Institute; L = left hemisphere.

2.4.3. Nucleus accumbens / reward-motivated behaviors

The NAc is associated with reward, food-related reward, and reward-motivated behavior. We used the right NAc region as defined in the Harvard-Oxford subcortical atlas [91, 92, 93, 94] (volume = 472 mm³ [59 voxels]) (Fig. 2). After reviewing results using the right NAc, we examined an alternative, *post hoc* neural model using the left NAc.

Note that animal studies are able to distinguish the NAc shell from its core. However, given the current spatial resolution of these fMRI scans, acquired at 3 Tesla, we were unable to resolve the NAc shell from the core in intact humans. The NAc shell is associated with reward salience, wanting, and positive reinforcement [95]. The NAc core is associated with motor function related to reward [96].

2.5. Negative control neural model

Our negative control model was comprised of three regions: (1) auditory cortex; (2) foot motor cortex; and (3) NAc (Fig. 2). We used Neurosynth to identify an *a priori* brain region associated with “auditory cortex.” We created a spherical ROI with radius 5 mm (volume = 648 mm³ [81 voxels]), centered on a peak *z*-score of 19.6 at (60, -14, 4) (Fig. 2). We also identified an *a priori* brain region associated with “foot” motor cortex. We created a spherical ROI with

radius 5 mm (volume = 648 mm³ [81 voxels]), centered on a peak *z*-score of 8.3 at (−6, −20, 54) (Fig. 2). We used the same right NAc region as defined above.

2.6. Magnetic resonance images

MRI scans were acquired on a Siemens 3T MAGNETOM TrioTim at NKI and Montclair State University. A high-resolution anatomical T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) scan with TR = 1900 ms and voxel size = (1 × 0.98 × 0.98) mm³ was acquired from each participant. Each subject participated in a 9.4-min blood oxygenation level-dependent (BOLD) resting-state multiband [87] T2-weighted echo planar image scan, collected with repetition time (TR) = 1400 ms, 404 dynamics, 64 slices, and voxel size = (2 × 2 × 2) mm³. Children were scanned while resting quietly with eyes closed with no overt stimuli.

2.7. MRI preprocessing

We processed the MRI datasets with FMRIB Software Library (FSL) v6.00 [97]. Preprocessing included removal of non-brain tissue [98]; spatial smoothing using a Gaussian kernel of full-width at half maximum 3.0 mm; 4D grand-mean intensity normalization; highpass temporal filtering using Gaussian-weighted least-squares straight line fitting with sigma = 200 sec; motion correction [99]; and linear and nonlinear spatial normalization [99, 100, 101, 102] to an age-appropriate MRI brain atlas for ages [7.5–13.5] years old [89, 90]. We discarded any scan during which a participant moved more than 2 mm.

2.8. Resting state functional connectivity

Biswal *et al.*, observed that BOLD fMRI signals from the motor cortex during quiet rest were strongly correlated with signals in other brain regions associated with motor function [103]. This observation gave rise to the idea of “resting state” brain function: when the brain is not engaged in an explicit task, the low-frequency changes in neural response reflect inherent and meaningful brain function along with its attendant networks [104]. The functional coupling between distal brain regions can be quantified by the statistical correlation of BOLD fMRI signals. The pattern of correlation throughout the brain, called functional connectivity [103, 105, 106], is believed to reflect neurons firing together with a common purpose [107, 108, 109], and can reveal whole-brain functional connectivity patterns [110].

For each participant, we calculated mean BOLD signals from each region in our neural model. To reduce noise from non-grey matter activity, we regressed out the following confounders: mean relative motion correction distance [111]; mean

BOLD signal from white matter [112]; and mean BOLD signal from cerebral spinal fluid [113]. We removed unwanted signal fluctuation due to respiration and heartbeat via a 0.10 Hz lowpass filter [114]. Using partial correlation, we calculated the functional connectivity between pairs of BOLD signals from the three regions: (1) IPL and NAc, denoted as [IPL:NAc] rsFC; (2) frontal pole and NAc, denoted as [FPOLE:NAc] rsFC; and (3) frontal pole and IPL, denoted as [FPOLE:IPL] rsFC. We used partial correlation to remove common effects from the other region within the model. For example, the resulting [IPL:NAc] rsFC is the correlation between IPL and NAc over and above any correlation with the frontal pole, *i.e.*, controlling for the effects of the frontal pole.

We examined the partial correlation coefficient, often denoted as $\rho_{XY.Z}$, as it is a measure of the strength of the relationship between BOLD signals X and Y , after controlling for another BOLD signal, Z . $\rho_{XY.Z}$ is bounded by $[-1, +1]$. A $\rho_{XY.Z}$ approaching ± 1 indicates that X and Y are approaching a perfect linear relationship. A related, although different, measure is β , the effect (or slope) of BOLD signal X on BOLD signal Y , after controlling for BOLD signal Z (Eq. 1). β can be estimated via a simple general linear model (GLM):

$$Y = \alpha + \beta X + \gamma Z + \varepsilon \quad (1)$$

Equation 1. A simple general linear model. β is unbounded and indicates the change of the expected value of Y for each 1-unit change in X after controlling for Z . β is also called an “effect,” *i.e.*, when X is changed by +1 unit, the effect on Y is a change of β units. β and $\rho_{XY.Z}$ are related as shown in (Eq. 2) [115]. β and $\rho_{XY.Z}$ are equal only when $\text{std}(X)$ and $\text{std}(Y)$ are equal.

$$\beta = \rho_{XY.Z} \frac{\text{std}(X)}{\text{std}(Y)} \quad (2)$$

Equation 2. Relation of β and $\rho_{XY.Z}$ where $\text{std}(X)$ is the standard deviation of X and $\text{std}(Y)$ is the standard deviation of Y .

We chose not to investigate β as it is conceivable that the effect can be transformed via a change in neural response (*e.g.*, via a neural gain function) while the strength of the relationship remains unchanged. Changes in neural response may be altered due to different levels of CO₂ in the blood [116, 117]; changes in vasoconstriction, *e.g.*, from caffeine use [118, 119]; or changes in metabolic demand [120]. However, the partial correlation coefficient, $\rho_{XY.Z}$, quantifies the strength of the relationship between X and Y regardless of the effect quantified by β .

We computed partial correlation coefficients via MATLAB's partialcorr (Release 2014a, The MathWorks, Inc., Natick, MA). We designated functional connectivity as statistically significant if the association has a p -value ≤ 0.05 . If $(0.05 < p\text{-value} \leq 0.10)$, then we designated functional connectivity as trending toward statistical significance.

To capture in a single measure the relative difference in functional connectivity between response inhibition-associated [IPL:NAC] rsFC and impulsivity-associated [FPOLE:NAC] rsFC, we calculated a simple difference measure that reflects resting state functional connectivity imbalance (Eq. 3):

$$DELTA = ([fPole : NAc]rsFC - [IPL : NAc]rsFC) \quad (3)$$

Equation 3. Difference between rsFC measures indicating imbalance in resting state functional connectivity. DELTA values can range from [-2, +2] where positive values indicate greater impulsivity-associated [FPOLE:NAC] rsFC relative to response inhibition-associated [IPL:NAC] rsFC; negative values indicate greater [IPL:NAC] rsFC relative to [FPOLE:NAC] rsFC. For example, if the BOLD signal from the frontal pole is perfectly in-sync with the BOLD signal from the NAc, then [FPOLE:NAC] rsFC = +1. And if the BOLD signal from the IPL is perfectly out-of-sync with the BOLD signal from the NAc, then [IPL:NAC] rsFC = -1. In this example, then:

$$DELTA = ([fPole : NAc]rsFC - [IPL : NAc]rsFC) = (+1 - (-1)) = +2 \quad (4)$$

Equation 4. Example of maximal difference between rsFC measures that is biased toward impulsivity-associated [FPOLE:NAC] functional connectivity.

DELTA = +2 indicates that the two functional connectivity measures to the NAc are maximally different with greater “in sync” functional connectivity between the frontal pole and NAc. To clarify, DELTA is not a measure of functional connectivity. Rather, DELTA is a single measure that indicates the relative imbalance between the two functional connectivity measures with respect to the NAc. DELTA = 0 indicates that impulsivity-associated [FPOLE:NAC] rsFC is in balance with response inhibition-associated [IPL:NAC] rsFC, regardless of the actual value of the functional connectivity measures. For example, DELTA = 0 when [FPOLE:NAC] = [IPL:NAC] = 0.8, or when [FPOLE:NAC] = [IPL:NAC] = -0.1. We also computed simple linear regressions between adiposity and DELTA via Python's `scipy.stats.linregress`.

2.9. Relationship of adiposity with brain functional connectivity (Fig. 1, Path A)

We also computed linear regressions between BMI z-score and DELTA, the relative imbalance in functional connectivity. To evaluate the effect of age on the relationships between BMI z-score and rsFC and with DELTA, we computed ordinary least squares (OLS) linear regression via Python's `statsmodels.formula.api.ols`.

2.10. Relationships of eating behaviors with brain functional connectivity (Fig. 1, Path B)

To evaluate the relationship between eating behavior and resting state functional connectivity, we computed simple linear regressions between CEBQ scores and each of the functional connectivity values, [IPL:NAC] rsFC, [FPOLE:NAC] rsFC, and

[FPOLE:IPL] rsFC, via Python's `scipy.stats.linregress`. We also computed linear regressions between CEBQ scores and DELTA, the relative imbalance in functional connectivity. In the initial validation of the CEBQ by Wardle *et al.*, they noted that only FF showed a sex difference, which was greater among boys ($t = 2.4$; $p \leq 0.02$) [76]. We therefore performed a *post hoc* linear regression with interaction analysis of brain functional connectivity by sex with FF via Python's `statsmodels.formula.api.ols`.

2.11. Relationship between eating behaviors and adiposity (Fig. 1, Path C)

To evaluate the relationship between eating behavior and adiposity, we computed simple linear regressions between CEBQ scores and BMI z -scores via Python's `scipy.stats.linregress`. We also performed *post hoc* linear regression with interaction analysis of FF by sex with BMI z -score via Python's `statsmodels.formula.api.ols`.

3. Results

3.1. Participants

Data from 38 children (F = 17; M = 21), ages 8-13 (mean = 11.2; std = 1.7) years old, were acquired from the NKI-RS (Table 1). Fig. 3 shows the distribution of BMI z -score vs. age. There was no significant relationship of BMI z -score with age ($p = 0.766$; $R^2 = 0.002$; $N = 38$). Nor is there a relationship of BMI z -score with by sex (girls: $p = 0.981$; $R^2 = 0.000$; $N = 17$; boys: $p = 0.730$; $R^2 = 0.006$; $N = 21$). Five of the 38 participants (13%) were classified as obese. This is comparable to 17% of US children who were classified as obese in 2010 [1]. Six of the 38 participants (16%) were classified as overweight, which is comparable to 15% of US children classified as overweight in 2010 [1]. Twenty-four of the 38 participants (63%) completed the CEBQ as the CEBQ was administered only to children younger than 12 years old (mean = 10.1; std=1.1 years old). Of these 24 children, 11 (46%) were girls and 13 (54%) were boys. Of the 24 children who were administered the CEBQ, 3 (12.5%) were classified as obese; 3 (12.5%) were classified as overweight; and 18 (75%) were classified as healthy weight. Forty-two percent of participants were scanned between 8:30-10:00 am; 18.4% were scanned between 10:00 am-noon; 39.5% of participants were scanned between noon-2:00 pm.

3.2. Adiposity is associated with resting state functional connectivity (Fig. 1, Path A)

Increasing BMI z -scores trended toward significance with decreasing response inhibition-associated [IPL:NAC] rsFC ($p = 0.084$; $R^2 = 0.080$; $r = -0.284$;

Table 1. Clinical and demographic summary of participants.

N = 38	Count (%)	
Sex		
Female	17 (44.7)	
Male	21 (55.3)	
Handedness (N = 36)		
Right	30 (83.3)	
Left	5 (13.9)	
Ambidextrous	1 (2.8)	
Race		
American Indian or Native Alaskan	3 (7.89)	
Asian	2 (5.26)	
Black or African American	16 (42.11)	
Native Hawaiian or Other Pacific Islander	0 (0.00)	
White	17 (44.74)	
Other Race	0 (0.00)	
	Mean (std)	Min, Max
Age (yrs)	11.2 (1.7)	8.4, 13.9
Weight (kg)	44.0 (13.9)	25.9, 81.7
BMI z-score	0.4 (1.1)	-1.4, 2.4
BMI%	59.9 (30.4)	8.4, 99.2
Tanner stage (N = 36)		
Girls (N = 17)	2.3 (1.0)	1, 4
Boys (N = 19)	2.2 (1.2)	1, 5

Table 2; Fig. 4A). In contrast, increasing BMI z-scores trended toward significance with increasing impulsivity-associated [FPOLE:NAC] rsFC ($p = 0.089$; $R^2 = 0.078$; $r = 0.280$; Table 3; Fig. 4B). There was no significant relationship between BMI z-scores and [FPOLE:NAC] rsFC ($p = 0.525$; $R^2 = 0.011$; $r = -0.106$; Table 4). BMI z-scores increased with increasing DELTA ($p = 0.035$; $R^2 = 0.117$; $r = 0.342$; Table 5; Fig. 4C). There was no significant association of age in the relationship between BMI z-score and any rsFC measure or DELTA (all $p \geq 0.688$). Table 2 lists the relationships between eating behaviors and [IPL:NAC] rsFC. Table 3 lists the relationships between eating behaviors and [FPOLE:NAC] rsFC. Table 4 lists the relationships between eating behaviors and [FPOLE:NAC] rsFC. And Table 5 lists the relationships between eating behaviors and DELTA.

Recall that the partial correlation between IPL and NAc, [IPL:NAC] rsFC, the functional connectivity value plotted along the x-axis in Fig. 4, panels A, D, and

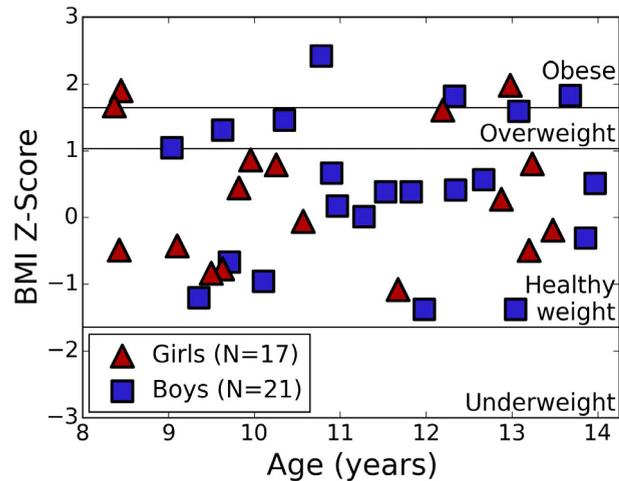


Fig. 3. Distribution of BMI z-score vs. age for $N = 38$ children. Healthy weight is ($-1.64 \leq \text{BMI z-scores} < 1.04$); overweight is ($1.04 \leq \text{BMI z-scores} < 1.64$); and obese is ($\text{BMI z-scores} \geq 1.64$).

G, was controlled for the effects of the frontal pole, fPole. Similarly, the partial correlation between fPole and NAc, [FPOLE:NAC] rsFC, the x -axis in Fig. 4, panels B, E, and H, was controlled for the effects of the IPL. The partial correlation between fPole and IPL, [FPOLE:IPL], was controlled for the effects of the NAc. Note that the functional connectivity values used to compute DELTA are these same partial correlation coefficients, [FPOLE:NAC] rsFC and [IPL:NAC] rsFC.

3.3. Eating behaviors are associated with resting state functional connectivity (Fig. 1, Path B)

3.3.1. Food approach eating behavior Enjoyment of Food (EF)

EF scores increased with decreasing response inhibition-associated [IPL:NAC] rsFC ($p = 0.020$; $R^2 = 0.223$; $r = -0.472$; Fig. 4D; Table 2). In contrast, the relationship between EF scores and impulsivity-associated [FPOLE:NAC] rsFC trended toward a positive increase ($p = 0.083$; $R^2 = 0.130$; $r = 0.361$; Fig. 4E; Table 3). There was no significant relationship between EF and [FPOLE:IPL] rsFC ($p = 0.271$; $R^2 = 0.055$; $r = -0.234$; Table 4). EF scores increased with increasing DELTA ($p = 0.017$; $R^2 = 0.232$; $r = 0.482$; Fig. 4F; Table 5).

3.3.2. Food avoidance eating behavior Satiety Responsiveness (SR)

Increasing SR scores trended toward significance with increasing [IPL:NAC] rsFC ($p = 0.092$; $R^2 = 0.124$; $r = 0.352$; Fig. 4G; Table 2). In contrast, SR scores decreased with increasing [FPOLE:NAC] rsFC ($p = 0.038$; $R^2 = 0.181$;

Table 2. Relationships between adiposity and rsFC, and eating behaviors and rsFC, between response inhibition-associated inferior parietal lobe and right nucleus accumbens.

Neural model: [IPL:NAC] [‡] resting state functional connectivity					
BMI z-score vs. [IPL:NAC]			<i>r</i>	<i>R</i> ²	<i>p</i>
N = 38			-0.284	0.080	0.084 [‡]
CEBQ eating behaviors vs. [IPL:NAC]			<i>r</i>	<i>R</i> ²	<i>p</i>
Food Approach	N = 24	DD: Desire to Drink	0.043	0.002	0.843
		EF: Enjoyment of Food	-0.472	0.223	0.020 [*]
		EOE: Emotional Overeating	-0.371	0.138	0.074 [‡]
		FR: Food Responsiveness	-0.427	0.182	0.037 [*]
Food Avoidance	N = 24	EUE: Emotional Under-Eating	0.047	0.002	0.827
		FF: Food Fussiness	0.224	0.050	0.294
		SE: Slowness in Eating	0.345	0.119	0.098 [‡]
		SR: Satiety Responsiveness	0.352	0.124	0.092 [‡]

IPL: inferior parietal lobe; NAc: nucleus accumbens; BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; rsFC: resting state functional connectivity; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

^{*} *p* ≤ 0.05.

[‡] *p* ≤ 0.10.

[‡] Partial correlation between IPL and NAc BOLD signals was controlled for the effects of the frontal pole (fPole).

r = -0.425; Fig. 4H; Table 3). There was no significant relationship between SR and [FPOLE:IPL] rsFC (*p* = 0.871; *R*² = 0.001; *r* = 0.035; Table 4). SR scores decreased with increasing DELTA (*p* = 0.025; *R*² = 0.208; *r* = -0.456; Fig. 4I; Table 5). Our *post hoc* analysis of FF scores with functional connectivity by sex showed no statistically significant main effects for functional connectivity or for sex (all *p* ≥ 0.388).

3.4. Adiposity is associated with eating behaviors (Fig. 1, Path C)

Table 6 lists the relationships between BMI z-score and each CEBQ score. BMI z-scores increased with increasing food approach behaviors in a statistically significant way (all *p* ≤ 0.002), with the exception of DD (*p* = 0.917). Concomitantly, BMI z-scores decreased with increasing food avoidance behaviors SE (*p* = 0.002; *R*² = 0.353; *r* = -0.594) and SR (*p* = 0.005; *R*² = 0.311; *r* = -0.558). EUE and FF show no statistically significant relationships (EUE: *p* = 0.176; FF: *p* = 0.103). Our *post hoc* analysis of BMI z-scores as a function of FF by sex showed no statistically significant main effects for FF or for sex (FF: *p* = 0.427; *t* = -0.811; sex: *p* = 0.835; *t* = -0.211) and no significant interaction between FF and sex (*p* = 0.758; *t* = -0.312).

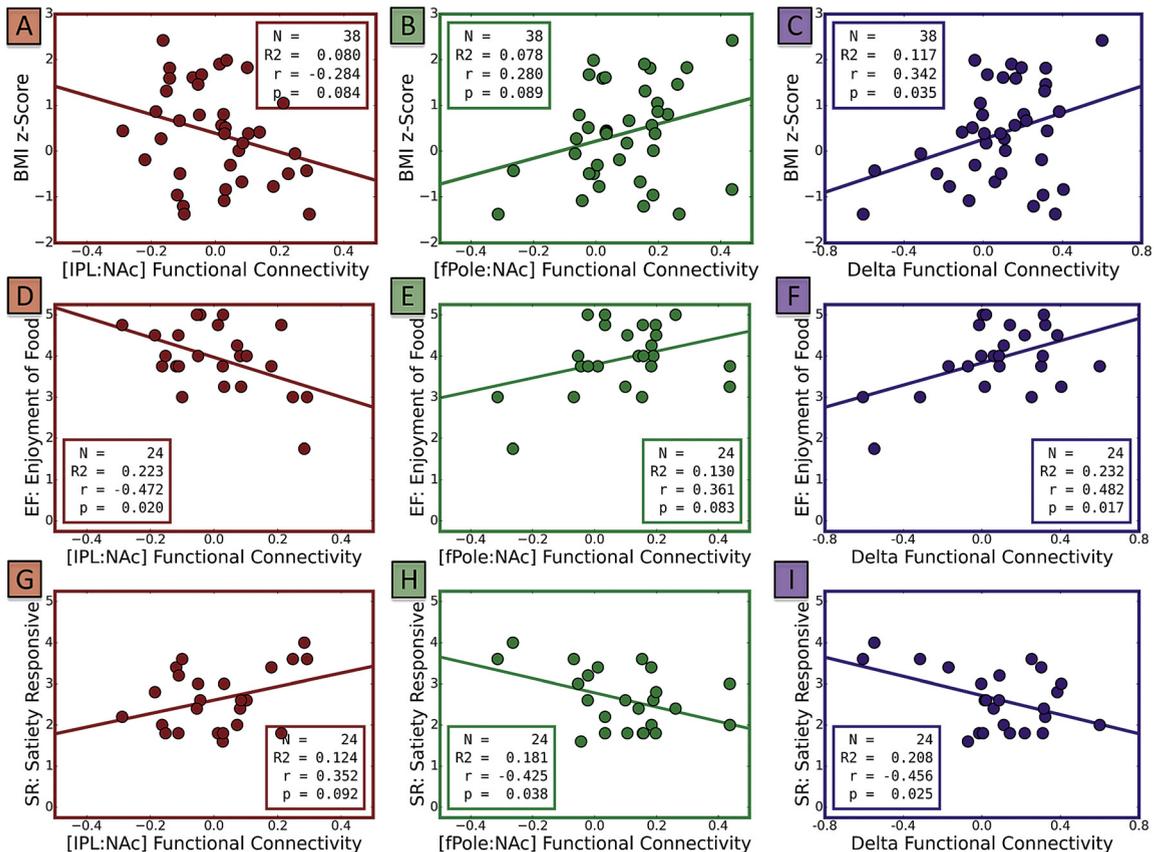


Fig. 4. Relationships within a neural model associated with non-homeostatic eating.

(A) Decreasing BMI z -score is associated with increasing response inhibition-associated [IPL:NAC] resting state functional connectivity. (B) Increasing BMI z -score is associated with increasing impulsivity-associated [FPOLE:NAC] resting state functional connectivity. (C) Increasing BMI z -score is associated with increasing impulsivity-biased imbalance Δ in functional connectivity. (D) Decreasing food approach eating behavior Enjoyment of Food (EF) is associated with increasing response inhibition-associated [IPL:NAC] resting state functional connectivity. (E) Increasing EF is associated with increasing impulsivity-associated [FPOLE:NAC] resting state functional connectivity. (F) Increasing EF is associated with increasing impulsivity-biased imbalance Δ in functional connectivity. (G) Increasing food avoidance eating behavior Satiety Responsiveness (SR) is associated with increasing response inhibition-associated [IPL:NAC] resting state functional connectivity. (H) Decreasing SR is associated with increasing impulsivity-associated [FPOLE:NAC] resting state functional connectivity. (I) Decreasing SR is associated with increasing impulsivity-biased imbalance Δ in functional connectivity. [IPL:NAC] Functional Connectivity: resting state functional connectivity between inferior parietal lobe (IPL) and nucleus accumbens (NAC); [FPOLE:NAC] Functional Connectivity: resting state functional connectivity between frontal pole (fPole) and NAC; Δ Functional Connectivity: The difference in functional connectivity measurements ([FPOLE:NAC] - [IPL:NAC]).

Table 3. Relationships between adiposity and rsFC, and eating behaviors and rsFC, between impulsivity-associated frontal pole and right nucleus accumbens.

Neural model: [FPOLE:NAC] [‡] resting state functional connectivity					
BMI z-score vs. [FPOLE:NAC]			<i>r</i>	<i>R</i> ²	<i>p</i>
N = 38			0.280	0.078	0.089 [†]
CEBQ eating behaviors vs. [FPOLE:NAC]			<i>r</i>	<i>R</i> ²	<i>p</i>
Food Approach	N = 24	DD: Desire to Drink	−0.208	0.043	0.330
		EF: Enjoyment of Food	0.361	0.130	0.083 [†]
		EOE: Emotional Overeating	0.296	0.088	0.160
		FR: Food Responsiveness	0.256	0.066	0.227
Food Avoidance	N = 24	EUE: Emotional Under-Eating	−0.216	0.047	0.311
		FF: Food Fussiness	−0.474	0.224	0.019 [*]
		SE: Slowness in Eating	−0.416	0.173	0.043 [*]
		SR: Satiety Responsiveness	−0.425	0.181	0.038 [*]

fPole: frontal pole; NAc: nucleus accumbens; BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; rsFC: resting state functional connectivity; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

^{*} *p* ≤ 0.05.

[†] *p* ≤ 0.10.

[‡] Partial correlation between fPole and NAc BOLD signals was controlled for the effects of the inferior parietal lobe (IPL).

3.5. Post hoc neural model with left nucleus accumbens

We performed a *post hoc* analysis of an alternative model with the left NAc. With one exception, there were no statistically significant associations between functional connectivity measures with BMI z-scores or with eating behaviors (Tables 7, 8, 9 and 10). We found a negatively trending relationship between EUE and [FPOLE:IPL] rsFC (*p* = 0.063; *R*² = 0.149; *r* = −0.386; Table 9).

3.6. Negative control neural model

To investigate whether our results were due to global, brain-wide phenomena, we defined a second neural model as a negative control. This functional brain network included auditory and foot motor cortex regions and the right NAc. With one exception, we found no associations between adiposity and functional connectivity, or between eating habits and functional connectivity (Tables 11, 12, 13 and 14). EF scores increased with increasing [FOOT:NAC] functional connectivity (*p* = 0.028; *R*² = 0.201; *r* = 0.448; Table 11).

4. Discussion

Intensive lifestyle interventions in adults do not typically lead to long-lasting weight loss, and co-morbidities such as diabetes and cardiovascular disease

Table 4. Relationships between adiposity and rsFC, and eating behaviors and rsFC, between impulsivity-associated frontal pole and response inhibition-associated inferior parietal lobe.

Neural model: [fPOLE:IPL] [‡] resting state functional connectivity					
BMI z-score vs. [fPOLE:IPL]			<i>r</i>	<i>R</i> ²	<i>p</i>
N = 38			-0.106	0.011	0.525
CEBQ eating behaviors vs. [fPOLE:IPL]			<i>r</i>	<i>R</i> ²	<i>p</i>
Food Approach	N = 24	DD: Desire to Drink	-0.110	0.012	0.608
		EF: Enjoyment of Food	-0.234	0.055	0.271
		EOE: Emotional Overeating	-0.070	0.005	0.746
		FR: Food Responsiveness	0.002	0.000	0.992
Food Avoidance	N = 24	EUE: Emotional Under-Eating	-0.337	0.114	0.107
		FF: Food Fussiness	0.071	0.005	0.743
		SE: Slowness in Eating	0.067	0.005	0.754
		SR: Satiety Responsiveness	0.035	0.001	0.871

fPole: frontal pole; IPL: inferior parietal lobe; BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; rsFC: resting state functional connectivity; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

[‡]Partial correlation between fPole and IPL BOLD signals was controlled for the effects of the nucleus accumbens (NAc).

develop over many years. Therefore an understanding of the developing neurobiology of obesity would provide unique insight into successful obesity treatment strategies. Furthermore, identification of children at risk for obesity would permit the development of novel prevention efforts. To better understand the organization and communication of the young obese brain, we investigated a neural model in a cohort of children using *a priori*-defined, seed-based resting-state functional connectivity. We focused on the relationships of resting state functional connectivity with adiposity and with eating behaviors. We investigated functional connectivity between regions associated with response inhibition (inferior parietal lobe [IPL]), impulsivity (frontal pole [fPole]), and reward (nucleus accumbens [NAc]). Our results suggest the following key findings.

4.1. Finding 1: Eating behaviors and adiposity

In agreement with other childhood obesity studies, increasing food approach behavioral scores – enjoyment of food (EF), food responsiveness (FR), and emotional overeating (EOE) – and decreasing food avoidance behavioral scores – slowness in eating (SE) and satiety responsiveness (SR) – are associated with increasing adiposity.

Table 5. Relationships between adiposity and the difference in rsFC, and eating behaviors and the difference in rsFC.

Neural model: DELTA = [fPOLE:NAC][‡] - [IPL:NAC][#]					
BMI z-score vs. DELTA			r	R²	p
N = 38			0.342	0.117	0.035 [*]
CEBQ eating behaviors vs. DELTA			r	R²	p
Food Approach	N = 24	DD: Desire to Drink	-0.153	0.023	0.477
		EF: Enjoyment of Food	0.482	0.232	0.017 [†]
		EOE: Emotional Overeating	0.386	0.149	0.062 [†]
		FR: Food Responsiveness	0.392	0.154	0.058 [†]
Food Avoidance	N = 24	EUE: Emotional Under-Eating	-0.160	0.026	0.455
		FF: Food Fussiness	-0.417	0.174	0.043 [*]
		SE: Slowness in Eating	-0.447	0.200	0.028 [*]
		SR: Satiety Responsiveness	-0.456	0.208	0.025 [*]

fPole: frontal pole; IPL: inferior parietal lobe; NAc: nucleus accumbens; BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; rsFC: resting state functional connectivity; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

^{*} *p* ≤ 0.05.

[†] *p* ≤ 0.10.

[‡] Partial correlation between fPole and NAc BOLD signals was controlled for the effects of the IPL.

[#] Partial correlation between IPL and NAc BOLD signals was controlled for the effects of the fPole.

Table 6. Relationships between adiposity and eating behaviors.

BMI z-score vs. CEBQ eating behaviors					
			r	R²	p
Food Approach	N = 24	DD: Desire to Drink	-0.022	0.001	0.917
		EF: Enjoyment of Food	0.591	0.349	0.002 ^{**}
		EOE: Emotional Overeating	0.623	0.388	0.001 ^{**}
		FR: Food Responsiveness	0.698	0.487	0.000 ^{**}
Food Avoidance	N = 24	EUE: Emotional Under-Eating	0.286	0.082	0.176
		FF: Food Fussiness	-0.341	0.116	0.103
		SE: Slowness in Eating	-0.594	0.353	0.002 ^{**}
		SR: Satiety Responsiveness	-0.558	0.311	0.005 ^{**}

BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

^{**} *p* ≤ 0.01.

Table 7. Relationships between adiposity and rsFC, and eating behaviors and rsFC, between response inhibition-associated inferior parietal lobe and left nucleus accumbens.

Left NAc Neural model: [IPL:NAC] [‡] functional connectivity					
BMI z-score vs. [IPL:LEFTNAC]			<i>r</i>	<i>R</i> ²	<i>p</i>
N = 38			0.000	0.000	0.998
CEBQ eating behaviors vs. [IPL:LEFT NAC]			<i>r</i>	<i>R</i> ²	<i>p</i>
Food Approach	N = 24	DD: Desire to Drink	0.123	0.015	0.568
		EF: Enjoyment of Food	-0.341	0.116	0.103
		EOE: Emotional Overeating	0.023	0.001	0.915
		FR: Food Responsiveness	0.076	0.006	0.725
Food Avoidance	N = 24	EUE: Emotional Under-Eating	0.072	0.005	0.740
		FF: Food Fussiness	0.123	0.015	0.568
		SE: Slowness in Eating	0.202	0.041	0.344
		SR: Satiety Responsiveness	0.140	0.020	0.514

This *ad hoc* brain model includes the left nucleus accumbens (NAc). Response inhibition-associated inferior parietal lobe (IPL) region remains in the right hemisphere. BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; rsFC: resting state functional connectivity; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

[‡]Partial correlation between IPL and left NAc BOLD signals was controlled for the effects of the frontal pole (fPole).

4.2. Finding 2: Resting state functional connectivity and adiposity

Adiposity is associated with resting state functional connectivity within our neural model among children ages 8–13 years old. As response inhibition-associated functional connectivity increases, adiposity decreases in a statistically trending relationship. As impulsivity-associated functional connectivity increases, adiposity increases in a statistically trending relationship. As the difference between these two functional connectivity measures – response inhibition-associated and impulsivity-associated resting state functional connectivity with the NAc – is increasingly biased toward impulsivity, adiposity increases in a statistically significant manner.

4.3. Finding 3: Resting state functional connectivity and eating behaviors

Eating behaviors are associated with resting state functional connectivity within our neural model among children ages 8–13 years old. As response inhibition-associated functional connectivity increases, food approach behaviors EF and FR decrease, while food avoidance behaviors SE and SR

Table 8. Relationships between adiposity and rsFC, and eating behaviors and rsFC, between impulsivity-associated frontal pole and left nucleus accumbens.

Left NAc Neural model:[FPOLE:NAC] [‡] functional connectivity					
BMI z-score vs. [FPOLE:LEFT NAC]					
	N = 38		<i>r</i>	<i>R</i> ²	<i>p</i>
			-0.001	0.000	0.997
CEBQ eating behaviors vs. [FPOLE:LEFT NAC]					
	N = 24	DD: Desire to Drink	<i>r</i>	<i>R</i> ²	<i>p</i>
Food Approach		EF: Enjoyment of Food	-0.038	0.001	0.860
		EOE: Emotional Overeating	-0.272	0.074	0.198
		FR: Food Responsiveness	-0.328	0.108	0.117
			-0.352	0.124	0.091 [†]
Food Avoidance	N = 24	EUE: Emotional Under-Eating	0.030	0.001	0.890
		FF: Food Fussiness	-0.093	0.009	0.666
		SE: Slowness in Eating	-0.025	0.001	0.908
		SR: Satiety Responsiveness	-0.016	0.000	0.943

This *ad hoc* brain model includes the left nucleus accumbens (NAc). Impulsivity-associated frontal pole (fPole) region remains in the left hemisphere. BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; rsFC: resting state functional connectivity; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

[†]*p* ≤ 0.10.

[‡]Partial correlation between fPole and left NAc BOLD signals was controlled for the effects of the inferior parietal lobe (IPL).

trend toward an increasing relationship. As impulsivity-associated resting state functional connectivity increases, food approach behavior EF trends toward an increasing relationship, while food avoidance eating behaviors food fussiness (FF), SE, and SR decrease. As the difference between these two functional connectivity measures is increasingly biased toward impulsivity, food approach behaviors increase while food avoidance behaviors decrease in a statistically significant manner.

4.4. Finding 4: Resting state functional connectivity relationships are not a global, brain-wide phenomenon

The relationships of resting state functional connectivity with adiposity and with eating behaviors are not a global, brain-wide phenomenon, with the exception of enjoyment of food.

Taken together, these results suggest that, in the absence of any explicit food-related stimuli, the developing brain is primed toward food approach and away from food avoidance behavior with increasing adiposity. While this bias is advantageous in an evolutionary sense, it is detrimental in today's environment of easy accessibility to high-energy dense food, as indicated by an associated

Table 9. Relationships between adiposity and rsFC, and eating behaviors and rsFC, between impulsivity-associated frontal pole and response inhibition-associated inferior parietal lobe, controlling for the effects of the left nucleus accumbens.

Left NAc Neural model: [FPOLE:IPL] [‡] functional connectivity					
BMI z-score vs. [FPOLE:IPL]		<i>r</i>	<i>R</i> ²	<i>p</i>	
N = 38		−0.068	0.005	0.683	
CEBQ eating behaviors vs. [FPOLE:IPL]		<i>r</i>	<i>R</i> ²	<i>p</i>	
Food Approach	N = 24	DD: Desire to Drink	−0.149	0.022	0.487
		EF: Enjoyment of Food	−0.212	0.045	0.320
		EOE: Emotional Overeating	−0.076	0.006	0.726
		FR: Food Responsiveness	−0.013	0.000	0.952
Food Avoidance	N = 24	EUE: Emotional Under-Eating	−0.386	0.149	0.063 [†]
		FF: Food Fussiness	0.050	0.002	0.817
		SE: Slowness in Eating	0.040	0.002	0.853
		SR: Satiety Responsiveness	0.013	0.000	0.951

This *ad hoc* brain model includes the left nucleus accumbens (NAc). Response inhibition-associated inferior parietal lobe (IPL) region remains in the right hemisphere. Impulsivity-associated frontal pole (fPole) region remains in the left hemisphere. BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; rsFC: resting state functional connectivity; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

[†] $p \leq 0.10$.

[‡] Partial correlation between fPole and IPL signals was controlled for the effects of the left NAc.

increase in adiposity and unhealthy eating habits among children. Although our results suggest a persistent relationship between resting state functional connectivity and enjoyment of food, additional brain regions should be probed to better understand the extent of this relationship. If this relationship is a brain-wide phenomenon, we speculate that this is indicative of the importance of enjoying food for survival.

Also of note, resting state functional connectivity imbalance associated with adiposity and eating habits develops during childhood, as early as 8–13 years of age. This early development indicates the importance of identifying children at risk for obesity for earlier intervention.

Our results indicate that associations with increased adiposity and unhealthy eating behaviors are driven not solely by decreased response inhibition-associated resting state functional connectivity and not solely by increased impulsivity-associated resting state functional connectivity. Rather, increased adiposity and unhealthy eating behaviors are most strongly associated with the *imbalance* between response inhibition- and impulsivity-associated functional connectivity.

Table 10. Relationships between adiposity and the difference in rsFC, and eating behaviors and the difference in rsFC, with left nucleus accumbens.

Left NAc Neural model: DELTA = [fPOLE:NAC] [‡] - [IPL:NAC] [#]					
BMI z-score vs. DELTA			<i>r</i>	<i>R</i> ²	<i>p</i>
N = 38			0.001	0.000	0.997
CEBQ eating behaviors vs. DELTA			<i>r</i>	<i>R</i> ²	<i>p</i>
Food Approach	N = 24	DD: Desire to Drink	0.113	0.013	0.600
		EF: Enjoyment of Food	-0.076	0.006	0.726
		EOE: Emotional Overeating	0.223	0.050	0.294
		FR: Food Responsiveness	0.277	0.077	0.190
Food Avoidance	N = 24	EUE: Emotional Under-Eating	0.033	0.001	0.878
		FF: Food Fussiness	0.147	0.022	0.492
		SE: Slowness in Eating	0.162	0.026	0.449
		SR: Satiety Responsiveness	0.111	0.012	0.605

This *ad hoc* brain model includes the left nucleus accumbens (NAc). Response inhibition-associated inferior parietal lobe (IPL) region remains in the right hemisphere; impulsivity-associated frontal pole (fPole) region remains in the left hemisphere. BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; rsFC: resting state functional connectivity; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

[‡]Partial correlation between fPole and left NAc BOLD signals was controlled for the effects of the IPL.

[#]Partial correlation between IPL and left NAc BOLD signals was controlled for the effects of the fPole.

This neural imbalance suggests that mindfulness may help treat and/or prevent childhood obesity. Mindfulness is described as paying attention *on purpose* and being in the present moment with acceptance and without judgment [121]. Mindfulness is associated with increased response inhibition [122, 123] and decreased impulsivity [124, 125, 126]. As brain regions associated with response inhibition, impulsivity, and reward are recognized as potent modulators of non-homeostatic eating habits, mindfulness may recalibrate the imbalance in neural systems associated with childhood obesity. The use of mindfulness for weight loss and weight control among adults has produced mixed results [127, 128]. This may indicate the extreme tenaciousness of adult obesity, perhaps reflecting a relative lack of “plasticity” in the adult brain, further arguing for the importance of early identification and treatment of children at risk for increased adiposity. While mindfulness is readily translatable to children, and encourages them to respond to everyday adversity in healthy ways [129, 130], few studies report mindfulness for weight loss, weight maintenance, or eating healthfully among children.

Among food approach behaviors, DD was not associated with brain network imbalance (*p* = 0.495), nor with BMI *z*-score (*p* = 0.917). Some studies have reported no relationship between DD and weight [131], while others have

Table 11. Relationships between adiposity and rsFC, and eating behaviors and rsFC, between foot motor cortex and right nucleus accumbens.

Negative control model: [FOOT:NAC] [‡] functional connectivity					
BMI z-score vs. [FOOT:NAC]			<i>r</i>	<i>R</i> ²	<i>p</i>
N = 38			0.101	0.010	0.548
CEBQ eating behaviors vs. [FOOT:NAC]			<i>r</i>	<i>R</i> ²	<i>p</i>
Food Approach	N = 24	DD: Desire to Drink	-0.346	0.120	0.098
		EF: Enjoyment of Food	0.448	0.201	0.028 [*]
		EOE: Emotional Overeating	0.202	0.041	0.345
		FR: Food Responsiveness	0.033	0.001	0.879
Food Avoidance	N = 24	EUE: Emotional Under-Eating	0.042	0.002	0.844
		FF: Food Fussiness	-0.246	0.061	0.246
		SE: Slowness in Eating	-0.229	0.053	0.281
		SR: Satiety Responsiveness	-0.362	0.131	0.082 [‡]

Relationships between adiposity and [FOOT:NAC] rsFC, and eating behaviors and [FOOT:NAC] rsFC. BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; rsFC: resting state functional connectivity; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

* $p \leq 0.05$.

† $p \leq 0.10$.

‡ Partial correlation between foot motor cortex and right NAc BOLD signals was controlled for the effects of the auditory cortex.

reported associations with the consumption of *sweetened* drinks with weight [132]. Given these mixed results, we advocate the view put forth by Sweetman *et al.*, that the type of drink consumed influences this relationship [131]. Among food avoidance behaviors, EUE was not associated with brain network imbalance ($p < 0.450$), nor with BMI z-score ($p < 0.176$). While developing the CEBQ, Wardle *et al.*, noted that EUE decreased with increasing age. Therefore our results may be attributable to the older ages of the children in this study.

While FF was associated with brain network imbalance ($p = 0.046$), it was not quite trending toward statistical significance with BMI z-score ($p = 0.103$). In the initial validation of the CEBQ, Wardle *et al.*, noted that only FF showed a sex difference, in which boys had higher FF scores. Our *post hoc* analyses showed no significant interactions of FF association by sex. We conclude that in our cohort FF is not dependent on the sex of the child. Food fussiness is characterized by restricted eating in both the amount and types of food eaten, along with an unwillingness to try new food [133]. Food fussiness is typically associated with low weight. However, it has also been associated with increased weight [134, 135] as fussy eaters often restrict the consumption of fruits and

Table 12. Relationships between adiposity and rsFC, and eating behaviors and rsFC, between auditory cortex and right nucleus accumbens.

Negative control model: [AUDITORY:NAC] [‡] functional connectivity					
BMI z-score vs. [AUDITORY:NAC]			<i>r</i>	<i>R</i> ²	<i>p</i>
N = 38			0.280	0.079	0.088 [†]
CEBQ eating behaviors vs. [AUDITORY:NAC]			<i>r</i>	<i>R</i> ²	<i>p</i>
Food Approach	N = 24	DD: Desire to Drink	0.026	0.001	0.905
		EF: Enjoyment of Food	0.207	0.043	0.332
		EOE: Emotional Overeating	0.193	0.037	0.367
		FR: Food Responsiveness	0.237	0.056	0.264
Food Avoidance	N = 24	EUE: Emotional Under-Eating	-0.033	0.001	0.879
		FF: Food Fussiness	-0.074	0.005	0.731
		SE: Slowness in Eating	-0.130	0.017	0.545
		SR: Satiety Responsiveness	0.013	0.000	0.953

Relationships between adiposity and [AUDITORY:NAC] rsFC, and eating behaviors and [AUDITORY:NAC] rsFC. BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; rsFC: resting state functional connectivity; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

[†]*p* ≤ 0.10.

[‡]Partial correlation between auditory cortex and right NAC BOLD signals was controlled for the effects of the foot motor cortex.

Table 13. Relationships between adiposity and rsFC, and eating behaviors and rsFC, between foot motor cortex and auditory cortex.

Negative control model: [FOOT:AUDITORY] [‡] functional connectivity					
BMI z-score vs. [FOOT:AUDITORY]			<i>r</i>	<i>R</i> ²	<i>p</i>
N = 38			-0.078	0.006	0.642
CEBQ eating behaviors vs. [FOOT:AUDITORY]			<i>r</i>	<i>R</i> ²	<i>p</i>
Food Approach	N = 24	DD: Desire to Drink	-0.059	0.004	0.783
		EF: Enjoyment of Food	0.022	0.000	0.918
		EOE: Emotional Overeating	-0.241	0.058	0.257
		FR: Food Responsiveness	-0.243	0.059	0.252
Food Avoidance	N = 24	EUE: Emotional Under-Eating	0.100	0.010	0.642
		FF: Food Fussiness	-0.064	0.004	0.767
		SE: Slowness in Eating	0.315	0.099	0.134
		SR: Satiety Responsiveness	0.117	0.014	0.587

Relationships between adiposity and [FOOT:AUDITORY] rsFC, and eating behaviors and [FOOT:AUDITORY] rsFC. BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; rsFC: resting state functional connectivity; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

[‡]Partial correlation between foot motor cortex and auditory cortex BOLD signals was controlled for the effects of the right nucleus accumbens.

Table 14. Relationships between adiposity and the difference in rsFC, and eating behaviors and the difference in rsFC, with right nucleus accumbens.

Negative control model: Δ = [FOOT:NAC][‡] - [AUDITORY:NAC][#]					
BMI z-score vs. Δ			<i>r</i>	<i>R</i>²	<i>p</i>
N = 38			-0.134	0.018	0.424
CEBQ eating behaviors vs. Δ			<i>r</i>	<i>R</i>²	<i>p</i>
Food Approach	N = 24	DD: Desire to Drink	-0.235	0.055	0.268
		EF: Enjoyment of Food	0.145	0.021	0.500
		EOE: Emotional Overeating	-0.001	0.000	0.995
		FR: Food Responsiveness	-0.138	0.019	0.521
Food Avoidance	N = 24	EUE: Emotional Under-Eating	0.049	0.002	0.822
		FF: Food Fussiness	-0.106	0.011	0.622
		SE: Slowness in Eating	-0.058	0.003	0.788
		SR: Satiety Responsiveness	-0.237	0.056	0.265

Relationships between adiposity and Δ , the difference in functional connectivity measures [FOOT:NAC] and [AUDITORY:NAC], and between eating behaviors and Δ . NAc: nucleus accumbens; BMI: body mass index; CEBQ: Child Eating Behaviour Questionnaire; rsFC: resting state functional connectivity; *r*: correlation coefficient; *R*²: coefficient of determination; *p*: indicators for statistical significance.

[‡]Partial correlation between foot motor cortex and right NAc BOLD signals was controlled for the effects of the auditory cortex.

[#]Partial correlation between auditory cortex and right NAc BOLD signals was controlled for the effects of the foot motor cortex.

vegetables. Decreased consumption of fruits and vegetables is associated with increased consumption of fats [136], contributing to increased adiposity. Our lack of negative association between BMI z-scores and FF may be due to restricted eating that includes an increase in high-energy dense food.

We found no statistically significant associations between eating behaviors and brain network imbalance in an alternative model in which the NAc was located in the left hemisphere. These results may be due to hemispheric laterality. There are two prominent hypotheses of laterality:

1. The right hemisphere is associated with punishment / avoidance; and
The right hemisphere is associated with punishment / avoidance.
2. The left hemisphere is associated with emotions with positive valence; and
The right hemisphere is associated with emotions with negative valence.

However, numerous studies support or contradict either hypothesis [137, 138, 139, 140]. Miller *et al.*, hypothesize that laterality may change across temporal and spatial domains, depending upon circumstances [141].

In light of this hypothesis, future work is needed to investigate resting state functional connectivity in relation to hemispheric laterality.

Our overarching hypothesis is that disrupted resting state functional connectivity within a neural model related to non-homeostatic eating is associated with increased adiposity and unhealthy eating behaviors among children. Previously published resting state functional connectivity studies in childhood obesity compared categorical weight classes: children who were severely obese with healthy weight children. Here we examined children across a continuous range of adiposity values to better understand functional connectivity and its imbalance as a function of adiposity.

Future work will consider larger brain networks using graph-based analyses and machine learning-based connectivity classification. A limitation of all functional connectivity analyses is that correlation does not imply causality. It is therefore important not to over-interpret functional connectivity results. Nonetheless, functional connectivity can be used to distinguish disease states and as a summary of neuronal activity.

Longitudinal studies are needed to better understand whether functional connectivity imbalance is present at birth or if imbalance develops during childhood. Longitudinal studies, beginning during very early childhood, are necessary to identify children who are at risk for developing obesity, to follow the development and integrity of resting state functional connectivity, and to develop and assess obesity interventions. Of note, Fig. 4C shows a cluster of four children who have lower BMI z -scores but higher impulsivity-biased imbalance. Following these children over time would reveal whether they are at risk for developing obesity.

5. Conclusions

Our results establish the interplay among resting state functional connectivity, adiposity, and eating behaviors during childhood. We reported novel results from a resting state functional connectivity study of childhood obesity in which we examined children across a range of adiposity values. To our knowledge, no previous childhood obesity resting state functional connectivity studies have examined adiposity as a continuous measure. Our results suggest that resting state functional connectivity can identify neural models that are associated with adiposity and with eating habits. Furthermore, the identification of an imbalance in resting state functional connectivity that is associated with adiposity and unhealthy eating habits contributes to our knowledge of non-homeostatic factors involved in childhood obesity. Long-lasting weight loss maintenance may be elusive because, in addition to changing eating habits and physical activities, one must also change brain function.

Declarations

Author contribution statement

BettyAnn Chodkowski: Conceived and designed the experiments; performed the experiments; analyzed and interpreted the data; contributed reagents, materials, analysis tools or data; wrote the paper.

Ronald L. Cowan; Kevin D. Niswender: Conceived and designed the experiments; contributed reagents, materials, analysis tools or data; wrote the paper.

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Competing interest statement

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Additional information

Data associated with this study is available through the Collaborative Informatics and Neuroimaging Suite (COINS; Scott et al., 2011) via the Nathan Kline Institute Rockland Sample Data Use Agreement (http://fcon_1000.projects.nitrc.org/indi/enhanced/data/DUA.pdf).

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