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Tonic Hyper-Connectivity of Reward Neurocircuitry in Obese Children

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Abstract

Objective—Obese children demonstrate less activation in prefrontal regions associated with self-control and inhibition when presented with food cues and advertisements. The current study evaluates the differences between obese and healthy weight children in resting-state functional connectivity to these brain regions.

Design and Methods—Seed regions in bilateral middle frontal gyri were chosen based on previous task-based analysis showing differences between obese and healthy weight children's responses to food-associated stimuli. Functional connectivity to these seed regions was measured in resting-state scans collected in obese and lean children undergoing fMRI.

Results—Obese children exhibited greater resting-state functional connectivity than healthy weight children between the left middle frontal gyrus and reward-related regions in the left ventromedial prefrontal cortex, as well as the left lateral OFC.

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Conclusion—Previously published results demonstrate that obese children exhibit less activity in brain regions associated with self-control when viewing motivationally salient food advertisements. Here we show that obese children also have tonically greater input to these self-control regions from reward neurocircuitry. The greater functional connectivity between reward and self-control regions, in conjunction with weaker activation of self-control neurocircuitry, may render these children more susceptible to food advertisements, placing them at elevated risk for over-feeding and obesity.

Keywords

children; functional magnetic resonance imaging (fMRI); resting-state; impulsivity; orbitofrontal cortex; ventromedial prefrontal cortex

Introduction

Recent research has demonstrated that differences between healthy and obese children are not limited merely to brain activity in the presence of food images per se[1–3] but extend to food-*associated* stimuli as well. In a first-of-its-kind study, Bruce and colleagues asked obese and healthy children to view food and non-food advertising logos while undergoing functional Magnetic Resonance Imaging (fMRI).[4] When viewing the food logos, healthy weight children exhibited greater activation bilaterally in the middle frontal gyrus (BA 10), a region associated with self-control and inhibition.[5–7] This finding was significant because it implies that inhibitory processes may automatically mediate neural responses of healthy-weight children in the presence of food logos, thereby facilitating behavioral restraint. What remains unclear from this and previous functional neuroimaging studies of obese and healthy weight children, is whether group differences reflect only abnormal *stimulus-driven* activity in obese children, or rather extend to *intrinsic* functional differences in the brains of obese children. Put another way, is the activity in obese children's brains abnormal only in the presence of food, and food-associated stimuli, or is the activity in their brains tonically abnormal? One tool for examining intrinsic (task-independent) brain activity is resting-state functional connectivity analysis, which measures the coupling of spontaneous fluctuations of the fMRI signal among brain regions.[8]

To date there are no published studies of resting-state functional connectivity differences between healthy and obese children. To better understand how differences in intrinsic activity may contribute to differential responses to food-associated stimuli in obese and healthy adolescents, we examined resting-state functional connectivity to the middle frontal gyrus region identified in the earlier task-based study of responses to food and non-food logos. We hypothesized that obese children would exhibit greater resting-state functional connectivity than healthy children between this region involved in self-control and regions implicated in reward valuation processing, including the orbitofrontal and ventromedial prefrontal cortices.

Methods and procedures

Participants

Eighteen right-handed, native English speaking children participated in the study (see Table S1 for demographics); nine healthy weight (mean BMI percentile = 51.33 ± 20.43%) and nine obese children (5 males; mean BMI percentile = 97.80 ± 1.81%). Exclusion criteria included Axis I psychiatric diagnosis or neurologic illness. The study protocol was approved by the Human Subjects Committee at the University of Kansas Medical Center. Informed consent and assent were obtained from each child's guardian and child before study participation.

fMRI Resting-state data collection

The resting-state scan followed a structural scan and two task-based functional runs.[4,9] Data were acquired with a 3-Tesla Siemens Allegra scanner. See online Supporting Information for scan parameters.

Data Preprocessing

Data preprocessing and statistical analysis were conducted using AFNI[10] and a modified version of the ANATICOR method[11] to reduce spurious effects related to motion and physiological noise. In addition, further motion correction procedures (i.e. 'scrubbing') were utilized to reduce the possibility of false group differences due to uncontrolled subject motion.[12,13] See online Supporting Information for descriptions of the preprocessing.

Seed Region Selection and Identification

Seed regions were chosen based on analysis of the functional activation data from the study participants, as previously discussed.[4] These analyses demonstrated greater activity in the middle frontal gyrus in healthy weight, compared to obese adolescents, when viewing food advertising logos. Because this area of the brain has been linked to cognitive control and self-control, and activation differences in this region between weight groups has already been established, the current study defined 2 mm seed regions bilaterally in middle frontal gyrus at the peak voxels identified in the analysis of the task data (Talairach coordinates 42,44,−5 and −42,44,−5).

Functional Connectivity Analyses

At the subject-level, the seed time-series for both of the seed regions was constructed by calculating the average time series during the resting-state scan within the spherical regions around the seed coordinate. Using multiple regression analysis, we produced maps of the time-course correlations between each of the seed regions separately and all brain voxels. These *r*-values were then transformed to *z*-scores. To identify voxels exhibiting differences in spontaneous BOLD fluctuations correlated with each prefrontal seed region, we implemented group-level random effects *t*-tests comparing healthy weight and obese subjects z-scores. The resulting statistical maps were corrected for multiple comparisons at $p < .05$ (see online Supporting Information for detailed descriptions of multiple comparisons corrections).

Results

Compared to healthy weight children, obese children exhibited greater functional connectivity between the left middle frontal gyrus and the left vmPFC (Peak t = −5.03 at Talairach coordinate 7,−21,−14; cluster size = 30.63 mm^3; see Figure 1). Though the statistical peak voxel was located in the left hemisphere, the cluster branched laterally and dorsally into the corresponding region of the right hemisphere, spanning the posterior region of Brodmann's area 10 to the frontal and polar regions of BA10. Additionally, the obese children exhibited greater FC between the left middle frontal gyrus and the left lateral OFC (Peak t = −5.44 at Talairach coordinate 31,−33,−4; cluster size = 3.52 mm^3; see Figure 1).

Discussion

Although previous functional neuroimaging studies have documented differences in healthy-weight and obese children's response to food-associated stimuli[2–4,9] prior to the present study, it was yet unknown whether these group differences reflect only abnormal *stimulus-driven* activity in obese children, or *intrinsic* functional differences in the brains of obese children's brains. Here we observed that, even while at rest, obese children exhibit greater functional connectivity between left middle frontal gyrus and the ventromedial prefrontal cortex and OFC.

The bilateral middle frontal gyrus, used as the seed region in the current analyses, is associated with cognitive control and response inhibition.[5–7] This area was chosen as a seed due to findings from a previous study using the same participants, in which healthy weight children showed greater activation in this area than obese children when viewing food-related logos.[4]

The region of the OFC exhibiting group differences in functional connectivity in the present study is associated with reward anticipation and evaluation,[14] as well as the processing of emotionally latent tasks,[15] and the lateral OFC more specifically is associated with cognitive aspects of emotional stimuli.[2] The vmPFC region exhibiting group differences in functional connectivity has been linked to the processing of emotional stimuli and valuation of goods.[16] Taken together, the findings of the present study show that obese children have increased functional connectivity between areas associated with cognitive control and those associated with the judgment of emotional stimuli and reward anticipation.

Although the present study includes a relatively small sample, the results presented here survive multiple comparisons correction, which testifies to the robustness of the reported effects. The study has additional important strengths. First, the seed regions were based on group differences from an analysis of functional data within these same individuals.[4] This ensured that the seeds were specific to participants in this study, which is important given previous work demonstrating that children's brains are structurally different from adult brains, making it difficult to pick seeds from related adult studies.[17,18] Second, the analyses utilized advanced procedures for motion 'scrubbing'[11,12] that account for signal artifacts due to movement.

Due to the cross-sectional nature of this study, it is impossible to determine whether these differences are a cause, correlation, or consequence of the increased body weight. Another potential limitation pertains to the data collection order, as the task-based data were collected prior to resting state scans, though there is little evidence to suggest this significantly impacts functional connectivity findings.

The present findings are consistent with previous studies evaluating cortical activation in obese children[2] and functional connectivity in overweight and obese adults.[19] Combined with previous reports from our group, we have demonstrated that though healthy weight children exhibit greater activation in the middle frontal gyrus while viewing food logos[4] (see Figure 2) functional connectivity between this region and the vmPFC and OFC is greater in obese participants. Our interpretation of the findings suggests that in obese children, cognitive control regions may tonically receive greater input from reward motivation regions of the brain, perhaps resulting in less self-control and greater value assigned to food-related stimuli. An alternative account may suggest that in obese children, the middle frontal gyrus exhibits greater functional connectivity with vmPFC and lateral OFC, which have also been implicated in inhibitory control.[20] Future studies should examine whether there are also functional connectivity differences present during a stimulus-based task.

The present findings have important implications for society's debate about whether, and how, to protect children from what some have described as "predatory" food marketing.[21] This debate must now occur in the context of the present findings, which strongly suggest that some children have brains that predispose them to these advertisements, and thus the concomitant health consequences of obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- fMRI studies have demonstrated obese and healthy weight children's brain activity differs in response to food and food-related stimuli.
- Brain activity in regions associated with reward, motivation, and cognitive control differ between obese and healthy weight children.

WHAT THIS STUDY ADDS

- This is the first evidence that brain functional connectivity during a resting state differs between obese and healthy weight children.
- Obese children show greater functional connectivity than healthy weight children between reward brain regions and self-control brain regions.

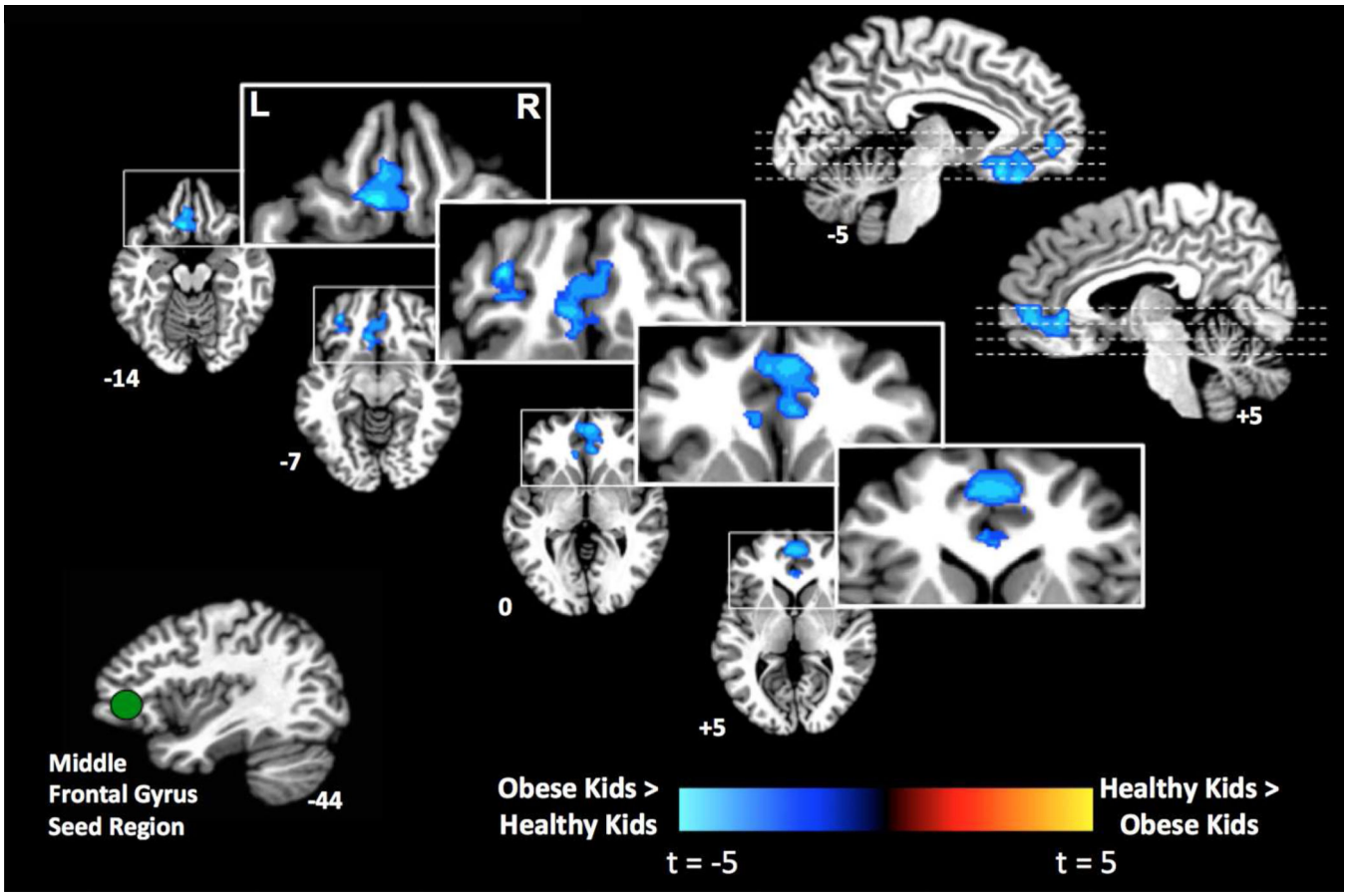

Figure 1. Functional Connectivity Differences Between Obese and Healthy Weight Children

Obese children exhibit stronger resting-state functional connectivity between orbitofrontal and ventromedial prefrontal reward regions and middle frontal gyrus regions involved in self-control.

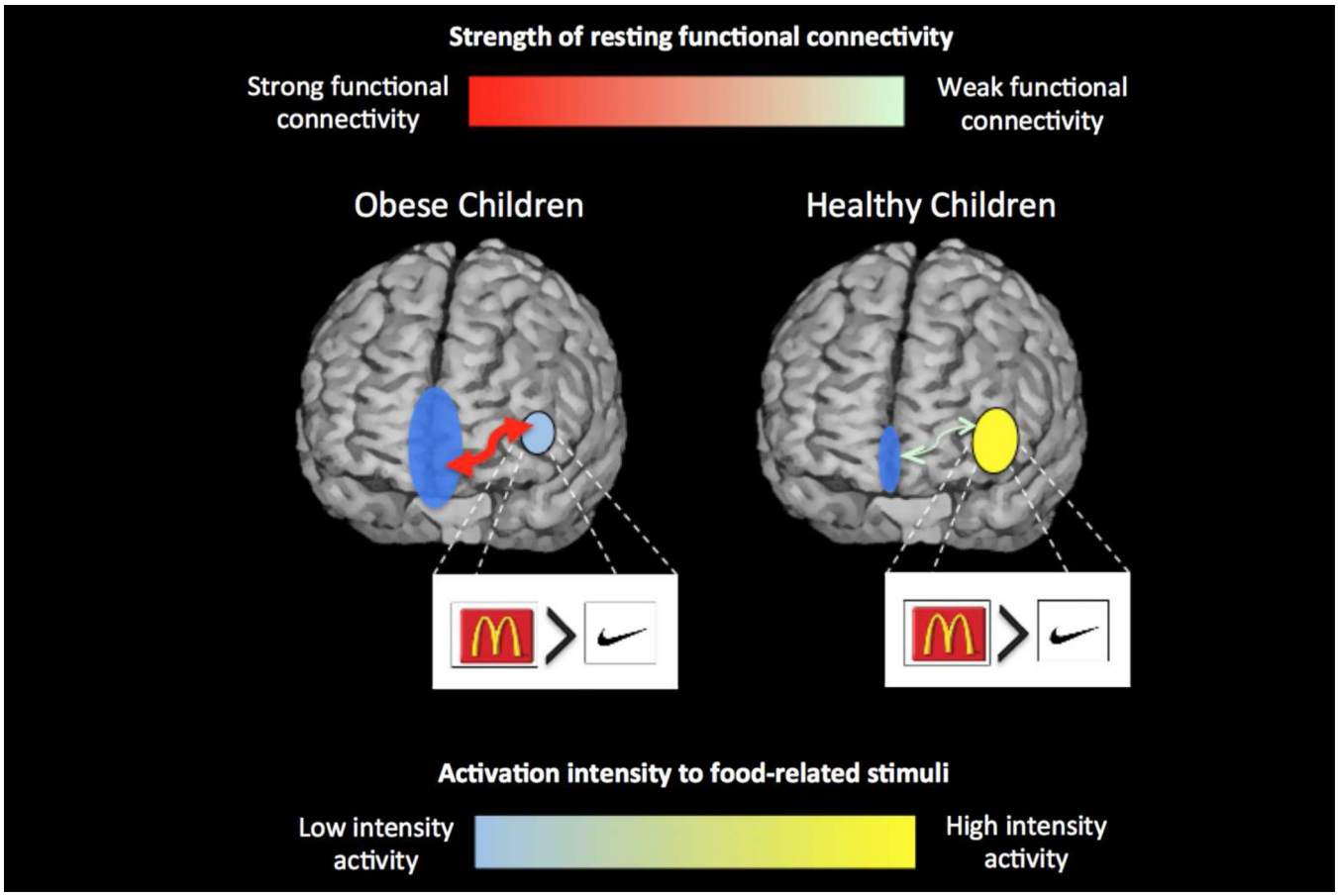

Figure 2. Differences in Neural Activation Between Obese and Healthy Weight Children When Viewing Food-Related Stimuli

Obese children exhibit less intense activation in self-control regions (middle frontal gyrus) while viewing food-related stimuli (Bruce, et al. 2013), but greater tonic functional connectivity between those control regions and reward regions in orbitofrontal and ventromedial prefrontal cortex.