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Reward-related neural correlates in adolescents with excess body weight

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ABSTRACT

The functional and connectivity reward processing in adults with excessive body weight is well documented, though is relatively less researched during adolescence. Given that reward and inhibition may be highly malleable during adolescence, it is unknown how impulsive behaviors, potentially stemming from impaired inhibitory control and heightened sensitivity to rewarding cues, relate to increases in body weight in adolescents. Adolescents (N = 76; mean age = 14.10 years, *SD* = 1.92) with varied body mass index (BMI) performed a child-friendly monetary incentive delay task during functional magnetic resonance imaging, to study reward processing during the anticipation of rewards (cue) and reactions to feedback about rewards (feedback). Our results show that adolescents with greater BMI z-score show neural activation and ventral striatum connectivity alterations in networks implicated in reward, salience detection, and inhibitory control. These bottom-up reward and top-down inhibitory control networks, as well as interactions between these networks were prevalent during the anticipation period (when the cue is presented) as well as when receiving feedback about whether one has received a reward. Specifically, our results were mainly driven by failure to receive a reward in the feedback period, and the anticipation of a potential reward in the anticipation period. Overall, we provide evidence for heightened reward salience as well as inhibitory control deficits that, in combination, may contribute to the impulsive behaviors that lead to higher BMI in adolescents.

1. Introduction

The prevalence of overweight/obesity and related negative health consequences are steadily increasing in adolescents in the United States (Skinner et al., 2018). The most significant driver of weight gain in this population is excessive calorie intake due to the wide availability of palatable energy-dense foods (Johnson and Wardle, 2014). Over time, such an obesogenic environment can alter neurobiological systems in a way that fosters overconsumption of highly rewarding foods (Stice et al., 2013; Stice and Yokum, 2016), thus, leading to weight gain and increased adiposity. In recent years, studies on childhood weight gain have mainly focused on impulsive behavior. This body of research suggests that children with self-regulation difficulties show a higher weight status and faster weight gain than their peers with greater self-regulation (Francis and Susman, 2009). While this is an important finding, it is critical to understand that impulsive behavior is not a unitary construct but rather a product of multiple neurocognitive processes mediated by related but distinct neural circuitry (Dalley et al., 2011; Stahl et al., 2014). Moreover, such processes are rapidly developing and highly vulnerable during adolescence (Walker et al., 2017) Therefore, a better understanding of how component neurocognitive processes underlying impulsive behavior may contribute to high body weight in adolescents is important.

Impulsive behaviors may stem from the combination of two neurocognitive mechanisms: impaired inhibitory control and heightened sensitivity to rewarding cues. Research shows that both these constructs are associated with high body weight in adults (Emery and Levine, 2017). With regards to the inhibitory control substrate of impulsive behavior, it is likely that confrontation with appetizing high-caloric food provokes the prepotent reaction to consume it. As a consequence, it is theorized that children with poor inhibitory control towards food may develop higher body weight (Reyes et al., 2015; van Meer et al., 2019).

Abbreviations: BMI, Body mass index; PDS, Pubertal Development Scale; gPPI, generalized psychophysiological interaction analysis; AFNI, Analysis of Functional Neuro Images.

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Intriguingly, research on the association between inhibition behavior and body weight has yielded inconsistent findings. Some studies report decreased inhibitory control, measured behaviorally, in children and young adults with excessive body weight as compared to healthy body weight (Nederkoorn et al., 2012; Thamotharan et al., 2013), while others found no such relation (Bartholdy et al., 2016). For the reward processing substrate of impulsive behaviors, individuals with greater sensitivity to rewards are thought to assign greater salience to reward cues and show increased approach behavior and neural response with reward exposure (Gray, 1970). Indeed, such sensitivity towards anticipatory food cues has been reported to be associated with elevated activation of reward and emotional-regulatory brain regions and predict future weight gain in both adolescents (Burger et al., 2016; Winter et al., 2017) and adults (Burger et al., 2016). While there is some evidence from prior research showing a non-food specific elevated hyper-responsivity in these brain regions in youths at risk for obesity (Stice et al., 2011), it is unclear if this domain-general sensitivity to reward may also be related to weight gain in adolescents.

Impaired inhibitory control and reward hypersensitivity are typically considered as independent risk factors for a range of problematic behaviors and thus are assessed in isolation. However, a growing body of literature has suggested that an overlap between these two constructs at both neural and dopaminergic system level (Jentsch and Pennington, 2014) may increase the risk of maladaptive behavior. Moreover, the brain regions related to these two constructs, including executive control (e.g., prefrontal/frontal cortex), salience (e.g., insula), and reward (e.g., basal ganglia: ventral striatum/nucleus accumbens), participate in large functional networks (Shirer et al., 2012). A disruption in the communication or connectivity among these regions may contribute to impulsive eating behavior and weight gain (Shapiro et al., 2019). Furthermore, the domain-specific (food-related) variance may have an overlap with domain general variance in impulsive behavior. To date, however, little is known about this network neurobiology, particularly in context of non-food related cues in adolescents. Given that 80% of adolescents with obesity will maintain excessive body weight into adulthood (Reilly et al., 2003; Simmonds et al., 2016; Ward et al., 2017) and general reward- and inhibition-related neural circuits undergo significant changes during this key developmental transition (Walker et al., 2017), such brain function studies are important to provide insight into the neural circuitry underlying weight gain. A clear understanding of these neural mechanisms may help inform the development of mechanistic treatment targets and appropriate interventions to prevent future weight gain.

Here we sought to examine the relation between body mass index (BMI) and reward related neural processes during adolescence. We aimed to compare brain activations evoked by monetary rewards to understand non-food-specific (domain general) mechanisms, in young adolescents with a range of BMI z-scores. Specifically, we aimed to test how reward processing is modulated by BMI z-score, using a child-friendly monetary incentive delay task. We are interested in both the anticipation of rewards (cue) as well as reactions to feedback about rewards (feedback) as increased reward salience may be manifest in altered activation during both periods (Oldham et al., 2018). This study focused on network connectivity as a function of reward/no-reward context. Our analyses focused on the ventral striatum, since this subcortical region is recognized as a pivotal center for motivation and reward (Cauda et al., 2011). Moreover, data shows that activity in ventral striatum predicts activity in regions implicated in reward circuitry due to functional and anatomical connectivity (Cauda et al., 2011). We hypothesized that, in response to monetary reward we will see alterations in connectivity in neural networks involved in both reward processing and inhibitory control as a function of BMI. In particular, we hypothesized that neural connections during the reward anticipation and feedback in a non-food cue domain may be explained by BMI status of the adolescents

2. Method

2.1. Participants

Data were acquired from 76 youths (mean age = 14.10 years, *SD* = 1.92), recruited from the community (n = 58), as well as from a local research clinic (n = 18), as part of a larger set of studies on reward and emotion. Data collection procedures were identical for each sample, and samples did not differ on sociodemographic variables (age, sex, monthly income). See Supplementary Table 4 for details regarding the recruitment procedures for each sample and sample comparisons. Exclusion criteria included magnetic resonance imaging (MRI) contraindications (e.g., orthodontic braces) or presence of a major co-occurring neurological disorder. Parental permission and child assent were obtained for participants under 18, and participants aged 18 and above provided written informed consent. The University of California San Diego Institutional Review Board, in joint agreement with the San Diego State University Institutional Review Board, approved all procedures.

2.2. BMI data collection

Height and weight data were available for each subject via the self- and parent-reported Pubertal Development Scale (PDS, n = 51) as well as manual data collection (n = 25). This information, along with data collection date, birthdate, and sex was used to generate BMI z-score using the CDC calculator (https://www.cdc.gov/healthyweight/bmi/calculator.html). This metric was used in the subsequent analyses. Additional details are available in Supplement 1.

2.3. Child-friendly monetary incentive delay task

This event-related task, performed during functional magnetic resonance imaging (fMRI) acquisition, captures neural correlates of reward processing during reward anticipation and performance feedback (including reward omission and receipt) in youths and reliably elicits reward-related brain activation in children, including in the striatum, thalamus, insula, and prefrontal cortex (Dougherty et al., 2018; Helfinstein et al., 2013; Wiggins et al., 2017). First, a cue appears, signaling whether the trial includes a potential reward or not. After a variable delay, the target appears, which the participant is instructed to try to hit on all trials, regardless of whether there is a reward. Time to hit the target is titrated in real-time to maintain an approximate 2/3 hit, 1/3 miss ratio. Participants then receive feedback as to whether they successfully received a reward (stars in basket). Stars corresponded to money earned after the scan. Please see previous work (Dougherty et al., 2018) and Supplement 1 for additional details. The script for the task is available at the following link: https://osf.io/ytfs5/.

2.4. Neuroimaging acquisition

Data were acquired on two scanners, both in the San Diego area. The first site utilized a 3 T General Electric MRI scanner with a 32-channel head coil to acquire anatomical and functional brain images of 51 subjects. The remaining 25 subjects were scanned with a Siemens Magnetom Prisma using a 30-channel head coil. During data collection, we used a mock scanner with real-time feedback on head motion to acclimate research participants to the scanner environment and train them to stay still. This permitted children in our study to become accustomed to our research procedure and minimized head motion. Subsequent analysis was completed to account for potential confounding influences of scanner/recruitment source. Multiband procedures increased spatial and temporal resolution from both sources (Moeller et al., 2010). Additional details are in Supplement 1.

2.5. fMRI data preprocessing

Preprocessing protocols were implemented using Analysis of Functional NeuroImages (AFNI; https://afni.nimh.nih.gov/afni/) and included functional image realignment, slice-time correction, 4 mm spatial smoothing, and non-linear registration for spatial standardization to the Talairach template. We also applied censoring by removing image volume pairs with frame-wise displacement >1 mm from individual-level analysis. A maximum of 33% of image volumes could be censored before the subject was removed from analysis (no participant met this bar and thus all participants were retained). These procedures and thresholds are in line with past task-based fMRI studies with children (Kryza-Lacombe et al., 2020). Mean frame-wise displacement (head motion) was ≤0.20 mm across all participants.

2.6. fMRI data analysis

2.6.1. First-level models

Activation. Individual-level general linear models generated estimates of brain activation during anticipation and feedback periods. For the anticipation period, the regressor of interest (Reward Condition [reward, no reward]) was convolved with AFNI's 'dmBLOCK' basis function over the variable length delay between cue and target. The regressors of interest for the feedback period included Reward Condition (reward, no reward) and Performance (hit, miss), and were both convolved with the 'BLOCK' function over the period when participants learned that they received or did not receive a reward. Beta coefficients at each voxel for each condition (anticipation period: reward, no reward; feedback period: reward/hit, reward/miss, no reward/hit, and no reward/miss) were output as a result of this analysis.

Connectivity. We used generalized psychophysiological interaction analysis (gPPI) (McLaren et al., 2012) to assess the functional connectivity between brain areas during the reward anticipation and feedback. In particular, we tested the change in correlations between a seed region of interest and each voxel in the rest of the brain for each condition compared to implicit baseline. As compared to the standard PPI approach, generalized methods are advantageous because they allow for the evaluation of all task conditions and their interaction in a single, omnibus model. This approach leads to improved model fit suggesting greater sensitivity to true positive findings and greater specificity to true negative findings (McLaren et al., 2012). However, it is also important to recognize that this approach cannot determine directionality or causality between functionally connected regions but can provide powerful means for generating specific hypotheses regarding functional relationships, which can be tested using causal models.

Given prior fMRI work implication the role of ventral striatum in reward processing (Dougherty et al., 2018; Helfinstein et al., 2013) and research studies implicating this region in obesity (Gearhardt et al., 2020; Ikeda et al., 2019; Legget et al., 2018), we utilized left and right ventral striatum as seeds for gPPI analyses (Fig. S1). Masks of the seeds were identified using the Talairach atlas in AFNI (left ventral striatum = 136 mm^3; right ventral striatum = 168 mm^3). These analyses resulted in voxel-wise images representing connectivity between the seed region and the rest of the brain, for each condition (anticipation period: reward, no reward; feedback period: reward/hit, reward/miss, no reward/hit, and no reward/miss). The PPI models for both activation and connectivity also included nuisance regressors head motion in x, y, z, roll, pitch, yaw directions and third-degree polynomials to model low-frequency drift as nuisance regressors.

2.6.2. Second-level models

To assess how reward processing is modulated by BMI z-score, a whole-brain, repeated-measures ANCOVAs using AFNI's 3dMVM program computed associations of BMI z-score with reward-related brain function (activation, connectivity) was conducted. To explore our interest in network connectivity as a function of reward/no-reward context, and to study the anticipation of rewards refers to motivational processes that are mobilized to obtain rewards as a function of their value of salience, as well as reactions to feedback about rewards, we conducted analyses for left and right ventral striatum connectivity images and whole brain activation separately, and for feedback and anticipation periods separately. Contrasts of interest included highest-order interactions between task conditions and BMI z-score (anticipation models: BMI z-score × Reward Condition; feedback models: BMI z-score × Reward Condition × Performance) as well as other lower-order terms that included BMI z-score (anticipation models: BMI z-score main effect; feedback models: BMI z-score × Reward Condition, BMI z-score × Performance, BMI z-score main effect). Beta coefficients at each voxel across participants for each condition (anticipation period: reward, no reward; feedback period: reward/hit, reward/miss, no reward/hit, and no reward/miss) were output. Cluster thresholds for each analysis were calculated with AFNI's 3dClustSim using the mixed-model spatial autocorrelation function (−acf) and the NN1 2-sided option, per the most recent recommendations on cluster correction (Cox et al., 2017). With a conservative height threshold of $p < .005$, the cluster extent threshold was ks ≥ 58–61 (varying slightly depending on analysis) to generate an equivalent whole-brain corrected $p < .05$. Values from significant clusters were extracted and averaged and exported to SPSS for post-hoc analyses to decompose interactions of interest; post-hoc decomposition of the interactions was false discovery rate (FDR) corrected for multiple comparisons within each analysis. Extracted data were also examined for outliers and potential confounding variables in SPSS (see Supplement 1). The syntax for analysis is available at the following link: https://osf.io/ytfs5/.

3. Results

Please see Table 1 for participant characteristics. Based on the World Health Organization's BMI z-score classification categories, 53.9% (n = 41) of children were healthy weight, 32.9% (n = 25) were overweight, and 13.2% (n = 10) were obese. BMI z-score did not differ by sex (t = 0.347, df = 74, p = 0.729). Additionally, BMI z-score was not correlated with age (r = 0.010, p = 0.928) or monthly income (r = −0.029, p = 0.836). Overall, we found that BMI z-score relates to neural activation and ventral striatum connectivity in networks implicated in reward, salience detection, and inhibitory control. Functional alterations in these regions were found in both the anticipation and feedback periods of the monetary incentive delay task; the direction of the differences depended on task condition (Reward, No Reward) and performance (Hit, Miss). Our results were mainly driven by failure to receive a reward in the feedback period, and the anticipation of a potential reward in the anticipation period.

3.1. Activation

Anticipation Period. There were no significant clusters related to

Table 1
Demographic and clinical characteristics.

Characteristic (N = 76)	
Sex (% female)	55.26%
Age (years)	
Mean (SD)	14.10 (1.93)
Range	9.69–19.44
BMI z-Score	
Mean (SD)	61 (1.22)
Range	−3.14–2.58
Monthly Income	
Median (SD)	5000 (5467.22)
Range	1000–27300

Note: SD = Standard Deviation; BMI = Body Mass Index

BMI z-score in the anticipation period.

Feedback Period. Significant BMI z-score × Performance interactions were detected in insula and caudate nucleus as well as prefrontal regions (superior and inferior frontal gyri) during the feedback period. All clusters were driven by BMI z-score related differences during the miss condition: In the insula and caudate nucleus as well as the superior frontal gyrus, higher BMI z-score was associated with less activation when the target was missed, whereas in the inferior frontal gyrus, higher BMI z-score was associated with greater activation when the target was missed. There was no relation between BMI z-score and activation when the target was hit in any of these clusters (Fig. 1).

3.2. Ventral striatum connectivity

Areas involved in both bottom-up reward and top-down inhibitory control networks show ventral striatum connectivity alterations in relation to BMI z-score during both the anticipation and feedback periods.

Anticipation Period. During the anticipation period, both left and right ventral striatum exhibited BMI-related connectivity alterations with insula, ventromedial prefrontal cortex, and parietal regions. In the right insula, there was a main effect of BMI z-score, such that higher BMI z-score was associated with decreased connectivity with the left ventral striatum across task conditions (Fig. 2**A**). Additionally, four parietal clusters showed significant main effects of BMI z-score, as decreased connectivity between these regions and right ventral striatum across task conditions was associated with increased BMI z-score (**Table S3**). For left ventral striatum connectivity, BMI z-score × Condition interactions were significant in the right insula and ventromedial prefrontal cortex, such that youths with higher BMI z-scores showed less connectivity when anticipating a reward but stronger connectivity (or a trend toward stronger connectivity, for the ventromedial prefrontal cortex) during trials without a reward (Fig. 2**B**).

Feedback Period. During feedback, the main effect of BMI z-score was significant for right ventral striatum connectivity with right inferior parietal lobule and middle frontal gyrus, such that higher BMI z-score related to weaker connectivity (**Table S3**). BMI z score × Condition interactions were significant for left and right ventral striatum connectivity with several prefrontal/frontal regions. Specifically, higher BMI z-score was associated with stronger left ventral striatum connectivity with two bilateral superior frontal clusters and left middle temporal gyrus during reward trials, yet weaker connectivity (or a trend toward weaker connectivity, for bilateral superior frontal gyri) during no reward trials (Fig. 3**A**).

BMI z-score × Condition × Performance was significant for right ventral striatum connectivity with right superior temporal gyrus. Here, the direction of effects depended on whether the subject hit or missed the target, and whether the trial had a potential reward or not: When participants missed the target in which no reward was expected (no reward miss), higher BMI z-score was associated with stronger striatum-superior temporal connectivity. By contrast, during trials where the participants missed a potential reward (reward miss) or hit the pinata but did not receive a reward (no reward hit), higher BMI z-score was associated with weaker connectivity; BMI z-score was not related to connectivity during trials in which the participant hit the target and received the reward (reward hit) (Fig. 3**B**).

3.3. Additional analyses

Additional analyses were conducted to evaluate the potential impact of age, sex, symptoms of depression and anxiety, recruitment source, scanner, and BMI z-score measurement method on our results. To summarize, the analyses demonstrated that these potential factors were not primarily driving our results (**see** Supplemental Material).

4. Discussion

The present study is the first to examine reward-related neural correlates of BMI z-scores in adolescents. Overall, we found that adolescents with greater BMI z-score show activation and connectivity alterations in both bottom-up reward and top-down inhibitory control networks as well as interactions between these networks. These neural aberrations

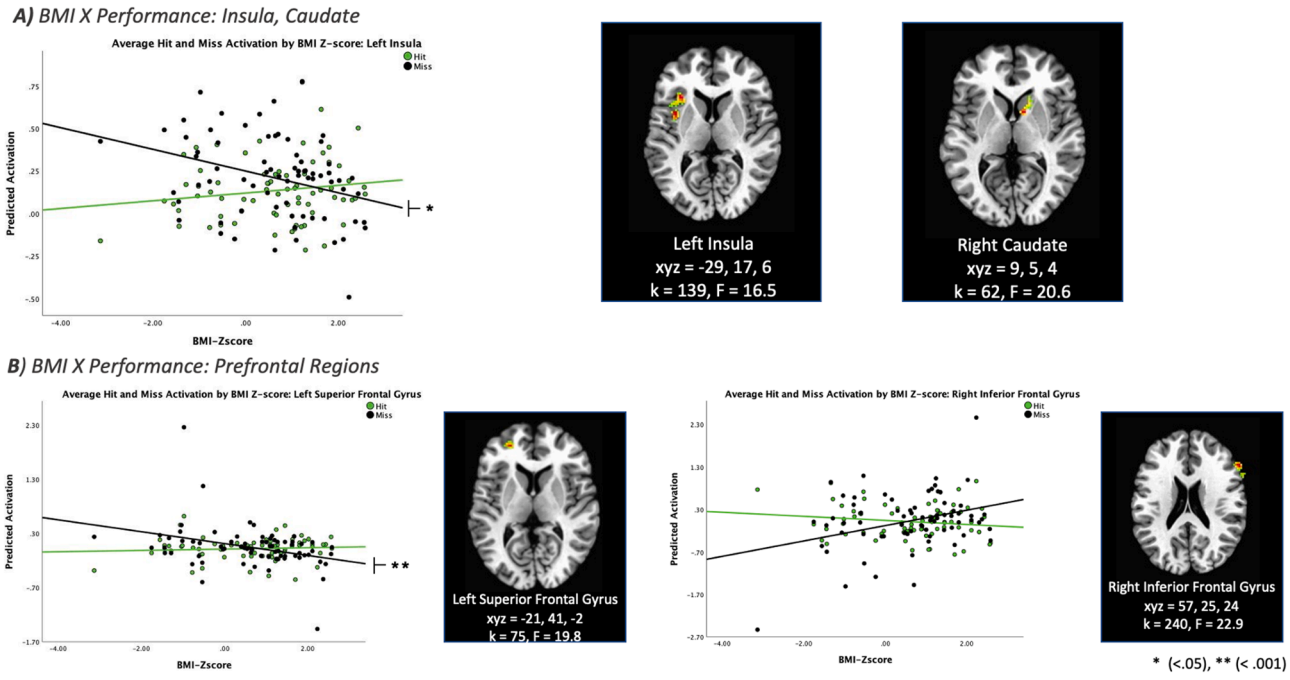

Fig. 1. Whole-brain Activation Analysis – Feedback Period. Graphs display predicted activation for indicated clusters. Because the pattern for insula and caudate were highly similar, the insula graph is shown as a representation of both. Post-hoc decomposition of the interactions was FDR corrected for multiple comparisons within each analysis and are displayed for illustrative purposes; significant post-hoc correlations are indicated with asterisks. Left = left on brain images, with threshold set at whole brain cluster corrected $p < .05$.

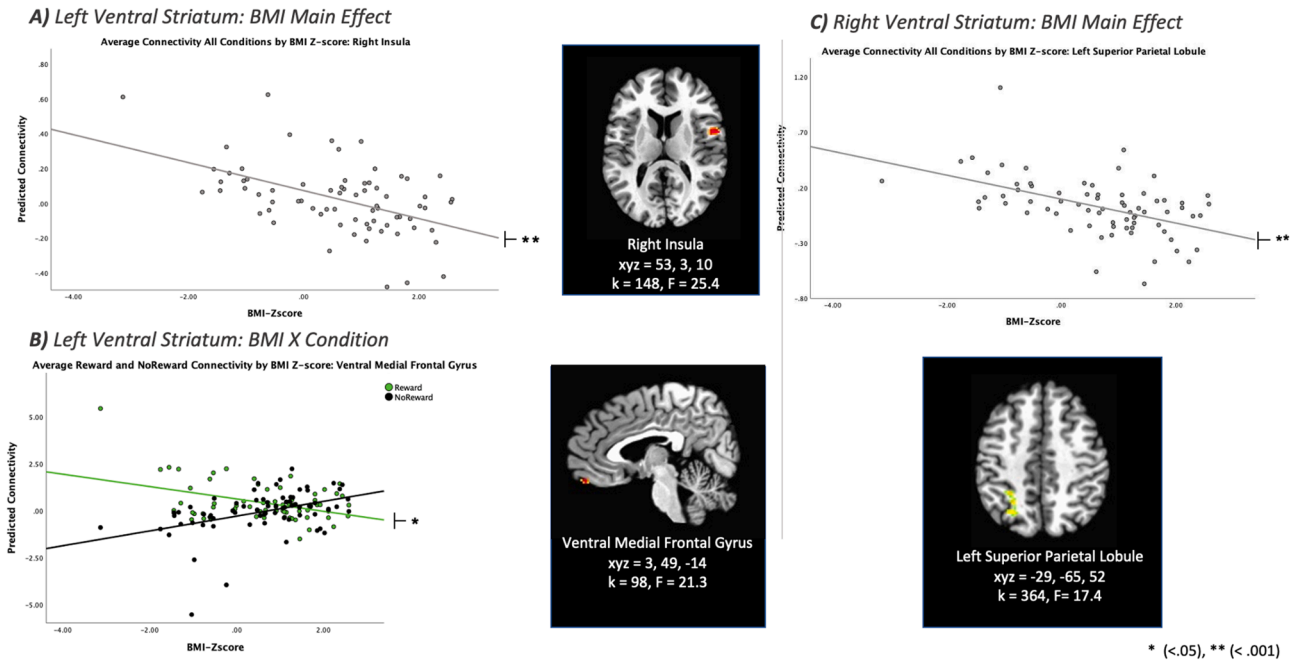

Fig. 2. Ventral Striatum Connectivity – Anticipation Period. Graphs display predicted connectivity for indicated clusters. Post-hoc decomposition of the interactions was FDR corrected for multiple comparisons and are displayed for illustrative purposes; significant post-hocs correlations are indicated with asterisks. Left = left on brain images, with threshold set at whole brain FDR corrected $p < .05$.

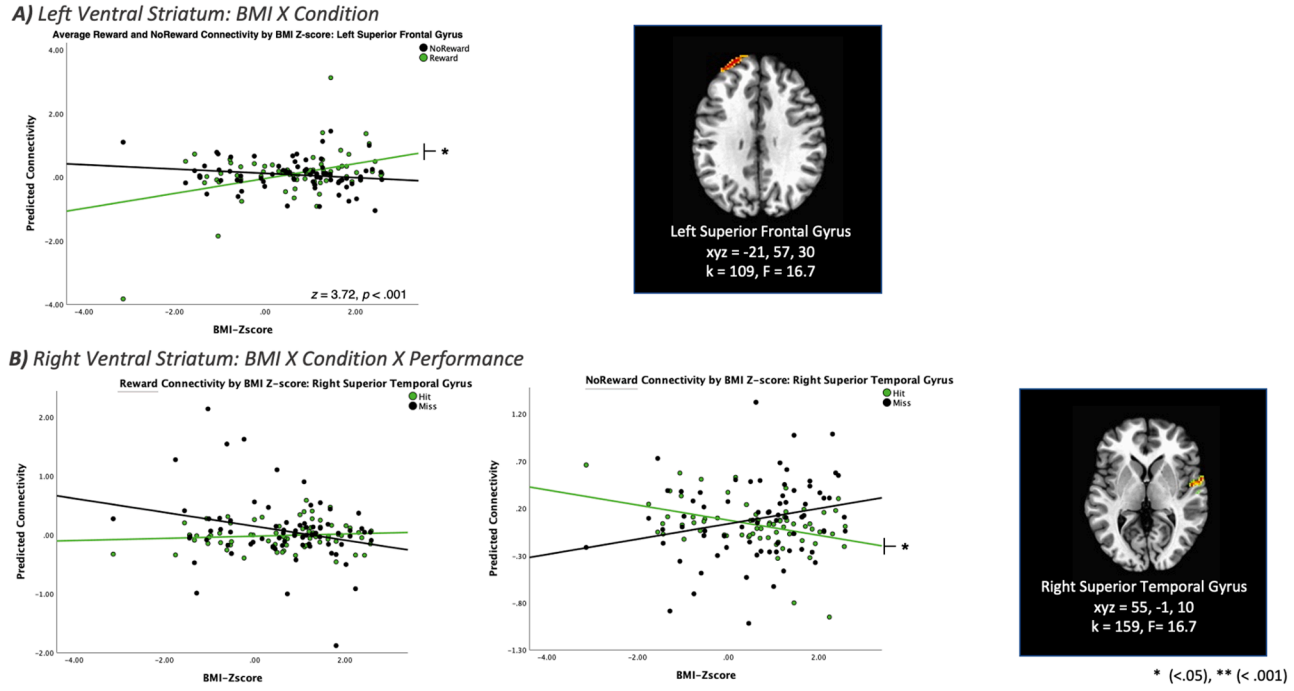

Fig. 3. Ventral Striatum Connectivity – Feedback Period. Graphs display predicted connectivity for indicated clusters. Post-hoc decomposition of the interactions were FDR corrected for multiple comparisons and are displayed for illustrative purposes; significant post-hocs correlations are indicated with asterisks (**). Left = left on brain images, with threshold set at whole brain FDR corrected $p < .05$.

were apparent across multiple contexts assessing reward salience (i.e., during anticipation of a reward as well as when receiving feedback about whether one has received a reward) in a developmentally appropriate fMRI paradigm. Overall, our results provide evidence for heightened reward salience as well as inhibitory control deficits that, in combination, may be associated with the impulsive behaviors that lead to higher BMI z-score in adolescents.

Building on other fMRI studies that used food-related reward cues, this study is the first to show that non-food (monetary) rewards are related to BMI z-score in adolescence, suggesting that changes in reward seen in adolescence are likely domain general and impact a variety of arenas, including food intake. Our work here applies a rich literature on reward and inhibition development (Galvan, 2014), typically studied within the context of psychopathology (O'Callaghan and Stringaris,

2019) in an innovative manner to understand adiposity. Indeed, prior work has shown that food rewards and monetary rewards activate common neural networks (Sescousse et al., 2013), with some reporting greater activation with food reward cues (Simon et al., 2015). This highlights that domain general related aberrant neural networks in adolescents with higher BMI z-scores will likely extend to food related stimuli and preference for energy dense rewarding foods. Within this context, our results are important because adolescence is a sensitive period of marked neuroplasticity, in which the brain undergoes considerable maturation. Overtime, failure to regulate dietary decisions, as a consequence of self-regulatory deficits, can disrupt the natural course of development of neurocircuitry, thus exacerbating reward processing/salience assignment and cognitive dysfunction (Reichelt, 2016). Moreover, literature suggests that inhibitory and reward processing evolves with development (Shulman et al., 2016), further compounding the risk of diet-induced obesity into adulthood.

Although prior literature had focused on inhibitory control and reward dysfunction separately in relation to overeating behavior, we found that brain regions associated with both reward and inhibitory control were implicated within a wide range of BMI z-scores. This suggests that both aspects are likely to contribute to impulsive eating behavior in adolescents. With regards to reward, we showed that adolescents towards the higher range of continuous BMI z-scores have alterations in brain connectivity during both reward anticipation and receipt, compared to adolescents in the lower range of the BMI z-scores. In particular, an increased connectivity between left ventral striatum and left insula in adolescents with higher BMI z-scores independent of trial types in our data set suggests an overall greater integration of information about the motivational significance of cues (Cao et al., 2019). When we parsed the neural differences in anticipation and receipt of rewards, different connectivity patterns were observed. Specifically, the connectivity between right insula and ventral striatum declined when these adolescents with higher BMI z-score anticipated a reward after a cue was presented, while it increased significantly when the reward was not received. The ventral striatum is one of the primary projection targets for dopaminergic neurons and therefore is heavily associated with incentive salience and motivational drive (Volkow et al., 2011). Similarly, insula is associated with bottom-up events such as differential value of reward cues (Duerden et al., 2013; Menon and Uddin, 2010). The aberrant connectivity patterns observed between these two regions in high BMI z-score adolescents may reflect that high BMI z-score adolescents show inappropriate modulation when the stakes are high, and they are anticipating reward; but also, when they do not receive the reward they expected.

In addition to the bottom-up reward network, an increase in BMI z-score was also associated with altered patterns of neural circuitry involved in top-down inhibitory control. Notably, weaker communication was observed between executive control regions and ventral striatum when the reward was anticipated in relation to higher BMI z-score. Previous studies in rodents and humans have consistently reported that prefrontal cortex has direct glutamatergic projections to ventral striatum (Sesack et al., 1989; Voorn et al., 2004) and that these regions exhibit strong functional connectivity (Cauda et al., 2011; Choi et al., 2012). Moreover, literature shows that prefrontal cortex is necessary for modulating ventral striatum responses to the anticipation of reward (Pujara et al., 2016). Thus, we speculate that excess body weight in our adolescent population reduced the signaling from higher order brain regions to prefrontal cortex, leading to modulated reward valuation in ventral striatum during the anticipation of reward (Lowe et al., 2019); though a potential bidirectionality cannot be overlooked. In adolescents this may increase the likelihood of overconsumption of hyperpalatable calorie-dense foods and increase weight gain. Additionally, recent fMRI studies utilizing tasks that elicit activation of prefrontal/executive function regions also have shown a close relationship with weight gain and obesity (Yang et al., 2018). Particularly, these studies suggest that individuals with higher BMI show functional neural deficits in areas mediating executive function and related behavioral deficiencies. In line with these findings, we also reported altered activity in superior and inferior frontal gyri with increasing BMI z-score, which was driven by missed reward targets. These results may indicate that weight gain in adolescents may be associated with dysfunctional communication between cognitive control and reward networks.

Our findings that insula and caudate nucleus activity declined in adolescents with greater BMI z-score when the target was missed is consistent with prior research where neurophysiological underpinnings of emotion regulation were explored in young adults with obesity and with healthy weight (Steward et al., 2016) and adolescents (Verdejo-Garcia et al., 2015). Their data showed that when adults with excess body weight experience negative emotions, activation in right anterior insula decreases. This reduction in insular activity also predicted poor intentional impulsiveness performance in these individuals with excess body weight. Collectively, the authors suggested that excess weight may be linked to a decreased ability to allocate attentional resources to engage physiological reactions that guide behavior, when facing negative emotion (Steward et al., 2016; Verdejo-Garcia et al., 2015). Moreover, the insula is important for gustatory processing and integrating homeostatic feedback with expected outcomes (Nelson et al., 2010). Thus, it is plausible that disrupted insula activation with increased BMI z-score in our population group may lead to abruption in these interoceptive inputs, as well as risk signaling, which may further the risk for weight gain (Mata et al., 2015). Collectively, our study suggests that increase in BMI z-score in adolescents may result in aberrant neural response in brain regions that my impact homeostatic/physiological response as well as executive functioning and reward, possibly leading to excess calorie intake and further weight gain.

Interestingly, our BMI z-score findings are primarily driven by trials in which participants did not receive a reward, i.e., they missed the target, or they hit the target but did not receive a reward (no reward condition). In addition to other reward regions, ventral striatum in particular is sensitive to situations when an expected reward is not delivered, as shown in other work with adolescents performing a monetary incentive delay task (Cao et al., 2019). Thus, our findings with altered reward system activation and connectivity may speak to both rewards being more salient and inhibitory control being more difficult in these non-reward situations for youths with greater BMI z-score. Youths who have more difficulty with non-reward (e.g., increased frustration and negative emotionality in response to non-reward) due to alterations in reward and inhibitory control may react more impulsively, including around food, potentially contributing to detrimental eating behavior and weight gain.

There are several limitations to the study. First, it is important to note that, in this cross-sectional study, we cannot assign causality; although there are theoretical reasons for interpreting reward/inhibition alterations as affecting BMI z-score, the opposite is possible as well. Longitudinal studies will be necessary to determine whether higher BMI or neural alterations occur first. Second, although this study broke new ground in examining BMI-related reward deficits in adolescents, because this secondary data analysis was part of a larger study, for 67% of our sample size, height and weight measures were solely self- and parent-reported, whereas 33% were measured by a trained examiner in addition to self- and parent report. Although post-hoc analyses suggest that source of height and weight measures to assess BMI z-score did not primarily drive our results, future studies specifically designed to build on our findings should have all anthropometric measurements collected in a clinical setting for greater accuracy.

Taken together, these findings support the hypothesis that adolescents with high BMI z-score show impairments in reward processing and inhibitory control related neural networks. Moreover, although we did not test domain generality directly and thus, our results should be confirmed with direct comparison among multiple types of reward (food, monetary, in addition to other types of reward such as social reward) within the same study/participants, our findings also suggest

that reward processing alterations associated with higher BMI z-score may be domain general, affecting multiple types of reward, including monetary and food-specific cues. Our work has important clinical implications and helps to set the stage for additional translational work to inform interventions. Specifically, understanding the reward and inhibitory mechanisms that contribute toward weight gain in this crucial developmental period, when such systems are rapidly shifting and thus may be more amenable to change, may be key to altering life-long trajectories, promoting weight loss and long-term healthy eating habits.

Author contributions

S.B., J.L.W. and I.R.C. conceived the idea; I.R.C. and D.P. performed data collection; I.R.C., J.L.W., and S.B. analyzed and interpreted the data; S.B., J.L.W., I.R.C., and D.P. contributed towards manuscript preparation. All authors reviewed the manuscript before submission.

CRediT authorship contribution statement

Surabhi Bhutani: Conceptualization, Methodology, Formal analysis, Writing - original draft. **Isaac Ray Christian:** Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing - original draft, Data curation. **Danielle Palumbo:** Formal analysis, Writing - review & editing. **Jillian Lee Wiggins:** Conceptualization, Methodology, Formal analysis, Writing - original draft.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102618.

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