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RESEARCH ARTICLE

Altered neural reward processing is associated with reward-related decision-making in adolescents with severe obesity

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ABSTRACT

Obesity is associated with altered food-related reward processing, but its impact on non-food reward remains unclear. This question is both timely due to rising rates of severe obesity and important because adolescence is a period of heightened reward seeking behavior. We used computational modeling and functional magnetic resonance imaging to examine monetary reward processing using classic experimental tasks in 35 adolescents (14-18 years-old, 13 male) with severe obesity (n=18) and without obesity (n=17). Participants completed the Balloon Analog Risk Taking Task to assess reward-related decision-making and the Monetary Incentive Delay task to assess neural correlates of reward anticipation. Reward-related decision-making model parameters revealed no differences in reward sensitivity but less adaptive decision-making (response consistency) in those with obesity compared to without obesity. Other metrics (e.g., number of balloons popped, number of pumps, and total points) did not differ between groups. During reward anticipation, those with obesity had lower activation than without obesity in ventral tegmental area and prefrontal cortex, canonical regions for reward and cognitive control, respectively. Weight status moderated associations between ventral tegmental area activation and reward-related decision-making metrics such that higher ventral tegmental area activation was associated with more risky decision-making (more popped balloons) in those with but not without obesity. Functional connectivity of ventral tegmental area with right inferior frontal gyrus and left superior temporal gyrus was greater higher in OB than nonOB. Associations between value-related ventral tegmental area-superior temporal gyrus connectivity and reward-related decision-making metrics were moderated by weight status such that higher connectivity was associated with greater number of pumps and points for without obesity and less risky decision-making for those with obesity. Therefore, differences in activation and connectivity between groups may suggest differences in decision-making strategies. Together, findings reveal that ventral tegmental area, prefrontal, and temporal engagement during monetary reward anticipation differs between adolescents with and without obesity and may contribute to individual differences in reward-related decision-making. Such domain-general alteration of reward processing may have far reaching consequences, not only for food intake but also functions central to motivational behavior such as learning and socialization during adolescence, a sensitive period in development. These findings highlight the importance of considering reward more broadly when designing and tailoring behavioral interventions in adolescent obesity.

Introduction

The development and maintenance of pediatric obesity is facilitated, in part, by altered reward functioning[1–3]. This has been well-studied in the context of food, given that altered food-related reward responsivity increases vulnerability to obesogenic behaviors such as eating in the absence of hunger[4]. However, it is not well understood how such findings generalize beyond food, which is a primary reinforcer, or how underlying neural differences in individuals with obesity may contribute to aberrant reward-related decision-making. The importance of answering those questions grows as rates of obesity continue to rise globally, particularly in children. According to the World Obesity Federation, world-wide rate of obesity expected to reach 20% and 18% by 2035 for boys and girls aged 5-19-years-old, respectively by 2035[5]. In the United States, 26% of adolescents (12-19-years-old) currently meet criteria for obesity[6]. Adolescence is a critical developmental period typically marked by heightened reward-seeking[7,8] which poses greater risk for maladaptive appetitive behaviors. Therefore, any obesity-related alterations in reward processing may amplify risk in this already-vulnerable age group. Understanding how reward-related decision-making differs in adolescents with obesity is of great importance in light of the long-term impact of choices on lifelong health outcomes[9], quality of life[10], and adaptive functioning[11,12].

Reward-related decision-making, both conscious and unconscious, plays a critical role in eating behavior[13] and, thus, contributes to risk for obesity. The same neural circuit that is activated by anticipation of primary rewards such as food and sex is also involved in processing of secondary rewards such as money and social stimuli[14]. Central to this neural circuit is the ventral tegmental area (VTA)[15] in the midbrain which integrates signals related to hunger (ghrelin), satiety (leptin), and energy metabolism (insulin)[16]. These hormones modulate dopaminergic tone, or background level of dopaminergic signaling, and subsequently influence food intake[17]. Other key regions in the reward processing circuit include the ventral and dorsal striatum[18] and prefrontal cortex[19]. These regions, along with the VTA, are engaged during anticipation of monetary and social reward, and therefore, any alterations associated with weight status may have broader impacts on areas of motivational behavior beyond the food context.

Limited prior literature suggests that obesity directly impacts brain function in the context of non-food reward anticipation. The most compelling evidence for a causal relationship showed that bariatric surgery-induced weight loss normalized ventral caudate and putamen activation during monetary reward anticipation in a small sample of adolescents with severe obesity such that activation no longer differed from peers with healthy weight[20]. In adults, degree of excess adiposity moderates neural engagement such that anticipation of monetary reward in adults with overweight, but not obesity, showed greater VTA, striatal, and prefrontal activation compared to adults with healthy weight[21]. Further, despite no difference in activation[21], adults with obesity showed hyperconnectivity between frontal, parietal, and striatal regions during reward anticipation relative to adults

with healthy weight[22]. Taken together, this prior work suggests that neural processing of reward anticipation is influenced by weight status. However, there is a paucity of studies focusing on monetary reward in adolescence and no prior study has elucidated how neural differences associated with weight status are relevant for maladaptive reward-related decision-making behavior that does not concern food intake.

The present study aimed to characterize potential neural mechanisms of altered domain-general reward-related decision-making in adolescents with severe obesity. To achieve this, we examined monetary reward-related functioning using a classic behavioral decision-making task, the Balloon Analogue Risk Task (BART), and a classic functional magnetic resonance imaging (fMRI) task of reward anticipation, the Monetary Incentive Delay (MID) task. The BART has been widely used to assess impulsive risk-taking behavior and the extent to which one learns to maximize money earned over trials[23,24]. The MID has been widely used to reveal the brain's response to symbolic cues that predict different monetary values of expected gain or loss[25]. We examined neural engagement with complementary measures, activation indicating the magnitude of evoked responses to reward value during anticipation and the functional connectivity of the responsive regions to characterize the network of regions involved in reward anticipation. Finally, to determine how altered neural reward processing impacts decision-making, we examined associations between indices of decision-making on the BART and differences in activation and functional connectivity during reward anticipation. In doing so, this study makes three novel contributions: First, this is one of the few studies to examine how pediatric, rather than adult, obesity impacts neural response to domain-general reward. Second, previous work has not connected neural activation or connectivity to decision-making behavior or characterized what aspects of reward behavior are impacted. Third, the study population focuses on the severe obesity phenotype, which is increasing in prevalence globally[26,27] and faces greater risk for negative health outcomes compared to overweight or less extreme obesity. Taken together, this study aims to identify neural mechanisms subserving altered reward-related decision-making in adolescents with severe obesity by using a paradigm that highlights vulnerability for risky decisions and highlights the need to consider reward more broadly when designing and tailoring behavioral interventions in adolescent obesity.

Materials and Methods

PARTICIPANTS

Thirty-five adolescents with severe obesity (body mass index (BMI) 120% above 95th percentile for age and sex; n=18, 6 males, 12 females) or without obesity (BMI < 95th percentile for age and sex, n=17, 7 males, 10 females) participated in this study. This sample overlaps partially or completely with previous studies (Author et al. 2017, Author et al. 2019). Adolescents with severe obesity were recruited from Children's National Hospital (CNH) in Washington, DC and those without obesity were recruited from the area community. Informed consent and assent were obtained according to the guidelines of the Institutional Review Boards at both Georgetown University and CNH. Inclusion

criteria included a full-scale IQ ≥ 75 (estimated from the vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Intelligence Scale-II)[28], and based on parent report: no past or current diagnosis of Type 2 diabetes, psychiatric or neurological disorder, no past or current prescription for psychotropic medication. All participants had a BMI < 50 due to size constraints of the scanner. While BMI was higher among adolescents with severe obesity, adolescents with and without obesity did not differ in IQ, age, gender, ethnicity, race, years of maternal education, or annual family income (Table 1).

EXPERIMENTAL DESIGN AND STATISTICAL ANALYSIS

After collection of height and weight, participants underwent fMRI during a reward anticipation task (Monetary Incentive Delay – MID) and performed a reward-related decision-making task (Balloon Analog Risk Taking – BART) task[23] on a laptop outside the scanner within a week of the scanning session. All tasks were administered using E-Prime[29] and were practiced prior to the experimental runs. For fMRI, task stimuli were viewed through a head coil-mounted mirror and presented using a magnet-compatible projector. For both tasks, participants were informed that the points earned during the tasks would be exchanged for a monetary reward. Unbeknownst to the participants, all received $5 for each task in order to ensure equity in compliance with our ethical guidelines.

ANTHROPOMETRICS.

Participants wore light clothing that would be comfortable in the scanner (i.e., no buttons, snaps, zippers) and no shoes while weight and height were measured three times using a digital scale (Health-O-Meter Professional 394KLX) and stadiometer (SECA 216 Wall-mount Mechanical measuring rod). The average of these measurements was used to calculate BMI (m^2/kg). Participants' weight status was characterized based on Center for Disease Control (CDC) BMI percentiles for age and sex such that participants with BMI under the 95th percentile were considered to not have obesity[30,31] while those with BMI 120% or more above the 95th percentile were considered to have severe obesity[32,33]. For descriptive purposes, Table 1 reports mean and standard deviation in BMI rather percentiles, since all adolescents with obesity had BMI >99th percentile.

Table 1. Demographic Characteristics

		Severe Obesity	Without Obesity
BMI Baseline		42.08 (5.78)***	21.53 (2.65)***
Age, yr		16.57 (1.23)	16.34 (1.26)
IQ		98.24 (13.17)	104.53 (12.76)
Maternal Education, yrs		14.00 (4.43)	15.65 (2.57)
Gender, N			
	Male	6	7
	Female	12	10
Handedness, N			
	Right	15	15
	Left	3	2
Ethnicity, N			
	Hispanic/Latino	4	2
	Not Hispanic/Latino	13	15
	Not Reported	1	0
Race, N			
	Black/African American	9	6
	White	5	9
	Other/Mixed	4	2
	Not Reported	0	0
SES, N			
	>$80,000	8	8
	$50,000-$80,000	4	4
	<$50,000	6	5
	Not Reported	0	0

BMI: body mass index; SES: Socio-economic Status; IQ estimated from the vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Intelligence Scale-II; Group differences tested with t-tests or Fisher's Exact test; *p<0.05; **p<0.01; ***p<0.005

REWARD RELATED DECISION-MAKING.

The Balloon Analog Risk Taking task (BART)[24] required participants to pump up a balloon as large as they could without popping, on each trial (n=30). Participants earned 10 points for each successful pump, but lost all points if the balloon popped. Participants could save their points and get the next balloon at any time. Each balloon had a different point of popping and the probability of a balloon popping changed with each pump such that the first pump represented a 1/128 chance of popping, the second a 1/127 chance, and so on until the 128th pump which would result in a 1/1 chance of popping.

REWARD ANTICIPATION

(Figure 1). The Monetary Incentive Delay (MID) task is optimized to assess reward anticipation[25]. Each trial began with one of nine cue shapes (2000 ms), followed by the target, a solid white square presented for a

variable duration (160-360 ms) and feedback (1920 ms). Cue shapes signaled either no response (triangles, n = 18), potential for gain (circles = 36), or potential for loss (squares, n = 36), with the number of lines inside the cue shapes indicating the points at stake: no lines—0 pts, 1 line—0.5 pts, 2 lines—1 pt, and 3 lines—5 pts (n = 9 each for gain and loss). After the target, feedback was presented indicating points gained/lost and the current total number of points. Adolescents were instructed to respond to the target as quickly as possible because if they could only win points (gain/circle cue trials) or avoid losing points (loss/square cues) if they responded while the target remained on the screen. If they responded too slowly, they would miss gaining points (gain/circle cues) or lose points (loss/square cues). Target duration was adjusted trial-by-trial (increased or decreased by 20 ms as needed) to maintain 66% target accuracy. Starting target durations were determined from individuals' average reaction time during out-of-scanner practice. Fixations before and after the target were adjusted trial-by-trial to ensure each trial lasted 8 s, resulting in two runs of 6 min each.

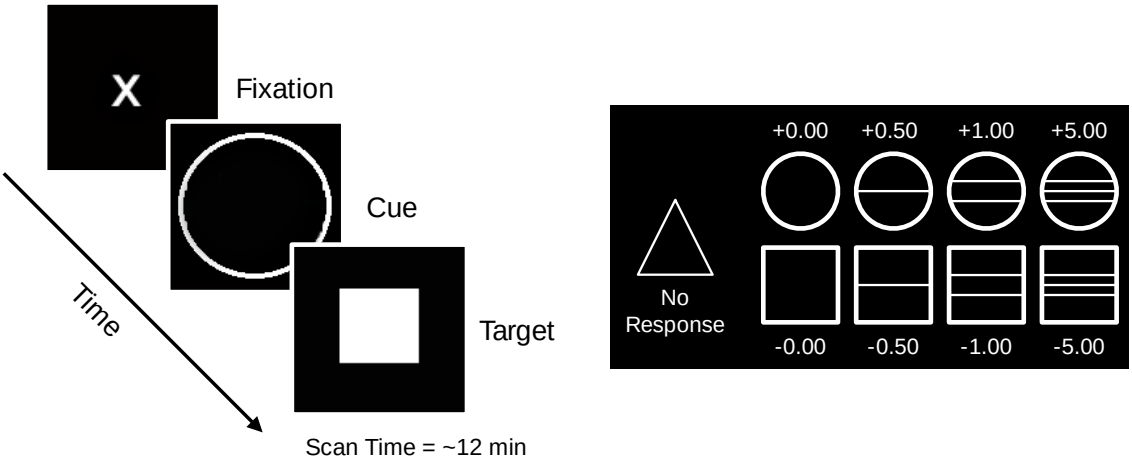

Figure 1. Monetary Incentive Delay task. The right panel shows the sequence of stimuli in a trial and the left panel shows the cues and their associated monetary values, with circle cues signaling gains and squares signaling loss, if response to the subsequent target is made successfully.

IMAGE ACQUISITION AND PREPROCESSING. Imaging was performed on a 3T Trio Siemens scanner (Erlangen, Germany). A high resolution T1-weighted structural scan (MPRAGE) was acquired lasting 7.23 mins with the parameters: TR/TE=2300/2.94ms, TI=900ms, 90-degree flip angle, 1 slab, 160 sagittal slices with a 1.0 mm thickness, FOV=256x256mm^2, resulting in an effective resolution of 1.03mm isotropic voxels. Two functional runs of the MID task were acquired using a T2*-sensitive gradient echo pulse sequence with parameters: TR/TE=2000/30ms, 90-degree flip angle, 43 interleaved slices (width = 2.5mm, gap width = 0.5mm, effective width = 3mm) ascending in the transverse plane, FOV=192x192mm^2. Slice acquisition was parallel to orbitofrontal cortex to minimize susceptibility artifacts. Head movement was minimized with padding between the head and coil.

MONETARY INCENTIVE DELAY (MID) TASK ACTIVATION.

Images were analyzed using SPM12 (Wellcome Department of Cognitive Neurology, London, UK). Preprocessing included discarding the first 4 TRs for signal stabilization, motion correction[34], slice-time correction, co-registration to each participant's MPRAGE, and smoothing with an 8mm FWHM Gaussian kernel. Reward anticipation was modeled using a canonical hemodynamic response function, convolved with cue onsets for neutral (0 point), low (0.5 point) and high (5 points) reward trials. Medium reward (1 point) trials were not modeled to maximize the comparison between reward conditions. Loss cues were also not modeled, as reward anticipation was the outcome of interest. For each participant, the general linear model included two contrasts: low reward (0.5 points > neutral) and high reward (5 points > neutral) and 7 regressors of no interest: 6 realignment parameters derived to estimate the effect of head motion on signal[34] and 1 parameter which de-weighted volumes with greater than 1.5 mm motion scan-to-scan (STS). Participants with more than 10% of volumes with half a voxel (1.5 mm) or greater motion STS were excluded from analyses (N=1 with severe obesity), resulting in a final sample of 34 participants. Deformation fields derived from each participant's MPRAGE were applied to individual contrast maps to normalize into MNI standard stereotaxic space.

GENERALIZED PSYCHOPHYSIOLOGICAL INTERACTION (gPPI).

All participants included in activation analyses were also included in gPPI analyses, as all had <0.5mm of mean STS motion. Voxel-wise whole brain functional connectivity of a seed was characterized via gPPI using the CONN Toolbox v18a (Whitfield-Gabrieli and Nieto-Castanon, 2012). A component-based noise correction method (CompCor)[35] was employed by including regressors of no interest for principal components related to white matter and cerebrospinal fluid. Two separate gPPI models were tested to discern connectivity patterns related to reward anticipation: 1) general reward anticipation: all reward trials (5 and 0.5 pts) > neutral (0 pts); and 2) sensitivity to reward value: high (5 pts) > low (0.5 pts) anticipated reward. For each subject, the general linear model included a regressor for the time series of the seed region, a regressor for the experimental task contrast, and an interaction term representing the PPI regressor of interest.

Statistical Analyses.

BEHAVIORAL DATA.

All behavioral analyses for the BART and MID were completed in R[36]. Group differences were assessed controlling for IQ and maternal education as an index of socioeconomic status, which were included as covariates. For the BART, measures of interest included reaction time, number of pumps on trials where the balloon didn't pop, number of balloons popped, and total points. Although the latter three measures contain similar information, there is nuance in the behavior being captured. Number of pumps on trials where the balloon didn't pop reflects the participant's estimation of optimal number of pumps, while number of balloons popped reflects how many times the estimation of optimal behavior was incorrect or too risky. Total points capture overall task performance. A low point total could be due to behavior that is either too cautious or too risky, while

higher totals signal better optimization of behavior. Differences between adolescents with and without obesity were tested using one-way (severe obesity vs without obesity) analyses of covariance (ANCOVAs) for continuous variables and Poisson generalized linear models (GLM) for count-based variables. For the MID, reaction time and total points were examined using Group (severe obesity vs without obesity) x Reward Value (Low vs Medium vs High) ANCOVAs. Effect sizes were calculated using Cohen's d (t-tests) and partial eta-squared (ηp2; ANCOVAs). Multiple comparisons were controlled for at $p < 0.05$ using Tukey-corrected pairwise post-hoc tests.

A well-established Bayesian decision-making model was used to assess biases in each participant's responses on the BART task[37] using maximum likelihood (MLL) methods (for model details see[37]). The two parameters of interest for this study indexed reward sensitivity (γ^+) and response consistency (β). Reward sensitivity reflects sensitivity to increases in gains with greater reward sensitivity resulting in a higher estimation of optimal number of pumps. In contrast, response consistency reflects the extent to which an individual's behavior is consistent with their own evaluation of the 'optimal' number of pumps. Greater response consistency reflects greater likelihood of adapting behavior to changing reward contingencies. These non-parametric parameters were analyzed using gamma generalized linear models (GLM) with a log link function[38].

MONETARY INCENTIVE DELAY (MID) TASK ACTIVATION.

Group differences in neural response during reward anticipation were tested with a Group (severe obesity vs without obesity) x Reward (Low>Neutral, High>Neutral) mixed-effects repeated measures Analysis of Variance (ANOVA) controlling for age and mean motion STS using GLM Flex Fast2 (http://mrtools.mgh.harvard.edu/). Multiple comparisons were controlled at $p < 0.05$ with whole-brain Monte-Carlo simulations using 3dclustsim[39] (2-sided, nearest neighbor 2; p=0.005; k=121).

GENERALIZED PSYCHOPHYSIOLOGICAL INTERACTION (gPPI) CONNECTIVITY.

Task-modulated connectivity was used to explore the extent to which canonical reward-related regions (e.g., striatum, globus pallidus, and VTA) showing altered activation in adolescents with severe obesity also show obesity-associated differences in connectivity. Canonical reward-related regions that showed a group difference in activation were used as seed regions for connectivity analyses. Group differences in connectivity for reward anticipation (reward > neutral) and sensitivity to reward value (high > low reward) were tested separately using two sample t-tests, controlling for age and mean STS motion as in activation analyses. Multiple comparisons were controlled for at cluster thresholding at $p < 0.05$ FDR corrected.

BRAIN-BEHAVIOR ASSOCIATIONS.

We tested interactions between Group (severe obesity vs without obesity) and extracted activation or connectivity values to determine whether MID-evoked neural engagement or connectivity was differentially related to reward-related decision making (BART) by obesity status. The following BART performance measures were used: reward sensitivity, response consistency, total

number of points on trials where the balloon didn't pop, number of balloons popped, and total points. For activation, the average beta parameters from the low > neutral and high > neutral contrasts were extracted from regions showing group differences. For task-evoked connectivity, Fischer transformed Z values were extracted from regions showing group differences in connectivity.

Results

BEHAVIORAL RESULTS

Across both groups, behavioral outcomes were not associated with the covariates. Maternal education was not associated with any outcomes of interest for BART performance (*ps* > 0.115; Table 2) or MID (*ps* > 0.215; Table 3). Similarly, IQ was not associated with BART (*ps* > 0.066) or MID (*ps* > 0.119) outcomes.

Table 2. Behavioral Performance During Balloon Analog Risk Taking Tasks

	Obese Mean (SD)	Without Obesity Mean (SD)	d[a]
Adjusted Number of Pumps[b]	33.43 (14.33)	31.72 (10.86)	0.13
Balloons Popped	8.39 (4.33)	8.76 (2.71)	0.10
Total Points	6,666.13 (1,822.37)	6,493.45 (1,682.88)	0.10

a: Cohen's d

b: Average number of pumps for balloons that did not pop

Table 3. Behavioral Performance During the Monetary Incentive Delay

	Obese Mean (SD)	Without Obesity Mean (SD)	d[a]
Total Points	11.71 (12.15)	12.12 (10.85)	0.04
Reaction Time, ms			
Neutral: 0 points	193.86 (19.84)	175.84 (25.63)	0.64
Low: 0.5 points	193.94 (19.32)	174.85 (29.80)	0.76
Medium: 1 point	195.22 (24.29)	172.79 (31.36)	0.80
High: 5 points	191.64 (19.67)	170.57 (24.19)	0.96

a: Cohen's d

REWARD-RELATED DECISION MAKING.

After adjusting for maternal education and IQ, there was no difference between adolescents with and without obesity for the number of balloons popped, number of pumps on non-pop trials, or total points earned (*ps* > 0.396)

during the BART, indicating that obesity status did not impact observable behavior during reward-related decision making.

Decision-making model fit was tested as in previous studies[40,41] using Bayesian Information Criteria. Ninety-four percent of participants (severe obesity: 16, without obesity: 16) showed a better fit for the Bayesian learning model than a model assuming no learning (binomial test: t(33)=9.60, p<.0001) with no difference in fit between groups (p = 0.350). Only those with a better fit for the Bayesian learning model were included in analyses of decision-making parameters. Additionally, one participant was excluded from analyses for response consistency due to an outlier value; inclusion of the outlier did not change the results. After controlling for maternal education and IQ, analysis of reward sensitivity (γ^+) and response consistency (β) revealed distinct results – while reward sensitivity did not differ between groups (β(se)=-.002 (0.18), p=.992), response consistency was almost 33% lower in adolescents with severe obesity compared to those without obesity (β(se)=-0.42 (0.20), e^{β} = 0.656, p=0.041). Therefore, despite no differences in behavioral outcomes (e.g., balloons popped), adolescents with severe obesity showed decision making that was less consistent with their own reward/risk evaluations.

REWARD ANTICIPATION.

After adjusting for maternal education and IQ, adolescents with severe obesity did not differ from those without obesity for total points earned on the MID (p = 0.869). In contrast, adolescents with severe obesity reacted more slowly compared to those without obesity (F(1, 29)=4.50, p=0.043, η_p^2 = 0.05), regardless of reward level (neutral, low, medium, high). There was no difference in reaction time for the entire sample across reward level (neutral, low, medium, high) and no interaction between Group and Reward (ps > 0.655). Together, this indicates that the difference in response speed between adolescents with severe obesity and those without obesity was similar across levels of reward.

Functional Magnetic Resonance Imaging Results

MONETARY INCENTIVE DELAY (MID) TASK ACTIVATION.

In both adolescents with severe obesity and those without obesity, there was greater activation during anticipation of high than low reward in widespread regions distributed across the frontal, parietal, and occipital lobes and subcortically in striatal, thalamic, and cerebellar regions (Main effect of Reward of Value, Table 4). The largest cluster included bilateral superior, middle, and inferior frontal gyri, extending into bilateral pre/postcentral gyri, supplementary motor area, anterior, middle, and posterior cingulate cortex, insula, caudate, thalamus, inferior parietal lobule, and cerebellum. Additionally, there were clusters in right inferior parietal lobule and left middle occipital gyrus extending into the angular gyrus and middle cingulate cortex. Overall, numerous regions of the adolescent brain were more active during higher anticipated reward value regardless of weight status.

However, there were cortical and subcortical regions sensitive to obesity status, regardless of reward value. Adolescents with severe obesity showed reduced activation compared to those without obesity during anticipation of

reward than neutral trials in right middle and inferior frontal gyri, left precuneus extending into inferior parietal gyrus, and in the midbrain in ventral tegmental area (VTA) extending into the periaqueductal grey (PAG; Main effect of Obesity Status, Table 4; Figure 2A). Importantly, differences between adolescents with and without obesity depended on reward value in the left precentral gyrus such that activation during anticipation of high (5 > 0; p_{Tukey} = 0.007) but not low reward (0.5 > 0; p_{Tukey} = 0.810) was reduced in adolescents with severe obesity compared to those without obesity (Obesity status X Reward value interaction, Table 4; Figure 2B). Further, adolescents with severe obesity showed greater activation for anticipation of low (0.5 > 0) than high reward (5 > 0; p_{Tukey} = 0.008) while adolescents without obesity showed a trend for greater activation for high (5 > 0) than low reward (0.5 > 0; $p_{Corrected}$ = 0.096; Figure 2B). The same pattern of results was seen when one outlier was removed from the analyses. Thus, during anticipation of monetary reward, adolescents with severe obesity showed reduced cortical and subcortical engagement relative to those without obesity, and precentral engagement during high reward relative to low reward.

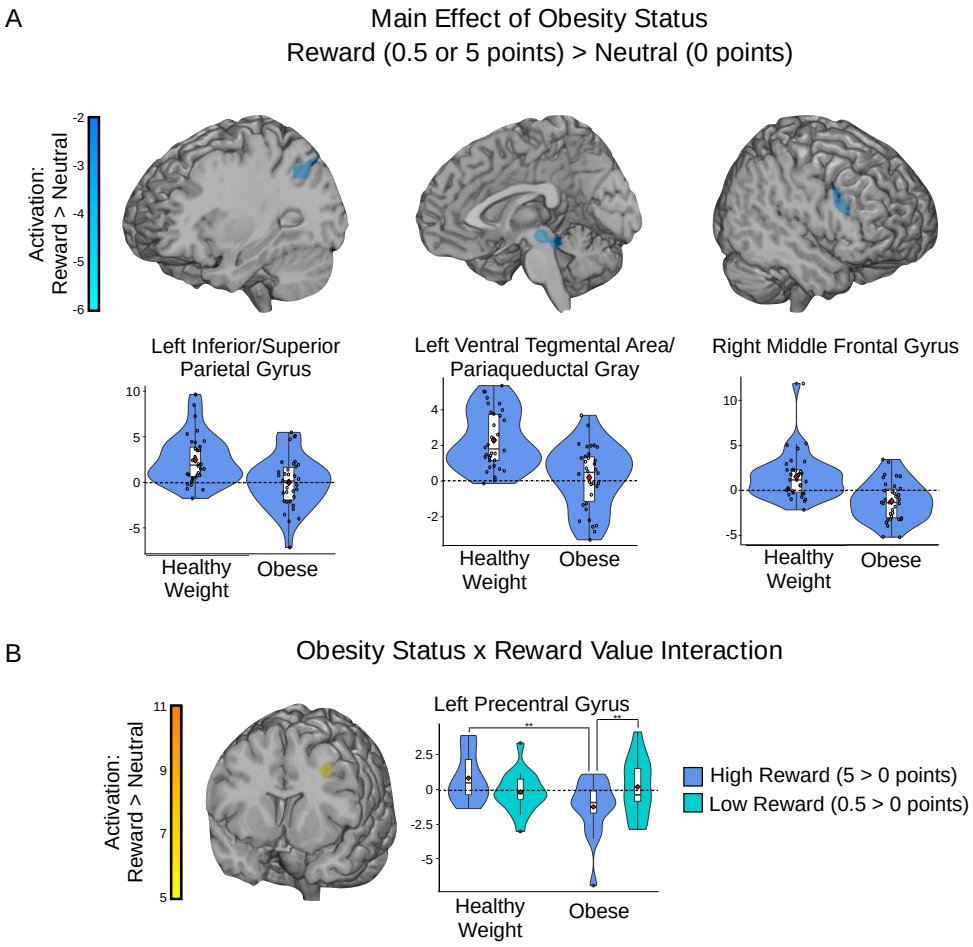

Figure 2. Monetary Incentive Delay Task-Evoked Activation during Reward Anticipation. A) Main effect of Obesity Status: OB < nonOB for the contrast Reward (5 or 0.5 points) > Neutral (0 points). B) Interaction between Obesity Status and Reward Value: OB showed lower activation for 5 > 0 points than nonOB and 5 > 0 points compared to 0.5 > 0 points.

Table 4. Group x Reward Value Analysis of Variance: Peak Activations from Significant Clusters for the Monetary Incentive Delay Task, Controlling for Mean Motion Scan-to-Scan and Age

Monetary Incentive Delay Task: Reward Value > No Gain						
		Volume				
Region (BA)	H	[a]	F[b]	x	y	z
Main Effect of Obesity Status: Without Obesity > Severe Obesity						
Middle and Inferior Frontal Gyrus (9)	R	291	-3.6	51	27	25
Ventral Tegmental Area extending into	L	246	-4	-2	-22	-10
Pariaqueductal Grey			-3.8	-4	-34	-14
Inferior and Superior Parietal Gyrus (7, 39)	L	163	-3.5	-33	-63	47
Main Effect of Value						
Superior, Middle, Inferior Frontal Gyri,	R/L	40,312	9.3	-10	8	-4
Insula, Caudate, Thalamus,			8.2	24	-92	-4
Precentral/Postcentral Gyri,			7.3	11	12	-7
Supplementary Motor Area, Anterior,			7	20	-98	12
Middle, and Posterior Cingulate Cortex,			6.2	34	56	-12
Precuneus, Inferior Parietal Lobule,						
Superior and Middle Occipital Gyri, and						
Cerebellum			6	28	21	-7
Inferior Parietal Lobule (7, 40)	R	358	4.5	36	-44	36
Middle Occipital Gyrus. Angular Gyrus,	L	312	4.7	-28	-52	28
and Middle Cingulate Cortex (17, 39)			3.5	-28	-62	58
Group X Reward Value Interaction						
Precentral Gyrus (6)	L	132	22.5	-36	8	42

a: volume measured in mm^3; b: peak F value derived from the Group x Reward Value analysis of variance
BA: Broadmann's Area; H: hemisphere

GENERALIZED PSYCHOPHYSIOLOGICAL INTERACTION (gPPI) CONNECTIVITY.

Among the canonical reward regions, only the ventral tegmental area (VTA) showed a significant group (severe obesity vs without obesity) difference in activation. Therefore, the identified VTA cluster was used as a seed to characterize the effect of reward anticipation on functional connectivity to every other voxel in the brain. Functional connectivity of the VTA was greater in adolescents with severe obesity than those without obesity during reward anticipation, when examining both sensitivity to reward (5 and 0.5 > 0) trials and sensitivity to reward value (5 > 0.5). Specifically, during anticipation of any reward relative to neutral, adolescents with severe obesity showed higher connectivity between VTA and right inferior frontal gyrus (IFG) and pars triangularis (Table 5, Figure 3A) compared to those without obesity. During anticipation of high than low reward, those with severe obesity had higher connectivity between VTA and left

superior temporal gyrus (STG; Table 5, Figure 3B) compared to those without obesity. No regions showed lower connectivity with VTA in adolescents with severe obesity compared to those without obesity for either sensitivity to reward (5 and 0.5 > 0) or reward value (5 > 0.5). Overall, adolescents with obesity showed hyperconnectivity of VTA with ventral prefrontal and superior temporal cortex during reward processing.

Table 5. Generalized Psychophysiological Interaction Analysis: Seed-to-Voxel Connectivity of Significant Clusters for the Monetary Incentive Delay Task, Controlling for Mean Motion Scan-to-Scan and Age

Monetary Incentive Delay Task: High > Low Reward Value					
Region (BA)	Volume[a]	T[b]	x	y	z
Severe Obesity > Without Obesity					
VTA - Left superior temporal gyrus (22)	119	5	-56	-50	12

Monetary Incentive Delay Task: Reward > Neutral					
Region (BA)	Volume[a]	T[b]	x	y	z
Severe Obesity > Without Obesity					
VTA - Right inferior frontal gyrus, pars triangularis (45,47)	223	2.8	58	26	6

a: volume measured in mm^3; b: peak T value derived from the Group difference
BA: Broadmann's Area; H: hemisphere

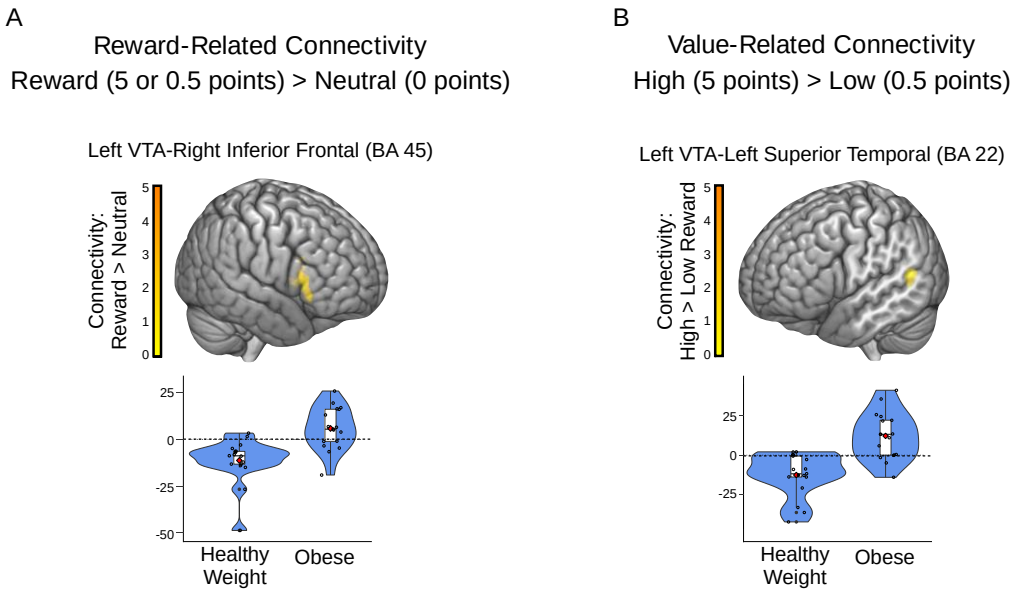

Figure 3. Monetary Incentive Delay Task-Evoked Connectivity during Reward Anticipation. A) Reward-Related Connectivity: Greater connectivity for OB than nonOB for Reward (0.5 or 5 points) > Neutral (0 points) contrast. B) Value-Related Connectivity: Greater connectivity for OB than nonOB for High (5 points) > Low (0.5 points) contrast.

Brain Behavior Associations

ACTIVATION.

The number of balloons popped on the BART showed a significant Group x VTA interaction such that for adolescents with severe obesity, a unit increase in VTA activation was associated with a 16% (e^{β} = 1.16, p = 0.007) increase in the number of balloons popped. In contrast, the association between number of pops and VTA activation did not differ from zero for adolescents without obesity (p = 0.067; Figure 4A). There were no significant main effects of VTA activation, Group, or an interaction between them for other indices of BART performance (Table 5).

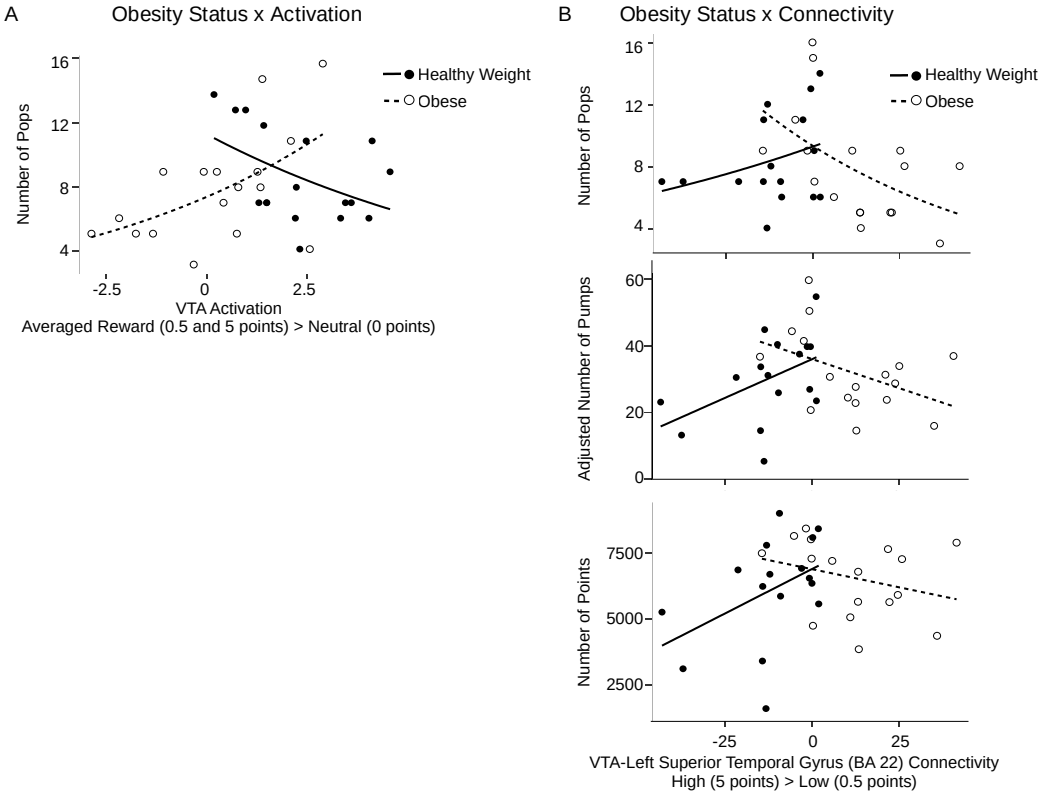

Figure 4. Associations between Balloon-Analog Risk-Taking Decision-Making Outcomes and Monetary Incentive Delay Task-Evoked Activation and Connectivity during Reward Anticipation. A) Obesity Status x Activation for Balloons Popped, B) Obesity Status x Connectivity interaction for Balloons Popped (top), Adjusted Number of Pumps (middle), and Number of Points (bottom)

GENERALIZED PSYCHOPHYSIOLOGICAL INTERACTION (gPPI) CONNECTIVITY.

Only the three BART performance measures showed a significant Group X VTA-left STG interaction (high > low) whereas no significant associations were observed for VTA-right IFG connectivity (Table 5; Figure 4B). In adolescents with severe obesity, a one standard deviation increase in connectivity was associated with a 2% (e^{β} = 0.98, p=0.011) decrease in balloons popped, while no association was seen for those without obesity (p = 0.231). In contrast, while there was no association between connectivity and adjusted number of pumps for adolescents with severe obesity (p=0.076), there was a positive association for those without obesity such that as connectivity became less negative the adjusted number of pumps increased (p=0.049). Similarly, while there was

no association between total points and connectivity for those with severe obesity (p=0.321), there was a positive association for adolescents without obesity such that as connectivity became less negative the number of points earned increased (p=0.046). Overall, increased VTA-left STG connectivity was associated with fewer balloons popped in adolescents with severe obesity while stronger negative connectivity was associated with greater adjusted number of pumps and total points in adolescents without obesity. There were no significant main effects of VTA-left STG connectivity, Group, or an interaction between group and connectivity for parameters of reward sensitivity and response consistency (Table 5). None of the behavioral or decision-making parameters for the BART were related to VTA-right IFG functional connectivity for reward anticipation (Table 5).

Discussion

This study characterized domain-general reward processing in adolescents with severe obesity and identified altered patterns of neural engagement that were differentially associated with reward-related decision-making by obesity status. In doing so, this work was able to provide novel insight into the impact of severe obesity on neural processing of non-food reward during adolescence, a period of development marked by heightened reward-seeking[7,8]. Specifically, we saw patterns similar to the prior finding that severe obesity in adolescents is behaviorally associated with slower response times on the MID[20] and reduced ability to adapt decisions to changing reward consistencies, indexed by response consistency on the BART[38]. Severe obesity was associated with reduced prefrontal, parietal and VTA activation during anticipation of monetary reward. Adolescents with severe obesity also showed greater value-related (high vs small) VTA-temporal cortex connectivity compared to peers without obesity. While obesity was not associated with behavioral metrics on the BART (e.g., balloons popped), VTA activation and value-related (high vs low) connectivity were differentially associated with number of balloons popped, number of pumps, and total number of points by obesity status. Taken together, these findings suggest obesity-associated alterations in neural engagement of the VTA, a key region in the dopaminergic pathway mediating reward processing, may have consequences for the learning and decision-making components of reward behavior.

Altered patterns of neural engagement during domain-general reward anticipation in adolescents with severe obesity were similar to altered response patterns seen in studies utilizing food reward. During anticipation of monetary reward, adolescents with severe obesity showed reduced activation relative to adolescents without obesity in precuneus and right middle frontal gyrus. This parallels reduced precuneus activation seen for food than non-food commercials[42] and logos[43] in children and adolescents. Similarly, recent meta-analyses show reduced prefrontal activation to food stimuli in adults and children with obesity relative to those without[44,45]. The precuneus is functionally connected to prefrontal and premotor cortices[46] and is associated with several higher order functions that may impact reward processing, including directing attention

during goal-directed behavior, processing visuo-spatial stimuli, and processing of internal state and agency[46]. Obesity, therefore, appears to be associated with altered activity in regions subserving cognitive control and goal directed behavior regardless of reward type (i.e., food or domain-general).

Although overall reduced frontal lobe engagement is consistent with the existing obesity neuroimaging literature, we also saw that premotor cortex response to reward value differed by obesity status. Adolescents with severe obesity had reduced premotor activation compared to adolescents without obesity during high reward and showed decreased activation for high than low reward. These results suggest variability in the fidelity of response to reward value in adolescents with obesity, rather than an overall blunting of response to reward. Premotor cortex is involved in integrating motivation with a planned motor response[47], in this case, responding to a cue to obtain an expected reward. Neurophysiological work in primates suggests that premotor cortex encodes reward-related information such as expected value[48], with evidence that neuronal firing rate tracks increasing magnitude of expected reward[49]. Behaviorally, adolescents with obesity showed slower response times during the MID, replicating a well-known finding that obesity is associated with slower motor responses[50]. This slower response to reward may be rooted in atypical activation for reward value in premotor cortex. Overall, our findings suggest that severe obesity may alter reward processing in motor planning brain regions, resulting in slower motor performance during goal directed behaviors.

The only canonical reward region that differed by obesity status was VTA, a finding consistent with both the adult and food reward literature. Adolescents with obesity, relative to those without, showed reduced VTA activation and greater VTA connectivity. During reward anticipation in the same task in a prior study, VTA activation in adults showed a curvilinear relationship with BMI such that adults with overweight, but not obesity, had greater VTA engagement than adults with healthy weight[21]. However, adults with obesity did show globally increased connectivity during reward anticipation[22]. While our study did not examine global connectivity, adolescents with obesity had greater connectivity of the VTA with IFG, which is known to subserve inhibitory control[51], and with STG, which has been posited to play a role in integrating past actions and successful outcomes into decision-making strategy[52]. Obesity-associated increased VTA connectivity has also been observed in response to food stimuli, but with the cerebellum and hippocampus[53]. Taken together, these data support the conclusion that the VTA is specifically important in altered reward-processing in obesity regardless of reward type or age.

The observed decreases in VTA neural activation and behavioral response consistency in decision-making may be the result of an obesity-related shift in the dopaminergic signaling. It is not fully understood what population of neurons is represented by BOLD signal in the VTA, but prior work suggests VTA activity may in part reflect reward prediction error (D'Ardenne, et al. 2008). This process is subserved by momentary or phasic firing of dopaminergic

neurons (Schultz et al 1997), which is posited to be decreased in severe obesity based on human PET studies[54]. In contrast, the overall background level of dopaminergic signaling and responsivity, termed dopaminergic tone, is greater in human severe obesity[54], possibly due to obesity-associated decreased activity of inhibitory (i.e., GABAergic) neurons that typically modulate tonic dopamine release (Koyama et al. 2013). Adolescents with obesity made less adaptive choices (i.e., less consistent with their own evaluation of risk), reflecting a deficit in updating future behavior based on past experience. Work from animal models of elevated dopaminergic tone reveals that that higher tone leads to behavior less influenced by recent reward, reflecting reduced integration of one's own reward estimation and behavior[55]. Ultimately, further investigation is needed to fully characterize how altered dopamine dynamics may underly neural and behavioral differences in adolescents with severe obesity.

VTA engagement and connectivity were differentially associated with behavioral performance on the BART by weight status, likely reflecting different decision-making strategies. In adolescents with severe obesity, greater VTA activity was associated with more popped balloons while increased value-related (high vs low) VTA-STG connectivity was associated with fewer balloons popped. Number of balloons popped has been associated with real-life risk taking behavior[56]; therefore, greater VTA activity during reward anticipation may contribute to risk taking in adolescents with obesity. Greater value-related VTA-STG connectivity in some adolescents with severe obesity may represent an alternate neural decision-making strategy, providing a compensatory mechanism for less risky, more adaptive, decision-making behavior. In adolescents without obesity, VTA and STG were less functionally associated compared to their peers with severe obesity; however, even among adolescents with healthy weight, less negative value-related VTA-STG connectivity was associated with more overall points and greater number of pumps on trials where the balloon did not pop. Together, these data suggest that VTA activity and modulation of connectivity with other regions during reward anticipation may influence risk-taking versus adaptive reward-related decision-making in adolescents with severe obesity.

The results of this study should be interpreted in light of several contextual factors. First, although the sample was matched for IQ and socioeconomic status (indexed by maternal education), both are independently associated with pediatric obesity[57,58]. While these factors were statistically controlled for, it is important to disentangle their association with obesity in the design of future studies. Second, the phenotype explored in this study is uncomplicated obesity such that none of the adolescents with obesity had diabetes or metabolic syndrome. Although this limits the possibility that our findings are a result of clinically significant insulin resistance, the potential role of subclinical insulin resistance was not explored. Additionally, our fMRI protocol did not draw a direct comparison between food and monetary reward or examine reward anticipation versus receipt. As prior literature has shown that processing of reward anticipation may be more domain-general than receipt[59], future studies are needed to determine the impact of obesity on

anticipation versus receipt of non-food reward. These data are also subject to limitations common in studies with special populations. First, the sample size is small due to the special nature of the population being studied and size limitations of the MRI scanner. Adolescents with a BMI greater than 50 had to be excluded from the study because the circumference of the scanner bore was too small for them to lie comfortably, thereby imposing an artificial ceiling on the range of BMIs in the study. This also limited statistical power by limiting sample size; therefore, some effects may have been too small to detect. Lastly, our results leave open the question of the extent to which they reflect causes versus consequences of obesity. In order to disentangle causes and consequences of pediatric obesity related to neurocognitive functioning, future studies should incorporate physiological measures such as insulin or inflammatory cytokines in longitudinal or weight loss intervention designs. Despite these limitations, this study provides initial evidence for altered neural processing of domain-general rewards in adolescents with obesity and highlights the potential that obesity may increase susceptibility for risk-taking behaviors in youth.

Conclusion

This study showed altered functional neural circuitry subserving domain-general reward processing in adolescents with severe obesity. Importantly, VTA neural engagement and circuitry was associated with risk-taking behavior and reward-related decision-making outside the scanner. Since the VTA is important for both hedonic and homeostatic eating[16], these data suggest the VTA may play an important role in behaviors that increase risk for obesity (e.g., eating in the absence of hunger). Additionally, these finding highlights that altered reward processing in adolescents with obesity may increase their susceptibility to making risky decisions more broadly. Therefore, understanding altered reward processing associated with pediatric obesity is important for both food and non-food related behaviors because it has the broader potential to impact multiple domains of health and adaptive functioning throughout the lifespan.

Conflicts of Interest Statement:

The authors have no conflicts of interest to declare.

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