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ORIGINAL ARTICLE

Increased brain response to appetitive tastes in the insula and amygdala in obese compared with healthy weight children when sated

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OBJECTIVE: There is evidence of altered neural taste response in female adolescents who are obese (OB), and in adolescents who are at risk for obesity. To further understand risk factors for the development of overeating and obesity, we investigated response to tastes of sucrose and water in 23 OB and healthy weight (HW) children.
METHODS AND DESIGN: Thirteen HW and 10 OB 8–12-year-old children underwent functional magnetic resonance imaging while tasting sucrose and water. Additionally, children completed an eating in the absence of hunger paradigm and a sucrose-liking task.
RESULTS: A region of interest analysis revealed an elevated BOLD response to taste (sucrose and water) within the bilateral insula and amygdala in OB children relative to HW children. Whole-brain analyses revealed a group by condition interaction within the paracingulate, medial frontal, middle frontal gyri and right amygdala: *post hoc* analyses suggested an increased response to sucrose for OB relative to HW children, whereas HW children responded more strongly to water relative to sucrose. In addition, OB children, relative to HW, tended to recruit the right putamen as well as medial and lateral frontal and temporal regions bilaterally.
CONCLUSION: This study showed increased reactivity in the amygdala and insula in the OB compared with HW children, but no functional differentiation in the striatum, despite differences in the striatum previously seen in older samples. These findings support the concept of the association between increased neural processing of food reward in the development of obesity, and raise the possibility that emotional and interoceptive sensitivity could be an early vulnerability in obesity.

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INTRODUCTION

Approximately one-third of children in the United States are overweight or obese (OB),[1] affecting 4–5 million children. Children who are OB are at an increased risk for negative health sequelae in childhood and adulthood, including orthopedic and endocrine conditions, cardiovascular disease, cancer and all-cause mortality.[2–5] Unfortunately, obesity tracks well from childhood to adolescence and adulthood, with over 80% of OB youth remaining OB in adulthood.[6]

Although several factors contribute to weight gain, eating above and beyond daily caloric requirements plays a primary etiological role in obesity across the life span.[7] Appetite regulation as a whole is a complex process that involves the integration of multiple physiological signals, including energy needs in the body, neural processes and cognitive processes. Neural mechanisms, in particular motivation and reward, are considered central components in regulating eating behavior.[8] Recent studies of obesity suggest that top-down neural processes, which encode the rewarding, emotional and cognitive aspects of food ingestion, may lead to important understandings of why some individuals over-consume food, even in the presence of satiety and replete energy stores.[9,10]

A number of models regarding the neural processes of obesity and overeating have been proposed. One model suggests that OB compared with normal weight people have decreased neural processing of food reward,[11] whereas another suggests an increase in neural processing of food reward.[12] Others have proposed that those at risk for obesity have an initial hyperreactivity in the striatum and somatosensory and gustatory regions, which drives overeating. Over time, there is a decrease in striatal response and increases in regions that encode incentive salience of food cues, which leads to further overeating and weight gain.[13,14] All of these models implicate neural regions associated with dopamine functioning, including the striatum, mesolimbic pathway and mesocortical pathways.[15,16] The primary gustatory pathway, which partially overlaps with the above circuits but extends to the insula, is responsible for the integration of sensory information and taste from the mouth. Additionally, the insula has been implicated in the anticipation of reward and outcomes.[17,18] Together with the anterior cingulate cortex and orbitofrontal cortex, the insula codes the sensory-hedonic response to taste, is implicated in the anticipation of outcomes and innervates a broad region of the rostral ventral-central striatum.[19–22] This network is thought to play a crucial role in linking sensory-hedonic experiences to the motivational components of reward[19] that may govern eating behavior.

The functional development of these regions is not well understood, and very little is known about the development of the reward pathways in childhood, let alone about the reward pathways related to taste and food consumption. Studying taste reward in children earlier in life will allow for a greater understanding of the conflicting reports of the hypo- vs

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hyper-reward sensitivity seen in obesity. Understanding the development of the taste reward pathways in childhood is crucial for understanding the development of reward over the life span and will assist in the development of interventions to address overeating.

To date, there are relatively few studies evaluating the neural responsivity to food in OB and healthy weight (HW) youth, and these studies have used paradigms that include both pictures of food[23,24] and food delivery[25,26] to assess reward, motivation and interoceptive circuitry. The studies that have evaluated the delivery of reward have compared the taste of chocolate milkshake and tasteless solution in OB and HW female adolescents. Results indicated that OB compared with HW teens showed increased activation in the gustatory cortex (anterior and mid insula, frontal operculum) and in the somatosensory regions (parietal operculum and rolandic operculum) in anticipation of consumption of a chocolate milkshake compared with actual consumption. However, OB compared with HW females showed decreased activation in the caudate nucleus in response to consumption of chocolate milkshake compared with a tasteless solution.[25] Another study by the same group compared normal weight female adolescents determined to be at high or low risk of obesity (based on parent's obesity status) and found that adolescents at high risk for obesity showed activation in the caudate, parietal operculum and frontal operculum in response to chocolate milkshake compared with a tasteless solution,[26] suggesting that many of these neural changes may exist prior to adolescence and prior to obesity onset. To date, there are no data on food reward delivery in younger children, which is crucial in understanding the development of food reward, overeating and obesity development.

To address these gaps in the literature, we chose to study neural processing of taste in preadolescent children, as there are developmental changes in dopamine receptors,[27] reward-seeking behaviors[28,29] and reactivity to sweet substances[30] as children transition to puberty. Owing to the significant developments in dopamine receptors throughout childhood, it is important to carefully stratify children and use tightly controlled age ranges when examining factors that activate the reward system.[27] Additionally, we are specifically interested in neural responsivity to taste when sated, as eating past nutritional needs is a key contributor to the obesity epidemic. Thus, the purpose of this study was to compare neural taste responsivity to sucrose and water in OB and HW preadolescent children when sated. We hypothesized that OB children would show increased activation to sucrose in the insula, amygdala and anterior striatum consistent with the hyperreactivity model and prior studies.[25] As an exploratory aim, we evaluated correlations between BOLD responses and behavioral task performance evaluating sucrose liking and overeating.

METHODS

Subjects

Ten OB children (5 boys, 5 girls) aged 8–12 (body mass index (BMI) percentile > 95th for age) were recruited from the community. Thirteen age-matched HW (BMI < 85th%) children (8 boys, 5 girls) were recruited through local advertisements and pediatric clinics. Inclusion criteria included willingness to participate in the study, meeting weight criteria for the two groups (OB or HW), right-handedness, fluent in English (for speaking, reading and writing) and liking of cheese pizza (necessary to complete the Eating in the Absence of Hunger (EAH) assessment). Exclusion criteria included any eating disorder (diagnosed by chEDE-C)[31] or other significant psychiatric disorder (MINI-kid),[32] or other medical or neurologic concerns and conditions contraindicative to magnetic resonance imaging (MRI). Child height was measured using a portable Schorr height board (Schorr Inc, Olney, MD, USA) in duplicate. Height was recorded to the nearest 0.1 cm for both trials. Body weight in kilograms was measured in duplicate on a Tanita Digital Scale (model WB-110A; Tanita Corporation of America, Inc., Arlington Heights, IL, USA). Body weight was recorded to the nearest 0.1 kg. The average of the two values for height and weight was converted to BMI (BMI = [kg m^{-2}]). Because children are growing, BMI was translated to BMI for age percentile score using the CDC growth charts.[33]

The study was conducted according to the Institutional Review Board regulations of the University of California, San Diego. Participants gave written informed assent, and their parents gave written informed consent. Participants completed an EAH evaluation and a Monell forced-choice paired-comparison task for assessing sweet taste preference (that is, sucrose liking). Between group comparisons of assessment scores were performed using Student's t-tests and assumed unequal variance when indicated (Table 1).

Experimental design

In the first visit, the children completed psychiatric interviews, sucrose liking and the EAH paradigm. Experienced interviewers (graduate students trained to competency by a licensed psychologist) used the MINI-KID[32] to rule out significant anxiety, depression and attentional disorders in children. The EAH paradigm has been described in publications with children from preschool to age 12 and yields a measure of percent of daily caloric needs consumed when sated in a free access session (EAH%).[34,35] Additionally, based on methods described by Small,[36] we also calculated percent of daily calories consumed in the EAH free access procedure using only the sweet foods (to correlate with BOLD response to the sweet taste of sucrose). Children also completed a Monell forced-choice paired-comparison task, which yields a measure of aqueous sucrose solution preference (sucrose liking).[37] On a separate day, following a standardized breakfast, functional MRI (fMRI) images were acquired using the taste paradigm task developed in our laboratory.[38] One milliliter fluid sample of 10% sucrose or ionic water was delivered to children with a semi-automatic programmable customized syringe pump (J-Kem Scientific, St Louis, MO, USA) in four blocks of 20 pseudorandom trials each using a manifold. Four runs were acquired, each lasting 6 min 40 s, and fluid was delivered every 20 s. Children were trained to perform one tongue motion (swishing the solutions across the tongue) after each application of taste stimulant, to wash the taste stimulus around the mouth and stimulate taste buds. Children were instructed to remain still with eyes closed during the paradigm.

Table 1. Clinical and demographic characteristics

Characteristic	HW (N = 13)	OB (N = 10)	T or χ^2 value	DF	P value	Hedge's g
Age at time of scanning (years)	10.4 ± 0.3 (8.0–12.0)	9.9 ± 0.3 (8.0–11.0)	1.03	20.97	0.31	0.4
Child BMI[a]	17.7 ± 0.5 (14.8–20.0)	26.1 ± 1.0 (22.3–30.7)	− 7.60	14.27	< 0.001	− 3.1
Child % BMI[a]	53.9 ± 6.9 (7.0–83.0)	96.8 ± 0.5 (94.0–98.0)	− 6.18	12.13	< 0.001	− 2.5
Child BMI-z[a]	0.1 ± 0.2 (−1.5–1.0)	2.0 ± 0.1 (1.6–2.3)	− 8.68	16.54	< 0.001	− 3.5
Sucrose liking	0.6 ± 0.1 (0.2–1.1)	0.6 ± 0.1 (0.1–1.1)	− 0.23	18.10	0.82	− 0.1
EAH %[b]	10.4 ± 3.1 (0.5–33.6)	16.6 ± 2.5 (6.0–30.2)	− 1.54	19.81	0.14	− 0.6

Abbreviations: BMI, body mass index; DF, degrees of freedom; EAH, Eating in the Absence of Hunger percent calories consumed; HW, healthy weight; OB, obese. [a]Equal variances not assumed. [b]One HW was missing responses on this measure. Note: Entries are of the form mean ± s.d. (min–max). Statistical comparisons were by means of Welsh's t-tests.

Apparatus

The macronutrient solutions were contained in two 25 ml syringes, which were attached to a semiautomatic and programmable customized syringe pump (J-Kem Scientific), positioned in the scanner control room.[39] Tastes were delivered to the subjects via two separate approximately 10-m long Food and Drug Administration-approved food grade Teflon tubes (Cole-Parmer, Vernon Hills, IL, USA). The syringes were also attached to a computer-controlled valve system, which enabled the two solutions to be delivered independently along the tubing. Taste delivery was controlled by E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA, USA) software operating on a PC positioned in the control room. The stimuli were also synchronized with MR scanning.

Functional MRI (fMRI)

Imaging data were collected with a 3T Signa Excite scanner (GE Medical Systems, General Electric Healthcare, Waukesha, WI, USA). FMRI was performed with gradient-recalled echoplanar imaging (TR = 2000 ms, TE = 30 ms, flip angle = 80°, 64×64 matrix, ASSET factor = 2, 40 2.6-mm ascending interleaved axial slices with a 0.4-mm gap, 200 volumes).[40,41] The first four volumes of each run were discarded so as to discount T1 saturation. Echo planar imaging (EPI)-based field maps were acquired for correcting susceptibility-induced geometric distortions. A high resolution T1-weighted image (SPGR, TI = 600 ms, TE = min full, flip angle = 8°, 256×192 matrix, 170 1.2 mm contiguous slices) was obtained for subsequent spatial normalization.

Definition of anatomical regions of interest

Regions of interest (ROI) were chosen based on the neurocircuitry of reward to include both the sensory aspects of taste (for example, insula), and limbic areas that modulate pleasure, motivation and the cognitive aspects of taste, including the amygdala and anterior ventral striatum.[15,42,43] Insula and amygdala ROIs were derived from the Harvard-Oxford Atlas.[44] We attempted to include the orbitofrontal cortex in our ROI analysis for its involvement in the gustatory circuit, but owing to signal drop-out and artifact, we do not report these results. The anterior striatum ROI was defined *a priori* based upon known functional distinctions to include the nucleus accumbens, and segments of the dorsal caudate and dorsal putamen residing anterior to the anterior commissure. Using the anterior commissure in the coronal plane, the caudate nucleus and putamen were sliced into anterior and posterior subdivisions, and only anterior subdivisions were retained for analysis.

Statistical analysis

Functional images were preprocessed and analyzed using Analysis of Functional NeuroImages (AFNI) software[45] and R statistical packages (http://www.r-project.org). EPI images were motion-corrected and aligned to high-resolution anatomical images.[46] Time points with isolated head movements not corrected by coregistration were censored from the statistical analysis. Outliers were generated using AFNI's 3dToutcount. Volumes with more than 10% of the voxels marked as outliers were censored from subsequent analyses. Approximately 5.2% of all volumes were censored overall (for all subjects, M = 36.4 volumes; s.d. = 8.1; range = 18–55).

Statistical analyses were performed using a general linear model, whereby taste blocks were modeled using AFNI's SPMG function. Six motion parameters (three rotations and three translations) were used as nuisance regressors to account for motion artifact. Within-voxel auto-correlations of time-series data were controlled with AFNI's 3dREMLfit. Registration to the MNI-152 atlas was performed using FMRIB's Non-linear Image Registration Tool (FNIRT), part of FSL (http://fsl.fmrib.ox.ac.uk/fsl/), resulting in 2×2×2 mm voxels. Functional data were scaled to percent signal change and smoothed with a 4 mm FWHM Gaussian kernel. The percent signal change map for each individual was visually inspected for outliers before inclusion in the group analyses.

To better account for morphometric variation and constrain extracted fMRI signal to gray matter tissue, we segmented each individual's anatomical image into gray matter, white matter and cerebrospinal fluid volumes using FMRIB's Automated Segmentation Tool (FAST).[47] ROIs applied to the fMRI data were constrained to exclude cerebrospinal fluid or white matter but retain gray matter.

A linear mixed effects analysis in R was performed for each voxel within each of the limbic ROIs.[48] Two separate models were constructed: in both models, subject was treated as a random effect. In one model, diagnosis (OB, HW) was treated as the between-subjects factor and condition (sucrose, water) as the within-subjects factor. As no group × condition interaction was observed in any of the ROIs, we reduced the model to include diagnosis (OB, HW) and condition (sucrose, water) as the between-subjects factors. Small volume correction was determined with Monte-Carlo simulations (via AFNI's 3dClustSim) to guard against false positives. To achieve an *a posteriori* ROI-wise probability of $P < 0.05$, an *a priori* voxel-wise probability of $P < 0.05$ in a cluster of 112 mm^3 comprised of 14 connected voxels in the amygdala, a cluster of 178 mm^3 comprised of 22 connected voxels in the insula, a cluster of 160 mm^3 comprised of 20 connected voxels in the left striatum and a cluster of 152 mm^3 comprised of 19 connected voxels in the right striatum was required. *Post hoc* analyses were conducted using Tukey's HSD. Effect size was computed with Hedge's *g*, which provides a better estimate for smaller sample sizes.

Pearson product-moment correlation coefficients using the mean percent signal change of each ROI and raw scores of behavioral measures of interest (EAH%, sugar liking) were computed to explore potential correlations, using FDR correction to control for multiple comparisons ($P < 0.05$).[49]

We also performed an exploratory voxel-wise analysis using a 2 group (OB, HW) by 2 condition (sucrose, water) linear mixed effects model as performed with the ROIs. A threshold adjustment based upon Monte-Carlo simulations (via AFNI's 3dClustSim) was used to guard against false positives. On the basis of the whole-brain analysis, an *a priori* voxel-wise probability of $P < 0.05$ in a cluster of 488 μl with 61 connected voxels (faces touching) resulted in an *a posteriori* cluster-wise probability of $P < 0.05$. The results of the main effect of group were more robust than the main effect of condition or the interaction of group by condition. Thus, a more stringent *a priori* voxel-wise probability of $P < 0.01$ in a cluster of 168 μl with 21 connected voxels (faces touching) which resulted in an *a posteriori* cluster-wise probability of $P < 0.01$ was implemented to discern distinct regions of activation for the group contrast.

RESULTS

Demographics and clinical assessments

OB and HW were of similar age (Table 1), but as expected, OB had higher BMI. Groups did not differ on percent calories consumed during the EAH free access protocol (EAH%).

ROI analyses

There were main effects of group and condition detected in the left and right amygdala and insula ROIs, but no main effects were seen in the anterior striatum ROIs (Figure 1, Table 2). *Post hoc* analyses revealed that, relative to HW, OB children had a stronger response to taste (for example, sugar and water collapsed across condition) within regions of the bilateral amygdala, left anterior insula and bilateral posterior insula. In addition, regions of the bilateral amygdala demonstrated a main effect of condition (Figure 1, Table 2). *Post hoc* analyses revealed this was driven by a stronger response to sucrose relative to water.

Whole-brain analysis

Multiple areas showed a significant group by condition (Table 3) interaction in the whole-brain voxel-wise analysis. *Post hoc* analyses suggested that OB children demonstrated elevated brain response compared with HW children for sucrose in nearly all significant clusters, and that for HW children, brain response was elevated for water compared with sucrose. These areas included the left and right paracingulate gyrus, right medial frontal gyrus, left and right lingual gyrus, left and right middle frontal gyrus, right amygdala, and left posterior middle temporal gyrus.

Multiple areas showed a main effect of group (Table 3, Figure 1), even at a more conservative statistical threshold ($P < 0.01$). Overall, OB children tended to recruit medial and lateral frontal and temporal regions bilaterally, including the anterior cingulate, inferior and middle frontal gyri, insula, and middle temporal gyrus more than HW children, whereas HW children did not recruit any regions more than OB children. There was also a main effect of
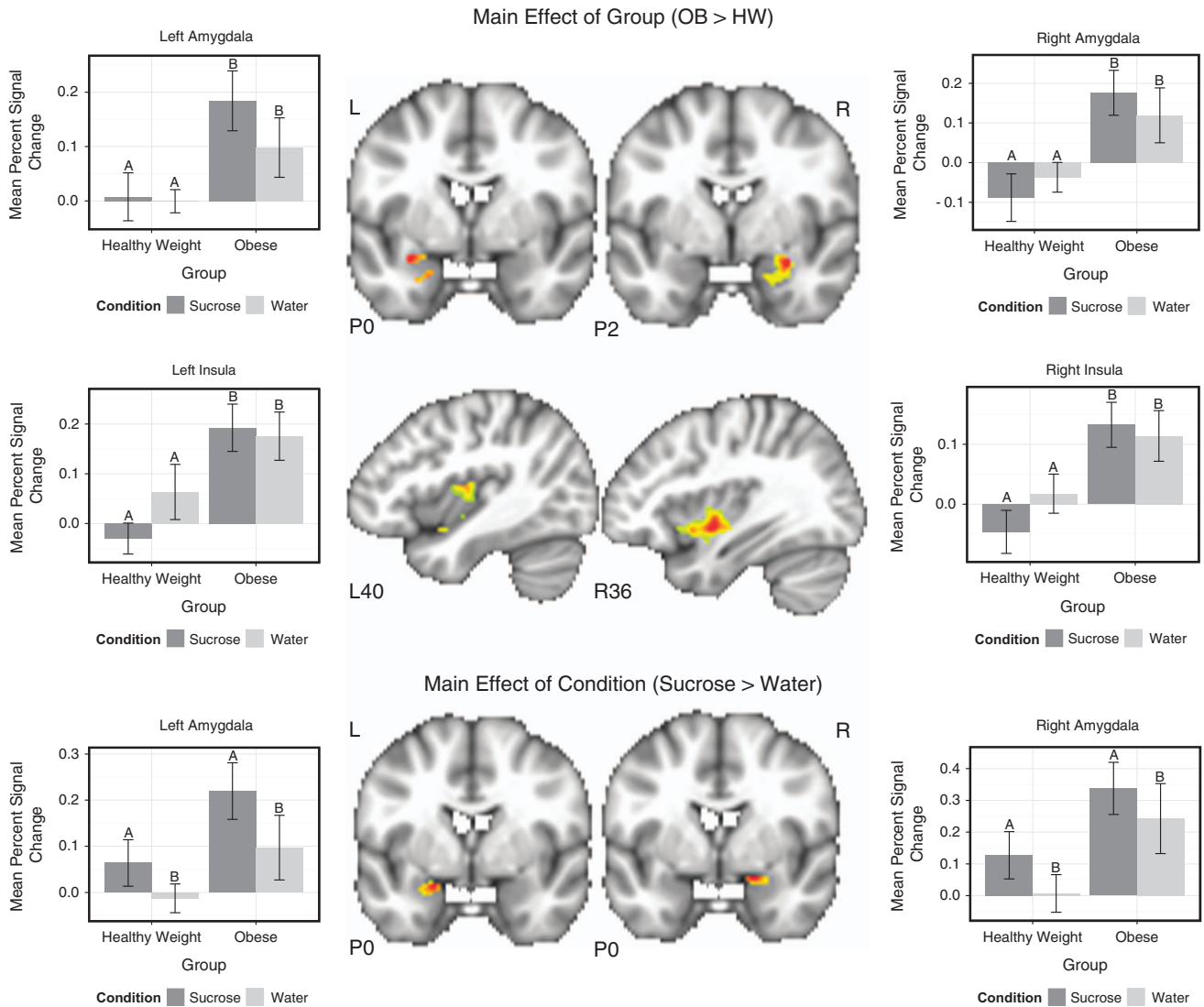
Figure 1. Plots demonstrating main effects of group (upper) and condition (lower) within ROI for the sucrose task. Upper: within the bilateral amygdala and insula, overweight children had an elevated response to sucrose and water. Lower: within the bilateral amygdala, brain response was elevated for sucrose relative to water across all participants. Error bars represent the standard error for each group. Bars with different letters (A vs B) are significantly different from one another. Hot colors indicate voxels reflecting a greater response to sucrose or water within the ROI, all voxels $P < 0.05$. L, left; R, right; P, posterior.

Table 2. Anatomically constrained limbic regions of interest analysis of variance results

| Region | L/R | Group (OB > HW) | | | | | | | Condition (sucrose > water) | | | | | | |
		Volume (μl)	x	y	z	F	t	g	Volume (μl)	x	y	z	F	t	g
Amygdala	L	184	−30	0	−16	7.2	2.8	1.1	—	—	—	—	—	—	—
	L	160	−20	−2	−26	6.3	2.5	1.0	208	−20	0	−18	10.0	3.2	1.3
	L	144	−28	−12	−14	7.6	2.8	1.1	—	—	—	—	—	—	—
	R	1064	30	−2	−18	10.1	3.2	1.3	184	20	0	−16	8.8	3.0	1.2
Insula (anterior)	L	488	−38	0	−16	8.3	2.9	1.2	—	—	—	—	—	—	—
(posterior)	L	472	−42	−12	6	13.6	3.7	1.5	—	—	—	—	—	—	—
(posterior)	R	1984	36	−4	−6	12.2	3.5	1.4	—	—	—	—	—	—	—
Anterior striatum	L	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	R	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Abbreviations: HW, healthy weight; L, left; MNI, Montreal Neurological Institute template; OB, obese; R, right. Small volume correction was determined with Monte-Carlo simulations (via AFNI's 3dClustSim) to guard against false positives resulting in an *a posteriori* ROI-wise probability of $P < 0.05$; minimum cluster size for amygdala = 112 μl, insula = 178 μl, left anterior striatum = 160 μl, right anterior striatum = 152 μl. Coordinates given in MNI space.

Table 3. Voxel-wise analysis of variance reporting significant clusters for an interaction of group × condition and significant main effects of group and of condition

Region	BA	L/R	Volume (µl)	x	y	z	F	g	Contrast	t
Group × Condition[a]										
Medial frontal gyrus/superior frontal gyrus, paracingulate gyrus	10/9/32	R	7256	20	56	10	11.4	1.4	Sucrose: OB>HW	2.9
									Water: OB>HW	1.1
									OB: sucrose>water	2.2
									HW: water>sucrose	2.6
Anterior cingulate/paracingulate gyrus, superior frontal gyrus	9/32	L	3624	−20	54	16	17.5	1.7	Sucrose: OB>HW	3.3
									Water: OB>HW	1.5
									OB: sucrose>water	1.3
									HW: water>sucrose	4.0
Cuneus, lingual gyrus/calcarine gyrus	17/18	L/R	3456	8	−84	−6	13.4	1.5	Sucrose: OB>HW	3.0
									Water: OB>HW	1.1
									OB: sucrose>water	1.3
									HW: water>sucrose	4.0
White matter/middle frontal gyrus	9	L	1840	−22	20	28	14.9	1.6	Sucrose: OB>HW	2.2
Sucrose: OB>HW									Water: OB>HW	1.1
Water: OB>HW									OB: sucrose>water	4.1
OB: sucrose>water									HW: water>sucrose	1.1
Amygdala/parahippocampal gyrus/anterior fusiform gyrus	37/36	R	1168	18	−2	−28	7.1	1.1	Sucrose: OB>HW	3.2
									Water: OB>HW	0.9
									OB: sucrose>water	0.7
									HW: water>sucrose	3.3
Paracingulate gyrus	32/9	R	824	10	38	32	7.3	1.1	Sucrose: OB>HW	3.2
									Water: OB>HW	1.0
									OB: sucrose>water	0.3
									HW: water>sucrose	3.7
Inferior frontal gyrus/middle frontal gyrus	45/9	R	800	40	18	18	9.6	1.3	Sucrose: OB>HW	2.6
									Water: OB>HW	0.9
									OB: sucrose>water	1.6
									HW: water>sucrose	2.8
Middle temporal gyrus/inferior temporal gyrus	21/20	L	728	−62	−18	−20	24.3	2.0	Sucrose: OB>HW	1.4
									Water: OB>HW	0.2
									OB: sucrose>water	4.5
									HW: water>sucrose	2.3
Cingulate gyrus/precentral gyrus	31/4	L	576	−16	−28	48	11.2	1.4	Sucrose: OB>HW	2.1
									Water: OB>HW	0.5
									OB: sucrose>water	3.4
									HW: water>sucrose	1.2
Anterior parahippocampal gyrus	36	L	512	−32	−16	−30	12.7	1.4	Sucrose: OB>HW	1.9
									Water: OB>HW	1.5
									OB: sucrose>water	2.8
									HW: water>sucrose	2.2
Main effect of group (OB vs HW)[b]										
Calcarine sulcus/occipital pole	19/18/17	L/R	3336	0	−90	2	13.2	1.5	OB>HW	3.6
Brain stem		L/R	3264	−12	−16	−26	16.0	1.6	OB>HW	4.0
Cerebellum (culmen)		L	1384	−4	−42	−14	13.6	1.5	OB>HW	3.7
Superior frontal gyrus	6	L	1376	−14	14	62	13.5	1.5	OB>HW	3.7
Superior temporal gyrus/insula	22/13	R	1280	60	−10	−2	15.6	1.6	OB>HW	3.9
Posterior cingulate gyrus	29/30	L/R	1152	−8	−50	20	13.8	1.5	OB>HW	3.7
Calcarine sulcus/occipital pole	17/18	R	1000	14	−98	0	28.9	2.2	OB>HW	5.4
Superior frontal gyrus/frontal pole	10	L	768	−10	66	18	12.9	1.5	OB>HW	3.6
Postcentral gyrus/precentral gyrus	3/2/1/4	R	752	12	−34	70	15.7	1.6	OB>HW	4.0
Anterior cingulate gyrus (dorsal)/paracingulate gyrus	32/24	R	744	6	30	26	14.0	1.5	OB>HW	3.7
Middle temporal gyrus (posterior)	21	L	712	−58	−30	−14	14.3	1.5	OB>HW	3.8
Inferior frontal gyrus (pars triangularis)	45	L	616	−34	34	14	13.6	1.5	OB>HW	3.7
Hippocampus/parahippocampal gyrus	27/36/35	R	608	28	−36	−2	18.3	1.7	OB>HW	4.3
Insula/putamen	13/14	R	472	36	−4	−6	12.2	1.4	OB>HW	3.5
Insula/superior temporal gyrus	13/38	L	456	−44	16	−12	14.3	1.5	OB>HW	3.8
Middle temporal gyrus (posterior)	21	R	432	56	−38	−4	11.8	1.4	OB>HW	2.8
Middle temporal gyrus (posterior)	37/19	L	424	−48	−58	0	14.1	1.5	OB>HW	3.8
Middle frontal gyrus/superior frontal gyrus	8	L	392	−28	32	52	10.8	1.3	OB>HW	3.3
Parahippocampal gyrus	36	L	336	−30	−42	−10	11.7	1.4	OB>HW	3.4

Table. 3. (Continued)

Region	BA	L/R	Volume (μl)	x	y	z	F	g	Contrast	t
Posterior cingulate gyrus	23/31	L	320	−14	−40	40	10.8	1.3	OB > HW	3.3
Posterior insula	13	L	272	−42	−12	6	13.6	1.5	OB > HW	3.7
Thalamus (ventral lateral nucleus, ventral anterior nucleus)		L	248	−6	−8	−2	11.5	1.4	OB > HW	3.4
Middle frontal gyrus	8	L	248	−48	20	44	10.9	1.3	OB > HW	3.3
Parahippocampal gyrus/fusiform gyrus	36/37	L	208	−40	−30	−16	11.6	1.4	OB > HW	3.4
Cerebellum (lobules I–IV)		L/R	208	0	−54	2	10.6	1.3	OB > HW	3.3
Posterior cingulate	30/29	R	208	14	−52	24	11.8	1.4	OB > HW	3.4
Middle temporal gyrus	21	L	200	−56	−16	−22	12.4	1.4	OB > HW	3.5
Inferior occipital gyrus/fusiform gyrus	37/19	L	200	−38	−68	−8	11.4	1.4	OB > HW	3.4
Middle temporal gyrus/angular gyrus	39	L	200	−44	−68	32	9.7	1.3	OB > HW	3.1
Main effect of taste (sucrose vs water)[a]										
Cerebellum		R	31088	24	−34	−26	15.7	1.6	Sucrose > Water	3.8
Precentral gyrus/postcentral gyrus	3/4	L	7928	−46	−16	24	22.9	1.9	Sucrose > Water	5.0
Precentral gyrus/postcentral gyrus	40/43/4	R	3352	44	−14	26	15.1	1.6	Sucrose > Water	4.1
Superior temporal gyrus	38	R	2200	42	16	−30	12.5	1.4	Sucrose > Water	3.4
Anterior cingulate	32	R	1728	12	42	−20	19.4	1.8	Sucrose > Water	4.1
Lingual gyrus/cuneus	30	L	1392	−26	−72	6	29.3	2.2	Sucrose > Water	5.3
Inferior parietal lobe	40	R	1392	26	−34	26	10.7	1.3	Sucrose > Water	3.2
Cingulate gyrus	24	L	1160	−22	10	24	15.0	1.6	Sucrose > Water	4.0
Caudate tail/posterior cingulate	23	L	904	−20	−40	22	13.6	1.5	Sucrose > Water	3.6
Anterior cingulate/medial frontal gyrus/subcallosal cortex	32/11/12	L	752	−12	32	−18	8.7	1.2	Sucrose > Water	3.0
Superior temporal gyrus	41/42	R	712	62	−22	10	16.1	1.6	Sucrose > Water	4.1
Middle temporal gyrus	21/36	L	592	−38	0	−28	10.4	1.3	Sucrose > Water	3.2
Cingulate gyrus	24	R	512	20	2	28	8.3	1.2	Sucrose > Water	2.9
Medial frontal gyrus	10	L	6912	−16	68	4	16.6	1.7	Water > Sucrose	4.0
Middle frontal gyrus/medial frontal gyrus	8/9	R	5104	24	30	40	17.0	1.7	Water > Sucrose	4.0
Middle frontal gyrus/superior frontal gyrus	8/9	L	4392	−22	30	52	16.2	1.6	Water > Sucrose	3.8
Parahippocampal gyrus/middle temporal gyrus	36/21	L	2216	−40	−22	−18	15.8	1.6	Water > Sucrose	3.8
Middle occipital gyrus/lingual gyrus	17/18	R	1784	24	−100	12	11.2	1.4	Water > Sucrose	3.1
Superior occipital gyrus	19	L	1448	−38	−78	32	12.1	1.4	Water > Sucrose	3.3
Inferior frontal gyrus	44	L	1128	−52	14	20	8.3	1.2	Water > Sucrose	2.8
Middle occipital gyrus/lingual gyrus	17/18	L	1048	−14	−94	12	7.2	1.1	Water > Sucrose	2.3
Precentral gyrus/postcentral gyrus	4/3	L/R	976	4	−36	72	10.1	1.3	Water > Sucrose	3.1
Superior parietal lobule	7	L	840	−26	−52	52	9.0	1.2	Water > Sucrose	2.9
Middle temporal gyrus/temporal pole	38/21	L	808	−52	2	−38	9.5	1.3	Water > Sucrose	2.8
Middle frontal gyrus	46/9	R	800	32	32	20	7.8	1.1	Water > Sucrose	2.5
Middle temporal gyrus	21	R	648	58	−14	−10	9.6	1.3	Water > Sucrose	2.9
Lateral occipital cortex	19	R	616	46	−74	30	9.8	1.3	Water > Sucrose	3.1
Precentral gyrus/postcentral gyrus	4/3	R	552	36	−18	64	7.8	1.1	Water > Sucrose	2.5
Superior frontal gyrus	6	L	536	−2	16	68	12.3	1.4	Water > Sucrose	3.2
Parahippocampal gyus/uncus	34/36	R	496	28	−6	−34	10.2	1.3	Water > Sucrose	2.9

Abbreviations: BA, Brodmann area; HW, healthy weight; L, left; MNI, Montreal Neurological Institute template; OB, obese; R, right. [a]Statistical threshold was determined with Monte–Carlo simulations (via AFNI's 3dClustSim) to guard against false positives resulting in an a posteriori ROI-wise probability of $P < 0.05$; minimum cluster size = 488 mm^3. [b]Statistical thresholding was determined with Monte-Carlo simulations (via AFNI's 3dClustSim) to guard against false positives resulting in an a posteriori ROI-wise probability of $P < 0.01$; minimum cluster size = 168 mm^3. Statistics relate to the peak voxel within each functional cluster. Coordinates given in MNI space.

condition (Table 3); a greater response to sucrose relative to water was reported for several clusters, including the inferior temporal lobe, operculum, caudate and insula. Regions more responsive to water relative to sucrose included the middle frontal gyrus, inferior frontal gyrus and occipital cortex.

Relationships to other measures

We conducted separate exploratory correlations between behavioral measures (EAH%, sucrose liking) for each group (OB or HW) and BOLD response to sucrose and water averaged across the entire ROI. When evaluating EAH, we also evaluated sweet food consumption and found comparable results to the full EAH paradigm, so results are not presented. Several comparisons were significant when uncorrected, but did not survive after correcting for multiple comparisons (Table 4). Overall, an interesting but non-significant pattern emerged in the OB and HW children's response

to sucrose. In OB children, there was a positive correlation between EAH% and bilateral striatum and bilateral insula, whereas the same relationships were negative in HW children. Similarly, there was a positive correlation in OB children between sucrose liking and bilateral amygdala, whereas the same relationships were negative in HW children.

DISCUSSION

To ultimately develop interventions to address overeating, it is crucial to understand the development of the taste reward pathways in childhood and the development of reward over the lifespan. To our knowledge, this is the first study to compare brain activation to sucrose and water administration in preadolescent (8–12-year-old) OB and HW children. Our ROI results showed that OB children had a significantly greater neural response to taste

Table 4. Correlations between behavioral measures (EAH%, sucrose liking) and sucrose and water in obese and healthy weight children

| | Sucrose | | | | | | Water | | | | | |
| | Obese | | | Healthy weight | | | Obese | | | Healthy weight | | |
	r	P	p (FDR-corr)	r	P	p (FDR-corr)	r	P	p (FDR-corr)	r	P	p (FDR-corr)
EAH%												
L Anterior striatum	0.61	0.057	0.26	− 0.53	0.079	0.26	0.75	0.012	0.13	0.44	0.15	0.34
R Anterior striatum	0.65	0.044	0.23	− 0.64	0.025	0.18	0.75	0.013	0.13	0.33	0.29	0.45
L Insula	0.69	0.026	0.18	− 0.35	0.26	0.43	0.76	0.01	0.13	0.56	0.06	0.26
R Insula	0.74	0.014	0.13	− 0.31	0.328	0.48	0.84	0.002	0.10	0.52	0.08	0.26
L Amygdala	0.55	0.1	0.30	0.13	0.69	0.71	0.57	0.08	0.26	0.36	0.26	0.43
R Amygdala	0.51	0.14	0.34	0.53	0.2	0.40	0.65	0.042	0.23	0.46	0.13	0.33
Sucrose liking												
L Anterior striatum	0.38	0.28	0.45	0.35	0.24	0.43	0.29	0.42	0.54	0.24	0.43	0.54
R Anterior striatum	0.4	0.25	0.43	0.26	0.4	0.53	0.36	0.3	0.45	0.23	0.46	0.57
L Insula	0.14	0.7	0.71	0.38	0.21	0.40	0.15	0.69	0.71	0.14	0.65	0.71
R Insula	0.32	0.38	0.52	0.46	0.12	0.32	0.22	0.54	0.63	0.18	0.55	0.63
L Amygdala	0.44	0.21	0.40	− 0.51	0.07	0.26	0.14	0.7	0.71	− 0.2	0.51	0.61
R Amygdala	0.54	0.11	0.31	− 0.41	0.17	0.37	0.32	0.37	0.52	−0.08	0.81	0.81

Abbreviations: EAH, eating in the absence of hunger; FDR, false discovery rate; L, left; R, right.

(for example, sugar and water collapsed across condition) within regions of the bilateral amygdala, left anterior insula and bilateral posterior insula compared with HW children. Surprisingly, there were no significant differences seen between OB and HW children in the ventral striatum. Our whole-brain analyses showed a main effect of group in that OB children tended to recruit medial and lateral frontal and temporal regions bilaterally, whereas HW children did not recruit any regions more than OB. We also found that OB children had an elevated neural response to sucrose compared with water in the paracingulate gyrus, medial frontal gyrus, middle frontal gyrus and amygdala, compared with HW children. Taken together, our data support the hypothesis that OB children relative to HW children show a neural hyperreactivity to the taste of sucrose and suggest that increased emotional and interoceptive susceptibility could be a vulnerability marker of obesity in youth.

Surprisingly, we did not find differences between OB and HW youth in response to sucrose/water administration in the anterior striatum. However, differences did emerge between OB and HW youth in the putamen in response to the task in the whole-brain analyses. Studies have suggested that the striatum is less responsive to food reward in OB compared with HW controls.[50] It is possible that our sample was too small to detect differences in this study, or alternatively, there is wider variation in the neural taste responsivity of children in this age range. It is also possible that sucrose alone was not as stimulating as administration of chocolate milkshake or that water was more rewarding than artificial saliva, resulting in smaller differences than in other studies.[25,26] Studies evaluating the development of food reward in children may need to target children younger than the preadolescent age range, to understand developmental issues related to higher levels of food reward.

Children had enhanced neural processing not only to sucrose but also to water in this study, although the activation was higher for sucrose compared with water in most of the regions studied. This is not surprising, as attempting to taste water produces large, bilateral activations in the insula, opercular, rolandic and cerebellar cortices relative to resting or smelling and it is not considered a neutral substrate.[51] For this reason, we collapsed sucrose and water activation to analyze group differences, which were found in the amygdala and insula ROIs. Our whole-brain analysis suggests that the differences were driven by increased

neural processing of sucrose, but our sample size may have been too small to allow us to detect this potential difference. These results suggest that OB children have higher activation to sucrose and water solutions, which may be a result of a focus on the liquid in the mouth, expectation of reward or the attempt to taste it.

This is also the first study to evaluate the associations between these regions associated with reward and a laboratory measure of overeating and sucrose liking in youth. Of note, the two groups (OB and HW) did not differ on overeating or sucrose liking at baseline. Although our results suggest an interesting differential pattern between OB and HW youth, after adjusting for multiple comparisons, these patterns were no longer significant. Larger studies are needed to explore these patterns further, and to determine whether neural activation can be associated with behavioral data.

The age of the children should be considered when interpreting these results. One study demonstrated that adult levels of dopaminergic neuromodulation of the subcortical structures are reached by the age of 9,[52] while another observed adult levels of striatal D1 and D2 receptors at the age of 10.[53] Published studies comparing OB with HW youth using food delivery [25] were conducted with adolescents, while those using pictures of food[23,24] were conducted with youth in late childhood and adolescence (10–17 years of age). Although the subcortical dopiminergic system matures early in life, some of the children in our study may not have reached full maturity in the striatum at the time of the study, impacting our ability to detect differences between groups. Clearly, more information is needed about the development of higher levels of food reward in youth.

There are several strengths and limitations that should be noted. This is the first study to interrogate the reward regions using sucrose in a tight age range (8–12 years of age) of preadolescent children. The restricted age range in this study should provide some reduced concern regarding developmental variability. Additionally, we studied delivery of a taste in children when sated, which is important to elucidate the mechanisms that drive eating past nutritional needs. Furthermore, we used laboratory paradigms to assess overeating and sucrose liking. Limitations include the relatively small sample size; further studies with larger samples are necessary to support its validity. There are potential concerns about using transformation to adult stereotaxic space in children, because of differences in brain size and

morphometry (for example, because of synaptic pruning and myelination). Other evidence, however, suggests the developing brain achieves 95% of its peak size by age six, and aligning the brains of children over the age of seven to an adult template does no worse than when aligning typical adults.[54–56] To address this limitation, we used nonlinear registration to the template atlas so as to improve accuracy. We did not report results for the ventromedial regions of the PFC because of susceptibility artifact. This signal drop out in the OFC limits our ability to make comparisons with frontal opercular findings in other studies. Additionally, this study utilized sucrose and water, which did not differentiate in the manner expected. Overall, OB children responded more to both sucrose and water compared with HW children. Other studies have used artificial saliva, which could be considered an aversive stimulus, potentially enhancing differentiation. Finally, this is a cross-sectional study, and causal relationships cannot be inferred. There may be unmeasured variables that could contribute to these findings, such as socioeconomic status among others. Future studies should replicate these results in larger samples, and extend them longitudinally to evaluate developmental differences between OB and HW children over time, and how changes relate to overeating.

Although these data from this study join a very small base of research on the development of food reward and overeating and obesity in children, they do provide some intriguing hypotheses regarding overeating. Our data support the hypothesis that OB children are hyperresponsive to the taste of sucrose and water compared with HW children during the preadolescent years. Although non-significant in this small sample, the overeating paradigm and sucrose-liking tasks could be used to evaluate the differences in neural substrates of liking and wanting. As this research is in its infancy, it is an important first step toward the goal of understanding neural development that may contribute to overeating, and to the development of tailored obesity interventions and prevention for youth in the future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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