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Elevated thalamic response to high sugar milkshake in ethnic and racial minorities

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Abstract

In the US, Hispanics and African Americans show elevated obesity, yet little is known about possible ethnic/racial differences in brain response during intake of palatable foods. To examine potential differences between non-Hispanic white (nHW) and racial/ethnic minority individuals, we used functional magnetic resonance imaging (fMRI) to assess brain response to intake of eucaloric milkshakes that were either high-sugar or high-fat and a calorie-free, tasteless control solution. Our sample included healthy-weight adolescents who identified as African American and/or Hispanic (minority, n=27) and non-Hispanic white (nHW, n=106). Minority participants showed elevated response in the pre/post central gyrus, precuneus, and left thalamus in response to the high sugar milkshake compared to high fat milkshake. To confirm these effects were not driven by differences in body mass or a function of unequal cell sizes, we performed the same analyses in minority participants and a randomly selected subsample of nHW participants (n=27) that were matched on BMI percentile. Similar to the full sample, we observed an elevated ventral posterior thalamic response to high sugar milkshake in minority participants. This effect held after controlling for self-reported sugar and fat intake. These results suggest that African American and Hispanic groups may have elevated response to specifically high-sugar foods in regions of the brain associated with sensory processing, providing novel information regarding the possible neural underpinnings of the disproportional risk for obesity seen in African American and Hispanic populations.

Keywords

obesity; minority; fMRI; thalamus; food intake

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The authors declare no conflicts of interest.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Introduction

The incidence and prevalence of obesity is disparately seen in racial and ethnic minority groups [1]. The odds of obesity among non-Hispanic black and Hispanic American adolescents is almost double that of non-Hispanic white adolescents [2]. While overall trends suggest the prevalence of childhood overweight/obesity is plateauing [3], other studies demonstrate that minority adolescents have an increasing risk of obesity [4–6], suggesting that obesity is still an epidemic among minority groups. Low socioeconomic status, early life adversities, and obesogenic environments have all been suggested as potential mediators of the relationship between minority status and obesity [7–9]. However, individual behavioral or biological factors that may confer minorities' high susceptibility for obesity have not been widely considered.

One factor associated with overweight and obese weight status is brain response to food. Studies that use neuroimaging to understand the association between brain response and eating behavior have significantly contributed to our understanding of obesity. Functional magnetic resonance imaging (fMRI), which measures blood-oxygen level dependent (BOLD) response as a proxy for neural activity, has consistently demonstrated aberrant brain response in obese individuals during intake as compared to lean counterparts. Obese individuals show reduced striatal response to food intake across multiple studies [10–13]. Critically, reduced striatal response to palatable food intake is associated with risk of weight gain in healthy-weight samples, such that greater response in the caudate and frontal operculum and parietal operculum was observed in youth at risk of obesity [14], and greater response in the nucleus accumbens was associated with weight gain in adults [15].

Elevated intake of high-fat and high-sugar food is also associated with overweight and obese weight status [16–19] and is characteristic of dietary patterns in racial and ethnic minorities in the US [20]. While there is consensus that a high-fat, high-sugar diet is obesogenic, the specific contributions of a high-fat diet versus a high-sugar diet to obesity are less clear. Results are mixed whether fat intake or sugar intake is more associated with obesity [21], or if macronutrient content contributes at all to weight gain, holding caloric intake the same [22]. Brain response to food intake does vary by macronutrient content [23]. Compared to a high-sugar, intake of a high-fat milkshake is associated with greater activation in the caudate, postcentral gyrus, hippocampus, and inferior frontal gyrus. Conversely, intake of a high-sugar milkshake was linked to activation in the insula, rolandic operculum, and thalamus. The unique effects of sugar versus fat on brain response to intake demonstrate that macronutrient is important to consider.

Neuroimaging studies often have small, homogeneous samples, due likely to the high cost of neuroimaging. To date, the most samples include predominantly nHW participants, or purposefully recruit only minority participants to look at brain response unique to that sample. As such, to date, no studies have directly compared differences in brain response to taste between racial and ethnic groups. As obesity is known to disparately affect minority populations, research should consider potential racial/ethnic differences in brain response to consumption. Therefore, this study aimed to examine differences in brain response to food intake in a racially and ethnically diverse sample of healthy-weight adolescents. To examine

if differential brain response is dependent on energy intake or specific nutrient intake, we examined differences in response to eucaloric, milkshakes of varying macronutrient content.

Methods

We completed analysis of fMRI data to examine racial and ethnic differences in blood oxygen level dependent (BOLD) activation in response to intake of high-fat milkshake, high-sugar milkshake, and a calorie-free tasteless solution in 133 adolescents. The initial results paper from this sample [23] reported main effects of high fat milkshake (as compared to high sugar) conferring greater BOLD response in oral somatosensory region, caudate, hippocampus and inferior frontal gyrus. High sugar milkshake elicited greater activation in the insula, rolandic operculum, and thalamus. The paper did not examine differences in BOLD response to milkshake across racial and ethnic groups, which gave opportunity for the present analysis.

Participants

Participants were 133 adolescents (BMI (mean $\pm$ SD) = 21.1 ± 0.2 kg/m², Male: 62, Female: 71) recruited for a study examining brain response to milkshake varying in fat and sugar content. Adolescents were recruited through flyers and mailings from the Pacific Northwest. Eligibility criteria included: 14–16 years old, BMI between 25th and 75th percentile at baseline. Individuals who reported binge eating or compensatory behavior in the past 3 months, weekly or more frequent use of psychotropic medications or illicit drugs, head injury with a loss of consciousness, or Axis I psychiatric disorder in the past year (including anorexia nervosa, bulimia nervosa, or binge eating disorder) were excluded from the study. Parents and adolescents provided informed written consent for this project. Participants self-reported their racial and ethnic identity. The overall sample included the following racial and ethnic background: 6% Asian, 11% African American, <1% American Indian/Alaskan Native, 76% Caucasian, and 6% multi-race/other. We selected data from all individuals who self-identified as African American (AA) and/or Hispanic (H; n=27, AA:15, H:11, AA and H:1), and non-Hispanic white (nHW) participants (n=106) to be included in this analysis. This analysis included African American and Hispanic adolescents in a single group because there is no evidence to support that the two groups would vary in BOLD response from each other, as only elevated weight gain risk is shown to be associated with differential brain response to food [14]. The BMI-matched nHW sample was selected to closest match BMI percentile of the minority sample. Local Institutional Review Boards approved all methods.

Participants were asked to consume their regular meals but to refrain from eating or drinking for 4 hours immediately preceding their imaging session for standardization.

Upon arrival to their session, participants rated their hunger on a scale from 1 (not hungry at all) to 10 (extremely hungry); if a 7 or higher was indicated, they were offered a small snack to bring their hunger to a neutral state. About 20% of participants (n=26) consumed the snack before their imaging session. Prescan VAS ratings of hunger did not significantly vary from the neutral rating of 0 [23].

Measures

Body Mass—Height was measured to the nearest millimeter using a stadiometer, and weight was measured to the nearest 0.1 kg using digital scale, following standard procedure. Body mass index (BMI) was calculated as $\text{weight(kg)}/\text{height(m)}^2$. BMI-percentile was calculated using the 2000 Center for Disease Control gender-specific growth charts [24].

Hunger and Hedonics—Participants completed hunger ratings using visual analog scales (VAS). The 20cm cross-modal VAS were anchored by –10 ‘not at all’, 0 ‘neutral’, 10 ‘never been more hungry’ for hunger. To complete hedonic ratings, participants sampled a small amount of each milkshake and the tasteless solution (order counterbalanced), rating pleasantness on a scale ranging from 0 ‘most unpleasant sensation ever’ to 20 ‘most pleasant sensation ever’. Participants completed VAS ratings immediately prior to complete the scan to confirm all participants were in a neutral hunger state during the scan. Visual analog scales are demonstrated to be reliable in measuring hedonic and hunger ratings [25].

Dietary Assessment—Participants completed the Block Food Frequency Questionnaire (FFQ; [26]) to assess dietary pattern over the past 2 weeks. Mean daily proportion of fat and sugar intake was calculated using reported frequencies and estimate macronutrient content in an average serving of each item.

fMRI Scanning Procedure

Functional MRI was used to measure BOLD response to a block version of the milkshake paradigm [23]. This paradigm assessed BOLD activity in response to receipt of 4 milkshakes varying in sugar and fat content, and a control solution. The milkshakes’ nutritional contents were: high-fat/low-sugar (high fat), low-fat/high-sugar (high sugar), low-fat/low-sugar, and high-fat/high-sugar. The current analysis does not include results from the low-fat/low-sugar milkshake due to low reported palatability, thus BOLD responses to 4 of the 5 conditions are presented. Each milkshake included the same ice cream base and chocolate syrup. Milkshake fat and sugar content was manipulated by variance of type of milk and simple syrup content. High fat/low sugar and high sugar/low fat milkshakes were matched for energy density (1.28 kcal/mL vs. 1.24 kcal/mL). Nutritional content of the high-fat/high-sugar, high fat, and high sugar milkshakes is summarized in Table 1. The control condition was a tasteless, odorless solution that matched the ionic components of saliva (12.5 mM KCl, 1.25 mM NaHCO₃ in distilled water).

Milkshake and tasteless beverages were delivered through a gustometer that was anchored the scanner bed. Tastants were cued with a picture (glass of a milkshake or water). The milkshake image was the same for all milkshakes. Cues were presented for 1s, then replaced with a fixation cross as tastant was delivered for 5s. A 3s swallow cue and 9–11s jitter followed each tastant delivery. Tastants were administered in a variable block paradigm with 4, 5, or 7 events (1 event = cue + tastant + swallow + jitter) in two runs. The order of each milkshake block was randomized, and all participants consumed the same total amount of each milkshake during the scan. The paradigm included 6 blocks over a total of 27 minutes.

Imaging Processing and Analysis

Scans were completed using a Siemens Tim Trio 3T MRI scanner. Functional scans used a T2* weighted gradient single-shot echo planar imaging (EPI) sequence (TE = 30ms, TR = 2000ms, flip angle=80°) with an in plane resolution of $3.0 \times 3.0 \text{ mm}^2$ (64×64 matrix; $192 \times 192 \text{ mm}^2$ field of view). Thirty-two 4mm slices (interleaved acquisition, no skip) were acquired along the AC-PC transverse oblique plane, as determined by the midsagittal section. Rather than including motion regressors in analyses, prospective acquisition correction (PACE) was used to adjust slice position and orientation, as well as to re-grid residual volume-to-volume motion in real-time during data acquisition for the purpose of reducing motion-induced effects (19). Head motion greater than 2 mm or degrees in any direction was our *a priori* exclusion criteria, but no participants were excluded on this basis. A high-resolution inversion recovery T1 weighted sequence (MP-RAGE; FOV = $256 \times 256 \text{ mm}^2$, 256×256 matrix, thickness = 1.0 mm, slice number ≈ 160) was also acquired.

Data were pre-processed and analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, London, England) in MATLAB (Mathworks, Inc., Sherborn, MA). Images were manually reoriented to the AC-PC line and skull stripped. Functional images were realigned to the mean and both the anatomical and functional images were normalized to the standard Montreal Neurological Institute (MNI) T1 template brain (ICBM152). Normalization resulted in a voxel size of 3 mm^3 for functional images and a voxel size of 1 mm^3 for high-resolution anatomical images. Functional images were smoothed with a 6 mm FWHM isotropic Gaussian kernel. A 128 second high-pass filter removed low-frequency noise and signal drift.

To identify brain regions showing increases in BOLD activation in response to intake of each milkshake, we entered the individual level contrasts of (milkshake intake > tasteless solution intake) into the 2nd level, one-sample t-test separately for each of the 4 milkshakes. To test whether BOLD response to the milkshakes varied between racial and ethnic groups, we compared group data from the milkshakes of interest in 2nd level models using between-subject t-tests as implemented in SPM12 (e.g., [Minority vs nHW]). fMRI analyses were also performed controlling for menstrual phase in females and BMI; no differences in results were observed when menstrual phase/BMI was statistically controlled. We tested for differences between males and females in the presented contrasts using between group t-tests in SPM, no significant differences in BOLD response were observed.

Whole brain analyses were used throughout; activity surviving a threshold of $P < 0.001$, with a cluster (k) 19 was considered significant for all analyses. This significance level resulted from 10,000 Monte Carlo simulations of random noise distribution through an average grey matter mask (3 mm^3) using the 3dClustSim module of AFNI [27,28]. For use in the Monte Carlo simulations, the inherent smoothness was calculated from the residual mean squares for each of the main effects analyses (receipt of the 2 milkshakes vs. tasteless solution) using 3dFWHM module of AFNI [27] and then averaged. The mean grey matter mask of the whole brain was derived from the sample using DARTEL segmentation in SPM following standard methods in VBM8 [23]. All stereotactic coordinates are presented in MNI space.

Questionnaire Analysis

VAS ratings of milkshake hedonics, hunger, and fullness and FFQ percent kilocalories from fat and sugar intake were compared between groups using a two-sided, independent sample t-test, with a significance level of 0.05.

Results

Demographics, hedonic ratings, and self-reported dietary pattern

Characteristics of the full and BMI-matched samples are described in Table 2. The minority (Mi) and nHW groups did not significantly differ in age (M: 15.1 ± 0.8 ; nHW: 15.0 ± 0.9 ; $t=0.394$, $p=0.998$) or gender (Mi: male=15, female=12; nHW: male=47, female=59; $X^2(2, N=133)=1.088$, $p=0.297$). Body mass index and BMI-percentile significantly differed between the minority and nHW groups (BMI: Mi: 21.9 ± 2.10 ; nHW: 20.9 ± 2.25 ; $t=2.04$, $p=0.044$; BMI-percentile: Mi: 69 ± 16 ; nHW: 58 ± 24 ; $t=2.17$, $p=0.032$). To account for differences in BMI, we randomly selected a sample of nHW participants to be matched to minority participant on BMI percentile. The matched nHW sample and minority group did not differ significantly on BMI percentile ($t=0.015$, $p=0.988$).

The mean VAS hedonic rating of the high-fat milkshake significantly differed between minority and nHW participants (Mi: 10.3 ± 3.5 ; nHW: 12.4 ± 3.84 ; $t=2.04$, $p=0.044$) such that the minority group reported higher pleasantness ratings on average than the nHW group. The minority and BMI-percentile matched nHW groups did not differ on pleasantness ratings for the high-fat milkshake. No other ratings hedonic ratings of the tastetants examined differed significantly between the groups (p 's: 0.07, 0.16, 0.50).

The minority group and full nHW group did not report significantly different proportions of percent daily kilocalories from sugar intake (Mi: 14.2 ± 3.5 %kcal; nHW: 14.7 ± 3.5 %kcal; $t=-0.64$, $p=0.52$) on the Food Frequency Questionnaire (FFQ). Nor did the groups differ for proportions of percent daily kilocalories from fat intake (Mi: 15.9 ± 1.7 ; nHW: 15.9 ± 1.6 ; $t=0.03$, $p=0.97$).

Response to Intake

BOLD response to milkshake consumption significantly differed between minority participants and nHW participants. First, in comparing high sugar milkshake versus high fat milkshake, minority participants showed elevated brain response in the precentral gyrus, precuneus, and left thalamus (Table 3, Figure 1a).

Controlling for BMI-percentile, in comparison of the minority and BMI-percentile matched nHW group, the elevated response in the left thalamus remained (Table 4, Figure 1b). No significant differences between minority and nHW groups in brain response to intake of high-sugar milkshake compared to tasteless solution, high-fat milkshake compared to tasteless solution, or high-fat/high-sugar milkshake compared to tasteless solution were observed.

Discussion

Neuroimaging results demonstrate that in African American and Hispanic participants, high sugar milkshake increased activity in salience encoding (precuneus), motor planning (precentral gyrus) and gustatory stimulation (thalamus) regions of the brain, as compared to non-Hispanic white participants. The elevated response in the precuneus, precentral gyrus, and thalamus is observed when contrasted against brain response to high fat milkshake, suggesting that elevated sensory, gustatory, and salience encoding response is driven by the high sugar content, versus caloric content of the milkshake. To account for BMI differences between the minority and nHW participants, our study also examined brain response in African American and Hispanic participants compared to a BMI-matched subset of the nHW group. Controlling for differences in BMI, minority participants showed higher thalamus response to the high sugar milkshake, comparing to the BMI-matched subset of nHWs. The difference in results between the full sample and BMI-matched sample suggests that elevated precuneus and precentral gyrus activity found in minority participants is driven by differences in BMI, rather than race/ethnicity. Other studies found that elevated precuneus response to taste is associated with obesity in children [29], and obese binge eaters showed elevated precentral gyrus response to palatable food images, as compared to lean individuals [30]. These studies support that elevated response in the precuneus and precentral gyrus are found in obese-lean comparisons.

Elevated thalamic response to high sugar milkshake in African American and Hispanic minority participants remains after controlling for BMI. Based on thalamic mapping studies [32,33], the response we observed appears to be centered in the ventral thalamus. The ventral thalamus is thought to project to the primary gustatory cortex, and responds to tastant sensation, but not anticipation [34]. Elevated thalamic response to high sugar milkshake in the minority group may confer stronger sweet sensation in the gustatory thalamus. Interestingly, however this result does not manifest in perceived sweetness of the beverages, as there was no difference in the self-reported sweetness of the high sugar milkshake between minority and nHW participants. Therefore, any differences in sweetness sensation are limited to non-conscious processing. Critically, the pattern of thalamic response seen in minority participants in our sample in response to high sugar milkshake is similar to previous reports of weight gain-prone response to milkshake [14]. This suggests that the elevated thalamic response seen in the minority group may confer a high risk of weight gain in the future.

The observed differential brain response to milkshake raises important considerations in understanding these results. First, we must consider if the differences observed between minority and nHW are driven by differences in prior behavior or other external factors. Differences between minority and nHW participants in dietary patterns could explain results, as other studies have demonstrated that frequent consumption of a food alters brain response to that food [35,36], however self-reported percent of daily kilocalories from fat and sugar intake did not differ between the two groups. Additionally, there are known genetic factors that alter brain response to intake [37], which may contribute to the observed effects. In the present analyses, we are unable to determine if the observed neural differences lead to weight gain in minorities, since these analyses were completed in a cross-sectional study,

however, data support that elevated responsivity to taste predicts weight gain in nHW samples [38]. It is likely that this result holds in minority samples, and considering the higher prevalence of obesity in minorities, it's possible that the relationship between elevated gustatory response to food and future weight gain could be more highly predictive in minority populations.

Limitations

While this study is one of the first to examine the difference in brain response to food intake between African-American and Hispanic and non-Hispanic White adolescents, the methods used have noted limitations. First, while the overall sample size is large compared to other neuroimaging studies, the AA and H minority group in this study is relatively small, since the original sample this analysis drew from was not recruited to have high minority representation. Also, while self-reported dietary intake of sugar and fat did not differ between the minority and nHW groups, the Block FFQ used to assess diet has limited precision in its measurement of macronutrient intake, and may not capture true differences between our two groups.

Conclusions

In consideration of these limitations, this study demonstrates that brain response to high sugar milkshake differs between racial and ethnic groups in a region of the brain associated with taste processing, and that the observed pattern of response may confer the disproportional risk for future weight gain seen in minority populations. Of note, the statistical approach used aims to identify differences in brain response between *a priori* groups; the similarity of response between non-Hispanic white and minority groups should be acknowledged. Additional analyses should attempt to replicate this effect in existing, diverse samples. Also, future studies or secondary analysis of existing samples should test for racial and ethnic differences in response to images of highly palatable high-sugar and high-fat foods.

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Figure 1.

A) Brain response to high sugar milkshake > high-fat milkshake in minority participants (n=27) > non-Hispanic white participants (n=106) B) Brain response to high sugar milkshake > high-fat milkshake in minority participants (n=27) > body mass index- matched non-Hispanic white participants (n=27)

Table 1

Caloric and Macronutrient Content of Milkshake Stimuli per 100 mL

Milkshake	Calories (kcal)	Sugar (g)	Fat (g)
High Fat, High Sugar	170 kcal	23 g	7.5 g
High Fat	129 kcal	7.3 g	9.0 g
High Sugar	124 kcal	23.7 g	1.9 g

Table 2

Differences in body mass index (BMI), diet, and hedonic ratings between minority participants and non-Hispanic white (nHW)

Measure	Mean	SD	T-value	p-value
BMI				
Minority (n=27)	21.9	2.1	2.04	0.044
nHW (n=106)	20.9	2.3		
BMI percentile				
Minority	68.9	15.7	2.17	0.032
nHW	58.4	23.8		
Percent of daily Kcal from sugar				
Minority (n=27)	3.57	0.8	0.506	0.61
nHW (n=106)	3.67	0.9		
Hunger				
Minority	11.0	4.9		
nHW	10.9	4.2	.107	0.091
Fullness				
Minority	6.54	4.5	0.021	0.98
nHW	6.56	4.3		
High sugar milkshake pleasantness				
Minority	14.1	4.0	1.50	0.14
nHW	12.6	4.7		
High fat milkshake pleasantness				
Minority	10.3	3.5	2.51	0.013
nHW	12.4	3.8		
<i>Subsample analyses</i>				
BMI percentile				
Minority (n=27)	68.9	15.7	0.0148	0.99
nHW (n=27)	68.8	15.5		
High sugar milkshake pleasantness				
Minority (n=27)	10.3	3.5	1.74	0.088
nHW (n=27)	12.1	3.9		

Brain response to high sugar milkshake > high fat milkshake in minority participants (n=27) > non-Hispanic white participants (n=106)

Table 3

Region	MNI Coordinates	Cluster size (k)	Peak Z-value	Effect Size (r)	Peak p-value
Right precuneus	30 -58 13	22*	3.88	0.336	5.27 e-5
	27 -49 13		3.70	0.321	1.06 e-4
Left frontal pole	-42 -43 25	16	3.76	0.326	8.66 e-5
Left Precentral gyrus	-18 -25 55	36*	3.67	0.318	1.23 e-4
	-15 -28 -46		3.66	0.317	1.28 e-4
	-12 -19 49		3.60	0.312	1.61 e-4
Left thalamus	-12 -19 -8	22*	3.50	0.303	2.36 e-4
	-12 -13 -2		3.44	0.298	2.92 e-4
Left precuneus	-33 -46 10	12	3.44	0.298	2.86 e-4
	-30 -61 13		3.35	0.290	4.05 e-4
Visual Cortex	-24 -52 22	14	3.33	0.289	4.36 e-4

* : meets minimum cluster size threshold

Brain response to high sugar milkshake > high-fat milkshake in minority (n=27) > body mass index (BMI) percentile matched nHW (n=27)

Table 4

Region	MNI Coordinates	Cluster size (k)	Peak Z-value	Effect Size (r)	Peak p-value
Left thalamus *	-15 -19 -5	29 *	4.11	0.559	1.9815e-5
Left pallidum	-12 -4 -2	11	3.72	0.506	1.0326e-4

* : meets minimum cluster size threshold