Relative ability of fat and sugar tastes to activate reward, gustatory, and somatosensory regions

Eric Stice, Kyle S Burger, and Sonja Yokum

ABSTRACT

Background: Although the intake of high-fat and high-sugar food activates mesolimbic reward, gustatory, and oral somatosensory brain regions, contributing to overeating, few studies have examined the relative role of fat and sugar in the activation of these brain regions, which would inform policy, prevention, and treatment interventions designed to reduce obesity.

Objective: We evaluated the effect of a high-fat or high-sugar equicaloric chocolate milkshake and increasing fat or sugar milkshake content on the activation of these regions.

Design: Functional magnetic resonance imaging was used to assess the neural response to the intake of high-fat/high-sugar, high-fat/low-sugar, low-fat/high-sugar, and low-fat/low-sugar chocolate milkshakes and a tasteless solution in 106 lean adolescents (mean ± SD age = 15.00 ± 0.88 y). Analyses contrasted the activation to the various milkshakes.

Results: High-fat compared with high-sugar equicaloric milkshakes caused greater activation in the bilateral caudate, postcentral gyrus, hippocampus, and inferior frontal gyrus. High-sugar compared with high-fat equicaloric milkshakes caused greater activation in the bilateral insula extending into the putamen, the Rolandic operculum, and thalamus, which produced large activation regions. Increasing sugar in low-fat milkshakes caused greater activation in the bilateral caudate, postcentral gyrus, and thalamus, which produced large activation regions. Increasing fat content did not elicit greater activation in any region.

Conclusions: Fat caused greater activation of the caudate and oral somatosensory regions than did sugar, sugar caused greater activation in the putamen and gustatory regions than did fat, increasing sugar caused greater activity in gustatory regions, and increasing fat did not affect the activation. Results imply that sugar more effectively recruits reward and gustatory regions, suggesting that policy, prevention, and treatment interventions should prioritize reductions in sugar intake. This trial was registered at clinicaltrials.gov as DK092468. Am J Clin Nutr 2013;98:1377–84.

INTRODUCTION

The obesity epidemic has prompted a focus on the role of high-fat and high-sugar food consumption in overeating. High-fat/high-sugar food intake activates mesolimbic reward (midbrain and striatum) and gustatory regions (frontal operculum and insula) (1–4). The dopamine midbrain and striatum play a role in encoding the reward value of stimuli and reward learning (5), and striatal dopamine release correlates with ratings of meal pleasantness (6). The taste of fat in the mouth has been shown to activate the primary taste cortex as well as the orbitofrontal cortex and amygdala (7–10), and the texture of fat in the mouth has been shown to activate the taste and somatosensory insula, orbitofrontal cortex, and anterior cingulate cortex (11). Neural activity in the midorbitofrontal and anterior cingulate cortex has been correlated with the pleasantness of oral fat texture (12). The primary taste cortex (ie, the anterior insula and adjoining frontal operculum) appear to play a key role in the encoding of tastes [eg, sweet and bitter (8)], and the activation in the primary taste cortex had been correlated with the subjective reward from food (6, 13). The taste of glucose has also activated the amygdala (14), with perceived pleasantness correlated with the degree of activation (15). Rolls (8) argued that brain regions that represent the reward value of food are distinct from those that represent the viscosity of food (which reflects the fat content) and tastes such as sweet because eating to satiety reduces the activation of reward-valuation regions (eg, the caudate, amygdala, and orbitofrontal cortex), but not the activation in regions that represent fat and sweet tastes. Thus, data have suggested that high-fat and high-sugar food intake recruits brain reward regions, and the elevated perceived pleasantness of such food may contribute to overeating and consequent weight gain.

Although studies have advanced understanding of brain regions that represent the hedonic value of palatable foods, sweet tastes, and fat tastes, few studies have examined the relative role of sugar and fat-food contents in the activation of reward, gustatory, and oral somatosensory regions. Such an examination is important because knowing whether fat or sugar plays a more potent role in the activation of these regions would inform policy interventions, such as whether to tax high-fat or high-sugar foods, or both, to reduce intakes of energy-dense foods and the prevalence of obesity. This information may also inform the design of more-effective obesity-prevention and -treatment interventions.

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Experiments with rodents have indicated that high-fat diets resulted in greater weight gain than did high-carbohydrate diets, in part because the rodents ate more of the high-fat than high-carbohydrate foods (16), which implied that high-fat foods might be more effective than high-sugar diets in the activation of reward, gustatory, and somatosensory regions. However, the finding that a regular intake of sugar but not fat is associated with naltrrexone-precipitated signs of withdrawal (17) implies that sugar may more effectively activate these brain reward regions. The primary aim of the current study was to evaluate the effect of a high-fat or high-sugar equicaloric chocolate milkshake in the activation of these brain regions by using milkshakes that were equal in energy density and matched for flavor and palatability. The secondary aim was to test whether increasing fat or sugar milkshake content caused greater increases in the activation of these brain regions.

SUBJECTS AND METHODS

We used fMRI to examine BOLD activation in response to intakes of high-fat/high-sugar, high-fat/low-sugar, low-fat/high-sugar, and low-fat/low-sugar chocolate milkshakes and a calorie-free tasteless solution in 106 healthy-weight adolescents (Table 1). Participants reported the following racial and ethnic backgrounds: 7% of subjects were Asian, 6% of subjects were African American, 3% of subjects were American Indian or Alaskan Native, 71% of subjects were white, 9% of subjects were Hispanic, and 5% of subjects were multirace or other. Individuals who reported binge eating or compensatory behavior in the past 3 mo, weekly or more frequent use of psychotropic medications or illicit drugs, a head injury with a loss of consciousness, or an Axis I psychiatric disorder in the past year (including anorexia nervosa, bulimia nervosa, or binge-eating disorder) were excluded. Parents and adolescents provided informed written consent for the project. Oregon Research Institute’s Institutional Review Board approved all methods.

Sensory and hedonic measures

Participants were asked to consume their regular meals but to refrain from eating or drinking for 4 h immediately preceding their imaging session for standardization. On arrival to the session participants rated their hunger on a scale from 1 (not hungry at all) to 10 (extremely hungry); if a score ≥7 was indicated, subjects were offered a small snack to bring their hunger to a neutral state. After questionnaires were completed and paradigms explained, just before the scan, hunger and hedonic ratings of the tastants were assessed on 20-cm crossmodal visual analog scales (VASs). VAS ratings were anchored by −10 (not at all), 0 (neutral), and 10 (never been more hungry) for hunger. For hedonic ratings, participants sampled a small amount of each milkshake and the tasteless solution (order counterbalanced) and rated the pleasantness on a scale that ranged from 0 (most unpleasant sensation ever) to 20 (most pleasant sensation ever). The mean (±SD) hunger rated immediately before the scan on the VAS was neutral (0.8 ± 4.3; Table 1), which confirmed that participants were in a neutral hunger state during the scan.

fMRI milkshake receipt paradigm

We used a block version of our milkshake paradigm (4), which assessed BOLD activity in response to the receipt of milkshakes that varied in sugar and fat contents. Each milkshake included the same ice-cream base and chocolate syrup. No fat substitutes or thickeners (eg, olestra or guar gum) or artificial sweeteners (eg, aspartate or sucralose) were included. Fat contents of the milkshakes were manipulated by varying the type of milk (half and half compared with 2% milk). The sweetness was manipulated by varying the simple-syrup content. We investigated the response to the following milkshakes (16 fl oz is equivalent to a typical medium-sized, fast-food milkshake): a high-fat/high-sugar milkshake (804 kcal, 35.4 g fat, and 106.4 g sugar/16 fl oz; 170 kcal, 7.5 g fat, and 23 g sugar/100 mL), a high-fat/low-sugar milkshake (605 kcal, 42.6 g fat, and 34.5 g sugar/16 fl oz; 129 kcal, 9.0 g fat, and 7.3 g sugar/100 mL), a low-fat/high-sugar milkshake (587 kcal, 8.9 g fat, and 121.2 g sugar/16 fl oz; 124 kcal, 1.9 g fat, 23.7 g sugar/100 mL), and a low-fat/low-sugar milkshake (350 kcal, 11.4 g fat, 41.2 g sugar/16 fl oz; 74 kcal, 2.4 g fat, and 8.7 g sugar/100 mL). Pilot testing showed these differences in fat and sugar contents were detectable without varying the flavor. In addition, the high-fat/low-sugar and low-fat/high-sugar milkshakes were designed such that they had similar energy densities (1.28 kcal/mL for the high-fat/low-sugar milkshake compared with 1.24 kcal/mL for the low-fat/high-sugar milkshake). We included a tasteless, odorless solution that

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td>Subject characteristics and behavioral measures (n = 106)</td>
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<tr>
<td>M (n = 47)</td>
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<td>---</td>
</tr>
<tr>
<td>Age (y)</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>Handedness (percentage of right-handed subjects)</td>
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<tr>
<td>Hunger</td>
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<tr>
<td>Milkshake pleasantness (high fat/high sugar)</td>
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<td>Milkshake pleasantness (high fat/low sugar)</td>
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<td>Milkshake pleasantness (low fat/high sugar)</td>
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<td>Milkshake pleasantness (low fat/low sugar)</td>
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<tr>
<td>Tasteless solution pleasantness</td>
</tr>
</tbody>
</table>

1Mean ± SD (all such values).
2Scale was from −10 (not at all hungry) to 10 (I have never been more hungry).
3Scale was from 0 (most unpleasant sensation ever) to 20 (most pleasant sensation ever). Different superscript letters indicate significant differences in pleasantness ratings (P < 0.01) assessed by using within-subject t tests.
contained the main ionic components of saliva (25 mmol/L KCl and 2.5 mmol/L NaHCO₃ in distilled water) as a control contrast. The receipt of the tasteless solution compared with the baseline activity produced significant activation in brain regions previously associated with taste, including oral somatosensory regions (bilateral postcentral gyrus and Rolandic operculum: right: 54, −7, 25; k = 300; Z = 7.7; left: −54, −7, 25; k = 300; Z = 7.5) and bilateral putamen extending into the insula (right: 30, −10, −11; k = 37; Z = 5.8; left: −27, −7, −11; k = 33; Z = 6.1).

Subjects received the tastants through individual beverage tubes that were connected to a 5-channel gustometer that was anchored to the scanner bed and delivered the tastes in the same area of the mouth. Participants were cues with a picture (glass of milkshake or water). All milkshake variants were preceded by the same image of a milkshake to not confound the neural response to receipt with expectations (18). During milkshake and tasteless delivery, the cue (1 s) was presented followed by a fixation cross during delivery of the tastant. The delivery of the milkshake and tasteless solution occurred in variable-length blocks (1 block presented 4, 5, or 7 events in each of the 2 runs). An event was considered when a tastant was delivered (0.7 cc) over 5 s followed by 3 s to swallow. Four, 5, or 7 events in a row of the same tastant were considered a block. After a block was completed, subjects received a rinse of the tasteless solution followed by a swallow cue (0.5 s) and a jitter (9–11 s). The tasteless solution followed the same pattern without a rinse. The order of the presentation of blocks (ie, different tastants) was randomized. Two runs (13 min; 40 s/run) were performed. Each run presented 3 blocks of each of the 4 milkshake types and the tasteless solution in a randomized order. In total, there were 6 blocks (32 events) of each of the 5 tastants presented.

**fMRI data acquisition and preprocessing**

Scanning was performed by a Siemens Tim Trio 3 Tesla MRI scanner (Siemens). Functional scans used a T²*-weighted gradient single-slice echo planar imaging sequence (echo time (TE): 30 ms; repetition time: 2000 ms; flip angle: 80°) with an in-plane resolution of 3.0 × 3.0 mm² (64 × 64 matrix; 192 × 192-mm² field of view). Thirty-two 4-mm slices (interleaved acquisition, no skip) were acquired along the anterior-commissure–posterior-commissure transverse oblique plane, as determined by the midsagittal section. Rather than include motion regressors in the model, the cue (1 s) was presented followed by a fixation cross during delivery of the tastant. The delivery of the milkshake and tasteless solution occurred in variable-length blocks (1 block presented 4, 5, or 7 events in each of the 2 runs). An event was considered when a tastant was delivered (0.7 cc) over 5 s followed by 3 s to swallow. Four, 5, or 7 events in a row of the same tastant were considered a block. After a block was completed, subjects received a rinse of the tasteless solution followed by a swallow cue (0.5 s) and a jitter (9–11 s). The tasteless solution followed the same pattern without a rinse. The order of the presentation of blocks (ie, different tastants) was randomized. Two runs (13 min; 40 s/run) were performed. Each run presented 3 blocks of each of the 4 milkshake types and the tasteless solution in a randomized order. In total, there were 6 blocks (32 events) of each of the 5 tastants presented.
### TABLE 2
Effects of BOLD responsivity to milkshake intake varied by macronutrient content

<table>
<thead>
<tr>
<th>Hemisphere of the brain</th>
<th>MNI coordinates ( x, y, z )</th>
<th>( k^2 )</th>
<th>Peak Z</th>
<th>( r^1 )</th>
<th>Peak P</th>
</tr>
</thead>
</table>
| **High-fat/high-sugar milkshake intake**  
(high-fat/high-sugar compared with tasteless solution intakes) | | | | | |
| Postcentral gyrus | Right | 54, –7, 22 | 557 | 5.77 | 0.56 | \( 3.9 \times 10^{-9} \) |
| Insula (mid) | Right | 36, –7, 7 | 562 | 0.55 | 9.3 \times 10^{-9} |
| Rolandic operculum | Right | 63, –13, 25 | 5.22 | 0.51 | |
| Postcentral gyrus | Left | –57, –7, 28 | 378 | 5.40 | 0.52 | \( 3.4 \times 10^{-8} \) |
| Insula | Left | –36, –10, 10 | 4.39 | 0.43 | 5.7 \times 10^{-6} |
| Temporal operculum | Left | –45, –19, 7 | 4.01 | 0.39 | 2.9 \times 10^{-5} |
| Cerebellum | Right | 15, –61, –26 | 56 | 4.82 | 0.47 | 7.6 \times 10^{-7} |
| Thalamus | Right | 9, –19, –2 | 99 | 4.62 | 0.45 | 1.9 \times 10^{-6} |
| Thalamus | Left | –6, –22, –2 | 4.55 | 0.44 | 2.6 \times 10^{-6} |
| Thalamus | Right | 9, –7, 10 | 3.75 | 0.36 | 8.7 \times 10^{-5} |
| Cerebellum | Left | –15, –64, –26 | 40 | 4.41 | 0.43 | 3.1 \times 10^{-6} |
| Anterior cingulate cortex | Right | 0, 20, 19 | 43 | 3.97 | 0.39 | 3.5 \times 10^{-5} |
| | | 0, 29, 25 | 3.62 | 0.35 | — |
| **High-fat/low-sugar milkshake intake**  
(high-fat/low-sugar compared with tasteless solution intakes) | | | | | |
| Postcentral gyrus | Right | 60, –7, 22 | 98 | 4.47 | 0.43 | \( 3.9 \times 10^{-6} \) |
| Postcentral gyrus | Right | 51, –10, 25 | 4.16 | 0.40 | — |
| | | 57, 5, 19 | 3.73 | 0.36 | — |
| Postcentral gyrus | Right | 54, –19, 34 | 20 | 4.01 | 0.39 | 3.1 \times 10^{-5} |
| Postcentral gyrus | Left | –57, –10, 31 | 69 | 3.86 | 0.38 | 5.6 \times 10^{-5} |
| | | –63, –10, 19 | 3.79 | 0.37 | — |
| | | –60, –19, 22 | 3.73 | 0.36 | — |
| Anterior cingulate cortex | Right | 3, 38, 19 | 17 | 3.73 | 0.36 | 9.7 \times 10^{-5} |
| | | 3, 26, 19 | 3.22 | 0.31 | — |
| **Low-fat/high-sugar milkshake intake**  
(low-fat/high-sugar compared with tasteless solution intakes) | | | | | |
| Insula (mid) | Right | 39, –7, 7 | 963 | 7.30 | 0.71 | \( 1.5 \times 10^{-13} \) |
| Postcentral gyrus | Right | 60, –13, 22 | 6.73 | 0.65 | 8.7 \times 10^{-12} |
| Putamen | Right | 24, –4, 4 | 5.81 | 0.56 | 3.0 \times 10^{-9} |
| Insula (mid) | Left | –36, –10, 10 | 729 | 6.41 | 0.62 | 7.4 \times 10^{-11} |
| Postcentral gyrus | Left | –60, –7, 31 | 6.38 | 0.62 | 8.6 \times 10^{-11} |
| | | –48, –10, 28 | 5.93 | 0.58 | — |
| Thalamus | Right | 9, –19, –2 | 88 | 5.57 | 0.54 | 1.3 \times 10^{-5} |
| Caudate | Right | 12, 8, 4 | 4.08 | 0.40 | 2.2 \times 10^{-5} |
| Thalamus | Right | 12, –1, 10 | 4.03 | 0.39 | 2.7 \times 10^{-5} |
| Thalamus | Left | –12, –22, 7 | 74 | 5.33 | 0.52 | 4.9 \times 10^{-5} |
| Caudate | Left | –9, 5, 1 | 4.94 | 0.48 | 3.9 \times 10^{-5} |
| Thalamus | Left | –12, –1, 10 | 4.77 | 0.46 | 9.0 \times 10^{-7} |
| Cingulate cortex | Right | 0, –22, 25 | 33 | 4.30 | 0.42 | 8.7 \times 10^{-6} |
| | | 6, –31, 25 | 3.55 | 0.34 | — |
| | Left | –3, –16, 34 | 3.44 | 0.33 | — |
| Cerebellum | Right | 15, –61, –26 | 23 | 4.13 | 0.40 | 1.8 \times 10^{-5} |
| Cingulate cortex | Left | –6, 11, 34 | 43 | 4.07 | 0.40 | 8.7 \times 10^{-6} |
| Cerebellum | Left | –21, –67, –26 | 28 | 4.00 | 0.39 | 3.2 \times 10^{-3} |
| Cingulate cortex | Right | 3, 38, 19 | 40 | 3.97 | 0.39 | 3.6 \times 10^{-5} |
| **Low-fat/low-sugar milkshake intake**  
(low-fat/low-sugar compared with tasteless solution intakes) | | | | | |
| Rolandic operculum | Right | 60, –4, 13 | 179 | 4.90 | 0.48 | 4.8 \times 10^{-7} |
| Postcentral gyrus | Right | 51, –10, 25 | 4.82 | 0.47 | 7.1 \times 10^{-7} |
| | | 60, –13, 4 | 4.12 | 0.40 | — |
| Cerebellum | Right | 21, –67, –23 | 82 | 4.55 | 0.44 | 2.7 \times 10^{-6} |
| | | 12, –58, –17 | 3.42 | 0.33 | — |

(Continued)
TABLE 2 (Continued)

<table>
<thead>
<tr>
<th>Hemisphere of the brain</th>
<th>MNI coordinates $x, y, z$</th>
<th>$k^2$</th>
<th>Peak Z</th>
<th>$r^1$</th>
<th>Peak P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postcentral gyrus</td>
<td>Left $-57, -7, 28$</td>
<td>165</td>
<td>4.49</td>
<td>0.44</td>
<td>$3.5 \times 10^{-6}$</td>
</tr>
<tr>
<td></td>
<td>$-60, -7, 16$</td>
<td>4.02</td>
<td>0.39</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>$-57, 5, 25$</td>
<td>3.93</td>
<td>0.38</td>
<td>$4.3 \times 10^{-5}$</td>
<td></td>
</tr>
<tr>
<td>Lingual gyrus</td>
<td>Left $-21, -64, -14$</td>
<td>108</td>
<td>4.38</td>
<td>0.43</td>
<td>$5.9 \times 10^{-6}$</td>
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<td></td>
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<td>3.52</td>
<td>0.34</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Temporal operculum</td>
<td>Left $-48, -19, 4$</td>
<td>41</td>
<td>4.28</td>
<td>0.42</td>
<td>$9.3 \times 10^{-6}$</td>
</tr>
<tr>
<td></td>
<td>$-39, -28, 10$</td>
<td>3.99</td>
<td>0.39</td>
<td>—</td>
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</tr>
<tr>
<td>Thalamus</td>
<td>Right $6, -22, 1$</td>
<td>33</td>
<td>3.99</td>
<td>0.39</td>
<td>$3.2 \times 10^{-5}$</td>
</tr>
<tr>
<td></td>
<td>$12, -16, 7$</td>
<td>3.87</td>
<td>0.38</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cingulate cortex</td>
<td>Right $3, 14, -46$</td>
<td>30</td>
<td>3.86</td>
<td>0.38</td>
<td>$5.8 \times 10^{-5}$</td>
</tr>
<tr>
<td></td>
<td>$3, 20, 34$</td>
<td>3.71</td>
<td>0.36</td>
<td>—</td>
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</tr>
</tbody>
</table>

1 MNI, Montreal Neurological Institute.
2 Cluster size. Clusters may contain more than one brain region as indicated by multiple names or $P$ values under one cluster size.
3 $r$ = Pearson’s product-moment correlation (calculated as $Z = \frac{r}{\sqrt{n}}$). Notes: $r$ values under one cluster size.
4 Peaks were shown in the putamen ($k = 7$) and caudate ($k = 11$) for high-fat/low-sugar milkshake, but they fell under the minimum cluster size ($k \geq 15$).

RESULTS

Pleasantness ratings varied significantly between the 4 milkshakes and tasteless solution (Table 1), with the exceptions of ratings of the high-fat/low-sugar milkshake compared with low-fat/high-sugar milkshake ($P = 0.33$) and low-fat/lowsugar milkshake compared with the tasteless solution ($P = 0.15$). Main effects of the 4 types of milkshakes compared with the tasteless solution on the BOLD response are shown in Table 2. High-fat/high-sugar milkshake (compared with the tasteless solution) intake elicited robust activity in the bilateral postcentral gyrus that extended into the insula and right Rolandic operculum. High-fat/low-sugar milkshake (compared with tasteless solution) intake also elicited significant activity in the bilateral postcentral gyrus and right anterior cingulate cortex. Low-fat/high-sugar milkshake (compared with tasteless solution) intake resulted in activity in the bilateral Rolandic operculum and right thalamus, and right cingulate cortex.

Direct comparison of equicaloric high-fat compared with high-sugar milkshakes on BOLD response

When we directly compared the BOLD response to the receipt of equicaloric high-fat compared with high-sugar milkshakes, we contrasted the high-fat/low-sugar compared with low-fat/high-sugar milkshakes, thereby controlling for energy density. High-fat compared with high-sugar equicaloric milkshakes caused greater activation in the bilateral hippocampus, caudate (Figure 1A), postcentral gyrus, left inferior frontal gyrus (Table 3; Figure 1A). The reverse contrast showed that the high-sugar compared with high-fat milkshakes caused greater activation in the bilateral insula (Figure 1B) extending into the putamen and the Rolandic operculum (Figure 1B) and left thalamus (Table 3).

Effect of increasing fat content in low- and high-sugar milkshakes on BOLD response

When we examined the effect of increasing fat content in low- and high-sugar milkshakes (high-fat/low-sugar compared with low-fat/low-sugar milkshakes), we did not observe significant activation. Similarly, when we examined the effect of increasing fat in high-sugar milkshakes (high-fat/high-sugar compared with low-fat/high-sugar milkshakes), we did not observe significant activity.

Effects of increasing sugar content in low- and high-fat milkshakes on BOLD response

Increasing sugar in low-fat milkshakes (low-fat/high-sugar compared with low-fat/low-sugar milkshakes) resulted in increased activity in the bilateral insula (Figure 1C) and right Rolandic operculum (Table 4). When we examined the effect of increasing sugar content in high-fat milkshakes (high-fat/high-

![FIGURE 1](https://academic.oup.com/ajcn/article-abstract/98/6/1377/4577250/fig1){/}
High-fat compared with high-sugar milkshakes (high-fat/low-sugar compared with low-fat/high-sugar milkshakes)

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Hemisphere</th>
<th>MNI Coordinates</th>
<th>Z-score</th>
<th>Peak P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>Left</td>
<td>−21, −37, 10</td>
<td>5.15</td>
<td>1.3 × 10⁻⁷</td>
</tr>
<tr>
<td>Caudate</td>
<td>Left</td>
<td>−15, −23, 1</td>
<td>4.97</td>
<td>3.4 × 10⁻⁷</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>Left</td>
<td>−21, −37, 70</td>
<td>4.46</td>
<td>4.2 × 10⁻⁶</td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>Left</td>
<td>−15, −31, 73</td>
<td>3.86</td>
<td>3.7 × 10⁻⁶</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Right</td>
<td>15, −34, 10</td>
<td>4.38</td>
<td>5.3 × 10⁻⁷</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Right</td>
<td>15, −76, −32</td>
<td>4.19</td>
<td>1.4 × 10⁻⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9, −79, −41</td>
<td>3.77</td>
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<td></td>
<td></td>
<td>27, −79, −41</td>
<td>3.76</td>
<td>—</td>
</tr>
<tr>
<td>Caudate</td>
<td>Right</td>
<td>18, 23, 1</td>
<td>4.06</td>
<td>2.4 × 10⁻⁵</td>
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<tr>
<td>Postcentral gyrus</td>
<td>Right</td>
<td>21, −37, 70</td>
<td>3.97</td>
<td>3.6 × 10⁻⁵</td>
</tr>
<tr>
<td>Frontal pole</td>
<td>Left</td>
<td>−24, 59, 7</td>
<td>3.61</td>
<td>1.5 × 10⁻⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−12, 62, 4</td>
<td>3.42</td>
<td>3.3</td>
</tr>
</tbody>
</table>
| High-sugar compared with high-fat milkshakes (low-fat/high-sugar compared with high-fat/low-sugar milkshakes)

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Hemisphere</th>
<th>MNI Coordinates</th>
<th>Z-score</th>
<th>Peak P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insula</td>
<td>Right</td>
<td>36, −7, 7</td>
<td>5.32</td>
<td>5.1 × 10⁻⁸</td>
</tr>
<tr>
<td>Putamen</td>
<td>Right</td>
<td>30, −13, −5</td>
<td>3.70</td>
<td>1.8 × 10⁻⁴</td>
</tr>
<tr>
<td>Insula</td>
<td>Right</td>
<td>42, 5, −5</td>
<td>3.51</td>
<td>2.2 × 10⁻⁴</td>
</tr>
<tr>
<td>Insula/putamen</td>
<td>Left</td>
<td>−36, −7, 7</td>
<td>4.59</td>
<td>2.2 × 10⁻⁷</td>
</tr>
<tr>
<td>Rolandic operculum</td>
<td>Left</td>
<td>−51, 5, −2</td>
<td>4.41</td>
<td>5.2 × 10⁻⁶</td>
</tr>
<tr>
<td>Insula</td>
<td>Left</td>
<td>−36, −4, −2</td>
<td>4.22</td>
<td>1.2 × 10⁻⁵</td>
</tr>
<tr>
<td>Rolandic operculum</td>
<td>Right</td>
<td>63, −13, 19</td>
<td>4.18</td>
<td>1.4 × 10⁻⁵</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Left</td>
<td>−15, −25, 7</td>
<td>3.68</td>
<td>1.2 × 10⁻⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−9, 16, 7</td>
<td>3.34</td>
<td>4.2 × 10⁻⁴</td>
</tr>
</tbody>
</table>

1 MNI, Montreal Neurological Institute.
2 Cluster size. Clusters may contain more than one brain region as indicated by multiple names or P values under one cluster size.
3 Pearson’s product-moment correlation (calculated as Z + √n).

sugar compared with high-fat/low-sugar milkshakes), we did not observe significant activation.

**DISCUSSION**

Main-effects analyses indicated that the various milkshakes activated reward (putamen, caudate), gustatory (insula), and oral somatosensory regions (Rolandic operculum) as well as attention regions (anterior cingulate cortex), which converged with findings from previous sensory neuroscience studies (1, 2, 7–11, 22, 23). The low-fat/high-sugar milkshake tended to activate more classic reward regions (eg, putamen and caudate) than did the high-fat/high-sugar and other milkshakes. It was also noteworthy that the low-fat/low-sugar milkshake activated gustatory and somatosensory but not traditional reward regions. Thus, main-effects analyses provide evidence for the validity of our fMRI food-receipt paradigm.

The first aim of the current study was to evaluate the effect of a high-fat or high-sugar chocolate milkshake in the activation of these brain regions by using equicaloric milkshakes matched for flavor. Results indicated that high-fat compared with high-sugar milkshake receipt elicited greater activation in the bilateral caudate, postcentral gyrus, hippocampus, and left inferior frontal gyrus. In contrast, the high-sugar compared with high-fat milkshakes elicited greater activation in the bilateral insula extending into the putamen and the Rolandic operculum and left thalamus. This pattern of findings suggested that tastes of high-fat compared with high-sugar milkshakes prompted greater activation in regions involved in associative learning processes (caudate and hippocampus) and somatosensory regions (postcentral gyrus), whereas tastes of high-sugar compared with high-fat milkshakes prompted greater activation in regions associated with reward and motivation (insula and putamen), oral somatosensation (Rolandic operculum), and gustatory stimulation (thalamus) (24–28). To our knowledge, these findings make a novel contribution to the literature in that it appears that no previous study has compared the neural response to foods that are high in fat compared with high in sugar, with control for energy density and flavor.

The second aim was to evaluate the effects of increasing the fat or sugar milkshake content on the neural response in reward, gustatory, and oral somatosensory regions. Analyses revealed that increasing the fat contents of both low-sugar and high-sugar milkshakes did not lead to changes in the responsivity of brain regions implicated in these processes. In juxtaposition, the increased sugar content of low-fat milkshakes caused greater activation in the bilateral insula and right Rolandic operculum. Thus, increasing sugar content of a low-fat milkshake resulted in greater activity in gustatory regions, but increasing fat content did
changes in sugar. However, the milkshakes were specifically
on a neural level was weaker relative to the ability to detect
ceiling effect), or the ability to detect differences in the fat content
floor effect), the high-fat milkshake contained too much fat (a
less-consistent findings regarding fat manipulation could have
been because the low-fat milkshake contained too-little fat (a
project more directly to reward-valuation regions than oral so-
matosensory regions that encode viscosity and, therefore, the fat
content of foods. Collectively, results from the current study
supported the notion that increasing the sugar content of food
results in a greater neural response than increasing the fat content.
Specifically, in every contrast that examined a relative increase in
sugar, we observed increased activation in the insula and con-
sistently observed greater activity in the Rolandic operculum
and regions along typical dopaminergic pathways (ie, caudate,
putamen, and anterior cingulate cortex). In addition, when we
examined the degree of activation caused by individual milk-
shakes compared with the tasteless solution, the low-fat/high-
sugar milkshake elicited the most robust activity in regions
previously associated with rewarding food intake (striatum,
insula, and oral somatosensory regions) relative to the other types
of milkshakes.

Note that the pattern of results from the main-effects analyses
did not suggest any type of interaction between fat and sugar
contents (ie, high-fat/high-sugar did not consistently activate
regions more than high-fat/low-sugar or low-fat/high-sugar).
Thus, results implied that fat and sugar contents did not interact
in the degree to which these macronutrients activated reward,
gustatory, and oral somatosensory regions. This null finding is
particularly interesting because of how fat and sugar are often
paired in energy-dense foods in the food environment (31).

Collectively, the current results supported the notion that in-
creases in the sugar content of food results in a greater neural
response relative to changes in fat. Particularly, fat manipulation
had less of an impact on the neural response particularly in
hypothesized reward regions. However, results tended to show
that increases in fat resulted in activity in oral somatosensory
regions in most contrasts, dovetailing previous evidence (11). The
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been because the low-fat milkshake contained too-little fat (a
floor effect), the high-fat milkshake contained too much fat (a
ceiling effect), or the ability to detect differences in the fat content
on a neural level was weaker relative to the ability to detect
changes in sugar. However, the milkshakes were specifically
designed for the current study and were done so in the most
generalizable and controlled fashion possible by maintaining
flavor and palatability without the use of artificial sweeteners or
texture manipulation and presenting detectable differences in fat
and sugar contents.

In conclusion, the current study showed neural differences of
a generalizable food item that varied the fat and sugar contents
without changes of flavor. The current results indicate that the
high-sugar milkshake more-effectively recruited reward regions
than did the equicaloric high-fat milkshake, and in addition,
increasing the sugar content compared with increasing the fat
content of milkshakes caused greater activity in brain regions
previously associated with the intake of rewarding foods. Last, fat
and sugar contents of the milkshakes did not appear to operate
interactively to activate reward regions, which may highlight the
need for examining individual differences surrounding the rel-
ative preference, taste sensitivity, and habitual intake of these
macronutrients.

We thank the Lewis Center for Neuroimaging at the University of Oregon
for their assistance in data collection for these projects.

The authors’ responsibilities were as follows—ES, KSB, and SY: de-
signed and conducted the research and wrote the manuscript; KSB and
SY: performed statistical analyses; ES: had primary responsibility for the
final content of the manuscript; and all authors: read and approved the final
manuscript. None of the authors had a conflict of interest.

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4. Stice E, Yokum S, Burger K, Epstein L, Smolen A. Multilocus genetic
composite reflecting dopamine signaling capacity predicts reward cir-
5. Schultz W. Behavioral theories and the neurophysiology of reward.
release in the dorsal striatum correlates with meal pleasantness ratings
representations of the viscosity, fat texture, temperature, grittiness,

TABLE 4
Effect of increasing sugar on BOLD responsivity to low-fat milkshakes

<table>
<thead>
<tr>
<th>Hemisphere of the brain</th>
<th>MNI coordinates</th>
<th>Peak</th>
<th>Z</th>
<th>r</th>
<th>Peak P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insula Right</td>
<td>36, −7, 7</td>
<td>63</td>
<td>4.63</td>
<td>0.45</td>
<td>1.8 × 10^{-6}</td>
</tr>
<tr>
<td>Rolandic operculum/postcentral gyrus Right</td>
<td>60, −16, 22</td>
<td>23</td>
<td>4.05</td>
<td>0.39</td>
<td>2.5 × 10^{-5}</td>
</tr>
<tr>
<td>Insula Left</td>
<td>−36, −4, 4</td>
<td>30</td>
<td>3.81</td>
<td>0.37</td>
<td>7.0 × 10^{-5}</td>
</tr>
<tr>
<td></td>
<td>−36, −10, 10</td>
<td>3.72</td>
<td>0.36</td>
<td>1.0 × 10^{-4}</td>
<td></td>
</tr>
</tbody>
</table>

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