Differential effects of fructose versus glucose on brain and appetitive responses to food cues and decisions for food rewards

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Prior studies suggest that fructose compared with glucose may be a weaker suppressor of appetite, and neuroimaging research shows that food cues trigger greater brain reward responses in a fasted relative to a fed state. We sought to determine the effects of ingesting fructose versus glucose on brain, hormone, and appetitive responses to food cues and food-approach behavior. Twenty-four healthy volunteers underwent two functional magnetic resonance imaging (fMRI) sessions with ingestion of either fructose or glucose in a double-blinded, random-order cross-over design. fMRI was performed while participants viewed images of high-calorie foods and nonfood items using a block design. After each block, participants rated hunger and desire for food. Participants also performed a decision task in which they chose between immediate food rewards and delayed monetary bonuses. Hormones were measured at baseline and 30 and 60 min after drink ingestion. Ingestion of fructose relative to glucose resulted in smaller increases in plasma insulin levels and greater brain reactivity to food cues in the visual cortex (in whole-brain analysis) and left orbital frontal cortex (in region-of-interest analysis). Parallel to the neuroimaging findings, fructose versus glucose led to greater hunger and desire for food and a greater willingness to give up long-term monetary rewards to obtain immediate high-calorie foods. These findings suggest that ingestion of fructose relative to glucose results in greater activation of brain regions involved in attention and reward processing and may promote feeding behavior.

fructose | glucose | fMRI | food cue | decision making

Obesity is a major public health problem, and increases in the consumption of fructose as a sweetener may be an important contributor to the current obesity epidemic (1). Fructose and glucose are both monosaccharides with the same number of calories, but they are metabolized differently. In the glycolytic pathway, glucose metabolism is regulated through feedback inhibition by the end products ATP and citrate, but fructose bypasses the main regulatory step, catalyzed by phosphofructokinase (2). Whereas glucose is the main circulating sugar in the blood, the majority of fructose is extracted from the bloodstream into the liver, where unregulated fructose metabolism can lead to increased lipogenesis (3). Similarly, unregulated fructose metabolism in the hypothalamus may lead to rapid depletion of hypothalamic ATP and consequently to increased food intake (4). Moreover, unlike glucose, fructose does not stimulate the secretion of insulin (5), a hormone that signals the brain to increase satiety and to blunt the reward value of food (6, 7). These unique properties of fructose versus glucose may help explain their differential effects on brain appetite pathways (4, 8). The central administration of fructose was shown to decrease hypothalamic satiety signaling and increase feeding in animals, whereas glucose increased satiety signaling and reduced food intake (4). Likewise, the hypothalamus was found to respond differently to the ingestion of fructose and glucose in humans (8). Ingestion of glucose relative to fructose resulted in a reduction in hypothalamic cerebral blood flow, a marker of neural activation, in healthy volunteers (8). Less is known, however, about differential effects of fructose compared with glucose ingestion on brain reward responsivity and food-approach behavior.

Thus, the current study was aimed at determining the effects of fructose versus glucose on brain and behavioral food-cue reactivity and on decisions between immediate food rewards versus delayed monetary rewards. We hypothesized that ingestion of fructose compared with glucose would result in greater food-cue reactivity in brain reward regions, greater appetitive responses to food cues, and increased decisions for immediate food rewards over delayed monetary rewards. To test these hypotheses, 24 healthy volunteers participated in a double-blinded, random-order cross-over study with ingestion of either fructose or glucose. A subset of 18 volunteers additionally underwent a water control session and rated the pleasantness of each drink. Functional magnetic resonance imaging (fMRI) was used to study the effects of ingestion of fructose compared with glucose on brain reward and appetitive responses to food cues. Motivation for food was probed by pitting immediately available food rewards against delayed monetary bonuses (the latter delayed by 1 mo, to explicitly model the delayed benefits of forgoing attractive high-calorie foods).

Results

Plasma Metabolites and Hormones. Baseline levels of plasma glucose, fructose, insulin, glucagon-like peptide 1 (GLP-1), peptide YY (PYY), leptin, ghrelin, and lactate were not different between the glucose and fructose conditions (Table S1). Glucose ingestion caused significantly greater elevations in plasma glucose [mean (±SE) area under the curve (AUC) difference:

Significance

Fructose compared with glucose may be a weaker suppressor of appetite. Here we sought to determine the effects of fructose versus glucose on brain, hormone, and appetitive responses to food cues and food-approach behavior. We show that the ingestion of fructose compared with glucose resulted in smaller increases in plasma insulin levels and greater brain responses to food cues in the visual cortex and left orbital frontal cortex. Ingestion of fructose versus glucose also led to greater hunger and desire for food and a greater willingness to give up long-term monetary rewards to obtain immediate high-calorie foods. These findings suggest that ingestion of fructose relative to glucose activates brain regions involved in attention and reward processing and may promote feeding behavior.

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960.47 ± 172.17 mg/dL, $P < 0.001$] and insulin (1931.44 ± 421.16 μU/mL, $P < 0.001$) concentrations (Fig. 1) compared with fructose ingestion, whereas the mean AUC difference in plasma fructose (104.00 ± 48.68 mg/dL, $P < 0.05$) and lactate (108.39 ± 38.83 mg/dL, $P < 0.01$) levels were greater after fructose relative to glucose ingestion. Mean AUC plasma PYY, GLP-1, leptin, and ghrelin levels were not different following fructose compared with glucose ingestion, but plasma PYY levels were higher 60 min after fructose compared with glucose ingestion (Table S1).

In-Scanner Food Cue-Induced Appetite Ratings. There were no significant differences in baseline (predrink) ratings of hunger or desire for food on the different study days. Ratings of drink pleasantness were similar for both the fructose and glucose drinks [fructose vs. glucose mean difference ± SE: −0.389 ± 0.325, $t(1, 17) = -1.197$, $P = 0.248$]. 2 × 2 ANOVA with drink (fructose or glucose) and condition (food or nonfood images) on ratings of hunger and desire for food (combined in a single composite) showed significant main effects of drink (Fig. 2) reflecting greater appetite after fructose than glucose [$F(1, 23) = 5.851$, $P = 0.024$] as well as greater appetite after food relative to nonfood images [$F(1, 23) = 12.393$, $P = 0.002$]. Although the interaction of drink and condition was not significant [$F(1, 23) = 2.609$, $P = 0.12$], it was in the direction of greater differentiation of appetite ratings between the food-cue and nonfood-cue conditions after fructose relative to glucose ingestion. Relative to water, both glucose and fructose resulted in decreased hunger and desire for food [$t(1, 17) = -3.198$, $P = 0.005$ for glucose vs. water; $t(1, 17) = -2.203$, $P = 0.042$ for fructose vs. water] in the subset of participants who completed the water session. Exploratory analysis was performed on hunger and desire for food ratings separately (Fig. S1), and similar patterns were observed.

Food Decision Task Results. Fructose relative to glucose ingestion resulted in greater willingness to give up delayed monetary rewards for immediate food [willingness to pay (WTP)-delayed] (mean difference ± SE: 1.45 ± 0.45 dollars, $Z = 2.305$, $P = 0.015$) (Fig. 2). Using a subset of participants who additionally completed a water session, we observed that, relative to water, glucose but not fructose resulted in significantly decreased WTP-delayed ($Z = -2.245$, $P = 0.025$ for glucose vs. water; $Z = -0.346$, $P > 0.05$ for fructose vs. water). Similar results were observed using mixed-effects logistic regression: greater WTP-delayed after fructose ingestion than glucose (mean difference ± SE: 1.23 ± 0.24 dollars, $Z = 2.278$, $P < 0.0227$).

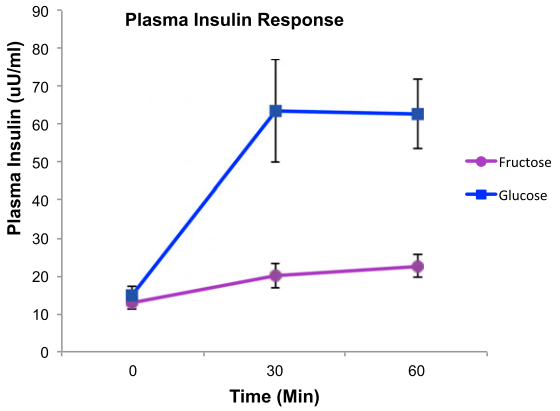

Fig. 1. Plasma insulin response to fructose and glucose ingestion. The *x* axis represents time points when plasma insulin was measured at baseline (0 min) and after the ingestion of the fructose (circles) or glucose (squares) drink, and the *y* axis represents the SE of mean plasma insulin levels in μU/mL. To convert insulin values to pmol/L, multiply by 6.945. Data are based on 24 participants.

Whole-Brain Analysis: Drink x Cue Interaction. When whole-brain contrast maps were directly compared between fructose and glucose sessions, we observed significant drink differences in the visual cortex (Table S2). In particular, the increase in visual cortex activity when food pictures were presented was significantly greater during the fructose relative to glucose session (Fig. 3).

Region-of-Interest Analysis: Food-Cue Reactivity in Brain Reward and Motivation Regions After Fructose vs. Glucose. Region-of-interest (ROI) analysis of sugar effects included signal extracted from food vs. nonfood contrast in eight brain regions that were reported to be responsive to food cues in a prior meta-analysis (9). Repeated-measures ANOVA indicated a significant interaction of drink and region [$F(7, 161) = 2.698$, $P = 0.011$] and a significant main effect of region [$F(7, 161) = 7.113$, $P < 0.001$]. This interaction was driven by significantly greater fructose vs. glucose difference in the left orbital frontal cortex (OFC) [$t(1, 23) = 2.909$, $P = 0.008$] and marginally significant in the left ventral striatum [$t(1, 23) = 2.070$, $P = 0.050$], whereas signal values from several other regions did not suggest a similar sugar differential (Fig. S2).

Discussion

In this study, we measured differential effects of fructose vs. glucose ingestion on hormonal responses, behavioral and neural food-cue reactivity, and decisions between immediate food rewards and delayed monetary rewards in healthy volunteers. We found that ingestion of fructose compared with glucose was associated with greater brain reward responsivity to food cues. Parallel to the neuroimaging findings, we also observed behavioral and hormonal differences such that fructose relative to glucose ingestion led to smaller increases in plasma insulin levels, greater increases in hunger and desire for food, and a greater willingness to pay for food rewards.

Whereas previous studies (8, 10) reported on resting-state differences in brain activity after glucose versus fructose ingestion, here our dependent variables were measured in experimental contexts designed to model situations relevant to eating behavior. Here we examined response to food cues, both subjective hunger and desire for food and cue-related increases in brain activity. We also reported on how much future money participants were willing to give up for actual opportunities to eat visually depicted food (modeling real-world food-consumption decisions). Thus, the data here, which importantly included circulating hormone levels, provide a window on physiological and central nervous system sugar differential effects that are considerably closer to the behavior of ultimate interest—food consumption.

The ingestion of fructose compared with glucose resulted in significantly greater food- vs. nonfood-cue responsiveness in the visual cortex in whole-brain analysis. Although the visual cortex is not believed to be a direct modulator of appetitive responses, visual system processing of stimuli is robustly sensitive to motivational factors. Although rarely emphasized, visual cortex activation is consistently apparent in studies using visual cues to probe craving (11, 12), and visual cortex response to high-calorie foods has been shown to be modulated by positive affect (13). Given top-down influences over visual processing (14) and evidence that higher-value targets recruit greater visual activation (15), it is also reasonable to hypothesize that altered valuation mediates the robust effect that food cues had on activity within the visual cortex. Thus, greater food-cue reactivity in the visual cortex after fructose than glucose may indicate a greater incentive value of food cues.

The ROI analysis suggested a significant region x drink interaction, which was driven by significantly greater left OFC and marginally significant ventral striatum response to food cues after fructose than glucose and a nonsignificant opposite pattern in the middle insula and precuneus. The OFC and ventral striatum play an important role in reward processing, with a meta-analysis

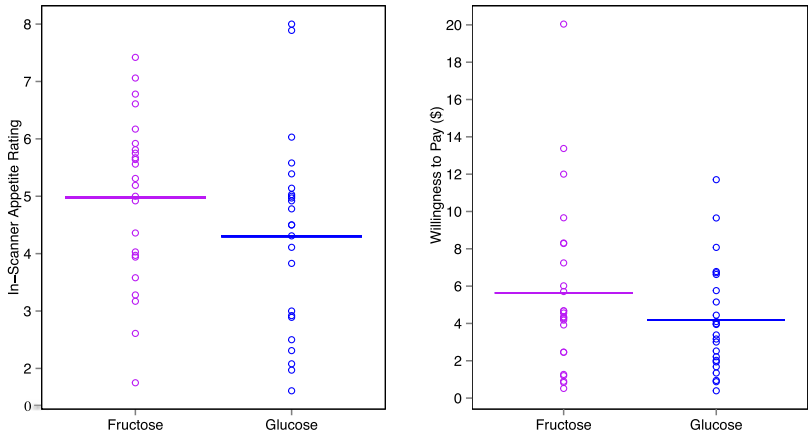

Fig. 2. Fructose vs. glucose effects on appetite rating and willingness to pay. The *x* axis indicates drink type; fructose is labeled in purple and glucose is labeled in blue. (*Left*) The *y* axis indicates the composite in-scanner appetite rating score, with each circle representing each participant's rating across food- and nonfood-cue conditions and the solid line indicating the mean rating score. (*Right*) The *y* axis indicates the willingness-to-pay amount for immediate food rewards from the mixed-effects model (see *Materials and Methods* for details). Each circle represents each participant's modeled average WTP amount, and the solid line indicates the mean WTP amount. Data are based on 24 participants.

showing a positive relationship between MRI signal change in this region and reward magnitude (16–18). Specific to food rewards, prior neuroimaging studies have shown an increase in OFC activity in response to high-calorie food cues compared with nonfood cues (9, 19), and the increased activity was modulated by homeostatic state (19–21). Greater food-cue reactivity in the OFC after ingestion of fructose relative to glucose in the current study suggests greater reward and motivation signaling for food cues, which may be modulated at least in part by a lower sating effect of fructose relative to glucose. Although it is important to note that glucose vs. fructose differences in the middle insula and precuneus were not significant, it may be the case that these regions are important in processing satiety signals, as suggested by Wang et al., who found a positive association between gastric balloon distension volume (a mechanical stimulus for satiety) and insula and precuneus signal change (22).

In addition to probing food-cue reactivity, we examined food-choice behavior, where participants were required to make decisions between immediate high-calorie food rewards and delayed monetary bonuses. The paradigm was a simple laboratory model of the common real-world situation in which the individual conceives a long-term potential reward (e.g., health, mobility, appearance) for avoiding attractive high-calorie foods. Here that long-term reward was made explicit as a 1-mo delayed monetary bonus. We used a titration procedure that allowed us to quantify the long-term reward the individual was willing to give up for each food. This was made incentive-compatible by selecting one trial at random for actual payout (see *Materials and Methods* for details). Fructose relative to glucose was associated with actual eating decisions that reflected greater willingness to trade off long-term rewards. We think the findings are an important contribution to the evidence regarding a possible obesogenic impact of dietary substitution of glucose with fructose.

Consistent with prior studies, we found significantly higher plasma insulin levels after glucose compared with fructose ingestion (8, 23–26), which may help explain differential effects of the two monosaccharides on brain reward and appetitive responses to food cues. Insulin receptors are found in the dopaminergic neurons in the ventral tegmental area (VTA) and striatum, which indicates its potential role in the reward system (27). Administration of insulin to the VTA in rodents is associated with decreased food intake, particularly highly palatable foods (28–30). Similarly, human imaging studies show that intranasal insulin increases satiety and suppresses food intake, potentially through enhancement of brain energy levels (31, 32). Moreover, higher circulating insulin levels were associated with reduced limbic system responses to food cues and decreased food cue-induced appetite (33, 34). However, the relationship between circulating insulin levels and the brain response to food cues is complicated, because insulin resistance (hyperinsulinemia accompanied by decreased insulin signaling) may impair the modulatory role of insulin on brain responsivity. Indeed, a recent imaging study found that insulin resistance was positively correlated with brain responses to food cues in the OFC (35). Thus, insulin resistance may affect the relationship between circulating insulin levels and brain responses to food cues after glucose vs. fructose consumption. Although the current study was not designed to test this, future studies could be directed at examining how insulin resistance affects the differential brain responses to fructose versus glucose ingestion. Higher circulating glucose levels after ingestion of glucose compared with fructose may also modulate brain reward processing. Animal studies have shown that glucose modulates the release of GABA and dopamine within the VTA and substantia nigra (36), and that hyperglycemia suppresses the firing of midbrain dopaminergic neurons (37). Moreover, a neuroimaging study in humans showed that higher circulating glucose levels are predictive of enhanced prefrontal inhibitory control and decreased desire for food (38). The sweeter taste of fructose relative to glucose (39) may be another potential mechanism to help explain the

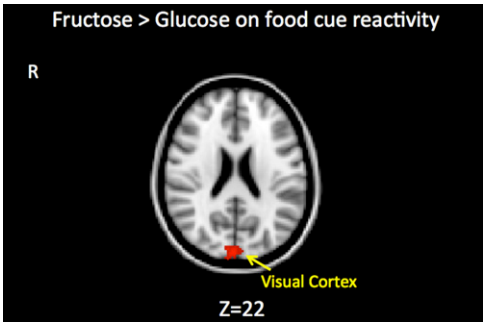

Fig. 3. Fructose vs. glucose effect on brain responsivity to food cues. The visual cortex showed greater responses to food cues after fructose than glucose ingestion. These contrast maps were based on whole-brain analysis of drink (fructose vs. glucose) x cue (food vs. nonfood) in every voxel ($Z > 2.3$, $p < 0.05$ corrected for multiple comparison problems). Data are based on 24 participants.

differential responses of fructose vs. glucose on hedonic feeding centers. Brain imaging studies have shown that sweet taste activates brain pathways involved in reward and motivation (40, 41). It is worth noting that participants rated the pleasantness of fructose to be equivalent to that of glucose. Thus, the observed differences in the neurobehavioral responses to the two sugars are not attributable to differences in subjective measures of pleasantness.

As expected, fructose relative to glucose ingestion resulted in higher circulating levels of fructose and lactate (8, 26). In contrast to glucose, the majority of fructose is metabolized in the liver, and the conversion of fructose into lactate allows fructose-derived carbons to be released from the liver for extrahepatic metabolism (2, 42). Circulating (AUC) levels of leptin, GLP-1, PYY, and ghrelin were similar following ingestion of fructose and glucose. Some studies reported that ingestion of glucose relative to fructose produced higher levels of the anorexigenic hormones GLP-1 (8, 24) and leptin (26) and reduced levels of the orexigenic hormone, ghrelin (26). Differences in the timing of hormone measurements, study populations, and/or study conditions may explain the disparities in these results.

We did not observe significant hypothalamic reactivity to food compared with nonfood cues in the present study. Whereas some prior studies have found a significant MRI signal change in the hypothalamus to food vs. nonfood cues (13, 43–45), others have not (46–48). Inconsistent findings could be due to variations in study design, differences in participant characteristics, and/or variations in image acquisition, which may be important in the hypothalamus, a small region that is affected by signal loss due to magnetic susceptibility artifacts in blood oxygen level-dependent (BOLD) imaging.

It is important to note that we included only young, healthy, nondieting participants within a narrow age range to limit potential confounding effects of dietary changes, age, and medical conditions. We included almost equal numbers of male and female participants, and did not observe sex-specific effects on the neuroimaging, hormone, or behavioral results. We included participants with a large range of body mass index (BMI). Although we observed no significant associations between BMI and neuroimaging or behavioral results, it is important to emphasize that given the small sample size, we were not well-powered for these analyses. Larger studies are necessary to determine potential sex- and BMI-specific effects on neurobehavioral responses to fructose and glucose. Future studies are also needed to determine whether neurobehavioral responses to fructose compared with glucose feeding are influenced by age, diet, and/or specific medical conditions, such as diabetes.

In summary, we found that ingestion of drinks containing 75 g of fructose compared with an equivalent dose of glucose resulted in greater recruitment within brain regions previously linked to food-cue reactivity. Moreover, we observed that ingestion of fructose compared with glucose resulted in a greater appetite and desire for food and greater willingness to give up long-term monetary rewards to obtain immediate high-calorie food rewards. These disparate brain and behavioral responses to fructose relative to glucose may promote appetitive behavior.

Materials and Methods

Participants. Twenty-four volunteers (14 female; 10 male; mean age 21.6 ± 2, range 16–25 y; mean BMI 29.0 ± 7.4, range 19.6–45.4 kg/m^2) with no history of eating disorders, fructose intolerance, diabetes, or other medical illnesses participated in the study. Participants were all right-handed with normal or corrected-to-normal vision, nonsmokers, and not on weight-loss diets or taking medications (with the exception of oral contraceptives). Participants were asked to maintain their typical diet and physical activity levels throughout this study, and female participants were studied during the follicular phase of their menstrual cycle. Participants gave written informed consent to all experimental procedures approved by the Institutional Review Board of the University of Southern California.

Overview of Experimental Protocol. All participants underwent a screening visit during which height and weight were measured and 24-h dietary and physical activity recalls were administered. A 75-g fructose tolerance test was also performed. Only individuals who reported no gastrointestinal discomfort (e.g., bloating, nausea, diarrhea) on a questionnaire administered 1 h after the ingestion of 75 g fructose were included in the study to limit confounding effects of fructose malabsorption. Two participants were excluded on this basis.

MRI sessions were performed in random order on separate days between 2 and 30 d apart with ingestion of either a fructose or glucose drink (75 g in 300 mL water with cherry flavoring) at the Dana & David Dornsife Cognitive Neuroscience Imaging Center at the University of Southern California. A subset of 18 participants (10 female; 8 male; mean age 21.9 ± 2, range 19–25 y; BMI 28.5 ± 6.8, range 21.6–40.0 kg/m^2) also underwent a water (300 mL with cherry flavoring) drink session as a control condition, and scans were randomized across fructose, glucose, and water sessions. The water control session was added to allow us to determine whether fructose vs. glucose differences relate to differential satiation or to increases in appetitive drive. MRI sessions were conducted in the morning after a 12-h overnight fast. Participants were asked to maintain similar dietary intake and physical activity levels during study participation. Participants were weighed on the morning of each study session, and 24-h physical activity and dietary recalls were recorded to limit between-session variability in homeostatic state.

Blood samples were obtained for measurement of plasma glucose, fructose, lactate, insulin, leptin, ghrelin, PYY, and GLP-1 levels at baseline (before drink ingestion) and at 30 and 60 min following drink ingestion. Participants completed visual analog scales (VAS) to rate baseline hunger and motivation for food on a scale from 1 to 10, where 1 was "not at all" and 10 was "very much." They then ingested the study drink (i.e., fructose, glucose, or water) before entering the MRI scanner, where they performed a food-cue task in which 12 visual activation task blocks including food cues and nonfood cues were presented in a randomized block design. Each block consisted of four photographs presented in random order. Each photograph was presented for 4 s with a 1-s waiting time between photographs. No photograph was presented more than once. Stimulus presentation was achieved using MATLAB (The MathWorks) and Psychtoolbox on a Mac laptop. Pictures were selected from various websites and from the International Affective Picture System (49) and were previously matched for visual appeal (38). Food cues consisted of high-calorie, palatable food items such as candy, cookies, pizza, and hamburgers. The control stimuli consisted of nonfood, neutral pictures such as buildings and baskets. At the end of each block, VAS appeared, and participants were given 15 s to rate hunger and desire for food by clicking on a number (1–10, 1 being not at all, 10 being very much) using a computer mouse-like device. All participants finished rating within a 15-s window, and the screen turned blank for the period from the moment participants finished responding to the beginning of the next block. This procedure allowed us to determine the effects of fructose and glucose ingestion on food-cue reactivity (i.e., hunger and desire for food in response to food cues).

Following the food-cue task, participants underwent a decision-making task. In each trial, participants made choices between (*i*) a visually presented high-calorie food reward and (*ii*) a visually presented monetary reward, always delayed by 1 mo. The delay was used to model real-life situations in which the benefits of turning down high-calorie foods come later in time. Participants were also asked to express whether each indicated preference was "strong" or "weak." Ten individualized high-calorie food items were used during the task. These included only food items rated as very attractive by the individual participant during pretesting. The food item presentation was pseudorandom, with each session including six presentations of each of the 10 food items. On a food item's first presentation within a session, the monetary alternative was set to the market price for the item, "discounted" for the 1-mo delay using participant-specific estimated discounting. This discounting estimate was obtained based on a monetary intertemporal choice procedure completed at the baseline session (for details, see ref. 50). On subsequent presentations of the food item, the amount of money offered as its alternative was adjusted according to the following rules: (*i*) it increased after the food alternative was selected and decreased after the money was selected; (*ii*) if the item had been presented in two or more prior trials and if the same alternative (whether food or money) was selected in the previous two or more presentations, then the magnitude of the adjustment of the money alternative was either 25% or 50%, based on whether the preference was indicated to be weak or strong; and (*iii*) if the item had been presented in only one prior trial, or if the choice in the two most recent presentations of the item included one selection of food and one of money, then the magnitude of the adjustment was either 10% or 20%, based on whether the preference was indicated to be weak or strong. At the end of each fMRI session, bonus earnings were determined by randomly drawing a trial from the food-decision task. If the food reward was selected, participants were provided the selected food item to eat immediately after the scan as a bonus reward. Alternatively, if

the delayed monetary reward was selected, participants received a Visa gift card in that amount 1 mo after the study session. To control for the extra time involved in eating food, the reimbursement session had a fixed duration of 30 min for all participants. During this time, participants either consumed the selected food item or were required to sit in and wait (in the case where a money reward was drawn) until the end of the session. Participants were instructed that they were not allowed to take the bonus food reward home.

Metabolite and Hormonal Analysis. Plasma glucose and lactate were measured enzymatically using glucose oxidase and lactate oxidase, respectively (Yellow Springs Instruments). Fructose was measured with a quantitative colorimetric assay (Abnova). Insulin, GLP-1 (active), PYY (total), and leptin and ghrelin (active) were measured using Luminex multiplex technology (Millipore). AUC was calculated for metabolites and hormones using the trapezoid method (51). Plasma metabolite and hormone levels were analyzed using repeated-measures ANOVA with drink type (fructose or glucose) and time (0, 30, 60 min) as within-subject factors. Linear contrasts were used to compare glucose and fructose conditions at each individual time point, and paired *t* tests were performed to compare differences in mean AUC. *P* values were adjusted for multiple comparisons using the Bonferroni correction. A value of $P < 0.05$ was considered significant.

In-Scanner Behavioral Ratings Analysis. Baseline (predrink) appetite ratings were compared using paired *t* tests. For the primary analysis, we computed a composite appetite score by averaging ratings across questions (hunger, desire for food) to determine the effects of each drink on appetitive responses to food and nonfood cues. Repeated-measures 2×2 ANOVA with drink (fructose or glucose) and condition (food or nonfood images) was performed on the composite score. Exploratory analysis was done on each appetite question separately and is reported in *Supporting Information*.

Decision-Making Task Analysis. Willingness to pay for each food item and each session was based on observed "cross-over" points for each item during titration. Cross-over points were cases where either (*i*) an increase in the monetary alternative to a particular food resulted in a switch to preference for the money or (*ii*) a decrease in the monetary alternative to a particular food resulted in a switch to preference for the food item. The average of the amount offered in the two trials comprising the cross-over was computed as a WTP estimate. When multiple cross-over points were present for the same food item during the same session, these points were averaged to obtain the item's overall WTP for that session. Items in which no cross-over point was obtained during a session were excluded. We analyzed data with mixed-effects models using the R lmer function of the lme4 library (cran.r-project.org/web/packages/lme4/). A base model included drink as both a fixed-effects predictor and random slope nested within a random intercept participant term that captures consistent individual differences in WTP. Alternatively, we performed a mixed-effects logistic regression to calculate cross-over points (or WTP-delayed) using the R glmer function. In the logistic regression model, choice was the dependent variable, drink was included as both a fixed-effects predictor and random slope nested within a random intercept participant term, and the amount of delayed monetary reward was included as a fixed-effects predictor.

Subjective Rating on Pleasantness of Drink. At the end of each session, participants were asked to rate the pleasantness of the drink on a scale from 1 to 10, 1 being not pleasant at all and 10 being very pleasant. The effects of fructose compared with glucose on subjective ratings of pleasantness were also compared in a subset of 18 participants using paired *t* tests.

MRI Parameters. MRI data were collected using a 3T Siemens MAGNETOM Tim/Trio scanner with a standard birdcage head coil. Participants laid supine on a scanner bed, viewing stimuli through a mirror mounted on the head coil. For each session, 278 functional T2*-weighted echo planar imaging (EPI) volumes of data were acquired with following parameters: repetition time (TR), 2 s; echo time (TE), 30 ms; flip angle, 90°; field of view, 192; in-plane resolution, 64×64; voxel dimensions, $2 \times 2 \times 2$ mm. A total of 32 axial slices was used to cover the whole brain with no gap. The slices were tilted 30° along the anterior commissure–posterior commissure plane to gain better signal in the orbital frontal cortex. Additionally, during the same session, a high-resolution anatomical image (matrix size: $256 \times 256 \times 176$) with $1 \times 1 \times 1$ mm^3 resolution was obtained using a T1-weighted 3D magnetization prepared rapid gradient echo (MP-RAGE) sequence (inversion time, 900 ms; TR, 1,950 ms; TE, 2.26 ms; flip angle, 90°).

fMRI Analysis. All fMRI data were processed using fMRI Expert Analysis Tool version 6.00, part of the Oxford University Centre for Functional MRI of the Brain Software Library (www.fmrib.ox.ac.uk/fsl). A total of four functional volumes (four TRs) was discarded to account for magnetic saturation effects. Translational movement parameters never exceeded one voxel in any direction for any participant. The fMRI data were motion-corrected, high pass-filtered (100 s), and spatially smoothed with a Gaussian kernel of full-width at half-maximum of 5 mm. The functional volumes were realigned to each participant's respective T1-weighted anatomical image and then normalized into standard space (Montreal Neurological Institute; MNI) using affine transformation with FLIRT (52) to the avg152 T1 MNI template.

The general linear model (GLM) was used to determine the contributions of each block type to the fMRI BOLD signal. Food and nonfood events were added to the model after convolution with a canonical hemodynamic response function: food stimuli and nonfood stimuli. An additional explainable variable was also added to the model for the 15-s VAS rating period. Temporal derivatives and temporal filtering were added to increase statistical sensitivity. For each subject and for each session, the following contrasts were made: food cues vs. nonfood cues.

First, we performed a whole-brain analysis exploring the interaction of drink x cue in every voxel. This analysis was thresholded using cluster detection statistics with a height threshold of $Z > 2.3$ and a cluster probability of $P < 0.05$ corrected for multiple comparisons (corresponding to voxelwise $P < 0.02$).

In addition, we performed a region-of-interest analysis to determine the differentiation between fructose and glucose ingestion on food-cue reactivity within brain regions, which showed stronger responses to food cues than nonfood cues in a meta-analysis report (9). A total of 11 regions was reported in the meta-analysis paper, of which three regions (fusiform gyrus, occipital lobe, and lingual gyrus) were outside the current study's slice position coverage. Thus, eight ROIs (left OFC, left ventral striatum, left amygdala, left hippocampus, bilateral anterior insula, bilateral middle insula, bilateral precuneus, and left postcentral gyrus) were defined by drawing a 4-mm-radius sphere around the peak voxel (see detailed information in Table S3). For the ventral striatum, a 2-mm-radius sphere was drawn because of its smaller size. Individual percentage signal change was extracted from each ROI for food vs. nonfood contrast, for each drink and each subject. It is important to keep in mind that the ROIs are based on meta-analysis of food-cue reactivity studies, and thus it is likely that the signal differential (food vs. nonfood) represents a difference between activations rather than deactivations, although these data do not directly distinguish these possibilities. Repeated measures of 2×8 ANOVA with drink (fructose or glucose) and region (eight ROIs) as within-subject factors was performed, and paired *t* tests were also conducted to examine the drink effect on each individual ROI.

Correlation Analysis. We used Spearman's correlation analyses to compare (*i*) differential effects of fructose vs. glucose (in subjective ratings, decisions, and brain food-cue reactivity) with (*ii*) demographics (age, education, BMI, waist, hip, waist/hip ratio). Given the sample size, these comparisons are underpowered for detection of moderate effects, and so these analyses are presented only for descriptive purposes (Table S4).

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