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Sweet Cognition: The Differential Effects of Glucose Consumption on Attentional Food Bias in Individuals of Lean and Obese Status

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Abstract

In general, glucose consumption improves cognitive performance; however, it is unknown whether glucose specifically enhances attentional food bias, and how this process may vary by BMI status. We hypothesized that glucose consumption would increase attentional food bias among individuals of obese BMI status more so than among individuals of lean BMI status. Participants (N=35) completed the n-back, a working memory task modified to assess attentional food bias (ATT-Food), under fasting and glucose challenge conditions. We computed pre-post changes in ATT-Food, blood glucose and insulin (ΔBG & ΔBI), and perceived task-stress (Δstress). After the second cognitive test and blood draw, participants ate lunch and completed a "taste test" of highly palatable foods, and we recorded food consumption. Pre-post changes in ATT-Food were greater among participants of obese (relative to lean) BMI status (F(1,33)=5.108, p=.031). Greater ΔATT-Food was significantly associated with greater ΔBG (r=.462, p=.007) and reduced Δstress (r=−.422, p=.011), and marginally associated with greater taste-test eating (r=.325, p=.057), but was not associated with ΔBI. Our findings suggest that individuals of obese BMI status may exhibit "sweet cognition," as indexed by greater attentional food bias following glucose ingestion. Among individuals of obese BMI status, sweet cognition may arise from difficulty broadening attention toward non-food cues after consuming a high glucose load, thereby potentially perpetuating sugar consumption. If confirmed by further research, measures of sweet cognition may help identify

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individuals with a phenotype of risk for obesity and greater sugar consumption, who may benefit from tailored interventions.

Keywords

Food Cues; Obesity; Cognitive Performance; Eating Behavior; Oral Glucose Tolerance Task

Introduction

Most people who lose weight will go on to regain much of what they lose[1]. Although many different diets can work when people adhere to them[2], the modern food environment, replete with cues to overeat, makes dietary adherence particularly challenging. Thus, it is not surprising that food cravings and an inability to control one's eating in the presence of highly processed foods, which are often high in sugar and fat, are commonly cited reasons for dietary non-adherence[3–5]. Relative to individuals of lean BMI status, individuals of overweight and obese BMI status report more intense cravings for highly processed food and more difficulty with controlling one's eating of these foods[6–8]. Though self-regulation is central to successful weight loss[9], most major diet interventions do not specifically target control-related cognitive processes and behaviors, but rather focus on diet and exercise. Clarifying the cognitive drivers of food self-regulation and non-homeostatic eating will help identify at risk individuals and optimize outcomes through targeted interventions[10].

Excessive attention to food-related cues in the environment (attentional biases toward food) may underpin food cravings and non-homeostatic eating. Studies of attention to food-related cues have reported increased risk for craving-related eating[11], and weight gain prevention attention-training interventions have begun to show short-term impacts on eating behavior[12–14]. We propose that one of the modifiable intervention targets that may impact attention to food-related cues in the environment is consumption of sugar, in particular, glucose. The brain relies on glucose as a primary fuel source[15], which may explain why people often crave sugar-laden foods[5,16,17]. Indeed, tasks that impose cognitive load deplete peripheral blood glucose[18], whereas ingestion of glucose enhances cognitive performance, particularly on tasks of verbal episodic memory[18–20]. These observations – that cognitive effort uses glucose, and that glucose facilitates cognitive performance – may reflect an underlying feedback loop seeking to achieve balance. In obesity, this balance may become disturbed as a result of exerting cognitive effort, overeating to compensate for glucose expended, and decrements in glucoregulatory control. However, it is unclear whether individuals with obesity (potentially due to underlying decrements in insulin sensitivity) exhibit more or less glucose facilitation relative to their lean counterparts.

Many studies report that executive function performance is reduced overall among individuals of overweight and obese BMI status relative to those of lean BMI status[21]. For example, on average, relative to individuals of lean BMI status (<25), individuals of obese BMI status (>30) show deficits on correct identifications in a one-back visual working memory task[22]. Similarly, on average, individuals of lean BMI status perform better on measures of attention, such as digit span and choice reaction time, as well as better on

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measures of executive function, such as verbal interference and maze errors[23]. However, neuroscientific evidence has shown that individuals of obese and lean status can differ in functional connectivity across visual and salience networks associated with responses to food cues and heightened attention[24]. Consistent with this, people with greater levels of impulsivity and of obese BMI status can detect high-calorie foods more quickly than people of normal BMI status[25]. From an evolutionary perspective, upon finding calorie-dense food in the wild, it would be adaptive to optimally encode the food source by directing more attentional and working memory resources toward that endeavor. Hence, glucose consumption may trigger this relative cognitive enhancement, manifesting as attentional biases to food-related cues, relative to non-food cues. Thus, sugar-laden foods may have the potential to enhance relative attentional bias toward food cues, which may be more pronounced for individuals of obese BMI status.

Evidence suggests that the hypothalamic set-point, which helps establish energy balance[26], is altered among individuals with obesity, and that these alterations may impact homeostatic regulatory processes following caloric intake. Chronic overnutrition can induce hypothalamic neuroinflammation, potentially disrupting normal regulation of weight and glucose homeostasis[27]. We might expect that lean individuals with healthy homeostatic regulation would attend more to food cues than other cues (attentional food biases) only when physiologically hungry. However, once lean individuals consume glucose and their brains detect a corresponding increase in blood glucose, it would theoretically become adaptive for these individuals to shift their focus back toward non-food cues that are important for survival. To enable these shifts in focus, executive function brain networks operate flexibly on salience networks, thereby directing attention toward or away from stimuli such as hunger, food rewards, and emotional threats so that an individual can decide how to act[28]. Whereas lean individuals may exhibit more cognitive flexibility such that food cues hold salience only under appropriate conditions (e.g., hunger or a fasted state), individuals with obesity may continue to seek glucose regardless of their state. In so doing, they may fail to employ the executive control needed to shift their attention toward non-food cues, thereby promoting over-eating. Per this model of attentional food bias, we would expect to see increased attention to non-food cues after consuming glucose among individuals of lean, but not obese, BMI status. In sum, both the glucose-facilitation and the homeostatic models predict that individuals of obese BMI status will exhibit a greater attentional food bias than lean individuals after consuming glucose. However, each model predicts different drivers among individuals of lean versus obese BMI status, in terms of whether bias arises due to: 1) glucose facilitation of attention to *food cues*, or 2) the absence of flexible salience-shifting to *non-food cues* when blood glucose is high (compared to fasted, lower blood glucose states).

The operant conditioning model[29] can shed light on the means by which the effects of glucose consumption on cognitive processes and affect drive habitual consumption of sugar-laden foods. Individuals may seek out a sugar-laden food or drink because sugar can provide strong neuropsychological reinforcement (reward). Specifically, sugar-induced enhancements in cognitive performance may be experienced as positive reinforcement (the addition of rewarding stimuli), and sugar-related relief from a stressor or negative emotion may provide negative reinforcement (removal of noxious stimuli)[30]. The extent to which the

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reinforcer successfully improves cognitive performance or affect should in theory increase the probability that an individual will repeat the behavior (i.e., sugar consumption). For example, if we drink a sugar-laden beverage (e.g., chocolate Frappuccino) at 2:30 PM while working with a stressful deadline at work, and find ourselves getting more work done or notice ourselves feeling relief from work stress, we are more likely to form a memory of the connection between the circumstance under which we drank the beverage and its associated benefits. Through this repeated behavior, we may strengthen the "bad habit" of consuming sugar during stress.

The Present Study

The enhancing effect of sugar (herein specifically glucose) consumption on attention in general, and on attention to food cues, might be thought of as "sweet cognition." This study sought to test the utility of a novel cognitive measure of sweet cognition based on the n-back task, which can assess selective attentional processes. In this study, we employed specific cues (food- and non-food-cues) and an experimental paradigm involving glucose consumption. This measure assesses the impact of sugar consumption on attentional biases toward food cues, with the aim of better identifying individuals at risk for sugar-consumption habits. To unpack associations between sugar consumption and attentional food bias (i.e., glucose enhancement of attention to food-related cues), we tested the hypothesis that individuals of obese BMI status and individuals of lean BMI status would differ in terms of their attentional focus following sugar consumption. Specifically, we hypothesized that such sugar consumption would increase attentional food bias ("sweet cognition") among individuals of obese BMI status more so than among individuals of lean BMI status. We administered cognitive tasks to individuals of lean and obese BMI status (and without diabetes) twice: once before and once 60 minutes after they consumed a sugar drink (75 g glucose beverage, specifically, Glutol).

Second, we tested whether sweet cognition (operationalized as increased attentional bias for food-related cues after glucose consumption) correlates with other behavioral, psychological, and biological measures, which together may characterize a reward-driven phenotype of obesity[31]. To do this, we administered self-report measures of eating behavior, specifically food cravings and reward-based drive to eat; administered an unobtrusive non-homeostatic eating task; and collected blood samples to test for insulin and glucose levels at each pre- and post-Glutol consumption. We hypothesized that greater sweet cognition would be associated with: 1) greater food cravings and reward-based drive to eat, 2) greater non-homeostatic eating of highly processed foods during the eating task, and 3) greater increases in blood glucose (BG) from pre- to post-Glutol consumption.

Methods

Participants and Recruitment

Participants were recruited from a multi-ethnic cohort of both individuals of lean and obese BMI status at UCSF (Inflammation Diabetes Ethnicity and Obesity; IDEO; NCT03022682) through paper and email invitations to participate. We did not invite participants of the multiethnic cohort to participate if they had a diagnosis of Type 1 or Type 2 Diabetes. We

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invited participants only if they were able to read and speak English, but participants were permitted to complete the self-report measures and cognitive tasks in Spanish if they felt more comfortable doing so (two individuals did, and we included task language as a statistical covariate). Of 37 initially recruited, a total of 35 individuals provided sufficient non-exclusionary data for inclusion in this study (18 categorized as obese per BMI>30, 17 categorized as lean per BMI<25). We excluded one participant with obesity from all analyses because his/her fasting glucose level was 162 mg/dL, which was consistent with a possible diagnosis of diabetes. All participants provided written consent.

Procedure

All study procedures were approved by the UCSF Institutional Review Board (IRB). On the morning of their participation, participants presented to the clinical research facility in a fasted state. After consenting procedures, participants completed the computerized cognitive task (n-back, described below), followed by a blood draw. Participants then completed an oral glucose tolerance test (OGTT) wherein they drank a glucose solution (Glutol; 75 g glucose) within 5 minutes, and waited in a seated position in a dedicated study room for one hour[32] before completing a second blood draw. During this hour, participants completed questionnaires (~15 minutes) and then could read magazines, books, or other leisure materials, which they had been instructed to bring. Participants then repeated the computerized cognitive task before receiving a standard lunch (white bagel, peanut butter or cream cheese, banana). Participants were instructed to eat lunch to satiety. After lunch, participants completed a taste test that involved tasting jelly beans and chips, of which they were presented 340 grams and 180 grams, respectively, in identical bowls. We informed participants that they would have 10 minutes during which they should taste each food and rate them in terms of sweetness, saltiness, and likeability, on paper forms according to a visual analogue scale (range: −100 to 100). They were told that after rating them, they could enjoy as much of these foods as they wished. Participants were alone during the taste test, and the experimenter knocked on the door to indicate that the time period had expired before waiting for 15 seconds before entering the room. After participants departed, we weighed the foods to compute amounts eaten. We compensated participants in cash ($75) for their time.

Measures

Attentional food bias (ATT-Food).—We used the n-back computerized cognitive task[33] to assess selective attention to food versus non-food cues (here, a 2-back task). In this paradigm, cues were either words for highly processed foods (e.g., high-fat and high-sugar foods, such as “milkshake” and “pie”) or non-food words (e.g., “medallion”, “website”). See Appendix A for all cues (Inquisit script available upon request). Participants clicked a computer mouse to indicate whether the most recent cue was presented n trials (here, 2 trials) earlier or not. Food and non-food cues were matched for length (number of letters) and first letter. Trial duration was set at 2500 ms, and cues were exposed for 2200 ms. If the participant failed to respond within these 2200 ms, the screen turned empty for 300 ms before exposing the next cue. If the participant responded within 2200 ms, the screen immediately turned empty for the remainder of the trial (the empty screen facilitates fixation, allowing the viewer to classify the cue). Figure 1 depicts the general procedure,

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where, on the left, “flan” represents a target food stimulus, and on the right, “paper” represents a target non-food stimulus. Other cues (e.g., “flower”, “float”) had not been shown in at least four consecutive trials to prevent any effects of familiarity. We derived a variable for attentional food bias (ATT-Food) by calculating the difference between the number of correct identifications (“Hits” or true positives) of food cues minus correct identifications of non-food cues. We computed this variable at each of two administrations (pre- and post-Glutol consumption).

Sweet cognition (ΔATT-Food).—We computed glucose facilitation of attentional food bias as the post-glucose ATT-Food score minus the pre-glucose ATT-Food score. Greater sweet cognition reflects a glucose-induced increase in the selective attention to food (relative to non-food) cues.

BMI status.—Participants were categorized as being of lean or obese status per standard BMI scaling: BMI≤25 (lean), BMI≥30 (obese for White American participants) or BMI≥27 (obese for Chinese-American participants)[34,35].

Blood glucose (BG) and blood insulin (BI).—We assayed each participant’s blood samples for glucose and insulin (LabCorp) both in a fasted state and 60 minutes after drinking a glucose beverage (Glutol; 75 g glucose). Although fasting BG values were not part of the inclusion criteria, we confirmed that only one participant had a fasting glucose level above 100 and in the prediabetes range (=110)[36].

Glycemic control (ΔBG, ΔBI).—We indexed glycemic control as pre- to post changes in BG and BI following an oral glucose tolerance test (OGTT), which involves the consumption of Glutol, a liquid beverage containing 75 g glucose. The OGTT indexes the extent to which an individual can efficiently maintain glucose levels in the normal range[37].

Laboratory measures of non-homeostatic eating (jelly bean and chip consumption).—We presented participants with 60 grams of jelly beans, a sweet food with a high glycemic index (GI=80)[38], and 180 grams of salted potato chips, a savory food with a lower glycemic index (chips; GI=54)[39]. Glycemic index values above 70 are considered high, while those below 55 are considered low[40]. We asked participants to taste the jelly beans and chips during a 10-minute period and rate them in terms of sweetness, saltiness, and likeability. After the participant departed, we weighed the jelly beans and chips to calculate total consumption.

Food Craving Questionnaire-Trait-Reduced (FCQ-T-R)[41].—The 15-item FCQ-T-R assesses (1) preoccupation with food, or obsessive thoughts about food and eating, (2) loss of control over eating, or difficulty regulating eating behavior when exposed to food cues, (3) positive outcome expectancy, or believing that eating is positively reinforcing, and (4) emotional craving, or the tendency to crave food when experiencing high levels of emotion. Higher FCQ-T-R scores have been associated with more frequent thinking and eating of high calorie snacks[42] and weight gain over time via increases in disinhibited eating[43]. A cut-off score of 50 or greater discriminates between individuals with and without “food addiction” with high sensitivity (85%) and specificity (93%)[44]. Items are answered on a 6-point scale

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from 1 (never) to 6 (always). The total score was computed as the sum of all items, with higher sores indicating greater trait food craving. Internal consistency in this sample was high (α = .96).

Reward-based Eating Drive (RED-9)[45].—The 9-item RED assesses reward-driven eating. Sample items include, "When I start eating, I just can't seem to stop" (lack of control), "I don't get full easily" (lack of satiety), and "Food is always on my mind" (preoccupation with food). Participants answered items on a scale from 1 (strongly disagree) to 5 (strongly agree). Greater RED scores have been associated with greater weight and weight gain over time[45], whereas reductions in RED scores have been prospectively associated with weight loss[46]. The total score was computed as the sum of all items, with higher scores reflecting higher reward-based eating drive. Internal consistency in this sample was good (α = .86).

Acute task-related mental stress (Δstress).—We asked participants to respond to the prompt, "The task was very stressful," on a scale from 1 (*strongly disagree*) to 7 (*strongly agree*). Participants responded to this item after each time they completed the computerized cognitive task (n-back), once fasted, and once 60 minutes post-Glutol ingestion (but before eating lunch and completing the taste test). To compute the reduction in task stress pre-to-post Glutol (Δstress), we computed change in post-task stress levels from the first to the second administration of the tasks as the second administration post-task stress score minus the first administration post-task stress score, where lower change scores indicate greater reductions in task stress.

Covariates.—We collected demographic information including age, education, race/ethnicity, and handedness. We collected potential confounds related to the cognitive task including n-back language (coded as English=1, Spanish=0) and administration variability, specifically, the interruption of the post-OGTT cognitive task administration due to a fire drill (one occasion), and receipt of three blocks of the task instead of two due to a scripting error (three occasions). We coded these variables as 0 (standard) and 1 (non-standard).

Data Analysis

Data preparation.—We examined distributions of variables and transformed when necessary to meet statistical assumptions of normality. Specifically, we log-transformed and standardized jelly bean and chips consumption to improve normality of the distribution and mean imputed one missing data-point. We used repeated measures to confirm that, as designed, BG significantly increased from pre-to-post Glutol consumption. We were unable to assess BG and BI at 60-min following Glutol consumption in one individual due to needle stick complications; hence, BG and BI analyses use an n=34. We winsorized to 2 standard deviations (95% CI) of ΔBG for one individual and of ΔBI of another, which were statistical outliers and could potentially have biased the regression results. However, the pattern of significance did not ultimately change when using the original or winsorized ΔBG and ΔBI values.

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Covariate selection.—We included a limited number of covariates in adjusted analyses due to small sample size. The covariates selected were those that differed across BMI status groups (handedness, see Table 1), as well as age, which prior literature suggests may influence the degree of glucose facilitation[47], and factors that could potentially introduce variability into the cognitive task protocol.

Group comparisons.—We conducted group comparisons (individuals with obesity versus individuals of lean status) on potential covariates as ANOVA or Chi-Square tests for continuous versus categorical variables, respectively. We used similar repeated measures tests to investigate differences in 60-minute increases in blood glucose and insulin levels across individuals of lean versus obese status.

Speed-Accuracy Trade-Offs.—We considered that a definition of sweet cognition based solely on correct identifications could conceivably yield misleading results if there were substantial speed-accuracy trade-offs present[48]; however, prior evidence suggests that accuracy and speed may diverge in the 2-back, diminishing trade-offs[49]. To assess for speed-accuracy tradeoffs, we calculated the correlation between ΔATT-Food (sweet cognition) and the corresponding reaction time (RT) index for targets.

Hypothesis 1.—To test the hypothesis that glucose ingestion facilitates attentional food biases (“sweet cognition”), differentially among individuals of obese vs. lean BMI status, we used repeated measures ANOVA. We entered the n-back scores for ATT-Food at pre- and post-Glutol ingestion as outcomes to create a within-subjects “Time” effect, BMI status as a between-subjects main effect, and the Time*BMI status interaction term.

Hypothesis 2.—We tested the associations between sweet cognition and biological, behavioral, and psychological factors associated with weight gain over time[50–52] using Pearson correlations. For significant effects, we also report partial correlations adjusting for the covariates listed above (entered singly due to the small sample size and number of covariates).

Hypothesis 2a.: Biological mechanisms: To test indices of glycemic control (ΔBG and ΔBI) as metabolic drivers of ΔATT-Food (sweet cognition) and non-homeostatic eating of highly processed foods, we assessed Pearson correlations between measures of glycemic control (ΔBG and ΔBI), and each ΔATT-Food and non-homeostatic eating (consumption of jelly beans and chips). To determine whether the associations between glycemic control (ΔBG and ΔBI), ΔATT-Food, and consumption of highly processed foods are independent of BMI status, we assessed separate regression models in which we enter both ΔBG and BMI status as simultaneous predictors of ΔATT-Food and each type of highly processed food.

Hypothesis 2b.: Non-homeostatic eating: To test the hypothesis that attentional food bias reflects the neurocognitive basis for real-word non-homeostatic eating of highly processed foods, we examined Pearson correlations between ΔATT-Food and consumption of jelly beans and chips during the taste test. We also report correlations between static assessments of attentional food bias (pre- and post-Glutol ATT-Food) and non-homeostatic eating.

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Hypothesis 2c.: Psychological factors: To explore whether ΔATT-Food is associated with self-reported dimensions of food reward, we tested the following hypotheses: (1) greater sweet cognition (ΔATT-Food) will be associated with higher self-reported reward-related eating drive (RED-9) and food cravings (FCQ-T-R); (2) greater ΔATT-Food will be concurrently associated with greater reductions in acute task-related mental stress (ΔStress).

Results

Group Comparisons

Differences between participants by BMI status appear in Table 1. Participants of obese status did not have higher fasting glucose (FG) than participants of lean status (p=.418). However, as expected, relative to participants of lean status, participants of obese status evidenced significantly greater 60-min ΔBG (p=.007) and ΔBI (p=.007). Participants did not differ by age, gender, race/ethnicity, or educational attainment across BMI status. Participants of obese status were significantly more likely to be left-handed (n=5, 28%) than were participants of lean status (n=0, 0%), p=.045; hence, we included handedness as a covariate in adjusted models. Relative to participants of lean status, participants of obese status reported a significantly higher reward-based drive to eat (RED-9; p=.017), but did not differ in self-reported food cravings (FCQ-T-R; p=.281). Relative to participants of lean status, participants of obese status also ate significantly more jelly beans (p=.029), but not chips, during the post-lunch taste test.

Glutol ingestion and blood glucose control.—As expected, ingestion of Glutol (75 g glucose) resulted in a significant 60-min ΔBG and ΔBI among all participants (ΔBG: $F(1,32)=40.777$, $p<.001$; ΔBI: $F(1,32)=47.556$, $p<.001$; Table 1). These increases were significantly greater among participants of obese status relative to those of lean status (Time*BMI Status effect; ΔBG: $F(1,32)=8.163$, p=.007; ΔBI: $F(1,32)=11.805$, p=.002), indicating that participants of obese status had significantly poorer glycemic control relative to participants of lean status (no participants had diabetes). The Time*BMI Status effects for ΔBG and ΔBI remained significant after adjusting for covariates.

Speed-Accuracy Trade-Offs

We did not find a significant correlation between the ΔATT-Food (sweet cognition) and the corresponding RT metric (r=−.064, p=.733). To minimize tests conducted, and because correct identifications exhibited better distributions, we did not include further analyses of RT.

Hypothesis Testing

Hypothesis 1: Glucose facilitation of attentional food bias.—As hypothesized, glucose ingestion differentially impacted ΔATT-Food among participants of obese versus lean status ($F(1,33)=5.108$, p=.031; Time*BMI status interaction). ΔATT-Food decreased among participants of lean BMI status, but increased among participants of obese BMI status. The interaction effect remained significant after adjusting for age or task language (all p's<.035), and was marginally significant after adjusting for handedness or administration variability (all p's<.082). To better understand whether what drove this effect,

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we split the sample by BMI status and examined food and non-food cues separately in follow-up repeated measures tests of the main effect of Time, which were uncorrected due to the small sample size. Figure 2 demonstrates that individuals of lean BMI status exhibit significant glucose facilitation (or an increase in correct identifications) of non-food cues ($F(1,16)=5.108$, $p=.037$), with no significant change in food cues ($p=.532$), whereas individuals of obese status show no significant Time effects for either food or non-food cues (all p's$>.30$).

Hypothesis 2a: Biological mechanisms

Glycemic control and sweet cognition.: As shown in Table 2 (Figure 3, Panel A), we found that greater ΔBG was associated with greater ΔATT-Food (sweet cognition; $r=.433$, $p=.012$), which remained significant in partial correlations adjusting for each covariate. In contrast, we did not observe a significant association between ΔATT-Food and ΔBI. Figure 3 also demonstrates how ΔBG tracked with changes in correct identifications for food cues (Figure 3B) and non-food cues (Figure 3C) separately. Just as Figure 2 finds the effects are driven by non-food items, Figure 3 shows a significant association of ΔBG with the change in non-food correct identifications. Given that direction of the associations between glucoregulation (ΔBG) and correct identifications of food cues and non-food cues differ, we focused subsequent tests on attentional food bias, or sweet cognition, as opposed to overall performance (i.e., the combination of food and non-food cues).

Hypothesis 2b: Non-homeostatic eating.—As shown in Table 3, we observed a marginally significant association between jelly beans consumption and ΔATT-Food ($r=.325$, $p=.057$; Figure 4, Panel A), which remained marginal ($p<.10$) in partial correlations adjusting for each covariate, and also after adjusting for jelly bean liking. Also of note, jelly beans consumption and post-Glutol ATT-Food were significantly positively correlated ($r=.341$, $p=.045$) whereas baseline ATT-Food was not associated with jelly bean consumption. We did not observe significant associations between any ATT-Food variable and chip consumption.

Glycemic control and non-homeostatic eating.: As shown in Table 2, greater jelly bean consumption was significantly correlated with greater increases in BG (ΔBG: $r=.462$, $p=.007$; Figure 4, Panel B) and not correlated with BI (ΔBI: $r=.290$, $p=.101$)[1]. This pattern of significance did not differ in partial correlations accounting for age. After accounting for jelly bean liking, the associations between jelly bean consumption and BG became stronger (ΔBG: $r=.448$, $p=.009$), whereas the association between jelly bean consumption and BI became non-significant (ΔBI: $r=.265$, $p=.136$). Of note, since these analyses did not involve n-back performance, we did not covary for task-specific covariates (e.g., task-language, administration variability). We did not observe significant associations between either glycemic control variable (ΔBI and ΔBG) and chip consumption (*all* p's$>.75$).

Role of BMI status.: We first established that ΔBG and BMI (lean versus obese BMI status) were significantly and moderately correlated ($r=.451$, $p=.007$). Next, regression analyses that

[1]When the non-winsorized ΔBG and ΔBI factors were analyzed instead, ΔBG remained significant and ΔBI was marginal.

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inputted both ΔBG and BMI status as simultaneous predictors of 1) ΔATT-Food or 2) jelly bean consumption as outcomes revealed that ΔBG marginally predicted ΔATT-Food (*ß*=.325, *t*(31)=1.825, *p*=.078), whereas BMI status did not (*ß*=.221, *t*(31)=1.240, *p*=.224). Furthermore, ΔBG significantly predicted jelly bean consumption (*ß*=.359, *t*(31)=2.045, *p*=.049), whereas BMI status did not (*ß*=.210, *t*(31)=1.197, *p*=.240).

Hypothesis 2c: Psychological factors

Acute task-related mental stress.: Consistent with our hypothesis, greater sweet cognition was associated with larger decreases in acute task-related mental stress, as indicated by the significant negative correlation between ΔATT-Food and Δstress (*r*=−.422, *p*=.011; Figure 4, Panel C). This association remained significant after adjusting for covariates. We also confirmed that acute task-related mental stress decreased significantly from pre to post-Glutol ingestion (*F*(1,32)=8.858, *p*=.005), and these decreases did not differ across BMI status groups (*p*=.439); however, due to the research design, we cannot determine what changes might have occurred in the absence of glucose (Glutol) ingestion.

Psychological Factors: Food craving and reward-related eating.: Greater ΔATT-Food (sweet cognition) was marginally associated with greater reward-related eating (RED-9; *r*=.320, *p*=.061; Table 3; Figure 4, Panel D), but was not associated with food cravings (FCQ-T-R; *r*=.258, *p*=.134). This pattern was unchanged when adjusting for covariates.

Discussion

Just as the terms “hot” and “cold” cognition communicate that our thinking is influenced by emotion, we use the term “sweet cognition” to communicate how reward processes can be influenced by the ingestion of sugar. This study provides a novel method to assess “sweet cognition,” which we define herein as the effect of consuming glucose on attentional food bias (i.e., greater attention to food than non-food cues). Individuals of obese BMI status exhibit greater sweet cognition relative to individuals of lean BMI status. Furthermore, these data provide supporting evidence that glucose-induced cognitive changes may strengthen the reinforcement value of sweet foods and contribute to non-homeostatic sweet eating. Specifically, individuals with greater sweet cognition tend to eat more sugary snack foods (jelly beans), experience greater decreases in task-related mental stress, and report marginally greater reward-related eating (one’s self-reported ability to control one’s eating-related behavior and thoughts around delicious foods). Measures of sweet cognition may help to identify individuals with a phenotype of higher risk for obesity, and thereby inform intervention development.

These data suggest that glycemic control, rather than obesity per se, may drive these cognitive changes. Specifically, when we included both blood glucose changes and BMI status in regression models predicting sweet cognition or sweet eating, blood glucose emerged as a significant or marginally significant predictor, whereas BMI status was not a significant predictor. In contrast, increases in insulin were not significantly correlated with greater sweet cognition. Strikingly, these results are based on consuming a standardized beverage containing 75g of glucose, which is still below the 82g of sugar per day reportedly consumed by the average American[53]. This standard beverage may be somewhat comparable

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to sugar-sweetened beverages that are widely available in gas stations, food marts, and vending machines: For example, a 20-ounce bottle of Coca-Cola contains 65g of sugar. It is noteworthy that this sample *excluded* individuals with diabetes, and only one individual met criteria for prediabetes. Hence, these effects operate among individuals along the spectrum of glycemic control that includes the normative range. This finding is particularly important, as it suggests that these measures may have the potential to identify individuals at the earliest stages of risk for elevated blood glucose, which can be associated with increased diabetes risk (i.e., developing prediabetes).

These findings map onto the operant conditioning framework[29] in several important ways. First, individuals exhibiting greater sweet cognition also endorsed greater decreases in task-related mental stress, suggesting a *negative reinforcement* value of glucose. In other words, consuming glucose may provide emotional comfort and relief from the mental and emotional stress associated with a difficult cognitive task. Similarly, if an individual experiences this boost in accuracy as a "benefit" in their day to day lives, it stands to reason that sugar ingestion might provide *positive reinforcement*.

Second, individuals of lean BMI status experienced greater cognitive performance changes; specifically, enhanced accuracy for non-food cues following glucose ingestion. In contrast, individuals of obese BMI status did *not* evidence such increased accuracy for non-food cues following glucose ingestion (Figure 2). Taken together, this suggests that individuals of lean BMI status may have greater cognitive flexibility to shift their attention back toward non-food cues once they are no longer in a fasted state. In the modern "obesogenic" food environment, this ability to shift cognition away from food after glucose ingestion represents an adaptive ability among individuals of lean status. In contrast, although arguably adaptive in times of famine, a lacking ability to divert attention away from food after glucose ingestion in individuals of obese status may be maladaptive in the modern food environment. This failure to shift attention away from food after receiving caloric load represents an important cognitive and mechanistic difference that may contribute to the obesogenic processes.

This study ostensibly resembles a possible real-world scenario: After consuming an initial dose of glucose similar to one and a half cans of soda, we found that individuals of obese BMI status more accurately identified food cues, *and* ate more jelly beans, despite having just eaten lunch (non-homeostatic eating). Particularly in the modern work environment, which, for many, transcends the physical office and invades the home via myriad communication channels (e.g., email, chat, text), sugar may provide relief from constant demands on attention and working memory. It is therefore noteworthy that a recent meta-analysis of 17 studies found that job stress – defined as high demands/effort and low rewards – had a stronger association with glucoregulatory control (fasting glucose) than global perceived stress[54]. This highlights the notion that in order to truly understand how stress, sugar, and visceral obesity are related, it is crucial to employ paradigms such as the one presented herein, which quantify "psychological stress" in the context of acute cognitive demands placed on the attentional control system, food cues, and the metabolic presence or absence of glucose. It also suggests that sweet cognition might be appropriate to study in a context of high job demands in relation to longitudinal visceral obesity increases.

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Neuroimaging research examining reward system activation (particularly in dopaminergic circuits) has identified some similarities across individuals of obese BMI status and individuals with substance dependence on alcohol, opiates, or other drugs of abuse[55,56]. Some findings from this study (e.g., glucose enhancing the salience of food cues, which in turn predicted greater sweet-eating) contribute to the question of whether some individuals with obesity may experience glucose as having addictive properties, as in animal models[57,58]. Currently, there is no clinical diagnostic tool that can identify these at-risk individuals. We propose that this experimental paradigm of "sweet cognition" may lay the groundwork for the development of a clinical diagnostic tool. If confirmed by further research, such a tool may provide a critical step toward identifying at-risk individuals and providing them with tailored interventions. Several promising interventions, ranging from pharmacotherapies that may reduce loss of control over eating (e.g., Contrave[59,60]) to mindful eating practices[46,61], may more directly address behavioral factors that perpetuate problematic overeating relative to standard lifestyle interventions. Indeed, a recent trial demonstrated that, among individuals high in reward-related eating, training in mindful eating resulted in greater decreases in food addiction symptoms than a cognitive behavioral intervention[46]. In sum, the sweet cognition paradigm may fill an existing gap in identifying individuals who may differentially benefit from interventions that target craving-related eating and dietary adherence[62,63].

In the taste test used to quantify non-homeostatic eating, we observed associations between sweet cognition and eating of jelly beans, but not with eating of chips. We note that jelly beans have a high glycemic index (GI) of 80[64]. In contrast, chips have a lower GI of approximately 54[39]. Because the increases in BG appear to drive cognitive changes, it is notable that these glucose-induced cognitive changes are only predictive of non-homeostatic eating for the higher glycemic food that was offered. While this is a pilot study, if replicated in a larger sample, this observation might suggest that sweet cognition is a specific marker for reward sensitivity to sugar, and that helping at-risk individuals to identify and reduce the amount of high glycemic foods in their diet could be beneficial in helping reduce cravings and improve dietary adherence.

Limitations and Future Directions

It is true that the lack of a control group precludes analysis of learning effects due to repeated testing; however, learning effects, if present, would most likely result in improvement in accuracy for *both* food and non-food items (rather than in changes in bias), which is inconsistent with these observations. Furthermore, learning effects would presumably have equally affected individuals of obese and lean BMI status. Instead, we observed a pattern of interaction effects that is not consistent with these predictions. Additionally, we observed a robust correlation between blood glucose increases from pre- to post-Glutol ingestion and the change in attentional food bias, which is consistent with published neuroscientific evidence that glucose serves as the primary fuel for the brain[15] and supports the notion that glucose ingestion is the most likely proximal cause of the observed cognitive effects. We note that the groups (lean vs. obese BMI status) did not differ on education, which removes a potential confound. Many other studies have tested control groups and have observed glucose facilitation effects on measures of attention and executive

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function outcomes[20,65,66]. As the sample size was relatively small, and we found no clear indication of speed-accuracy trade-offs, we focused these results on correct identifications; however, future work might further examine reaction time as a secondary outcome.

We report both statistically significant and marginally significant associations; hence, interpretation of marginal effects should be made cautiously. Nonetheless, in smaller samples, effect sizes (e.g., *r* values and standardized regression coefficients) may communicate more meaningful information than significance testing. Future work should replicate these associations in larger, independent samples. Although 25 g or 50 g of glucose may be optimal for memory enhancement[20], we elected to use a dose of 75 g because it is used for the Oral Glucose Tolerance Test (OGTT), a clinical tool used to diagnose diabetes. This dose therefore establishes that the effects observed here are detectable in individuals with obesity even when deficits in glucose control are subclinical. Notably, the optimal dose of glucose to maximize facilitation effects has yet to be determined, and future studies should consider varying doses. Furthermore, although we provided participants with standardized lunches, we did not measure the amount of lunch that participants actually ate. Although our experimental design lacked a control beverage matched for sweetness but without glucose, many previous studies have included such controls and established glucose facilitation effects[20,67,68]. A critical future step is to establish whether individuals with higher scores on sweet cognition are less likely to adhere to dietary plans, and therefore, are less likely to lose weight with traditional lifestyle interventions.

As a future direction, obesity-associated neuroinflammation is one potential mechanism that might explain the intriguing pattern of group differences found herein. Specifically, we found that *only* individuals of lean BMI status exhibited a relative reduction in the salience of food cues after consuming glucose, which might be viewed as an evolutionarily adaptive cognitive function. Individuals with obesity produce more inflammatory cytokines[69], and peripheral inflammation has been shown to *reduce* glucose metabolism in the anterior cingulate, anterior insula, and parahippocampal regions[70,71], with implications for reward processing, motivation, and memory. Hence, future studies might examine whether obesity-associated inflammation contributes to attentional food bias.

Conclusions

From an evolutionary perspective, it might be adaptive to focus on survival needs, such as hunger or threats, and then to flexibly shift attention toward the broader world once these survival needs are met. Accordingly, individuals of lean and obese BMI status performed similarly on cognitive tests of attention and working memory after a night of fasting. After consuming 75 g of liquid glucose, *only* the lean individuals experienced an enhanced ability to focus on and to remember non-food cues (e.g., everyday words such as “digit” and “pen”). In contrast, individuals with obesity remained relatively more focused on highly processed food-related cues (“donut” and “pie”). This phenomenon, which we call “sweet cognition,” hints at the neurocognitive bases of cravings and habit formation, which may underlie persistent non-homeostatic eating of sugar-laden foods. The more likely an individual was to experience “sweet cognition,” the more likely that individual was to also experience relief from mental stress after drinking the glucose beverage and to eat more

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sweets. This experimental paradigm may lay the groundwork for the development of precision medicine tools to identify and treat individuals at risk for obesity. If further validated, this battery may provide a novel experimental paradigm worthy of consideration for identifying individuals with heightened sensitivity to sugar rewards, and may provide guidance for novel treatments for the reward-driven phenotype of obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Individuals of obese BMI status show greater attentional food bias after consuming glucose
- We refer to changes in attention to food cues following glucose ingestion as “sweet cognition”
- Greater sweet cognition was associated with greater decreases in acute mental stress
- Greater sweet cognition was associated with greater non-homeostatic eating of sugar-laden food
- Sweet cognition may be due to greater capacity among lean individuals to attend to non-food cues after consuming glucose.

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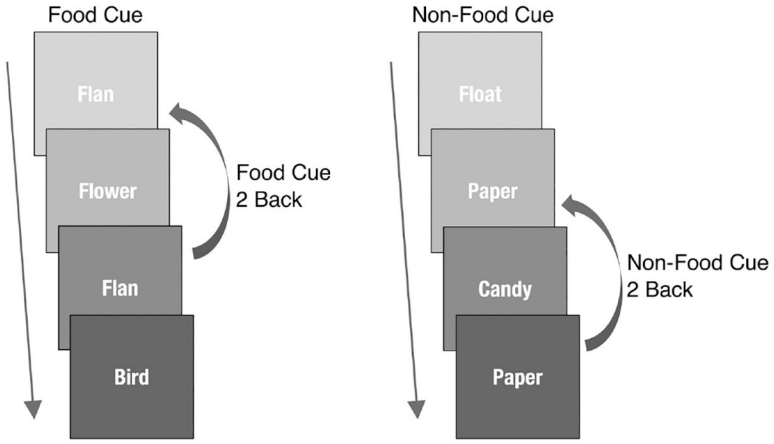

1.

The n-back cognitive task: An illustrative example of food and non-food cues

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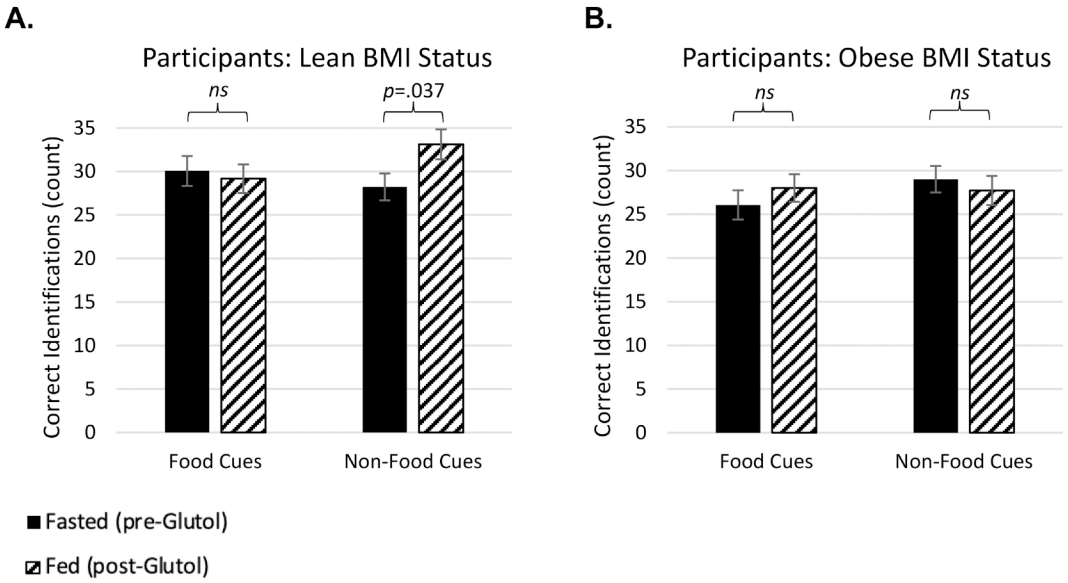

2.

Figure depicting differential attention to food and non-food cues among individuals of lean and obese BMI status

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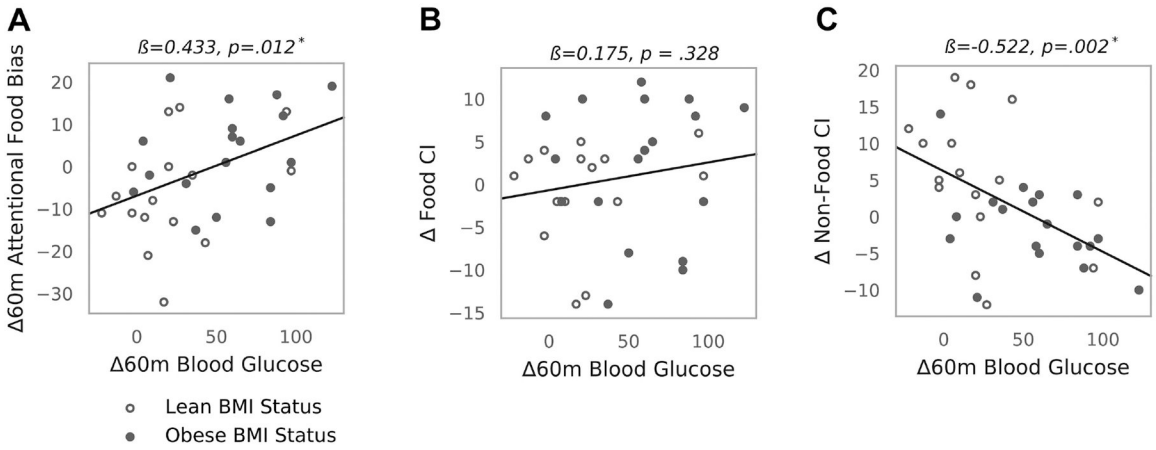

3.

Associations between glucoregulation, attentional food bias, and the two components of attentional bias (food and non-food cues)

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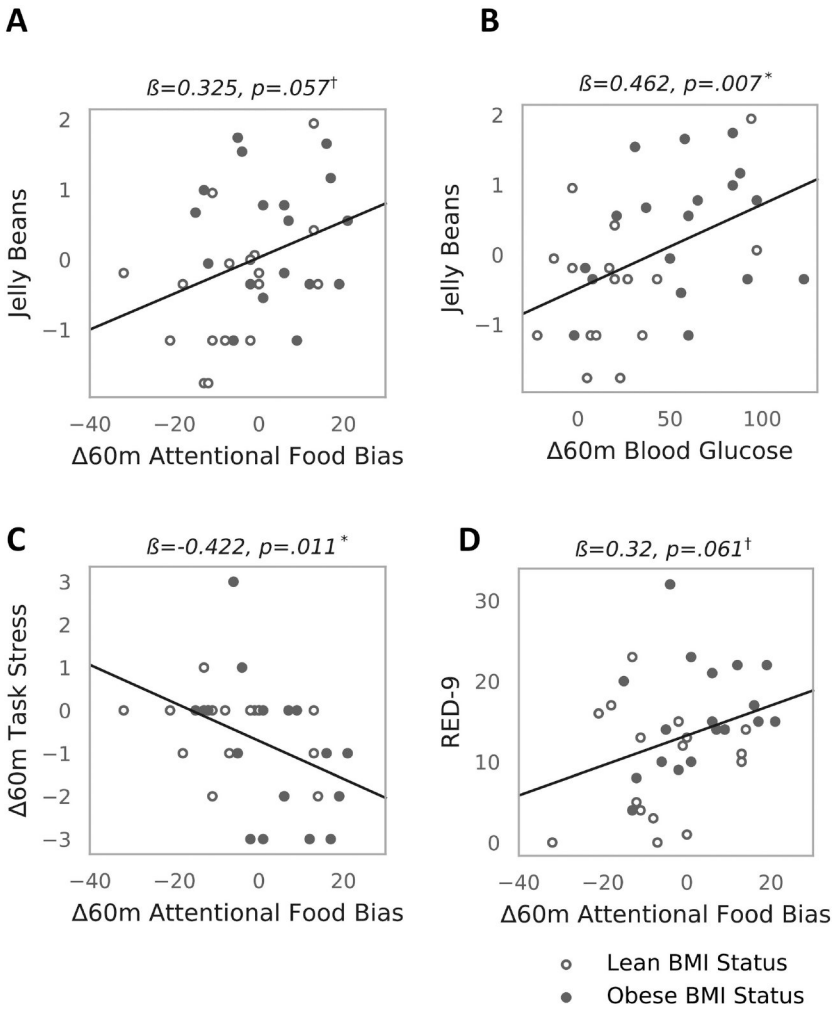

4.

Associations of cognition, eating behavior, and psychological factors

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Table 1.

Differences in study variables by BMI status

	BMI Status	
	BMI>27 (*n*=18)	**BMI≤25 (*n*=17)**
Age, years (*M*, SD)	45.94 (12.86)	45.06 (13.38)
Sex, male (*n*, %)	8 (44%)	6 (35%)
White / non-Hispanic (*n*, %)	4 (22%)	6 (35%)
Asian / non-Hispanic (*n*, %)	9 (50%)	7 (41%)
Hispanic (*n*, %)	5 (28%)	4 (24%)
Education (*M*, SD)	3.39 (0.92)	3.42 (1.38)
Handedness, left-handed (*n*, %)	5 (28%)	0 (0%) *
Body mass index (BMI: *M*, SD)	33.86 (6.78)	22.48 (1.85) **
Fasting blood glucose (*M*, SD)	89.33 (8.30)	87.24 (6.68)
Fasting blood insulin (*M*, SD)	15.46 (9.46)	6.51 (4.49) **
Δ Blood glucose (BG: *M*, SD)	56.43 (34.93)	22.31 (33.21) **
Δ Blood insulin (BI: *M*, SD)	132.89 (85.99)	47.47 (24.26) **
Reward-based Eating Drive scale (RED-9: *M*, SD)	15.83 (6.70)	10.12 (6.77) *
Food Cravings Questionnaire, Trait-Reduced (FCQ-T-R: *M*, SD)	23.44 (16.36)	17.76 (14.17)
Jelly bean consumption (*M*, SD)	0.35 (0.91)	−0.37 (0.95) *
Chips consumption (*M*, SD)	0.17 (0.92)	−0.18 (1.05)

Note.

** $p \leq .01$,

* $p \leq .05$,

† $p \leq .10$.

Education was scored with 6 categories ranging from having not graduated high school (0) to having completed a graduate or advanced degree (5). Jelly bean and chip consumption variables were log-transformed and standardized to improve the distribution for regression analyses. Δ indicates change from pre- to post-Glutol ingestion.

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Table 2.

Associations of metabolic factors with attentional food bias (ATT-Food) and non-homeostatic eating

	Blood Glucose (BG)			Blood Insulin (BI)		
	Pre-Glutol (Fasted)	**60 min Post-Glutol**	**Δ BG**	**Pre-Glutol (Fasted)**	**60 min Post-Glu**	**Δ BI**
ATT-Food (Pre-Glutol, Fasted)	−.009	−.038	−.024	−.042	.089	.139
ATT-Food (Post-Glutol, 60 min)	.045	.530 *	.550 **	.432 *	.466 **	.457 **
Δ ATT-Food	.041	.423 *	.433 *	.349 *	.282	.238
Jelly Bean Consumption	.270	.439 **	.462 **	.365 *	.311 †	.290
Chips Consumption	−.078	.039	.032	−.039	−.076	−.112

Note.

** $p \leq .01$,

* $p \leq .05$,

† $p \leq .10$.

See Tables 1 and 2 for variable abbreviations and descriptions. Values are results of Pearson correlations (r). We report Δ BG and Δ BI with one statistical outlier winsorized to prevent biasing the correlation coefficients; however, we also confirmed that the overall pattern of significance is not changed when we used the unwinsorized Δ BG and Δ BI variables.

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Table 3.

Associations of attentional food bias with non-homeostatic eating and trait psychological factors

	ATT-Food: Pre-Glutol (Fasted)	ATT-Food: 60 min Post-Glutol	Δ ATT-Food
Jelly Bean Consumption	−.092	.341 *	.325 †
Chips Consumption	−.038	.038	.057
RED-9	−.109	.318 †	.320 †
FCQ-T-R	−.047	.298 †	.258

Note. ** $p \leq .01$,

* $p \leq .05$,

† $p \leq .10$.

N=35. ATT-Food=Attentional food bias. Δ ATT-Food = “sweet cognition,” or the change in attentional food bias from pre- to post-Glutol. See Table 1 for further variable abbreviations and descriptions. Values are results of Pearson correlations (r).