

Gastric bypass surgery for obesity decreases the reward value of a sweet-fat stimulus as assessed in a progressive ratio task^{1–3}

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ABSTRACT

Background: Obesity is among the leading causes of disease and death. Bariatric surgery is the most effective treatment of obesity. There is increasing evidence that after gastric bypass surgery, patients and animal models show a decreased preference for sweet and fatty foods. The underlying mechanism may include alterations in taste function.

Objective: We hypothesize that a gastric bypass reduces the reward value of sweet and fat tastes.

Design: In this prospective case-control study, 11 obese patients who were scheduled to undergo a gastric bypass and 11 normal-weight control subjects in the fed state clicked a computer mouse to receive a sweet and fatty candy on a progressive ratio schedule 10 wk apart (in patients, testing took place 2 wk before and 8 wk after gastric bypass surgery). Subjects worked progressively harder to obtain a food reward (reinforcer) until they stopped clicking (ie, the breakpoint), which was a measure of the reinforcer value. Breakpoints were assessed by the number of mouse clicks in the last completed ratio. The experiment was repeated in a different cohort by using vegetable pieces as the reinforcer.

Results: Breakpoints in the test sessions of control subjects correlated highly for both reinforcers. The median breakpoint for candies, but not vegetables, was reduced by 50% in the obese group after gastric bypass. Patients with the largest reduction in the breakpoint had the largest decrease in BMI.

Conclusions: Gastric bypass surgery resulted in the selective reduction of the reward value of a sweet and fat tastant. This application of the progressive ratio task provided an objective and reliable evaluation of taste-driven motivated behavior for food stimuli after obesity surgery. This trial was registered at clinicaltrials.gov as NCT01531738. *Am J Clin Nutr* 2012;96:467–73.

INTRODUCTION

Obesity is among the leading causes of disease and death throughout the world. A healthy lifestyle, including a balanced diet and regular physical activity, is crucial in the prevention of obesity but offers little benefit for its treatment in the long term (1). Dieting can reduce body weight, but this reduction is followed by the activation of protective neural circuits that cause a return in weight for many patients (2). Bariatric surgery is currently the most effective treatment of obesity and its associated comorbidities because it causes significant weight loss, most of which can be maintained for decades after the operation (3).

Observations from the clinic, which have gained some empirical support and other human and animal studies, suggested that after a gastric bypass, patients show a decreased preference for high-calorie sweet and fatty food compared with before the operation and compared with patients who were undergoing different bariatric procedures (such as gastric banding or gastroplasty) or relative to the general population (4–12). The preference for vegetables after a gastric bypass has been reported to be lower (9, 13), higher (7, 14, 15), or unchanged (4) in similar comparisons. It is possible that bariatric surgery could exert its effects on food selection and preference through alterations in the sensory-discriminative, motivational, or physiologic domains of taste function (16). In regard to the sensory-discriminative domain, we have shown that after gastric bypass, patients decrease their sucrose-detection threshold and, thus, increase their sensitivity to low concentrations of this sweet stimulus (17), which confirmed previous findings (18).

Visual analog scale (VAS) techniques, including the generalized labeled magnitude scale, have also been used to measure the hedonic evaluation of food stimuli to provide an assessment of responsiveness in the motivational or affective domain of taste function (19–21). These techniques are relatively easy, efficient, and inexpensive to use. Nevertheless, a common limitation is that they cannot be used in animal subjects because they rely on verbal report. This reduces the translational relation between results collected from animal models and those derived from clinical research.

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Although there are suggestions in animal models that the rewarding and aversive properties of sweet and fat stimuli may change after a gastric bypass (17, 22–26), very little work has been conducted in humans to determine whether there are postoperative changes in the motivational domain of taste function. The purpose of the current article was to begin addressing this question through the use of the progressive ratio schedule of reinforcement, which is an operant task first developed by Hodoss (27) for use in animals. During the task, the animal is trained to perform a certain number of responses required to obtain a reinforcer (ie, reward). After delivery of each reward, the response requirement progressively increases until it is so great, the animal stops responding, which is referred to as the breakpoint. The number of responses completed for the last reward received can be used as a proxy of the reward value of the reinforcer and is a pure assessment of appetitive responsiveness driven by properties of the reinforcer such as its taste. We adapted this technique in humans and predicted that breakpoints to a sweet, high-fat candy would decrease and that breakpoints for vegetable pieces would remain unchanged or even increase after gastric bypass surgery for obesity.

SUBJECTS AND METHODS

This was a prospective case-control study. Obese patients with BMI (in kg/m^2) >35 and approved for obesity surgery on the basis of United Kingdom National Institute of Clinical Excellence guidelines were recruited consecutively from the Imperial Weight Centre, Imperial College Healthcare Hospital Trust (London, United Kingdom) between July 2011 and July 2012. Exclusion criteria for all patients and control subjects in the study included a lack of understanding of the test instructions, a diagnosis of diabetes mellitus, active smoking, pregnancy, breastfeeding, substance abuse, >3 alcoholic units/d, psychiatric illness, chronic medical conditions that would make it unsafe to have a general anesthetic, and a dislike for or allergy to the stimulus ingredients. Two different cohorts of normal-weight participants (controls) with BMI between 19 and 25 were recruited from the community. Written informed consent was obtained from all of the subjects. The study was conducted in accordance with the Declaration of Helsinki, and all procedures were approved by the West London 2 Research Ethics Committee (reference 10/H0711/22).

Experiment 1

The first cohort of obese patients who were undergoing a gastric bypass and normal-weight participants were instructed to have their usual breakfast until they felt comfortably full before attending. Testing occurred 2–3 h after breakfast in a quiet room within the clinical research facility. Room temperature was maintained at 22°C . The instructor, who was the same instructor throughout the experimental period, provided patients and controls with exactly the same test information and information sheet. Subjects were told, “Press as little or as much as you like. There are no right or wrong answers in the task. When you no longer want to continue, press the space bar. This is not a competition.” Hunger scores were obtained just before testing by using a horizontal 100-mm VAS with the anchors “not at all hungry” and “extremely hungry” on either end.

Subjects were placed in front of a computer screen and a plate of 20 chocolate candies (M&M crispy candies; Mars UK Ltd). Each candy contained a mean of 4 kcal (energy contribution: 43.7% sugars and 44.1% fat). The following prompt appeared on the screen: “You can earn food by clicking on the mouse button. Click as much or as little as you like. When you no longer want to continue, press the spacebar to stop the session.” On completion of each ratio a message box appeared on the screen: “You have earned food. Enjoy your reward and after you have swallowed it completely you may click on OK to continue with the programme.” After ingesting the reward, subjects pressed the OK button in the message box only if they wished to progress to the next ratio to obtain another chocolate candy. The starting ratio was 10 clicks with a geometric increment of 2 (ie, 10, 20, 40, 80, etc). This progression schedule was chosen based on pilot experiments in both obese and normal-weight volunteers. Presumably, when the effort in pressing the mouse button was greater than the rewarding value of the chocolate candy, subjects pressed on the space bar to terminate the session, which indicated that the breakpoint was reached. One trial run was initially performed by using the first ratio without reinforcement to allow participants to become familiar with the computer software. After this trial, the instructor left the room, and subjects were left on their own to complete the task. No food or fluid was offered after termination. The same number of chocolate candies ($n = 20$) was presented to all participants. The number of candies that remained after completion of the experiment was subtracted from 20 to give the total number consumed. The total number of candies consumed was correlated with the number of completed ratios from the computer software to ensure that participants followed the instructions correctly. Patients who were scheduled to receive a gastric bypass underwent testing 2 wk preoperatively and 8 wk postoperatively, whereas normal-weight controls were tested on 2 occasions 10 wk apart.

Experiment 2

A cohort of obese patients who were undergoing gastric bypass and normal-weight participants underwent testing by using the paradigm described in experiment 1, but the sweet and fat stimulus was replaced with vegetable pieces. Participants were offered a combination of 20 vegetable pieces that included tinned sweet corn, baby peas, and carrots, which were preserved in water and presented at 22°C after being cut to pieces of a volume similar to the that of the chocolate candies. A small plastic fork was used to pick each piece of vegetable. The approximate calorie content of each vegetable piece was 0.78 kcal (energy contribution: 15.0% sugars and 11.5% fat).

In both experiments, we aimed to match cases to control subjects for the potential confounders of age and sex and also keep hunger scores stable between the first and second testing sessions of each experiment. To limit bias, patients were recruited in the order in which they attended the clinic by an investigator who was blinded to the hypothesis of the study. The investigator who performed the experiments was not present during the task, as this influenced the responses to the task in our pilot studies. Experiments 1 and 2 were performed by 2 different investigators. In addition, participants were blinded to the study hypothesis, given exactly the same verbal and written instruction, and

specifically instructed that there were no right or wrong responses to the task.

The variables measured included hunger ratings in millimeters and mouse clicks in the last completed ratio (breakpoint). Comparisons between and within groups were made by using the Mann-Whitney *U* test and Wilcoxon matched-pairs test, respectively. Correlations were made by using Spearman's non-parametric test, but the graphs included a parametric linear regression curve for visual comparison. Patient-characteristic data were normally distributed, and thus, *t* tests were used for within- and between-group comparisons for age and BMI, whereas sex comparisons were made by using Fisher's exact test. Results are expressed either as means \pm SEMs or medians and interquartile ranges. Statistical comparisons were done with GraphPad Prism software (version 5). Because, to our knowledge, this experiment has not been performed in this setting before, our study size was determined from previously published data from our group on the effects of gastric bypass on thresholds of sweet-taste detection (17).

RESULTS

Basic characteristics of participants are shown in **Table 1**. All eligible normal-weight participants were recruited and completed the study ($n = 11$ in experiment 1, $n = 10$ in experiment 2). In the obese group of experiment 1 ($n = 21$ eligible and recruited), 4 patients did not complete the study because their operations were cancelled, 4 patients had a different type of obesity surgery for technical reasons, and 2 patients did not understand the study instructions ($n = 11$ completers). In experiment 2, of the 15 obese patients who were eligible and recruited for the study, 6 patients had a surgical procedure different from the gastric bypass ($n = 9$ completers). Data from noncompleters were not used. In experiment 1, groups were matched for age and sex at baseline; in experiment 2, normal-weight volunteers were younger than obese patients. There was no significant change in the BMI of the normal-weight control groups between the 2 sessions. There was no significant difference in the percentage of BMI loss between obese patient groups who were undergoing a gastric bypass surgery in experiments 1 and 2 ($14.5\% \pm 0.8\%$ compared with $15.9\% \pm 0.7\%$; $P = 0.21$). There were no discrepancies between the number of reinforcers actually consumed and the number predicted to have been

consumed on the basis of software results for either the patient or normal-weight volunteer group in either experiment.

In both experiments 1 and 2, breakpoints as assessed by the number of mouse clicks in the last completed ratio of the test did not significantly differ in the normal-weight control group between the 2 sessions for either chocolate candies or vegetables ($P = 0.78$ and $P = 0.85$, respectively) (**Figure 1**). Moreover, there was a high and significant correlation between the breakpoints for sessions 1 and 2 for control subjects for both chocolate candies and vegetables (**Figure 2, A and C**). There was no significant difference in breakpoints between normal-weight and obese groups for chocolate candies and vegetables at baseline ($P = 0.53$ and $P = 0.51$, respectively) (Figure 1). However, there was a 50% reduction in the median breakpoint of the obese group after gastric bypass surgery for chocolate candies but not for vegetables ($P = 0.015$ and $P = 0.400$, respectively). There was a significant correlation between breakpoints for sessions 1 and 2 for obese subjects when vegetables, but not chocolate candies, were used as the reinforcer (Figure 2, B and D). The postoperative decrease in BMI in patients was correlated with the decrease in breakpoint for chocolate candy but not for vegetables (**Figure 3**).

The results of hunger ratings are summarized in **Table 2**. Hunger was unchanged in the normal-weight control group in both experiments 1 and 2. Hunger ratings were significantly reduced after gastric bypass surgery in experiment 1 and did not significantly change in experiment 2. Hunger ratings did not correlate with breakpoints in either the normal-weight control or obese patient group for any test session in both experiments. Moreover, the change in hunger ratings also did not correlate with the change in breakpoints between sessions in either the normal-weight or the obese group.

DISCUSSION

To our knowledge, this was the first study to use the progressive ratio task to assess changes in the rewarding properties of a food item after gastric bypass surgery. The reinforcing efficacy of the sweet and fat candy stimulus decreased by a factor of 2 after gastric bypass surgery and remained unchanged across a similar test-retest interval in normal-weight control subjects. There was no change in the reinforcer efficacy of vegetable stimuli by using the same testing paradigm in a separate group of

TABLE 1
Participant characteristics¹

	Normal-weight control group		Obese patient group		<i>P</i> (between-group comparisons) ²	
	Experiment 1	Experiment 2	Experiment 1	Experiment 2	Experiment 1	Experiment 2
Sex [total <i>n</i> (M/F)]	11 (4/7)	10 (4/6)	11 (4/7)	9 (4/5)	1.00	1.00
Age (y)	38.2 \pm 2.9 ³	39.4 \pm 4.6	44.4 \pm 3.0	56.0 \pm 0.9	0.15	0.004
BMI at first session (preoperatively) (kg/m ²)	22.7 \pm 0.8	22.6 \pm 0.7	49.3 \pm 1.5	46.9 \pm 1.4	<0.0001	<0.0001
BMI at second session (postoperatively) (kg/m ²)	22.7 \pm 0.7	22.5 \pm 0.7	42.2 \pm 1.6	39.5 \pm 1.3	<0.0001	<0.0001
<i>P</i> (within-group comparisons for BMI) ⁴	0.84	0.71	<0.0001	<0.0001		

¹ In experiment 1, chocolate candies were used as reinforcers; in experiment 2, vegetables were used as reinforcers.

² Fisher's exact test was used for sex comparisons, and the unpaired Student's *t* test was used for continuous data.

³ Mean \pm SEM (all such values).

⁴ Paired Student's *t* test.

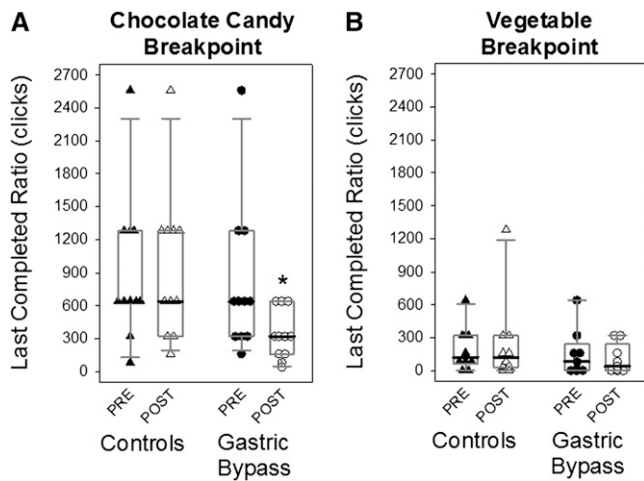


FIGURE 1. Box plot of the breakpoint (ie, clicks in the last completed ratio) for chocolate candies (A) in the normal-weight control group (triangles; $n = 11$ in panel A; $n = 10$ in panel B) and gastric bypass group (circles; $n = 11$ in panel A; $n = 9$ in panel B) for session 1 (preoperatively; filled symbols) and session 2 (postoperatively; open symbols). Lower and upper boundaries of the box represent 25th and 75th percentiles, respectively. Lower and upper whiskers represent 10th and 90th percentiles, respectively. The median is denoted by the bold black line inside the box. *Significant differences within groups between sessions 1 (preoperatively) and 2 (postoperatively) as determined by using Wilcoxon matched-pairs test. POST, postoperatively; PRE, preoperatively.

obese patients undergoing gastric bypass surgery with similar weight loss.

We adapted this operant technique that is widely used in animals to investigate the hedonic value of a reinforcer (28–31). Our method built on the literature involving the use of progressive ratio tasks in humans (32–38) and the reliability of our adaptation in the context of gastric bypass was validated in part

by the high correlation between breakpoints for sessions 1 and 2 in the normal-weight control groups in 2 separate experiments.

One of the key merits of the task used here is that the assessment was based on the actual behavior of the subject and was not burdened by some of the interpretive limitations associated with scaling procedures. Our study answered the question of how hard a subject was willing to work for a given reinforcer. Our model used simple computer software and entailed participants actually tasting the reinforcer during the task rather than postponing the consumption to the end. Thus, appetitive responsiveness was determined directly by the orosensory properties (eg, taste) of the reward and did not depend on the association between a stimulus such as a token, money, or images with the reward. The completion of the schedule was not dependent on computer skills or the completion of an intellectually demanding task. In an attempt to minimize postingestive effects, reinforcers were of minimal volume and calories. It is this property that makes it beneficial for the study of changes in appetitive responsiveness in gastric bypass patients so that the ingestion of a food reward may not lead to premature satiation and interfere with its orally based evaluation. Participants were briefed about each experiment by the same investigator who was not present during the task to minimize bias in responses. These methodologic features differentiate our paradigm from others used in humans in previous studies (32–38).

The literature regarding gastric bypass from human and animal experiments has broadly described a reduced food preference for refined sugars and fat without pinpointing taste or postingestive effects as the cause for this change to more healthy choices (4–12). It is reassuring that the change in breakpoints observed in our study matches the reports of reduced preference, but as noted, our assessment was actually quantified on the basis of the measurement of the objective behavior of the subject. Accepting the limitations of the VAS, there was no correlation between

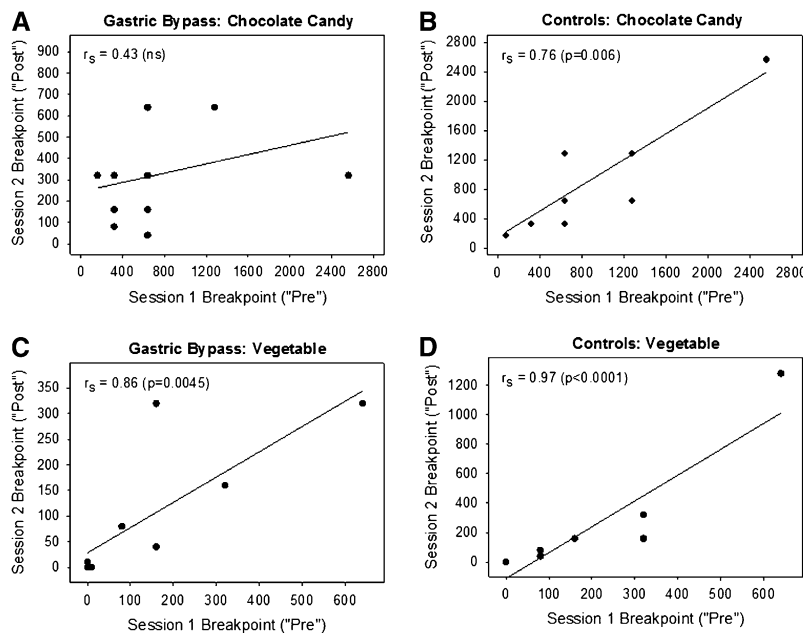


FIGURE 2. Correlation of the breakpoint (ie, clicks in the last completed ratio) in the normal-weight control group for chocolate candies (A; $n = 11$), the gastric bypass group for chocolate candies (B; $n = 11$), the normal-weight control group for vegetables (C; $n = 10$), and the gastric bypass group for vegetables (D; $n = 9$) between sessions 1 (preoperatively) and 2 (postoperatively) by using Spearman's correlation coefficient (r_s). Post, postoperatively; Pre, preoperatively.

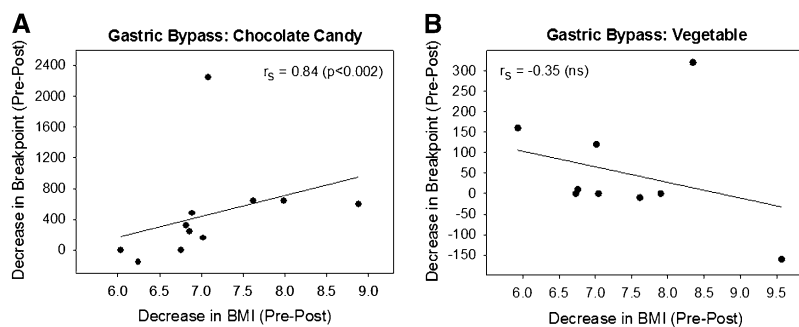


FIGURE 3. Correlation of the change in BMI compared with the change in the breakpoint (ie, clicks in the last completed ratio) in the gastric bypass group for chocolate candies (A; $n = 11$) and vegetables (B; $n = 9$) by using Spearman's correlation coefficient (r_s). Pre-post, preoperatively-postoperatively.

hunger ratings and the breakpoint or between the across-session change in hunger ratings and the change in breakpoints in either control subjects or patients. These results would suggest that the change in breakpoints may have been related to the evaluation of the affective orosensory properties of the reinforcer and not to changes in physiologic drive state at the start of each test. Breakpoints of the unoperated obese and normal-weight groups were the same in both experiments, which suggested that the subjects in these groups were prepared to work equally hard for the reward of chocolate candies or vegetables.

Importantly, the same task could, in principle, be conducted in an animal model of gastric bypass, which may open up the field to more in-depth interrogation of mechanisms that underlie the change in behavior. The investigation of effects of gastric bypass surgery on sweet and/or fat taste reward in animals has yielded mixed and complex results. Some groups have shown postoperative decreases in consummatory responsiveness to high concentrations of sucrose (22, 24, 25) and a fat emulsion (22), and in one case, at low concentrations of these stimuli, rats increased their licking responses after a gastric bypass (22). Still, other authors have shown no changes in consummatory responsiveness to these stimuli (26, 39). Some studies have shown increases in appetitive responsiveness to sweet-tasting stimuli (22, 39), but other studies have not (25). What is clear about many of these studies is that they differed in methodologically significant ways,

including the maintenance diet used, the body weights of animals at surgery, the size of the stomach pouch and relative limb lengths, the preoperative diet, and the choice of procedural variables in the behavioral tests conducted. The last variable is critical because it can have a strong influence on how much a behavioral measure reflects appetitive compared with consummatory processes. The progressive ratio task is a pure measure of appetitive responsiveness to a taste stimulus and should prove useful in the clarification of the effects of gastric bypass on motivated behavior.

Weight loss after a gastric bypass is associated with increased concentrations of anorexigenic gut hormones (40), which may influence the taste system at multiple sites including the peripheral (41) and central (24) gustatory system as well as reward circuits in the brain (42). Only recently was it shown that rat models of the vertical sleeve gastrectomy, which is a procedure that also leads to increased gut hormone concentrations, showed shifts in food choices very similar to those seen after the gastric bypass (43). The study of progressive ratio responses in patients treated experimentally with gut hormones or their antagonists and rodents with a gene knockout that emulates or reverses the consequences of obesity will be crucial in the elucidation of the mechanisms responsible for changes in taste.

Our methodologic adaptation of the progressive ratio task to study the appetitive responsiveness to taste stimuli can be

TABLE 2
 Summary of hunger-rating results

	<i>n</i>	Hunger rating ¹	<i>P</i> ²	Correlation of hunger rating with breakpoint	Correlation of change in hunger rating with change in breakpoint
<i>mm</i>					
Experiment 1					
Session 1: normal-weight group	11	26.00 (11.00–45.00)	0.26	$r_s^3 = -0.30, P = 0.37$	$r_s = 0.11$
Session 2: normal-weight group	11	42.00 (18.00–53.00)		$r_s = -0.14, P = 0.69$	$P = 0.73$
Preobese patient group	11	24.00 (11.00–45.00)	0.05	$r_s = -0.32, P = 0.34$	$r_s = -0.67$
Postobese patient group	11	13.00 (3.00–28.00)		$r_s = 0.05, P = 0.88$	$P = 0.17$
Experiment 2					
Session 1: normal-weight group	10	49.50 (23.50–67.50)	0.33	$r_s = 0.34, P = 0.33$	$r_s = 0.54$
Session 2: normal-weight group	10	26.50 (20.50–55.75)		$r_s = 0.16, P = 0.65$	$P = 0.11$
Preobese patient group	9	21.00 (4.00–75.00)	0.18	$r_s = -0.14, P = 0.71$	$r_s = 0.10$
Postobese patient group	9	5.00 (2.00–34.00)		$r_s = -0.54, P = 0.13$	$P = 0.81$

¹ All values are medians; interquartile ranges in parentheses.

² Within-group comparisons (session 1 compared with session 2 in normal-weight groups and preoperatively compared with postoperatively in obese patient groups) by using the Wilcoxon matched pairs test.

³ r_s , Spearman's correlation coefficient.

improved further. Ideally, it should be fully automated and camera recorded to minimize any investigator bias in the way instructions are given and to ensure that the reinforcer is actually ingested. The administration of a fixed preload under supervised controlled conditions to try to standardize the physiologic state and perceived hunger levels before the task would be ideal but could prove difficult in a postgastric surgery population. Peri-operative dietary advice may have introduced the confounding element of unintentional prejudging toward sweet and fatty foods. Blinding participants to the reinforcers used so that they rely purely on their orosensory properties for evaluation may, therefore, prove useful in future experiments. These adaptations may also include a control group of obese subjects who are not undergoing surgery. To investigate whether the effects of a gastric bypass on a sweet and fat taste reward are chronic, the same experiments should be repeated in the same patient cohort 1 y after surgery when weight loss has plateaued.

We cannot entirely dismiss the possibility that subject responses were influenced by their own cognitive expectations regarding how they thought they were supposed to behave toward the reward stimuli. However, this is an inescapable limitation of any assessment of food preference and hedonics in an experimental setting. Subjects were clearly instructed that there was no right or wrong performance. Indeed, the small volumes of rewards ingested coupled with the simple response requirement associated with the task probably helped to circumvent the influence of cognitive factors on the outcome. It is impossible to objectively assess a subject's intent, but we can measure a subject's behavior, and in the context of these experiments, behavioral outcomes correspond remarkably well with the changes in BMI observed after a gastric bypass and were consistent with at least some reports in the literature regarding changes in food preferences.

In conclusion, the progressive ratio task showed a reduction in appetitive behavior for a reward that contained sugar and fat but not for vegetables after gastric bypass surgery for obesity. We showed that the direct measurement of appetitive behavior is possible and informative in humans after a gastric bypass. The underlying mechanisms responsible for this change can now be studied in both animal and human experiments. The goal will be the mimicry of these mechanisms with novel pharmacologic agents that can promote weight loss and improve health for obese patients without risks associated with surgery. In particular, manipulation of the brain taste-reward network through less invasive means could limit any systemic side effects and, therefore, improve patient concordance.

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The authors' responsibilities were as follows—ACS, CWIR, TH, and TO: designed the research; ADM and RNJ: conducted the research; ACS: provided essential materials; ADM, SNJ, APG, ACS, and CWIR: analyzed data; ADM, ACS, and CWIR: wrote the manuscript; ACS and CWIR: 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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