Neuronal Food Reward Activity in Patients With Type 2 Diabetes With Improved Glycemic Control After Bariatric Surgery

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OBJECTIVE

Obesity and type 2 diabetes mellitus (T2DM) are associated with altered food-related neuronal functions. Besides weight loss, substantial improvement of glucose metabolism in patients with T2DM can be achieved by bariatric surgery. We aimed to target the neuronal and behavioral correlates of improved glycemic control after bariatric surgery.

RESEARCH DESIGN AND METHODS

Two patient groups with T2DM were recruited. The treatment group (n = 12) included patients after Roux-en-Y gastric bypass (RYGB) surgery and a control group of patients who did not undergo surgery (n = 12). The groups were matched for age and current BMI. HbA_{1c} was matched by using the presurgical HbA_{1c} of the RYGB group and the current HbA_{1c} of the nonsurgical group. Neuronal activation during a food reward task was measured using functional MRI (fMRI). Behavioral data were assessed through questionnaires.

RESULTS

RYGB improved HbA_{1c} from 7.07 ± 0.50 to 5.70 ± 0.16% ($P < 0.05$) and BMI from 52.21 ± 1.90 to 35.71 ± 0.84 kg/m^2 ($P < 0.001$). Behavioral results showed lower wanting and liking scores as well as lower eating behavior–related pathologies for the patients after RYGB than for similar obese subjects without surgery but impaired glycemic control. The fMRI analysis showed higher activation for the nonsurgical group in areas associated with inhibition and reward as well as in the precuneus, a major connectivity hub in the brain. By contrast, patients after RYGB showed higher activation in the visual, motor, cognitive control, memory, and gustatory regions.

CONCLUSIONS

In obese patients with diabetes, RYGB normalizes glycemic control and leads to food reward–related brain activation patterns that are different from obese patients with less-well-controlled T2DM and without bariatric surgery. The differences in food reward processing might be one factor in determining the outcome of bariatric surgery in patients with T2DM.

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Obesity, which is associated with various comorbidities, especially type 2 diabetes mellitus (T2DM), can shorten life expectancy by up to 20 years (1). In the past few decades, the prevalence of obesity and diabetes has increased dramatically (2,3) and has led to a growing interest in unraveling the underlying mechanisms of obesity and diabetes. Besides altered behavioral and metabolic processes, obesity (4) and T2DM (5) have been shown to be associated with altered neuronal mechanisms related to eating behavior and food and reward processes. When stimulated with food items, obese subjects show higher activation in gustatory, reward, and frontal control regions than lean subjects (6–8). Patients with T2DM have increased responses to food pictures in gustatory and reward regions, which are modulated by dietary self-care (5).

In terms of behavior, food reward can be divided into a wanting and a liking component. Liking is explained as the hedonic reaction to the pleasure of a reward, whereas wanting is described as the incentive salience linked with the motivation toward an item. Animal research has shown that wanting and liking are associated with different neuronal circuits (9). Finlayson et al. (10) used behavioral studies to demonstrate that this concept can be used in human research, and several brain imaging studies have shown that food reward–associated brain structures are specifically involved in the processing of wanting and liking (11–13).

Although various treatment options for obesity exist, long-term weight loss maintenance is difficult to achieve, and the majority of patients regain weight within the first year after losing weight by a conventional weight loss therapy (14,15). The most successful, as well as most invasive, therapy for weight loss is bariatric bypass surgery (16). A recent review summarized the hormonal, neuronal, and metabolic consequences of bariatric surgery and emphasized that the interplay of these factors leads to changes in feeding behavior (17). Long-term follow-up studies on weight development after bariatric surgery showed an excess weight loss of >50% and, in some cases, >70% after 10 years (18). In addition to being an effective form of weight loss treatment, bariatric surgery successfully prevents the development of T2DM, particularly in patients with impaired glucose control but independent of presurgical BMI (19). Furthermore, a remission of T2DM after Roux-en-Y gastric bypass (RYGB) surgery has been reported in the majority of patients (20–22). Several independent factors, including weight loss and diabetes duration, predict T2DM improvement (23). The effectiveness of successful long-term weight loss and diabetes remission thus depends on various factors that might also include neuronal food reward processes.

On a neuronal level, bariatric surgery results in altered neuronal responses to food cues, particularly in the reward, gustatory, and homeostatic regions (11,24–26). A comparison of neuronal responses to food items between patients postsurgery and a lean and an obese control group showed that severely obese women who underwent RYGB at least 1 year earlier showed a normalization of obesity-associated alterations in brain activity (25). This neuronal normalization is also supported by a partial reversal of hypothalamic dysfunction after glucose intake in postoperative patients without diabetes (27).

These studies mainly focused on the effect of weight loss and changes in the activity of eating-related hormones and did not specifically address the effect of changes in glycemic control. In the present cross-sectional study, we aimed to determine whether neuronal food reward–related activation patterns depend on improvement of glycemic control in a population with T2DM after bariatric surgery. We studied two groups with T2DM: One group underwent RYGB and experienced substantially improved HbA_{1c}, and the other group had a comparable BMI but did not undergo bariatric surgery. This design allowed us to compare brain activation patterns in patients with T2DM who mainly differed in glycemic control achieved by bariatric surgery.

RESEARCH DESIGN AND METHODS

Study Population

In total, 24 obese, right hand–dominant subjects with T2DM participated in the study. Twelve underwent RYGB at least 6 months prior and had experienced substantial weight loss and improved glycemic control (RYGB group). The other 12 did not undergo bariatric surgery (nonsurgical group). Patient characteristics are shown in Table 1. Patients were matched for age (50.0 ± 2.7 vs. 50.7 ± 3.3 years, $P = 0.88$) and current BMI (35.71 ± 0.84 vs. 37.81 ± 1.38 kg/m^2, $P = 0.21$). HbA_{1c} was matched by using the presurgical level of the RYGB group with the current level of the nonsurgical group (7.07 ± 0.50 vs. 7.04 ± 0.37%, $P = 0.97$). The study protocol was approved by the ethics committee of the medical faculty of the University of Tübingen, and all subjects gave written informed consent.

Study Design

Subjects arrived at the study site after fasting for at least 3 h and taking their usual medication as instructed. They completed questionnaires to assess their current hunger, mood, and eating behavior traits (the Three Factor Eating Questionnaire with the scales cognitive

Table 1—Patient characteristics

	T2DM group		
	RYGB	Nonsurgical control	*P* value
No. patients (female/male)	12 (10/2)	12 (6/6)	0.08
Age (years)	50.0 ± 2.67	50.7 ± 3.29	0.88
BMI (kg/m^2)	35.71 ± 0.84	37.81 ± 1.38	0.21
RYGB-induced change in BMI	−16.5 ± 1.53		
HbA_{1c} (%)	5.70 ± 0.16	7.04 ± 0.37	0.005
RYGB-induced change in HbA_{1c}	−1.37 ± 0.48		
Years since diabetes diagnosis	11.17 ± 1.91	6.46 ± 1.09	0.043
Months since RYGB surgery	17.73 ± 2.68		
Oral diabetes medication	2	8	0.005
Insulin therapy	0	2	0.078

Data are mean ± SEM. Medication is given as the number of subjects taking oral medication or undergoing insulin therapy.

restraint, disinhibition, experienced hunger [28] and the Power of Food Scale measuring the power of food that is available, present, or tasted [29]). The Beck Depression Inventory (30) was used to address depressive symptoms. A blood sample was taken to determine the HbA_{1c} level. Presurgery BMI and HbA_{1c} (measured by using the same method as for the presurgery HbA_{1c}) was retrieved from clinical records.

For the functional MRI (fMRI) measurement, subjects were positioned in the scanner with their heads fixed in a 12-channel head coil. An intercom system was used for communication. During the scanning session, subjects were stimulated with 40 food pictures (20 high calorie and 20 low calorie) within the wanting (run 1) and liking (run 2) tasks. During these two runs, subjects were asked to first rate each picture for wanting ("How much do you want to eat this food now?") and then for liking ("How much do you like this food in general?") on a 5-point Likert scale using an fMRI–compatible button box. Each picture was presented for 3 s, with an interstimulus interval of 1–12 s. The task was programmed with Presentation version 10.2 software (www.neurobs.com). After completion of the task, an anatomical scan was recorded and hunger ratings obtained.

Imaging Procedures and Analyses

Whole-brain fMRI blood oxygen level–dependent data were obtained with a 3-T fMRI scanner (MAGNETOM Trio, A Tim System; Siemens Healthcare, Erlangen, Germany) equipped with a 12-channel head coil. During the stimulation paradigm, each session consisted of 150 scans (repetition time 2 s, echo time 30 ms, matrix 64×64, flip angle 90°, voxel size $3.3 \times 3.3 \times 3.2$ mm^3, slice thickness 3.2 mm, 0.8-mm gap, 30 slices [images acquired in ascending order]). Resting state measurements had already been taken beforehand with 176 scans (repetition time 2 s, echo time 30 ms, matrix 64×64, flip angle 90°, voxel size $3.3 \times 3.3 \times 3.6$ mm^3, slice thickness 3.6 mm, 0.9-mm gap, 26 slices [images acquired in ascending order]). At the end of the scanning period, high-resolution T1-weighted anatomical images (magnetization-prepared rapid gradient-echo 160 slices, matrix 256×224, $1 \times 1 \times 1$ mm^3) of the brain were acquired.

Analyses of the fMRI data during visual stimulation were performed using Statistical Parametric Mapping 8 software (www.fil.ion.ucl.ac.uk/spm). Data were preprocessed, beginning with slice timing and realignment of the images to the mean image. To account for susceptibility by movement artifacts, unwarping of time series was performed. The anatomical T1-weighted image was coregistered to the mean functional image. Normalization into Montreal Neurological Institute (MNI) space (3-mm isotropic voxel size) and Gaussian spatial smoothing (full width at half maximum 6 mm) were then performed. Data were high-pass (cut off 128 s) filtered and global AR(1) autocorrelation corrected.

For each subject, a general linear model was applied for the high- and low-caloric food wanting and liking conditions. For each condition, a separate regressor was modeled by using a canonical hemodynamic response function that included time derivatives. Movement parameters were modeled as confounders.

Because imaging results also depend on vascularity effects and neuronal vascularity depends on age, medication, and diabetes (31), we controlled the analyses for vascularization. We implemented the method by Tsvetanov et al. (31) by using a scaling of the first-level contrast images by the individual resting state fluctuation amplitude before group analyses. Resting state measurements were analyzed using Data Processing Assistant for Resting-State fMRI running on Statistical Parametric Mapping 8 software (32). Functional images were realigned and coregistered to the T1 structural image. Images were normalized into MNI space (3-mm isotropic voxel size) and smoothed with a three-dimensional isotropic Gaussian kernel (full width at half maximum 6 mm). A temporal filter (0.01–0.08 Hz) was applied to reduce low-frequency drifts and high-frequency physiological noise. The resulting amplitude of low frequency fluctuations maps were then used to scale the contrast images obtained during the stimulation protocol.

Statistical Second-Level Analyses

For the fMRI data, block design $2 \times 2 \times 2$ full factorial analyses were used, including the factors group (nonsurgical, RYGB), task (wanting, liking), and food (high calorie, low calorie). Analyses were controlled for age, BMI, and hunger. Results were considered significant at $P < 0.05$ family-wise error-corrected on cluster level as a function of an uncorrected primary threshold level of $P < 0.001$ (33).

Statistical analyses of behavioral data were performed using SPSS version 22 software (IBM Corporation, Armonk, NY). Differences in eating behavior traits, descriptive data, and blood measurements between the two groups were analyzed using two-sample *t* tests. Group differences in the hunger state (pre- and postmeasurement) were analyzed by using a repeated-measures ANOVA with the within factor time and the between factor group. Repeated measurements of HbA_{1c} levels and BMI for the RYGB group (pre- and postsurgery) were analyzed using paired *t* tests. An ANOVA was performed with the factors group and task and the covariates age and BMI to test for group and task-related differences. Group differences in medication and sex distribution were calculated by χ^2 tests. Results of behavioral analyses were considered significant at $P < 0.05$ (Table 1).

RESULTS

Weight, Glycemic Control, and Medication

All subjects had preexisting T2DM (duration since diagnosis: 6.46 ± 1.09 vs. 11.17 ± 1.91 years for RYGB vs. nonsurgical, respectively) and were severely obese before surgery. The two study groups were matched for age, postsurgical BMI, and presurgical HbA_{1c}.

The HbA_{1c} level significantly improved after surgery in the RYGB group from 7.07 ± 0.50 to 5.70 ± 0.16% ($P < 0.05$). BMI also improved from 52.21 ± 1.90 to 35.71 ± 0.84 kg/m^2 ($P < 0.001$).

Medication was documented as the number of subjects taking oral diabetes-specific drugs and/or undergoing insulin therapy. Diabetes medication was significantly lower in the RYGB group than in the nonsurgical group (Table 1).

Behavioral Results

Behavioral results of the wanting and liking ratings during the scanning sessions revealed higher ratings in both tasks for the nonsurgical group than for the RYGB group ($P < 0.001$) and generally higher liking than wanting ratings

(P = 0.002). No interaction effect of the factors group and task was observed (Fig. 1). Hunger scores were low and increased over time (P = 0.019) but did not significantly differ between the two groups (P = 0.115) (Supplementary Fig. 1). Mood parameters showed no group differences.

In general, the RYGB group showed lower scores in eating behavior–related traits than did the nonsurgical group. In particular, the RYGB group scored significantly lower in cognitive restraint (Three Factor Eating Questionnaire) and power of food (Power of Food Scale) (Supplementary Table 1).

Neuronal Differences

We found significant main effects for the factors group and task but not for the factor food. No significant interaction between factors were observed.

For the main effect group, the nonsurgical subjects displayed higher activity in regions associated with inhibition (inferior frontal gyrus) and reward (globus pallidus) and in a general connectivity hub (precuneus) than subjects in the RYGB group (Fig. 2*A* and Table 2). In comparison, the RYGB surgical group showed higher activation in visual (primary visual, fusiform gyrus), frontal control regions (frontal middle gyrus, anterior cingulate cortex), somatosensory cortex, motor regions (supplementary motor area, supramarginal gyrus), memory-related areas (hippocampus), and gustatory regions (anterior insula, operculum) than the nonsurgical group (Fig. 2*B* and Table 2).

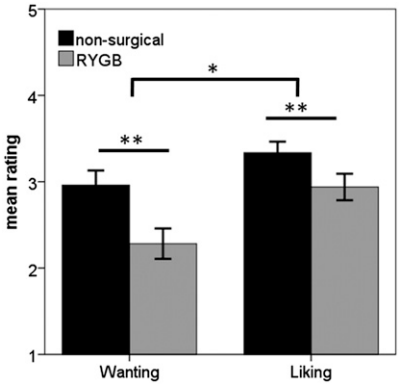

Figure 1—Mean wanting and liking rating for food pictures within the scanning sessions for the nonsurgical and RYGB groups. Error bars represent SEM. *P < 0.01, **$P \leq$ 0.001.

In an exploratory analysis, we tested whether improved glycemic control (change in HbA_{1c}) is associated with specific changes in brain activation within the RYGB group. The analysis with an uncorrected threshold level of $P <$ 0.01 revealed a significant correlation of the HbA_{1c} reduction with activity in the orbitofrontal cortex (OFC) (Supplementary Fig. 2). Greater HbA_{1c} reduction was associated with higher activity in the OFC during food reward processing.

For the main effect task, activation differences were detected in the somatosensory cortex (postcentral gyrus), showing higher activation in the wanting task than in the liking task (Supplementary Fig. 3 and Table 2).

CONCLUSIONS

The aim of this study was to investigate the effect of a food reward–related task (wanting, liking) on brain functions in two groups of similarly obese subjects with T2DM: one group after RYGB surgery and one group without surgery. The RYGB group showed substantially improved glycemic control in the normal range, whereas the nonsurgical group had impaired glycemic control.

On a behavioral level, we observed lower scores in questionnaires examining eating behavior–related pathologies in the RYGB group, which has also been reported in previous studies (25,34–36). Furthermore, the lower wanting and liking scores after bariatric surgery are in line with previous findings of a reduced desire to eat after RYGB (11).

Neuronal activation patterns showed distinct differences between the groups and between the two task conditions. Obese patients with T2DM without surgery and impaired glycemic control showed substantially higher activations in brain areas associated with inhibition (inferior frontal gyrus) and reward (globus pallidus) compared with their counterparts who experienced improved glycemic control after RYGB. Also in the nonsurgical subjects, we found higher activity in the precuneus, a central hub in the brain with strong and multiple connections to various brain areas and, thus, involvement in high-level cognitive functions, including episodic memory, self-related processing, and aspects of consciousness (37,38). One may speculate that in the nonsurgical subjects, the visual stimulation of food items during the wanting and liking tasks triggers an increase in self-related processes associated with palatable food, which has to be actively modulated by inhibitory processes. Similarly, Bruce et al. (39) reported that patients who had undergone gastric banding surgery showed higher inferior frontal activity during the processing of food pictures before than after surgical intervention. In addition, changes in food reward–related brain regions were reported soon after bariatric surgery (24) and after a weight loss of at least 8% (40). The globus pallidus is proposed to directly initiate reward-related signals (41). Changed food reward–related activation patterns, therefore, might be a direct consequence of the surgery, even without weight loss. Likewise, an improvement of glycemic control can be observed immediately after surgery before weight loss is measurable (21). Hence, the mesolimbic reward system might play a crucial role in diabetes remission after bariatric surgery.

The RYGB subjects with normalized glycemic control showed increased activity in a large number of brain areas compared with the nonsurgical control group. A large cluster was found in the visual area, including the fusiform gyrus. The fusiform gyrus is consistently activated in visual food processing (42), and higher activity in patients after RYGB than in an obese control group without surgery has also been reported (25). In addition, the fusiform gyrus was found to be more highly activated after stimulation with high-caloric food pictures in lean subjects after ingestion of water, whereas glucose ingestion resulted in an enhanced activity of the fusiform gyrus to low-caloric stimuli in lean subjects. Obese subjects showed no such differential reaction pattern in the fusiform gyrus (43). This region, therefore, appears to be sensitive to postprandial glycemic and hormonal actions. In this regard, it is important that food-related fusiform gyrus activity is specifically modulated by insulin (44). Thus, the higher activity in the fusiform gyrus may indicate an improved insulin sensitivity of the brain region after bariatric surgery with improved glycemic control. Because impaired insulin action in the human brain has negative consequences for metabolism, improvement of brain insulin action might be one reason for

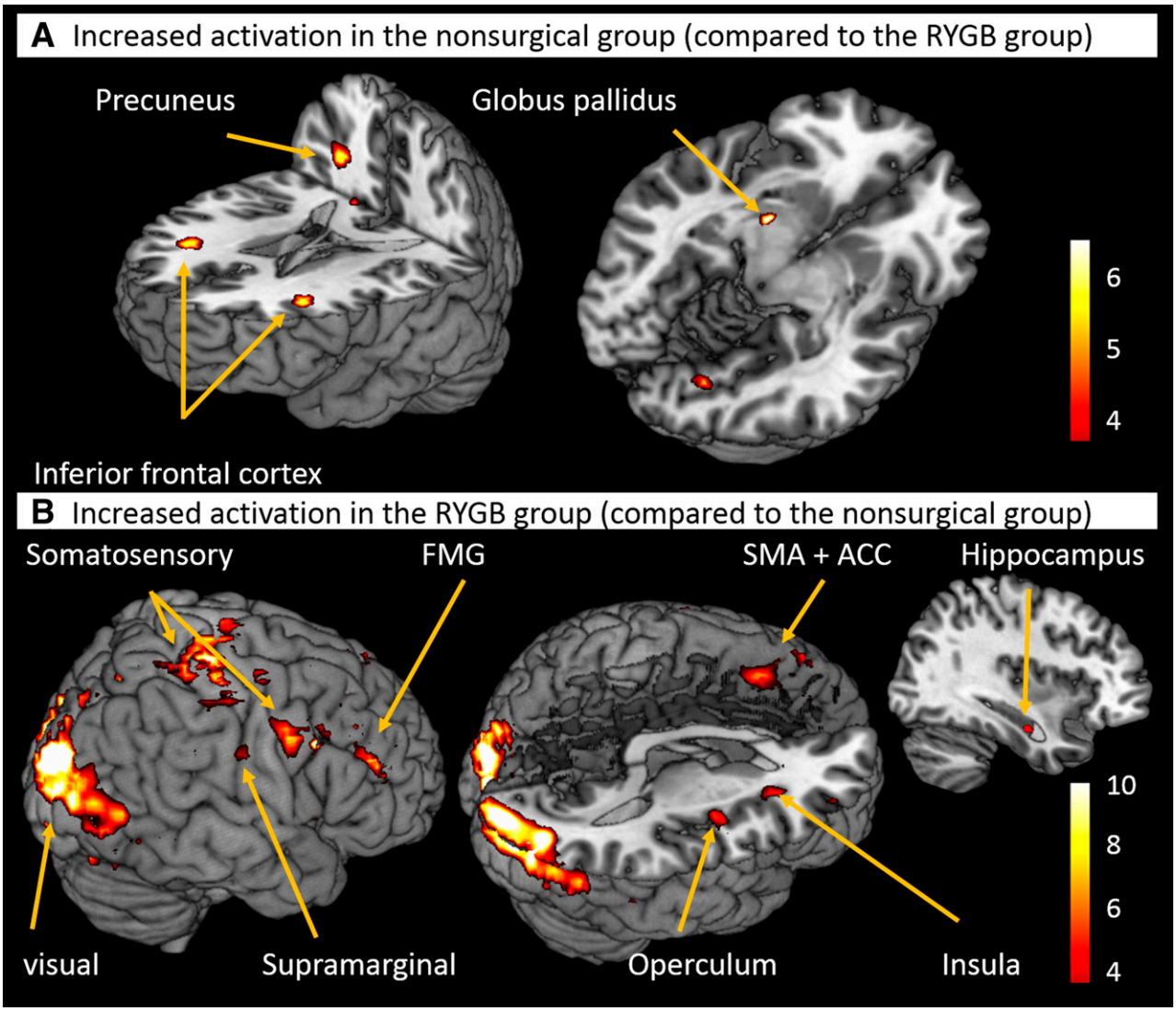

Figure 2—*A*: Regions with higher activation in the nonsurgical group than in the RYGB group. *B*: Regions with higher activity in the RYGB group than in the nonsurgical group. Results are significant at $P < 0.05$ family-wise error-corrected after an initially uncorrected threshold of $P < 0.001$. The color bar represents *T* values. ACC, anterior cingulate cortex; FMG, frontal middle gyrus; SMA, supplementary motor area.

improved metabolic control (45). However, the current study cannot distinguish between cause and consequence in this regard.

The increased activity in the anterior insula and the rolandic operculum may also be associated with food evaluation. The anterior insula is part of the primary gustatory cortex (46). Scholtz et al. (40) also observed higher activation in the anterior insular cortex with food stimuli after bariatric bypass surgery. In addition, we observed increased activity in the hippocampus, a major memory-related area. In conjunction with the other areas, the hippocampus may be responsible for the establishment of new memory traces for food in relation to the metabolic and eating behavior–related changes after improved glycemic control.

In an exploratory analysis, change in the HbA_{1c} level in the RYGB group was associated with increased activation in the OFC. This area is part of the secondary gustatory cortex and is involved in the integration of perceived stimuli, evaluative processes, and reward. Larger HbA_{1c} reduction and, therefore, improvement of glycemic control are associated with higher OFC activity. This goes along with our findings in the RYGB group of increased activity in the primary gustatory cortex (insula, operculum) (Fig. 2*B*), which seems to be more sensitive after surgery. According to the present exploratory analyses, the secondary gustatory cortex seems to be sensitive to HbA_{1c} change within the RYGB group.

Independent of the groups, the main effect task revealed higher activation in the somatosensory cortex for wanting than for liking, suggesting that each of the two food-reward components has a different evaluation process. In a previous study, we investigated a leaner (mean BMI 27 kg/m^2) nonsurgical study population and found higher activation for wanting than for liking in a large brain network, including the visual, reward, memory, food processing, emotion, and frontal control regions (12). Therefore, one might speculate that the different task effect compared with healthy subjects is associated with severe obesity and/or diabetes.

Table 2—Significant differences in brain activation for the nonsurgical and RYGB groups during the wanting and liking rating tasks

Effect	Brain region	MNI Coordinates			Cluster size (voxels)§	*T* value
		x	*y*	*z*		
Task-related activation						
Nonsurgical > RYGB	Lateral globus pallidus	21	−7	−8	10	5.60
	Inferior frontal gyrus	33	26	19	22	5.58
		−39	29	16	16	4.88*
	Precuneus	33	−55	34	44	5.18
RYGB > nonsurgical	Fusiform gyrus/visual cortex	39	−79	−5	2,975	10.61
	Supplementary motor area/anterior cingulate cortex	0	23	52	315	6.96
	Supramarginal gyrus	−54	−37	34	32	6.75
	Rolandic operculum	−39	−7	16	70	6.09
	Frontal middle gyrus	−39	38	22	88	6.07
	Somatosensory cortex (postcentral gyrus)	−42	−40	61	110	5.75
		39	−37	64	42	5.50
	Primary motor cortex (precentral gyrus)	−54	2	40	126	5.38
	Hippocampus	39	−13	−23	11	6.04
	Anterior insula	−33	29	4	60	5.33
		33	29	1	23	4.23*
Wanting > liking	Somatosensory cortex (postcentral gyrus)	39	−34	58	70	5.21

§Results are significant with $P < 0.05$ family-wise error-corrected on cluster level after an initially uncorrected threshold of $P < 0.001$. *$P < 0.001$ uncorrected. Result included to show the bilateral activation pattern.

Overall, in the current study, patients who underwent RYGB surgery are characterized by reduced eating pathologies associated with a reduced need for inhibitory processes, higher cognitive control, and increased gustatory activity. Thus, brain areas involved in the control of temptations to eat are altered in food reward processes after bariatric surgery, which is especially noteworthy because the surgery changes eating behavior based not only on smaller stomach size but also on neuronal and psychological processes related to eating behavior. This finding suggests a general change in the reaction to food-related temptations after RYGB in T2DM.

The use of bariatric surgery as a diabetes and weight loss treatment has to be considered carefully because some patients have shown a relapse of diabetes (47,48) and weight regain (20). A driving factor for successful diabetes remission and weight loss maintenance could be bariatric surgery–associated neuronal changes as reported in the current study. However, further studies are needed to determine the effect of neuronal plasticity on success or nonsuccess of bariatric surgery in relation to diabetes relapse and weight regain.

Whether the observed differences in neuronal activation are due to either the change in HbA_{1c} and BMI in the RYGB group or the difference in current HbA_{1c} between the groups cannot be ruled out. To our knowledge, only one study compared food-related neuronal processes between an obese group and an equally obese group with diabetes (5) wherein a higher activation was reported in gustatory and reward regions for patients with diabetes than for the control subjects. In the current study, we also found higher activation in a reward-associated region (pallidus) as well as in inferior frontal regions associated with inhibition. In addition, we found a rather large network of higher activation in the RYGB group, including gustatory, frontal control, visual, motor, and memory-related regions. Thus, the results of the current study clearly differ from the previous study, indicating that the improvement of HbA_{1c} induced by the surgery might be causal.

Several limitations of the study remain to be mentioned. Because of the cross-sectional study design, we cannot assess a causal role of changes in glycemic control on neuronal function. In addition, the tasks were not counterbalanced, which might have affected the main effect task. Groups were not matched for individual duration since T2DM diagnosis. Diabetes-related medication in the RYGB group was lower than in the nonsurgical group at the time of measurement. Moreover, Duarte et al. (49) showed that functional brain activation can be influenced by impaired vascular coupling in patients with diabetes. Thus, we controlled the analyses for the individual vascularity as proposed by Tsvetanov et al. (31).

In summary, in obese patients with T2DM, we show distinct neuronal differences between those who underwent bariatric surgery with improved/normalized glycemic control and those who did not undergo surgery with worse glycemic control. On the basis of the BMI-matched sample, the observed neuronal effects do not depend on BMI differences. Instead, differences in food reward–associated brain functions might be based on substantial weight loss and an improvement in glycemic control. Those neuronal activation patterns might be one factor in improved eating pathologies and in gaining long-lasting remission of diabetes.

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