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BARIATRIC AND METABOLIC SURGERY ORIGINAL ARTICLE

Altered brain activity in severely obese women may recover after Roux-en Y gastric bypass surgery

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OBJECTIVE: Neuroimaging studies have demonstrated alterations in brain activity in obese (OB) subjects that might be causally linked to their disorder. Roux-en Y gastric bypass (RYGB) surgery induces a marked and sustained weight loss and may affect brain activity. The aim of this study was to compare brain activity pattern between severely OB women ($n = 11$), normal-weight women (NW, $n = 11$) and previously severely OB women who had undergone RYGB surgery (RYGB, $n = 9$) on average 3.4 ± 0.8 years (all >1 year) before the experiment.

DESIGN: Brain activity was assessed by functional magnetic resonance imaging during a one-back task containing food- and non-food-related pictures and during resting state. Hunger and satiety were repeatedly rated on a visual analog scale during the experiment.

RESULTS: As compared with NW and also with RYGB women, OB women showed (1) a higher cerebellar and a lower fusiform gyrus activity during the visual stimulation independently of the picture category, (2) a higher hypothalamic activation during the presentation of low- vs high-caloric food pictures, (3) a higher hippocampal and cerebellar activity during the working memory task and (4) a stronger functional connectivity in frontal regions of the default mode network during resting state. There were no differences in brain activity between the NW and RYGB women, both during picture presentation and during resting state. RYGB women generally rated lower on hunger and higher on satiety, whereas there were no differences in these ratings between the OB and NW women.

CONCLUSION: Data provide evidence for an altered brain activity pattern in severely OB women and suggest that RYGB surgery and/or the surgically induced weight loss reverses the obesity-associated alterations.

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INTRODUCTION

Bariatric surgery represents the most effective therapy for long-term weight loss in severely obese (OB) subjects[1] and the Roux-en Y gastric bypass (RYGB) is currently the most frequently performed bariatric procedure.[2] While mechanical restriction of food intake in conjunction with malabsorption of nutrients may represent the main effects of the surgery promoting weight loss, profound modulation of the secretion of hunger/satiety regulating gut hormones may also contribute to the weight loss by reducing hunger and appetite.[3–7]

One major contributor to obesity is overeating. Growing evidence indicates an impaired homeostatic regulation of food intake and altered food reward-related processes in OB subjects.[8,9] In general, different eating disorders show differential neural responses to food items.[10] Specifically, obesity is associated with greater activation in food reward-related brain regions and a lower activation of frontal brain regions due to food stimulation.[11,12] Furthermore, satiation after a meal is associated with greater reduction in the neuronal activity of homeostatic, reward and emotion-related brain areas, but an enhanced activation in prefrontal areas in OB subjects.[13,14] These food-related neuronal alterations in OB subjects may also be mediated by impaired anorexic hormonal pathways as suggested by previous neuroimaging[15,16] and behavioral studies.[17] In addition, a recent study[18] has pointed to an altered 'resting state' brain activity within the default mode network (DMN) in OB subjects. It remains unknown, however, whether functional brain changes constitute a cause or a consequence of obesity.

Only little is known on the putative effects of RYGB surgery on central nervous processes regulating eating behavior. One recent functional magnetic resonance imaging (fMRI) study showed a partial normalization (in comparison to a normal-weight (NW) control group) of the preoperatively impaired hypothalamic response to an oral glucose challenge 9 months after surgery.[19] Other recent fMRI studies found reduced activation in mesolimbic reward circuits[20] as well as an association between postoperative reduction in wanting for high- (HC) vs low-caloric (LC) food and diminished activity within mesolimbic as well as dorsolateral prefrontal brain areas[21] 1 month after RYGB surgery as compared with preoperative responses. Interestingly, such early postoperative changes in the neural activity response to food pictures appear to be even more pronounced in the fasting as

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compared with the postprandial state.[22] Lastly, two positron emission tomography studies yielded contradictory results of the density of dopamine type 2 receptors within mesolimbic brain structures after RYGB surgery, that is, one showing an increased density after 6 months[23] and the other showing a decrease after 7 weeks.[24]

Of note, in all of these studies changes in brain functions after RYGB were assessed relatively shortly after the surgery, that is, a phase characterized by a profoundly negative energy balance and thus catabolic state. Also, most of these studies did not include a NW control group, so that it remained unclear as to how the observed changes after the RYGB related to the NW state.

We performed a cross-sectional case–control study recording brain activity by fMRI in women who had undergone RYGB surgery at least 1 year before as well as in severely OB women and NW control women. On the background of previous findings showing an influence of food cues on working memory in subjects with eating disorders,[10,25] we presently assessed brain activity during the visual presentation of food and non-food (NF)-related pictures while performing a one-back working memory task, that is, an approach that has not previously been used in studies comprising bariatric surgery. Furthermore, for the first time we assessed resting state in these patients and assessed subjective ratings on hunger and satiety in parallel. Whole head analyses were performed as well as region of interest (ROI) analyses for hypothesized brain regions. Overall, we hypothesized differential effects of obesity and RYGB surgery on brain activity pattern in homeostatic, reward-related and prefrontal inhibitory control regions.

SUBJECTS AND METHODS

Subjects

Severely OB ($n = 11$; body mass index (BMI) all $>35\,kg\,m^{-2}$) and previously severely OB women who had undergone an RYGB surgery at least 1 year before ($n = 9$) were recruited from the Interdisciplinary Obesity Center (St Gallen, Switzerland) and the adiposity platform of the University of Tübingen (Tübingen, Germany). NW (BMI: 19–25 $kg\,m^{-2}$) women ($n = 11$) were recruited in St Gallen and in Tübingen. Exclusion criteria were contraindications for the fMRI scanning (for example, metal implants), any kind of known psychiatric or neurological diseases as well as a current medication with drugs acting on the central nervous system or affecting eating behavior. The upper weight limit of the fMRI scanner was 150 kg, so that women with a higher body weight had to be excluded. Giving this weight limit and even more important limitations regarding the body circumference due to the interior diameter of the scanner, we decided to restrict the study to women and not to include men. All participants gave written informed consent and the study protocol was approved by the ethics committees of the Canton St Gallen and the Medical Faculty of the University Tübingen.

RYGB procedure

The average time after surgery for the RYGB group was 3.4 ± 0.8 years (range: 1.1–8.7 years). Six of the women had undergone a proximal RYGB surgery with a Roux limb length of 150 cm, while the remaining three women had undergone a distal RYGB surgery with the common channel length ranging between 60 and 100 cm.[26] The biliopancreatic limb length was about 60 cm in the proximal and 60–100 cm in the distal RYGB procedures. In both RYGB procedures, the largest part of the stomach was transected, thereby creating a small gastric pouch of about 30 ml, which was anastomized to the proximal jejunum. The diameter of this pouch–jejunal anastomosis was standardized as to 12 mm by using a round stabler.

Study protocol

fMRI measurements were performed in the afternoon. Food intake was standardized by providing the subjects a liquid meal (300 ml; Protiline balance vanilla (Vifor Pharma, Villars-Sur-Glane, Switzerland), in total: 246 kcal, 25.6% protein, 64.2% carbohydrates; 10.2% fat) 30 min before the fMRI measurements. Before, 25 min after the liquid meal and immediately after the fMRI scanning procedure, participants rated their perceived hunger, satiety, fullness and prospective food consumption on a 100 mm visual analog scale.[27]

To assess eating behavior-related traits, we applied the German version of the Three-Factor Eating Questionnaire (TFEQ).[28] In addition, subjects were asked about their highest education on a four-point rating scale (1 = 9-year school (Hauptschule), 2 = 9-year school (Hauptschule) with further apprenticeship, 3 = 10-year school (Realschule), 4 = 12/13-year school (Abitur/University). Body composition was assessed by multifrequency bioelectrical impedance analysis (Nutriguard M, Data Input, Darmstadt, Germany). Percentage of fat mass was computed by using the manufacturer's software (NutriPlus 5.4.1). Capillary blood glucose concentrations were measured using a glucometer (One touch Ultra 2, LifeScan, Johnson & Johnson, Milpitas, CA, USA) before the ingestion of the liquid meal.

fMRI scanning protocol

Participants were lying in the scanner with their head fixated in an 8-channel head coil. They were instructed not to move, and for communication, an intercom supply was used. The fMRI scanning procedure started with three sessions of an established stimulation protocol.[29] Food and NF pictures were presented to the subjects during the fMRI scanning by using a custom-made visual stimulation device (mirror to project the visual cues into the field of view of the subjects) and the Presentation software (Version 10.2, www.neurobs.com). Food pictures included HC and LC foods. Pictures of the different categories were matched for complexity, valence and arousal. Pictures were presented within a block design with two different task conditions: one was a one-back memory task in which participants had to press a button with the index finger of the right hand as fast as possible to indicate whether the shown picture was the same as the picture immediately shown before (left button) or not (right button). The other condition was a control task during which participants always had to press the left button whenever a picture appeared. During both tasks reaction time was recorded. The order of the task conditions, that is, one-back and control task, was randomly alternated within each session. Details on the stimuli material and experimental paradigm have been described previously.[29]

Following these stimulation sessions, a 6-min resting state measurement[30] was performed during which subjects were instructed to close their eyes but not to fall asleep and not to think of anything particular.

Imaging procedures and analyses

Whole-brain fMRI blood oxygen-level dependent data were obtained by using a 1.5 T fMRI scanner (Siemens Vision, Erlangen, Germany). During the stimulation paradigm, each session consisted of 310 scans and 178 scans were recorded during resting state (repetition time = 2 s; echo time = 40 ms; matrix: 64×64; flip angle: 90°; voxel size: $3 \times 3 \times 4\,mm^3$; slice thickness: 4 mm; 1 mm gap; 27 slices; images acquired in ascending order). At the end of the scanning period, high-resolution T1-weighted anatomical images (MPRage: 176 slices; matrix: 256×224, $1 \times 1 \times 1\,mm^3$) of the brain were obtained.

Analyses of the fMRI data were performed using the Statistical Parametric Mapping 8 (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/). Data were preprocessed starting with realignment of the images to the mean image. To account for susceptibility by movement artifacts, unwarping of geometrically distorted echo-planar images was performed using the FieldMap Toolbox available for SPM8. The anatomical T1-weighted image was coregistered to the mean functional image. Thereafter, normalization into Montreal Neurological Institute (MNI) space (3 mm isotrop voxel size) and Gaussian spatial smoothing (full-width at half-maximum: 6 mm) was performed. Data were high-pass filtered (cut off: 128 s) and auto correlation corrected (AR(1)). For each condition, a separate regressor was modeled using a canonical hemodynamic response function including time derivatives. Movement parameters were modeled as confounds.

Resting state data were analyzed using a group spatial independent component analysis.[31] Using the GIFT software (http://icatb.sourceforge.net/), the smoothed and normalized fMRI images were decomposed into 18 components. To determine the number of components, dimensionality estimate was used using the minimum description length criteria, modified to account for spatial correlation. Data from all participants were then concatenated and this aggregated data set was reduced to 18 temporal dimensions using principal component analysis, followed by an independent component estimation

using infomax algorithm. For each subject, spatial maps were reconstructed and converted to *z*-values. To investigate differences in the DMN, the components matching the DMN were selected. For the selection, a DMN mask was used including precuneus, posterior cingulate and Brodmann area 7, 10 and 39.[31]

Statistical analyses

Data are provided as mean ± s.e.m. Participants' characteristics and questionnaires scores were compared across the three groups by analyses of variance (ANOVA). Visual analog scale ratings were analyzed by ANOVA models, which included the factor 'group' (NW, OB, RYGB) and the repeated-measure factor 'time'. Significant results were further evaluated by Tukey's honestly significant difference *post hoc* tests. For ordinal variables (level of education), Kruskal–Wallis test was used to examine group differences. All of these statistical analyses were carried out by using SPSS 18 (SPSS Inc., Chicago, IL, USA).

Stimulus-dependent fMRI data were analyzed using a full factorial design, including the within-subject factors 'picture' (HC, LC, NF) and 'task' (one-back, control) and the between-subject factor 'group'. To assess the effects of food, the contrasts 'HC vs NF' and LC vs NF' from the first-level analyses was used for the multivariate analysis. For the factor 'task', the contrast 'one-back vs control' was entered in a separate ANOVA. For a detailed analysis with respect to the calorie content of the food pictures, the 'HC vs LC' contrast was included in respective ANOVA models. To evaluate general differences in brain activity, a whole brain analysis was performed. In addition, ROI analyses were performed for specific brain regions (hypothalamus, striatum, dorsolateral prefrontal cortex) in which we, based on previous studies,[19–22,32,33] expected significant differences across the three groups. All analyses were corrected for age. Results of the main effects were considered significant at a *P*-value <0.05 family-wise error (FWE) corrected. For interaction effects and resting state analysis, results were considered significant at an uncorrected *P*-value <0.001 with respective analyses also controlling for age.

RESULTS

Subjects

The characteristics of the participants are summarized in Table 1. Although NW women were on average younger than OB women and women with an RYGB, this difference did not reach significance in overall ANOVA ($P=0.41$). However, to account for a potential biasing influence of age differences, all analyses on outcome variables were corrected for age. There were no differences in the highest educational level across the three study groups ($P=0.65$). The average BMI significantly differed across the three study groups ($P<0.001$), with OB women showing the highest and NW women the lowest BMI. The mean BMI of the women with RYGB was significantly lower than that of the OB women ($P<0.001$), but still significantly higher than that of the NW women ($P<0.001$). The mean BMI of the RYGB women before they had undergone the surgery was $43.3 \pm 0.38\,kg\,m^{-2}$, which thus tended to be even higher than that of OB women ($P=0.061$). At the time of the experiment, the percentage of body fat was significantly higher in OB women than in the other groups (both $P<0.001$), whereas there was no significant difference between the RYGB and NW group ($P=0.20$). Blood glucose levels were similar in all three study groups ($P=0.65$).

Eating behavior questionnaire

The 'disinhibition' and 'hunger' domain score showed significant differences across the three study groups (Table 1; overall ANOVA both $P<0.05$). OB women showed significantly higher scores on the 'disinhibition' and on the generally experienced 'hunger' scale than the NW women (both $P<0.05$). Respective 'disinhibition' scores of women with an RYGB were not significantly different from those of OB or NW women (both $P>0.5$). Experienced 'hunger' however tended to be lower than in the OB group ($P=0.08$), but similar to those of the NW group ($P>0.5$). The NW women show a trend for a lower score on the 'cognitive restrained' domain of the TFEQ compared with OB women and women with an RYGB ($P=0.094$ for overall ANOVA).

Table 1. Participant's characteristics and results on eating behavior questionnaires

	NW	*RYGB*	*OB*	P-*value*
Age (years)	36.6 ± 3.8	42.0 ± 2.8	42.6 ± 4.0	0.412
BMI ($kg\,m^{-2}$)	21.4 ± 0.5	27.1 ± 0.9[a]	40.2 ± 0.8[a,b]	<0.001
Body fat (%)	26.1 ± 1.8	31.1 ± 2.2	49.2 ± 1.5[a,b]	<0.001
Plasma glucose ($mmol\,l^{-1}$)	5.2 ± 0.3	4.9 ± 0.15	5.0 ± 0.2	0.649
Education	3 (2–4)	3 (2–4)	3 (2–4)	0.652
TFEQ				
Cognitive restraint (1–21)	6.00 ± 1.30	10.56 ± 1.56	9.55 ± 1.61	0.094
Disinhibition (1–16)	3.89 ± 0.79	6.33 ± 0.78	8.55 ± 1.10[c]	<0.01
Hunger (1–14)	2.94 ± 0.93	3.78 ± 0.94	7.18 ± 1.10[a]	<0.05

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; NW, normal-weight group; OB, obese group; RYGB, Roux-en Y gastric bypass group; TFEQ, Three-Factor Eating Questionnaire. Data are mean ± s.e.m. for interval scaled variables and median (range) for ordinal variables. *P*-values derive from overall ANOVA, except for the variable education (1 = 9-year school (Hauptschule), 2 = 9-year school (Hauptschule) with further apprenticeship, 3 = 10-year school (Realschule), 4 = Abitur/University), which was analyzed by using the nonparametric Kruskal–Wallis test. For pair-wise comparisons Tukey's honestly significant difference *post hoc* tests were used. [a]$P<0.001$ vs NW group. [b]$P<0.001$ vs RYGB group. [c]$P<0.05$ vs NW group.

Visual analog scales

Overall ANOVA on visual analog scale data revealed significant changes in hunger, satiety, fullness and prospective food consumption across the experimental period (all $P<0.03$ for the 'time' main effect; Figure 1) and also significant differences in ratings of these symptoms across the three study groups (all $P<0.05$ for the group main effect). While the NW and OB women overall showed very similar rating scores during the experiment, women with an RYGB rated markedly lower on hunger and prospective food consumption and higher on satiety and fullness. The differences between the RYGB and the other two groups was particularly pronounced immediately before the beginning of the scanning, although the respective interaction term reached significance only for the satiety and the prospective food consumption score (both $P=0.04$ for group × time).

Analyses of fMRI data during visual stimulation

During the task in the scanner, no differences in reaction times were observed between the three study groups ($P=0.19$).

Significant functional group differences were observed during the presentation of pictures (irrespective of the category) in the cerebellum at Crus 1 and the fusiform gyrus (Table 2). OB women showed a weaker fusiform and stronger cerebellar activation in response to the pictures than NW women and also women with an RYGB (Figure 2).

Analyses on the effects of the factor 'task' revealed, as expected,[29] a higher activation during the one-back task compared with the control task in brain areas related to motor functions and working memory such as parietal, temporal and cerebellar regions (Supplementary Material Table S1). In contrast, a higher activation in superior frontal regions and the precuneus, which can be attributed to regions of the DMN, was observed during the control task. Analyses of the contrast 'one-back task vs control task' revealed significant differences across the study groups reflecting a higher activation in the hippocampus and the cerebellum at Crus 1 in the OB women as compared with the NW and the RYGB women (Table 2 and Figure 3a).

Analyses of the distinct responses to the different pictures revealed group-independent effects for the contrasts 'HC vs NF',

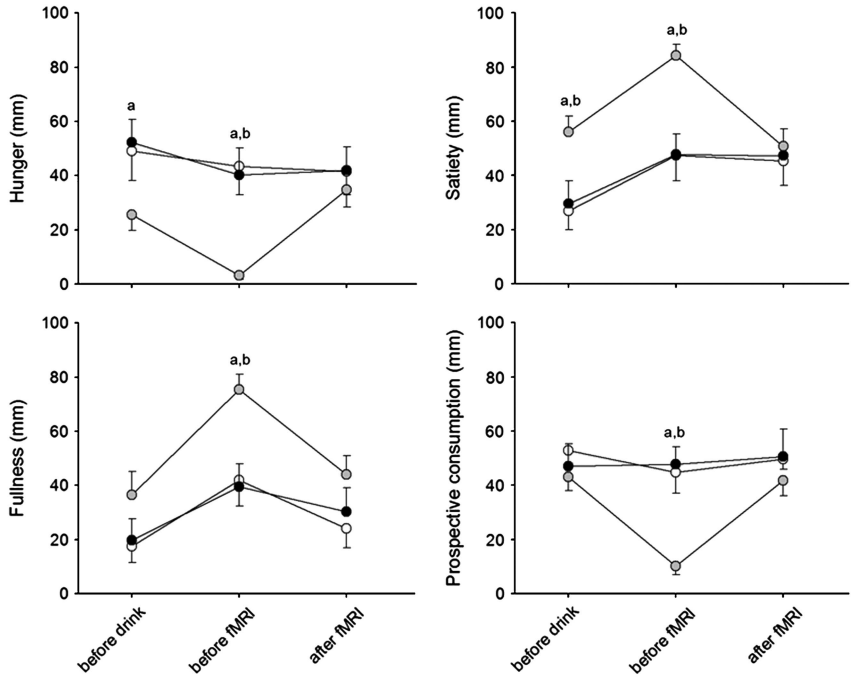

Figure 1. Mean ± s.e.m. visual analog scale ratings on hunger, satiety, fullness and prospective food intake in the NW (open circles), RYGB (gray circles) and the OB (black circles) group before, 25 min after the liquid meal and after the fMRI measurements. Overall ANOVA revealed significant changes in hunger, satiety, fullness and prospective food consumption over time (all $P<0.05$ for the 'time' main effect) and significant differences across the three study groups (all $P<0.05$ for the 'group' main effect) as well as a significant 'group × time' interaction term for satiety and prospective food consumption (both $P=0.04$). [a]$P<0.05$ RYGB vs OB; [b]$P<0.05$ RYGB vs NW by Tukey's honestly significant difference *post hoc* tests.

Table 2. Significant results of the fMRI analyses related to differences across the study groups

Paradigm	*Effect*	*Brain region*	*MNI coordinates*			*Cluster size (in voxels)*	*Z-value*
			x	*y*	*z*		
All pictures	Main group	Cerebellum (Crus 1)	24	−78	−30	39	6.07
		Fusiform gyrus	33	−51	−18	7	5.40
All pictures	Group x task	Hippocampus	30	−30	−6	11	3.86
		Cerebellum (Crus 1)	21	−72	−36	12	3.68
HC vs LC	Group x food	Hypothalamus	3	−9	−9	7	4.33[a]
Resting state	Main group	ACC	−3	33	−6	12	3.97
			9	36	6	88	3.36
		FSG	−21	51	3	49	3.71
			18	57	3	88	3.31
		OFC	9	42	−12	13	3.57

Abbreviations: ACC, anterior cingulate cortex; ANOVA, analysis of variance; FWE, family-wise error; fMRI, functional magnetic resonance imaging; FSG, frontal superior gyrus; HC, high-caloric; LC, low-caloric; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; ROI, region of interest. Results are reported using the MNI coordinate system. Results are based on ANOVAs. Main effects are significant at $P_{FWE}<0.05$, FWE corrected. Interaction effects and resting state analysis are significant at $P<0.001$ uncorrected (ACC, FSG, OFC). [a]ROI analysis: ($P_{FWE}<0.05$, FWE corrected).

'LC vs NF' and 'HC vs LC' (Supplementary Material Table S2). HC food pictures elicited a stronger activation in food-related brain areas such as the orbitofrontal cortex (OFC), the insular cortex, the amygdala, ACC and the fusiform gyrus than NF-related pictures. HC food pictures also elicited a stronger activation than the LC food pictures in gustatory and reward-related areas (OFC, ACC) and also in frontal control regions, that is, in the frontopolar cortex. When contrasted against NF-related pictures, LC food pictures elicited a higher activation in the fusiform gyrus.

No significant differences in responses to food vs NF-related pictures were found across the three study groups. However, when HC food pictures were contrasted against LC food pictures, a group by caloric content interaction with distinctly different activity pattern emerged within the hypothalamus across the three study groups (Table 2). Severely OB women showed a much stronger hypothalamic activation during the presentation of LC than HC food pictures, whereas NW and RYGB women showed a reverse pattern (Figure 3b).

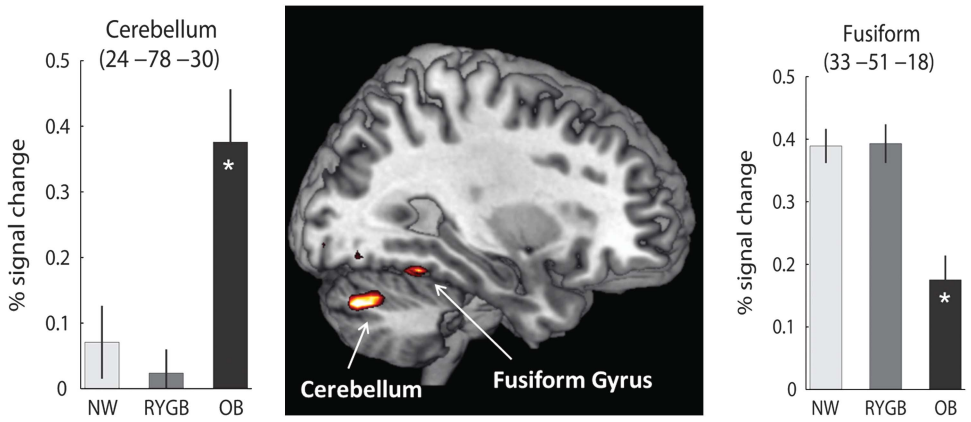

Figure 2. Left: Bar graphs of the activation in the cerebellum upon the presented pictures independent of the category in the NW, RYGB and the OB group. Middle: Sagittal view of mean activation of the main effect 'group' during visual stimulation (pictures). Right: Bar graphs of the activation in the fusiform gyrus during stimulation. *Significantly different ($P_{FWE} < 0.05$, FWE corrected for multiple comparison) from the two other groups.

Analyses of resting state fMRI data

Resting state analysis revealed a much stronger functional connectivity within the DMN comprising the ACC bilaterally, in the frontal superior gyrus bilaterally and in the right OFC in the OB than in NW women, and also than in women with an RYGB (Table 2 and Figure 4). Of note, the NW and RYGB group showed very similar connectivity strength within the DMN.

DISCUSSION

For the first time, we assessed brain activity responses to food- and NF-related pictures presented within a one-back and control task as well as resting state brain activity in severely OB and NW women in addition to previously severely OB women who had undergone RYGB surgery on average 3.4 years before. We found a markedly altered brain activity pattern in severely OB as compared with NW women during the presentation of food and NF pictures as well as during resting state conditions. Also, severely OB women showed a much stronger hypothalamic activation during the presentation of LC food pictures and a weaker response to HC food pictures. Furthermore, eating behavior questionnaires indicated generally enhanced disinhibition and hunger scores in the severely OB women. Ratings of the OB group on hunger, satiety, fullness and prospective food consumption did not differ with that of the NW women throughout the experiment. Most intriguing, however, are our observations in the RYGB women. Here, the brain activity during visual stimulation as well as during resting state distinctly differed from respective pattern in severely OB women, but showed no difference to the NW women despite higher ratings on satiety and fullness and lower ratings on hunger and prospective food consumption immediately before the scanning period. Taken together, our data suggest that alterations in brain activity associated with severe obesity may recover after RYGB surgery.

The clinical significance of the found alterations in brain activity in severely OB women can only be speculated on. The connectivity strength that was found to be enhanced within the DMN is known to depend on the amount of cognitive loads.[34,35] Furthermore, the Crus 1 part of the cerebellum, which showed a stronger activation in severely OB women than in the other two groups during visual stimulation, is involved in executive control networks.[36] In contrast, the fusiform gyrus, which has an important role in visual object recognition,[37] showed a diminished activation during visual stimulation in severely OB women. Furthermore, hippocampal and cerebellar activity during the one-back contrasted against the control task was highest in the OB women. In the light of previous findings suggesting diminished cognitive performance,[38,39] especially executive functions,[25,40,41] in OB subjects, it might be speculated that the distinct brain activity pattern may relate to cognitive alterations. While reaction times during the tasks were similar in all three study groups, the stronger hippocampal and cerebellar activity response to the one-back task in OB women may indicate that the task represented a higher cognitive load to this study group than to the NW and RYGB women. This higher cognitive load may lead to an increased food intake, as was shown in previous studies.[42] Of note, a recent study demonstrated an improvement of cognitive domains in severely OB patients 12 weeks after they had undergone bariatric surgery,[43] suggesting that the unaltered brain activity pattern in RYGB women compared with NW women may represent a neuronal correlate of such postoperative changes.

Severely obese women showed an altered connectivity strength during rest in frontal reward areas (OFC, ACC), which confirms previous results on the ACC.[18] The OFC is crucially involved in food reward processing[44] and has been shown to display a distinct activation in obese compared with NW subjects in response to food stimuli.[11–14] Extending these findings, our present resting state analyses suggest that the OFC of severely obese women displays functional alterations that do not depend on a stimulation. The unaltered resting state brain activity in RYGB as compared with NW women on the other hand suggest that the functional connectivity may recover after RYGB surgery, that is, an assumption that is supported by a recent study showing similar results already <1 year after the bariatric operation.[19]

Within the hypothalamus, severely OB women showed a greater activation during the presentation of LC food pictures and a lower activation during the presentation of HC food pictures as compared with the NW and RYGB women. While the hypothalamus is well known to be critically involved in the mediation of hunger and satiety,[45] the observed differences in hypothalamic responses across the three study groups unlikely rely on respective differences in the hunger and satiety state. Severely OB women showed an altered hypothalamic response, while they did not show different self-rated hunger and satiety scores in comparison to the NW women. In contrast, the RYGB group rated markedly lower on hunger and higher on satiety than the other two study groups, but showed a hypothalamic response that was very similar to that of the NW but distinct from that of the severely OB group. While our data do not allow for any conclusion on the underlying mechanism of the calorie content-dependent differential hypothalamic processing of food stimuli in severely OB women, they imply that this altered hypothalamus activity response is not necessarily a function of the hunger and satiety state.

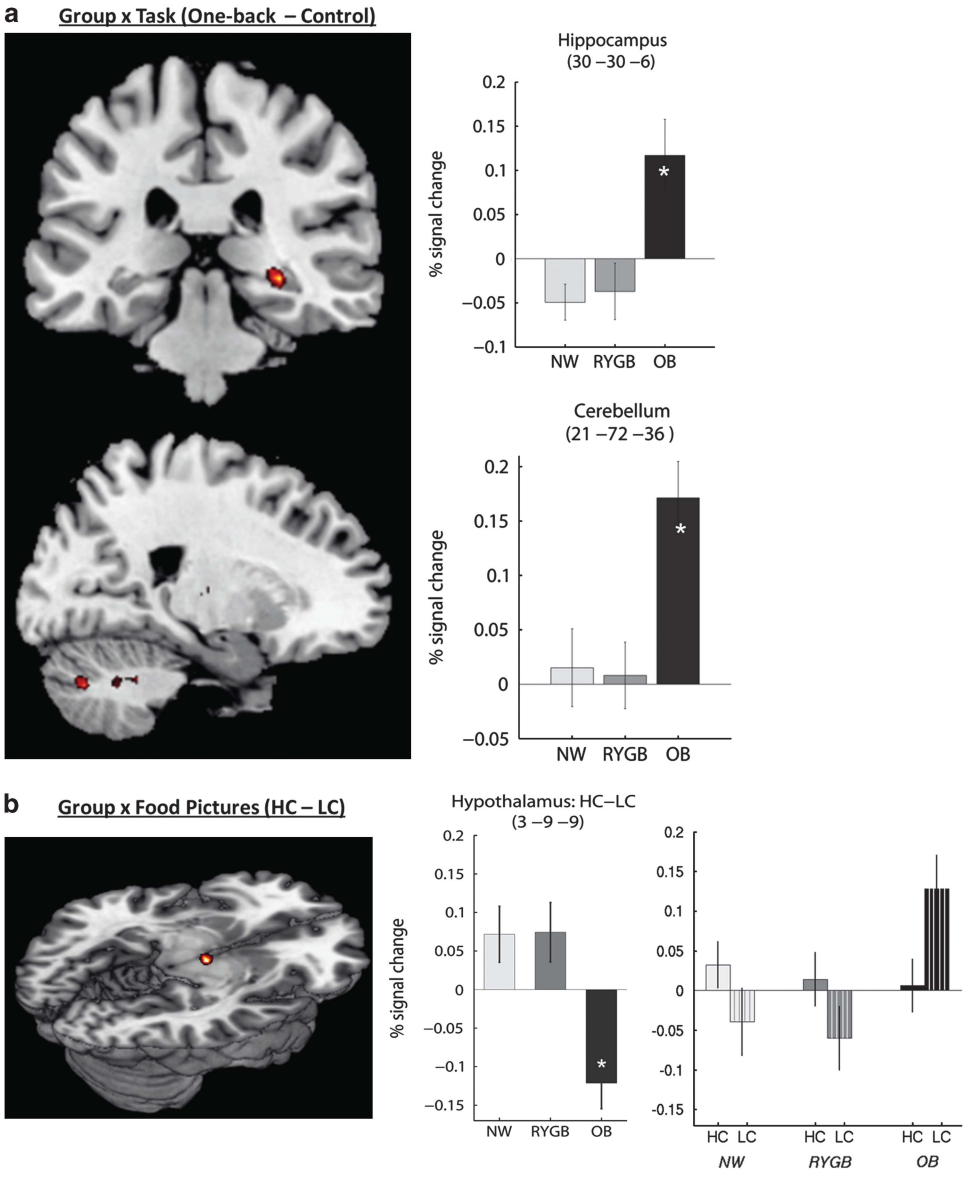

Figure 3. (**a**) Left: Coronal view of the hippocampus and sagittal view of the cerebellum at Crus 1 for the interaction 'group × task'. Right: Differences (Delta) in the activation in the hippocampus and the cerebellum in the task contrast 'one-back-control'. *Significantly different ($P<0.001$, uncorrected) from the other two groups. (**b**) Left: Transversal view of the activation in the hypothalamus for the interaction 'group × picture'. Right: Differences (Middle: Delta) in the activation in the hypothalamus during the presentation of HC–LC food pictures. *Significantly different ($P_{FWE}<0.05$, FWE corrected for multiple comparison) from the other two groups; ROI analyses. Bar plots represent mean percentage signal change ± s.e.m., all results are based on ANOVA.

While our findings overall suggest a 'normalization' of brain activity in previously severely OB women after undergoing RYGB surgery, it needs to be emphasized that the cross-sectional nature of our study precludes any conclusion upon postoperative changes. However, further support for the notion of a recovery of obesity-associated brain activity alterations after RYGB drives from previous longitudinal fMRI studies that showed marked brain activity changes soon (<1 year) after the surgery.[19–21] Interestingly, one of those studies[19] also showed an increase in cerebrospinal fluid concentrations of the anti-inflammatory cytokines interleukin-6 and -10 after RYGB. This finding suggests that the surgical procedure can reduce obesity-associated neuroinflammation, that is, an effect that could also represent an important mechanism for the recovery of brain activity patterns. Our study extents these previous findings by suggesting that the putative central nervous effects of RYGB surgery persist over a long duration keeping in mind that our RYGB women had undergone the surgery already on average 3.4 years before.

Although a change in brain activity after RYGB surgery appears to be likely, it remains unknown whether these changes represent a direct consequence of the surgery or result from marked weight loss induced by the surgery. RYGB is well known to modulate the secretion of many gastrointestinal hormones,[3,4] which are known to exert central nervous effects.[46] It might be speculated that these hormonal changes mediate the changes in brain activity after RYGB. However, weight loss *per se* is also associated with distinct endocrine and metabolic changes,[47,48] which could also affect central nervous processes.[49] The dissociation of putative effects of weight loss from inherent effects of RYGB represents a difficult challenge since weight loss in a comparable extent as observed after the RYGB surgery is hard to achieve and even

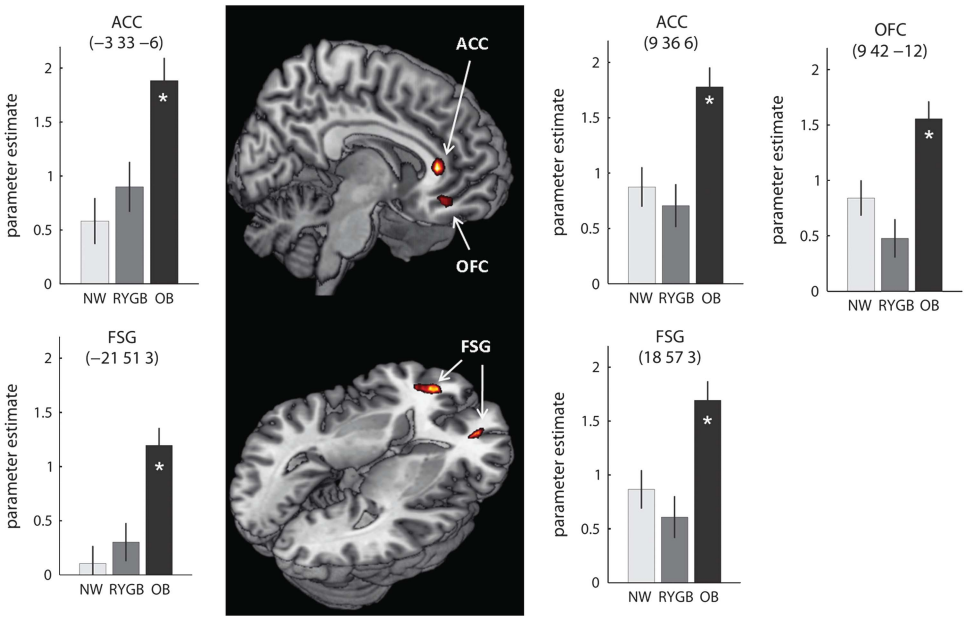

Figure 4. Top: Sagittal view of mean activation in the main effect 'group' during rest in the ACC and OFC. Bottom: Transversal view of mean activation in the main effect 'group' during rest in the frontal superior gyrus. Left and right: Bar plots for parameter estimate ± s.e.m., all results are based on ANOVA. *Significantly different ($P<0.001$ uncorrected) from the other two groups.

harder to maintain over several years with non-surgical measures. Here, comparing the effects of RYGB surgery with other bariatric procedures such as gastric banding might be a promising approach to gain further insights on the mechanism leading to changes in brain activity after RYGB surgery.

Several limitations of our study, beside the lack of any longitudinal follow-up data, need to be put forward. Firstly, while none of our tested women complained about sleep or mood disorders, we cannot exclude that discrete, clinically inapparent alterations in these domains have influenced our results, as both of these conditions are associated with obesity.[50–52] Secondly, the number of subjects studied in each group was relatively small, thereby limiting the statistical power to detect more subtle differences across the study groups. This may also explain why, in contrast to our expectations and previous studies,[20,21] we were not able to detect differential responses in reward-related brain areas during the presentation of food stimuli as a function of obesity. Finally, our study included women only, which precludes a generalization of the results to men. To overcome these limitations, further neuroimaging studies including a larger number of OB women and men undergoing bariatric surgery are needed.

In summary, our study shows distinct alterations in visually stimulated and—for the first time—resting state brain activity in severely OB women who are not found in patients after RYGB surgery. While the clinical correlates of the altered brain activity in OB women remain to be elucidated, our findings suggest that RYGB surgery exerts profound and persisting effects on the brain that results in an activity pattern comparable to that in NW women.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

The author contributions are as follows: study design (BE, BS, BW, HP, MT, NB, SF), data acquisition (BE, BW, RV, SF), data analysis (BW, SK, SF), data interpretation (BS, HP, NB, RV, SF), manuscript writing (BS, SF) and manuscript revision and approval (all authors).

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