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# Preoperative brain $\mu$ -opioid receptor availability predicts weight development following bariatric surgery in women

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**Key words:** Obesity; brain; positron emission tomography; reward; opioid; dopamine; receptors; bariatric surgery; weight loss

**Abstract**

Bariatric surgery is the most effective method for weight loss in morbid obesity. There is significant individual variability in the weight loss outcomes, yet factors leading to postoperative weight loss or weight regain remain elusive. Alterations in the  $\mu$ -opioid receptor (MOR) and dopamine D<sub>2</sub> receptor (D<sub>2</sub>R) systems are associated with obesity and appetite control, and the magnitude of initial brain receptor system perturbation may predict long-term surgical weight loss outcomes. We tested this hypothesis by studying 19 morbidly obese women (mean BMI 40) scheduled to undergo bariatric surgery. We measured their preoperative MOR and D<sub>2</sub>R availabilities using positron emission tomography (PET) with [<sup>11</sup>C]carfentanil and [<sup>11</sup>C]raclopride, respectively, and then assessed their weight development association with regional MOR and D<sub>2</sub>R availabilities at 24-month follow-up. MOR availability in the amygdala consistently predicted weight development throughout the follow-up period, but no associations were found for D<sub>2</sub>R. This is the first study to demonstrate that neuroreceptor markers prior to bariatric surgery are associated with the postoperative weight development. Postoperative weight regain may derive from dysfunction in the opioid system, and weight loss outcomes after bariatric surgery may be partially predicted based on preoperative brain receptor availability opening up new potential for treatment possibilities.

## Introduction

The prevalence of obesity is constantly increasing and reaching global pandemic levels. Accumulating evidence suggests that dysfunctions in appetite control and reward processing mechanism significantly contribute to weight gain and maintenance, and particularly brain's dopamine and opioid systems in the reward circuit are dysfunctional in obesity. Dopamine D<sub>2</sub> receptor (D<sub>2</sub>R) expression and function are altered in obesity (1-3), whereas endogenous opioid system is consistently linked to hedonic aspects of feeding in animals (4, 5). In humans, feeding triggers endogenous opioid release (6) and accordingly pharmacological challenge studies have found that both  $\mu$ -opioid receptor (MOR) antagonists and inverse agonists reduce human eating behaviour (7, 8). MOR levels are also downregulated in obese subjects, underlining the importance the opioid system perturbation in overeating (9, 10).

Bariatric surgery is currently the most effective method for weight loss in obesity. Mean postoperative total weight loss of 27 % has been shown among patients even after 12 years (11). Bariatric surgery procedures are also much more effective than intensive medical therapy to reach glycemic control (12). For weight loss, there is currently some consensus to use standardized reporting guidelines in bariatric surgery literature (13), but similar uniform consensus needs to be achieved regarding postoperative weight regain in order to assess the durability of weight loss and to reliably evaluate potential treatment options (14). Weight regain following bariatric surgery occurs in one fifth (15-17) up to one third of the patients (18-20).

Factors leading to weight regain following surgery remain poorly understood, yet cross-sectional studies point towards a possible role of the brain in regulating the treatment response. Impulsivity and disinhibition are traits often associated with poorer weight loss after surgery, but both psychosocial issues and psychiatric comorbidities may also have a major impact on weight loss outcomes (21-24). However, only few neuroimaging studies have examined neural predictors of weight loss after surgery. To our knowledge, there are only two small MRI studies that have investigated brain markers that might affect the weight loss outcome of the surgery. Functional connectivity and alterations in brain activity in some of the key areas of

reward circuit predicted weight loss 12 months after sleeve gastrectomy (25, 26). However, the role of specific neurotransmitter systems – such as D<sub>2</sub>R and MOR implicated in feeding and reward processing – on post-surgical weight gain and loss remain unknown. In the present study, we addressed this issue by measuring obese subjects' MOR and D<sub>2</sub>R availability with positron emission tomography (PET) before they underwent bariatric surgery. We followed the subjects for two years and predicted their weight loss outcomes with regional MOR and D<sub>2</sub>R availabilities. We show that MOR availability particularly in the amygdala predicts long-term outcome of the bariatric surgery, suggesting a causal role of this region in appetite control and food intake.

## Results

Mean MOR availability in the subjects is presented in Figure 1. As reported earlier (9, 27), preoperative BMI was negatively correlated with MOR availability in all the tested regions (mean  $r = -0.56$ ). Mean weight loss at 3 months was  $20.8 \pm 5.6$  kg, at 6 months was  $25.7 \pm 7.7$  kg, at 12 months was  $28.3 \pm 12.1$  kg, and at 24 months was  $30.7 \pm 15.1$  kg. Postoperative weight development is shown in the Figure 2. Roux-en-Y gastric bypass was performed on 6 subjects and sleeve gastrectomy on 13 subjects. Effect of different surgery types on MOR availability and weight loss were not analyzed due to insufficient statistical power.

Correlations between preoperative MOR availabilities and subject weight are shown in the Table 1. Preoperative MOR availabilities were significantly associated with the subject weight in the amygdala ( $r = -0.54$ ) (Figure 3), insula ( $r = -0.46$ ), ventral striatum ( $r = -0.48$ ) and putamen ( $r = -0.49$ ) at 3 months. Significant association was also found in the amygdala at 6 months ( $r = -0.53$ ) and at 12 months ( $r = -0.49$ ) (Figure 3). Moreover, significant association was observed in the amygdala ( $r = -0.50$ ) (Figure 3) and thalamus at 24 months ( $r_s < -0.49$ ).

Preoperative weight did not correlate with MOR availabilities in any brain area. We did not find any significant correlation between preoperative D<sub>2</sub>R availability and subject weight in any brain area at any time point. No significant correlations between BDI-II and STAI scores and MOR and D<sub>2</sub>R availabilities in any brain area were observed. BDI-II and STAI scores did not predict weight loss at any time point.

Five subjects experienced clinically significant weight regain (median 6.4 kg). We could not find significant association between weight gain and receptor availabilities.

## Discussion

Our main finding was that neuroimaging markers predict the weight development after bariatric surgery. MOR availability in the amygdala consistently predicted weight development throughout the 24-month follow-up period, even though MOR availability was not initially associated with preoperative weight. MOR availabilities were predictive of future gross weight but not with weight change normally evaluated using standardized outcome definitions of percent excess weight loss (%EWL), percent excess BMI loss (%EBMIL), or percent total weight loss (%TWL). No associations were found for D<sub>2</sub>R. These results show that neuromolecular phenotypes may contribute to the outcome of weight loss after bariatric surgery, possibly providing novel predictive biomarkers for postoperative weight loss after bariatric surgery. However, our finding suggestive of a potential predictive impact of MOR availability in postoperative weight loss needs to be evaluated in larger patient cohorts.

Obesity is expensive for the society, especially due to the obesity related comorbidities. Bariatric surgery reduces mean costs to the health service compared with usual care (28). However, a significant number of the patients experience weight regain (18), which was also seen in our study (Figure 2). Determining patient characteristics leading to sustainable weight loss at long-term is important, but so far there have not been reliable markers. Some metabolic markers may predict weight regain after surgery (29), also taste preference towards salty or sucrose-sweetened foods may contribute to some extent (30, 31). Our study is the first PET study to predict the outcome of bariatric surgery from neuroimaging markers, and only two small MRI studies exist (25, 26). Smith et al. also showed that Roux-en-Y gastric bypass can lead to increased weight loss in subjects who have a preference for sweet foods, which was also coupled with specific changes in ventral tegmental area response assessed by fMRI (30). Our study shows that molecular organization of the brain's reward circuit is an important determinant of the surgery-induced weight loss.

Bariatric surgery alleviates depressive and anxious symptoms (32, 33), yet psychiatric comorbidities are associated with weight gain following surgery (23, 24). Surgery has a more positive impact

on the depressive disorders than anxiety disorders (34), but preoperative symptoms also likely affect the results of the surgical methods. Preoperative depression is also associated with lower postoperative weight loss (35). Although MOR availability is associated with depressive and anxious symptoms (36), we observed no association between depressive and anxiety symptoms and weight loss. This may be due to low statistical power for the questionnaire-based measures, as well as relative crudeness of questionnaires (in comparison with structural interviews such as MADRS).

Human PET studies have shown that feeding activates the endogenous opioid system (6), and consequently dysfunction of the endogenous opioid system is a key component underlying overeating, and thus a feasible target for pharmacological and behavioural interventions. Previous studies have investigated effects of bariatric surgery and following weight loss to separate receptor systems, showing mainly unaltered D<sub>2</sub>R availability and normalized MOR availability (27, 37-39), although two animal studies have yielded contradictory findings (40, 41). Our study highlights the importance of MOR in the amygdala in predicting the weight management after the surgery. Opioidergic circuits in the amygdala are critical for emotions including fear and anxiety (42), but it is also one of the key regions in appetite control (43). MOR availability in amygdala is associated with subclinical depressive and anxiety symptoms (36), and it is likely that individual differences in MOR availability also in the amygdala may explain the differences in eating behaviour (44). It has also been shown that bariatric surgery can recover initially downregulated MOR in the amygdala of obese patients (27).

Our study has several limitations. Only female subjects were studied, and the results may not be generalizable to male subjects. Sample size was relatively small possibly precluding establishing associations between MOR availabilities, weight development, and preoperative psychiatric symptoms. However, original power analysis suggested that the study has sufficient power (27) and the employed radioligand has high affinity for MOR (45) and high test-retest reliability (46), further improving the validity of the data. We only followed the subjects for two years as part of their standard clinical visits, but longer follow-up might have showed different trajectories. However, longer follow-up studies are planned in the future (47).

In summary, preoperative MOR availability in the amygdala predicts weight outcomes after bariatric surgery. Postoperative weight regain or primary weight loss failure may partially depend on dysfunctional opioid system. There is growing evidence that opioidergic system plays an important role in governing multitude of reward functions (44), and this study further confirmed its significance in the aspects of feeding (6). Downregulation of the MOR system can be reversed by surgical (27) and non-surgical weight loss (10). The present study extended these findings by establishing the role of MOR in long-term weight maintenance. Future prospective studies should address whether MOR availability is also predicative of weight gain in normal-weight subjects, and whether it predicts weight loss success by conventional dieting-based approaches.

## Methods

### Study population

We studied 19 morbidly obese women (mean BMI 40, mean age 43) scheduled to undergo bariatric surgery, i.e. Roux-en-Y gastric bypass or sleeve gastrectomy, according to their standard clinical treatment. Subject characteristics are shown in the Table 2. Clinical screening of the subjects included history, physical examination, anthropometric measurements, and laboratory tests. Exclusion criteria for this study involved opiate drug use, neurological and severe mental disorders, substance abuse, and excessive alcohol consumption determined by clinical interviews, medical history, and blood tests. Seven subjects were smokers (3-15 cigarettes per day). Antidiabetic, antihypertensive and cholesterol lowering drugs were paused prior to the study. Subject weight was recorded before surgery as well as at 3, 6, 12, and 24 months after surgery during a standard hospital visit. Two subjects dropped out of the study before 24 months follow-up visit, but their weight data at 3, 6, and 12 months were included in the analysis. Baseline depressive and anxiety symptoms were recorded using Beck Depression Inventory II (BDI-II) and State-Trait Anxiety Inventory (STAI), respectively (48, 49).

### Image acquisition and quantification of receptor availability

We measured  $\mu$ -opioid receptor availability with the high-affinity agonist [ $^{11}\text{C}$ ]carfentanil (45) and  $\text{D}_2$  receptor availability with the antagonist [ $^{11}\text{C}$ ]raclopride (50) using positron emission tomography (PET). Brain scans were performed before the start of the standard very low-calorie diet. Radiotracer production has been described previously (9). [ $^{11}\text{C}$ ]carfentanil and [ $^{11}\text{C}$ ]raclopride scans were performed on separate days. Both radiotracers had high radiochemical purity (>99 %). Before scanning, a catheter was placed in the subject's left antecubital vein for tracer administration. Head was strapped to the scanner table in order to prevent head movement. Subjects fasted two hours prior to scanning. A CT scan was performed to serve as attenuation map. Clinical well-being of subjects were monitored during the scanning.

We injected both tracers as bolus ( $252.2 \pm 10.8$  MBq [ $^{11}\text{C}$ ]carfentanil and  $248.4 \pm 21.9$  MBq [ $^{11}\text{C}$ ]raclopride). After the injection, radioactivity in brain was measured with the GE Healthcare Discovery™ 690 PET/CT scanner (General Electric Medical Systems, Milwaukee, WI, USA) for 51 minutes, using 13 time frames. MR imaging was performed with Philips Gyroscan Intera 1.5 T CV Nova Dual scanner to exclude structural abnormalities and to provide anatomical reference images for the PET scans. High-resolution anatomical images (1 mm<sup>3</sup> voxel size) were acquired using a T1-weighted sequence (TR 25 ms, TE 4.6 ms, flip angle 30°, scan time 376 s).

All alignment and coregistration steps were performed using SPM8 software ([www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/)) running on Matlab R2012a (The Mathworks Inc., Sherborn, Massachusetts). To correct for head motion, dynamic PET images were first realigned frame-to-frame. The individual T1-weighted MR images were coregistered to the summation images calculated from the realigned frames. Regions of interest (ROIs) for reference regions were drawn manually on MRI images using PMOD 3.4 software (PMOD Technologies Ltd., Zurich, Switzerland). Occipital cortex was used as the reference region for [ $^{11}\text{C}$ ]carfentanil and cerebellum for [ $^{11}\text{C}$ ]raclopride. Receptor availability was expressed in terms of  $BP_{\text{ND}}$ , which is the ratio of specific to non-displaceable binding in brain.  $BP_{\text{ND}}$  was calculated applying basis function method for each voxel using the simplified reference tissue model (SRTM) with reference tissue time activity curves (TAC) as input data (51).

### Statistics

The subject-wise parametric  $BP_{\text{ND}}$  images were normalized to the MNI space using the T1-weighted MR images, and smoothed with a Gaussian kernel of 8 mm FWHM. Anatomic regions of interest were generated in ventral striatum, dorsal caudate, putamen, insula, amygdala, thalamus, orbitofrontal cortex, anterior cingulate cortex, medial cingulate cortex, and posterior cingulate cortex using the AAL (52) and Anatomy (53) toolboxes. Regional [ $^{11}\text{C}$ ]carfentanil and [ $^{11}\text{C}$ ]raclopride binding potentials ( $BP_{\text{ND}}$ ) were extracted and correlated with subject weights at 3, 6, 12, and 24 months after surgery. Moreover, BDI and STAI scores were

correlated with [<sup>11</sup>C]carfentanil and [<sup>11</sup>C]raclopride binding potentials as well as subject weight at different time points. A P value less than 0.05 was considered significant. Group differences in receptor availabilities between normal-weight and morbidly obese subjects have been previously reported for a subset of the subjects (9, 27).

#### Study approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the Hospital District of South-Western Finland (SleevePET2, NCT01373892, <http://www.clinicaltrials.gov>). All participants signed ethical committee-approved, informed consent form prior to scans.

### Author contributions

LN and PN designed the experiments. PS recruited the study subjects. SH produced the radiotracers. HK acquired PET data. HK and LT analyzed PET data. HK, LT, SH, PS, PN, and LN wrote the manuscript. All authors interpreted the data and submitted the manuscript.

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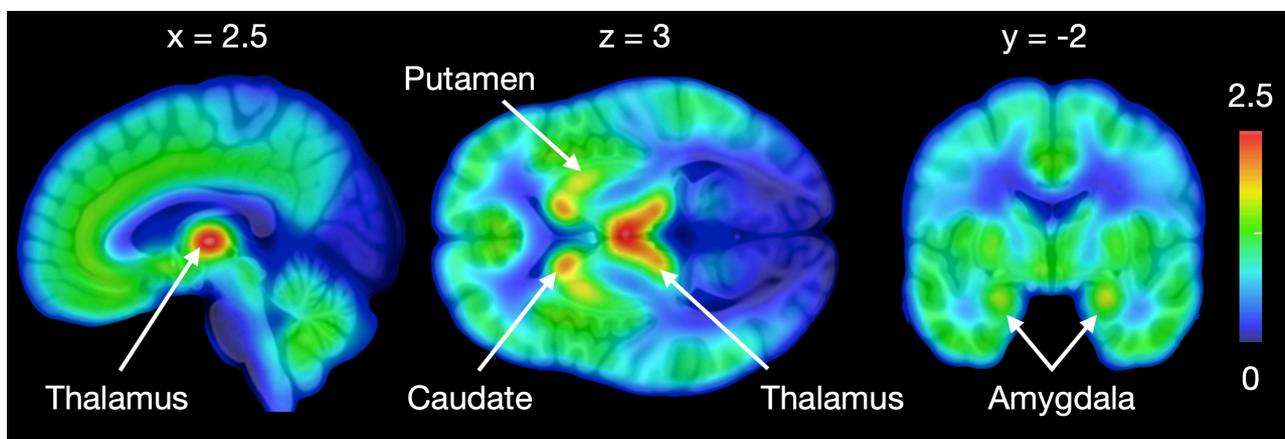
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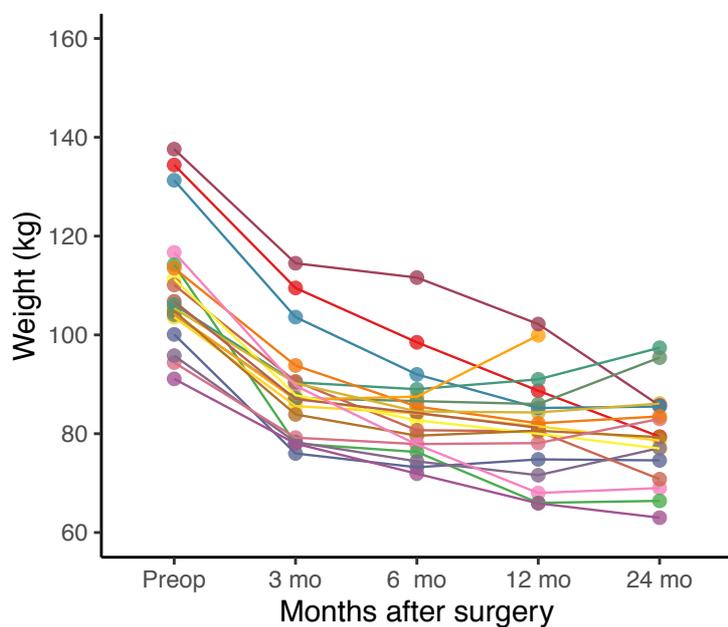
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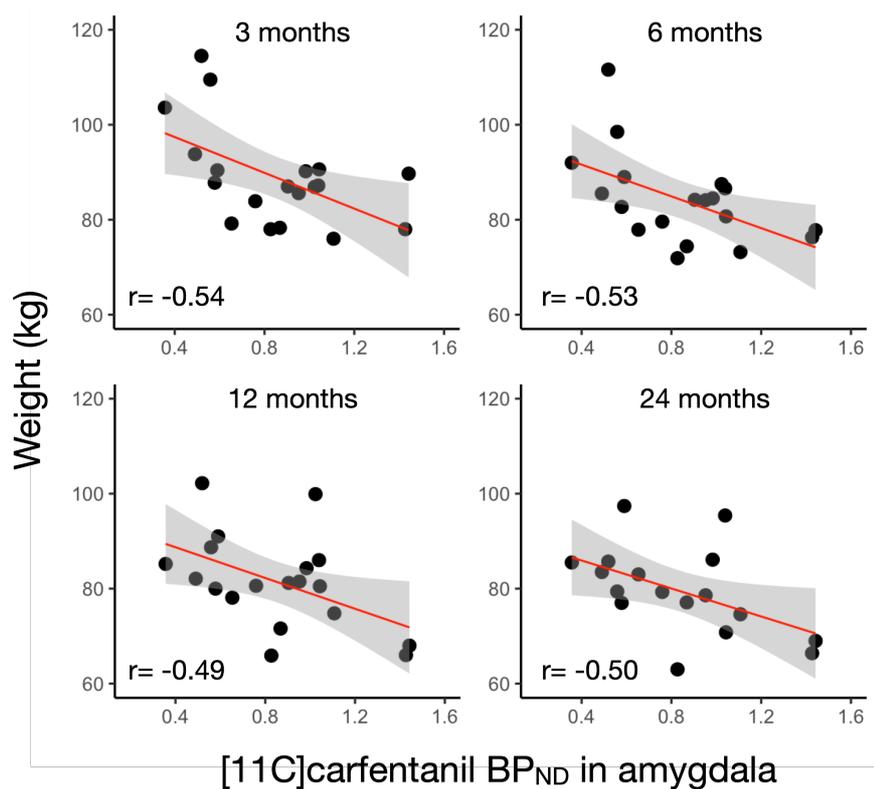
## Figures and figure legends



**Figure 1.** Mean  $[^{11}\text{C}]$ carfentanil  $BP_{\text{ND}}$  in morbidly obese subjects before surgery.



**Figure 2.** Weight development after bariatric surgery for each subject ( $N = 19$ ). Two subjects discontinued the study before 24 months follow-up visit.



**Figure 3.** Correlations between preoperative [<sup>11</sup>C]carfentanil  $BP_{ND}$  in amygdala and subject weight at 3, 6, 12, and 24 months.

## Tables

**Table 1.** Pearson correlations between regional [<sup>11</sup>C]carfentanil  $BP_{ND}$  and weight at different time points.

Statistically significant correlations are shown in boldface.

Timepoint	ACC	MCC	OFC	PCC	Amygdala	Dorsal caudate	Insula	Putamen	Thalamus	Ventral striatum
3 months	-0.43	-0.40	-0.42	-0.42	<b>-0.54</b>	-0.44	<b>-0.46</b>	<b>-0.49</b>	-0.43	<b>-0.48</b>
6 months	-0.37	-0.35	-0.38	-0.39	<b>-0.53</b>	-0.33	-0.42	-0.41	-0.41	-0.45
12 months	-0.38	-0.34	-0.32	-0.39	<b>-0.49</b>	-0.26	-0.37	-0.35	-0.32	-0.42
24 months	-0.42	-0.43	-0.38	-0.43	<b>-0.50</b>	-0.31	-0.46	-0.39	<b>-0.49</b>	-0.42

**Table 2.** Characteristics of the participants ( $N = 19$ ). Data are presented as mean  $\pm$  SD.

Age (y)	43.3 $\pm$ 8.2
Preoperative weight (kg)	109.8 $\pm$ 12,8
Height (cm)	164.5 $\pm$ 5.0
BMI (kg/m <sup>2</sup> )	40.4 $\pm$ 4.1
Surgery type (Roux-en-Y gastric bypass / sleeve gastrectomy)	6 / 13
Amount of alcohol use (units per week)	1.5 $\pm$ 1.7
Tobacco smokers / non-smokers ( $N$ )	7 / 12
BDI-II score	5.4 $\pm$ 5.5
STAI score (Trait anxiety)	37.7 $\pm$ 8.1
Injected activity of [ <sup>11</sup> C]carfentanil (MBq)	252.2 $\pm$ 10.8
Injected activity of [ <sup>11</sup> C]raclopride (MBq)	248.4 $\pm$ 21.9