

# Bariatric Surgery Induces White and Grey Matter Density Recovery in the Morbidly Obese: A Voxel-Based Morphometric Study

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**Abstract:** Obesity is associated with lowered brain's grey (GM) and white matter (WM) density as measured by voxel-based morphometry (VBM). Nevertheless, it remains unknown whether obesity has a causal influence on cerebral atrophy. We recruited 47 morbidly obese subjects (mean BMI = 42.2, (mean BMI = 42.2, SD = 4.1, 42 females and five males) eligible for bariatric surgery and 29 non-obese subjects (mean BMI 23.2, SD 2.8, 23 females, six males) served as controls. Baseline scans were acquired with T1-weighted magnetic resonance imaging (MRI) at 1.5 Teslas; obese participants were scanned again six months after the surgery. Local GM and WM densities were quantified using VBM. Full-volume analyses were used for comparing baseline between-group differences as well as the effects of surgery-induced weight loss in the morbidly obese. Metabolic variables were used in linear models to predict WM and GM densities in the clusters identified in the full-volume analyses. Obese subjects had initially lower GM densities in widespread cortical areas including frontal, parietal, and temporal regions as well as insulae. Lower WM densities were observed throughout the WM. Bariatric surgery and concomitant weight loss resulted in global increase in WM density. Grey matter increase was limited to occipital and inferior temporal regions. Metabolic variables were associated with brain densities. We conclude that weight loss results in global recovery of WM as well as local recovery of grey matter densities. These changes likely represent improved brain tissue integrity. *Hum Brain Mapp* 00:000–000, 2016. © 2016 Wiley Periodicals, Inc.

**Key words:** structural MRI; voxel-based morphometry; obesity; bariatric surgery; weight loss

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## INTRODUCTION

Overeating and resulting obesity have adverse effects on the central nervous system, increasing its susceptibility to dysfunction and degeneration. Cross-sectional studies in humans have shown that obesity is associated with brain volume reductions in both grey (GM) and white matter (WM) as measured by voxel-based morphometry (VBM), and loss of structural integrity of the WM as measured by diffusion tensor imaging (DTI) [Karlsson et al., 2013; Raji et al., 2010; Stanek et al., 2011; Verstynen et al., 2012]. These findings parallel with findings showing brain volume decreases as a function of age especially in frontal areas, yet obesity further amplifies the observed volume reductions even in the elderly [Brooks et al., 2013]. These volumetric changes may be detrimental to cognitive performance, and obesity-induced structural brain changes may translate to cognitive dysfunction later in life [Walther et al., 2010]. Interestingly, metabolic changes that accompany obese phenotype seem to mediate these changes.

Accumulating evidence suggests that increase in adipose tissue, elevated blood pressure, hyperglycemia, hyperlipidemia, and low-grade systemic inflammation underlie obesity-related loss of structural integrity of the brain [Cazettes et al., 2009; Friedman et al., 2014; Karlsson et al., 2013; Korf et al., 2007]. However, because focal volume reductions have been observed in the brain areas governing reward, inhibition, and appetite control, it has also been proposed that these abnormalities in brain structure may have preceded obesity and thus caused overeating [Diekhof et al., 2012; Lopez et al., 2012; Mizuhiki et al., 2012; Pannacciulli et al., 2006; Raji et al., 2010; Small, 2010; Scharmüller et al., 2012; Walther et al., 2006]. Cross-sectional studies cannot determine whether these brain volume changes are due to obese phenotype or whether they reflect risk factor for developing one, yet currently experimental studies on the effects of body weight loss or gain on human brain structure are scarce.

Bariatric surgery provides effective means for weight loss in the morbidly obese, inducing rapid weight loss and subsequent improvement of metabolic health [Chang et al., 2013; Glov et al., 2013]. Moreover, it provides a powerful

approach for studying the effects of weight loss on the brain. Here we used magnetic resonance imaging (MRI) and VBM to study the effects of bariatric surgery on morbidly obese patients' WM and GM densities at a baseline state and six months after bariatric surgery and concomitant weight loss. First, we predicted that GM and WM densities would be initially lowered in the morbidly obese subjects in comparison with healthy controls. Second, we hypothesized that the rapid weight loss after bariatric surgery would recover at least some of the obesity-related volume reductions.

## METHODS

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 (Sleeve-pass NCT00793143 and SleevePET2 NCT01373892, <http://www.clinicaltrials.gov>). All participants signed ethical committee-approved, informed consent form prior to study. The study population encompasses some subjects from our previous study [Karlsson et al., 2013].

## PARTICIPANTS

We initially scanned 30 non-obese participants and 51 morbidly obese participants. One non-obese and one obese subject were excluded from the study due to microvascular lesions in the WM, as revealed by neuroradiological examinations. Three further obese participants were excluded due to motion artifacts in the T1 images. The final sample included 42 morbidly obese females and five males (mean BMI = 42.2, SD = 4.1) about to undergo bariatric surgery and 23 non-obese females and six males (mean BMI 23.2, SD 2.8) (Table I). Subject groups were matched for age and height. Exclusion criteria for all subjects included binge-eating disorders, neurological or mental disorders, as well as substance abuse and excessive alcohol consumption determined by clinical interviews, medical history, and blood tests. The screening procedure entailed routine doctor checkup and taking of blood samples for assessing metabolic health. Weight and conductance-derived fat percentages were measured with Omron BF 400-E (Omron Healthcare Europe, Netherlands) scale. The patients did not use their medications before the screening measurements.

Because depression might associate with similar adverse brain changes as obesity [Cole et al., 2013], participants also completed the Beck Depression Inventory II as a part of the screening procedure. Some participants had mild depressive symptoms (Table I), but they were deemed non-depressive clinically prior to measurements. Some of the morbidly obese subjects had disturbed glucose and/or cholesterol metabolism, but they were currently medicated. Three obese individuals had diagnosed sleep apnea. Altogether, 14 of the morbidly obese group had pre-

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### Abbreviations

DTI	Diffusion tensor imaging
FWHM	Full width at half maximum
GLM	General linear model
GM	Grey matter
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
MRI	Magnetic resonance imaging
OGTT	Oral glucose tolerance test
SAT	Subcutaneous adipose tissue
VAT	Visceral adipose tissue
VBM	Voxel-based morphometry
WM	White matter

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TABLE I. Group characteristics

	Normal weight subjects, N=29, six males			Morbidly obese subjects Preoperative, N=47, five males			Morbidly obese subjects, 6 months postoperative, N=40, THREE males			P <sup>b</sup>
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	
Age (years)	45.9	11.8	19-65	44.9	9.0	24-60	91.3	14.4	70-129	***
Weight (kg)	66.8	11.3	49-93	117.3	13.8	91-149	32.7	4.1	27-44	***
BMI (Body mass index)	23.2	2.8	17.8-29.9	42.2	4.0	35-53	101.5	11.8	70-127	***
Waist circumference (cm)	75.1	8.4	63-92	120.8	11.0	110-159	42.5	5.4	27-53	***
Fat percent	30.25	6.7	16-42	49.4	5.6	33-55	125.8	11.3	109-155	*
Systolic blood pressure (mmHg)	127.5	12.5	105-150	132.6	17.8	97-187	80.0	9.5	63-101	**
Diastolic blood pressure (mmHg)	80.1	8.3	65-96	85.9	9.1	66-107	5.6	0.6	4.3-7.5	NS
HbA1c (%)	5.6	0.3	5-6	5.9	0.7	5-8	5.7	0.9	4.4-8.5	NS
Fasting glucose (mmol/l)	5.4	0.4	4-6	6.2	1.2	5-12	1.1	0.4	0.5-2.2	NS
Triglycerides (mmol/l)	0.7	0.3	0.3-1.0	1.3	0.5	1.0-3.0	1.4	0.3	0.9-2.0	NS
HDL (mmol/l)	1.8	0.4	0.9-2.7	1.2	0.2	1.0-2.0	3.1	4.3	1.3-4.3	NS
LDL (mmol/l)	2.5	0.9	1.1-4.0	2.5	0.7	1.0-4.0	32.4	9.4	15-53	NS
HDL/Kol ratio (%)	40.4	8.9	27-56	29.4	7.1	15-47	2.3	2.1	0.2-8.6	NS
sensitive CRP (mg/l)	0.73	1.0	0-4	4.4	3.8	0.2-19.0	1.3	1.4	0.4-2.5	NS
Thyroid stimulating hormone (mU/l)	1.25	0.4	1-2	1.74	1.4	0-4	2.8	3.6	0-15	NS
Beck depression inventory II	3.7	4.4	0-15	4.4	4.4	0-19	0.15 <sup>S</sup>			***
Educational background <sup>c</sup>	Low		N=14	Low		N=31				
	High		N=13	High		N=14				

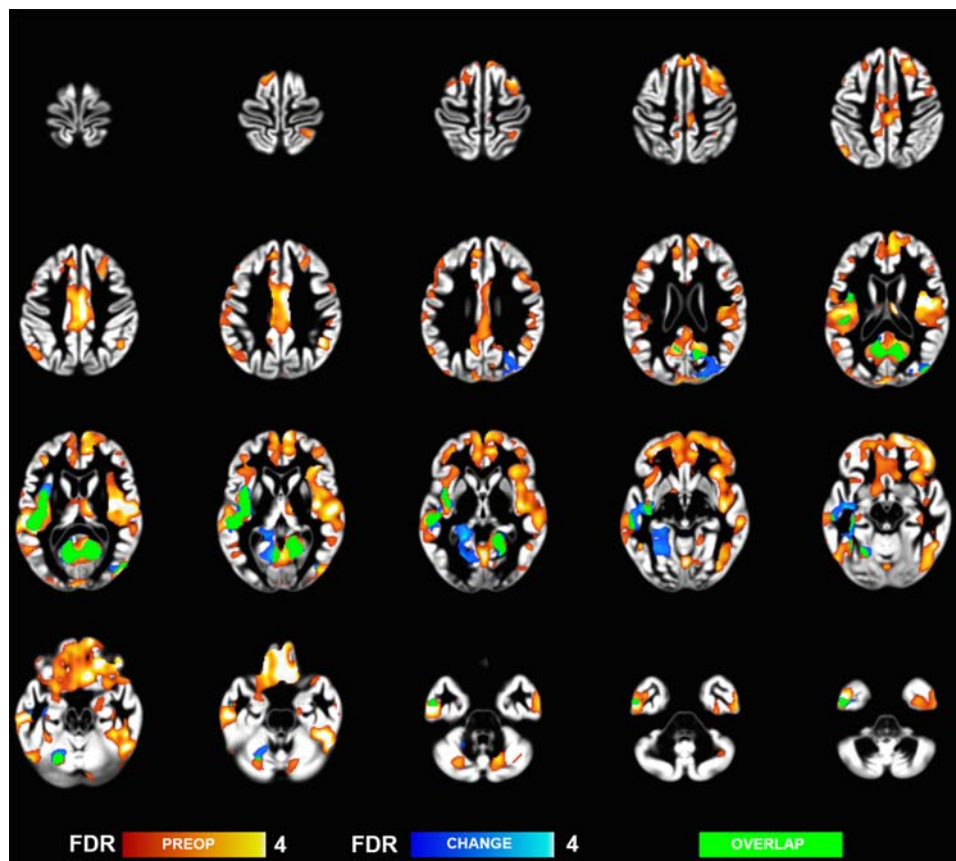
\*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001, NS = non-significant.

<sup>a</sup>Independent samples *t*-test.

<sup>b</sup>Paired samples *t*-test.

<sup>c</sup>High refers to university or polytechnical school degree, low to all other backgrounds. <sup>S</sup> Mann-Whitney U test.

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**Figure 1.**

Grey matter regions, where morbidly obese subjects had decreased brain densities as compared to normal weight controls and density increase postoperatively (whole brain FDR corrected  $P < 0.05$ ). SPM contrasts have been overlaid to mean GM template (derived from the data via SPM ImCalc-function) by using Mango software.

diabetes (IFG – impaired fasting glucose or IGT – impaired glucose tolerance) and 18 had diabetes as defined by ADA criteria in oral glucose tolerance test (OGTT). The non-obese subjects had healthy glucose metabolism. 19 subjects underwent gastric bypass and 21 subjects underwent sleeve gastrectomy. 14 morbidly obese patients were light smokers 5-20 cigarettes per day.

The screening checkups, interviews and laboratory measurements were repeated 6 months postoperatively. Altogether seven obese subjects opted to drop out from the study prior to the postoperative scan or did not undergo the surgery. They did not differ from the participants that were included in the follow up.

using a T1-weighted sequence (TR 25ms, TE 4.6 ms, flip angle 30°, scan time 376 s). To assess the volume of abdominal subcutaneous (SAT) and visceral (VAT) adipose tissue, axial T1-weighted dual fast field echo images covering the abdominal area were acquired (TE 2.3 and 4.6 ms, TR 120 ms, slice thickness 10 mm without gaps). Abdominal subcutaneous and visceral fat was counted from top of liver until the top of femoral bone appeared on both sides were analyzed with the SliceOmatic software version 4.3 (<http://www.tomovision.com/products/sliceomatic.htm>). Sets of images were opened in SliceOmatic and the borders of adipose tissues were drawn manually (by TP).

### IMAGE ACQUISITION

MR imaging was performed with Philips Gyroscan Intera 1.5 T CV Nova Dual scanner at Turku PET Centre. Anatomical images with 1 mm<sup>3</sup> resolution were acquired

### VBM METHODS

Prior to analysis, the image quality was checked visually and the origo of each T1 image was set to anterior commissure. Structural images were analyzed with Matlab

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**TABLE II. Regional maxima for brain regions identified in preoperative comparison (normal weight > morbidly obese)**

Region	MNI coordinates			T value
	x	y	z	
<b>Grey matter</b>				
Left middle temporal lobe	-52	-30	4	6.9
	3	36	-30	6.1
	9	21	-30	5.9
Right thalamus	10	-16	16	5.1
	14	-6	15	2.7
	-8	10	15	2.5
Left calcarine gyrus	-6	-99	12	4.5
	-6	-96	24	4.0
	16	-94	21	4.0
Right angular gyrus	44	-49	33	4.4
Left inferior occipital lobe	-52	-69	-17	4.3
	-48	-55	-9	4.1
	-36	-52	-11	3.8
Right inferior temporal lobe	60	-8	-35	3.9
	57	0	-38	3.7
	34	-4	-44	3.3
Right cerebellum	16	-66	-32	3.9
	39	-63	-35	3.1
	10	-85	-21	3.0
Left middle occipital gyrus	-22	-97	12	3.5
	-32	-93	12	2.9
	-40	-88	15	2.8
Right postcentral gyrus	33	-46	66	3.4
	32	-48	57	3.0
Left cerebellum	-27	-72	-32	3.4
	-22	-66	-17	3.1
Left inferior temporal lobe	-38	-27	-15	3.2
	-34	-42	-21	3.1
Right fusiform gyrus	38	-25	-17	3.2
Right parahippocampal gyrus	20	-16	-24	2.7
	22	-7	-20	2.6
<b>White matter</b>				
Left inferior frontal	-33	54	-11	6.36
	-42	42	-8	5.7
	8	-4	34	5.16
Left medial frontal	-8	8	39	3.4
Right inferior occipital	38	-87	-9	3.39
Right medial frontal	8	44	28	2.95
	20	38	37	2.92
	18	47	31	2.91
Left cerebellum	-38	-66	-38	2.59
	-33	-60	-35	2.39

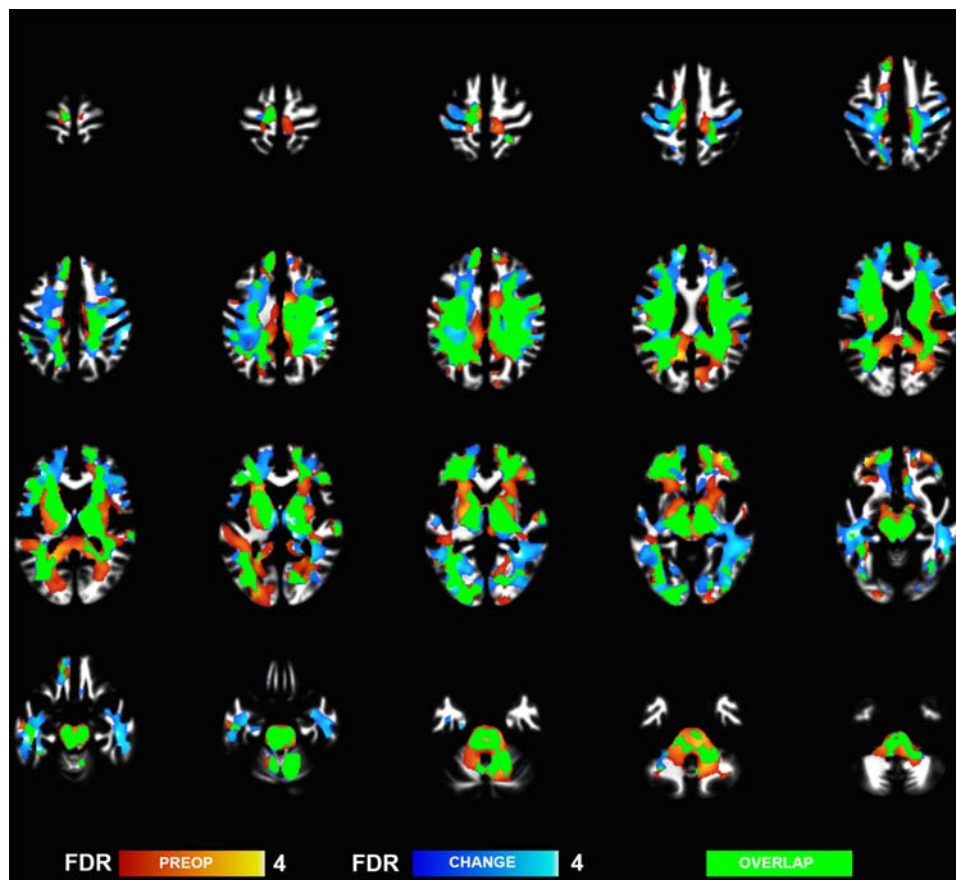
The data are thresholded at  $P < 0.05$  (FDR corrected).

2012a (Math Works, Natick, MA) using the SPM8 ([www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/)) software and vbm8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/download/>), which enables automated spatial normalization, tissue classification and radio-frequency bias correction to be combined with the segmentation step. Cut-off of spatial normalization was 25 mm and medium affine regularization 0.01 was used. Following normalization and segmentation

into GM and WM, a modulation step was incorporated to take into account volume changes caused by spatial normalization. Importantly, the modulation step corrects for the differences in total brain size across subjects. Finally, the segmented, normalized, and modulated “m0” GM and WM images were smoothed using a Gaussian kernel of 8 mm full width at half maximum (FWHM).



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**Figure 2.**

White matter regions, where morbidly obese subjects had decreased brain densities as compared to normal weight controls and density increase postoperatively (whole brain FDR corrected  $P < 0.05$  for WM and  $P < 0.05$ , FDR corrected at the cluster level for GM). SPM contrasts have been overlaid to mean white matter template (derived from the data via SPM ImCalc-function) by using Mango software.

### STATISTICAL ANALYSIS

The smoothed images were analyzed using general linear model [GLM; Friston et al., 1994] in SPM8. First, a between-subjects model (one-way ANOVA) was used to compare GM and WM densities between controls and obese patients, as well as for non-diabetic obese versus diabetic obese in the baseline state before surgery. Second, to answer the main hypothesis of the study, a within-subjects model (one-way within-subjects ANOVA) was used to estimate GM and WM changes following bariatric surgery by comparing patients' postoperative and preoperative scans with each other. An absolute threshold mask in the 2nd level designs was set at 0.2 for all comparisons to avoid possible edge effects around the border between GM and WM. Subjects' ages in years were entered into the between groups comparison models as a regressor of no interest to account for age-related changes across subjects.

Primary statistical threshold was set at whole brain FDR corrected  $P < 0.05$ . Additionally, more lenient threshold ( $P < 0.05$ , FDR corrected at the cluster level) was used to explore possible weaker effects. To determine which metabolic variables best predict initial abnormalities and surgery-induced changes in brain structure, we extracted GM and WM densities from the clusters resulting from the full-volume analyses using Marsbar (<http://marsbar.sourceforge.net>). Cortical regions were identified from MNI coordinates of the SPM output with AAL atlas.

We also conducted complementary SPM analysis to reveal possible confounding effects of diabetic status and type of surgical technique on GM and WM atrophy. First, we used one-way ANOVA to reveal possible differences between diabetic groups using one-way ANOVA (non-diabetic vs. IFG/IGT/diabetic; obese subjects only). Second, we also tested, whether there are linear associations between preoperative brain densities and preoperative

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**TABLE III. Spearman correlations between grey matter densities and metabolic variables in normal weight and morbidly obese participants (preoperative)**

	Left cere bellum	Right cere bellum	Left calcarine Gyrus	Right fusiform gyrus	Right angular gyrus	Left middle occipital gyrus	Left inferior occipital lobe	Right thalamus	Right inferior temporal lobe	Left inferior temporal lobe	Left middle temporal lobe	Right para hippo campal Gyrus	Right post central gyrus
Age (years)			-0.287*			-0.240*	-0.251*			-0.416**			-0.259*
BMI	-0.469**	-0.397***	-0.271*	-0.411***	-0.294*	-0.352**	-0.399***		-0.472***	-0.484***	-0.291*	-0.259*	-0.273*
Waist circumference (cm)	-0.358**	-0.295*	-0.332**	-0.305*					-0.408**	-0.267*			-0.267*
Fat percent				-0.297*	-0.307**	-0.251*	-0.388**		-0.318**	-0.363**	-0.280*		
Systolic blood pressure													
diastolic blood pressure													
HbA1c(%)				-0.271*									
Fasting glucose (mmol/l)									-0.294*				
Triglycerides (mmol/l)	-0.358**	-0.283*	-0.313*	-0.273*	-0.263*			-0.288*	-0.262*	-0.537***			
HDL (mmol/l)													
LDL (mmol/l)								0.355**	0.311**	0.288*			
HDL/Kol ratio (%)								0.379**	0.391**	0.351**		0.274*	
sensitive CRP (mg/l)									-0.322*	-0.265*			
Thyroid stimulating hormone (mU/l)													
Beck depression inventory II													-0.273*

Only statistically significant correlations ( $P < 0.05$ ) are shown. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

**TABLE IV. Spearman correlations between white matter densities and metabolic variables in normal weight and morbidly obese participants (preoperative)**

	Left Cerebellum	Right inferior Occipital	Left Inferior Frontal	Left Medial Frontal	Right Medial Frontal
Age (years)	0.256*				
BMI	-0.251*	-0.268*	-0.322**	-0.439***	-0.320**
Waist circumference (cm)				-0.280*	
Fat percent	-0.300**	-0.307**	-0.294*	-0.467***	-0.324**
Systolic blood pressure		-0.242*			
diastolic blood pressure					
HbA1c(%)				-0.325*	
Fasting glucose (mmol/l)	-0.276*	-0.321*		-0.326**	
Triglycerides (mmol/l)	-0.293*			-0.297*	
HDL (mmol/l)			0.270*	.318**	
LDL (mmol/l)					
HDL/Kol ratio (%)					
sensitive CRP (mg/l)	-0.264*		-0.313*	-0.345**	
Thyroid stimulating hormone (mU/l)					
Beck depression inventory II					

Only statistically significant correlations ( $P < 0.05$ ) are shown. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

BMI and change in BMI after the weight loss surgery (preoperative minus postoperative) and within the obese group that completed the follow up ( $N = 40$ ) within one sample  $t$ -test and used BMI as a regressor of interest. These two cross sectional comparisons were corrected for age. Third, we analyzed the effects of the surgical technique to changes in brain using a  $2 \times 2$  mixed ANOVA (gastric bypass – sleeve gastrectomy  $\times$  preop - postop).

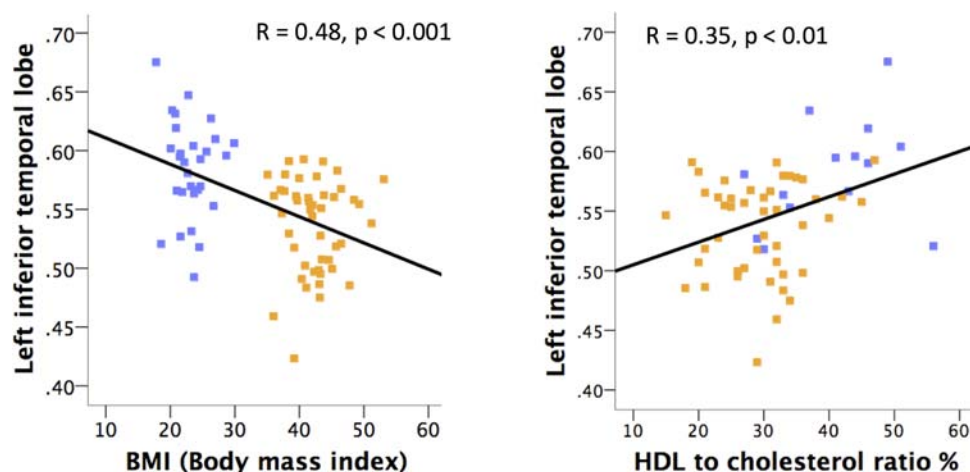
All further between groups comparisons and correlational statistical analysis were carried out in IBM SPSS Statistics version 22. Additionally, we evaluated the possible confounding effects of smoking and depressive symptoms in the ROI analysis by correlating local GM and WM

densities with smoking status and BDI scores. Finally, the metabolic characteristics of the morbidly obese that dropped out from the study were compared to those participating to all scans.

## RESULTS

### Cross-Sectional Differences Between Normal-Weight and Morbidly Obese Subjects

Preoperatively, the morbidly obese subjects had widespread decreases in grey matter (GM) density in bilateral inferior orbitofrontal and frontal regions and bilateral



**Figure 3.**

Linear relationship between brain densities, BMI and total cholesterol-to-HDL ratio. See Tables III–VI for full report on the correlations between brain tissue densities and metabolic variables.



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**TABLE V. Regional maxima for brain regions identified in follow up comparison of the morbidly obese (postop. > preop.)**

Region	MNI coordinates			T value
	x	y	z	
<b>Grey Matter</b>				
Right lingual gyrus	21	-63	0	4.3
	-20	-45	-2	3.8
	-42	-15	-14	3.8
<b>White matter</b>				
Left inferior temporal	-42	-28	-18	5.8
	-8	-10	-12	5.2
	10	-12	1	5.1
Left inferior temporal	-28	-13	-30	3.9
Left superior temporal	-52	-4	-9	3.3
	-54	-13	-3	3.1
Left cerebellum	-30	-45	-35	2.9
	-32	-58	-39	2.6

The data are thresholded at  $P < 0.05$ , FDR corrected.

F1 insula (Fig. 1). We also found lower densities in temporal,  
T2 cerebellar, and occipital regions (Fig. 1 and Table II). WM  
reductions were most prominent beneath bilateral orbito-  
F2 frontal gyri and midbrain/medulla (Fig. 2, Table II).

In general, many metabolic variables linked with obesity  
(BMI, waist circumference, fat percent, abdominal and vis-  
ceral fat volumes, systolic blood pressure, fasting glucose  
and plasma lipids) were negatively associated with grey  
and WM densities (Tables III and IV). Plasma HDL chole-  
sterol levels were positively associated with both GM  
T3 T4 and WM in most brain regions in (Tables III and IV and  
F3 Fig. 3). The results remained essentially unchanged when  
including only female participants and leaving smokers  
out of the analysis did not change the overall pattern of  
results. BDI-scores did not correlate systematically with  
brain densities in ROI analysis (Tables III and IV). Also,  
no differences between smokers and non-smokers in meta-  
bolic variables or brain densities were found. No differen-  
ces were found in GM densities between morbidly obese  
with and without disturbances in glucose metabolism.  
However, brain stem WM densities were lower in mor-  
bidly obese subject with (versus without) disturbed

glucose metabolism (data not shown). Finally, BMI did not  
have linear associations to BMI within the obese group  
preoperatively.

**Effects of Bariatric Surgery and Weight Loss**

Bariatric surgery led to significant weight loss ( $M = 26$   
kg + SD 14) and decrease in fat percentage ( $M = 6.9\% + SD$   
5.4) (Table I). Nine subjects with initial diabetes and four  
with IGT were in remission postoperatively. At brain level  
we found extensive WM volume recovery, spanning  
throughout the WM (Fig. 2 and Table V). GM recovery  
was observed only by using more lenient statistical thresh-  
old ( $P < 0.05$  FDR corrected at cluster level) and spanned  
occipital and temporal cortical regions (Fig. 1 and Table  
V). These effects partially overlapped with initial volume  
differences observed in the non-obese versus obese com-  
parison in the preoperative state (see Figs. 1 and 2).

The postoperative GM and WM changes were similar  
between the two surgical procedures (sleeve gastrectomy  
and gastric bypass). The dropped out obese participants  
did not differ from the ones that concluded the study with

**TABLE VI. Pearson correlations between changes of brain densities and metabolic metrics after surgical weight loss**

	Right lingual gyrus	Left inferior temporal white matter	Left cerebellar white matter	Left inferior temporal white matter	Left superior temporal white matter
BMI					
Triglycerides (mmol/l)			0.433**		
LDL cholesterol (mmol/l)		0.330*			
HbA1c(%)			0.402*		

Brain density increase is correlated with decreases in metabolic metrics. Only statistically significant correlations ( $P < 0.05$ ) are shown.  
\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ .

respect to demographic and metabolic variables. We found no significant correlations between preoperative grey or WM brain densities and surgery-induced BMI changes in the ROI analysis. Correlation analysis between the postoperative increases in brain densities and changes in metabolic variables showed only limited correlations with each other and the changes did not appear directly proportional to BMI change (Table VI). Decreases in plasma triglycerides, LDL cholesterol and long term glucose balance marker HbA1c correlated positively with the density increases (Table VI). Finally, we used complementary full-volume GLM to test whether preoperative regional GM and WM densities would be associated with surgery-induced weight loss. Significant positive associations with GM density were found in right-hemispheric frontotemporal and insular cortices, right thalamus, and bilateral cerebellum. In WM positive associations with weight loss were found beneath bilateral posterior temporal cortex, and precentral and superior frontal cortex. Negative associations with weight change and GM or WM density were not found.

## DISCUSSION

Morbidly obese subjects had initially decreased grey and WM volumes, yet bariatric surgery and the following weight loss resulted in global WM recovery six months after the surgery. GM recovery was also observed but it was not as prominent. Some—but not all—of these changes occurred at sites where atrophy was observed in the preoperative comparison to control subjects (Figs. 1 and 2). At the preoperative state, increased adiposity and brain densities were associated negatively (Tables III and IV) and decreases in plasma triglycerides, LDL cholesterol, and HbA1c after weight loss were positively associated with increased brain densities (Table VI). Altogether these findings suggest that weight loss has a causal influence on brain tissue densities.

### Obesity Is Associated With Fronto-Insular Atrophy

At the baseline state, obesity was associated with lowered grey and WM densities. GM atrophy was observed in frontal and orbitofrontal cortices and insulae, and tissue densities were lower throughout the WM. This accords with previous evidence suggesting that brain volume reductions are a common feature of obesity [Karlsson et al., 2013], even though few opposing findings have also been reported [Haltia et al., 2007; Taki et al., 2008]. The insular cortex is involved in homeostatic and motivational control and has also recently been found to be critical in maintenance of addictions [Mizuhiki et al., 2012; Naqvi and Bechara, 2009; Small, 2010], whereas the orbitofrontal cortex links rewards to hedonic experience [Kringelbach, 2005]. Accordingly, alterations in these circuits may make

the obese individuals prone to eat regardless of internal state of hunger or satiety [Diekhof et al., 2012; Karlsson et al., 2013; Scharmüller et al., 2012], but the changes may also reflect the consequences of obesity-related adverse metabolic health profile.

### Brain Integrity Is Associated With Metabolic Factors

Preoperatively, GM and WM atrophy was associated with multiple metabolic parameters including fat percentage, systolic blood pressure, fasting glucose, and triglycerides. However, clear tissue type specific trends were not revealed in the analyses and none of the used parameters appeared prominent as compared to others (Tables III and IV). Yet, preoperative regional GM and WM densities were not associated with subsequent weight loss. Complementary full-volume analysis, however, revealed that fronto-temporal, insular, thalamic, and cerebellar GM densities, as well as frontotemporal WM densities were positively associated with the magnitude of weight loss.

Based on previous studies, adverse cellular effects in the brain could follow vascular damage caused by hypertension [Breteler et al., 1994; Korf et al., 2007] and elevated plasma lipids [Cohen et al., 2011], which are features of obesity [Cazettes et al., 2011; Hotamisligil, 2006; Lumeng and Saltiel, 2011; Pannaciulli et al., 2007; Vachharajani and Granger, 2009]. On the other hand, brain volume alterations among obese may also result from chronic hyperglycemia and glucose neurotoxicity through increased amount of oxygen radicals [Tomlinson and Gardiner, 2008; Tuulari et al., 2013], as weight gain and peripheral insulin resistance are generally thought to cause adverse structural and functional brain changes [Craft, 2006; Messier, 2005; Williamson et al., 2012]. In the current study, plasma HDL cholesterol levels were positively associated with GM and WM densities, which highlights possible positive effects of healthy lipid profile on brain health (Tables III and IV). Thus, the associations between metabolic variables and brain tissue integrity accord with some of the well-known risk/protecting factors for atherosclerosis, vascular diseases [Friedman et al., 2014] and cognitive decline with increasing age [Jagust et al., 2005; Pannaciulli et al., 2007; Walther et al., 2010], yet their specific and individual contributions to cerebral atrophy cannot be resolved on the basis of the present data, in part because the study lacks longitudinal follow up prior to surgery.

### Possible Causal Links Between Weight Gain, Weight Loss, and Brain Tissue

Given that obesity is associated with brain tissue volume reductions, it could be expected that losing weight would reverse these changes. This was the case in the current study, where we observed widespread recovery of WM

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and less profound recovery of GM densities (Figs. 1 and 2). WM may be the most vulnerable part of the brain under the multifaceted metabolic stress caused by obesity. Furthermore, WM may have greater capacity for regeneration, here probably through recovery in myelination [Bhatt et al., 2014]. It is generally thought that neurons within the cortical GM are not able to recover after cellular insult. Should more extensive recovery within the GM take place, in terms of what can be quantified with VBM, it may be that brain gray matter needs more time than current six-month follow-up to recuperate.

The initial GM atrophy might reflect an obese-prone endophenotype rather than consequence of obesity [Karls-son et al., 2013]. Supporting this view, we observed GM atrophy in components of the homeostatic and reward circuitry, whose atrophy has been shown to predict future weight gain in prior prospective studies [Smucny et al., 2012; Yokum and Stice, 2012]. GM in these regions did not exhibit as strong recovery as in WM regions after bariatric surgery. It is thus possible that lowered brain densities in these regions involved in appetite and eating control may predispose an individual to overeating and obesity, whereas the WM changes might be caused by obese phenotype.

Although our results imply that extreme obese phenotype is associated with decreased tissue integrity, recent large epidemiological study highlights that obesity might even protect against the onset of dementia [Qizilbash et al., 2015]. This implies that the association between adiposity and cognitive performance is not as straightforward as has previously been thought. Overall, the metabolic variables explained a rather small amount of the tissue changes after bariatric surgery. It is thus imperative to assess the effects of additional factors such as changes of non-adipose body composition, exercise habits [Coen et al., 2015], sleep quality [Peromaa-Haavisto et al., 2015] and gastrointestinal hormone secretion [McIntyre et al., 2013; Meek et al., 2015] to brain tissue after the bariatric surgery changes in future studies.

### LIMITATIONS

The age range of our obese subjects was fairly broad (Mean ca. 45 years; range 19-65), but some changes (both structural and functional) may unfold only after decades of hyperglycemia, hyperlipidemia and low-grade inflammation - or may manifest only with more extreme degrees or prolonged length of these states. The obese subjects diagnosed for type 2 diabetes, hypertension, and hypercholesterolemia were using oral medication, which may have resulted in flattened associations to brain volumes. Further, our sample comprised mainly of females thus the present findings may not directly generalize to males [Mueller et al., 2011]. Although grey reductions may be associated with decreased functional capability, VBM does not address brain function per se and that cellular changes

corresponding to volumetric changes as observed here are not yet fully understood or characterized. Finally, although our study establishes a causal link between weight loss and brain tissue recovery, it remains unresolved whether weight gain actually leads to the atrophy observed in the morbidly obese subjects at the preoperative stage.

### CONCLUSIONS

We show that obesity is associated with cerebral atrophy, yet its influences particularly in the WM, but in GM as well, are recoverable by weight loss. This suggests a causal link between weight loss and brain tissue integrity, which might reflect improved brain health after surgical weight loss. Finally, obesity-related accumulation of cardiovascular risk factors best explains the degree of atrophy and recovery to some extent, suggesting that efficient vascular risk factor control in clinical setting is also beneficial to brain integrity.

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