

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

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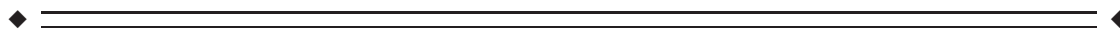
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Abstract: Obesity is associated with lowered brain's grey (GM) and white matter (WM) density as measured by voxel-based morphometry (VBM). Nevertheless, it remains unknown whether obesity has a causal influence on cerebral atrophy. We recruited 47 morbidly obese subjects (mean BMI = 42.2, SD = 4.0, 42 females and five males) eligible for bariatric surgery and 29 non-obese subjects (mean BMI = 23.2, SD = 2.8, 23 females and six males) served as controls. Baseline scans were acquired with T1-weighted magnetic resonance imaging (MRI) at 1.5 Tesla; 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. 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 reflect improved brain tissue integrity. *Hum Brain Mapp* 37:3745–3756, 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 those 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., 2011; 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; Mizuhiki et al., 2012; Pannacciulli et al., 2006; Raji et al., 2010; Small, 2010; Scharmüller et al., 2012; Walther et al., 2010]. Cross-sectional studies cannot determine whether such cerebral changes are due to the obese phenotype or whether they reflect a risk factor for weight gain. 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; Gloy 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 lower 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 = 4.0) 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 at the day of the screening measurements.

Because depression might be associated 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 subjects from the morbidly obese group had pre-diabetes (IFG – impaired fasting glucose or IGT – impaired glucose tolerance) and 18 had diabetes as

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

TABLE I. Group characteristics

	Normal weight subjects N = 29, 6 males			Morbidly obese subjects Preoperative, N = 47, 5 males			Morbidly obese subjects 6 months postoperative, N = 40, 3 males			p ^b
	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	91.3	14.4	70–129	***
BMI (Body mass index)	23.2	2.8	17.8–29.9	42.2	4.0	35–53	32.7	4.1	27–44	***
Waist circumference (cm)	75.1	8.4	63–92	120.8	11.0	110–159	101.5	11.8	70–127	***
Fat percent	30.25	6.7	16–42	49.4	5.6	33–55	42.5	5.4	27–53	***
Subcutaneous fat mass (kg)	4.2	1.3	2–7	19.2	5.1	9–35	10.7	3.4	6.1–20.4	***
Visceral fat mass (kg)	0.8	0.4	0.2–2.0	4.2	1.5	2–8	1.8	1.0	0.5–4.2	***
Systolic blood pressure (mmHg)	127.5	12.5	105–150	132.6	17.8	97–187	125.8	11.3	109–155	*
Diastolic blood pressure (mmHg)	80.1	8.3	65–96	85.9	9.1	66–107	80.0	9.5	63–101	**
HbA1c (%)	5.6	0.3	5–6	5.9	0.7	5–8	5.6	0.6	4.3–7.5	NS
Fasting glucose (mmol/l)	5.4	0.4	4–6	6.2	1.2	5–12	5.7	0.9	4.4–8.5	NS
Triglycerides (mmol/l)	0.7	0.3	0.3–1.0	1.3	0.5	1.0–3.0	1.1	0.4	0.5–2.2	NS
HDL (mmol/l)	1.8	0.4	0.9–2.7	1.2	0.2	1.0–2.0	1.4	0.3	0.9–2.0	NS
LDL (mmol/l)	2.5	0.9	1.1–4.0	2.5	0.7	1.0–4.0	3.1	4.3	1.3–4.3	NS
HDL/Kol ratio (%)	40.4	8.9	27–56	29.4	7.1	15–47	32.4	9.4	15–53	NS
sensitive CRP (mg/l)	0.73	1.0	0–4	4.4	3.8	0.2–19.0	2.3	2.1	0.2–8.6	NS
Thyroid stimulating hormone (mU/l)	1.25	0.4	1–2	1.74	1.4	0–4	1.3	1.4	0.4–2.5	NS
Beck depression inventory II	3.7	4.4	0–15	4.4	4.4	0–19	2.8	3.6	0–15	NS
Educational background ^c	Low		N = 14	Low		N = 31	High		N = 14	0.15 ^d
	High		N = 13	High		N = 14				***

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

^aIndependent samples t-test.

^bPaired samples t-test.

^cHigh refers to university or polytechnical school degree, low to all other backgrounds.

^dMann-Whitney U test.

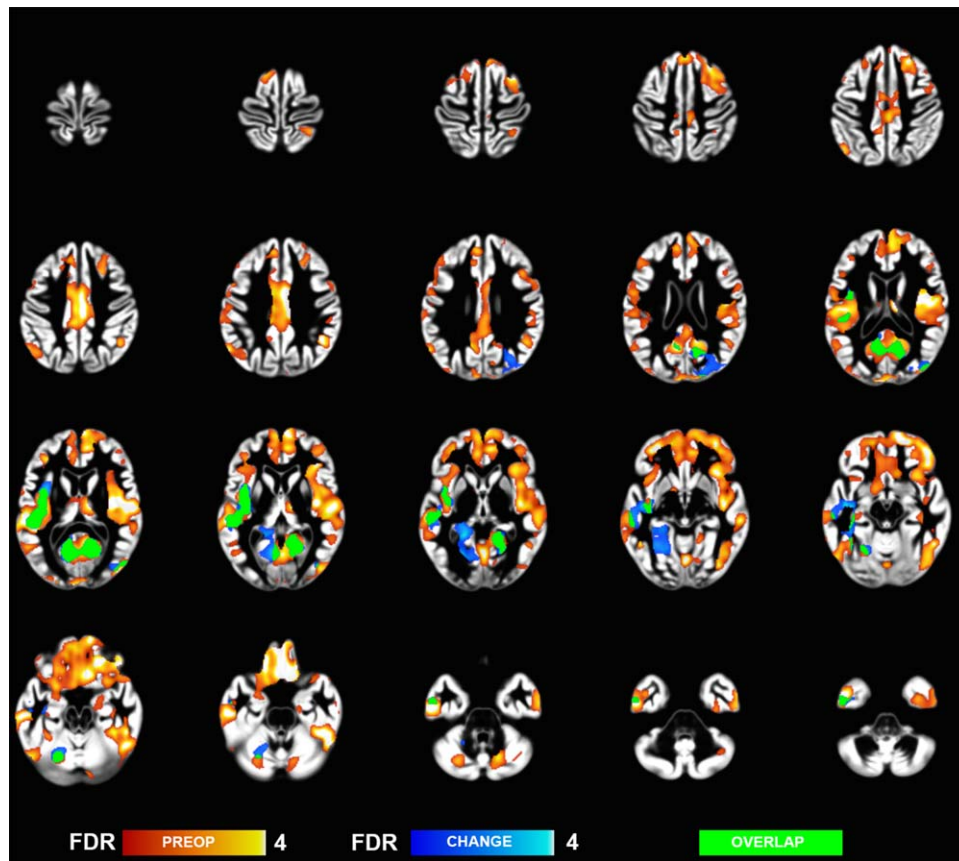


Figure 1.

Grey matter regions where morbidly obese subjects had decreased brain densities as compared to non-obese controls (hot colors), and regions showing postoperative density changes (cool colors) (whole brain FDR corrected $p < 0.05$).

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 in terms of metabolic parameters (Table 1).

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^3 resolution were acquired using a T1-weighted sequence (TR 25ms, TE 4.6 ms, flip angle 30° , scan time 376 s). To assess the volume of abdominal subcu-

taneous (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).

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 2012a (The MathWorks Inc., Natick, MA) using the SPM8 (<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

TABLE II. Regional maxima for brain regions identified in preoperative comparison (non-obese > morbidly obese)

Region	MNI coordinates			T value
	x	y	z	
Grey matter				
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
Left inferior temporal lobe	-22	-66	-17	3.1
	-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
White matter				
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).

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

GM and WM images were smoothed using a Gaussian kernel of 8 mm full width at half maximum (FWHM).

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

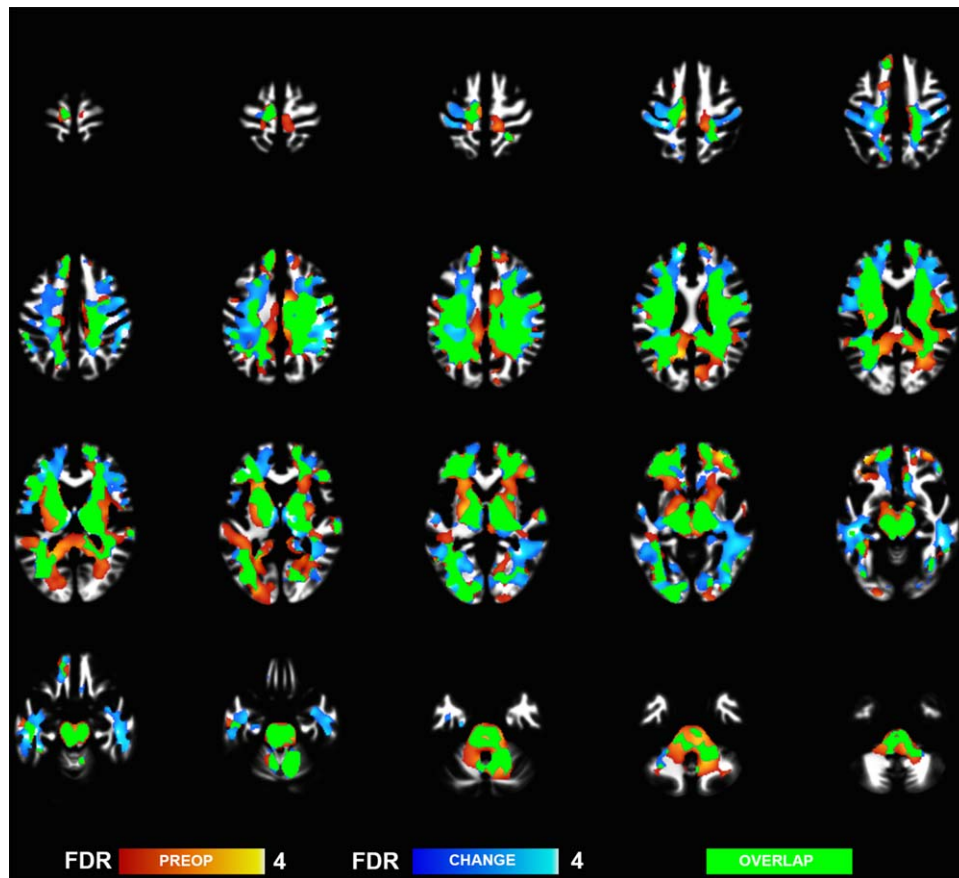


Figure 2.

White matter regions where morbidly obese subjects had decreased brain densities as compared to non-obese controls (hot colors), and regions showing postoperative density changes (cool colors) (whole brain FDR corrected $p < 0.05$).

compare GM and WM densities between controls and obese patients, 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 brain densities 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 BMI as well as preoperative brain densities and BMI change after surgery (preoperative minus postoperative) within the obese group that completed the follow up ($N = 40$). These two cross sectional comparisons were corrected for age. Third, we analyzed the effects of the surgical technique to changes in brain using a 2×2 mixed ANOVA (gastric bypass – sleeve gastrectomy \times preop - postop).

All region-of-interest (ROI) based between groups comparisons and correlational statistical analysis were

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

	Left Cerebellum	Right Cerebellum	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 hippocampal Gyrus	Right Post central Gyrus
Age (years)			-.287*			-.240*	-.251*			-.416**		-.259*	-.259*
BMI	-.469**	-.397***	-.271*	-.411***	-.294*	-.352**	-.399***	-.297**	-.472***	-.484***	-.291*	-.273*	-.267*
Waist Circumference (cm)	-.358**	-.295*	-.332**	-.305*					-.408**	-.267*			
Fat percent	-.335**	-.237*		-.297*	-.307**		-.388**		-.318**	-.363**	-.280*		
Subcutaneous fat mass (kg)	-.420**	-.366**	-.289*	-.405**		-.295*	-.363**		-.429**	-.382**			
Visceral fat mass (kg)	-.417**	-.289*		-.472**	-.280*	-.334*			-.392**				
Systolic blood pressure						-.251*				-.318**			
diastolic blood pressure													
HbA1c(%)										-.417**			
Fasting glucose (mmol/l)				-.271*					-.294*	-.461***			
Triglycerides (mmol/l)	-.358**	-.283*	-.313*	-.273*	-.263*			-.288*	-.262*	-.537***			
HDL (mmol/l)		.368**						.355**	.311**	.288*			
LDL (mmol/l)													
HDL/Kol ratio (%)		.376**						.379**	.391**	.351**		.274*	
sensitive CRP (mg/l)									-.322*	-.265*			
Thyroid stimulating hormone (mU/l)													
Beck depression inventory II													-.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)	.256*				
BMI	-.251*	-.268*	-.322**	-.439***	-.320**
Waist Circumference (cm)				-.280*	
Fat percent	-.300**	-.307**	-.294*	-.467***	-.324**
Systolic blood pressure		-.242*			
Subcutaneous fat mass (kg)	-.299*			-.366**	-.284*
Visceral fat mass (kg)	-.384**			-.462**	-.317*
diastolic blood pressure					
HbA1c (%)				-.325*	
Fasting glucose (mmol/l)	-.276*	-.321*		-.326**	
Triglycerides (mmol/l)	-.293*			-.297*	
HDL (mmol/l)			.270*	.318**	
LDL (mmol/l)					
HDL/Kol ratio (%)					
sensitive CRP (mg/l)	-.264*		-.313*	-.345**	
Thyroid stimulating hormone (mU/l)					
Beck depression inventory II					

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

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 Non-obese and Morbidly Obese Subjects

Preoperatively, the morbidly obese subjects had widespread decreases GM density in bilateral inferior orbito-frontal and frontal regions and bilateral insula (Fig. 1). We also found lower densities in temporal, cerebellar, and

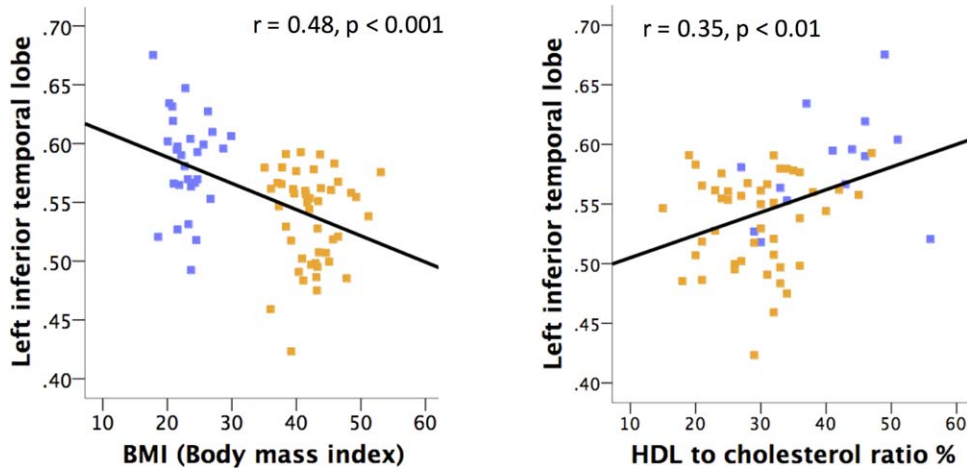


Figure 3.

Linear relationship between grey matter densities, BMI and total cholesterol-to-HDL ratio (in the scatter plot, non-obese subjects appear in dark blue and obese subjects in orange). See Tables III, IV and VI for full report on the correlations between brain tissue densities and metabolic variables. [Color figure can be viewed at wileyonlinelibrary.com]

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	
Grey Matter				
Right lingual gyrus	21	-63	0	4.3
	-20	-45	-2	3.8
	-42	-15	-14	3.8
White matter				
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.

occipital regions (Fig. 1 and Table II). WM reductions were most prominent beneath bilateral orbitofrontal gyri and midbrain/medulla (Fig. 2, Table II).

In general, multiple metabolic variables linked with obesity (BMI, waist circumference, fat percent, abdominal and visceral fat volumes, systolic blood pressure, fasting glucose and plasma lipids) were negatively associated with GM and WM densities (Tables III and IV). Plasma HDL cholesterol levels were positively associated with both GM and WM in most brain regions in (Tables III and IV and 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 metabolic variables or brain densities were found. No differences were found in GM densities between morbidly obese with and without disturbances in glucose metabolism. However, brain stem WM densities were lower in morbidly obese subjects with versus without disturbed glucose metabolism (data not shown).

Finally, BMI did not have linear associations to brain densities 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 threshold ($p < 0.05$ 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 comparison 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 respect to demographic and metabolic variables. We found no significant correlations between preoperative GM 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

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					
Subcutaneous fat mass (kg)				-.459*	.396*
Triglycerides (mmol/l)			.433**		
LDL cholesterol (mmol/l)		.330*			
HbA1c (%)			.402*		

Brain density increase is correlated with decreases in metabolic metrics.

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

superior frontal cortex. Negative associations with weight change and GM or WM density were not found (data not shown).

DISCUSSION

Morbidly obese subjects had initially decreased GM and WM densities 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). Furthermore, decreases in plasma triglycerides, LDL cholesterol, and HbA1c after weight loss were associated positively 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 GM 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 results suggesting that brain volume reductions are a common feature of obesity [Karlsson et al., 2013], even though opposite 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 in the ROI analysis. 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 the 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 and 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 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 six months to recuperate.

The obesity-related GM atrophy might reflect an obese-prone endophenotype rather than consequence of obesity [Karlsson 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 the extreme obese phenotype is associated with decreased tissue integrity, a 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 age of the groups was ca. 45 years; range 19-65). It is thus possible that 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 particularly the WM (and to some extent GM) atrophy is 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 vas-

cular risk factor control in clinical setting is also beneficial to brain integrity.

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