GREY MATTER VOLUME DIFFERENCES IN OBESE AS COMPARED TO NORMAL-WEIGHT INDIVIDUALS: A VOXEL-BASED MORPHOMETRIC STUDY

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ABSTRACT

Background: Signs of declined cognitive function as well as cerebral volume reduction can be found in obese individuals earlier and to a greater extent than in the normal-weight population. We aimed at finding cerebral volume differences in young adults when using Magnet Resonance Imaging (MRI)-based volumetry to compare normal-weight and obese individuals.

Material/Methods: Twenty-four young (mean age 28.4±5.9 yrs.) female adults (12 obese patients, mean BMI 36.6±,12 controls) underwent isotropic 3D-MPRAGE MR imaging in a 1.5T scanner. Image data were then post-processed by using the VBM-DARTEL algorithm and compared for subtle volume differences using a two-tailed *t*-test ($p<0.05$).

Results: VBM-based regional brain volume differences were encountered in the cingulate gyrus, oribitofrontal cortex, parts of the temporal lobe and the cerebellum. Neither total intracranial volumes (TIV) nor cerebrospinal fluid (CSF) volumes or brain volumes differed when a whole brain approach with conventional volumetric analysis was applied.

Conclusion: Our findings suggest that measurable effects of obesity on brain volumes appear already in young adults. Focal grey matter thinning involves cingulate gyrus, orbitofrontal cortex and also partially affects the temporal lobe and cerebellum.

KEYWORDS — Obesity, Volumetry, Cingulate Gyrus, Voxel-based Morphometry (VBM), Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL), MRI

INTRODUCTION

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health; BMI>25 (BMI= kg/m^2) is defined as overweight, BMI>30 as obesity (WHO-definition). Obesity has been described to be associated with reduced brain volumes in late adulthood. A trend of functionally reduced skills concerning planning, goal-oriented behaviour and decision-making as assessed by cognitive testing have been shown in child, teen and adult obese individuals (Smith 2011). Even though these findings are controversially discussed, we hypothesized that structural differences might already be found in younger adults when using MRI-based volumetry. Voxel-based morphometry (VBM) is a mean by which even subtle volumetric differences can be detected where conventional volume analysis does not show volume effects yet.

Obesity is becoming one of the major epidemics of the 21st century. The prevalence amounts to about 50% in Western Europe. More than one in ten of the world´s adult population is obese. It is globally the 5th leading risk factor for death (WHO Fact sheet N°311, 2013). Obesity may lead to a substantial decrease in quality of life and is considered as a risk factor for a number of diseases such as hypertension, diabetes and Alzheimer disease (AD). Reasons for obesity are seen in generally changes of life styles, with increased intake of energy-dense food and decreased expend of energy. However, this is true for many more people than those suffering from obesity but only a certain percentage of people at risk finally fall ill.

CT-based volumetric studies showed a correlation between BMI and higher risk for atrophy in temporal lobes during aging in obese patients (Gustafson, 2004). An MRI-based volumetric study resumed a general reduction in brain volume with higher BMI (Ward, 2005). Recently published studies using more precise VBM-techniques showed focal volume reductions of gray matter (GM) in various brain regions of obese patients (Pannacciulli et al., 2006; Taki et al., 2008; Maayan et al., 2011).

There are only sparse studies based on MRI-based morphometry data in obese individuals, even less with respect to young obese adults. The purpose of this

study was to evaluate possible volume differences between normal-weight and obeseyoung adults in order to detect obesity-related volume effects while excluding age-related decline.

METHODS

Subjects

We examined 24 young adult female subjects, 12 obese patients (mean age 29.3 ±7.3) with a mean BMI 36.3 ± 4.8 and 12 normal-weight (age-matched) subjects (mean age 27.5 ± 4.3yrs., mean BMI of 20.9±1.7), all right-handed (Oldfield, 1971). Exclusion criteria comprised a history of severe pain, stroke, epilepsy or other neurological illnesses, diabetes, substance abuse or addiction, hypertension, claustrophobia or any psychiatric illnesses. For further details see table 1. None of the study subjects had a binge eating disorder. Prior to scanning, both groups had their last meal 1.5 hours before the experiment. Hence, they were neither hungry nor just satiated. Recruitment of the subjects was done through newspaper advertisement. Written informed consent was obtained from all participants prior to scanning. The study was approved by the local Human Subjects Committee and adhered to the Declaration of Helsinki.

Data acquisition

MRI measurements were performed on a 1.5 T scanner (Siemens Magnetom Vision, Erlangen, Germany) with a standard head coil. Head motion was minimised by using a vacuum pad. Subsequent to the scout scan, structural data were acquired using a T1-weighted sagittal 3D magnetization-prepared rapid gradient-echo (MP-RAGE): TR/TE 11.4/4.4ms, flip angle 15°, FOV= 256 mm, voxel size 1mm^3, no gap. Prior to processing, all data sets were inspected for artifacts and structural pathologies.

Data analysis

Imaging data were analyzed using SPM8 (Statistical Parametric Mapping), Welcome Department of Imaging Neuroscience, University College London, UK) running under the MATLAB R2010a environment (Mathworks. Inc., Natick, MA, USA).

The origin of all source images was set on the anterior commissure (AC). A Native Space Analysis was performed to get global tissue volumes, GM-, White Matter (WM)-, cerebrospinal fluid (CSF)-volumes. First, we segmented all correctly aligned data by the SPM tool "VBM- estimate and write" function. The specific volumes of the native spaces of each individual were read out by the VBM8 function "read raw volumes" (as described in the VBM8 Manual). The raw data volumes were then statistically analyzed with SPSS 18 (SPSS Inc, Chicago, IL, USA) by using two-tailed t-tests with the significance level set to $p<0.05$.

Afterwards we performed a VBM-DARTEL analysis. VMB-DARTEL is an algorithm implemented in a toolbox of the SPM8 algorithms; it is able to detect very sensitively systematic differences in GM including subtle volume differences (Ashburner, 2001). Additionally, the VBM-DARTEL algorithm has been shown to improve precision of inter-subject alignments compared to conventional VBM algorithms (Takahasi, 2010).

Basically, the VBM-DARTEL analysis was performed as described by Ashburner (2010 "VBM tutorial"). As far as no other values are mentioned we used the default values of SPM8. Rigidly transformed tissue classification as well as accurate warping of individual brains into GM population templates were performed. Smoothing was done with a Gaussian kernel of 8 mm full width at half maximum (FWHM). Data were spatially normalized to MNI. Within the framework of the general linear model (GLM) the data were analyzed in SPM8. Statistical Analysis was performed using a two-tailed t-test. No confounding covariates were identified. Results were thresholded at $p <0.05$; corrected for multiple comparison using false discovery rate (FDR). This last correction guarantees that no more than 1% of the significant voxels are false positive. The VBM data was masked using an absolute threshold of 0.2 as recommended in the Ashburner tutorial. No a priori identification of a region of interest was done as VBM-DARTEL provides a whole brain analysis.

Testing war performed for two hypotheses:

Hypothesis 1: K > P (controls have more GM volume than obese); a minimal number of contiguous voxels was set at a cluster size of 25.

Hypothesis 2: K < P (controls have less GM brain volume than obese), cluster size of 25 voxels. Additionally, one analysis was done by using a cluster size of 5 voxels in order not to overlook any effect.

For better anatomical depiction the resulting statistical data were visualized by using the program MRIcron (Chris Rorden).

RESULTS

Subjects

Table 1 shows anthropometric and metabolic data of the study groups. The two groups differed significantly in BMI values ($p< 0,001$). Obesity was prevailing since 17 ±8.9 yrs. in the obese subjects group. All examined subjects were right-handed. The two groups did not differ significantly with respect to age, gender, and medication. No other illness than obesity was present in the study participants.

Global volume changes

No significant differences in the global volume parameters (TIV, GM, WM and CSF) were encountered (see Table 2). The TIV was about equal in both groups, with approximately 1.3 litres each.

Region-specific GM changes evaluated by VBM

The VBM- study showed some regional foci, where GM volume was significantly reduced (see Figures 1 and Table 2). Region-specific significant volume reduction ($p < 0.05$) in GM in obese participants was found in four major clusters, including the cingulate gyrus, orbitofrontal cortex, parts of the temporal lobe and the cerebellum. Table 3 displays MNI-coordinates of the most significant statistical values together with their localization and corresponding cluster sizes. When regarding cluster sizes, most extended volume differences in GM were observed in the anterior cingulate gyrus (255 R + 96 L voxels), followed by the orbitofrontal gyrus (274 voxels), the right cerebellar hemisphere (245 voxels) and the left cerebellar hemisphere (192 voxels).

Significantly smaller GM volumes in normal-weight controls where only encountered when reducing the cluster size from 25 to 5 voxels; two small clusters, counting less than 16 voxels each, could be found bilaterally in the frontal lobe (BA 10) with significantly smaller GM volumes in normal as compared to obese subjects (Table 4).

DISCUSSION

Following a hypothesis of Peters (2009) decreased brain volumes might be an effect of an insufficient metabolic supply of this organ. Especially reduction of grey matter or neurons might be explained by energy deficits as neurons are the most energy demanding cells. This hypothesis is supported by results of a phosphorus 31 magnetic resonance spectroscopy (31p MRS) study that showed an inverse correlation between BMI and intracranial adenosine triphosphate (ATP) levels (Schmoller 2009). Also, well-documented increases of cytokines and other inflammatory mediators in obese subjects might contribute to brain volume reductions (Rizvi 2010). A correlation between elevated fibrinogen levels and diminished brain volumes in orbitofrontal cortex was demonstrated in a recent study by Cazettes and co-workers (Cazettes 2011). Also, our results indicate subtle GM volume effects rather than extended volume differences between obese and control subjects.

TIV= intracranial brain volume

Regarding total brain volumes, no significant volume difference was found in our study collective of young adult women between obese and normal-weight participants. Their WM/GM-ratios did not differ significantly from each other. Following a study of Groeschel et al. (2010), in which brain development from birth through the age of 30 were analyzed using

TABLE 1. Anthropometric Group Data

all data, mean (SD)	Normal-weight group (n=12)	Obese group (n=12)	T or Z value	p
Age, years	27.5 (4.3)	29.25 (7.28)		ns
BMI, years	20,9 (1,7)	36,3 (4,8)	T(24)=-10,8	<0,001
Handedness (riųght)	12	12	-	ns
Current medication	none	none	-	ns
Time since suffering from obesity, in years	none	17,2 (8,9)	-	ns

TABLE 2. Comparison of NATIVE SPACE VOLUMES between obese and controls

all data, mean (SD)	Normal-weight group (n=10)	Obese group (n=13)	T or Z value	p
TIV (ml)	1359,83	1316,42	0,94	0,36
GM volume (ml)	641,90	613,55	1,32	0,20
WM volume (ml)	526,26	525,47	0,03	0,98
CSF volume (ml)	191,69	177,47	2,08	0,05
Neuroparenchym (ml)	1168,16	1139,01	0,64	0,53
grey of total (in %)	47	47	0,52	0,61
white of total (in %)	39	40	-0,93	0,37
CSF of total (in %)	14	14	1,03	0,31

algorithms based on voxel-based morphometry (VBM), we conclude that all study participants were at about the same level of brain maturity. Our TIV findings are also in accordance with other studies showing no volume differences on macroscopic levels between obese and nomal-weight women such as the study of Peters et al. (2011), underlining the need for advanced imaging techniques, such as VBM.

VBM

Our findings of GM diminishment in obese subjects are supported by various other studies (Maayan et al., 2011, Walther et al., 2010, Raji et al., 2010, Taki et al., 2008, Gunstad et al., 2008 and Panacciulli et al., 2006), even though different study designs hamper their comparability. In

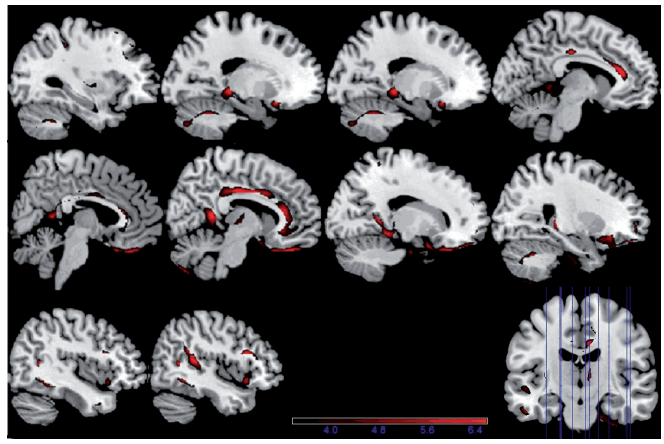

FIG. 1. Results of VBM-study. Comparison Obese < Controls. Statistical threshold: p<0,05. FDR-corrected. Results visualized in MRICRON

TABLE 3. VOXEL BASED MORPHOMETRIE, Obese < controls. Two-tailed t-test, p < 0.05; FDR Maximal Voxel Cluster >25

Region	H	BA	T	Z	MNI-coordinates	Cluster Size
Cingulate Gyrus; Limbic Lobe	R	24	13.22	6.88	11; 13; 33	255
Cingulate Gyrus; Limbic Lobe	R	24	7.98	5.41	8; -5; 35	
Cingulate Gyrus; Limbic Lobe	L	24	5.55	4.87	-9; 22, 24	96
Orbital Gyrus, Frontal Lobe	R	11	9.90	6.05	12; 36; -28	274
Sub-Gyral; Temporal Lobe	R	37	8.24	5.51	48; -48; -9	30
Gyrus fusiforme; Temporal Lobe	R	37	5.85	4.95	50; -41; -13	
Culmen; Anterior Lobe	R	Cerebellum	11.54	6.49	11; -39; -4	245
Culmen; Anterior Lobe	L	Cerebellum	10.0	6.08	-12; -35; -6	156
Cerebellar Tonsil; Posterior Lobe	L	Cerebellum	6.60	4.85	-27; -54; -34	36
Anterior Lobe;	L	Cerebellum	5.31	4.72	-18; -54; -28	

TABLE 4. VOXEL BASED MORPHOMETRIE, Obese > controls. Two-tailed t-test, p < 0.05; FDR Maximal Voxel Cluster >5

Region	H	BA	T	Z	MNI-coordinates	Cluster Size
Middle Frontal Gyrus; Frontal Lobe	R	10	7,27	5,14	12; 52; 6 R=3	9
Middle Frontal Gyrus; Frontal Lobe	L	10	6,63	4,87	-11; 46; 6 R=1	16

contrast to Taki et al. (2008) who did not detect brain volume differences but in men solely, we found BMI - associated parenchymal volume differences in women. By examining exclusively right-handed young adults with neither prior CNS illnesses nor medication, we were able to rule out confounding variables such as aging or drug related effects and attributed brain volume changes to the BMI differences of our study groups.

The nature of GM volume reduction in VBM studies has not been described on a cellular level yet. It remains unclear whether the described selective volume effects are due to apoptosis of neurons or just represent neuronal volume shrinkage. Also, the reversibility of GM volume differences has not been established up to now, i.e. the beneficial effects of dietary measures and weight reduction in obese patients. A recent study suggests that salutogenesis/decrease in brain volume in the obese seems possible when an adequate therapy is applied (Matochik 2005a); in that study leptin-deficient patients showed increasing grey matter volumes after Leptin-substitution. It might also be speculated that the selective GM volume changes

in obese subjects are a constitutive factor rather than a sequel of BMI increases.

Anatomical and physiological context

In the following, we address the potential functional impacts of subvolume differences of the brain parenchyma in obese patients as compared to healthy controls.

Cingulate gyrus

We found a significant volume reduction of GM in obese individuals as compared to control subjects bilaterally in the anterior cingulate gyrus. These findings are in agreement with the studies of Raji et al. (2010) and Taki et al. (2008) in which volume reductions in the cingulate gyrus were detected as well. Representation of sense and flavour can be found in the anterior cingulate cortex, as well as in the orbitofrontal cortex and the insular taste cortex (Grabenhorst 2007).

Neurons of the cingulate gyrus express leptinreceptors. Leptin seems to be essential in several differentiating steps of fetal neurons and may maintain neuronal stem cells (Udagawa et al., 2006). In Leptin-deficient mice an elevated number of pycnotic cells could be found in cingulate gyrus with reduced sizes of cerebrum and cerebellum. The authors hypothesized that leptin deficiency leads to an elevated rate of neuronal apoptosis (Udagawa, 2006). In addition, leptin is secreted by adipocytes and regulates food intake and homeostasis of metabolism as could be shown in some knock out mutations (Udagawa 2006). Leptin deficiency as well as -resistance of receptors is associated with elevated weight. Leptin-deficient mice show elevated body weights, reduced brain weight, reduced grey matter, maturation deficits of neuronal and glial cells and an elevated tendency towards neurodegeneration (Sriram 2002). The role of Leptin in idiopathic obesity is less clear, yet leptin seems to have trophic effects on brain tissue and at least in some cases sustained GM volumes increases could be shown in leptin-deficient patients by VBM measurements, following replacement therapy of recombinant methionyl human leptin (Matochik 2005a). Altogether, these findings suggest a context between leptin metabolism, obesity and pathomorphology of the cingulate gyrus, that fits into our current study findings.

Orbitofrontal cortex (OFC)

The prevailing study showed reduced OFC volumes, which has also been reported in obese subjects by Maayan (2011). The OFC plays a key role in impulse control as indicated by functional studies (Rothemund 2007, Weygandt 2013) and impulse control in turn does have an important impact on food uptake.

Cerebellum

Some cerebellar regions showed reduced volumes in obese young women as compared to controls. The cerebellum is not only involved in the control of movement but also in that of visceral activity (Triarhou 2008) and it participates in modulating the function of higher centres. Direct cerebello – thalamic projections have been described. Finally also homeostasis undergoes cerebellar modulation (Schmahmann 2007).

Middle frontal gyrus/ temporal lobe

Volume reductions in the temporal lobe have been described to a greater extent in an CT -based study on elderly women (Gustafson, 2004), showing that elevated body weight leads to disproportional volume decreases in this region throughout the process of aging. Our results in young female adults only showed sparse comparable effects, yet further decline within following decades might be expected for obese participants.

LIMITATIONS

A major limitation of this study is the relatively small sample size, resulting in reduced statistical power. All participants were young adult women, making our findings less generalizable, even though this fact in turn strengthened the statistical power by reducing the within sample variation.

Data acquisition itself is a potential source of imprecision of VBM studies; usage of different scanners can have a negative effect on data analysis (Focke et al. 2011). To avoid this, we made only use of a data sample made on one single scanner within a time span where acquisition conditions could be kept stable even though this in turn limited the study period and thus the number of patients to be included.

The comparability of our results with previously published VBM studies on the obese also suffers from the varying study designs

CONCLUSION

Comparison of global brain tissue volumes in obese versus normal-weight young women showed no significant differences.

Yet, our data suggest subtle foci of reduced gray matter volumes in the cingulate gyrus, orbitofrontal gyrus, temporal lobe, fusiforme gyrus, anterior lobe and in the cerebellum of young, adult, obese females, some of these regions have previously been put into context with control of food intake.

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