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Association between waist circumference and gray matter volume in 2344 individuals from two adult community-based samples

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ABSTRACT

We analyzed the putative association between abdominal obesity (measured in waist circumference) and gray matter volume (Study of Health in Pomerania: SHIP-2, N = 758) adjusted for age and gender by applying volumetric analysis and voxel-based morphometry (VBM) with VBM8 to brain magnetic resonance (MR) imaging. We sought replication in a second, independent population sample (SHIP-TREND, N = 1586). In a combined analysis (SHIP-2 and SHIP-TREND) we investigated the impact of hypertension, type II diabetes and blood lipids on the association between waist circumference and gray matter. Volumetric analysis revealed a significant inverse association between waist circumference and gray matter volume. VBM in SHIP-2 indicated distinct inverse associations in the following structures for both hemispheres: frontal lobe, temporal lobes, pre- and postcentral gyrus, supplementary motor area, supramarginal gyrus, insula, cingulate gyrus, caudate nucleus, olfactory sulcus, para-/hippocampus, gyrus rectus, amygdala, globus pallidus, putamen, cerebellum, fusiform and lingual gyrus, (pre-) cuneus and thalamus. These areas were replicated in SHIP-TREND. More than 76% of the voxels with significant gray matter volume reduction in SHIP-2 were also distinct in TREND. These brain areas are involved in cognition, attention to interoceptive signals as satiety or reward and control food intake. Due to our cross-sectional design we cannot clarify the causal direction of the association. However, previous studies described an association between subjects with higher waist circumference and future cognitive decline suggesting a progressive brain alteration in obese subjects. Pathomechanisms may involve chronic inflammation, increased oxidative stress or cellular autophagy associated with obesity.

Introduction

Obesity has recently been classified as a disease by the American Medical Association (Pollack, 2013). More than one-third of U.S. (Ogden et al., 2014) and one-fourth of the German adults are obese (Mensink et al., 2013; Völzke et al., 2015). Obesity is a serious individual and public health problem: in many patients it affects most organ systems including the central nervous system, and is associated with increased risk for poor cognitive function and neurodegenerative disorders, such as dementia (Gustafson et al., 2003; Loef and Walach, 2013; Whitmer et al., 2005).

A well-established metric to reflect body proportions is the body mass index (BMI). The World Health Organization defined obesity as a BMI ≥ 30 (WHO, 2014). There is growing evidence that higher BMI is associated with lower brain volume (Pannacciulli et al., 2006; Raji et al., 2010; Taki et al., 2008; Ward et al., 2005; Yokum et al., 2012). In a recent genome-wide-association analysis including 339,224 individuals a pathway analysis provided strong support for an important role of the central nervous system in obesity susceptibility. BMI-associated genes were enriched for expression in the brain and central nervous system (Locke et al., 2015).

However, the BMI does not reflect the pattern of fat distribution. The abdominal or central obesity appears to be more closely linked to

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adverse health outcomes than a high BMI would indicate in studies investigating cardiovascular diseases and risk factors of chronic diseases (de Koning et al., 2007; Janssen et al., 2004; Staiano et al., 2012). Different fat distribution patterns even showed distinct genetic components (Shungin et al., 2015). Abdominal obesity is defined as a waist circumference of more than 102 cm for men and 88 cm for women (WHO, 2008).

Only little is known about the associations between abdominal obesity and gray matter volume. Previous studies focused on middle aged participants or were conducted in relatively small study populations. For example, Debette et al. showed that total brain volume is inversely associated with CT-measured visceral adiposity (Debette et al., 2010) and with waist-to-hip ratio (Debette et al., 2011). Kurth et al. investigated the effect of waist circumference and BMI on the gray matter volume in 115 healthy, unmedicated subjects without hypertension, type II diabetes or lipid disorder (Kurth et al., 2013). Results were more pronounced for waist circumference than for BMI with most prominent effects on hypothalamus, prefrontal, anterior temporal and inferior parietal cortices and the cerebellum. While there is converging evidence for regional gray matter differences in obesity (measured in BMI), the precise gray matter pattern has not been clearly defined in abdominal obesity. Kurth et al. summarized that waist circumference is a more sensitive indicator than BMI in determining the adverse effects of obesity on the brain and associated risks to health (Kurth et al., 2013).

Common comorbidities of obesity, hypertension and type II diabetes, are significantly linked to obesity-related morbidity and mortality (Mokdad et al., 2003). These conditions may affect the brain and gray matter (Firbank et al., 2007; Glodzik et al., 2012; Moulton et al., 2015; Roberts et al., 2014). Additionally, little is known about the influence of blood lipids on the gray matter volume, since lipid disorders are often an exclusion criterion from voxel-based morphometry (VBM) analyses on obesity (Horstmann et al., 2011; Kurth et al., 2013). However, results from one previous study indicated an inverse association between the temporal lobe volume and total cholesterol levels in men (Qiu et al., 2012).

We examined 2344 subjects from two epidemiological samples with brain magnetic resonance imaging (MRI) and applied the VBM 8 for the global analysis of brain structure without an a priori restriction to a region of interest (Ashburner and Friston, 2000).

Based on findings from the studies mentioned above, we hypothesized that subjects with abdominal obesity have smaller volumes of gray matter structural networks, specifically in areas involved in behavioral control, reward processing (e.g. the prefrontal cortex in the frontal lobe or striatum with caudate nucleus, globus pallidus and putamen), homeostasis (hypothalamus) and motor control (cerebellum and gyrus precentralis). We specifically assessed the putative effects of obesity-related comorbidities (type II diabetes and hypertension) and corresponding medication on gray matter volumes and also considered serum lipid levels as potential mediator.

Material and methods

Data from two independent samples from the Study of Health in Pomerania (SHIP) project were used (Grabe et al., 2005; John et al., 2001; Volzke et al., 2011). The target population for SHIP-0 was comprised of adult German residents in northeastern Germany living in three cities and 29 communities, with a total population of 212,157. A two-stage stratified cluster sample of adults aged 20–79 years (baseline) was drawn from local registries. The net sample (without migrated or deceased persons) comprised 6267 eligible subjects, of which 4308 Caucasian subjects participated at baseline SHIP-0 between 1997 and 2001. From 2008 to 2012 the second follow-up examination (SHIP-2, N = 2333) was carried out. Concurrent with SHIP-2 a new independent sample from the same area was drawn and similar examinations were undertaken between 2008 and 2012 (SHIP-TREND, N = 4420). The only exclusion criterion for SHIP-TREND was participation in SHIP-0.

Subjects from SHIP-2 and SHIP-TREND were invited to undergo whole-body MRI. After exclusion of subjects who refused participation or who fulfilled exclusion criteria against MRI (e.g. cardiac pacemaker, pregnancy) N = 1182 subjects from SHIP-2 and 2186 subjects from SHIP-TREND underwent the MRI scanning. T1-weighted MRI of the brain were available for n = 1163 subjects from SHIP-2 and N = 2154 subjects from SHIP-TREND (Hegenscheid et al., 2013). All images were obtained from the same 1.5 Tesla scanner (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany). For our structural investigations we used the three-dimensional T1-weighted axial MRI sequence with the following parameters: 1900 ms repetition time, 3.4 ms echo time, flip angle = 15° and a voxel size of 1.0 × 1.0 × 1.0 mm. We used SPM 8 with VBM 8 toolbox and MATLAB R2014a. The images were bias-corrected, spatially normalized by using the high-dimensional DARTEL normalization, segmented into the different tissue classes, modulated for non-linear warping only and smoothed by a Gaussian kernel of 8 mm FWHM (full-width at half maximum). Absolute threshold masking was altered from defaults with 0.2. We used t-contrast for inverse associations with waist circumference/BMI as a single-ended test.

Exclusion criteria for analyses

We excluded subjects with following medical conditions from the present analyses: history of cerebral tumor, stroke, Parkinson's disease, multiple sclerosis, epilepsy, hydrocephalus, enlarged ventricles and pathological lesions (remaining subjects in SHIP-2: N = 1045 and SHIP-TREND: N = 2010). Furthermore, images with strong movement artefacts or severe inhomogeneities of the magnetic field (remaining subjects in SHIP-2: N = 1011 and SHIP-TREND: N = 1934) and subjects with incomplete datasets for clinical data were excluded (remaining subjects in SHIP-2: N = 1009 and SHIP-TREND: N = 1934).To minimize neurodegenerative effects we excluded subjects with age above 65 years (residual subjects in SHIP-2: N = 771 and SHIP-TREND: N = 1611). Homogeneity check within the VBM 8 toolbox was conducted separately for each sample (residual subjects in SHIP-2: N = 758 and SHIP-TREND: N = 1586). In total, N = 2344 subjects with N = 758 subjects from SHIP-2 and N = 1586 subjects from SHIP-TREND were included in the final analyses.

Interview and clinical examination

Sociodemographic factors and medical history were assessed by a computer-assisted face-to-face interview. All subjects were asked to bring their packing containers of all medication they had taken during the last 7 days, as well as their drug prescription sheets. Every compound was recorded and categorized according to the Anatomical Therapeutic Chemical classification (ATC-Index, 2007). We focused on antidiabetics ATC-code (A10*) and antihypertensive medication (C02*, C03*, C07*, C08* and C09*).Having completed the interview, patients underwent medical examinations. This included the measurement of height and weight to calculate the BMI (kg/m^2). Waist circumference was measured in cm. After a 5-min resting period, systolic and diastolic blood pressure was measured three times on the right arm of seated subjects using a digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan) with each reading being followed by a further resting period of 3 min. One of two differently sized cuffs was applied according to the circumference of the participant's arm. The mean of the second and third measurement (mm Hg) was used for the present analyses.

Laboratory analyses

Non-fasting blood samples were drawn from the cubital vein in the supine position in SHIP-2. Fasting blood samples were drawn with the same procedure in SHIP-TREND. The samples were taken between 07:00 a.m. and 04:00 p.m., and serum aliquots were prepared for

immediate analysis or storage at −80 °C. High-density lipoprotein cholesterol (HDL-C) concentrations were measured photometrically (Hitachi 704, RocheDiagnostics, Mannheim, Germany), whereas follow-up HDL-C concentrations were quantified by lipid electrophoresis (HELENA SAS-3 system, Helena 7 BioSciences Europe, Tyne & Wear, UK). To ensure comparability in the longitudinal HDL-C analyses, we used baseline HDL-C concentrations as the reference and calculated corrected follow-up HDL-C concentrations based on a previously published conversion formula (HDL_fu_corr = −80 + (1.158 × HDL_fu)) (Nauck et al., 1995). Serum low-density lipoprotein (LDL-C) was measured by applying a precipitation procedure using dextran sulfate (Immuno, Heidelberg, Germany) on an Epos 5060 (Eppendorf, Hamburg, Germany). Total cholesterol, LDL-C and HDL-C were measured in mmol/l as dimensional scores.

Glycated hemoglobin (HbA1c, measured in %) concentrations were determined by high-performance liquid chromatography (Bio-Rad Diamat, Munich, Germany). All assays were performed according to the manufacturer's recommendations by skilled technical personnel. In addition, the laboratory participates in official quarterly German external proficiency testing programs.

Statistical analysis

We used SPM 8 with VBM 8 toolbox and MATLAB R2014a. Associations of waist circumference on local gray matter volume were tested using multiple regression analyses in a general linear model. Age and gender were included as covariates for the VBM-analyses of SHIP-2 and SHIP-TREND. We applied age, gender, hypertension, type II diabetes, and serum lipids as covariates in the combined sample. In a separate analysis, serum lipids as covariate were excluded to specifically evaluate this association (see supplement table 4 and supplement Fig. 2). Hypertension was defined by a systolic blood pressure (BP) of ≥140 mm Hg and/or a diastolic BP of ≥90 mm Hg and/or intake of antihypertensive medication (ATC-Code: C02*, C03*, C07*, C08* and C09*). Type II diabetes was defined as HbA_{1c} ≥6% and/or intake of antidiabetic medication (ATC-code: A10*) (ATC-Index, 2007). Age, gender, hypertension, type II diabetes, and serum lipids were included as covariates. Hypertension and type II diabetes were included as categorical covariates. Serum lipids included LDL-C, HDL-C and total cholesterol as dimensional covariates. All results were corrected for multiple comparisons by controlling the family wise error rate (FWE) at 0.05 on voxel level.

Two additional comparisons were conducted: For sensitivity analysis using VBM8 we included 435 TREND participants without hypertension, without type II diabetes and with HDL-C > 1 mmol/l in men and >1.3 mmol/l in women, LDL-C < 4.2 mmol/l and total cholesterol < 5.2 mmol/l, triglyceride <2.3 mmol/l from SHIP-2 and SHIP-TREND.

We conducted a multiple regression analysis in a general linear model with age and gender as covariates (see supplement). For comparison reasons we additionally performed a VBM analysis for the association between gray matter volume and BMI in the combined sample of SHIP-2 and SHIP-TREND, analyses of interactions with waist circumference and gender and the association of whole brain volume/gray matter with waist circumference (see supplement).

MRIcroGL and OrthoView were used for graphics. Reports were labeled with the AAL Toolbox (Tzourio-Mazoyer et al., 2002) and xjview.

Results

Characteristics of the study population

Table 1 depicts the characteristics and clinical information of the two study populations. Significant differences for following characteristics were observed: age, systolic and diastolic blood pressure, consequentially hypertension, triglyceride levels, HbA_{1c} levels and education.

Table 1
Description of the SHIP-2 and SHIP-TREND study populations.

Variable		
Mean +/− sd; N	SHIP-2	SHIP-TREND
	N = 758	N = 1586
Age in years	49.8 +/− 9.3	46.3 +/− 11.3***
Men/women	350/408	737/849
Waist circumference in cm	88.7 +/− 12.8	87.9 +/− 12.6
Body height in cm	170.3 +/− 9.2	170.8 +/− 9.2
Weight in kg	79.6 +/− 15.5	79.5 +/− 15.2
BMI	27.4 +/− 4.5	27.2 +/− 4.4
Systolic BP in mm Hg	128.9 +/− 17.7	124 +/− 16.4***
Diastolic BP in mm Hg	80.9 +/− 9.9	77.2 +/− 10.0***
HbA_{1c} in %	5.3 +/− 0.8	5.2 +/− 0.7**
Trigycerides in mmol/l	1.8 +/− 1.4	1.5 +/− 1.1***
LDL-C in mmol/l	3.4 +/− 0.9	3.4 +/− 0.9
HDL-C in mmol/l	1.5 +/− 0.4	1.5 +/− 0.4
Total cholesterol in mmol/l	5.5 +/− 1.06	5.5 +/− 1.1
Type II diabetes	64	107
Hypertension	347	586***
Education		
<10 years	69	101 **
10 years	495	984
>10 years	194	497
Smoking nicotine		
Current	277	603
Former	293	539
Never	187	441
Medication		
Antihypertensive	210	371
Antidiabetic	24	37

Abbreviations: sd = standard deviation, N = Number, cm = centimeter, kg = kilogram, BMI = body mass index, BP = blood pressure, HbA_{1c} = glycated hemoglobin, mm HG = millimeter of mercury, mmol/l = millimol per liter, LDL-C = low density lipoproteins, HDL-C = high density lipoproteins.
** P ≤ 0.01.
*** P ≤ 0.0001.

VBM revealed significant inverse associations with waist circumference and gray matter volume in SHIP-2 (supplement table 1). The following structures were distinct in SHIP-2 for both hemispheres: frontal lobe, temporal lobes, pre- and postcentral gyrus, supplementary motor area, supramarginal gyrus, insula, cingulate gyrus, caudate nucleus, olfactory sulcus, (para-) hippocampus, gyrus rectus amygdala, globus pallidus, putamen, cerebellum, fusiform and lingual gyrus, (pre-) cuneus, thalamus and small areas unilateral in the temporal, parietal and occipital lobe.

In a second VBM analysis we replicated these results in SHIP-TREND (supplement table 2). In SHIP-TREND very similar brain areas differed with even more pronounced associations in the occipital lobe and the cerebellum. More than 76% of the voxels associated with waist circumference in SHIP-2 overlapped with the voxels associated with waist circumference in SHIP-TREND (Table 2). Overlapping brain structures between SHIP-2 and SHIP-TREND are exemplarily presented in Fig. 1a. The affected clusters were only marginally smaller when adjusting for hypertension, type II diabetes and blood lipids (combined sample of SHIP-2 and SHIP-TREND) (supplement table 3). Fig. 1b presents brain areas of smaller gray matter volumes in SHIP-2 and SHIP-TREND combined. We found the thalamus and the frontal cortex to show particularly smaller volumes.

The overlap of associated brain areas between the analyses adjustment Level 1 (adjusted for gender and age) and for adjustment Level 2 (adjusted for gender, age, hypertension, diabetes and blood lipids) is presented in Fig. 2. The overlap of associated brain areas between the analyses adjustment Level 2 (adjusted for gender, age, hypertension, diabetes and blood lipids) and for adjustment Level 3 (adjusted for gender, age, hypertension and diabetes without blood lipids) is presented in supplement table 4 and supplement Fig. 2.

In a sensitivity analysis we investigated a healthy subsample (N = 435) for gray matter structures and inverse associations with waist

Table 2
Overlapping voxels of the association between waist circumference and gray matter volumes between different adjustment level in SHIP-2 and SHIP-TREND.

Condition	Number of voxels §	Number of overlapping voxels § (%)
A = SHIP-2 adjustment Level 1*	34,266	26,088 (76.1% of A in overlap with B)
B = SHIP-TREND adjustment Level 1*	76,843	
C = SHIP-2 + SHIP-TREND adjustment Level 1*	116,343	79,737 (68.5% of C in overlap with D)
D = SHIP-2 + SHIP-TREND adjustment Level 2*	81,101	
E = SHIP-2 + SHIP-TREND waist circumference adjustment Level 2*	81,101	52,307 (64.5% of E in overlap with F)
F = SHIP-2 + SHIP-TREND BMI adjustment Level 2*	55,032	

Adjustment Level 1 * = adjusted for gender, age.
Adjustment Level 2 * = adjusted for gender, age, hypertension, diabetes, HDL-C >1 mmol/l in men and >1.3 mmol/l in women, LDL-C <4.2 mmol/l and total cholesterol <5.2 mmol/l.
Abbreviations: BMI = body mass index, mmol/l = millimol per liter, LDL-C = low density lipoproteins, HDL-C = high lipoproteins.
§ Significant ($p < 0.05$) after FWE correction.

circumference (supplement table 5). The gray matter volumes of the right gyrus rectus, bilateral frontal lobes, left insula, left temporal pole and small part of the left cerebellum were inversely associated with waist circumference.

Furthermore we conducted VBM analyses for using BMI instead of waist circumference in the combined sample (supplement table 6, supplement Fig. 1). All involved areas of the waist circumference/gray matter analysis were replicated, but measured regions were smaller. Correlation between waist circumference and BMI were r = 0.84 in the dataset with N = 2344 subjects (in detail: SHIP-2: r = 0.82 (N = 758) and SHIP-TREND: r = 0.84 (N = 1586)).

We regressed the voxels of relative gray matter volume (controlled for total brain volume) obtained by VBM in the combined SHIP-2 and SHIP-TREND sample on waist circumference adjusted for age, gender, hypertension, type II diabetes and serum lipids. The median of the significant associations (FWE corrected p-values < 0.05) was $-8.98e^{-04}$

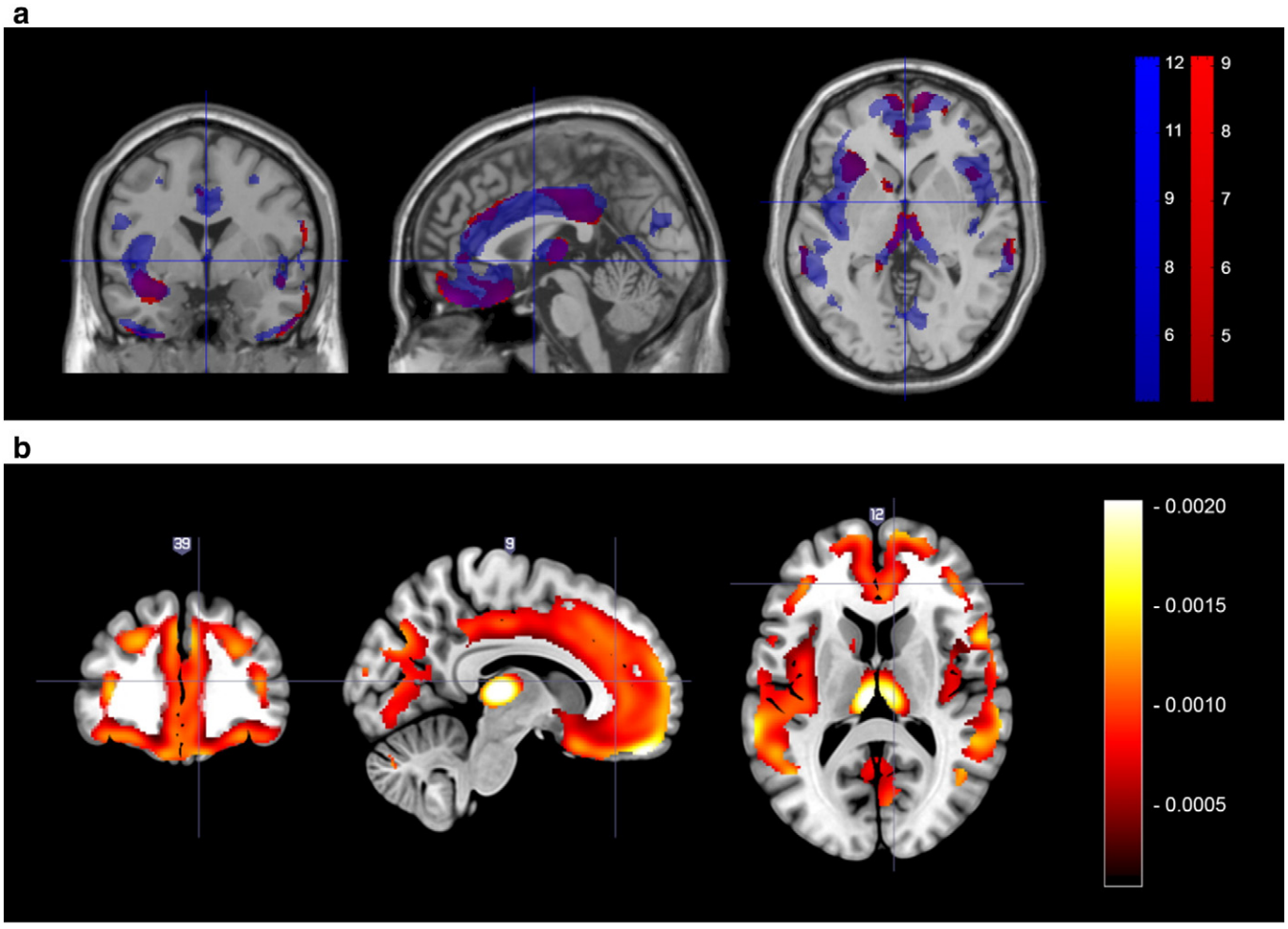

Fig. 1. a: Overlapping brain areas of inversely associated gray matter volumes in SHIP-2 and SHIP-TREND. Inverse association of gray matter volume with waist circumference in two independent samples (adjustment for age and gender) displayed by maximum intensity projections (i.e., a glass brain) in sagittal, coronal, and transaxial orientations. Maps are thresholded at $P < 0.05$, after false-discovery rate (FDR) correction for multiple comparisons. Overlapping areas of inversely associated gray matter volumes in SHIP-2 and SHIP-TREND are displayed in violet. Involved areas of gray matter volume differences exclusively in SHIP-2 (N = 758) subjects are displayed in red, whereas blue color codes for areas of gray matter volumes exclusively identified in SHIP-TREND subjects (N = 1586). b: Brain areas of inversely associated gray matter volumes in SHIP-2 and SHIP-TREND combined. b: Inverse association of gray matter volume with waist circumference (adjustment for age and gender) displayed by maximum intensity projections (i.e., a glass brain) in sagittal, coronal, and transaxial orientations (N = 2344). Maps are thresholded at $P < 0.05$, after false-discovery rate (FDR) correction for multiple comparisons. Particularly involved are thalamus and frontal cortex.

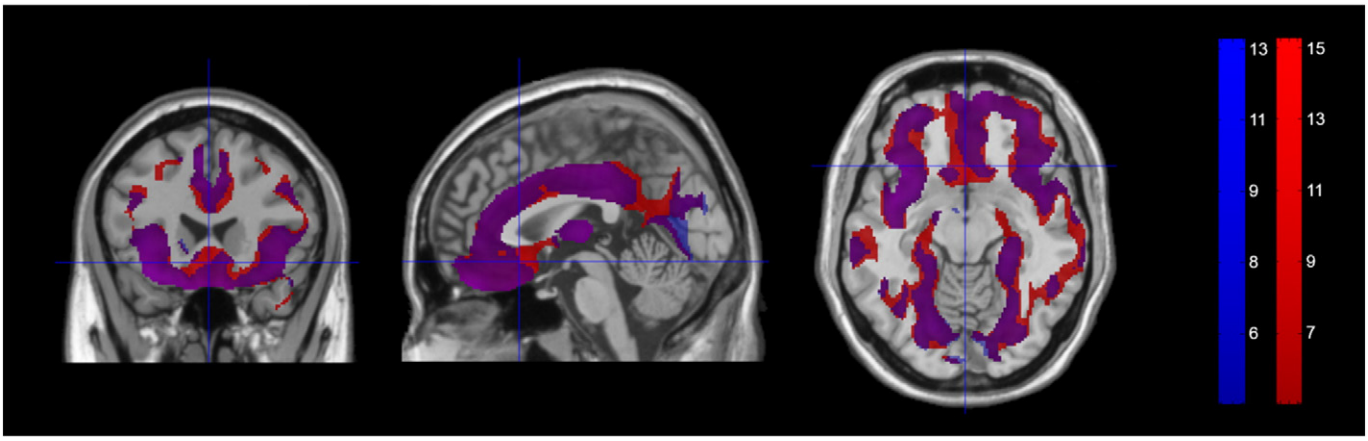

Fig. 2. Overlaps between adjustments. Inverse association of gray matter volume with waist circumference in a combined sample (SHIP-2 and SHIP-TREND): Overlapping areas in violet indicate negatively associated gray matter volume after adjustment for age and gender and after additional adjustment for hypertension, type II diabetes and blood lipids. Red areas indicate gray matter volumes exclusively associated with waist circumference after adjustment for age and gender. Blue areas exclusively indicate gray matter volume associations after adjustment for age, gender, hypertension, type II diabetes and blood lipids.

(interquartile range: $-7.5548e^{-04}$, -0.0011), which corresponds to an average negative association of 0.1% gray matter volume per cm waist circumference.

Discussion

This cross-sectional study investigated the relationship between abdominal obesity (measured in waist circumference) and both global and regional gray matter volumes in two large samples from the general population. Given the higher statistical power due to double quantity of participants in SHIP-TREND the replication-sample showed even larger regions with gray matter differences than SHIP-2. SHIP-2 is a sample at the third examination (10 years after baseline recruitment) compared with SHIP-TREND at the first examination. Both samples significantly differed for following characteristics: age, systolic and diastolic blood pressure, hypertension, triglycerides, HbA_{1c} and education. However, most of the differences are fully explained by the higher age of subjects in SHIP-2 (Völzke et al., 2015). Therefore, despite these differences, replication of the results succeeded.

As hypertension and type II diabetes have been shown to be negatively associated with the gray matter by themselves (Firbank et al., 2007; Glodzik et al., 2012; Moulton et al., 2015; Roberts et al., 2014) and are common conditions of obesity (Mokdad et al., 2003) we adjusted our analyses for both conditions. However, only a minor effect upon adjustment was identified suggesting that the association between waist circumference and gray matter was not largely mediated by type II diabetes or hypertension. The adjustment for blood lipids additionally to age, gender, hypertension and type II diabetes did not change the associations found before (supplement table 4 and supplement Fig. 2).

We identified new and confirmed previously described differences of gray matter in the following structures: frontal lobe, temporal lobe, pre- and postcentral gyrus, supplementary motor area, supramarginal gyrus, insula, cingulate gyrus, caudate nucleus, olfactory sulcus, (para-) hippocampus, gyrus rectus amygdala, globus pallidus, putamen, cerebellum, fusiform and lingual gyrus, (pre-) cuneus, thalamus and small areas unilateral in the temporal, parietal and occipital lobe.

The distributed and regionally specific nature of these distinctions provides compelling support for considering abdominal obesity as a condition that involves the impairment of specific networks across the brain. We focus in our discussion on whole brain analyses in the literature. Previous cross-sectional studies have used MRI to detect brain structural abnormalities in subjects with increased BMI but frequently, heterogeneous and often conflicting results have emerged: lower gray matter volume in regions implicated in taste processing and interception (postcentral gyrus and frontal operculum/extended insula), executive control (middle frontal gyrus) and reward (putamen) (Pannacciulli et al., 2006), reduced global brain volume (Ward et al., 2005) and differences in the orbitofrontal cortex, inferior- and middle frontal gyri, parahippocampal gyrus, lingual gyrus, and cerebellum (Walther et al., 2010). Similar results were found for BMI and gray matter differences controlled for acute depression (Opel et al., 2015b). Raji et al. investigated in a tensor-based morphometry (N = 94; mean age 77 years) and found inverse associations between BMI and gray matter volume in the ACC, hippocampus, frontal cortex and thalamus (sensory relay motor regulation) (Raji et al., 2010). Inverse associations were reported in male but not in female subjects in 1428 participants between BMI and gray matter volume in the medial temporal lobes, cerebellum, occipital lobe, frontal lobe, midbrain, hippocampus, and precuneus (Taki et al., 2008). Ethnic differences and the use of self-report data instead of measured somatometric data may account for different results. Waist-to-hip ratio and older age were inversely related to hippocampal volumes in 112 participants. The association was not affected by adjustment for BMI, total cholesterol, fasting blood glucose, and insulin levels or systolic blood pressure (Jagust et al., 2005).

The relationship of both BMI and waist circumference was explored with gray matter volumes in a group of 115 healthy subjects and revealed significant inverse associations (hypothalamus, prefrontal, anterior temporal and inferior parietal cortices, and the cerebellum) (Kurth et al., 2013). In an additional analysis, we examined a subsample of healthy subjects (n = 435) to enable a comparison with the results from Kurth et al. We found different inverse associations in the right gyrus rectus, bilateral frontal, left insula, left temporal pole and small part of the left cerebellum. These differences may have occurred because of younger age (mean age 39.7 years; +/− 9.91) and lower waist circumference (mean waist circumference 80.6 cm; +/− 10.1) of the subjects in our healthy subsample compared to our combined sample. Our combined sample (SHIP-2 and SHIP-TREND) was older and more obese than the sample of Kurth et al. The gray matter disparity was more widespread. Similar to Kurth et al. we saw distinct inverse associations with waist circumference compared to BMI (Kurth et al., 2013).

To develop a model on the causal relationship between waist circumference and gray matter difference longitudinal studies may be especially informative. Longitudinal data over 5 years reported declines in temporal and occipital gray matter associated with baseline BMI (Bobb et al., 2014). They suggested persistence and possibly progression of gray matter distinctions in some lobar areas. In a longitudinal study, increasing waist-to-hip ratio was associated with progressive decline in total brain volume (Debette et al., 2011). These longitudinal data indicate a progressive volume reduction of the gray matter as being a dynamic process particularly in obese subjects. Additionally, gray matter

volume was found to be different in the orbitofrontal cortex, insula, and cerebellum in obese prone subjects compared to obese resistant subjects (aged from 25 to 40 years), independent of fat mass (Smucny et al., 2012). They defined obese prone or obese resistant based on self-identification, BMI, and personal/family weight history and concluded that the gray matter volume reduction has occurred prior to the onset of obesity.

The longitudinal studies found evidence supporting these possible models:

First: pre-existing gray matter volume deficits in neurocircuits controlling food intake may lead to impaired behavioral control of eating habits and therefore contribute to future obesity. Second: abdominal obesity itself may be associated with progressive gray matter loss.

The results from our study tend to support the first model: Our whole-brain analysis approach lead to findings without an *a priori* regional bias. The two different aged independent samples showed very similar results. The magnitude of the gray matter volume differences found in this study is striking. The brain regions identified in our study have an established functional role in the pathophysiology of obesity. Initial gray matter deficits may appear in specific regions which regulate appetite, satiety, behavioral control or reward processing and lead to overindulge and abdominal obesity. A meta-analysis about response to food images—comparing obese to normal weight subjects—yielded increased activation in the left dorsomedial prefrontal cortex, right parahippocampal gyrus, right precentral gyrus and right anterior cingulate cortex, and reduced activation in the left dorsolateral prefrontal cortex and left insular cortex (Brooks et al., 2013). They conclude that the prefrontal cortex areas linked to cognitive evaluation processes, such as evaluation of rewarding stimuli as well as explicit memory regions, are more activated in response to images of food in obese probands. However, a reduced activation in brain regions associated with cognitive control and interoceptive awareness of sensations in the body might refer to a weakened control system, combined with hyposensitivity to satiety and unease (Brooks et al., 2013). Obese subjects showed increased BOLD (blood oxygenation level dependent) response to reward in prefrontal and subcortical areas compared to subjects of normal weight, which might reflect dysfunction in reward-related brain circuits in obese (Opel et al., 2015a). Several brain regions found to be smaller in obese versus lean individuals in the present study showed hyperresponsiveness in the food image studies (e.g., insula, caudate nucleus, amygdala, and putamen). This suggests a `disconnect´ between brain volume and BOLD signal.

Chronic brain damage secondary to obesity has been suggested as another possible mechanism for the negative association between waist circumference and gray matter volume. For example, chronic stress in abdominal obesity increases cortisol secretion, which may entail to brain volume changes (Bjorntorp, 2001; Lupien et al., 1998; Salehi et al., 2005; Simmons et al., 2000). Leptin modulates the inflammatory signaling in microglia (Pinteaux et al., 2007; Tang et al., 2007) which impacts on inflammatory and oxidative pathways. Oxidative stress in the brain could potentially mediate the pathogenesis of overnutrition-related metabolic diseases. This is associated with a decline of levels and activity of Nuclear factor erythroid-derived 2-like 2 (Nrf2), a transcription factor, suggesting a potential role for decreased antioxidant response. The impaired Nrf2 signaling and increased cerebral oxidative stress as mechanisms underlying high fat diet-induced obesity may lead to declines in cognitive performance (Morrison et al., 2010).

Furthermore, adipose tissue produces both pro-inflammatory and anti-inflammatory factors (Bays et al., 2008). There are clear findings that genes associated with abdominal obesity affect early development respectively differentiation of adipocytes from mesenchymal stem cell (Shungin et al., 2015). How could potentially damaging circulating factors interact with the brain tissue? An animal model showed changes in the blood-brain barrier induced by high-energy diet with increased permeability with a decrease in mRNA level of tight junction proteins, notably Claudin-5 and -12 in the hippocampus (Kanoski et al., 2010).

Brains of mice receiving a high fat/low carb diet showed 5% lower weight than normal fed mice brains (especially the volume of the hippocampal region CA3) (Pedrini et al., 2009).

Finally, one should also take into account that prolonged diminished movement patterns in obese may lead to changes in brain structure (Benedict et al., 2013; Colcombe et al., 2003). Chronic inflammation and multiple reactions like increased cortisol, decreased antioxidant response etc. may induce further unspecific progressive lesions. Overeating may serve as a function to generate more energy to fight the chronic inflammation. Regions of motoric control might perish as well to save energy or due to motoric inactivity.

This may include autophagy-mechanism in these regions. Mice with autophagy deficiency showed decreased fat mass and were protected from diet-induced obesity or insulin resistance and were accompanied by increased fatty acid oxidation (Kim et al., 2013).

In addition to the two models mentioned above, which were derived from longitudinal studies, a third model should be considered:

Additional factors, particularly genetic disposition, could influence gray matter volume and waist circumference independently. Results from a recent genome-wide-association analysis revealed that BMI-associated genes are enriched for expression in the brain and central nervous system (Locke et al., 2015).

There are several limitations to the present study. First, due to the cross-sectional design of our study, no causation can be clarified between waist circumference and gray matter volume. Second, there is potential selection bias in every MRI study due to non-participation of subjects. Additional subject selection (e.g. history of stroke) may have resulted in an unrepresentative sample. Third, neuropsychological or functional data are not assessed or included.

Strengths are the whole brain analyses without an *a priori* identification of a region of interest and the observation of long-term effects on abdominal obesity. Our study is the largest study to specifically examine gray matter volume differences in abdominal obesity and it provides a very robust level of evidence documenting the structural pattern of gray matter distinctions. Our cohorts are well characterized and non-geriatric. The enormous statistical power of two large epidemiological samples with measured waist circumference and no self-report in weight or height. To examine whether the waist circumference was associated with the gray matter volume in VBM, we adjusted for hypertension and type II diabetes, because these factors are known to be associated with regional gray matter volume. Additional controlling for blood lipids did not reveal considerable differences. We did not exclude probands with these comorbidities for a naturalistic observation. However, we cannot rule out other confounding factors that may have affected the association between waist circumference and the gray matter volume. Our study presents a highly powered, highly standardized (same MRI scanner, same scanning protocol), cross-sectional analysis of a well-described cohort, providing valuable and novel insights into the gray matter volume differences that characterize abdominal obesity.

Conclusion

In our study we could locate and quantify structural differences associated with central obesity. These gray matter distinctions are widespread and include key regions known to be functionally involved in food intake, behavior control and appetite regulation. Given the magnitude of the obesity related health- and economic problems and the paucity of treatments, there is a clear need to understand abdominal obesity in greater detail. Prospective studies with multiple measurements including both structural and functional imaging, correlated with genetics and clinical data in young cohorts, are needed to provide the data to answer these urgent questions. Further work is needed to understand the pathophysiological mechanism underlying the gray matter volume distinctions that we have demonstrated.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.07.086.

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