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Reduced cortical thickness associated with visceral fat and BMI

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ABSTRACT

Structural brain imaging studies have shown that obesity is associated with widespread reductions in gray matter (GM) volume. Although the body mass index (BMI) is an easily accessible anthropometric measure, substantial health problems are more related to specific body fat compartments, like visceral adipose tissue (VAT). We investigated cortical thickness measures in a group of 72 healthy subjects (BMI range 20–35 kg/m^2, age range 19–50 years). Multiple regression analyses were performed using VAT and BMI as predictors and age, gender, total surface area and education as confounds. BMI and VAT were independently associated with reductions in cortical thickness in clusters comprising the left lateral occipital area, the left inferior temporal cortex, and the left precentral and inferior parietal area, while the right insula, the left fusiform gyrus and the right inferior temporal area showed a negative correlation with VAT only. In addition, we could show significant reductions in cortical thickness with increasing VAT adjusted for BMI in the left temporal cortex. We were able to detect widespread cortical thinning in a young to middle-aged population related to BMI and VAT; these findings show close resemblance to studies focusing on GM volume differences in diabetic patients. This may point to the influence of VAT related adverse effects, like low-grade inflammation, as a potentially harmful factor on brain integrity already in individuals at risk of developing diabetes, metabolic syndromes and arteriosclerosis.

1. Introduction

Functional and morphological brain changes are associated with obesity. Previous neuroimaging studies demonstrated increased neural activation to food cues in obese compared to lean subjects in brain regions associated with reward, gustation, emotion, cognitive control and memory (Carnell et al., 2012). Furthermore, structural alterations in obesity have been investigated using volume-based morphometry (VBM). Hereby obesity was associated with reduced gray matter (GM) density compared to lean subjects in prefrontal, somatosensory, insular, temporal, cerebellar and subcortical regions (Kurth et al., 2013; Pannacciulli et al., 2006). In general, obesity is determined by the body mass index (BMI). However, it is well known that the risk of developing obesity related diseases is increased by specific body fat distribution and insulin resistance (Stefan et al., 2008). Individuals with abdominal adiposity, showing increased visceral adipose tissue (VAT), have an enhanced risk of metabolic complications. Raschpichler et al. (2013) demonstrated in young adults reduced GM volume exclusively in cerebellar areas with increased VAT. In comparison to BMI, Debette et al. (2010) found, in a middle-aged group, the strongest negative association between VAT and total brain volume. In old subjects, higher VAT was associated with reduced hippocampal volume and enlarged ventricles compared to lower VAT (Isaac et al., 2011).

Besides GM volume, cortical thickness is a more specific (Ashburner and Friston, 2001) and sensitive (Hutton et al., 2009) measure of GM alterations, and it is directly linked to cortical organization. Furthermore, studies investigating gray matter changes in autism (Jiao et al., 2010) and Parkinson diseases (Pereira et al., 2012) showed superior diagnostic classification using thickness-based models compared to VBM based models. Cortical thickness may therefore be a more appropriate measure when assessing structural brain alterations in diseased brains. Recently, cortical thinning was reported in obese compared to lean middle-aged adults in the anterior cingulate cortex (ACC), the anterior insula, the posterior parietal cortex (Hassenstab et al., 2012), the left superior frontal gyrus and the right medial orbitofrontal cortex (OFC) (Marques-Iturria et al., 2013) using atlas based averaged surface measures.

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Table 1
Anthropometric and metabolic characteristics.

	Mean	SD	Range
Age (years)	29.65	8.15	19–50
BMI (kg/m^2)	25.49	5.18	17.70–46.49
Waist-to-hip ratio	0.84	0.08	0.68–1.06
VAT (l)	2.39	1.56	0.31–7.58
Fasting glucose (mmol/l)	5.0	0.45	4–6.72
Fasting insulin (pmol/l)	69	65.9	20–529
Cholesterol (mg/dl)	177	31.4	119–259
HDL cholesterol (mg/dl)	55	14.1	31–101
LDL cholesterol (mg/dl)	95	25.5	43–152
Triglyceride (mg/dl)	93	47.5	34–317
C-reactive protein (mg/l)	0.25	0.44	0.01–2.52

Table 2
Significant differences in cortical thickness in relation to VAT and BMI.

Area	Size mm^2	Coordinates			*p*-Value
		x	y	z	
VAT					
Fusiform lh	3644	−40.4	−73.4	−14.6	0.0001
Insula rh	3022	34.8	−19.0	20.3	0.0206
Inferior temporal rh	1951	43.1	−10.1	−33.4	0.0487
BMI					
Inferior parietal lh	2056	−38.2	−78.2	13.0	0.0311
Inferior temporal lh	4401	−48.4	−61.5	−6.7	0.0004
Precentral rh	3713	51.8	4.3	13.6	0.0075
VAT (adjusted BMI)					
Transverse temporal lh	2190	−51.5	−15.0	3.0	0.0224

The listed areas represent the vertex with the maximum difference within the cluster. The *p*-values are corrected for multiple comparisons over both hemispheres using Monte Carlo simulation. lh = left hemisphere, rh = right hemisphere.

Thus far, the majority of the abovementioned structural studies focused on middle -aged to elderly individuals with severe obesity. It is, however, well known that additional factors are rather common in these populations like hypertension, elevated cholesterol and inflammatory processes, which potentially influence structural integrity and contribute to brain atrophy. Hence, in the current study we assessed surface based cortical thickness to investigate adipose tissue (i.e. VAT) related morphometric changes in lean, overweight and obese young to middle-aged adults.

2. Material and methods

A total of 72 subjects (30 females) were included in the study (mean age (years): 29.65 SD 8.15; mean BMI (kg/m^2): 25.49 SD 5.18). Of the 72 subjects, 42 were lean (BMI < 25), 17 overweight (BMI 25–30) and 13 obese (BMI > 30). There were no significant sex differences for age and BMI. All subjects had normal metabolic status, no chronic diseases or psychiatric and neurological diseases. In particular, in the present study the average VAT was 3.22 l in male and 1.80 l in female. Based on published studies normative values in subjects with BMI below 30 range from 2.0 to 4.0 l in men and 1.5 to 2.0 l in women (Maislin et al., 2012). C-reactive protein levels were determined using standard clinical measure to exclude subjects with acute infection (CRP > 10 mg/l). There was a significant difference between overweight/obese compared to lean subjects regarding their CRP levels (overweight/obese mean: 0.47 (SD 0.57) mg/l, lean mean: 0.10 (SD 0.21) mg/l; $t(68) = -3.79$, $p < 0.001$). The local Ethics Committee had approved the protocol and

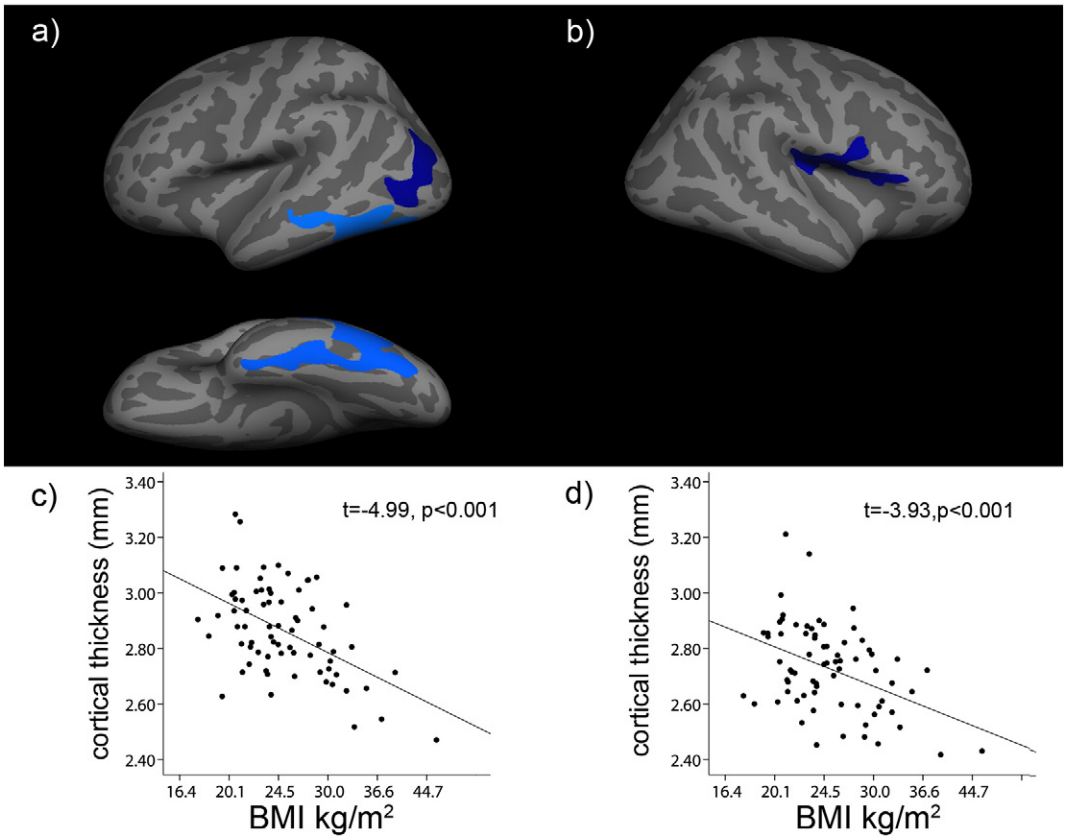

Fig. 1. Lateral and inferior views of the reductions in cortical thickness in relation to BMI adjusted for sex, age, total surface area and education. Significant clusters in the left inferior temporal and left inferior parietal cortex (a) and right precentral gyrus (b). Scatter plots represent the association between BMI and the averaged cortical thickness of each subject in the corresponding clusters representing the left inferior temporal cortex (c) and the right precentral gyrus (d). The t-value and the corresponding *p*-value are depicted.

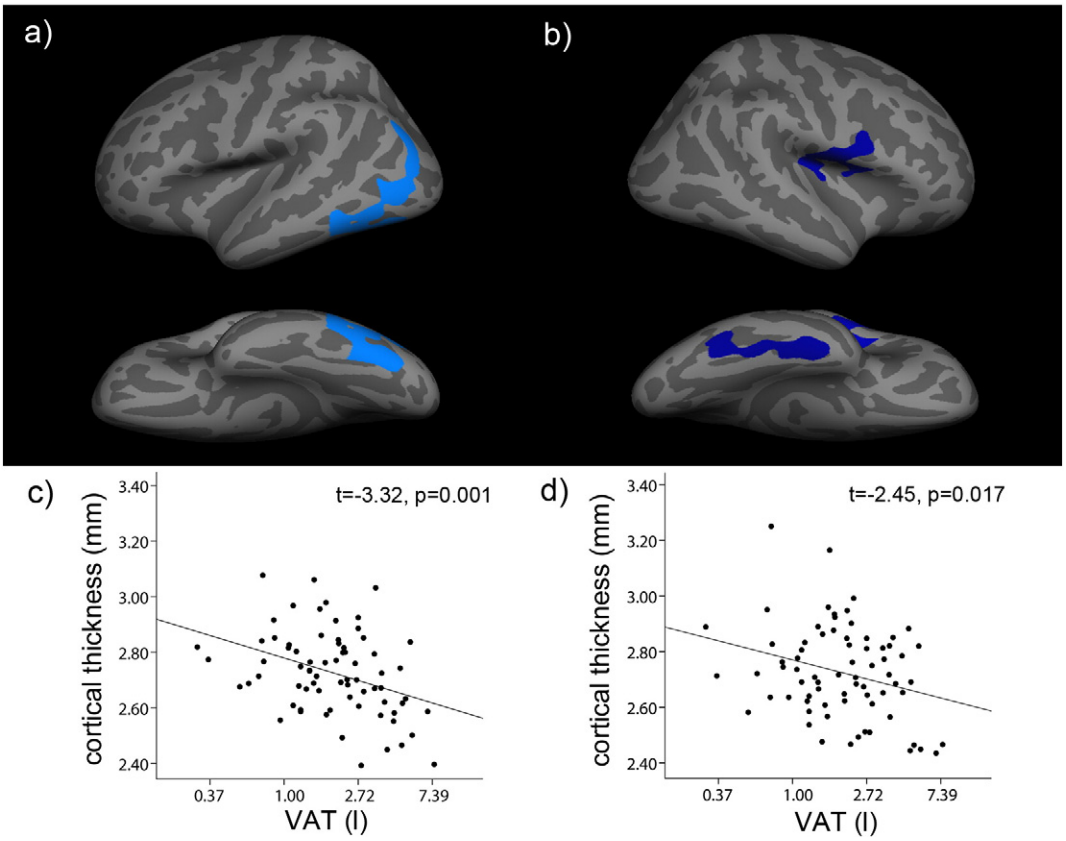

Fig. 2. (a) Lateral and inferior views of the reductions in cortical thickness in relation to visceral adipose tissue adjusted for sex, age, total surface area and education. Significant clusters in the left fusiform gyrus (a) and the right inferior temporal and mid-insular region (b). Scatter plots represent the association between VAT and the averaged cortical thickness of each subject in the cluster representing the left inferior temporal cortex (c) and the right mid-insular gyrus (d). The t-value and the corresponding *p*-value are depicted.

informed written consent was obtained from all subjects. An overview of anthropometric and metabolic characteristics are shown in Table 1.

2.1. Magnetic resonance imaging

Whole brain anatomical scans were recorded using a Magnetization Prepared Rapid Acquisition Gradient Echo sequence with the following parameters – TR: 2300 ms; TE: 2.98 ms; flip angle: 9°; 192 sagittal slices; matrix: 256 × 256 mm^2; bandwidth: 240 Hz/Px, voxel size: 1 × 1 × 11 mm^3 – on a Siemens Tim Trio scanner equipped with a 12-channel head coil.

For the determination of body fat distribution (i.e. VAT) a standardized measurement protocol was used (Machann et al., 2005). An axial T1-weighted fast spin echo sequence with a train length of 7 was applied (TR: 490 ms, TE: 12 ms, slice thickness: 10 mm with 10 mm gap between slices, field of view: 430–530 mm, matrix size: 256 × 178) on a 1.5 Tesla Siemens scanner (Magnetom Sonata, Siemens Healthcare, Erlangen, Germany).

2.2. Data processing

Cortical thickness analysis was performed using FreeSurfer software package (v5.10) (http://surfer.nmr.mgh.harvard.edu). Standard preprocessing of the structural images was performed including intensity normalization, Talairach transformation, skull stripping, white matter segmentation, and tessellation and inflation of the surface (Dale et al., 1999). The pial surface of each hemisphere was computed by using a deformable surface algorithm to extract white matter surface outward toward the gray matter boundary. After automatic correction of topological defects (Fischl et al., 2001), each individual image was visually checked for labeling inaccuracies in white matter and pial surface. In case of defective labels they were manually corrected and reexamined before surface generation. The distance between the white matter surface and pial surface yields an estimate of cortical thickness at each vertex (Fischl and Dale, 2000). For further analysis the data was transformed into a common template with a smoothing kernel of 10 mm which is in line with most cortical thickness studies. Higher smoothing kernels (20 mm and above) as suggested by other groups (Lerch and Evans, 2005) were not used to minimize artificial extension of cortical thinning patterns (Bernal-Rusiel et al., 2010).

Whole body image analysis was performed with customized MATLAB (Mathworks, Natick, MA) scripts. Volumetric assessment of different adipose tissues was based on intensity threshold values separating visceral adipose tissue (VAT) and abdominal subcutaneous tissue. The respective selected pixels were multiplied with the in-plane pixel dimensions and slice thickness and the resulting volumes were calculated in liters (Machann et al., 2005).

2.3. Statistical analysis

To compute differences in cortical thickness vertex-by-vertex analyses were performed separately for each hemisphere. In a first step, we defined two different general linear models (GLMs) using VAT or BMI respectively as predictors (continuous variable). We defined in both models sex (discrete variable), age and educational status as confounding variables. Educational level was coded on a discrete scale with three levels (middle school, high school, academics). To account for possible head size effects, we calculated the total surface area and included it as a covariate. BMI and VAT were tested for normality using the Shapiro–Wilk test. Both variables were non-normally distributed and were logarithmically transformed prior to GLM analysis. Furthermore, we tested whether the slope for males and females were different

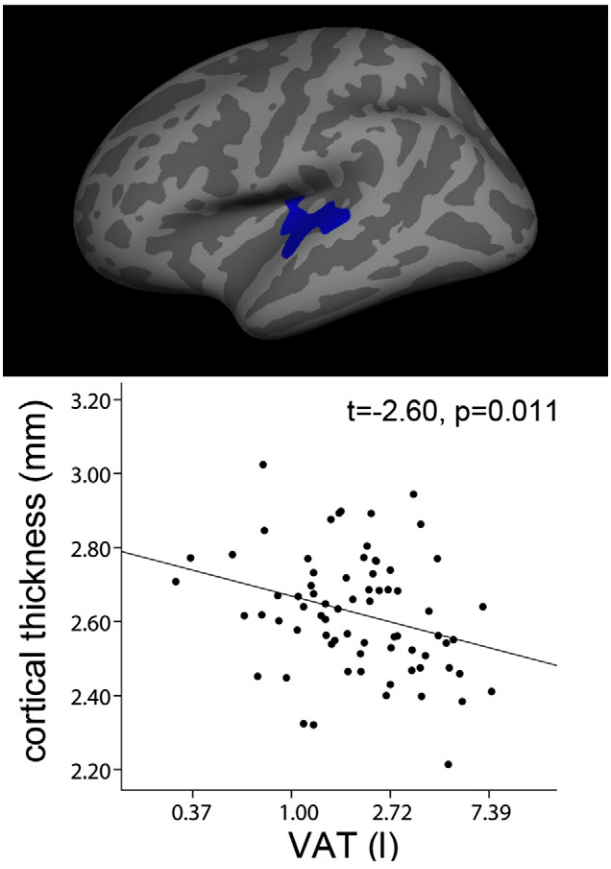

Fig. 3. Lateral view of the reductions in cortical thickness in relation to VAT adjusted for BMI, sex, age, total surface area and education. A significant cluster in the left transverse temporal gyrus extending into the superior temporal gyrus and mid-insula. Scatter plot represents the association between VAT and the averaged cortical thickness in the corresponding area in each subject. The t-value and the corresponding *p*-value are depicted.

regarding the continuous variables. We found no gender specific slopes and used a model with one regressor for each covariate.

To evaluate the specific contribution of each predictor to the changes in cortical thickness we defined a model with VAT and BMI as regressors, while age, sex, total surface area and education were kept as confounds. All continuous variables were mean centered. The results were corrected for multiple comparisons over both hemispheres using a Monte Carlo simulation to assign clusters surviving a cluster-wise significance threshold of $p < 0.05$. In addition to the vertex-wise analysis, we labeled the significant clusters and calculated the average cortical thickness of the vertices within each labeled cluster separately for each subject. Linear regression analyses were performed using the cluster-wise averaged thickness values as dependent variable. Additionally, we computed a partial correlation analysis with BMI, age, sex and educational status as control variables and VAT as dependent variable.

3. Results

The multiple regression analyses revealed that increasing BMI was associated with decreased cortical thickness in a cluster extending from the right precentral gyrus to the postcentral gyrus, the insula and the pars triangularis and pars opercularis. In the left hemisphere, there were two clusters with cortical thinning namely in the inferior temporal and the inferior parietal cortex (the clusters include also the middle temporal, lateral occipital and fusiform areas) (Fig. 1; Table 2). Increasing VAT was significantly related to cortical thinning in a cluster centered around the left fusiform gyrus extending into the inferior parietal, the inferior temporal and the lateral occipital cortex. In the right hemisphere, we found a significant reduction of cortical thickness in a cluster including the insula (extending into the precentral and postcentral gyrus) and a second cluster in the inferior temporal cortex including the fusiform gyrus (Fig. 2; Table 2). The GLM analysis using VAT and BMI as predictors revealed a VAT specific reduction (adjusted for BMI) in cortical thickness in a cluster including the transverse temporal gyrus, the superior temporal gyrus and the mid-insula (Fig. 3; Table 2). Partial correlation analysis using the average cortical thickness in the labeled cluster of the transverse temporal gyrus confirmed the unique contribution of VAT (adjusted for BMI) for the reduced cortical thickness. No significant correlations were found between BMI or VAT and global values of surface area and average cortical thickness.

4. Discussion

The present study aimed to investigate the relationship between visceral adipose tissue and BMI on changes in cortical thickness in a group of lean, overweight and obese young to middle-aged adults. In agreement with recent volumetric studies, reduced gray matter thickness was associated with both increased BMI and increased VAT in lateral occipital areas (e.g. fusiform gyrus) (Karlsson et al., 2013; Pannacciulli et al., 2006; Walther et al., 2010). Recent research has identified the fusiform gyrus as an important structure for discriminating high from low caloric food cues (van der Laan et al., 2011). Of note, overweight/obese subjects showed decreased activation in the fusiform gyrus to food items compared to lean subjects (Kullmann et al., 2013). On the other hand, in the current study, we observed more extended reductions in the right inferior temporal gyrus and the insula in relation to VAT but not BMI. However, there is large overlap of areas with significant reductions in relation to VAT and BMI, which is mainly due to the relative high correlation between both variables. Even independent of BMI, we were able to show that increasing VAT was related to reduced cortical thickness mainly in the temporal cortex and the mid-insular region. Concomitantly, volumetric reductions in gray matter volume of temporal areas have been repeatedly shown in obese adults (Karlsson et al., 2013; Kurth et al., 2013; Weise et al., 2013). Interestingly, in type 2 diabetes patients reduced cortical thickness was also identified in the medial temporal cortex (Brundel et al., 2010).

Considering the fact that the risk of developing obesity related diseases, such as type 2 diabetes and metabolic syndrome, is strongly related to abdominal adiposity, a possible pathomechanism underlying the relationship between cortical thinning and increasing VAT may arise from inflammatory responses. These are seen in connection with adipose tissue in obesity (Karlsson et al., 2013). In a recent study, Neeland et al. (2013) showed that VAT is only related to C-reactive protein (CRP) compared to other inflammatory markers. CRP is an important marker of infection or inflammation and CRP levels are often elevated in obese subjects (Choi et al., 2013), in particular in individuals with metabolic syndrome (Aronson et al., 2004). In the present sample, there was a significant difference between overweight/obese compared to lean subjects in relation to CRP levels. Increased CRP levels are markers of cardiovascular disease risk and current evidence suggests impaired microstructural integrity in relation to elevated CRP levels (Wersching et al., 2010). Taki et al. (2013) investigated the association between CRP and regional gray matter differences in a healthy elderly cohort. The authors found volumetric reductions in a strictly defined area in the left lateral temporal cortex almost exactly located in a region that we found in the present study. Although a causal linkage between CRP levels and gray matter reductions is difficult to establish, there is evidence that atherosclerosis affects cerebral blood flow regulatory processes (Nobili et al., 1993) in a way that ischemic states can occur more often and lead to tissue degeneration. Moreover, increased cardiovascular risk factors are associated with reduced cortical thickness in temporal and parietal areas (Cardenas et al., 2012). The gray matter loss in the

left temporal cortex can be an early indicator of low grade inflammatory processes that lead to tissue degeneration.

5. Conclusions

In this study we found cortical thinning in relation to BMI and VAT in a group of young to middle-aged adults. With increasing visceral adipose tissue, we identified extended cortical thinning in the left temporal cortex independent of BMI. Since VAT is strongly related to cardiac and metabolic risk factors, a possible mechanism may arise from adipose tissue related low grade inflammation processes as a potential harmful factor on brain integrity, although the exact mechanisms including hormonal, metabolic and lifestyle factors underlying structural changes warrant further investigations.

Conflicts of interest

The authors declare no conflicts of interest.

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References

Aronson, D., Bartha, P., Zinder, O., Kerner, A., Markiewicz, W., Avizohar, O., Brook, G.J., Levy, Y., 2004. Obesity is the major determinant of elevated C-reactive protein in subjects with the metabolic syndrome. International Journal of Obesity and Related Metabolic Disorders: Journal of the International Association for the Study of Obesity 28, 674–679. http://dx.doi.org/10.1038/sj.ijo.0802609149939 13.

Ashburner, J., Friston, K.J., 2001. Why voxel-based morphometry should be used. Neuroimage 14, 1238–1243. http://dx.doi.org/10.1006/nimg.2001.096111707080.

Bernal-Rusiel, J.L., Atienza, M., Cantero, J.L., 2010. Determining the optimal level of smoothing in cortical thickness analysis: a hierarchical approach based on sequential statistical thresholding. Neuroimage 52, 158–171.

Brundel, M., van den Heuvel, M., de Bresser, J., Kappelle, L.J., Biessels, G.J., Utrecht Diabetic Encephalopathy Study Group, 2010. Cerebral cortical thickness in patients with type 2 diabetes. Journal of the Neurological Sciences 299, 126–130. http://dx.doi.org/10.1016/j.jns.2010.08.04820869085.

Cardenas, V.A., Reed, B., Chao, L.L., Chui, H., Sanossian, N., DeCarli, C.C., Mack, W., Kramer, J., Hodis, H.N., Yan, M., Buonocore, M.H., Carmichael, O., Jagust, W.J., Weiner, M.W., 2012. Associations among vascular risk factors, carotid atherosclerosis, and cortical volume and thickness in older adults. Stroke 43, 2865–2870. http://dx.doi.org/10.1161/STROKEAHA.112.65972222984010.

Carnell, S., Gibson, C., Benson, L., Ochner, C.N., Geliebter, A., 2012. Neuroimaging and obesity: current knowledge and future directions. Obesity Reviews: an Official Journal of the International Association for the Study of Obesity 13, 43–56. http://dx.doi.org/10.1111/j.1467-789X.2011.00927.x21902800.

Choi, J., Joseph, L., Pilote, L., 2013. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. Obesity Reviews: an Official Journal of the International Association for the Study of Obesity 14, 232–244. http://dx.doi.org/10.1111/obr.1200323171381.

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9, 179–194. http://dx.doi.org/10.1006/nimg.1998.03959931268.

Debette, S., Beiser, A., Hoffmann, U., Decarli, C., O'Donnell, C.J., Massaro, J.M., Au, R., Himali, J.J., Wolf, P.A., Fox, C.S., Seshadri, S., 2010. Visceral fat is associated with lower brain volume in healthy middle-aged adults. Annals of Neurology 68, 136–144. http://dx.doi.org/10.1002/ana.2220820695006.

Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proceedings of the National Academy of Sciences of the United States of America 97, 11050–11055. http://dx.doi.org/10.1073/pnas.20003379710984517.

Fischl, B., Liu, A., Dale, A.M., 2001. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. IEEE Transactions on Medical Imaging 20, 70–80. http://dx.doi.org/10.1109/42.90642611293693.

Hassenstab, J.J., Sweet, L.H., Del Parigi, A., McCaffery, J.M., Haley, A.P., Demos, K.E., Cohen, R.A., Wing, R.R., 2012. Cortical thickness of the cognitive control network in obesity and successful weight loss maintenance: a preliminary MRI study. Psychiatry Research 202, 77–79. http://dx.doi.org/10.1016/j.pscychresns.2011.09.00822595506.

Hutton, C., Draganski, B., Ashburner, J., Weiskopf, N., 2009. A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. Neuroimage 48, 371–380. http://dx.doi.org/10.1016/j.neuroimage.2009.06.04319559801.

Isaac, V., Sim, S., Zheng, H., Zagorodnov, V., Tai, E.S., Chee, M., 2011. Adverse associations between visceral adiposity, brain structure, and cognitive performance in healthy elderly. Frontiers in Aging Neuroscience 3, 12. http://dx.doi.org/10.3389/fnagi.2011.0001221949507.

Jiao, Y., Chen, R., Ke, X., Chu, K., Lu, Z., Herskovits, E.H., 2010. Predictive models of autism spectrum disorder based on brain regional cortical thickness. Neuroimage 50, 589–599. http://dx.doi.org/10.1016/j.neuroimage.2009.12.04720026220.

Karlsson, H.K., Tuulari, J.J., Hirvonen, J., Lepomäki, V., Parkkola, R., Hiltunen, J., Hannukainen, J.C., Soinio, M., Pham, T., Salminen, P., Nuutila, P., Nummenmaa, L., 2013. Obesity is associated with white matter atrophy: a combined diffusion tensor imaging and voxel-based morphometric study. Obesity (Silver Spring) 21 (12), 2530–2537. http://dx.doi.org/10.1002/oby.2038623512884.

Kullmann, S., Pape, A.A., Heni, M., Ketterer, C., Schick, F., Häring, H.U., Fritsche, A., Preissl, H., Veit, R., 2013. Functional network connectivity underlying food processing: disturbed salience and visual processing in overweight and obese adults. Cerebral Cortex (New York, N.Y.: 1991) 23, 1247–1256. http://dx.doi.org/10.1093/cercor/bhs12422586138.

Kurth, F., Levitt, J.G., Phillips, O.R., Luders, E., Woods, R.P., Mazziotta, J.C., Toga, A.W., Narr, K.L., 2013. Relationships between gray matter, body mass index, and waist circumference in healthy adults. Human Brain Mapping 34, 1737–1746. http://dx.doi.org/10.1002/hbm.2202122419507.

Lerch, J.P., Evans, A.C., 2005. Cortical thickness analysis examined through power analysis and a population simulation. Neuroimage 24, 163–173. http://dx.doi.org/10.1016/j.neuroimage.2004.07.04515588607.

Machann, J., Thamer, C., Schnoedt, B., Haap, M., Haring, H.U., Claussen, C.D., Stumvoll, M., Fritsche, A., Schick, F., 2005. Standardized assessment of whole body adipose tissue topography by MRI. Journal of Magnetic Resonance Imaging: JMRI 21, 455–462. http://dx.doi.org/10.1002/jmri.2029215778954.

Maislin, G., Ahmed, M.M., Gooneratne, N., Thorne-Fitzgerald, M., Kim, C., Teff, K., Arnardottir, E.S., Benediktsdottir, B., Einarsdottir, H., Juliusson, S., Pack, A.I., Gislason, T., Schwab, R.J., 2012. Single slice vs. volumetric MR assessment of visceral adipose tissue: reliability and validity among the overweight and obese. Obesity (Silver Spring) 20, 2124–2132. http://dx.doi.org/10.1038/oby.2012.5322395811.

Marqués-Iturria, I., Pueyo, R., Garolera, M., Segura, B., Junqué, C., García-García, I., José Sender-Palacios, M., Vernet-Vernet, M., Narberhaus, A., Ariza, M., Jurado, M.Á, 2013. Frontal cortical thinning and subcortical volume reductions in early adulthood obesity. Psychiatry Research 214, 109–115. http://dx.doi.org/10.1016/j.pscychresns.2013.06.00424041490.

Neeland, I.J., Ayers, C.R., Rohatgi, A.K., Turer, A.T., Berry, J.D., Das, S.R., Vega, G.L., Khera, A., McGuire, D.K., Grundy, S.M., de Lemos, J.A., 2013. Associations of visceral and abdominal subcutaneous adipose tissue with markers of cardiac and metabolic risk in obese adults. Obesity (Silver Spring, Md.) 21, E439–E447. http://dx.doi.org/10.1002/oby.2013523687099.

Nobili, F., Rodriguez, G., Marenco, S., De Carli, F., Gambaro, M., Castello, C., Pontremoli, R., Rosadini, G., 1993. Regional cerebral blood flow in chronic hypertension. A correlative study. Stroke; a Journal of Cerebral Circulation 24, 1148–1153. http://dx.doi.org/10.1161/01.STR.24.8.11488342188.

Pannacciulli, N., Del Parigi, A., Chen, K., Le, D.S., Reiman, E.M., Tataranni, P.A., 2006. Brain abnormalities in human obesity: a voxel-based morphometric study. Neuroimage 31, 1419–1425. http://dx.doi.org/10.1016/j.neuroimage.2006.01.04716545583.

Pereira, J.B., Ibarretxe-Bilbao, N., Marti, M.J., Compta, Y., Junqué, C., Bargallo, N., Tolosa, E., 2012. Assessment of cortical degeneration in patients with Parkinson's disease by voxel-based morphometry, cortical folding, and cortical thickness. Human Brain Mapping 33, 2521–2534. http://dx.doi.org/10.1002/hbm.2137821898679.

Raschpichler, M., Straatman, K., Schroeter, M.L., Arelin, K., Schlögl, H., Fritzsch, D., Mende, M., Pampel, A., Böttcher, Y., Stumvoll, M., Villringer, A., Mueller, K., 2013. Abdominal fat distribution and its relationship to brain changes: the differential effects of age on cerebellar structure and function: a cross-sectional, exploratory study. BMJ Open 3. http://dx.doi.org/10.1136/bmjopen-2012-00191523355665.

Stefan, N., Kantartzis, K., Machann, J., Schick, F., Thamer, C., Rittig, K., Balletshofer, B., Machicao, F., Fritsche, A., Häring, H.U., 2008. Identification and characterization of metabolically benign obesity in humans. Archives of Internal Medicine 168, 1609–1616. http://dx.doi.org/10.1001/archinte.168.15.160918695074.

Taki, Y., Thyreau, B., Kinomura, S., Sato, K., Goto, R., Wu, K., Kakizaki, M., Tsuji, I., Kawashima, R., Fukuda, H., 2013. Correlation between high-sensitivity C-reactive protein and brain gray matter volume in healthy elderly subjects. Human Brain Mapping 34, 2418–2424. http://dx.doi.org/10.1002/hbm.2207322438310.

van der Laan, L.N., de Ridder, D.T., Viergever, M.A., Smeets, P.A., 2011. The first taste is always with the eyes: a meta-analysis on the neural correlates of processing visual food cues. Neuroimage 55, 296–303. http://dx.doi.org/10.1016/j.neuroimage.2010.11.05521111829.

Walther, K., Birdsill, A.C., Glisky, E.L., Ryan, L., 2010. Structural brain differences and cognitive functioning related to body mass index in older females. Human Brain Mapping 31, 1052–1064. http://dx.doi.org/10.1002/hbm.2091619998366.

Weise, C.M., Thiyyagura, P., Reiman, E.M., Chen, K., Krakoff, J., 2013. Fat-free body mass but not fat mass is associated with reduced gray matter volume of cortical brain regions implicated in autonomic and homeostatic regulation. Neuroimage 64, 712–721. http://dx.doi.org/10.1016/j.neuroimage.2012.09.00522974975.

Wersching, H., Duning, T., Lohmann, H., Mohammadi, S., Stehling, C., Fobker, M., Conty, M., Minnerup, J., Ringelstein, E.B., Berger, K., Deppe, M., Knecht, S., 2010. Serum C-reactive protein is linked to cerebral microstructural integrity and cognitive function. Neurology 74, 1022–1029. http://dx.doi.org/10.1212/WNL.0b013e3181d7b45b20350977.