The influence of body fat distribution on white matter integrity

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Abbreviations

λ_1:	eigenvalue of the major axis
λ_2/ λ_3:	eigenvalues of the minor axes
AD:	axial diffusivity
BMI:	body mass index
CRP:	C-reactive protein
DTI:	diffusion tensor imaging
FA:	fractional anisotropy
GM:	gray matter
MCI:	mild cognitive impairment
MD:	mean diffusivity
MRI:	magnetic resonance imaging
RD:	radial diffusivity
ROI:	region of interest
SCAT:	subcutaneous adipose tissue
TAT:	total adipose tissue
VAT:	visceral adipose tissue
VO_2:	maximal oxygen consumption
WHO:	World Health Organization
WM:	white matter

1. Introduction

1.1. Obesity

Obesity is a health problem that already concerns over 600 million adults worldwide. According to the World Health Organization (WHO), the prevalence of obesity has nearly doubled since 1980, and “most of the world’s population live in countries where overweight and obesity kills more people than underweight” (WHO, 2015). It is one of the most visible, but at the same time most neglected public-health problems not only of high-income countries but also low- and middle-income countries (WHO, 2015).

The definition of overweight and obesity is abnormal fat accumulation that presents a risk of health (WHO, 2015). It is determined by the body mass index (BMI) as a useful index of weight-for-height: $\text{BMI } [kg/m^2] = \frac{\text{weight } [kg]}{(\text{height } [m])^2}$

The WHO defines normalweight as BMI 18.5 - 24.9 kg/m², overweight as a BMI ≥ 25 kg/m² and obesity as BMI ≥ 30 kg/m² (WHO, 2015).

The main cause of obesity is over-consumption of energy together with decreased physical activity (for review, see (Haslam & James, 2005)). Beyond this putative simple explanation however, a complex disease with genetic, endocrinological and environmental aetiologies is a major risk factor for various chronic diseases (for review, see (Conway & Rene, 2004)). The main consequences are cardiovascular diseases, type 2 diabetes, musculoskeletal disorders and numerous cancers such as endometrial, breast and colon carcinomas (WHO, 2015). More precisely, inflammation, dyslipidemia, changes in blood pressure and insulin resistance are found to be the consequences of excessive peripheral accumulation of fat (for reviews see (Bastard et al., 2006; A. R. Johnson, Milner, & Makowski, 2012)). Furthermore, obesity is associated with reduced cognitive functioning such as an increased risk for dementia and reduced cognitive performance with changes in brain structure and function (Gunstad et al., 2007; D. Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003).

1.2. Body fat distribution

Even though BMI is a useful and common measure to get an idea of overweight and obesity within a population, it may not give exact information about the degree of adiposity of a person (for review, see (Machann, Horstmann, Born, Hesse, & Hirsch, 2013)). Adipose tissue is not a homogenous organ, but has to be subdivided, according to their location, into subcutaneous adipose tissue (SCAT), visceral adipose tissue (VAT) and ectopic depots such as in the skeletal muscle and in the liver (Stefan et al., 2008) with different functionality. Increased accumulation of visceral fat follows from the disability of fat to store excess energy in an appropriate way (Stefan et al., 2008). VAT is found to be hypoxic, poorly capilarized and hypertrophic adipocytes are present which lead to inflammation and fibrosis, SCAT in contrast is characterized by plenty of small adipocytes buffering excess of fatty acids and with better insulin sensitivity (Krotkiewski & Billing-Marczak, 2014). Because visceral fat in obese subjects is highly inflamed and is secreting free fatty acids and pro-inflammatory cytokines such as interleukin-1 and interleukin-6, adiponectin, leptin and tumor necrosis factor α , there is evidence that visceral adipose tissue is directly involved in the development of atherosclerosis and its complications (for reviews, see (Alexopoulos, Katritsis, & Raggi, 2014; Kaur, 2014)). In a large European cohort study, abdominal adiposity has been shown to associate with the risk of death, independently of general adipositiy (Pischon et al., 2008). Furthermore, abdominal adiposity is important for the clinical diagnosis of metabolic syndrome, which is defined by a combination of interconnected biochemical, physiological, metabolic and clinical factors that directly augments the risk of type 2 diabetes mellitus, cardiovascular disease and cause mortality (Wilson, D'Agostino, Parise, Sullivan, & Meigs, 2005), (for review, see (Grundy et al., 2005))

Thus, the measurement and differentiation of adipose tissue is of great relevance. Abdominal adiposity can be estimated by anthropometric measures such as waist circumference, waist-hip-ratio and waist-height-ratio. These measures are fast and simple to assess, but they are not capable to

differentiate or to quantify the different adipose tissue compartments such as visceral and subcutaneous adipose tissue (Schwenzer et al., 2010). Therefore, imaging techniques are needed for volumetric assessments. To quantify adipose tissue, dual energy X-ray absorptiometry, computed tomography and magnetic resonance imaging are available. Dual energy X-ray absorptiometry can differentiate between lean and fatty tissue, but not between VAT and SCAT. Yet computed tomography is capable to quantify adipose tissue distribution. However, it is not advised for scientific use because of high ionizing radiation (for review, see (Machann et al., 2013)).

Magnetic resonance imaging (MRI) offers not only a quantification and differentiation of whole-body adipose tissue without exposure to ionizing radiation, but can also assess lipids in pancreas, liver, skeletal muscle and heart (for review, see (Machann et al., 2013)). One of the MR techniques is based on relaxation times of lean and fatty tissues. Adipose tissue has a shorter relaxation time than lean tissue, hence it appears brighter in T1-weighted sequences and the different tissue compartments of the whole-body measurement can be calculated (figure 1) (for review, see (Machann et al., 2005)).

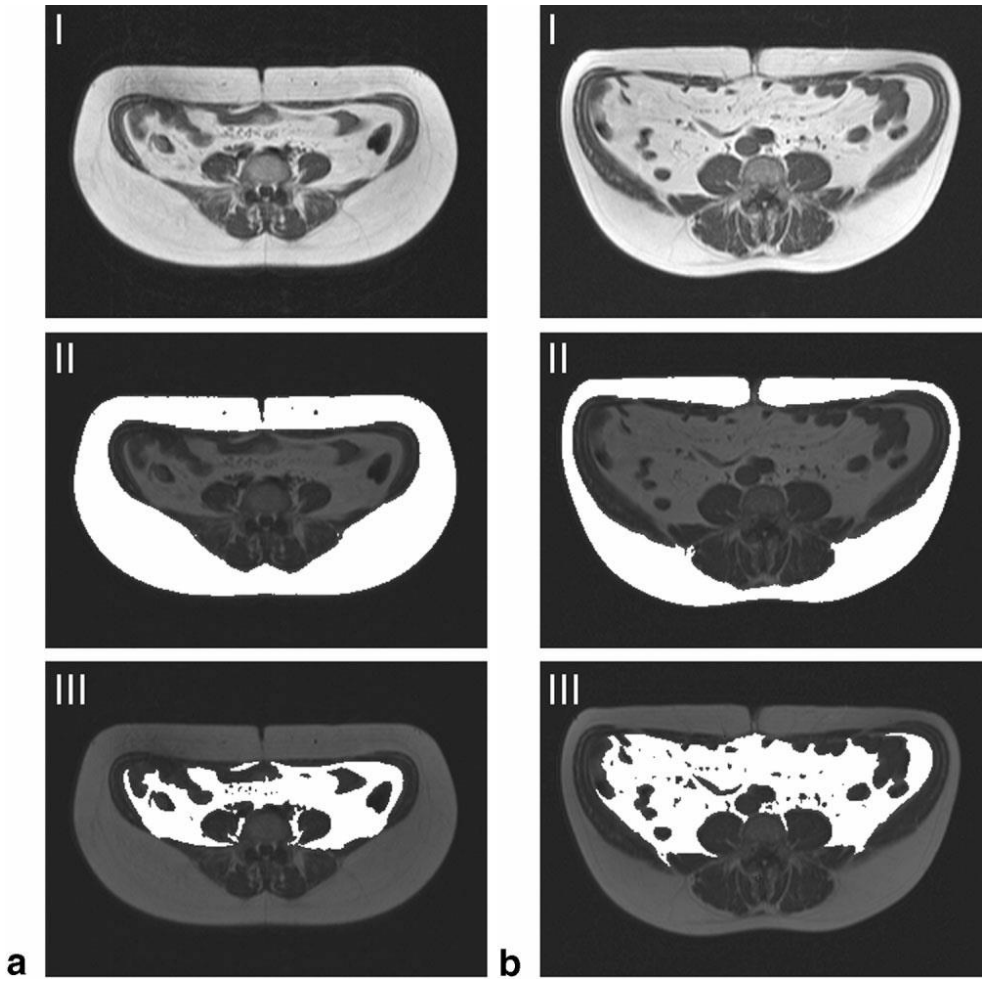

Figure 1 Principle of segmentation of visceral and subcutaneous fat in a female (a) and a male volunteer (b). I = original images, II = subcutaneous adipose tissue (SCAT), III = visceral adipose tissue (VAT). Differences in adipose tissue distribution become obvious, as the female volunteer is characterized by higher SCAT and lower VAT compared to the male volunteer (Machann et al., 2005).

1.3. Structural changes of the brain in obesity

Considering the structural obesity-related changes, the focus in the past years has been mainly on changes in gray (GM) and white matter (WM) volume and density measured by magnetic resonance imaging. Tensor-based morphometry and voxel-based morphometry are methods to localize and differentiate structural changes in GM and WM volume and density. Increased BMI was shown to be associated with lower GM volume mainly in frontal, occipital and temporal lobes as well as in the orbitofrontal and cingulate cortex and in thalamus, hippocampus and midbrain (Bobb, Schwartz, Davatzikos, & Caffo, 2014; Driscoll et al., 2012; D. R. Gustafson, Steen, & Skoog, 2004; He et al., 2015; Raji et al., 2010; Taki et al., 2008; Walther, Birdsill, Glisky, & Ryan, 2010; Ward, Carlsson, Trivedi, Sager, & Johnson, 2005; Yokum, Ng, & Stice, 2012). This association can already be observed in obese children and adolescents in frontal and limbic gray matter regions (Alosco et al., 2014). Prospective studies have shown that low GM volume in frontal brain areas, which are significant for inhibitory control, predicted future weight gain (Yokum et al., 2012) and also that GM volume of the insular cortex is affected in obesity prone persons (Smucny et al., 2012).
To investigate obesity-related brain alterations more specifically, recent studies measured waist to hip ratio, waist circumference, subcutaneous and visceral abdominal tissue, body fat percentage, fat free body mass and leptin, a hormone that correlates with adipose tissue. These markers correlate inversely with total brain volume, in which VAT showed the strongest association independent of insulin resistance and BMI (Debette et al., 2010). In addition, SCAT volume and high body fat percentage were found to be negatively associated with GM density (Karlsson et al., 2013).

However, changes in white matter volume paint a more complex picture. BMI was found to have a positive relationship with white matter volume in frontal, parietal and temporal lobes, in adolescents (Schwartz et al., 2014) as well as in older adults (Walther et al., 2010), and a negative association in the basal ganglia and corona radiata (Raji et al., 2010; Yokum et al., 2012).

1.4. White matter integrity in obesity

White matter is a collection of axons which occupies nearly 50% of the adult brain facilitating the transfer of information between gray matter structures, and therefore playing an essential role in cognition and emotion (Filley, 1998). White matter microstructure contains myelin, which is produced by oligodendrocytes, one type of glial cells (Benarroch, 2009). Myelin forms a concentric sheath around the axon leaving unwrapped small segments, the so called nodes of Ranvier which allow salutatory conduction (for review, see (Filley, 2005)). Thus, myelin is the key for increased conduction velocity (for review, see (Filley, 2010)). However, white matter fibers should not only be considered “mere conduits for the appropriate gray matter centers” (Ulmer, 2005), but are also likely to be involved in higher cortical function (for review, see (Filley, 2005)).

Changes in white matter volume reflect macrostructural alterations. To investigate the microstructural architecture of the white matter and to understand the previous findings, diffusion tensor imaging (DTI) has become of special interest. Below the methodological background of DTI and the previous findings of changes in white matter integrity associated with obesity will be described.

1.4.1. Methodology of diffusion tensor imaging

In the early 1990s, diffusion magnetic resonance imaging of the brain was introduced for clinical use, primarily to evaluate suspected acute ischemic stroke (Mukherjee, Berman, Chung, Hess, & Henry, 2008). Clinical diffusion MRI measures water self-diffusion. Diffusion is the constant movement of water molecules due to thermal energy (Le Bihan et al., 1986).

Diffusion tensor imaging maps and quantifies the directionality and rate of the three-dimensional diffusion of water within tissue in a noninvasive way (Basser, Mattiello, & LeBihan, 1994). At the level of the basic unit of the MRI, the voxel, diffusion mathematically represents an ellipsoid, or a tensor. Diffusion is

isotropic when the rates of diffusion (eigenvalues, λ) are nearly equal in all three directions of the ellipsoid such as in gray matter and cerebrospinal fluid where the movement of the water is randomly and equal in every direction, whereas it is considered anisotropic, or directional, when the eigenvalues significantly differ in magnitude (Alexander, Lee, Lazar, & Field, 2007). In areas with great physical barriers such as neurofilaments, axonal cell membranes and axon sheath, the movement of the water is forced to follow a particular direction and the rate of diffusion is greater along the fiber than across it. In regions of parallel orientated, compact fiber bundles like in the corpus callosum, anisotropy is highest. Therefore, more than one direction of the diffusion is required to describe and quantify anisotropic diffusion (Mukherjee et al., 2008).

1.4.1.1. Diffusion tensor imaging parameters

Established DTI parameters to investigate white matter integrity are fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) (figure 2).

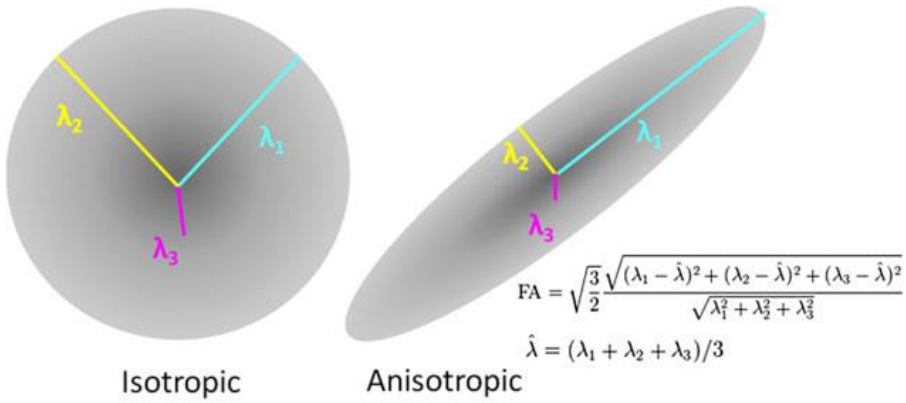

Figure 2 Graphical illustration of diffusion tensor imaging (DTI) parameters. λ1 = axial diffusivity (AD); (λ2 + λ3)/2 = radial diffusivity (RD); (λ1 + λ2 + λ3)/2 = mean diffusivity (MD) (Kullmann, Schweizer, Veit, Fritsche, & Preissl, 2015).

These parameters can all be calculated with the three eigenvalues and are markers for the microstructural composition of the white matter (Alexander et al., 2007).

Fractional anisotropy and mean diffusivity are summary parameters. FA is most commonly used in DTI studies and quantifies anisotropic diffusion. It reflects the fraction of the tensor that can be attributed to anisotropic diffusion and is independent of the rate of diffusion (Basser, 1995; Madden et al., 2012).

$$\mathrm{FA} = \sqrt{\frac{3}{2}}\frac{\sqrt{(\lambda_1\text{-MD})^2+(\lambda_2\text{-MD})^2+(\lambda_3\text{-MD})^2}}{\sqrt{\lambda_1^2+\lambda_2^2+\lambda_3^2}}$$ (Verstynen et al., 2012)

The range of the FA values is between 0 and 1 on a normalized scale. Zero indicates isotropic, spherical diffusion and 1 reflects infinitely anisotropic diffusion due to great physical barriers such as myelin and axons (Madden et al., 2012). FA gives information about white matter integrity (Karlsson et al., 2013), hence reduced FA may reflect damaged white matter due to demyelination or axonal loss, and higher FA values indicate increased white matter integrity. However it is important to recognize that FA is highly sensitive to microstructural change, i.e. crossing fiber tracts. FA may be lowered because less coherent local fiber architecture and not necessarily because of reduced white matter integrity (Pierpaoli et al., 2001; Pierpaoli & Basser, 1996; Virta, Barnett, & Pierpaoli, 1999). This variability can be reduced by focusing on specific white matter regions with fewer crossing tracts.

MD is the average of the three eigenvalues. It reflects the overall magnitude of diffusion and is independent of direction (Karlsson et al., 2013; Madden et al., 2012), increasing when diffusion is less bounded by fibers.

$$\mathrm{MD} = \frac{(\lambda_1+\lambda_2+\lambda_3)}{3}$$

It is equal to the apparent diffusion coefficient, a more traditional parameter of the energy of water diffusion (Chanraud, Zahr, Sullivan, & Pfefferbaum, 2010; Verstynen et al., 2012).

Although FA and MD are indices for general organization of the fibers, they may not be able to distinguish between myelin sheet and axon damage, therefore axial and radial diffusivity are useful to specify the changes in white matter

integrity (Song et al., 2003). AD and RD are parameters reflecting the rate of diffusion. AD is the eigenvalue of the major axis (λ_1) of the ellipsoid and therefore it reflects the rate of diffusion along the fiber orientation and indicates axonal integrity, whereas RD indicates myelin integrity and is the mean of the eigenvalues of the two minor axes (λ_2 and λ_3) which are orthogonal to the major axis (Basser, 1995; Mukherjee et al., 2008; Song et al., 2003; Song et al., 2002).

$$AD = \lambda_1$$

$$RD = \frac{(\lambda_2 + \lambda_3)}{2}$$

AD may be increased because of a great coherence of the fiber tracts or less crossing tracts and decreased due to axonal degeneration (Budde, Xie, Cross, & Song, 2009; Song et al., 2003) caused by different mechanisms such as diffuse axonal injury, Wallerian degeneration and axonal swelling which lead to hindered longitudinal water movement (for review, see (Aung, Mar, & Benzinger, 2013)). Increased RD was found to be the result of myelin degradation or demyelination causing increased water movement orthogonal to the major axis of the axon (Song et al., 2002), while decreased RD reflects remyelination after myelin damage or increased myelination.

All in all, in well-characterized, homogenous parallel regions of white matter, which are not confounded by crossing fibers, DTI seems to be a sensitive estimate of neuropathology. (Alexander et al., 2007).

Nevertheless, DTI parameters change during brain development. Fractional anisotropy increases while MD and RD decrease in white matter tracts from birth to adulthood. Additionally, FA values in the adult brain were found to have maximum values in the corpus callosum and minimum values in subcortical regions, showing a heterogeneous distribution, while MD values become distributed homogenously throughout the brain (Mukherjee et al., 2002; Oishi, Faria, Yoshida, Chang, & Mori, 2013; Snook, Paulson, Roy, Phillips, & Beaulieu, 2005).

1.4.1.2. Quantitative tractography

Tractography is a method to analyze fiber-tracts in white matter tissue. The basis of tractography is the directional relationship of tract orientation and the direction of greatest diffusivity (Alexander et al., 2007). Fiber tract trajectories can be estimated by pursuing coherent local patterns in the direction of the major eigenvectors (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000). This so called tracking starts from a seed voxel spreading a line in accordance to the major axis of the diffusion and its direction is reassessed voxel by voxel all over the brain. Regions of interest (ROI) can be defined from anatomical landmarks to identify the tract (Mori et al., 2002). New methods of tractography aim to be able to resolve the problem of crossing fibers (for review, see (Alexander et al., 2007)).

1.4.2. Diffusion tensor imaging-studies in obesity research

DTI has become of special interest in the past years but still there are only few studies that have examined the effect of obesity on the integrity of the white matter. Previous studies determined obesity mainly using BMI, but also associated factors such as dyslipidemia, hypertension and inflammation. With the aid of voxel-wise or region-of-interest analysis, these studies have shown a relationship between obesity and loss of integrity of the white matter, particularly in fiber bundles within the limbic system and in tracts that connect the frontal and temporal lobe (figure 3, for review, see (Kullmann et al., 2015)). Lower values of FA and MD, and higher values of RD respectively, were found all over the brain in obese compared to normal-weight (Stanek et al., 2011; Verstynen et al., 2012). More specific findings are described below.

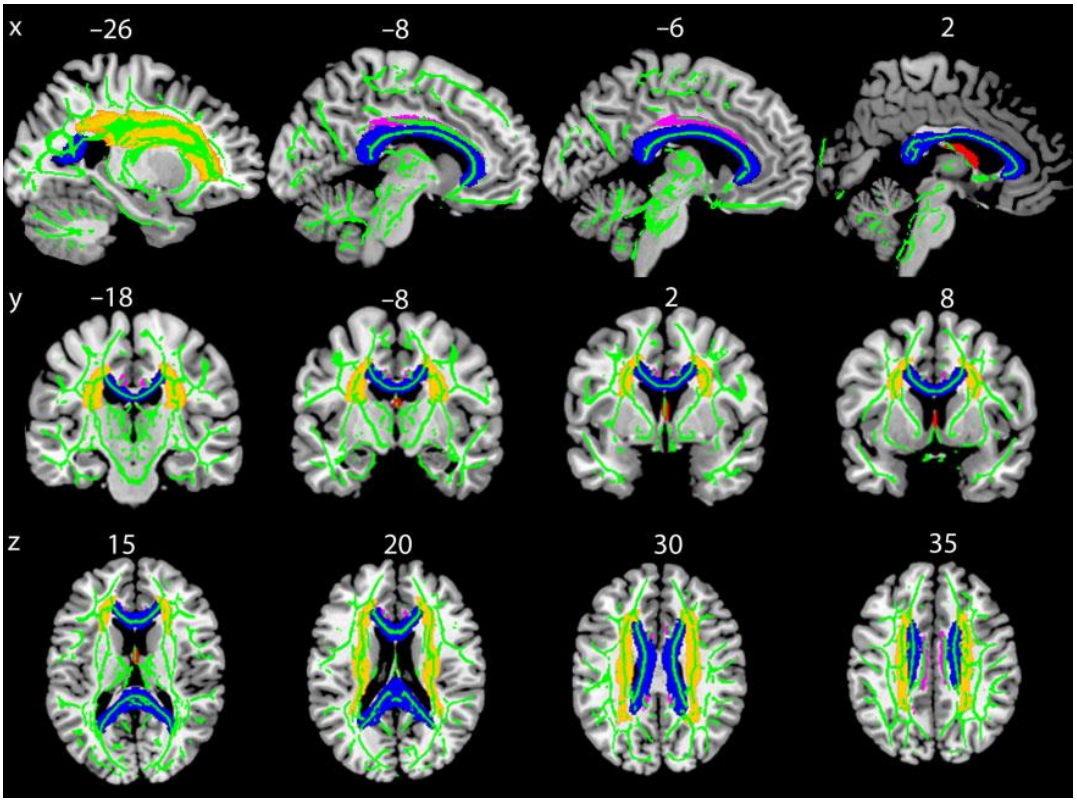

Figure 3 Major white matter tracts affected by obesity overlaid on a green fractional anisotropy skeleton (top row: sagital, middle row: coronal and bottom row: axial view of a standard brain) (blue: corpus callosum; magenta: cingulum; orange: corona radiate; red: fornix) (Kullmann et al., 2015).

1.4.2.1. Body mass index and white matter integrity

Corpus callosum

With more than 300 million axons, the corpus callosum is the largest fiber tract in the human brain consisting of four parts, the splenium, body, genu and rostrum (Huang et al., 2005). It interconnects the two hemispheres and is important for passing cognitive, sensory and motor information between the corresponding regions of the two hemispheres (Huang et al., 2005). Forceps major and minor are part of the callosal radiation connecting the corresponding hemispheres. Forceps major projects from the splenium into the occipital lobes, forceps minor projects from the genu of the corpus callosum into the frontal lobes (Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004).

Previous studies found a negative correlation between BMI and FA in the corpus callosum (Bettcher et al., 2013; Karlsson et al., 2013; Mueller et al., 2011; Stanek et al., 2011; Verstynen et al., 2013; Xu, Li, Lin, Sinha, & Potenza, 2013) with the strongest correlation in the genu of the corpus callosum remaining significant after controlling for inflammatory and vascular markers (Bettcher et al., 2013). With increased BMI, AD was also reduced in the entire corpus callosum (Mueller et al., 2011), especially in the body (Xu et al., 2013) and in the genu (Ryan & Walther, 2014) whereas MD and RD were increased in the splenium (Xu et al., 2013) and genu of the corpus callosum (Mueller et al., 2011; Verstynen et al., 2013). Altogether, these findings point to axonal damage as well as demyelination in the corpus callosum in obese.

Additional to these findings, physiological aging leads to the decline of white matter integrity which has been shown by age-related reduced fractional anisotropy and increased radial diffusivity (Inano, Takao, Hayashi, Abe, & Ohtomo, 2011; Salat et al., 2005). Within the relationship between BMI and white matter integrity in the corpus callosum, Stanek et al. found an interaction between age and BMI in the splenium and body of the corpus callosum (Stanek et al., 2011).

The sex also seems to interact within the relationship between BMI and white matter integrity. Within a sample of 857 healthy subjects, men showed significantly higher FA compared to women in a number of regions inclusive in the splenium of the corpus callosum (Inano et al., 2011). Mueller et al. (2011) found decreased FA with increased BMI in the entire corpus callosum and increased RD in the genu of the corpus callosum only in women whereas the apparent diffusion coefficient was decreased in the splenium of the corpus callosum in men (Mueller et al., 2011).

In addition, Mueller et al. (Mueller et al., 2014) showed a correlation between AD and RD in the corpus callosum and obesity-associated changes of gray matter density in areas of habit learning and executive control in the female brain. AD in the inferior and posterior regions of the body of the corpus callosum correlated negatively the gray matter density in the dorsal striatum whereas AD in the genu of the corpus callosum correlated positively with gray matter density in the dorsolateral prefrontal cortex. RD in the entire corpus callosum correlated negatively with densities in these regions (Mueller et al., 2014).

Limbic system: fornix and cingulum

Fornix and cingulum are the preeminent, C-shaped structures in the limbic system (Mori, Wakana, van Zijl, & Nagae-Poetscher, 2005).

The fornix provides information from the hippocampus to other brain regions, such as the hypothalamus, and is therefore involved in homeostatic functions and hedonic control of food intake (Haber & Knutson, 2010; Kim, Woods, & Seeley, 2012; Mori et al., 2008; Schoenbaum & Esber, 2010; Wakana et al., 2004). White matter integrity of the fornix was reduced with increased BMI indicated by decreased FA (Bettcher et al., 2013; Stanek et al., 2011) and increased MD, RD and AD (Metzler-Baddeley, Baddeley, Jones, Aggleton, & O'Sullivan, 2013; Xu et al., 2013), though after controlling for inflammatory and vascular markers, the relation with FA did not remain significant (Bettcher et al., 2013) indicating demyelination in the fornix.

The cingulum owns his name to its belt-like shape (Jones, Christiansen, Chapman, & Aggleton, 2013) carrying afferent connections from the cingulate gyrus to the entorhinal cortex (Mori et al., 2008; Mori et al., 2005), travelling along the ventral face of the hippocampus and dorsal to the corpus callosum (Wakana et al., 2004). At the level of the splenium of the corpus callosum, it can be separated in the cingulate part and the hippocampal part (Mori et al., 2008). The cingulum bundle contains short and long association fibers that potentially link the frontal lobe with the temporal lobe. Found as a complex tract with many different connections including many short fibers it is likely that different parts of the cingulum reflect different underlying functions. Effects on normal aging, depression, schizophrenia, Mild Cognitive Impairment (MCI), Alzheimer's disease and traumatic brain injury have been described (for review, see (Jones et al., 2013)).

With higher BMI and greater abdominal girth, FA values in the bilateral cingulum were found to be reduced, both in young and in elderly adults (Bettcher et al., 2013; He et al., 2015; Marks, Katz, Styner, & Smith, 2011), remaining significant after controlling for inflammatory and vascular markers (Bettcher et al., 2013). In a study with 336 young college students, using quantitative tractography, the total number of tracks passing the midcingulate cortex seed region was decreased with increased BMI (He et al., 2015). In addition, He et al. assessed the Iowa gambling task, which tested subjects in decision making under ambiguity and correlated it with the number of tracks which pass the midcingulate cortex. The task scores in the first 40 trials mediated the association between BMI and the number of tracks. The results remained the same when the sample was reduced to only normal-weight subjects (He et al., 2015). In a study with older adults, BMI and abdominal girth correlated negatively with FA in the posterior cingulum segment.

Temporal and frontal lobes

The superior longitudinal fasciculus is a major, intrahemispheric fiber tract in a C-shape (Makris et al., 2005; Wakana et al., 2004) connecting temporal, occipital, parietal and frontal lobes including Broca's, Wernicke's and Geschwind's territories (Mori et al., 2008). Interestingly a positive correlation was found between BMI and AD values in the superior longitudinal fasciculus, which may indicate a positive effect on axon integrity (Xu et al., 2013). After an exercise intervention with overweight children, FA values in the superior longitudinal fasciculus were increased while RD values were decreased (Krafft et al., 2014).

The uncinate fasciculus, which connects the anterior temporal lobe and the frontal lobe (Mori et al., 2008), showed higher FA and lower RD values after an exercise intervention (Schaeffer et al., 2014). Adipose tissue, measured by BMI, also affected white matter integrity of the uncinate fasciculus. Examining a group of older adults, Bolzenius et al. found reduced FA values with increased BMI (Bolzenius et al., 2014). MD was also found to be less in obese (Karlsson et al., 2013). Concomitantly, a reduction of FA and MD with increased BMI, was also described for the inferior fronto-occipital fasciculus (Karlsson et al., 2013), association fibers connecting the frontal and occipital lobes (Mori et al., 2008). The influence of aerobic fitness will be discussed in more detail later in the text.

In general, white matter integrity in the temporal lobe is reduced with increased BMI, shown by decreased FA and AD, increased RD and reduced fiber bundle length using quantitative tractography (Bolzenius et al., 2013; Ryan & Walther, 2014; Yau, Kang, Javier, & Convit, 2014).

Cerebellar regions

Obesity does not only alter WM integrity of fiber bundles connecting the limbic system and the hemispheres. Cerebellar regions also show correlations with increased BMI. Negative correlations between BMI and FA and AD values were

found, as well as a positive correlation between BMI and RD, especially in the inferior and superior cerebellar peduncles (Ryan & Walther, 2014; Verstynen et al., 2013). Apart from the motor function, white matter in the cerebellum is described to be involved into verbal working memory (Chen & Desmond, 2005). Reduced white matter integrity in cerebellar regions may therefore affect motor and nonmotor functions of the cerebellum.

Projection fibers

Projection fibers connect the cortex with the brainstem, the spinal cord or the thalamus and consist of afferent and efferent fibers (Mori et al., 2005). The corticospinal tract, a long corticofugal tract, projects from the pre and postcentral gyrus into the spinal cord passing the internal capsule (Mori et al., 2008; Wakana et al., 2004). Adiposity reduces the integrity of the white matter in the corticospinal tract, showed by reduced FA with increased BMI (Karlsson et al., 2013; Ryan & Walther, 2014). The same was found in the internal capsule (Shott et al., 2015). Corona radiata is also a projection fiber bundle and includes parts of the corticofugal pathways and the thalamic radiations (Mori et al., 2008). In studies with young and middle-aged adults, BMI correlated negatively with FA values and positively with AD and RD of the corona radiata (Shott et al., 2015; Verstynen et al., 2013; Xu et al., 2013) indicating axonal and myelin damage. Interestingly, a negative correlation between FA and the obesity-associated gene neural growth regulator 1 (NEGR1) was found most significantly in the corona radiata. However this association did not show a correlation with BMI, which indicates a gene-related effect on white matter integrity without influence of BMI (Dennis et al., 2014). Concerning genetic influence on white matter, in a study with 761 Mexican Americans, obesity and reduced white matter integrity were found to share the same genetic risk factors (Spieker et al., 2015). Another finding in the corona radiata is a positive correlation between FA values and dyslipidemia (Verstynen et al., 2013). The influence of dyslipidemia will be discussed below.

1.4.2.2. Mediators of obesity-associated effects on white matter integrity

Aerobic fitness

Aerobic fitness can be assessed by VO_2max, which is the maximal capacity of the cardiorespiratory system to take up and use oxgygen. Cognitive functions and academic performance were found to be positively affected by aerobic fitness (for review, see (Hillman, Erickson, & Kramer, 2008)). Concerning white matter integrity, aerobic fitness has been shown to have a positive correlation with FA in the left middle cingulum (Marks et al., 2011). Studies with exercise intervention have shown the beneficial influence of aerobic fitness on WM integrity in the temporal and frontal lobes, both in older adults and in overweight children (Schaeffer et al., 2014; Voss et al., 2013) and in the superior longitudinal fasciculi in children (Krafft et al., 2014). These findings indicate that the cingulum and uncinate fasciculus and other structures in the temporal and frontal lobes are susceptible to both aerobic fitness and high body weight.

Dyslipidemia, blood pressure, systemic inflammation, metabolic syndrome

The effect of vascular physiological factors on white matter integrity is very complex. Dyslipidemia is characterized by an abnormal quantity of lipids in the blood measured by increased circulating triglycerides, reduced high-density lipoprotein and increased small, dense low density lipoprotein (Carr & Brunzell, 2004). In a sample of 155 middle-aged adults, dyslipidemia, measured by circulating triglycerides and high-density lipoproteins, was shown to have a positive association with FA values in the corona radiate (Verstynen et al., 2013). Blood pressure was also found to have a local positive effect on the brain, correlating strongly positively with FA values in bilateral internal and external capsule (Verstynen et al., 2013). These findings lead to the assumption that dyslipidemia and blood pressure are localized positive vascular-linked factors while systemic inflammation and glucose regulation seem to be negative immunity-linked factors showing global distributed effects on white matter integrity. In the same study, glucose regulation and systemic inflammation

correlated strongly negatively with FA values throughout the white matter (Verstynen et al., 2013). Dyslipidemia and blood pressure seem to be competing pathways with glucose regulation and systemic inflammation (Verstynen et al., 2013). However, there are also contrary results, showing a negative, and not positive, correlation between abnormal cholesterol and FA values in the prefontal lobes (J. I. Cohen, Cazettes, & Convit, 2011). Nonetheless, after examining the groups individually, the negative correlation only remained significant in the group of overweight and obese subjects (J. I. Cohen et al., 2011). Additionally, the results of blood pressure having a positive effect on white matter integrity have also been contradicted by a large study with 4095 healthy middle-aged adults. High systemic blood pressure correlated with decreased FA, and subsequently increased MD values, in the inferior fronto-occipital fasciculi, the anterior corpus callosum and in fibers projecting from thalamus to the superior frontal gyrus (Maillard et al., 2012).

Systemic inflammation can be measured by C-reactive protein and Interleukin-6. Increased inflammation markers lead to a widespread reduction of FA values (Gianaros, Marsland, Sheu, Erickson, & Verstynen, 2013; Verstynen et al., 2013). It also seems to mediate in the association between BMI and white matter integrity in fornix and body and splenium of the corpus callosum, which didn't remain significant after controlling for vascular and inflammatory markers (Bettcher et al., 2013).

Abdominal obesity, increased blood pressure, dyslipidemia and elevated plasma glucose are risk factors for the metabolic syndrome (Grundy et al., 2005), which can lead to a pro-inflammatory state and further to type 2 diabetes mellitus, cardiovascular disease and mortality (Kaur, 2014). Metabolic syndrome risk factors were found to independently affect white matter integrity, shown by reduced FA values (Sala et al., 2014), especially in frontal lobes (Segura et al., 2009; Shimoji et al., 2013), the corpus callosum and the inferior fronto-occipital fasciculus (Shimoji et al., 2013) in patients with metabolic syndrome. Yet in adolescents with nondiabetic metabolic syndrome compared with the control group, FA was shown to be decreased in the medial longitudinal

fasciculi, the corpus callosum and optic radiations (Yau, Castro, Tagani, Tsui, & Convit, 2012). Hippocampal volumes also were found to be reduced in obese adolescents with metabolic syndrome (Yau et al., 2012). Cognitive impairment, mainly in the frontal lobe, was found in adults (Segura et al., 2010), as well as in adolescents with metabolic syndrome, shown also in lower scores in mental flexibility and attention (Yau et al., 2012).

Body fat distribution

Obesity itself is a risk factor for artherosclerosis, insulin resistance and type 2 diabetes mellitus, but visceral adipose tissue increases the risk for metabolic and cardiovascular complications (Stefan et al., 2008). Increased VAT has been shown to correlate with reduced total brain volume (Debette et al., 2010), especially gray matter volume in cerebellar regions (Raschpichler et al., 2013), and increased subcutaneous fat was associated with reduced gray matter density (Karlsson et al., 2013). In the adolescent brain, VAT is found to correlate with higher signal intensity in the white matter (Schwartz et al., 2014). Inflammation, due to of visceral fat accumulation, may be a link to reduced white matter integrity. However, the effect of visceral fat on white matter integrity has not been investigated until now.

1.5. Aim of study

Thus far, obesity-associated white matter integrity alterations are poorly understood. In most studies, the relationship between BMI and FA was used to describe the effect of obesity on white matter integrity. The effect of different fat compartments has not yet been investigated. Moreover, there are only few studies that examined the effect of obesity on white matter integrity in young to middle-aged samples.

The aim of the study was to investigate the influence of body fat distribution, more specifically visceral, subcutaneous and total adipose tissue, on white matter integrity in young to middle-aged adults. For this purpose, we performed diffusion tensor magnetic resonance imaging of the brain and whole body MRI to differentiate the body fat compartments. We then analyzed the relationship between BMI, body fat compartments and the four DTI parameters: FA, MD, AD and RD using a ROI-based approach. We hypothesized an obesity-associated reduction in whiter matter integrity with regional specific changes.

2. Material and methods

2.1. Subjects

For this study, we recruited 48 healthy lean, overweight and obese adult participants (23 women and 25 men; age range 21 to 37 years; BMI range 19.2 – 46.5 kg/m²), all students at the University of Tuebingen, by using broadcast emails. Subjects with a BMI greater than 25 kg/m² were defined as overweight and obese. The study protocol was approved by the local Ethics Committee and prior to examination all subjects provided informed written consent.

The characteristics of the participants are summarized in table 1 and in detail in table 2.

Table 1 Characteristics of the participants by weight group

	All n = 48	**Lean subjects** n = 25	**Overweight/ obese subjects** n = 23	**One-way ANOVA**	
				F-value (df = 1)	p
Sex (female/male)	n = 23/25	n = 11/14	n = 12/11		
	mean ± SD	**mean ± SD**	**mean ± SD**		
Age (years)	26.92 ± 3.71 range: 21 - 37	26.08 ± 3.54 range: 21 - 34	27.83 ± 3.75 range: 23 - 37	2.758	0.104
BMI (kg/m²)	26.63 ± 5.63 range: 19.20 - 46.50	22.53 ± 1.98 range: 19.20 - 27.60	31.10 ± 4.85 range: 25.90 - 46.50	66.076	<0.001
Total intracranial volume (liter)	1.45 ± 0.15	1.45 ± 0.13	1.45 ± 0.16	0.006	0.940
Total volume (liter)	79.08 ± 20.78	65.11 ± 10.02	94.26 ± 18.73	46.227	<0.001
Total adipose tissue (liter)	29.45 ± 15.75	17.63 ± 4.20	42.30 ± 13.40	117.728	<0.001
Visceral adipose tissue (liter)	2.45 ± 1.67	1.48 ± 0.83	3.51 ± 1.71	29.557	<0.001
Subcutaneous adipose tissue (liter)	9.95 ± 7.07	4.82 ± 1.67	15.52 ± 6.43	64.652	<0.001

Data are presented as mean ± standard deviation (SD). P = P-values for comparison of unadjusted $\log_e$-transformed data by ANOVA

Table 2 Detailed characteristics of each participant (P01-P48)

	Sex 1 female 2 male	Age (years)	Body mass index (kg/m²)	Total intracranial volume (liter)	Total volume (liter)	Total adipose tissue (liter)	Visceral adipose tissue (liter)	Subcutaneous adipose tissue (liter)
P01	2	34	24.52	1.64	75.20	17.33	2.34	4.53
P02	1	27	23.46	1.31	62.19	23.94	1.13	9.78
P03	1	33	20.33	1.18	49.00	17.47	1.25	4.65
P04	2	33	24.05	1.42	73.00	24.08	3.88	6.33
P05	2	24	27.59	1.42	68.93	10.09	1.62	2.71
P06	2	27	24.52	1.58	68.00	18.74	2.09	4.70
P07	2	28	23.10	1.46	74.59	16.85	1.13	4.59
P08	1	23	21.12	1.32	55.10	18.69	0.62	5.12
P09	2	29	21.79	1.65	82.32	12.14	1.86	2.54
P10	1	25	22.00	1.42	70.42	19.70	1.06	4.93
P11	1	22	19.20	1.38	50.57	16.00	0.31	3.67
P12	1	29	21.18	1.31	54.00	17.16	0.74	4.97
P13	1	26	21.41	1.55	55.00	17.66	0.36	4.74
P14	2	21	20.60	1.43	60.00	11.47	1.50	2.44
P15	1	26	21.20	1.40	57.00	19.49	0.95	4.75
P16	2	27	25.70	1.47	75.00	14.21	1.35	3.73
P17	2	24	22.42	1.42	76.00	15.53	2.66	4.16
P18	2	24	23.77	1.42	69.00	13.56	1.42	3.21
P19	2	25	23.33	1.44	73.00	17.52	2.15	4.23
P20	2	23	19.53	1.64	70.00	19.27	1.77	5.56
P21	2	24	22.79	1.58	64.00	19.58	2.24	5.64
P22	1	29	20.77	1.24	50.00	16.51	0.71	5.26
P23	2	23	23.62	1.71	75.00	20.48	2.21	5.98
P24	1	23	24.12	1.30	70.61	29.46	1.03	8.62
P25	1	23	21.16	1.48	49.80	13.71	0.59	3.65
P26	2	24	26.64	1.43	73.20	26.08	2.72	8.94
P27	2	26	46.49	1.52	156.00	75.80	7.58	34.97
P28	1	30	28.63	1.54	74.54	32.28	1.18	9.79
P29	1	37	33.35	1.40	94.00	48.03	2.83	17.59
P30	1	26	32.30	1.36	88.52	47.94	2.19	15.51
P31	2	33	29.03	1.90	98.23	27.20	5.15	9.08
P32	1	25	25.90	1.28	65.90	31.04	0.88	9.99
P33	1	27	37.23	1.24	112.08	64.33	4.02	26.47
P34	1	31	35.02	1.29	107.10	55.72	4.94	20.29
P35	2	26	27.90	1.53	88.22	33.28	3.38	10.34
P36	1	28	31.02	1.26	86.96	42.59	2.74	17.99
P37	1	23	32.30	1.26	90.00	49.29	2.61	18.53
P38	1	25	28.90	1.37	84.85	37.58	2.43	14.44
P39	2	31	33.00	1.47	107.17	44.44	3.70	17.60

P40	1	27	28.12	1.35	84.12	36.72	1.55	12.18
P41	1	23	27.68	1.47	95.00	53.46	2.08	20.34
P42	2	35	30.52	1.71	92.00	38.63	5.63	13.13
P43	2	28	29.46	1.56	84.00	35.83	3.39	13.34
P44	2	23	26.18	1.41	91.00	30.78	3.68	11.00
P45	2	27	29.76	1.51	100.00	43.39	4.38	14.51
P46	2	29	26.09	1.70	86.00	22.74	2.36	7.52
P47	2	26	30.25	1.34	84.00	33.18	4.42	11.47
P48	2	30	39.33	1.42	125.00	62.48	6.94	21.96

2.2. Study design

Before starting the experiment, all volunteers were medically examined to be sure they did not have neurological, metabolic nor psychiatric diseases. Exclusion criteria for the study were treated chronic diseases or any medication except for oral contraceptives.

2.3. Data acquisition

Whole body MRI measurements

MRI examinations were performed on a 1.5T whole body imager (Magnetom Sonata; Siemens Healthcare, Erlangen, Germany). A set of 90–120 parallel transverse slices was recorded according to a whole body imaging protocol described by Machann et al. (Machann et al., 2005). Applying T1-weighted contrast, fatty tissue and other types of tissue were semi-automatically quantified in each cross-section. This assessment quantified body volume, total adipose tissue (TAT) and total mass of specific adipose tissues such as subcutaneous adipose tissue and visceral adipose tissue. All slices between the heads of femora and the diaphragm were applied to calculate VAT.

Diffusion tensor imaging measurements

DTI measurements were performed at a 3T scanner (Tim Trio; Siemens) with a standard 12-channel head coil. Diffusion weighted images and a high-resolution T1-weighted anatomical image were measured using the following settings: MPRAGE; magnetization-prepared rapid gradient echo: matrix size = 256 x 256, 192 slices, voxel size 1 x 1 x 1 mm, TR = 2300 ms, TE = 2.98 ms, TI = 900 ms; DTI-EPI; single-shot echo planar imaging sequence: 35 nonlinear directions, 2 averages, 70 slices, diffusion weighting of b = 1000 s/mm^2, slice thickness of 2 mm, field of view = 196 mm, TR 9700 ms, TE 95 ms, acquisition matrix = 128 x 128, voxel size 1.5 x 1.5 x 2 mm. The total scanning time of the DTI measurement and the T1-weighted anatomical image was about 22 minutes for each participant.

2.4. Diffusion tensor imaging data analysis

With the aid of a MATLAB toolbox called “pipeline for analyzing brain diffusion images” (PANDA) (Cui, Zhong, Xu, He, & Gong, 2013), we analyzed the DTI data sets within the software library framework called FSL (FMRIB software library) which was written by the Functional Magnetic Resonance of the Brain (FMRIB) Analysis Group at Oxford University and contains analysis tools for brain imaging data of structural, functional and diffusion MRI (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012).

With an affine transformation, the diffusion-weighted images were registered to the b0 images to correct the raw data of each participant for eddy currents and head motions. The b0 images is an image of the anatomy that takes into account tissue signals and contrasts without diffusion weighting, hence these images are not contaminated by additional eddy current deformations of the directional scans. The b0 images were used to estimate a brain mask. Within this brain mask, diffusion tensor metrics, which contained fractional anisotropy, mean diffusivity, axial diffusivity and radial diffusivity, were calculated in a voxel-wise way (using *dtifit* of *FSL*). Then, by applying the FSL non-linear registration

tool (*FNIRT)* command, the FA images of the native space of each participant were registered to the FA template in MNI (Montreal Neurological Institute) space to normalize them.

The MNI brain templates were established at the Montreal Neurological Institute (MNI) and are based on a number of normal MRI volumetric data sets (Evans et al., 1993). As representing an average brain, the MNI templates are used as targets during spatial normalization (Laird et al., 2010).

For resampling the diffusion metrics images (MD, FA, AD, RD) into MNI space with a 2 x 2 x 2 mm spatial resolution, resulting warping transformations were used. For reduction of noise and misalignment between participants, the images, which were now in normalized format, were smoothed using a Gaussian kernel of 6 mm. Average DTI parameters of all major tracts, based on the Johns Hopkins University (JHU) white matter tractography atlas (Mori et al., 2008; Mori et al., 2005; Wakana et al., 2004), were extracted for further ROI-based analyses. Regions of interest are functionally or anatomically predefined brain regions (Poldrack, 2007). For each ROI, the mean of each DTI parameter was calculated for further statistical analyses. In contrast, voxel-wise whole brain analysis collects voxel by voxel data and with the aid of standard atlases inter-individual statistical comparisons can be performed. This method owns a lot more detailed information about specific brain alterations but is also prone to false-negative results (for review, see (Astrakas & Argyropoulou, 2010)).

2.5. Statistics

2.5.1. Metabolic parameters

Metabolic and anthropometric parameters were analyzed with a one-way ANOVA comparing the two weight groups for every parameter ($p<0.05$; IBM SPSS statistics version 22).

2.5.2. Diffusion tensor imaging parameters

Region-of-interest analyses were performed for all DTI parameters (FA, MD, AD and RD) of the major tracts including the anterior thalamic radiation, corticospinal tract, cingulum (cingulate gyrus and hippocampus), forceps major and minor, superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, the uncinate fasciculus and the temporal part of the superior longitudinal fasciculus.

Using partial correlation, we investigated the effect of BMI on all DTI parameters adjusted for age, total intracranial volume, and sex. Furthermore, we investigated the effect of different fat compartments (visceral, subcutaneous and total adipose tissue) on all DTI parameters by means of partial correlation adjusting for BMI, age, sex, and total intracranial volume. We used a statistical threshold of $p < 0.005$ corrected for number of tested regions (IBM SPSS statistics version 22).

Partial correlation is a method used to analyze the relationship between two variables whilst taking away the effects of another variable, or several other variables. The basic idea is to examine the correlations among residuals, which are errors of prediction. After regressing variable $\mathbf{x}=(x_i)$, i=1,N on variable $\mathbf{z}=(z_i)$, i=1,N and then subtracting the linear regression from **x**, we have a residual $\mathbf{x^*}=(x_i^*)$, i=1,N. This residual will be uncorrelated with **z**, so any correlation **x** shares with another variable $\mathbf{y}=(y_i)$, i=1,N cannot be due to **z**. Furthermore, variable **y** is regressed on variable **z** and then subtracted from **y**, leading to the residual $\mathbf{y^*}= (\mathbf{y}_i\mathbf{^*})$, i=1,N**.** The partial correlation is then achieved by correlating

the residuals $\mathbf{x_i^*}$ on $\mathbf{y_i^*}$ (Bortz & Schuster, 2011; J. Cohen, Cohen, West, & Aiken, 2013).

Equation for calculation residual $\mathbf{x_i^*}$:

$x_i^* = x_i - (\hat{a}_0 + \hat{a}_1 z) \qquad i=1,\ldots\ldots,N$

The equation for calculating the residual for $\mathbf{y_i^*}$

$y_i^* = y_i - (\hat{o}_0 + \hat{o}_1 z) \qquad i=1,\ldots\ldots,N$

For our analyses, we used the partial correlation syntax in IBM SPSS 22 to evaluate the relationship between visceral adipose tissue or BMI (variable **x**) and the DTI data (variable **y**) whilst partialling out the effect of multiple confounding variables (variables **z**). This analysis provided adjusted correlation coefficients and corresponding p-values as noted in the results section.

In order to plot the partial correlations, residuals were acquired using multiple regression implemented in SPSS. All partial correlation figures (figure 4 to figure 7) illustrated in this dissertation display residuals. For example, we were interested in the correlation between DTI data and visceral adipose tissue controlling for the effect of BMI, age, TIV and sex.

<u>Example:</u>

y= MD values of the left cingulum hippocampal part

x= visceral adipose tissue (log transformed)

$\mathbf{z_1}$= BMI (kg/m^2)

$\mathbf{z_2}$= Age

$\mathbf{z_3}$= TIV (Liter)

$\mathbf{z_4}$= sex (coded with 1 or 2)

The equation for calculating the residual for x_i^*

$x_i^* = x_i - (\hat{a}_0 + \hat{a}_1 z_{1i} + \hat{a}_2 z_{2i} + \hat{a}_3 z_{3i} + \hat{a}_4 z_{4i})$

Where $\mathbf{x_i}$ is the original VAT value and $\hat{\mathbf{a}}$ are the regression coefficients. Using multiple regression, VAT ($\mathbf{x_i}$) was added as the dependent variable and $\mathbf{z_1}$, $\mathbf{z_2}$, $\mathbf{z_3}$ and $\mathbf{z_4}$ as the independent variables. The unstandardized residual $\mathbf{x_i^*}$

(centered on zero) are then plotted on the x-axis of our partial correlation figures.

Regression coefficients of our example:

$\hat{a}_0$= -3.150

$\hat{a}_1$= 0.085

$\hat{a}_2$= 0.030

$\hat{a}_3$= -0.285

$\hat{a}_4$= 0.740

Using *participant P01* as an example.

y_{MD}= 0.00074

$x_{VAT\text{-}log}$=0.850151

z_{BMI}= 24.515596

z_{age}= 34

z_{TIV}= 1.635346

z_{sex}= 2

The residual $\mathbf{x_i^*}$ will be:

$x_i^* = x_i - (\hat{a}_0 + \hat{a}_1 z_{1i} + \hat{a}_2 z_{2i} + \hat{a}_3 z_{3i} + \hat{a}_4 z_{4i})$

= 0.85-(-3.150 + 0.085*24.51 + 0.030*34 - 0.285*1.635 + 0.740*2)

= -0.115

The equation for calculating the residual for $\mathbf{y_i^*}$

$y_i^* = y_i - (\hat{o}_0 + \hat{o}_1 z_{1i} + \hat{o}_2 z_{2i} + \hat{o}_3 z_{3i} + \hat{o}_4 z_{4i})$

Where $\mathbf{y_i}$ are the original MD values and $\hat{\mathbf{o}}$ are the regression coefficients. Using multiple regression, the MD values ($\mathbf{y_i}$) were added as the dependent variable and $\mathbf{z_1}$, $\mathbf{z_2}$, $\mathbf{z_3}$ and $\mathbf{z_4}$ as the independent variables. The unstandardized residual $\mathbf{y_i^*}$ are plotted on the y-axis of the partial correlation figures.

For this example:

$\hat{o}_0$= 0.001

$\hat{o}_1$= -1.197E-6

$\hat{o}_2$= -5.524E-7

$\hat{o}_3$= -7.119E-5

$\hat{o}_4$= -1.434E-5

Using *participant P01* as an example.

The residual $\mathbf{y_i^*}$ will be:

$y_i^* = y_i - (\hat{o}_0 + \hat{o}_1 z_1 + \hat{o}_2 z_2 + \hat{o}_3 z_3 + \hat{o}_4 z_4)$

= 0.00074 – (0.001+ (-1.197E-6*24.515596) + (-5.524E-7*34) + (-7.119E-5*1.635) + (-1.434E-5*2))

= -6.98E -5

3. Results

3.1. Statistic results

3.1.1. Metabolic parameters

The two weight groups showed no significant difference in age and total intracranial volume ($p = 0.104$ and $p = 0.940$, respectively, see table 1). Overweight and obese subjects had a significant higher BMI, total adipose tissue, visceral adipose tissue and subcutaneous adipose tissue than the lean ($p < 0.001$, see table 1).

3.1.2. DTI parameters

In table 3 and 4, the data of the region-of-interest analysis of the DTI parameters of the major tracts are presented as mean and standard deviation.

Table 3 Region-of-interest analysis of FA and MD of the major tracts presented as mean and standard deviation (SD)
(FA = fractional anisotropy; MD = mean diffusivity; SD = standard deviation; L = left; R = right)

	FA		**MD**	
	mean	**SD**	**mean**	**SD**
Anterior thalamic radiation L	4.06E-01	1.75E-02	7.47E-04	3.94E-05
Anterior thalamic radiation R	3.80E-01	1.54E-02	7.71E-04	3.45E-05
Corticospinal tract L	5.64E-01	1.64E-02	7.20E-04	2.27E-05
Corticospinal tract R	5.56E-01	1.62E-02	7.41E-04	2.07E-05
Cingulum (cingular part) L	5.31E-01	3.11E-02	6.98E-04	2.54E-05
Cingulum (cingular part) R	4.59E-01	3.79E-02	6.94E-04	2.58E-05
Cingulum (hippocampal part) L	3.84E-01	2.82E-02	7.36E-04	3.71E-05
Cingulum (hippocampal part) R	3.76E-01	2.62E-02	7.64E-04	3.57E-05
Forceps major	5.65E-01	1.90E-02	8.31E-04	5.64E-05
Forceps minor	4.51E-01	1.64E-02	8.06E-04	2.43E-05
Inferior fronto-occipital fasciculus L	4.51E-01	1.65E-02	7.37E-04	2.38E-05
Inferior fronto-occipital fasciculus R	4.43E-01	1.62E-02	7.57E-04	2.14E-05
Inferior longitudinal fasciculus L	4.39E-01	2.11E-02	7.39E-04	2.04E-05
Inferior longitudinal fasciculus R	4.51E-01	1.98E-02	7.52E-04	2.44E-05
Superior longitudinal fasciculus L	3.93E-01	1.74E-02	7.42E-04	2.36E-05
Superior longitudinal fasciculus R	3.93E-01	2.04E-02	7.58E-04	2.58E-05
Uncinate fasciculus L	4.08E-01	2.49E-02	7.84E-04	2.78E-05

Uncinate fasciculus R	3.90E-01	2.14E-02	8.09E-04	2.50E-05
Superior longitudinal fasciculus (temporal part) L	4.67E-01	3.59E-02	7.34E-04	2.90E-05
Superior longitudinal fasciculus (temporal part) R	5.23E-01	3.51E-02	7.32E-04	3.32E-05

Table 4 Region-of-interest analysis of AD and RD of the major tracts presented as mean and standard deviation (SD)

(AD = axial diffusivity; RD = radial diffusivity; SD = standard deviation; L = left; R = right)

	AD		**RD**	
	mean	**SD**	**mean**	**SD**
Anterior thalamic radiation L	1.08E-03	3.98E-05	5.80E-04	4.19E-05
Anterior thalamic radiation R	1.09E-03	3.74E-05	6.12E-04	3.54E-05
Corticospinal tract L	1.23E-03	3.87E-05	4.65E-04	2.20E-05
Corticospinal tract R	1.26E-03	3.61E-05	4.82E-04	2.02E-05
Cingulum (cingular part) L	1.16E-03	4.50E-05	4.66E-04	2.96E-05
Cingulum (cingular part) R	1.08E-03	4.14E-05	5.02E-04	3.49E-05
Cingulum (hippocampal part) L	1.06E-03	5.57E-05	5.76E-04	3.48E-05
Cingulum (hippocampal part) R	1.09E-03	5.43E-05	6.03E-04	3.36E-05
Forceps major	1.43E-03	7.58E-05	5.31E-04	5.19E-05
Forceps minor	1.23E-03	3.15E-05	5.95E-04	2.50E-05
Inferior fronto-occipital fasciculus L	1.13E-03	3.13E-05	5.40E-04	2.35E-05
Inferior fronto-occipital fasciculus R	1.16E-03	2.87E-05	5.57E-04	2.18E-05
Inferior longitudinal fasciculus L	1.12E-03	3.14E-05	5.50E-04	2.28E-05
Inferior longitudinal fasciculus R	1.15E-03	3.45E-05	5.54E-04	2.53E-05
Superior longitudinal fasciculus L	1.05E-03	2.50E-05	5.86E-04	2.64E-05
Superior longitudinal fasciculus R	1.08E-03	2.51E-05	5.97E-04	2.98E-05
Uncinate fasciculus L	1.15E-03	3.04E-05	6.01E-04	3.32E-05
Uncinate fasciculus R	1.17E-03	3.67E-05	6.27E-04	2.70E-05
Superior longitudinal fasciculus (temporal part) L	1.14E-03	4.94E-05	5.30E-04	3.50E-05
Superior longitudinal fasciculus (temporal part) R	1.20E-03	5.30E-05	4.98E-04	3.85E-05

3.2. Effects of body mass index

The region-of-interest analyses, after controlling for age, sex and total intracranial volume, revealed significant negative correlations between BMI and AD values in the left corticospinal tract (see figure 4), the hippocampal part of the right cingulum and the forceps minor with the strongest correlation in the left corticospinal tract ($p < 0.005$, corrected for number of tested regions).

Marginal significances in correlations with increased BMI were found with reduced AD in the right corticospinal tract, the hippocampal part of the left cingulum, the left inferior fronto-occipital fasciculus and the right inferior longitudinal fasciculus ($p < 0.05$) and with reduced MD in both left and right corticospinal tracts and the hippocampal part of the right cingulum ($p < 0.05$).

We found no significant correlation for FA, MD, AD and RD in the left and right anterior thalamic radiation, the cingular parts of the left and right cingulum, the forceps major, the right inferior fronto-occipital fasciculus, the left inferior longitudinal fasciculus, the left and right superior longitudinal fasciculus, the left and right uncinate fasciculus and the temporal part of the left and right superior longitudinal fasciculus. We also found no significant correlation for FA, MD and RD in the hippocampal part of the left cingulum, the forceps minor, the left inferior fronto-occipital fasciculus and the right inferior longitudinal fasciculus. And we found no significant correlation for FA and RD in the corticospinal tract and the hippocampal part of the right cingulum.

For detailed results of the ROI analysis with BMI see table 5.

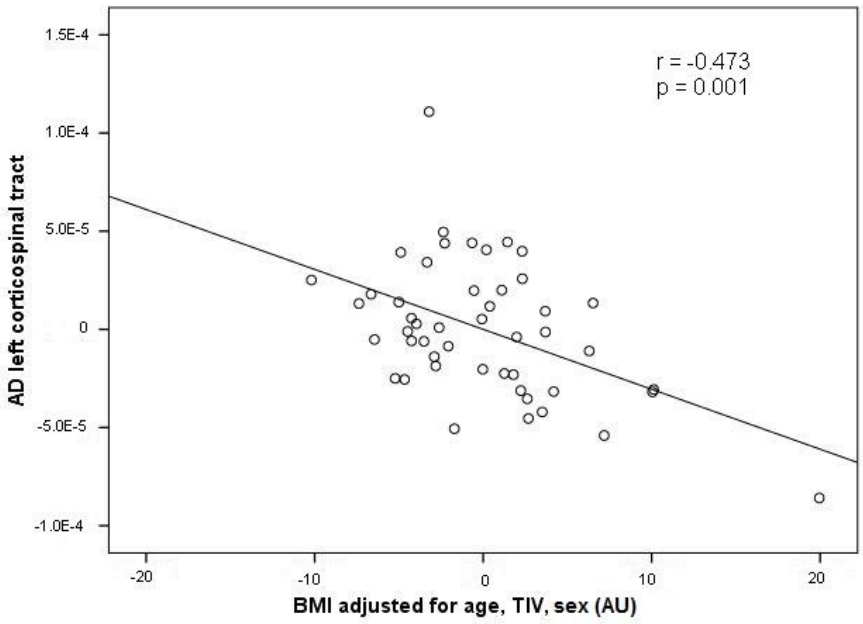

Figure 4 Partial correlation between BMI and AD of the left corticospinal tract adjusted for age, TIV and sex. Axes are mean centered. (AD=axial diffusivity; AU=arbitrary unit; BMI=body mass index; TIV=total intracranial volume).

Table 5 Region-of-interest analysis with partial correlations between BMI and DTI parameters

(FA = fractional anisotropy; MD = mean diffusivity; AD = axial diffusivity; RD = radial diffusivity; r r_{adj} = adjusted correlation coefficient; L = left; R = right)

	FA		**MD**		**AD**		**RD**	
	r_{adj} value	p-value	r_{adj} value	p-value	r_{adj} value	p-value	r_{adj} value	p-value
Anterior thalamic radiation L	0.078	0.610	-0.221	0.144	-0.353	0.095	-0.192	0.206
Anterior thalamic radiation R	0.114	0.457	-0.246	0.103	-0.256	0.090	-0.231	0.127
Corticospinal tract L	-0.106	0.489	-0.381	**0.010***	-0.473	**0.001****	-0.165	0.277
Corticospinal tract R	-0.076	0.619	-0.296	**0.049***	-0.364	**0.014***	-0.137	0.370
Cingulum (cingular part) L	-0.076	0.618	0.112	0.464	0.015	0.922	0.129	0.397
Cingulum (cingular part) R	-0.056	0.717	0.087	0.571	0.031	0.840	0.075	0.624
Cingulum (hippocampal part) L	-0.247	0.102	-0.190	0.212	-0.319	**0.033***	-0.042	0.786
Cingulum (hippocampal part) R	-0.164	0.283	-0.380	**0.010***	-0.432	**0.003****	-0.267	0.076
Forceps major	-0.137	0.370	-0.124	0.416	-0.157	0.303	-0.088	0.565
Forceps minor	-0.124	0.416	-0.269	0.074	-0.428	**0.003****	-0.129	0.400
Inferior fronto-occipital fasciculus L	-0.073	0.632	-0.180	0.237	-0.306	**0.041***	-0.080	0.602
Inferior fronto-occipital fasciculus R	0.026	0.864	-0.156	0.308	-0.214	0.159	-0.093	0.544
Inferior longitudinal fasciculus L	-0.098	0.521	-0.129	0.399	-0.234	0.122	-0.019	0.901
Inferior longitudinal fasciculus R	-0.063	0.681	-0.281	0.062	-0.370	**0.012***	-0.160	0.294
Superior longitudinal fasciculus L	-0.156	0.305	0.288	0.055	0.200	0.188	0.289	0.054
Superior longitudinal fasciculus R	-0.131	0.390	0.269	0.074	0.229	0.131	0.256	0.090
Uncinate fasciculus L	0.182	0.232	-0.198	0.193	-0.086	0.574	-0.211	0.165
Uncinate fasciculus R	0.285	0.058	0.051	0.739	0.237	0.117	-0.083	0.587
Superior longitudinal fasciculus (temporal part) L	-0.186	0.222	-0.066	0.665	-0.227	0.134	0.084	0.585
Superior longitudinal fasciculus (temporal part) R	-0.253	0.093	0.129	0.399	-0.073	0.633	0.212	0.162

* $p < 0.05$

** $p < 0.005$ corrected for number of tested regions

3.3. Effects of visceral adipose tissue

Controlling for age, sex, total intracranial volume and BMI, we found significant positive correlations between VAT and MD and RD values in the hippocampal part of the left cingulum ($p < 0.005$, corrected for number of tested regions, see figure 5 and 6) with the strongest correlation for the RD value.

However, increased VAT showed marginally significant correlations ($p < 0.05$) with increased MD and RD in the hippocampal part of the right cingulum and in the forceps major (see figure 7), decreased FA and increased RD in the right inferior longitudinal fasciculus and increased AD in the right anterior thalamic radiation and the hippocampal part of the left cingulum.

We found no significant correlation for FA, MD, AD and RD in the left anterior thalamic radiation, the left and right corticospinal tract, the cingular part of the left and right cingulum, the forceps minor, the left and right inferior fronto-occipital fasciculus, the left inferior longitudinal fasciculus, the left and right superior longitudinal fasciculus, left and right uncinate fasciculus and the temporal part of the left and right superior longitudinal fasciculus. No significant correlation was found for FA, MD and RD in the right anterior thalamic radiation, and for FA, AD and RD in the hippocampal part of the right cingulum. And we found no significant correlation for FA and AD in the forceps major, for MD and AD in the right inferior longitudinal fasciculus and for FA in the hippocampal part of the left cingulum.

For details about the results of the ROI analysis with VAT see table 6. The major white matter tracts that are affected by VAT are illustrated in figure 8.

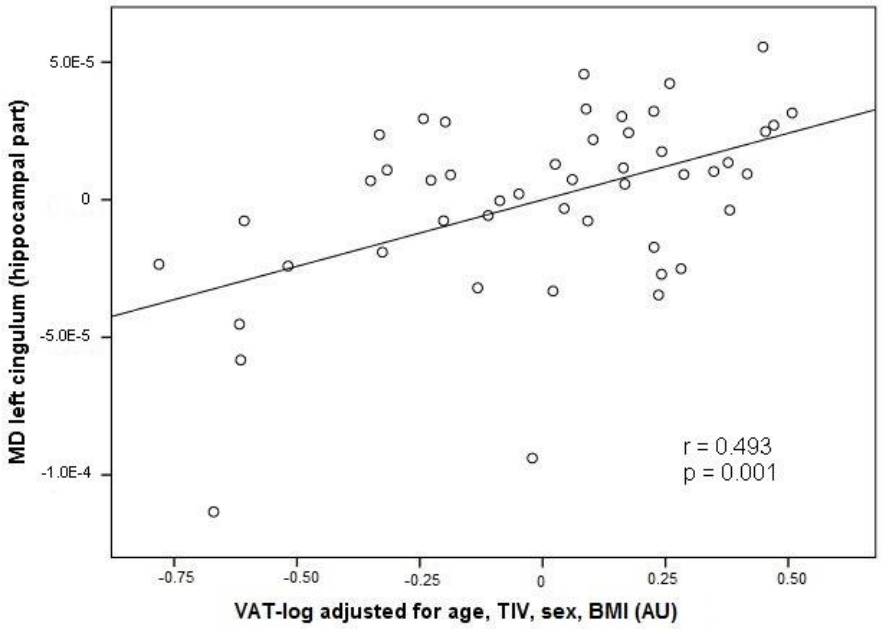

Figure 5 Partial correlation between VAT and MD of the hippocampal part of the left cingulum adjusted for age, TIV, sex and BMI. Axes are mean centered. (AU=arbitrary unit; BMI=body mass index; MD=mean diffusivity; TIV=total intracranial volume; VAT=visceral adipose tissue).

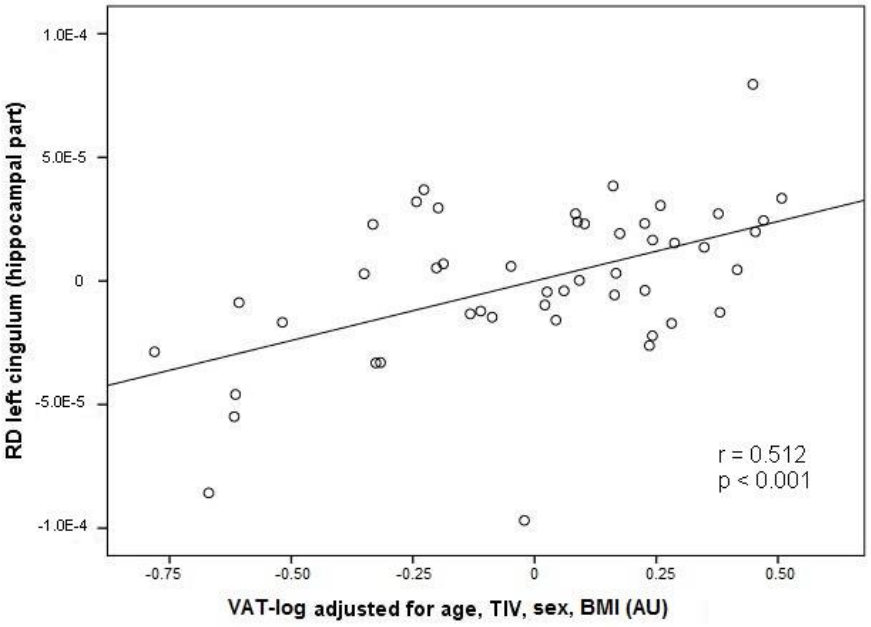

Figure 6 Partial correlation between VAT and RD of the hippocampal part of the left cingulum adjusted for age, TIV, sex and BMI. Axes are mean centered. (AU=arbitrary unit; BMI=body mass index; RD=radial diffusivity; TIV=total intracranial volume; VAT=visceral adipose tissue).

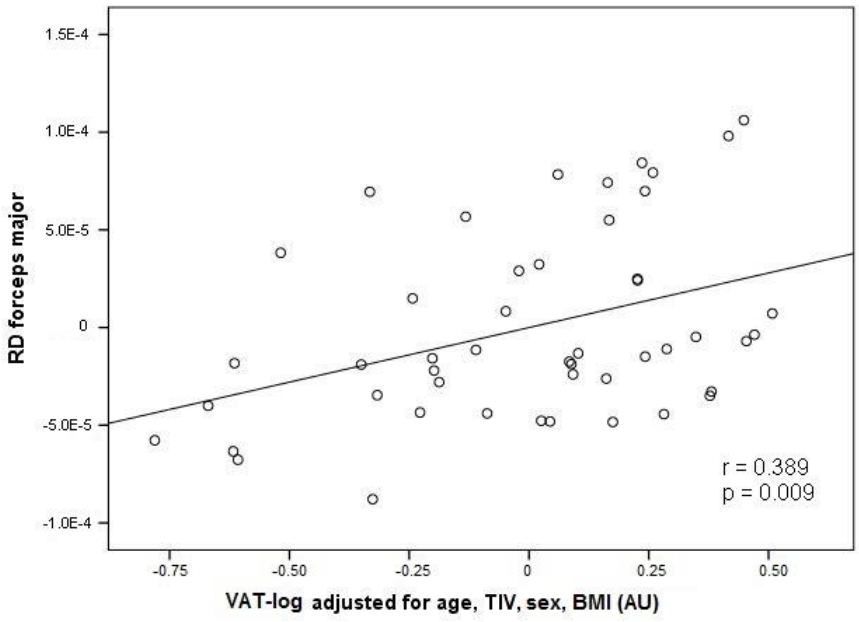

Figure 7 Partial correlation between VAT and the RD of the forceps major adjusted for age, TIV, sex and BMI. Axes are mean centered. (AU=arbitrary unit; BMI=body mass index; RD=radial diffusivity; TIV=total intracranial volume; VAT=visceral adipose tissue).

Table 6 Region-of-interest analysis with partial correlations between VAT and DTI parameters

(FA = fractional anisotropy; MD = mean diffusivity; AD = axial diffusivity; RD = radiaI diffusivity; r_{adj} = adjusted correlation coefficient; L = left; R = right)

	FA		**MD**		**AD**		**RD**	
	r_{adj} value	p-value	r_{adj} value	p-value	r_{adj} value	p-value	r_{adj} value	p-value
Anterior thalamic radiation L	-0.089	0.566	0.286	0.060	0.294	0.053	0.266	0,081
Anterior thalamic radiation R	-0.107	0.490	0.289	0.057	0.299	**0.049***	0.270	0.076
Corticospinal tract L	0.015	0.925	0.175	0.256	0.152	0.326	0.121	0.434
Corticospinal tract R	-0.019	0.900	0.036	0.816	0.035	0.822	0.016	0.915
Cingulum (cingular part) L	-0.068	0.661	0.056	0.719	-0.052	0.737	0.106	0.492
Cingulum (cingular part) R	0.108	0.487	0.013	0.935	0.105	0.497	-0.048	0.759
Cingulum (hippocampal part) L	-0.243	0.112	0.493	**0.001****	0.334	**0.027***	0.512	**< 0.001 ****
Cingulum (hippocampal part) R	-0.116	0.454	0.331	**0.028***	0.250	0.102	0.317	0.036*
Forceps major	-0.163	0.292	0.368	**0.014***	0.296	0.051	0.389	**0.009***
Forceps minor	-0.147	0.340	0.151	0.327	0.125	0.419	0.146	0.345
Inferior fronto-occipital fasciculus L	-0.192	0.212	0.209	0.173	0.140	0.366	0.222	0.148
Inferior fronto-occipital fasciculus R	-0.164	0.286	0.191	0.213	0.113	0.464	0.219	0.152
Inferior longitudinal fasciculus L	-0.299	0.135	0.234	0.127	0.056	0.716	0.262	0.086
Inferior longitudinal fasciculus R	-0.309	**0.041***	0.284	0.062	0.117	0.448	0.339	**0.024***
Superior longitudinal fasciculus L	-0.290	0.056	0.145	0.347	-0.007	0.963	0.204	0.185
Superior longitudinal fasciculus R	-0.179	0.244	0.177	0.250	0.084	0.588	0.187	0.225
Uncinate fasciculus L	-0.058	0.706	0.028	0.858	0.026	0.866	0.029	0.851
Uncinate fasciculus R	-0.071	0.646	0.131	0.397	0.120	0.436	0.103	0.507
Superior longitudinal fasciculus (temporal part) L	-0.238	0.120	0.139	0.368	-0.102	0.510	0.243	0.113
Superior longitudinal fasciculus (temporal part) R	0.046	0.764	0.119	0.442	0.171	0.266	0.031	0.844

* $p < 0.05$

** $p < 0.005$ corrected for number of tested regions

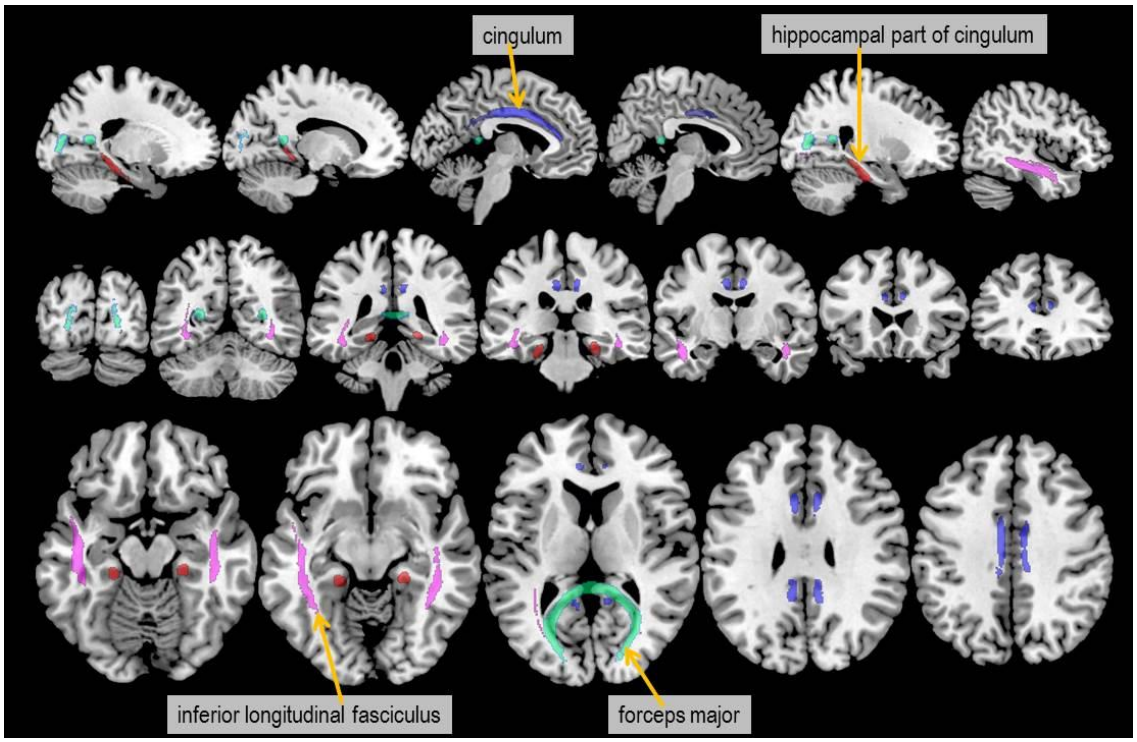

Figure 8 Major white matter tracts affected by visceral adipose tissue (top row: sagital, middle row: coronal and bottom row: axial view of standard brain) (Blue: cingulum; green: forceps major; magenta: inferior longitudinal fasciculus; red: hippocampal part of cingulum).

3.4. Effects of subcutaneous and total adipose tissue

After controlling for age, sex, total intracranial volume and BMI no significant correlation was observed between all DTI parameters and SCAT and TAT ($p < 0.005$, corrected for number of tested regions). However, we observed a positive trend ($p < 0.05$) between TAT and AD in both left and right anterior thalamic radiation and MD in the right anterior thalamic radiation. SCAT showed no significant nor marginally significant correlation with any of the DTI parameters.

4. Discussion

Given the impact of obesity on white matter integrity, the objective of this study was to examine the effect of body fat distribution, especially that of visceral adipose tissue on the microstructure of white matter. In our study with healthy, young to middle-aged subjects, we were able to show a relationship between obesity, particularly visceral adipose tissue, and reduced white matter integrity. Increased BMI correlated with reduced WM integrity in the corticospinal tract, in the cingulum and in the forceps minor. Moreover, visceral adipose tissue affected white matter integrity in the cingulum and forceps major, whereas subcutaneous adipose tissue and total visceral adipose tissue did not show any significant association with white matter integrity. These findings point to a special influence of VAT on white matter integrity and underline previous report of VAT being an unfavorable fat.

4.1 Body mass index-associated effects on white matter integrity

In previous studies, higher BMI was found to correlate with lower values of fractional anisotropy and axial diffusivity, and higher values of mean diffusivity and radial diffusivity respectively in obese compared to normal-weight, in samples with older subjects (Bettcher et al., 2013; Metzler-Baddeley et al., 2013; Ryan & Walther, 2014) as well as adolescents (Yau et al., 2014). Reduced white matter integrity was found especially in the limbic system and fiber bundles connecting the frontal and temporal lobe (for review, see (Kullmann et al., 2015)). In this present study, we were able to confirm these previous findings showing significant negative correlations between BMI and axial diffusivity in the left corticospinal tract, the hippocampal part of the right cingulum and in the forceps minor.

The finding that increased BMI was associated with reduced integrity of the corticospinal tract is in accordance with previous studies (Karlsson et al., 2013; Lou, Chen, Luo, & Dai, 2014; Ryan & Walther, 2014). The corticospinal tract projects from the primary motor and somatosensory cortex into the spinal cord

passing the internal capsule (Mori et al., 2008; Wakana et al., 2004) and is therefore carrying information of voluntary movement. Our results combined with previous findings suggest that the corticospinal tract is vulnerable to metabolic changes such as obesity and dyslipidemia.

BMI also correlated with axial diffusivity values in the forceps minor which is part of the callosal radiation containing commissural fibers of the corpus callosum and projects from the genu into the frontal lobes (Wakana et al., 2004). The genu of the corpus callosum and frontal pericallosal regions are found to be vulnerable to aging (for review, see (Madden et al., 2012)). Frontal white matter is important for cognitive processes such as memory, executive function and sustained attention and is therefore vulnerable to white matter disorders like dementia (for review, see (Filley, 2005)). In previous studies, obesity was already found to correlate with white matter integrity in the corpus callosum (Bettcher et al., 2013; Karlsson et al., 2013; Mueller et al., 2011; Ryan & Walther, 2014; Stanek et al., 2011; Verstynen et al., 2013; Xu et al., 2013), which confirms our results in the forceps minor as part of the callosal radiation. The significance of the decline of white matter integrity in the cingulum will be discussed below.

4.2 Visceral adipose tissue-associated effects on white matter integrity

With increased visceral adipose tissue, we found heightened mean and radial diffusivity particularly in the left hippocampal part of the cingulum tract. Additionally, we identified marginally significant correlations between VAT and the forceps major, inferior longitudinal fasciculus and the right hippocampal part of the cingulum tract, with the strongest effect on mean diffusivity and radial diffusivity. Hence we postulate that the VAT-associated effect on white matter integrity is related to demyelination rather than axonal damage, since both of these DTI indices increase with reduced myelination (for reviews, see (Alexander et al., 2007; Chanraud et al., 2010; Madden, Bennett, & Song, 2009)). Below, the effects of visceral adipose tissue on the cingulum and forceps major and its significance for human cerebral health are discussed.

4.2.1. Cingulum

The cingulum bundle contains association fibers and as part of the limbic system it carries afferent connections from the cingulate gyrus to the entorhinal cortex, which is an area located in the medial temporal lobe important for memory function (Mori et al., 2008; Mori et al., 2005; Trepel, 2012).

In our study, VAT correlated positively with MD and RD values in the hippocampal part of the cingulum, near the entorhinal cortex. Previous studies already pointed to axonal loss in white matter in the cingulum, showing lower FA values with higher BMI and greater abdominal girth (Bettcher et al., 2013; He et al., 2015; Marks et al., 2011). Both in elderly (Bettcher et al., 2013) and in young obese (He et al., 2015), white matter integrity in the cingulum was found to be reduced, even after controlling for inflammatory and vascular markers (Bettcher et al., 2013). Using quantitative tractography, the total number of tracks that pass the midcingulate cortex seed region was decreased with increased BMI (He et al., 2015).

The cingulum bundle is a complex tract with many connections including many short fibers, hence it is likely that different parts of the cingulum reflect different underlying functions having effects on normal aging, depression, schizophrenia, mild cognitive impairment and Alzheimer's disease (for review, see (Jones et al., 2013)). Because of the tight connection between cingulum and hippocampus, disruption of the cingulum bundle may cause reduced process ability of the hippocampus. The hippocampus is known to consolidate the declarative memory and to also regulate emotional and vegetative functions (Trepel, 2012). Hippocampal atrophy was found to serve as early marker of memory decline and future dementia (den Heijer et al., 2010). It is evident that obesity is related with deficits in cognitive performance, in learning and executive functions, and therefore it increases the risk of developing mild cognitive impairment, dementia and Alzheimer's disease ((Gunstad et al., 2007; D. Gustafson et al., 2003; Hassing, Dahl, Pedersen, & Johansson, 2010), for review, see (Nguyen, Killcross, & Jenkins, 2014)). Especially mid-life obesity leads to decline of executive function and reduced hippocampal volume and increases the risk of dementia (Debette et al., 2011; Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005) (for reviews, see (Emmerzaal, Kiliaan, & Gustafson, 2015; Nguyen et al., 2014)). Moreover, overweight and obese children already show reduced cognitive performance in learning and memory and reduced hippocampal volume (Bauer et al., 2015).

Cognitive decline is not only reported in subjects with reduced hippocampal volume, the microstructure of the cingulum bundle itself seems to relate to cognitive function such as working memory and sustained attention (Takahashi et al., 2010). Additionally, the ability of making decisions under ambiguity, assessed by the Iowa Gambling Task, was found to mediate the negative association between the structure of the midcingulate cortex and BMI (He et al., 2015). Patients with mild cognitive impairment show disruption in white matter in the anterior and inferior cingulum, which could be related to executive function, attention and process speed (Chang et al., 2015; Metzler-Baddeley et al., 2012). Hence, white matter integrity in the cingulum might be a sensitive

biomarker in early detection of Alzheimer's disease (Chang et al., 2015). These previous findings indicate that reduced white matter integrity in the cingulum, due to obesity, is potentially related to cognitive decline. Based on our finding that increased visceral adipose tissue is related to decreased white matter integrity in the hippocampal part of the cingulum, may point to a special role of visceral fat for the increased risk for future MCI, dementia and Alzheimer's disease. Longitudinal studies are needed to examine the effect of VAT on the development of MCI, dementia and Alzheimer's disease.

Furthermore, the cingulum is part of the emotion regulation system, and alterations within the cingulum bundle combined with other predisposing factors are associated with specific psychiatric disorders such as bipolar disorder, depression, anxiety disorders, schizophrenia, anorexia and post-traumatic stress disorder (Heilbronner & Haber, 2014), (for review, see (Fani et al., 2014)). Especially changes in the posterior part of the cingulum, which is proximal to the hippocampus, seem to influence both cognitive and affective processes (for review, see (Fani et al., 2014)). The posterior cingulum may be part of the hippocampal part of the cingulum that we examined.

Additionally, obesity is associated with mood disorders such as anxiety disorder and major depressive disorder (Scott, McGee, Wells, & Oakley Browne, 2008). Especially in depression, which is also found to correlate with hippocampal volume loss (Cole, Costafreda, McGuffin, & Fu, 2011), there is evidence for its relationship with obesity (for reviews, see (de Wit et al., 2010; Preiss, Brennan, & Clarke, 2013)). Several large longitudinal studies found that obese are more likely to have onset of depression than non-obese (Nigatu, Bultmann, & Reijneveld, 2015; Xiang & An, 2015). A recent meta-analysis of longitudinal studies showed bidirectional associations between obesity and depression and calculated a 55% increased risk to develop depression for obese persons (Luppino et al., 2010). These findings may provide a link between obesity-related changes in white matter integrity in the cingulum bundle and the development of depression.

Therefore, the changes in white matter integrity that we found not only point to future cognitive but also emotional impairment of the, to date, still healthy obese subjects of our study. Still longitudinal work is needed to prove these suggestions.

4.2.2. Forceps major

Forceps major is part of the callosal radiation containing commissural fibers of the corpus callosum. It projects from the splenium into the occipital lobes (Wakana et al., 2004) and thus connects the corresponding hemispheres of the occipital lobe (Trepel, 2012). Therefore it is important for passing cognitive, sensory and motor information between the corresponding regions (Huang et al., 2005). According to previous studies, the forceps major is relevant for cognitive performance. A study with patients with relapsing multiple sclerosis found a negative relationship between cognitive performance and the number of WM lesions in the forceps major and in the splenium of the corpus callosum (Rossi et al., 2012). Among very old subjects, white matter microstructure in the forceps major is positively related to perceptual speed (Laukka et al., 2013), which is part of the fluid cognitive ability. Reduced fluid cognition is particularly associated with age-related decline in white matter integrity (for review, see (Madden et al., 2012)). In this present study, we found that increased VAT correlates positively with mean diffusivity and radial diffusivity in the forceps major. These results indicate that increased VAT could lead to a loss of myelin (for review, see (Alexander et al., 2007)) in regions that are important for cognitive performance especially for perceptual speed. Therefore it is possible that VAT potentiates and accelerates the process of cognitive aging.

4.2.3 Effects of visceral adipose tissue

Increased visceral adipose tissue is related with decreased white matter integrity especially in regions involved in cognitive processes such as the cingulum and the forceps major. However, the underlying cause of this relationship is not known.

4.2.3.1 Effects on metabolism

Visceral adipose tissue has become of increasing interest in the last few years. There is now evidence that the amount of VAT is key correlate of the association between health risk and obesity (for review, see (Tchernof & Despres, 2013)). In particular, the risk for cardiovascular diseases and coronary artery disease, including myocardial infarction, is increased in subjects with a great portion of visceral adipose tissue (Mahabadi et al., 2009; Nakamura et al., 1994; Yusuf et al., 2005). Insulin resistance and the subsequent development of type 2 diabetes are associated with the accumulation of VAT independently of other diabetes risk factors (Boyko, Fujimoto, Leonetti, & Newell-Morris, 2000; Preis et al., 2010). Furthermore, the dyslipidemic state, represented by low high-density lipoprotein cholesterol and hypertriglyceridemia, which is found in subjects with increased visceral adipose tissue leads to the metabolic syndrome (Grundy et al., 2005). Even the risk of cancer, especially colorectal cancer, is higher with increased VAT ((Larsson & Wolk, 2007), for review, see (Tchernof & Despres, 2013)). These findings can conclude that visceral adipose tissue represents a risk for human health. In this present study, we were able to show that visceral adipose tissue also affects the microstructure of the human brain reducing white matter integrity.

One reasonable mechanism behind the visceral adipose tissue associated loss in white matter integrity may provide the effect of systemic inflammation. Visceral adipose tissue is known as unfavorable fat because of containing hypoxic, poorly capilarized and hypertrophic adipocytes leading to inflammation and fibrosis (Krotkiewski & Billing-Marczak, 2014). Accumulated visceral

adipose tissue causes chronic, low-grade inflammation with infiltration of macrophages and is secreting free fatty acids and pro-inflammatory cytokines such as Interleukin-1 and Interleukin-6, adiponectin, leptin and tumor necrosis factor α (for reviews, see (Alexopoulos et al., 2014; Kaur, 2014; Tchernof & Despres, 2013)).

4.2.3.2 Effects on cognition

Hence, increased inflammation not only contributes to the development of type 2 diabetes and cardiovascular disease (for review, see (Tchernof & Despres, 2013)) but also to a widespread reduced white matter integrity in the human brain (Gianaros et al., 2013; Verstynen et al., 2013). Cytokines, such as Interleukin-6 and Interleukin-1β, and C-reactive protein were found to disrupt neural circuits which are involved in memory and cognition and are associated with an increased risk of dementia (for reviews, see (Gemma & Bickford, 2007; Koyama et al., 2013)). Furthermore, oligodendrocytes of association fiber bundles are assumed to be susceptible to metabolic damage due to their major metabolic activity (Madden et al., 2012). Thus, a loss of oligodendrocytes due to systemic inflammation may be observed in reduced white matter integrity, in particular in increased radial diffusivity which indicates demyelination (Klawiter et al., 2011). This may explain why we predominantly identified reduced white matter integrity based on increased mean diffusivity and radial diffusivity in individuals with heightened visceral adipose tissue, while no such association was found with subcutaneous and total adipose tissue.

Since increased visceral adipose tissue is related to compromised white matter integrity, the question now arises whether this white matter decline can be attenuated or even reversed. First, physical activity seems to have an impact on both the amount of visceral adipose tissue and white matter integrity. Increased BMI is associated with lower physical fitness which could be shown in a large study with 2411 schoolchildren (Ceschia et al., 2015). In previous studies, high physical exercise was identified to reduce VAT and cardiometabolic risk factors even when only minimal body weight loss could be achieved (for reviews, see

(Ross & Janiszewski, 2008; Tchernof & Despres, 2013; Vissers et al., 2013)). Furthermore, aerobic fitness was found to have a positive effect on white matter integrity in the left middle cingulum (Marks et al., 2011) and in the temporal and frontal lobes, both in older adults and in overweight children (Schaeffer et al., 2014; Voss et al., 2013). Additionally, it is known to have beneficial effects on cognitive performance (for review, see (Loprinzi, Herod, Cardinal, & Noakes, 2013)). Another study suggests that high cardiorespiratory fitness extenuates age-related demyelination in the corpus callosum (N. F. Johnson, Kim, Clasey, Bailey, & Gold, 2012). Hence, physical activity seems to be a potential therapy to prevent and treat compromised white matter integrity and possible even accelerated cognitive decline in obesity.

Second, body weight loss is discussed to have a beneficial effect on cerebral health. Weight loss in short-term interventions appear to have a modest protective effect on cognitive function, especially on memory and executive functioning, in obese but not in overweight subjects (Siervo et al., 2011), while long-term interventions were found to have a cognitive benefit for overweight but not obese (Espeland et al., 2014). Still, other studies also found significant associations between weight loss and improved cognitive function among obese participants (Napoli et al., 2014; Siervo et al., 2012). Studies investigating neural activation before and after weight loss report higher functional activation to food cues after successful weight loss in right middle temporal and left superior frontal cortex (McCaffery et al., 2009), and in dorsolateral prefrontal cortex (Le et al., 2007), patterns that are normally found in lean subjects and are regions associated with cognitive control (Bruce et al., 2012). Increased white matter volumes in obese subjects with increased waist to hip ratio are found partially reversed after weight loss. Hence, it is suggested that increased visceral adipose tissue is related with fat accumulation in central myelin, which may be reversible by weight loss (Haltia et al., 2007). However, the effect of intentional weight loss on white matter integrity has not been investigated until now.

Third, cognitive training was found to have a positive effect on white matter integrity. With cognitive training including perceptual speed, working and episodic memory, changes in white matter integrity such as increased fractional anisotropy and decreased mean diffusivity have been shown. Therefore it is suggested that disordered intrahemispheric connectivity may be modifiable with cognitive training (Lovden et al., 2010).

Thus, cognitive training as well as physical activity, and presumably weight loss, may help to prevent or reverse cognitive decline caused by visceral adiposity.

4.3. Conclusion

We conclude that visceral adipose tissue, independently of BMI, is associated with altered white matter integrity, particularly in regions that are involved in cognitive and emotional functioning such as the cingulum and the forceps major. This DTI-study is the first in obesity research to examine the particular relationship between visceral adipose tissue and white matter integrity and therefore provides deeper understanding of the relevance of body fat distribution on cerebral health. Our results suggest that visceral adipose tissue may increase the risk for cognitive and emotional impairment, but still further direct examination is needed, particularly longitudinal studies. Further work is also required to determine clinical relevance and causal impact of visceral adipose tissue on white matter integrity and functionality.

5. Summary

Objective: Obesity has become a great health problem and increases the risk for cardiovascular and metabolic diseases as well as for cognitive impairments including brain alterations in gray and white matter structure and function. The differentiation of adipose tissue in visceral adipose tissue and subcutaneous adipose tissue was found to be greatly relevant due to its different composition and consequent potential for metabolic complications. Hence, the objective of this study was to investigate the relationship between body fat distribution, especially visceral and subcutaneous adipose tissue, and white matter integrity.

Methods: Diffusion tensor imaging (DTI) of the brain and whole body magnetic resonance imaging were performed of 48 healthy young to middle-aged lean, overweight and obese participants. The collected data included participant's sex, age, body mass index, total body volume, volume of total, subcutaneous and visceral adipose tissue, total intracranial volume and DTI data of the brain. By using a region-of-interest-based approach, the DTI parameters fractional anisotropy, mean diffusivity, axial diffusivity and radial diffusivity were analyzed and correlated with the body mass index, total adipose tissue, subcutaneous and visceral adipose tissue, controlling for age, sex, total intracranial volume and BMI.

Results: We found significant positive correlations between visceral adipose tissue and mean diffusivity and radial diffusivity values in the hippocampal part of the left cingulum ($p < 0.005$, corrected for number of tested regions) and marginally significant positive correlations in the forceps major and hippocampal part of the right cingulum ($p < 0.05$). Subcutaneous and total adipose tissue did not show significant correlations with DTI parameters.

Conclusion: Our DTI study contributed to the current knowledge of the relationship between visceral adipose tissue and white matter integrity. We conclude that increased visceral adipose tissue is associated with reduced white matter integrity in regions which are known to be important for emotional and cognitive functioning. Therefore we suggest that increased visceral adipose

tissue may increase the risk for emotional and cognitive impairment. Still further longitudinal studies may determine causal impact of visceral adipose tissue and its clinical relevance.

5.1. Deutsche Zusammenfassung

Ziel der Arbeit: Adipositas ist zu einen großen Gesundheitsproblem geworden und geht mit einem erhöhten Risiko für sowohl kardiovaskuläre und metabolische Erkrankungen als auch für kognitive Beeinträchtigungen einschließlich Veränderungen der Struktur und Funktion der grauen und weißen Substanz einher. Die Differenzierung des Körperfetts in Viszeralfett und subkutanes Fett ist aufgrund ihrer unterschiedlichen Zusammensetzung und dem daraus resultierenden Potential für metabolische Komplikationen von großer Bedeutung. Daher war es das Ziel der Arbeit, die Beziehung zwischen der Körperfettverteilung, insbesondere viszeralem und subkutanem Fett, und der Integrität der weißen Substanz zu untersuchen.

Methoden: Bei 48 gesunden, jungen bis mittelalten, normalgewichtigen bis adipösen erwachsenen Teilnehmern wurde jeweils eine Diffusions-Tensor-Bildgebung (DTI, abgekürzt von englisch: diffusion tensor imaging) des Gehirns und eine Ganzkörper-Magnetresonanztomographie durchgeführt. Die gesammelten Teilnehmerdaten beinhalteten das Geschlecht, das Alter, den Body-Mass-Index (BMI), die Volumina an Gesamtfett, subkutanem und viszeralem Fett, das Gesamthirnvolumen und die DTI-Daten des Gehirns. Mithilfe von „Region-of-interest“-basierter Annäherung wurden die DTI-Parameter fraktionelle Anisotropie, mittlere, axiale und radiale Diffusivität analysiert und mit dem BMI und den Volumina an Gesamtfett, subkutanem und viszeralem Fett korreliert, wobei für Alter, Geschlecht, Gesamthirnvolumen und BMI kontrolliert wurde.

Ergebnisse: Wir fanden signifikant positive Korrelationen zwischen vizeralem Fett und den Werten von mittlerer und radialer Diffusivität im hippocampalen Teil des linken Cingulums ($p < 0,005$; korrigiert für Anzahl der gestesteten Regionen) und grenzwertig signifikante positive Korrelationen im Forceps major und im hippocampalen Teil des rechen Cingulums ($p < 0,05$). Das subkutane Fett und das Gesamtfett zeigten keine signifikanten Korrelationen mit den DTI-Parametern.

Fazit: Unsere DTI-Studie trug zum Verständnis über die Beziehung zwischen viszeralem Fettgewebe und der Integrität der weißen Substanz bei. Somit gibt es eine Assoziation von vermehrtem Viszeralfett mit reduzierter Integrität der weißen Substanz in Hirnregionen, die für emotionale und kognitive Funktionen von Bedeutung sind. Darum vermuten wir, dass vermehrtes Viszeralfett das Risiko für emotionale und kognitive Beeinträchtigung erhöhen dürfte. Dennoch sind weitere longitudinale Studien erforderlich, um die kausale Auswirkung von Viszeralfett und ihre klinische Relevanz zu erfassen.

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7. Erklärung zum Eigenanteil

Die Arbeit wurde im Universitätsklinikum Tübingen/ fMEG-Zentrum unter Betreuung von Herr Prof. Dr. Hubert Preissl durchgeführt.

Die Konzipierung der Studie erfolgte in Zusammenarbeit mit Frau Dr. Stephanie Kullmann und Herr Prof. Dr. Hubert Preissl.

Die Daten der diffusionsgewichteten Magnetresonanztomographie (MRT) wurden von Frau Dr. Stephanie Kullmann und Maike Borutta erhoben und mir zur Verfügung gestellt. Die Daten der Ganzkörper-Magnetresonanztomographie wurden von PD Dr. Jürgen Machann erhoben und mir zur Verfügung gestellt.

Die erhobenen MRT Daten des Gehirns wurden von mir aufbereitet und ausgewertet. Hierfür habe ich selbstständig ein neues Datenauswertungsprogramm in der Arbeitsgruppe Prof. Dr. Hubert Preissl implementiert, um die Diffusions-Tensoren zu berechnen, die zur Quantifizierung der weißen Substanz im Gehirn dienen. Dieses neue Datenauswerteprogramm ermöglicht ein standardisiertes Verfahren um große DTI-Datensätze auszuwerten.

Die statistische Auswertung wurde von mir nach einer Einweisung durch Frau Dr. Stephanie Kullmann selbstständig durchgeführt.

Die Ergebnisse wurden von mir zusammengefasst und mit Prof. Dr. Hubert Preissl und Dr. Stephanie Kullmann besprochen. Die Diskussion der Ergebnisse wurde von mir erstellt.

Ich versichere, das Manuskript selbständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

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