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Specific white matter tissue microstructure changes associated with obesity

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ABSTRACT

Obesity-related structural brain alterations point to a consistent reduction in gray matter with increasing body mass index (BMI) but changes in white matter have proven to be more complex and less conclusive. Hence, more recently diffusion tensor imaging (DTI) has been employed to investigate microstructural changes in white matter structure. Altogether, these studies have mostly shown a loss of white matter integrity with obesity-related factors in several brain regions. However, the variety of these obesity-related factors, including inflammation and dyslipidemia, resulted in competing influences on the DTI indices. To increase the specificity of DTI results, we explored specific brain tissue properties by combining DTI with quantitative multi-parameter mapping in lean, overweight and obese young adults. By means of multi-parameter mapping, white matter structures showed differences in MRI parameters consistent with reduced myelin, increased water and altered iron content with increasing BMI in the superior longitudinal fasciculus, anterior thalamic radiation, internal capsule and corpus callosum. BMI-related changes in DTI parameters revealed mainly alterations in mean and axial diffusivity with increasing BMI in the corticospinal tract, anterior thalamic radiation and superior longitudinal fasciculus. These alterations, including mainly fiber tracts linking limbic structures with prefrontal regions, could potentially promote accelerated aging in obese individuals leading to an increased risk for cognitive decline.

Introduction

Besides the strong association with numerous health conditions and changes in blood pressure, inflammation, dyslipidemia and insulin resistance (Bastard et al., 2006; Johnson et al., 2012), obesity is also related to changes in cognitive functions. These alterations include an increased risk for dementia and an accelerated cognitive decline in older age, with complementary structural and functional brain changes (Gunstad et al., 2007; Gustafson et al., 2003). Hence, there has been an increased interest in investigating obesity-related structural brain alterations using magnetic resonance imaging (MRI).

Recent studies in this fast growing field have mainly focused on changes in volume or density of gray (GM) and white matter (WM) using voxel-based (VBM) and tensor-based morphometry (TBM). A widespread reduction in GM volume and density was distinctly shown with increased BMI throughout the brain (Bobb et al., 2014; Driscoll et al., 2012; Gustafson et al., 2004; He et al., 2015; Raji et al., 2010; Taki et al., 2008; Walther et al., 2010; Ward et al., 2005; Yokum et al., 2012). Moreover, cortical thickness, a more specific and direct measure of gray matter, recently confirmed these obesity-related GM alterations showing cortical thinning with increased BMI mainly in frontal, temporal and parietal regions (Hassenstab et al., 2012; Marques-Iturria et al., 2013; Veit et al., 2014).

Macrostructural WM changes in obesity showed a more complex and less consistent pattern, revealing a positive association between BMI and WM volume/density in frontal, temporal and parietal lobes (Schwartz et al., 2014; Walther et al., 2010) and a negative relationship

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in the basal ganglia and corona radiata (Raji et al., 2010; Yokum et al., 2012). To clarify these findings, the microstructural composition and architecture of the white matter have been investigated using diffusion tensor imaging (DTI), which is highly sensitive to changes at the cellular and microstructural level (Alexander et al., 2007), quantifying and mapping the rate and directionality of water movement within tissue (Basser et al., 1994). Fractional anisotropy (FA) and mean diffusivity (MD) are summary measures of WM diffusivity reflecting the coherence of fiber tracts and the average rate of water diffusion, respectively. Reduced myelin integrity results in decreased FA and increased MD. It is also possible to analyze the rate of diffusion along the individual axis of the tensor: axial diffusivity (AD) measures diffusivity along the primary axis and is associated with axonal integrity, whereas radial diffusivity (RD) measures diffusivity perpendicular to the major axis reflecting myelin integrity (Basser, 1995). Increased AD can result from heightened fiber coherence or decreased axonal branching (Budde et al., 2009), while axonal damage can lead to decreased AD. Reduced myelin integrity of the membrane or sheath can also increase RD (Song et al., 2003).

Studies using DTI have revealed a loss of white matter integrity showing an inverse association between body mass index (BMI) and FA mainly in tracts within the limbic system and those connecting the temporal and frontal lobes (Bolzenius et al., 2013; Gupta et al., 2015; Ryan and Walther, 2014; Shott et al., 2014; Xu et al., 2013; Yau et al., 2014) (for review see Kullmann et al., 2015). However, the variety of obesity-related factors, such as inflammation and dyslipidemia, result in competing influences on the DTI indices. Vascular physiological factors, such as dyslipidemia and blood pressure, were related to localized higher FA, while increased BMI and global inflammation were related to a widespread reduction in FA values (Verstynen et al., 2013).

The specificity of DTI can be complemented and improved through combination with other imaging techniques such as quantitative Multi-Parametric Mapping (MPM) (Weiskopf et al., 2013) to explore specific brain tissue properties by studying a number of key contrast parameters, namely effective proton density (PD*), magnetic transfer saturation (MT), longitudinal relaxation rate (R1) and effective transverse relaxation rate (R2*). These quantitative MRI (qMRI) measures each have differential sensitivity to underlying biological metrics. MT reflects macromolecular content, with myelin being the biggest contributor in the brain (Helms et al., 2010; Schmierer et al., 2004). Hence, demyelination would lead to a reduction in MT. R1 is sensitive to the relative contribution of myelin and water content, as well as to paramagnetic content, e.g. iron (Callaghan et al., 2015; Lutti et al., 2014; Rooney et al., 2007). Thus, a reduction in myelin or an increase in water content would lead to decreased R1 levels in the brain. It should be noted that iron decreases could also lead to a reduction in R1, but to a lesser extent (Callaghan et al., 2015; Rooney et al., 2007), particularly in white matter (Gelman et al., 2001). The R2* measure is sensitive to local dephasing agents, and has been shown to correlate with iron content in the brain (Langkammer et al., 2010). Since iron is a major co-factor for the production and maintenance of myelin, a reduction of iron in the white matter may promote demyelination. Proton density is sensitive to water content, which is increased by inflammatory processes, and has been used to estimate the macromolecular tissue volume fraction (Lerski et al., 1984; Mezer et al., 2013; Tofts, 2004). Here we refer to the effective proton density since this measure has residual T2* weighting.

In the current study, we used multi-parametric mapping, in addition to DTI, to acquire quantitative maps to investigate the effect of obesity on brain white matter microstructure in young healthy adults. Given that each acquired quantitative MRI parameter is associated with particular aspects of white matter tissue structure, we can begin to detect specific changes related to obesity. We hypothesized that increased BMI and altered lipid profiles would be associated with myelin loss, and changes in water diffusion characteristics.

Materials and methods

Subjects

We recruited 24 healthy lean, 12 overweight and 12 obese adult participants for this study (average BMI lean group: 22.31 ± 1.71 kg/m^2, overweight group: 27.73 ± 1.31 kg/m^2, obese group: 34.14 ± 4.8 kg/m^2; age range 21 to 37 years; 23 women and 25 men). DTI data were acquired in all participants. However, out of time constraints, the multi-parametric mapping protocol was additionally acquired only on 33 out of the 48 subjects (for details of this sub-cohort, please see Table 1). Informed written consent was obtained from all subjects and the local Ethics Committee approved the protocol. All participants were students at the University of Tübingen recruited using broadcast emails.

Study design

Prior to the experiment, all participants underwent a medical examination to confirm that they did not suffer from psychiatric, neurological or metabolic diseases. Diabetes was ruled out by a 75 g oral glucose tolerance test (OGTT). Any volunteer treated for chronic disease or taking any kind of medication other than oral contraceptives was excluded. To address psychiatric diseases, the Patient Health Questionnaire (PHQ) (Löwe et al., 2002) was used. Fasting blood samples were taken to determine individuals' lipid profile (cholesterol and triglycerides) and to exclude participants with acute infection (C-reactive protein > 10 mg/l). An overview of anthropometric and metabolic characteristics is shown in Table 1.

Data acquisition

Experiments were conducted after an overnight fast of at least 10 h and started between 8.00 and 10.00 a.m. Participants were examined on a 3T scanner (Tim Trio; Siemens) equipped with a standard 12-channel and 32-channel radio-frequency (RF) receiver head coil and RF body transmit coil. A high-resolution T1-weighted anatomical

Table 1
Participants' characteristics (n = 33).

	Lean	Overweight	Obese	p
Gender (female/male)	6/10	3/5	5/4	0.669
Age (y)	26.68 ± 3.68	26.12 ± 1.95	26.88 ± 4.45	0.902
Body mass index (kg/m^2)	22.43 ± 1.61	28.13 ± 1.38	33.16 ± 3.16	<0.001
Cholesterol (mg/dl)	174.93 ± 28.39	169.37 ± 19.92	172.33 ± 30.26	0.893
HDL cholesterol (mg/dl)	62.56 ± 4.15	49.75 ± 3.46	43.00 ± 2.90	0.002
LDL cholesterol (mg/dl)	85.37 ± 20.48	89.62 ± 12.79	92.33 ± 28.17	0.726
Triglyceride (mg/dl)	76.37 ± 20.71	92.00 ± 61.79	134.11 ± 78.66	0.047
C-reactive protein (mg/l)	0.12 ± 0.17	0.17 ± 0.15	0.50 ± 0.44	0.004
Ferritin (μg/dl)	4.83 ± 4.04	5.78 ± 4.83	8.14 ± 8.86	0.851

Data are presented as mean ± SD. p = p-Values for comparison of unadjusted $\log_e$ transformed data by ANOVA.