Psychoneuroendocrinology 91 (2018) 179–185

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Elevated body-mass index is associated with reduced white matter integrity in two large independent cohorts

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ARTICLE INFO

Keywords:
DTI
BMI
Obesity
White matter
Fractional anisotropy

ABSTRACT

Obesity has been associated with a variety of neurobiological alterations. Recent neuroimaging research has pointed to the relevance of brain structural and functional alterations in the development of obesity. However, while the role of gray matter atrophy in obesity has been evidenced in several well powered studies, large scale evidence for altered white matter integrity in obese subjects is still absent. With this study, we therefore aimed to investigate potential associations between white matter abnormalities and body mass index (BMI) in two large independent samples of healthy adults.

Associations between BMI values and whole brain fractional anisotropy (FA) were investigated in two independent cohorts: A sample of n = 369 healthy subjects from the Münster Neuroimaging Cohort (MNC), as well as a public available sample of n = 1064 healthy subjects of the Humane Connectome Project (HCP) were included in the present study. Tract based spatial statistics (TBSS) analyses of BMI on whole brain FA were conducted including age and sex as nuisance covariates using the FMRIB library (FSL Version 5.0). Threshold-free cluster enhancement was applied to control for multiple comparisons.

In both samples higher BMI was significantly associated with strong and widespread FA reductions. These effects were most pronounced in the corpus callosum, bilateral posterior thalamic radiation, bilateral internal capsule and external capsule, bilateral inferior longitudinal fasciculus and inferior fronto-occipital fasciculus. The association was found to be independent of age, sex and other cardiovascular risk factors. No significant positive associations between BMI and FA occurred.

With this highly powered study, we provide robust evidence for globally reduced white matter integrity associated with elevated BMI including replication in an independent sample. The present work thus points out the relevance of white matter alterations as a neurobiological correlate of obesity.

1. Introduction

Obesity is a major challenge for public health especially in developed countries with an estimated worldwide prevalence of 13% (World Health Organization, 2014). To avoid further spreading of this preventable condition, a better understanding of the etiological mechanisms leading to excessive weight gain appears crucial.

In this regard, genetic and neuroimaging research has cumulated evidence for neurobiological correlates of obesity pointing to a key role of altered brain structure and function in the development of excessive weight gain (Batterink et al., 2010; Bobb et al., 2014; Burger and Berner, 2014; Locke et al., 2015; Opel et al., 2015a, 2015b; Raji et al., 2010). More specifically, gray matter volume reduction in the medial prefrontal cortex and the striatum are among the most replicated findings in neuroimaging studies in obesity research (Opel et al., 2015b; Pannacciulli et al., 2006; Shott et al., 2014). Moreover, results from a recent study carried out by our group suggest that these prefrontal brain structural alterations might be an intermediate phenotype that

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https://doi.org/10.1016/j.psyneuen.2018.03.007
Received 5 January 2018; Received in revised form 6 March 2018; Accepted 13 March 2018

mediates the genetic risk for obesity (Opel et al., 2017).

However, while the relevance of gray matter atrophy in obesity has recently been confirmed by a number of highly powered studies including replication in several independent cohorts, large scale evidence for altered white matter integrity in obesity and replication of such findings is widely lacking up to now. Lack of statistical power in many studies as well as diverging methodological aspects (region-of-interest (ROI) vs. whole brain approaches, tract-based spatial statistics (TBSS) vs. tractography approaches) have prevented comparability and replication among diffusion tensor imaging (DTI) research in obesity.

Among the available studies that addressed white matter abnormalities in obesity, reduced white matter integrity in a variety of fiber tracts was frequently demonstrated in rather small samples (Karlsson et al., 2013; Mueller et al., 2014; Stanek et al., 2011; Xu et al., 2013). Up to now, evidence from the largest available study population of 268 healthy subjects comes from a TBSS study carried out by Papageorgiou et al. and suggests widespread reduced fractional anisotropy (FA) to be associated with higher body mass index (BMI) values in the thalamic radiation, the inferior fronto-occipital fasciculus and the inferior longitudinal fasciculus (Papageorgiou et al., 2017). Findings from a ROI based DTI study investigating white matter differences in the corpus callosum and the fornix support this association between higher BMI and reduced FA (Stanek et al., 2011). Fractional anisotropy (FA), which can be seen as a quantitative index of white matter coherence (Soares et al., 2013), has become the most common DTI measure in voxel-based analysis (Teipel et al., 2014). The current belief is that high FA values represent highly organized and normally myelinated axon structure. Thus, reduced FA can be interpreted as a loss of coherence in the main preferred diffusion direction and therefore points to deficits in white matter microstructure and integrity (Soares et al., 2013).

Interestingly, altered white matter integrity has also been associated with several obesity related conditions such as metabolic syndrome and hypertension (Alfaro et al., 2017; Maillard et al., 2012). Yet, to the best of our knowledge no previous DTI study investigating obesity related white matter alterations controlled for the presence of further cardiovascular risk factors such as hypertension or metabolic disorders.

Since reduced integrity of white matter tracts has been described for a variety of neurological (Kern et al., 2011; Melzer et al., 2013) and psychiatric diseases (Benedetti et al., 2015; Kochunov et al., 2017; Repple et al., 2017), large-scale investigation and replication of white matter microstructure alterations in obesity appears to be of great importance to provide a reliable basis for a better understanding of potential neurobiological overlaps between obesity and psychiatric disorders.

Therefore, with the present study we aimed to investigate whole brain white matter alterations associated with obesity in two large independent samples of healthy adults. Based on the previous findings of reduced FA in obesity in diverse white matter tracts, we hypothesized that elevated BMI values would be associated with significantly reduced FA in several, widespread white matter tracts including the thalamic radiation, the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, the fornix, and the corpus callosum and that these findings could be replicated in an independent sample. Regarding the previous evidence for associations between white matter alterations and hypertension as well as metabolic syndrome, we furthermore investigated whether the association between FA reductions and BMI would occur independently of further cardiovascular risk factors by controlling for Hemoglobin A1c (HbA1c) and systolic blood pressure in our analyses.

2. Material and methods

2.1. Participants

373 subjects participated in the present study as part of the Münster Neuroimaging Cohort (MNC). Subjects of the MNC study were recruited via newspaper advertisement with no apparent link to obesity. Exclusion criteria were any history of severe neurological (e.g., concussion, stroke, tumor, neuro-inflammatory diseases) and medical (e.g. cancer, chronic inflammatory or autoimmune diseases, diabetes mellitus, infections) conditions as well as any presence or history of psychiatric disorders according to the Structural Clinical Interview for DSM-IV-TR (SKID; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997). Subjects varying in age from 20 to 59 years were included in the present study. 4 subjects were excluded from all analyses due to anatomical anomalies resulting in a final sample of 369 subjects.

To replicate our findings, we investigated open-access brain imaging data from the Human Connectome Project (HCP) WU-Minn HCP 1200 Subjects Data Release (Van Essen et al., 2013) (for further information on details of data acquisition and processing in this sample please see: https://www.humanconnectome.org/study/hcp-young-adult/document/1200-subjects-data-release).

All 1064 subjects for whom BMI and DTI data were available were included in the present study. Additionally, in the HCP sample information on blood pressure and HbA1C, a glycated form of hemoglobin that informs about the three-month average plasma glucose concentration (measured as the ratio of glycated hemoglobin to total hemoglobin), were available. In both samples BMI was calculated as the body weight (in kilogram) divided by squared body height (in meters) ($mass_{kg}/height_m^2$). For demographic characteristics of both samples see Table 1.

2.2. DTI data acquisition

Data of the MNC sample was acquired using a 3T whole body MRI scanner (Gyroscan Intera, Philips Medical Systems, Best, the Netherlands). A circularly polarized transmit/receive birdcage head coil with an HF reflecting screen at the cranial end was used for spin excitation and resonance signal acquisition. The DTI data was acquired in 36 axial slices, 3.6 mm thick with no gap (acquired matrix 128 × 128), resulting in a voxel size of 1.8 × 1.8 × 3.6 mm^3. The echo time was 95 ms and the repetition time was 9473 ms. A *b*-value of 1000 s/mm^2 was used for 20 DW-images (20 diffusion directions), with isotropic gradient directions plus one non-DW ($b_0 = 0$) image. In sum, 21 images per slice were used for diffusion-tensor estimation. The total data acquisition time was approximately 8 min per subject.

Data for the HCP was acquired on a customized Siemens 3T "Connectome Skyra" housed at Washington University in St. Louis, using a standard 32-channel Siemens receive head coil and a "body" transmission coil designed by Siemens specifically for the smaller space available using the special gradients of the WU-Minn and MGH-UCLA Connectome scanners (Feinberg et al., 2010; Van Essen et al., 2012).

A full diffusion MRI session includes 6 runs (each approximately 9 min and 50 s), representing 3 different gradient tables, with each table

Table 1
Sociodemographic and clinical characteristics of the Münster Neuroimage Cohort study sample (MNC) consisting of 369 healthy subjects and the Humane Connectome Project sample (HCP) comprising 1064 healthy subjects.

	N	Mean	SD	Min	Max
MNC					
Sex (m/f)	369	183/186			
Age	369	39.39	11.24	20	59
BMI	369	24.65	4.08	18.17	42.21
HCP					
Sex (m/f)	1064	490/574			
Age	1064	28.75	3.68	22	37
BMI	1064	26.40	5.10	16.48	47.76
Systolic Blood Pressure	1052	123.38	13.79	87	185
HbA1C	741	5.23	0.37	1.32	9.6

Means, standard deviations (SD), minimal (Min) and maximal (Max) values are presented.