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Obesity Comorbidity/Pathophysiology

Compromised white matter integrity in obesity

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Summary

Obesity is associated with both structural and functional changes of the central nervous system. While gray matter alterations in obesity point to a consistent reduction with increasing body mass index (BMI), volumetric changes in white matter are more complex and less conclusive. Hence, more recently, diffusion tensor imaging (DTI) has been employed as a highly sensitive tool to investigate microstructural changes in white matter structure. Parameters of diffusivity and anisotropy are used to evaluate white matter and fibre integrity as well as axonal and myelin degeneration. Fractional anisotropy (FA) is the most commonly used parameter as it is the best estimate of fibre integrity. The focus of this review was on the relationship between obesity and brain alterations assessed by DTI. Altogether, these studies have shown a loss of white matter integrity with obesity-related factors, especially in tracts within the limbic system and those connecting the temporal and frontal lobe. More specifically, multiple studies found an inverse association between BMI and FA in the corpus callosum, fornix, cingulum and corona radiata in elderly and young adults as well as children. Furthermore, significant interactions were observed between BMI and age, pointing to accelerated ageing of white matter structure in obese.

Keywords: Brain, diffusion tensor imaging, obesity, white matter.

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Introduction

Obesity is a major public health concern because of its strong predispositions to numerous health conditions, as type 2 diabetes, cardiovascular disease and numerous cancers. In general, obesity is determined by the body mass index (BMI) and is associated with an excessive peripheral fat accumulation entailing changes in blood pressure, inflammation, dyslipidaemia and insulin resistance (1,2). However, changes in cognitive functions have also been shown in obesity including an increased risk for dementia and an accelerated cognitive decline in older age, with complimentary structural and functional brain changes (3,4).

For the obesity-related structural brain alterations, the focus in the past years has been mostly on changes in volume or density of gray (GM) and white matter (WM) assessed by magnetic resonance imaging. With the aid of voxel-based morphometry and tensor-based morphometry, structural changes in GM and WM volume/density can be differentiated and localized. Lower GM volume was distinctly shown with increased BMI, mainly in temporal, frontal and occipital lobes as well as in the cingulate and orbitofrontal cortex and also in the hippocampus, thalamus and midbrain (5–13). In frontal and limbic brain areas, this can already be observed in obese children and adolescents (14). In prospective studies, low GM volume in frontal regions, which are important for inhibitory control, was a predictor for future weight gain (11), and also GM volume in the insular cortex was identified to be especially affected in obesity-prone individuals (15).

Even though BMI is the most common measure to determine obesity, the risk to develop metabolic complications is more related to abdominal adiposity. Hence, recent studies

have used other obesity-associated factors like waist circumference, waist to hip ratio (WHR), the volume of fat-free body mass, abdominal subcutaneous fat (SAT) and visceral adipose tissue (VAT), body fat percentage and leptin, as a hormonal correlate of adipose tissue, to investigate obesity-related structural brain changes. These markers are inversely associated with total brain volume, in which VAT revealed the strongest association independent of BMI and insulin resistance (16). Additionally high body fat percentage and the volume of SAT was found to be associated with less GM density (17). Interestingly, fat-free mass, which is also increased in obesity, was significantly associated with a reduction in GM volume in temporal and frontal regions (18). Recently a more specific and direct measure of GM, cortical thickness, confirmed these obesity-related GM alterations. While mainly frontal and parietal regions showed cortical thinning with increased BMI (19,20), VAT correlated negatively with the insula and temporal cortex (21), which may indicate that especially abdominal adiposity has an adverse effect on brain regions vital for cognition.

Obesity-related WM volumetric alterations, reflecting macrostructural changes, show a more complex pattern, revealing a positive association with BMI in frontal, temporal and parietal lobes (10) and a negative relationship with the basal ganglia and corona radiata (11,12). The extensive larger WM volumes with BMI were found in older adults as well as adolescent (10,22). Interestingly, a 6-week diet partially reversed this effect (23). To clarify these findings, the microstructural composition and architecture of the WM have to be investigated. For this purpose, diffusion tensor imaging (DTI) has become of special interest to measure diffusion-weighted imaging data, which is highly sensitive to changes at the cellular and microstructural level (24).

In this review, we first describe the methodological background of DTI and then, in more detail, studies investigating the effect of obesity-related factors on WM integrity by means of DTI.

Methodological background of DTI

DTI quantifies and maps the rate and directionality of the three-dimensional diffusion of water within tissue (25). At the level of the voxel, as the basic spatial unit of magnetic resonance imaging, diffusion is represented by an ellipsoid, or more generally a tensor. When the rates of diffusion are similar in all three directions of the tensor, diffusion is isotropic, as observed in GM and cerebrospinal fluid (CSF), where water is moving randomly and equal in every direction. Whereas diffusion is considered anisotropic (directional), when the rate of diffusion is significantly different in magnitude for different directions (24). In regions with great physical obstructions such as axon sheath, axonal cell membranes and neurofilaments, water movement is bounded by a particular direction and diffusion is greater along the long axis of the fibre than across it. Anisotropy is highest in regions of compact, parallel-orientated fibre bundles such as the corpus callosum.

Parameters of diffusivity and anisotropy and their interpretation

Traditional DTI parameters include mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD) (Fig. 1, Table 1). Collectively, these parameters are indicators for WM microstructure; the most commonly used indices are MD and FA.

MD is the average rate of water diffusion independent of direction (17,26), decreasing with heightened myelination. It equals the apparent diffusion coefficient (ADC), which is a more traditional estimate of water diffusion (27,28). MD and ADC values are increased when water diffusion is less restricted by fibres, reflecting WM metabolism at a cellular level.

FA is most frequently used in DTI studies and is a measure of anisotropy, reflecting the coherence of the orientation of water diffusion independent of the rate of diffusion (Fig. 2) (29,30). The values of FA range between 0 and 1 on a normalized scale. FA values of 1 reflect increased directionality of diffusion, indicating that water moves in a perfect line because of constrains by surrounding barriers as axons and myelin, whereas a value of 0 indicates no barriers, and hence perfect spherical diffusion (29).To that extent, higher FA reflects greater WM integrity of the barriers constraining the directional diffusion of water. Thus, a reduction may indicate damaged or disordered WM and fibre structure caused by axonal loss or demyelization.

Both MD and FA are summary measures of WM diffusion; however, it is also possible to analyse the rate of diffusion along the individual axis of the tensor (eigenvector). The eigenvalue of the major axis (λ_1) of the tensor is called AD and measures diffusivity along this primary axis reflecting axonal integrity, whereas RD

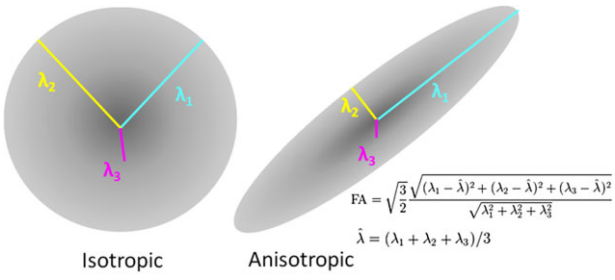

Figure 1 Graphical illustration of diffusion tensor imaging (DTI) parameters. λ_1 = axial diffusivity (AD); $(\lambda_2 + \lambda_3)/2$ = radial diffusivity (*RD*); $(\lambda_1 + \lambda_2 + \lambda_3)/2$ = mean diffusivity (*MD*).

Table 1 Interpretation of diffusion tensor imaging (DTI) parameters

DTI parameters	Definition	Potential meaning
Fractional anisotrophy (29,30)	Measures anisotropic diffusion Reflects the degree of directionality of water diffusion Values range between 0 and 1 on a normalized scale	Highest in regions of compact, parallel-orientated fibre bundles such as the corpus callosum Gives information about white matter integrity A reduction reflects damaged or disordered white matter and fibre structure caused by axonal loss or demyelization
Mean diffusivity (26,28)	Average of the three eigenvalues(λ_1, λ_2 and λ_3) Reflects the overall magnitude of diffusion Equals the apparent diffusion coefficient	Increased when water diffusion is less restricted by fibres Reflects white matter energy metabolism at a cellular level Decreases with heightened myelination
Axial diffusivity (24)	Eigenvalue of the major axis (λ_1) of the tensor Measures diffusivity along this primary axis	Reflects axonal integrity Increase can result from heightened fibre coherence or decreased axonal branching Decrease can results from axonal damage
Radial diffusivity (24)	Average of the eigenvalues of the two minor axes (λ_2 and λ_3) Measuring diffusivity perpendicular to the major axis of water diffusion	Reflects myelin integrity Increase can results from reduced myelin integrity of the membrane or sheath Decrease can results from increased level of myelination

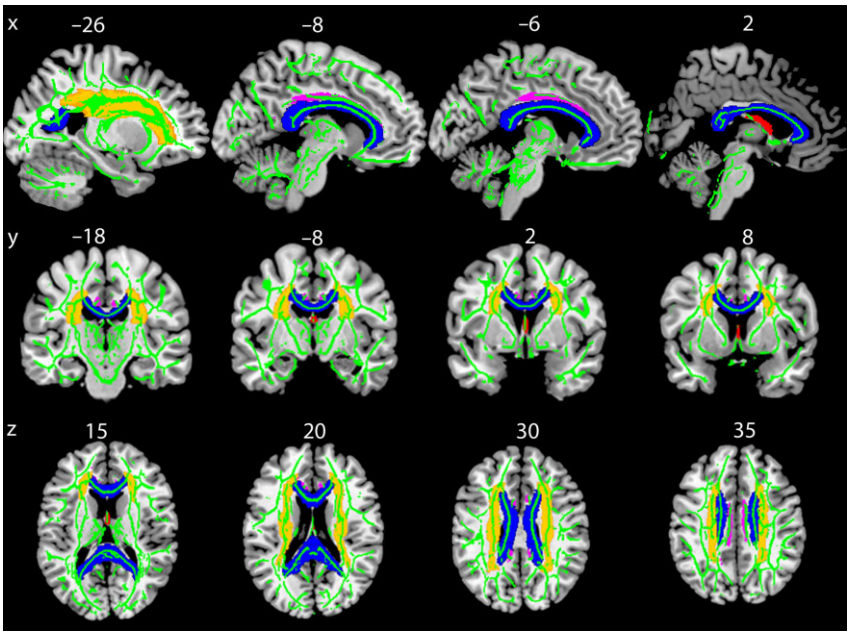

Figure 2 Major white matter tracts affected by obesity overlaid on a green fractional anisotropy skeleton (top row: sagital, middle row: coronal and bottom row: axial view of a standard brain) (blue: corpus callosum; magenta: cingulum; orange: corona radiate; red: fornix).

reflects myelin integrity and is the average of the eigenvalues of the two minor axes (λ_2 and λ_3), measuring diffusivity perpendicular to the major axis of water diffusion (30–32). Increased AD can result from heightened fibre coherence or decreased axonal branching (33), while axonal damage can lead to decreased AD. Reduced myelin integrity of the membrane or sheath results in higher RD, while increased level of myelination leads to decreased RD (31).

Especially in homogenous, anatomically characterized WM tissues, DTI is a very sensitive, but unspecific marker of neuropathology (24). Many studies have observed reduced FA in a broad range of diseases. In combination with all other diffusion parameters, more specific interpretation can be made. For example demyelination has been shown to increase RD without affecting AD. MD will increase with tissue water in oedema, while cell proliferation in neoplasia may decrease MD (for review see (24)),

which may alter FA in both cases. But also during normal brain development, DTI parameters are subject to change. While FA increases in WM tracts from birth to adulthood, MD values decrease primarily driven by decreasing RD. Furthermore, MD values become homogenous across the brain while FA values are heterogeneously distributed throughout the brain, showing the highest values in the corpus callosum and the lowest values in subcortical regions in the adult brain (34–36).

For more information about technical foundations and physical details see Beaulieu *et al.* (37), Basser *et al.* (38), Le Bihan *et al.* (39), Taylor *et al.* (40) and Mori *et al.* (41).

Tractography

Tractography is used to localize and quantify anatomical connections or pathways in the brain non-invasively and *in vivo* on the basis of the direction of greatest diffusivity of water (24). Fibre-tract trajectories can be estimated by following coherent local patterns in the major eigenvectors of the tensor (42). Tracking starts from a seed voxel propagating a line according to the major eigenvector and its direction is re-evaluated voxel by voxel throughout the brain. There are two major approaches: deterministic tractography, which assumes a single orientation at each voxel, and probabilistic tractography, which assumes a distribution of orientations producing a connectivity matrix for each voxel. Hence, probability tractography has a greater variability and is more sensitive to detect crossing fibres delineating a greater portion of WM tracts, while deterministic tractography provides fewer connections with greater connectivity values (43).

DTI studies in obesity research

So far, there are only few studies employing DTI to investigate the influence of obesity on WM integrity. In general, two study types can be differentiated: first, studies that examined the relationship between BMI and DTI parameters by either performing group comparisons (normal-weight versus overweight/obese) or using BMI in a regression model and second, studies including further obesity-associated factors, for example inflammation, into their study design. These studies investigate DTI indices either on a voxel-wise whole-brain level or using a region-of-interest (ROI) approach by evaluating mean FA, MD, AD or RD values of specific tracts.

We searched the scientific databases PubMed and Google scholar for potential studies for the present review. The search was performed using the keywords obesity, obese and BMI each combined with the terms WM integrity and brain, DTI and diffusion-weighted imaging and brain, FA and brain, respectively. Cross-references from eligible studies were also examined for inclusion in the review. Studies had to investigate at least one obesity-related parameter as BMI, waist circumference, WHR or body fat distribution. We excluded studies investigating WM integrity in patients with type 2 diabetes, Prader–Willi syndrome, Alström syndrome, metabolic syndrome and psychiatric diseases.

Thus far, 19 publications (see supporting information) in total have examined the effect of obesity, including a wider range of associated factors as inflammation, hypertension and dyslipidaemia, on WM integrity in adults. Altogether, these studies have shown a loss of WM integrity in obesity revealing an inverse relationship between BMI and FA, the most commonly used parameter.

Effect of obesity on WM integrity of the corpus callosum

The corpus callosum is the largest WM structure in the brain, divided into the rostrum, genu, body and splenium, facilitating communication between the two hemispheres (Fig. 2). Multiple studies, using a voxel-wise whole-brain analysis or an ROI approach, identified a negative correlation between BMI and microstructural architecture of the WM, primarily in the corpus callosum in all age and BMI groups. More specifically, FA values, were reduced with increased BMI and WHR in the entire corpus callosum with the most predominant changes in the genu even after correcting for vascular and inflammatory markers (17,44–48). AD was also decreased throughout the corpus callosum in the splenium (46), genu (49) and body (45) while RD showed high values in the genu (46,48) and splenum (45). Together, these results indicate that obesity is mainly associated with axonal damage accompanied with demyelination in some parts of the corpus callosum.

In addition, Stanek *et al.* (44) identified an interaction between BMI and age within the corpus callosum in a sample of 103 healthy adults displaying a wide age range. While age was generally associated with lower FA in all brain regions, a significant interaction with BMI was only observed in the splenum and body of the corpus callosum increasing the loss of WM integrity in otherwise normal ageing (44).

Besides age, gender influences the effect of BMI on brain structure. Generally, there is a difference in WM integrity between men and women. Significantly higher FA values were found in men compared with women in the splenum of the corpus callosum (50). Interestingly, Müller *et al.* identified reduced FA values of the corpus callosum with increased BMI only in women (46).

Effect of obesity on the WM integrity of the fornix and cingulum

Besides the corpus callosum, ROI-based analysis investigated the effect of obesity on the fornix and cingulum, which

are the most prominent tracts within the limbic system (Fig. 2). The fornix is a C-shaped fibre bundle providing strong connections from the hippocampus to other brain regions. Four studies explicitly investigated the obesity-related effects on the fornix, revealing reduced WM integrity. Decreased FA values (44,47) together with increased RD and MD values (45,51) were observed pointing to demyelination in the fornix with increasing BMI. However, one study showed that this effect was diminished after correcting for vascular and inflammatory markers (47).

The cingulum is another C-shaped structure of WM fibres wrapped around the frontal and temporal lobe above the corpus callosum. The anterior part is important for the processing of emotions while the posterior region is involved in cognition. With increased BMI, a negative correlation was observed between FA values of the bilateral cingulum in a large sample of young lean college students and elderly adults (13,47,52). Intriguingly, while BMI was negatively associated with FA of the posterior cingulum segment, aerobic fitness assed by VO_2 peak positively correlated with FA of the middle cingulum segment. VO_2 peak is the maximal capacity of the cardiorespiratory system to take up and use oxygen and has been shown to have a beneficial effect on brain function improving a number of aspects of cognition (53). Hence the authors speculate that aerobic fitness improves oxygen delivery up-regulating the expression of neuronal growth factors improving WM integrity (52). Interestingly, in older adults as well as overweight children, aerobic fitness improved WM integrity in the frontal and temporal lobes after an exercise intervention (54,55). Hence the cingulum and other prominent structures within the temporal and frontal lobes are vulnerable to body weight as well as aerobic fitness.

Effect of obesity on whole-brain WM integrity

Reduced WM integrity with increased BMI has been observed in further regions of the brain, especially in studies with large sample sizes. Additionally, studies including also severely and morbidly obese participants showed more extensive compromise in WM integrity. Overall, connections within the limbic system and especially those connecting the temporal and frontal lobe are susceptible to obesity, which can already be seen in children (54) and adolescents (56). Also in elderly women, higher BMI was associated with lower FA in the WM of the temporal cortex and the corticospinal tract with a wide spread AD reduction, pointing to mainly axonal damage in obesity (49). Furthermore, in a group of subjects including morbidly obese patients, compromised WM integrity were more extensive with lower FA, from the corticospinal tracts, mammillary bodies, optic radiations and right inferior occipitofrontal fascicle, significantly correlating with BMI and percentage of body fat (17). Lower MD values, on the other hand, were identified in both uncinate fascicles and inferior occipitofrontal fascicles of mainly frontal regions in morbidly obese adults (17). Even though type 2 diabetes was not explicitly investigated in this study, 9 out of the 23 obese participants were diagnosed with type 2 diabetes. Hence the extensive WM alterations could be disease-related. Nonetheless, no correlations were observed with Hb1Ac and blood sugar (17).

In young to middle-aged adults, BMI as well as waist circumference were negatively associated with FA values in the inferior and superior cerebellar peduncle (48) and the corona radiata (48,57), which also showed increased AD values (45). The corona radiata is an extensive WM structure with large fibres carrying information from and to the cerebral cortex. Interestingly, a recent study investigating the effect of 16 obesity-related genes in mostly normal-weight young adults showed the strongest association between the obesity-risk gene *neural growth regulator 1* (*NEGR1; rs2815752*) and lower WM integrity (lower FA values), especially in the corona radiata (58). *NEGR1* is important for neural development and the risk allele has been associated with a higher BMI (59,60). In rats, reduced NEGR1 in the periventricular hypothalamic area has been shown to increase BMI (61). However in the sample of mostly normal-weight young adults, the reduced WM integrity of the corona radiata showed no association with BMI, pointing to a gene-related effect on WM integrity (58). Whether this association holds in an obese sample still needs to be investigated.

Furthermore, FA values of the corona radiata were positively correlated with dyslipidaemia (48). While obesity and global inflammation were related to a wide spread reduction in FA values, vascular physiological factors as dyslipidaemia and blood pressure related to localized higher FA, suggesting competing effects of these factors on WM integrity (48). On the contrary, in another study including participants with obesity but not diabetes, dyslipidaemia resulted in reduced and not increased FA values in prefrontal regions (62). However, for individual groups (normal-weight versus overweight/obese), the negative association with the cholesterol profile was only significant for the overweight/obese group (63).

As dyslipidaemia, blood pressure also correlated positively with WM integrity, but mainly in the internal and external capsules (48). However, further studies investigating the effect of systemic blood pressure revealed reduced WM integrity (i.e. lower FA accompanied with higher MD values) especially in the corpus callosum and inferior fronto-occipital tract in young healthy adults (64). Hence, the effect of vascular physiological factors on WM integrity are currently difficult to interpret.

Dyslipidaemia, elevated blood pressure and blood glucose and abdominal adiposity are widely recognized risk factors for metabolic syndrome. Indeed, these factors were

identified as independent factors on WM microstructure in patients with metabolic syndrome (65), especially in the corpus callosum, external capsule and frontal lobes (66). Individuals with these risk factors commonly manifests a pro-inflammatory state (67), which is associated with a widespread drop in WM integrity with increased inflammation markers as interleukin-6 and C-reactive protein, displayed by reduced FA values throughout the brain (48,68). Generally, in the central nervous system, pro-inflammatory cytokines can affect cell integrity by a local inflammatory response in the microglia contributing to brain atrophy, reduced GM volume (69,70), increasing tissue water and therefore increasing MD, which can result in reduced FA. Furthermore, BMI was no longer significantly associated with the body and splenum of the corpus callosum and the fornix after controlling for vascular blood marker and inflammation; however, the negative association between BMI and FA values in the genu of the corpus callosum and cingulate fibres remained significant (47).

Interestingly, a low-grade inflammatory response is produced particularly by white adipose tissue. However, the effect of fat distribution (including visceral and subcutaneous fat) and obesity have hardly been investigated on WM integrity. Individuals with abdominal adiposity, showing increased VAT, have an enhanced risk for metabolic complications (71). Indeed, reduced GM volume exclusively in cerebellar areas in young adults were observed with increased VAT (72) and reduced GM density was observed with SAT (17) and fat-free mass (18). Total brain volume showed the strongest negative association with VAT independent of BMI, but not C-reactive protein, which attenuated the association (16). Hence inflammation provides a possible link between obesity and reduced WM integrity. Nonetheless, these studies identified changes in volume and not WM integrity with body composition in obesity. Hence, further studies are needed to investigate specific changes in WM integrity as assessed by DTI with changes in fat and fat-free mass.

Effect of obesity on WM paths using tractography

The effect of obesity on key fibres paths were determined only in a few studies by means of deterministic (13,51,54,73) and probabilistic tractography (57). In older adults, increased BMI was associated with reduced fibre bundle length exclusively in the temporal lobe (73), a region especially vulnerable in the development of Alzheimer's disease, which is known to have an increased prevalence in individuals with increased BMI (3). Moreover, already in young healthy adults, the association between fewer tracks passing the midcingulate cortex with BMI (13) was mediated by cognitive processes (i.e. decision-making ability). Fibres connecting frontal and temporal lobes, as the uncinate fasciculus, also showed disrupted integrity in obesity with improved integrity after an 8-month exercise intervention in overweight children (54,57). Similarly, patients with type 2 diabetes show consistent decrease in multiple brain areas especially in temporal and frontal regions (74,75) with strong correlations to cognitive functions (76,77). These results indicate that obesity-related WM alterations are already present in young healthy children and adults, and normal ageing could potentially be exacerbated by obesity. Yet, these findings could also reflect the adverse effect of increased BMI on brain development, emphasizing the need for longitudinal studies.

Limitations

The current lack of longitudinal studies is a major limitation for the interpretation of the reported microstructural changes in obesity. Hence, no conclusion can be made whether compromised WM integrity is present in individuals prior to becoming obese. Also, studies investigating WM integrity in children are not conclusive. While some obesity-related changes were identified especially in temporal regions (54,56), Alosco *et al*. (14) found no association between FA and BMI in 120 children and adolescent. Furthermore, the complexity of obesity-related factors, as inflammation and dyslipidaemia, could result in competing influences on the DTI indices. The specificity of DTI may be improved by combining with other techniques as quantitative multiparametric imaging to explore specific brain tissue properties, as myelin, water or iron content (78).

Furthermore, changes in FA are unreliable where fibres mix (signal mixing of GM, WM and CSF) (79), as FA depends on one dominant fibre direction. Hence FA may be lowered because the local fibre architecture is less coherent and not because of less WM integrity (80–82). So in areas of crossing fibre tracts reports of altered FA must be treated with caution. New diffusion imaging methods as Q-ball imaging or high angular diffusion imaging, which require higher diffusion weighting and more measurement time, seem promising to resolve this problem (24).

Summary and outlook

A number of cross-sectional DTI studies, investigating obesity-related changes in WM integrity, have been published over the last years revealing compromised WM integrity with obesity-related factors in one or more regions, mostly showing reduced FA. These results indicate that WM microstructural changes are already present in children and early adulthood as well as in older adults. Interestingly, BMI related WM alterations were observed in normal-weight and obese participants, but to a larger extent in the latter. Moreover, significant interactions were observed between BMI and age. Hence obesity could

potentially accelerate the normal ageing process. Given the fact that the elderly population will continue to increase, longitudinal studies are needed to evaluate the effect of obesity on WM integrity over a lifespan.

Conflict of interest statement

No conflict of interest was declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12248

Supporting Informtation. Summary of diffusion tensor imaging (DTI) studies investigating obesity-related changes in white matter integrity

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