A systematic review of diffusion tensor imaging studies in obesity

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Abstract

Obesity is a major global health problem leading to serious complications. It has been consistently associated with alterations in brain structure. One of the increasingly popular techniques to examine white matter structure is Diffusion Tensor Imaging, which allows to assess the dynamics of water diffusion. Fractional anisotropy and mean diffusivity are two main parameters measuring the directionality and rate of diffusion. Abnormal changes in these indices associated with obesity have been previously reported in numerous fiber tracts. This systematic review investigates microstructural white matter alterations in obesity using Diffusion Tensor Imaging. Computerized search based on the inclusion/exclusion criteria identified 28 studies comparing individuals with obesity and lean controls. The majority of included studies reported decreased

fractional anisotropy and increased mean diffusivity associated with obesity, suggesting white matter abnormalities that might contribute to weight gain. However, a pattern of alterations is still highly inconsistent across studies. Therefore, additional techniques such as a direct assessment of the extent and distribution of body fat is recommended for a more accurate characterization of brain-body relationship.

Abbreviations

BMI = Body Mass Index; VBM = Voxel-Based Morphometry; GM = Gray Matter; ACC = Anterior Cingulate Cortex; WM = White Matter; DTI = Diffusion Tensor Imaging; MRI = Magnetic Resonance Imaging; MD = Mean Diffusivity; ADC = Apparent Diffusivity Coefficient; FA = Fractional Anisotropy; AD = Axial Diffusivity; RD = Radial Diffusivity; WC = Waist Circumference; ROI = Region Of Interest; WHR = Waist-to-hip ratio; UF = Uncinate Fasciculus; CG = Cingulate Cortex; SLF = Superior Longitudinal Fasciculus; ILF = Inferior Longitudinal Fasciculus, IFOF = Inferior Fronto-Occipital Fasciculus; CC = Corpus Callosum; AC = Anterior Commissure; PC = Posterior Commissure; CT = Cortico-Spinal Tract; CBT = Cortico-Bulbar Tract; IC = Internal Capsule; EC = External Capsule; SCP = Superior Cerebellar Peduncle; MCP = Middle Cerebellar Peduncle; ICP = Inferior Cerebellar Peduncle; CR = Corona Radiata; ML = Medial Lemniscus; ATR = Anterior Thalamic Radiation; PTR = Posterior Thalamic Radiation.

Introduction

Obesity affects about 13% of the world's adult population. According to the World Health Organization (WHO[1]), approximately 11% of men and 15% of women were obese in 2016. The prevalence of obese and overweight has risen dramatically since 1975, and if the current tendency continues, by 2030 around 57% of the world's population will be either overweight or obese [2]. Globally, increased high-caloric food intake and reduced physical activity are two major hazards that promote obesity at a very young age predisposing to the risk of numerous comorbid conditions and higher mortality in mid- and late-life [3,4]. Obesity-associated complications may include cerebrovascular disease, type 2 diabetes mellitus, hypertension, several types of cancer, and dementia. Various neurological and psychiatric conditions have been consistently linked to structural alterations of the brain, which is also true for obesity. Multiple brain imaging studies showed altered activity in the reward circuitries that may predispose an individual to abnormal eating behavior and weight gain [5,6]. Although neuroimaging is a promising tool for detecting and examining brain abnormalities underlying obesity, causal links between brain alterations and obesity are still not clear.

Macrostructural Gray and White Matter Changes in Obesity

The most common measure used to classify the degree of obesity is Body Mass Index (BMI, kg/m^2). Numerous studies report associations between elevated BMI and volumetric brain changes in humans using volumetry and Voxel-Based Morphometry (VBM) approaches. Several studies reported volumetric gray matter (GM) reductions associated with increased BMI in the basal ganglia structures, as well as the orbitofrontal cortex, insula, amygdala, hippocampus, and anterior cingulate cortex (ACC)[7,8]. These brain areas have been previously associated with reward, emotion processing, memory and motivation, as well as impulse control and decision-making [9]. Previous meta-analyses on GM alterations in obesity suggest that degeneration in these brain regions may underlie impaired internal feedback within the circuits associated with reward, emotion, and impulse control and, therefore, contribute to weight gain [10–12].

Long considered to be of little importance, the role of white matter (WM) has recently gained significant recognition. Overall, compared to existing studies on GM changes in obesity, there is less evidence reporting volumetric WM alterations. Kennedy et al. showed reductions in WM volume associated with higher BMI in the anterior limb of the internal capsule and middle frontal gyrus [13]. The anterior limb contains fibers projecting from the thalamus to the frontal pole and ACC, as well as subcortical connections between the caudate nucleus and putamen [14,15]. Those fiber tracts are known to be involved in emotion processing, decision-making, and motivation. Moreover, reduced WM volume in the frontal lobe might explain a higher risk of developing dementia and cognitive decline individuals with obesity [16]. Inconsistencies in results and lack of research focusing on WM macrostructural abnormalities in healthy obesity limit the interpretation of existing findings. Besides, techniques investigating differences in brain volume/concentration are incapable of

assessing the microstructural changes in WM that may underlie obesity-related pathology. Diffusion Tensor Imaging (DTI) is an increasingly popular neuroimaging method that is capable of detecting subtle alterations in WM fiber tracts on a microstructural level.

DTI technique

DTI is a magnetic resonance imaging (MRI) technique used to assess microstructural changes in WM by measuring the diffusion of water molecules. The most frequently assessed DTI parameters are mean diffusivity (MD) also referred to as apparent diffusion coefficient (ADC) and fractional anisotropy (FA). MD or ADC reflects the mean water diffusion rate within a voxel and FA indicates the preferred orientation of water diffusion in a voxel [17,18]. FA values vary between 0 and 1, where higher values indicate the preference of water to diffuse in one direction (anisotropic diffusion), whereas low FA values suggest that water molecules can diffuse equally in all directions (isotropic diffusion). Diffusion in WM tracts is anisotropic, since it is restricted by axon fibers, while diffusion in GM and cerebrospinal fluid (CSF) is isotropic. [19,20]. Additional parameters that can be derived include axial (AD) and radial diffusivity (RD) reflecting the rate of diffusion along axonal fibers and perpendicular to axonal fibers, respectively. It has been proposed that altered DTI parameters may be associated with WM pathology e.g., axonal damage, demyelination, decreased fiber density [21,22].

DTI and obesity

A link between obesity and altered WM microstructure has been shown by several studies, however, the results are highly diverse[23–28]. FA reductions in several major WM fiber tracts have been linked to numerous cognitive processes including reward-related behavior, cognitive and inhibitory control, or memory and decision-making[8,29–34]. On the other hand, higher BMI or waist circumference (WC) was associated with increased FA in several studies [28,35]. Moreover, reported WM tracts vary across studies, which makes it challenging to interpret the pattern of alterations.

Several factors could contribute to such mixed findings. One possible explanation is the type of sample examined. In particular, sex-dependent differences in WM microstructure using DTI were indicated by multiple studies. Shin et al. showed higher FA values in CC of healthy men compared to women [36]. Other studies suggest that the degree of myelination, axonal fiber density, and axonal diameter as major modulators of FA vary between men and women[37–39]. Another crucial factor is age. The majority of studies investigating age-related differences in DTI parameters report a negative association between FA and age accompanied by lower cognitive performance [40–42]. Commonly reported areas affected by aging mainly include CC and prefrontal WM [43]. Although correction for age-related effects is a standard analysis step, one should be cautious when interpreting studies conducted in older individuals or children/teenage samples only. Furthermore, the specific data analysis approach might also contribute to the heterogeneity of results. DTI measures are commonly extracted by defining specific anatomical regions of interest (ROI) or by applying a whole-brain analysis. ROI-based analysis is a hypothesis-driven approach and is based on the manual or automatic delineation of *a priori*specified brain regions. Whole-brain analyses can be performed by applying voxel-based analysis or tract-based spatial statistics. This approach is hypothesis-free assuming that structural changes can be observed anatomically anywhere in the brain. Since the choice of ROIs is subjective, interpretation of ROI studies results can be limited. Moreover, the examination of only specific brain areas strongly constrains comparability across ROI and whole-brain studies[44,45]. . Additionally, studies examining samples with a wider range of BMIs consistently demonstrate a relationship between the severity of obesity and DTI measures. Specifically, individuals suffering from morbid obesity display significantly lower FA compared to overweight subjects [24,46].

Obesity-associated complications may further contribute to altered WM microstructure. Studies assessing microstructural brain alterations in individuals diagnosed with type 2 diabetes revealed WM abnormalities in several association fiber tracts including inferior and superior longitudinal and uncinate fasciculi (ILF, SLF, UF) [47]. Although numerous DTI studies point out the importance of obesity-associated comorbid conditions, there is only limited evidence on WM microstructure in "healthy" obesity in comparison to the

related disorders.

Aims

While the DTI method has been proven a powerful tool in detecting subtle microstructural WM abnormalities in obesity, existing results are inconsistent across studies due to aforementioned factors. The current paper therefore aims to systematically review the DTI studies reporting structural alterations in individuals suffering from obesity with no history of neurological or psychiatric conditions compared to healthy lean control subjects.

Methods

Full systematic searches on PubMed and Livivo databases were performed using the following search items: "obesity" OR "obese" OR "overweight" OR "body mass index" OR "waist circumference" OR "waist-to-hip ratio" OR "body mass" AND "diffusion tensor imaging" AND "white matter". 390 articles were identified in the first step. After the removal of duplicates, the titles and abstracts of the remaining 272 articles were screened, 214 studies that did not match the inclusion criteria were excluded. The remaining 58 articles were fully screened and 30 studies were excluded for reasons stated in the PRISMA Flow Diagram (see Figure 1). In the end, we included 28 articles that met the following inclusion criteria: 1) compared healthy controls and subjects with overweight/obesity; 2) used subjects with no metabolic or psychiatric disorders 3) used DTI to assess WM 4) was published as an original paper 5) was published in English.

Additionally, once the information on WM tracts had been extracted from the included studies, the IIT Human Brain Atlas (v.5.0) was used to uncover probable GM regions that are connected through reported WM tracts (www.iit.edu/~mri). Most frequently reported WM tracts were used to generate ROIs in an IIT space using the mean FA template. The "regionconnect" algorithm was used to integrate information across selected WM ROI voxels and generate probable pairs of GM regions connected through that ROI[48]. The analysis was performed in FSLeyes (FMRIB, University of Oxford, UK) using ICBM-DTI-81 white-matter labels and JHU white-matter tractography atlases.

3. Results

3.1. Sample types and DTI approach

Twenty-one out of twenty-eight retrieved studies[23–28,32,33,46,49–59] used samples of adults. Five studies [60–64] were performed on adolescents between 12 and 19 years, and two studies [65,66] were performed on children between 7 and 11 years. Twenty-six studies[23–28,32,33,46,50,52–54,56–58,60–69] used a sample composed of both men and women, while two studies[59,70] were performed on women only. All selected studies used a cross-sectional approach. The majority of the studies (n = 22) [23–26,32,46,49,51,52,55–66,70] used BMI as a measure of obesity, while the rest used WC (n = 1) [28], total body fat percentage (n = 1) [27], both BMI and WC (n = 3) [33,50,54], or both BMI and waist-to-hip ratio (WHR (n = 1)) [53].

Across selected studies, twenty studies[23–28,32,50–53,55,58,61–65,67,70] performed a whole-brain analysis, four studies [56,57,60,66]utilized an ROI approach, and four studies [33,46,54,59]used both approaches. An overview of the included studies is presented in Table 1.

3.2. Relationship between obesity and FA

The findings from studies included in this review will be divided into the following categories: "decrease in FA/increase in FA/no differences in FA" and "decrease in diffusivity coefficients/ increase in diffusivity coefficients/no differences in diffusivity coefficients". Note that some of the studies indicate mixed results and can therefore be found in more than one category. The results will be further subdivided into three major fiber pathways classified based on their course and connections within the brain: association, commissural, projection & thalamic pathways. The summary of DTI findings across selected studies is represented in Table 2.

3.2.1. Decrease in FA

Overall twenty studies[23–27,32,33,46,49–54,56,59–62,66,70] indicated significantly reduced FA in subjects with obesity compared to healthy controls.

3.2.1.1. Association fibers

Association fibers are axon fibers that connect different cortical areas within the same hemisphere. Major association pathways include the following: uncinate fascicle (UF) connecting frontal and temporal lobes; cingulum (CG) connecting cingulate gyrus and entorhinal cortex; superior longitudinal fasciculus (SLF) passing from occipital to frontal lobe; inferior longitudinal fasciculus (ILF) connecting occipital and temporal lobes; inferior fronto-occipital fasciculus (IFOF) connecting temporal and frontal lobes.

Fourteen out of twenty studies[23,25,27,32,49,52–54,56,59–62,70] associated a greater degree of obesity with a decrease in FA within CG[23,25,49,52], IFOF [27,32,35,70], UF[30,35,56,70], SLF [23,30,62,70], ILF[23,32,53,62], temporal stem [59,61], superior temporal WM [59], nucleus accumbens fibers[54] (see Figure 2).

3.2.1.2. Commissural fibers

Commissural fibers are axon fibers that connect two hemispheres and are comprised of corpus callosum (CC), anterior commissure (AC) and posterior commissure (PC). Ten out of twenty studies[24,26,27,32,33,46,52,53,60,61] reported significantly lower FA in subjects with obesity compared to healthy controls in CC (see Figure 3).

3.2.1.3. Projection & thalamic fibers

Projection and thalamic pathways are white matter tracts that connect the cortex with subcortical structures, e.g., thalamus, midbrain, spinal cord, etc. Major fibers connecting cortex and spinal cord include the cortico-spinal tract (CT), cortico-bulbar tract (CBT), internal capsule (IC), external capsule (EC), superior, middle, and inferior cerebellar peduncles (SCP, MCP & ICP), corona radiata (CR), medial lemniscus (ML). Fiber tracts connecting the thalamus to the frontal lobe, as well as parietal and occipital lobes are anterior and posterior thalamic radiations (ATR & PTR), respectively. The fornix, originating in hippocampus and connecting it to different subcortical structures such as thalamus, hypothalamus, septal nuclei and nucleus accumbens, is also considered a projection fiber.

Twelve studies [23,25,27,32,33,50,53,59,61,66,68,70]reported significant FA reductions within the following projection and thalamic pathways: CT [23,27,50,59] and CBT[59], SCP [25,33,53,66,70],

ICP [33,66], MCP [25,51], IC[25,32,53,61], EC [53,61,70], CR[25,33,53,70], ATR [30,70], PTR[23,32,53,61], fornix [26,52], brainstem[50], lemniscus, and infundibulum [25](see Figure 4).

3.2.2. Increase in FA

Four out of twenty-eight identified studies[25,28,60,65] reported elevated FA in participants with obesity compared to lean controls.

3.2.2.1. Association fibers

All four studies [25,28,60,65] reported increased FA in the following association fiber tracts: ILF [25], SLF[28,65], CG [28,60], IFOF[60,65].

3.2.2.2. Commissural fibers

Three studies [25,28,60] reported increased FA in genu, body and splenium, rostrum and genu of CC, accordingly.

3.2.2.3. Projection & thalamic fibers

Four studies [25,28,60,65] associated obesity with higher FA in the following WM tracts: CT [60], MCP and SCP [25], SCR [28,65], IC[28], EC [28].

3.3.1. No differences in FA

Six out of twenty-eight studies [54,55,57,58,63,64] did not indicate any significant differences in FA between subjects with obesity and healthy lean controls.

3.4. Relationship between obesity and diffusivity coefficients

Overall, seventeen out of twenty-eight studies[23–25,27,28,33,46,55,57,59,60,62,64–66,68,70]reported altered diffusivity parameters related to obesity. Four studies reported MD/ADC [25,27,66,70], eleven studies reported MD/ADC, AD and RD [23,24,28,46,51,55,57,60,62,64,65], and two studies reported only AD and RD indices in addition to FA[33,59].

Note that one study [65] reported a general reduction in RD, one study reported increased RD [33] and one more study [28] indicated a significant reduction in MD, AD, and RD throughout the brain, but WM fiber tracts were not specified.

3.4.1. Decrease in diffusivity coefficients

Two out of fifteen studies [27,46] reported decreased MD/ADC in subjects with obesity. Seven studies[24,28,46,55,58,59,68] indicated reduced AD and three studies [28,58,68] indicated reduced RD.

3.4.1.1. Association fibers

Two studies reported a decrease in diffusivity parameter[27,59] in the following fibers tracts: AD in bilateral AF, right UF and left SLF; AD in the right orbital, inferior and superior WM and temporal brainstem in the same study but using a ROI approach [59], MD in IFOF and UF [27].

3.4.1.2. Commissural fibers

Five studies [24,46,55,58,59] reported a reduction pattern in diffusivity parameters in the following commissural pathways: AD in left body of CC [24], AD in genu of CC[59], ADC in splenium of CC and AD in the entire CC[46], AD in forceps major [55], RD in the entire CC [58].

3.4.1.3. Projection & Thalamic fibers

Only two studies [51,59] reported significantly reduced diffusivity coefficients in the following WM tracts: AD in anterior IC, bilateral superior CR, superior and inferior CP [59] ; RD in the right MCP, AD and MD in bilateral CT and anterior TR[68].

3.4.2. Increase in diffusivity coefficients

Overall, eight studies [24,46,51,57,59,60,62,70]indicated an elevated diffusivity in WM. Five studies identified elevated MD/ADC [24,57,60,68,70] and RD[24,46,59,60,62], and four studies identified increased AD [24,51,57,60].

3.4.2.1. Associations fibers

Six studies [24,51,59,60,62,70] reported increased diffusivity coefficients in the following association tracts:

RD in SLF [63], AD in the right SLF[24,51], and MD in the right SLF [51] ; RD in right superior temporal and left medial tempoparietal WM[59] ; ADC in the right IFOF [70] ; ADC in ILF [70] and RD in ILF [63] ; MD in the right UF; AD in the left CG and left UF; RD in the right UF[60].

3.4.2.2. Commissural fibers

Four studies [24,46,57,60] reported an increase in diffusivity coefficients in the following commissural tracts: MD in the left and right splenium of CC [24] and RD in splenium of CC [24,46]; RD in genu of CC [46] ; AD in anterior frontal and orbital CC and RD in superior and orbital frontal CC [60] ; MD in fornix [24,57]and AD in fornix [57].

3.4.2.3. Projection & thalamic fibers

Three studies [24,60,70] reported increased diffusivity parameters in the following projection & thalamic fiber tracts: AD in CR [24] and ADC in superior CR [70] ; MD and AD in the left CT [60].

3.4.3. No differences in diffusivity coefficients

Only two out of sixteen studies did not find any differences in diffusivity measures between individuals with obesity and lean subjects[23,64].

3.5. GM connections

Most frequently reported WM clusters were used to examine probable pairs of GM projections passing through defined ROIs (see Table 3). The probability that a WM fiber passing through a voxel of defined ROI belongs to the pair of GM connection is expressed in percentage. Several possible pairs of GM are displayed for each ROI with the probabilities arranged in descending order.

3.6. Covariate correlations

3.6.1. Sex

Out of nine studies [23,27,33,46,52,57,60,66,68]examining the effect of gender on the DTI parameters, seven did not report any significant differences[23,27,33,52,57,66,68]. One study [60]found increased FA in men with obesity compared to women in the orbitofrontal tract of CC, left CG, the occipital portion of right IFOF, and decreased FA in left IFOF and superior frontal tract of CC. The same study detected decreased FA in women with obesity compared to men in the orbitofrontal portion of left UF and middle and temporal right UF. A separate study [46] indicated reduced FA in the entire CC in women with obesity but not in men.

3.6.2. Cognitive performance

Out of five studies assessing correlations between cognitive performance and BMI or DTI indices [30,56,59,61,62], one did not indicate any significant relationship with executive function or memory[56]. One study [57] associated elevated AD in fornix with higher free recall task scores, as well as elevated MD, AD, and RD in fornix with higher National Adult Reading Test scores. Another study [61] reported lower academic achievements in subjects suffering from obesity, particularly in spelling and arithmetic, as well as lower working memory performance and lower WRAML Attention-Concentration index. A separate study [53]indicated a negative relationship between WHR and memory performance. Similarly, the BMI percentile was inversely related to verbal and spatial memory accuracy and IQ [62]. Eventually, one study [59] on women with obesity associated lower AD in superior, inferior, and orbital frontal WM with reductions in executive functions and reduced memory was associated with increased RD in temporal stem and temporoparietal WM and decreased FA in posterior cingulate temporoparietal WM.

4. Discussion

4.1. Overall pattern of DTI changes

4.1.1. FA

Evidence from the reviewed studies suggests that there is a consistent pattern of microstructural WM changes in individuals with obesity compared to lean controls. Despite the high variability of results, the majority of studies associated reduced FA with a greater degree of obesity. This finding is, however, to be interpreted with caution, since little is known about the mechanisms underlying these alterations. FA is sensitive to the subtle cellular changes in WM, but it is not clear, which cellular constituents contribute to the changes in the DTI signal. Moreover, similar alteration patterns in DTI indices across various medical conditions may have different cellular mechanisms underlying the pathology. Alterations in FA metrics might have different neurobiological contributors such as demyelination and axonal loss/damage, on the one hand and inflammatory processes on the other hand [77].

Evidence from postmortem brain examination in humans with obesity revealed increased microglial activation suggesting neuroinflammation[78]. Moreover, obesity-induced neuroinflammation of the hippocampus in rodent models is associated with cognitive decline, which is consistent with obesity-associated cognitive deficits found in humans[79]. Inflammatory processes are linked to excessive extracellular free water volume and can be assessed in vivo by free water imaging [80]. It has been suggested that in obesity FA might be confounded

by inflammatory factors, however, existing evidence is limited. Furthermore, a separate study indicated lower axonal density in obese group suggesting that inflammatory factors further promote WM damage [81].

Overeating has been linked to addictive behaviors, since they share similar brain mechanisms. For example, both abnormal eating behavior and drug/alcohol abuse are associated with fewer dopamine D2 receptors. Thus, low dopamine activity might promote overeating and substance abuse to compensate for its rewarding properties [82]. A great deal of studies found an association between addictive behavior and abnormal WM changes, thus, considering obesity a result of addictive behavior might shed light on the underlying pathophysiology[82,83].

Altogether, it remains challenging to interpret FA findings of this review due to various pathologies that might underlie these alterations and their impact on WM microstructure. Therefore, incorporating techniques that assess specific WM properties (e.g., myelin content, axonal count, neuroinflammatory factors) is required to pinpoint sources of WM abnormalities and disambiguate the nature of FA alterations in obesity.

4.1.2. Diffusivity

When investigating pathology underlying altered WM microstructure, one should take into account both anisotropy and diffusivity metrics, since they are strongly interlinked. The pattern of diffusivity coefficients across included studies appears to be less consistent compared to FA. One of the reasons is that nearly one-third of the studies did not examine changes in diffusivity metrics. Half of those studies found no differences in MD/ADC and only a few studies reported an increase in these indices. However, despite highly inhomogeneous findings, about half of the studies reported decreased AD and increased RD along with reduced FA.

Reduction in FA caused by one of the factors discussed above is frequently associated with enhanced overall diffusivity due to the weakened directionality of diffusion. Such an alteration pattern has been observed in multiple sclerosis and schizophrenia[84,85]. However, similar to anisotropy, MD proves to have limited sensitivity to the type of changes in WM, whereas AD and RD display higher specificity to the WM microstructural components[86]. Greater diffusivity along the axon has been previously linked to neuronal maturation, while lower RD values have been observed in axons with thicker myelination. Thus, it has been suggested that AD is more sensitive to axonal injury, while RD rather reflects myelin related changes [100].

Overall, although FA and MD are the most frequently assessed DTI metrics, they provide little specificity of the microstructural WM abnormalities. Therefore, assessment of AD and RD might allow a better characterization of disease-specific WM changes. However, a lot of diseases show a more complex pattern of WM abnormalities, such as in MS. Therefore, it is still unclear, whether AD and RD relate to specific WM pathologies.

Interpretation of the diffusivity results of this review is challenging, since 1) little is known about microstructural brain alterations in obesity and 2) there is insufficient evidence from DTI studies to make inferences on the role of altered AD and RD. Thus, further quantification of diffusivity parameters is needed to determine, whether they can indeed be considered biomarkers of specific WM damage in obesity.

4.2.1. Projections to GM

The atlas-based analysis revealed that most of the selected WM clusters displayed connectivity within the frontal and temporal regions, particularly, superior frontal, middle frontal, and middle temporal areas, as well as subcortical structures, such as insula, putamen, and caudate. A recent meta-analysis on GM changes in obesity identified the largest GM reductions within the inferior frontal gyrus including insula[10]. This structure is a major component of gustatory cortex involved in the perception of taste and the control of appetite[87]. Several studies using functional MRI showed enhanced activation in the insular cortex in response to food cues in subjects with obesity relative to lean controls [88,89]. Furthermore, increased activation in the insular cortex in individuals with obesity has been observed during a drug- and food-craving[87,90]. This evidence suggests that reduced GM volume in this structure might promote abnormal processing of food cues and, therefore, contribute to weight gain. Another large cluster identified by Herrmann et al. is middle frontal

GM, which has previously been linked to working memory function [91]. Although only a few included studies examined the relationship between executive functions and WM integrity, several studies reported impaired working memory in subjects with obesity. Moreover, a separate fMRI study revealed increased activity in middle frontal GM during a food-related inhibition task, proposing that volumetric reductions in this region might contribute to impaired appetite control [92]. Changes in caudate and putamen, two components of the basal ganglia involved in reward processing, might further contribute to the disrupted functioning of the food-related reward circuitry [7].

4.2.2. Limitations

The majority of the included studies used BMI, WHR, or WC to characterize the degree of obesity. However, these indices may be inaccurate, since they use indirect ways to classify body composition. This, in turn, could potentially contribute to less consistent results across studies. Therefore, a more accurate delineation of body fat is required. Methods to quantify fat levels directly include bioelectrical impedance, air displacement plethysmography, as well as imaging techniques, such as MRI and computed tomography scan. Furthermore, although several studies suggest a link between the severity of obesity and brain alterations, the number of studies on subjects with grade 2 and grade 3 obesity is still limited. Although 7 out of 9 studies did not indicate any significant differences in DTI measures between men and women, this finding is difficult to interpret given the small sample sizes. Therefore, further subgroup analyses are required for a more comprehensive interpretation of brain changes in obesity with regard to severity, as well as age, gender, co-morbidities, and cognitive function.

4.2.3. Future Directions

The majority of studies investigating brain alterations in obesity use a correlational approach, however, correlations do not necessarily imply causation. Although studies have shown a causal relationship between obesity and brain changes, it still remains a matter of debate, whether brain abnormalities develop as a results of excess body fat, or whether brain changes promote weight gain. Intervention studies show that WM atrophy can be reversed by the effects of dieting and bariatric surgery[93]. Further, increase in GM volume in hippocampus and frontal lobe was observed following a 6-months physical exercise intervention [94,95]. Similarly, significant FA increase in WM tracts connecting temporal and frontal brain areas was observed after completing a 12-months aerobic exercise program[96]. Interestingly, changes in those brain regions have also been associated with normal aging, suggesting that obesity might accelerate aging-related brain abnormalities. Although behavioral interventions prove to reverse obesity-related brain alterations, their effects differ depending on the type of diet or physical activity[97].

Further, a direct assessment of the amount and distribution of fat in the intervention studies might be beneficial for a more accurate delineation of the brain-body interplay. For example, quantification of different adipose tissue depots (e.g., visceral and subcutaneous fat) and different types of adipose tissue (e.g., white and brown fat) can identify, which adipose tissue depots are more sensitive to specific behavioral interventions. The amount of visceral adipose tissue has been associated with cardiovascular disease and type 2 diabetes, therefore, developing and improving interventions that selectively target visceral adiposity can reduce obesity-related complications [98].

4.2.4. Conclusions

In summary, the present review demonstrates structural WM alterations in DTI metrics associated with increased degree of obesity. Those alterations are mostly characterized by reduced FA and elevated MD. Reported WM tracts are associated with executive and inhibitory control, reward, memory, and emotion regulation, suggesting that impaired communication within these brain networks potentially makes one more prone to obesity. Future studies should further investigate causal links between brain structure and function and body composition to establish more effective strategies for reducing obesity-related complications and maintaining brain health.

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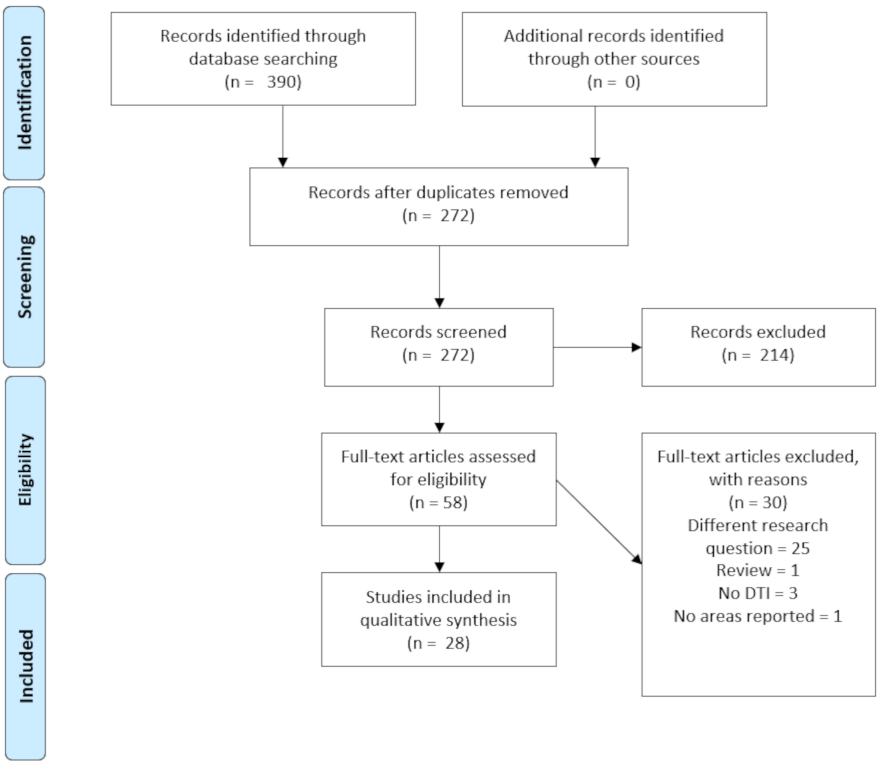

Figure 1: PRISMA 2009 Flow Diagram.

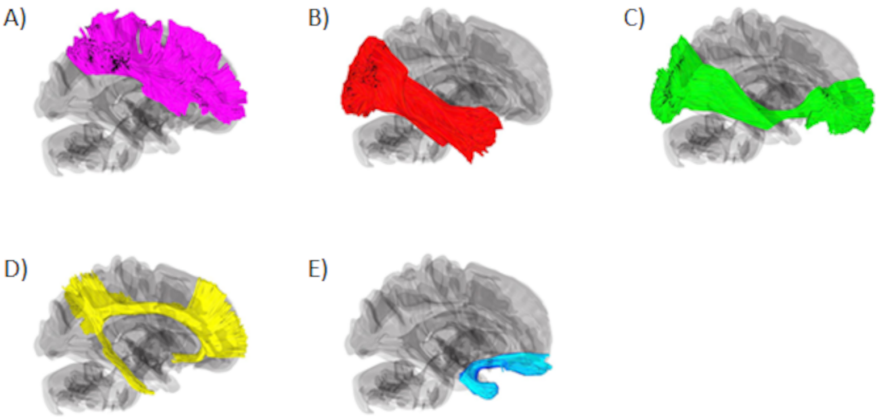

Figure 2: Association pathways. A) Superior longitudinal fasciculus. B) Inferior longitudinal fasciculus. C) Inferior fronto-occipital fasciculus. D) Cingulum. E) Uncinate fasciculus.

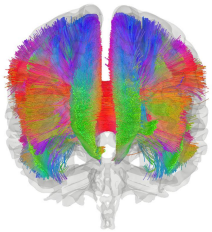

Figure 3: Commissural pathways. Corpus Callosum.

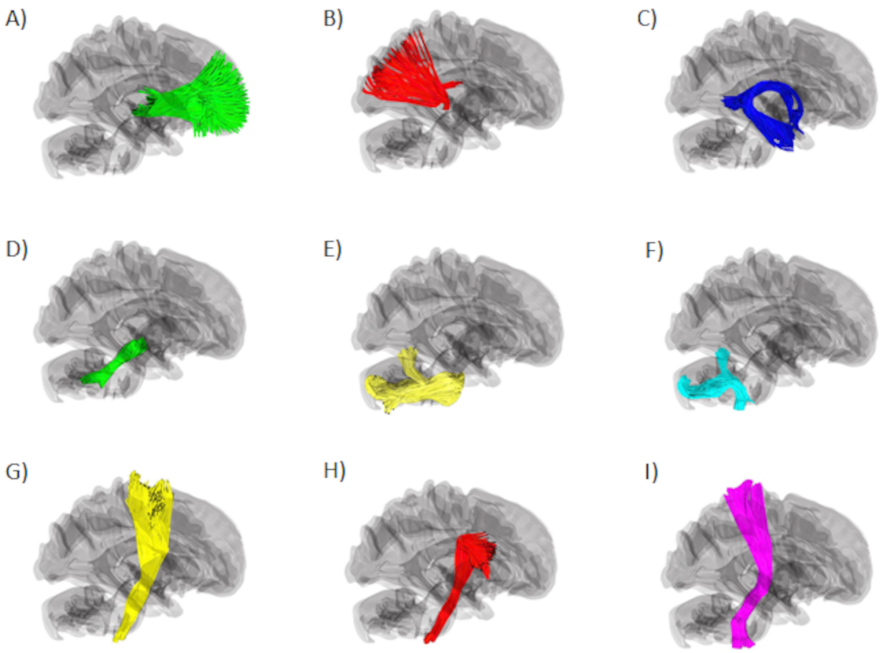

Figure 4: Projeciton & thalamic pathways. A) Anterior thalamic radiation. B) Posterior thalamic radiation. C) Fornix. D) Superior cerebellar peduncle. E) Middle cerebellar peduncle. F) Inferior cerebellar peduncle. G) Cortico-spinal tract. H) Cortico-bulbar tract. I) Medial lemniscus. Note that external and internal capsules are not represented in the HCP1065 tractography atlas. Posterior limb of internal capsule is a part of corticospinal tract.

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