Mechanisms linking obesity and its metabolic comorbidities with cerebral grey and white matter changes

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Abstract

Obesity is a preventable risk factor for cerebrovascular disorders and it is associated with cerebral grey and white matter changes. Specifically, individuals with obesity show diminished grey matter volume and thickness, which seems to be more prominent among fronto-temporal regions in the brain. At the same time, obesity is associated with lower microstructural white matter integrity, and it has been found to precede increases in white matter hyperintensity load. To date, however, it is unclear whether these findings can be attributed solely to obesity or whether they are a consequence of cardiometabolic complications that often co-exist with obesity, such as low-grade systemic inflammation, hypertension, insulin resistance, or dyslipidemia. In this narrative review we aim to provide a comprehensive overview of the potential impact of obesity and a number of its cardiometabolic consequences on brain integrity, both separately and in synergy with each other. We also identify current gaps in knowledge and outline recommendations for future research.

ABBREVIATIONS: BMI, body mass index; Cam-CAN, Cambridge Centre for Ageing and Neuroscience; FA, fractional anisotropy; FFA, free fatty acids; LBP, lipopolysaccharide binding protein; TG, triglycerides; TNF-alpha, tumor necrosis factor alpha; TOF, time-of-flight; T2DM, type 2 diabetes mellitus.

KEYWORDS: Body mass index; adiposity; vascular factors; metabolic; neuroanatomical; MRI

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1. Introduction

Obesity is defined as an excessive accumulation of adipose tissue in the body [1]. This excess of body fat tends to be biologically defended, which hampers successful weight loss in the long term and renders obesity as a chronic health problem [2]. Obesity is often accompanied by a state of low-grade inflammation and other cardiometabolic complications, namely hypertension, insulin resistance, diabetes mellitus type II, and dyslipidemia [1,3]. The cluster of abdominal obesity, hypertension, insulin resistance and dyslipidemia is referred to as the metabolic syndrome and it is an important risk factor for cerebrovascular disorders [4].

Obesity is traditionally measured using the body mass index (BMI), and individuals are categorized as obese when their BMI is equal to or exceeds 30 kg/m^2. However, the BMI sometimes fails to provide a good approximation of the cardiovascular risk associated with obesity. For instance, some individuals suffer from obesity-associated comorbidities (such as insulin resistance or low grade inflammation) despite having a BMI categorized as normal-weight [5]. It might be necessary to look at other adiposity-related indicators, such as waist circumference, waist-to-hip ratio, or lipid profile in order to study the effects of abdominal obesity and its complications [6]. For example, the combination of elevated waist circumference along with high concentrations of fasting triglycerides has been described as a good surrogate of abdominal fat deposition [6,7]. Unfortunately, neuroscientific research often fails to report an accurate characterization of obesity beyond the BMI.

Keeping in mind this limitation, obesity, or a high BMI, has been associated with diminished cerebral grey and white matter integrity in a number of cross-sectional as well as longitudinal studies [8,9]. However, the extent to which these findings can be attributed to obesity per se or to

its metabolic complications is still far from clear. The current review attempts to provide a comprehensive answer to this question. First, we will provide an overview of the neuroanatomical literature in obesity. Next, we will analyze the potential impact of each cardiometabolic factor on structural brain differences. Finally, we will highlight some open questions in the field for future research.

2. Method

In this narrative review, we looked for studies targeting the association between obesity and other metabolic comorbidities (inflammation, hypertension, diabetes, and dyslipidemia) and cerebral grey and white matter differences. We searched PubMed and Google Scholar combining the following keywords: obesity, body mass, adiposity, grey matter, white matter, white matter hyperintensities, inflammation, interleukin-6, interleukin-10, C-reactive protein, TNF-alpha, hypertension, insulin resistance, type 2 diabetes mellitus, HDL cholesterol, LDL cholesterol, triglycerides, dyslipidemia, atherosclerosis, and carotid stenosis. Studies were written in English and published between 2010 and 2021. The studies cited here were the ones deemed pivotal to the topic. Note however, that our search was not intended to be exhaustive and that some relevant papers might have been missed.

Throughout the paper, we will be referring to the distinction between cerebral grey and white matter. Grey matter contains neuronal bodies, unmyelinated fibers, and glial cells such as astrocytes and oligodendrocytes. It is in the grey matter where most synapses can be found and where most neuronal communication takes place [10]. White matter, on the other hand, is

composed predominantly of myelinated axons, which confers its pale color. Myelin sheaths enable the rapid transmission of electrical signals along the neuronal axon, supporting neural communication across brain regions [10].

2. Brain changes associated with obesity

Obesity has been associated with lower grey matter volume [11] and diminished cortical thickness [12]. The medial prefrontal cortex/orbitofrontal cortex, and temporal areas, such as the temporal pole, are some of the brain regions showing consistent reductions in volume and thickness associated with obesity in cross-sectional studies [8,13–17] (Figure 1A). Moreover, studies on obesity using longitudinal designs have also reported alterations in grey matter. For example, Franz et al., [18] (n=373) found that participants whose BMI increased steadily over the course of four decades showed thinner cortex in several frontal and temporal brain regions, compared to participants with a relatively stable BMI over time, when both groups were compared at age ~64. Similarly, longitudinal increases in BMI have been associated with grey matter reductions in structures such as the cingulate cortex, entorhinal cortex [9], and hippocampus [19,20]. Together, these longitudinal studies suggest that the negative effects of obesity on brain morphology accumulate over time.

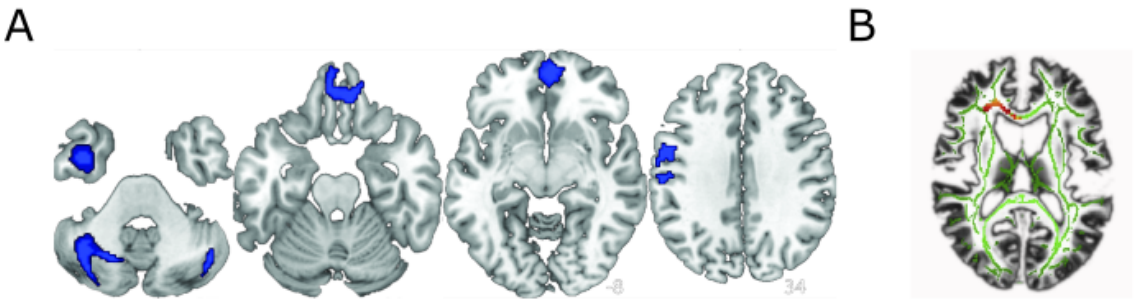

Fig. 1 Grey and white matter neuroanatomical differences associated with obesity-related measurements (such as BMI, waist circumference, waist-to-hip ratio, and body fat percentage). A) Meta-analysis results (21 studies, n=5882 participants) showing decreases in grey matter volume associated with obesity (figure adapted from García-García et al. [8]). B) Results of a meta-analysis (18 studies, n=4453 participants) showing that obesity was associated with lower fractional anisotropy (FA) values in the right genu of the corpus callosum (adapted from Daoust et al. [21], reproduced with editorial permission)

The findings presented here do not discount the possibility that some differences in grey matter structure might constitute risk factors, rather than consequences of obesity. Neuroanatomical differences in brain regions associated with the processing of food and other rewards, such as the medial prefrontal cortex/orbitofrontal cortex [22], could increase the risk for over-eating and weight gain, leading to obesity [23]. As such, some (cross-sectional) grey matter differences in obesity might be more plausibly regarded as causal agents of weight gain and obesity rather than as consequences of obesity. For example, Opel et al. [14] performed cross-sectional analyses in two independent samples (n=330 and n=347) and suggested that reductions in medial prefrontal volume could mediate the relationship between genetic risk for obesity and participants' BMI. To

reconcile some of the contradictory findings in the obesity literature, we suggested that the relationship between obesity and brain structure can be age dependent. Here, at a younger age certain brain changes can constitute a risk for the development of excess weight, while in older adults with chronic obesity, excess weight could lead to brain atrophy [24] .

Obesity has also been linked to white matter differences. The majority of studies (but see, e.g., [25] (n=168) for a negative result) report negative correlations between obesity-related measurements (such as BMI, waist circumference, waist-to-hip ratio, and body fat percentage) and fractional anisotropy (FA), a measure of white matter integrity [11,26,27] (Figure 1B). Results have been found in major white matter tracts, such as the corpus callosum [21], internal capsule, corona radiata, and superior longitudinal fasciculus [26], and indicate that obesity is associated with widespread reductions in white matter microstructural integrity (Figure 1B). Along similar lines, a recent study in 119 participants reported negative correlations between BMI or waist circumference and whole-brain myelin water fraction, suggesting that high body weight might be associated with lower myelin content [28]. Population studies in elderly individuals have additionally reported associations between obesity and macrostructural changes in white matter, such as white matter hyperintensities [11,20,29], which are a radiological marker of cerebral small-vessel disease [30]. For instance, Arnoldussen et al. [20] (n=286) showed that having an increased waist circumference (i.e., higher than 88 cm in women and higher than 102 in men) at baseline was associated with increased white matter hyperintensity load 9 years later. This result highlights that the potential role of abdominal obesity in demyelination, axonal loss, and small-vessel disease increases over time.

So far, we have shown that cross-sectional and longitudinal studies have related obesity with alterations in brain anatomy. The severity of these changes, however, range from subtle decreases in grey matter volume [8], to increased markers of cerebrovascular disease, with the devastating consequences that this entails [20,29]. Several factors might account for this heterogeneity of outcomes. The first one is the measurements used to quantify obesity. As aforementioned, BMI has its limitations as a predictor of obesity-related morbidity, and other indexes such as waist circumference or waist-to-hip ratio might prove a better indicator of abdominal obesity and its complications [6]. In addition, the effects of obesity on brain structure might be more marked at certain life stages, such as midlife. In this regard, Ronan et al. [31] analyzed a cohort of 473 participants aged 20 to 87 years old (belonging to the Cambridge Centre for Ageing and Neuroscience (CAM-Can) dataset) and suggested that the effects of obesity on white matter integrity might be largest at around 40 years old. Finally, obesity rarely occurs in isolation. Abdominal obesity can lead to a number of cardiometabolic complications, such as low-grade systemic inflammation, hypertension, dyslipidemia, and insulin resistance [3]. It is plausible that some of the neuroanatomical alterations associated with obesity might be attributed to its cardiometabolic consequences, which would act as intermediate factors. There is an increasing number of studies adopting this perspective and showing that cardiometabolic biomarkers mediate the link between obesity and its neuroanatomical outcomes (e.g., [27,29,32,33]). For instance, Morys et al., [32] (n~20,000) reported that obesity was associated with increased markers of cardiometabolic dysfunction, and that these markers were associated with prospective white matter hyperintensity volume. In turn, white matter hyperintensities were related to lower cortical thickness and diminished grey matter volume. At the same time, cardiometabolic factors might each exert harmful effects on brain anatomy that are independent of obesity [34]. In the following,

196 we explore these two possibilities further and analyze the potential impact of each cardiometabolic
197 factor on brain integrity, both separately and in synergy with obesity and other metabolic factors.
198
199 ## 3. Inflammation
200
201 Research over the past years has revealed that adipose tissue is a complex endocrine and metabolic
202 organ involved in energy homeostasis regulation [35]. In response to a chronic positive energy
203 balance, adipose tissue expands by increasing the size of mature adipocytes (adipose tissue
204 hypertrophy) and/or generating new adipocytes (adipose tissue hyperplasia) [6]. However, when
205 this adaptative response is sustained over time, the adipose tissue may reach a threshold at which
206 the adipocytes become dysfunctional leading to a limited lipid storage and reduced adipose tissue
207 expandability [35]. Adipose tissue dysfunction leads to ectopic fat deposition (fat accumulation in
208 the liver, skeletal muscle, heart, and pancreas) and represents one of the main mechanisms
209 underlying the link between visceral obesity and metabolic alterations including insulin resistance
210 [6,36]. Accumulating evidence suggests that the pathogenesis of adipose tissue dysfunction is
211 characterized by i) the enlargement of mature adipocytes (adipocytes hypertrophy) and impaired
212 adipogenesis; ii) increased number of immune cells infiltrating adipose tissue; iii) changes in the
213 cellular composition of adipose tissue and fibrosis; and iv) altered secretion of proinflammatory
214 cytokines [36]. It has been hypothesized that adipose tissue inflammatory response initiated and
215 sustained over time by adipose tissue dysfunction is involved in the systemic chronic, low-grade
216 inflammation associated with obesity (e.g. elevated systemic inflammatory cytokines including
217 interleukine-6 and high-sensitivity C-reactive protein) [6,36]. Obesity-associated inflammatory

responses have a harmful impact in many organs, including the brain [37], and it can potentially trigger insulin resistance [37–39].

Several studies in rodent models of diet-induced obesity suggest that hypercaloric diets induce neuroinflammation (e.g. activation of glial cells) in the hypothalamus, amygdala, hippocampus, cortex and cerebellum [40]. These increases in neuroinflammatory markers are often accompanied by decreases in synaptic density and by alterations in the rodents' behaviors (such as decreased spatial learning ability or increases in signs of anhedonia/depression) [40]. One possible mechanism to explain neuroinflammation is that hypercaloric diet induces disruption of blood brain barrier permeability [40]. Through this mechanism, the elevated levels of circulating inflammatory cytokines might trigger inflammatory processes within brain areas that control feeding behavior, energy homeostasis and cognitive function [40]. Interestingly, postmortem examination of brain from individuals with obesity also revealed hypothalamic gliosis and increased microglial dystrophy [41]. A recent study (n=141 healthy and non-diabetic individuals) also reported that higher BMI is associated with decreased mRNA expression of the anti-inflammatory cytokine IL-10 and increased mRNA expression of the pro-inflammatory enzyme iNOS in the frontal cortex [41].

Neuroimaging studies in humans have also investigated the association between obesity-induced chronic low-grade inflammation and alterations in grey and white matter. Cazettes et al. have examined the link between obesity-related inflammation and changes in brain structures involved in reward and eating behaviors in adult participants. They found, in participants with overweight and obesity (n=44), that increased levels of fibrinogen, a driver of inflammation, were associated with smaller lateral orbitofrontal volumes after controlling for age, hypertension, waist-to-hip ratio as well as lipid and glucose levels [42]. Another study in adolescents and young adults (aged 12

to 21 years old, n=65) first confirmed the existence of positive correlations between BMI and serum inflammatory markers. Subsequently, it showed that fibrinogen serum concentrations were partially explaining the association between BMI and lower cortical thickness in the lateral orbitofrontal cortex. Tumor necrosis factor alpha (TNF-alpha), another inflammatory cytokine, was partially explaining the relation between BMI and higher surface area in the superior frontal gyrus [43]. Peripheral inflammation does not necessarily translate into neuroinflammation. Nevertheless, results from these two studies suggest the possibility that increased serum levels of inflammation might be reflecting a general low-grade inflammatory state in participants with a high BMI or with obesity, which could in turn be involved in neuroanatomical differences. Both studies, moreover, seem to converge on showing results in the lateral orbitofrontal cortex, a region associated with compulsive eating patterns [44].

With regards to white matter differences, a strong positive correlation was also observed between fibrinogen levels and water diffusion coefficient in amygdala among participants with overweight and obesity [42]. In a sample of 733 middle-aged and older adults, Debette et al. found a negative association between visceral adiposity and brain volume independently of BMI [45]. This association was reduced after statistical adjustment for C-reactive protein, suggesting a potential role of systemic inflammation [45]. Using a large sample of neurologically healthy individuals (n=155), Verstynen et al. showed that adiposity-related metabolic alterations, including blood pressure, dyslipidemia (triglyceride and high-density lipoprotein levels), glucose homeostasis (fasting glucose and adiponectin levels) and inflammation (C-reactive protein and interleukin-6 levels) had more influence on white matter MRI measures than adiposity alone [27]. Interestingly, they found that systemic inflammatory score was the strongest mediator of the relationship between adiposity and white matter disruption (reduced fractional anisotropy) [27]. Other recent

studies have suggested that the relationship between visceral obesity and white matter alterations could be mediated by inflammation [29,46]. Using path analyses in a large sample (n=1,825 participants from the LIFE-adult study), Lampe et al. found that both waist-to-hip ratio and BMI contributed to higher deep-to-periventricular white matter hyperintensities via elevated interleukine-6 levels [29].

Other studies have examined the links between inflammation, white matter alterations and cognitive performance [46,47]. For instance, higher circulating levels of lipopolysaccharide binding protein (LBP), a specific obesity-related inflammatory marker, were associated cross-sectionally and longitudinally with lower fractional anisotropy values and with poorer working memory/short-term verbal memory (n=44) [47]. A recent study in 872 adolescents also showed that visceral adiposity-related systemic inflammation was associated with alterations in white matter microstructure and with lower processing speed [46]. A cross-sectional study in children with overweight and obesity (n=107) found negative and positive associations between inflammatory cytokine levels (interleukin-6, TNF-alpha, C-reactive protein) and regional grey and white matter volumes in small clusters, after statistical adjustment for sex, peak height velocity (i.e., an indicator of growth in adolescence), parental education university level, and BMI [48]. However, they did not find a significant association between inflammatory biomarkers and executive function.

Taken together, these findings suggest that obesity-associated inflammatory responses are related to disruptions in white matter integrity, cerebrovascular disease and, to a lesser extent, to changes in grey matter volume. These changes also appear to be linked to impaired cognitive performance.

4. Hypertension

Abdominal obesity confers a higher risk of hypertension [6]. Some of the mechanisms that have been proposed in order to explain the link between obesity and hypertension are increases in angiotensin II and aldosterone secretion [6], along with increases in sympathetic nervous system activity [49]. These mechanisms might lead to renal dysfunction and to elevated blood pressure in obesity [6,49].

Hypertension produces several changes in the morphology and function of the cerebral blood vessels. These changes include the formation of atherosclerotic plaques, increases in wall thickness, vascular stiffening, increments in the permeability of the blood-brain barrier, and endothelial dysfunction [50,51]. By facilitating the appearance of chronic hypoperfusion and vascular insufficiency, these alterations can increase the susceptibility of the brain to cerebrovascular diseases [50,52]. Indeed, hypertension is the most prevalent preventable risk factor for ischemic brain disease [53,54].

Hypertension has been associated with poorer outcomes in different indicators of brain health [55–58]. For instance, a population study (n=9722 participants from the UK Biobank study) showed that hypertension was associated with lower global measurements of grey matter volume and microstructural white matter integrity, as well as with greater white matter hyperintensity volumes. Elevated blood pressure during midlife is associated with increased risk of stroke [59], augmented white matter hyperintensity volumes, and decreased brain volumes in elderly individuals [60]. Moreover, hypertension has negative consequences on cognition, promoting the appearance of mild cognitive impairment and vascular dementia in aging [50,52]. Related to this, the vascular

damage caused by hypertension might promote the accumulation of amyloid protein underlying Alzheimer disease [61].

Some of the harmful consequences of high blood pressure in the brain might already appear in normotensive individuals. Some studies, for instance, have related subclinical-high systolic pressure with lower grey and white matter integrity in participants without diagnosed hypertension [33,62,63], indicating the possibility of a linear trend or a dose-dependent relationship.

The effects of high blood pressure on the brain are usually attributed to vascular damage and disruptions in cerebral blood flow [51,61]. We will refer to this mechanism more thoroughly in another paragraph. Moreover, studies suggest that the effects of hypertension on the brain might be described both as independent of and additive relative to other cardiometabolic factors. For example, the effects of hypertension on global atrophy and white matter hyperintensity volumes were statistically significant after adjusting for the presence of obesity, dyslipidemia, or type 2 diabetes mellitus (T2DM) [11], and hypertension, even in the absence of obesity and diabetes, is still a significant risk factor for cerebrovascular disease [50]. At the same time, the brain effects of hypertension might augment the deleterious effects of inflammation and diabetes mellitus [33].

5. Insulin resistance and type 2 diabetes mellitus

Insulin receptors are widely expressed in the brain in areas responsible for appetite regulation, cognitive function or autonomic activity [64]. Insulin regulates feeding behavior and energy homeostasis, but it also plays a role in processes specific to the central nervous system, such as neuronal survival, synaptic plasticity, memory, learning, and attention [64]. There is also evidence linking insulin resistance to neurodegeneration and cognitive decline. Although the literature

differentiates between peripheral and brain insulin resistance [65], both are highly interdependent and the exact contributions of each type of insulin resistance to neurocognitive consequences of adiposity are not known. What is known, however, is that it is likely that peripheral and brain insulin resistance work in a positive feedback loop. Recently, it has become clear that adiposity can lead to both peripheral and central insulin resistance [65].

There are several mechanisms by which obesity can lead to altered insulin signaling and insulin resistance. Most such mechanisms derive from the fact that adipose tissue is a secretory organ. Visceral adipose tissue releases free fatty acids (FFA) but also inflammatory factors, such as C-reactive protein, interleukins, or TNF-alpha [66–70]. An increase in blood level of these compounds leads to an increase in oxidative stress, which may drive both central and peripheral insulin resistance [64,69]. Interestingly, mechanisms that lead to insulin resistance are at the same time amplified by insulin resistance, which creates a positive feedback loop. For example, while inflammation can lead to insulin resistance, insulin resistance also increases inflammation [71]. In the same vein, oxidative stress, a common cause of insulin resistance, can also be caused by insulin resistance through a dysregulation of carbohydrate and lipid metabolism [71,72]. Interestingly, insulin resistance also leads to increased brain levels of phosphorylated tau protein and β-amyloid 42 - hallmarks of neurodegeneration and Alzheimer disease [71,73] - which are themselves also known to cause insulin resistance [74].

As such, brain insulin resistance was previously related to neurodegeneration and Alzheimer disease. This is because, in addition to leading to deposition of β-amyloid and phosphorylated tau, it can impact neurite outgrowth, impair neuroplasticity, or disturb neurotransmitter release and uptake [64]. On the other hand, peripheral insulin resistance may lead to neurodegeneration due to chronic hyperglycemia, hyperinsulinemia, or microvascular disease [73]. Animal studies show that

insulin resistance and T2DM are related to changes in hippocampal plasticity and decrease in neuronal densities in the hippocampus [73]. Studies in humans also show that adiposity, T2DM, and glucose levels are related to reductions in grey matter thickness, cerebrovascular disease, and disrupted white matter integrity [32,75,76]. A recent study by Morys et al. investigated a sample of over 20,000 individuals from the UK Biobank and showed that diabetes mellitus mediates the relationship between obesity and white matter hyperintensities, which in turn were related to poor cognition [32]. Lu and colleagues, in a sample of over 900 participants, showed that insulin resistance was related to lower cortical thickness in frontoparietal and temporal brain regions [75]. Those studies corroborated previous findings by Shin and colleagues, who showed similar cortical thinning patterns related to insulin resistance in a sample of over 500 participants [77]. A study by Dearborn in 900 individuals also showed that insulin resistance was positively related to cerebral small vessel disease [78]. In addition to these cross-sectional studies, a longitudinal study by Willette showed that insulin resistance was related to lower grey matter volume in the medial temporal lobe, prefrontal cortex, precuneus and parietal gyri at baseline and at 4-year follow-up [79]. Here, the authors also showed that insulin resistance-related medial temporal lobe atrophy was linked to poor cognitive performance [79].

In sum, excess weight and adiposity lead to insulin resistance via the secretory functions of adipose tissue and, indirectly, oxidative stress that affects most bodily organs. Insulin resistance together with hyperglycemia and hyperinsulinemia, in turn, leads to reductions in grey matter volume and thickness, disrupted white matter integrity, cerebrovascular disease, but also to Alzheimer disease-like changes in the brain and cognitive decline. All these alterations further potentiate insulin resistance, thus creating a positive feedback loop.

6. Dyslipidemia

Another constituent of metabolic syndrome, dyslipidemia, can also affect cerebral grey and white matter. Dyslipidemia is defined as increased or decreased levels of various blood lipids. In this review, we will focus on the high density lipoprotein cholesterol (HDL) and triglycerides (TG), as they are recognized as elements of the metabolic syndrome [4]. According to standard criterion for metabolic syndrome, dyslipidemia consists of reduced blood HDL and elevated TG levels [4]. There is limited research on the specific mechanisms by which HDL and TG blood levels might affect the brain. Some work suggests that one of the plausible mechanisms that mediates the relationship between dyslipidemia and neurodegeneration can be increased inflammation and bodily immune response [80]. On the other hand, hyperlipidemia is a risk factor for atherosclerosis and cerebrovascular disease, possibly leading to a disruption of the blood brain barrier [81,82]. This can further potentiate cerebrovascular disease and white and grey matter changes [83,84], and we refer to this mechanism in the next section.

In humans, past research seems to rather consistently point towards a negative impact of dyslipidemia on grey matter. In a small sample of 18 individuals with metabolic syndrome and 18 healthy controls, Schwarz and colleagues showed that lower HDL and higher TG levels were related to reduced cortical thickness in the parietal, frontal, and occipital cortices [85]. Similar results were found in studies using larger sample sizes, for example Ward and co-authors (n=183) showed that lower HDL levels were associated with lower grey matter volume in the temporal and temporo-occipital regions, but also with cognitive decline [86]. Shan and colleagues found that high TG levels are related to grey matter reductions in cognition-related brain areas in the parietal and occipital cortex and the cerebellum [87].

In terms of white matter changes, past work shows some consistency in results regarding the relationship between dyslipidemia and white matter lesions, but little consistency with regard to white matter integrity as measured by fractional anisotropy, mean diffusivity, axial diffusivity or radial diffusivity. Some studies point to an association between increased white matter hyperintensities, white matter lesions, and dyslipidemia [32,88,89]. Concerning white matter integrity, a study by Williams and co-authors in over 100 participants showed both increased and decreased fractional anisotropy associated with HDL levels [90]. Finally, a recent study in 273 participants by Iriondo points to negative associations between TG levels and mean diffusivity, radial diffusivity, and axial diffusivity, and a positive association between HDL levels and the same white matter integrity measures [91].

In sum, previous research shows that dyslipidemia is related to lower grey matter thickness and volume, an increased incidence of white matter lesions and hyperintensities, and altered white matter integrity. However, the number of studies investigating those relationships is small and those conclusions need to be supported by further work, ideally using larger samples and longitudinal designs.

7. Cerebrovascular disease

Obesity and other vascular risk factors, namely hypertension, T2DM, and dyslipidemia, might exert their negative effects by disrupting the cerebral blood flow. For instance, hypertension, visceral obesity, and dyslipidemia can cause or accelerate the formation of atherosclerosis [61,92]. Atherosclerosis can be extracranial, when it affects the internal and vertebral arteries, or

intracranial [50,61]. One manifestation of atherosclerosis is carotid stenosis, which is associated with cerebral ischemia and cognitive disfunction [30]. In addition, T2DM, insulin resistance, and systemic inflammation may also cause cerebrovascular impairment via endothelial dysfunction or disruption of the blood brain barrier [93,94] that can lead to brain hypoperfusion.

Cross-sectional studies have consistently shown that lower cerebral blood flow is associated with white matter hyperintensities [95]. Along the same lines, it has been suggested that functional and morphological alterations in the cerebral vessels might lead to vascular insufficiency, increasing the risk of small-vessel diseases [50]. Unfortunately, longitudinal results do not allow to extract firm conclusions on whether a compromised blood supply is the precursor of cerebral small-vessel diseases [30,95], and it is perhaps modulated by the presence of some neurodegenerative disorders, such as Alzheimer disease [96,97].

With regards to grey matter changes, in general, studies suggest that compromised cerebral blood flow is associated with reduced grey matter volumes [98,99]. For instance, a study on a large community-dwelling sample aged 73 years old (n=554 participants) showed that carotid stenosis was associated with lower cortical thickness and lower fluid intelligence scores [100]. Another study reported a negative association between carotid stenosis and grey matter changes (cortical thickness and hippocampal volume) in a group of participants with cognitive impairment (n=199). However, in healthy controls (n=281), this relationship was not significant [97]. The severity of the stenosis might be an important factor to consider. In this regard, a study (n=663) reported that severe stenosis (stenosis > 70%) was associated with the progression of brain atrophy after a 4 years follow up. Mild-to-moderate stenosis, however, did not show significant associations with longitudinal brain atrophy [99].

8. Concluding remarks and future directions

Cross-sectional and longitudinal evidence suggests that obesity, and more specifically visceral obesity, has a negative impact on brain structure. Extensive research has been done to characterize 'what' brain regions and circuits are associated with an excess of body weight [14,16,32]. Obesity-related grey matter differences seem to follow a frontal-temporal pattern, while studies examining white matter have found consistent micro- as well as macrostructural changes that can impact structural connectivity and white matter integrity. With this in mind, in the current review we have sought to provide an answer to the questions of 'how' and 'why' obesity jeopardizes grey and white matter health. We have delineated the possible effects of inflammation, hypertension, insulin resistance, and T2DM, as well as dyslipidemia on brain. All these factors seem to work together to affect the brain, making it difficult to discriminate between their possible individual effects. At the same time, substantial evidence indicates that inflammation, hypertension, T2DM, and dyslipidemia might act as intermediate variables (or mediators) of the effects of obesity on the brain [27,29,32,33]. The metabolic complications of obesity are heterogeneous [92]. To better define and personalize the risk that obesity poses for cerebral grey and white matter health, it is thus important to account for the cardiometabolic factors that often co-exist with obesity (Figure 2).

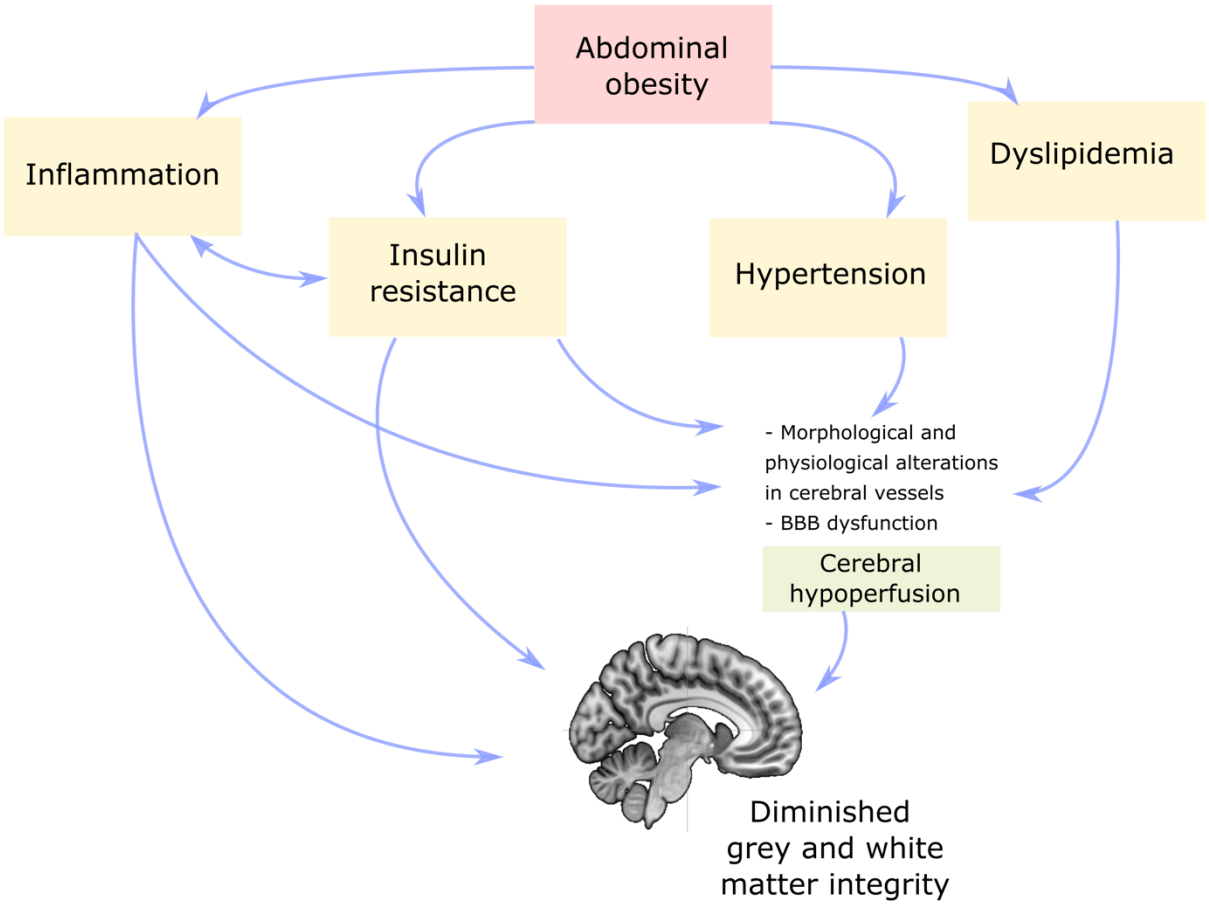

Fig. 2 Schema of the possible intermediate mechanisms mediating the link between abdominal obesity and poorer grey and white matter health

The neuroanatomical effects of abdominal obesity and its metabolic factors associated might prove somewhat difficult to disentangle from age effects. Aging is associated with increases in the prevalence of cardiometabolic factors [103]. For instance, in the American Heart Association 2019 Heart Disease and Stroke Statistical Update, the presence of hypertension in population aged 35 to 44 years old was 42.5% in males and 31.6% in females [103]. In population over 75 years old, however, the prevalence of hypertension is estimated to be 80.0% in males and 85.6% in females [103]. Aging is also associated with reductions in total brain volume, and the rate of annual

decreases has been estimated to be around 0.2-0.5% [104]. Some brain areas, such as the frontal and temporal lobes, seem to be especially prone to grey matter reductions associated with age [104]. White matter also shows age-related decreases in volume and microstructure, as well as increases in radiological markers of small-vessel diseases, such as white matter hyperintensities [105]. These changes are generally regarded as responsible for age-related declines in fluid intelligence [106,107]. It is thus possible that abdominal obesity and its related metabolic complications, accelerate some of the neuroanatomical effects of normative aging. Together, these results provide support for the importance of preventing cardiometabolic risk factors in lifestyle strategies promoting successful aging in older adults.

One of the paths by which all of the above cardiometabolic consequences seem to exert their negative effects in the brain is by compromising the cerebral blood supply. However, human research on the effects of vascular deficiency on grey and white matter integrity is surprisingly scarce. Therefore, one possible and important avenue of future research is to investigate how obesity and metabolic syndrome influence cerebrovascular function. This can be achieved using MRI sequences that do not need the administration of contrast, such as time-of-flight (TOF) sequence [101], or arterial spin labeling [102], which allow to image brain's vascular system anatomy and function.

With the increasing availability of open-access neuroimaging datasets (such as the UK Biobank [108], the Human Connectome Project [109], or the Cam-CAN database [110]) well-powered analyses are becoming the norm in neuroimaging studies in obesity. The effect sizes of obesity and other cardiometabolic factors on the brain seem to be small-to-medium (e.g., [8]). The use of open-access datasets thus represents a great opportunity for researchers to examine small effects associated with obesity and its interaction with cardiometabolic conditions. Open-access datasets

often contain general health data, such as the BMI, history of hypertension, or diagnosis of T2DM. However, they might lack information that is fundamental to provide an appropriate characterization of the effects of obesity, such as information that is more specifically related to abdominal obesity (i.e., visceral adipose tissue, waist-to-hip ratio, etc, the UK Biobank constitutes an exception here), or blood markers, such as inflammatory markers or lipids. This way, we believe that combining analyses in big population datasets along with smaller but deeply characterized studies will be crucial in the future.

Finally, we think that another important direction for future research is designing translational studies that can in depth investigate the basic mechanisms by which obesity together with other cardiometabolic consequences affect neurocognition. This should be achieved by collaborations between molecular, animal, and human researchers. Studies utilizing a number of techniques from different fields, such as, for example, molecular techniques, genetics, or brain imaging, will ultimately drive the field forward.

With all current advances in science and technology, we believe that the recommended steps will lead to a significant improvement in the understanding of obesity and how it relates to brain's health and cognition, which in turn will help improve the overall health prospects of the aging society.

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