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ETIOLOGY OF OBESITY (M ROSENBAUM, SECTION EDITOR)

Cognition, Brain Structure, and Brain Function in Individuals with Obesity and Related Disorders

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Abstract

Purpose of Review Obesity is one of the most serious public health concerns. Excess adipose tissue, particularly with a centralized distribution, is associated with cognitive decline. Indeed, obesity has been associated with a number of adverse changes in brain function and structure that can be detected by neuroimaging techniques. These obesity-associated changes in the brain are associated with cognitive dysfunction.

Recent Findings While the pathways by which excess adipose tissue affects brain function are not fully understood, available evidence points towards insulin resistance, inflammation, and vascular dysfunction, as possible mechanisms responsible for the observed relations between obesity and cognitive impairment.

Summary It appears that weight loss is related to better brain and cognitive outcomes and that cognitive impairment due to obesity may be reversible.

Keywords Neuroimaging · Metabolic syndrome · Overweight · Aging · Midlife

Introduction

Humans possess the remarkable capacity to store energy in the form of body fat when the opportunity to consume extra energy arises. From an evolutionary perspective, the storage of sufficient energy is essential for prevention of starvation and to protect reproductive integrity [1]. Obesogenic environments, characterized by abundant calorie dense foods and sedentary lifestyles, have contributed to the rising levels of obesity worldwide. Obesity constitutes a major public health threat because of deleterious effects on multiple tissues and organs [2, 3]. Obesity is closely associated with diabetes, metabolic syndrome (MetS), and cardiovascular diseases [3]. More recently identified consequences of obesity are cognitive deficits [4]. Neuroimaging studies have contributed to revealing morphological and neurophysiological changes in obesity and related disorders such as MetS [4].

The current review summarizes research evidence associating obesity and related disorders with cognitive function, brain structure, and brain neurophysiology (Fig. 1). Because obesity is a central feature of MetS and research on MetS is a logical extension of studies of obesity, the topic of MetS is highlighted. A primary focus is placed on middle-aged adults as neuropathological changes are known to precede the onset of clinically significant cognitive impairment and the relationships between obesity cognitive dysfunction appear nonlinear and most robust in midlife [5].

Obesity and Cognition

Overweight and obesity in middle-aged adults is linked to increased risk of incidental cognitive decline with relative risks of 1.26 and 1.64 [6], particularly on tasks that evaluate executive function and memory [7]. A systematic review of cross-sectional studies reveals a remarkably consistent relationship between obesity and cognitive performance with 14 of 15 studies showing a negative association between obesity

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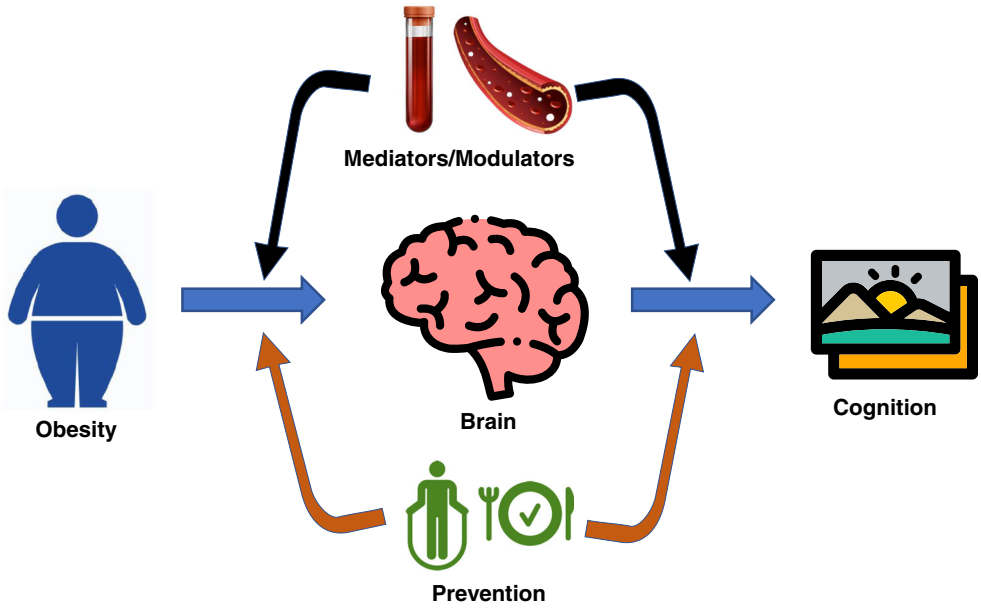

Fig. 1 Neurocognitive impacts of obesity

and cognition at 19–65 years of age [8]. The distribution of adipose tissue seems to selectively impact cognitive function. In particular, abdominal obesity is a more salient predictor of cognitive decline than whole-body adiposity [9]. The association between abdominal obesity and executive function appears to be mediated, at least in part, by brain-derived neurotropic factors (BDNF), a key neurotrophin crucial for neuronal regeneration and survival [7].

In contrast to cross-sectional studies, prospective and longitudinal studies are not consistent as the risk of cognitive decline in late life is no longer significant with a relative risk of 0.98 [6], evoking the concept of "obesity paradox." In midlife, being overweight or obese is associated with increased risk of cognitive decline, while the same conditions in late life appear to be neuroprotective [5]. Similarly, in a community-based longitudinal study that tracked changes in BMI for more than 28 years, obesity at age 50 years, but not at 60 or 70, is associated with risk of dementia [10]. Thus, prospective evidence indicates that obesity in midlife, but not in late life, is associated with dementia risk. The cause of the obesity paradox is often attributed to weight loss in the preclinical stage of dementia as BMI starts to decline 6–10 years prior to dementia diagnosis [11]. It should be noted that BMI does not directly assess body composition or fat distribution as individuals who are very muscular may be incorrectly labeled as having obesity [12].

Obesity and Subcortical Regional Atrophy

In meta-analysis of 10 investigations using voxel-wise measurements of gray matter, BMI is consistently associated with lower volume of subcortical regions [13]. Metabolically active adipose tissue around the central portion of the body has stronger associations with structural changes in the brain. Middle-aged adults with greater visceral fat possess lower total brain volume, independent of BMI or insulin resistance [14]. Additionally, individuals with overall and central obesity have lower gray matter volumes than their lean counterparts, even after adjustment for multiple covariates [15]. Specific impacted subcortical regions may differ between men and women [16]. Total body fat percentage was associated with smaller volume of the thalamus, caudate putamen, globus pallidus, hippocampus, and nucleus accumbens in men while only volume of the globus pallidus had a significant association in women [16].

Obesity and Cortical Thickness

In longitudinal studies, elevated BMI has been associated with cortical thinning of the posterior cingulate, a central region of the default mode network related to cognition, on long-term follow-up, but not at baseline [17]. Roughly speaking, an annual increase in BMI of 1% is associated with 0.5% reduction in cortical thickness [17]. In adults with overweight, greater BMI is associated with concurrent cortical thinning in the right ventromedial prefrontal cortex and the left lateral occipital cortex [18]. In contrast to these findings, our group has reported greater thickness of the posterior cingulate cortex with higher volume of visceral fat suggesting that the neuropathology of the brain may initiate with neuronal hypertrophy before subsequent atrophy [19]. In support, a cross-sectional study including a wider age range of participants indicates greater whole brain cortical thickness among individuals with obesity and overweight, compared with lean controls [20]. A similar

finding is reported among young adults with obesity who demonstrate greater cortical thickness in the right medial orbital frontal cortex as well as bilateral left rostral anterior cingulate cortex, inferior parietal gyrus, and superior parietal gyrus [21]. Increases in cortical thickness in adults at risk for cognitive impairment are attributed to neuronal hypertrophy and astrogliosis [22]. At the same time point, participants with obesity exhibit cortical thinning in the right entorhinal cortex and the temporal pole, bilaterally [21]. Clearly, more work is needed to understand the regional specificity and time course of cortical thickness changes associated with increases in adipose tissue.

Obesity and White Matter

There is a non-linear trajectory in white matter volume where peak volume occurs around midlife and decreases in late life, but this can be impacted by increased adiposity. Individuals with obesity have accelerated white matter brain aging at midlife compared with their lean counterparts [20]. There is also a reduction in the structural integrity of the white matter tracts that form connections between regions of the brain. Demyelination of these tissues results in less anisotropic diffusion of water along axons as highlighted by reduced fractional anisotropy (FA), indicative of reduced structural integrity, with increases in obesity [23]. Decreased FA is observed in various white matter tracts in obese and overweight adults [24]. Our group has shown that FA is significantly lower in the splenium of the corpus callosum and uncinate of adults with MetS [25]. Using a new technique, diffusion-based spectrum imaging, neuroinflammation is detected among hippocampal tracts where structural integrity is also lower in adults with obesity than in lean controls [26].

Obesity and Cerebral Lesions

Obesity is linked with increased number and volume of lesions in the brain. Such lesions indicate cerebral small vessel disease and increase susceptibility to cognitive impairment or dementia. Among a cohort of older participants, individuals with MetS demonstrate greater volume but similar number of white matter hyperintensities (WMH) [27]. Waist circumference is not an independent predictor of WMH volume, indicating that obesity may only be one component of a cluster of factors that result in neuropathological changes. In a middle-aged sample, visceral adipose tissue is a significant independent predictor of WMH and lacunar infarcts with odds ratios of 1.13 and 1.38 whereas the same association is not observed with BMI or subcutaneous adipose tissue [28]. Visceral fat is more strongly associated with deep WMH compared with periventricular WMH [29]. Interestingly, the presence of subcutaneous adipose tissue may have protective effects against the development of WMH [30]. These benefits are most pronounced among females and individuals with the greatest level of obesity. Investigations focused on obesity and changes in white matter may also reflect a more complex relationship between MetS and neuropathological changes. Individuals with MetS demonstrate greater odds of having silent brain infarcts regardless of obesity status [31]. In middle-aged adults without MetS, obesity is not associated with increased odds (odds ratio of 0.85) for silent brain infarcts [31].

Mediators/Mechanisms Underlying Associations Between Obesity and the Brain

Insulin Resistance In peripheral tissues, insulin plays a critical role in maintaining glucose homeostasis by regulating substrate metabolism. In the central nervous system, insulin is not required for glucose transport into most cells. Yet, it supports neurophysiological processes critical for successful cognitive function [32]. We have previously noted that memory performance benefits related to cardiorespiratory fitness might be mediated, at least in part, by plasma insulin concentrations [33].

Chronic hyperinsulinemia and insulin resistance in the periphery, primarily caused by obesity, tend to downregulate insulin receptors on the blood–brain barrier, inducing hypoinsulinemia in the brain and disrupting neurophysiological processes underlying learning and memory [34]. For example, insulin modulates glutamate, the primary excitatory neurotransmitter [35]. Thus, cerebral insulin deficit likely results in reduced glutamate receptor binding and higher than normal, potentially excitotoxic, levels of free glutamate [36]. Indeed, our team has detected higher free cerebral glutamate levels in adults with MetS [37]. These results fit with literature linking insulin resistance to reduced hippocampal synaptic plasticity and spatial memory deficits in rats fed a Western-style diet [38], hippocampal atrophy and impaired declarative memory in patients with diabetes mellitus [39], and cognitive decline in the general population [40].

Vascular Dysfunction Insulin is also involved in vascular function as a vasodilator via nitric oxide production in endothelial cells [41]. Thus, dysfunction of insulin metabolism could contribute to problems with vascular tone. Decreased insulin-mediated microvascular perfusion and cognitive problems have been reported in rats [42]. In humans, insulin resistance has been linked to increased risk for vascular dementia [43]. Consistent with these reports, we have observed reduced flow-mediated vasodilation, an index of endothelium-dependent vasodilation, in relation to increased burden of WMH [44] and lower cerebrovascular response to a working memory challenge [45]. However, insulin resistance may only partially explain

endothelial dysfunction; thus, attention must also be paid to other manifestations of insulin resistance such as obesity, dyslipidemia, and inflammation [46]. Obesity, insulin resistance, and dyslipidemia tend to accelerate age-related arterial stiffening [47], leading to cerebral hypoperfusion [48], cortical thinning [49], poorer white matter microstructural integrity [50], and weaker cognitive performance [51]. Thickening of the intimal and medial layers of the carotid arteries is associated with poorer neuronal integrity in midlife [52] and poorer cognitive function in older age [53]. Vascular stiffening reduces transducing capacity of arterial baroreflex and leads to autonomic nervous system dysfunction. Indeed, diet-induced obesity induces dysregulation of the baroreflex control of blood pressure, which in turn can lead to cerebral hypoperfusion [54].

Inflammation Heightened inflammation has been associated with diminished brain integrity and cognitive impairment. Relevant to obesity, systemic inflammation exacerbates the deleterious cognitive effects of MetS such that adults with MetS and elevated serum inflammatory markers demonstrate poorer cognitive test performance than those with MetS or inflammation alone [55]. Additionally, chronic low-grade inflammation appears to increase the probability of cognitive decline over time [55]. Markers of systemic inflammation in adults with obesity have related to neuroimaging markers of brain vulnerability such as WMH [29] and disordered water diffusion [56].

While activated microglia and astrocyte proliferation can be detected in the aging brains, whether those changes reflect neuroinflammation in the conventional sense and how they may relate to neurodegeneration are less clear [57]. Non-invasive early biomarkers of neuroinflammation are still scarce. Our team has reported higher cerebral *myo*-inositol levels in the brains of middle-aged adults with peripheral inflammation as indicated by higher C-reactive protein levels and speculated that *myo*-inositol may be a proxy for neuroinflammation [58], though *myo*-inositol is also a potential marker of gliosis that is related to obesity [59].

Treatment Measures

Weight Loss Weight loss is related to improved cognitive performance. In a meta-analysis, 2 out of 7 studies reported a positive effect of weight loss on memory (a small Cohen's effect size $d = 0.13$) and 5 out of 8 studies on executive function/attention [60]. Improvement in at least one cognitive function has been observed for individuals in the obese BMI range, but is not as consistent for those in the overweight range [60]. In a more recent review of 20 previously published studies, weight loss is associated with improvements in executive function, cognition, and language in longitudinal studies and randomized control trials in individuals with obesity and overweight [61].

Exercise In cross-sectional studies, habitual exercise is associated with reduced body adiposity, improved cognition, and brain function [25, 62] and has been reported to be protective against age-related cognitive decline as evidenced in older masters athletes [63]. Favorable effects of regular exercise for improving cognitive function appear to be obtained when the training intervention is performed for a longer duration, with each session lasting at least 30 min [63]. In our work, cardiorespiratory fitness is associated with both enhanced cognition and healthier brain, and this relationship may be in part mediated by plasma insulin concentrations [25, 33]. Another possible mechanism is that exercise may upregulate key factors in neurogenesis (e.g., BDNF) [64].

Bariatric Surgery Bariatric surgery in patients with morbid obesity leads to significant weight loss and has been reported to produce measurable improvements in cognitive functions. Systematic reviews examining post-surgical cognitive change have reported improvement in memory and executive functions [65, 66]. These improvements may be in part due to post-surgical changes in gray and white matter in the cerebral cortex of all lobes suggesting that brain plasticity and reorganization may occur [67].

Overall, it appears that weight loss that addresses obesity is related to better brain and cognitive outcomes and that cognitive impairment due to obesity may be reversible. This is promising as addressing weight loss and weight maintenance midlife may confer some protection against later cognitive decline and be the key to early interventions for cognitive decline.

Conclusions and Summary

Throughout the review, we have highlighted the impact of obesity on morphological and physiological changes in the brain that lead to cognitive impairment. Measures of visceral obesity are more strongly associated with cognitive dysfunction than whole-body or subcutaneous adiposity. Whether obesity is a cause or consequence of morphological and functional changes in the brain is a matter of debate as some studies support the premise that cognitive dysfunction precedes or causes increased levels of obesity via food reward, food restraint, etc. [8]. The present review supports the notion that obesity is a neurological disorder and highlights the need to invest in neuroimaging studies in obesity.

Compliance with Ethical Standards

Conflict of Interest None.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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