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Review

Does the brain shrink as the waist expands?

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ABSTRACT

Recent studies suggest that being overweight or obese is related to worse cognitive performance, particularly executive function. Obesity may also increase the risk of Alzheimer's disease. Consequently, there has been increasing interest in whether adiposity is related to gray or white matter (GM, WM) atrophy. In this review, we identified and critically evaluated studies assessing obesity and GM or WM volumes either globally or in specific regions of interest (ROIs). Across all ages, higher adiposity was consistently associated with frontal GM atrophy, particularly in prefrontal cortex. In children and adults <40 years of age, most studies found no relationship between adiposity and occipital or parietal GM volumes, whereas findings for temporal lobe were mixed. In middle-aged and aged adults, a majority of studies found that higher adiposity is associated with parietal and temporal GM atrophy, whereas results for precuneus, posterior cingulate, and hippocampus were mixed. Higher adiposity had no clear association with global or regional WM in any age group. We conclude that higher adiposity may be associated with frontal GM atrophy across all ages and parietal and temporal GM atrophy in middle and old age.

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1. Introduction

One-third of adults and 17% of children and adolescents in the United States are currently obese, where the prevalence of obesity continues to rise among boys and men and remains high for girls and women (Ogden et al., 2012a,b). It has been well established that obesity increases the risk for cardiovascular disease (Whitlock et al., 2009; Friedemann et al., 2012), type 2 diabetes (Haslam and James, 2005), various cancers (Vucenik and Stains, 2012), and overall mortality in children and adolescents (Flegal et al., 2007), as well as adults (Whitlock et al., 2009). Several studies have shown a negative association between anthropometric measures of obesity, such as body weight, body mass index (BMI), or waist circumference (WC), and cognitive performance (Elias et al., 2012), in particular worse executive function (Gunstad et al., 2007). However, other studies have found no such association with cognition (van Boxtel et al., 2007) or even small positive associations (Kuo et al., 2006).

Regarding children and adolescents, recent reviews (Liang et al., 2014; Reinert et al., 2013) indicate that higher adiposity (i.e., being overweight or obese) is consistently associated with poorer executive function, inhibitory control, and attention, as well as worse academic achievement. It has been speculated that these deficits reflect dysregulation of brain networks mediating these higher cognitive functions, as well as regulating appetitive drive. These networks include medial parietal areas, insula, hippocampus, prefrontal cortex (PFC), and cingulate cortex (Del Parigi et al., 2002; Martin et al., 2010; Mehta et al., 2012; Brooks et al., 2013b). By contrast, only half of the studies in that literature find an association with worse learning and memory performance.

Toward the other end of the lifespan, increased midlife adiposity has been linked to worse cognitive performance and higher risk for Alzheimer's disease (AD) (Elias et al., 2012), although sex effects and other factors appear to modify this risk. For example, for women but not men at age 70, every 1-point increase in BMI corresponded to a 36% increase in AD risk over a 10–18 years time span (Gustafson et al., 2003). A recent meta-analysis (Beydoun et al., 2008) found that increased AD risk was attributable to obesity (BMI > 30) but not being overweight (BMI 25–30), although Huang and Yu re-analyzed the same data and contest the distinction (2008). Obesity may increase AD risk not as an isolated factor, but as a component of the Metabolic Syndrome, which refers to the constellation of impaired glucose tolerance, abdominal or central obesity, hypertension, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol, and is progressively being recognized as a major mechanism underlying age-related cognitive decline and development of AD (Frisardi et al., 2010; Craft et al., 2012).

Based in part on the association between excess adiposity and AD risk, Gustafson and colleagues published one of the first papers examining excess adiposity and lobar brain volume (Gustafson et al., 2004). Specifically, in Swedish women, higher BMI measured at some point between midlife and old age predicted a small but significantly higher likelihood of atrophy (Odds Ratio 1.11–1.14) in temporal gray matter (GM) volume based on Likert scale ratings by expert radiologists. No relationship was found for frontal, parietal, or occipital lobes. Since this seminal report, many cross-sectional and a few longitudinal studies have examined anthropometric or quantitative measures of adiposity and brain structure using magnetic resonance imaging (MRI), microstructure using diffusion tensor imaging (DTI), and various magnetic resonance spectroscopy (MRS) techniques. Akin to the obesity literature in younger cohorts, these studies have also focused on hippocampus, PFC, precuneus and posterior cingulate cortex, and to a lesser extent insula, due in part to their relationship with late life cognitive decline and atrophy seen in AD (Whitwell et al., 2007; McDonald et al., 2009; Risacher et al., 2010).

Despite the remarkable number of recent publications addressing adiposity in relation to brain atrophy in these areas and others, there has been no systematic, critical review of this literature in younger or older age groups. It is important to distinguish between these age groups because the pathophysiology underlying excess adiposity and brain may differ across the lifespan. For example, aging is related to low-grade chronic expression of peripheral proinflammatory cytokines and chemokines, in part due to increased abdominal adiposity (Michaud et al., 2013). Peripheral proinflammatory cytokines and chemokines predict brain atrophy cross-sectionally in aged rhesus monkeys (Willette et al., 2010) and aged humans (Satizabal et al., 2012). Furthermore, comorbidities such as insulin resistance (IR), cardiovascular disease, hypertension, and hyperlipidemia preferentially affect older age groups (Michaud et al., 2013). Finally, the loss of lean muscle mass with ageing (i.e., sarcopenia) complicates direct age group comparisons based on BMI. Indeed, BMI is the most common adiposity index used in this literature, and this metric does not distinguish between non-fat mass and fat mass.

This review first focuses on defining brain atrophy and various measures of adiposity. After detailing search criteria and the analytic strategy, we summarize the literature in younger and then older cohorts, followed by a discussion of those studies and then potential underlying mechanisms and interventions.

1.1. Defining atrophy

In the context of pathology, atrophy is characterized by reduction of brain tissue volume and cortical thickness over time or compared to normal brains, due to various combinations of reduced synaptic density, dendritic arborization, corpuscular volume of neurons and glia, and cell death (Donkelaar, 2011). Given the paucity of neuroimaging studies longitudinally assessing brain volume and adiposity (Haltia et al., 2007; Debette et al., 2011; Bobb et al., 2014; Driscoll et al., 2012), the term "atrophy" has been mainly used to characterize lower GM or white matter (WM) volumes relative to various control groups (Yaffe et al., 2004). This usage presupposes established norms for regional GM and WM and that the various control groups represent the population distribution. This assumption becomes problematic for smaller studies, or newer methodologies where norms have not been well established (e.g., DTI, MRS). In neuroimaging studies, all available methodologies for tissue segmentation used to generate GM and WM maps remove voxels containing CSF (albeit with variable success). Therefore, reported associations refer to brain tissue volume free of CSF.

1.2. Defining adiposity using BMI

Various metrics have been devised to reflect central adiposity (i.e., fat tissue surrounding viscera in the peritoneum), subcutaneous adiposity (i.e., fat tissue underlying the skin), or total body adiposity. Body mass index, or BMI, is a simple anthropometric