



Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr



Review

Does the brain shrink as the waist expands?

Auriel A. Willette, Dimitrios Kapogiannis*

Laboratory of Neurosciences, National Institute on Aging, 3001 S. Hanover St, NM531, Baltimore, MD 21225, USA

ARTICLE INFO

Article history:
Received 4 February 2014
Received in revised form 25 March 2014
Accepted 28 March 2014
Available online xxx

Keywords:

Obesity
Adiposity
Brain atrophy
Gray matter
White matter
Body mass index
MRI
MRS
Frontal lobe
Cognition

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.

© 2014 Published by Elsevier B.V.

Contents

1.	Introduction	00
1.1.	Defining atrophy	00
1.2.	Defining adiposity using BMI	00
2.	Methods	00
2.1.	Search criteria	00
2.2.	Evaluation and organization of studies	00
3.	Results	00
3.1.	Adiposity and brain: search results	00
3.2.	Adiposity and brain atrophy: children and younger adults (<40 years of age)	00
3.2.1.	Summary of findings in children and younger adults (<40 years of age)	00
3.3.	Adiposity and brain atrophy: middle-aged to aged adults (>40 years of age)	00
3.3.1.	Summary of findings for middle-aged to aged participants (>40 years of age)	00
4.	Discussion	00
4.1.	Overall findings	00
4.2.	Adiposity and brain atrophy: potential mechanisms	00
4.2.1.	Inflammation	00
4.2.2.	Vascular risk factors	00
4.2.3.	Insulin resistance	00
4.2.4.	Glucocorticoid and brain-derived neurotrophic factor signaling	00
4.3.	Adiposity and brain atrophy: evidence from interventions	00
4.3.1.	Calorie restriction and weight loss	00

* Corresponding author. Tel.: +1 410 350 3953; fax: +1 410 350 7308.
E-mail address: kapogiannisd@mail.nih.gov (D. Kapogiannis).

4.3.2. Exercise.....	00
5. Conclusions.....	00
Appendix A. Supplementary data.....	00
References.....	00

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 (Vucenic 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., 2013; 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 (OR 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 (Satzibal et al., 2012), as well as longitudinally in middle-aged adults at risk for AD (Willette et al., 2013a). 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; Dobbie et al., 2011; Bobb et al., 2012; 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

surrogate of total body fat and is calculated by dividing kilograms of body weight by squared meters in height. The World Health Organization has created standardized BMI groups (2000) including lean (18.5–24.99), overweight (25–29.99), obese class I and II or obese (30–39.99), and obese class III or morbidly obese (≥ 40.00). As detailed in many other reports (e.g., Dalton et al., 2003), BMI does not distinguish between visceral and subcutaneous fat, as well as non-fat mass, and has major limitations as a disease biomarker, since it can be affected by *non-fat* mass loss, which typically occurs in old age (i.e., sarcopenia). Waist circumference (WC) is assessed by circumference around the umbilicus after breath release, while waist-to-hip ratio (WHR) utilizes both waist and hip circumference measurements. These measures preferentially reflect central adiposity and are more accurate predictors of type 2 diabetes and cardiovascular disease than BMI (Luchsinger et al., 2012). Given their greater relevance to metabolism, WC and WHR may also better reflect associations between adiposity and brain health across the lifespan.

2. Methods

2.1. Search criteria

Articles from 2004 to 2013 were reviewed. Searches prior to 2004 did not return any results that met criteria. The last search occurred in August 2013. Searches were performed in PubMed/Medline using combinations of the following terms: brain; atrophy; gray matter; white matter; obesity; fat; high fat diet; neurons; brain volume; magnetic resonance imaging; magnetic resonance spectroscopy; body mass index; waist circumference; waist to hip ratio; cortical density; body weight; histopathology. Human studies were included if they had: (1) been published in English; (2) included at least one brain scan; (3) examined global, lobar, regional brain volumes or measured metabolites that reflect brain tissue integrity using MRS; (4) included at least one anthropometric or quantitative assessment of central or global adiposity, such as body weight, BMI, WC or abdominal girth, WHR, visceral adipose tissue (VAT) and/or subcutaneous adipose tissue (SAT), percentage body fat (% body fat), and similar indices; and (5) focused on the weight spectrum from normal to class III obesity, which did not include studies on being underweight such as anorexia nervosa. An alternative criterion was a genetic predisposition toward obesity, such as Prader-Willi syndrome (Cassidy, 1997) or risk alleles for the fat mass and obesity associated (FTO) gene (Dina et al., 2007) when combined with an adiposity measure. While important, it was beyond the scope of this review to include articles examining adiposity and fMRI activation, brain metabolism, brain vascular pathology (e.g., white matter hyperintensities), or autopsy studies that only considered brain weight instead of composition.

2.2. Evaluation and organization of studies

First, we developed a set of criteria to critically evaluate studies for scientific and statistical rigor. Studies were considered optimal if they had: (1) large sample sizes, with balanced sampling of different weight groups, if applicable; (2) indices of adipose tissue (SAT, VAT) over anthropometric measures like BMI; (3) a clear study design, where hypotheses were clearly stated and based on pre-existing literature, the methodology and analytic strategy were rigorous and a priori driven, and the results confirmed at least some of the hypotheses; (4) stringent exclusion criteria including type 2 diabetes and related comorbidities, cardiovascular disease, psychiatric disorders, and central nervous system disorders, all of which may be independently associated with both obesity and brain volume and, therefore, are potential confounders; (5) adjustment for type

1 error; and (6) an intervention, were longitudinal, or otherwise novel.

Studies in children to young adults were evaluated and are presented separately from those in middle-aged to aged age groups. For the young adult or middle-aged to aged groups, we present findings for lobar GM posteriorly to anteriorly (i.e., from occipital to frontal lobe), as well as four regions of interest (ROI). Finally, findings for global and regional WM are discussed. The four GM ROIs we focus on are: precuneus or posterior cingulate cortex, hippocampus, insula, and any sub-region of PFC. These brain regions were selected because they are AD-sensitive areas (Whitwell et al., 2007; McDonald et al., 2009; Risacher et al., 2010), and the hippocampus, insula, and ventral PFC are also involved in appetitive drive and inhibitory control. Many of these regions are also important for declarative memory and executive function (Del Parigi et al., 2002; Martin et al., 2010; Mehta et al., 2012; Brooks et al., 2013b), processes that are thought to be dysregulated in obese participants.

3. Results

3.1. Adiposity and brain: search results

We found 44 articles that directly or indirectly addressed the possible link between adiposity and brain volume or metabolites reflecting tissue composition. Supplementary Table 1 summarizes the findings of these studies in detail and allows for direct comparisons. The table includes the publication date, sample size, brain modality, neuroimaging modality (structural MRI vs. MRS), whether categorical or continuous measures of adiposity were used, age group, and a color-coded chart indicating if and in what direction adiposity was associated with brain volumes and/or MRS metabolites. DTI findings from 5 studies that will be referenced in the discussion are also included. Table 1 highlights eight methodologically rigorous reports that either typify overall findings in the literature or present noteworthy findings.

BMI was the most common adiposity index in this literature, with 33 of the 44 studies reviewed exclusively using continuous BMI or BMI groups for associations with brain volume indices. WC, WHR, or equivalent measures were used separately or in concert with BMI in 7 of the 44 studies reviewed. Lastly, 3 studies (Anan et al., 2010; DeBette et al., 2010; Weise et al., 2013) directly measured adipose tissue in whole or in the separate subcutaneous and peritoneal compartments. Twenty-eight of the 44 studies used an anatomically defined region of interest approach to acquire volumetric measures for lobar volumes and/or the 4 ROIs. Eighteen of the 44 studies used voxel-wise statistics (Ashburner and Friston, 2000). Lastly, 2 of the 44 studies used Likert scale ratings of brain volume to qualitatively assess brain volumes. Most of the 44 studies included age or age and sex as covariates. Furthermore, many reports in older cohorts with large sample sizes assessed models that additionally covaried components of the metabolic syndrome, such as dyslipidemia and hypertension indices.

3.2. Adiposity and brain atrophy: children and younger adults (<40 years of age)

Fifteen studies have examined the association of global or regional brain volumes and adiposity in participants less than 40 years of age (Pannacciulli et al., 2006; Haltia et al., 2007; Miller et al., 2007, 2009; Maayan et al., 2011; Ogura et al., 2011; Brain Development Cooperative Group, 2012; Maudsley et al., 2012; Mueller et al., 2012; Smucny et al., 2012; Ursache et al., 2012; Yokum et al., 2012; Alosco et al., 2013; Melka et al., 2013; Weise et al., 2013). Thirteen of these 15 studies used BMI as a continuous variable or BMI groups, while one study used a quantitative index

Table 1
Q3 Examples of literature findings.

Report	Year	Age group	N	Neuroimaging method	Contrast type	Summary of findings
Zade et al.	2013	Middle-Aged	494	ROI	WHR Quartiles	Among the highest WHR quartile, higher WHR was associated with lower total brain volume, frontal GM volume, higher temporal horn volume reflective of less hippocampal volume, and more ventricular volume.
Taki et al.	2008	Middle-Aged	1428	VBM Voxel-Wise	(Q4 indicative of obesity) Continuous BMI	A BMI * Sex interaction showed no association for women. For men, higher BMI predicted less GM in temporal lobe, anterior cerebellum, fusiform gyrus, frontal lobes, precuneus, and midbrain. Positive associations were noted in IFG, posterior cerebellum, frontal and temporal lobes, thalamus, and caudate.
Ho et al.	2010	Aged	700	TBM Voxel-Wise	Continuous BMI	Higher BMI across AD and MCI participants predicted less GM predominantly in medial PFC, occipital lobe, less GM predominantly in medial PFC, occipital lobe, midline areas, cerebellum, brainstem, and deep WM. There was slight coverage in the ADNI-only cohort. Higher BMI predicted more GM in occipital lobe, posterior and anterior cingulate, and pre-central gyrus.
Walther et al.	2010	Aged	95	VBM Voxel-Wise	Continuous BMI	Higher BMI predicted lower GM in frontal lobe, inferior parietal area, parahippocampus to lingual gyrus, cerebellum, and other regions. Higher BMI predicted more WM predominantly in frontal and temporal areas.
Weise et al.	2013	Young Adult	76	VBM Voxel-Wise	Continuous Fat-Free Mass Index (FFMI) or Fat Mass Index (FMI)	Higher FFMI strongly predicted less GM in insula, temporal gyri, ventral and orbital PFC. Higher FMI was associated with smaller clusters in similar regions. Covarying FFMI rendered FMI associations non-significant.
Haltia et al.	2007	Young Adult	46	VBM Voxel-Wise	Obese (30) vs. Lean (16)	Obese participants showed no significant GM differences after type 1 error correction, but did show more WM near parahippocampus, temporal gyri, brainstem, and cerebellum. After 6 weeks of dieting in obese participants, there was significantly less WM near parahippocampal gyrus and temporal areas.
Brain Development Cooperative Group	2012	Child to Adolescent	325	ROI	Continuous BMI	Higher BMI had smaller to moderate associations with global, parietal, temporal, and occipital GM. No association was seen with frontal GM. Higher BMI predicted small positive correlations with global, frontal, parietal, and temporal WM.
Pannacciulli et al.	2006	Young Adult	60	VBM Voxel-Wise	Morbidly obese (24) vs. Lean (36)	Morbidly obese participants had less GM in cerebellum, post-central gyrus, putamen, MFG, and anterior insula. Obese participants also had more GM in occipital areas, cerebellum, and MFG, as well as more WM near striatum.

AD = Alzheimer's disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; BMI = Body Mass Index; CHS-CS = Cardiovascular Health Study Cognition Study; GM = Gray Matter; IFG = Inferior Frontal Gyrus; MCI = Mild Cognitive Impairment; MFG = Medial Frontal Gyrus; PFC = Prefrontal Cortex; ROI = Region of Interest; TBM = Tensor-Based Morphometry; VBM = Voxel-Based Morphometry; WHR = Waist to Hip Ratio; WM = White Matter.

of fat mass and non-fat mass (Weise et al., 2013). See Supplemental Table 1 for more details.

Six of these studies were deemed optimal based on our criteria. Weise and colleagues (2013) conducted a study in 76 healthy participants (mean age = 32.1 ± 8.8 years), where they examined fat-free mass index (FFMI) or fat mass index (FMI) and gray matter volume using voxel-wise regression. While higher FMI predicted less GM in superior temporal and prefrontal areas, these effects became non-significant after covarying FFMI; therefore, the authors suggest that overall body mass instead of adiposity may underlie brain associations. The Brain Development Cooperative Group (2012) studied a large cohort of 325 children and adolescents (~70% normal BMI) from 4.5 to 18 years of age and examined total brain, lobar, and ventricular ROI volumes. They found small to moderate correlations between higher BMI and lower global GM volume and GM volume in occipital, parietal, and temporal but not frontal lobes, whereas higher BMI predicted higher WM volume. In a comparably aged cohort, Alosco and colleagues (2013) used an ROI approach to examine if higher BMI predicted less GM in 120 children and adolescents (mean age = 13.5 ± 2.9 years). Higher BMI was associated with less GM in frontal lobe, as well as a "limbic lobe" ROI that included the hippocampus, parahippocampus, amygdala, cingulate, and cerebellum. Pannacciulli and co-workers (2006) examined regional WM and GM differences between 24 morbidly obese and 36 lean participants (mean age = 32.5 ± 8.5 years). Obese participants had less GM in parietal, temporal, and middle prefrontal areas, but also had more GM in occipital and inferior prefrontal regions, as well as more WM. A more recent study (Yokum et al., 2012) that considered the full BMI range, by including 17 obese, 36 overweight, and 31 lean adolescent females (mean age = 18.4 ± 2.8 years), found no volumetric differences between overweight participants and other groups. However, they did note medium to large effect sizes when comparing obese versus lean, where obese participants had less occipital GM and global WM, but more regional WM in inferior and temporal areas, as well as in rolandic operculum and dorsal striatum. Finally, Haltia et al. (2007) compared 30 obese and 16 lean participants (mean age = 37 ± 16.5 years) at baseline and after a 6-week very low calorie diet in the obese group. At baseline, regional WM volume was higher in obese participants. After the intervention, WM volumes did not significantly differ between the once obese participants who had become lean versus the always-lean participants. No GM differences were noted at either time-point.

3.2.1. Summary of findings in children and younger adults (<40 years of age)

Although these studies and the others produce several conflicting or non-replicable findings, some trends are clear. Two of the 4 studies that assessed total brain volume (Ogura et al., 2011; Melka et al., 2013) found negative associations with more adiposity. Three of 5 studies that assessed global GM (Brain Development Cooperative Group, 2012; Ogura et al., 2011; Yokum et al., 2012) also found that more adiposity predicted lower volume.

Two of 11 studies that examined occipital lobes reported more (Brain Development Cooperative Group, 2012; Yokum et al., 2012) atrophy associated with more adiposity, but one study showed the opposite association (Pannacciulli et al., 2006). Three of 11 studies that examined parietal lobes also found an association between less atrophy and more adiposity (Brain Development Research Group, 2012; Pannacciulli et al., 2006; Ogura et al., 2011). Of 8 reports examining precuneus or posterior cingulate, only one study by Alosco et al. (2013) shows a relationship between more adiposity and less volume in a 'limbic lobe' incorporating these areas.

Results for temporal lobe GM are mixed (i.e., no clear consensus among reports about the presence and direction of an association). Three of the 6 optimal studies to examine temporal lobes

(Pannacciulli et al., 2006; Brain Development Cooperative Group, 2012; Weise et al., 2013) and 2 of 3 other studies to examine temporal lobes (Mueller et al., 2011; Ogura et al., 2011) reported more atrophy with adiposity. Furthermore, only 2 of 9 studies that used a hippocampus ROI (Mueller et al., 2012; Alosco et al., 2013) found such an association between more adiposity and lower volumes. These findings parallel the mixed results noted between obesity and learning and memory (Liang et al., 2013). Similarly, only 3 of 7 reports examining the insula showed an association between more atrophy and either higher BMI or more fat mass (Pannacciulli et al., 2006; Smucny et al., 2012; Weise et al., 2013).

Five of 11 studies examining frontal lobes (Pannacciulli et al., 2006; Ogura et al., 2011; Smucny et al., 2012; Alosco et al., 2013; Weise et al., 2013) noted an association between higher BMI and lower GM, also suggesting mixed results. Interestingly, 6 of 9 reports specifically assessing PFC (Pannacciulli et al., 2006; Maayan et al., 2011; Ogura et al., 2011; Smucny et al., 2012; Ursache et al., 2012; Weise et al., 2013) found that higher BMI or fat mass predicted less GM volume. Furthermore, Maayan and colleagues (2011), found that obese participants performed markedly worse than lean controls on executive tasks, particularly on a Stroop task, and linked lower frontal volumes with worse executive performance. These findings may reflect the generally consistent relationship between more adiposity and worse executive performance in children and adolescents (Liang et al., 2013).

Finally, 4 of 7 reports examining global or regional WM (Pannacciulli et al., 2006; Haltia et al., 2007; Brain Development Cooperative Group, 2012; Yokum et al., 2012) found that more WM was related to more adiposity, whereas 2 of 7 reports examining global or regional WM (Ogura et al., 2011; Yokum et al., 2012) found that more adiposity was associated with less WM volume. Similar studies examining WM microstructure using DTI clarify these findings and will be discussed later in the review.

3.3. Adiposity and brain atrophy: middle-aged to aged adults (>40 years of age)

Many studies have been motivated by the link between obesity and AD risk (Gustafson et al., 2003; Beydoun et al., 2008; Elias et al., 2012) to examine associations between adiposity and regional brain volumes or metabolite concentrations in older cohorts. Twenty-nine studies have been published as of August 2013 in middle-aged (Ward et al., 2005; Gazdzinski et al., 2008; Gunstad et al., 2008; Taki et al., 2008; Ruehl et al., 2009; DeBette et al., 2010, 2011; Gonzales et al., 2012; Hassenstab et al., 2012; Haley et al., 2013; Karlsson et al., 2013; Kurth et al., 2013; Zade et al., 2013) or aged participants (Gustafson et al., 2004; Jagust et al., 2005; Soreca et al., 2009; Anan et al., 2010; Gazdzinski et al., 2010; Ho et al., 2010a,b, 2011a,b; Raji et al., 2010; Walther et al., 2010; Widya et al., 2011; Bobb et al., 2012; Driscoll et al., 2012; Brooks et al., 2013a; Metzler-Baddeley et al., 2013). Twenty-one reports used BMI continuously or used it to define subgroups from lean to morbidly obese categories, whereas the remainder used BMI and one or more other anthropometric indices (5), WHR quartiles (1), SAT and VAT with anthropometric indices (1), or VAT alone (1). Thirteen of these studies met our criteria for being optimal and will be briefly detailed before summarizing findings from the literature. We note that the Cardiovascular Health Study Cognition Study sample used by Raji et al. (2010) was likely used in a subsequent paper (Ho et al., 2011a), after more CHS-CS participants had been added to the analysis. We therefore highlight the Raji paper for its technical merits, but do not include it in our tallies below.

Taki et al. (2008) were the first group to examine BMI and voxel-wise GM associations with a very large cohort of 1428 middle-aged Japanese participants. In men but not women, higher BMI corresponded to less global GM, as well as less regional GM in inferior

and medial temporal, precuneus, anterior cerebellar, prefrontal, and midbrain regions. Unlike most groups using voxel-wise analyses, they also conversely tested if higher BMI corresponded to more GM and found significant clusters in frontal and temporal areas, thalamus, caudate, and posterior cerebellum. [Soreca et al. \(2009\)](#) examined baseline BMI and BMI change over a 15–20 year period from 1983–1984 (the time of initial evaluation) to 2005–2006 (when MRI was acquired) in 48 healthy, postmenopausal women (mean age at MRI = 67.1 ± 1.3). BMI increase of over time predicted less global GM volume, whereas no relationship was found for global WM. [Walther et al. \(2010\)](#) compared cognitive performance and regional GM and WM using voxel-wise analysis in 53 lean, 22 overweight, and 20 obese older women (mean age = 69.3 ± 9.3 years). Obese participants had worse executive function. Higher BMI corresponded to lower GM in frontal, inferior and medial temporal but not hippocampal, inferior parietal, and occipital areas, as well as cerebellum. Less GM in orbital frontal cortex was associated with poorer executive performance. In addition, BMI predicted less WM volume in all 4 lobes. [Widya et al. \(2011\)](#) tested if 140 lean, 256 overweight, and 75 obese, non-demented participants (mean age = 74.3 ± 3.1 years) varied in 7 sub-cortical volumes. Obese versus lean participants had significantly larger bilateral amygdala and left hippocampus, even after type 1 error and covariate correction. [Gonzales et al. \(2012\)](#) used MRS in occipitoparietal junction to examine brain tissue metabolites, cognition, and continuous BMI in 54 middle-aged participants (mean age = 50.7 ± 6.3 years). Higher BMI predicted higher Myoinositol/Creatine, a ratio thought to represent glial tissue content, but not N-Acetyl-Aspartate/Choline (NAA:Choline), a ratio thought to reflect neuronal density. Using structural equation modeling, higher values of Myoinositol/Creatine significantly mediated lower scores on a global cognitive index comprised of several memory, executive function, and general intelligence measures. [Gazdzinski et al. \(2008\)](#), in 50 middle-aged adults (mean age = 43.1 ± 8.03 years), in part examined associations between higher BMI and NAA metabolite concentrations in frontal, parietal, temporal, and occipital lobes. After Bonferroni correction, higher BMI was related to less NAA in frontal GM, as well as frontal, temporal, and parietal WM.

[Hassenstab et al. \(2012\)](#) examined 17 obese, 19 always-lean participants, and 17 successful weight loss maintainers who were once obese but had been lean for at least 3 years (mean age = 46.6 ± 9.1 years). An ROI approach was used to compare cortical thickness in anterior insula, dorsal anterior cingulate, dorsal PFC, and posterior parietal cortex including precuneus. Obese versus always-lean participants had less GM in anterior insula, dorsal anterior cingulate, and posterior parietal cortex. Importantly, weight loss maintainers had brain volumes between obese and lean groups and did not significantly differ from either of them. This result suggests that GM atrophy associated with obesity might be ameliorated with weight loss, but prospective interventional studies are needed to confirm this finding.

Several consistent findings have emerged in findings from large cohorts such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and/or CHS-CS cohorts. [Raji et al. \(2010\)](#) initially compared GM volume between 29 lean, 51 overweight, and 14 obese participants (mean age = 77.2 ± 3.1 years), or across groups using continuous BMI, with tensor-based morphometry (TBM). These participants had remained cognitively stable for at least 5 years after the brain scan, which minimized any potential atrophy due to dementia. Across participants, there were small to moderate correlations between higher BMI and lower GM in medial temporal lobe including hippocampus, frontal lobe, sub-cortical midline areas, anterior cingulate, and subcortical WM volume. Similarly, obese participants showed less GM volume in these regions versus lean participants. Ho and colleagues ([Ho et al., 2010b](#)) extended this work by examining not only continuous BMI and TBM in 206

ADNI participants (mean age = 76.2 ± 5 years), but also non-risk ($n=78$) versus risk ($n=128$) genotype groups for the FTO gene, which has been associated with increased fat mass and higher obesity prevalence ([Dina et al., 2007](#)). Higher BMI predicted lower volume predominantly in deep WM, and frontal and occipital GM, but not hippocampus unlike Raji and colleagues. Higher BMI also predicted higher GM in precuneus. Interestingly, FTO risk carriers showed less GM in occipital and frontal areas that overlapped with areas associated with BMI. Another noteworthy study ([Ho et al., 2010a](#)) examined BMI and TBM in 476 Mild Cognitive Impairment (MCI) and 224 AD participants. Each BMI point increase was related to a 0.5–1.5% decrease in WM volume in brainstem and cerebellum, as well as medial PFC, occipital lobe, globus pallidus, cerebellum, and brain stem GM. Relative increases were found in anterior cingulate, precuneus, occipital lobe, and dorsal PFC GM. One of the clusters partially covered the hippocampus, but it is unclear to us whether that coverage genuinely reflects contraction in hippocampus, or is due to the strength of the association between higher BMI and volume contraction within nearby WM.

Finally, the Framingham Heart Study has also produced several reports on obesity and brain. [DeBette et al. \(2010\)](#) cross-sectionally assessed 733 middle-aged participants (mean age = 60 ± 9 years) using standardized ROIs of total brain volume and temporal horn volume. Temporal horn volume is a CSF measure that increases as hippocampal volume decreases. Adiposity was measured using BMI, WC, and WHR, as well as SAT and VAT. Higher values for any adiposity measure predicted less TBV, especially VAT. In addition, WHR predicted increased temporal horn volume, suggesting relatively smaller hippocampi. Later, in a larger middle-aged cohort of 1352 participants ([DeBette et al., 2011](#)) (mean age = 54 ± 9 years), annual changes from baseline to roughly 7 years later were assessed for TBV, temporal horn volume, and cognition. Across all participants, no relationships between BMI, WHR, or WC were found with annual changes in MRI or cognition, although the authors note an unusually strong cross-sectional association between higher WHR and lower TBV (10.81 Odds Ratio) in those participants in the top quartile of change in brain or cognitive indices. Finally, [Zade et al. \(2013\)](#) examined TBV, lateral ventricle volume, frontal brain volume, and temporal horn volume in 494 middle-aged participants. The fourth quartile of WHR was used to represent central obesity. Fourth Quartile WHR was significantly associated with lower TBV, frontal volume, higher CSF volume in lateral ventricle and temporal horn, and worse performance on executive function and memory tasks. The inclusion of frontal volume and moderating effects of ApoE Genotype (see Supplemental Table 1) distinguish this analysis from [DeBette et al. \(2010\)](#).

3.3.1. Summary of findings for middle-aged to aged participants (>40 years of age)

For participants aged 40 years or older, 5 of the 8 reports that assessed total brain volume ([Ward et al., 2005](#); [Gunstad et al., 2008](#); [DeBette et al., 2010, 2011](#); [Zade et al., 2013](#)) found a negative association with more adiposity. Three of 6 reports assessing global GM also found that more adiposity predicted less volume ([Gunstad et al., 2008](#); [Taki et al., 2008](#); [Soreca et al., 2009](#)). Seven of 14 studies examining occipital lobes report negative associations with more adiposity and brain volume ([Ho et al., 2010a,b, 2011a](#); [Walther et al., 2010](#); [Bobb et al., 2012](#); [Karlsson et al., 2013](#); [Kurth et al., 2013](#)). While the Ho and Raji studies consistently noted this association ([Ho et al., 2010b, 2011a,b](#); [Raji et al., 2010](#)), studies with larger cohorts ([Taki et al., 2008](#)) have not found this relationship. Longitudinal studies examining occipital atrophy and adiposity are also mixed as either not finding ([Bobb et al., 2012](#); [Driscoll et al., 2012](#)) or finding ([Walther et al., 2010](#)) a link.

Seven of 13 studies examining parietal lobes report negative associations between lower volume and more adiposity ([Taki et al.,](#)

2008; Ho et al., 2010a,b, 2011a; Walther et al., 2010; Karlsson et al., 2013; Kurth et al., 2013). Three of these 13 studies using ADNI and/or CHS-CS data from different sub-samples simultaneously showed a positive association with posterior-medial parietal volume (Ho et al., 2010a,b, 2011a). Four of 14 studies examining precuneus and posterior cingulate volume (Taki et al., 2008; Driscoll et al., 2012; Hassenstab et al., 2012; Karlsson et al., 2013) report negative associations with more adiposity, whereas 3 of 14 studies examining precuneus and posterior cingulate volume (Ho et al., 2010a,b, 2011a) report positive associations with more adiposity.

Nine of 13 studies examining temporal lobe (Jagust et al., 2005; Taki et al., 2008; Ho et al., 2010a,b, 2011a; Walther et al., 2010; Bobb et al., 2012; Karlsson et al., 2013; Kurth et al., 2013) report negative associations with temporal lobe GM volumes and more adiposity, whereas Taki and colleagues (2008) report a positive relationship. While hippocampus has been the central focus of this literature, only 9 of 19 reports examining hippocampal volume (Jagust et al., 2005; Taki et al., 2008; Bruehl et al., 2009; Anan et al., 2010; Debetto et al., 2010; Ho et al., 2010a,b, 2011a; Kurth et al., 2013) found the expected relationship between greater hippocampal atrophy and more adiposity, while Widya et al. (2011) and Bobb et al. (2012) showed that more adiposity predicted less atrophy. Effect sizes or correlations were generally small. Five of 10 reports examining the insula (Ho et al., 2010a,b, 2011a; Raji et al., 2010; Hassenstab et al., 2012; Kurth et al., 2013) found a negative association between lower GM volume and more adiposity, whereas Taki et al. (2008) showed more adiposity predicted more insula volume.

Ten of 14 studies examining frontal lobe volume found that more adiposity corresponded to greater atrophy (Gazdzinski et al., 2008; Taki et al., 2008; Ho et al., 2010a,b, 2011a; Walther et al., 2010; Brooks et al., 2013b; Karlsson et al., 2013; Kurth et al., 2013; Zade et al., 2013). Two of these 15 studies examining frontal lobe volume showed that higher adiposity predicted higher GM volume (Taki et al., 2008; Ho et al., 2010a). Eleven of 14 studies examining PFC found that more adiposity was related to less GM volume (Taki et al., 2008; Gazdzinski et al., 2010; Ho et al., 2010a,b, 2011a; Walther et al., 2010; Hassenstab et al., 2012; Brooks et al., 2013a; Karlsson et al., 2013; Kurth et al., 2013; Zade et al., 2013). Among the 14 studies assessing PFC, Taki et al. (2008) conversely found that more adiposity predicted more GM in PFC.

Finally, 7 of 12 studies examining global or regional WM (Gazdzinski et al., 2008; Ho et al., 2010a,b, 2011a; Driscoll et al., 2012; Karlsson et al., 2013; Metzler-Baddeley et al., 2013) found a negative association between WM volume and more adiposity, while two other groups (Walther et al., 2010; Bobb et al., 2012) noted the opposite relationship.

4. Discussion

4.1. Overall findings

The most consistent finding of studies in both younger and older cohorts is that more adiposity is related to GM atrophy in frontal lobe and PFC. In middle-aged and aged adults, more adiposity is associated with temporal GM atrophy and to a lesser degree parietal GM atrophy. Adiposity is not consistently related to global and regional WM volume in any age group. The different findings for older and younger cohorts may be due to methodology. For instance, almost all of the reviewed studies in younger cohorts used BMI as an index of adiposity instead of WC, WHR, or direct measures of fat mass. Alternatively, younger people may not be affected by certain adiposity-related mechanisms of brain atrophy. For example, vascular disease requires chronicity, and secretion of proinflammatory cytokines from adipose tissue, increases with age (Michaud et al., 2013). Finally, younger

brains show greater plasticity in response to stressors and, which may partially or wholly mitigate any deleterious effects of adiposity (McEwen and Morrison, 2013).

For occipital lobe, most studies find no relationship with adiposity regardless of age. The few reported occipital associations come almost exclusively from voxel-wise analyses, often as part of a larger cluster that includes cerebellum. For parietal lobe, adiposity is associated with GM volume in older adults but not children and young adult cohorts. Generally, these associations are found within superior and to a lesser extent inferior parietal areas.

The temporal lobe has received an immense amount of attention for its role in AD (Beydoun et al., 2008) and learning and memory (Liang et al., 2013; Reinert et al., 2013). Reported associations with adiposity are more consistent for the temporal lobe as a whole than for hippocampus. Although no consistent pattern was apparent in young cohorts, almost all methodologically rigorous studies in older participants showed temporal atrophy with more adiposity (Taki et al., 2008; Ho et al., 2010a,b; Raji et al., 2010; Walther et al., 2010). Importantly, when higher visceral fat, a specific measure for central adiposity, was studied in young (Weise et al., 2013) and aged (Anan et al., 2010) adults, it also predicted lower temporal volume. In general, adiposity had no associations with hippocampus in younger cohorts. Among middle-aged and aged adults, on the one hand, none of the studies examining hippocampal atrophy longitudinally found any association with adiposity (Debetto et al., 2011; Bobb et al., 2012; Driscoll et al., 2012). Most null findings studies used categorical BMI comparisons, typically obese versus lean, and used voxel-wise analysis. On the other hand, most of the rigorous cross-sectional studies meeting our criteria did find a negative association between more adiposity and lower hippocampal volume (Taki et al., 2008; Debetto et al., 2010; Ho et al., 2010a; Raji et al., 2010; Zade et al., 2013), while a report from Widya et al. (2011) found a positive association with left hippocampal volume.

More adiposity predicting lower frontal GM, and in particular PFC volume, has by far been the most consistent finding in the literature. Among studies of younger cohorts that met our criteria, roughly half found a frontal relationship (Pannacciulli et al., 2006; Alosco et al., 2013; Weise et al., 2013) and half did not (Brain Development Cooperative Group, 2012; Haltia et al., 2007; Yokum et al., 2012). However, we note that the Haltia and Yokum reports found non-significant associations in frontal areas. *The Brain Development Cooperative Group sample was also relatively lean (mean \pm SD BMI = 19.24 \pm 4.3), which may explain the lack of association between BMI and frontal GM.* Among middle-aged and aged participants, studies that did not find an association with regard to frontal GM (Gustafson et al., 2004; Gunstad et al., 2008; Driscoll et al., 2012) either used overly stringent error correction, or a qualitative index of atrophy, or suffered from not including important covariates.

For global or regional WM, adiposity was related to variation in volume, but the directionality varied greatly, especially in participants less than 40 years of age. In the study by Haltia et al. (2007), six weeks of a very low calorie diet reduced WM volume, such that once obese participants no longer had more WM volume than lean controls (Haltia et al., 2007), suggesting a dynamic modulation of WM volume by obesity. Using DTI, which assesses the microstructural integrity of WM axons and myelin using fractional anisotropy or mean diffusivity of water (Song et al., 2002), several groups have found that more adiposity consistently predicted lower WM microstructural integrity among younger (Mueller et al., 2011; Xu et al., 2013), middle-aged (Alkan et al., 2008; Stanek et al., 2011; Karlsson et al., 2013), and aged (Marks et al., 2011; Metzler-Baddeley et al., 2013) participants. This consistency in DTI findings may be contrasted with the inconsistent associations found between BMI and WM volume, particularly in younger cohorts. In general, WM volumetric and DTI studies offer complementary information, since aging or insults of variable intensity may decrease WM microstructural integrity without

decreasing (or even while increasing) WM volume (Kou et al., 2013; Tseng et al., 2013). Collectively, these DTI results suggest that WM, regardless of age, may be less intact as adiposity increases.

4.2. Adiposity and brain atrophy: potential mechanisms

4.2.1. Inflammation

It is now well established that adipose tissue is not inert, but rather actively produces proinflammatory cytokines and chemokines primarily via macrophage activation (Johnson et al., 2012). Inflammatory activity in the gut and brain is highly integrated and bidirectional due to vagal innervation (Dantzer, 2004). Obesity can induce gliosis and damage in the hypothalamus in rodents and humans (Thaler et al., 2012), while a 5 month high-fat diet in male rodents leads to increased expression of prostaglandin E₂, cyclooxygenases, and reactive oxygen species in rat cortex, suggesting increased neuroinflammation and oxidative stress (Zhang et al., 2005). Neuroinflammation is generally thought to contribute to brain atrophy and worse cognitive performance (Wilson et al., 2002). Given their ease of acquisition, peripheral cytokines reflecting systemic, and to some degree brain, inflammation are often used in combined biomarkers-neuroimaging studies. Higher concentrations of peripheral interleukin-6, a proinflammatory cytokine, are associated with less hippocampal volume cross-sectionally in middle-aged (Marstrand et al., 2008) and aged (Satizabal et al., 2012) adults. It is also relevant to highlight recent voxel-wise studies in aged rhesus macaques on an ad libitum enriched diet or long-term calorie restriction (CR; see 4.3.1.). Higher peripheral levels of the proinflammatory cytokine IL-6 predicted less GM volume or tissue density in temporal, frontal, and parietal regions (Willette et al., 2010). Conversely, higher peripheral concentrations of the anti-inflammatory cytokine IL-10 among CR but not control monkeys was associated with more volume or greater microstructural integrity in similar regions, particularly dorsal PFC (Dantzer, 2004). Higher levels of the proinflammatory chemokine IL-8 have also been related to lower volume exclusively in bilateral hippocampus for control but not CR monkeys (Dantzer, 2004). Central IL-8 is predominantly released by microglia in brain, particularly in hippocampus and hypothalamus in at least rodents (Licinio et al., 1992), where IL-8 can have neurotoxic actions through secondary mediators like amyloid-beta (Franciosi et al., 2005; Liu et al., 2010).

4.2.2. Vascular risk factors

Cardiovascular risk factors, such as dyslipidemia (Launer, 2002), midlife hypertension (Fillit et al., 2008), and other components of the metabolic syndrome (Yaffe, 2007) can affect the brain vasculature and may additively contribute to increased AD risk. However, risk factors examined individually show complex or inconsistent results with respect to brain volume and cognition. For example, high-density but not low-density lipoprotein or total cholesterol concentrations have been associated with lower hippocampal volume and higher AD risk (Wolf et al., 2004), whereas hypercholesterolemia in cognitively normal elders either does not show this relationship (Debette et al., 2011) or predicts higher total cerebral volume, as suggested by the Rotterdam study (Hoogendam et al., 2012). Treatment with statins may decrease neurofibrillary tau pathology (Li et al., 2007) but not GM atrophy over time (ten Dam et al., 2005).

Midlife systolic hypertension predicts declines in executive function over roughly a decade later, but no changes in total brain or temporal horn volumes (Debette et al., 2011). Annualized medial temporal atrophy over 2.4 years, however, is significantly associated with higher systolic and diastolic blood pressure but not lipoproteins in elders (de Jong et al., 2014). Biomarkers of vascular stiffness induced by impaired nitric oxide production may contribute to the development of small vessel disease, which is

associated with brain atrophy in normally aging but not cognitively impaired participants (Barnes et al., 2013). Indeed, a peripheral biomarker of impaired nitric oxide synthase, asymmetrical dimethylarginine, predicts greater prevalence of stroke and subclinical vascular injury manifested as WM hyperintensities (Pikula et al., 2009).

4.2.3. Insulin resistance

In the brain, insulin normally facilitates microvascular blood flow, glucose uptake, and glucose oxidation for ATP generation (Cersosimo and DeFronzo, 2006). IR is defined broadly as reduced cellular responsiveness to insulin (Goldstein, 2002), and is characterized by higher insulin levels needed to maintain glucose levels in the periphery and brain. Critically, IR develops in up to 40% of late middle-aged adults who are overweight or obese (Matsuzawa et al., 2011). IR is found in AD patient brains (Giordano et al., 2007). For example, hippocampal tissue from AD patients versus cognitively normal controls shows impaired insulin signaling, reflecting brain IR, which strongly predicted worse antemortem cognitive performance (Talbot et al., 2012). IR may also increase AD risk (Craft and Watson, 2004; Schrijvers et al., 2010).

Higher IR also predicts less brain volume in AD-sensitive regions in primates. In aged rhesus macaques, long-term calorie restriction increased insulin sensitivity (i.e., lowered IR) derived from a glucose tolerance test. Higher insulin sensitivity in CR but not control monkeys was related to more volume in ventral PFC and bilateral hippocampus (Willette et al., 2012a). Higher baseline IR in middle-aged adults at risk for AD corresponded to less GM volume over 4 years, and IR was a mediator of worse memory performance (Willette et al., 2013a). Although there are many pathophysiological processes that may underlie these associations, Bomfim et al. (2012) found that amyloid beta oligomers injected into the brains of cynomolgus monkeys lead to neuron-specific increases in *c-Jun N-terminal kinase* (JNK) activity induced by tumor necrosis factor- α signaling, subsequent serine phosphorylation of *insulin receptor substrate-1* (IRS-1) in hippocampus, and axonal transport dysfunction. These results suggest that complex interactions between amyloid, inflammation, and insulin resistance may disrupt tissue function and could eventually lead to tissue atrophy.

4.2.4. Glucocorticoid and brain-derived neurotrophic factor signaling

Obesity can induce higher cortisol secretion through increased hypothalamic-pituitary-adrenocortical axis activity (Bjorntorp, 1996). Many studies, such as in Lupien et al. (1998), have shown that higher cortisol levels may be associated with brain atrophy and worse cognitive performance. In rodents, streptozocin-induced diabetes resulted in deficits in hippocampal synaptic plasticity partly via elevated corticosterone (Stranahan et al., 2008). More recent evidence suggests that obesity per se, in at least adolescents, mediates the relationship between higher waking cortisol response and atrophy in hippocampus and frontal lobe (Ursache et al., 2012). Indeed, mediation of the awakening cortisol secretion response by hippocampus and PFC is dysregulated in obesity (Dedovic et al., 2009).

One potential mechanism underlying the effects of cortisol may be decreased brain-derived neurotrophic factor (BDNF), a key modulator of synaptic activity in hippocampus and other areas (see Pluchino et al., 2013). Restraint stress in rodents raised peripheral cortisol and lowered BDNF mRNA expression in hippocampus (Walton et al., 2012). Dexamethazone, a synthetic glucocorticoid, lowered rodent BDNF levels in cultured hippocampal neurons (Strle et al., 2004). By contrast, lowering corticosterone levels in *diabetic/diabetic* (*db/db*) transgenic mice selectively restored BDNF mRNA expression in hippocampal dentate gyrus (Stranahan et al., 2011). Thus, increased glucocorticoid signaling may have

downstream effects via BDNF that may have downstream effects such as reduced synaptic plasticity and induced atrophy.

4.3. Adiposity and brain atrophy: evidence from interventions

4.3.1. Calorie restriction and weight loss

Calorie restriction, or CR is defined as limiting caloric intake without loss of nutrient content. CR reduces central adiposity in rhesus monkeys (Colman et al., 2009) and humans (Johnson et al., 2007; Harvie et al., 2011, 2013). In the longitudinal University of Wisconsin-Madison study on 30% long-term, chronic CR in aged rhesus macaques (see Colman et al., 2009 for an overview), long-term CR helped to preserve GM volume bilaterally in temporal and frontal cortices, insula, cingulate cortex, and sub-cortical areas (Colman et al., 2009), as well as WM volume in the centrum semiovale, corpus callosum, and several occipital and parietal tracts (Bendlin et al., 2011).

Furthermore, beneficial effects of CR were noted for peripheral inflammation, vascular factors, insulin sensitivity, and other blood-based parameters that may have indirect ameliorative effects on brain volume, tissue microstructural integrity, and cognition. As noted above, long-term CR reduced IL-6 and IL-8 while increasing concentrations of IL-10 (Dantzer, 2004; Willette et al., 2010, 2013b). CR monkeys showed a weaker or non-significant association with lower PFC and hippocampal volume or microstructure per point increase in IL-6 or IL-8, whereas associations between higher IL-10 and brain indices were significantly stronger. These results suggest an ameliorative effect of CR on brain atrophy via reduced pro-inflammatory and increased anti-inflammatory peripheral interleukins, which to a degree reflect their central concentrations.

In addition CR monkeys showed less WM atrophy and more microstructural density per point higher homocysteine levels primarily in brainstem and cerebellum, as well as less GM atrophy in occipital, hippocampal, caudoputamen, and anterior cingulate areas (Willette et al., 2012b). CR also considerably reduced stress reactivity (Willette et al., 2012c), where aged monkeys on CR showed less corresponding atrophy per point increase in a z-scored stress factor in many WM tracts, as well as similar amelioration in GM volume or microstructural density for orbital PFC and hippocampus. Finally, CR monkeys had many fewer perseverative errors and achieved task criterion in fewer trials for the most complicated Wisconsin Card Sort Test set-shifting tasks (Sridharan et al., 2012). Fewer errors corresponded to more GM in orbital PFC, an area where CR monkeys have more volume.

In regards to human weight loss intervention studies, we have already referred to the study by Haltia et al. (2007) that found that WM, but not GM, volume may change after a 6 week very low calorie diet. This result is inconsistent with the retrospective study by Hassenstab et al. (2012) that found that previously obese people who had maintained weight loss for 3 years did not have different GM or WM thickness from either lean or obese groups. More dietary intervention studies are needed to determine whether or not weight loss has any effects on adiposity and brain associations.

4.3.2. Exercise

Non-sedentary adults are less likely to develop AD (Rockwood and Middleton, 2007). Cardiorespiratory fitness in early AD, but not cognitively normal controls, is associated with less whole brain atrophy (Burns et al., 2008). A 24-week moderate-intensity exercise program can modestly reduce cognitive decline in cognitively impaired adults without dementia (Lautenschlager et al., 2008). By extension, moderate aerobic exercise can also have beneficial effects on the brain. Erickson et al. (2011) recently found in 60 aged, previously sedentary adults that moderate aerobic exercise (i.e., walking) led to increased anterior hippocampal volume

1 year after baseline by roughly 2%, whereas 60 controls showed age-typical atrophy over 1 year of roughly 1.4%. Nevertheless, cognitive performance on word list recall and ADAS-Cog remained comparable between groups. Curiously, however, 93 aged women who engaged in once- or twice-weekly resistance training showed improved Stroop executive function performance, but not set-shifting or working memory, after 1 year compared to 42 controls (Liu-Ambrose et al., 2010). Curiously, the resistance training group but not the controls showed a modest decrease in total brain volume.

5. Conclusions

Obesity is a common health concern that clearly increases the risk for developing cardiovascular disease, various cancers, and AD. Contrary to many statements that appear in the literature and suggest a strong association between more adiposity and brain atrophy, our systematic review demonstrated that more adiposity has regionally selective and typically modest to moderate associations with brain atrophy. Frontal lobe atrophy, and in particular PFC, is most consistently associated with more adiposity in younger and older cohorts. Associations between more adiposity and lower parietal volumes were seen only in older cohorts, but not in precuneus or posterior cingulate areas, which are of particular interest for their role in AD. Hippocampal atrophy is not consistently linked with adiposity. The association between more adiposity and increased AD risk (Beydoun et al., 2008) may be mediated by factors other than hippocampal atrophy.

To further clarify these associations, it is important for future studies to quantitatively assess visceral fat mass and non-fat mass, and obtain longitudinal measures of brain atrophy. Weise et al. (2013), for example, found that associations between higher non-fat mass and brain atrophy were robust, whereas findings with fat mass were rendered non-significant after covarying non-fat mass. Longitudinal TBM has been used to assess modest associations with insulin resistance and brain atrophy using Jacobian determinant maps (Willette et al., 2013a), which may be more sensitive to regional variation than anatomical ROI approaches. Neuroimaging approaches optimized for longitudinal studies could be included in studies that study anti-obesity interventions, such as in calorie restriction, not only to establish associations between brain volume loss over time and adiposity, but also to assess the reversibility of underlying pathophysiological mechanisms.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.arr.2014.03.007>.

References

- Alkan, A., Sahin, I., Keskin, L., Cikim, A.S., Karakas, H.M., Sigirci, A., Erdem, G., 2008. Diffusion-weighted imaging features of brain in obesity. *Magnet. Reson. Imag.* 26, 446–450.
- Alosco, M.L., Stanek, K.M., Galioto, R., Korgaonkar, M.S., Grieve, S.M., Brickman, A.M., Spitznagel, M.B., Gunstad, J., 2013. Body mass index and brain structure in healthy children and adolescents. *Int. J. Neurosci.*
- Anan, F., Masaki, T., Shimomura, T., Fujiki, M., Umeno, Y., Eshima, N., Saikawa, T., Yoshimatsu, H., 2010. Abdominal visceral fat accumulation is associated with hippocampal volume in non-dementia patients with type 2 diabetes mellitus. *NeuroImage* 49, 57–62.
- Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry—the methods. *NeuroImage* 11, 805–821.
- Barnes, J., Carmichael, O.T., Leung, K.K., Schwarz, C., Ridgway, G.R., Bartlett, J.W., Malone, I.B., Schott, J.M., Rossor, M.N., Biessels, G.J., DeCarli, C., Fox, N.C., 2013. Vascular and Alzheimer's disease markers independently predict brain atrophy rate in Alzheimer's Disease Neuroimaging Initiative controls. *Neurobiol. Aging* 34, 1996–2002.
- Bendlin, B.B., Canu, E., Willette, A., Kastman, E.K., McLaren, D.G., Kosmatka, K.J., Xu, G., Field, A.S., Colman, R.J., Coe, C.L., Weindruch, R.H., Alexander, A.L., Johnson,

- S.C., 2011. Effects of aging and calorie restriction on white matter in rhesus macaques. *Neurobiol. Aging* 32 (2319), e2311.
- Beydoun, M.A., Beydoun, H.A., Wang, Y., 2008. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obesity Rev.: Off. J. Int. Assoc. Study Obesity* 9, 204–218.
- Bjorntorp, P., 1996. The regulation of adipose tissue distribution in humans. *Int. J. Obesity Related Metab. Disord.: J. Int. Assoc. Study Obesity* 20, 291–302.
- Bobb, J.F., Schwartz, B.S., Davatzikos, C., Caffo, B., 2012. Cross-sectional and longitudinal association of body mass index and brain volume. *Human Brain Mapp.*
- Bomfim, T.R., Forny-Germano, L., Sathler, L.B., Brito-Moreira, J., Houzel, J.C., Decker, H., Silverman, M.A., Kazi, H., Melo, H.M., McClean, P.L., Holscher, C., Arnold, S.E., Talbot, K., Klein, W.L., Munoz, D.P., Ferreira, S.T., De Felice, F.G., 2012. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated Abeta oligomers. *J. Clin. Invest.* 122, 1339–1353.
- Brooks, S.J., Benedict, C., Burgos, J., Kempton, M.J., Kullberg, J., Nordenskjold, R., Kilander, L., Nylander, R., Larsson, E.M., Johansson, L., Ahlstrom, H., Lind, L., Schioth, H.B., 2013a. Late-life obesity is associated with smaller global and regional gray matter volumes: a voxel-based morphometric study. *Int. J. Obes. (Lond.)* 37, 230–236.
- Brooks, S.J., Cedernaes, J., Schioth, H.B., 2013b. Increased prefrontal and parahippocampal activation with reduced dorsolateral prefrontal and insular cortex activation to food images in obesity: a meta-analysis of fMRI studies. *PLoS One* 8, e60393.
- Bruehl, H., Wolf, O.T., Sweat, V., Tirsi, A., Richardson, S., Convit, A., 2009. Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. *Brain Res.* 1280, 186–194.
- Burns, J.M., Cronk, B.B., Anderson, H.S., Donnelly, J.E., Thomas, G.P., Harsha, A., Brooks, W.M., Swerdlow, R.H., 2008. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. *Neurology* 71, 210–216.
- Cassidy, S.B., 1997. Prader-Willi syndrome. *J. Med. Genet.* 34, 917–923.
- Cersosimo, E., DeFronzo, R.A., 2006. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. *Diabetes/Metab. Res. Rev.* 22, 423–436.
- Colman, R.J., Anderson, R.M., Johnson, S.C., Kastman, E.K., Kosmatka, K.J., Beasley, T.M., Allison, D.B., Cruzen, C., Simmons, H.A., Kemnitz, J.W., Weindruch, R., 2009. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science* 325, 201–204.
- Craft, S., Foster, T.C., Landfield, P.W., Maier, S.F., Resnick, S.M., Yaffe, K., 2012. Session III: mechanisms of age-related cognitive changes and targets for intervention: inflammatory, oxidative, and metabolic processes. *J. Gerontol. A Biol. Sci. Med. Sci.* 67, 754–759.
- Craft, S., Watson, G.S., 2004. Insulin and neurodegenerative disease: shared and specific mechanisms. *Lancet Neurol.* 3, 169–178.
- Dalton, M., Cameron, A.J., Zimmet, P.Z., Shaw, J.E., Jolley, D., Dunstan, D.W., Welborn, T.A., 2003. Waist circumference, waist-hip ratio and body mass index and their correlation with cardiovascular disease risk factors in Australian adults. *J. Int. Med.* 254, 555–563.
- Dantzer, R., 2004. Innate immunity at the forefront of psychoneuroimmunology. *Brain, Behav. Immun.* 18, 1–6.
- de Jong, L.W., Forsberg, L.E., Vidal, J.S., Sigurdsson, S., Zijdenbos, A.P., Garcia, M., Eiriksdottir, G., Gudnason, V., van Buchem, M.A., Launer, L.J., 2014. Different susceptibility of medial temporal lobe and basal ganglia atrophy rates to vascular risk factors. *Neurobiol. Aging* 35, 72–78.
- Debette, S., Beiser, A., Hoffmann, U., Decarli, C., O'Donnell, C.J., Massaro, J.M., Au, R., Himali, J.J., Wolf, P.A., Fox, C.S., Seshadri, S., 2010. Visceral fat is associated with lower brain volume in healthy middle-aged adults. *Ann. Neurol.* 68, 136–144.
- Debette, S., Seshadri, S., Beiser, A., Au, R., Himali, J.J., Palumbo, C., Wolf, P.A., DeCarli, C., 2011. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology* 77, 461–468.
- Dedovic, K., Duchesne, A., Andrews, J., Engert, V., Pruessner, J.C., 2009. The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. *NeuroImage* 47, 864–871.
- Del Parigi, A., Gautier, J.F., Chen, K., Salbe, A.D., Ravussin, E., Reiman, E., Tataranni, P.A., 2002. Neuroimaging and obesity: mapping the brain responses to hunger and satiation in humans using positron emission tomography. *Ann. N. Y. Acad. Sci.* 967, 389–397.
- Dina, C., Meyre, D., Gallina, S., Durand, E., Korner, A., Jacobson, P., Carlsson, L.M., Kiess, W., Vatin, V., Lecoq, C., Delplanque, J., Vaillant, E., Pattou, F., Ruiz, J., Weill, J., Levy-Marchal, C., Horber, F., Potoczna, N., Hercberg, S., Le Stunff, C., Bougneres, P., Kovacs, P., Marre, M., Balkau, B., Cauchi, S., Chevre, J.C., Froguel, P., 2007. Variation in FTO contributes to childhood obesity and severe adult obesity. *Nat. Genet.* 39, 724–726.
- Donkelaar, H.J., 2011. *Clinical Neuroanatomy: Brain Circuitry and its Disorders*. Springer, Heidelberg, New York.
- Driscoll, I., Beydoun, M.A., An, Y., Davatzikos, C., Ferrucci, L., Zonderman, A.B., Resnick, S.M., 2012. Midlife obesity and trajectories of brain volume changes in older adults. *Human Brain Mapp.* 33, 2204–2210.
- Elias, M.F., Goodell, A.L., Waldstein, S.R., 2012. Obesity, cognitive functioning and dementia: back to the future. *J. Alzheimer's Dis.: JAD* 30 (Suppl. 2), S113–S125.
- Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kim, J.S., Heo, S., Alves, H., White, S.M., Wojcicki, T.R., Mailey, E., Vieira, V.J., Martin, S.A., Pence, B.D., Woods, J.A., McAuley, E., Kramer, A.F., 2011. Exercise training increases size of hippocampus and improves memory. *Proc. Natl. Acad. Sci. U. S. A.* 108, 3017–3022.
- Fillit, H., Nash, D.T., Rundek, T., Zuckerman, A., 2008. Cardiovascular risk factors and dementia. *Am. J. Geriatr. Pharmacother.* 6, 100–118.
- Flegal, K.M., Graubard, B.I., Williamson, D.F., Gail, M.H., 2007. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA: J. Am. Med. Assoc.* 298, 2028–2037.
- Franciosi, S., Choi, H.B., Kim, S.U., McLarnon, J.G., 2005. IL-8 enhancement of amyloid-beta (Abeta 1-42)-induced expression and production of pro-inflammatory cytokines and COX-2 in cultured human microglia. *J. Neuroimmunol.* 159, 66–74.
- Friedemann, C., Heneghan, C., Mahtani, K., Thompson, M., Perera, R., Ward, A.M., 2012. Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis. *BMJ* 345, e4759.
- Frisardi, V., Solfrizzi, V., Seripa, D., Capurso, C., Santamato, A., Sancarolo, D., Vendemi-ale, G., Pilotto, A., Panza, F., 2010. Metabolic-cognitive syndrome: a cross-talk between metabolic syndrome and Alzheimer's disease. *Ageing Res. Rev.* 9, 399–417.
- Gazdzinski, S., Kornak, J., Weiner, M.W., Meyerhoff, D.J., 2008. Body mass index and magnetic resonance markers of brain integrity in adults. *Ann. Neurol.* 63, 652–657.
- Gazdzinski, S., Millin, R., Kaiser, L.G., Durazzo, T.C., Mueller, S.G., Weiner, M.W., Meyerhoff, D.J., 2010. BMI and neuronal integrity in healthy, cognitively normal elderly: a proton magnetic resonance spectroscopy study. *Obesity (Silver Spring)* 18, 743–748.
- Giordano, V., Peluso, G., Iannucelli, M., Benatti, P., Nicolai, R., Calvani, M., 2007. Systemic and brain metabolic dysfunction as a new paradigm for approaching Alzheimer's dementia. *Neurochem. Res.* 32, 555–567.
- Goldstein, B.J., 2002. Insulin resistance as the core defect in type 2 diabetes mellitus. *Am. J. Cardiol.* 90, 3G–10G.
- Gonzales, M.M., Tarumi, T., Eagan, D.E., Tanaka, H., Vaghias, M., Haley, A.P., 2012. Indirect effects of elevated body mass index on memory performance through altered cerebral metabolite concentrations. *Psychosom. Med.* 74, 691–698.
- Brain Development Cooperative Group, 2012. Total and regional brain volumes in a population-based normative sample from 4 to 18 years: the NIH MRI Study of Normal Brain Development. *Cereb. Cortex* 22, 1–12.
- Gunstad, J., Paul, R.H., Cohen, R.A., Tate, D.F., Spitznagel, M.B., Gordon, E., 2007. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Compreh. Psychiatry* 48, 57–61.
- Gunstad, J., Paul, R.H., Cohen, R.A., Tate, D.F., Spitznagel, M.B., Grieve, S., Gordon, E., 2008. Relationship between body mass index and brain volume in healthy adults. *Int. J. Neurosci.* 118, 1582–1593.
- Gustafson, D., Lissner, L., Bengtsson, C., Bjorkelund, C., Skoog, I., 2004. A 24-year follow-up of body mass index and cerebral atrophy. *Neurology* 63, 1876–1881.
- Gustafson, D., Rothenberg, E., Blennow, K., Steen, B., Skoog, I., 2003. An 18-year follow-up of overweight and risk of Alzheimer disease. *Arch. Internal Med.* 163, 1524–1528.
- Haley, A.P., Gonzales, M.M., Tarumi, T., Tanaka, H., 2013. Dyslipidemia links obesity to early cerebral neurochemical alterations. *Obesity (Silver Spring)*.
- Haltia, L.T., Viljanen, A., Parkkola, R., Kempainen, N., Rinne, J.O., Nuutila, P., Kaasinen, V., 2007. Brain white matter expansion in human obesity and the recovering effect of dieting. *J. Clin. Endocrinol. Metab.* 92, 3278–3284.
- Harvie, M., Wright, C., Pegington, M., McMullan, D., Mitchell, E., Martin, B., Cutler, R.G., Evans, G., Whiteside, S., Maudsley, S., Camandola, S., Wang, R., Carlson, O.D., Egan, J.M., Mattson, M.P., Howell, A., 2013. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. *British J. Nutr.* 1, 1–14.
- Harvie, M.N., Pegington, M., Mattson, M.P., Frystyk, J., Dillon, B., Evans, G., Cuzick, J., Jebb, S.A., Martin, B., Cutler, R.G., Son, T.G., Maudsley, S., Carlson, O.D., Egan, J.M., Flyvbjerg, A., Howell, A., 2011. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. *Int. J. Obes. (Lond.)* 35, 714–727.
- Haslam, D.W., James, W.P., 2005. Obesity. *Lancet* 366, 1197–1209.
- Hassenstab, J.J., Sweet, L.H., Del Parigi, A., McCaffery, J.M., Haley, A.P., Demos, K.E., Cohen, R.A., Wing, R.R., 2012. Cortical thickness of the cognitive control network in obesity and successful weight loss maintenance: a preliminary MRI study. *Psychiatry Res.* 202, 77–79.
- Ho, A.J., Raji, C.A., Becker, J.T., Lopez, O.L., Kuller, L.H., Hua, X., Lee, S., Hibar, D., Dinov, I.D., Stein, J.L., Jack Jr., C.R., Weiner, M.W., Toga, A.W., Thompson, P.M., 2010a. Obesity is linked with lower brain volume in 700 AD and MCI patients. *Neurobiol. Aging* 31, 1326–1339.
- Ho, A.J., Stein, J.L., Hua, X., Lee, S., Hibar, D.P., Leow, A.D., Dinov, I.D., Toga, A.W., Saykin, A.J., Shen, L., Foroud, T., Pankratz, N., Huentelman, M.J., Craig, D.W., Gerber, J.D., Allen, A.N., Corneveaux, J.J., Stephan, D.A., DeCarli, C.S., DeChairo, B.M., Potkin, S.G., Jack Jr., C.R., Weiner, M.W., Raji, C.A., Lopez, O.L., Becker, J.T., Carmichael, O.T., Thompson, P.M., 2010b. A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in the healthy elderly. *Proc. Natl. Acad. Sci. U. S. A.* 107, 8404–8409.
- Ho, A.J., Raji, C.A., Becker, J.T., Lopez, O.L., Kuller, L.H., Hua, X., Dinov, I.D., Stein, J.L., Rosano, C., Toga, A.W., Thompson, P.M., 2011a. The effects of physical activity, education, and body mass index on the aging brain. *Human Brain Mapp.* 32, 1371–1382.
- Ho, A.J., Raji, C.A., Saharan, P., DeGiorgio, A., Madsen, S.K., Hibar, D.P., Stein, J.L., Becker, J.T., Lopez, O.L., Toga, A.W., Thompson, P.M., 2011b. Hippocampal volume is related to body mass index in Alzheimer's disease. *Neuroreport* 22, 10–14.
- Hoogendam, Y.Y., van der Geest, J.N., van der Lijn, F., van der Lugt, A., Niessen, W.J., Krestin, G.P., Hofman, A., Vernooij, M.W., Breteler, M.M., Ikram, M.A., 2012. Determinants of cerebellar and cerebral volume in the general elderly population. *Neurobiol. Aging* 33, 2774–2781.
- Huang, T.L., Yu, W.W., 2008. Weight loss occurs over a decade prior to dementia diagnosis: comment on meta-analysis of obesity as a risk factor for dementia

- and its subtypes. *Obesity Rev.: Off. J. Int. Assoc. Study Obesity* 9, 631–632 (author reply 633–634).
- Jagust, W., Harvey, D., Mungas, D., Haan, M., 2005. Central obesity and the aging brain. *Arch. Neurol.* 62, 1545–1548.
- Johnson, A.R., Milner, J.J., Makowski, L., 2012. The inflammation highway: metabolism accelerates inflammatory traffic in obesity. *Immunol. Rev.* 249, 218–238.
- Johnson, J.B., Summer, W., Cutler, R.G., Martin, B., Hyun, D.H., Dixit, V.D., Pearson, M., Nassar, M., Telljohann, R., Maudsley, S., Carlson, O., John, S., Laub, D.R., Mattson, M.P., 2007. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Radic. Biol. Med.* 42, 665–674.
- Karlsson, H.K., Tuulari, J.J., Hirvonen, J., Lepomaki, V., Parkkola, R., Hiltunen, J., Hanunkainen, J.C., Soinio, M., Pham, T., Salminen, P., Nuutila, P., Nummenmaa, L., 2013. Obesity is associated with white matter atrophy: A combined diffusion tensor imaging and voxel-based morphometric study. *Obesity* (Silver Spring).
- Kou, Z., Gattu, R., Kobeissy, F., Welch, R.D., O'Neil, B.J., Woodard, J.L., Ayaz, S.I., Kulek, A., Kas-Shamoun, R., Mika, V., Zuk, C., Tomasello, F., Mondello, S., 2013. Combining biochemical and imaging markers to improve diagnosis and characterization of mild traumatic brain injury in the acute setting: results from a pilot study. *PLoS One* 8, e80296.
- Kuo, H.K., Jones, R.N., Milberg, W.P., Tennstedt, S., Talbot, L., Morris, J.N., Lipsitz, L.A., 2006. Cognitive function in normal-weight, overweight, and obese older adults: an analysis of the Advanced Cognitive Training for Independent and Vital Elderly cohort. *J. Am. Geriatr. Soc.* 54, 97–103.
- Kurth, F., Levitt, J.G., Phillips, O.R., Luders, E., Woods, R.P., Mazziotta, J.C., Toga, A.W., Narr, K.L., 2013. Relationships between gray matter, body mass index, and waist circumference in healthy adults. *Human Brain Mapp.* 34, 1737–1746.
- Launer, L.J., 2002. Demonstrating the case that AD is a vascular disease: epidemiologic evidence. *Ageing Res. Rev.* 1, 61–77.
- Lautenschlager, N.T., Cox, K.L., Flicker, L., Foster, J.K., van Bockxmeer, F.M., Xiao, J., Greenop, K.R., Almeida, O.P., 2008. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA: J. Am. Med. Assoc.* 300, 1027–1037.
- Li, G., Larson, E.B., Sonnen, J.A., Shofer, J.B., Petrie, E.C., Schantz, A., Peskind, E.R., Raskind, M.A., Breitner, J.C., Montine, T.J., 2007. Statin therapy is associated with reduced neuropathologic changes of Alzheimer disease. *Neurology* 69, 878–885.
- Liang, J., Matheson, B.E., Kaye, W.H., Boutelle, K.N., 2013. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. *Int. J. Obes. (Lond)*.
- Licinio, J., Wong, M.L., Gold, P.W., 1992. Neutrophil-activating peptide-1/interleukin-8 mRNA is localized in rat hypothalamus and hippocampus. *Neuroreport* 3, 753–756.
- Liu, Y.J., Guo, D.W., Tian, L., Shang, D.S., Zhao, W.D., Li, B., Fang, W.G., Zhu, L., Chen, Y.H., 2010. Peripheral T cells derived from Alzheimer's disease patients overexpress CXCR2 contributing to its transendothelial migration, which is microglial TNF- α -dependent. *Neurobiol. Aging* 31, 175–188.
- Liu-Ambrose, T., Nagamatsu, L.S., Graf, P., Beattie, B.L., Ashe, M.C., Handy, T.C., 2010. Resistance training and executive functions: a 12-month randomized controlled trial. *Arch. Int. Med.* 170, 170–178.
- Luchsinger, J.A., Cheng, D., Tang, M.X., Schupf, N., Mayeux, R., 2012. Central obesity in the elderly is related to late-onset Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* 26, 101–105.
- Lupien, S.J., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Nair, N.P., Thakur, M., McEwen, B.S., Hauger, R.L., Meaney, M.J., 1998. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat. Neurosci.* 1, 69–73.
- Maayan, L., Hoogendoorn, C., Sweat, V., Convit, A., 2011. Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. *Obesity* (Silver Spring) 19, 1382–1387.
- Marks, B.L., Katz, L.M., Styner, M., Smith, J.K., 2011. Aerobic fitness and obesity: relationship to cerebral white matter integrity in the brain of active and sedentary older adults. *Brit. J. Sports Med.* 45, 1208–1215.
- Marsland, A.L., Gianaros, P.J., Abramowitch, S.M., Manuck, S.B., Hariri, A.R., 2008. Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. *Biol. Psychiatry* 64, 484–490.
- Martin, L.E., Holsen, L.M., Chambers, R.J., Bruce, A.S., Brooks, W.M., Zarcone, J.R., Butler, M.G., Savage, C.R., 2010. Neural mechanisms associated with food motivation in obese and healthy weight adults. *Obesity* (Silver Spring) 18, 254–260.
- Matsuzawa, Y., Funahashi, T., Nakamura, T., 2011. The concept of metabolic syndrome: contribution of visceral fat accumulation and its molecular mechanism. *J. Atheroscler. Thromb.* 18, 629–639.
- Maudsley, A.A., Govind, V., Arheart, K.L., 2012. Associations of age, gender and body mass with 1H MR-observed brain metabolites and tissue distributions. *NMR Biomed.* 25, 580–593.
- McDonald, C.R., McEvoy, L.K., Gharapetian, L., Fennema-Notestine, C., Hagler Jr., D.J., Holland, D., Koyama, A., Brewer, J.B., Dale, A.M., 2009. Regional rates of neocortical atrophy from normal aging to early Alzheimer disease. *Neurology* 73, 457–465.
- McEwen, B.S., Morrison, J.H., 2013. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron* 79, 16–29.
- Mehta, S., Melhorn, S.J., Smeraglio, A., Tyagi, V., Grabowski, T., Schwartz, M.W., Schur, E.A., 2012. Regional brain response to visual food cues is a marker of satiety that predicts food choice. *Am. J. Clin. Nutr.* 96, 989–999.
- Melka, M.G., Gillis, J., Bernard, M., Abrahamowicz, M., Chakravarty, M.M., Leonard, G.T., Perron, M., Richer, L., Veillette, S., Banaschewski, T., Barker, G.J., Buchel, C., Conrod, P., Flor, H., Heinz, A., Garavan, H., Bruhl, R., Mann, K., Artiges, E., Lourdusamy, A., Lathrop, M., Loth, E., Schwartz, Y., Frouin, V., Rietschel, M., Smolka, M.N., Strohle, A., Gallinat, J., Struve, M., Lattka, E., Waldenberger, M., Schumann, G., Pavlidis, P., Gaudet, D., Paus, T., Pausova, Z., 2013. FTO, obesity and the adolescent brain. *Human Mol. Genet.* 22, 1050–1058.
- Metzler-Baddeley, C., Baddeley, R.J., Jones, D.K., Aggleton, J.P., O'Sullivan, M.J., 2013. Individual differences in fornix microstructure and body mass index. *PLoS One* 8, e59849.
- Michaud, M., Balardy, L., Moulis, G., Gaudin, C., Peyrot, C., Vellas, B., Cesari, M., Nourhashemi, F., 2013. Proinflammatory cytokines, aging, and age-related diseases. *J. Am. Med. Directors Assoc.* 14, 877–882.
- Miller, J.L., Couch, J., Schwenk, K., Long, M., Towler, S., Theraque, D.W., He, G., Liu, Y., Driscoll, D.J., Leonard, C.M., 2009. Early childhood obesity is associated with compromised cerebellar development. *Dev. Neuropsychol.* 34, 272–283.
- Miller, J.L., Couch, J.A., Schmalfuss, I., He, G., Liu, Y., Driscoll, D.J., 2007. Intracranial abnormalities detected by three-dimensional magnetic resonance imaging in Prader-Willi syndrome. *Am. J. Med. Genet. Part A* 143, 476–483.
- Mueller, K., Anwander, A., Moller, H.E., Horstmann, A., Lepsien, J., Busse, F., Mohammadi, S., Schroeter, M.L., Stumvoll, M., Villringer, A., Pleger, B., 2011. Sex-dependent influences of obesity on cerebral white matter investigated by diffusion-tensor imaging. *PLoS One* 6, e18544.
- Mueller, K., Sacher, J., Arelin, K., Holiga, S., Kratzsch, J., Villringer, A., Schroeter, M.L., 2012. Overweight and obesity are associated with neuronal injury in the human cerebellum and hippocampus in young adults: a combined MRI, serum marker and gene expression study. *Translat. Psychiatry* 2, e200.
- Ogden, C.L., Carroll, M.D., Kit, B.K., Flegal, K.M., 2012a. Prevalence of obesity in the United States, 2009–2010. *NCHS Data Brief*, 1–8.
- Ogden, C.L., Carroll, M.D., Kit, B.K., Flegal, K.M., 2012b. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. *JAMA: J. Am. Med. Assoc.* 307, 483–490.
- Ogura, K., Fujii, T., Abe, N., Hosokai, Y., Shinohara, M., Takahashi, S., Mori, E., 2011. Small gray matter volume in orbitofrontal cortex in Prader-Willi syndrome: a voxel-based MRI study. *Human Brain Mapp.* 32, 1059–1066.
- Pannacciulli, N., Del Parigi, A., Chen, K., Le, D.S., Reiman, E.M., Tataranni, P.A., 2006. Brain abnormalities in human obesity: a voxel-based morphometric study. *NeuroImage* 31, 1419–1425.
- Pikula, A., Boger, R.H., Beiser, A.S., Maas, R., DeCarli, C., Schwedhelm, E., Himali, J.J., Schulze, F., Au, R., Kelly-Hayes, M., Kase, C.S., Vasan, R.S., Wolf, P.A., Seshadri, S., 2009. Association of plasma ADMA levels with MRI markers of vascular brain injury: Framingham offspring study. *Stroke: J. Cerebr. Circulat.* 40, 2959–2964.
- Pluchino, N., Russo, M., Santoro, A.N., Litta, P., Cela, V., Genazzani, A.R., 2013. Steroid hormones and BDNF. *Neuroscience* 239, 271–279.
- Raji, C.A., Ho, A.J., Parikshak, N.N., Becker, J.T., Lopez, O.L., Kuller, L.H., Hua, X., Leow, A.D., Toga, A.W., Thompson, P.M., 2010. Brain structure and obesity. *Human Brain Mapp.* 31, 353–364.
- Reinert, K.R., Po'e, E.K., Barkin, S.L., 2013. The relationship between executive function and obesity in children and adolescents: a systematic literature review. *J. Obesity* 2013, 820956.
- Risacher, S.L., Shen, L., West, J.D., Kim, S., McDonald, B.C., Beckett, L.A., Harvey, D.J., Jack Jr., C.R., Weiner, M.W., Saykin, A.J., 2010. Longitudinal MRI atrophy biomarkers: relationship to conversion in the ADNI cohort. *Neurobiol. Aging* 31, 1401–1418.
- Rockwood, K., Middleton, L., 2007. Physical activity and the maintenance of cognitive function. *Alzheimer's Dementia: J. Alzheimer's Assoc.* 3, S38–S44.
- Satizabal, C.L., Zhu, Y.C., Mazoyer, B., Dufouil, C., Tzourio, C., 2012. Circulating IL-6 and CRP are associated with MRI findings in the elderly: the 3C-Dijon Study. *Neurology* 78, 720–727.
- Schrijvers, E.M., Witteman, J.C., Sijbrands, E.J., Hofman, A., Koudstaal, P.J., Breteler, M.M., 2010. Insulin metabolism and the risk of Alzheimer disease: the Rotterdam Study. *Neurology* 75, 1982–1987.
- Smucny, J., Cornier, M.A., Eichman, L.C., Thomas, E.A., Bechtel, J.L., Tregellas, J.R., 2012. Brain structure predicts risk for obesity. *Appetite* 59, 859–865.
- Song, S.K., Sun, S.W., Ramsbottom, M.J., Chang, C., Russell, J., Cross, A.H., 2002. Demyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *NeuroImage* 17, 1429–1436.
- Soreca, I., Rosano, C., Jennings, J.R., Sheu, L.K., Kuller, L.H., Matthews, K.A., Aizenstein, H.J., Gianaros, P.J., 2009. Gain in adiposity across 15 years is associated with reduced gray matter volume in healthy women. *Psychosom. Med.* 71, 485–490.
- Sridharan, A., Willette, A.A., Bendlin, B.B., Alexander, A.L., Coe, C.L., Voytko, M.L., Colman, R.J., Kennitz, J.W., Weindrich, R.H., Johnson, S.C., 2012. Brain volumetric and microstructural correlates of executive and motor performance in aged rhesus monkeys. *Front. Aging Neurosci.* 4, 31.
- Stanek, K.M., Grieve, S.M., Brickman, A.M., Korgaonkar, M.S., Paul, R.H., Cohen, R.A., Gunstad, J.J., 2011. Obesity is associated with reduced white matter integrity in otherwise healthy adults. *Obesity* (Silver Spring) 19, 500–504.
- Stranahan, A.M., Arumugam, T.V., Cutler, R.G., Lee, K., Egan, J.M., Mattson, M.P., 2008. Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. *Nat. Neurosci.* 11, 309–317.
- Stranahan, A.M., Arumugam, T.V., Mattson, M.P., 2011. Lowering corticosterone levels reinstates hippocampal brain-derived neurotrophic factor and TrkB expression without influencing deficits in hypothalamic brain-derived neurotrophic factor expression in leptin receptor-deficient mice. *Neuroendocrinology* 93, 58–64.

- 1267 Strle, K., Broussard, S.R., McCusker, R.H., Shen, W.H., Johnson, R.W., Freund, G.G.,
1268 Dantzer, R., Kelley, K.W., 2004. Proinflammatory cytokine impairment of insulin-
1269 like growth factor I-induced protein synthesis in skeletal muscle myoblasts
1270 requires ceramide. *Endocrinology* 145, 4592–4602.
- 1271 Taki, Y., Kinomura, S., Sato, K., Inoue, K., Goto, R., Okada, K., Uchida, S., Kawashima,
1272 R., Fukuda, H., 2008. Relationship between body mass index and gray matter
1273 volume in 1,428 healthy individuals. *Obesity (Silver Spring)* 16, 119–124.
- 1274 Talbot, K., Wang, H.Y., Kazi, H., Han, L.Y., Bakshi, K.P., Stucky, A., Fuino, R.L.,
1275 Kawaguchi, K.R., Samoyedny, A.J., Wilson, R.S., Arvanitakis, Z., Schneider, J.A.,
1276 Wolf, B.A., Bennett, D.A., Trojanowski, J.Q., Arnold, S.E., 2012. Demonstrated
1277 brain insulin resistance in Alzheimer's disease patients is associated with IGF-
1278 1 resistance IRS-1 dysregulation, and cognitive decline. *J. Clin. Invest.* 122,
1279 1316–1338.
- 1280 ten Dam, V.H., Box, F.M., de Craen, A.J., van den Heuvel, D.M., Bollen, E.L., Murray,
1281 H.M., van Buchem, M.A., Westendorp, R.G., Blauw, G.J., 2005. Lack of effect of
1282 pravastatin on cerebral blood flow or parenchymal volume loss in elderly at risk
1283 for vascular disease. *Stroke; J. Cerebr. Circul.* 36, 1633–1636.
- 1284 Thaler, J.P., Yi, C.X., Schur, E.A., Guyenet, S.J., Hwang, B.H., Dietrich, M.O., Zhao, X.,
1285 Sarruf, D.A., Izgur, V., Maravilla, K.R., Nguyen, H.T., Fischer, J.D., Matsen, M.E.,
1286 Wisse, B.E., Morton, G.J., Horvath, T.L., Baskin, D.G., Tschop, M.H., Schwartz, M.W.,
1287 2012. Obesity is associated with hypothalamic injury in rodents and humans. *J.*
1288 *Clin. Invest.* 122, 153–162.
- 1289 Tseng, B.Y., Gundapuneedi, T., Khan, M.A., Diaz-Arrastia, R., Levine, B.D., Lu, H.,
1290 Huang, H., Zhang, R., 2013. White matter integrity in physically fit older adults.
1291 *Neuroimage* 82, 510–516.
- 1292 Ursache, A., Wedin, W., Tirsi, A., Convit, A., 2012. Preliminary evidence for obesity
1293 and elevations in fasting insulin mediating associations between cortisol
1294 awakening response and hippocampal volumes and frontal atrophy. *Psychoneu-*
1295 *roendocrinology* 37, 1270–1276.
- 1296 van Boxtel, M.P., Baars, L., Jolles, J., 2007. Obesity, blood pressure and cognitive func-
1297 tion: a reply to Waldstein and Katzel. *Int. J. Obes. (Lond.)* 31, 1186 (author reply
1298 1187–1188).
- 1299 Vucenic, I., Stains, J.P., 2012. Obesity and cancer risk: evidence, mechanisms, and
1300 recommendations. *Ann. N. Y. Acad. Sci.* 1271, 37–43.
- 1301 Walther, K., Birdsill, A.C., Glisky, E.L., Ryan, L., 2010. Structural brain differences and
1302 cognitive functioning related to body mass index in older females. *Human Brain*
1303 *Mapp.* 31, 1052–1064.
- 1304 Walton, J.C., Grier, A.J., Weil, Z.M., Nelson, R.J., 2012. Photoperiod and stress regula-
1305 tion of corticosteroid receptor, brain-derived neurotrophic factor, and glucose
1306 transporter GLUT3 mRNA in the hippocampus of male Siberian hamsters
1307 (*Phodopus sungorus*). *Neuroscience* 213, 106–111.
- 1308 Ward, M.A., Carlsson, C.M., Trivedi, M.A., Sager, M.A., Johnson, S.C., 2005. The effect of
1309 body mass index on global brain volume in middle-aged adults: a cross sectional
1310 study. *BMC Neurol.* 5, 23.
- 1311 Weise, C.M., Thiyyagura, P., Reiman, E.M., Chen, K., Krakoff, J., 2013. Fat-free body
1312 mass but not fat mass is associated with reduced gray matter volume of cortical
1313 brain regions implicated in autonomic and homeostatic regulation. *NeuroImage*
1314 64, 712–721.
- 1315 Whitlock, G., Lewington, S., Sherliker, P., Clarke, R., Emberson, J., Halsey, J., Qizilbash,
1316 N., Collins, R., Peto, R., 2009. Body-mass index and cause-specific mortality in
1317 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 373,
1318 1083–1096.
- 1319 Whitwell, J.L., Przybelski, S.A., Weigand, S.D., Knopman, D.S., Boeve, B.F., Petersen,
1320 R.C., Jack Jr., C.R., 2007. 3D maps from multiple MRI illustrate changing atrophy
1321 patterns as subjects progress from mild cognitive impairment to Alzheimer's
1322 disease. *Brain: J. Neurol.* 130, 1777–1786.
- 1323 Widya, R.L., de Roos, A., Trompet, S., de Craen, A.J., Westendorp, R.G., Smit, J.W., van
1324 Buchem, M.A., van der Grond, J., 2011. Increased amygdala and hippocampal
1325 volumes in elderly obese individuals with or at risk of cardiovascular disease.
1326 *Am. J. Clin. Nutr.* 93, 1190–1195.
- 1327 Willette, A.A., Bendlin, B.B., McLaren, D.G., Canu, E., Kastman, E.K., Kosmatka, K.J., Xu,
1328 G., Field, A.S., Alexander, A.L., Colman, R.J., Weindruch, R.H., Coe, C.L., Johnson,
1329 S.C., 2010. Age-related changes in neural volume and microstructure associ-
1330 ated with interleukin-6 are ameliorated by a calorie-restricted diet in old rhesus
1331 monkeys. *NeuroImage* 51, 987–994.
- 1332 Willette, A.A., Bendlin, B.B., Colman, R.J., Kastman, E.K., Field, A.S., Alexander, A.L.,
1333 Sridharan, A., Allison, D.B., Anderson, R., Voytko, M.L., Kemnitz, J.W., Weindruch,
1334 R.H., Johnson, S.C., 2012a. Calorie restriction reduces the influence of glucoreg-
1335 ulatory dysfunction on regional brain volume in aged rhesus monkeys. *Diabetes*
1336 61, 1036–1042.
- 1337 Willette, A.A., Gallagher, C., Bendlin, B.B., McLaren, D.G., Kastman, E.K., Canu, E.,
1338 Kosmatka, K.J., Field, A.S., Alexander, A.L., Colman, R.J., Voytko, M.L., Weindruch,
1339 R.H., Coe, C.L., Johnson, S.C., 2012b. Homocysteine, neural atrophy, and the effect
1340 of caloric restriction in rhesus monkeys. *Neurobiol. Aging* 33, 670–680.
- 1341 Willette, A.A., Coe, C.L., Colman, R.J., Bendlin, B.B., Kastman, E.K., Field, A.S., Alexan-
1342 der, A.L., Allison, D.B., Weindruch, R.H., Johnson, S.C., 2012c. Calorie restriction
1343 reduces psychological stress reactivity and its association with brain volume
1344 and microstructure in aged rhesus monkeys. *Psychoneuroendocrinology* 37,
1345 903–916.
- 1346 Willette, A.A., Xu, G., Johnson, S.C., Birdsill, A.C., Jonaitis, E.M., Sager, M.A., Hermann,
1347 B.P., La Rue, A., Asthana, S., Bendlin, B.B., 2013a. Insulin resistance, brain atro-
1348 phy, and cognitive performance in late middle-aged adults. *Diabetes Care* 36,
1349 443–449.
- 1350 Willette, A.A., Coe, C.L., Birdsill, A.C., Bendlin, B.B., Colman, R.J., Alexander,
1351 A.L., Allison, D.B., Weindruch, R.H., Johnson, S.C., 2013b. Interleukin-8 and
1352 interleukin-10, brain volume and microstructure, and the influence of calorie
1353 restriction in old rhesus macaques. *Age (Dordr)*
- 1354 Wilson, C.J., Finch, C.E., Cohen, H.J., 2002. Cytokines and cognition—the case for a
1355 head-to-toe inflammatory paradigm. *J. Am. Geriatrics Soc.* 50, 2041–2056.
- 1356 Wolf, H., Hensel, A., Arendt, T., Kivipielto, M., Winblad, B., Gertz, H.J., 2004. Serum
1357 lipids and hippocampal volume: the link to Alzheimer's disease? *Ann. Neurol.*
1358 56, 745–748.
- 1359 World Health Organization, 2000. Obesity: Preventing and Managing the Global
1360 Epidemic.
- 1361 Xu, J., Li, Y., Lin, H., Sinha, R., Potenza, M.N., 2013. Body mass index correlates nega-
1362 tively with white matter integrity in the fornix and corpus callosum: a diffusion
1363 tensor imaging study. *Human Brain Mapp.* 34, 1044–1052.
- 1364 Yaffe, K., 2007. Metabolic syndrome and cognitive disorders: is the sum greater than
1365 its parts? *Alzheimer Dis. Assoc. Disord.* 21, 167–171.
- 1366 Yaffe, K., Kanaya, A., Lindquist, K., Simonsick, E.M., Harris, T., Shorr, R.I., Tylavsky,
1367 F.A., Newman, A.B., 2004. The metabolic syndrome, inflammation, and risk of
1368 cognitive decline. *JAMA: J. Am. Med. Assoc.* 292, 2237–2242.
- 1369 Yokum, S., Ng, J., Stice, E., 2012. Relation of regional gray and white matter volumes
1370 to current BMI and future increases in BMI: a prospective MRI study. *Int. J. Obes.*
1371 (Lond.) 36, 656–664.
- 1372 Zade, D., Beiser, A., McGlinchey, R., Au, R., Seshadri, S., Palumbo, C., Wolf, P.A., DeCarli,
1373 C., Milberg, W., 2013. Apolipoprotein epsilon 4 allele modifies waist-to-hip ratio
1374 effects on cognition and brain structure. *J. Stroke Cerebrovasc. Dis.: Off. J. Natl.*
1375 *Stroke Assoc.* 22, 119–125.
- 1376 Zhang, X., Dong, F., Ren, J., Driscoll, M.J., Culver, B., 2005. High dietary fat induces
1377 NADPH oxidase-associated oxidative stress and inflammation in rat cerebral
1378 cortex. *Exp. Neurol.* 191, 318–325.