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Review

Is obesity a brain disease?☆

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ABSTRACT

That the brain is involved in the pathogenesis and perpetuation of obesity is broadly self-intuitive, but traditional evaluation of this relationship has focused on psychological and environment-dependent issues, often referred to as the "it's all in the head" axiom. Here we review evidence that excessive nutrition or caloric flux, regardless of its primary trigger, elicits a biological trap which imprints aberrant energy control circuits that tend to worsen with the accumulation of body fat. Structural and functional changes in the brain can be recognized, such as hypothalamic inflammation and gliosis, reduction in brain volume, reduced regional blood flow or diminished hippocampal size. Such induced changes collectively translate into a vicious cycle of deranged metabolic control and cognitive deficits, some of which can be traced back even to childhood or adolescence. Much like other components of the obese state, brain disease is inseparable from obesity itself and requires better recognition to allow future therapeutic targeting.

Contents

1. Introduction

Overeating and sedentary behavior are typically viewed as reflective of cultural, psychological or otherwise acquired addictive traits, abetted by seemingly controllable external cues, the availability of calorie-rich food and the growing ease of life, which now allows lessening linkage between voluntary movement and survival. As such, these behavioral patterns are often the target of moral judgment, which eventually contributes to physician–patient mistrust, in the treatment of obesity and its sequels, when facing the failure of the "eat less, exercise more" approach. Here we will assess existing evidence that obesity indeed is a disease of the brain. Whether brain disease in obesity is the primary event or at least a partly reversible sequel of obesity may

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matter less than expected from traditional rigid "cause and effect" analysis.

2. Overnutrition is a biological trap, not simply a willful choice

Animal studies may offer good insights into biologically entrenched choices of diet, as they are uncomplicated by cultural and social habituation or the complexity of human cognition. Earlier beliefs that animals can select food with precision sufficient to allow just normal growth and survival have been challenged more than two decades ago (Galef, 1991). Even if such biological precision is accepted, recent data suggest that early exposure of rats to fatty foods during the growth period predisposes these animals to favor high fat diet in adult life (Nakashima and Yokokura, 2010). Long-term, fat- and sugar-rich cafeteria feeding can, in turn, increase energy intake in rats by 25% (Vallerand et al., 1986). It is therefore not surprising that in the setting of multiple choice cafeteria diet in rats, hyperphagia and obesity rapidly evolve (Naim et al., 1985). Further, spontaneously hypertensive rats that were offered a choice between cafeteria diet and regular chow diet not only experienced increased body weight but also featured leptin and insulin resistance and higher blood pressure than control rats fed on regular chow (Miesel et al., 2010). These experiments may have replicated the human metabolic syndrome (MetS) on the genetic background of hypertension. Finally, obesity can be facilitated by ill-programming generated not only by self-feeding, but also by prenatal and postnatal maternal exposure, as the feeding of rats with cafeteria diet during gestation and lactation results in offspring adiposity (Bayol et al., 2005, 2008). Such adipose accumulation is already complicated by the presence of non-alcoholic fatty liver, independent of actual diet of the pups themselves (Bayol et al., 2010; Hennige et al., 2009).

Both the caloric source and time of eating may be as important as the high caloric value of the consumed food. In one study, mice fed a diet supplemented with monounsaturated fatty acids displayed more efficient insulin action in the brain and enhanced brain cortical activity and locomotion than mice receiving a calorically equal food containing saturated fatty acids only (Sartorius et al., 2012). Restricting high fat diet to several hours a day leads to lesser weight gain than a calorically equivalent diet given with continued free access to food (Sherman et al., 2012). Conversely, there is evidence that "out of phase" consumption of food (during hours which are normally spent in the inactive, food-free state, typical of the undisturbed circadian rhythm) can facilitate weight gain without an overall increase in caloric intake (Salgado-Delgado et al., 2010).

3. Early life overnutrition and exposure to maternal obesity reprograms eating control in adult life

Brain structural maturation is not completed in-utero but extends into the first phases of life. Hence, exposure to excessive nutrition during this critically vulnerable pre- and postnatal development periods can impair the brain in general and disrupt the finely tuned normal brain-governed feeding behavior. Such responses to over-nutrition are probably mediated through the induction of structural and functional alterations which can lead to obesity, dysmetabolism and/or cognitive disadvantage later in life. For example, in one study high fat diet resulted in increased body fatness when administered either in weaning or adult mice, but only juvenile exposure to fatty food reduced hippocampal neurogenesis and relational memory flexibility (Boitard et al., 2012). Maternal high fat diet maintained from pre-mating through lactation led to increased offspring hippocampal lipid peroxidation and decreased neuogenesis (Tozuka et al., 2009). Newborn rat pups raised on a high-carbohydrate (HC) milk formula develop chronic peripheral hyperinsulinemia and adult-onset obesity despite subsequent placement on regular rat chow. This is associated with impaired hypothalamic energy control manifested by increased mRNA expression of hypothalamic orexigenic hormones such as neuropeptide Y (NPY), agouti-related polypeptide, and galanin and decreased mRNA expression of feeding down regulators including proopiomelanocortin (POMC), melanocortin receptor-4, cocaine- and amphetamine-regulated transcript, and corticotrophin-releasing factor which persisted at least into young adulthood (Srinivasan et al., 2008).

Although caloric restriction can later reduce body weight gain, the earlier life-entrained hypothalamic predisposition to hyperphagia appears irreversible (Srinivasan et al., 2013). Apparently, early life exposure to unnecessarily enriched nutrition imprints hypothalamic feeding related aberrations that may be *macronutrient-dependent* rather than *calorie-related*: for example, as compared to maternal high-fat diet, high carbohydrate diet resulted in lower arcuate nucleus POMC expression (which encodes at this site the appetite curbing hormone α melanocyte-stimulating-hormone, α MSH) and higher paraventricular nucleus NPY and orexin peptide concentrations in their young adult rat offspring (Beck et al., 2012). Not only direct nutritional effects are important but also maternal obesity status per se may be a dominant factor: cross-fostering of offspring of lean rat dams by obese dams resulted in an exaggerated dysmetabolic, insulin-resistant phenotype compared to offspring lean dams nursed by their natural mothers (Oben et al., 2010). In humans, where calorie-rich diet is normally excessive in terms of both fat and carbohydrates, a mixed deleterious hypothalamic derangement may therefore evolve.

This complex pattern may be, however, further modulated by intestinal signals generated by colonic microbiota. Dietary fibers such as inulin-type fructans, which are non-digestible by human enzymes but are easily fermented by gut bacteria can modify the gut microbioata profile in association with increases in circulating gut hormones which tend to curb appetite such as Glucagon-Like-Peptide 1 (GLP-1), peptide YY and decrease of the gastric-derived orexigenic hormone ghrelin (Cani et al., 2005; So et al., 2007). Accordingly, in mice, supplementation of a high fat diet with oligofructose-enriched inulin was shown to reduce accrued fat deposition and increase arcuate nucleus neuronal activity as captured by manganese-enhanced MRI (Anastasovska et al., 2012).

4. Overnutrition elicits brain disease: relation to obesity

Cafeteria diet reportedly disrupts the blood brain barrier in the hippocampus in rats through down regulation of mRNA expression of tight junction proteins, particularly Claudin-5 and -12, in the choroid plexus (Kanoski et al., 2010), thus exposing the brain tissue to potentially damaging circulating factors which cannot normally interact with brain cells. Chronic high fat intake can lead to inflammatory changes in the brain cortex as evidenced by the presence of increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-generated reactive oxygen species and accelerated prostaglandin E2 production along with up-regulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling in mice fed a fat-rich diet leading to obesity (Zhang et al., 2005). This indicates that brain oxidative stress could potentially mediate the pathogenesis of overnutrition-related metabolic diseases. Obesity related inflammatory changes within the brain have selective sequels affecting energy homeostasis and general functional along with structural implications. For example, obesity linked to mitochondrial dysfunction in hypothalamic POMC neurons can cause impairment in central glucose sensing (Parton

et al., 2007). Moroz et al. demonstrated that in mice developing obesity in response to high fat diet (HFD), mild neuropathological lesions were seen along with significant impairment in insulin receptor binding in the temporal lobe region. HFD feeding caused brain insulin resistance manifested by reduced maximum binding capacity (Bmax) for insulin receptor and modestly increased brain insulin gene expression. However, HFD-fed mice did not exhibit the brain histopathology of Alzheimer's disease (AD), such as increases in Amyloid-β or phospho-tau, or impairment in insulin-like growth factor 1 (IGF) signaling or acetylcholine homeostasis. That obesity and type 2 diabetes mellitus (T2DM) cause brain atrophy with brain insulin resistance, oxidative stress, and neuronal cytoskeleton degradation, in the absence of many features that typify AD, suggests that obesity and T2DM may contribute to, but are not sufficient to cause, AD (Moroz et al., 2008). It has been recently observed that some parallel increases in tumor necrosis factor-alpha (TNF-α) and macrophage/microglial activation can be induced in adipose tissue and brain from HFD fed animals. Most interestingly, however, both the brain and adipose tissue had elevated amyloid precursor protein (APP) in neurons and macrophages/adipocytes, respectively. The presence of APP in itself may not only harbor subsequent amyloid deposition, but also exert proinflammatory effects since APP agonist antibody increased specific cytokine secretion in macrophage cultures (Puig et al., 2012). It is noteworthy that there is increased expression of APP in adipose tissue from obese human subjects and that plasma Amyloid-β is positively related to body fat, even in normal subjects (Lee et al., 2008). In one study (Thirumangalakudi et al., 2008) unconfirmed by another (Moroz et al., 2008), high fat/high cholesterol diet induced increased brain expression of APP, Amyloid-β and several proinflammatory proteins in association with memory impairment.

Insulin resistance is a hallmark of obesity and caloric excess and can play an important role in brain dysfunction. Hyperinsulinemia and insulin resistance develop rapidly in response to increased caloric intake (Danielsson et al., 2009; Lee et al., 2011) and weight gain, even prior to the evolution of obesity and therefore precedes the evolution of confounding conditions such as hypertension, hyperglycemia, the metabolic syndrome and diabetes. Peripheral insulin resistance has been linked to subtle cognitive deficits and reduced spontaneous cortical activity in otherwise cognitively healthy humans afflicted with obesity, prediabetes or diabetes (Baker et al., 2011). Functional brain magnetic resonance imaging (fMRI) studies showed that the homeostasis model of assessment (HOMA-IR), a standard measure of insulin resistance derived from fasting circulating glucose and insulin, was inversely correlated with functional connectivity in the right inferior frontal gyrus and precuneus in patients with T2DM. Such patients with impaired peripheral insulin sensitivity also showed reduced functional connectivity in the brain's default mode network, which was associated with insulin resistance in selected brain regions (Musen et al., 2012). In elderly subjects, insulin sensitivity was positively related to verbal fluency performance, brain size, and temporal lobe gray matter volume in regions known to be involved in speech production (Benedict et al., 2012). The mechanisms underlying this association may be rapidly unfolding. Insulin can cross the blood brain barrier and has a wide range of physiological actions, which apparently depend on the signaling through its receptors. Insulin receptors are expressed particularly in brain areas related to cognitive processing such as the hippocampus, and are involved in synaptic plasticity and behavior (Agrawal et al., 2009). Cumulative evidence now supports an array of molecular and functional effects elicited through central nervous system (CNS) insulin signaling such as enhancement of synaptic long-term potentiation (Lee et al., 2009), attenuation of pathological binding of Amyloid-β-derived diffusible ligands to synapses of neurons (De Felice et al., 2009), reduction in food intake and improvement in declarative memory (Hallschmid et al., 2008). Obesity is associated with alterations in at least some of insulin's CNS effects. For example, intra-nasally administered insulin, presumably acting through the CNS, lowers food intake in normal weight but not in obese men (Hallschmid et al., 2008). Insulin enhances spontaneous cerebrocortical activity in the theta frequency band, which is mainly controlled by the hippocampus and linked to locomotor activity and voluntary movement, but this effect is blunted in obese subjects proportional to visceral fat mass and circulating fatty acid concentrations (Tschritter et al., 2009). Insulin administered intra-cerebro-ventricularly (ICV) increased locomotor activity in lean, but not in obese, mice (Hennige et al., 2009). Some of these associations not only reflect the loss of cerebral sensitivity to insulin's action in obesity, but can by themselves sustain or aggravate obesity: reduced locomotor activity and lack of suppression of eating by insulin can obviously foster weight gain and obesity.

5. What is the actual culprit: high caloric intake, increased dietary fat, excessive carbohydrate consumption or the presence of obesity per se?

Identification of the critical instigator(s) of brain anomalies in the obese state is highly desirable, but unfortunately not necessarily practical. Presently, this cannot be viewed as a simple "Chicken and Egg" question, but is most likely a highly complex series of impairments, encompassing inherited defects predisposing to obesity (e.g., leptin deficiency as an extreme example), the stress imposed on the brain by increased overall caloric load, selective deleterious brain effects of fat-rich diet or excessive intake of simple carbohydrates and, eventually, an ongoing insult to the brain secondary to the obese state. Western type diet, which is most commonly associated with obesity in humans, is both fat- and carbohydrate rich and their separate effects are hard to discern except for artificially generated and time-limited conditions. As reflected thus far in the present review, high fat diet/"cafeteria diet" protocols comprise the single largest source of information on the impact of nutritional and weight gain related effects on the brain, even in experimental models in animals (Table 1).

Still, emerging evidence indicates that excessive carbohydrate intake or the ensuing alteration in circulating insulin and insulin signaling may have distinct negative effects in the brain (Table 2). High fructose diet alone was found sufficient to impair memory in rats (Agrawal and Gomez-Pinilla, 2012). Both hypertriglyceridemia, a frequent sequel of insulin resistance, and insulin resistance per se may play a role in this setting as a positive correlation was noted between fructose induced memory deficits and triglyceride levels as well as with insulin resistance index. In human adolescents, post-breakfast cognitive performance is better following a low-glycemic index meal than with an eucaloric high-glycemic index breakfast (Cooper et al., 2012).

High fructose diet was also associated with regional brain increased lipid peroxidation and insulin resistance as reflected by reduced insulin signaling in the hippocampus: lower insulin receptor tyrosine- and Akt phosphorylation. Chronic fructose consumption can induce leptin resistance in terms of deficient appetite suppression *prior* to the increase in body weight, adiposity, serum leptin, insulin, or glucose and this fructose-induced leptin resistance accelerates high-fat induced obesity (Shapiro et al., 2008). In rats, high-sucrose diet resulted in increased brain phosphorylated-phospholipase A_2 ($cPLA_2$) protein, $cPLA_2$ activity and 12-lipoxygenase mRNA, but decreased brain-derived nuclear-factor (BDNF) mRNA and protein, all of which can collectively contribute to the reduced synaptic plasticity and cognitive impairment seen in rats and humans with the MetS (Taha et al., 2012).

Table 1
Effects of high fat (HF) diets with and without the induction of obesity on the brain.

Source	Species	Diet period	Weight gain	Body fat	Detected signal	Special feature(s)/effects
Lee et al. (2013a,b)	Mice	21 weeks	+/−	++	Gliosis: (1) T2 on brain MRI; (2) histology	MRI confirms gliosis in mediobasal hypothalamus
Pepping et al. (2013)	Mice		++	++	Western blots of frontal cortex injury	Less blood brain barrier proteins; more metalloproteinase 2
Scherer et al. (2012)	Rats	3 days	−	ND	Blunted hypothalamic response to insulin	Resulted in increased peripheral lipolysis and hepatic glucose output
Jeon et al. (2012)	Mice		+++	ND	Brain volume declined, hippocampal inflammatory markers increased	Hippocampal neurodegeneration, TNF-α and microglial marker Ila-1 increased
Thaler et al. (2012)	Mice; humans		−− in 1 day; +++ later	+++	Hypothalamic inflammation within 1 day	Gliosis in mediobasal hypothalamus preceded by acute inflammation prior to weight gain
Zhang et al. (2005)	Rats		++	ND	Cerebral cortex: high ROS, expression of gp91(phox), p22(phox), p47(phox), and p67(phox) NADPH oxidase subunits	Evidence for high NADPH oxidase-induced oxidative stress in cortex
Cintra et al. (2012)	Rats and mice	16 weeks	++	+	Induction of inflammatory gene expression in the hypothalamus 2w after HF diet introduction. Increased expressions of the orexigenic, anti-thermogenic NPY and MCH and reduced expressions of the anorexigenic, pro-thermogenic POMC and CART	Hypothalamic inflammation upon HF diet was reversed by ICV administration of ω3 and ω9 pure fatty acids, which also leads to reduction in spontaneous food intake and body mass gain
De Souza et al. (2005)	Rats	16 weeks	+	++	Proinflammatory cytokines, as TNF-α and interleukin-1 beta (IL-1β) were released in the hypothalamus and activated apoptotic signaling in the hypothalamus	HF diet induced a local proinflammatory status in the hypothalamus, which results in impaired anorexigenic insulin signaling
Jeon et al. (2012)	Mice	20 weeks	++ND	Not reported, but likely increased	Memory deficits and elevated expression of protein levels of TNF-α and Iba-1 expression, as well as phosphorylation of tau in the hippocampus	HF diet resulted in increased hippocampal TNF-α expression and activated microglia
Milanski et al. (2012)	Rats and mice	8 weeks	+	+	Intracerebroventricularl immunoneutralizing antibodies against TLR4 or TNF-α reduced hypothalamic inflammation and attenuated hypothalamic resistance to leptin, improved insulin signal transduction in the liver and improved liver steatosis	Hypothalamic inflammation, presumably acting through activation of the sympathetic nervous system, can also blunt the hepatic response to insulin
Moroz et al. (2008)	Mice	16 weeks	++		Marginal reduction in brain weight together with increased tau, IGF-I receptor, IRS-1, IRS-4, ubiquitin, glial fibrillary acidic protein, and 4-hydroxynonenol (marker of lipid peroxidation)	HF diet seemed to be dissimilar to typical Alzheimer's disease
Park et al. (2010)	Mice	7 weeks	++	++	HF diet impaired hippocampal neurogenesis and neuronal progenitor cell proliferation through increased lipid peroxidation and decreased BDNF	
Parton et al. (2007)	Mice	20 weeks	++		Mitochondrial dysfunction in hypothalamic proopiomelanocortin (POMC) neurons was associated with impaired central glucose sensing	Loss of glucose sensing by POMC neurons has a role in the development of type 2 diabetes
Pistell et al. (2010)	Mice	21 weeks	++		Very high fat (60% fat; HFL) and 41% fat (western diet) increased weight, but only HFL impaired cognition, reduced brain BDNF and induced brain inflammation.	During high fat diet, brain inflammatory damage and the associated cognitive decline may depend on the dietary formulation, not only on weight gain.

Table 1 (*Continued*)

Source	Species	Diet period	Weight gain	Body fat	Detected signal	Special feature(s)/effects
Puig et al. (2012)	Mice	22 weeks	++		Elevated proinflammatory, neurodegenerative phenotype of HF diet fed brains correlated with similar increase in APP and TNF-α levels in adipose tissue	APP protein levels increased in primarily neurons in the brain and macrophage and adipocytes in adipose tissue
Sartorius et al. (2012)	Mice	8 weeks	+++ in saturated fatty acids (SFA) vs. monoun-saturated fatty acids (MUFA)	++	Mice fed on MUFA displayed efficient insulin action in the brain and enhanced brain cortical activity and locomotion than mice receiving a calorically equal food containing SFA only	In humans, SFA-enriched diet led to a decrease in hippocampal and cortical activity determined by fMRI
Scherer et al. (2012)	Rats	3 days			Insulin delivered to the mediobasal hypothalamus did not inhibit lipolysis through central pathways	Short-term HF intake interfered with hypothalamic insulin signaling, an effect seen even before the evolution of peripheral insulin resistance in white adipose tissue
Thirumangalakudi et al. (2008)	Mice	8 weeks	NO		(1) Deficient handling of increasing working memory load; (2) activated microglia and astrocytes in the hippocampi; (3) increased expression of the key amyloid precursor protein (APP) processing enzyme i.e. beta-site APP cleaving enzyme 1; (4) enhanced hippocampal mRNA expression of IL-1β, IL-6, and TNF-α as well as proinflammatory enzymes: COX2, iNOS	
Tozuka et al. (2010)	Mice	Eembryo to end of lactation			HF diet offspring (1) increased hippocampal lipid peroxidation during early postnatal development; (2) less hippocampal BDNF; (3) impaired spatial learning in the young but not adult period	
Witte et al. (2009)	Healthy humans; normal, over-weight	3 months	Caloric restriction	No change	Exercise raises plasma BDNF while caloric restriction improved memory in old subjects without affecting circulating BDNF	
Tozuka et al. (2009)	Mice	6 weeks pre-mating most of lactation	++ (offsprings)	Larger adipocytes	Maternal obesity impaired neurogenesis during offspring postnatal development. In this condition, oxidative stress was promoted in the dentate gyrus of HFD offsprings	Maternal HF diet led to increased offspring hippocampal lipid peroxidation and decreased neuogenesis
Boitard et al. (2012)	Mice	17 weeks	++		Same duration of HF diet consumption in early life, but not in adulthood, results in loss of relational memory flexibility and decreased hippocampal neurogenesis	

ND, not determined.

Attempted reversal of the overweight/obese state through preferential dietary deprivation of carbohydrates or fat can also shed light on the role of these nutrients on brain function, but these studies are thus far inconclusive. Brinkworth et al. assessed cognitive function in 106 adult overweight and obese subjects assigned either to an isocaloric very low-carbohydrate, high-fat diet or to a high-carbohydrate, low-fat diet, for 1 year. Both diets achieved similar weight loss and improvement in working memory but neither affected the speed of processing (Brinkworth et al., 2009). However in another study, low-carbohydrate high-fat diet resulted in smaller improvement in speed of processing relative to low-fat, high-carbohydrate diet, despite a higher achieved weight loss (Halyburton et al., 2007).

6. Structural changes

Multiple structural alterations have been reported in the brain of obese subjects, some of which may be difficult to conclusively discern from the effects of aging or the concomitant presence of hypertension, atherosclerosis, dyslipidemia or abnormal glucose metabolism. Still, cross-sectional regression studies associate increased body mass index (BMI) with decreased brain volume (Ward et al., 2005) and obese humans were found to have decreased brain volumes independent of age or disease (Gunstad et al., 2008). A recent report indicates that increased BMI is linked to reduction in white matter integrity throughout the brain (Verstynen et al., 2012). Clinical obesity is also reportedly linked to reduction in focal

Table 2
Effects of carbohydrate-modified diets on the induction of obesity or weight loss.

Source	Species	Diet	Diet period	Weight gain	Detected signal/effect	Special feature(s)/effects
Agrawal and Gomez-Pinilla (2012)	Rats	High-fructose	6 weeks		Impaired cognitive abilities and disrupted insulin signaling	The presence of docosahexaenoic acid, an $n-3$ fatty acid, restored metabolic homeostasis
Brinkworth et al. (2009)	Humans; overweight and obese	Very low carbohydrate (LC) and low-fat (LF)	1 year	Weight loss	Similar weight loss and improvement in working memory, neither diet affected speed of processing	Favorable effect of LF vs. isocaloric LC diet on mood and affect in overweight and obese
Halyburton et al. (2007)	Humans; overweight or obese	Low-carbohydrate, high-fat (LCHF) and high-carbohydrate, low-fat (HCLF)	8 weeks	+++ in LCHF	LCHF diet resulted in smaller improvement in speed of processing relative to HCLF diet	Higher achieved weight loss in LCHF vs. HCLF diet
Kanoski et al. (2010)	Rats	High saturated fat (lard) and glucose	90 days	++	Impairment in hippocampal-dependent discrimination problems and no effect on tasks that do not rely on the hippocampus. Compromised BBB integrity	Some learning and memory processes, particularly those that rely on the integrity of the hippocampus are due to disruption by diets containing saturated fat and refined carbohydrates
Taha et al. (2012)	Rats	High sucrose	8 weeks	NO	Lower synaptic plasticity and cognitive impairment, along with increased brain phosphorylated-phospholipase A_2 ($cPLA_2$) protein, $cPLA_2$ activity and 12-lipoxygenase mRNA, but decreased brain-derived nuclear-factor mRNA and protein	Reduced whole brain BDNF mRNA and protein levels were not mediated by pro-inflammatory eicosanoids
Srinivasan et al. (2008)	Rat pups	High-carbohydrate (HC) milk formula	12/24 days then weaning onto standard chow for 76 days	++ (postnatal days 40, 100)	Hyperphagia and increased weight gain in the post-weaning period with hypothalamic: (1) increase in mRNA levels of neuropeptide Y, agouti-related polypeptide, and galanin and decreased levels of POMC, melanocortin receptor-4, cocaine- and amphetamine-regulated transcript, and (2) decrease in corticotrophin-releasing factor mRNA, insulin receptor β (IR-β) and leptin receptor protein; changes persisted into adult life (100 days).	Newborn pups raised on HC milk formula develop chronic peripheral hyperinsulinemia and adult-onset obesity despite subsequent placement on regular chow, associated with impaired hypothalamic energy control
Srinivasan et al. (2013)	Rat pups	High-carbohydrate (HC) milk formula	12 and 24 days then weaning onto standard or HC chow until day 140	++	Pair-feeding implemented from postnatal days 24–140 did not reverse the programmed effects in islets and hypothalamus, which supported chronic hyperinsulinemia and hyperphagia	Earlier life-entrained hypothalamic predisposition to hyperphagia appears irreversible
Beck et al. (2012)	Rat dams	Gestating dams were fed a restricted normal diet with the opportunity to complete energy requirements with either high-fat (HF) or a high-carbohydrate (HC) food	Day 12 of gestation until delivery	+ HF; −HC	Compared to maternal HF diet, HC diet induced lower arcuate nucleus POMC expression and higher paraventricular nucleus NPY and orexin peptide concentrations in young adult rat offspring	Early life exposure to unnecessarily enriched nutrition imprints hypothalamic feeding related aberrations (supporting hyperphagia) that may be macronutrient-dependent rather than calorie-related

Table 2 (*Continued*)

Source	Species	Diet	Diet period	Weight gain	Detected signal/effect	Special feature(s)/effects
So et al. (2007)	Mice	60% resistant starch (HRS), or readily digestible starch (LRS)	4 weeks	No change	Mice on both diets had similar weights, yet total body adiposity, subcutaneous and visceral fat, plasma: leptin, adiponectin and insulin/glucose ratios were greater in LRS. MRI data from the ventromedial and paraventricular hypothalamic nuclei show a satiating effect of the HRS diet despite a lower energy intake	Adipocytes isolated from LRS mice were larger and had lower insulin-stimulated glucose uptake
Anastasovska et al. (2012)	Mice	High fat (HF) diet supplemented with oligofructose-insulin enriched (In) or corn starch (Cs)	9 weeks	– on In diet	HF diet with oligofructose-enriched inulin (In diet) reduced accrued fat deposition and increase arcuate nucleus neuronal activity	Supplementation of a HF diet with oligofructose-enriched insulin induced beneficial metabolic and hypothalamic neuronal activity effects

Table 2 Effect of carbohydrate-modified diets on the induction of obesity or weight loss.

gray matter volume and enlarged orbitofrontal white matter, particularly in the frontal lobe (Pannacciulli et al., 2006). Functional alterations may accompany these structural and morphological changes in the obese brain. For example, in healthy subjects increased BMI was associated with decreased regional blood flow in the prefrontal cerebral cortex (Willeumier et al., 2011).

7. Differing functional brain MRI (fMRI) responses between obese and lean individuals

Imaging studies conducted in the postprandial state (i.e., after a meal) argue that the excess energy intake in obesity is at least partly due to eating in the absence of hunger (nonhomeostatic eating) presenting evidence that overweight/obese participants have greater brain activity in response to the presence of food (cues or taste) and enhancement of anticipated reward compared with normal-weight participants. For example, in the fasted state preceding a breakfast that provided 20% of subject-specific calculated daily energy requirements to achieve satiety, food reward-related brain signaling (FRS) was higher in overweight subjects, but when sufficiently satiated, FRS was lower compared to normal weight subjects. Inhibitory control, represented by prefrontal cortex signaling, however, was lower in the satiated overweight individuals; this may result in eating in the absence of hunger or, perhaps more precisely stated, lack of a true biological need to provide just adequate caloric supply (Martens et al., 2013) (see Table 3 for additional information about brain reward circuits). Interestingly, increased responsiveness to food cues in some reward-related brain regions not only persists in "formerly obese" individuals that lost weight and maintained normal BMI, but is also associated with weight gain. For example, 8 obese or overweight women who experienced >2.5% increase in BMI over a 6-month follow-up period, showed reduced striatal response to chocolate milkshake consumption vs. a tasteless control solution compared with 12 women who showed <2% change in BMI. Six women that lost weight did not show significant changes in caudate activation upon milkshake intake compared to the weight gain or weight stable groups. These results suggested that weight gain may be associated with reduced sensitivity of reward circuitry which may be a fundamental mechanism responsible for overeating (DelParigi et al., 2004; Stice et al., 2010) (see Table 3 for additional studies regarding reward circuits). DelParigi et al. showed that in response to a liquid meal (Ensure Plus) there was a significant difference in the activity of the posterior cingulate and amygdala between obese and the lean individuals, but not between lean and post-obese subjects. However, increased neural activity in the middle insula and decreased activity in the posterior hippocampus was found in obese and post-obese compared with lean individuals. Collectively, then, some functionally demonstrable alterations in the "obese brain" may be reversible with weight loss, whereas the persistence of other anomalous patterns is compatible with the concept that they may be involved in the pathophysiology of obesity (DelParigi et al., 2004). fMRI studies also showed that there are differences in brain activity between successful dieters (past-obese individuals that lost weight and achieved and maintained normal BMI) to non- successful dieters that remain obese. The dorsal prefrontal cortex (DPFC), involved in controlling inappropriate behavioral responses, was activated in successful-compared to non-successful dieters upon meal consumption, and there was an association between the degree of dietary restraint (assessed by questionnaires) and the coordinated neural changes in the DPFC and orbitofrontal cortex (DelParigi et al., 2007). Compared to normal weight and obese individuals, sustained weight losers (past obese individuals that achieved normal BMI and maintained it for at least 3 years) that were shown images of food items had enhanced activation of primary and secondary visual cortices, i.e., enhanced visual attention to food cues, together with greater engagement of inhibitory control regions (frontal regions) in response to food cues. These differences could comprise a possible contributory mechanism to improved control of food intake in successful weight-losers (McCaffery et al., 2009).

8. Overnutrition, hypothalamic inflammation and hypothalamic dysfunction

Proinflammatory cytokines, such as TNF-α and interleukin-1 beta (IL-1β) were shown to be released in the hypothalamus and activate apoptotic signaling in the hypothalamus of rodents placed on a high fat diet (De Souza et al., 2005). This process may be particularly prominent in the mediobasal hypothalamus. Short-term high-fat intake interferes with insulin signaling in the hypothalamus as measured by the inability of insulin delivered to the mediobasal hypothalamus to inhibit lipolysis through central pathways, an effect seen even before the evolution of peripheral insulin

Table 3
Effects of food-related measures/measurements on human brains.

Source	Type of patients	Type of intervention/study	Duration of assessed intervention	Change in weight and/or fat	Detected signal	Special feature(s)/effects
Gunstad et al. (2011)	Obese	Bariatric surgery	12 weeks post-operative	–	Several cognitive tests improved in bariatric surgery patients relative to obese controls, including multiple memory indices and a test of psychomotor speed	Obesity-related cognitive dysfunction was at least partly reversible
Martens et al. (2013)	Normal weight, overweight	10 h fast followed by a large breakfast			Overweight subjects had a more pronounced food-reward anticipating brain signaling in the fasted state in the anterior cingulate cortex (ACC) vs. normal-weight subjects When sufficiently satiated, food reward–related brain signaling was less pronounced in overweight vs. normal-weight subjects in the ACC and the prefrontal cortex.	
Stice et al. (2010)	Obese/lean teenagers	Observation	6 months	Weight increase seen in association with brain reward activity and genetic variation in dopamine receptors' polymorphisms	Weaker activation of the frontal operculum, lateral orbitofrontal cortex, and striatum in response to imagined consumption palatable vs. unpalatable foods or water, predicted future increases in body mass for those with the DRD2 TaqIA A1 allele or the DRD4-7R allele	Findings suggest that low responsivity of dopamine-based reward circuitry to food intake predicts future weight gain and that this difference is likely determined by genetic variation (polymorphisms) in dopamine receptors 2 and 4
Witte et al. (2009)	Healthy, normal, over-weight	Caloric restriction	3 months		Increase in verbal memory which correlated with decreases in fasting insulin and C-reactive protein. Best results in subjects with best adherence to the diet	

resistance in white adipose tissue (Scherer et al., 2012). Activation of hypothalamic inhibitor of kappaB kinase beta (IKKβ)/NF-κB, at least in part through elevated endoplasmic reticulum stress in the hypothalamus, is another important link between overnutrition and hypothalamic inflammation. In fact, direct forced activation of hypothalamic IKKβ/NF-κB can interrupt central insulin/leptin signaling and actions (Zhang et al., 2008). Notably, direct activation of IKKbeta/NF-κB in the pro-opiomelanocortin (POMC) neurons in the mediobasal hypothalamus accounts for obesity-induced hypertension, operating downstream via activation of the sympathetic nervous system (Purkayastha et al., 2011). Conversely, site- or cell-specific suppression of IKKβ either across the brain in general or targeting the mediobasal hypothalamus, or even more specifically, the hypothalamic agouti-related protein (AGRP) neurons, provides significant protection from high fat diet-induced obesity and glucose intolerance (Zhang et al., 2008). Hence, mediobasal hypothalamic inflammation may be a mediator of obesity and obesity-related hypertension depending on the involvement of specific cell types within this area. It has been recently clarified that unlike inflammation in peripheral tissues, which develops as a consequence of obesity, hypothalamic inflammatory signaling can be detected in both rats and mice as early as 1–3 days from the onset of high fat intake, prior to weight gain. Ensuing reactive gliosis and markers suggestive of neuron injury were found in the hypothalamic arcuate nucleus within the first week of fat-rich diet. Whereas these changes were initially entirely reversible, with continued consumption of fat excess, they re-emerged permanently at the mediobasal hypothalamus. Examination of human brain MRI studies likewise showed increased gliosis in the mediobasal hypothalamus of obese subjects (Thaler et al., 2012). Apparently, potential local neuroprotective repair mechanisms may be overpowered under the chronic insult of overnutrition and/or obesity. This is suggested by the observation that long term HFD feeding leads to both depletion and functional impairment in the neurogenic capacity of adult hypothalamic neural stem cells (htNSCs; a multipotent cell population residing predominantly in the mediobasal hypothalamus of adult mice), associated with local IKKβ/NF-κB activation. Hence, IKKβ/NF-κB-mediated impairment of adult htNSCs may be a critical neurodegenerative mechanism in obesity (Li et al., 2012). Acutely inflamed hypothalamus due to short term overnutrition or structurally modified hypothalamus secondary to chronic obesity and/or inflammation can become dysfunctional. This might disrupt the normally precise coupling between caloric intake and energy expenditure, fostering overeating and further weight gain. An example to this effect is the observation that short-term HFD feeding led to a 37% increase in caloric intake, hyperinsulinemia, and, even prior to impairment in insulin signaling in white adipose tissue (WAT), loss of the ability of the mediobasal hypothalamus to suppress WAT lipolysis and hepatic glucose production

as assessed by glycerol and glucose flux. This was associated with increased hypothalamic levels of the endocannabinoid 2-arachidonoylglycerol (2-AG) after only 3 days (Scherer et al., 2012).

The hypothalamic inflammation seen in mice with diet-induced obesity can be reversed by direct ICV administration of ω3 and ω9 pure fatty acids, which also leads to reduction in spontaneous food intake and body mass gain (Cintra et al., 2012). Finally, specificity of the inflammatory profile, site and affected cell population appear critical to the induction of overeating and hypothalamic dysfunction: for example, hypothalamic TNF-α can also produce anorexigenic and negative energy balance effects (Arruda et al., 2010).

9. Hypothalamic inflammation affects insulin release and action

Recent evidence indicates that hypothalamic inflammation results not only in impaired central regulation of energy balance but also in disruption of normal insulin secretion and reduced peripheral insulin sensitivity. ICV injection of a low dose of TNF-α leads to a dysfunctional increase in insulin secretion and activates the expression of a number of markers of apoptosis in pancreatic islets. Experimentally induced hypothalamic inflammation induced by the ICV injection of stearic acid produced an impairment of insulin secretion, accompanied by increased expression of pancreatic islet markers of apoptosis. Thus, the signals generated in concert with or secondary to hypothalamic inflammation can be a negative modulator of pancreatic islet function (Calegari et al., 2011). Hypothalamic inflammation, presumably acting through activation of the sympathetic nervous system, can also blunt the hepatic response to insulin. In fact, when obese rodents received ICV injections of immunoneutralizing antibodies against Toll-like receptor (TLR) 4 or TNF-α, hypothalamic inflammation was reduced, resulting in attenuation of hypothalamic resistance to leptin, improved insulin signal transduction in the liver and lessening of liver steatosis (Milanski et al., 2012).

10. Hippocampal inflammation and atrophy

The hippocampus is a vital structure for cognition, processing of short to long term memory, learning, spatial navigation and emotions, whose function may be preserved through continued neurogenesis in adult life. As recently reviewed by Fotuhi et al. (2012), obesity and obesity-related conditions such as diabetes, hypertension, cardiovascular disease, obstructive sleep apnea, vitamin B12 deficiency, atrial fibrillation, mood disorders are known to adversely influence hippocampal size (Fotuhi et al., 2012). However, direct studies with careful matching of controls and hypertensive subjects failed to identify a role for hypertension hippocampal volume (Gold et al., 2005; Raz et al., 2003). Some insight into the effect of obesity on the hippocampus is offered by a recent study, in which HFD resulted in increased hippocampal TNF-α expression and activated microglia (Jeon et al., 2012). HFD in mice also increased lipid peroxidation as indicated by high 4-hydroxynonenol levels in the hippocampus (Moroz et al., 2008). High fat diet can induce local pro-apoptotic signaling such as increased expression of caspase-3 and gliosis in the hippocampus, particularly in the dentate gyrus (Rivera et al., 2013). Such local incitement of inflammation and cell damage may eventually lead to loss of hippocampal tissue. There is evidence for reduced hippocampal size in obesity, which could harbor accelerated cognitive impairment in late life (Ho et al., 2011; Jagust et al., 2005; Raji et al., 2009; Whitmer et al., 2008). Furthermore, a high BMI in midlife is a marker of increased rate of hippocampal atrophy in late life (Jagust et al., 2005; Knopman, 2008; Raji et al., 2010; Taki et al., 2007). In one analysis, an increase in one standard deviation (SD) in the waist-to-hip ratio was reportedly linked to a 0.2 SD decrease in hippocampal volume (Jagust et al., 2005). While obesity per se and or high fat intake can contribute to the hippocampal atrophy, very recent evidence indicates that glucose, even at the high normal range, may be an additional important player in hippocampal volume shrinkage (Cherbuin et al., 2012). In a 4 year MRI-based follow up study of non-diabetic subjects, blood glucose was linked to hippocampal and amygdalar atrophy, explaining 6–10% in volume change after controlling for age, sex, body mass index, hypertension, alcohol, and smoking.

Novel insights into how self-perpetuating this association may be is offered by emerging evidence that hippocampal injury may, in itself, adversely affect feeding behavior, thus potentially further perpetuating obesity by uncontrolled feeding. Not only are receptors for negative regulators of feeding such as GLP-1, leptin and insulin expressed in the hippocampus, but also the direct hippocampal exposure to leptin reduces food intake (Kanoski et al., 2011). Brain leptin resistance, a well-studied aspect of the obese state, as well as hippocampal injury that is secondary to obesity could, thus, play a role in disrupted feeding behavior. In vivo studies show that low adiponectin levels, typical of obesity and the metabolic syndrome, are inversely related to hippocampal volume in T2DM (Masaki et al., 2012). In vitro studies showed that adiponectin protects cultured hippocampal neurons from excitotoxicity (Qiu et al., 2011).

11. Obesity and cognitive decline

Experimental evidence links very HFD-induced obesity to cognitive decline. For example, in one study, very HFD but not moderate fat diet elicited impaired cognition, increased brain inflammation, and decreased brain-derived neurotrophic factor (BDNF), along with increased body weight. Hence some, but not all, diet formulations which increase body weight can induce brain inflammation and disrupt cognition in mice (Pistell et al., 2010). While this appears to suggest that some types of excessive nutrition per se impair cognition independent of obesity, a wealth of studies nevertheless links the obese state, either alone or in association with its comorbidities/sequels, to cognitive disadvantage.

The linkage between obesity and/or the MetS and cognitive impairment is strongly supported not only by epidemiological cross-sectional and prospective studies (Case et al., 2002; Yaffe et al., 2004) but even more so by improvement of cognitive measures following effective intervention addressing individual components of the MetS (Siervo et al., 2011). First, obesity is associated with cognitive impairment across the human life span (Smith et al., 2011), beginning with some deficits seen as early as during childhood or adolescence (Maayan et al., 2011). These early deficits include reduction in executive functioning and attention, decreased global functioning or lesser intelligence quotient (IQ) (Yates et al., 2012). Of interest is the possibility that deficient executive function may actually play a role in the development or persistence of obesity, particularly if weak inhibitory control performance leads to overeating (Pauli-Pott et al., 2010). Second, even healthy obese subjects have some deficits in learning, memory, and executive function relative to nonobese individuals (Elias et al., 2003, 2005; Waldstein and Katzel, 2006), which appears to reflect the effect of obesity per se (Gunstad et al., 2006, 2007; Jeong et al., 2005). Third, cognitive performance also declines with decreased physical activity and aerobic fitness, which often accompany, if not simply underlie or contribute to, increased fatness and high energy consumption. These factors likely adversely affect cognition not only on a rudimentary level but also at the level of scholastic performance

(Donnelly et al., 2009). Fourth, obesity, particularly in the setting of the MetS, may be a marker of future cognitive decline (Yaffe et al., 2004). Cognitive deficits have been recently reported to be more likely associated with MetS in the presence of markers of peripheral inflammation such as elevated circulating levels of c-reactive protein (CRP) or Interleukin 6 (IL-6) (Roberts et al., 2010). Fifth, as recently reviewed by Siervo et al., weight loss improves cognitive function (Siervo et al., 2011) affecting some of the very same cognitive parameters impaired in the obese state: memory and attention/executive functioning (see Table 3 for additional examples). In fact, weight loss may result in rapid improvement of some cognitive functions. For example, in one study, improved memory was noted as early as 12 weeks following bariatric surgery (Gunstad et al., 2011) (see Table 3 for another example for the effect of caloric restriction and cognitive function). At the present time, potential effects of weight loss cannot be fully separated from those elicited by the associated improvement in the metabolic control secondary to weight loss (Ryan et al., 2006). Likewise, weight loss associated improvement in hemodynamic factors such as blood pressure, arterial flow and endothelial function, sleep quality and nutrient composition and load could also contribute to the beneficial cognitive effects of weight loss. Sixth, midlife obesity per se is an apparent risk factor for Alzheimer's disease (AD), independent of other conditions (Beydoun et al., 2008; Fitzpatrick et al., 2009; Kivipelto et al., 2005; Profenno and Faraone, 2008; Profenno et al., 2010; Whitmer et al., 2007). Somewhat reminiscent of the differential effects of various dietary fat types on the brain in mice, the ingestion of saturated, but not unsaturated fat, at midlife appears to increase the risk of developing AD (Eskelinen et al., 2008; Laitinen et al., 2006).

Brain function is sensitive to inflammatory pathways and mediators, the expression of which is enhanced in the peripheral tissues in the obese state, and possibly, at least under some conditions, in the brain. Hence, both peripheral inflammation and central inflammatory processes may affect the brain in the obese state. It is now well accepted that the expression of inflammatory cytokine can be induced in brain cells, which then leads to neuronal apoptosis and impaired cognition (Gemma and Bickford, 2007). Direct injection of IL-1β to the dorsal hippocampus impairs context memory in mice (Barrientos et al., 2002). However, even peripheral exposure to lipopolysaccharide can disrupt working memory, an effect which cannot be exerted in IL-6 knockout mice and involves increased hippocampal expression of IL-6 (Sparkman et al., 2006). Notably, the highest levels of cytokine binding during experimentally induced acute sickness or inflammation have been demonstrated particularly in specific brain areas associated with learning and memory, including regions of the cortex and hippocampus (Parnet et al., 2002). The contribution of inflammatory mechanisms to cognitive impairment is further suggested by its association with elevated increased circulating levels of CRP in the MetS. Cognitive function is strongly affected by mood and elevated circulating levels of IL-6 were also found to correlate with mood symptoms (Soczynska et al., 2011).

12. Hormonal alterations and cognitive function in obesity

Leptin replacement was shown to improve cognitive function in a boy with leptin deficiency, but the interpretation of this effect is complex, since the effects of the induced weight loss are difficult to discern from the effect of leptin per se (Paz-Filho et al., 2008). There is growing interest in the possibility that leptin and leptin analogs have neuroprotective effects (Frolich et al., 2011) and in this respect, the brain leptin resistance seen in obesity might adversely affect naturally existing neuroprotective mechanisms.

GLP-1, a hormone that increases food induced insulin release has modulatory effects on both fat tissue homeostasis and learning capacity which appear to be blunted in the obese state. The injection of GLP-1 ICV in mice potently decreases lipid storage in white adipose tissue, an effect which is blunted in obese mice (Nogueiras et al., 2009). Such decreased central GLP-1 effects in obesity could likewise affect cognitive ability as GLP-1 receptor knockout mice display memory impairment which can be overridden by viral-borne GLP-1 gene therapy (During et al., 2003). There is now experimental evidence that GLP-1 treatment can improve neurodegenerative processes in animal models of Alzheimer's (Gengler et al., 2012) and Parkinson's disease (Li et al., 2009) and also can preserve cognitive functions in HFD-fed mice, a model which is highly relevant to human diet-induced obesity.

BDNF is widely recognized as a key regulator of neuronal development, survival, and differentiation and is functionally implicated in memory and cognitive ability. BDNF also suppresses food intake and is activated via the monocyte chemoattractant proteins 4 (MCP-4) receptor pathway and leptin such that when it is administered to mice, it leads to weight loss (Liao et al., 2012; Xu et al., 2003). Intact hippocampal BDNF signaling restrains anxiety-like behavior patterns (Bergami et al., 2008). Moreover, hippocampal BDNF mRNA expression and signal transduction are negatively regulated by proinflammatory cytokines (Barrientos et al., 2004).

Given this background on BDNF and in light of the inflammation and volume atrophy noted in the hippocampus in obesity, the observation that HFD impairs hippocampal neurogenesis and retards the proliferation of neural progenitor cells through increased lipid peroxidation and decrease in BDNF expression is of interest (Park et al., 2010). Such effects can be prenatally programmed since high fat diet-induced maternal obesity impairs hippocampal BDNF production and spatial learning performance in young mouse offsprings (Tozuka et al., 2010). Genetic obesity, such as seen in the leptin receptor deficient db^{-}/db^{-} mouse model is also linked to reduced hippocampal BDNF expression, in association with hippocampal inflammation and increased expression of the cytokines interleukin-1β, TNF-α and IL-6. Concomitant behavioral alterations consistent with hippocampal impairment were noted, mainly increased anxiety-reflecting movement patterns in the open-field, and impaired spatial recognition memory, the latter being an established hippocampus-dependent task (Dinel et al., 2011). Increased brain levels of TNF-α and IL-6 induced by consumption of HFD in mice are associated with reduced BDNF levels and cognitive performances (Pistell et al., 2010).

Obesity and obesity-related phenotypes are associated with variations in the BDNF gene (Hotta et al., 2011) but do not necessarily translate into simple effects on circulating BDNF. The potential importance of alteration in BDNF expression with respect to both weight regulation and cognitive function is exemplified by a rare human genetic disease in which BDNF haplotype insufficiency results in obesity along with significant cognitive impairment (Gray et al., 2006).

While plasma BDNF is positively related to body mass index (BMI) in human females but not in males, and declines with age (Golden et al., 2010) there is insufficient information on the source and regulation of circulating BDNF. Physical exercise raises plasma BDNF but caloric restriction improves memory in older subjects without an effect on circulating BDNF (Witte et al., 2009).

13. Sleep deprivation

Sleep deprivation and circadian disruption in the urban, western style, "24/7 Society" have been long suspected as facilitators of the spread of obesity and the MetS. On functional MRI studies, sleep restriction in normal weight adults reportedly leads to increased overall neuronal activation in response to food, particularly of brain areas involved in reward, including the putamen, nucleus accumbens, thalamus, insula, and prefrontal cortex

(St-Onge et al., 2012). Obesity, in turn, interferes with normal sleep, most commonly by eliciting night-time sleep apnea and daytime sleepiness, in association with memory and spatial orientation deficits (Telakivi et al., 1988). Experimentally induced circadian disruption in mice results in increased weight gain which is accompanied by remodeling of neocortical neuronal structure, reduction in some applied learning capacities and increased emotionality (Karatsoreos et al., 2011). In mice, disruption of the clock gene that codes for a transcription factor known to regulate circadian rhythm, brain and muscle Arnt-like 1 (Bmal1), led to adipocyte hypertrophy and obesity (Barclay et al., 2012). Sleep abnormalities may also turn on inflammatory mechanisms, a potential link to mood changes and cognitive derangement. For example, in one study increases in habitual sleep duration was associated with elevations in CRP and IL-6 levels whereas reduced sleep duration was linked to increase in circulating TNF-α, thus suggesting that extreme sleep habits can differentially activate pro-inflammatory pathways (Patel et al., 2009). Interference with sleep, then, impairs cognition and fosters weight gain, whereas obesity itself is a sleep disruptor, thus forming a vicious self amplifying path which facilitates obesity and hampers cognitive performance through obesity-related abnormal sleep.

14. Brain disease in obesity: dissecting the role of obesity from its confounders, hypertension, diabetes and the metabolic syndrome

Although obesity facilitates the evolution of dysglycemia, diabetes, hypertension and the metabolic syndrome, fat accumulation usually precedes the emergence of these sequels. Further, although concomitant realization of the presence of these conditions in cluster is not uncommon in humans, there is an actual lag time ranging between a few years to several decades between obesity and its sequels. A primary role for obesity can be therefore assumed on the basis of this chronological sequence alone, yet the relative role of each of these conditions vis-à-vis brain function in obesity merits reconsideration. The two key fields for such scrutiny are the (a) potential a priori brain anomalies in obesity and or the primacy of abnormal control mechanisms in food-related brain centers leading to appetite deregulation, overeating and obesity; and (b) the chronic brain damage which evolves secondary to obesity.

The phenomenon that preceding exposure to excessive nutrition is linked to subsequent dysfunction of brain food control centers, resulting in hyperphagia and weight gain comprises perhaps the best example of clear separation between obesity and its confounders. In man, maternal pre-pregnancy BMI is a risk factor for childhood overweight (Weng et al., 2013), but this linkage is obviously complicated by genetic factors. A more visible proof for a primary insult induced by improper excessive feeding is the experimental data (reviewed in Section 3) that overfeeding in early life imprints hypothalamic anomalies which intensify eating drive into adulthood and result in weight gain. In brief, early hyper-nutritional cues generate long terms hypothalamic dysfunction, hyperphagia and obesity. Further, hypothalamic inflammatory response can be induced within 24 h of exposure to high fat diet (Thaler et al., 2012). Collectively then, impairment in feeding control centers can be triggered by improper excessive caloric or fatty food flux, even before any weight gain, let alone the evolution of obesity, hypertension or diabetes.

The potential contributory role of obesity sequels or of aging per se to obesity-linked brain functional and structural aberrations is far more difficult to exclude in adult life. Changes detected in neuroimaging studies in obese, hypertensive diabetic and elderly subjects overlap to some extent, but some important differences are depicted in Table 4. In this context, studies in healthy children provide the best opportunity to assess the brain effects of obesity independent of its metabolic or elder age-related confounders, particularly diabetes and hypertension. An inherent caveat in this setting is that children's "health" in such studies is often assumed based on the absence of known diseases rather than on careful direct testing. Even when examined however, subtle effects of shifts in indices of metabolic and vascular factors, namely, rises in blood glucose or blood pressure within the normal range cannot be entirely excluded. Nevertheless, emerging evidence is consistent with obesity-associated brain changes in otherwise healthy children. In a recent study of 120 children and adolescents obesity was associated with decreased volume of frontal and limbic

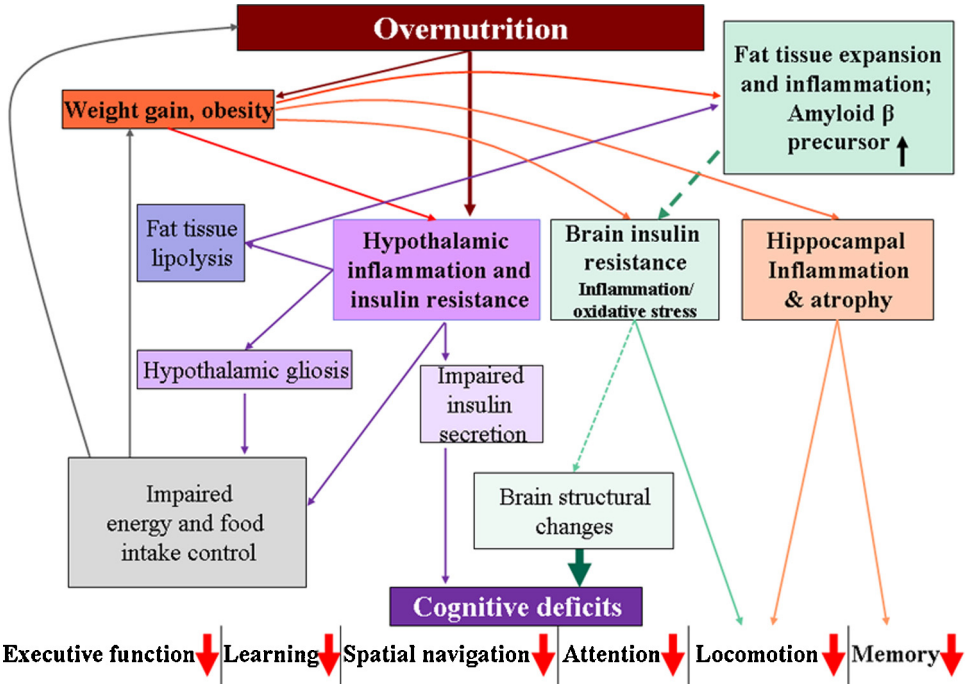

Fig. 1. Effects of overnutrition and obesity on the brain and cognitive function. Dashed lines represent hypothetical interactions.

Table 4
Effects of obesity as compared to hypertension, diabetes and aging on human brain structural changes as detected by neuroimaging, particularly MRI studies.

	Obesity	Hypertension	Diabetes	Aging
White matter intensities on MRI	+ in older subjects (Jagust et al., 2005) − in children and adolescents (Alosco et al., 2013)	++ (Valdes Hernandez et al., 2013)	++ (Reijmer et al., 2011; van Harten et al., 2007)	++
Reduced brain volume in children/adolescents-frontal and limbic cerebral gray matter regions	+ in obese children/adolescents (Alosco et al., 2013)	NR	+ in comparison with obese adolescents (Bruehl et al., 2011)	NA
Temporal lobe atrophy	++, but not linked to FTO risk allele (Ho et al., 2010)	− (Korf et al., 2007)	++ (Korf et al., 2007)	+ (Yao et al., 2012)
Frontal/prefrontal lobe atrophy	++ Even in adolescents (Alosco, 2013)	+ (Gold et al., 2005; Raz et al., 2003)	+ (Lee et al., 2013b)	+ (Mander et al., 2013)
Hippocampal atrophy	(+)(+) (Whitmer et al., 2008; Ho et al., 2011; Raji et al., 2009; Jagust et al., 2005)	− (Gold et al., 2005; Raz et al., 2003)	+ even with rising normal glucose (Cherbuin et al., 2012)	In proportion to total brain volume reduction with age (Knoops et al., 2012)

NR, not reported; NA, not applicable.

cerebral gray matter regions (Alosco et al., 2013). These findings are dissimilar to studies in obese and overweight adults, in that they do not reveal any linkage between BMI and microstructural, MRI-detected, white matter changes, which are more typically observed in association with hypertension, diabetes or aging. Such early brain changes in children may interact with rather prevalent genetic factors. Defined variations (rs9930333) in the fat mass- and obesity (FTO)-associated gene, which affect more than 15% of the population and are known to exert a small incremental effect on human body weight, in the vicinity of 3 kg (Frayling et al., 2007), have been linked to reduced brain volume in elderly subjects (Ho et al., 2010). Notably, this reduction was not related to common confounders of obesity, including hypertension, and hypercholesterolemia and was also independent of white-matter hyperintensities. More impressive, perhaps, is the finding of a shared *inverse* variance between the brain volume and total body fat in a population-based cohort of 598 adolescents recruited from the French Canadian founder population which was subsequently verified in two additional population samples of adolescents (Melka et al., 2013). In fact, in this report, analysis of co-expression networks supported the possibility that the underlying FTO effects may occur as early as during embryogenesis. Rather than a cause and effect relationship of obesity to lower brain volume, then, this finding highlights the formerly unpredicted possibility that FTO, and perhaps other genes as well, exert inverse effects on adipose and brain tissues. Finally, in the ARIC prospective cohort study of the development of atherosclerosis in 15,792 individuals aged 45–64 years at baseline, the FTO allele linked to weight gain and smaller brain volume was strongly associated decline in verbal memory independent of age, gender, education, diabetes, hypertension and BMI (Bressler et al., 2013).

15. Conclusion

In conclusion, the evidence reviewed here suggests that excessive nutrition elicits early hypothalamic inflammatory effects, which likely disrupt the normal homeostasis of energy intake and expenditure as well as insulin secretion and sensitivity.

Structural changes in the hypothalamus, hippocampus and cortex may perpetuate these initially reversibly anomalies. Additionally, these structural changes may reflect genetic background as well as the added burden of the accrued fat mass with the associated sequels of systemic anomalies in carbohydrate and lipid metabolism as well as in the vasculature. The “obese brain” is also functionally modified over time, which translates into a vicious cycle of poor control of eating and increasing harmful peripheral signaling, eventually culminating in cognitive impairment. Defining which of these putative steps, if any, can be therapeutically targeted, might offer much needed additional tools in the search for brain protection in obesity (see Fig. 1).

Author contribution

GS, YM and NS wrote, reviewed and edited the manuscript.

Conflicts of interest

GS, YM and NS declare that no conflicts no conflict of interest exists.

References

Agrawal, R., Gomez-Pinilla, F., 2012. ‘Metabolic syndrome’ in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition. Journal of Physiology 590, 2485–2499.
Agrawal, R., Tyagi, E., Shukla, R., Nath, C., 2009. A study of brain insulin receptors, AChE activity and oxidative stress in rat model of ICV STZ induced dementia. Neuropharmacology 56, 779–787.
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. International Journal of Neuroscience, http://dx.doi.org/10.3109/00207454.2013.817408, Posted online on July 19, 2013.
Anastasovska, J., Arora, T., Sanchez Canon, G.J., Parkinson, J.R., Touhy, K., Gibson, G.R., Nadkarni, N.A., So, P.W., Goldstone, A.P., Thomas, E.L., Hankir, M.K., Van Loo, J., Modi, N., Bell, J.D., Frost, G., 2012. Fermentable carbohydrate alters hypothalamic neuronal activity and protects against the obesogenic environment. Obesity (Silver Spring) 20, 1016–1023.
Arruda, A.P., Milanski, M., Romanatto, T., Solon, C., Coope, A., Alberici, L.C., Festuccia, W.T., Hirabara, S.M., Ropelle, E., Curi, R., Carvalheira, J.B., Vercesi, A.E., Velloso, L.A., 2010. Hypothalamic actions of tumor necrosis factor alpha provide the thermogenic core for the wastage syndrome in cachexia. Endocrinology 151, 683–694.
Baker, L.D., Cross, D.J., Minoshima, S., Belongia, D., Watson, G.S., Craft, S., 2011. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Archives of Neurology 68, 51–57.
Barclay, J.L., Husse, J., Bode, B., Naujokat, N., Meyer-Kovac, J., Schmid, S.M., Lehnert, H., Oster, H., 2012. Circadian desynchrony promotes metabolic disruption in a mouse model of shiftwork. PLoS ONE 7, e37150.
Barrientos, R.M., Higgins, E.A., Sprunger, D.B., Watkins, L.R., Rudy, J.W., Maier, S.F., 2002. Memory for context is impaired by a post context exposure injection of interleukin-1 beta into dorsal hippocampus. Behavioural Brain Research 134, 291–298.
Barrientos, R.M., Sprunger, D.B., Campeau, S., Watkins, L.R., Rudy, J.W., Maier, S.F., 2004. BDNF mRNA expression in rat hippocampus following contextual learning is blocked by intrahippocampal IL-1β administration. Journal of Neuroimmunology 155, 119–126.
Bayol, S.A., Simbi, B.H., Bertrand, J.A., Stickland, N.C., 2008. Offspring from mothers fed a ‘junk food’ diet in pregnancy and lactation exhibit exacerbated adiposity that is more pronounced in females. Journal of Physiology 586, 3219–3230.

Bayol, S.A., Simbi, B.H., Fowkes, R.C., Stickland, N.C., 2010. A maternal junk food diet in pregnancy and lactation promotes nonalcoholic fatty liver disease in rat offspring. Endocrinology 151, 1451–1461.
Bayol, S.A., Simbi, B.H., Stickland, N.C., 2005. A maternal cafeteria diet during gestation and lactation promotes adiposity and impairs skeletal muscle development and metabolism in rat offspring at weaning. Journal of Physiology 567, 951–961.
Beck, B., Richy, S., Archer, Z.A., Mercer, J.G., 2012. Early and persistent up-regulation of hypothalamic orexigenic peptides in rat offspring born to dams fed a high-carbohydrate supplement during gestation. Brain Research 1477, 10–18.
Benedict, C., Brooks, S.J., Kullberg, J., Burgos, J., Kempton, M.J., Nordenskjöld, R., Nylander, R., Kilander, L., Craft, S., Larsson, E.-M., Johansson, L., Ahlström, H., Lind, L., Schiöth, H.B., 2012. Impaired insulin sensitivity as indexed by the HOMA score is associated with deficits in verbal fluency and temporal lobe gray matter volume in the elderly. Diabetes Care 35, 488–494.
Bergami, M., Rimondini, R., Santi, S., Blum, R., Götz, M., Canossa, M., 2008. Deletion of TrkB in adult progenitors alters newborn neuron integration into hippocampal circuits and increases anxiety-like behavior. Proceedings of the National Academy of Sciences 105, 15570–15575.
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 Reviews 9, 204–218.
Boitard, C., Etchamendy, N., Sauvant, J., Aubert, A., Tronel, S., Marighetto, A., Laye, S., Ferreira, G., 2012. Juvenile, but not adult exposure to high-fat diet impairs relational memory and hippocampal neurogenesis in mice. Hippocampus 22, 2095–2100.
Bressler, J., Fornage, M., Demerath, E.W., Knopman, D.S., Monda, K.L., North, K.E., Penman, A., Mosley, T.H., Boerwinkle, E., 2013. Fat mass and obesity gene and cognitive decline: the Atherosclerosis Risk in Communities Study. Neurology 80, 92–99.
Brinkworth, G.D., Buckley, J.D., Noakes, M., Clifton, P.M., Wilson, C.J., 2009. Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. Archives of Internal Medicine 169, 1873–1880.
Bruehl, H., Sweat, V., Tirsi, A., Shah, B., Convit, A., 2011. Obese adolescents with type 2 diabetes mellitus have hippocampal and frontal lobe volume reductions. Neuroscience and Medicine 2, 34–42.
Calegari, V.C., Torsoni, A.S., Vanzela, E.C., Araujo, E.P., Morari, J., Zoppi, C.C., Sbragia, L., Boschero, A.C., Velloso, L.A., 2011. Inflammation of the hypothalamus leads to defective pancreatic islet function. Journal of Biological Chemistry 286, 12870–12880.
Cani, P.D., Neyrinck, A.M., Maton, N., Delzenne, N.M., 2005. Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like peptide-1. Obesity Research 13, 1000–1007.
Case, C.C., Jones, P.H., Nelson, K., O'Brian Smith, E., Ballantyne, C.M., 2002. Impact of weight loss on the metabolic syndrome. Diabetes, Obesity and Metabolism 4, 407–414.
Cherbuin, N., Sachdev, P., Anstey, K.J., 2012. Higher normal fasting plasma glucose is associated with hippocampal atrophy: the PATH Study. Neurology 79, 1019–1026.
Cintra, D.E., Ropelle, E.R., Moraes, J.C., Pauli, J.R., Morari, J., Souza, C.T., Grimaldi, R., Stahl, M., Carvalheira, J.B., Saad, M.J., Velloso, L.A., 2012. Unsaturated fatty acids revert diet-induced hypothalamic inflammation in obesity. PLoS ONE 7, e30571.
Cooper, S.B., Bandelow, S., Nute, M.L., Morris, J.G., Nevill, M.E., 2012. Breakfast glycaemic index and cognitive function in adolescent school children. British Journal of Nutrition 107, 1823–1832.
Danielsson, A., Fagerholm, S., Ost, A., Franck, N., Kjolhede, P., Nystrom, F.H., Stralfors, P., 2009. Short-term overeating induces insulin resistance in fat cells in lean human subjects. Molecular Medicine 15, 228–234.
De Felice, F.G., Vieira, M.N., Bomfim, T.R., Decker, H., Velasco, P.T., Lambert, M.P., Viola, K.L., Zhao, W.Q., Ferreira, S.T., Klein, W.L., 2009. Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the pathogenic binding of Abeta oligomers. Proceedings of the National Academy of Sciences of the United States of America 106, 1971–1976.
De Souza, C.T., Araujo, E.P., Bordin, S., Ashimine, R., Zollner, R.L., Boschero, A.C., Saad, M.J., Velloso, L.A., 2005. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology 146, 4192–4199.
DelParigi, A., Chen, K., Salbe, A.D., Hill, J.O., Wing, R.R., Reiman, E.M., Tataranni, P.A., 2004. Persistence of abnormal neural responses to a meal in postobese individuals. International Journal of Obesity and Related Metabolic Disorders 28, 370–377.
DelParigi, A., Chen, K., Salbe, A.D., Hill, J.O., Wing, R.R., Reiman, E.M., Tataranni, P.A., 2007. Successful dieters have increased neural activity in cortical areas involved in the control of behavior. International Journal of Obesity 31, 440–448.
Dinel, A.L., Andre, C., Aubert, A., Ferreira, G., Laye, S., Castanon, N., 2011. Cognitive and emotional alterations are related to hippocampal inflammation in a mouse model of metabolic syndrome. PLoS ONE 6, e24325.
Donnelly, J.E., Greene, J.L., Gibson, C.A., Smith, B.K., Washburn, R.A., Sullivan, D.K., DuBose, K., Mayo, M.S., Schmelzle, K.H., Ryan, J.J., Jacobsen, D.J., Williams, S.L., 2009. Physical Activity Across the Curriculum (PAAC): a randomized controlled trial to promote physical activity and diminish overweight and obesity in elementary school children. Preventive Medicine 49, 336–341.
During, M.J., Cao, L., Zuzga, D.S., Francis, J.S., Fitzsimons, H.L., Jiao, X., Bland, R.J., Klugmann, M., Banks, W.A., Drucker, D.J., Haile, C.N., 2003. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nature Medicine 9, 1173–1179.
Elias, M.F., Elias, P.K., Sullivan, L.M., Wolf, P.A., D'Agostino, R.B., 2003. Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. International Journal of Obesity and Related Metabolic Disorders 27, 260–268.
Elias, M.F., Elias, P.K., Sullivan, L.M., Wolf, P.A., D'Agostino, R.B., 2005. Obesity, diabetes and cognitive deficit: the Framingham Heart Study. Neurobiology of Aging 26 (Suppl. 1), 11–16.
Eskelinen, M.H., Ngandu, T., Helkala, E.-L., Tuomilehto, J., Nissinen, A., Soininen, H., Kivipelto, M., 2008. Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study. International Journal of Geriatric Psychiatry 23, 741–747.
Fitzpatrick, A.L., Kuller, L.H., Lopez, O.L., Diehr, P., O'Meara, E.S., Longstreth Jr., W.T., Luchsinger, J.A., 2009. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Archives of Neurology 66, 336–342.
Fotuhi, M., Do, D., Jack, C., 2012. Modifiable factors that alter the size of the hippocampus with ageing. Nature Reviews Neurology 8, 189–202.
Frayling, T.M., Timpson, N.J., Weedon, M.N., Zeggini, E., Freathy, R.M., Lindgren, C.M., Perry, J.R.B., Elliott, K.S., Lango, H., Rayner, N.W., Shields, B., Harries, L.W., Barrett, J.C., Ellard, S., Groves, C.J., Knight, B., Patch, A.M., Ness, A.R., Ebrahim, S., Lawlor, D.A., Ring, S.M., Ben-Shlomo, Y., Jarvelin, M.R., Sovio, U., Bennett, A.J., Melzer, D., Ferrucci, L., Loos, R.J.F., Barroso, I., Wareham, N.J., Karpe, F., Owen, K.R., Cardon, L.R., Walker, M., Hitman, G.A., Palmer, C.N.A., Doney, A.S.F., Morris, A.D., Smith, G.D., Hattersley, A.T., McCarthy, M.I., 2007. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316, 889–894.
Frolich, M.A., Esame, A., Warren Iii, W.M., Owen, J., 2011. High-dose oxytocin is not associated with maternal temperature elevation: a retrospective cohort study of mid-trimester pregnancy with intrauterine fetal demise. International Journal of Obstetric Anesthesia 20, 30–33.
Galef Jr., B.G., 1991. A contrarian view of the wisdom of the body as it relates to dietary self-selection. Psychological Review 98, 218–223.
Gemma, C., Bickford, P.C., 2007. Interleukin-1beta and caspase-1: players in the regulation of age-related cognitive dysfunction. Reviews in the Neurosciences 18, 137–148.
Gengler, S., McClean, P.L., McCurtin, R., Gault, V.A., Holscher, C., 2012. Val(8)GLP-1 rescues synaptic plasticity and reduces dense core plaques in APP/PS1 mice. Neurobiology of Aging 33, 265–276.
Gold, S.M., Dziobek, I., Rogers, K., Bayoumy, A., McHugh, P.F., Convit, A., 2005. Hypertension and hypothalamo-pituitary–adrenal axis hyperactivity affect frontal lobe integrity. Journal of Clinical Endocrinology and Metabolism 90, 3262–3267.
Golden, E., Emiliano, A., Maudsley, S., Windham, B.G., Carlson, O.D., Egan, J.M., Driscoll, I., Ferrucci, L., Martin, B., Mattson, M.P., 2010. Circulating brain-derived neurotrophic factor and indices of metabolic and cardiovascular health: data from the Baltimore Longitudinal Study of Aging. PLoS ONE 5, e10099.
Gray, J., Yeo, G.S., Cox, J.J., Morton, J., Adlam, A.L., Keogh, J.M., Yanovski, J.A., El Gharbawy, A., Han, J.C., Tung, Y.C., Hodges, J.R., Raymond, F.L., O'Rahilly, S., Farooqi, I.S., 2006. Hyperphagia, severe obesity, impaired cognitive function, and hyperactivity associated with functional loss of one copy of the brain-derived neurotrophic factor (BDNF) gene. Diabetes 55, 3366–3371.
Gunstad, J., Paul, R.H., Brickman, A.M., Cohen, R.A., Arns, M., Roe, D., Lawrence, J.J., Gordon, E., 2006. Patterns of cognitive performance in middle-aged and older adults: a cluster analytic examination. Journal of Geriatric Psychiatry and Neurology 19, 59–64.
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. Comprehensive 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. International Journal of Neuroscience 118, 1582–1593.
Gunstad, J., Strain, G., Devlin, M.J., Wing, R., Cohen, R.A., Paul, R.H., Crosby, R.D., Mitchell, J.E., 2011. Improved memory function 12 weeks after bariatric surgery. Surgery for Obesity and Related Diseases 7, 465–472.
Hallschmid, M., Benedict, C., Schultes, B., Born, J., Kern, W., 2008. Obese men respond to cognitive but not to catabolic brain insulin signaling. International Journal of Obesity 32, 275–282.
Halyburton, A.K., Brinkworth, G.D., Wilson, C.J., Noakes, M., Buckley, J.D., Keogh, J.B., Clifton, P.M., 2007. Low- and high-carbohydrate weight-loss diets have similar effects on mood but not cognitive performance. American Journal of Clinical Nutrition 86, 580–587.
Hennige, A.M., Sartorius, T., Lutz, S.Z., Tschritter, O., Preissl, H., Hopp, S., Fritsche, A., Rammensee, H.G., Ruth, P., Haring, H.U., 2009. Insulin-mediated cortical activity in the slow frequency range is diminished in obese mice and promotes physical inactivity. Diabetologia 52, 2416–2424.
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., 2011. The effects of physical activity, education, and body mass index on the aging brain. Human Brain Mapping 32, 1371–1382.
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, C.R., Weiner, M.W., Raji, C.A., Lopez, O.L., Becker, J.T., Carmichael, O.T., Thompson, P.M., Alzheimer's Disease Neuroimaging Initiative,

2010. A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in the healthy elderly. Proceedings of the National Academy of Sciences of the United States of America 107, 8404–8409.
Hotta, K., Kitamoto, T., Kitamoto, A., Mizusawa, S., Matsuo, T., Nakata, Y., Kamohara, S., Miyatake, N., Kotani, K., Komatsu, R., Itoh, N., Mineo, I., Wada, J., Yoneda, M., Nakajima, A., Funahashi, T., Miyazaki, S., Tokunaga, K., Masuzaki, H., Ueno, T., Hamaguchi, K., Tanaka, K., Yamada, K., Hanafusa, T., Oikawa, S., Yoshimatsu, H., Sakata, T., Matsuzawa, Y., Nakao, K., Sekine, A., 2011. Association of variations in the FTO, SCG3 and MTMR9 genes with metabolic syndrome in a Japanese population. Journal of Human Genetics 56, 647–651.
Jagust, W., Harvey, D., Mungas, D., Haan, M., 2005. Central obesity and the aging brain. Archives of Neurology 62, 1545–1548.
Jeon, B.T., Jeong, E.A., Shin, H.J., Lee, Y., Lee, D.H., Kim, H.J., Kang, S.S., Cho, G.J., Choi, W.S., Roh, G.S., 2012. Resveratrol attenuates obesity-associated peripheral and central inflammation and improves memory deficit in mice fed a high-fat diet. Diabetes 61, 1444–1454.
Jeong, S.K., Nam, H.S., Son, M.H., Son, E.J., Cho, K.H., 2005. Interactive effect of obesity indexes on cognition. Dementia and Geriatric Cognitive Disorders 19, 91–96.
Kanoski, S.E., Hayes, M.R., Greenwald, H.S., Fortin, S.M., Gianessi, C.A., Gilbert, J.R., Grill, H.J., 2011. Hippocampal leptin signaling reduces food intake and modulates food-related memory processing. Neuropsychopharmacology 36, 1859–1870.
Kanoski, S.E., Zhang, Y., Zheng, W., Davidson, T.L., 2010. The effects of a high-energy diet on hippocampal function and blood-brain barrier integrity in the rat. Journal of Alzheimer's Disease 21, 207–219.
Karatsoreos, I.N., Bhagat, S., Bloss, E.B., Morrison, J.H., McEwen, B.S., 2011. Disruption of circadian clocks has ramifications for metabolism, brain, and behavior. Proceedings of the National Academy of Sciences 108, 1657–1662.
Kivipelto, M., Ngandu, T.L.F., et al., 2005. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Archives of Neurology 62, 1556–1560.
Knoops, A.J., Gerritsen, L., van der Graaf, Y., Mali, W.P., Geerlings, M.I., 2012. Loss of entorhinal cortex and hippocampal volumes compared to whole brain volume in normal aging: the SMART-Medea study. Psychiatry Research 203, 31–37.
Knopman, D.S., 2008. Go to the head of the class to avoid vascular dementia and skip diabetes and obesity. Neurology 71, 1046–1047.
Korf, E.S., van Straaten, E.C., de Leeuw, F.E., van der Flier, W.M., Barkhof, F., Pantoni, L., Basile, A.M., Inzitari, D., Erkinjuntti, T., Wahlund, L.O., Rostrup, E., Schmidt, R., Fazekas, F., Scheltens, P., 2007. Diabetes mellitus, hypertension and medial temporal lobe atrophy: the LADIS study. Diabetic Medicine 24, 166–171.
Laitinen, M.H., Ngandu, T., Rovio, S., Helkala, E.L., Uusitalo, U., Viitanen, M., Nissinen, A., Tuomilehto, J., Soininen, H., Kivipelto, M., 2006. Fat intake at midlife and risk of dementia and Alzheimer's disease: a population-based study. Dementia and Geriatric Cognitive Disorders 22, 99–107.
Lee, C.C., Kuo, Y.M., Huang, C.C., Hsu, K.S., 2009. Insulin rescues amyloid beta-induced impairment of hippocampal long-term potentiation. Neurobiology of Aging 30, 377–387.
Lee, D., Thaler, J.P., Berkseth, K.E., Melhorn, S.J., Schwartz, M.W., Schur, E.A., 2013a. Longer T2 relaxation time is a marker of hypothalamic gliosis in mice with diet-induced obesity. American Journal of Physiology. Endocrinology and Metabolism 304 (11), E1245–E1250.
Lee, J.H., Yoon, S., Renshaw, P.F., Kim, T.S., Jung, J.J., Choi, Y., Kim, B.N., Jacobson, A.M., Lyoo, I.K., 2013b. Morphometric changes in lateral ventricles of patients with recent-onset type 2 diabetes mellitus. PLoS ONE 8, e60515.
Lee, Y.-H., Tharp, W.G., Maple, R.L., Nair, S., Permana, P.A., Pratley, R.E., 2008. Amyloid precursor protein expression is upregulated in adipocytes in obesity. Obesity 16, 1493–1500.
Lee, Y.S., Li, P., Huh, J.Y., Hwang, I.J., Lu, M., Kim, J.I., Ham, M., Talukdar, S., Chen, A., Lu, W.J., Bandyopadhyay, G.K., Schwendener, R., Olefsky, J., Kim, J.B., 2011. Inflammation is necessary for long-term but not short-term high-fat diet-induced insulin resistance. Diabetes 60, 2474–2483.
Li, J., Tang, Y., Cai, D., 2012. IKKbeta/NF-kappaB disrupts adult hypothalamic neural stem cells to mediate a neurodegenerative mechanism of dietary obesity and pre-diabetes. Nature Cell Biology 14 (10), 999–1012.
Li, Y., Perry, T., Kindy, M.S., Harvey, B.K., Tweedie, D., Holloway, H.W., Powers, K., Shen, H., Egan, J.M., Sambamurti, K., Brossi, A., Lahiri, D.K., Mattson, M.P., Hoffer, B.J., Wang, Y., Greig, N.H., 2009. GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. Proceedings of the National Academy of Sciences of the United States of America 106, 1285–1290.
Liao, G.-Y., An, J.J., Gharami, K., Waterhouse, E.G., Vanevski, F., Jones, K.R., Xu, B., 2012. Dendritically targeted Bdnf mRNA is essential for energy balance and response to leptin. Nature Medicine 18, 564–571.
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.
Mander, B.A., Rao, V., Lu, B., Saletin, J.M., Lindquist, J.R., Ancoli-Israel, S., Jagust, W., Walker, M.P., 2013. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. Nature Neuroscience 16, 357–364.
Martens, M.J., Born, J.M., Lemmens, S.G., Karhunen, L., Heinecke, A., Goebel, R., Adam, T.C., Westerterp-Plantenga, M.S., 2013. Increased sensitivity to food cues in the fasted state and decreased inhibitory control in the satiated state in the overweight. American Journal of Clinical Nutrition 97, 471–479.
Masaki, T., Anan, F., Shimomura, T., Fujiki, M., Saikawa, T., Yoshimatsu, H., 2012. Association between hippocampal volume and serum adiponectin in patients with type 2 diabetes mellitus. Metabolism: Clinical and Experimental 61, 1197–1200.
McCaffery, J.M., Haley, A.P., Sweet, L.H., Phelan, S., Raynor, H.A., Del Parigi, A., Cohen, R., Wing, R.R., 2009. Differential functional magnetic resonance imaging response to food pictures in successful weight-loss maintainers relative to normal-weight and obese controls. American Journal of Clinical Nutrition 90, 928–934.
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 Molecular Genetics 22, 1050–1058.
Miesel, A., Muller, H., Thermann, M., Heidbreder, M., Dominiak, P., Raasch, W., 2010. Overfeeding-induced obesity in spontaneously hypertensive rats: an animal model of the human metabolic syndrome. Annals of Nutrition and Metabolism 56, 127–142.
Milanski, M., Arruda, A.P., Coope, A., Ignacio-Souza, L.M., Nunez, C.E., Roman, E.A., Romanatto, T., Pascoal, L.B., Caricilli, A.M., Torsoni, M.A., Prada, P.O., Saad, M.J., Velloso, L.A., 2012. Inhibition of hypothalamic inflammation reverses diet-induced insulin resistance in the liver. Diabetes 61, 1455–1462.
Moroz, N., Tong, M., Longato, L., Xu, H., de la Monte, S.M., 2008. Limited Alzheimer-type neurodegeneration in experimental obesity and type 2 diabetes mellitus. Journal of Alzheimers Disease 15, 29–44.
Musen, G., Jacobson, A.M., Bolo, N.R., Simonson, D.C., Shenton, M.E., McCartney, R.L., Flores, V.L., Hoogenboom, W.S., 2012. Resting-state brain functional connectivity is altered in type 2 diabetes. Diabetes 61, 2375–2379.
Naim, M., Brand, J.G., Kare, M.R., Carpenter, R.G., 1985. Energy intake, weight gain and fat deposition in rats fed flavored, nutritionally controlled diets in a multichoice ("cafeteria") design. Journal of Nutrition 115, 1447–1458.
Nakashima, Y., Yokokura, A., 2010. Consumption of a high-fat diet containing lard during the growth period in rats predisposes them to favorably respond to the diet in later life. Journal of Nutritional Science and Vitaminology 56, 380–386.
Nogueiras, R., Perez-Tilve, D., Veyrat-Durebex, C., Morgan, D.A., Varela, L., Haynes, W.G., Patterson, J.T., Disse, E., Pfluger, P.T., Lopez, M., Woods, S.C., DiMarchi, R., Dieguez, C., Rahmouni, K., Rohner-Jeanrenaud, F., Tschop, M.H., 2009. Direct control of peripheral lipid deposition by CNS GLP-1 receptor signaling is mediated by the sympathetic nervous system and blunted in diet-induced obesity. Journal of Neuroscience 29, 5916–5925.
Oben, J.A., Mouralidarane, A., Samuelsson, A.M., Matthews, P.J., Morgan, M.L., McKee, C., Soeda, J., Fernandez-Twinn, D.S., Martin-Gronert, M.S., Ozanne, S.E., Sigala, B., Novelli, M., Poston, L., Taylor, P.D., 2010. Maternal obesity during pregnancy and lactation programs the development of offspring non-alcoholic fatty liver disease in mice. Journal of Hepatology 52, 913–920.
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.
Park, H.R., Park, M., Choi, J., Park, K.Y., Chung, H.Y., Lee, J., 2010. A high-fat diet impairs neurogenesis: involvement of lipid peroxidation and brain-derived neurotrophic factor. Neuroscience Letters 482, 235–239.
Parnet, P., Kelley, K.W., Bluthe, R.M., Dantzer, R., 2002. Expression and regulation of interleukin-1 receptors in the brain. Role in cytokines-induced sickness behavior. Journal of Neuroimmunology 125, 5–14.
Parton, L.E., Ye, C.P., Coppari, R., Enriori, P.J., Choi, B., Zhang, C.Y., Xu, C., Vianna, C.R., Balthasar, N., Lee, C.E., Elmquist, J.K., Cowley, M.A., Lowell, B.B., 2007. Glucose sensing by POMC neurons regulates glucose homeostasis and is impaired in obesity. Nature 449, 228–232.
Patel, S.R., Zhu, X., Storfer-Isser, A., Mehra, R., Jenny, N.S., Tracy, R., Redline, S., 2009. Sleep duration and biomarkers of inflammation. Sleep 32, 200–204.
Pauli-Pott, U., Albayrak, Ö., Hebebrand, J., Pott, W., 2010. Association between inhibitory control capacity and body weight in overweight and obese children and adolescents: dependence on age and inhibitory control component. Child Neuropsychology 16, 592–603.
Paz-Filho, G.J., Babikian, T., Asarnow, R., Delibasi, T., Esposito, K., Erol, H.K., Wong, M.L., Licinio, J., 2008. Leptin replacement improves cognitive development. PLoS ONE 3, e3098.
Pepping, J.K., Freeman, L.R., Gupta, S., Keller, J.N., Bruce-Keller, A.J., 2013. NOX2 deficiency attenuates markers of adiposopathy and brain injury induced by high-fat diet. American Journal of Physiology. Endocrinology and Metabolism 304, E392–E404.
Pistell, P.J., Morrison, C.D., Gupta, S., Knight, A.G., Keller, J.N., Ingram, D.K., Bruce-Keller, A.J., 2010. Cognitive impairment following high fat diet consumption is associated with brain inflammation. Journal of Neuroimmunology 219, 25–32.
Profenno, L.A., Faraone, S.V., 2008. Diabetes and overweight associate with non-APOE4 genotype in an Alzheimer's disease population. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 147B, 822–829.
Profenno, L.A., Porsteinsson, A.P., Faraone, S.V., 2010. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. Biological Psychiatry 67, 505–512.
Puig, K.L., Floden, A.M., Adhikari, R., Golovko, M.Y., Combs, C.K., 2012. Amyloid precursor protein and proinflammatory changes are regulated in brain and adipose tissue in a murine model of high fat diet-induced obesity. PLoS ONE 7, e30378.
Purkayastha, S., Zhang, G., Cai, D., 2011. Uncoupling the mechanisms of obesity and hypertension by targeting hypothalamic IKK-[beta] and NF-[kappa]B. Nature Medicine 17, 883–887.

Qiu, G., Wan, R., Hu, J., Mattson, M.P., Spangler, E., Liu, S., Yau, S.Y., Lee, T.M., Gleichmann, M., Ingram, D.K., So, K.F., Zou, S., 2011. Adiponectin protects rat hippocampal neurons against excitotoxicity. Age (Dordrecht, Netherlands) 33, 155–165.

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 Mapping 31, 353–364.

Raji, C.A., Lopez, O.L., Kuller, L.H., Carmichael, O.T., Becker, J.T., 2009. Age, Alzheimer disease, and brain structure. Neurology 73, 1899–1905.

Raz, N., Rodrigue, K.M., Acker, J.D., 2003. Hypertension and the brain: vulnerability of the prefrontal regions and executive functions. Behavioral Neuroscience 117, 1169–1180.

Reijmer, Y.D., van den Berg, E., de Bresser, J., Kessels, R.P., Kappelle, L.J., Algra, A., Biessels, G.J., 2011. Accelerated cognitive decline in patients with type 2 diabetes: MRI correlates and risk factors. Diabetes/Metabolism Research and Reviews 27, 195–202.

Rivera, P., Perez-Martin, M., Pavon, F.J., Serrano, A., Crespillo, A., Cifuentes, M., Lopez-Avalos, M.D., Grondona, J.M., Vida, M., Fernandez-Llebrez, P., de Fonseca, F.R., Suarez, J., 2013. Pharmacological administration of the isoflavone daidzein enhances cell proliferation and reduces high fat diet-induced apoptosis and gliosis in the rat hippocampus. PLoS ONE 8, e64750.

Roberts, R.O., Geda, Y.E., Knopman, D.S., Cha, R.H., Boeve, B.F., Ivnik, R.J., Pankratz, V.S., Tangalos, E.G., Petersen, R.C., 2010. Metabolic syndrome, inflammation, and nonamnestic mild cognitive impairment in older persons: a population-based study. Alzheimer Disease and Associated Disorders 24, 11–18.

Ryan, C.M., Freed, M.I., Rood, J.A., Cobitz, A.R., Waterhouse, B.R., Strachan, M.W., 2006. Improving metabolic control leads to better working memory in adults with type 2 diabetes. Diabetes Care 29, 345–351.

Salgado-Delgado, R., Angeles-Castellanos, M., Saderi, N., Buijs, R.M., Escobar, C., 2010. Food intake during the normal activity phase prevents obesity and circadian desynchrony in a rat model of night work. Endocrinology 151, 1019–1029.

Sartorius, T., Ketterer, C., Kullmann, S., Balzer, M., Rotermund, C., Binder, S., Hallschmid, M., Machann, J., Schick, F., Somoza, V., Preissl, H., Fritsche, A., Haring, H.U., Hennige, A.M., 2012. Monounsaturated fatty acids prevent the aversive effects of obesity on locomotion, brain activity, and sleep behavior. Diabetes 61, 1669–1679.

Scherer, T., Lindtner, C., Zielinski, E., O'Hare, J., Filatova, N., Buettner, C., 2012. Short-term voluntary overfeeding disrupts brain insulin control of adipose tissue lipolysis. Journal of Biological Chemistry 287 (39), 33061–33069.

Shapiro, A., Mu, W., Roncal, C., Cheng, K.Y., Johnson, R.J., Scarpace, P.J., 2008. Fructose-induced leptin resistance exacerbates weight gain in response to subsequent high-fat feeding. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology 295, R1370–R1375.

Sherman, H., Genzer, Y., Cohen, R., Chapnik, N., Madar, Z., Froy, O., 2012. Timed high-fat diet resets circadian metabolism and prevents obesity. FASEB Journal 26, 3493–3502.

Siervo, M., Arnold, R., Wells, J.C., Tagliabue, A., Colantuoni, A., Albanese, E., Brayne, C., Stephan, B.C., 2011. Intentional weight loss in overweight and obese individuals and cognitive function: a systematic review and meta-analysis. Obesity Reviews 12, 968–983.

Smith, E., Hay, P., Campbell, L., Trollor, J.N., 2011. A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. Obesity Reviews 12, 740–755.

So, P.W., Yu, W.S., Kuo, Y.T., Wasserfall, C., Goldstone, A.P., Bell, J.D., Frost, G., 2007. Impact of resistant starch on body fat patterning and central appetite regulation. PLoS ONE 2, e1309.

Soczynska, J., Kennedy, S., Woldeyohannes, H., Liauw, S., Alsuwaidan, M., Yim, C., McIntyre, R., 2011. Mood disorders and obesity: understanding inflammation as a pathophysiological nexus. Neuromolecular Medicine 13, 93–116.

Sparkman, N.L., Buchanan, J.B., Heyen, J.R., Chen, J., Beverly, J.L., Johnson, R.W., 2006. Interleukin-6 facilitates lipopolysaccharide-induced disruption in working memory and expression of other proinflammatory cytokines in hippocampal neuronal cell layers. Journal of Neuroscience 26, 10709–10716.

Srinivasan, M., Mahmood, S., Patel, M.S., 2013. Metabolic programming effects initiated in the suckling period predisposing for adult-onset obesity cannot be reversed by calorie restriction. American Journal of Physiology. Endocrinology and Metabolism 304, E486–E494.

Srinivasan, M., Mitrani, P., Sadhanandan, G., Dodds, C., Shbeir-ElDika, S., Thamotharan, S., Ghanim, H., Dandona, P., Devaskar, S.U., Patel, M.S., 2008. A high-carbohydrate diet in the immediate postnatal life of rats induces adaptations predisposing to adult-onset obesity. Journal of Endocrinology 197, 565–574.

St-Onge, M.P., McReynolds, A., Trivedi, Z.B., Roberts, A.L., Sy, M., Hirsch, J., 2012. Sleep restriction leads to increased activation of brain regions sensitive to food stimuli. American Journal of Clinical Nutrition 95, 818–824.

Stice, E., Yokum, S., Blum, K., Bohon, C., 2010. Weight gain is associated with reduced striatal response to palatable food. Journal of Neuroscience 30, 13105–13109.

Taha, A.Y., Gao, F., Ramadan, E., Cheon, Y., Rapoport, S.I., Kim, H.W., 2012. Upregulated expression of brain enzymatic markers of arachidonic and docosahexaenoic acid metabolism in a rat model of the metabolic syndrome. BMC Neuroscience 13, 131.

Taki, Y., Kinomura, S., Sato, K., Inoue, K., Goto, R., Okada, K., Uchida, S., Kawashima, R., Fukuda, H., 2007. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. Obesity 16, 119–124.

Telakivi, T., Kajaste, S., Partinen, M., Koskenvuo, M., Salmi, T., Kaprio, J., 1988. Cognitive function in middle-aged snorers and controls: role of excessive daytime somnolence and sleep-related hypoxic events. Sleep 11, 454–462.

Thaler, J.P., Yi, C.-X., Schur, E.A., Guyenet, S.J., Hwang, B.H., Dietrich, M.O., Zhao, X., Sarruf, D.A., Izgur, V., Maravilla, K.R., Nguyen, H.T., Fischer, J.D., Matsen, M.E., Wisse, B.E., Morton, G.J., Horvath, T.L., Baskin, D.G., Tschöp, M.H., Schwartz, M.W., 2012. Obesity is associated with hypothalamic injury in rodents and humans. Journal of Clinical Investigation 122, 153–162.

Thirumangalakudi, L., Prakasam, A., Zhang, R., Bimonte-Nelson, H., Sambamurti, K., Kindy, M.S., Bhat, N.R., 2008. High cholesterol-induced neuroinflammation and amyloid precursor protein processing correlate with loss of working memory in mice. Journal of Neurochemistry 106, 475–485.

Tozuka, Y., Kumon, M., Wada, E., Onodera, M., Mochizuki, H., Wada, K., 2010. Maternal obesity impairs hippocampal BDNF production and spatial learning performance in young mouse offspring. Neurochemistry International 57, 235–247.

Tozuka, Y., Wada, E., Wada, K., 2009. Diet-induced obesity in female mice leads to peroxidized lipid accumulations and impairment of hippocampal neurogenesis during the early life of their offspring. FASEB Journal 23, 1920–1934.

Tschritter, O., Preissl, H., Hennige, A.M., Sartorius, T., Grichisch, Y., Stefan, N., Guthoff, M., Dusing, S., Machann, J., Schleicher, E., Cegan, A., Birbaumer, N., Fritsche, A., Haring, H.U., 2009. The insulin effect on cerebrocortical theta activity is associated with serum concentrations of saturated nonesterified fatty acids. Journal of Clinical Endocrinology and Metabolism 94, 4600–4607.

Valdes Hernandez, M.D., Booth, T., Murray, C., Gow, A.J., Penke, L., Morris, Z., Maniega, S.M., Royle, N.A., Aribisala, B.S., Bastin, M.E., Starr, J.M., Deary, I.J., Wardlaw, J.M., 2013. Brain white matter damage in aging and cognitive ability in youth and older age. Neurobiology of Aging, pii:S0197-4580(13)00245-5.

Vallerand, A.L., Lupien, J., Bukowiecki, L.J., 1986. Cold exposure reverses the diabetogenic effects of high-fat feeding. Diabetes 35, 329–334.

van Harten, B., Oosterman, J.M., Potter van Loon, B.J., Scheltens, P., Weinstein, H.C., 2007. Brain lesions on MRI in elderly patients with type 2 diabetes mellitus. European Neurology 57, 70–74.

Verstynen, T.D., Weinstein, A.M., Schneider, W.W., Jakicic, J.M., Rofey, D.L., Erickson, K.I., 2012. Increased body mass index is associated with a global and distributed decrease in white matter microstructural integrity. Psychosomatic Medicine 74, 682–690.

Waldstein, S.R., Katzel, L.I., 2006. Interactive relations of central versus total obesity and blood pressure to cognitive function. International Journal of Obesity 30, 201–207.

Ward, M.A., Carlsson, C.M., Trivedi, M.A., Sager, M.A., Johnson, S.C., 2005. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. BMC Neurology 5, 23.

Weng, S.F., Redsell, S.A., Nathan, D., Swift, J.A., Yang, M., Glazebrook, C., 2013. Estimating overweight risk in childhood from predictors during infancy. Pediatrics 132 (2), e414–e421.

Whitmer, R.A., Gunderson, E.P., Quesenberry Jr., C.P., Zhou, J., Yaffe, K., 2007. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Current Alzheimer Research 4, 103–109.

Whitmer, R.A., Gustafson, D.R., Barrett-Connor, E., Haan, M.N., Gunderson, E.P., Yaffe, K., 2008. Central obesity and increased risk of dementia more than three decades later. Neurology 71, 1057–1064.

Willeumier, K.C., Taylor, D.V., Amen, D.G., 2011. Elevated BMI is associated with decreased blood flow in the prefrontal cortex using SPECT imaging in healthy adults. Obesity 19, 1095–1097.

Witte, A.V., Fobker, M., Gellner, R., Knecht, S., Floel, A., 2009. Caloric restriction improves memory in elderly humans. Proceedings of the National Academy of Sciences of the United States of America 106, 1255–1260.

Xu, B., Goulding, E.H., Zang, K., Cepoi, D., Cone, R.D., Jones, K.R., Tecott, L.H., Reichardt, L.F., 2003. Brain-derived neurotrophic factor regulates energy balance downstream of melanocortin-4 receptor. Nature Neuroscience 6, 736–742.

Yaffe, K., Kanaya, A., Lindquist, K., Simonsick, E.M., Harris, T., Shorr, R.I., Tylavsky, F.A., Newman, A.B., 2004. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 292, 2237–2242.

Yao, Z.J., Hu, B., Liang, C.J., Zhao, L.N., Jackson, M., 2012. Alzheimer's disease neuroimaging initiative a longitudinal study of atrophy in amnestic mild cognitive impairment and normal aging revealed by cortical thickness. PLoS One 7 (11), e48973.

Yates, K.F., Sweat, V., Yau, P.L., Turchiano, M.M., Convit, A., 2012. Impact of metabolic syndrome on cognition and brain: a selected review of the literature. Arteriosclerosis, Thrombosis, and Vascular Biology 32, 2060–2067.

Zhang, X., Dong, F., Ren, J., Driscoll, M.J., Culver, B., 2005. High dietary fat induces NADPH oxidase-associated oxidative stress and inflammation in rat cerebral cortex. Experimental Neurology 191, 318–325.

Zhang, X., Zhang, G., Zhang, H., Karin, M., Bai, H., Cai, D., 2008. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 135, 61–73.