REVIEW

Imaging of brain glucose uptake by PET in obesity and cognitive dysfunction: life-course perspective

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Abstract

The prevalence of obesity has reached epidemic proportions and keeps growing. Obesity seems implicated in the pathogenesis of cognitive dysfunction, Alzheimer's disease and dementia, and vice versa. Growing scientific efforts are being devoted to the identification of central mechanisms underlying the frequent association between obesity and cognitive dysfunction. Glucose brain handling undergoes dynamic changes during the life-course, suggesting that its alterations might precede and contribute to degenerative changes or signaling abnormalities. Imaging of the glucose analog ^{18}F-labeled fluorodeoxyglucose (^{18}FDG) by positron emission tomography (PET) is the gold-standard for the assessment of cerebral glucose metabolism *in vivo*. This review summarizes the current literature addressing brain glucose uptake measured by PET imaging, and the effect of insulin on brain metabolism, trying to embrace a life-course vision in the identification of patterns that may explain (and contribute to) the frequent association between obesity and cognitive dysfunction. The current evidence supports that brain hypermetabolism and brain insulin resistance occur in selected high-risk conditions as a transient phenomenon, eventually evolving toward normal or low values during life or disease progression. Associative studies suggest that brain hypermetabolism predicts low BDNF levels, hepatic and whole body insulin resistance, food desire and an unfavorable balance between anticipated reward from food and cognitive inhibitory control. Emerging mechanistic links involve the microbiota and the metabolome, which correlate with brain metabolism and cognition, deserving attention as potential future prevention targets.

Key Words
▶ obesity
▶ metabolism
▶ development/fetal nutrition
▶ cognitive dysfunction
▶ brain PET imaging

Introduction

The prevalence of obesity has reached epidemic proportions and is growing in most world regions. Obesity is a risk factor for a series of chronic morbidities, the most frequent being type 2 diabetes. According to the World Health Organization (WHO), overweight and obesity have been estimated to account for about 65–80% of new cases of type 2 diabetes (http://www.euro.who .int/en/health-topics/noncommunicable-diseases/dia betes/data-and-statistics). Obesity and type 2 diabetes have been implicated in the pathogenesis of cognitive dysfunction (1). A number of studies have documented that people with obesity (especially in middle-age) and/or type 2 diabetes have a greater risk to develop dementia and Alzheimer's disease (2, 3, 4, 5). Clustering of these morbidities is fostered by population aging, whose rate of progression seems especially marked in Europe, North America and China, with 30% or more people reaching ≥60 years of age in 2050 (https://www.who.int /ageing/events/world-report-2015-launch/en/). Notably, the prevalence of overweight and obesity is enriched in

these same countries. Nearly 60% of Europeans and North Americans are affected, and China hosts 20% of the world overweight population (http://www.euro.who.int/en/health-topics/noncommunicable-diseases/obesity/data-and-statistics). These concepts are summarized in Fig. 1.

The risk of obesity is settled, at least in part, during the earliest phases of life, as the brain undergoes its major development, involving a five-fold volumetric spurt in the first 5 years of life (6). Several early-life factors may affect the propensity of infants to become obese children, adolescents, and adults. These include maternal exposures (obesity, diabetes, stress) (7, 8, 9), mode of delivery (e.g. C-section) (10), early nutrition (11, 12, 13, 14, 15). Interestingly, these early risk factors have been also associated with a greater risk of premature cognitive decline, from early life to elderly age (16, 17, 18, 19, 20).

Growing scientific efforts are being devoted to the identification of central mechanisms underlying the mutual reinforcement exerted by obesity on cognitive dysfunction and vice versa. Both have been associated with morphological reductions in brain volume, relating to systemic dysmetabolism and insulin resistance and/or to the degree of cognitive impairment (21, 22, 23). Glucose is the most important brain fuel and central

signaling factor. Glucose brain handling undergoes dynamic changes during the life-course, suggesting that its alterations might precede and contribute to degenerative changes or signaling abnormalities (24, 25). Imaging of the glucose analog ^{18}F-labeled fluorodeoxyglucose (^{18}FDG) by positron emission tomography (PET) is the gold standard for the assessment of cerebral glucose metabolism *in vivo*. In this manuscript, we review evidence on brain glucose uptake measured by PET imaging, trying to embrace a life-course vision in the identification of patterns that may explain (and contribute to) the frequent association between obesity and cognitive dysfunction.

Brain glucose metabolism and PET imaging

The brain relies primarily on glucose as its main energy source. Given its elevated utilization of circulating glucose, the brain may contribute to regulate peripheral glucose levels in a direct manner, by subtracting glucose from blood. Beyond nourishing the tissue, glucose is a signaling factor, informing central regulatory circuits on the metabolic and feeding conditions of the body (26, 27). In the brain, glucose stimulates the production of
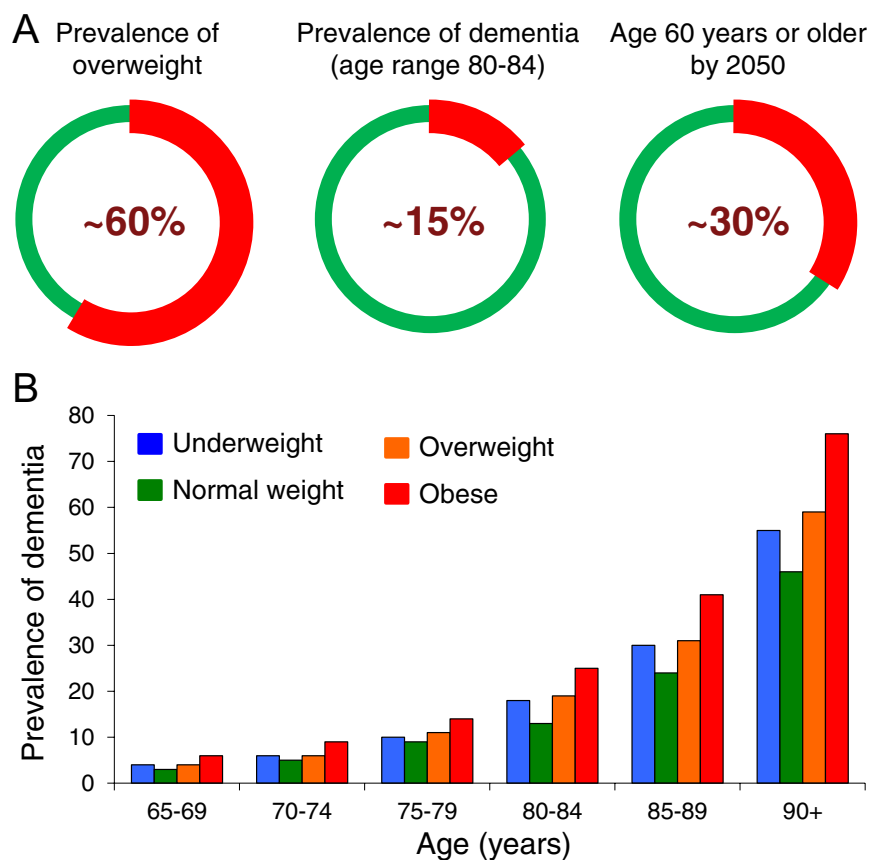

A Prevalence of overweight — **~60%**

Prevalence of dementia (age range 80-84) — **~15%**

Age 60 years or older by 2050 — **~30%**

B

Figure 1
The three circles in panel A show the current prevalence of overweight (left) or dementia (middle) in Europe, and (on the right) the estimated aging of the European population in 2050, further promoting these conditions. Panel B (from data presented by Laurie Brown at the National Dementia Congress, Melbourne 2014 and (115)) depicts the prevalence of dementia by BMI status, across age categories.

rewarding neurotransmitters (28, 29, 30, 31), thereby contributing to appetite control and more in general to mental well-being. Brain sensing translates in the regulation of metabolically relevant organs and processes, including insulin secretion by pancreatic beta-cells (32, 33, 34, 35), hepatic glucose production (36, 37, 38, 39) and fatty acid release by adipose tissue lipolysis (40, 41). This partly occurs via afferent and efferent nerves. In turn, insulin can cross the blood–brain barrier to tune central control (42), and fatty acids can reach the brain (43), representing its main structural constituent (44). The characterization of brain glucose uptake in groups of individuals of progressive ages has shown important changes occurring throughout the lifespan. Supporting the five-fold expansion in gray matter observed in the first 5 years of life (6), brain glucose uptake undergoes a >four-fold increase from birth to pre-scholar and early-scholar periods (24). This is followed by a relatively rapid decline, already from the age of 7–8 years and throughout the teenage period, reducing brain glucose uptake by 20–30% of its maximum, as opposed to only 10% gray matter losses. A brain volume reduction of 30% is achieved in late adulthood, a time in which glucose uptake has fallen by 60% from its maximum (24, 25). These time trends suggest that functional, namely metabolic changes are larger and detectable in advance of their morphological counterpart. It is therefore not surprising that FDG-PET imaging provides the earliest biomarker predicting neurodegenerative disease, as compared to other imaging (amyloid PET, magnetic resonance) or clinical modalities (signs and symptoms, cerebrospinal fluid markers) (45).

Compared to alternative methods to assess brain glucose metabolism *in vivo*, including arterial-venous catheterization or micro-dialysis, PET imaging is minimally invasive, and provides regional information, best reflecting the functional diversification between highly specialized brain areas. Once injected in a study subject, ^{18}FDG undergoes extraction by the brain and body tissues in proportion to their requirements. Graphical (46) and compartmental models (47) have been widely used to translate tissue and blood concentrations into biologically meaningful rate constant values, describing the transfer of ^{18}FDG from blood to brain cells and its subsequent phosphorylation. The fractional tissue extraction rate constant describes the relative amount (or percentage) of ^{18}FDG that is extracted from the circulation in a unit of time and tissue volume (or mass). In order to convert this factor into an absolute rate of glucose uptake, one has to account for the organ-specific lumped constant and

the level of circulating glucose (48). The former corrects for different affinities of transporters and enzymes (hexokinases) for glucose compared to ^{18}FDG, whereas the latter translates fractional (%) into absolute rates of glucose influx into the target tissue (e.g. μmol/min/g). Hence, the actual amount of glucose entering the tissue is given by the product of fractional extraction rate constant of ^{18}FDG and plasma glucose level, divided by the lumped constant term. Though the term glucose uptake may have been used interchangeably in the literature to define either absolute (glucose) or relative (^{18}FDG) tissue influxes, there is an important conceptual and numerical difference between these two processes. In neurodegenerative diseases, the extraction is frequently reported, with fewer studies quantifying absolute brain glucose uptake rates. The opposite is true in obesity studies. In this review, we primarily refer to the absolute value.

Homeostatic regulation of brain glucose metabolism in obesity

In humans, brain glucose metabolism has been studied in the fasting state or during euglycemic insulin stimulation. In adults, data from PET imaging studies indicate that the brain accounts for at least 50% of whole-body glucose disposal during the fasting state and 10–20% during euglycemic insulin stimulation, supporting an important direct role of this organ in affecting glycemia (42, 49, 50, 51, 52). Studies have compared obese and lean individuals, as well as patients with glucose intolerance and normo-tolerant BMI-matched controls (42, 52). The evidence from these studies indicates that fasting insulin levels may serve to maintain a physiological tone of brain glucose uptake, since the inhibition of insulin secretion suppresses glucose uptake values in healthy individuals (49), whereas the elevation of insulinemia toward post-prandial levels does not further affect cerebral glucose uptake compared to fasting values in non-obese healthy subjects (50, 51, 52).

Compared to lean, obese subjects showed higher fasting metabolism in the parietal somatosensory cortex regions where sensation of the mouth, lips and tongue are located (53), and in regions regulating executive function (54). Other studies could not find differences between fasted lean and obese individuals, but observed elevated uptake of glucose in most brain regions during insulin stimulation in glucose-intolerant or morbidly obese patients (42, 52). In the latter, the elevation in brain glucose uptake was associated with greater endogenous

glucose release (indicative of hepatic insulin resistance), and lower peripheral glucose consumption (primarily reflecting skeletal muscle insulin resistance), suggesting that brain hypermetabolism is the expression of central insulin resistance (55). In the same study, high brain glucose uptake was also shown to negatively predict the improvement in glucose levels occurring after weight loss in morbidly obese patients, thus contrasting one of the most relevant clinical benefits of bariatric surgery, that is, the recovery from type 2 diabetes. Consistent with the above evidence, the injection of glucose in cerebral ventricles caused a suppression of hepatic glucose production in healthy mice (38), but a 4-week infusion failed to provoke any effect in type 2 diabetic rats (56). Controlled studies in pigs replicate the human findings, by showing no brain glucometabolic response to euglycemic hyperinsulinemia (compared to fasting state) in control pigs, as opposed to an elevated response in pigs fed a high-fat diet (57). Studies in Zucker fatty or diabetic rats have shown that their brain glucose uptake is chronically elevated under fasting and glucose loading conditions, lacking the excursion that normally signals the transition from a fasted to fed state (58). We also reported that young pre-obese Zucker fatty rats, showing normal body weight but impaired glucose tolerance, already manifest brain hypermetabolism

during a glucose tolerance test (59). Overall, the available evidence in human and animal studies, as exemplified in Fig. 2, suggests that a chronic overexposure of the brain to glucose may interrupt relevant feedback loops.

Hedonic regulation of brain glucose metabolism in obesity

Glucose can stimulate the production of reward-promoting neurotransmitters in the brain (29, 30, 31, 60, 61). Few studies have used FDG PET imaging to address the involvement of brain glucose uptake in the hedonic regulation of appetite and body weight, which is an important underlying element in the pathogenesis of obesity. One early study suggested that an enhanced metabolic activity in regions involved with sensory processing of food in obese subjects could make them more sensitive to the rewarding properties of preferred foods, contributing to excessive food consumption (53). Upon sensory (visual, taste, olfactory) stimulation with palatable food, all brain regions experience a rise in glucose uptake, compared to neutral sensing (62). Gender differences were noted in this response, since women showed greater metabolic activation than men
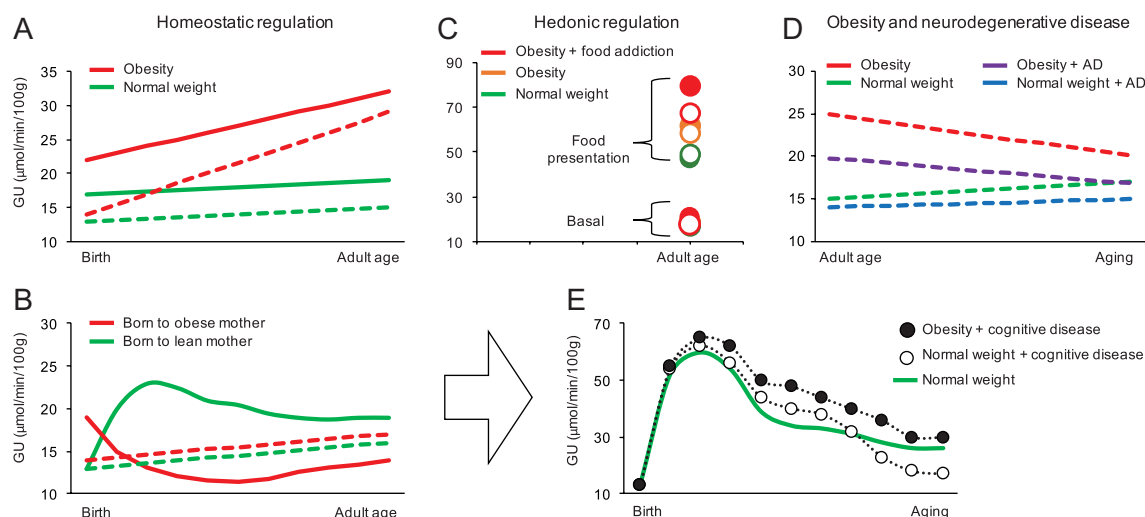

Figure 2

The figure summarizes the patterns of brain glucose metabolism described in this review. Panel A shows that the development of obesity in a genetic rodent model (Zucker rat) is characterized by brain hypermetabolism both in fasting condition (dashed lines) and during oral glucose tolerance test (solid line) (59). Panel B illustrates the effect of exposure to maternal obesity, resulting in a hypermetabolic brain response to isoglycemic insulin stimulation (solid line) in very early life (70), and mild brain hypermetabolism in fasting conditions (dashed lines) (92). Panel C shows the progressive increase of brain glucose uptake in response to food presentation in inhibitory control regions (open circles) and in reward related regions (closed circles) from normal weight women to women with obesity without and with food addiction (62, 64) in adult age. In panel D, a progressive increment in fasting brain glucose uptake from normal weight mice with Alzheimer's disease (AD, blue line), to normal weight mice without AD (green line), obese mice with AD (purple line) and obese mice without AD (red line) is shown (69). Based on the above observations, panel E provides a simulation of how cognitive disease, with or without obesity, may modify (black lines) the physiological time-course (green line, (24) of brain metabolism over life.

in several brain regions, and minimal response to an inhibitory control cognitive task against their preferred food stimulation, as opposed to men in whom the cognitive task diffusely suppressed brain metabolism (right insula, right striatum, amygdala, hypothalamus, anterior cingulate, hippocampus, parahippocampal gyrus, orbitofrontal cortex, cerebellum) and hunger ratings (63). Unfortunately, the study did not involve obese patients. We have recently hypothesized that the magnitude and regional distribution of hedonic food responses might differ between similarly obese individuals, opening the opportunity for mechanistic based stratification, and personalized management of obese patients. In order to prove this concept, we studied two groups of obese women, who had similar metabolic profile and BMI, but different severity of food addiction symptoms, as based on the DMS Yale Food Addiction Scale (64). Compared to women with few symptoms, the more severely affected group showed greater brain metabolic activation in response to palatable versus neutral food cues, especially in reward-related regions, and less in inhibitory control regions (64). A lower response in inhibitory regions was predictive of a greater number of symptoms and hunger, which recalls the negative association described by others between BMI and prefrontal metabolism (65). Brain glucose responses and hunger ratings were reduced after modest diet-induced weight loss in the group with a food addicted profile, whereas no change was observed in control women (64). These proof-of-principle results strengthen the evidence of different obesity types, showing distinct metabolic brain reactions to food cues and to inhibitory control. Notably, the observation that the normalization of brain (hyper)metabolism during food sensing occurred together with a decreased perception of hunger was common to the acute cognitive inhibitory task in men (63) or the more prolonged diet-control effort in women (64). Animal studies exploring brain glucose uptake during hedonic (olfactory) stimulation with palatable food (bacon) show that caloric restriction, food desire and (Zucker) genotype influence central glucose metabolic responses via a complex interplay, especially in the hippocampus (a brain region that is increasingly involved in food behaviors) and superior colliculus (a brain region that modulates the saliency value of food reinforcers) (66). Figure 2 exemplifies the above observations, collectively suggesting that (a) brain metabolism relates to perceived hunger but does not respond similarly to palatable foods and food restriction in all individuals; (b) gender, obesity, ability to cognitively control, food addiction symptoms (shown in humans), and obesity-prone genotype versus food accessibility (reported in rodents) contribute to differentiate brain glucose responses; (c) more studies are definitely needed to understand to what extent the amount of glucose entering brain regions involved in homeostatic, hedonic, and cognitive control can modulate feeding behavior; (d) better understanding and account of the above interactions is likely to lead to tailored weight control interventions.

Brain metabolism as common feature in obesity and neurodegenerative disease

In the context of obesity research, the literature summarized above indicates that high cerebral metabolic rates occur in obese and glucose-intolerant subjects during fasted or homeostatic stimuli (i.e. hyperinsulinemia during eu- or hyperglycemia). Brain glucose uptake is normally increased in response to hedonic stimuli in lean individuals, especially in regions related with food sensing and reward (62). This effect is particularly pronounced in obese food addicted women in the whole brain (63, 64), though more markedly in regions related with food sensing and reward, and in the hypothalamus. The current evidence also supports the concept that insufficient metabolic hyperactivation in orbitofrontal inhibitory regions may predict greater food dependency (64), possibly because the degree of hypermetabolism observed in sensing and reward-related regions is not sufficiently balanced by areas of executive function. The observation that an inhibitory cognitive task reduces brain glucose uptake in all regions, resulting in lower hunger ratings, further supports the existence of a metabolic network in which cognition prevails (metabolically) over anticipated reward. Interestingly, one study showing that BMI and cognition were inversely related (65) highlighted that low frontal glucose metabolism was associated with both BMI (negative) and cognitive function (positive), involving domains beyond inhibitory glucose metabolism, for example memory and recall, executive function, verbal and non-verbal intelligence quotients. So far, we are left with the dual hypothesis that obesity may independently affect frontal metabolism and cognition or that dysfunctional prefrontal metabolism due to for example cognitive disease may fail to inhibit overeating, contributing to obesity. Animal studies support both possibilities. On one side, lesions of the hippocampus lead to overeating (67, 68), and mouse models of Alzheimer's disease (AD) type pathology show overeating compared to controls (69). On the other hand, high-fat feeding

in these genetically predisposed animals accelerates neurodegeneration and cognitive decline. Metabolically, a high-fat diet elevated brain glucose uptake in middle-aged mice, but this elevation was blunted in the AD type model and followed by a remarkable metabolic and cognitive fall throughout aging (69). Exposure to a high-fat diet or maternal obesity during early life development predicts premature cognitive decline and obesity along the lifespan in humans (7, 8, 16, 17, 18, 20). In a minipig model, such exposure led to a marked elevation in brain glucose uptake in the initial post-natal period, due to hyperglycemia, followed by a rapid decline resulting in brain hypometabolism in later life stages (70). Accordingly, brain glycogen levels were depleted in adult offspring born to high-fat diet mothers.

The above studies suggest that, as we attempt to establish cerebral glucose metabolism as predictor or hallmark of disease, it is fundamental to consider that brain glucose uptake may vary depending on brain regions, disease type, staging, duration and severity. This is supported by for example mouse models of AD that are characterized by different temporal patterns of disease development, as brain metabolism was found to be deficient in animals showing advanced neurodegeneration and cognitive decline (71) already at 7 months of age, but not in 3xTg mice showing only mild signs of dysfunction and structural loss at 8 months of age (69). Along these spectra, brain hypermetabolism can appear as an early trait, occurring during early- or mid-life periods and vanishing along aging or advanced disease or after prolonged high-fat diet exposure. Reinforcing this conclusion, a study in patients with different degrees of cognitive impairment has shown that cerebral glucose metabolism was high in subjects with mild disease, and low in advanced disease compared to healthy controls (45). The authors speculate that brain hypermetabolism may serve as transient compensatory reaction to the initial neurodegenerative insult, but is progressively replaced by hypometabolism, as tissue loss becomes more severe in the chronic situation. The authors surmise that in spite of being compensatory, the initial glucose excess may overstimulate and exhaust neural networks, accelerating the degenerative process. The same compensatory theory was suggested to explain the preservation of cognitive function in a study in morbidly obese women, showing brain hypermetabolism (54). Again these authors refer to the initial phase of neurodegeneration, in which inhibitory synapses are first destroyed, and excitatory synapses prevail with increased local activity (72), which may justify brain hypermetabolism in obese patients.

Figure 2 illustrates the above concepts, providing a hypothetical time-course of brain glucose uptake along the progression of life, in relation to cognitive disease with and without obesity.

As potential mechanisms whereby an excessive uptake of glucose by the brain can result in a simultaneous dysregulation of appetite, systemic metabolism and cognitive function, brain-derived neurotrophic factor (BDNF) stems as a credible candidate. BDNF has been implicated in the pathogenesis of obesity, type 2 diabetes, and neurodegeneration (73, 74, 75). BDNF deficiency is a recognized correlate of memory impairment and has been described in patients with obesity and type 2 diabetes (76). The administration of BDNF in animal models was shown to improve the control of food intake and weight loss, peripheral glucose homeostasis, neuropreservation and cognition (77, 78, 79, 80, 81). Few studies have addressed the relationship linking BDNF production and brain glucose uptake. Elegant human experiments, using arterial-venous catheterization across the brain, have documented that BDNF release by the human brain is suppressed by brain glucose overexposure, that is, high blood glucose levels during a hyperglycemic clamp (73). In Zucker fatty rats, we have shown that brain glucose uptake, as measured by FDG PET imaging correlates inversely with circulating levels of BDNF (59). The relationship was stronger in young, pre-obese (but already glucose intolerant) animals, and we confirmed the dependency of BDNF on glucose levels already in human fetal cord plasma. Since the latter were in turn dependent on maternal glycemia at the time of delivery, we suggested that the establishment of optimal glycemic conditions at the time of birth might be a unique opportunity to protect cognitive and metabolic health.

Emerging mechanistic hypotheses leading to preventive perspectives

Animal studies have shown that some of the actions of glucose in the brain occur only in the presence of concurrent insulin delivery (82). Secreted insulin can reach the brain and its receptors are present in most brain regions, as reviewed by Blazquez *et al.* and Ghasemi *et al.* (83, 84). Insulin is a growth and metabolic regulator, whose cerebral actions have been implicated in the pathogenesis of obesity (suppression of appetite (85), regulation of adipose tissue lipolysis and lipogenesis (41, 86)), type 2 diabetes (modulation of endogenous glucose production and glucose levels (37, 38), and of pancreatic insulin

secretion (87, 88, 89)), and Alzheimer's disease (90). Most of these actions are lost in experimental models of obesity induced by high fat feeding (91). The role of insulin on brain glucose metabolism remains to be fully established. As detailed in the previous sections, compared to fasting, the induction of euglycemic hyperinsulinemia does not provoke any change in brain glucose uptake in healthy individuals, whereas it elicits a positive response in obese or glucose-intolerant patients. However, it is of note that the euglycemic–hyperinsulinemic clamp technique does not allow to dissect the direct role of insulin on the brain from the many peripheral actions occurring concomitantly. It is also important to recognize that insulin clamp studies prevent the reduction of glucose levels, which is the most important insulin effect in physiological conditions. Intranasal insulin injections have been recently used as a way to dissect central insulin roles, with translational perspectives in humans. Animal studies have shown that when insulin is delivered to the brain via the intranasal route, brain glucose uptake is reduced, mainly due to a centrally mediated hypoglycemic effect of the hormone (69). According to this, brain insulin resistance can be defined as failure of insulin to suppress brain glucose uptake, which is coherent with the finding of high glucose uptake under human euglycemic insulin clamp conditions. Comparing healthy lean mice of different ages, we observed that the central hypometabolic action of insulin was significant in adult and old mice, but was not present in early post-natal life (69, 92). It is plausible that brain glucose suppressing signals are not yet operative in the first period of life, to ensure sufficient energy provisions during this demanding phase of rapid brain growth. Interestingly, mice born to high fat fed dams showed brain hypersensitivity to insulin in this early period and brain insulin resistance during (mid-life) adulthood (92), and minipigs born to high fat fed sows showed greater brain-specific insulin receptor density few days post-natally, followed by deficiency in insulin receptors and insulin-dependent glucose transporters (GLUT4) in the cortex and hypothalamus (70). Also the combination of high fat dieting and AD type pathology in mice is characterized by an absent response of brain glucose metabolism to intranasal insulin. These mice showed similar brain hypermetabolism during fasting and during insulin stimulation. Again this trait was clearly detectable during mid-life, but not after aging. In these mice, the chronic administration of intranasal insulin, starting in early adulthood resulted in a normalized mid-life brain metabolism and insulin response, together with a full preservation of cognitive function and hippocampus size

throughout the lifespan (69). Insulin therapy also reduced food intake, body weight and peripheral glucose levels. Brain PET imaging studies with intranasal insulin in obese humans are lacking. In non-obese patients with clinically confirmed symptomatic cognitive disease, the chronic administration of intranasal insulin improved memory and slowed the decline in brain metabolism linked to tissue degeneration (93). Subsequent observations by the same authors indicate that the insulin formulation may importantly interfere with the outcome, as the effects of rapid insulin on cognition could be reproduced, whereas long-acting insulin was less effective and not consistent (93); unfortunately, PET imaging was not carried out in these comparative studies. In the field of obesity, acute intranasal insulin studies addressing functional responses by magnetic resonance imaging, systemic insulin sensitivity or hunger ratings (94, 95) support the suppressive effects of intranasal insulin on peripheral glucose levels, hypothalamic activity, and appetite control in humans. These metabolic effects await for chronic intervention trials to be tested for longer term efficacy and safety in obese patients.

Omics technologies represent another field of intensive investigation due to their potential to identify and/or confirm early biomarkers and mechanistic links related to obesity and neurodegenerative disease. Among them, the study of the microbiome emerges as a promising candidate for treatment, since pioneer trials with probiotics or fecal transplant have shown some benefit in dysmetabolic and Alzheimer's patients (96, 97), and probiotics have been safely administered to pregnant women or infants (98), opening an opportunity of primary prevention (99, 100). Many studies have shown differences in microbiota composition between lean and obese individuals (101, 102, 103). Seminal studies have produced first evidence in human Alzheimer's pathology (104, 105). In one animal study in which brain glucose metabolism was measured, we have shown that microbiota composition differs in mice fed a high fat diet and in mice with genetically determined AD type pathology in the early course of the disease, leading to additive effects when the two conditions are combined (106). We have also documented that fecal and serum metabolomes were different between groups and that numerous metabolites correlated with relative bacteria abundances. Some of these bacteria were associated with cognitive dysfunction and brain metabolism. Emerging bacteria patterns include depletion of Bifidobacterium, and overabundance *Turicibacteraceae*, *Christensenellaceae*, *Anaeroplasmataceae* and *Ruminococcaceae*. Emerging metabolites were amino

acids (leucine, isoleucine, glycine), ketone bodies, lactate, TMA-TMAO, and inflammatory indicators, all present in greater concentrations in diseased cases, together with a reduction in fatty acids. It is of translational interest that several of these metabolites were recently reported to be elevated in morbidly obese humans in association with an elevation in brain glucose metabolism (55).

Bariatric surgery represents a model of treatment in which all the elements above improve in combination (55, 107, 108). It can therefore substantiate their involvement, though it does not dissect and provide in itself a cause-effect demonstration for each factor. Interestingly, bariatric surgery leads to an amelioration in cognitive function, appetite regulation and weight loss. Brain glucose hypermetabolism and the related circulating metabolites are normalized after the intervention (52, 54). Transplantation of human microbiota following bariatric surgery into mice suggests that bacterial changes induced by the gastrointestinal operation are partly responsible for the effects of surgery on circulating metabolites (108). Though the gut–brain axis is focus of intensive investigation, and the microbiota can potentially influence brain development, structure and function by several mechanisms, a direct effect of bacteria or their metabolic products on brain glucose metabolism has not been yet clarified in the published literature.

Technical considerations

There are a number of technical differences between PET imaging studies, involving image acquisition and processing that might influence the interpretation of results in the reports quoted in this review; the available information is summarized in Table 1. First, dynamic scans allow to follow the progressive concentration of [18]FDG radioactivity in the brain over time (time-activity curve) starting from tracer injection, whereas static images provide a single-activity value, usually delayed from injection to avoid the initial blood flow-dependent phase, and primarily reflect the accumulation of [18]FDG that is induced by metabolic needs. Dynamic images allow sophisticated mathematical for example graphical and compartmental modeling (based on the changing levels of tissue to blood activities over time, to generate one or multiple rate constants) compared to simpler approaches and parameters that can be reliably obtained by static images (e.g. the ratio of tissue to injected dose per unit of body weight, or – if an input function is available – the

ratio of tissue to integrated blood activity). In these ways, dynamic and static scanning modes provide different but tightly correlated absolute values of brain glucose uptake and are both widely accepted and valid. However, when complex modeling (suited to dynamic imaging) is forcefully applied to a static image in the attempt to go beyond the simple parameters it can provide, several assumptions are required, including the use of a set of predefined and fixed rate constants, introducing some degree of arbitrariness in the results. Interestingly, this method led to low absolute frontal glucose uptake values in obese individuals (65), as opposed to either normal or tendentially elevated values in conservative approaches. Second, the input function (i.e. the tracer concentration that is available in blood for tissue extraction, as used in the above computations) should ideally be obtained by arterial blood sampling. To circumvent this invasive procedure, several groups have replaced arterial with arterialized (by heating pad or box) venous blood, which is accepted and common practice in metabolic (non-imaging) insulin clamp studies since their origin (109). In theory, oxygen saturation should be measured to confirm proper arterialization of venous blood; *de facto*, this measurement is rarely pursued. In few studies in Table 1, an image-derived input function (from cardiac cavities or carotid images) has been used, to avoid any frequent blood sampling, especially during the peak-phase after tracer injection, with few cross-check blood samples needed. In other few cases, normalization of regional to whole brain values was done in place of any mathematical modeling (66, 93) or in addition to the quantification of brain glucose uptake (63). Normalization requires caution as it can introduce a degree of cross-dependency and amplification of results. Third, different scanners and reconstruction methods are likely to lead to different absolute values. In recent years, iterative reconstruction methods (approximating the real image by an iterative process) have replaced the (raw data-driven) filtered-backprojection, leading to images that are of superior visual quality, but less consistently accurate. PET scanner and reconstruction affect image resolution, influencing the extent of partial volume/spill-over effects (contamination from surrounding tissue) in brain sub-regions whose size is close to or lower than the resolution. Though this error can be satisfactorily corrected in post-processing, such operation was not clearly reported in most Table 1 studies. Fourth, reconstructed images reflect radioactivity concentrations in kBq/cc, which can be converted into metabolic maps, by applying mathematical modeling to each image voxel

Table 1 Technical features in PET image acquisition, reconstruction and analysis methods.

Reference	PET acquisition	Scanner		Glucose uptake quantification		Normalization	
		Reconstruction		Input function		Analysis method	
		Resolution		Lumped constant (LC)		Statistical correction	
Hirvonen et al. ([42])	Dynamic	GE Advanced PET camera – Resolution of parametric image 12 mm FWHM		CMRglu by Gjedder-Patlak plot Arterial input function LC = 0.52		– SPM analysis + ROI-based analysis Significance voxel level uncorrected *P* < 0.05, cluster level corrected *P* < 0.05	
Bingham et al. ([49])	Dynamic 90-min	Siemens/CTI ECAT 951R tomograph FBP reconstruction Resolution 8.5 mm FWHM		CMRglu by Gjedder-Patlak plot Arterial input function LC = 0.52		Whole-brain uptake as confounding covariate SPM analysis + ROI-based analysis Significance at clusters level uncorrected *P* < 0.001	
Hasselbach et al. ([50])	Dynamic 45-min or 95-min	Therascan 3128 PET camera – Plane resolution 20 mm		CMRglu by 3K and 4K models Arterial input function LC experimentally determined		– ROI-based analysis –	
Cranston et al. ([51])	Dynamic 60-min	Siemens/CTI ECAT 951R tomograph – Resolution 8.5 mm		CMRglu by 4K model Arterial input function LC = 0.52		– ROI-based analysis –	
Tuulari et al. ([52])	Dynamic 40-min	GE Advanced PET camera Reconstruction using Hann filter with cut-off frequency of 0.5 and MRP method Resolution of parametric images 10 mm FWHM		CMRglu by Gjedder-Patlak plot Arterial input function LC = 0.80 or experimentally determined		– SPM analysis + ROI-based analysis Voxel level analysis FDR corrected, cluster level uncorrected	
Wang et al. ([53])	Static 20-min	CTI-931 tomograph (Computer Technologies) – Resolution 6.5 mm FWHM, final resolution of parametric image 16 mm FWHM		CMRglu computed using published k constants (4K) Arterial input function LC = 0.52		– SPM analysis Significance at voxel level uncorrected *P* < 0.003	
Marques et al. ([54])	Static 15-min	Siemens/CTI PET/CT Biograph 3D-OSEM reconstruction Final resolution 8 mm FWHM		Not calculated, only statistics reported		– SPM analysis Voxel level analysis with FWE correction	
Rebelos et al. ([55])	Dynamic 40-min	GE Advanced PET camera Reconstruction using Hann filter with cut-off frequency of 0.5 and MRP method Resolution of parametric images 10 mm FWHM		CMRglu by Gjedder-Patlak plot Arterial input function LC = 0.65		– SPM analysis + ROI-based analysis Cluster level analysis with FDR correction	
Bahri et al. ([57])	Dynamic 55-min	– FBP reconstruction Resolution 8.5 mm FWHM		CMRglu by 3K model, Patlak plot for calculation of parametric map, and spectral analysis Arterial input function LC = 0.45		– SPM analysis + ROI-based analysis Threshold for cluster size 100 voxels, FDR correction	
Liistro et al. ([58])	Static 20-min	YAP(S)PET microPET (ISE s.r.l.) OSEM reconstruction Resolution 1 mm FWHM		FURglu Image-derived input function –		Spillover correction of the image-derived input curves ROI-based analysis –	
Guzzardi et al. ([59])	Static 20-min	YAP(S)PET microPET (ISE s.r.l.) OSEM reconstruction Resolution 1 mm FWHM		SUVglu – –		– ROI-based analysis –	

(Continued)

Table 1 Continued

Reference	PET acquisition	Scanner		Glucose uptake quantification		Normalization	
		Reconstruction		Input function		Analysis method	
		Resolution		Lumped constant (LC)		Statistical correction	
Wang *et al*. (62)	Static 20-min	Siemens HR + PET scanner – Resolution 4.5 mm FWHM, resolution of parametric image 16 mm FWHM		CMRglu by using published k constants (4K) Arterialized plasma input function LC = 0.52		Normalization to whole brain SPM analysis + ROI-based analysis Threshold for cluster size 100 voxels, multiple test correction via the random filed theory, significance at cluster level corrected *P* < 0.05	
Wang *et al*. (63)	Static 20-min	Siemens HR+ PET scanner – Resolution 4.5 mm FWHM, resolution of parametric image 16 mm FWHM		CMRglu by using published k constants (4K) Arterialized plasma input function LC = 0.52		Normalization to whole brain SPM analysis + ROI-based analysis Threshold for cluster size 100 voxels, multiple test correction via the random filed theory, significance at cluster level corrected *P* < 0.05	
Guzzardi *et al*. (64)	Dynamic 40-min	GE discovery VCT PET/CT scanner OSEM reconstruction Resolution 5.8 mm FWHM		CMRglu by Gjedder-Patlak plot Image-derived input function –		– ROI-based analysis –	
Volkow *et al*. (65)	Static 20-min	Siemens/CTI ECAT HR+ PET scanner – Resolution 4.5 mm FWHM, resolution of parametric image 16 mm FWHM		CMRglu by using published k constants (4K) Arterialized plasma input function LC = 0.52		– SPM analysis + ROI-based analysis Threshold for cluster size set at 100 voxels, significance at uncorrected *P* < 0.005	
Thanos *et al*. (66)	Static 80-min	Siemens R4 uPET tomograph, FBP and OSEM3D/MAP reconstruction methods Resolution 2 mm FWHM.		Not reported, only statistics reported		Normalization to global activity SPM analysis Significance uncorrected *P* < 0.001	
Sanguinetti *et al.* (69)	Dynamic 60-min	IRIS PET/CT microPET-CT tomograph (Inviscan SAS) OSEM reconstruction Resolution 1 mm FWHM		SUVglu –		– ROI-based analysis –	
Sanguinetti *et al.* (70)	Static	Siemens ECAT HR+ tomograph FBP reconstruction Resolution 5–8 mm FWHM		FURglu Image-derived input function –		– ROI-based analysis –	
Bouter *et al.* (71)	Static 20-min	Small animal 1 Tescal nanoScan PET/MRI (Mediso) – –		SUVglu –		– ROI-based analysis –	
Sanguinetti *et al.* (92)	Dynamic 60-min	IRIS PET/CT microPET-CT tomograph (Inviscan SAS) OSEM reconstruction Resolution 1 mm FWHM		SUVglu –		– ROI-based analysis –	
Craft *et al*. (93)	Static 15-min	GE Advance PET scanner FBP reconstruction Resolution 5 mm FWHM		Not reported, only statistics reported		Normalization to cerebellar and pontine values SPM analysis + ROI-based analysis Voxel wise analysis corrected for multiple comparison	

The hyphen (–) indicates that the information was not reported and not obtained by previous publications.
3K and 4K, pharmacokinetic three-compartment three- or four-rate-constant models; CMRglu, cerebral metabolic rate of glucose calculated as FDG rate of extraction (ki) multiplied by plasma glucose concentration; FBP, filtered back projection; FDR, false discovery rate; FURglu, glucose fractional uptake rate (ratio of tissue radioactivity concentration at time T and integral of plasma activity from time 0 to T) multiplied by plasma glucose concentration; FWE, family wise error; FWHM, full width half maximum; MRP, median root prior; OSEM, ordered subsets expectation maximization; ROI, region of interest; SPM, standardized parametric mapping; SUVglu, standardized uptake value (ratio of tissue radioactivity concentration at time T and administered dose at time of injection divided by body weight) multiplied by plasma glucose concentration.
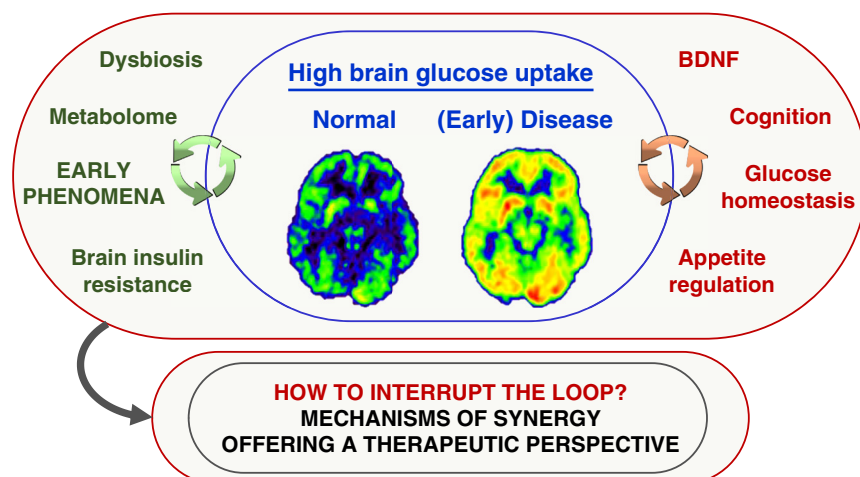
Figure 3
The central panel highlights that high brain glucose uptake occurs in selected stages of metabolic and neurodegenerative diseases, and may be offensive and/or defensive. The right panel addresses conditions that might be fostered by brain hypermetabolism, whereas the left panel lists early phenomena that might be promising prevention targets.

(46, 47, 110). Then, statistical analyses can be done automatically on a voxel-by-voxel basis, after brain alignment to a reference space (statistical parametric mapping (SPM)) across all brain voxels. In this multiple comparisons approach it is important to correct for the risk of false positive findings, by applying e.g. family-wise error or false discovery rate corrections. To reduce the impact of interdependency, one may restrict these corrections to a selected number of voxels in a given target region (small volume correction) or extract values from few larger regions of interest, corresponding to anatomically or functionally meaningful areas of the brain, and/or utilize non-SPM based analysis. Original images (kBq/cc) can also be used to extract tissue time-activity-curves from brain subregions and apply mathematical modeling outside of the image domain (non-parametric image and non-SPM based analysis), reducing the noise related to the modeling of time-activity-curves in each very small voxel, though introducing some degree of operator dependency in the definition of the region of interest.

Deeper technical insights are beyond the scope of this review, and can be found in (111), focusing on the relevance of *a priori* validation in PET data simplification, and in (112, 113, 114), covering statistical concepts that are common to MRI, PET, and other neuroimaging modalities.

Conclusions

In this review, we have addressed brain glucose metabolism determinations by FDG PET imaging, as a potential unifying marker in the synergy linking obesity and cognitive disease. Figure 3 provides a graphic representation of the following conclusions, as supported by the current evidence: (a) brain glucose metabolism undergoes changes across the lifespan, increasing in first life years and declining from late childhood through aging in the normal situation; (b) compared to healthy individuals, brain glucose metabolism is high during mid-life in adults with obesity or with mild cognitive dysfunction and in animal models of AD pathology fed a high-fat diet or animal models of metabolic syndrome, as well as during early life days in offspring born to obese mothers; (c) most observations indicate that brain hypermetabolism may be a transient phenomenon, eventually evolving toward normal or low values during life or disease progression; (d) associative studies suggest that brain hypermetabolism predicts low BDNF levels, hepatic and whole body insulin resistance, food desire and an unfavorable balance between anticipated reward and cognitive control; (e) the effect of (intranasal) insulin is to reduce brain glucose exposure, that is, brain insulin resistance manifests as failure of insulin to achieve this suppression; (f) according to this definition, brain insulin resistance occurs in obese individuals, in mice born to obese mothers, and in mice with AD pathology when combined with high fat feeding; (g) emerging mechanistic links, showing summative alterations in AD, obesity and high-fat diets involve the microbiota and the metabolome, which correlate with brain metabolism and cognition. Though brain hypermetabolism is considered a potential compensatory reaction against initial brain damage, its consequences may still be deleterious. Research priorities in this area require clarification of whether brain hypermetabolism, and its reversal play a causative or protective role in obesity, neurodegeneration and their combination, and whether metabolites or bacteria or hormones (insulin and beyond) can be an effective strategy to prevent or mitigate the risk of neurodegeneration.

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