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REVIEW ARTICLE

Brain functional imaging in obese and diabetic patients

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Abstract
Obesity and type 2 diabetes are associated with greater risk of brain damage. Over the last decade, functional imaging techniques (functional magnetic resonance imaging, fMRI, positron emission tomography, PET, electroencephalography, magnetoencephalography, near infrared spectroscopy) have been exploited to better characterize behavioral and cognitive processes, by addressing cerebral reactions to a variety of stimuli or tasks, including hormones and substrates (e.g., glucose, insulin, gut peptides), environmental cues (e.g., presentation of sensory stimuli), and cognitive tasks. Among these techniques, fMRI and PET are most commonly used, and this review focuses on results obtained with these techniques in relation to brain substrate metabolism, appetite control and food intake, and cognitive decline in obesity and type 2 diabetes. The available knowledge indicates that there are a series of cerebral abnormalities associating with, or preceding obesity and type 2 diabetes, including impaired substrate handling, insulin resistance, disruption of inter-organ cross-talk and of resting state networking. Some of these abnormalities are reversed by metabolic interventions, suggesting that they are partly a consequence rather than cause of disease. Therefore, causal implications and mechanisms remain to be determined.

Keywords Brain substrate metabolism · Appetite control · Cognitive processes · Functional magnetic resonance imaging · Positron emission tomography

Introduction

The prevalence of obesity and type 2 diabetes (T2D) is high and growing worldwide, associating with brain damage. Over the last decade, brain functional imaging techniques have been exploited to achieve deeper understanding of neural mechanisms underlying behavioral and cognitive processes. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are the most used functional imaging techniques. The first exploits the different magnetic proprieties of oxygenated and deoxygenated hemoglobin (the so-called blood-oxygen-level dependent contrast—BOLD), providing an indirect measure of neural connectivity, and a fine localization of neural activation during resting state or in response to external stimuli. PET employs molecules labeled with positron-emitting radioisotopes to provide a direct and specific measure of biochemical processes in organs and regions of interest. In Fig. 1, the basic principles of these neuroimaging techniques are illustrated.

The present review summarizes results of functional imaging of brain in obese and diabetic patients, focusing on (1) cerebral substrate metabolism, (2) central and peripheral regulation of appetite, and (3) cognitive processes.

Brain substrate metabolism

Glucose is the main fuel for brain survival. Though glucose uptake primarily responds to cerebral energy requirements, systemic glucose levels and brain aging or neurodegeneration are strong modulators [3, 4].

During the fasting state, the brain represents the predominant glucose consumer among body organs. Following a meal, insulin secretion directs most of the glucose into insulin-dependent organs, such as muscle, myocardium and fat [5]. It also suppresses endogenous glucose production by the liver, favoring glucose storage in this organ [5]. Insulin receptors are highly expressed in the

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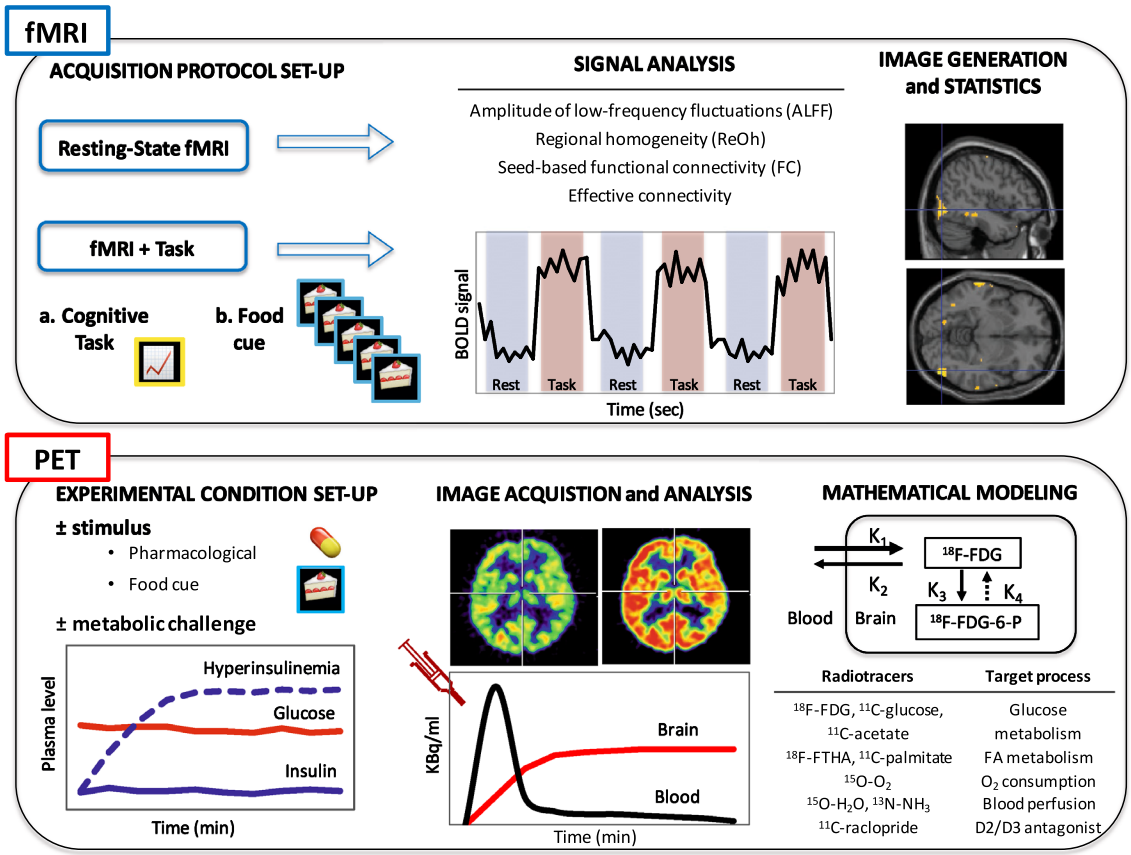

Fig. 1 In magnetic resonance imaging (MRI), the application of a magnetic field and of a radiofrequency pulse results in the alignment of nuclear spins (for instance, hydrogen nuclei in water) within the human body. When the radiofrequency ceases, the spins return in the original orientation generating a signal that is detected by a coil placed around the subjects or the area of interest. Modulating MRI acquisition parameters allows to spatially encode the detected signals, generating structural images with high contrast between different tissues. In functional MRI (fMRI), an indirect measure of brain activation is obtained based on the different magnetic proprieties of oxygenated and deoxygenated hemoglobin, and it is called blood-oxygen-level dependent contrast (BOLD). Under resting state, fMRI allows to measure intrinsic activity within the brain, and the neural network and connectivity operating in absence of any sensory or cognitive stimuli. By combining fMRI with external stimuli or tasks, it is possible to assess and localize specific brain functions. Over the years, sophisticated techniques of signal analysis and statistical parametric mapping have been developed to examine and extrapolate differences in brain activation [1]. Positron emission tomography (PET) is a nuclear imaging technique employing short-lived positron-emitting radioisotopes to label molecules of interest (e.g., metabolic substrates, perfusion markers), to directly measure a biochemical process in individual organs and regions of interest. The biochemical process can be measured during a stimulus (e.g., administration of a pharmaceutical interacting with the target process, or sensory stimuli), or under a metabolic challenge (e.g., hyperinsulinemic-euglycemic clamp to measure organ-specific insulin sensitivity). The radiotracer is administered to the subject, emitted positrons annihilate when combined with an electron in the body tissue, generating two 511 keV photons in opposite directions, which are recorded by detectors arranged around the area of interest (e.g., the brain). Each couple of photons is used to generate the image, and consecutive images can be acquired to provide kinetic data. Time-activity concentrations of tracer in blood and tissues can be used in combination with mathematical modeling to quantify biochemical processes within the target tissue area. The radiolabeled glucose analogue ^{18}F-fluorodeoxyglucose (FDG) is the most commonly used PET tracer to quantify regional brain glucose metabolism, which represents a direct measure of neuronal metabolism [2]. The table in the right bottom panel provides a non-exhaustive list of PET tracers and their target biological processes. *^{18}F-FDG-6-P* ^{18}F-FDG-6-phosphate, *^{18}F FTHA* ^{18}F-fluoro-thia-heptadecanoic acid, *FA* fatty acids

brain, and insulin can cross the blood–brain barrier to exert appetite suppressive and anti-neurodegenerative actions, being a growth factor. However, the ability of insulin to enhance glucose uptake in the brain remains incompletely defined. Eastman et al. [6] used FDG-PET to show that patients with T2D were characterized by normal net glucose retention in the brain during insulin stimulation, in spite of greater washout of glucose from the brain. This may suggest that the unidirectional uptake of glucose (given by the sum of efflux and retention) could be higher in the diabetic than control brain. In fact, more recent PET imaging studies support the possibility that the response to insulin in terms of glucose uptake is enhanced in the brain of morbidly obese subjects [7] and patients

with impaired glucose tolerance [3]. In addition, results combining brain PET imaging and plasma FDG kinetics data to calculate endogenous glucose production, suggest that higher insulin-mediated brain glucose uptake in morbidly obese individuals may disturb the cross-talk occurring between brain and liver, elevating hepatic glucose release [8]. The above findings were obtained by increasing insulin to post-prandial levels and maintaining euglycemia (insulin clamp). At basal insulin levels, the brain response was low in insulin-resistant individuals [9]. Interestingly, bariatric surgery in humans was shown to reduce the excessive uptake of glucose observed in the insulin-stimulated brain before surgery [7]. Likewise, short-term interval training effectively decreased insulin-stimulated brain glucose uptake in sedentary subjects with insulin resistance [10].

One important factor to consider is that the primary action of insulin is to modify glycemia, whereas the forceful maintenance of euglycemia in insulin clamp studies cannot recapitulate the full physiological outcome occurring under free-living conditions. Human PET studies under free living situations to compare, e.g., meal or glucose load in lean and metabolically diseased subjects are lacking. Obese and diabetic rodents undergoing glucose loading show chronic brain glucose over-exposure and limited metabolic flexibility from the fasted to fed states [4, 11]. Brain glucose uptake was shown to inversely relate to the release of brain-derived neurotrophic factor, which regulates peripheral metabolism and energy balance, beyond neuroprotection. Thus, brain glucose overexposure and low metabolic flexibility might explain the combination of neuronal damage and systemic dysmetabolism characterizing obesity and diabetes. Clearly, a prolonged duration of brain glucose overexposure may result in cell loss and brain hypometabolism. Therefore, the expected metabolic brain pattern is dynamic and may change from hyper to hypo along disease progression. This was shown to occur, e.g., in the offspring of obese minipigs [12], representing a risk model of adulthood obesity, diabetes and brain damage.

Considering that systemic insulin levels in the above studies may not necessarily reflect brain insulin concentrations, recent investigations have adopted the intranasal route of administration to directly stimulate the brain [13]. In humans, this paradigm has been mostly used to examine peripheral consequences of central insulin action, and combined with the systemic insulin clamp, showing that central insulin delivery suppresses hepatic glucose release and tends to elevate whole-body glucose uptake in healthy humans [13]. Brain insulin sensitivity was assessed by fMRI, showing action in the hypothalamus and insula. Importantly, these insulin-mediated effects were lacking in overweight subjects [13]. In healthy mice studied under free-living fasting conditions, intranasal insulin administration led to a reduction in peripheral glycemia, and brain glucose uptake, whereas it failed to reduce peripheral glucose levels in obese mice, resulting in higher brain glucose uptake [14].

Though the primary fuel for the brain is glucose, PET imaging of ^{18}F-fluoro-thia-heptadecanoic acid (reflecting fatty acid uptake) and ^{11}C-palmitate (informing on fatty acid oxidation) has revealed that fatty acids contribute to brain energy provisions [15]. Patients with the metabolic syndrome were characterized by a marked elevation in brain fatty acid uptake, which was more pronounced in white than gray matter. The fraction of fatty acids undergoing oxidation was lower in these patients. Weight loss by low calorie diet alleviated these abnormalities in patients with the metabolic syndrome [15], whereas exercise training did not seem to affect fatty acid uptake in the brain of insulin resistant individuals [10].

In summary, in spite of the importance of brain substrate metabolism on brain health and peripheral homeostasis, the available PET imaging studies in human diabetes and obesity are relatively few, and technically different. The current evidence seems to indicate that there is an excess of substrate uptake in the brain of patients with metabolic disorders. More studies are needed to characterize free-living conditions, cause–effect mechanisms and brain responses and/or contributions to disease progression (Fig. 2).

Brain control of appetite and food intake

Eating behavior is regulated by an integrated neural network, involving homeostatic, reward and inhibitory control regions to respond to food cues and peripheral signals [16].

Response to food cues

fMRI studies have shown that the oral ingestion of glucose [17] leads to a transient reduction of hypothalamic ventromedial and paraventricular nuclei activation in normal-weight volunteers. However, this reduction was attenuated and delayed in obese subjects [17], and absent in patients with T2D [18], suggesting that impaired hypothalamic nutrient processing might have a role in disease etiology or progression. Impairment in reward processes has also been shown [19–21]. In healthy normal-weight volunteers, exposure to images of palatable and high-calorie food triggered brain reward-related response [22, 23], involving amygdala, striatum, insula and orbitofrontal cortex (OFC), in fasted [24, 25] more than in fed state [24]. Furthermore, fMRI hyperactivation (ventral pallidum) in response to milkshake vision, and hypoactivation (caudate) after milkshake ingestion predicted BMI gain over 2 years [26]. In obese compared to lean subjects, exposure to high-calorie food images caused greater activation of reward (anterior cingulated cortex, striatum,

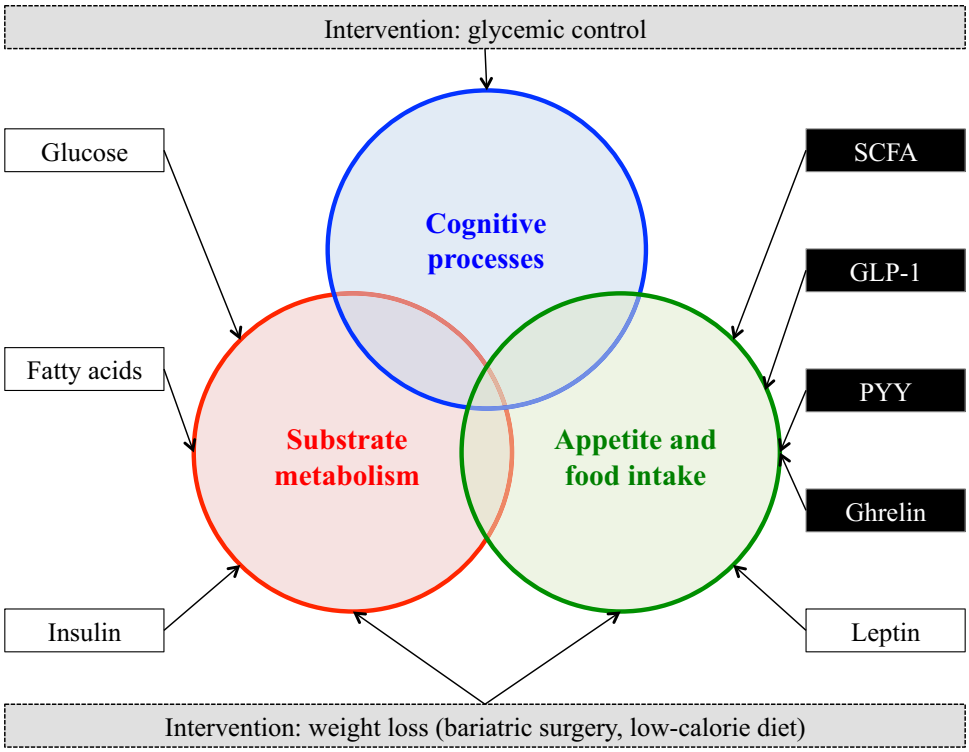

Fig. 2 Brain substrate metabolism, appetite regulation and food intake, and cognitive processes (shown in circles) are dysfunctional in obesity and diabetes. The intersection between circles suggests a mutual interaction, which remains to be understood. Molecules produced by peripheral organs, and having abnormal plasma levels in metabolic disorders, have been involved in the above cerebral (dys) functions. Substrates and insulin (white boxes) have been implicated in the regulation of brain metabolism, and molecules derived from the gut, such as peptides and short-chain fatty acids (SCFA produced by the gut microbiota) (black boxes) have been mostly studied in connection with brain patterns of appetite control. Intervention studies (gray boxes) have demonstrated that brain functional abnormalities observed in obese and diabetic patients are, at least partially, reversible, prompting for the need to dissect causal from compensatory processes

insula) and somatosensory associative regions (postcentral gyrus, OFC) [19–21]. These studies suggest that a high anticipated reward before food consumption, together with an impaired reward after food consumption may contribute to the development of obesity.

These results are in line with PET findings in obese subjects, showing enhanced metabolic activity in areas involved in taste perception and food intake [27], and low activity in areas encoding food reward and inhibitory control [28], or reduced blood flow in posterior cingulate, temporal and orbitofrontal cortex in response to meal ingestion compared to lean subjects [29]. Together with the reduction of striatal dopamine receptor density observed in overweight subjects [30, 31], these studies suggest that the dopamine-dependent reward system is down-regulated in obese subjects, in whom a higher caloric intake may be required to experience a given level of reward. This concept supports the food addiction hypothesis, as a debated mechanism underlying the proneness to obesity development [32]. Several reviews [32, 33] address this controversy, whose conclusive demonstration or confutation has not been reached. We underscore that the comparison of lean and obese individuals cannot dissect different causes of obesity within the obese population, and studies aimed at stratifying similarly obese subjects based on their brain functional/metabolic reaction are lacking.

Appetite regulating gut peptides

Enteric hormones, like ghrelin, GLP-1, PYY, and the adipostatic hormone leptin, affect neural functionand eating behavior [34]. Ghrelin is released by gastric cells during fasting, stimulating hunger, and its release decreases postprandially [34]. Ghrelin administration to healthy fed subjects [35] resulted in fMRI activation patterns that are typical of the fasting/hungry state, in regions encoding the incentive value of food cues, including the amygdala, OFC, insula and striatum [36]. It increased corticolimbic system responses to visual food cues, and blunted hypothalamic, brainstem and limbic activation after food ingestion [37]. In obese compared to lean adolescents, glucose ingestion failed to suppress plasma ghrelin and fMRI activity in homeostatic and hedonic (hypothalamus,

thalamus and hippocampus), while suppressing activity in executive control regions (prefrontal cortex) [38]. These fMRI data are consistent with PET findings, showing that fasting ghrelin levels correlate negatively with the dopaminergic binding potential in the midbrain and nucleus accumbens in lean, but not in obese women [39]. A defective decrement of post-prandial ghrelin levels observed in obese compared to lean subjects might stimulate continuing eating in these subjects.

$PYY_{3–36}$ and GLP-1 are anorectic enteroendocrine hormones released during a meal [34]. A fMRI study showed that $PYY_{3–36}$ administration to fasted lean subjects [40] reduced food intake, activating the hypothalamus and OFC [40], and dampening corticlimbic activation in response to visual food cues to a level comparable to that observed under fed conditions, especially when co-administered with $GLP\text{-}1_{7–36\ amide}$ [41]. Although PYY deficiency could reduce satiety in post-prandial subjects [42], functional imaging studies exploring its neural mechanisms in obesity are lacking.

GLP-1 agonists have been largely investigated in the treatment of diabetes, as they improve glycaemic control, by promoting insulin release and decelerating gastric empting. They also exert appetite suppressive effects [43]. fMRI studies have demonstrated that the intravenous administration of the GLP-1 agonist exenatide reduced brain hyper-responsiveness to food pictures in insula, amygdala, putamen and OFC and food intake seen in obese (normoglycemic and T2D) patients compared to lean controls [43, 44], and the antagonist exendin 9-39 abolished this effect [43]. Ten days of treatment with the GLP-1 agonist liraglutide in obese T2D patients improved the response to chocolate milk receipt in the right insula and caudate nucleus, predicting weight changes after 12 weeks [45].

In a PET study in male subjects with post-prandial hyperglycemia, exenatide injection during oral glucose ingestion increased cerebral glucose metabolism in reward-related regions (OFC, thalamus, insula, posterior cingulate, putamen, limbic system), and reduced hypothalamic metabolism [46]. The GLP-1-dependent enhancement of reward responsiveness to food ingestion may contribute to the induction of weight loss observed during treatment.

Leptin is an adipokine, informing the brain on body fat stores. Its decline during fasting stimulates hypothalamic signals to increment food intake [34]. Two important fMRI studies [47, 48] have shown that treatment of leptin-deficient (genetic mutation) individuals with recombinant leptin reduces hunger ratings in the fasting state, in association with lower response to food images in regions linked to hunger and reward, and increases post-prandial satiety [47], enhancing activation in regions linked to inhibition and satiety [48]. Overall, in the human genetic model of hypoleptinemia, leptin administration attenuates food reward, increasing satiety after food consumption.

During weight loss, there is a substantial reduction in plasma leptin, and there are changes in neural activity that are consistent with a state of leptin deficiency, e.g., greater activation in response to visual food stimuli in reward-related regions, and lower activation in homoeostatic and inhibitory regions [49]. It has been hypothesized that leptin treatment might help prevent weight regain and support weight maintenance [49]. Two fMRI studies demonstrated that leptin treatment in obese subjects reversed weight loss-induced changes in neural activity [49]. Moreover, during weight maintenance with leptin repletion, functional connectivity of the hypothalamus increased with the mid-insula and central and parietal operculae, and decreased with OFC and dorsal anterior cingulate, suggesting the restoration of the homeostatic control of energy intake, and reduced sensitivity to the rewarding properties of food [50]. The main drawback of leptin treatment in weight-loss maintenance is the potential onset of leptin resistance, which is often observed in overweight and obese subjects.

Other gut-derived appetite regulators

Recently, the gut microbiota and its metabolites, e.g., short-chain fatty acids acetate propionate and butyrate, are being explored as appetite and eating behavior modulators. By combining ^{11}C-acetate-PET with manganese-enhanced MRI in a preclinical mouse model, Frost et al. [51] showed that intraperitoneal injection of acetate suppressed appetite via activation of the hypothalamic arcuate nucleus, whereas no significant differences were observed in the ventral medial hypothalamus, and in the paraventricular nucleus. More recently, human fMRI data [52] indicated that acute increased colonic propionate, resulting from consumption of inulin-propionate ester compared to control inulin, reduced neural activation in the caudate and accumbens nuclei during a food-image evaluation task, in healthy lean volunteers. Interestingly, neural functional changes were associated with a reduced subjective appeal of high-energy foods and energy intake in the subsequent ad libitum meal, independent of circulating glucose, insulin and anorectic gut hormones PYY and GLP-1.

Pharmacological and surgical weight-loss interventions

A recent fMRI study has shown that the combination of naltrexone and bupropion, as used in treating obesity, may improve control of eating behavior, by increasing functional connectivity between the superior parietal cortex and regions involved in saliency (dorsal anterior cingulate gyrus) and reward (insula), while reducing functional connectivity density in craving-related regions (medial prefrontal cortex) [53]. Bariatric surgery is currently the most effective

treatment of obesity [54]. fMRI showed that post-roux-en-Y gastric bypass (RYGB) weight loss normalized functional connectivity between hypothalamus and orbitofrontal and somatosensory cortices in pre-surgery obese compared to lean controls [55]. Moreover, RYGB reduced the activation of reward-related regions (OFC, amygdala, caudate, nucleo accumbens, hippocampus) in response to high-calorie food images compared to pre-surgery values [56], and compared to gastric banding surgery [54]. These effects might be mediated by the rise in PYY and GLP-1 reported in post-RYGB patients [54]. In fact, they were not seen after suppressing post-prandial PYY and GLP-1 with the somatostatin analogue octreotide [57]. A recent FDG-PET study [58] compared brain regional response to eating between normal weight, non-operated obese and post-RYGB patients. Post-RYGB subjects showed enhanced homeostatic (hypothalamus) and hedonic (left medial orbital cortex) response to eating compared to normal weight, and the restoration of inhibitory control (reduced activation in dorsolateral frontal cortex and in regions of the default mode network) compared to non-operated obese individuals. Again, these effects were partially reversed by blocking gut peptide release by somatostatin infusion [58].

Taken together, these data indicate that enhanced secretion of satiety hormones might be a causal mechanism by which obesity surgery modifies appetite control and food intake (Fig. 2).

Cognitive processes

Obesity, insulin resistance and diabetes have been associated with poor cognitive health and increased risk of cognitive disorders, including dementia and Alzheimer's disease [59–61]. Structural brain imaging studies combining magnetic resonance imaging (MRI) with neuropsychological assessments revealed that both metabolic and cognitive diseases are characterized by brain structural abnormalities (e.g., total brain or hippocampal atrophy), and reduced cognitive performance [59, 62–66]. This review is focused on functional, rather than structural imaging, and a comprehensive description of brain structural abnormalities associated with cognitive decline in obesity and diabetes is out of our scope; main outcomes are summarized as they provide the rationale to functional studies.

Already in childhood [67] and adolescence [68], obesity and metabolic syndrome have been associated to lower verbal fluidity [67], and lower working memory, attention, psychomotor efficiency cognitive scores in spelling and arithmetic tasks [68]. MRI analysis revealed structural abnormalities, including reduced volume of left hippocampus and thickness of orbitofrontal and anterior cingulate cortices, at both ages [67, 68]. In a population-based MRI study conducted in 1352 adults without dementia belonging to the prospective Framingham offspring study [64], it was shown that obesity and high waist-to-hip ratio in midlife are associated with an increased rate of reduction in brain volume and decline in executive function a decade later, and diabetes is associated with a more rapid increase in temporal horn volume (surrogate marker of accelerated hippocampal atrophy). Other MRI population-based studies revealed that plasma glucose or HbA_{1c} levels and years of diabetes were positively related to brain atrophy [63], white matter lesions, and presence of cerebral infarcts [62], and inversely related to cognitive function [62]. On the same line, Moran et al. [65] showed significantly greater gray and white matter losses (mainly in medial temporal, anterior cingulate, medial frontal lobes, and in frontal and temporal regions, respectively), in addition to hippocampal reductions, in T2D patients compared to controls. Since this cortical atrophy is also seen in preclinical dementia [69], the authors speculate that it might underscore the role of glucose dysmetabolism on the pathophysiology of Alzheimer's disease [65]. Consistently, in a population of middle-aged cognitively healthy individuals, Willette et al. [66] demonstrated that insulin resistance predicted medial temporal lobe atrophy at baseline and after 4 years, mediating a worse performance in the Rey Auditory Verbal Learning Test. The Memory in Diabetes (MIND), substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, was conducted in 52 clinical sites in north America [70], involving ~3000 participants (mean age 62) with T2D, high HbA_{1c} (> 7.5%) and high risk for cardiovascular events, to assess the efficacy of intense glycemic control (target $HbA_{1c} < 6\%$) compared to standard therapy (target HbA_{1c} 7.0–7.9%). After 80 months of treatment, there was no difference between treatment arms in total brain volume and in the primary cognitive outcome. Substantial loss to follow-up may have limited the power of the study. In addition, the authors speculated that the duration (10 years on average) of T2D at trial entry might have hampered the potential of an intensive glycaemic intervention to reverse changes already present in the brain.

The evidence of structural abnormalities associated with cognitive decline in obese and diabetic patients pave the way to the exploitation of functional brain imaging techniques to achieve deeper insight in functional causal mechanisms.

Resting state fMRI (RS-fMRI) and fMRI during cognitive tasks are common protocols applied to reveal abnormal neural activity and connectivity in background patterns (such as the default mode network—DMN—that is activated at rest and suppressed during cognitive activity) or in response to active tasks, which might precede structural and cognitive changes. Impaired activation of hippocampus, temporal and prefrontal regions is a functional characteristic in Alzheimer's disease [71]. In T2D patients compared to healthy controls, functional connectivity in several regions of the

DMN, including middle temporal gyri, right inferior and left medial frontal gyri and left thalamus, was reduced and inversely correlated with insulin resistance [59], in spite of no group differences in hippocampal volume and cognitive performance. Moreover, reduced connectivity between hippocampus and other brain regions, including fusiform, frontal, temporal, anterior cingulate, medial frontal, and posterior cingulate gyri, precuneus and inferior parietal lobule, was accompanied by lower cognitive performance in tasks assessing memory and executive functions in elderly subjects with T2D [72]. Interestingly, in the same population, cognitive performance was inversely related to BMI and HbA_{1c} [72].

Analysis of amplitude of low-frequency fluctuation (ALFF) and of regional homogeneity (ReHo) are two methods characterizing global RS-fMRI signals, as they measure neural intensity and neural coherence, respectively [73]. Decreased ALFF and RoHo in the occipital lobe and postcentral gyrus (typically associated to visual and sensory loss) and in middle temporal gyrus [74] were observed in T2D patients compared to healthy controls, in spite of no brain structural differences [73]. Furthermore, these abnormalities were related to impaired cognitive function, higher HbA_{1c}, impaired beta-cell function and HOMA-IR [74]. In a subsequent study, the same authors [75] showed that in T2D patients hypoconnectivity of the occipital lobe was correlated with impaired visual memory and executive function performance, while anterior cingulate cortex hyperconnectivity was related to better executive function.

fMRI during cognitive tasks showed that neural activation patterns in patients with metabolic syndrome [76], obesity, insulin resistance [60] or T2D [61] are affected. Patients with the metabolic syndrome compared to controls were characterized by reduced activation in right superior frontal gyrus, right superior parietal lobule and left inferior parietal lobules during verbal working memory test [76]. In a more recent fMRI study, obesity (BMI > 30 kg/m^2) and HOMA-IR > 1.94 were found to be associated with reduced activity of the core recollection network, including hippocampus and dorsloateral prefrontal cortex during an episodic memory task [60]. Reduced activation of task-relevant brain regions (dorsolateral prefrontal cortex) and impaired deactivation of DMN were also found in T2D patients during encoding and recognition tasks, and were significantly related to high glucose and HbA_{1c} levels and insulin resistance [61]. These findings suggest that glucose dysmetabolism may affect neural patterns, becoming similar to those observed in populations at risk of cognitive decline and Alzheimer's disease [61].

PET studies, conducted during resting state [77, 78] or cognitive tasks [79], indicated associations between insulin resistance and reduced cerebral metabolism in cognitive-relevant regions. In patients with normal cognitive performance to mild dementia, a higher Framingham cardiovascular risk profile (FCRP) was associated with lower glucose metabolism in superior medial frontal, superior frontal and superior orbital frontal cortex and the ventrolateral prefrontal cortex [77]. Among FCRP components, diabetes was associated with lower metabolism in bilateral supplementary motor areas, bilateral paracentral lobule, left supramarginal, and left postcentral gyri. In a population-based study of cognitively normal adults [78], insulin resistance was associated with lower total brain and regional (large portions of frontal, lateral parietal, lateral temporal, and medial temporal lobe) glucose metabolism. In addition, left medial temporal lobe hypometabolism was related to worse memory performance. In cognitively healthy adults with new diagnosis of prediabetes or T2D, insulin resistance was associated with reduced cerebral metabolism (FDG-PET) in frontal, temporal–parietal and cingulate regions during resting state [79]. A memory-encoding task scan resulted in a more widespread activation pattern, including bilateral orbital-medial and inferior prefrontal regions, subcortical regions (right putamen, left thalamus) and right cerebellar vermis, in prediabetic or T2D patients compared to healthy controls, which is typical of adults with prodromal or early dementia [79].

Taken together, the data suggest that disruption of functional connectivity, especially in the middle temporal gyrus and occipital lobe, is associated with insulin resistance, preceding structural changes, and can be used to predict cognitive decline and risk of dementia in patients with impaired glycemic control or T2D. Control of glycemic homeostasis is important to maintain neural metabolism and cognitive function, but further studies are needed to identify timing and intensity of preventive and therapeutic interventions (Fig. 2).

Conclusion: knowledge gaps

Imaging studies have revealed brain metabolic, functional and structural abnormalities, involving brain patterns of eating behavior, neural connectivity and cognition, and associating with, or preceding obesity and type 2 diabetes, as exemplified in Fig. 2. Most studies have focused on one or the other of the above aspects, whereas their interaction remains to be understood. Furthermore, the few existing longitudinal studies suggest that metabolic and functional alterations change during the course of the metabolic disorder, and some are reversed by metabolic interventions. Therefore, causal implications and mechanisms remain to be dissected from disease consequences and compensatory or defense responses. Future studies should overcome the associative nature of previous investigations, using longitudinal and standardized, possibly multi-imaging designs able to dissect the cause–effect link underlying disease progression, potentiate the predictive value of functional imaging

data, and identify and validate brain processes that should be targets of prevention and treatment.

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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