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Human Cognitive Function and the Obesogenic Environment

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Abstract

Evidence is accumulating which suggests that, in addition to leading to unprecedented rates of obesity, the current food environment is contributing to the development of cognitive impairment and dementia. Recent experimental research indicates that many of the cognitive deficits associated with obesity involve fundamental inhibitory processes that have important roles in the control of food intake, implicating these cognitive impairments as a risk factor for weight gain. Here, we review experiments that link obesity with deficits in memory, attentional, and behavioral control and contemplate how these deficits may predispose individuals to overeat. Specifically, we discuss how deficits in inhibitory control may reduce one's ability to resist eating when confronted with the variety of foods and food cues that are ubiquitous in today's environment. Special attention is given to the importance of memory inhibition to the control of eating and appetitive behavior, and the role of the hippocampus in this process. We also discuss the potential etiology of both obesity and obesity-related cognitive impairment, highlighting non-human animal research which links both of these effects to the consumption of the modern "Western" diet that is high in saturated fats and simple carbohydrates. We conclude that part of what makes the current food environment "obesogenic" is the increased presence of food cues and the increased consumption of a diet which compromises our ability to resist those cues. A multi-dimensional intervention which focuses on improving control over food-related cognitive processing may be useful not only for combating the obesity epidemic but also for minimizing the risk of serious cognitive disorder later in life.

Keywords

obesity; Western diet; memory; hippocampus; inhibition

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The current food environment in Western and westernized societies is characterized by the widespread availability of low cost, energy-dense, highly-palatable, foods and beverages, and an abundance of external cues that keep thoughts of these foods and beverages almost constantly in mind. It has often been claimed that this combination of factors has helped to create an “obesogenic” environment that overwhelms the physiological controls that normally maintain energy balance and body weight (e.g., 1, 2). Along with excess energy intake and body weight gain, this environment is associated with increased incidence of Type II diabetes (T2DM), cardiovascular disease, hypertension, depression, and certain types of cancer (e.g., 3).

Accumulating evidence suggests that cognitive dysfunction should also be prominent on the list of the adverse health consequences of living in an obesogenic environment. A number of recent epidemiological studies have reported links between obesity and cognitive dysfunction (4, 5). In addition, well-controlled non-human animal studies indicate that consuming an energy-rich “Western”-style diet (WD) that is high in sugar and saturated fat can promote not only obesity but also impairments in specific types of cognitive functions. Such WD-induced impairments are accompanied by signs of pathology in the brain substrates for those functions. Furthermore, animals that are most sensitive to this diet-induced obesity are also most sensitive to the effects of that diet on brain pathophysiology and learning and memory function. These findings are discussed in recent reviews (7-9).

The purpose of the present paper is to (a) summarize findings that link excess energy intake and body weight to cognitive dysfunction in humans; (b) describe the types of cognitive processes that might be involved with energy and body weight regulation; and (c) discuss how impairments in these cognitive processes could contribute to the capacity of the obesogenic environment to promote overeating and weight gain.

Links between excess intake, body weight, and cognitive dysfunction across the lifespan

There is concern that the obesity “epidemic” heralds a coming epidemic of Alzheimer’s Disease (AD) and other dementias. Being obese or overweight in mid-life is associated with higher incidence of cognitive dementia in old age, independent of T2DM and cardiovascular-related co-morbidities (10). Furthermore, it appears that people with high levels of central adiposity (i.e., excess accumulation of abdominal body fat) in middle-age are at increased risk of dementia in late-life, even if they possess an otherwise normal body weight (11).

There is also evidence that links being overweight or obese to cognitive decline not only during old-age but across the lifespan. For example, BMI and body adiposity were found to be negatively related to academic achievement and response inhibition in children 7-9 years old (12, 13). In another study (14) which compared obese and lean 12-year-old boys, obesity was associated with reduced attention endurance and increased perseverative errors in a test of set-shifting abilities, the Wisconsin Card Sorting Task. Similar results were reported by

Verdejo-Garcia et al. (15), who found that obese adolescents aged 13-16 years performed worse than normal weight adolescents on indexes of inhibition, cognitive flexibility, and decision-making. Based on the results of these and other studies, it appears that excessive body weight is associated with deficits in some types of cognitive capabilities and that these deficits are not restricted to late-life but are present even in children and adolescents.

Other evidence suggests that both cognitive dementia and milder cognitive deficits are also associated with intake of Western diet. For example, Gustaw-Rothenberg (16) reported that the dietary pattern of Polish patients with AD was characterized by a high intake of meat, butter, high-fat dairy products, eggs, and refined sugar, whereas the dietary pattern of non-demented age-matched controls was characterized by a high intake of grains and vegetables. Furthermore, according to Eskelinen et al. (17) consuming a diet containing a high compared to a low level of saturated fat (a main component of the Western diet) at midlife was associated with an increased risk of mild cognitive impairment in late adulthood.

Similar links between WD consumption and cognitive impairment have been observed in younger adults and children. Cohen et al. (18) reported that adults aged 50-69 exhibited fewer perseverative errors and better attention/concentration and processing speed on tests of cognitive function if they were lean than obese. Notably, the lean group also self-reported consistently consuming more “high quality” food (defined as farm produce, fish, whole grains, and nuts) and less “low quality” food (defined as meats, refined carbohydrates, fried food, fast food, junk food, and alcohol). Similarly, Jasinska et al. (19) found that weaker control over attention and motor responses was associated with higher preference for “junk foods” (potato chips, nachos, candy bars) and lower preference for “healthy” snacks (apples, bananas, carrots) in a cohort of college undergraduates. In a study of 4th graders (ages ~9-10 years), Riggs et al. (20) found that greater self-reported snack food intake and less consumption of fruits and vegetables were associated with poorer performance on an index of cognitive functioning that was comprised of measures of inhibitory control, emotional control, working memory, and planning/organizational ability (separate scores for each subscale were not presented).

Riggs et al. suggested that the relationship between increased intake of snack food and reduced cognitive functioning might be bi-directional. The possibility of a bi-directional relationship was also suggested by Guxens et al. (21), who reported that for children 4 years of age, higher scores on a test of general cognitive function were associated with less risk for becoming overweight by age 6. Thus, deficits in certain types of cognitive functions may not only be a consequence of obesity and consumption of the Western diet, but they may also *promote* excessive weight gain and caloric intake, potentially creating a detrimental developmental cascade. This possibility is discussed in detail later on in this paper, when we identify the types of cognitive impairments that are most likely to influence food intake control and review the evidence linking each of these deficits to overeating and obesity.

Obesogenic environments and progressive cognitive decline

Our hypothesis is that the same dietary factors that lead to obesity (e.g., consumption of a high carbohydrate / high fat diet) also impair cognitive functioning, and that these cognitive

deficits have the potential to compromise energy and weight regulation. Viewed this way, the same environmental risk factors for obesity (e.g., increased availability of low cost, high-calorie food) can also be viewed as risk factors for cognitive decline in that they encourage consumption of a Western diet. One of the implications of this view is that childhood obesity and/or consumption of obesogenic diets may have lasting consequences on cognitive functioning in adulthood. While these impairments are likely to be subtle early in life, there are reasons to suspect that when combined with the normal aging process these deficits, and the pathologies that underlie them, may become increasingly serious. Consistent with this possibility are recent attempts to trace the progression over time of brain pathologies that are thought to lead first to mild cognitive impairment, then to full-blown AD. Several analyses of this progression agree that the first signs of brain disease can occur at least 50 years prior to the emergence of serious cognitive dysfunction (22). These signs originate in the hippocampal formation, an area in the medial temporal lobe of the brain, which is comprised of four subregions: the dentate gyrus, the hippocampus proper (i.e., the CA1, CA2, and CA3 subfields), the subicular complex (i.e., the subiculum, presubiculum, and parasubiculum), and the entorhinal cortex (23, 24). Over time, these pathological changes spread into the orbitofrontal cortex, striatum, lateral hypothalamus and other areas that are interconnected with the hippocampus (25, 26).

Consistent with the possibility that early life, diet-induced brain pathologies may have detrimental effects on cognition later in life, consumption of a WD has been shown to have adverse effects on the hippocampus and has also been identified as a potential contributor to the pathogenesis of AD. Specifically, research from several laboratories shows that intake of WD in nonhuman animals reduced hippocampal neurogenesis, increased hippocampal inflammation, and increased permeability of the blood-brain barrier (BBB) leading to the accumulation of exogenous substances in the hippocampus (27, 28, 140). At the same time, independent research has provided evidence that reduced hippocampal neurogenesis (e.g., (29, 30), increased brain inflammation (31, 32), and increased BBB permeability (33-35) and integrity are at least as important as amyloidosis in the pathogenesis of AD (e.g., (36, 37). In the following section, we describe the types of cognitive impairments that might occur as a result of these pathologies and describe how these deficits could contribute to energy and body weight dysregulation.

Cognitive and behavioral inhibitory processes and energy regulation

It is well known that cues such as the sight, smell, and even thought of palatable food can induce appetite and promote eating (for recent reviews, see 38, 39). Thus, in order to lose weight or prevent weight gain, one must resist the urge to eat when confronted with these food cues. This ability to resist involves both behavioral and cognitive control. That is, in addition to prevent oneself from engaging in the physical act of eating, one must also refrain from thinking about the positive qualities of food that make eating desirable in the first place. This ability to interrupt, stop, or suppress physical and mental activity is generally referred to as “inhibition” (40). Inhibition plays a critical role in cognitive and behavioral control by enabling individuals to suppress unwanted thoughts, ignore distracting stimuli in their environment, and resist engaging in maladaptive behaviors. Thus, inhibitory control underlies many aspects of behavior that are considered to be indicative of increased

“impulsivity”. Here, we review evidence showing that overeating and obesity is associated with deficits in these inhibitory processes. We also highlight the role of episodic memory in food intake control.

Memory inhibitory contributions to food intake control

One of the primary ways in which inhibition contributes to cognitive performance is by enabling individuals to control unwanted or intrusive thoughts. Memory inhibition contributes to this type of cognitive control by helping individuals deliberately suppress unwanted thoughts, as well as by automatically and unconsciously modulating memory retrieval (e.g., reducing the retrievability of memories that are contextually-inappropriate or irrelevant) (41). These functions of memory inhibition can also contribute to food intake control by influencing the likelihood that food cues in the environment will retrieve representations of the positive outcomes of eating, and by influencing how well an individual can put those thoughts out of mind once they are retrieved. For instance, Davidson et al. (42, 43) has proposed that memory inhibition plays a critical role in preventing memories of food from being retrieved in situations where food intake is undesirable, such as when an individual is already satiated or “full”. This automatic suppression of food-related information in response to satiety is thought to help individuals refrain from overeating in situations that would otherwise evoke food intake, such as when encountering food or food cues in the environment.

Consistent with the idea that reduced memory inhibition could contribute to overeating by failing to modulate the retrieval of food-related thoughts, studies in rats have shown that the same manipulations which increase an animals’ susceptibility to memory intrusions also increase cue-reactivity, food intake, and weight gain (for reviews, see 8, 9). In humans, it appears that memory control can also discriminate between individuals who do and do not lose control over their eating. For instance, “restrained eaters” (i.e., individuals who show an above-average preoccupation with monitoring their food intake in order to avoid overeating and weight gain; see (44)) are more likely experience memory intrusions, including intrusive memories of food, if they are obese versus normal weight (45). There are also reports that restrained eaters are more likely to experience memory intrusions if they are susceptible to external eating (i.e., eating in response to food cues in the environment; (46), but see 47). These findings are consistent with the possibility that individuals who tend to lose control of their food intake may have deficits in memory control that make it difficult for them to resist thinking about food when confronted with food cues.

In addition to modulating the likelihood that food cues in the environment will subconsciously and automatically evoke food-related thoughts, memory inhibition is important for enabling individuals to deliberately stop, suppress, or otherwise forget unwanted thoughts about food and eating. The influence of these two processes on food intake control are presumably linked, as it is typically those individuals who are the least capable of preventing food-related thoughts from being retrieved automatically by food cues in their environment who are the most likely to require deliberate thought-suppression in order to control the urge to eat. Unfortunately, attempting to suppress unwanted thoughts can often backfire, leading to an unusual increase in the frequency of those thoughts (48). In

regards to food intake control, this means that trying to control one's thoughts about food could lead to an undesirable increase in food-related thoughts, particularly in individuals who are predisposed to require effortful thought control (e.g., people who are preoccupied with thinking about food and/or exhibit decreased control over their food-related thoughts).

Consistent with this possibility, studies have shown that individuals who exhibit both an increased preoccupation with food and a reduced ability to control their food intake (i.e., restrained eaters who are obese and/or engage in external eating) are more likely to show a paradoxical increase in their frequency of food-related thoughts after attempting to suppress those thoughts (45) and are more likely to overeat after engaging in thought-suppression strategies (49, 50). These findings suggest that trying to resist thinking about food may have undesirable effects on food intake, particularly for individuals who already exhibit biased food->related processing and/or reduced cognitive control (e.g., weakened implicit memory inhibitory processing).

Attentional inhibition as a contributor of food intake control

Inhibition is thought to play a role in attentional control by enabling individuals to direct attention away from distracting stimuli in the environment (51). This type of inhibitory ability has obvious relevance to food intake control because our ability to resist eating when confronted by food cues depends partly on our ability to ignore those cues (see 52). It is likely that attentional inhibition and memory inhibition will interact to influence food intake (e.g., 53). Indeed, a recent study by Higgs et al. (54) showed that an attentional bias to food cues could be produced experimentally simply by increasing an individuals' preoccupation with thoughts of food. These results suggest that a reduced ability to control one's thoughts about food may increase one's risk of food-cue reactivity and external eating.

Evidence is mixed as to whether attentional biases to food (i.e., faster detection and or slower disengagement of attention to foods) causally contribute to weight gain in humans. Attentional biases to food cues have been reported in individuals who exhibit decreased control over eating, such as "external eaters" (i.e., individuals who eat in response to food-related stimuli, regardless of the internal hunger or satiety state (55-60)), obese individuals (61-65; but see 66-69), and binge eaters (70, 71). However, attentional biases have also been observed in individuals who exhibit increased control over eating, such as restrained eaters and anorexics (see 72). This observation is consistent with Higgs et al. (54) in that it suggests that anyone who shows an increased preoccupation with food and eating will probably exhibit an attentional bias to food, regardless of whether that preoccupation is with calorie-counting versus craving.

The types of foods that are the targets of the attentional bias may be one factor that determines whether an increased distractibility to food contributes to overeating. Calitri et al. (73) found that individuals who showed an attentional bias to unhealthy food words showed an 11 increase in BMI during a 12-week weight loss intervention; conversely, individuals who showed an attentional bias to healthy food words showed a decrease in BMI. Attentional biases to high-calorie food cues have also been associated with lower dieting success in individuals who engage in effortful food intake control, such as restrained eaters (e.g., 74). Thus, it appears that attentional biases could either help or hinder efforts to

control food intake depending on the types of foods that are attended to. Capitalizing on the possibility that healthy eating might be promoted by modifying participants' attention towards certain types of foods, recent experiments have attempted to increase subjects' attention to healthy foods (75) and decrease their attention to unhealthy foods (76). While these experiments have had mixed success in altering eating habits, they highlight the importance of multi-dimensional approaches to modifying eating behavior and acknowledge the importance of improving control over food-related cognitive processing.

While most of the work linking attentional control to control of food intake has focused on food-directed processing, there is some evidence that these attentional biases may occur as a result of more general attentional impairments, at least for individuals who are characterized by external eating. Compared to individuals with low external eating scores, individuals with high external eating scores report greater difficulty controlling their cognitive processes, specifically those related to task-shifting, distractibility, and preventing unwanted thoughts (77). Higher disinhibition scores and BMIs have also been related to slower completion of a traditional color-word Stroop task (78); but see (69). While speculative, these findings suggest that general attentional impairments might be at least partially responsible for the attentional bias to food cues observed in individuals who tend to lose control over their food intake.

Memory for recent eating as an inhibitor of food intake

So far we've discussed how basic inhibitory processes that minimize interference from memory intrusions and external distractors can also act to influence energy regulation by enabling us to suppress unwanted thoughts about food and ignore food cues in the environment. In particular, we've talked about how being able to prevent the retrieval of memories pertaining to food can help reduce external eating. However, there are times when our memories of food can benefit energy regulation.

Several studies have shown that our ability to correctly recall what we've eaten in the past plays an important role in limiting food intake in the present. For instance, it is well-known that our experience with eating a food can influence our expectations of its satiety (79) and, in turn, can influence how much of that food we decide to consume (80-82). In addition, studies in rats have shown that manipulations which promote uncertainty about the energy density / caloric content of a given food also disrupt the animal's ability to compensate for those foods at a subsequent meal, promoting overeating and weight gain (6, 83, 84). Thus, our ability to correctly and reliably recall the energy-density or satiating quality of a food can influence portion selection and meal size, thereby contributing to long term energy regulation.

What we recall about our prior eating can also exert more immediate effects on food intake. A variety of studies have shown that manipulations which decrease our ability to encode or retrieve the memory of one meal can result in increased food intake at the next meal (for reviews, see 85, 86). For instance, amnesic individuals who are unable to encode the memory of having recently eaten will eat two meals in succession and even begin consuming a third meal before it is taken away (87). Eating while distracted by the television or other media can also reduce encoding of a meal, leading to increased food

intake later on (88-90). Conversely, manipulations which increase participants' encoding of a meal have been shown to decrease subsequent food intake (91, 92). These results have led researchers to encourage people to engage in more "mindful" eating as a way to avoid overeating and potentially combat obesity (see 93).

One way in which our memory for recent eating may reduce future food intake is by altering our perceptions of hunger and satiety (94-96). For instance, a novel study conducted by Wansink et al. (96) used self-refilling soup bowls to examine the degree to which visual cues about portion size influence perceptions of satiation. They found that subjects who ate from self-refilling bowls did not report any increase in satiation, despite eating 73% more soup than individuals who ate from regular soup bowls. Using a similar procedure, Brunstrom et al. (95) had subjects eat from bowls that contained either a small (300 ml) or large (500 ml) portion of soup that was either surreptitiously filled or emptied by a peristaltic pump while the subject ate. Thus, the subjects' perception of how much soup they consumed was sometimes congruent (e.g., see 300 ml, consume 300 ml) and sometimes incongruent (e.g., see 300 ml, consume 500 ml) with the amount of soup they actually consumed. They found that subjects who were led to believe they consumed the larger portion of soup reported feeling less hungry 2-3 hours after eating than subjects who were led to believe they consumed the smaller portion of soup, regardless of their actual intakes. These findings suggests that people rely on their memory of what they've eaten when deciding whether or not they are hungry, implicating memory processes in the determination of satiation and satiety.

Behavioral inhibitory contributions to food intake control

A variety of evidence has emerged linking overeating and obesity with deficits in behavioral control. Researchers have found that obese subjects are less successful at withholding prepotent behavioral responses (12, 97) and have difficulty stopping their actions once they have been initiated (98-102). Obesity has also been associated with deficits in behavioral tasks that assess cognitive flexibility, the ability to adjust one's thinking, attention, and behavior in response to changing goals and/or environmental stimuli (e.g., 103), processes which depend heavily on inhibition (104). For instance, obese individuals are less successful at shifting away from previously-learned behavioral patterns than normal weight individuals (15, 68, 105, 106); but see 107), with increases in adiposity and BMI predicting worse task-shifting ability (14, 108, 109). Obese individuals also exhibit impairments in working memory and self-monitoring, processes that play a central role in cognitive flexibility (110-112).

Of particular relevance to the control of food intake are results indicating that obese individuals are at increased risk of losing control over their actions when those actions earn incentives. For instance, when given a choice between receiving an immediate small reward (i.e., food, money) or a larger delayed reward, obese individuals are more likely to choose the immediate reward whereas normal weight subjects are more likely to wait for the larger reward (113-116; but see 117, 101). Obese individuals also respond more *persistently* for rewards compared to non-obese subjects, even when the likelihood of earning those rewards declines the longer they respond (102, 99). These findings suggest that obese individuals are

more likely to start eating (and less likely to stop) when confronted by highly-palatable foods and food cues, implicating inhibitory deficits as a risk factor for overeating and obesity.

Supporting this possibility, studies have shown that deficits in behavioral control are associated with increased food intake (98, 118, 119), as well as increased body weight. For instance, studies in obese individuals have found that the ability to inhibit behavioral responses in a go / no-go task is inversely related to an individual's body weight and adiposity (12, 97). Others have observed that the degree to which an obese individual is successful at losing weight during a treatment program depends upon how much behavioral control they exhibit at baseline, with poorer behavioral control being associated with worse treatment outcomes (99, 100, 120). Particularly worrisome are studies linking impaired behavioral control with increased weight gain in children. For instance, studies have shown that children who are the least capable of delaying gratification (i.e., waiting to receive an incentive, such as a food or toy) at age 3-5 are more likely to be overweight at age 11-12 (121, 122). Weight-related differences in neural activation of brain areas associated with behavioral control have also been reported, with reduced activation predicting higher body weights and weight gain (123, 124) and increased activation being associated with maintenance of weight loss (125).

Perhaps the most compelling evidence implicating behavioral control as a causal factor contributing to obesity are studies showing that experimental procedures which reduce the ability to inhibit responses (or increase impulsivity) also increase food intake and vice versa. A study by Guerrieri et al. (126) showed that subjects who perform a stop signal task consisting of "go" trials and "stop" trials eat more food at a later ad-libitum "taste test" if they are administered a version of the task that prioritizes the "go" trials over the "stop" trials. Similar effects on food intake have been obtained simply by having subjects imagine themselves as being a more or less impulsive person (127, 128). Other studies have shown that interventions that enable individuals to "practice" inhibiting their responses to food cues can sometimes be successful at decreasing intake of that food (129; but see 130). Together, these results indicate that behavioral control is closely related to food intake control and that factors which reduce one's control over their actions may increase one's risk of overeating and weight gain.

Relationships between behavioral control and cognitive control of energy intake

It is worth pointing out that deficits in behavioural control are not necessarily distinct from the deficits in cognitive control discussed earlier in this paper (see 104, 131, 132). For instance, the ability to inhibit responding in a test of behavioral inhibition like the go/no-go task is likely to be influenced by the extent to which the retrieval of memories or stored associations that underlie the evocation of those responses can be inhibited (e.g., the memory that "X" → "go" and "Y" → "no-go"; see 133). Contemporary views accept the idea that Pavlovian conditioning involves memory, expectations, outcome revaluation and other cognitive processes (134-136). Accordingly, failures to inhibit responding in Pavlovian situations are interpretable as failures not merely in the control of behaviour but also in the control of the learning and memory processes that *underlie* behaviour. Indeed, as

noted previously, a variety of findings with animal models have identified important roles of the hippocampus and other structures critical for memory formation and associative learning in the control of behavior, including appetitive behaviors related to food-seeking and energy regulation (e.g., 137). It would seem odd if interpretation of the decrements in behavioral inhibition shown by humans failed to similarly acknowledge a potential role for these types of cognitive processes. Similar overlaps are likely to exist between the concepts of attentional control and memory control (e.g., 104). As mentioned earlier, the probability of attending to environmental stimuli will partly depend upon what information those stimuli retrieve from memory. Thus, the ability of food cues to catch our attention and evoke eating behavior will likely depend upon the extent to which an individual can inhibit the retrieval of the food-related memories associated with those cues. Future research investigating the links between these various inhibitory processes on food intake control will no doubt provide valuable information regarding the basis of obesity-related inhibitory impairments in humans and for devising multi-disciplinary interventions that can successfully counter the detrimental effects of these inhibitory deficits on energy regulation.

How does the obesogenic environment “overwhelm” the regulatory control of energy intake?

The very concept of an “obesogenic” environment implies that the environment causes obesity. While it is easy to suggest that factors such as the widespread availability of low-cost, energy-rich, and highly-palatable food “overwhelm” the physiological controls of energy-regulation, describing the mechanisms that underlie this loss of physiological control has been much more difficult. In an attempt to address this difficulty, we proposed a “vicious cycle” model of obesity and cognitive decline (7, 9, 42, 43). This model suggests that *eating* a WD rich in high-fat and high-sugar foods and fluids may lead to brain pathologies which decrease one’s ability to inhibit responding to food and food-related environmental cues, which in turn leads to *overeating* WD and excess weight gain.

Consistent with this account, a variety of studies have shown that consuming a WD can have adverse effects on the hippocampus and potentially other brain circuits and structures that contribute to the cognitive inhibitory control of behaviour. Studies in rats have shown that as little as 35 days of eating a WD is sufficient to compromise the integrity of the BBB (139) and that this loss of BBB protection impacts the hippocampus more than other brain structures. For instance, studies in WD-fed animals have shown that exogenous agents that are normally prevented from entering the brain are able to penetrate the BBB and gain increased access to the hippocampus but not the striatum, prefrontal cortex, or cerebellum (138-140). These findings suggest that consuming a WD could disrupt the ability of the BBB to “filter” out foreign, toxic, or other unwanted agents that could compromise hippocampal health and function. Indeed, eating a WD has been associated with a variety of pathological changes in the hippocampus, such as increased infiltration of microglia (27), decreased synaptic plasticity (152), and decreased neurogenesis (28)-- effects that are indicative of hippocampal dysfunction. Even more compelling is evidence showing that rats fed a WD are selectively impaired in solving learning and memory problems that are known to depend on the functional integrity of the hippocampus, but are unimpaired in solving

problems that do not depend on the hippocampus (for a review of these effects of WD on brain pathology and cognitive performance, see 8, 9). This latter finding argues against the hypothesis that performance deficits on hippocampal-dependent problems are the result of nonspecific deficits in motivational, reward, sensory processes, general behavioral competence, or global cognitive functioning because in many studies both the hippocampal-dependent and hippocampal-independent problems were trained concurrently in the same rats under the same conditions, with the same stimuli, rewards, and response requirements.

Like people, not all rats gain excessive amounts of weight when maintained on WD (141). Interestingly, some evidence suggests that the likelihood of weight gain depends upon the development of hippocampal dysfunction. Recent reports from our laboratory (138, 139) show that rats that exhibit WD-induced obesity (e.g., “diet-induced obese” or DIO animals) also exhibit greater impairments in both hippocampal-dependent learning and memory performance and BBB integrity compared to rats that resist the obesity-promoting effects of WD (e.g., “diet-resistant” or DR animals). These findings substantiate the link between WD intake, impaired hippocampal-dependent cognitive functioning, and excess body weight gain by showing that whether or not an animal gains weight on an obesogenic, Western-style diet is related to whether or not that animal exhibits hippocampal-dependent, cognitive-inhibitory deficits.

These data, combined with others described in this review, provide a basis for approaching question “how does the obesogenic environment overwhelm the physiological controls of intake?” It may be that the environment has become obesogenic because the cognitive mechanisms that normally moderate the ability of food-related cues to evoke appetitive and eating behavior are failing. One reason they are failing is because the consumption of WD interferes with the brain substrates (i.e., the hippocampus and related circuits) that underlie the operation of those cognitive mechanisms.

Impaired cognitive functioning: a “cause” or an “effect” of overeating?

Whether overeating produces cognitive dysfunction or cognitive dysfunction produces overeating may be another instance of the chicken and the egg. Indeed, we described our model as a vicious cycle of obesity and cognitive decline and it is often difficult to determine where such cycles begin. For example, environmental food cues may provoke overeating prior to the development of any cognitive-inhibitory problems. Likewise, overeating could originate from changes in brain areas (e.g., hypothalamas) or regulatory physiology (e.g., metabolic or hormonal disorders) that have little to do with cognition. Thus, one possibility is that overeating WD produces brain pathologies that subsequently disrupt the cognitive processes that help to inhibit intake. However, it is also possible that individual differences in cognitive-inhibitory control may predict one’s susceptibility to environmental food cues and, thus, act as a risk factor for overeating WD and obesity.

There are some data that favour the latter possibility. As noted above Riggs et al. (20) and Guxens (21) reported that, for at least some children, poor cognitive performance predicts subsequent excess gains in body weight. A recent study in our laboratory further explored this possibility. Davidson et al. (138) used cross-lagged panel correlations to provide information about the direction of the potential causal relationship between WD-induced

weight gain, adiposity, and cognitive dysfunction (Figure 1). For rats maintained on a Western-style diet, weaker performance on a hippocampal-dependent cognitive task at Day 24 was predictive of higher body weight and adiposity at Day 90. In contrast, the correlation between body weight and percent body fat at Day 24 with cognitive performance at Day 90 were both much lower and nonsignificant. Thus, while the adverse effect of consuming WD on cognitive function was a good predictor of subsequent weight gain and increased adiposity, the effect of that diet on weight gain and adiposity did not reliably predict subsequent cognitive deficit. Notably, neither of these cross-lagged correlations were significant for a control group maintained on a standard chow diet. These findings support the hypothesis that cognitive deficits precede and promote excessive energy intake and body weight gain.

Summary and Implications

We have reviewed a variety of evidence showing that Western diet, obesity, and cognition functioning are inter-related. This evidence suggests that mechanisms which underlie one's capacity to inhibit retrieval of memories related to food and eating, attention to environmental food cues, and the appetitive behaviors that are evoked by these memories and cues may be degraded for people who are overweight or obese or have been overweight or obese during their lifetime. We have also reviewed evidence which suggests that both excess body weight and cognitive dysfunction is related to intake of the Western diet, which includes high amounts of sugars and saturated fats. These types of food cues and this type of diet are ubiquitous in what has been referred to as our current obesogenic environment. We've suggested that Western diet-induced pathologies are partly responsible for making the current environment obesogenic because they interfere with the brain substrates important for providing cognitive inhibitory control, including control over food intake. We also considered the possibility that such diet-induced cognitive impairments precede and promote overeating of Western diets by reducing our ability to resist eating in response to food-related cues, subsequently promoting increased body weight and adiposity. This pattern of intake, interference with brain function, reduced cognitive inhibitory control, and increased responding to environmental food cues could lead to a vicious-cycle of progressively increasing intake of Western diet, increasing body weight, and cognitive decline.

One implication of this analysis is that deficits in memory inhibition are poised to impact cognitive function in more ways than simply promoting overeating. Indeed, our model suggests that a failure to resist engaging in external eating may be a symptom of a more systemic problem with memory interference control. By this account, it does not seem surprising that the majority of deficits that have been described in obese individuals are related to regulating, monitoring, and changing one's behavior — “executive functions” which are not only fundamental to carrying out any kind of goal-directed behavior but are also known to be highly dependent on inhibition and interference control (104). Deficits in the control of food-directed responding may appear sooner and be more obvious compared to deficits in inhibiting responses to other types of cues because food cues and food memories are more powerful elicitors of behavior compared to other types of cues and memories. More general interference effects, such as those assessed with typical memory

batteries, may emerge later in life as these cognitive impairments become more pronounced. Supporting this possibility are studies showing that individuals who exhibit midlife obesity are more likely to exhibit a variety of cognitive impairments later in life, including Alzheimer's Disease (AD)—a disorder characterized primarily by deficits in cognitive control and increased susceptibility to interference (142). Thus, efforts to counteract the obesity epidemic may be important not only for protecting one's physical and cognitive health in the short term but also for minimizing the risk of serious cognitive disorder over the long-term.

Much research with nonhuman animal models has focused on the role of the hippocampus as a substrate for the types of cognitive impairments we have discussed. However, it is likely that the hippocampus is a component of a larger system of structures and circuits that have a role in memory inhibition, in general, and energy regulation more specifically. Research in humans indicates that the inhibitory processes reviewed here are also involved in frontally-mediated "executive functions", some of which appear to involve important neuroanatomical connections to the hippocampus (see 53, 143-145). Studies exploring the link between Western-diet consumption, hippocampus and frontal lobe connectivity, and the contribution of this brain circuit to executive function are needed to further clarify how these brain systems interact to influence inhibitory processing and, thus, might be disrupted by consuming a Western diet.

Another question of interest relates to how quickly these WD-induced effects on cognition occur. In rodents, impairments in cognitive performance have been reported after 3 -7 days of continuous maintenance on the diet (146, 147) and signs of brain inflammation have been recorded after as little as 3 days (148). Interestingly, there is evidence that these early impairments in both cognitive function and inflammation undergo a transient recovery period before re-emerging after further exposure to the diet. These effects could be indicative of different mechanisms of early versus late-onset cognitive impairment. Alternatively, it is possible that early deficits are overcome by a compensatory neuroprotective response that becomes exhausted after continued exposure to the pathogenic diet, leading to the re-emergence of deficits. Further research is needed to elucidate the processes that are involved with the time course of the effects of WD on brain and cognitive functioning.

Finally, while we have talked rather broadly about the effects of WD on brain and cognitive functioning, we have not discussed all of the possible mechanisms by which WD might exert those effects. For example, WD is associated with a number of metabolic and hormonal changes that have been linked with deficits in hippocampal-dependent and other types cognitive functioning. These include changes in glucoregulation, insulin resistance, leptin resistance, and many others (e.g., 149-151). The relative importance of these changes and their potential roles as causes or effects of weight gain and/or cognitive dysfunction is a continuing question of interest.

The data and ideas discussed in this review also have implications for the types of treatment strategies that might be effective for both combating obesity and for preventing cognitive decline. It is more than a matter of reducing the intake of WD. While reducing intake of

unhealthy foods may be a sure way to reduce body weight and protect cognitive functioning, many of us are just not able to it. It may be that one of the reasons efforts at dieting and weight loss fail is because the cognitive inhibitory processes that fundamentally contribute to the control of behavior are compromised. This review suggests that one way to maintain or regain this control is to develop therapies that improve cognitive inhibitory functions and/or target emergent pathologies in the brain areas that underlie those functions.

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Highlights

Obesity is associated with cognitive impairment both in early and late life.

Certain cognitive impairments may reduce the inhibitory control of food intake.

These cognitive impairments can develop as a result of eating a Western diet (WD).

The “obesogenic” environment may be a product of WD-induced cognitive impairment.

Figure 1.
A vicious-cycle model of obesity and cognitive decline.