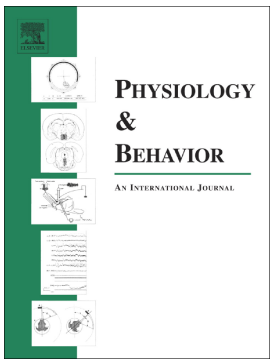

Dietary influences on cognition

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PII: S0031-9384(18)30113-6
DOI: doi:10.1016/j.physbeh.2018.02.052
Reference: PHB 12112

To appear in: *Physiology & Behavior*

Received date: 20 December 2017
Revised date: 27 February 2018
Accepted date: 28 February 2018

Please cite this article as: A.C. Reichelt, L.E. Stoeckel, L.P. Reagan, C.A. Winstanley, K.A. Page , Dietary influences on cognition. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Phb(2017), doi:10.1016/j.physbeh.2018.02.052

DIETARY INFLUENCES ON COGNITION

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Abstract

Obesity is a world-wide crisis with profound healthcare and socio-economic implications and it is now clear that the central nervous system (CNS) is a target for the complications of metabolic disorders like obesity. In addition to decreases in physical activity and sedentary lifestyles, diet is proposed to be an important contributor to the etiology and progression of obesity. Unfortunately, there are gaps in our knowledge base related to how dietary choices impact the structural and functional integrity of the CNS. For example, while chronic consumption of hypercaloric diets (increased sugars and fat) contribute to increases in body weight and adiposity characteristic of metabolic disorders, the mechanistic basis for neurocognitive deficits in obesity remains to be determined. In addition, studies indicate that acute consumption of hypercaloric diets impairs performance in a wide variety of cognitive domains, even in normal non-obese control subjects. These results from the clinical and basic science literature indicate that diet can have rapid, as well as long lasting effects on cognitive function. This review summarizes our symposium at the 2017 Society for the Study of Ingestive Behavior (SSIB) meeting that discussed these effects of diet on cognition. Collectively, this review highlights the need for integrated and comprehensive approaches to more fully determine how diet impacts behavior and cognition under physiological conditions and in metabolic disorders like type 2 diabetes mellitus (T2DM) and obesity.

Keywords: Fructose; insulin; obesity; impassivity; dementia; diabetes

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1. Introduction

There is emerging evidence for a direct effect of diet on neurocognition and mood and emotional function independent of effects due to obesity and cardiometabolic dysfunction. In non-obese individuals, short-term high fat diet exposure elicits decreases in cognitive function in the absence of changes in endocrine measures (plasma insulin or glucose levels) or increases in body weight [1,2]. Acute access to a high saturated fat and sugar breakfast also impairs hippocampal-dependent learning and memory in non-obese young adults and these cognitive deficits were correlated with changes in blood glucose levels [3]. These results from this study raise two important issues. First, it may well be that fasting glucose and insulin levels are not sensitive enough to capture subtle, but key changes in metabolism. Indeed, using the hyperinsulinemic/euglycemic clamp Hernandez and colleagues reported that even a single exposure to an oral saturated fat load can decrease whole-body insulin sensitivity by 25% [4]. This suggests that diet can have a rapid impact on metabolic function, which could in turn influence cognition. Collectively, these studies indicate that acute access to hypercaloric diets impairs cognitive function in otherwise non-obese participants. In addition, studies have also examined the relationship between chronic consumption of hypercaloric diets, metabolic disorders and cognitive function. In view of these observations, the goal of this review is to discuss how clinical and preclinical studies have begun to identify the underlying mechanisms through which diet impacts cognitive function. In addition, we discuss how diet contributes to the development of neurocognitive deficits observed in metabolic disorders like type 2 diabetes mellitus (T2DM) and obesity.

While the sections below describe how our ongoing studies contribute to the growing literature that is examining the effects of diet on different neurocognitive domains, we recognize that hypercaloric diets, high fat diets and highly palatable diets are not interchangeable as it relates to their compositions/formulations. For example, ‘high fat diet’ is a rather ambiguous

term since it is used classify a wide variety of diets that can differ significantly in their fat content (percentage fat), as well as the types of fats used. In addition, some investigators may supplement their HFD with sugars to further promote and/or accelerate metabolic and endocrine changes in rodents. This review highlights that perhaps it is more important to recognize that in spite of the differences in these dietary approaches (i.e. hypercaloric, sucrose/fructose, HFD, highly palatable diets), consumption of these diets consistently leads to impairments in cognitive function in both rodents and humans. Such observations suggest that common mechanistic mediators are likely responsible for the diet-induced cognitive deficits and that identification of these neural substrates represent an important advance in our ultimate goal of effectively managing the neurological consequences of metabolic disorders like T2DM and obesity.

2. Impact of high sucrose diets on memory encoding and retrieval

Excessive consumption of high sugar (sucrose) foods and drinks, which are cheap and readily available, plays a central role in the development of obesity and metabolic disturbances [5]. This increase in dietary sugar has been attributed to the widespread availability of relatively cheap sugar-sweetened beverages (SSBs); the largest single source of added sugar consumption worldwide [6]. Diet composition is known to have a profound impact on brain function [7,8]. Emerging research indicates that high sugar diets (HSDs) impair cognitive functioning even in the absence of extreme weight gain or excessive energy intake. [9,10]. Such observations suggest that the effects of HSDs on cognition may be insidious in nature, only becoming apparent when cognitive systems are taxed. The hippocampus, which is critically involved in spatial, contextual and episodic memory encoding, is particularly vulnerable to the deleterious effects of HSDs [10-14].

Neuropathological changes have been observed within the hippocampus following HSD consumption. In animal studies, markers of neuroinflammation, such as microglia activation

measured by IBA-1 immunoreactivity and increased hippocampal levels of pro-inflammatory cytokines such as interleukin(IL)-1β, IL6 and tumor necrosis factor-α (TNF-α), were observed in rats and mice exposed to HSDs [9,12,15]. Brain-derived neurotrophic factor (BDNF) is a signaling molecule that is intimately related to both energy metabolism [16] and synaptic plasticity [17], and promotes the survival, maintenance, and growth of neurons [18]. As it relates to the current discussions, consumption of hypercaloric diets high in both fat and sugar have been shown to reduce BDNF mRNA expression in the hippocampus [19,20]. These studies suggest that the mechanisms through which consumption of HSDs impair hippocampal neuroplasticity may include increases in pro-inflammatory cytokines, as well as decreases in neurotrophic factor expression, which may ultimately contribute to diet-induced cognitive deficits [21].

The hippocampus is important for place recognition memory [22,23], and as such many studies have utilized spatial memory protocols to examine the functional impact of hypercaloric (high fat and high sugar) diets on hippocampal function in rodents [11-13,19,24]. The benefit of these exploratory tasks is that they exploit the natural tendency of rodents to explore novel objects, and do not require animals to be motivated for foods, which may have altered incentive values following extended exposure to palatable diets. As such laboratories have utilized place recognition and object recognition as a non-spatial control test, regulated by the perirhinal cortex, and have found spatial-specific deficits in rats fed hypercaloric diets in as little as 5 days [19,24]. However, the diet induced spatial memory deficits are not present when discrete spatial cues are placed in the arena [24]. Such results suggest that hypercaloric diets may impact different aspects of learning and memory and that diet-induced behavioral deficits may become more apparent when task difficulty and cognitive demand are increased.

Studies have also examined cellular/molecular mechanisms of the cognitive deficits elicited by hypercaloric diets. For example, within the hippocampus the dentate gyrus (DG) plays a

critical role in memory encoding [25]. The DG is a site where proliferation of neuronal progenitor cells and their subsequent differentiation, migration and functional integration into the pre-existing circuitry occurs throughout the lifespan - a process called adult neurogenesis [26-29]. Animal studies indicate that diet, environmental enrichment and physical activity can modulate levels of hippocampal neurogenesis [30-35]. Conversely, HSD consumption in rats resulted in decreased markers of hippocampal neurogenesis in the DG measured by BrdU [15] and the neuroproliferation markers doublecortin and proliferating cell nuclear antigen (PCNA) immunoreactivity [36]. Adult neurogenesis in the DG is proposed to be a neural substrate for specific aspects of memory formation [37], in particular “pattern separation” - the process distinguishing and coding similar patterns of neural activity as distinct representations during memory encoding and storage. This is thought to decrease the probability of interference during memory recall [38]. In contrast, pattern completion refers to the process of recovering stored patterns from degraded retrieval cues during recall and retrieval of memory [38].

The Trial Unique Non-Match to Location (TUNL) task is a DG-dependent touchscreen automated test that measures pattern separation performance in rats [39] and mice [40]. The TUNL task uses two locations, a sample location which must be responded to by nose-poking the screen, followed by presentation of the sample and target location, and a correct response to the novel target location is reinforced with a food reward. As this task employs multiple locations across trials, a range of locations on the touchscreen are presented, allowing the systematic manipulation of the distance, and therefore the pattern separation load, between response locations (Figure 1, Panel A). Accordingly, the TUNL has the flexibility to place variable demand on pattern separation capacity [39-41]. The Reichelt lab has recently examined the effects of HSD on behavioral performance in the TUNL test. In this regard, preliminary data (Figure 1, Panel B) indicated that rats that were exposed to a HSD for 4 weeks prior to training and testing on the TUNL task showed impairments when there was a small

separation between the sample and target location, but not when there was a large separation. This indicates that HSD impaired performance when the pattern separation load was increased, again illustrating that test difficulty/increased cognitive demand are adversely affected by HSD. Furthermore, it is of note that these cognitive changes are observed in absence of weight differences between HSD and control animals, demonstrating that diet, rather than obesity, underpins the cognitive deficits.

An adapted version of the Spontaneous Location Recognition (SLR) task has been utilized to examine behavioral pattern separation in rodents [36,42-44]. In the SLR task (See Figure 2, Panel A), a rat is exposed to a spatial arrangement where identical objects are further apart (d-SLR; low pattern separation) or closer together (s-SLR; high pattern separation). After a 24 hour retention interval, the rat is then exposed to the arena again, which contains one object in a familiar location, and another, identical object is located mid-way between the other two objects (novel location). The s-SLR condition, which is cognitively taxing for rodents, requires greater demand on behavioral pattern separation processes than the d-SLR condition as the novel location is closer in spatial separation to the sample object arrangement. There is also evidence to suggest that performance on the s-SLR component is enhanced through intrahippocampal infusion of BDNF [42,43] and systemic administration of the gut-derived hormone ghrelin, indicating that hunger peptides may have an important role in pattern separation [44]. In these experiments, only performance on the small separation condition was affected, indicating separation-dependent effects. The SLR task has also been utilized to explore the effects of HSD-induced impairments in hippocampal learning and memory [36]. In this study, daily intake of 10% sucrose over 28 days induced deficits in spatial memory when objects were closer together (s-SLR) and spared performance when locations were spatially distinct (d-SLR), suggesting that HSD adversely effects hippocampal-dependent forms of learning involved in spatial pattern separation (Figure 2, Panel B).

Overall, these studies present evidence to suggest that hippocampal-mediated learning and memory can be assessed with pattern-separation tasks to determine subtle diet induced cognitive deficits that only become apparent when memory systems are taxed. Importantly, understanding that alterations in neuroplasticity and neuroproliferation underpin these deficits provides rationale for interventions that enhance these processes, such as aerobic exercise.

3. Neuroendocrine and behavioral responses to sugar

The results described above clearly indicate that exposure to hypercaloric diets impact behavioral performance in rodents. One important question is how these animal studies translate to the human condition. Such questions are clinically relevant and important since American diets (for example) are loaded with sugar. Recent estimates show that adults in the United States consume an average of 13% of their daily calories from added sugar, and children and adolescents consume about 16% of their daily calories from added sugars [45,46]. Excessive sugar consumption has been linked to increased risk for obesity, T2DM and cardiovascular disease [6,47-49]. In response to these findings, the World Health Organization issued recommendations that adults and children limit their intake of added sugars to less than 10% of daily calories and preferably less than 5% of daily calories (WHO, 2015). Similarly, the American Heart Association recommended that men consume no more than 9 teaspoons of added sugar and women and children no more than 6 teaspoons in a day [45,50].

The most common consumed sugar sweeteners are sucrose, a disaccharide containing 50% fructose and 50% glucose, and high fructose corn syrup, which is a mixture of free fructose and glucose in various ratios, but most commonly containing 55% fructose and 45% glucose [51]. While glucose and fructose are typically consumed together, evidence suggests that fructose and glucose have different effects on neuroendocrine systems involved in the regulation of appetite and food intake. Glucose and fructose are both monosaccharides with the chemical formula $C_6H_{12}0_6$, but they have different structures. Glucose contains an aldehyde

group at position 1 of the carbon chain, and it forms a six member pyranose ring structure in solution. In contrast, fructose contains a keto group in position 2 of its carbon chain and is present in solution as either a five member furanose ring structure or a pyranose ring structure [51].

In addition to having different molecular structures, fructose and glucose are handled differently by the body and the brain. Glucose is the main circulating sugar the bloodstream and the main fuel source for all of the cells in our body including the brain, which relies on a constant supply of glucose to meet its high energy requirements [52]. In contrast, very little fructose circulates in the bloodstream because the majority of fructose is extracted into the liver where it is metabolized [53]. In the glycolytic pathway, glucose metabolism is tightly regulated whereas fructose enters the glycolytic pathway at the triose phosphate level and bypasses the major control point catalyzed by phosphofructokinase. Thus, excessive fructose consumption can serve as an unregulated source of glycerol-3 phosphate and acetyl-coA, leading to increased lipogenesis [53,54]. Fructose and glucose also have different effects on the release of hormones involved in the regulation of appetite and food intake. When compared to the consumption of glucose, fructose results in a smaller rise in circulating levels of insulin, glucagon-like polypeptide-1 (GLP-1), and leptin, which are hormones that increase satiety and reduce hedonic related feeding [55-57]. Fructose consumption also fails to suppress the hunger hormone, ghrelin, to the same degree as glucose [56]. Thus, fructose may be less effective at suppressing hunger when compared to glucose. Furthermore, fructose was shown to reach a higher peak sweetness intensity compared to glucose [58] and may have different effects on taste pathways.

Over the last decade, emerging evidence has shown differential effects of fructose and glucose on brain pathways involved in appetite and hedonic feeding have been examined in both rodent models and in humans. Fructose and glucose were shown to have opposing effects

on brain pathways involved in appetite regulation in mice [59]. In this regard, the direct delivery of glucose into the brain of mice led to decreased food intake, whereas fructose stimulated food intake through differential effects on energy signaling pathways in the hypothalamus [59]. Evidence from studies in rat models also suggests that fructose and glucose have different effects on brain circuits involved in reward processing. For example, two weeks of fructose, but not glucose, consumption resulted in upregulation in the expression of hypothalamic endocannabinoid 1 receptor (CB1), a receptor involved in the rewarding aspects of feeding [60]. Behavioral studies in animals have also found differences in glucose and fructose on the hedonic aspects of feeding behavior. A recent study showed that intermittent access to 8% solutions of sucrose, glucose, or fructose resulted in different effects on sugar bingeing behavior in rats [61]. Fructose was shown to produce greater sugar bingeing than glucose after 4 to 6 days of intermittent access to the sugar solutions whereas sucrose had an intermediate effect relative to its monosaccharide components. Rorabaugh et al., suggest two potential interpretations of these findings: (1) the results could suggest that fructose produced greater sugar bingeing than glucose because it has a higher hedonic value; (2) glucose bingeing is more rewarding and produces less tolerance than fructose bingeing, and thus less glucose is needed to achieve a reward [61]. The work of Scalfini and colleagues have shown that intragastric infusions of glucose are more effective than isocaloric fructose infusions in conditioning flavor preferences and increasing intake in mice, which suggests that the post-oral actions of fructose may be less effective at engaging brain reward circuits than glucose in mice [62-64]. Species differences as well as variations in experimental procedures could contribute to differing findings on neurobehavioral components of reward-related responses to fructose and glucose, which highlights the need for future work in this area.

Collectively, studies in animal models have suggested that fructose and glucose engage brain energy signaling and reward pathways differently. Studies in the Page laboratory have

been aimed at understanding the brain, endocrine, and behavioral responses to acute ingestion of fructose relative to glucose in humans. In our first study, we used a magnetic resonance imaging (MRI) method called pulsed arterial spin labeling (PASL) to examine the hypothalamic cerebral blood flow (CBF) response to an acute ingestion of drinks containing fructose or glucose (75 grams in 296 mL) using a blinded, random order crossover design [57]. Twenty normal weight participants were studied in the morning after an overnight fast. Blood samples were collected at baseline and at 10-minute intervals after drink ingestion throughout the 60 minute MRI session, and appetite ratings were obtained before and 60-minutes after drink ingestion. We observed significantly greater increases in circulating glucose, insulin, and GLP-1 levels after glucose compared to fructose ingestion. Glucose and fructose also had significantly different effects on hypothalamic CBF (95% CI of mean difference, 1.87-14.70; P=0.014). Specifically, glucose but not fructose resulted in a significant reduction in hypothalamic CBF within 15 minutes of consumption. These findings support animal studies showing differential effects of fructose and glucose on hypothalamic satiety signaling pathways [59]. From an endocrine perspective, the disparate hypothalamic responses to acute fructose relative to glucose ingestion were associated with smaller increases in circulating levels of glucose, insulin and GLP-1, which may play a role in promoting feeding behavior.

To better understand the effects of fructose and glucose on brain and behavioral responses mediating the motivation for food, the Page laboratory embarked on another study that paired the ingestion of fructose or glucose with visual food cues, behavioral ratings of desire for food, and a decision making task that pitted immediately available food rewards against monetary bonuses delayed by one month [65]. Twenty-four non-obese volunteers participated in a blinded, random order, crossover study with ingestion of either fructose or glucose (75 grams in 296 ml). Study sessions were performed in the morning after an overnight fast. Blood samples were obtained at baseline and at 30 and 60 min following drink ingestion for analysis of

hormones involved in appetite regulation. The food cue task examined the effects of fructose and glucose ingestion on both neural and behavioral food-cue reactivity and included twelve blocks of food cues and nonfood cues presented in a randomized block design. At the end of each block, participants rated their hunger and desire for food. Blood oxygen level dependent (BOLD)-functional magnetic resonance imaging (fMRI) was used to study the effects of acute ingestion of fructose compared to glucose on brain food cue reactivity.

Following the food-cue task, participants underwent a decision-making task in which they made choices between a visually presented high-calorie food reward available immediately after the session and a visually presented monetary reward delayed by 1 month. The delay was used to model real-life situations in which the benefits of turning down high-calorie foods come later in time. Each session included six presentations of each of 10 food items that were rated as very attractive by the participant during pretesting. On a food item's first presentation within a session, the monetary alternative was set to the market price for the item, "discounted" for the 1 month delay using a participant specific estimated discounting based on a monetary intertemporal choice procedure completed during pretesting [65]. On subsequent presentations of the food item, the amount of money offered as its alternative was titrated up or down in order to find a switch point, or a point at which the alternative item was selected. At the end of each fMRI session, bonus earnings (i.e., immediate food reward or delayed monetary reward) were determined by randomly drawing a trial from the food-decision task. The results from this study revealed that the ingestion of fructose compared with glucose resulted in smaller increases in plasma insulin levels and greater brain responses to food cues in the visual cortex (in whole brain analyses, corrected for multiple comparisons) and left orbital frontal cortex (in region of interest analysis). Parallel to the neuroimaging findings, fructose compared to glucose provoked greater ratings of hunger and desire for food and a greater willingness to give up long-term monetary rewards to obtain immediate high-calorie food rewards [65]. These findings

suggest that the acute ingestion of fructose relative to glucose results in greater activation of brain regions involved in attention and reward processing and may promote feeding behavior.

Collectively, both animal and human studies have shown differential effects of fructose and glucose on brain and endocrine systems involved in the regulation of appetite and food intake. These studies provide new insights into how the individual components of added sugar sweeteners may influence feeding behavior. It is important to note that our proof of concept studies in humans used relatively high doses of fructose and glucose to maximize the chances of detecting differences. In addition, fructose and glucose are rarely consumed in isolation because, as mentioned earlier, common sugar sweeteners include both fructose and glucose in almost equal amounts. Moreover, these studies were aimed at understanding the acute effects of fructose and glucose on neuroendocrine pathways, and the effects of chronic consumption of these monosaccharides were not studied. Therefore, there are a number of important questions that will require further investigation. Future work should examine neurobehavioral and hormone responses to lower doses of fructose and glucose and to "real-world" added sugar sweeteners (i.e., high fructose corn syrup or sucrose). Determining the effects of habitual consumption of high amounts of sugar (total sugar as well as the monosaccharides, fructose and glucose) on neuroendocrine circuits is also an important future direction. Moreover, while the studies discussed in this section were focused on the effects of fructose compared to glucose on neural processes related to appetite, reward, and motivation, the differential effects of fructose vs. glucose on cognitive processes such as executive function, memory, and impulsivity remains an important area of investigation.

4. Macronutrient intake and impulse control

As the studies described above were performed in otherwise non-obese humans and animals, an important question is whether these responses to hypercaloric diets and sugars are modulated in individuals with obesity or insulin resistance. Indeed, no country in the world has

successfully decreased the proportion of its populations now classified as obese or overweight, despite numerous public health campaigns and fitness initiatives [66]. It would appear that something is missing in our understanding of how the food we eat affects our weight, and that factors are at work beyond a simple "calories in-calories out" equation. The ingestion of highly palatable foods, particularly those containing substantial amounts of fat or sugar, has been unequivocally linked to weight gain and obesity. Our widely-acknowledged tendency to lose control over consumption of these appetitive foods has led to debate over whether obesity should be considered as part of the addiction spectrum rather than purely a metabolic disorder [67-70].

From a neurobiological perspective, both addictive drugs and highly palatable foods increase dopamine release in the reward centers of the brain, and maladaptive changes in dopamine signaling have long been implicated in the etiology of addiction. In particular, a reduction in striatal $D_{2/3}$ receptor density has been observed repeatedly in diverse populations of drug users [71], and has also been documented in obese subjects [72]. Impulsivity—the tendency to act without sufficient forethought or concern for the outcome—has likewise been strongly associated with both drug addiction and weight gain (e.g. [73-76]. Furthermore, significant comorbidity has been reported for obesity, as defined as a body mass index greater than 30, and psychiatric disorders associated with high impulsivity, such as attention-deficit hyperactivity disorder [77-79], bipolar disorder [80-82], and pathological gambling [83,84].

One explanation for this relationship is that high impulsivity, and low striatal $D_{2/3}$ receptor expression, may act as pre-existing vulnerability factors for obesity and other addictive behaviors, and simply facilitate consumption of appetitive food and drug rewards [85,86]. However, newer findings are challenging the directionality of this relationship. For example, recent data suggests that obesity may drive the symptom manifestation and severity of bipolar disorder [87]. It has also been shown that chronic consumption of high-fat diets, even in the

absence of excessive weight gain, can alter the behavioral response to dopaminergic drugs in rats [88-90], and that such effects may be particularly pronounced using diets rich in saturated fats [91]. Similarly, other rodent studies have suggest that individual differences in the degree to which ingestion of high-fat diets modulate striatal dopaminergic signaling can dissociate obesity-prone vs obesity-resistant animals [92,93]. As such, data from animal models suggest that both pre-existing and hypercaloric diet-induced changes in the sensitivity of the dopamine system may contribute to vulnerability to obesity [94,95].

Rodent models of impulsivity, based on neuropsychological tests used to measure this behavior clinically, have been extensively validated, and can be useful in parsing the causal nature of relationships that is otherwise difficult to deduce from clinical data alone [96-98]. Importantly, it has been found that rats which make high levels of impulsive actions are more likely to take cocaine and eat highly palatable food in a compulsive manner, and also show reduced striatal $D_{2/3}$ receptor expression [99-101]. Recent data from the Winstanley lab using one such behavioral assay of impulsivity, the five-choice serial reaction time task (5CSRT), suggest that macronutrients themselves may be able to alter this form of cognition. In this regard, long-term (twelve weeks) consumption of a high fat diet decreased impulse control and D_2 receptor expression in the rat striatum [102]. Furthermore, these changes happened in animals that were food-restricted; their daily calorie intake was designed to maintain their weight at 85% of a free-feeding animal. These animals were therefore not obese, but the diet they were fed caused behavioral and neurobiological changes that would theoretically put them at risk for compulsive overeating that could increase risk for obesity or lead to more severe obesity. Animals eating the same number of calories, but from a high-sugar diet, did not exhibit any such increase in impulsivity, and their behavior and dopamine receptor levels matched those of animals eating the calorie-equivalent amount of a control diet.

The potential significance of these findings may be considerable. Firstly, they imply that eating a disproportionately high number of calories from fat, even if total caloric intake is within recommended levels, could put individuals at risk of developing obesity due to the changes such a diet has on the brain and behavior. These observations could explain why some attempts at dieting still result in excessive weight gain over time, and caution against unbalanced diets. Such data also re-emphasize the necessity of considering the brain to be an organ of the body as much as an organ of the mind. The idea that nutritional variables will affect heart rate and blood pressure is well-accepted by most. However, the realization that dietary changes can also affect the biological functioning of the brain and seriously impact cognitive function has yet to fully penetrate our social consciousness, with possibly disastrous consequences as the obesity pandemic threatens to overwhelm healthcare services. These data also support the hypothesis that targeting impulse control with therapeutic interventions may be useful in improving health outcomes [103,104].

However, oversimplifying the relationship between cognitive processes and weight gain risks severely limiting the benefits of their discovery. With this in mind, it is important to note that obesity and excessive weight gain isn't necessarily associated with elevated impulsivity. As a further example of such dissociations, leptin knockout rats, which exhibit an obese phenotype characterized by numerous markers of metabolic dysfunction, are not more impulsive at baseline (Adams, Winstanley and co-workers, *submitted to this special issue*). Although these animals took longer to learn the 5CSRT, their performance was largely indistinguishable from their wild-type (WT) litter mates once a stable, asymptotic behavioral baseline has been reached. Switching animals onto a high fat diet for four weeks also did not differentially affect WT vs leptin knockout rats, with all animals showing signs of enhanced motivation on task. Although leptin knockout rats were more sensitive to the ability of the psychostimulant amphetamine to subsequently promote impulsive responses, potentially indicative of alterations

in the mesolimbic dopamine system, no difference in levels of accumbal D_2 receptors were observed ex vivo. As such, leptin deficiency is not associated with marked impairment in cognitive processes in a manner that may facilitate weight gain, even though this genetic manipulation engenders obesity. The ability of certain hypercaloric macronutrients to increase impulsivity, and thereby potentiate pathological overeating, is just one route to weight gain, and such neurocognitive changes may not be a hallmark of overconsumption. These findings fit with current thinking and suggest that obesity can arise through a variety of biological and environmental factors, including hormonal imbalance and the breakdown of homeostatic control over food intake [105]. Successful treatment may depend on the targeting of different mechanisms across individuals, requiring a "personalized medicine" approach rather than "one treatment fits all".

5. Diet and Obesity: linking obesity and dementia

Along with a sedentary lifestyle, diet is also considered to be a causative factor in the development of obesity and T2DM [106]. In addition to the well described consequences in the periphery, metabolic disorders also have structural and functional consequences in the CNS. For example, epidemiological studies revealed that both T2DM patients [107] and obese subjects [108] have increased risk of developing dementia. Moreover, consumption of diets high in saturated fats and refined carbohydrates are associated with neurocognitive dysfunction, including increased risk for mild cognitive impairment and dementia [109]. Moreover, obesity is associated with impairments in decision-making, planning and problem solving (all of which are features of executive function) with less evidence for associations with other cognitive domains, such as verbal fluency and learning and memory [110]. Beyond executive function, obesity is associated with alterations in appetitive functions, such as, reinforcement learning and effort, food cue reactivity and incentive motivation, all of which are regulated by neural systems that support executive functions [111,112]. Obese individuals are also more impulsive [113], show

increased delay discounting or greater preference for immediate vs. future rewards [114], and have impairments in negative outcome learning [115]. Indeed, many studies suggest that incentive motivation, reward learning and executive function are most affected in adults with obesity [116]. However, it should be noted that these behavioral changes could be due to increased incentive salience and reactivity to appetitive cues, decreased control of behavior by goal directed circuits, or decreased self-control due to impairment in learning to avoid negative outcomes [112].

From a mechanistic perspective, these cognitive deficits in obesity may result from decreases in neurotrophic factor expression, increases in oxidative stress and neuroinflammation, as well as structural and functional deficits in brain regions like the hippocampus and prefrontal cortex [109]. For example, impairments in executive function may be related to obesity-associated structural brain changes and reduced brain connectivity in the parietal and prefrontal cortex (among other brain regions/networks) that link to reward and associated brain networks of relevance to obesity [117-121]. Altered reward-related neural responses to food cues appears to be more pronounced in obese individuals with prediabetes and more components of the so-called metabolic syndrome [122]. In addition to cortical connectivity, metabolic disorders also impact the structural and functional integrity of the hippocampus. In this regard, deficits in hippocampal-dependent (associative), but not hippocampal-independent (item), memory is associated with central, but not whole body adiposity [123]. Moreover, hippocampal atrophy is observed in humans with obesity [124], as is altered hippocampal white matter connectivity [125] and functional connectivity [126] 2017). An important caveat associated with these structural analyses in humans is that metabolic function was not assessed. This may be particularly relevant to how deficits in brain insulin signaling contribute to these cognitive impairments.

Brain insulin resistance is the failure of brain cells to respond to insulin and may result from decreased BBB transport of insulin, decreased insulin receptor binding activity or faulty activation of insulin signaling cascades [127]. Brain insulin resistance reduces neuroplasticity, which may manifest itself through impaired receptor regulation or neurotransmitter release in neurons, impaired neuronal glucose uptake in neurons expressing insulin responsive GLUT4, or impaired inflammatory responses in glial cells in response to insulin. Additionally, the existing literature strongly support the concept that brain insulin resistance is a causative factor in cognitive decline [128]. For example, studies by Arnold and coworkers determined that AD patients exhibit hippocampal insulin resistance and that the degree of cognitive decline observed in these patients was associated with the magnitude of hippocampal insulin resistance [129]. Such studies provide an example of the important relationship between hippocampal insulin resistance, AD and metabolic disorders [130,131]. In support of these observations in humans, the Reagan lab has demonstrated that insulin resistance restricted to the hippocampus induces deficits in hippocampal neuroplasticity that include impairments in hippocampal-dependent learning and memory in rats [132]. These results support the concept that brain insulin resistance may occur somewhat independently of changes in glucose homeostats and insulin sensitivity in the periphery [116,128]. Since intranasal insulin (INI) administration enhances cognitive function in normal non-obese controls [133] and in patients with AD [134], INI combined with neuroimaging and neuropsychological testing may be a useful paradigm for the *in vivo* assessment of “brain insulin resistance” [135].

6. Summary and Perspectives

While the studies described above highlight the provocative advances related to how diet modulates behavior and cognition, many questions remain. To begin, these studies highlight the need for integrated and comprehensive approaches that include cellular/molecular, endocrine/metabolic, structural and functional neuroimaging, and detailed neuropsychological

and behavior measures to represent the complexity of how diet impacts cognition. Just as importantly, such analyses will need to be performed in both non-obese subjects and in subjects with metabolic disorders (T2DM, obesity, insulin resistance). Indeed, while epidemiological studies provide essential information related to the world-wide obesity crisis, these studies cannot identify the mechanistic basis for the increasing rate of obesity and perhaps more importantly how obesity reduces synaptic plasticity in the CNS. This includes the increased risk of neuropsychiatric co-morbidities like depression, bipolar disorder, anxiety, and addiction among individuals with metabolic disorders. Such analyses will not only be critical to determine the neuronal circuits through which diet modulates higher cognitive function, but are also a requisite first step towards identifying and developing practical interventions in the treatment of the neurological consequences of obesity. Indeed, epidemiological studies suggest that introduction of a more healthy diet positively impacts cognitive domains. In this regard, review of the clinical literature indicates that Mediterranean-style diets combined with DASH (Dietary Approaches to Stop Hypertension), referred to as MIND (Mediterranean-DASH for Neurodegenerative Delay) slow the progression of age-related cognitive decline and the development of Alzheimer's disease [136,137]. Moreover, weight loss induced by dietary changes [138-140] reverses neuroplasticity deficits in obese rodents, thereby supporting data indicating that lifestyle interventions effectively improve cognitive function in obese patients. This includes studies indicating that weight loss achieved through bariatric surgical procedures is associated with elevations in cognition and mood [141-146]. Such results suggest that the deleterious effects of diet on cognitive measures may be amenable to intervention. Nonetheless, these studies have not yet unequivocally identified the factors that are necessary for the beneficial effects of weight loss in the CNS, or have they identify which metabolic parameters are not responsive to intervention. Moreover, it is unlikely that a single factor is responsible for the neuroplasticity deficits observed in obesity, insulin resistance and T2DM. Only through appreciation and understanding of these limitations can we identify opportunities

to effectively address the long-term consequences of metabolic disorders on the structural and functional integrity of the CNS.

Acknowledgments

Supported by Australian Research Council (Discovery Early Career Research Award DE140101071; ACR); the Department of Veterans Affairs (IO1 BX001804 and I21 BX002085; LPR); Canadian Institutes of Health Research (CAW: PJT148631), Natural Sciences and Engineering Council of Canada (CAW: RGPIN 341483-12), philanthropic donations provided by Paul and Diane Erickson and the Gillespie Family (CAW). Michael Smith Foundation for Health Research (CAW); National Institutes of Health, NIDDK R01DK102794 (PI: KP), Doris Duke Charitable Foundation Clinical Scientist Development Award 2012068 (PI: KP), and American Heart Association Beginning Grant in Aid (PI: KP).

Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the above stated funding agencies. The authors have no conflicts of interest to declare.

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Figure legends

Figure 1. A) Schematic of the TUNL task showing the location of a sample stimulus, followed by the sample and target on an array with either a large or small separation. B) Preliminary data showing TUNL performance (% correct) in control and high sucrose diet rats [N=8 / group, One way ANOVA with between subjects factor of diet (control, sucrose). Large separation ($F(1,14) = 0.043$, $P = 0.84$; small separation ($F(1,14) = 7.34$, $P = 0.02$). * = $P<0.05$].

Figure 2. Figure 2. A) Schematic representation of the SLR task and spatial arrangement of the objects in the d-SLR and s-SLR component. B) Performance of control and high sucrose diet rats during the d-SLR and s-SLR tasks. Discrimination ratio = (Time novel – Time familiar) / (novel + familiar) (Time novel + Time familiar). N's = 6 per group. *** = $P<0.001$. Adapted (with permission) from Reichelt, A.C., Morris, M.J., Westbrook, R.F., 2016. Daily access to sucrose impairs aspects of spatial memory tasks reliant on pattern separation and neural proliferation in rats. Learning & memory 23, 386-390.

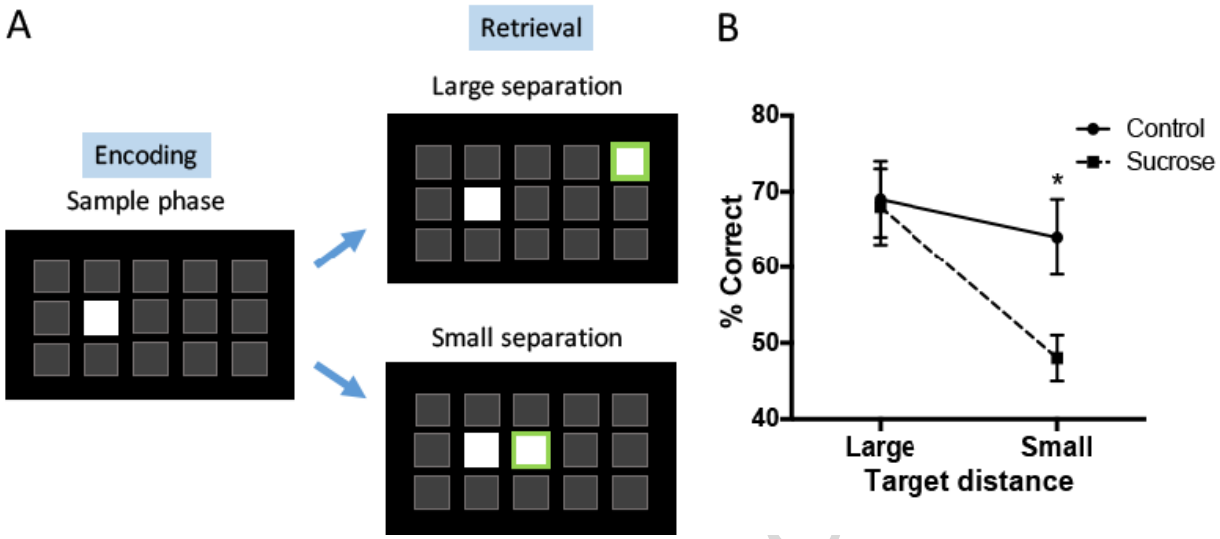

Fig. 1

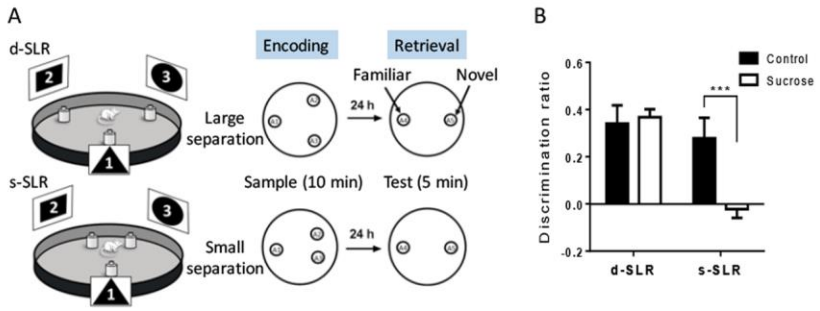

Fig. 2

Highlights

- Acute intake of hypercaloric diets impairs cognition, even in healthy subjects
- Diet is proposed to be an important contributor to the development of obesity
- High sucrose consumption elicits neuropathological changes in the hippocampus
- Fructose ingestion activates brain regions involved in attention and reward
- High fat diet decreases impulse control and striatal D_2 receptor expression
- Brain insulin resistance is a mechanistic link between obesity and dementia