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The Outward Spiral: A vicious cycle model of obesity and cognitive dysfunction

Sara L. Hargrave[a], **Sabrina Jones**[b], and **Terry L. Davidson**[c]

Sara L. Hargrave: Hargrave@american.edu; Sabrina Jones: sj8677a@student.american.edu; Terry L. Davidson: terryd@american.edu

[a]Center for Behavioral Neuroscience, Department of Psychology. American University. Washington, DC 20016, USA

[b]Center for Behavioral Neuroscience, Department of Psychology. American University. Washington, DC 20016, USA

[c]Center for Behavioral Neuroscience, Department of Psychology. American University. Washington, DC 20016, USA

Abstract

Chronic failure to suppress intake during states of positive energy balance leads to weight gain and obesity. The ability to use context – including interoceptive satiety states – to inhibit responding to previously rewarded cues appears to depend on the functional integrity of the hippocampus. Recent evidence implicates energy dense Western diets in several types of hippocampal dysfunction, including reduced expression of neurotrophins and nutrient transporters, increased inflammation, microglial activation, and blood brain barrier permeability. The functional consequences of such insults include impairments in an animal's ability to modulate responding to a previously reinforced cues. We propose that such deficits promote overeating, which can further exacerbate hippocampal dysfunction and thus initiate a vicious cycle of both obesity and progressive cognitive decline.

Introduction

There is mounting neuroanatomical and behavioral evidence that the hippocampus is a primary brain substrate for the control of food intake (for reviews see [1, 2]). For example, the hippocampus receives neural input from brain areas involved with the detection of metabolic signals, the perception of internal cues, taste, and reward. It is also the site of receptors for a multitude of neurochemical signals (e.g., cholecystokinin, leptin, insulin, glucose, ghrelin) that are known to contribute to energy intake and body weight regulation. In addition, hippocampal neurons project to multiple brain areas that are important substrates for energy balance and ingestive behavior [3, 4]. Furthermore, the hippocampus is

Correspondence to: Sara L. Hargrave, Hargrave@american.edu.

critically involved with cognitive processes (e.g., memory, decision-making) that animals may use to determine when to eat [5, 6]. Accordingly, it should not be surprising that interference with hippocampal functioning would have adverse consequences for the control of eating and appetitive behavior.

Recent evidence shows that consuming energy dense "western" diets has harmful effects on the hippocampus [7–9]. We and others have proposed that intake of such diets could invoke a vicious cycle (see F.1) of hippocampal dysfunction and impaired inhibitory cognitive control of responding to environmental food cues, resulting in excess intake, obesity, and further hippocampal dysfunction [2, 10–12]. In this review we describe the associative underpinnings of this vicious cycle and highlight recent findings pointing to the neurobehavioral mechanisms that may initiate and perpetuate it.

The Model

Functions of the hippocampus

The hippocampus is recognized as an important substrate for the encoding and retrieval of both spatial and several nonspatial forms of memory [13]. Recent data indicate that the hippocampus is also needed for decision-making processes, especially those involved with response selection in the face of conflicting or ambiguous information [14]. For example, the hippocampus has been implicated in resolving approach-avoidance discrepancies in situations in which two opposing response tendencies are experienced simultaneously [15, 16]. Other findings suggest adaptive response selection is based on the contribution of the hippocampus to the context-dependent inhibition of approach tendencies [14, 17, 18]. The retrieval of situationally-appropriate memories by contextual cues and the reduction of interference by memories formed in other contexts are also considered functions of the hippocampus [19, 20].

Contextual control of conflict resolution in ingestive behavior

The model diagrammed in F.2 (adapted from [11]) shows how interoceptive "satiety" states may serve as contextual stimuli that animals can use to resolve ambiguities associated with whether or not to perform appetitive responses. Specifically, that diagram indicates that food and food-associated environmental stimuli are embedded concurrently in two conflicting associations. The excitatory association enables food cues to retrieve the memory (formed when animals eat food when *they are not food sated*) of hedonically-positive post-ingestive consequences. The retrieval of this memory promotes appetitive responding to food-related external cues.

However, food cues do not always signal that the post-ingestive consequences of intake will be positive. For example, when an animal's energy needs have been satisfied (i.e., *they are food sated*), the post-ingestive consequences may be neutral, or even aversive. This circumstance results in the formation of an inhibitory association that opposes the capacity of the excitatory association to excite the memory of the post-ingestive reward. Thus, when encountering external food cues animals must resolve the ambiguity produced by these conflicting associations to determine whether or not to engage in appetitive behavior. According to F.2, animals can solve this problem because their satiety signals act as

contextual stimuli [21] that retrieve the memory of the inhibitory association, thereby antagonizing the ability of the excitatory association to retrieve the reward memory. The conflict is thus resolved in favor of refraining from engaging in appetitive and consummatory behaviors. As discussed above, this role for satiety signals describes a hippocampal-dependent function.

Supporting data

Hippocampal insult disrupts the inhibitory control of feeding

The case of Henry Moliason (a.k.a. H.M.) provided early evidence for hippocampal involvement in the control of intake [22] Following bilateral medial temporal lobectomy that damaged his hippocampus, H.M. not only exhibited anterograde amnesia so severe that he was unable to recall a meal he consumed a few minutes earlier, he would consume a second full meal minutes later and rate himself no more satiated after, compared to before, eating. Subsequent studies showed that rats with hippocampal damage more selective than H.M.'s increase their meal frequency [23], exhibit greater response perseveration on progressive ratio schedules [24] and show impairments in their ability to discriminate among their deprivation states [25, 26].

Recent findings also substantiate hippocampal involvement in feeding behavior. For example, temporary inactivation of the dorsal hippocampus in rats decreases intermeal intervals [27], suggesting a diminished capacity for satiety signals to inhibit intake during the period following a meal. Furthermore, the conversion of circulating triglycerides to fatty acids increases following food intake, providing a source of satiety signals detectable in the brain [28]. Interference with this conversion in the dorsal hippocampus increases weight gain in rodents [29]. In the ventral hippocampus, activation of receptors for the anorectic peptides leptin and GLP-1 decreases food intake and appetitive behavior based on food rewards [30, 31], whereas direct administration of the orexigenic hormone ghrelin (which presumably antagonizes satiety signaling) increases meal frequency and the ability of environmental food-related cues to stimulate eating [32]. These results suggest that interference with the hippocampal processing of either anorectic or orexigenic promotes positive energy balance.

Imaging studies in humans also provide evidence that the hippocampus is included among a group of feeding-related brain substrates that are influenced by both interoceptive satiety signals and external food cues. For example, consistent with the rodent findings noted above, a recent fMRI study with humans showed that the effect of satiation on the hippocampal response to palatable and energy-dense food was specifically associated with the meal's ability to increase triglyceride, and reduce ghrelin, levels [33]. Hippocampal activation is also modulated as a function of obesity and feeding state by interoceptive signals of gastric distension [34] and by visual images of foods [35].

Such findings supports the associative model depicted in F.2, by providing evidence that (a) the hippocampus is sensitive to physiological signals that are informative about energy state; (b) appetitive behavior is altered by manipulations that influence the detection of those signals hippocampal receptors; (c) that hippocampal activation in responses to food-related

cues is modulated by those signals; and (d) that disruption of hippocampal function has adverse effects on the ability to detect or use energy state cues to control the power of food cues to evoke eating and appetitive behavior after energy homeostasis has been achieved.

Links between diet, obesity and hippocampal dysfunction

Saturated fat and simple sugar intake is strongly associated with weight gain, and diets high in these macronutrients are common throughout the United States [36, see F.3], Europe [37], and other Western and Westernized societies with high obesity rates. There is increasing evidence that consumption of these "Western Diets" (WD) can induce cognitive deficits and perturb hippocampal function. Recent evidence indicates that even relatively short-term consumption of a WD is associated with signs of hippocampal pathology. For example, 10 days maintenance on a WD led to reduced hippocampal and hypothalamic mRNA expression of GLUT1 and MCT1, genes involved in the transport of glucose and monocarboxylates (e.g., ketones, lactate, pyruvate), respectively [38]. Elevated levels of cell death in the hippocampus have also been reported after three days of WD exposure [39].

Extended maintenance on a WD leads to more pronounced neurological consequences. It has been known for some time that WD can lead to neuroinflammation [40–45] and reduced hippocampal and hypothalamic levels of brain-derived neurotrophic factor (BDNF) [46–48], a protein that serves to promote neurogenesis, synaptic transmission, and memory performance [46, 49–51]. Current research has demonstrated that sustained WD access can also impair long-term potentiation (a potential cellular mechanism for learning and memory) in the hippocampus and greater hippocampal formation [52, 53]. Further, WD consumption induces microglial activation in the hippocampus, which is improved following roux-en-y gastric bypass surgery and caloric restriction [54, 55]. Contemporary research by our laboratory has established that WD maintenance can alter the blood-brain barrier (BBB), a critical interface between the cirulatory and nervous systems. This BBB damage is indicated by reduced expression of the tight-junction proteins that comprise the BBB [56], and increases in BBB permeability to molecular tracers such as sodium fluorescein. These pathologies are most pronounced in the hippocampal formation [56, 57], which is believed to be especially vulnerable to insult as a result of its high nutrient demands and pronounced cellular plasticity [58].

It is currently unclear whether these pathological events influence each other, or occur independently. Neuroinflammation, for instance, has been shown to induce neurodegeneration [41, 59, 60] and BBB remodelling [61–63] under some circumstances. However, BBB damage (and the subsequent infiltration of blood-borne toxins) can also promote inflammation, microglial activation, and cell death; for this reason, BBB breakdown is hypothesized to contribute to the progression of neurodegenerative conditions such as Alzheimer's disease and multiple sclerosis [64].

Maintenance on a WD impairs performance on hippocampal-dependent tasks

Consistent with evidence of hippocampal injury, WD-fed rodents are selectively impaired at numerous hippocampal-dependent tasks. The earliest of these reports indicated that diet could alter spatial performance in the Morris Water Maze [47, 65]. Subsequent reports

confirmed and expanded these findings, first indicating that WD maintenance led to increased spatial reference and working memory errors on a radial-arm maze [66] and more recently demonstrating delayed acquisition and a bias toward a non-spatial "response" strategy on a two-arm choice task [67].

Another recent study showed that WD-fed rats that become obese, exhibit elevated hippocampal expression of the cytokine IL-1β, and show impairments on tasks of contextual fear conditioning. This behavioral effect was normalized after maintenance on standard laboratory chow or antagonism of the IL-1 receptor, indicating cytokines may influence hippocampal-dependent cognition, though the mechanism behind this effect is not yet known [42]. Recently, it has been demonstrated that performance on hippocampal-dependent relational memory was perturbed in children with high levels of abdominal adiposity [68], or high saturated fatty acid intake [69], indicating these effects translate to humans and may impact individuals even at a young age.

We have also observed impairments in hippocampal-dependent serial feature negative (sFN) discrimination performance [see 70] after WD exposure [56]. This finding is of special interest because sFN perforamnce appears to require rats to learn a set of associative relations analogous to that shown in F.2, except that external cues are substituted for satiety signals [11]. Performance of the same rats on a hippocampal-independent simple discrimination problem involving the same reinforcer and response requirements was not impaired by WD, indicating that motivational or physical deficits did not underlie impaired sFN performance. Recent evidence suggests WD intake is associated with a distinct temporal pattern of sFN deficits. Performance is temporarily impaired after short-term (10 day) access, remits, then returns again after a more extended (e.g., 90 day) period [57]. These deficits often correlate with the pernicous brain changes associated with WD intake and obesity [56, 57, 71]. Our research program has observed the greatest degree of pathology (e.g., BBB permeability) in rodents that also showed hippocampal-dependent cognitive dysfunction and excess weight gain [57, 67, 72]. This suggests that these diets promote weight gain as a result of their ability to disrupt hippocampal function, and therefore the inhibitory control of food intake.

Further, WD-fed animals are less adept at using interoceptive food cues to exert discriminative control over appetitive behavior. In a recent example [73], rats were simultaneously trained to use interoceptive (deprivation state) and exteroceptive (tone, white noise) cues to predict the presence of a sucrose reward. Rats were then either maintained on chow or switched to the WD, the latter of which weakened the ability of deprivation state to modulate food intake. WD-fed rats maintained the ability to utilize exteroceptive cues to predict reward, suggesting that a WD dimishes the discriminatory power of internal cues, relative to external stimuli.

The "outward" spiral

Here, we have described a vicious cycle in which high-energy diets harm the hippocampus (see F.1). This progressively weakens the ability of satiety signals to inhibit the capacity of environmental food-related stimuli to elicit appetitive behaviors, and results in positive

energy balance, weight gain, and further harm to the hippocampus. We have described how this cycle may be initiated by WD consumption or the obesity that results from WD maintenance. However, it could commence with hippocampal injury resulting from disease, trauma, exposure to environmental toxins, or other factors. Rather than damaging the hippocampus directly, the effects of a WD, toxic substances, or illnesses could also alter hippocampal function indirectly by compromising the integrity of the BBB.

This model does not deny the possibility that, in addition to the dampening of inhibitory controls, external cues have become more powerful and prevalent elicitors of appetitive behavior. So-called obesogenic environments, which are rife with cheap, palatable, energy-dense foods, are common throughout the industrialized world. Residents of these communities are bombarded with advertising and marketing materials that serve as almost constant reminders to eat [74–77]. However, we suggest that at least part of the rise in the power of environmental stimuli to evoke intake is a reduced ability of interoceptive satiety signals to offset that power.

In addition to obesogenic environmental stimuli, western and westernized societies contain numerous external cues designed to inhibit intake, such as nutritional information labels, public service announcements describing the health risks associated with obesity, frequent advertisements for dietary interventions, and widespread cultural penchants for slimness. Given the continuing obesity pandemic, the effectiveness of these “obesolytic” cues can also be questioned [but see 75, 78]. It may be that, like external cues in sFN discrimination problems, WD intake also reduces the ability of obesolytic environmental stimuli to antagonize the eating evoked by obesogenic environmental cues. This speculation suggests that interference with hippocampal-dependent mechanisms may diminish the potential for both interoceptive and exteroceptive stimuli to inhibit appetitive and consummatory behaviors.

Regardless of its etiology, new findings summarized here indicate that the “outward spiral” may arise based, at least in part, on WD-induced pathologies that interfere with hippocampal function. In rats, this interference can be observed after relatively brief exposure (90 days or less) to a WD and may be manifested in the form of reduced ability to use interoceptive satiety signals to counter the power of food-related environmental stimuli to evoke appetitive and eating behaviors.

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discriminative control over conditioned responding to that of discrete auditory cues. After maintenance on Western diet, rats were unable to use deprivation state to predict reinforcement in the appetitive task above, but retained the ability to use discrete auditory cues. This indicates that Western diet and obesity diminish the potency of interoceptive, relative to external, cues to elicit behavior.

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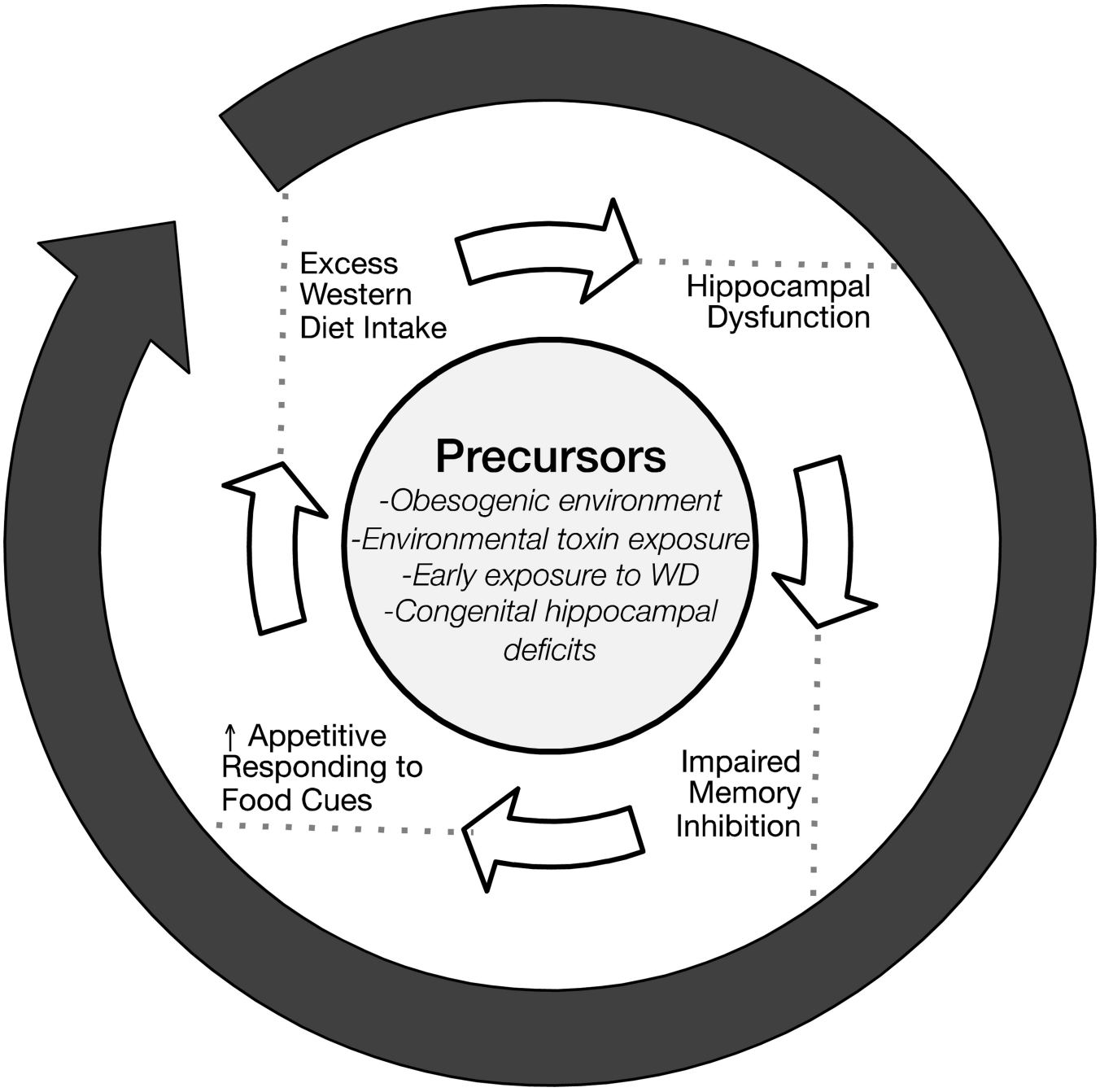
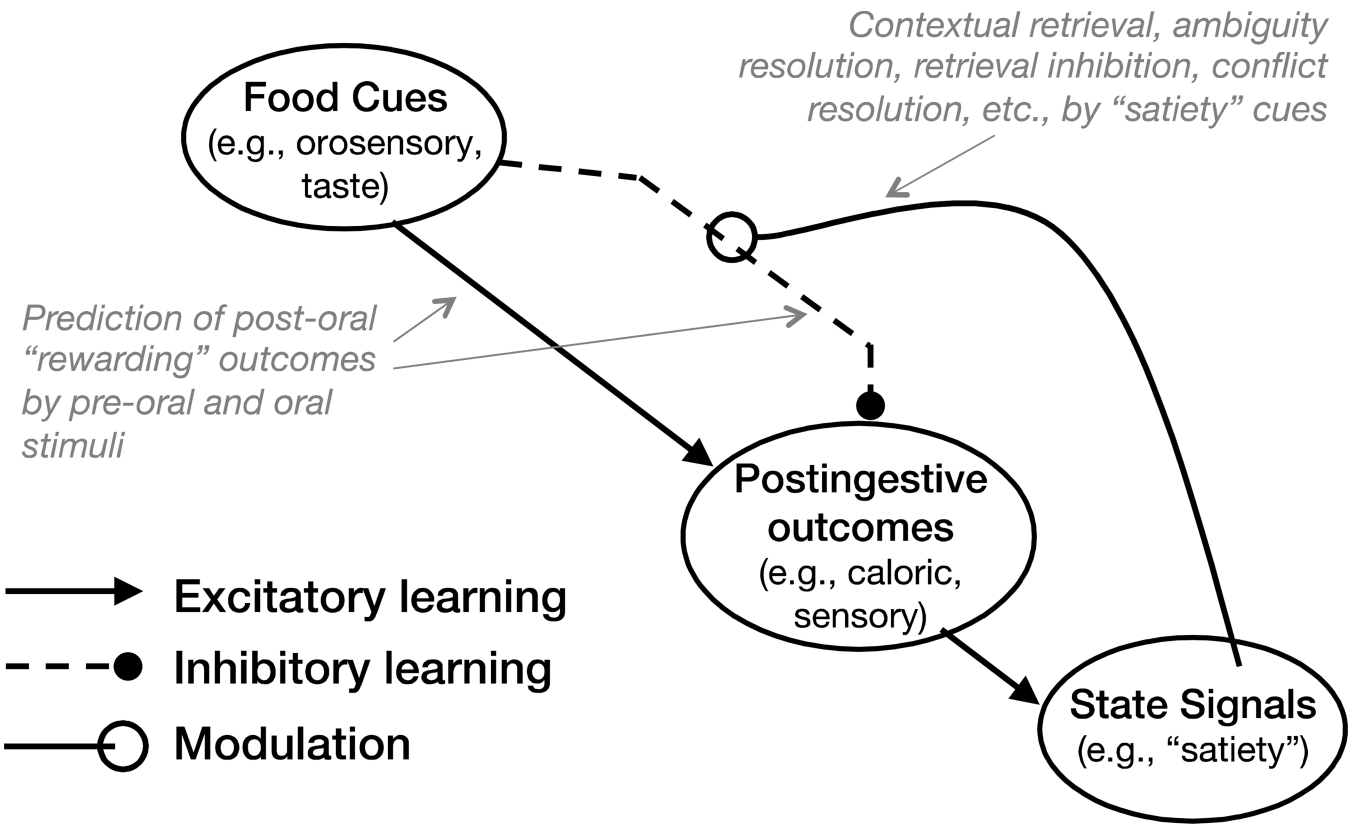
Highlights

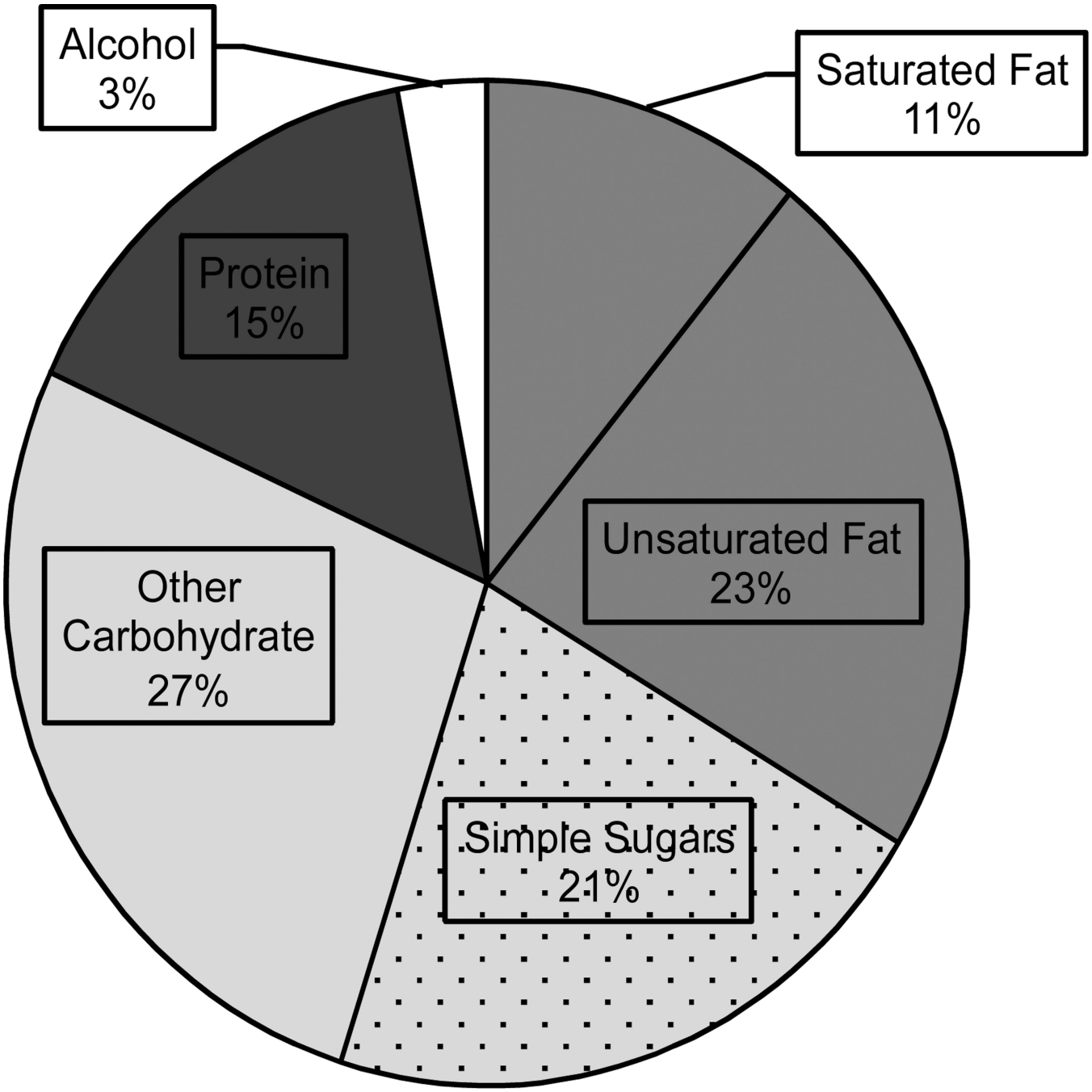
- The hippocampus is a substrate for the contextual stimulus control of behavior.
- Satiety signals are contextual cues that underlie the inhibitory control of eating.
- The Western diet (WD) is associated with hippocampal pathology and dysfunction.
- Both hippocampal damage and WD impair discriminative control by satiety cues.
- WD may induce a vicious cycle of overeating and hippocampal-based memory decline.



F.1.
A vicious cycle model of obesity and cognitive decline.



F.2.
An associative model of energy intake and body weight regulation.



F.3.
Average macronutrient consumption for US adults, 2011–2012